The effect of common infections on cognition and dementia in people with and without diabetes

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Thesis submitted in accordance with the requirements for the degree of Doctor of Philosophy of the University of London

NOVEMBER 2021

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Declaration

I, Rutendo Muzambi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in this thesis.

Signed: Rutendo Muzambi
Date: November 2021

Acknowledgements

I am incredibly grateful for the constant support, encouragement and guidance of my supervisors Charlotte Warren-Gash, Krishnan Bhaskaran and Liam Smeeth. Without their expertise and dedicated involvement throughout my PhD, this thesis would not have been possible.

I am also deeply grateful to my advisory panel, Carol Brayne, Nish Chaturvedi and Christopher Rentsch, for offering their extensive knowledge and expertise. I would like to extend my gratitude to my co-authors Victoria Garfield and Dylan Williams for their expertise and advice.

I wish to also thank the Alzheimer's Society for funding this PhD and the Alzheimer's Society research monitors Gillian Andrew and Sue Boex for their insightful comments, suggestions and support throughout my PhD.

To my fellow PhD students, colleagues and friends, particularly Liang-Yu Lin, Charlotte Kerr, Alexandra Richards, Jennifer Davidson, Jeremy Brown, Steady Chasimpha, Deji Oloko and many others: thank you for the chats, laughter and support over the years.

Finally, I cannot begin to express my gratitude to my partner, Ben, for his relentless support and words of encouragement. I am also immensely grateful to my mum and sister Rebecca for their tremendous understanding and support with all my studies.

Abstract

Introduction: Dementia is a major contributor to disability and dependence worldwide and is currently the leading cause of death in England. As the global burden of dementia continues to rise, identification of modifiable risk factors for dementia has become an urgent public health priority. Common infections may be associated with risk of dementia or cognitive impairment, but the nature, temporality or magnitude of any relationship is unclear.

Objectives and data sources: The objectives of this thesis were to 1) systematically review evidence from longitudinal studies on the association between common clinically symptomatic bacterial infections and risk of incident dementia or cognitive decline, 2) examine the association of late-life infections with incident dementia using data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES), 3) investigate the association of midlife infections and incident dementia using data from the UK Biobank study, 4) investigate the association between midlife infections, cognitive decline and neuroimaging measures using data from the UK Biobank study.

Results: Evidence from 7 studies included in the systematic review (chapter 3) suggested that common clinically symptomatic bacterial infections were associated with an increased risk of dementia, with effect estimates ranging from HR 1.10 (95% CI; 1.02–1.19) to OR 2.60 (95% CI; 1.84–3.66) in a narrative synthesis of findings. However, studies were either from the United States or Taiwan, predominantly focused on hospitalised infections, mainly pneumonia or sepsis, and faced other methodological limitations including small sample sizes or inadequate confounder adjustment. Findings from my CPRD and HES study (chapter 5) showed that late life infections were associated with dementia risk in a population of 989,800 individuals aged 65 years and older. Dementia risk was higher for sepsis, pneumonia, infections resulting in hospital admission and among individuals with diabetes. In the third study (chapter 6) which compared the association of infections and dementia in a younger healthier population (the UK Biobank study), a lack of association was observed between the presence, site and setting of common midlife infections and dementia though consistent with the CPRD and HES study, an association was found for hospitalised infections. In the final study (chapter 7) which included 16,728 participants (median age 56.0 years [IQR 50.0-61.0]) midlife infections were not associated with cognitive decline on the mean correct response time, fluid intelligence and prospective memory tests. However, urinary tract infections and increasing numbers of infections were associated with slight declines in visual memory performance over time. No association was found between infections, hippocampal and white matter hyperintensity volume.

Conclusion: Common late-life infections were associated with an increased risk of dementia, particularly for more severe infections (sepsis, pneumonia and infections resulting in hospital admission). However, mid-life infections were not associated with cognitive decline, hippocampal or white matter hyperintensity volume, with the exception of visual memory. Clinical trials are needed to investigate whether strategies to prevent infections lower subsequent dementia risk. In terms of cognitive decline, further studies with sufficient sample sizes for infection types and hospitalised infections, are needed to confirm the findings in this thesis.

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Abbreviations

BMI	Body Mass Index
BNF	British National Formulary
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
CTV3	Clinical Terms Version 3
dm+d	Dictionary of Medicines and Devices
EHRs	Electronic Health Records
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HES	Hospital Episode Statistics
HES APC	Hospital Episode Statistics Admitted Patient Care
HR	Hazard Ratio
ICD-10	International Classification of Diseases, Tenth revision
IMD	Index of Multiple Deprivation
ISAC	Independent Scientific Advisory Committee
LRTIs	Lower Respiratory Tract Infections
LSOA	Lower Layer Super Output Area
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NHSCR	NHS Central Register
ONS	Office for National Statistics
OR	Odds Ratio
PPV	Positive Predictive Value

PROSPERO	International Prospective Register of Systematic Reviews
QOF	Quality and Outcomes Framework
SSTIs	Skin and Soft Tissue Infections
UK	United Kingdom
US	United States
UTIs	Urinary Tract Infections
UTS	Up To Standard

Chapter 1: Background

1.1 Introduction

In this chapter, I describe the background and rationale for this thesis. I provide an overview of dementia which includes the definition, epidemiology, underlying neuropathology and risk factors for dementia. I then describe the epidemiology of infections and the potential association and mechanisms linking infections and dementia. Lastly, I discuss the epidemiology of diabetes and its relationship with both infections and dementia. In chapter 2, I outline the aims and objectives of this thesis informed by the present chapter.

1.2 Dementia

1.2.1 Dementia definition

Dementia is a complex, multifactorial syndrome characterised by a progressive deterioration in cognitive function that interferes with an individual's ability to perform activities of daily living.[1] Characteristics of dementia may include a decline in memory and reasoning capabilities, impaired language and visuospatial abilities, behavioural and psychological changes such as apathy and depression, and eventually difficulty walking, speaking or swallowing.

1.2.2 Epidemiology of dementia

Dementia is a major public health challenge and poses a significant burden to individuals, healthcare givers and the healthcare system. The total cost of dementia is rising. Worldwide, the total cost of dementia is expected to double to US $2 trillion by 2030. [2,3] In the UK, the current cost of dementia is projected to rise from £26 billion to £55 billion by 2040.[4,5] Besides its economic burden, dementia is a major contributor of disability and dependence worldwide. In 2016, dementia was the fifth leading cause of death in the world and it is currently the leading cause of death in England as of August 2021, accounting for 10.9% of all deaths.[6]

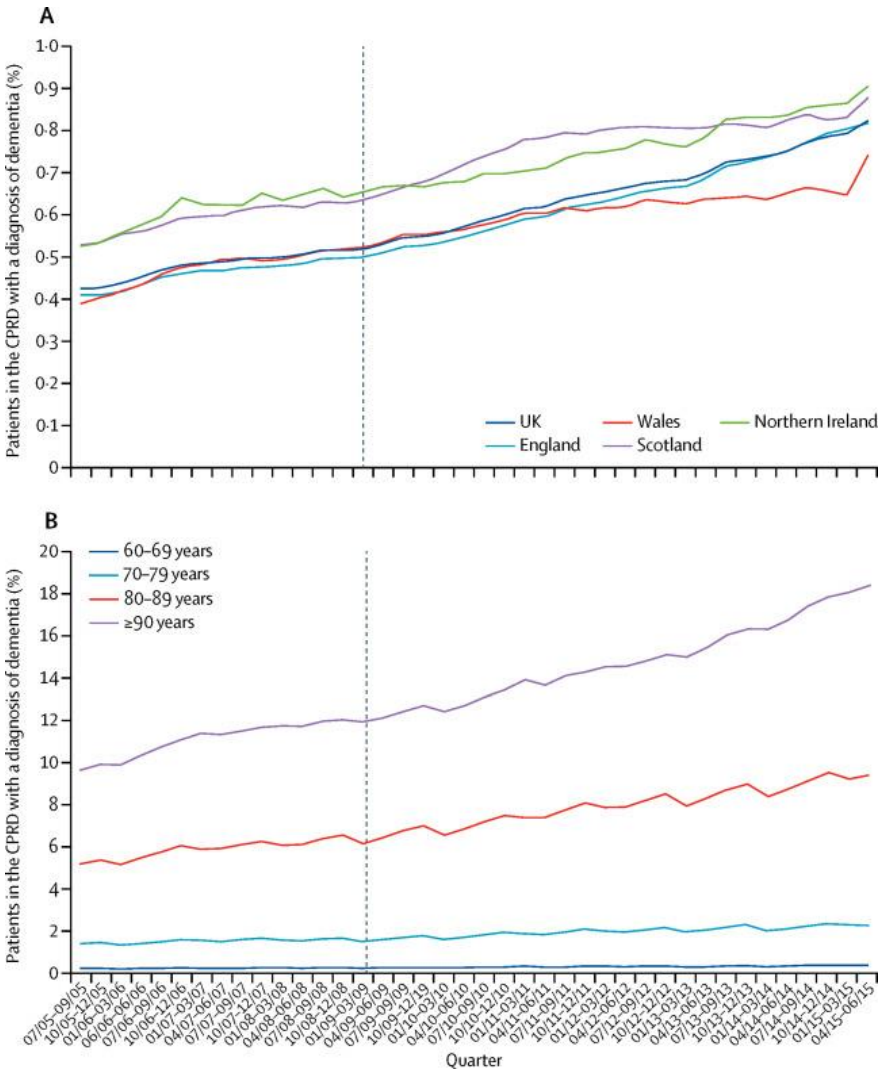

Figure 1.1 Proportion of individuals diagnosed with dementia in the UK in the Clinical Practice Research Datalink data source between July, 2005, and June, 2015 by (A) region and (B) age.

Reproduced from The Lancet, Vol 2, Donegan et al 2017, Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study, pages e149-e156 (2017). This article is open access distributed under the terms of the creative commons CC BY 4.0 license.[7,8]

The number of people living with dementia worldwide has more than doubled in the last few decades, from 20.2 million in 1990 to 43.8 million in 2016.[9] In the UK, the number of individuals diagnosed with dementia in primary care doubled over a 10 year period from 0.4% in 2005 to 0.8% in 2015 (Figure 1.1). Hospital dementia diagnoses also increased over time in the UK. It is estimated that the number of people living with dementia will increase by 57% between 2016 and 2040; globally the number of people living with dementia is projected to increase to 152 million by 2050.[3,10] This rise in the burden of dementia is being fuelled by population ageing and growth. Worldwide, the population of adults aged 65 years and older rose from 6% in 1990 to 9% in 2019 and is projected to rise to 16% by 2050.[11]

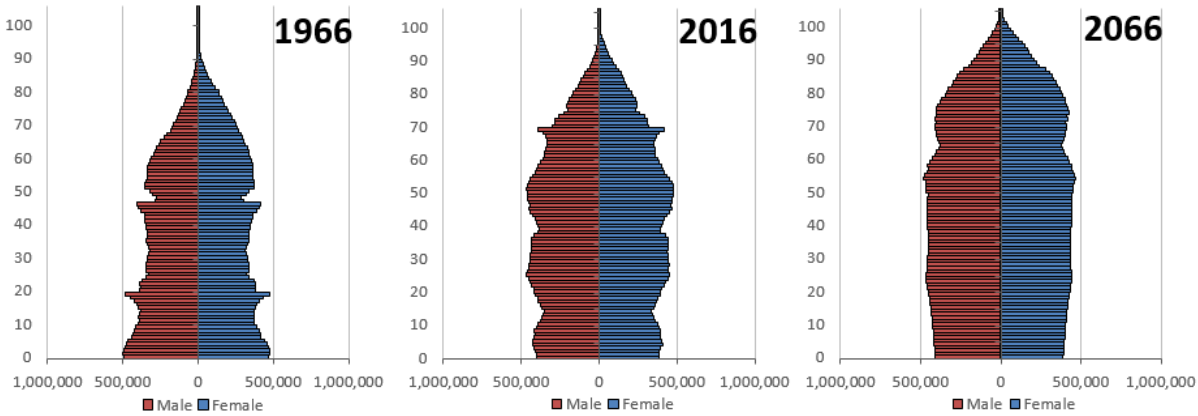

Figure 1.2: UK population pyramids in 1966, 2016 and 2066.

Reproduced from population estimates, Principal population projections, 2016-based, Office for National Statistics (ONS) obtained under the Open Government Licence v3.0.[12,13] Licensing terms compatible with Creative Commons Attribution License 4.0.[8]

Figure 1.2 displays the population estimates of the UK population every 50 years from 1966. The population pyramids illustrate the ageing UK population with 4.3 million adults aged 65 years and older in 1966 which increased to 6.5 million in 2016.[12] The most recent estimates from the Office for National Statistics (ONS) show that the UK

population has grown from 56.3 million in 1982 and reached 66.8 million in 2019 with an additional 7.5 million people aged 65 years and older estimated to be living in the UK in 50 years' time.[14]

1.2.3 Dementia age-specific incidence

Recently, population-based studies from high income countries such as the UK,[15] Netherlands,[16,17] France,[18] Sweden,[19] and the US[20,21] have reported a declining trend in the age-specific incidence of dementia among older adults. Evidence from the Cognitive Function and Ageing Studies suggested a 20% decline in dementia incidence over 2 decades (Figure 1.3). A UK modelling study using data from the English Longitudinal Study of Ageing cohort also found a decline in the age-specific incidence of dementia in England and Wales at a relative rate of decline of 2.7% annually, after accounting for the competing effect of mortality and dropouts. The decline in the age-specific incidence rate of dementia has been attributed to improvements in educational attainment and vascular risk factors.[10]

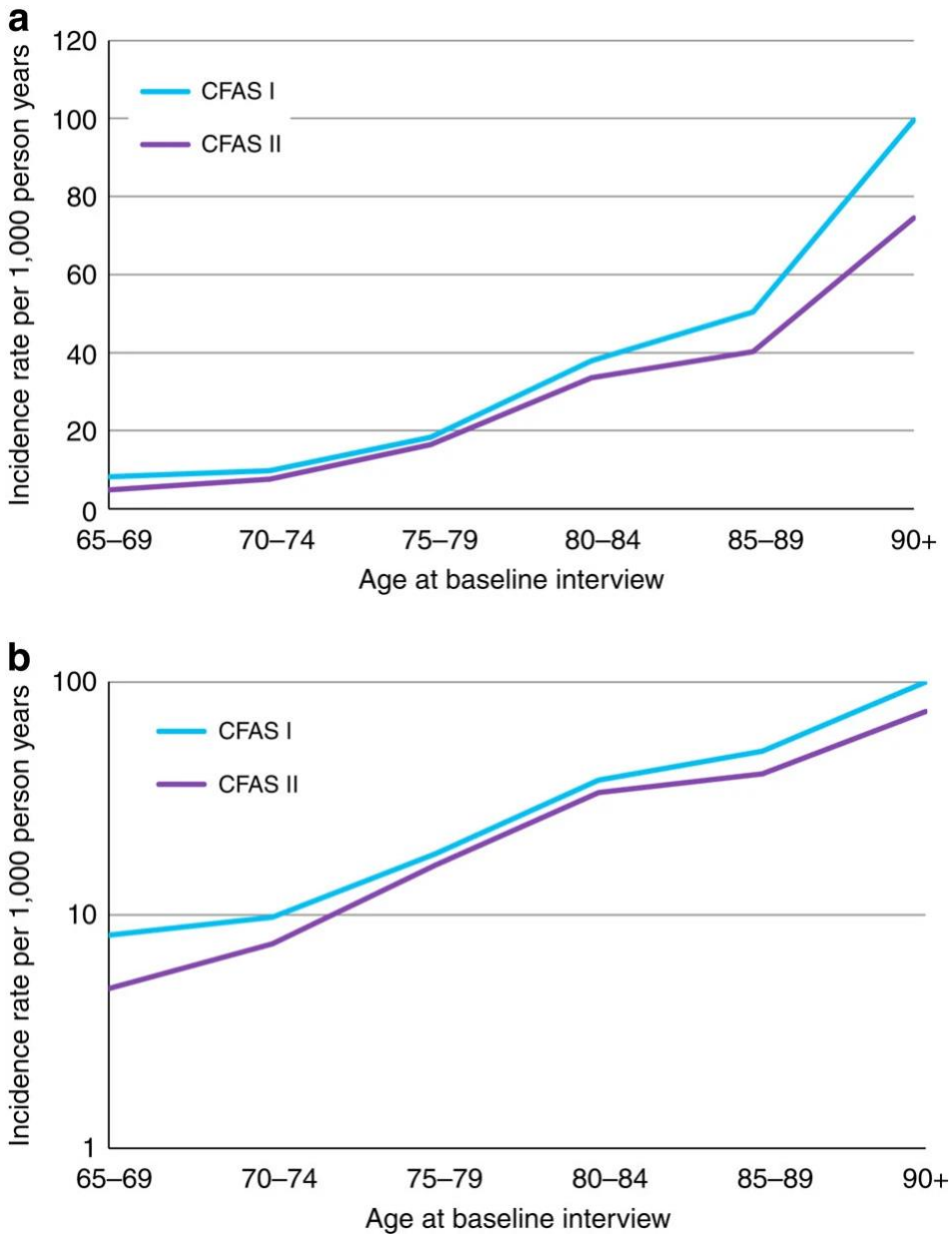

Figure 1.3. Incidence rate of dementia per 1,000-person years in CFAS I and CFAS II by age at baseline interview using (a) a natural scale and (b) a logarithmic scale. CFAS; Cognitive Function and Ageing Studies. Reproduced from Nature Communications, Vol 7, Matthews et al, A two-decade dementia incidence comparison from the Cognitive Function and Ageing Studies I and II (2016) under the CC BY 4.0 license.[8,15]

1.2.4 Pathological processes of dementia

Alzheimer's disease is the most commonly diagnosed dementia sub-type in adults aged 65 years and older, [22,23] though population-based neuropathology studies have found that the majority of individuals have mixed dementia with pathology consistent with

Alzheimer's disease and vascular dementia. [24,25] Classical histopathological hallmarks of Alzheimer's disease include accumulation of β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau protein.[26,27] Updated biomarker models of Alzheimer's disease suggest that vascular dysregulation is implicated in the early pathological processes associated with dementia progression. [28]

Vascular dementia is a severe form of vascular cognitive impairment. Vascular cognitive impairment includes cognitive disorders associated with cerebrovascular disease and has been defined as "a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain."[29] Other subtypes of dementia include, but are not limited to, mixed dementia, frontotemporal dementia, Lewy body dementia and Parkinson's disease dementia.

1.2.5 The trajectory of dementia

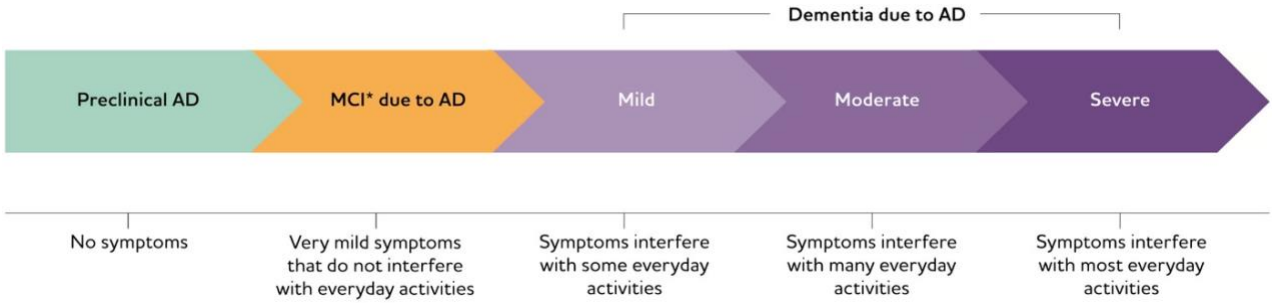

Figure 1.4. Alzheimer's disease continuum.
*MCI; Mild Cognitive Impairment. Reproduced from Alzheimer's & Dementia, Vol. 16, 2020 Alzheimer's disease facts and figures, Pages No. 70, Copyright (2020), with permission from John Wiley and Sons.[30]

Dementia has a long preclinical phase which can take many years to develop before the clinical onset of dementia.[31] Figure 1.4 depicts of the progression of Alzheimer's disease from the preclinical phase to severe dementia. During the preclinical phase of dementia, individuals do not exhibit impaired cognitive abilities however the prodromal

(predementia) stage is characterised by mild cognitive impairment. This prodromal stage not only encompasses early clinical symptoms of dementia but also biomarker of cerebrospinal fluid evidence consistent with the pathological changes of dementia.[32] The preclinical and prodromal phases of dementia are important for informing dementia prevention studies and for developing accurate biomarkers of these early stages before a clinical diagnosis of dementia. However, it is important to also acknowledge that not all individuals with subclinical cognitive impairment such as mild cognitive impairment will progress to dementia; some never progress to dementia while some have been shown to regain cognitive function.[33-35]

1.2.6 Delirium

Delirium is an example of an acute, rather than chronic, form of cognitive impairment. Delirium is a serious neuropsychiatric syndrome characterised by acute cognitive dysfunction and inattention.[36] Specifically, symptoms of delirium include reduced concentration, confusion, auditory and visual hallucinations, reduced mobility and movement and changes in communication, mood or attitude.[37] Delirium is associated with adverse outcomes such as increased length of hospital stay, hospital acquired complications, morbidity, cognitive decline, dementia and mortality.[37,38] Evidence from 3 population-based studies of 987 autopsied brains suggests that delirium is not only independently associated with faster trajectories of cognitive decline but may interact with the pathological processes of dementia to accelerate cognitive decline.[39] Other studies, including a meta-analysis of 23 studies, also confirm that delirium is strongly associated with an increased risk of long term cognitive decline and dementia.[40,41] Conversely, delirium frequently occurs in people with dementia.[42] Given the similarities between the clinical presentation of delirium and dementia, it can be challenging to

distinguish between delirium and dementia which can potentially lead of misclassification.

1.2.7 Neuroimaging measures

Early studies of brain magnetic resonance imaging (MRI) examined the cerebral anatomy of the human brain and brain morphology changes with advancing age. These studies suggested that increasing age was associated with a decline in regional brain volume such as the hippocampus, white matter and grey matter volume. [43-45] The hippocampus, located in the medial temporal lobe, plays an important role in declarative memory and spatial navigation. White matter hyperintensities are lesions in the brain associated with cerebrovascular disease, cognitive decline and dementia.[46,47] Hippocampal atrophy, white matter hyperintensities and whole brain atrophy accelerate in the early stages of Alzheimer's disease and in cognitively normal individuals before mild cognitive impairment.[48-55] These structural brain MRI markers can occur years before a dementia diagnosis and as such are important biomarkers for the early signs of dementia. [54,56]

1.2.8 Dementia diagnosis

According to the UK National Institute for Health and Care Excellence guidelines, the process of a dementia diagnosis involves an initial assessment in a non-specialist setting. During the initial assessment, an individual's cognitive, behavioural and psychological symptoms and the effect of these symptoms on an individual's daily life are investigated. Further assessments include a physical examination, cognitive testing using validated measures and blood and urine testing to rule out reversible causes of

cognitive decline. An individual is then referred to specialist dementia diagnostic services where a dementia diagnosis including dementia subtype is made using validated criteria such as the National Institute on Aging criteria for Alzheimer's disease or National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences criteria for vascular dementia.[57] Individuals may be diagnosed with dementia in primary care without referral to specialist settings.

Dementia diagnosis is based on diagnostic criteria which do not have clear thresholds or specific measures relating to the level of cognitive decline and its impact. Therefore, diagnosis is based on clinical judgement or consensus. [58] In primary care, dementia has tended to be underdiagnosed with some past studies suggesting that over 50% of dementia cases were not detected.[59,60] In recent years, the proportion of cases receiving a diagnosis appears to have increased and recent evidence suggests that around two thirds of people living with dementia have a diagnosis in primary care.[61] A dementia primary care record could have been diagnosed in primary care or in a specialist setting such as a memory clinic. Accuracy on the number of people living with dementia is affected by a number of factors which include differences in individuals' health seeking behaviour and UK policy initiatives such as the Quality Outcomes Framework (QOF) in 2004 and National Dementia strategy in 2009 which aimed to increase the recording of dementia.[62-64]

1.2.9 Dementia pharmacological therapy

Current pharmacological therapy for dementia works to alleviate the symptoms of dementia. Acetyl-cholinesterase inhibitors (donepezil, rivastigmine or galantamine) are

recommended for patients with mild or moderate Alzheimer's disease.[57] They work by inhibiting the enzyme acetylcholinesterase, which is responsible for breaking down the neurotransmitter acetylcholine, thus increasing the concentration of acetylcholine. Another pharmacological intervention licensed in the UK for dementia is memantine. Memantine is recommended as an alternative therapy for those with moderate or severe Alzheimer's disease.[57] It is a glutamate receptor antagonist, which works by increasing the receptivity of nicotinic receptors to acetylcholine. Although pharmacological management of dementia exists, there are currently no disease modifying treatments that can alter the pathology or course of dementia.[65] In the decade of 2002 to 2012, over 400 drug trials for Alzheimer's disease were performed, and of these 99.6% failed to reach marketing approval.[66] This failure in finding disease modifying pharmacological therapy for dementia has led to increased focus on dementia risk reduction.

1.2.10 Modifiable risk factors

Age is the single greatest risk factor for dementia, with the risk doubling every 5 years after the age of 65, however, it has been estimated that around a third of dementia cases worldwide can be accounted for by modifiable risk factors.[67,68] In 2017, evidence from the Lancet Commission on dementia prevention, intervention and care suggested that around 35% of dementia, calculated using population attributable fractions (PAF), was attributed to nine potentially modifiable risk factors in early, mid- and late-life. Low educational attainment was identified as an early life risk factor, midlife risk factors were hearing loss, hypertension and obesity, and late life risk factors were smoking, depression, physical inactivity, social isolation and diabetes.[68] In 2020, the Lancet commission was updated and the new life course model found that 40% of dementia

could be eliminated by accounting for potentially modifiable risk factors with the addition of three new risk factors; traumatic brain injury, air pollution and excessive alcohol consumption (Figure 1.5).[69] However, these PAFs were calculated using data from observational studies as a result residual confounding and reverse causality cannot be ruled out.[70] Therefore, these estimates may reflect non-causal associations. Nonetheless, Identification of modifiable risk factors for dementia and subsequent treatment of these risk factors could be crucial in reducing the risk and overall burden of dementia. This highlights the importance of identifying other preventable risk factors of dementia.

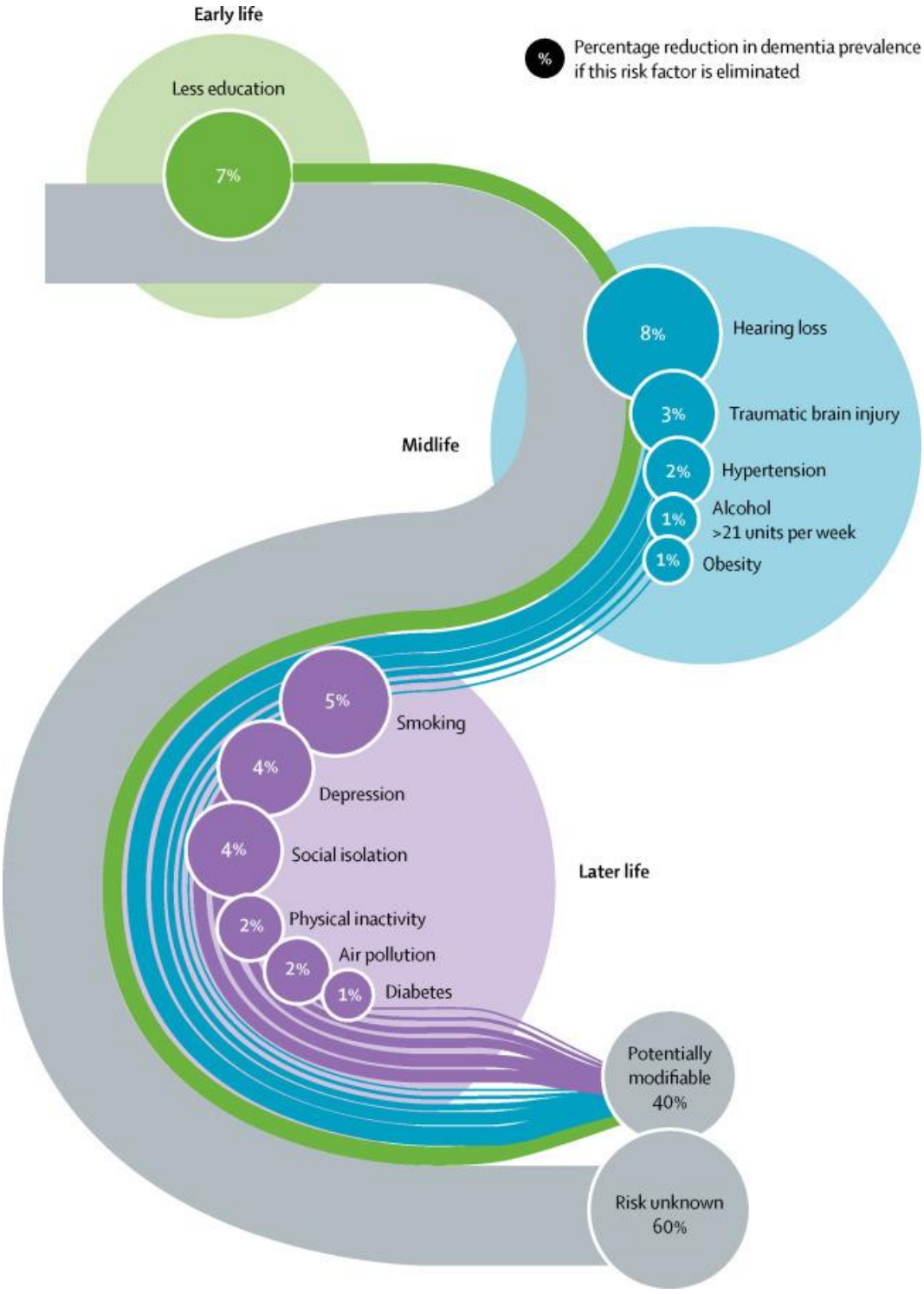

Figure 1.5. Population attributable fraction of potentially modifiable risk factors for dementia. Reprinted from The Lancet, Vol. 396, Livingston et al, Dementia prevention, intervention, and care: 2020 report of the Lancet Commission, Pages No. 413-446, Copyright (2020), with permission from Elsevier.

1.2.11 Challenges in dementia epidemiology

Studies investigating dementia incidence face important challenges. Firstly, given that dementia has a long preclinical phase, which may take years (or decades) to develop, studies need a sufficient follow up period to reduce the potential for reverse causality.[31,71,72] Second, loss to follow up is a concern given the long duration of follow up required for dementia to develop and given that individuals experiencing cognitive decline and dementia may be more likely to drop out from a prospective study.[73] Loss to follow up is minimised in routinely collected healthcare datasets, however, these datasets rely on individuals seeking healthcare service and thus healthcare seeking behaviour can influence the likelihood of receiving a dementia diagnosis. Third, under-ascertainment of dementia is an issue particularly in routinely collected electronic health records which might miss undiagnosed dementia or dementia during the early or milder stages.[59,60] Fourth, when investigating associations between potential dementia risk factors and dementia incidence, confounding by factors such as age, the single greatest risk factor for dementia, is of concern and raises challenges in disentangling the contributions of age on dementia risk and the independent effects of other dementia risk factors. The aetiology of dementia is likely to be multifactorial with a wide range of risk factors which are unlikely to be measured in any single dataset therefore there is a risk of residual confounding in observational studies. Fifth, the underlying biology of dementia remains poorly understood which limits the ability to understand potential risk factors and mechanisms contributing to dementia as well as the potential to discover effective disease modifying agents. Sixth, different exposures may have differing effects on dementia risk over a person's life-course (early, mid or late-life), highlighting the need to examine dementia risk at different life stages.

1.3 Infections

1.3.1 Infection definitions and causative agents

Lower respiratory tract infections (LRTIs), urinary tract infections (UTIs) and skin and soft tissue infections (SSTIs) are among the most acute infections affecting the elderly in the UK and worldwide.[74] LRTIs include bronchiolitis, bronchitis and pneumonia, with pneumonia one of the most severe infections commonly associated with mortality risk. LRTIs can be caused by bacteria, viruses or fungi. *Streptococcus pneumoniae* is a common bacterial causative agent for pneumonia.[75] Other bacterial agents responsible for pneumonia and other LRTIs include *Haemophilus influenzae* and *Chlamydia pneumoniae.*[76,77]

UTIs include infections of the bladder, kidney, urethra and ureters, for example, cystitis, pyelonephritis and urethritis.[78]. UTIs are predominantly caused by gram-negative bacteria with *Escherichia coli* bacteria accounting for between 65 to 75% of all urinary tract infections. Other pathogens such as gram-positive bacteria (e.g., *Staphylococcus aureus*) and fungi (e.g., *Candida spp)* are less common causative agents for urinary tract infections.[79,80]

SSTIs encompass a range of conditions which affect the skin and subcutaneous tissue, muscle or fascia. These infections, which differ in severity from superficial infections to severe necrotising infections, include impetigo, erysipelas and cellulitis.[81] Gram-positive and gram-negative bacteria are responsible for SSTIs with *Staphylococcus aureus and Streptococcus pyogenes* among the most common pathogens implicated in SSTIs. [82]

LRTIs, UTIs and SSTIs can lead to sepsis. Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection."[83] Although viral, parasitic and fungal pathogens may be responsible for sepsis, gram positive bacteria (e.g. Staphylococcus aureus and Streptococcus pyogenes) are the most common cause of sepsis. [84,85]

1.3.2 Infection epidemiology

According to the 2016 Global Burden of Diseases study, LRTIs are the sixth leading cause of mortality in the world. In the US, pneumonia hospitalisation rates have increased over time by 20% from 1988-1990 to 2000-2002 in adults aged 65 years and older.[86,87] In England, hospital admissions for pneumonia have increased by approximately 4% per year from 1998 to 2008 and at a much faster rate of around 9% per year from 2009 to 2014.[88] Other studies have reported an increase in pneumonia hospital admissions in England. [89,90] Evidence from UK primary care electronic health records (EHRs) among adults, including those aged 65 years and older, suggests an increase incidence of clinically diagnosed LRTIs and pneumonia between the years 1997 to 2017.[91,92]

UTIs are one of the most common infections in adults aged 65 years and older. In a large-scale UK primary care records study of almost one million adults aged 65 years and older, the incidence of clinically diagnosed UTIs has increased over a 10 year period from 2004 to 2014.[93] Similarly, evidence from UK primary care suggests the rates of hospital admission for UTIs as well as pneumonia has increased over a 10-year period.[94] Likewise, a similar increase in hospitalisation of UTIs has been observed in the US.[95]

SSTIs have increased in incidence rapidly in the US [96,97]. Complications of SSTIs include increased mortality, hospitalisation and prolonged length of hospital stay.[98]

The incidence of sepsis hospitalisations and mortality rates is increasing.[99,100] According to the global burden of disease study, an estimated 48.9 million incident cases of sepsis and 11.0 million deaths were recorded worldwide in 2017, with estimates double that of previous global figures.[101] The incidence of sepsis diagnosed in primary care rose in the years between 2002-2017.[102] Survivors of sepsis have been associated with long term adverse outcomes such as poor quality of life,[103,104] functional disability,[105] depression,[106] recurrent infections,[107] and cognitive impairment.[105]

1.4 Infections, dementia and cognitive impairment

1.4.1 Association between infections, delirium and Alzheimer's disease

Common infections in older adults such as UTIs, LRTIs, SSTIs and sepsis are well known to be associated with short term reversible changes in cognition manifested as delirium, however, whether there is long-term cognitive impairment, after resolution of delirium, is less well known.[108-111] .

Although the relationship between common clinically symptomatic infections and dementia has been understudied, infectious agents have been hypothesised to be involved in the pathogenesis of dementia for decades and a wide range of pathogens have been implicated in this association. Reactivated herpes simplex virus was hypothesised to travel from the trigeminal ganglia into the limbic areas of the brain most impacted by Alzheimer's disease in 1982 by Ball.[112] This work led to subsequent studies investigating the presence of infectious agents in post-mortem brain tissue of

individuals with Alzheimer's disease. These pathogens include herpes simplex virus infections,[113-115] spirochetes bacteria,[116] *Borrelia burgdorferi*,[117,118], *Chlamydia pneumoniae*,[119,120] and other viral, bacterial, fungal and protozoal microorganisms.[121] Over the last three decades, there has been a large body of evidence to support the role of chronic infections in the aetiology of Alzheimer's disease, though this evidence is largely cross-sectional. Additionally, these studies have faced important methodological limitations such as small sample sizes and inadequate adjustment for confounding.[121]

1.4.3 Mechanisms

The mechanisms underlying the association between infections and subsequent dementia are uncertain. Systemic inflammation has been suggested as a potential pathway linking infections and dementia.[122] The inflammatory response to infection triggers the release of pro-inflammatory mediators and activation of cytotoxic microglia which may result in deterioration of cognitive function and thus increasing the risk of dementia. In support of this mechanism, evidence from a growing number of longitudinal studies suggests that markers of systemic inflammation are involved in the pathogenesis of dementia.[123]

Severe acute systemic inflammation such as severe sepsis or prolonged systemic inflammation from inflammatory comorbidities such as diabetes, arthritis and obesity can activate microglia and is associated with cognitive decline and dementia risk in a normal healthy brain. Mild or moderate acute systemic inflammation in a pathological brain can exacerbate inflammation in the central nervous system, leading to synaptic loss, neuronal death, memory dysfunction and other damage in the brain which increase long term cognitive decline. [124]

The association between infections and dementia may also be driven by delirium. Infections may trigger delirium through systemic inflammation. Infections can lead to the secretion of inflammatory mediators, activation of microglia which produce pro-inflammatory cytokines and can eventually lead to neuronal dysfunction or cell death contributing to manifestations of delirium.[36] Systemic inflammation in delirium may in turn lead to neurodegeneration or an exaggerated inflammatory response resulting in neuronal injury and subsequently cognitive decline and dementia.[125-127] Therefore, given the relationship between systemic inflammation, delirium and dementia, it is possible that delirium may lie on the causal pathway of the association between infections and dementia. However, the biological mechanisms underlying delirium and dementia remain poorly understood.

Lastly, the potential association between infections and dementia could be explained by vascular damage. Common infections have been associated with the increased risk of a range of cardiovascular diseases including stroke and myocardial infarction which are in turn associated with an increased risk of dementia.[128-130] Therefore, systemic inflammation and vascular damage may be potential mechanisms in the association of infections and dementia.

1.5 Diabetes

1.5.1 Epidemiology of diabetes

Diabetes mellitus is a group of chronic metabolic diseases characterised by elevated blood glucose levels, hyperglycaemia, and insulin deficiency or resistance.[131]

Worldwide, 462 million individuals (6.3% of the world's population) were estimated to be living with type 2 diabetes in 2017. It is estimated that by 2040 the prevalence of diabetes will increase to 7,862 individuals per 100,000 from 6059 cases per 100,000 person years.[132] In the UK, over 4.9 million people are living with diabetes, with approximately 90% living with type 2 diabetes. This number is estimated to rise to 5.5 million people by 2030.[133] Diabetes is associated with a range of outcomes including microvascular and macrovascular vascular complications, infections and dementia.[134-136]

1.5.2 Diabetes, infections, cognition and neuroimaging markers

People with diabetes have an impaired immune response, thought to be caused by hyperglycaemia, which increases their susceptibility to infections.[137] Evidence from a large body of literature including a systematic review and meta-analysis of 345 cohort and case control studies suggests that diabetes is associated with a wide range of infections, with a stronger associations for skin, genitourinary, respiratory and bloodstream infections. [138] In a large English population-based cohort of 100,000 individuals, diabetes was associated with higher rates of serious and severe infections, including pneumonia, sepsis, infections requiring hospitalisation or infection-related mortality.[139]

Diabetes is also a well-known risk factor for cognitive decline and dementia.[136,140,141] In a recent systematic review and meta-analysis comprising 2.3 million individuals from 14 prospective studies, diabetes was associated with a 60% increased risk of all cause dementia and a 40% increased risk of non-vascular dementia.[142] Numerous neuropsychological studies have consistently found that people with diabetes perform

worse on multiple domains of cognitive function, including speed processing and mental flexibility, compared to the general population.[143-145] Diabetes has also been associated with neuropathological markers of cognitive dysfunction, such as hippocampal atrophy and white matter hyperintensities in neuroimaging studies.[146,147]

While diabetes has well-established relationships with both infections and dementia, it is unknown whether inflammatory comorbidities such as diabetes modify any effect of infections on cognitive trajectories and dementia risk.

1.6 Summary

Dementia has been identified as a public health priority by the World Health Organization. Although the age-specific incidence of dementia is declining in the UK and other high-income countries, the increasing burden of dementia, owing to population growth and ageing, and the absence of a disease modifying pharmacological therapy, emphasises the need to identify modifiable risk factors to mitigate the projected burden of dementia.

The focus of this thesis will be on common infections as a potentially modifiable risk factor for dementia or cognitive decline. Infections may be modifiable through strategies to minimise the risk of infections such as vaccines and antibiotic therapy. Given that diabetes is also a preventable risk factor for dementia and its co-occurrence with infections, I will also explore the potential for effect modification by diabetes on the association of common infections with dementia or cognitive decline.

Chapter 2: Research aims

Research aim 1: to summarise evidence from literature investigating the association between common clinically symptomatic bacterial infections and incident cognitive decline or dementia in longitudinal studies.

Research aim 2: to investigate the association between common infections and incident dementia using UK primary care electronic health records from the Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES).

Objectives:

(a) To describe the age-specific incidence rates of dementia in adults aged 65 years and older with and without common infections.

(b) To investigate whether the presence of common infections is associated with dementia risk.

(c) To investigate whether the type, clinical setting, frequency and timing of common infections are associated with dementia risk.

(d) To investigate whether diabetes modifies any association between infections and incident dementia.

(e) To investigate whether the presence and type of common infections are associated with evidence of cognitive impairment (secondary outcome).

Research aim 3: to investigate the association of common infections with the risk of dementia using data from the UK Biobank study and linked primary and secondary care electronic health records.

Objectives:

(a) To investigate whether the presence, type and clinical setting of infections are associated with dementia risk.

(b) To investigate the association between common infections and dementia, stratified by dementia-subtype

Research aim 4: to investigate the association between common infections, cognitive decline or neuroimaging measures using data from the UK Biobank study and linked primary and secondary care electronic health records.

Objectives:

(a) To investigate whether the presence of infections is associated with cognitive decline.

(b) To investigate whether the type, clinical setting, frequency and timing of infections are associated with cognitive decline.

(c) To investigate whether diabetes modifies any association between common infections and cognitive decline.

(d) To investigate the association of common infections with hippocampal volume, white matter hyperintensity volume and total brain volume.

Chapter 3: Systematic review of the association between common clinically symptomatic bacterial infections and incident dementia or cognitive decline

3.1 Introduction

In this chapter I addressed the first research aim of this thesis which was to conduct a systematic review of existing longitudinal studies investigating the association between common symptomatic bacterial infections and incident dementia or cognitive decline. The main sections of this chapter include two published papers (a systematic review protocol and systematic review), a brief update on the articles published since the systematic review and a summary of the chapter.

Numerous reviews and meta-analyses have been published addressing the association of specific infectious agents, regardless of symptom status, and dementia risk. These reviews, which have yielded mixed findings, have focused on herpes virus infections,[148-152] cytomegalovirus,[150,152] *helicobacter pylori*,[151-154], periodontitis,[151,152,155,156] spirochaetal bacteria,[152,157] *Chlamydophila pneumonia*,[151,152,157] and other infectious agents.

However, to my knowledge, no systematic reviews had been published specifically focusing on the association of clinically symptomatic common bacterial infection syndromes such as sepsis, LRTIs, UTIs and SSTIs with dementia or cognitive decline. Therefore, I aimed to address this gap in literature and specifically focused on longitudinal studies in order to explore the temporality of this association and avoid capturing studies focusing on short term reversible cognitive impairment.

Prior to conducting this systematic review, a protocol of the systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) to 1) ensure there were no other similar systematic reviews addressing the same research questions being conducted thus avoiding duplicating systematic reviews, and 2) to provide transparency by documenting the methodology for the review and recording any changes to the review process.

3.2 Systematic review protocol

A detailed protocol of the systematic review was published in a peer reviewed journal in 2019, The BMJ Open. The protocol includes the search strategy for one of the electronic databases searched, as well as the rationale, objectives and planned methodology for the review. The search strategy is presented in appendix 10.1.

3.3 Research paper 1

Common bacterial infections and risk of incident cognitive decline or dementia: a systematic review protocol

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SECTION A – Student Details

Student ID Number	1802273	**Title**	Ms
First Name(s)	Rutendo		
Surname/Family Name	Muzambi		
Thesis Title	The effect of common infections on cognition and dementia in people with and without diabetes		
Primary Supervisor	Dr Charlotte Warren-Gash		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	BMJ Open		
When was the work published?	12/09/2019		
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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author of this paper. I conceived and designed the study, drafted and revised the protocol and developed and revised the search strategy. The co-authors contributed to the conception and design of the study. They also provided comments to the search strategy and manuscript.

SECTION E

Student Signature	[redacted]
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Common bacterial infections and risk of incident cognitive decline or dementia: a systematic review protocol

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To cite: Muzambi R, Bhaskaran K, Brayne C, *et al*. Common bacterial infections and risk of incident cognitive decline or dementia: a systematic review protocol. *BMJ Open* 2019;**9**:e030874. doi:10.1136/bmjopen-2019-030874

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-030874).

Received 04 April 2019
Revised 09 August 2019
Accepted 13 August 2019

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ABSTRACT

Introduction The global burden of dementia is rising, emphasising the urgent need to develop effective approaches to risk reduction. Recent evidence suggests that common bacterial infections may increase the risk of dementia, however the magnitude and timing of the association as well as the patient groups affected remains unclear. We will review existing evidence of the association between common bacterial infections and incident cognitive decline or dementia.

Methods and analysis We will conduct a comprehensive search of published and grey literature from inception to 18 March 2019. The following electronic databases will be searched; MEDLINE, EMBASE, Global health, PsycINFO, Web of Science, Scopus, Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature, Open Grey and the British Library of Electronic Theses databases. There will be no restrictions on the date, language or geographical location of the studies. We will include longitudinal studies with a common clinically symptomatic bacterial infection as an exposure and incident cognitive decline or dementia as an outcome. Study selection, data extraction and risk of bias will be performed independently by two researchers. We will assess the risk of bias using the Cochrane collaboration approach. The overall quality of the studies will be assessed using the Grading of Recommendations, Assessment, Development and Evaluations criteria. We will explore the heterogeneity of relevant studies and, if feasible, a meta-analysis will be performed, otherwise we will present a narrative synthesis. We will group the results by exposure and outcome definitions and differences will be described by subgroups and outcomes.

Ethics and dissemination Ethical approval will not be required as this is a systematic review of existing research in the public domain. Results will be disseminated in a peer-reviewed journal and presented at national and international meetings and conferences.

PROSPERO registration number CRD42018119294.

Strengths and limitations of this study

- To the best of our knowledge, this will be the first systematic review assessing the association between common clinically symptomatic bacterial infections and the risk of incident cognitive decline and dementia in longitudinal studies.
- We will perform a comprehensive search of published and grey literature with no restrictions on date, language or geographical location.
- The review will develop existing evidence to generate better knowledge on the magnitude and direction of the relationship between common bacterial infections and subsequent cognitive decline or dementia.
- Heterogeneity in the way infections, cognitive decline and dementia are defined is expected, which could affect the feasibility of performing a meta-analysis and interpretation of findings.
- There may be difficulty ascertaining whether lower respiratory tract infections are bacterial or viral.

INTRODUCTION

Rationale

Dementia is a clinical syndrome that significantly contributes to disability and dependence worldwide, with a devastating impact on individuals, caregivers and healthcare services.[1–3] It is characterised by a progressive deterioration in cognition and behaviour that interferes with an individual's ability to perform activities of daily living.[4] In 2018, approximately 50 million people worldwide were estimated to be living with dementia, and this figure is projected to rise to 152 million by 2050.[5]

Age is the single biggest risk factor for dementia, with the risk doubling every 5 years after the age of 65.[6] Despite this, there have been some indications that the risk for dementia can be reduced, with more recent cohorts in the UK demonstrating a significantly lower risk at any given age.[7] It has become clear from clinical and neuropathological studies that the risk for dementia is complex, not driven by genetics, vascular factors or age alone. Given the rapidly increasing ageing population and the absence of pharmacological treatments that can delay the onset or progression of dementia, identification of effective strategies to reduce risk, as age increases, has become a public health

priority.[8] As a result, recent literature has focused on modifiable risk factors. It has been estimated that around a third of dementia cases worldwide can be attributed to modifiable risk factors.[9–11]

Bacterial infections have been identified as potential risk factors for dementia. For the past few decades, a large body of research has been published on the association between bacterial pathogens and Alzheimer's disease, particularly in postmortem brain tissue.[12–14] Despite this, the temporality of this relationship remains unclear due to the cross-sectional nature of the data collected in these studies. A recent meta-analysis of 27 serological, cerebrospinal fluid and postmortem brain studies found that infections due to *Chlamydia pneumoniae* and Spirochaetes were associated with a 5-fold (OR 5.66; 95% CI 1.83 to 17.51) and 10-fold (OR 10.61; 95% CI 3.38 to 33.29) increased risk of Alzheimer's disease, respectively.[15] However, temporality could not be assessed in these studies. The meta-analysis was further limited by the inclusion of studies with small sample sizes and the focus on Alzheimer's disease rather than all types of dementia.

Common bacterial infections are well recognised to be associated with acute changes in cognition, manifested as delirium, among older adults.[16] In turn, delirium is strongly associated with an increased risk of subsequent cognitive decline and dementia.[17–19] This raises the challenge of disentangling the relative contribution of the (potentially reversible) ageing immune system's response to acute infections, from ongoing neuropathological processes, both of which may affect cognition.

Longitudinal studies with a follow-up time sufficient enough for delirium to resolve, are important in distinguishing between delirium and long-term cognitive impairment. Additionally, longitudinal studies that compare incidence of cognitive decline or dementia in individuals with and without common bacterial infections provide evidence for the temporality and magnitude of this association. Although the prevalence of common bacterial infections, such as pneumonia and urinary tract infections, in individuals with dementia is well known,[20 21] the incidence of cognitive decline and dementia is less established.

The mechanisms by which bacterial infections may increase the risk of cognitive decline and dementia are unclear but may involve inflammation.[22 23] Bacterial infections may trigger an inflammatory response in the brain resulting in the release of pro-inflammatory mediators and activation of cytotoxic microglia. This may result in deterioration of cognitive function, possibly increasing the risk of dementia.[12]

To date, no systematic review has been performed on the incidence of cognitive decline and dementia in individuals with a common bacterial infection causing clinical illness. As these infections frequently occur in the community, early recognition, treatment or prevention of common bacterial infections could have important public health implications in reducing the burden of dementia.

Objectives

The primary objective of the proposed systematic review is to summarise the current literature investigating the association between common clinically symptomatic bacterial infections (sepsis, lower respiratory tract infections, urinary tract infections and skin and soft tissue infections) and incident cognitive decline and dementia in longitudinal studies. A secondary objective will be to identify gaps in literature and recommendations for future research on this topic.

METHODS

The present systematic review protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) statement and was registered on the PROSPERO database.[24 25] Any amendments to the protocol will be updated in PROSPERO.

We will report the systematic review in line with the PRISMA statement.[26] If a meta-analysis is feasible, it will be reported according to the Meta-analysis of Observational Studies in Epidemiology statement.[27]

Eligibility criteria

Studies will be eligible for inclusion into the present study if they meet the inclusion criteria mentioned below.

Study design

We will include longitudinal studies; retrospective and prospective cohort studies, case-control studies and randomised controlled trials (RCTs). We will include studies specifically investigating the association between common bacterial infections and cognitive decline or dementia. Although it would not be possible to perform RCTs specifically addressing our research question, we will consider studies derived from RCTs which could include cohort or case-control studies from an RCT data source. We will include studies in which the exposure is ascertained prior to the occurrence of the outcome events in order to investigate the temporal relationship between common bacterial infections and subsequent cognitive decline or dementia. Additionally, to avoid including studies focusing on short-term reversible changes in cognition, rather than long-term cognitive decline, we will include studies in which cognitive decline was measured at least 3 months following infection.

Study population

We will include human studies of adults aged 18 years and over with no restrictions on the sex, ethnicity, prior health status or residence of participants. We will include studies conducted in any healthcare setting.

Exposure

We will include studies in which exposure is defined as symptomatic illness due to common bacterial infections, either suspected clinically or confirmed by isolation of a bacterial pathogen. Types of bacterial infections will be

subdivided into sepsis, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections. The possible pathophysiological mechanisms of bacterial infections on cognitive decline or dementia may differ depending on the site of infection, and thus we will only include studies assessing the independent effect of each type of infection on our outcomes. In addition, infections are likely to differ in terms of severity, particularly sepsis, which further highlights the need to assess their effect separately. We will exclude studies that focus on a specific bacterial pathogen as the exposure rather than the symptomatic disease (ie, isolation of a bacterium by PCR alone in the absence of clinical symptoms).

Comparators

Studies eligible for inclusion will include a comparison group. For cohort studies and secondary analyses of longitudinal RCT data, individuals exposed to common bacterial infections will be compared with those unexposed to infections. For case-control studies, cases with dementia or cognitive decline will be compared with a control group without dementia or cognitive decline.

Outcomes

We will have two primary outcomes. These will be (1) incident cognitive decline and (2) incident dementia (all types). Cognitive decline will be defined clinically. Dementia will also be defined clinically, with or without neuroimaging or histopathology. If a sufficient number of eligible studies are available, dementia will be subdivided into dementia types.

Literature searches

We will systematically search electronic databases of published and grey literature from inception to 18 March 2019. The following databases will be searched: MEDLINE (Ovid interface), EMBASE (Ovid interface), Global health (Ovid interface), PsycINFO (Ovid Interface), Web of Science, Scopus, Cochrane Library, the Cumulative Index to Nursing and Allied Health Literature, Open Grey and the British Library of Electronic Theses databases. Additionally, we will search the reference lists of the included studies to identify any relevant articles not captured in the search strategy. We will search the databases using subject headings, where possible, and keywords related to the exposure, outcome and study design. These search terms will be combined using Boolean logical operators.

We carried out a preliminary search on PubMed to ensure we would capture a sufficient number of studies for inclusion into the review. We developed a search strategy for the MEDLINE database which is provided in online supplementary appendix 1. The search strategy was developed in consultation with a librarian at the London School of Hygiene and Tropical Medicine and was subsequently peer reviewed based on the Peer-Review for Electronic Search Strategies.[28] We will translate our search strategy in all databases using search syntaxes specific to each database. No restrictions will be placed on the geographical location, language or date of publication of the studies. Any potentially relevant non-English studies will be translated.

Study records

Data management

We will import the search results into the reference manager software EndNote (X8.0.2). Duplicate entries will be identified and removed.

Study selection

Two researchers will independently screen all titles and abstracts against the eligibility criteria. The researchers will then independently screen the full-text articles of potentially eligible articles and decide on whether the inclusion criteria have been met. Any disagreements between the reviewers will be discussed and if necessary a third reviewer will be consulted. Reasons for exclusion of studies will be recorded. We will document the study selection process using the PRISMA flow diagram.[26] If multiple papers arise from the same population, we will include the paper with the largest sample size and most detailed information about the exposure and outcome. We pilot tested our study selection process to ensure that the inclusion criteria can be reliably applied.

Data collection process

Two researchers will independently extract data from included papers onto a predesigned form. If necessary, the authors will be contacted directly to obtain any missing information. We will perform pilot testing on the data extraction form to identify any missing or irrelevant criteria, and we will modify the form accordingly.

Data items

We will use the Population, Exposure, Comparator, Outcomes and Study characteristics framework to design our data extraction form. The following information will be extracted:

1. Population: age (mean, median or range), sex, inclusion and exclusion criteria.
2. Exposure: definition of exposure, type of bacterial infection, cause of sepsis, number of exposed.
3. Comparators: identification and definition of comparator, number of comparators.
4. Outcomes: definition of outcome and identification of cognitive decline and dementia, number of participants with the outcome.
5. Study characteristics: authors, name of study, year of publication, study design, type of longitudinal study, healthcare setting, country, sample size, duration of follow-up.

Regarding the study results, we will extract unadjusted and adjusted estimates and their corresponding 95% CI for each exposure and outcome. Data on subgroup or sensitivity analyses will be extracted. We will extract additional data on antibiotic treatment, if indicated, given that antibiotics have been associated with delirium,[29]

which is in turn a risk factor for cognitive decline and dementia. We will also extract data on confounding variables. Factors considered to be potential confounders include age,[30] sex,[31] socioeconomic status,[32] ethnicity,[33] smoking,[34] alcohol consumption,[35] cardiovascular disease,[36] diabetes,[37] renal dysfunction,[38] psychiatric disorders,[39] cerebrovascular disease,[40] chronic obstructive pulmonary disease[41] and immunodeficiency disorders.[42] We will assess whether studies have adequately assessed for potential confounders as part of our risk of bias and study quality assessments.

Risk of bias in individual studies

We will use a sample of studies to pilot test the risk of bias form to ensure the criteria can be applied consistently by both reviewers. Two researchers will independently assess the risk of bias in line with the Cochrane collaboration approach.[43 44] We will examine the risk of bias for RCTs using the following domains: sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting and other potential threats to validity.[44] We will assess the risk of bias for observational studies using the following domains: confounding, selection of participants, misclassification of variables, missing data, reverse causation, generalisability and study power.

Data synthesis and meta-bias(es)

We will group studies according to the outcome (cognitive decline or dementia) and exposure (type of common bacterial infection) and synthesise them narratively. Data will be summarised in predefined tables. We will consider subgroup analyses according to age group, gender, dementia subtype and risk of bias. If possible, we will explore the effect of antibiotic treatment on cognitive decline or dementia.

A meta-analysis will be considered feasible if there are a minimum of at least two studies that are homogeneous in terms of study design, type of common bacterial infection and type of outcome. We will pool effect measures (ORs, risk ratios or HRs) from the studies in order to perform the meta-analysis.

We will assess statistical heterogeneity through the use of forest plot, χ^2 test and I^2 statistic. Depending on the level of heterogeneity, a fixed or random effects model will be selected to calculate the pooled incidence and corresponding 95% CI. A χ^2 test with a p value of 0.1 will be considered statistically significant. We will consider an I^2 value of >25% to indicate moderate heterogeneity, which will guide the use of a random effects model.[45 46] We will assess publication bias and small study effects using funnel plots, provided that there are 10 or more studies eligible for inclusion into the meta-analysis.[47]

Confidence in cumulative evidence

We will assess the overall quality of evidence for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation tool.[48] The domains assessed will include study limitations, inconsistency, indirectness, imprecision and publication bias.[49] The strength of the evidence will be categorised as high, moderate, low and very low.

Patient and public involvement

No patients or public were directly involved in the design of this study. However, we sought advice on the dissemination of our findings from lay volunteers assigned to Rutendo Muzambi's PhD studentship by the Alzheimer's Society.

ETHICS AND DISSEMINATION

This systematic review will provide evidence for the role of common bacterial infections in the development of cognitive decline and dementia. The systematic review will be submitted for publication in a peer-reviewed journal and the results may be presented at national and international conferences and meetings relevant to the field. This review will highlight gaps in current literature and identify future research directions.

Contributors CW-G, KB and LS conceived and designed the study, revised the protocol and search strategy critically. RM conceived and designed the study, drafted and revised the protocol and developed and revised the search strategy. CB contributed to the design of the study and revised the protocol and search strategy critically. The final version of the protocol was read and approved by all authors.

Funding RM is supported by an Alzheimer's Society PhD studentship 379 (AS-PhD-17-013). CWG is supported by a Wellcome Intermediate Clinical Fellowship, Wellcome Trust (201440_Z_16_Z).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Ethical approval will not be required as the review will summarise data from previous studies.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

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3.4 Systematic review

The systematic review accompanying the systematic review protocol was published in a peer reviewed journal in 2020, the Journal of Alzheimer's disease. The supplementary material for this paper which includes the search strategy for each database, changes to the protocol and secondary analyses is provided in Appendix 10.1. The findings of this systematic review informed the types of infections addressed in the second and third research aim (sepsis and a separate category for pneumonia and lower respiratory infections), as well as the secondary analyses performed (e.g. analyses investigating the effect of clinical setting on dementia risk).

3.5 Research paper 2

Common Bacterial Infections and Risk of Dementia or Cognitive Decline: A Systematic Review

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Student ID Number	1802273	**Title**	Ms
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Thesis Title	The effect of common infections on cognition and dementia in people with and without diabetes		
Primary Supervisor	Dr Charlotte Warren-Gash		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Journal of Alzheimer's Disease		
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Date	11/11/2021

Journal of Alzheimer's Disease 76 (2020) 1609–1626
DOI 10.3233/JAD-200303
IOS Press

Common Bacterial Infections and Risk of Dementia or Cognitive Decline: A Systematic Review

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Accepted 29 May 2020

Abstract.
Background: Bacterial infections may be associated with dementia, but the temporality of any relationship remains unclear.
Objectives: To summarize existing literature on the association between common bacterial infections and the risk of dementia and cognitive decline in longitudinal studies.
Methods: We performed a comprehensive search of 10 databases of published and grey literature from inception to 18 March 2019 using search terms for common bacterial infections, dementia, cognitive decline, and longitudinal study designs. Two reviewers independently performed the study selection, data extraction, risk of bias and overall quality assessment. Data were summarized through a narrative synthesis as high heterogeneity precluded a meta-analysis.
Results: We identified 3,488 studies. 9 met the eligibility criteria; 6 were conducted in the United States and 3 in Taiwan. 7 studies reported on dementia and 2 investigated cognitive decline. Multiple infections were assessed in two studies. All studies found sepsis ($n = 6$), pneumonia ($n = 3$), urinary tract infection ($n = 1$), and cellulitis ($n = 1$) increased dementia risk (HR 1.10; 95% CI 1.02–1.19) to (OR 2.60; 95% CI 1.84–3.66). The range of effect estimates was similar when limited to three studies with no domains at high risk of bias. However, the overall quality of evidence was rated very low. Studies on cognitive decline found no association with infection but had low power.
Conclusion: Our review suggests common bacterial infections may be associated with an increased risk of subsequent dementia, after adjustment for multiple confounders, but further high-quality, large-scale longitudinal studies, across different healthcare settings, are recommended to further explore this association.

Keywords: Cognition, dementia, infections, prevention, systematic review

Systematic review registration number: CRD42018119294, registered in December 2018

INTRODUCTION

Dementia is a major global health challenge. Worldwide, approximately 50 million people are currently living with dementia, and this number is projected to rise to over 152 million by 2050 [1]. Given the increasing life expectancy and absence of a cure or disease-modifying therapy, dementia prevention has become a public health priority [2]. Recent evidence suggests modifiable risk factors may have contributed to a decline in the age-specific incidence of dementia in Europe and the United

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States [3–9], highlighting the importance of identifying and targeting modifiable risk factors, as age increases. Bacterial infections have been identified as one potentially important risk factor for dementia [10, 11].

Symptomatic bacterial infections such as pneumonia and urinary tract infections are common, and complications frequently occur among older people. One of the hallmark complications of common bacterial infections is delirium; a serious neuropsychiatric syndrome characterized by acute cognitive dysfunction and inattention [12]. Delirium is strongly associated with an increased risk of subsequent cognitive decline and dementia [13–15]. Increasing evidence suggests cognitive impairment may persist for years after sepsis hospitalization [16, 17]. However, it is unclear whether there are long term effects of common infections on cognition and dementia, independent of delirium.

Previous reviews have investigated the role of bacterial pathogens on Alzheimer's disease; however, evidence is inconsistent, and the exact nature of this association remains unclear. In a meta-analysis of predominantly case-control studies Maheshwari and Eslick found that *Chlamydia pneumonia*, a bacterium responsible for pneumonia and other respiratory tract infections, was associated with a five-fold (OR 5.66; 95% CI 1.83–17.51) increased occurrence of Alzheimer's disease [11]. However, due to the cross-sectional nature of the data collected in these studies, it was not possible to assess temporality. Additional drawbacks of this meta-analysis included differences in methodology and the relatively small sample sizes of the studies included (total sample size ranging from 2 to 200 samples). Furthermore, other bacterial microorganisms have also been implicated in previous and subsequent reviews [10, 18] and differing conclusions have been drawn on the role of *Chlamydia pneumonia* with Alzheimer's disease as evidenced in a comprehensive review by Mawanda and Wallace [18]. However, studies included in these reviews also faced the same limitations in terms of sample size and cross-sectional study designs.

We aimed to summarize current evidence from longitudinal studies of the association between common clinically symptomatic bacterial infections (sepsis, lower respiratory tract infections, urinary tract infections, and skin and soft tissue infections) and risk of subsequent incident dementia or cognitive decline in adults aged 18 years and older. A secondary objective was to identify gaps in literature and recommendations for future research.

METHODS

Protocol and registration

We registered this systematic review with the International Prospective Register of Systematic Reviews in December 2018 (PROSPERO 2018; CRD42018119294) and published a more detailed protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA) reporting guidelines [19].

Study design

Studies eligible for inclusion were longitudinal studies such as prospective and retrospective cohort studies, secondary analyses of randomized controlled trial data, and case control studies. We included studies in which cognitive decline was measured at least 3 months following infection, to avoid associations dominated by short term, reversible cognitive impairment. Further, to assess temporality, we restricted our search to studies in which infections occurred prior to cognitive decline or dementia.

Study population

Only studies with human participants aged 18 years and older were eligible for inclusion.

Exposure

Exposure was defined as symptomatic illness due to common bacterial infections, either suspected clinically or confirmed by isolation of a bacterial pathogen. We identified studies investigating the following major infection types: sepsis, lower respiratory tract, skin and soft tissue, and urinary tract infections. Studies identifying specific bacterial agents alone, rather than the symptomatic disease, were excluded.

Comparators

We only included studies in which a comparison group was present. This comparison group comprised of individuals unexposed to common bacterial infections in cohort studies and secondary analyses of longitudinal randomized controlled trial data, or a control group without dementia or cognitive decline in case control studies.

Outcomes

Our two primary outcomes of interest were (1) incident dementia (all types) and (2) cognitive decline. We included studies in which our outcomes were defined clinically, which for dementia could be with or without neuroimaging or histopathology results.

Information sources

We performed a comprehensive search across eight databases of published literature (MEDLINE, EMBASE, Global Health, PsychInfo, CINAHL Plus, Cochrane Library, Scopus, and Web of Science) and two grey literature databases (Open grey and the British Library electronic Theses Online Service) from inception to 18 March 2019. Additionally, we searched the reference lists of the included studies to identify any relevant articles not captured in our search strategy.

Search

We searched the databases using subject headings, specific to each database, and keywords related to common bacterial infections, cognitive decline or dementia, and longitudinal study designs. These search terms were then combined using Boolean logical operators. No restrictions were placed on the language, country, or health care setting of the studies. Our search strategy was developed in consultation with a librarian at the London School of Hygiene and Tropical Medicine and was subsequently peer reviewed based on the Peer-Review for Electronic Search Strategies. We translated the final search strategy across all databases which is shown in the Supplementary Material 1.

Study selection

The study selection process was carried out by two reviewers (RM and JAD), using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. The two reviewers independently screened all titles, abstracts and full text articles against the eligibility criteria. A third reviewer (CWG) was consulted when there were any discrepancies.

Data items

Data extraction was performed independently by two reviewers for all studies. We used the Population, Exposure, Comparator, Outcomes and Study characteristics framework to extract data from eligible studies (Supplementary Material 2). We pilot tested our data extraction form and modified the form accordingly. We extracted key study results, namely unadjusted and adjusted incidence effect estimates and their corresponding 95% CIs. Data on confounding variables adjusted for in each study and pre-specified sub-groups were also extracted.

Risk of bias in individual studies

The risk of bias was assessed independently by two reviewers in line with the Cochrane collaboration approach. We classified studies as at high, medium, low or unclear risk of bias in each of the following domains: confounding, selection of participants, misclassification of variables, missing data, reverse causation, generalizability, and study power [20, 21].

Synthesis of results

We grouped studies according to their outcome (cognitive decline or dementia) and exposure definition (common bacterial infection) and synthesized them narratively. Heterogeneity was assessed using the I squared statistic if there were two or more studies with effect estimates for the same exposure definition, outcome, and study design. Geographical location and risk of bias were explored as potential sources of heterogeneity. Other sources of heterogeneity could not be explored due to the limited data available. We also carried out sub-group analyses by age, sex, and dementia subtype where sufficient data were available.

Quality of evidence

We assessed the overall quality of evidence for each outcome using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool. The following domains were assessed: study limitations, inconsistency, indirectness, imprecision, and publication bias. We rated the strength of evidence as high, moderate, low, or very low. The criteria for grading are stated in Supplementary Material 3.

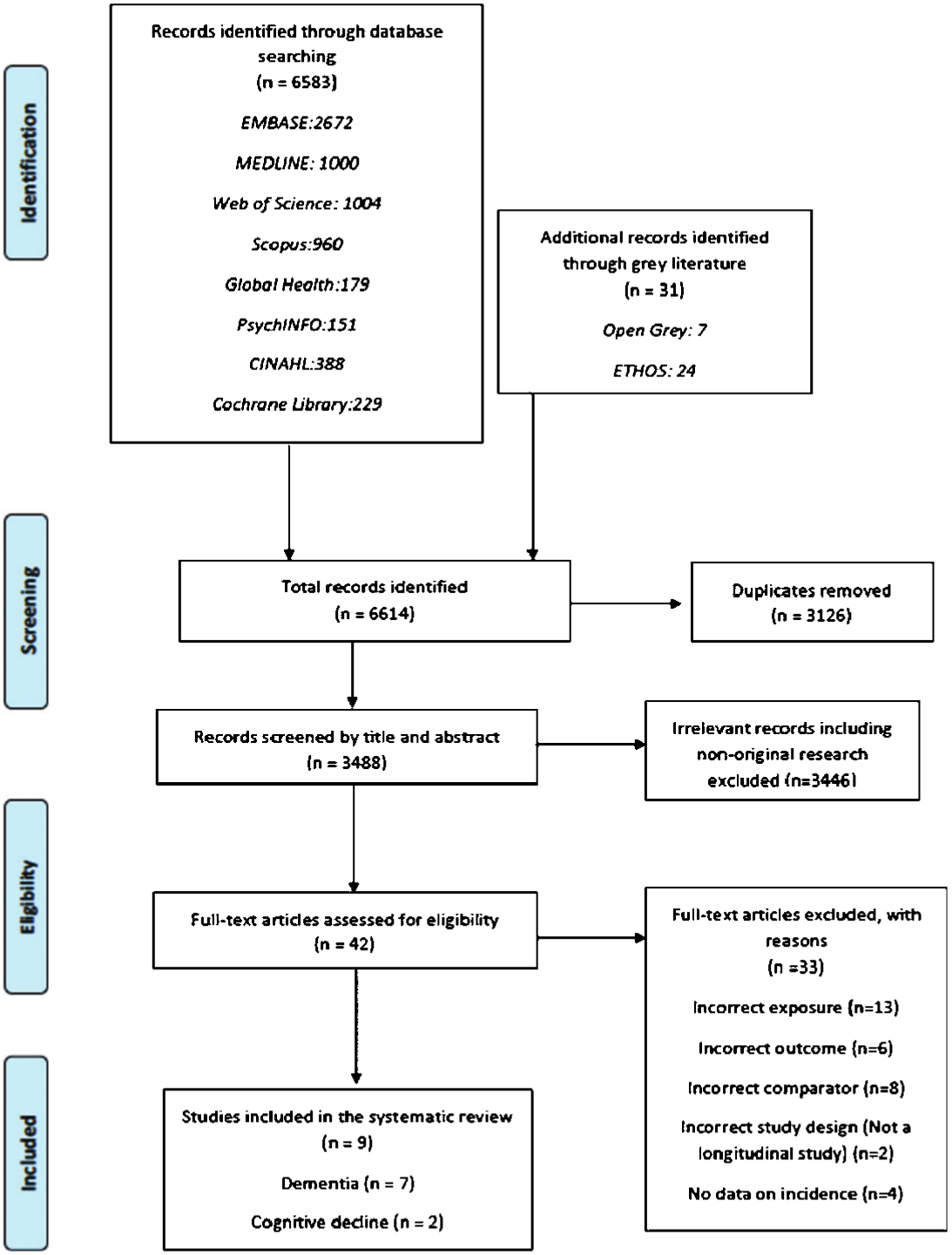


Fig. 1. Study selection PRISMA flow diagram.

RESULTS

Study characteristics

In total, 3,488 studies were identified from 10 databases, after de-duplication, as outlined in Fig. 1. Of these, 42 were included in the full text screening and the reasons for exclusion were noted. Finally, 9 studies were included in the present systematic review. The study characteristics and results are summarized in Tables 1 and 2, respectively. Forest plots of the results are displayed in Figs. 2 and 3.

Table 1
Characteristics of studies included in the review

First Author, year of publication	Study design	Study period	Setting	Study population at recruitment	Definition and ascertainment of exposure	Definition and ascertainment of comparator	Outcome	Definition and ascertainment of outcome	Study population characteristics (Age and male %)
					Dementia				
Cohort studies									
Shah et al., 2013 [23]	Prospective cohort study	1997-unknown follow up	United States, Community dwelling adults	Adults aged 65 y or older	Pneumonia and sepsis defined using ICD-9 diagnosis codes.	Pneumonia exposure: comparators were participants never hospitalized with pneumonia. Severe sepsis exposure: comparators were participants never hospitalized with infection.	Dementia	Neuropsychiatric testing, magnetic resonance imaging evaluations and annually with the (3MS) examination.	Age 72.8 y (5.6) (mean) 42.4% male
Guerra et al., 2012 [22]	Retrospective cohort study	2005-2008	United States, Medicare beneficiaries	Adults aged 66 y and older who received intensive care and survived hospital discharge.	Diagnoses of severe sepsis assessed using a standard definition, ICD-9-CM codes.	Participants without infection	Dementia	Dementia defined using ICD-9-CM codes (290.x, 294.x, 331.x, 797.x)	Age 76.6 $y \pm 6.8$. 48.7% male
Mawanda et al., 2016 [25]	Retrospective cohort study	2003-2012	United States, National sample of US Veterans database	Veterans aged 56 y and older during fiscal year 2003 enrolled and receiving health care at any Veterans Health Administration care facility.	Septicemia, bacteremia, pneumonia, UTI and cellulitis diagnosed using ICD-9 diagnosis codes.	Participants without a diagnosis of an extra-CNS bacterial infection	Dementia	Dementia diagnosed from using ICD-9	Age 67.7 (8.1) y (mean) and 97.9% male.
Chou et al., 2017 [29]	Retrospective cohort study	2001-2011	Taiwan, Longitudinal Health Insurance Database	Participants hospitalized with septicemia without prior dementia, age and sex matched at 1 : 2 ratio to cohort without septicemia or prior dementia.	Septicemia defined according to according to ICD-CM codes (003.1, 036.2, and 038)	Age and sex matched cohort without septicemia or prior dementia.	1. All Dementia 2. Alzheimer's disease 3. Non-Alzheimer's dementias	Dementia defined using ICD-9-CM codes. (290, 294.1 and 331.0)	Exposed: 65.6 y (16.8), 56% male Unexposed: Age: 65.4 y (16.7), 56% male

(*Continued*)

Table 1
(*Continued*)

First Author, year of publication	Study design	Study period	Setting	Study population at recruitment	Definition and ascertainment of exposure	Definition and ascertainment of comparator	Outcome	Definition and ascertainment of outcome	Study population characteristics (Age and male %)
Chou et al. 2018 [28]	Retrospective cohort study	2001-2011	Taiwan, Longitudinal Health Insurance Database	-	Septicemia. Ascertainment not reported.	Age and sex matched cohort without septicemia or prior dementia	Vascular dementia	-	-
Tate et al., 2014 [24]	Cohort study - secondary analysis of a randomized trial	2000-2008	United States, Community dwelling adults	Adults aged 75 y and older.	ICD-9-CM codes and textual search of discharge diagnoses to identify pneumonia hospitalizations	Participants without ICD-9-CM pneumonia hospitalization codes or without pneumonia recorded in diagnoses fields	Dementia	Participants screened using 3MSE exam, ADAS-Cog scale and the clinical dementia rating.	Age=78.6 y (mean), 54% male. Exposed age = 79.5 y and 63.3% male. Unexposed Age = 78.5 y and 53.1
Case control study									
Kao et al. 2015 [30]	Nested case control study	2003-2011	Taiwan, Longitudinal Health Insurance Database	Adults aged 45 y and older, sex, age and year of index date matched (1 : 1) with healthy controls.	Participants hospitalized with a diagnosis of sepsis using ICD-9-CM codes within 5 y prior to the index date.	Age, sex, and year of index matched healthy controls without dementia.	Dementia	First time diagnosis of dementia using ICD-9-CM codes.	Age 75.4 (10.4 y) (mean) 44% male
Cognitive Decline									
Cohort study									
Davydow et al., 2013 [26]	Prospective cohort study	1998-2010	United States, Community dwelling adults with pneumonia, myocardial infarction and stroke hospitalizations	Adults aged over 50.	Pneumonia was diagnosed using ICD-9-CM principal diagnostic codes and to identify hospitalizations	Participants with principal discharge stroke or myocardial infarction hospitalization	Moderate to severe cognitive impairment	Cognitive impairment was assessed versions of the modified TICS interview.	Age (median) Pneumonia 77.1 (9.4), myocardial infarction, 75.5 (8.2) and stroke 77.0 (8.4)

Case control study

Sakusic 2018 [27]	Nested case-control study	July 2004 - November 2015	United States, critically ill patients in ICU	Adults aged 18 y and older admitted to ICU. Excluded were those admitted to neuroscience ICU, those with cognitive impairment prior to ICU stay and those only with cognitive impairment documented within 3 months of ICU discharge.	Sepsis. Ascertainment not reported.	Cognitive impaired cases were matched to cognitively normal controls based on age, sex and having had an ICU admission	Persistent cognitive impairment	Defined as the onset of new cognitive impairment within 3-24 months after ICU discharge. Cognitive impairment identified by manually reviewing electronic health records using algorithms for cognitive impairment and dementia.	65.9 (mean age) and 54.6% male

ICD-9-CM, International Classification of Diseases, 9th revision, Clinical Modification; 3MS, Modified Mini-Mental State Examination, ADAS-Cog, Alzheimer's Disease Assessment Scale Cognitive Subscale; ICU, Intensive Care Unit; TICS-M, Modified Telephone Interview for Cognitive Status

Table 2
Results of studies included in the review

First Author, year of publication	Population size (N), follow-up time (y)	Subjects with outcome (or exposure for case-control studies) (N, %)	Statistical analysis method used	Main reported crude results	Main reported adjusted results	Adjusted for
			Dementia			
Cohort studies						
Shah et al., 2013 [23]	5888. Dementia assessed in 3,602 participants. Followed for over 10 y.	707 (19.6%)	Cox proportional hazards regression models	**Pneumonia** HR 2.24 (95% CI; 1.62–3.11) **Severe sepsis** HR 1.98 (95% CI; 1.38–3.77)	**Pneumonia** HR 1.57 (95% CI; 1.11–2.22)	Demographics, health behaviors, other chronic health conditions, trajectories of physical and cognitive decline before pneumonia hospitalization.
Guerra et al., 2012 [22]	25,368 ICU survivors. Sepsis: 3,145, no infection: 17,151. Average follow up 2.5 $y \pm 0.9$.	4,519 (17.8%)	Extended cox proportional hazards regression models	HR 1.63 (95% CI; 1.50,1.77)	HR 1.40 (95% CI; 1,28–1.53)	Risk factors for dementia and time dependent coefficients: Age, race, gender, cerebrovascular disease, Parkinson's disease, alcohol abuse, hypertension, hypoglycemia and chronic renal failure.
Mawanda et al., 2016 [25]	417,172. Mean follow up 9.03 (1.1)	25,639 (6.2%)	Extended cox proportional hazards regression models	**Pneumonia** HR 1.54 (95% CI; 1.43–1.67) **Septicemia** HR 2.09 (95% CI; 1.75–2.49) **Urinary tract infection** HR 1.44 (95% CI; 1.38–1.51) **Cellulitis** HR 1.49 (95% CI; 1.42–1.56)	**Pneumonia** HR 1.10 (95% CI; 1.02–1.19) **Septicemia** HR 1.39 (95% CI; 1.16–1.66) **Urinary tract infection** HR 1.13 (95% CI; 1.08–1.18) **Cellulitis** HR 1.14 (95% CI; 1.09–1.20)	Demographic characteristics (age, gender, race/ethnicity, and annual income), medical comorbidity and psychiatric covariates (traumatic brain injury, hypertension, ischemic heart disease, cerebrovascular disease, atherosclerosis, diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, peptic ulcer disease/gastritis, bipolar disorder, PTSD, schizophrenia, and alcohol abuse).
Chou et al., 2017 [29]	Exposed: 20,466 Unexposed: 40,932	**Exposed:** All dementia: 832 (4.1%), Alzheimer's disease: 46 (0.2%), non-Alzheimer's dementias 786 (3.8%). **Unexposed:** All dementia: 1945 (4.8%), Alzheimer's disease: 222 (0.5%) and non-Alzheimer's dementias: 1723(4.2%)	Cox proportional hazards regression	**All dementia**: HR 1.79 (95% CI; 1.65–1.94) **Alzheimer's disease**: HR 0.89 (95% CI;0.64–1.22) **non-Alzheimer's dementias** 1.91 (95% CI; 1.75–2.07)	**All dementia:** HR 2.09 (95% CI; 1.92–2.28) **Alzheimer's disease:** HR 1.15 (95% CI; 0.83–1.60) **non-Alzheimer's dementias** 2.20 (95% CI; 2.01–2.41)	Age, sex, stroke, DM, hyperlipidemia, hypertension, depression, ARD, smoking, and NSAID use.

Chou et al. 2018 [28]	Exposed: 20,466 Unexposed: 40,932	-	Cox proportional hazards regression	HR 2.26 (95% CI; 2.07–2.47)	-	-
Tate et al., 2014 [24]	3069. Median follow up 6.1 y	523 (17.0%)	Cox proportional hazards regression models	HR 2.4 (95% CI; 1.7–3.3)	HR 1.9 (95% CI; 1.4–2.8)	Age, sex, race, site, education and baseline cognitive function.
Case-control studies						
Kao et al. 2015 [30]	Cases: 5,955	Cases: 122/5,955 (2.05%)	Conditional logistic regression	OR 2.68 (95% CI; 1.91–3.77)	OR 2.60 (95% CI; 1.84–3.66)	Monthly income, urbanization level, hyperlipidemia and diabetes.
	Controls: 5,955	Controls: 46/5,955 (0.77%)				
			Cognitive decline			
Cohort studies						
Davydow et al., 2013 [26]	1,434 survivors. 1,711 hospitalizations; Pneumonia ($n = 827$), myocardial infarction ($n = 450$) or stroke hospitalization ($n = 434$). Follow up range (7.7–9.8 y)	Unclear	Within-person regressions	**Pneumonia versus Myocardial Infarction** OR 1.46 (95% CI; 0.69, 3.09) **Pneumonia versus Stroke** OR 0.64 (95% CI; 0.3,1.34)	-	-
Case-control studies						
Sakusic 2018 [27]	Cases: 2,401. Controls: 2,401. Follow up between 3-24 months	Cases: 793/2,401 (33.0%)	Conditional logistic regression	OR 1.28 (95% CI; 1.16– 1.41)	OR 1.08 (95% CI; 0.97–1.21)	Charlson Comorbidity Index and N. of ICU stays.
		Controls: 736/2,401 (30.7%)				

HR, hazard ratio; PTSD, post-traumatic stress disorder; DM, diabetes mellitus; ARD, alcoholism-related disease; NSAID, non-steroidal anti-inflammatory drug; ICU, intensive care unit, OR, odds ratio.

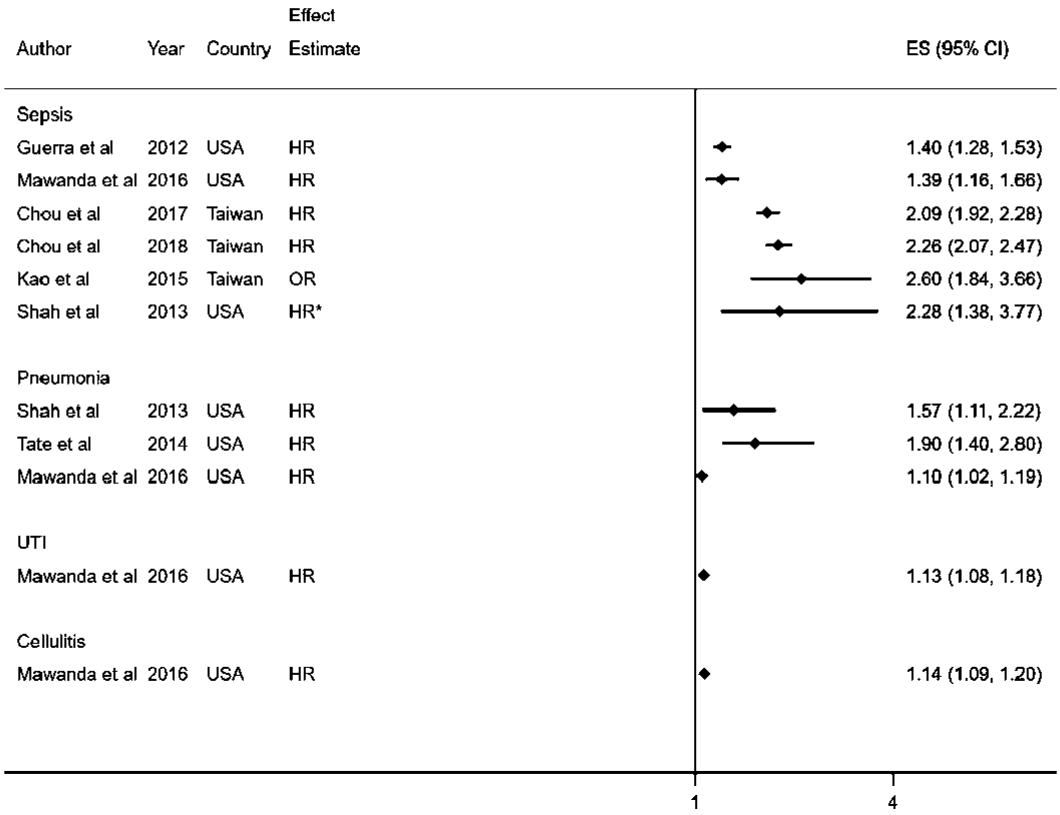


Fig. 2. Forest plot showing the effect of infections on dementia. *Unadjusted effect estimates. The mean age (SD) in this study was 72.8 years (5.6).

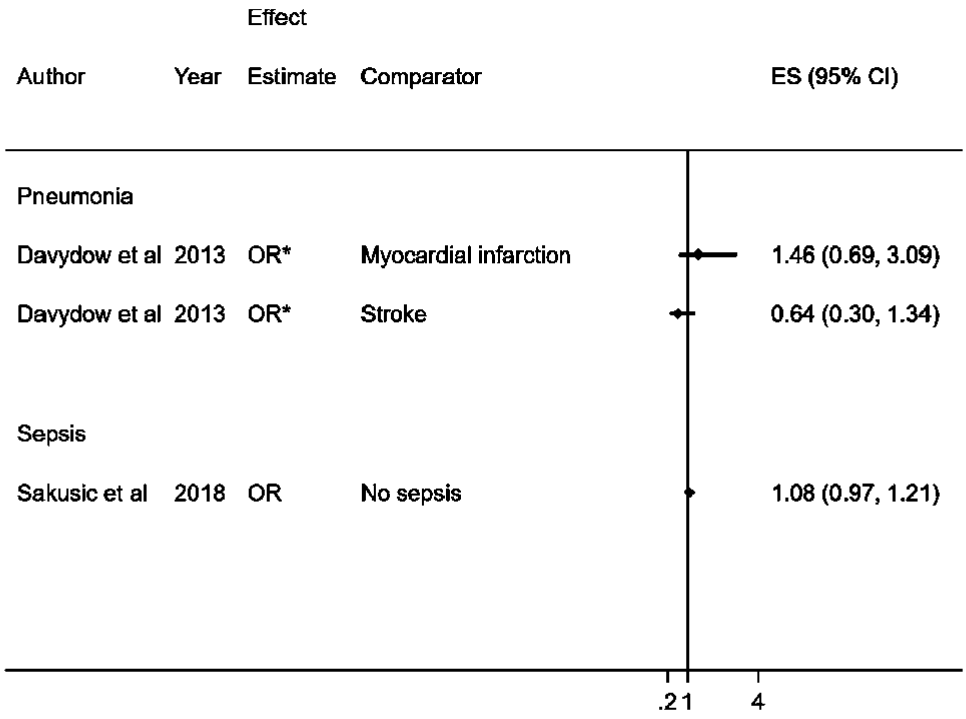


Fig. 3. Forest plot showing the effect of common bacterial infections on cognitive decline. *Unadjusted effect estimates for the study by Davydow et al., 2013 [26]. The median age in years (SD) in this study for each exposure was as follows: pneumonia 77.1 (9.4), myocardial infarction, 75.5 (8.2) and stroke 77.0 (8.4).

Of the studies included, six studies were conducted in the United States [22–27], and three in Taiwan [28–30]. Four were historical cohort studies, which used data derived from electronic health records [22, 25, 28, 29], two were prospective cohort studies [23, 26], one was a secondary analysis from a randomized controlled trial [24], and two were case-control studies [27, 30].

In total, seven studies investigated sepsis [22, 23, 25, 27–30], four assessed pneumonia [23–26], and only one study considered urinary tract infections and cellulitis [25]. Two studies investigated the effect of multiple infections on dementia [23, 25]. Infections were defined using ICD-9 (International Classification of Diseases, Ninth Revision) or ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes [22–26, 29, 30]. Ascertainment of infection was unclear in two studies [27, 28]. In terms of the setting in which infections were diagnosed, all studies defined infections in secondary care, with the exception of one study which included individuals receiving care at veterans health administration facilities [25]. These facilities comprise secondary care, outpatient sites and primary care settings. Two studies reported on the association between sepsis and dementia from the same study population in the Taiwanese health insurance database. Of these studies, one reported on vascular dementia as an outcome [28], while the other study reported on all types of dementia, Alzheimer's disease, and non-Alzheimer's disease dementia [29].

Ascertainment of dementia and cognitive decline varied across studies. Four studies defined dementia using the ICD-9 or ICD-9-CM diagnostic codes [22, 25, 29, 30], while two studies used multiple validated clinical tests to diagnose dementia [23, 24]. One study did not specify the ascertainment of dementia [28]. In one study, cognitive decline was defined using a modified version of the Telephone Interview for Cognitive Status, which is a validated measurement of cognitive impairment [26]. The other study ascertained cognitive impairment through manual review of medical records, and the use of algorithms to capture terms for cognitive impairment and dementia [27].

Sample sizes were generally smaller for studies assessing cognitive decline, ranging from 1,434 to 2,401 total population, compared to 3,602 to 417,172 in dementia studies. The age at which participants were recruited ranged widely between 18 to 75 years and older, but the mean age ranged between 65.5 to 78.6 years old.

The duration of follow up differed widely. In studies assessing cognitive decline, follow-up ranged from 3 months to 9.8 years. Among studies assessing dementia, only 3 studies reported the mean or median follow time which ranged from 2.5 to 9.0 years.

Effect of infections on dementia

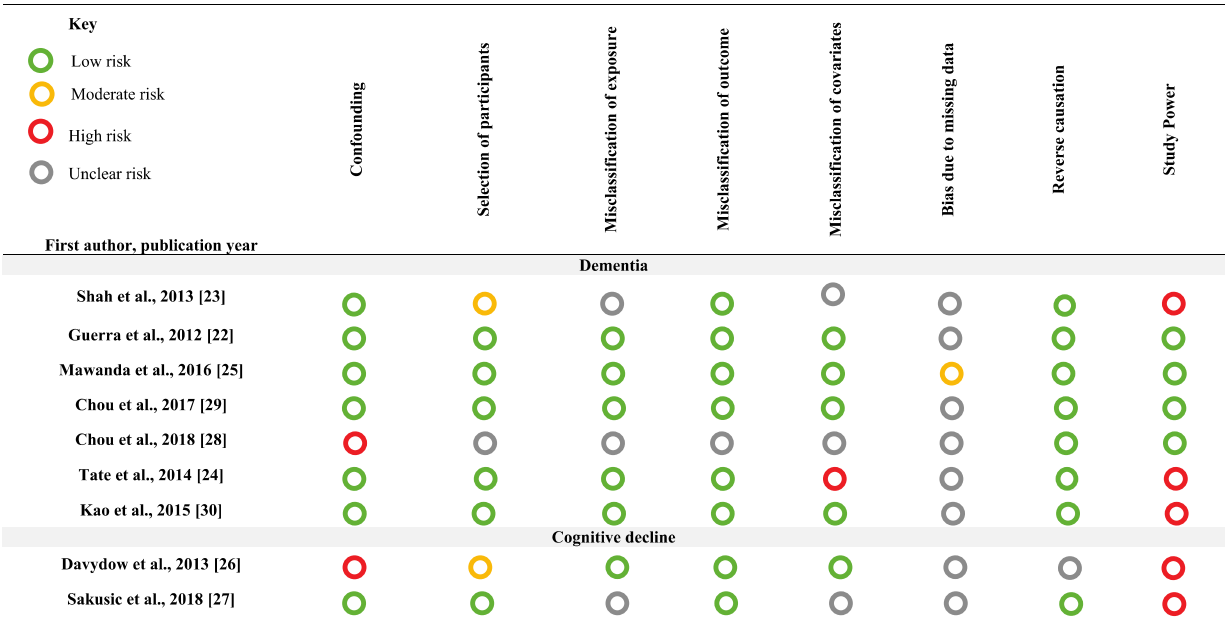
Seven studies assessed dementia as an outcome (Table 2, Fig. 2) [22–25, 28–30]. In all studies, infections were associated with an increased risk of all cause dementia or vascular dementia, with effect estimates ranging from HR 1.10 (95% CI;1.02–1.19) to OR 2.60 (95% CI;1.84–3.66).

To determine whether a meta-analysis was appropriate, we calculated heterogeneity when a sufficient number of studies were available. We decided not to meta-analyze data for the associations between sepsis or pneumonia with incident dementia due to evidence of substantial heterogeneity, $I^2 = 93.6\%$, $p = <0.01$ and $I^2 = 83.9\%$, $p < 0.01$. Due to the limited number of studies available, we could only explore geographical location and risk of bias as potential sources for heterogeneity. Heterogeneity was explored in studies assessing incident dementia following sepsis infection as shown in Supplementary Figures 1 and 2. Removing studies conducted in Taiwan reduced heterogeneity substantially ($I^2 = 0\%$, $p = 0.406$); however, when studies with a domain of high risk of bias were removed, heterogeneity remained high ($I^2 = 95.6\%$, $p < 0.01$).

Subgroup analyses

All three studies from Taiwan reported data on subgroup analyses for age, sex, and dementia subtype as shown in Supplementary Figures 3–5. Of these, two studies reported on the association of sepsis on dementia subtype [28, 29]. In one study, sepsis was associated with an increased risk of all types of dementia 2.09 (95% CI; 1.92–2.28) and non-Alzheimer dementias 2.20 (95% CI; 2.01–2.41) [29]. However, the association of sepsis and Alzheimer's disease HR 1.15 (95% CI; 0.83–1.60) was not statistically significant. In the other study, individuals with sepsis had an increased risk of vascular dementia HR 2.26 (95% CI; 2.07–2.47) [28]. In sub-group analysis we also explored whether the effect of infections on dementia differed by sex [29, 30]. Findings from these studies showed the association of sepsis on dementia was greater in men compared to women.

Table 3
Risk of bias summary assessments for individual domains



Only one study investigated the effect of age on infections and dementia [30]. Kao et al. found that compared with individuals aged 45 to 64, participants aged 65 and older showed a lower risk of dementia following sepsis HR 1.80 (95% CI; 1.65–1.97) than those aged under 45 HR 7.32 (95% CI; 1.85–28.9). However, these results are difficult to interpret due to the small number of events in the under 45 years age group ($n = 11$) compared to the 65 years and older group ($n = 2492$). This study also investigated the effect of sepsis severity on dementia and found that dementia incidence increased with mild HR 1.20 (95% CI; 1.06–1.37), moderate HR 3.37 (95% CI; 3.02–3.76) and severe HR 5.04 (95% CI; 3.98–6.37) sepsis severity. Another study also reported an increasing trend for developing dementia with increasing sepsis severity [28].

Effect of infections on cognitive decline

Two studies assessed cognitive decline as an outcome: one following hospitalization with pneumonia and the other following admission to an intensive care unit with sepsis (Table 2, Fig. 3) [26, 27]. In one study, the effect of pneumonia hospitalization on moderate/severe cognitive impairment was compared to individuals hospitalized with stroke OR 0.64 (95% CI; 0.3–1.34) and to those with myocardial infarction OR 1.46 (95% CI; 0.69–3.09) [26]. In the other study, there was no association between sepsis and cognitive decline OR 1.08 (95% CI; 0.97–1.21) in adjusted estimates [27]. Given that the definition of infections was inconsistent in these studies, we could not pool the results into a combined effect estimate and perform a meta-analysis.

Risk of bias

Our classifications and justifications for the risk of bias assessments are presented in Supplementary Table 1 and summarized in Table 3. Overall, none of the studies were classified as at low risk of bias across all domains. All studies assessing cognitive decline and three looking at dementia outcomes were considered at high risk of bias for study power. Studies assessing cognitive decline had particularly small sample sizes and wide confidence intervals compared to the dementia studies. The majority of studies assessing dementia scored a low risk of bias for confounding as these studies adjusted for age, sex, and other important covariates. Three studies did not have any domains at high risk of bias [22, 25, 29]. These studies all investigated the effect of sepsis on dementia, with hazard ratios ranging from 1.39 (95% CI; 1.16–1.66) to 2.09 (95% CI; 1.92–2.28). All studies were given a low rating for reverse causality as all outcomes were assessed after infection; however, three studies reported a relatively short follow up period from infection to dementia diagnosis [22, 24, 30]. Given that dementia has a long pre-clinical phase, it is thus unclear whether follow up time was long enough for dementia to develop. Further, none of the studies

reported sufficient information on loss of follow up or how missing data were accounted for.

Study quality

The overall evidence on the associations of sepsis or pneumonia with dementia were classified as of very low quality using the GRADE assessment tool. This is because these studies were rated "serious" or "very serious" for risk of bias, inconsistency, imprecision, and indirectness (Supplementary Table 2). We did not assess the overall quality of evidence for the association of other infections on dementia or cognitive decline as only a single study was available for each exposure and outcome.

DISCUSSION

Our comprehensive systematic review identified 9 longitudinal studies examining the association of common bacterial infections with incident dementia or cognitive decline. Although a meta-analysis was not performed due to the heterogeneity of the studies, evidence from all seven studies assessing dementia found a positive association following infection with sepsis, pneumonia, urinary tract infections, or cellulitis. This association remained consistent in studies with no domains at high risk of bias. However, the overall quality of evidence was rated very low for these studies due to risk of bias, consistency, imprecision, and indirectness. Of the two studies assessing the effect of pneumonia or sepsis on cognitive decline, a lack of association was observed. However, these studies had a number of important methodological limitations including a lack of power or poor comparability, limiting the ability to draw accurate conclusions from the findings.

Heterogeneity

The high heterogeneity observed between the studies assessing incident dementia precluded a meta-analysis, despite the studies being homogenous in terms of exposure, outcome, and study design. A major source of heterogeneity may have been the differences in the country in which the study was conducted. Studies assessing the effect of sepsis on dementia were either from the United States or Taiwan, with studies from Taiwan reporting much greater effect estimates compared to those from the United States. When studies from Taiwan were removed from the meta-analysis, heterogeneity reduced substantially. However, due to the small number of studies available, we were unable to quantitatively explore heterogeneity in studies from Taiwan. Studies assessing pneumonia were all conducted in the United States, but also had high heterogeneity, however, the paucity of studies limited the ability to quantitatively explore sources of the heterogeneity.

There are a number of possible explanations for the substantial heterogeneity observed. Varying assessments were used to diagnose dementia including neuropsychological tests, ICD-9 or ICD-9-CM codes, and magnetic resonance imaging. Studies using electronic health records rely on routine medical diagnoses which can result in misclassification given that dementia is frequently under-diagnosed in these databases [31, 32]. However, further evidence suggests that recording of dementia diagnoses is changing over time, with improvements observed in more recent years [33, 34]. Another potential issue arising from routine healthcare data is that individuals with illnesses encounter health services more frequently compared to healthy people, which could increase the likelihood of getting a dementia diagnosis. This may, however, be more likely to occur among those with chronic illnesses requiring ongoing management than with acute infections.

Another source of heterogeneity could have come from differences in the adjustment of confounders, given that the study that adjusted for a wide range of confounders including demographics, psychiatric and medical comorbidity reported weaker effect estimates in comparison to the other studies [25]. Additionally, differences in the age at recruitment and mean age of the study populations may also account for the heterogeneity. This is of importance as the risk of developing infections increases with age [35] and in turn older adults have a greater chance of developing dementia, with the risk doubling every 5 years after the age of 65 [36]. Additionally, sex representation, which ranged from 44% to 97% for men, may have contributed to heterogeneity. In our subgroup analyses, we observed differences in sex in the Taiwanese studies looking at the association between sepsis and dementia, with men at a greater risk of dementia compared to women [29, 30]. Studies from Europe and the United States suggest that there is gender variation in the reduction of age-specific dementia, with some reporting a greater decline in men [3, 6, 9] and others in women [5, 8].

One study did not find an association between sepsis and Alzheimer's disease. The study suggested a

reason for this may be due to the low prevalence for a causative pathogen of Alzheimer's disease, *B. burgdorferi*, in Taiwan [29]. Another reason could be the potential to misdiagnose Alzheimer's disease. A systematic review investigating the validation of dementia cases in routine health care data from Europe, North America, and Australia found that positive predictive values of Alzheimer's disease ranged from 57% to 100% [37].

Cognitive decline

Evidence for any association of common bacterial infections with cognitive decline was limited. The study by Davydow et al. faced a number of limitations. First, there was no adjustment for confounders in this study [26]. Second, individuals hospitalized with pneumonia were compared to those with stroke and myocardial infarction. This raises issues on the suitability of these comparator groups as stroke and myocardial infarction are both risk factors for dementia and may increase the risk of pneumonia [38, 39]. The authors stated that these analyses were based on a hypothetical population, and as such the results may not be generalizable to a particular group of people. Taken together, these limitations make it difficult to extrapolate any meaningful conclusions from these results.

Comparison with previous studies

Although the association between common bacterial infections and cognitive decline was unclear, evidence from previous longitudinal studies suggests that individuals with bacterial infections are associated with worsening cognitive impairment [16, 40], with one study showing a decline in the mean score of cognitive ability, assessed using the Danish intelligence test, following hospitalization with sepsis, skin, respiratory and urological infections [41]. Other studies have found a link between sepsis and specific cognitive domains after long-term follow up [42].

Regarding the link between bacterial infections and dementia, our findings are consistent with evidence from a nested-case control study using UK primary care data which suggested that episodes of infections were associated with an increased likelihood of a dementia diagnosis [43]. This study assessed the overall effect of infections on dementia, including urinary tract and skin infections, rather than the individual effect of each infection on dementia. Because of this, the study was not eligible for inclusion.

Individual bacterial pathogens including *Helicobacter pylori*, *Chlamydia pneumoniae, Borelia burgdorferi*, and oral *spirochetal Trepenoma* have been linked to Alzheimer's disease, primarily in serology based and post mortem brain studies [10, 18]. *Chlamydia pneumonia* and *spirochetes* are the focus of previous reviews and have been frequently associated with Alzheimer's disease [10, 11, 44–46]. In their review, Mawanda and Wallace suggested chronic bacterial infections, such as tuberculosis, are associated with amyloid deposition, a key hallmark of Alzheimer's disease. This is further supported in a study by Emery et al., which demonstrated an increase in *actinobacteria* in the brains of individuals with Alzheimer's disease compared to controls [47]. However, no single microorganism has been identified as the sole pathogen responsible for Alzheimer's disease.

Mechanisms

Mechanisms underlying the association between infections and subsequent dementia are unclear [48, 49], but several plausible pathophysiological pathways have been proposed. One such potential pathway is through systemic inflammation. Infections can induce systemic inflammation through the release of pro-inflammatory mediators which can cross the blood-brain barrier and activate cytotoxic microglia. This may result in a deterioration of cognitive function and thus increasing the risk of developing dementia [10]. In support of this mechanism, evidence from a growing number of longitudinal studies suggests that markers of systematic inflammation, such as tumor necrosis factor, nitric oxide synthase, and interleukin IL-1β, IL-6, and IL-18, are involved in the pathogenesis of dementia [50, 51]. Recent findings demonstrate that when sepsis is induced in animal models, it triggers systemic inflammation which leads to accumulation of amyloid-β and cognitive dysfunction [52, 53].

Alternatively, it is also possible that the association between infections and dementia is non-causal and may be a result of the co-occurrence of age-related pathologies. The immune system deteriorates with age, increasing incidence of infection. Conversely, the aging immune system also induces a chronic inflammatory state which leads to tissue damage and inflammatory disease and accelerates age-related diseases such as Alzheimer's disease

[54, 55]. Nevertheless, the present review focused only on longitudinal studies which provide evidence of appropriate temporality between infections and dementia, thus adding to the likelihood of a possible causal relationship.

Strengths and limitations

Strengths of our study include a comprehensive search using multiple databases of published and grey literature, with no restrictions on the date, language or geographical location of the studies. Our search strategy was detailed and peer reviewed. We registered and published our protocol in order to increase the transparency of our findings. Other strengths include the inclusion of longitudinal studies to minimize reverse causality, a minimum 3 month follow up period to avoid capturing short term cognitive impairment, and requiring the use of a comparator group without infections in order to provide evidence on causality.

There are several limitations to this systematic review. First, there was a small number of longitudinal studies available, particularly for cognitive decline outcomes. Second, the high heterogeneity between the studies meant that it was not feasible to perform a meta-analysis. Third, given the long pre-clinical phase of dementia and the evidence that individuals with dementia are at a greater risk of hospitalizations and common bacterial infections [56], we cannot rule out the possibility of reverse causality. Fourth, these studies did not account for past hospitalizations with infections, as such we cannot rule out the effect of previous infections on the risk of dementia. Fifth, the generalizability of these studies is of concern. All studies were conducted in the United States or Taiwan, and there were no studies from Europe or low- or middle-income countries. Further to this, infections were predominantly diagnosed in a hospital setting. These findings may thus not be representative of individuals with less severe infections that did not require hospitalization. This may have led to an underestimation of people with infections.

Implications for research and practice

The paucity of studies available highlights the need for further large scale, longitudinal studies from populations across the world.

Our sub-group analyses suggested that the severity of sepsis is associated with an increased risk of dementia. Further research on the effect of severity, frequency, and timing of infections on cognitive decline and dementia is warranted. This will be important for identifying the sub-populations most at risk of dementia. In line with this rationale, previous studies have identified a dose-response relationship between hospital contacts with infection and cognitive ability [41]. Additionally, there is evidence of gender variation between infections and dementia, as such, more work is needed to explore this possible link further as it may have implications on prevention strategies in men and women.

A key drawback of the studies included was the fact that infections were predominantly diagnosed in secondary care. This is an issue as hospitalization itself has been associated with incident cognitive decline and dementia [57–59]. Hospitalized patients are at a greater risk of nosocomial infections [60], delirium [61], and functional decline [62], which may also increase the risk of dementia. Therefore, individuals hospitalized with infections may not be representative of those with infections diagnosed in primary care. In future, studies could investigate the effect of infections diagnosed in different health care settings. Additionally, the bacterial agents responsible for infections acquired in the community or in hospital settings differ, and as such it is possible that these pathogens could have differing effects on dementia, if any at all. Future longitudinal studies investigating the link between laboratory confirmed bacterial agents and dementia could shed further light on causality.

Research on infections as potential risk factors for dementia faces a number of challenges. Firstly, the etiology of dementia is multifactorial and is likely to involve an interplay of genetic, environmental, and lifestyle factors. In addition, the fact that age is the single greatest risk factor for dementia raises challenges in disentangling the pathophysiological effects of age on dementia with the independent effects of infections on dementia. Secondly, the pathophysiological processes of dementia may begin years before dementia is diagnosed, and as such it is possible that the preclinical phase of dementia may be underway before infection occurs. Future studies with a follow up time sufficient enough for dementia to develop are recommended in order to minimize the possibility of reverse causality. Moreover, given that infections may trigger delirium, it is important for future studies to ensure that individuals are followed up long enough for delirium to resolve in order to help distinguish between delirium and long-term cognitive decline. However, as delirium itself is associated with

cognitive decline and dementia, there is a need to better understand whether the pathological processes of infections on long-term cognitive decline are independent of delirium. Third, prospective cohort studies on infections and dementia are susceptible to selection bias. Individuals with more severe infections are associated with attrition as they are more likely to experience greater morbidity and an increased risk of mortality compared to those with less severe infections. Additionally, cognitive decline and dementia are associated with attrition during follow up and drop-out due to death [63, 64], which may underestimate the true effect of infections on dementia. Further studies could tackle this limitation by performing an analysis of attrition to investigate whether those lost to follow up were more likely to have impaired cognitive function. Loss of follow up is minimized in routine healthcare datasets; however, one of the limitations of these datasets is that they rely on individuals seeking health care services. As a result, health seeking behavior could affect the likelihood of a dementia diagnosis. Future studies should consider accounting for health-seeking behavior in their design or analysis.

This review suggests that infections may be involved in the development of dementia. These findings could have clinical implications in the early recognition and treatment of infections, particularly in the older population who are more susceptible to infections and are at a greater risk of dementia. Additionally, other implications include the need for strategies to improve infection control and to identify sub-populations at risk of infections and dementia.

Conclusions

Our systematic review suggests that sepsis, pneumonia, urinary tract infections, and cellulitis may be associated with an increased risk of dementia, after adjustment for multiple confounders. However, due to the paucity of longitudinal studies, further evidence from high quality studies is needed to confirm this association. Given that evidence on cognitive decline was limited by a lack of studies and small sample sizes, further large scale, well-powered studies are needed to investigate the effect of infections on cognitive decline. Infections are well-recognized to trigger delirium, as such, it is important for future work to distinguish whether the potential association between infections and cognitive decline is independent of delirium. Common bacterial infections frequently occur in the elderly, who are at an increased risk of dementia, and thus a better understanding of their role in dementia development could inform dementia risk reduction strategies.

ACKNOWLEDGMENTS

Rutendo Muzambi is supported by an Alzheimer's Society PhD studentship 379 (AS-PhD-17-013). We would like to thank the lay volunteers assigned to Rutendo's PhD studentship for their input and advice. Charlotte Warren-Gash is supported by a Wellcome Intermediate Clinical Fellowship, Wellcome Trust (201440_Z_16_Z) and Krishnan Bhaskaran holds a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0303r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-200303.

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3.6 Relevant studies published after the systematic review search

The search period for the published systematic review ended in March 2019, therefore, to update the search, I repeated the search between March 2019 and August 2021. An additional six studies were published that would have been eligible for inclusion into the published systematic review. One of these studies is the third research paper in this thesis which aimed to address the evidence gaps identified in the systematic review. As I describe this paper in detail in chapter 5, this section will focus on the five other additional studies that would have been eligible for inclusion.

Of these five studies, two were conducted in the UK,[158,159] one in Sweden,[160] one in Germany,[161] and one in Finland.[162] All studies used data from linked EHRs; 4 were retrospective cohort studies,[158-161] and one was a prospective cohort study linked to EHRs.[162] The size of the study populations for these studies was generally much larger than the studies previously included in the systematic review. Study sizes from these updated studies ranged from 60,392 to 4,262,092 individuals and the age of the study population at recruitment ranged from 18 to 65 years and older. Follow up was generally longer for these studies compared to those in the published systematic review. In all studies, individuals were followed up for at least up to 9 years with two studies having a median follow up of over 10 years. [159,162] Overall, while all 5 included the use of EHRs, studies were heterogeneous in terms of study design, study population (with some studies comprising of selective population groups i.e only stroke survivors or intensive care unit survivors), type and setting of infections and dementia subtype (all-cause dementia or Alzheimer's disease).

The results of these studies were broadly consistent with the findings of the systematic review, though one study did not find an association between common infections and dementia. Three of the updated studies investigated the association of sepsis and dementia. In a historical cohort study using German health claims data consisting of 161,567 adults aged 65 years and older, Fritze et al found that individuals hospitalised with sepsis were at an increased risk of a dementia diagnosis (HR 3.14, 95% CI 2.83-3.49) compared to those without sepsis, with the risk lower for sepsis patients admitted to intensive care units HR 2.22 (95% CI, 1.83–2.70).[161] Similarly, in a Finnish primary cohort of this study which included 260,490 people aged 18 years or older, Sipilä et al found that individuals who had bacterial infection with sepsis were at an increased risk of dementia compared to those without infection HR 1.69 (95% CI, 1.29-2.21).[162] Findings from the German and Finnish study thus corroborated with the results of the published systematic review. In constrast, a Swedish retrospective study of 210,334 intensive care unit survivors aged 18 years and older.[160] In this study, Ahlström et al found no association between sepsis and dementia (HR 1.01, 95% CI, 0.91–1.11) after adjustment for baseline characteristics include those related to intensive care admission. Discrepancies between findings could be attributed to differences in clinical setting and study population.

Two studies from the UK investigated the association of urinary tract infections, skin and soft tissue infections and lower respiratory tract infections with incident dementia. In a UK historical cohort study using EHR data from the Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) consisting of 60,392 stroke survivors aged 40 years and older, Morton et al found an association between lower respiratory tract infections HR 1.44 (95% CI, 1.14 – 1.81) and urinary tract infections

HR 1.63 (95% CI, 1.28 – 2.07) with early post-stroke dementia.[158] No association was found between skin and soft tissue infections and early post-stroke dementia, HR 0.89 (95% CI, 0.52 – 1.51), though the number of people diagnosed with dementia in this group were small (n=22). In addition, no association was found between lower respiratory tract-, urinary tract-, and skin and soft tissue infections with late post-stroke dementia. The studies included in the systematic review had predominantly focused on hospitalised infections while the study by Morton et al was the first study to show individual associations between primary and secondary care infections. The authors found that hospitalised infections were associated with a greater risk for early post-stroke dementia and the risk of late-life dementia only increased following hospital-record infections, and not GP recorded infections. The effect of frequency of infections on dementia risk was also investigated in this study and evidence of a dose-response relationship between an increasing number of GP recorded infections and early dementia was found. In another UK study, no evidence was found of a dose-response relationship between the cumulative infections and risk of Alzheimer's disease. This study, by Douros et al, was a case-control study using primary care data from the CPRD, which comprised 4,262,092 individuals aged 50 years and older. Douros et al found an association between urinary tract infections and Alzheimer's disease OR 1.03 (95% CI, 1.00 to 1.06) but no association between pneumonia and Alzheimer's disease OR 0.92 (95% CI, 0.84 to 1.01).[159] In contrast to the studies included in the systematic review, this study only included infections diagnosed in community general practice. Only one study included in the systematic review assessed Alzheimer's disease as an outcome and this study found no association between sepsis and Alzheimer's disease.[163]

3.7 Summary

- In summary, this systematic review was the first to summarise evidence from existing longitudinal studies to investigate the association of common clinically symptomatic bacterial infection with dementia or cognitive decline.
- Of the seven studies included in the systematic review investigating dementia as an outcome, all studies found that sepsis, pneumonia, urinary tract infection and cellulitis were associated with an increased risk of dementia. Only two of the included studies assessed cognitive decline as an outcome, and both studies found no association between sepsis or pneumonia hospitalisations and cognitive impairment.
- Existing literature was limited by focusing solely on sepsis, pneumonia or hospitalised infections and the studies were predominantly conducted in Taiwan or the United States. Other limitations included relatively small study population sizes, short follow-up periods, inadequate confounder adjustment or limited generalisability. The overall quality of these studies was rated very low.
- Although 5 of the relevant studies published after this systematic review overcame some of these limitations, they still faced a number of key drawbacks particularly in terms of generalisability.
- Heterogeneity in terms of study population, study design, type of common infection and dementia subtype of the studies included in the systematic review precluded a meta-analysis as such the magnitude and direction of any association remains uncertain.
- This systematic review highlighted the need for further large-scale longitudinal studies focusing on a range of common infections, including urinary tract- and

skin and soft tissue infections, from different clinical and geographical settings (primary and secondary care) assessing the association of common infections with dementia. Moreover, current literature on common infections and cognitive decline is scarce and limited warranting further research in this field.

Chapter 4: Data sources

4.1 Introduction

In this chapter I describe the two data sources used to address the second, third and fourth research aims of this thesis. To investigate the second research aim which investigated the association between common infections and incidence of dementia and cognitive impairment, I used data from the Clinical Practice Research Datalink (CPRD) which is a large UK dataset of routinely collected primary care EHRs from general practitioner (GP) practices. Data from CPRD were linked to Hospital Episode Statistics (HES) for GP practices that had consented to participate in the CPRD linkage scheme. For the third and fourth research aim which assessed the association of common infections with dementia, cognitive decline and neuroimaging measures, I used data from the UK Biobank study, an ongoing prospective, population-based cohort study. Data from the UK Biobank study were linked to routinely collected electronic healthcare datasets including primary care records and hospital admissions data.

4.2 Clinical Practice Research Datalink

4.2.1 Background and overview of CPRD data

The CPRD is a large dataset of anonymous UK primary care EHRs that is sponsored by the Medicines and Healthcare Regulatory Agency and the National Institute of Health Research.[164] The CPRD was established in 1987 when it was known as the small Value Added Medical Products dataset until 1993 and then as the General Practice Research Database (GPRD) until 2012.[165] Since its inception, CPRD data have contributed to clinical practice and epidemiological research with over 2,800 peer reviewed publications using the database by September 2021.[166]

The UK has a unique health care system, the National Health Service (NHS), which is free at the point of use and includes over 98% of the UK population who are registered with a GP.[167] GPs are the first point of contact for patient care and are also responsible for referrals to secondary or specialist health care services. Regarding consent for data collection and sharing, no consent is needed for data collection as data are collected for routine clinical purposes, but practices opt in to sharing anonymised data with CPRD for use in research. The CPRD GOLD database contains data sourced from GP practices in the UK using the Vision system software. Around 9% of GP practices in England used vision software in 2016.[168] In this thesis, I used data from the CPRD GOLD database which consisted of over 16 million ever patients (including patients who transferred out of the database and deceased patients) from 761 participating general practices in January 2019. Of these patients, 2.3 million were registered at GP practices currently contributing to CPRD GOLD and these patients covered 3.5% of the UK population at the time.

Figure 4.1 shows the spatial mapping of GP practices using Vision software in 2016 at the Clinical Commissioning Group level. Primary care databases using Vision were largely concentrated in London, the South, Greater Manchester and Birmingham and were the least geographically representative of the UK population compared to other primary care databases in England.[168] However, the CPRD database is representative of the UK population in terms of age, sex and ethnicity.[164,169]

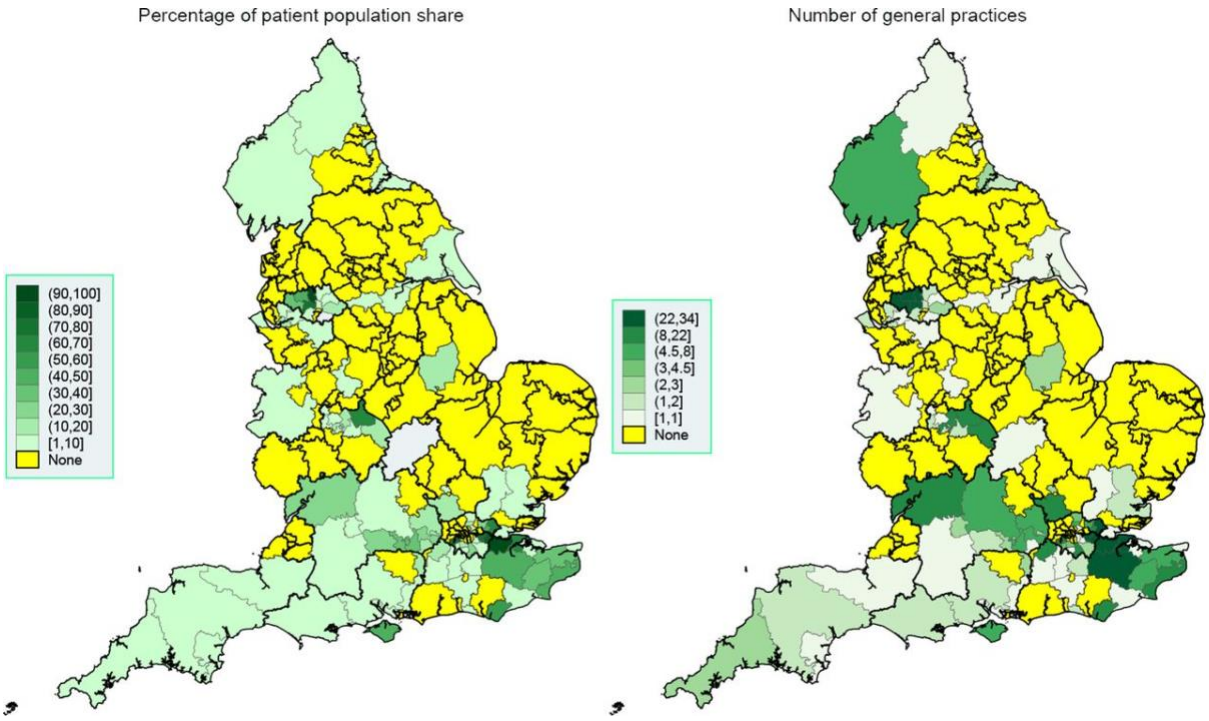

Figure 4.1. Spatial mapping at the Clinical Commissioning Group (CCG) in September 2016 for GP practices using the Vision computer system.
Image from Kontopantelis et al, 2018 under a CC-BY license. [168]

4.2.2 Data structure

CPRD GOLD data is delivered to users in the form of 10 files per practice, which contain information on patient and practice demographics, clinical information, tests, therapies, health-related behaviours and referrals to secondary care (Table 4.1).[170] Clinical events in CPRD are recorded by GPs using a hierarchical clinical classification system of Read codes. Read codes are a clinical coding system mapped to a dictionary of clinical terms. GPs also record details of a consultation using free text however due to the possibility of patient identifiable information included in the free text, this information is not collected by CPRD.

Table 4.1 Description of the datasets in the CPRD GOLD database

Dataset	Description	Examples of data fields
Patient	Patient demographics and patient registration information	Patient identification number, age and year of birth, gender, date of death, first and current registration date
Practice	Practice information	Practice identification number, region, last collection date and up to standard date
Consultation	Types of consultation (e.g. emergency, surgery consultation)	Consultation identifier (which links consultations and events), consultation date and event date
Clinical	Patient's medical history information (e.g. signs, symptoms and diagnoses)	Medical code for medical terms, date of event entered by the GP
Therapy	Prescription data on the GP system. All prescriptions issued by the GP	Product code relating to therapy prescribed by GP, BNF code, total quantity of product
Referral	Referrals to secondary care settings (e.g. hospitals) and other external care centres	Source of referral (e.g. self, GP), In Patient (type of referral),
Test	Details of tests and examinations performed in the GP practice	Entity type (number assigned to each type of test), medical code, data field data1-data8 contain details of the test results
Immunisation	GP Vaccination records	Type, stage, source, status, reason and method of immunisation
Additional Clinical Details	Structured data areas that contain information that is not stored as coded data e.g. smoking and alcohol intake	Entity type (number assigned to type of clinical data)
Staff	Details of the GP practice staff members	Staff identification number, gender of staff and role of staff

BNF (British National Formulary)

4.2.3 Data quality and completeness

All GP practices contributing to CPRD GOLD are provided with recording guidelines to improve the completeness and quality of the data. However, the data quality in CPRD can still vary between practices.

The CPRD provides researchers with a flag for checking the quality of data. In the patient dataset, there is a data field indicating whether a patient has met specific quality standards and thus whether their data are acceptable for use in research or not. Patients with poor recording of data or non-continuous follow up are labelled as unacceptable. A few examples of patients labelled as unacceptable include those with missing first or current registration dates, missing year of birth and those with events recorded prior to year of birth. To ensure patient data are of research standard, patients labelled as unacceptable are not recommended by CPRD for use in research. Another quality assurance procedure by CPRD is the use of the 'Up To Standard (UTS)' date in the practice dataset. The UTS date is the date at which data from the practice is deemed to be of high quality and thus suitable for use in research. This date is derived using information on gaps in the data to ensure the continuity of data recording from the UTS date onwards. Therefore, to ensure data are of research standard, the CPRD recommend using data from the practice's UTS date.[164]

The quality of data recording in primary care has improved over the last two decades as a result of the introduction of the QOF in 2004.[171] The QOF set standards for recording data and financially incentivized GPs for the accurate recording of data. This has led to improvements in recording of outcomes in CPRD data over the years, thus improving the completeness of the data. Other government initiatives have led to an increase in the

diagnosis of certain health outcomes, such as the National Dementia Strategy which encouraged the diagnosis of dementia and led to an increase in the recording of dementia diagnoses in GP practices per primary care trust per year.[64] In England, the recorded dementia diagnosis rate increased over time to 67.8% by August 2018 though there were variations in dementia diagnosis rates across the UK.[61]

4.3 Linked data

4.3.1 Linked data overview

Data in CPRD can be linked to other datasets including the Hospital Episode Statistics dataset and Index of Multiple Deprivation (IMD) data. A Trusted Third Party, NHS Digital, performs the CPRD data linkage in England as it is legally allowed to receive identifiable patient data.[172,173] Linkage of CPRD data is only available for GP practices that have consented to participate in the linkage scheme and GP practices can withdraw their consent at any time.

All participating GP practices submit de-identified patient data to CPRD through their electronic software suppliers. To facilitate linkage, practices that have consented to data linkage, submit identifiable patient data (e.g. NHS number, date of birth) and system patient and practice identifiers via their GP software suppliers to NHS Digital. After data cleaning, data are merged with the previous data submission and ready for record linkage to other health care datasets. Secondary care and other external data sources also submit data to NHS digital. These data include identifiable patient data and pseudonymised identifiers which will allow the CPRD dataset to be merged with external data sourced for example HES or IMD data.[173]

4.3.2 Linked Hospital Episode Statistics Admitted Patient Care data

The HES database contains data on all admissions, outpatient and accident and emergency attendances to English NHS hospitals, or independent hospitals funded by the NHS.[174] The NHS is estimated to fund 98-99% of hospital activity.[175] The HES database consists of four datasets with different clinical information and coverage. These include the HES Admitted Patient Care (APC) dataset, HES Outpatients records, Accident and Emergency Records and Adult critical care records.[176] In this thesis, I used the HES APC dataset. HES APC has the longest patient coverage from 1989-90 onwards and data linkage from 1997-98 onwards. The dataset contains information on hospital admissions which include any episode that requires a hospital bed (elective or emergency). This includes day cases, emergency and planned admissions, births and associated deliveries, inpatient or day care hospital admissions. [174] Diagnostic data recorded in HES are coded using the International Classification of Diseases version 10 (ICD-10) coding frame. [174]

4.3.3 Linked Index of Multiple Deprivation data

The Index of Multiple Deprivation (IMD) is a measure of relative deprivation for small areas in England and is calculated for every Lower Layer Super Output Area (LSOA).[177,178] The most recent IMD measure at the time of conducting analyses for this thesis was the IMD 2015. The IMD 2015 is based on 37 indicators across seven domains and these domains include income deprivation, employment deprivation, health deprivation and disability, education, skills and training deprivation, crime, barriers to housing and services and living environment deprivation.[178] Domains can be divided into groups ranking from least to most deprived.[177] CPRD GOLD data can be linked to patient or practice level IMD. Quintiles or deciles of the deprivation scores are provided.

The IMD can be used as a proxy for socioeconomic status. To facilitate the linkage of the IMD data the practices' postcode or postcode of where the patient resides is mapped to a LSOA boundary which is then mapped to IMD data.

4.4 CPRD Strengths and limitations

CPRD GOLD is a large-scale, longitudinal primary care database of UK routinely collected HER data with 2.3 million active patients in January 2019 and a median follow up of 11.88 years (4.34 – 23.25). An important strength of CPRD data is the large size of the dataset which increases the statistical power for precise estimates of associations, the ability to adjust for multiple confounding variables and to undertake well-powered analyses in population subgroups. CPRD includes a large number of variables including sociodemographic, lifestyle and morbidity which allows the possibility to investigate a wide range of associations including those of rare outcomes. Additionally, CPRD has a relatively long follow up which is particularly important for assessing causal relationships where they may be a long length of time between the initial exposure and clinical outcomes such as dementia which can take years to develop. Another key strength of CPRD is the ability to link primary care data to other data sources including hospitalisation data which improves the ascertainment of outcomes, exposures and covariates, facilitates follow up of health outcomes and also allows for the investigation of associations in different clinical settings. CPRD has an advantage over electronic health databases that only include selective patient groups or populations such as elderly individuals or veterans. CPRD uses data from GP practices and 98% of the UK population are registered with a GP. Evidence suggests that the dataset is representative of the UK in terms of age, sex and ethnicity which therefore improves generalisability of research findings.[164,169]

Primary care data are not recorded with the sole aim of using it for research purposes. As such data completeness, accuracy and consistency are key limitations of CPRD data. Misclassification of variables is a potential issue given that the absence of a Read code for a particular condition is regarded as the absence of that condition. However, for a Read code to be recorded patients first need to consult with their GP and some patients, for example those with greater health seeking behaviour, may be more likely to present to the GP than others. Patients with more mild conditions (e.g. mild acute infections) may also be less likely to seek care from a GP and thus missed records for these conditions will be likely. Furthermore, some outcomes such as dementia have been shown to be frequently underdiagnosed in primary care, though dementia recording in primary care has been improving in recent years.[59-61] The possibility of misclassification is also increased by the differences in the coding of diagnoses amongst GPs. As a result, it is possible that researchers may fail to include relevant codes relating to a condition which will then led to misclassification. However, the use of multiple data sources to ascertain variables will limit the possibility of misclassification. Additionally, CPRD has been validated numerous times since its inception, [179-182] with high positive predictive values for a wide range of outcomes including dementia.[183] Missing data, particularly for lifestyle and behavioural variables such as smoking status and body mass index (BMI), is a key drawback of CPRD. Recording of these variables may vary between patients depending on their health condition. Additionally, data on diet, physical activity or education is not well recorded in CPRD.

4.5 UK Biobank

4.5.1 Rationale

The UK Biobank is an ongoing prospective, population-based cohort study established by the Medical Research Council and Wellcome Trust. The overall aim of the UK Biobank study is to improve the prevention, diagnosis and treatment of illnesses including diabetes and dementia.[184] Between 2006-2010, over 500,000 adults between 40-69 years of age enrolled in the UK Biobank study. This age group was selected as it includes people at risk of developing a range of key conditions including diabetes and dementia over the next following decades.[185] According to the UK Biobank protocol, the age-range also enables the ascertainment of events at an age where cause-specific outcomes are generally well recorded with less co-morbidity than older age groups. The rationale for the large size of the UK Biobank population was based on power calculations for nested case-control studies.[185] Ethical approval for the UK Biobank study was granted by the Research Ethics Committee (reference 11/NW/0382). After participants have consented to take part in the UK Biobank study, they can withdraw from the study at any time.

4.5.2 Recruitment

Participants were recruited through direct mailing of invitations to 9, 238,453 individuals who lived within 40 km of one of the 22 UK Biobank assessment centres in England, Scotland and Wales using contact details obtained for NHS central registers.[184] The locations of the assessment centres are shown in Figure 4.2. The response rate was low with 503, 317 (5.5%) consenting and participating in the baseline assessment.[186] UK cohorts drawn from selected populations such as the British Doctors study and the Whitehall II study of British civil servants had a high response rate of 69% and

73%.[187,188]. Nationally sampled UK cohorts such as the Health Survey for England (HSE) and the Scottish Health surveys (SHS) had a mean response rate of 68%. However, when associations between well-established risk factors and mortality were compared between the HSE-SHS studies and the UK Biobank study close agreement was found.[189] The participation rate in the UK Biobank study increased with age. Participation rate was higher among older age groups (9% in 60-64 age group and 3% in 40-44 age group). Participant rate was also higher among women (6.4% in women and 5.1% in men) and highest for people residing in less deprived areas (8% in least deprived area and 3% in most deprived area).[186]

Figure 4.2. Map of the location of the 22 UK Biobank assessment centres.
Image obtained with permission from the UK Biobank website.[190]

Table 4.2. Key characteristics of UK Biobank participants at baseline

	Total participants N=502,444
Age at baseline assessment (Mean, standard deviation)	56.53 (8.10)
Age (years)	
<40	7 (0.0%)
40-44	51,784 (10.3%)
45-49	66,061 (13.1%)
50-54	76,315 (15.2%)
55-59	90,807 (18.1%)
60-64	121,470 (24.2%)
65+	96,000 (19.1%)
Sex	
Female	273,342 (54.4%)
Male	229,102 (45.6%)
Ethnicity	
White European	472,641 (94.1%)
South Asian	8,066 (1.6%)
African Caribbean	8,060 (1.6%)
Mixed or other	10,901 (2.2%)
Missing	2,776 (0.6%)
Baseline quintiles Townsend deprivation index	
Least deprived	100,348 (20.0%)
2nd least deprived	100,350 (20.0%)
Median deprivation level	100,379 (20.0%)
2nd most deprived	100,352 (20.0%)
Most deprived	100,392 (20.0%)
Missing	623 (0.1%)
Baseline alcohol intake frequency	
Rarely or never	98,633 (19.6%)
1-8 times per month	185,122 (36.8%)
16 times per month- every day	217,189 (43.2%)
Missing	1,500 (0.3%)
Smoking category	
Never smoker	332,271 (66.1%)
Previous smoker	115,285 (22.9%)
Current smoker	52,969 (10.5%)
Missing	1,919 (0.4%)

Total UK Biobank population, excluding those who withdrew from the study as of August 2021

Table 4.2 shows the key characteristics of UK Biobank participants at baseline. In total there were 502,444 UK Biobank participants, excluding participants who withdrew from the study as of August 2021. The mean age was 56.5 years with the greatest proportion of participants in the 60-64 years age group. 54.4% of participants were female and 66.1% were never smoker.

Fry et al, 2017 used nationally representative data sources to compare characteristics of UK Biobank participants with the UK general population.[186] UK Biobank participants were more likely to be healthy than the general population; they had fewer self-reported health conditions, were less obese, less likely to smoke, had lower rates of all-cause mortality and lower total cancer incidence. Therefore, there is evidence of a "healthy volunteer" bias in the UK Biobank study which limits representativeness of the study. However, this may not be a limitation when investigating exposure and outcome associations and the findings may still be widely generalisable.

4.5.3 Baseline assessment

The baseline assessment visit took place between 2006-2010 at 22 centres in England, Scotland and Wales. The baseline assessment lasted between two to three hours during which participants provided written consent and completed touch screen questionnaires, a face-to-face nurse interview, physical examinations and provided blood, saliva and urine samples (Table 4.3). Data collected at baseline included information on family history and early life exposures, lifestyle, health status, hearing threshold, cognitive function, sociodemographic, psychosocial and environmental factors.[184] Physical measures included blood pressure and heart rate, grip strength, anthropometrics, spirometry, bone density, arterial stiffness, eye examination and fitness test.

Table 4.3 Baseline examinations for UK Biobank study participants between 2006-2010

Assessment type	Characteristics	Details
Touchscreen	Sociodemographic factors, Lifestyle and environment, early life factors, family history, cognitive function, psychosocial factors, health and medical history and sex-specific factors	○ Household, employment, education, ethnicity etc ○ physical activity, smoking alcohol, diet etc

		○ Medical conditions, medication, cancer screening, general health etc ○ Reaction time, fluid intelligence, numeric memory, pairs matching, prospective memory etc
Verbal interview	Early life factors, employment, medical conditions, medications, operations	○ Birth weight, country and place of birth etc ○ Cancer and non-cancer illnesses, pregnancy
Physical measures	Blood pressure, carotid ultrasound, arterial stiffness, hearing test, eye measures, hand grip strength, anthropometry, spirometry and electrocardiogram	○ Diastolic and systolic blood pressure, method of blood pressure, pulse rate ○ Eye surgery, visual acuity, intraocular pressure etc ○ Body size measures, body composition by impedance
Biological sampling	Blood, saliva and urine sample collections	

4.5.3.1 Cognitive function tests

At baseline, participants undertook a brief 15-minute cognitive test battery to assess cognitive function using a touchscreen computer. Participants were given instructions for the test on the screen and completed the assessment without supervision. These tests included reaction time (mean correct response time), visual memory, fluid intelligence and prospective memory. The fluid intelligence and prospective memory were added part way through the baseline assessment and only used at ten assessment centres as such baseline data on these tests were missing for the majority of participants. The numeric memory test was removed during the baseline assessment and not included in the first repeat assessment. For reaction time, visual memory, fluid intelligence and prospective memory tests, some participants attended only one follow

up assessment and some attended both follow up assessments.[191,192] The cognitive tests used in this thesis are described in more detail below.

Reaction time

The reaction time test was used to assess speed processing and was measured using 12 rounds of a computer version of the card game "snap". During this test, participants were shown two cards on a touch screen and were instructed to press a button as quickly as possible when the symbols on the cards matched. The outcome measure for reaction time used was the mean time (milliseconds) taken for a participant to press a button when two matching pairs of cards were displayed on the screen.

Visual memory

Visual memory was assessed using the pairs matching test. For this test, participants were shown 6 pairs of cards with symbols for 5 seconds. Participants were instructed to memorise the position of as many matching pairs of cards, in the fewest tries, as possible. The outcome measure was the total number of incorrect matches in participants who completed the test.

Fluid intelligence

Verbal and numerical reasoning was assessed using the fluid intelligence test. For this test, participants were given two minutes to answer as many questions as possible. Participants were given a number of possible responses to select from. An example of a verbal reasoning question was "If Truda's mother's brother is Tim's sister's father, what relation is Truda to Tim?". An example of a numeric reason question was: "If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from

eighty-five." The outcome measure for this test was the total number of incorrect answers to the 13 questions.

Prospective memory

The prospective memory test assessed participants' ability to remember to perform an action in the future. Before participants completed the other tests, they were first instructed the following: "At the end of the games we will show you four coloured shapes and ask you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead". Participants were scored 0 for the correct answer and 1 for an incorrect answer at first attempt.

4.5.4 Follow up assessments

A subset of UK Biobank participants have undergone various further follow up assessments after baseline. Figure 4.3 summaries baseline assessments and 2 post baseline visits of relevance to this thesis where cognitive function or brain imaging data were collected.

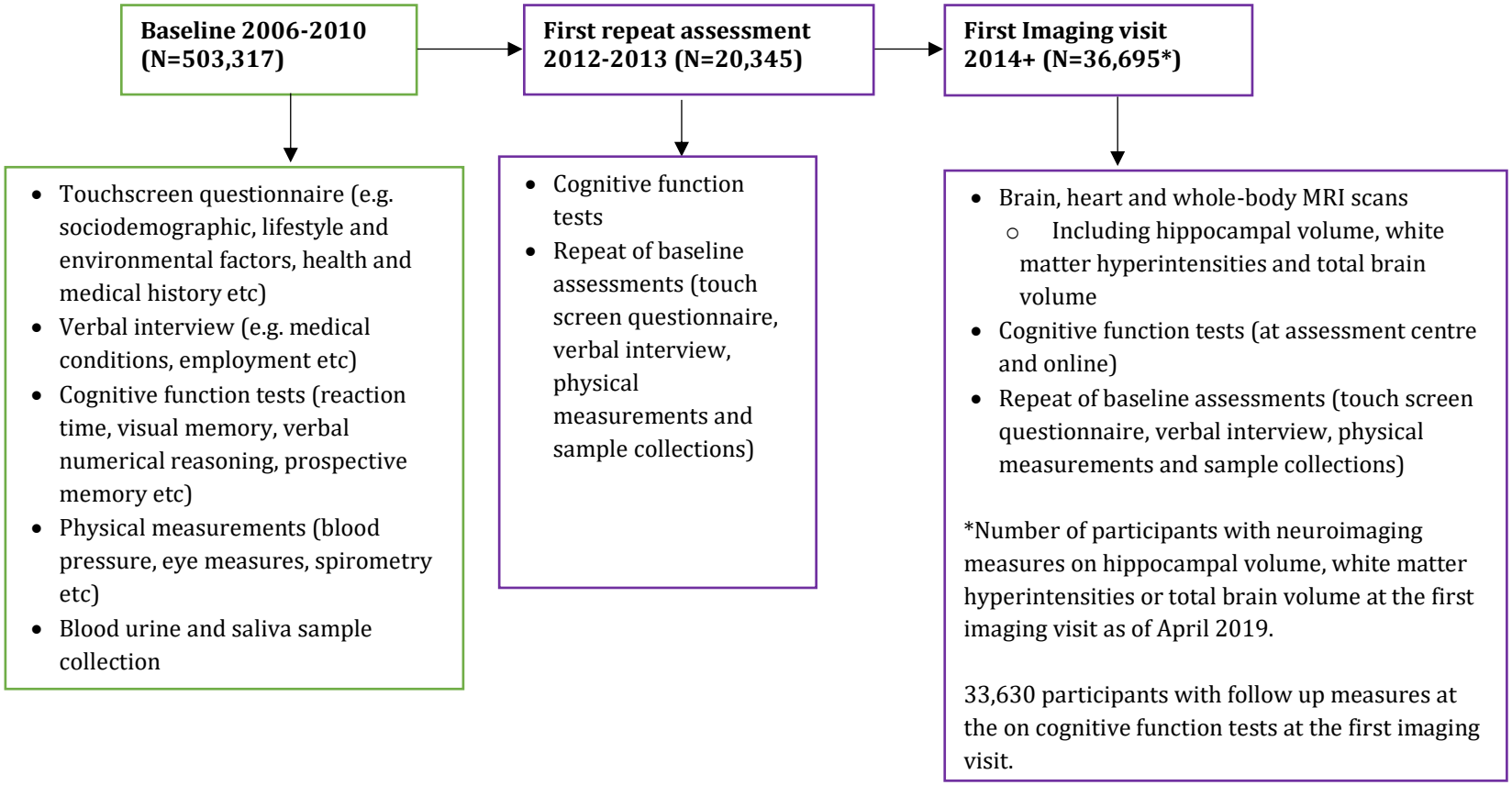

Figure 4.3. Baseline and follow up assessments of participants in the UK Biobank study

4.5.4.1 First repeat assessment

The first repeat assessment took place between August 2012 and June 2013. 103,514 participants who lived within approximately a 30m radius of the assessment centre were invited via email to attend a repeat assessment visit. During this visit, a touch screen questionnaire and brief verbal interview was used to capture participants' information on their health and lifestyle factors, physical measurements and cognitive function. [193]

Table 4.4 compared the characteristics of participants who attended, declined, cancelled or did not attend the first repeat assessment and those who did not respond to the invitation. Table 4.4 shows that participants who attended the repeat assessment were more likely to be older, have a lower BMI, better educated (72.5% had a degree or other higher education/professional qualifications), less deprived, lived closer to repeat assessment centre, never smoked and less likely to have a long-standing illness. These data were obtained directly from the UK Biobank website.[193]

Table 4.4. Characteristics of invited participants who attended repeat assessment vs participants who did not attend

	Attended n (%)	Declined, cancelled, no show n (%)	No response n (%)	Total
Total participants	20,345	23,650	59,519	103,514
Age category at recruitment (baseline visit)				
<45 years	1,557 (7.7%)	1,802 (7.6%)	7,515 (12.6%)	10,874 (10.5%)
45 to <50 years	2,176 (10.7%)	2,532 (10.7%)	9,377 (15.8%)	14,085 (13.6%)
50 to <55 years	2,970 (14.6%)	3,170 (13.4%)	10,011 (16.8%)	16,151 (15.6%)
55 to <60 years	4,539 (22.3%)	4,418 (18.7%)	10,496 (17.6%)	19,453 (18.8%)
60 to <65 years	5,731 (28.2%)	6,603 (27.9%)	12,936 (21.7%)	25,270 (24.4%)
65+ years	3,372 (16.6%)	5,125 (21.7%)	9,184 (15.4%)	17,681 (17.1%)
Sex				
Female	10,405 (51.1)	13,921 (58.9)	30,341 (51.0)	54,667 (52.8)
Male	9,940 (48.9)	9,729 (41.1)	29,178 (49.0)	48,847 (47.2)
Ethnicity				
White	19,852 (97.6%)	23,085 (97.6%)	56,698 (95.3%)	99,635 (96.3%)
Other	443 (2.2%)	491 (2.1%)	2,585 (4.3%)	3,519 (3.4%)
Don't know	2 (0.01%)	6 (0.03%)	14 (0.02%)	22 (0.02%)
Prefer not to answer	44 (0.2%)	46 (0.2%)	168 (0.3%)	258 (0.3%)
Missing	4 (0.02%)	22 (0.09%)	54 (0.09%)	80 (0.08%)
Body Mass Index (BMI)				
<25	7,629 (37.5%)	7,862 (33.2%)	17,198 (28.9%)	32,689 (31.6%)
25 to 30	8,590 (42.2%)	10,007 (42.3%)	26,090 (43.8%)	44,687 (43.2%)
30+	4,080 (20.1%)	5,669 (24.0%)	15,883 (26.7%)	25,632 (24.8%)
Missing	46 (0.2%)	112 (0.5%)	348 (0.6%)	506 (0.5%)
Qualifications				
Degree/NVQ, HDN, HNC/Other professional qualifications	14,748 (72.5%)	13,068 (55.3%)	35,642 (59.9%)	63,458 (61.3%)
A-level or equivalent	1,060 (5.2%)	1,218 (5.2%)	2,977 (5.0%)	5,255 (5.1%)

GCSE/CSE or equivalent	2,648 (13.0%)	4,500 (19.0%)	10,632 (17.9%)	17,780 (17.2%)
None of the above	1,800 (8.9%)	4,615 (19.5%)	9,638 (16.2%)	16,053 (15.5%)
Prefer not to answer	85 (0.4%)	228 (1.0%)	581 (1.0%)	894 (0.9%)
Missing	4 (0.02%)	21 (0.09%)	49 (0.08%)	74 (0.07%)
Townsend deprivation index				
Least deprived <-2	12,544 (61.7%)	13,433 (56.8%)	32,257 (54.2%)	58,234 (56.3%)
-2 to 2	5,707 (28.1%)	7,218 (30.5%)	18,110 (30.4%)	31,035 (30.0%)
Most deprived 2+	2,083 (10.2%)	2,977 (12.6%)	9,084 (15.3%)	14,144 (13.7%)
Missing	11 (0.05%)	22 (0.09%)	68 (0.1%)	101 (0.1%)
Home area population density				
Urban	17,418 (85.6%)	21,030 (88.9%)	52,944 (89.0%)	91,392 (88.3%)
Rural	2,778 (13.7%)	2,492 (10.5%)	6,056 (10.2%)	11,326 (10.9%)
Missing	149 (0.7%)	128 (0.5%)	519 (0.9%)	796 (0.8%)
Distance from home residence to repeat assessment centre				
<10 miles	5,670 (27.9%)	2,675 (11.3%)	9,533 (16.0%)	17,878 (17.3%)
10 to <20 miles	5,180 (25.5%)	5,208 (22.0%)	11,177 (18.8%)	21,565 (20.8%)
20 to <30 miles	4,938 (24.3%)	7,309 (30.9%)	17,929 (30.1%)	30,176 (29.2%)
30+ miles	4,411 (21.7%)	8,332 (35.2%)	20,372 (34.2%)	33,115 (32.0%)
Missing	146 (0.7%)	126 (0.5%)	508 (0.9%)	780 (0.8%)
Smoking status				
Never	11,971 (58.8%)	12,876 (54.4%)	31,612 (53.1%)	56,459 (54.5%)
Previous	7,042 (34.6%)	8,520 (36.0%)	20,868 (35.1%)	36,430 (35.2%)
Current	1,283 (6.3%)	2,153 (9.1%)	6,786 (11.4%)	10,222 (9.9%)
Prefer not to answer	45 (0.2%)	86 (0.4%)	206 (0.4%)	337 (0.3%)
Missing	4 (0.02%)	15 (0.06%)	47 (0.08%)	66 (0.06%)
Alcohol drinker status				
Never	617 (3.0%)	813 (3.4%)	2,280 (3.8%)	3,710 (3.6%)
Previous	521 (2.6%)	788 (3.3%)	1,964 (3.3%)	3,273 (3.2%)
Current	19,197 (94.4%)	22,017 (93.1%)	55,171 (92.7%)	96,385 (93.1%)
Prefer not to answer	6 (0.0%)	17 (0.1%)	56 (0.1%)	79 (0.1%)
Missing	4 (0.0%)	15 (0.1%)	48 (0.1%)	67 (0.1%)

Long-standing illness, disability or infirmity				
No	13,873 (68.2%)	15,229 (64.4%)	38,632 (64.9%)	67,734 (65.4%)
Yes	6,085 (29.9%)	7,831 (33.1%)	19,326 (32.5%)	33,242 (32.1%)
Do not know	370 (1.8%)	525 (2.2%)	1,412 (2.4%)	2,307 (2.2%)
Prefer not to answer	13 (0.06%)	42 (0.2%)	94 (0.2%)	149 (0.1%)
Missing	4 (0.02%)	23 (0.1%)	55 (0.09%)	82 (0.08%)

NVQ; National vocational qualification, HDN; Higher National Diploma, HNC; Higher National Certificate. These data were obtained directly from the UK Biobank website.[193]

4.5.4.2 First Imaging visit

Overview

The second follow up assessment also known as the imaging visit commenced in 2014 and aims to scan 100,000 participants by 2023.[194,195] The sample size of 100,000 was selected based on prior sample size calculations. Participants were re-invited via email (postal invitations were also sent in 2020 given that not all participants provided an email address) to undergo magnetic resonance imaging of the brain, heart, body, carotid arteries, bone and joints. Brain imaging included regional grey matter volumes (e.g. volume of brain-stem or cerebellum), subcortical volumes (e.g. volume of amygdala or hippocampus) and other brain MRI imaging including volume of white matter hyperintensities. Body imaging included bone size and mineral density, and body composition. Abdominal MRI included kidney, liver, pancreas MRI and abdominal composition. Heart MRI included left ventricular size and function and pulse wave analysis. [195,196] In addition to MRI imaging, for the imaging visit, participants also completed web-based assessments which included online cognitive function tests. The fourth research aim of this thesis focuses on baseline and repeat cognitive function assessments and brain MRI imaging.

Recruitment

Between 2014 and 2015, a pilot study of approximately 5000 participants was conducted after which funding was released for 95,000 participants. Imaging examinations took place at four assessment centres in Stockport, Newcastle-upon-Tyne, Reading and Bristol (in 2020). These centres were chosen in order to limit travel times for the majority of participants.[195] Participants were first invited for the first imaging visit in 2014 and are still being invited for the imaging assessment. As of early 2020,

44% of the 503,000 UK Biobank population were invited to the imaging visit, of these 31% expressed interest in attending. 29% of these participants were ineligible to attend after pre-screening. Reasons for ineligibility include having metal implants, certain surgeries and claustrophobia. Of the 71% of interested participants who were eligible, 97% have attended the assessment visit. The response rate for booking an appointment after invitation was 12%.[195]

Quality assurance

Quality assurance across all imaging centres was managed through a centralised training and monitoring team. A six-week training programme was attended by all staff members prior to the opening of centres and monthly training was provided by the magnetic resonance physicist. Across all centres, a standardised training programme for all radiographers, standard operating procedures and other quality assurance and control measures were employed. Identical protocols, scanner models, software, types of coils and adjustment and tuning methods were used in each centre to ensure fully harmonised imaging data.[195]

4.5.4.2.1 Brain imaging

Brain imaging at the UK Biobank assessment centres was completed within 35 minutes due to the large size of the UK Biobank population.[197] The brain imaging data acquisition includes 6 modalities which encompass three structural MRI scans, diffusion MRI, resting-state functional MRI and task functional MRI. The structural imaging includes a T1-weighted, T2-weighted fluid attenuation inversion recovery (FLAIR) structural imaging and susceptibility-weighted imaging. The T1 weighted structural

technique provides imaging-derived phenotypes relating to volumes of brain tissues and structures. T1-weighted imaging processed using FIRST (FMRIB's Integrated Registration and Segmentation tool) was used in this thesis to determine the volume of the left and right hippocampus (data fields 25019 and 25020) and total brain volume of grey and white matter normalised for head size (data fields 25009). This technique depicts brain anatomy with high resolution and strong contrast between grey and white matter. The T2-weighted imaging structural technique is mainly related to pathology and depicts alterations to tissue areas linked with pathology.[197] In this thesis, T1 and T2 FLAIR images were used to determine the total volume of white matter hyperintensities. To obtain a more accurate model T2 FLAIR was used with the T1 structural imaging as noted in the UK Biobank brain imaging documentation.

4.5.4.3 First repeat imaging visit

The first repeat imaging visit commenced in 2019 with the aim of 10,000 participants undergoing repeat imaging assessment. This visit is scheduled to complete in 2023.[198] For this visit, participants who attended the first imaging visit are being invited via email and postal invitations (in 2020) and the response rate is currently high at approximately 65%, although invitations are still ongoing.

Due to the paucity of data released for the first repeat imaging visit, this thesis only focused on the first imaging visit for data on neuroimaging measures.

4.5.5 Linked data

4.5.5.1 Overview

Besides the repeat assessment visits, participants of the UK Biobank study are followed up over time for health outcomes through linked with routinely collected healthcare datasets including primary care records, national hospital admissions and mortality records. These linked routinely collected datasets enable follow-up for outcomes such as diabetes and dementia. Primary care linkage was available for approximately 230,000 participants (45%) of the total UK Biobank population.[199] The primary care data comprises of registration, clinical and prescription data from England, Wales and Scotland.

4.5.5.2 Linked primary care data

GP registration data

The linked GP registration dataset consists of 228,924 participants (45.6% of total UK Biobank population) after exclusion of those who had withdrawn from the study. This dataset included information on participants' registration date and date of removal from practice lists. I performed quality checks on this dataset which showed that 9,764 participants had implausible registration dates (registered in the years 1901, 1902, 1903 and 2037). After excluding these participants, a total of 219,160 remained. The vast majority of linked GP data came from England, with 71.8% from practices using TPP and 8.1% from those using Vision software. 10.6% of the linked GP registration data was from practices in Scotland and 9.6% from Wales.

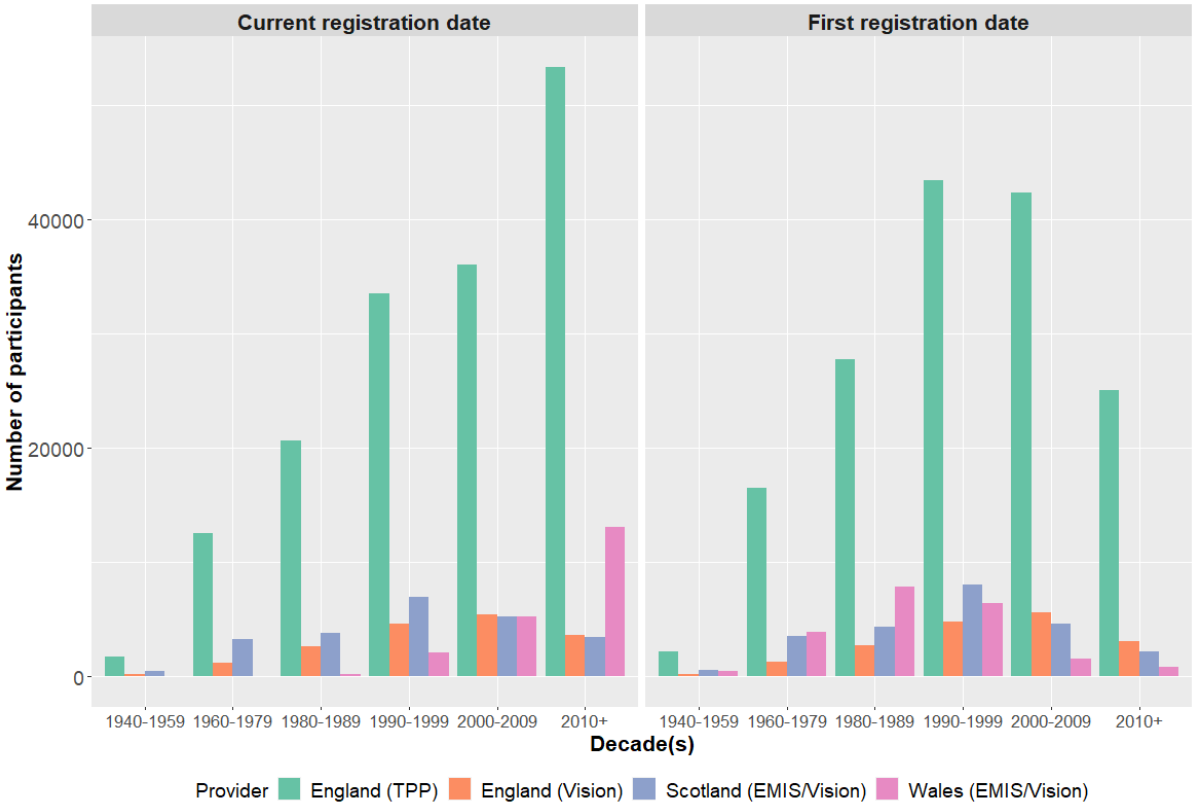

Figure 4.4. Number of participants registered with a GP practice in each decade(s) for each data provider using participants' most recent (current) or first registration date

Figure 4.4 shows that, among participants with linked primary care data, participants' first registration with GP practices began in the 1940s and peaked in the decade of 1990-1999. Registrations were highest for participants in England whose practice used the TPP computer software system. The most recent GP practice registration dates were in the decade of 2010 and onwards. This reflects changes in participants' GP practices over time. I explored the number of years participants were registered in primary care using their most recent registration date prior to baseline. Among the 185,212 participants registered with a GP practice before baseline, the majority (81%) were registered with the same GP practice for 5 or more years, and only 4% were registered with the same practice for less than a year.

GP Clinical data

The GP clinical dataset included 230,078 participants after excluding participants who withdrew from the study. This dataset includes information on participants' symptoms, diagnoses, consultations, laboratory tests results, procedures and other administrative information. Clinical events were recorded using Read v2 or Clinical Terms Version 3 (CTV3) coding classification. Examples of data fields in this dataset include participant identifier, clinical event date, Read v2 or CTV3 code. All data providers used the Read v2 coding system, with the exception of TPP which used CTV3 codes.

I performed data quality checks on the clinical dataset before using the dataset to create codelists or running any analyses. For the clinical dataset, data quality checking showed that some participants had implausible clinical event dates in the years 1901,1902,

1903 and 2037. I excluded participants with these implausible data which left 230,076 individuals this dataset.

GP Prescription data

Prescription data was coded using Read v2, BNF or Dictionary of Medicines and Devices (dm+d) coding classifications. Linked primary care data on prescribed medication is also available. Data from the four providers in England, Wales and Scotland is either coded using BNF, dm+d and Read v2 codes.

I also performed data quality checks on the prescription dataset and similar to the clinical dataset some participants had implausible dates (prescription dates in the years 1901,1902, 1903 and 2037) and after excluding these participants the number of participants there were 222,096 participants left in the prescription dataset.

Data recording and quality

Recording of data varied over time for each data provider in the clinical and prescription dataset as illustrated in Figure 4.5. Data was recorded prior 1990 but due to the small number of observations, it was not included in the figure. Figure 4.4 shows that recording of clinical events and medication increased over time, with most observations from the England TPP GP system. The reason for the increase between the decade of 1990-1999 and 2000-2009 could be due to the QOF introduced in 2004 which led to an increase in the recording of clinical data.

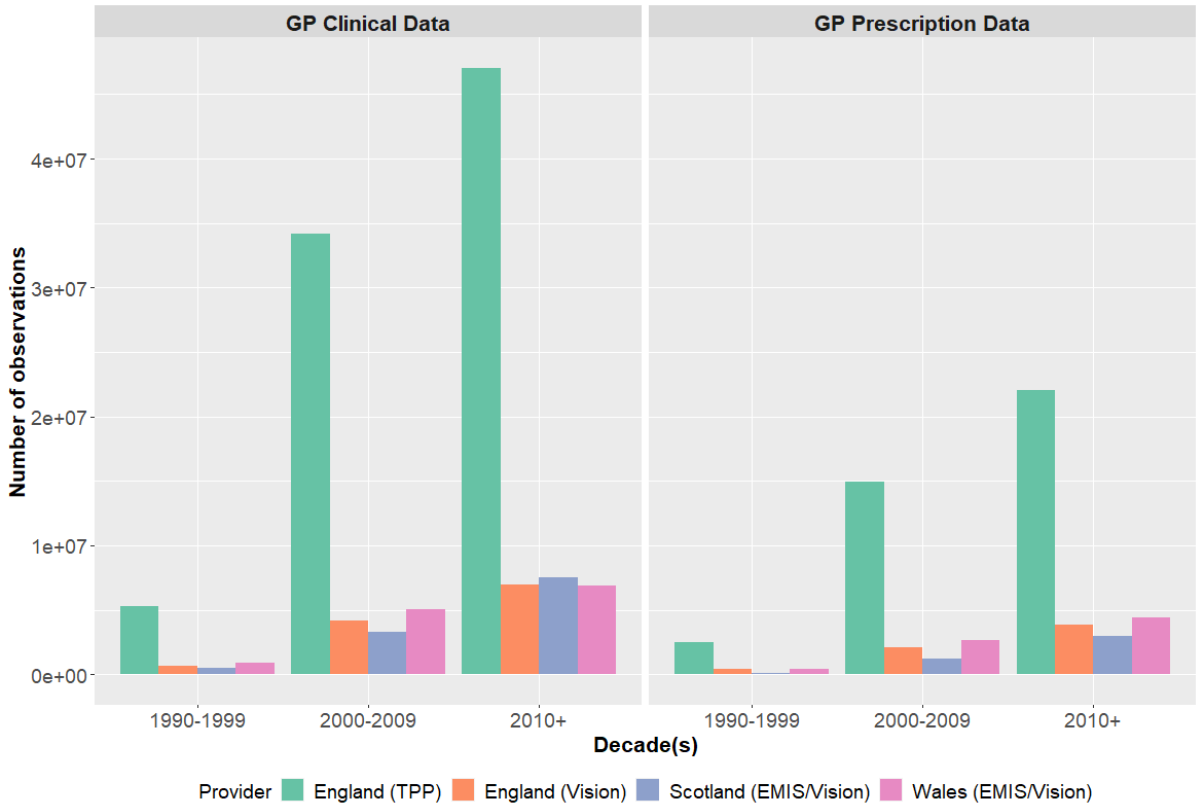

Figure 4.5 Number of observations per decade in the GP clinical and GP prescription dataset

Recording of clinical and prescription data varied across GP providers. Although the clinical and prescription dataset contain Read v2, CTV3, BNF and dm+d codes, they do not contain a description accompanying each clinical and prescription codes. To create codelists, I used look up tables and mapping files from the UK Biobank data showcase website which were derived from the NHS Digital Technology Reference Data Update Distribution and NHS Business Services Authority.

There are inconsistencies between the mapping files and prescriptions data. For the England Vision GP system, the length of dm+d codes vary from 8 to 18 characters and some dm+d codes present in the prescription dataset are not present in the mapping file. Similarly, for the Scottish dataset, the length of BNF codes varied from 0 to 15 characters and approximately 3,900 participants in the dataset did not have BNF and

Read codes. Prescription data from the England TPP and Wales was well recorded with no missing codes and corresponding codes in the mapping files.

4.5.5.3 Linked Hospital data

Linked hospital data for the UK Biobank cohort was obtained for the entire dataset. Table 4.5 describes the hospital data used for linkage in the UK Biobank study. To summarise, in England, the Hospital Episode statistics APC database was obtained from NHS digital. In Wales, the Patient Episode Database for Wales (PEDW) admitted patient care dataset of the Secure Anonymised Information Linkage Database (SAIL) was used. This dataset included information on inpatient and day cases. In Scotland, the general acute inpatient day case dataset from the Scottish Morbidity Record 1a and 1b was used. Coverage for these datasets was between 1981-1997 and 1997 to present, respectively. Data fields from the three hospital providers in England, Scotland and Wales such as clinical diagnostic codes were standardised across the data providers. Hospital records from all providers were combined into a single hospital data set for the UK Biobank population.[200,201]

Table 4.5 Description of linked hospital data in the UK Biobank study

Country and data provider	Hospital Database	Coverage	Clinical coding system	Dataset	Description of dataset
England, NHS Digital	Hospital Episode Statistics	1996-present	ICD-10 and OPCS-4	HES APC dataset	Includes all admissions to NHS or independent providers by the NHS. Admissions requiring a hospital bed including emergency, elective day cases and births and associated deliveries.[174]
Wales, Secure Anonymised Information Linkage Database (SAIL)	Patient Episode Database for Wales (PEDW)	1999 - present	ICD-10, OPCS-4	PEDW Admitted Patient Care dataset	Includes data on inpatient and day cases and contains demographic, clinical and administrative, diagnostic and operative procedures.[202]
Scotland, Information Services Division (ISD)	Scottish Morbidity Record 1a	1981-1997	ICD-9, ICD-10, OPCS-3, OPCS-4	General Acute Inpatient and Day case – Scottish Morbidity Record	Includes general acute, inpatient and day case data. Excludes data on maternity and mental health admission.[201]
	Scottish Morbidity Record 1b	1997-present	ICD-10, OPCS-4		

4.5.5.4 Linked Mortality records

Mortality records for the UK Biobank study are obtained from death registries which include NHS Digital for participants in England and Wales, and from the NHS Central Register (NHSCR) for participants in Scotland. Data includes the date of death and the primary and contributory causes of death. The records use the ICD-10 coding system . Mortality data are currently updated from NHS Digital and NHSCR every month. [203]

4.6 UK Biobank Strengths and limitations

The UK Biobank study is one of the largest longitudinal studies in the world with extensive data on MRI imaging, genetics, lifestyle, environmental and health outcomes. The wealth of data on over 500,000 participants at baseline and follow up is thus a key strength of the UK Biobank study. This enables the use of UK Biobank data in investigating a wide range of exposures and outcomes, including cognitive function, and adjustment for multiple confounders. Another advantage of the UK Biobank study is the use of detailed questionnaires, physical examinations, biological samples at repeat assessments and the ability to link participants to primary, secondary and mortality EHRs which allows researchers to follow participants over time for health outcomes. Details on exposures and outcomes in the UK Biobank is more detailed and extensive than that of routinely collected EHRs such as the CPRD.

However, there are a number of limitations to this data source. First, given that individuals aged 40-69 were recruited into the UK Biobank study, the findings of this study may not be generalisable to older adults, who are at a greater risk of outcomes associated with increasing age such as dementia. Second, the UK Biobank had a low response rate of 5.5% which may also limit the generalisability of the findings. In addition, differences were found between responders and non-responders and UK Biobank participants were healthier than the general population which is suggestive of selection bias. Third, the UK Biobank cohort is not representative of the general population in terms of ethnicity, with only 5.4% of participants belonging to minority ethnic groups compared to 13% according to the 2011 UK census.[204] Fourth, loss of follow up is an issue in the UK Biobank cohort as participants who undertook the repeat assessments were better educated, less deprived and less likely to have a long-standing

illness. This difference between those included and excluded at follow up may bias associations between exposures and outcomes towards the null. Fifth, only a subset of participants were invited for repeat assessments which reduced the number of individuals able to take part in the follow up assessments. These individuals were invited for follow up assessments by email as such those without a working email address would not have been invited for follow up assessments which may have led to selection bias. Sixth, there are issues of data completeness and inconsistencies in the linked primary care dataset, particularly in the GP prescriptions dataset which contains missing or inaccurate dm+d or BNF codes. This increases the likelihood of information bias from poor recording of prescription data.

4.7 Confounder selection

The data sources mentioned in this chapter (CPRD, HES, IMD, UK Biobank and linked EHRs) were used to identify potential confounders for infections and dementia. These potential confounders include a wide range of sociodemographic and lifestyle characteristics and comorbidities. They were selected based on whether they were associated with infections, were risk factors for cognitive decline or dementia and were not on the causal pathway of infections and cognitive decline or dementia. Potential sociodemographic and lifestyle confounders include age, sex, ethnicity, social economic status, education, BMI, physical activity, alcohol intake and smoking.[67,69,92,205-211] Comorbidities include cardiovascular, inflammatory conditions, psychiatric conditions and other comorbidities. Inflammatory conditions such as inflammatory bowel disease, rheumatoid arthritis, psoriasis have been associated with infections such as pneumonia, skin and soft tissue infections and urinary tract infections.[212-215] These inflammatory comorbidities are also potential risk factors for dementia.[216-218] Psychiatric conditions

have been associated with infectious diseases, including pneumonia.[219] Evidence from a large study English national dataset linked to hospital episode statistics found that severe mental illness (hospitalisation of schizophrenia, bipolar, depression or anxiety) was associated with greater incidence of pneumonia.[220] In turn, severe mental illness has also been associated with dementia.[221] Cardiovascular diseases such as stroke, hypertension and heart failure are associated with infections, particularly lower respiratory tract infections, and risk of dementia.[222-224] Respiratory tract infections are a risk factor for MI, stroke, and AF , and thus these factors could act as mediators. [225-227] Other conditions such as traumatic brain injury and obstructive sleep apnoea have been associated with respiratory tract infections and are emerging potential risk factors for dementia. [228-231] Medication use such as benzodiazepines, systemic corticosteroids and proton pump inhibitors are also potential confounders associated with infections and cognitive impairment and dementia risk.[232-236] The code lists used in this thesis are available at https://datacompass.lshtm.ac.uk/id/eprint/2073/ (chapter 5) and https://doi.org/10.17037/DATA.00002573 (chapter 6 and 7). Other codelists for chapter 6 are included in appendix 10.3.

4.8 Summary

- This thesis uses data from the CPRD linked to HES (chapter 5) and data from the UK Biobank study linked to primary and secondary care records (chapter 6 and 7).
- The CPRD is a large-scale (over 16 million individuals ever patients and 2.3 million active patients in January 2019) anonymous primary care dataset which includes information on patient demographics, diagnoses and symptoms, prescriptions and referrals to secondary care.
- Strengths of the CPRD include the large size of the dataset, ability to link to other datasets (e.g. IMD and HES), longitudinal follow up data (median follow-up of 11.9 years (IQR, 4.34 – 23.25)) and the representativeness of the data to the UK population in terms of age, sex and ethnicity.
- Limitations include potential misclassification of exposures, outcomes and covariates, missing data and poor recording of certain factors related to health such as physical activity and education.
- The UK Biobank is a large prospective cohort study of over 500,000 participants recruited between 40-69 years of age. It includes extensive and detailed baseline information on participants' sociodemographic characteristics, lifestyle factors and medical conditions.
- The UK Biobank study is the largest imaging study in the world which consists of wealth of imaging data, including hippocampal and white matter hyperintensity volume, and multiple repeat cognitive function tests assessing different domains of cognition. Other strengths of the UK Biobank data include the ability to link participants' data to routinely collected data sources such as GP, hospital and mortality records.
- Drawbacks of the UK Biobank study include limited generalisability, selection bias, loss of follow up in participants invited for repeat assessments and issues with data completeness and poor recording of data in the linked primary care dataset.

Chapter 5: Association of common infections with incident dementia and cognitive impairment using UK primary and secondary care records

5.1 Introduction

In this chapter I examine the association of common infections with incident dementia and cognitive impairment using UK primary care EHRs from the CPRD linked to secondary care records from HES. This association is the focus of research paper 3 which was published in The Lancet Healthy Longevity journal. Appendix 10.2 includes a protocol of this study which was approved by the Independent Scientific Advisory Committee (ISAC) and ethical approval which was obtained from the London School of Hygiene and Tropical Medicine prior to conducting this study. In addition, the supplementary material to research paper 3 is also provided in appendix 10.2.

Findings from the systematic review in chapter 3 suggested an association between common bacterial infections and incident dementia, though findings from the updated studies were conflicting. None of the studies included in the original systematic review were conducted in the UK, with studies either from Taiwan or the US. Other important limitations of existing studies, which were highlighted in chapter 3, motivated some of the analyses in this chapter. Here, I explore a wider range of common infections instead of only pneumonia or sepsis infections as in the majority of previous studies. Previous studies also mainly focused on hospitalised infections, therefore in this chapter, I investigated the association of infections in both primary and secondary care settings and explored any differences in association in these settings. The systematic review also found that data on infections and cognitive decline was scarce. The present chapter addresses this by exploring the association of infections and cognitive impairment in one of the largest datasets of UK primary care records with analyses adjusted for multiple confounders. Datasets used in this study were described in detail in Chapter 4.

5.2 Research paper 3

Assessment of common infections and incident dementia using UK primary and secondary care data: a historical cohort study

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SECTION A – Student Details

Student ID Number	1802273	**Title**	Ms
First Name(s)	Rutendo		
Surname/Family Name	Muzambi		
Thesis Title	The effect of common infections on cognition and dementia in people with and without diabetes		
Primary Supervisor	Dr Charlotte Warren-Gash		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	The Lancet Healthy Longevity		
When was the work published?	18/06/2021		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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Where is the work intended to be published?	
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Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author of this paper. I conceived and designed the study, drafted and revised the manuscript. The co-authors contributed to the conception and design of the study and provided comments to the manuscript.

SECTION E

Student Signature	[redacted]
Date	11/11/2021

Supervisor Signature	[redacted]
Date	11/11/2021

Assessment of common infections and incident dementia using UK primary and secondary care data: a historical cohort study

Rutendo Muzambi, Krishnan Bhaskaran, Liam Smeeth, Carol Brayne, Nish Chaturvedi, Charlotte Warren-Gash

Summary

Background Common infections have been associated with dementia risk; however, evidence is scarce . We aimed to investigate the association between common infections and dementia in adults (≥65 years) in a UK population-based cohort study.

Methods We did a historical cohort study of individuals who were 65 years and older with no history of dementia or cognitive impairment using the Clinical Practice Research Datalink linked to Hospital Episode Statistics between Jan 1, 2004, and Dec 31, 2018. Multivariable Cox proportional hazard regression models were used to estimate the association between time-updated previous common infections (sepsis, pneumonia, other lower respiratory tract infections, urinary tract infections, and skin and soft tissue infections) and incident dementia diagnosis. We also tested for effect modification by diabetes since it is an independent risk factor for dementia and co-occurs with infection.

Findings Between Jan 1, 2004, and Dec 31, 2018, our study included 989 800 individuals (median age 68·6 years [IQR 65·0–77·0]; 537 602 [54·3%] women) of whom 402 204 (40·6%) were diagnosed with at least one infection and 56 802 (5·7%) had incident dementia during a median follow-up of 5·2 years (IQR 2·3–9·0). Dementia risk increased in those with any infection (adjusted hazard ratio [HR] 1·53 [95% CI 1·50–1·55]) compared with those without infection. HRs were highest for sepsis (HR 2·08 [1·89–2·29]) and pneumonia (HR 1·88 [1·77–1·99]) and for infections leading to hospital admission (1·99 [1·94–2·04]). HRs were also higher in individuals with diabetes compared with those without diabetes.

Interpretation Common infections, particularly those resulting in hospitalisation, were associated with an increased risk of dementia persisting over the long term. Whether reducing infections lowers the risk of subsequent dementia warrants evaluation.

Funding Alzheimer's Society, Wellcome Trust, and the Royal Society.

Lancet Healthy Longev 2021; 2: e426–35

Published Online June 18, 2021 https://doi.org/10.1016/S2666-7568(21)00118-5

See Comment page e391

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Introduction

Dementia (also known as major neurocognitive disorder) is a leading contributor to disability and dependence worldwide. In the UK, the number of people living with dementia is projected to rise from 850 000 in 2015 to more than 2 million by 2051, owing to population growth and ageing.[1] Because the established modifiable risk factors of dementia account for only 40% of dementia cases, identification of other preventable risk factors has become an urgent public health priority.[2]

Common infections are an established risk factor for acute cognitive impairment in older adults (≥65 years) and increasing evidence from longitudinal studies suggests that common infections are associated with an increased risk of dementia.[3] However, previous studies have mainly focused on sepsis or pneumonia hospitalisations rather than on a wide range of infections in different clinical settings,[4–8] and have had short follow-up periods (3–5 years),[4,7] relatively small sample sizes (between 3069 and 5955 participants or cases),[5–7] or inadequate adjustment for confounding.[6–8] Large-scale longitudinal studies published since 2016 have overcome some of these limitations; however, these studies have only been done in veterans,[9] stroke survivors,[10] or patients in intensive care unit,[11] restricting the generalisability of their findings. Furthermore, evidence of an association between infections and dementia risk is conflicting.[11] Moreover, few studies have assessed the effect of type, clinical setting, and frequency of infections on dementia risk, restricting the potential for public health intervention.

Serious infections, including sepsis, infections requiring hospitalisation or infections resulting in mortality, frequently occur in older adults (≥70 years) with diabetes.[12] Diabetes is an independent risk factor for dementia,[13] and, given its co-occurrence with infections, diabetes could potentially modify the association between

Research in context

Evidence before this study

We updated our previously published systematic review of longitudinal studies investigating the association between common bacterial infections and dementia or cognitive decline by searching Embase and MEDLINE for articles published between March 1, 2019, and Dec 22, 2020, without language or geographical location restrictions. We used medical subject heading terms and key words including "dementia", "cognitive decline", "sepsis", "lower respiratory tract infections", "urinary tract infections", and "skin and soft tissue infections." A full list of search terms is reported in the appendix (pp 1–4). Our updated search yielded two new studies. Overall, most of the identified studies, which were mainly done in the USA or Taiwan, suggested an association between common infections and dementia. One study did not find an association; however, this study was done only in patients in an intensive care unit setting, restricting the generalisability of these findings. Other studies also had limitations, including short follow-up periods, relatively small sample sizes, or inadequate adjustment for confounders. Additionally, previous studies mainly focused on sepsis or pneumonia hospitalisations. Two studies also investigated the effect of frequency of infections on dementia, and only one investigated the effect of clinical setting of infections on dementia.

See Online for appendix

Added value of this study

To our knowledge, our longitudinal study of almost 1 million individuals aged 65 years and older, with up to 14 years of follow-up, is the largest to date reporting on the association between common infections and incident dementia. Our study finds novel evidence of effect modification by diabetes on the association between infections and dementia. Our finding of a higher dementia risk for infections likely to be severe, such as hospitalised infections, sepsis, and pneumonia, also extends the existing literature as does our finding that the association between infections and dementia persists continues long term. We also confirm findings from previous longitudinal population-based studies in the USA and Taiwan that sepsis and pneumonia are associated with incident dementia, and findings from a US study of predominantly male veterans and a UK study of stroke survivors, which also showed associations between urinary tract infections and skin and soft tissue infection and incident dementia.

Implications of all the available evidence

Our findings highlight the need for future studies investigating whether reducing infections lowers the risk of subsequent dementia. More work is needed to understand the underlying mechanisms in the association between infections and dementia and to investigate the association between common infections and cognitive decline using validated repeated measures of cognition.

common infections and dementia; however, to our knowledge, no studies have explored this link.

We aimed to investigate the association between common infections and dementia or cognitive impairment in a large population-based cohort study of adults aged 65 years and older using UK electronic health records data. We hypothesised that all common infections, regardless of type of infection (sepsis, pneumonia, other lower respiratory tract infections, urinary tract infections, and skin and soft tissue infections), clinical setting, number of infections, and time since infection, increased the risk of dementia and that diabetes modified the association between infections and dementia.

Methods

Study design and participants

In this historical cohort study, we used data from the Clinical Practice Research Datalink (CPRD) GOLD linked to secondary care data from the Hospital Episode Statistics (HES). CPRD is a large primary care database of anonymous electronic health records representative of the UK population in terms of age, sex, and ethnicity, and it includes information on demographics, diagnoses, therapies, and referrals.[14] The HES database includes data on admissions to English National Health Service hospitals and independent health-care providers.[15] Clinical diagnoses in CPRD were coded using Read, and diagnoses with HES were coded with International Classification of Diseases (ICD)-10.

We included adults aged 65 years and older present in CPRD GOLD with linked HES data who were registered in CPRD between Jan 1, 2004, and Dec, 31, 2018. Only individuals who were registered in CPRD at least 12 months before the start of follow-up and who had no history of dementia or cognitive impairment were included. Follow-up began on Jan 1, 2004, participants' 65th birthday, or 12 months after registration in CPRD, whichever occurred first, and participants were followed up to the earliest incident dementia diagnosis, date of death, deregistration from CPRD, the last data collection date by the general practitioner, or end of the study period, whichever occurred first. To avoid misclassifying delirium, which often results from infection and is characterised by acute cognitive dysfunction and inattention, as dementia, we excluded the first 3 months of follow-up after infection.

Procedures

Our primary exposure was a time-updated variable capturing whether an individual had ever had a recorded

common infection during follow-up. Exposure status changed after diagnosis of infection. Therefore, individuals initially contributed person-time to the unexposed category (no infection) but once diagnosed with an infection they contributed person-time to the exposed category (infection). These infections included sepsis, pneumonia, other lower respiratory tract infections, urinary tract infections, and skin and soft tissue infections. In HES, ICD-10 codes were used to define all infections. In CPRD, sepsis, pneumonia, and other lower respiratory tract infections were defined using read codes; individuals were defined as having urinary tract infections or skin and soft tissue infections if they had a Read code and a prescription for antibiotics on the same date. In our secondary analyses, we explored the effect of type, clinical setting (hospital-recorded or general practitioner-recorded), frequency, and timing of infections on dementia incidence. Time since infection was split into overlapping periods (3 months to <1 year, 3 months to <2 years, and 3 months to <3 years, 3 months to <4 years, 3 months to <5 years, 3 months to <6 years, 3 months to <7 years, 3 months to <8 years, 3 months to <9 years, and 3 months to ≥9 years). The association between infections and dementia was assessed in these time periods. We considered infections that occurred within 28 days of each other as a single episode of infection.

We used a directed acyclic graph to identify potential confounders and mediators of the association between infections and dementia (appendix p 5). Potential confounders included age (years), sex (male and female), ethnicity (White, south Asian, Black, and mixed ethnicity or other), time updated calendar period (split into 2004–08, 2009–13, or 2014–18) to account for clinical and administrative changes over the study period that might influence the recording of infections and dementia diagnoses in our study, patient-level quintiles of the Index of Multiple Deprivation (IMD) as a proxy for socioeconomic status, heavy alcohol consumption, smoking status (current smoker, former smoker, or never-smoked) and body-mass index (BMI; according to WHO categories). We identified the following comorbidities as potential confounders at any time before the start of follow-up: severe mental illness (schizophrenia and bipolar disorder), depression and anxiety, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, hypertension, heart failure, type 1 and type 2 diabetes mellitus, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, obstructive sleep apnoea, stroke, and traumatic brain injury. The following covariates relating to medication use were identified in the 2 years before the start of follow-up: benzodiazepines, proton pump inhibitors, corticosteroids, and polypharmacy (concurrent use of five or more medications). Diabetes was also identified as an effect modifier. Atrial fibrillation, stroke, and myocardial infarction were identified as potential mediators and were measured after infection diagnosis. The ascertainment of variables is reported in the appendix (pp 6–9).

Outcomes

Our primary outcome was an incident dementia diagnosis. When individuals were diagnosed with dementia in both CPRD and HES, we used the earliest dementia diagnosis. We used a broad definition of dementia that included Alzheimer's disease, vascular dementia, unspecified dementia, and secondary dementia related to other diseases. Our secondary outcome was cognitive impairment, which was defined using Read and ICD-10 codes relating to symptoms and diagnoses of cognitive impairment.

Statistical analysis

Our statistical analysis plan was specified in the study protocol before doing our analyses. We described the study characteristics of individuals with and without common infections during follow-up and examined age-specific incidence rates of dementia in person-time with and without common infections.

For the **study protocol** see https://datacompass.lshtm.ac.uk/id/eprint/2134/

We used Cox proportional hazards regression, with age as the underlying timescale, to calculate hazard ratios (HRs) and 95% CI to investigate the association between common infections and risk of dementia. In our minimally adjusted model, we adjusted for age, sex, patient-level IMD, and calendar period. In our fully adjusted model, we adjusted for age, sex, patient-level IMD, calendar period, ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids, and polypharmacy. BMI was not adjusted for in our main analysis because a low BMI might be a consequence of dementia. However, we explored the possible confounding effect of BMI in an additional analysis. We adjusted for potential mediators (atrial fibrillation, stroke, and myocardial infarction) in separate analyses. A complete case analysis approach was used when HRs were adjusted for BMI, ethnicity, and smoking status. We did not do multiple imputation because these data were unlikely to be missing at random.[16]

To test the robustness of our findings, we did a range of sensitivity analyses (appendix p 10). First, we repeated our primary analyses excluding individuals with secondary dementia causally related to other conditions because infections are unlikely to be causally associated with this type of dementia. Second, to improve the accuracy of our definition of cognitive impairment, we excluded codes relating to symptoms of cognitive impairment. Third, we repeated our primary analyses defining all infections in

	Patients (n=989 800)
Length of CPRD follow-up in years	5·2 (2·3–9·0)
Mean age, years	71·7 (7·9)
Median age, years	68·6 (65·0–77·0)
Age groups, years	
65–69	528 580 (53·4%)
70–74	153 969 (15·6%)
75–79	124 514 (12·6%)
80–84	97 505 (9·9%)
85–89	50 785 (5·1%)
≥90	34 447 (3·5%)
Sex	
Male	452 198 (45·7%)
Female	537 602 (54·3%)
Ethnicity	
White	865 338 (87·4%)
South Asian	16 901 (1·7%)
Black	8749 (0·9%)
Mixed/Other	9938 (1·0%)
Missing	88 874 (9·0%)
Patient-level Index of Multiple Deprivation	
1 (least deprived)	238 449 (24·1%)
2	233 517 (23·6%)
3	213 430 (21·6%)
4	172 086 (17·4%)
5 (most deprived)	132 318 (13·4%)
Body-mass index	
Underweight (<18·5)	17 480 (1·8%)
Normal weight (18·5–24·9)	313 044 (31·6%)
Overweight (25·0–29·9)	356 014 (36·0%)
Obese or morbidly obese (≥30·0)	210 051 (21·2%)
Missing	93 211 (9·4%)
Smoking status	
Never-smoked	441 851 (44·6%)
Current smoker	149 104 (15·1%)
Former smoker	374 654 (37·9%)
Missing	24 191 (2·4%)
Heavy alcohol consumption	54 663 (5·5%)

(Table 1 continues in next column)

	Patients (n=989 800)
(Continued from previous column)	
Comorbidities	
Depression or anxiety	109 672 (11·1%)
Severe mental illness	7659 (0·8%)
Inflammatory bowel disease	31 971 (3·2%)
Multiple sclerosis	3168 (0·3%)
Rheumatoid arthritis	20 486 (2·1%)
Psoriasis	37 872 (3·8%)
Asthma	120 429 (12·2%)
Chronic kidney disease	40 220 (4·1%)
Chronic liver disease	18 609 (1·9%)
Chronic obstructive pulmonary disease	109 199 (11·0%)
Diabetes	118 148 (11·9%)
Heart failure	50 976 (5·2%)
Hypertension	424 439 (42·9%)
Myocardial infarction	55 590 (5·6%)
Obstructive sleep apnoea	7278 (0·7%)
Stroke	44 430 (4·5%)
Traumatic brain injury	10 692 (1·1%)
Medication use	
Benzodiazepines	42 066 (4·2%)
Proton pump inhibitors	191 895 (19·4%)
Systemic corticosteroids	85 594 (8·6%)
Polypharmacy	296 201 (29·9%)

Data are n (%), mean (SD), or median (IQR). Comorbidities were assessed at any time before the start of follow-up. Medication use was captured in the 12 months prior to baseline. Polypharmacy as the concurrent use of five or more medications using British National Formulary chapters. CPRD=clinical practice research datalink.

Table 1: **Baseline characteristics**

CPRD with a diagnostic code and prescription for antibiotics to improve the accuracy of our infection definition. Finally, we repeated our primary analysis excluding individuals diagnosed with infections from two different sites (eg, skin and soft tissue infections and pneumonia) on the same date to avoid the potential biases introduced from including these infections.

A p value of less than 0·05 was considered to be statistically significant.

Using Cox regression models, we assessed the effect of type, clinical setting, frequency, and timing of infections on the risk of dementia. For our analyses on timing of infections, follow-up was split into overlapping periods to account for depletion of susceptible bias.[17] We tested for the presence of effect modification by diabetes using the likelihood ratio test. For our secondary outcome, we explored the effect of common infections on cognitive impairment.

We did three additional secondary analyses: (1) we investigated whether the association between infections and dementia differed across subtypes of dementia (Alzheimer's disease, vascular dementia, and unspecified dementia); (2) we assessed whether the association between infections and dementia varied by sex; and (3) we used Kaplan-Meir survival plots and the log-rank test to explore proximity to death after dementia diagnosis in people with and without infections, given that serious cognitive impairment can occur in the phase before death.

We tested the Cox proportional hazards assumption using log-log plots and the Schoenfeld residuals test. We found evidence of non-proportionality for our infection variable, suggesting that the association between infections and dementia differed with age. To deal with this, we did additional analyses in which we stratified our primary analyses by age. Other variables

	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	Age-adjusted HR (95% CI)*	Age, sex, IMD, and calendar period adjusted HR (95% CI)†	Fully adjusted HR (95% CI)‡
No infection	25 314	3 895 032	6·50 (6·42–6·58)	1 (ref)	1 (ref)	1 (ref)
Any infection	31 488	1 754 956	17·94 (17·75–18·14)	1·78 (1·75–1·81)	1·64 (1·61–1·66)	1·53 (1·50–1·55)
Sepsis	427	16 814	25·40 (23·10–27·92)	2·48 (2·26–2·73)	2·18 (1·98–2·40)	2·08 (1·89–2·29)
Pneumonia	1247	47 836	26·07 (24·66–27·56)	2·27 (2·15–2·41)	1·98 (1·87–2·10)	1·88 (1·77–1·99)
Other LRTI	13 429	910 432	14·75 (14·50–15·00)	1·57 (1·54–1·60)	1·39 (1·36–1·42)	1·34 (1·31–1·37)
UTI	10 513	481 341	21·84 (21·43–22·26)	2·04 (1·99–2·08)	1·80 (1·75–1·84)	1·73 (1·69–1·78)
SSTI	5535	291 603	18·98 (18·49–19·49)	1·78 (1·73–1·83)	1·58 (1·53–1·62)	1·54 (1·49–1·58)

HR=hazard ratio. IMD=Index of multiple deprivation. LRTIs=lower respiratory tract infections (excluding pneumonia). UTIs=urinary tract infection. SSTI=skin and soft tissue infection. *Age as underlying timescale. †Adjusted for age, sex, patient level IMD, and calendar time period over follow-up (2004–08, 2009–13, and 2014–18). ‡Adjusted for age, sex, patient level IMD, and calendar time period over follow-up (2004–08, 2009–13, and 2014–18), ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids, and polypharmacy.

Table 2: **Association between common infections and dementia overall and stratified by type of infection**

showed evidence of non-proportionality (appendix p 22), so we did additional analyses with interaction terms between age and these variables to check whether the observed association between infections and dementia differed from the association in our primary analyses.

Our study was approved by the Independent Scientific Advisory Committee (approval 19_129R) and the London School of Hygiene & Tropical Medicine (reference 17752). Our study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guideline. Analyses were done with STATA MP (version 16) and the analysis codes are available online.

Role of the funding source

The funders had no role in the study design, collection, analysis and interpretation of the data, or writing of the report. The corresponding author (RM) had full access to all the data in the study and accepts responsibility for the decision to submit for publication.

Results

Between Jan 1, 2004, and Dec, 31, 2018, we included a total of 989 800 individuals in our final study population (appendix p 11), with a median follow-up of 5·2 years (IQR 2·3–9·0). Median age was 68·6 years (65·0–77·0), and 537 602 (54·3%) participants were women (table 1).

402 204 (40·6%) individuals were diagnosed with a first-ever infection during the study. Of these individuals, 6046 (1·5%) had sepsis, 16 391 (4·1%) had pneumonia, 197 823 (49·2%) had other lower respiratory tract infections, 110 759 (27·5%) had urinary tract infections, and 68 222 (17·0%) had skin and soft tissue infections. 2488 (0·6%) individuals were diagnosed with multiple infections, other than sepsis, at different sites on the same date. 56 802 (5·7%) of 989 800 individuals had a first-ever diagnosis of dementia during follow-up. The age-specific incidence rate of dementia was higher per person-time with previous infections compared with person-time without previous infections (appendix p 12). Of the individuals diagnosed with dementia, the mean time from an infection diagnosis to a first-ever dementia diagnosis was 4·3 years (SD 3·5) and the median time was 3·7 years (IQR 1·7–6·4). For individuals without an infection diagnosis, the mean time from the start of follow-up to dementia diagnosis was 4·8 years (SD 3·5) with a median time of 4·1 years (IQR 1·8–7·2).

A history of any infection was associated with an increased risk of subsequent dementia compared with no history of infection in our age-adjusted models (HR 1·78 [95% CI 1·75–1·81]; table 2). After fully adjusting for potential confounders, the association between any infection and dementia risk attenuated (HR 1·53 [1·50–1·55]). In the fully adjusted analysis, when we stratified our primary analysis by type of infection, dementia risk was highest for individuals previously infected with sepsis (HR 2·08 [1·89–2·29]) and for individuals with previous pneumonia (HR 1·88 [1·77–1·99]; table 2). Multiple infections diagnosed from different sites on the same date were strongly associated with dementia risk (HR 2·68 [2·40–2·99]). After adjustment for potential mediators, the risk of dementia following infections increased; adjustment for BMI did not change our effect estimates (appendix p 13).

Hospital-recorded infections were associated with an increased risk of dementia (HR 1·99 [95% CI 1·94–2·04; table 3). This association attenuated, but remained strong, when adjusted to only consider hospital-recorded primary diagnosis of infection (HR 1·84 [1·78–1·91]). Evidence of an association for infections recorded in general practice was weak (HR 1·02 [1·00–1·04]).

There was a small association between an increasing number of infections and an increasing risk of dementia (HR 1·02 [95% CI 1·01–1·02]; likelihood ratio test for trend p<0·0001; table 4). The risk of dementia was highest between 3 months and 1 year after an infection (HR 1·86 [1·80–1·92]; figure). Dementia risk attenuated over longer

For the **analysis codes** see https://github.com/RutendoMuzambi/Common-infections-and-incident-dementia

	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	Age-adjusted HR (95% CI)*	Age, sex, IMD, and calendar period adjusted HR (95% CI)†	Fully adjusted HR (95% CI)‡
General practitioner recorded infections						
No infection	37 298	4 115 228	9·06 (8·97–9·16)	1 (ref)	1 (ref)	1 (ref)
Any infection	24 314	1 554 615	15·64 (15·44–15·84)	1·20 (1·18–1·22)	1·09 (1·07–1·11)	1·02 (1·00–1·04)
Hospital recorded infections						
No infection	51 127	5 534 732	9·24 (9·16–9·32)	1 (ref)	1 (ref)	1 (ref)
Any infection	7166	200 320	35·77 (34·95–36·61)	2·28 (2·22–2·34)	2·15 (2·10–2·20)	1·99 (1·94–2·04)
Hospital recorded infections (primary diagnosis)						
No infection	57 142	5 641 094	10·13 (10·05–10·21)	1 (ref)	1 (ref)	1 (ref)
Any infection	3630	104 147	34·85 (33·74–36·01)	2·10 (2·03–2·17)	1·99 (1·92–2·06)	1·84 (1·78–1·91)

HR=hazard ratio. IMD=Index of multiple deprivation. *Age as underlying timescale. †Adjusted for age, sex, patient level IMD, and calendar time period over follow-up (2004–08, 2009–13, and 2014–18). ‡Adjusted for age, sex, patient level IMD, and calendar time period over follow-up (2004–08, 2009–13, and 2014–18), ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids, and polypharmacy.

Table 3: **Association between common infections and dementia stratified by clinical setting**

	Total number of incident dementia diagnoses	Total person-years at risk	Age-adjusted HR (95% CI)*	Age, sex, IMD, and calendar period adjusted HR (95% CI)†	Fully adjusted HR (95% CI)‡
No infection	25 314	3 895 425	1 (ref)	1 (ref)	1 (ref)
First infection	11 209	859 035	1·52 (1·49–1·55)	1·42 (1·39–1·45)	1·34 (1·32–1·37)
Second and additional infections§	14 112	731 026	1·04 (1·03–1·04)¶	1·02 (1·02–1·03)¶	1·02 (1·01–1·02)¶

HR=hazard ratio. IMD=Index of multiple deprivation. *Age as the underlying timescale. †Adjusted for age, sex, patient level IMD, and calendar time period over follow-up (2004–08, 2009–13, and 2014–18). ‡Adjusted for age, sex, patient level IMD, and calendar time period over follow-up (2004–08, 2009–13, and 2014–18), ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids, and polypharmacy. §Quantitative variable of number of infections from a count of two or more infections alongside a binary variable for yes or no infections in all models. Likelihood ratio test for trend, p<0·0001 in fully adjusted model. ¶Per additional infection.

Table 4: **Association between the number of common infections and dementia**

periods of follow-up, but risk remained high up to 9 years or more after infection (HR 1·53 [1·50–1·55]). This is also depicted in non-overlapping periods (appendix p 14).

There was evidence of effect modification by diabetes on the association between common infections and dementia (p=0·00014; appendix p 15), with a higher risk of dementia in individuals with diabetes (HR 1·70 [95% CI 1·61–1·79]) compared with those without diabetes (HR 1·50 [1·47–1·53]; appendix p 15). We found an association between common infections and an increased risk of cognitive impairment (HR 1·29 [1·27–1·32]; appendix p 16), but this association was weaker than that between infections and dementia (appendix p 16).

Stratifying our main analyses by dementia subtype showed that the association between infections and dementia was highest for unspecified dementia (HR 1·72 [95% CI 1·67–1·76]) and vascular dementia (HR 1·69 [1·62–1·76]), but was markedly weaker for Alzheimer's disease (HR 1·09 [1·05–1·13]; appendix p 17). Stratifying our primary analyses by sex showed that the association between infections and risk of dementia was stronger in men than in women; however, CIs overlapped (appendix p 18). Finally, analyses exploring the proximity to death following a dementia diagnosis show that Kaplan-Meier survival curves were steepest shortly after a dementia diagnosis, indicating that a larger proportion of people died in this period (appendix p 19). The curves also show that survival was worse in those with a history of infections compared with those without a history of infections (p<0·0001).

Due to evidence of non-proportionality for our main infection variable and residual non-proportionality (Schoenfeld residuals test, p=0·02 and p<0·0001), we stratified our primary analyses by age (appendix pp 20–21). The risk of dementia following infections increased with age, with the risk highest in those aged 90 years and older. When we included interaction terms between age and other variables that showed evidence of non-proportionality, our results were consistent with our primary analysis (appendix p 22).

In our sensitivity analyses, we observed minimal change in our effect estimates for our analyses on infections and dementia (appendix pp 23–24). When we excluded symptoms of cognitive impairment, the magnitude of the association between infections and cognitive impairment diagnoses increased (HR 1·62 [95% CI 1·56–1·68]; appendix p 25).

Discussion

In this population-based study of almost 1 million adults aged 65 years and older, we found that common infections were associated with an increased risk of dementia, with the risk strongest risk following sepsis and pneumonia. Of note, infections resulting in hospital admission—therefore, probably being more severe—

were associated with approximately double the risk of dementia compared with no infections, whereas a weak association was found for infections treated in community general practice. The risk of dementia was strongest between 3 months and 1 year following infection, which might be due to reverse causality (undiagnosed dementia increasing risk of infection); however, the association persisted for more than 9 years. Dementia risk increased with an increasing number of infections, although the magnitude of this trend was small. Furthermore, we found evidence that the association between infection and subsequent dementia was stronger in those with diabetes.

To our knowledge, with almost 1 million individuals followed up for up to 14 years, our study is the largest to investigate the association between common infections and incident dementia. Other strengths of our study include the exclusion of the first 3 months of follow-up after infection to prevent misclassification of delirium as dementia and the use of linked primary and secondary care electronic health records, representative of the English population and thus probably generalisable to the English population aged 65 years and older. Our findings were also robust across a range of sensitivity analyses.

Consistent with our findings, previous longitudinal studies have found an association between sepsis,[4,5,7–9] pneumonia,[5,6,9] urinary tract infections,[9,10] skin and soft tissue infections,[9,10] with dementia. Only two studies investigated the effect of a range of infections on dementia: a US cohort study of 417 172 veterans and a UK cohort study using primary and secondary care data of 60 392 stroke survivors. These studies found that risk of dementia increased with increasing number of infections,[9,10] and was highest in individuals with sepsis[9] and for infections requiring hospitalisation.[10] To our knowledge, only one study did not show an association between infection and dementia: a retrospective Swedish study of 210 334 patients (≥18 years) who had been admitted to an intensive care unit, which found no association between sepsis and dementia.[11] Discrepancies between the findings of the Swedish study and the rest of the published literature might be due to differences in clinical setting and study population. Similarly, our findings were in contrast with a longitudinal study from the USA that found no risk of cognitive impairment in individuals hospitalised due to sepsis compared with individuals without infection hospitalisation. However, another USA longitudinal study found an association between pneumonia hospitalisation and moderate-to-severe cognitive impairment. In this study, no association was found when individuals hospitalised with pneumonia were compared with individuals who were hospitalised with myocardial infarction or stroke. However, these studies were limited by small sample sizes (both studies included <2402 patients) or unsuitable comparator groups.[18,19] Our finding of a higher dementia risk in patients aged 80 years and older is in agreement with a case-control study using UK primary care data that reported a stronger association of infections and dementia in adults aged 84 years and older compared with younger age groups.[20] However, in this study infections were captured only 4 years before a dementia diagnosis. By contrast, a retrospective Taiwanese cohort study reported a lower risk of dementia following sepsis in individuals aged 65 years and older compared with those younger than 65 years. However, confidence intervals in the younger age groups were wide and the number of individuals with dementia was small.

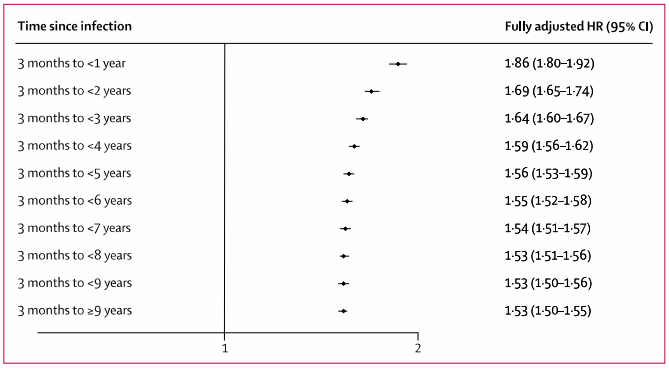

Figure: **The association between common infections and dementia, stratified according to time since infection**
Time periods are overlapping. Adjusted for age, sex, patient level index of multiple deprivation, calendar period, ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids, and polypharmacy. HR=hazard ratio.

Our study expands on existing literature by examining the association between infections and dementia using a wide range of secondary analyses, including exploring effect modification by diabetes and investigating the association between common infections and cognitive impairment, after resolution of delirium preventing misclassifying delirium as dementia.

The underlying mechanisms driving the association between infections and dementia are unclear, but they might be partly explained by systemic inflammation. Infections trigger the release of proinflammatory cytokines resulting in systemic inflammation, with such inflammation associated with cognitive decline and dementia.[21,22] Our finding of a larger effect on dementia risk of infections resulting in hospitalisation, such as pneumonia and sepsis, supports the role for notion of more severe infections having a stronger association with dementia risk. Severe infections are more likely to lead to systemic inflammation and are more prevalent in patients with diabetes due to immune dysfunction, probably caused by hyperglycaemia. Systemic inflammation has also been proposed as

one of the potential pathways linking diabetes and dementia.[23] Common infections, particularly respiratory tract infections, have been shown to trigger acute cardiovascular events, including myocardial infarction and stroke, and cause subclinical vascular damage in association with increased inflammation.[24] This increased inflammation in turn has been associated with vascular dementia.

We found marked differences between the association of common infections and dementia by dementia subtype, with the risk highest for vascular dementia and weakest for Alzheimer's disease. However, caution must be applied when interpreting the weaker associations found for Alzheimer's disease because misclassification of dementia subtype is probable because of the clinical challenges in classifying dementia. Additionally, in older adults, dementia is predominantly associated with mixed pathologies consistent with both vascular dementia and Alzheimer's disease.[25] Nonetheless, the substantial differences in the strengths of associations between common infections, vascular dementia, and Alzheimer's disease suggest that there might be underlying distinctions between dementia subtypes. Furthermore, mechanisms potentially linking infections with vascular dementia, such as potentiating vascular damage and inflammation, could explain the higher risk observed for vascular dementia.

We found that the risk of dementia following infection was higher in older age groups (≥90 years). This finding might be explained by immune dysfunction, which increases with age. Older adults (≥65 years) are more susceptible to infections and might experience recurrent and more severe infections. The effects of infections on systemic inflammation or vascular damage might accumulate over time, resulting in a higher risk of dementia in older adults. An alternative explanation could be that older adults often have multiple comorbidities and might, therefore, encounter health-care services more frequently, which in turn might increase their likelihood of a dementia diagnosis.[26]

Our study showed that the risk of dementia was highest between 3 months and 1 year after an infection. Dementia diagnosed shortly after infection is likely to reflect previously undiagnosed dementia, which is likely to be more prevalent in older adults because the prevalence of dementia increases with age. Systemic inflammation induced by systemic infections has been suggested to accelerate trajectories of cognitive decline in individuals with Alzheimer's disease.[27,28] Hence, accelerated cognitive decline and dementia progression could have increased the likelihood of a dementia diagnosis. Therefore, our finding of a higher dementia risk shortly after infection supports the need for future studies to clarify whether common infections accelerate cognitive decline and dementia progression in individuals with pre-existing cognitive impairment. Another explanation for this finding could be that older adults presenting with infections in primary care or during hospitalisation who are experiencing cognitive impairment might be referred for cognitive assessment after recovery, which could also increase their chances of receiving a dementia diagnosis.

A common consequence of serious infections is delirium. Delirium itself is a strong risk factor for dementia and can accelerate cognitive decline in individuals with dementia.[29,30] Delirium can also result in hospitalisation, and, in turn, hospitalisation, particularly in cases requiring intensive care unit admission, has been associated with long-term cognitive impairment.[31]

There are several limitations to our study. First, missed dementia diagnoses were possible because dementia is known to be frequently underdiagnosed in primary care.[32] However, the number of missed diagnoses has reduced as a result of government policies and strategies, such as the introduction of the Quality and Outcomes Framework in 2004 and the National Dementia Strategy in 2009 and dementia ascertainment in our study was probably improved by using two different data sources.[33–36] Misclassification of dementia subtype was probable, particularly in the older age groups in whom dementia is often associated with mixed pathologies.[25] Furthermore, it is possible that individuals diagnosed with infections had greater health-seeking behaviours; therefore, they were more likely to encounter health services, increasing the likelihood of a dementia diagnosis. This bias would probably be differential and would bias effect estimates away from the null. However, because individuals could be diagnosed with infections at any point during follow-up, we could not explore health-seeking behaviours in people with and without infections before follow-up. Second, ascertainment of cognitive impairment has not been validated in CPRD, and individuals were unlikely to have had their cognitive function tested at multiple timepoints by their general practitioner. However, we excluded individuals with evidence of cognitive impairment before the start of the study, reducing the potential for misclassification. Third, infections are often diagnosed without microbiological data, which increases the possibility of overdiagnosis. To minimise this, individuals were only defined as having urinary tract infections or skin and soft tissue infections if they were treated with antibiotics. Including antibiotic use in the definition of urinary tract infections or skin and soft tissue infections probably increased the specificity of our infection definition; however, defining these infections with antibiotics means that the associations we observed will have incorporated any mitigating effect of antibiotic treatment. As such, the observed associations for these infections might have been underestimated. Asymptomatic infections might also be missed by general practitioners, but these milder infections are less likely to lead to significant systemic inflammation and other pathophysiological mechanisms underlying the association between infections and dementia. Additionally, this bias due to milder infections

being missed is probably non-differential by dementia status and would bias effect estimates towards the null. Fourth, adjustment for confounders had a modest effect on our effect estimates, suggesting that our observed association was driven either by residual confounding or a possible causal effect. Although we accounted for a wide range of confounders, which were ascertained with both primary and secondary care data to minimise residual confounding, we cannot rule out the possibility of residual confounding through unmeasured confounders, such as frailty and genetic susceptibility, adjustment for categorical variables, and complex interaction between variables. Frailty is associated with a poor inflammatory response and slower recovery after infections. Therefore, individuals who develop more severe infections might be frailer, which could increase their risk of dementia. Frailty is also associated with adverse outcomes and more comorbidities, some of which we accounted for in our analyses. Finally, due to the long preclinical phase of dementia, we cannot rule out the possibility of reverse causality. People living with dementia are more susceptible to infections and have an increased risk of hospitalisation, with urinary tract infections and pneumonia being two of the most common complications in those hospitalised.[37] However, to minimise the possibility of reverse causality, we excluded individuals with a history of dementia; furthermore, the association of infections on dementia persisted for more than 9 years, making reverse causality highly unlikely to account for all of the observed effect.

In conclusion, our findings suggest that common infections are associated with an increased risk of dementia in adults (≥65 years), with the risk varying according to type, clinical setting, frequency, and timing of infections, and to the presence of diabetes. Future large-scale, longitudinal studies with a long follow-up period are needed to confirm our findings and to improve our understanding of the mechanisms underlying the associations between infections, diabetes, and dementia. To translate our findings into clinical practice, future studies should investigate whether infection prevention and control interventions reduce the risk of dementia in high-risk populations. Our findings highlight the importance of managing long-term neurological complications following other infections, such as COVID-19, which uniquely has been associated with cognitive dysfunction soon after illness and might also more generally be associated with cognitive decline and dementia in line with the observations made in this study.[38] Infections, such as periodontitis, for which patients do not typically present to the general practitioner, have been associated with Alzheimer's disease, but these infections were not included in our study; more research is needed in this area.[39] Additional research is warranted to identify potential microorganisms responsible for the association between infections and dementia. Future studies are also needed to investigate the association between infections and biomarkers related to cognitive impairment and dementia, and to examine the effect of infections on cognitive decline, using validated repeated measures assessing multiple domains of cognition.

Contributors

CW-G, CB, LS, KB, and RM conceptualised and designed the study. RM searched the literature, analysed the data, and wrote the first draft of the manuscript. CW-G, KB, RM, LS, CB, and NC were involved in data interpretation and revision of the manuscript. RM, KB and CW-G accessed and verified the patient-level data.

Declaration of interests

We declare no competing interests.

Data sharing

All code lists used in this study and the study protocol online. Data are not publicly available. Access to data is obtained through Clinical Practice Research Datalink and is dependent upon approval of a study protocol by the independent scientific advisory committee.

For **code lists and the protocol** see https://doi.org/10.17037/data.00002073

Acknowledgments

This research was funded in whole, or in part, by the Wellcome Trust (201440/Z/16/Z). RM is supported by an Alzheimer's Society PhD studentship 379 (AS-PhD-17-013). We thank the Alzheimer's Society research monitors assigned to RM's studentship for their input. CW-G is supported by a Wellcome Intermediate Clinical Fellowship. KB holds a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society.

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5.3 Summary

- This chapter investigates the association of common infections with incident dementia and evidence of cognitive impairment in a large-scale historical cohort study using UK primary and secondary care EHRs of almost one million adults aged 65 years and older.
- Common infections (sepsis, pneumonia, other lower respiratory tract infections, urinary tract infections and skin and soft tissue infections) were associated with an increased risk of dementia HR 1.53 (95% CI, 1.50–1.55) with the risk highest for infections likely to be severe i.e. sepsis HR 2.08 (95% CI, 1.89–2.29), pneumonia HR 1.88 (95% CI, 1.77–1.99) and infection resulting in hospital admission HR 1.99 (95% CI, 1.94–2.04].
- There was evidence that the association between infections and dementia was higher among individuals with diabetes than among those without diabetes. However, future studies are needed to understand the potential biological mechanism underpinning the association between infections, diabetes and dementia.
- In secondary analyses, common infections were also associated with an increased risk of cognitive impairment HR 1.29 (95% CI, 1.27–1.32), however, ascertainment of cognitive impairment has not been validated in primary care and it is unlikely that cognitive impairment was assessed repeatedly over time by the GP. Therefore, further studies are needed to assess the association of common infections on the trajectory of cognitive decline assessment at multiple time points in different domains of cognitive function.
- This study overcame limitations of previous studies mentioned in the systematic review of chapter 3 through its large study population, long follow up period of up to 14 years which limited the possibility of reverse causality, adjustment for multiple confounders, and exploration of the association of infections and dementia in different clinical settings through the use of primary and secondary care records.
- Adjustment for potential confounders such as education and physical activity was not possible as these variables are not well captured in EHRs.

- The focus of this study was on infections occurring in late life (65 years or older), however, the association of early to mid-life infections remains understudied.

Chapter 6: The assessment of the effect of common infections on dementia using data from the UK Biobank study linked to routinely collected electronic health records

6.1 Introduction

In chapter 5, I investigated the association between common infections and dementia using UK EHRs from the CPRD and HES databases. In this chapter, I also examined the association between infections and dementia in a younger and healthier study population using data from the UK Biobank study in order to compare the findings of these two studies. Therefore, I conducted analyses investigating the association between the presence, site and setting of common infections with dementia incidence. I also assessed whether the association of infections on dementia differed by dementia sub-type. The main sections of this chapter include the methodology, results, discussion and summary of the chapter.

6.2 Methodology

Study design and population

To conduct this study, I used data from the UK Biobank study, an ongoing prospective cohort study which recruited over 500,000 participants aged 40-69 between 2006-2010 from 22 assessment centres in England, Wales and Scotland. I describe the UK Biobank study in detail in chapter 4.

I also used linked primary, secondary and mortality data in this study. All UK Biobank participants provided consent for linkage of their health records but linkage to primary care records was only available for approximately 45% of the UK Biobank cohort owing

to difficulties in accessing the data for some primary care data providers.[199] As a result of this, I excluded participants without linked primary care records. I also excluded participants who had less than 12 months registration with a GP practice. Previous studies of UK EHRs suggest historical diagnoses may be recorded within the first 12 months a patient registers with a practice. Therefore, I only included participants with at least one year of follow up.

Assessment of exposure

As in the previous chapter, infections were the main exposure. These infections included sepsis, pneumonia, other LRTIs, UTIs and SSTIs. Infections were defined using linked primary and secondary care records and were identified up to 5 years prior to participants' baseline assessment visit. A period of up to 5 years was chosen due to issues with data recording and completeness in the linked primary care dataset. Similar to chapter 5, participants were defined as having UTIs and SSTIs if they were prescribed antibiotics on the same day as an infection diagnosis.

Assessment of dementia

Using a broad definition of dementia (including Alzheimer's disease, vascular dementia and dementia causally related to other conditions), I defined dementia using a previously described algorithm which used Read codes in linked GP records and ICD-10 codes in hospital and mortality records.[237] When participants had multiple records of dementia diagnosis, I used the earliest dementia record.

Assessment of covariates

The covariates used in this study were similar to those in chapter 5. Covariates were ascertained using baseline assessment questionnaires, nurse interview and linked primary and secondary care data. Covariates such as educational attainment, physical

activity and alcohol consumption were not well captured in the CPRD database and thus I was able to additionally adjust for them in the present study. In the CPRD and HES study, I adjusted for polypharmacy however due to the issues with completeness and inconsistencies in the prescription dataset of the linked UK Biobank primary care records, I did not adjust for this covariate.

Comorbidities ascertained in EHRs were defined within 10 years prior to baseline. Demographic variables included age, sex and ethnicity (white, south Asian, black, mixed or other), years in education based on the International Standard Classification of Education (ISCED) 1997, [238,239] and socioeconomic status measured using the Townsend Deprivation score. [240] Lifestyle covariates included BMI (kg/m^2), smoking (never smoker, former smoker or current smoker), alcohol intake frequency (rarely or never, 1-8 times per month and 16 times per month) and physical activity (number of days a week where participants spent >10 minutes of moderate physical activity). Diabetes was ascertained using HbA1c, medication history at baseline questionnaire and nursing interview and linked EHRs. Other comorbidities were ascertained using baseline assessment questionnaires/interviews as well as primary and secondary care records. Comorbidities were defined up to 10 years before baseline. These comorbidities include anxiety and depression, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, heart failure, hypertension, inflammatory bowel disease, multiple sclerosis, obstructive sleep apnoea, rheumatoid arthritis, psoriasis, severe mental illness, stroke and traumatic brain injury. Medication use was also adjusted for using linked primary care data. This included at least two prescriptions of proton pump inhibitors, benzodiazepines or systemic corticosteroids in the year before baseline.

Statistical analyses

I described the characteristics of the study population according to history of infection in the 5 years prior to baseline assessment. Categorical data was described using numbers and percentages and for continuous data, mean and median values with standard deviations or interquartile range were used.

Cox proportional hazards regression models were used to estimate hazard ratios for the association between common infections and dementia. Participants were followed from the date of baseline assessment to the earliest of either their date of dementia diagnosis, date of death or last date of hospital admission (14th February 2018). The underlying time scale was follow up (years) from baseline assessment. In the fully adjusted models, the following covariates were accounted for: age (years), sex, ethnicity, education, socioeconomic status, physical activity, alcohol intake, diabetes, anxiety and depression, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, heart failure, hypertension, inflammatory bowel disease, multiple sclerosis, obstructive sleep apnoea, rheumatoid arthritis, psoriasis, severe mental illness, stroke, traumatic brain injury, proton pump inhibitors, benzodiazepines and systemic corticosteroids.

Secondary analyses were performed on site and setting of infections and dementia subtype (Alzheimer's disease, vascular dementia and unspecified dementia). Due to a small number of dementia events, I adjusted for covariates that changed the effect estimates by approximately a 10%. The Cox proportional hazards assumption was checked using log-log plots and Schoenfeld residuals. No evidence of non-proportionality was found for the infection variable (p=0.41) though I found evidence of

non-proportionality for the global test (p=0.047). As a result, I performed additional analyses stratifying analyses by follow up time (0-6 years and 6-12 years).

6.3 Results

In total, there were 502,444 participants in the UK Biobank study. After excluding those without linked primary and secondary care records, those registered in primary care for less than 12 months and those with a history of dementia and cognitive impairment at baseline, 176,207 participants were included in the final study population (Figure 6.1).

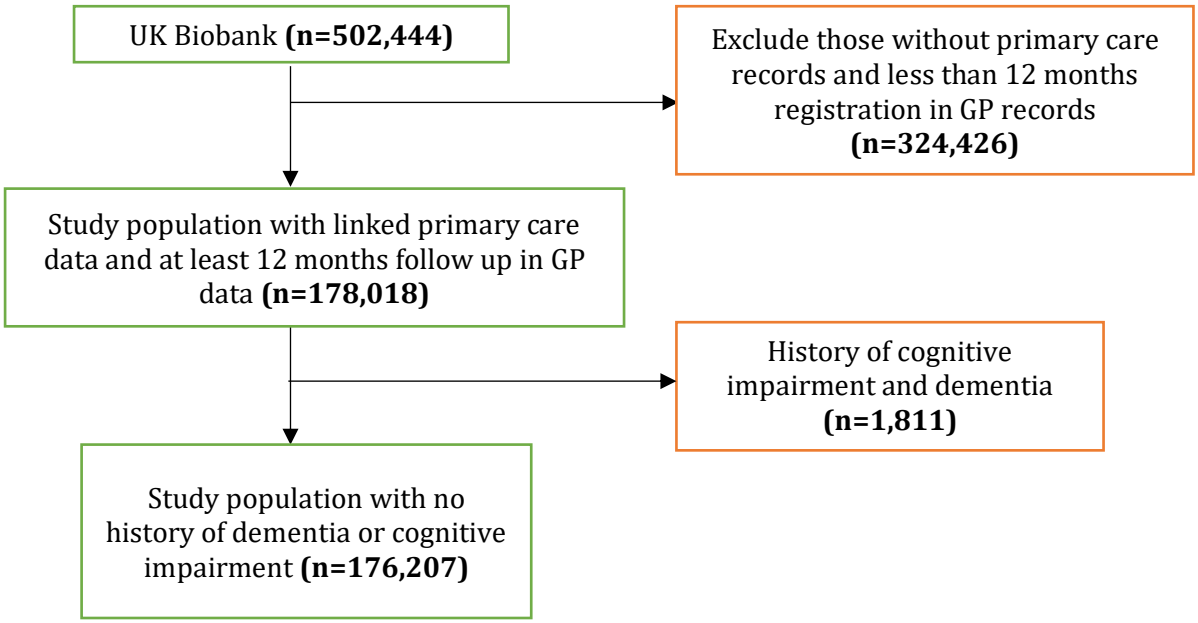

Figure 6.1. Flow chart for inclusion and exclusion into study population for analyses on common infections and dementia incidence

Table 6.1. Baseline characteristics of 176,207 UK biobank participants by status of history of infection

	Total (N=176,207)	**No Infection (N=141,558)**	**Any Infection (N=34,649)**
Age at baseline assessment (mean, sd)	56.62 (8.05)	56.33 (8.06)	57.84 (7.90)
Age at baseline assessment (median)	58.00 (50.00-63.00)	57.00 (50.00-63.00)	60.00 (52.00-64.00)
Age (years)			
40-44	17,504 (9.9%)	14,770 (10.4%)	2,734 (7.9%)
45-49	23,104 (13.1%)	19,377 (13.7%)	3,727 (10.8%)
50-54	26,614 (15.1%)	21,977 (15.5%)	4,637 (13.4%)
55-59	31,912 (18.1%)	25,883 (18.3%)	6,029 (17.4%)
60-64	43,156 (24.5%)	33,839 (23.9%)	9,317 (26.9%)
65+	33,917 (19.2%)	25,712 (18.2%)	8,205 (23.7%)
Female	96,168 (54.6%)	75,437 (53.3%)	20,731 (59.8%)
Ethnicity			
White European	167,614 (95.1%)	134,754 (95.2%)	32,860 (94.8%)
South Asian	3,028 (1.7%)	2,331 (1.6%)	697 (2.0%)
African Caribbean	1,746 (1.0%)	1,403 (1.0%)	343 (1.0%)
Mixed or other	3,036 (1.7%)	2,456 (1.7%)	580 (1.7%)
Missing	783 (0.4%)	614 (0.4%)	169 (0.5%)
Education attainment (years)	14.89 (5.14)	15.08 (5.08)	14.13 (5.29)
BMI (mean)	27.49 (4.78)	27.30 (4.63)	28.28 (5.27)
Baseline Townsend deprivation index	-1.44 (2.97)	-1.49 (2.95)	-1.23 (3.04)
Baseline number of days/week moderate physical activity >10 mins (median)	3.0 (2.00-5.00)	3.00 (2.00-5.00)	3.00 (2.00-6.0)
Smoking status			
Never smoker	117,384 (66.6%)	95,946 (67.8%)	21,438 (61.9%)
Previous smoker	40,255 (22.8%)	31,340 (22.1%)	8,915 (25.7%)
Current smoker	18,030 (10.2%)	13,873 (9.8%)	4,157 (12.0%)
Missing	538 (0.3%)	399 (0.3%)	139 (0.4%)
Baseline alcohol intake frequency - 3 categories			
Rarely or never	33,825 (19.2%)	25,900 (18.3%)	7,925 (22.9%)
1-8 times per month	66,253 (37.6%)	53,222 (37.6%)	13,031 (37.6%)
16 times per month- every day	75,737 (43.0%)	62,156 (43.9%)	13,581 (39.2%)
Missing	392 (0.2%)	280 (0.2%)	112 (0.3%)
Comorbidities			
Anxiety and depression	22,992 (13.0%)	16,411 (11.6%)	6,581 (19.0%)
Severe mental illness	2,371 (1.3%)	1,715 (1.2%)	656 (1.9%)
Inflammatory bowel disease	8,558 (4.9%)	6,072 (4.3%)	2,486 (7.2%)
Multiple Sclerosis	671 (0.4%)	482 (0.3%)	189 (0.5%)

Rheumatoid Arthritis	2,440 (1.4%)	1,695 (1.2%)	745 (2.2%)
Psoriasis	4,711 (2.7%)	3,549 (2.5%)	1,162 (3.4%)
Asthma	23,245 (13.2%)	15,618 (11.0%)	7,627 (22.0%)
Chronic kidney disease	2,114 (1.2%)	1,441 (1.0%)	673 (1.9%)
Chronic liver disease	7,117 (4.0%)	4,923 (3.5%)	2,194 (6.3%)
Chronic obstructive pulmonary disease	2,956 (1.7%)	988 (0.7%)	1,968 (5.7%)
Diabetes mellitus	9,183 (5.2%)	6,384 (4.5%)	2,799 (8.1%)
Heart failure	4,528 (2.6%)	2,787 (2.0%)	1,741 (5.0%)
Hypertension	36,729 (20.8%)	27,149 (19.2%)	9,580 (27.6%)
Obstructive sleep apnoea	1,688 (1.0%)	1,177 (0.8%)	511 (1.5%)
Stroke	1,895 (1.1%)	1,342 (0.9%)	553 (1.6%)
Traumatic brain injury	1,391 (0.8%)	978 (0.7%)	413 (1.2%)
Medication use (two prescriptions within a year)			
Systemic corticosteroids	2,452 (1.4%)	1,260 (0.9%)	1,192 (3.4%)
Benzodiazepines	973 (0.6%)	638 (0.5%)	335 (1.0%)
Proton pump inhibitors	16,920 (9.6%)	11,339 (8.0%)	5,581 (16.1%)

The baseline characteristics of participants included in this study are presented in Table 6.1. Overall participants had a mean age of 56.6 (sd, 8.1) and median age of 58.0 (IQR, 50.0-63.0). 54.6% of participants were female. The median follow up of 8.9 years (8.3-9.7). Participants with a history of infection were slightly older, more likely to be female (59.8%), more likely be have diabetes and had less years in education compared to those without infection. 19.7% (34,649) of the study population was diagnosed with any common infection in the 5 years before their baseline assessment.

Of the participants with a history of infection, 0.8% (279) were diagnosed with sepsis, 2.0% (707) had pneumonia, 60.5% (20,952) were diagnosed with other LRTIs, 19.7% (6,809) had UTIs and 16.9% (5,849) had SSTIs. 53 participants (0.2%) were diagnosed with multiple infections from different sites on the same date. In terms of the clinical setting of infection, 31,278 (17.8%) had a GP recorded infection and 3,371 (1.9%) had a hospital recorded infection. In total, 1,201 participants were diagnosed with dementia.

For dementia subtype, 479 participants had Alzheimer's disease, 171 had vascular dementia, 466 had unspecified dementia and 85 had other types of dementia
Table 6.2 shows the association of common infections with dementia stratified by site and clinical setting. The presence of common infections was associated with incident dementia, in the age and sex adjusted models. However, in the fully adjusted models, there was no longer an association between common infections and dementia HR 1.10 (95% CI, 0.95-1.27). In analyses stratified by site of infection, no association was found between infection sites and dementia in fully adjusted models. Due to a small number of dementia events for pneumonia (n<5), sepsis (n=5) and for multiple infections diagnosed on the same date (n<5), the association of these infections with dementia were not presented. When I stratified analyses by clinical site, an association was found between hospital recorded infections and dementia HR 1.60 (95% CI, 1.19-2.16) while no association was found for infections recorded in GP records HR 1.05 (95% CI, 0.92-1.21).

Table 6.3 shows the association between common infections and dementia subtype. In these analyses, I found no association between common infections and Alzheimer's disease HR 0.93 (95% CI, 0.75-1.17). However, common infections were associated with a 49% increased risk of vascular dementia HR 1.49 (95% CI, 1.07-2.07).

Due to evidence of non-proportionality, I conducted sensitivity analyses stratified by follow up in years as shown in Table 6.4. These results did not change the conclusions of the primary analysis.

Table 6.2. Association of common infections with dementia incidence, stratified by type and setting of infections

Infection	Total dementia events	Person-years at risk	Crude incidence rate (95% CI)	*Age and sex adjusted HR (95% CI)	**Fully adjusted HR (95% CI)
Type of infections					
No infection	882	1262898	0.70(0.65-0.75)	1.00	1.00
Any Infection	319	300563	1.06(0.95-1.18)	1.28 (1.13-1.46)	1.10 (0.95-1.27)
LRTIs	204	182341	1.12(0.98-1.28)	1.31 (1.12-1.53)	1.12 (0.96-1.32)
UTIs	58	59056	0.98(0.76-1.27)	1.26 (0.96-1.65)	1.17 (0.90-1.54)
SSTIs	48	50363	0.95(0.72-1.26)	1.22 (0.91-1.63)	1.15 (0.86-1.54)
Setting of infections					
No infection	927	271595	0.72(0.67-0.77)	1.00	1.00
GP recorded	274	271595	1.01(0.90-1.14)	1.19 (1.04-1.37)	1.05 (0.92-1.21)
No infection	1156	1534493	0.75(0.71-0.80)	1.00	1.00
Hospital record	45	28969	1.55(1.16-2.08)	1.74 (1.29-2.34)	1.60 (1.19-2.16)

HR, hazard ratio. HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTIs; urinary tract infections, SSTIs, skin and soft tissue infections. Follow up time (years) as underlying time scale ** Adjusted for age and sex, **additional adjusted for ethnicity, socioeconomic status, smoking status, alcohol intake, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, heart failure, hypertension, obstructive sleep apnoea, traumatic brain injury, benzodiazepines, proton pump inhibitors and systemic corticosteroids. For analyses on setting of infection fully adjusted analyses adjust for age, sex, COPD and anxiety and depression.

Table 6.3. Association of common infections with dementia incidence, stratified by dementia subtype

Infection	Total dementia events	Person-years at risk	Crude incidence rate (95% CI)	*Age and sex adjusted HR (95% CI)	**Fully adjusted HR (95% CI)
Alzheimer's disease					
No infection	371	1262898	0.29(0.27-0.33)	1.00	1.00
Any Infection	108	300563	0.36(0.30-0.43)	1.01 (0.81-1.25)	0.93 (0.75-1.17)
Vascular dementia					
No infection	115	1262898	0.09(0.08-0.11)	1.00	1.00
Any Infection	56	300563	0.19(0.14-0.24)	1.70 (1.24-2.35)	1.49 (1.07-2.07)
Unspecified Dementia					
No infection	329	1262898	0.26(0.23-0.29)	1.00	1.00
Any Infection	137	300563	0.46(0.39-0.54)	1.50 (1.23-1.83)	1.27 (1.03-1.56)
HR, hazard ratio. Follow up time (years) as underlying time scale. Fully adjusted analyses include age, sex, COPD and anxiety and depression.					

Table 6.4. Association of common infections with dementia incidence, split by follow up time

Infection	Person-years at risk	No. of dementia events	Crude incidence rate (95% CI)	*Age and sex adjusted HR	**Fully adjusted HR
0 to < 6 years follow up time					
No Infection	508	842501	0.60 (0.55-0.66)	1.00	1.00
Any Infection	178	204804	0.87 (0.75-1.01)	1.23 (1.03-1.45)	1.10 (0.91-1.34)
6 to < 12 years follow up					
No infection	374	420398	0.89 (0.80-0.98)	1.00	1.00
Any infection	141	95759	1.47(1.25-1.74)	1.36 (1.12-1.65)	1.17 (0.94-1.45)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
*Follow up time as underlying time scale. ** Adjusted for age and sex, **additional adjusted for ethnicity, socioeconomic status, smoking status, alcohol intake, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, heart failure, hypertension, obstructive sleep apnoea, traumatic brain injury, benzodiazepines, proton pump inhibitors and systemic corticosteroids.

6.4 Discussion

Summary

Overall, in this large population of 176,207 participants in the UK Biobank study, no association was found between the presence and site of common infections occurring in midlife and dementia risk. An association, however, was found between hospital recorded infections and dementia. Additionally, an association was also found between infections and vascular dementia while no association was found for Alzheimer's disease.

Comparison with existing literature

Analyses on hospital recorded infections and dementia incidence in this study are similar to those observed in a recent UK Biobank study which focused solely on hospital-treated infections and found an association between infections and dementia.[162] Differences in the magnitude of this association may be attributed to differences in the infection definition. The study by Sipilä et al, used a broad definition of infections, rather than focusing on common infections, and these infections included a wide range of over 900 infectious diseases including bacterial, viral, parasitic and fungal infections. In this study, the risk of dementia was greatest for CNS infections. In addition, the study by Sipilä et al had a much greater proportion of participants with hospital recorded infections (n=94,112) compared to the present study (n=3,371), which increased the power to detect an association between hospital infections and dementia. Other differences between the present study and the study by Sipilä et al, include differences in the timing of the ascertainment of infections. Sipilä et al, defined participants as having infections prior to or at baseline and participants with infections during follow up were also classified as having infections whereas in the present study

infections were only ascertained up to 5 years prior to baseline. Similar to the present study, the Sipilä et al found evidence of a dose-response relationship between the number of infections and dementia. Also, consistent with the present study, Sipilä et al also found a greater association for vascular dementia than Alzheimer's disease. The non-significant association between GP recorded infections and dementia, and infections and Alzheimer's disease are consistent with two other studies using UK primary care records. A recent case-control study using CPRD data found no association between infectious disease and Alzheimer's disease.[159] In another case control study of 19,463 individuals with Alzheimer's disease using CPRD data, influenza was not associated with Alzheimer's disease.[241]

Comparison with research paper 3 in chapter 5

Findings in this chapter on the presence and site of common infections differ with those in chapter 5. In chapter 5, common infections were associated with a 21% increased risk of dementia, whereas no association was found in the present chapter, though the 95% confidence interval in this study includes a HR of 1.21 which is consistent with chapter 5. Although the presence and site of infections were not associated with an increased risk of dementia in this study, the point estimates overall went in the same direction as the findings in chapter 5.

Explanations for this difference could be due to the much larger sample size of the previous study (almost a million individuals of whom 56,802 were diagnosed with dementia), an older population aged 65 years and older with a mean age of 71.7 years, and a much greater proportion of infections likely to be severe (hospital recorded infections, sepsis and pneumonia) whose risk of dementia was greater compared to less

severe infections. The mean age for the present study was 56.6 years thus findings may not be generalisable to older populations. Participants of the UK Biobank were healthier than the general population, therefore the present study likely underrepresented individuals at a greater risk of dementia. These differences could also explain the differences in magnitude of the associations on hospital recorded infections and dementia, and infections and vascular dementia.

Similar to chapter 5, in this study, a stronger association was seen for participants hospitalised with infection, suggesting a gradient of association with infection severity. Additionally, findings on common infections and dementia subtype were consistent with those of chapter 5 which found a stronger association for common infections and vascular dementia.

Strengths and limitations

Strengths of this study include the extensive information on a wide range of covariates including education and physical activity, which were not well recorded and adjusted for in chapter 5. However, there were several limitations to the present study. Firstly, although the present study had a large study population size of over 176,000 participants, the number of dementia events for site and setting of infections and dementia subtype were small thus the study was not large enough to fully adjust for all potentially covariates for these analyses. Secondly, the age distribution of participants in this study was fairly young (median age 58.00, IQR 50.00-63.00) for a dementia study given that dementia is uncommon under of the 60 and the risk of dementia doubles every 5 years after the age of 65.[67] Therefore, the generalisability of these findings to older adults who are at a greater risk of cognitive decline and dementia may be limited.

Generalisability may also be limited because UK Biobank participants are healthier than the general population thus cognitive decline may be delayed in this population, reducing the likelihood of detecting an association between common infections and dementia. Third, as with all observational studies, residual confounding cannot be ruled out. One such potential unmeasured confounder may have been hospitalisation severity which could have biased effect estimates between hospital recorded infections and dementia away from the null.

Conclusion

In summary, no association was found between the presence and site of common infections and incident dementia in this longitudinal cohort study using UK Biobank data linked to primary and secondary care records. However, an association was found between hospital recorded infections and dementia, and common infections and vascular dementia. Further studies, with larger population sizes from different settings (including primary and secondary care) in different age groups are required to strengthen the evidence base on infections and dementia. Studies aimed at investigating whether reducing common infections also reduces the risk of dementia are needed in order to inform dementia risk reduction strategies.

6.5 Summary

- In this chapter I examined the association of common infections occurring in midlife with incident dementia to compare the findings of the CPRD and HES study in a younger and healthier cohort which used data from the UK Biobank study.
- Unlike the CPRD and HES study, the presence and site of common infections in this study were not associated with incident dementia however confidence intervals overlapped and the point estimates overall were in the same direction.
- Consistent with the CPRD and HES study, participants hospitalised with common infections were at a greater risk of dementia and the risk of dementia was higher for participants with vascular dementia.
- Strengths of this study include the extensive information on covariates including education and physical activity. Education and physical activity are not well recorded in primary care and were therefore not adjusted for in the CPRD and HES study.
- Limitations of this study include the age of the participants (mean age 56.6), the population which is healthier than the general public and the small number of dementia events was small in sub-group analyses which limited the ability adjust for all potential covariates.
- Future large-scale studies examining this association in different clinical settings and age groups are warranted.
- While this study investigated the association between common midlife infections and incident dementia, the association of these infections with changes in cognitive function over time before clinical onset of dementia is unclear.

Chapter 7: Common infections and cognitive decline in the UK Biobank

7.1 Introduction

This chapter addresses the fourth research aim of this thesis which was to investigate the effect of common infections on cognitive decline, structural neuroimaging measures and dementia using data from the UK Biobank study linked to routinely collected primary and secondary care EHRs. In this chapter, I include a draft of the research article to be submitted for publication which will focus on the association of common infections with cognitive decline, hippocampal volume and white matter hyperintensity volume, a description of cognition function scores stratified by age and infection status, an additional section focusing on the association of common infections and total brain volume, and a summary of the chapter.

In the CPRD and HES study (chapter 5), an association was found between infections occurring in late life and evidence of subsequent cognitive impairment. However, while this was a large-scale population-based study of almost a million individuals, it was limited by the use of EHRs to ascertain cognitive impairment. Cognitive impairment in the CPRD and HES study was also assessed at one point in time rather than using repeated measurements of neuropsychological assessments to assess longitudinal changes in cognition over time. Therefore, in the previous chapter it was not possible to assess trajectories of cognitive decline following infection given that data on repeated measurements of cognitive function is lacking in routinely collected health records. Additionally, in EHRs there is a lack of routine, systematically collected information on neuroimaging measures such as hippocampal volume and white matter hyperintensities

which are early neuroimaging markers associated with dementia risk. Identifying potential modifiable risk factors for cognitive decline and early subclinical neuroimaging measures associated with dementia, could play a crucial role in delaying or preventing the onset of dementia.[31,72] The UK Biobank study overcame the aforementioned limitations of the CPRD and HES study as it includes data on repeated measures of multiple domains of cognition and a subset of the population had data on neuroimaging measures.

Therefore, in this chapter, I used data from the UK Biobank study to examine the association of common infections with cognitive decline, hippocampal volume and white mater hyperintensity volume (research paper 4). The null hypothesis was that there would be no difference in the rate of cognitive decline over follow up for participants with a history of common infections compared to participants without infections in each cognitive test, and no association between the association of infections with hippocampal volume and white matter hyperintensities. The alternative hypothesis was that participants with a history of common infections would have an increased rate of cognitive decline over follow up in each cognitive test, a decline in hippocampal volume and an increase in WMH volume. In a supplementary section of this chapter, I performed exploratory analyses on the association between common infections and total brain volume.

7.2 Research paper 4

Are infections associated with cognitive decline and neuroimaging outcomes? A historical cohort study using data from the UK Biobank study linked to primary and secondary care electronic health records

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SECTION A – Student Details

Student ID Number	1802273	**Title**	Ms
First Name(s)	Rutendo		
Surname/Family Name	Muzambi		
Thesis Title	The effect of common infections on cognition and dementia in people with and without diabetes		
Primary Supervisor	Dr Charlotte Warren-Gash		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	n/a		
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Where is the work intended to be published?	European Journal of Neurology
Please list the paper's authors in the intended authorship order:	Rutendo Muzambi, Krishnan Bhaskaran, Christopher Rentsch, Liam Smeeth, Carol Brayne, Victoria Garfield, Dylan M Williams, Nish Chaturvedi, Charlotte Warren-Gash
Stage of publication	**Not yet submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I am the first author of this paper. I conceived and designed the study, drafted and revised the manuscript. CWG, KB, LS, CB, NC, CR, VG and DMW also contributed to the conception and/or design of the study. CWG, KB, LS, NC, VG and DMW provided comments to the manuscript.

SECTION E

Student Signature	[redacted]
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Supervisor Signature	[redacted]
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Are infections associated with cognitive decline and neuroimaging outcomes? A historical cohort study using data from the UK Biobank study linked to primary and secondary care electronic health records

Short running title: Infections and cognitive decline

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Journal: European Journal of Neurology

Tables and figures: 4 tables and 4 figures

Abstract

Background and purpose:

While there is growing evidence of associations between common infections and dementia risk, associations with cognitive impairment, and potential structural correlates of cognitive decline, remain underexplored. Here we aimed to investigate the presence and nature of any association between common infections, cognitive decline, and neuroimaging parameters in a large volunteer cohort.

Methods:

The UK Biobank is a large cohort with linkage to primary and secondary care records. Using linear mixed effects models we compared participants with and without a history of common infections for changes in cognitive function during follow up. Linear regression models were then used to investigate the association of common infections with hippocampal and white matter hyperintensity (WMH) volume.

Results:

16,728 participants (median age 56.0 years [IQR 50.0-61.0; 51.3% women) had baseline and follow up cognitive measures. We found no association between the presence, site and setting of infections with cognitive decline for mean correct response time, fluid intelligence and prospective memory tests. UTIs were associated with a slight increase of 0.011 (95% CI: 0.004-0.018) per year in the log visual memory errors compared to those with no prior infection. A slight increase in the log of visual memory errors per year was also found for each additional infection (β 0.0064, 95% CI: 0.0019-0.011). 14,712 participants had neuroimaging measures. We found no association between common infections and hippocampal and WMH volume.

Conclusion:

Our findings do not support a major role for common midlife infections in contributing to cognitive decline for this cohort. Further research is warranted in individuals with more severe infections and for infections occurring later in life.

Introduction

Growing evidence from longitudinal studies supports the role of common infections such as sepsis,[242-245] pneumonia,[158,245] other lower respiratory tract infections (LRTIs),[245] urinary tract infections (UTIs),[158,245] and skin and soft tissue infections (SSTIs)[158,245] in increasing the risk of dementia, though evidence has been conflicting.[160]

Dementia has a long preclinical phase which can take decades to develop.[246] Before the clinical expression of dementia, cognitive and neuropathological changes associated with dementia progression can be observed but it is unclear whether infections are relevant during this process.[247,248] Common infections are well established risk factors for acute reversible changes in cognition manifested as delirium which is in turn associated with cognitive decline and dementia.[36,39] However, the association of common infections with long term cognitive impairment, after resolution of delirium, is less well known. Identifying the point at which infections may act before clinical onset of dementia might allow interventions to be targeted and timed appropriately to prevent or delay the onset of dementia.

Infection-related hospitalisations, particularly for sepsis and pneumonia, have been associated with cognitive decline in US longitudinal studies of adults aged 50 years or older.[105,106,249-251] There is limited understanding of the relationship of other sites of common infections in different clinical settings such as primary care with changes in cognitive function over time. Other limitations of existing studies include either relatively small study sizes, the use of a single global measure of cognition rather than individual cognitive domains, or inadequate confounder adjustment, given the wide

range of potential confounders (e.g. sociodemographic and lifestyle factors and comorbidities including cardiovascular, inflammatory, psychiatric and other conditions).[69,213,214,216,217,220,221,228-230] To our knowledge, no studies using repeated measures of cognition over time have investigated the association between the frequency and timing of common infections and cognitive decline.

Besides cognitive decline, neuroimaging measures such as hippocampal atrophy and white matter hyperintensities (WMH) are frequently studied subclinical markers of dementia risk that predict the incidence and progression of dementia. [252] However, evidence on the link between common infections and these neuroimaging markers is scarce. Compared to cognitive function measures, neuroimaging measures may be less prone to the effects of sociodemographic influences such as education and investigating cognitive decline and neuroimaging measures may allow us to triangulate our findings across different outcomes associated with dementia risk.

Therefore, we aimed to explore the association between common infections and cognitive decline (using four repeated measures of cognition), hippocampal volume and WMH volume. We then assessed whether these associations differed by infection site, clinical setting, frequency and timing of infections.

Methods

Study design and population

We used data from the UK Biobank study, an ongoing prospective study which recruited over 500,000 participants aged 40-69 between 2006-2010 from 22 assessment centres based in England, Wales and Scotland with a low response rate of 5.5%.[186]. Participants identified from National Health Service (NHS) central registers were invited to take part through postal invitations. The methodology and design of the UK Biobank has been described previously and is summarised in supplementary methods.[184]

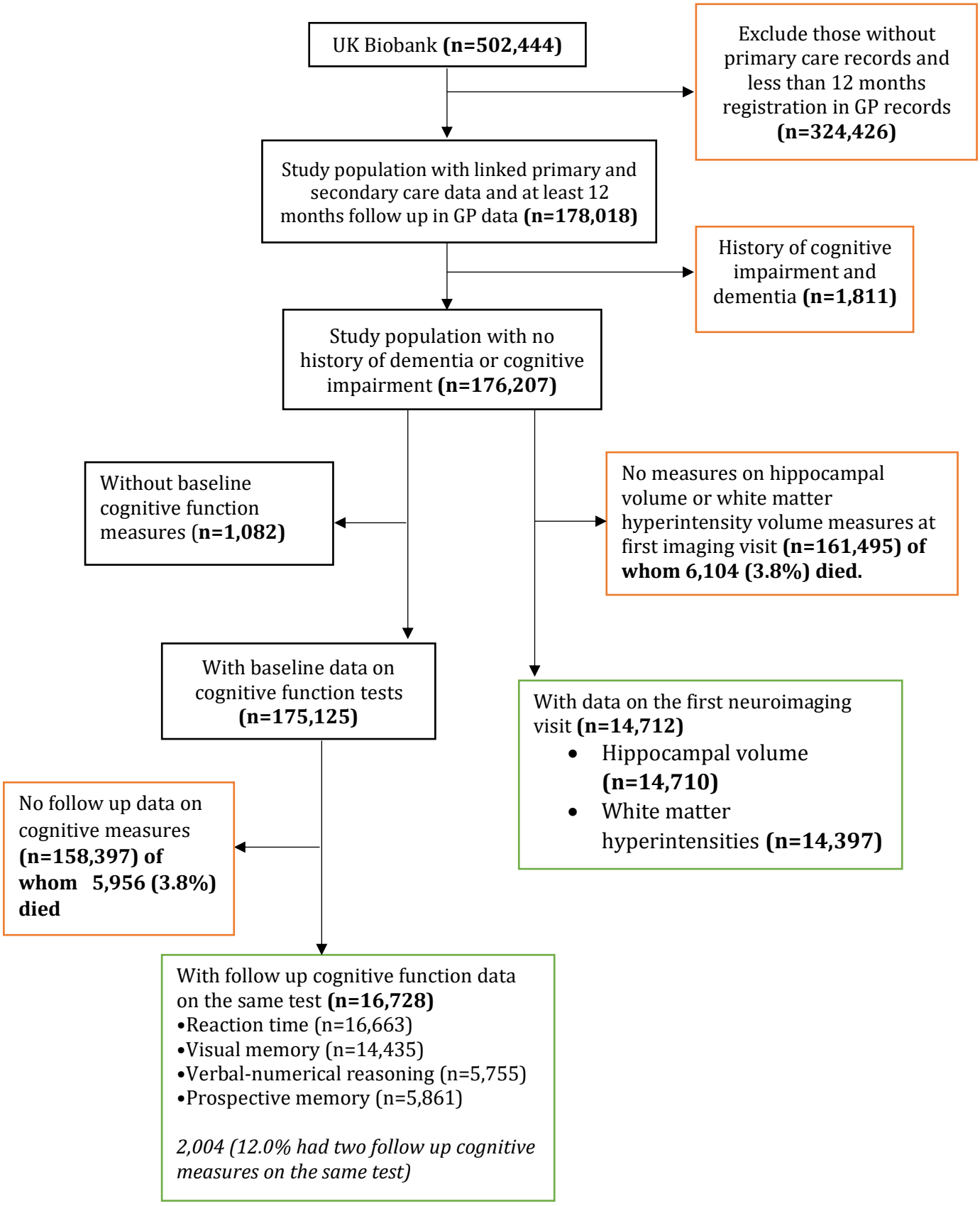


Figure 7.1. Flow chart of study population

Due to difficulties in collecting primary care data from different GP software providers, linkage to primary care data has been obtained by the UK Biobank for approximately 45% of the cohort.[199] Therefore, to minimise exposure misclassification, our study population was limited to only participants with linked primary and secondary care records (Figure 7.1). Baseline was defined as the date participants attended the UK Biobank baseline assessment. A subset of participants who lived within a 35km radius of the Stockport coordinating centre were invited via email to attend the first repeat assessment (2012 and 2013) and the first wave of the neuroimaging assessments (2014+). Cognitive function was assessed at all three assessments.

Our study explored two subsets of the UK Biobank population, a cognition subset and a separate neuroimaging subset. For our cognition analytical sample, we only included participants with valid measures of cognitive function completed at baseline and at least one follow-up measure on the same test. For our neuroimaging cohort, we included only participants with data on hippocampal or WMH volume who attended the first neuroimaging visit. Some participants attended the baseline and follow up cognition visits and as well as the neuroimaging visit and thus were included in both cohorts. We excluded participants with dementia or cognitive impairment at baseline in both cohorts using data from baseline questionnaires, nurse interview and linked primary and secondary care records.

Outcomes

Cognitive function

Participants completed a 15-minute battery of computerised cognitive function tests including measurement of reaction time which is referred to in this study as the mean correct response time test, visual memory (pairs matching test), fluid intelligence (assessing verbal-numerical reasoning) and prospective memory. Details of these tests have been reported elsewhere.[191] The association of these cognitive measures with age has been previously described by Cornelis et al.[253]

Our outcome measures for these tests were the mean correct response time (milliseconds) taken for a participant to correctly identify matching pairs of cards for reaction time (Data-field 404). For visual memory we assessed the total number of incorrect matches in participants who completed the test (Data-field 399). For fluid intelligence, we measured the total number of incorrect answers (Data-field 20016). For the prospective memory test participants were scored 0 for the correct answer and 1 for an incorrect answer at the first attempt (one minus data-field 20018). For all cognitive tests, lower scores indicated better cognitive performance.

Exposure

Our exposure was common infections which included sepsis, pneumonia, other LRTIs, UTIs and SSTIs. Sepsis is defined as a serious, life-threatening condition caused by a dysregulated host response following a range of infections.[83] Infections were identified in the 5 years up to UK Biobank participants' baseline assessment visit. This time period of 5 years was chosen due to issues with the completeness of historical linked primary care data. If participants were diagnosed with more than one infection during this

period, the infection date was taken from the earliest record of infection. Infections were defined using Read codes in linked primary care records and International Classification of Diseases (ICD)-10 codes in hospital records. To increase the specificity of our infection definition, participants were defined as having UTIs or SSTIs if they were also prescribed antibiotics on the same date as an infection diagnosis. Infection site, clinical setting of infections (general practitioner-recorded or hospital-recorded) frequency of infections and timing of infection (year(s) since infection diagnosis in the 5 years up to baseline) was explored in secondary analyses. For the analysis on infection frequency, infections diagnosed within 28 days of each other were classified as a single episode of infection.

Neuroimaging measures

Hippocampal volume (Data-fields 25019 and 25020) and WMH volume (Data-field 25781) were measured at the imaging visit from 2014 onwards (supplementary material). We assessed the total volume of WMH volume using postprocessed measured from T1 and T2 weighted fluid attenuation inversion recovery (FLAIR) imaging technique derived by the UK Biobank study.[195,197]

Covariates

Data from baseline assessment questionnaires, nurse interview and linked primary and secondary care data were used to define covariates. Demographic variables included age, sex and ethnicity (white, south Asian, black, mixed or other). Other demographic variables included education, defined as years in education using qualifications entered during baseline questionnaires. Years in education was coded based on the International Standard Classification of Education (ISCED) 1997 (supplementary table

1).[238,239] Socioeconomic status was measured using the Townsend Deprivation scores, based on residential post codes at baseline.[240] Potential lifestyle factors included body mass index (kg/m^2), smoking (never smoker, former smoker or current smoker), alcohol intake frequency (rarely or never, 1-8 times per month and 16 times per month) and physical activity (number of days a week where participants spent >10 minutes of moderate physical activity). Diabetes was ascertained using HbA1c, medical history at baseline questionnaire, nurse interview and linked electronic health records. Diabetes was included as a confounder and effect modifier. Other comorbidities also ascertained using self-reported information and linked primary and secondary care records include anxiety and depression, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, heart failure, hypertension, inflammatory bowel disease, multiple sclerosis, obstructive sleep apnoea, rheumatoid arthritis, psoriasis, severe mental illness, stroke and traumatic brain injury. Comorbidities ascertained in electronic health records were defined within 10 years prior to baseline. All code lists used in this study for linked primary and secondary care records can be accessed at: https://doi.org/10.17037/DATA.00002573.

Approval for the UK Biobank study was obtained from the North West Multi-Centre Research Ethics Committee and the present research was conducted under application number 7661. All participants of the study provided written informed consent. Ethical approval was also obtained from the London School of Hygiene and Tropical Medicine.

Statistical Analysis

Prior to conducting our analyses, we established the potential for bias in relation to participation into this study by describing the characteristics of participants included and excluded from our study. We found missing data on ethnicity, BMI, years in

education, alcohol consumption, smoking, physical activity and Townsend deprivation scores for the cognition and neuroimaging cohorts. Missing data was minimal (≤3.6% in total) in both cohorts and not all of these covariates were adjusted for in each analysis thus we used a complete case analysis for all analyses.

Association between common infections and cognitive decline

For each continuous cognitive measure (mean correct response time, visual memory and fluid intelligence), we fitted linear mixed models with random intercept and slope effects using an unstructured covariance matrix to estimate the rates of cognitive decline over follow up in participants with and without a history of common infections. Interaction terms were fitted between infections and time since baseline to assess the difference in cognitive decline over follow up. The beta coefficient represents the additional change in outcome per year for participants with infection compared to those without infections. Due to skewed distribution and zero value inflation of the visual memory error scores, a value of one was added to the scores which were then transformed using natural log. For the dichotomous test (prospective memory), we used logistic regression models for participants with correct recall at baseline to examine the association between common infections and cognitive decline with a binary variable (coded as 0 for correct recall and 1 for incorrect recall at follow up). For linear mixed models, minimally adjusted models included age, sex and an interaction term between time and infection. For all other analyses, minimally adjusted models included age and sex. For each analysis, we considered adjustment for all potential confounders described above and adjusted for covariates that changed the main association estimates by an important amount (approximately 10% change in association magnitude) in the fully adjusted model.

In our secondary analyses, we investigated the association between site (sepsis, pneumonia, other LRTIs, UTIs and SSTIs), clinical setting (GP or Hospital recorded infections), frequency (with the number of infections modelled as a continuous variable) and timing of infections prior to baseline (0 to <1 year, 1 to < 2 years, 2 to <3 years, 3 to <4 years and 4 to 5 years). Given the potential interaction between inflammatory comorbidities, such as diabetes, and dementia pathogenesis,[254] we explored whether the associations of infections on cognition differs by diabetes category (using a binary variable of diabetes) and tested for the presence of effect modification by fitting an interaction term. We performed additional analyses to compare the association of common infections on cognitive decline by age group (40-49, 50-59 and 60+) and sex. This is because increasing age is associated with greater trajectories of cognitive decline and some studies have reported sex differences in cognitive decline.[206,255]

Association of common infections with hippocampal and WMH volume

We log transformed WMH volume due to a positively skewed distribution. We used linear regression models to estimate the association between common infections and each structural neuroimaging measure. We used the same strategy to confounder adjustment as the approach described for our cognitive decline analyses. To aid interpretation, log transformed WMH volume was reported using exponentiated betas and was interpreted as percentages. For example, exponentiated beta 1.01 refers to a 1% increase in WMH volume.

Sensitivity analyses

We found evidence of non-normal distribution for the mean correct response time outcome. However, when we inverse or log transformed this variable, we were unable to fit the models due to unstable standard errors and models failing to converge. Thus, we used raw scores in our main analyses and in a sensitivity analysis we specified an independent covariance structure instead of unstructured which allowed us to re-run our models using the inverse transformed variable which showed evidence of a normal distribution (supplementary methods). We conducted a range of other sensitivity analyses which is described in further detail in supplementary table 2.

Statistical analyses were performed in Stata MP (version 16.0) and RStudio (version 4.1.0).

Results

Of the 176,207 participants with linked primary and secondary care records and no history of cognitive impairment or dementia at baseline, 16,728 had baseline and at least one follow-up cognitive measure on the same test of whom 2,004 (12.0%) had two follow up cognitive measures. 14,712 participants completed neuroimaging measurements at the first imaging visit (Figure 1.1). The mean time interval between baseline and the first or second repeat cognitive function assessment was 4.0 years (sd 0.78) and 8.27 years (sd 1.6), respectively. In our cognition cohort, the median age was 56.0 (IQR, 50.0-61.0) and 51.3% were female. 2,971 (17.8%) participants were diagnosed with a previous infection at least 5 years prior to baseline (Table 7.1). Compared to participants without follow up cognitive measures, participants included in our study were slightly younger, less likely to be female, had more years in education, fewer infections and performed better on baseline cognitive tests. Further descriptive

information on infections in participants included and excluded from the study is presented in supplementary table 3. Infection related mortality in participants excluded from the study was 323 (1.0%) compared to 5 (0.2%) for participants included in the study.

Table 7.1: Baseline Characteristics of participants included and excluded from the study for the cognitive function and neuroimaging cohorts

	Cohort with cognitive function measures		**Cohort with neuroimaging measures**	
Characteristics	Included (n=16,728)	Excluded because of no follow up cognition measures (158,383)	Included (14,712)	Excluded because of no neuroimaging measures (161,495)
Any Infection	2,971 (17.8%)	31,381 (19.8%)	2,435 (16.6%)	32,214 (19.9%)
Age at baseline assessment (mean)	55.59 (7.50)	56.73 (8.10)	54.82 (7.46)	56.79 (8.08)
Age at baseline assessment (median)	56.00 (50.00-61.00)	58.00 (50.00-63.00)	55.00 (49.00-61.00)	58.00 (50.00-63.00)
Age category				
40-44	1,650 (9.9%)	15,744 (9.9%)	1,680 (11.4%)	15,824 (9.8%)
45-49	2,458 (14.7%)	20,519 (13.0%)	2,336 (15.9%)	20,768 (12.9%)
50-54	2,887 (17.3%)	23,606 (14.9%)	2,781 (18.9%)	23,833 (14.8%)
55-59	3,721 (22.2%)	27,994 (17.7%)	3,267 (22.2%)	28,645 (17.7%)
60-64	4,048 (24.2%)	38,855 (24.5%)	3,231 (22.0%)	39,925 (24.7%)
65+	1,964 (11.7%)	31,665 (20.0%)	1,417 (9.6%)	32,500 (20.1%)
Women	8,576 (51.3%)	87,051 (55.0%)	7,781 (52.9%)	88,387 (54.7%)
Ethnicity				
White European	16,323 (97.6%)	150,683 (95.1%)	14,275 (97.0%)	153,339 (94.9%)
South Asian	110 (0.7%)	2,776 (1.8%)	135 (0.9%)	2,893 (1.8%)
African Caribbean	76 (0.5%)	1,630 (1.0%)	76 (0.5%)	1,670 (1.0%)
Mixed or other	177 (1.1%)	2,787 (1.8%)	185 (1.3%)	2,851 (1.8%)
Missing	42 (0.3%)	507 (0.3%)	41 (0.3%)	742 (0.5%)

Diabetes status				
No diabetes	14,762 (88.2%)	134,585 (85.0%)	13,203 (89.7%)	136,823 (84.7%)
Pre-diabetes	370 (2.2%)	5,109 (3.2%)	279 (1.9%)	5,256 (3.3%)
Undiagnosed diabetes	1,104 (6.6%)	10,157 (6.4%)	884 (6.0%)	10,579 (6.6%)
Controlled diabetes	362 (2.2%)	5,593 (3.5%)	256 (1.7%)	5,781 (3.6%)
Uncontrolled diabetes	130 (0.8%)	2,939 (1.9%)	90 (0.6%)	3,056 (1.9%)
Educational attainment (years in education)	16.63 (4.37)	14.73 (5.17)	16.75 (4.32)	14.72 (5.17)
Baseline BMI (mean)	26.74 (4.37)	27.57 (4.81)	26.53 (4.19)	27.58 (4.82)
Townsend deprivation score (mean)	-2.15 (2.53)	-1.38 (2.99)	-2.07 (2.56)	-1.38 (3.00)
Baseline number of days/week moderate physical activity >10 mins	3.00 (2.00-5.00)	3.00 (2.00-5.00)	3.00 (2.00-5.00)	3.00 (2.00-5.00)
Smoking status				
Never Smoker	12,060 (72.1%)	104,733 (66.1%)	10,670 (72.5%)	106,714 (66.1%)
Ex-Smoker	3,650 (21.8%)	36,455 (23.0%)	3,138 (21.3%)	37,117 (23.0%)
Current smoker	1,001 (6.0%)	16,901 (10.7%)	889 (6.0%)	17,141 (10.6%)
Missing	17 (0.1%)	294 (0.2%)	15 (0.1%)	523 (0.3%)
Baseline alcohol intake frequency				
Rarely or never	2,192 (13.1%)	31,244 (19.7%)	1,860 (12.6%)	31,965 (19.8%)
1-8 times per month	6,159 (36.8%)	59,815 (37.8%)	5,399 (36.7%)	60,854 (37.7%)
16 times per month-every day	8,374 (50.1%)	67,161 (42.4%)	7,447 (50.6%)	68,290 (42.3%)
Missing	<5	163 (0.1%)	6 (0.0%)	386 (0.2%)
Comorbidities				
Anxiety and depression	1,968 (11.8%)	20,832 (13.2%)	1,660 (11.3%)	21,332 (13.2%)
Severe mental illness	187 (1.1%)	2,150 (1.4%)	155 (1.1%)	2,216 (1.4%)
Inflammatory bowel disease	708 (4.2%)	7,788 (4.9%)	611 (4.2%)	7,947 (4.9%)
Multiple Sclerosis	51 (0.3%)	612 (0.4%)	41 (0.3%)	630 (0.4%)

Rheumatoid Arthritis	155 (0.9%)	2,269 (1.4%)	126 (0.9%)	2,314 (1.4%)
Psoriasis	460 (2.7%)	4,227 (2.7%)	402 (2.7%)	4,309 (2.7%)
Asthma	2,099 (12.5%)	20,981 (13.2%)	1,835 (12.5%)	21,410 (13.3%)
Chronic kidney disease	141 (0.8%)	1,950 (1.2%)	119 (0.8%)	1,995 (1.2%)
Chronic liver disease	479 (2.9%)	6,576 (4.2%)	328 (2.2%)	6,789 (4.2%)
Chronic obstructive pulmonary disease	114 (0.7%)	2,798 (1.8%)	75 (0.5%)	2,881 (1.8%)
Heart failure	208 (1.2%)	4,233 (2.7%)	149 (1.0%)	4,379 (2.7%)
Hypertension	2,613 (15.6%)	33,785 (21.3%)	1,982 (13.5%)	34,747 (21.5%)
Obstructive sleep apnoea	126 (0.8%)	1,547 (1.0%)	97 (0.7%)	1,591 (1.0%)
Stroke	116 (0.7%)	1,756 (1.1%)	80 (0.5%)	1,815 (1.1%)
Traumatic brain injury	118 (0.7%)	1,260 (0.8%)	92 (0.6%)	1,299 (0.8%)
Baseline cognitive function test performance				
Mean correct response time score baseline (milliseconds)	540.33 (102.23)	561.26 (118.80)	536.20 (99.76)	549.31 (106.86)
Pairs matching test score (incorrect matches)	5.14 (2.94)	5.50 (3.25)	5.07 (2.84)	5.30 (3.14)
Fluid intelligence test score (incorrect answers)	6.25 (2.03)	7.08 (2.14)	6.25 (2.03)	6.25 (2.02)
Prospective Memory test (incorrect answer)	761 (13.0%)	14,323 (24.6%)	532 (12.7%)	229 (13.7%)

For data protection, table cells containing fewer than 5 participants were recorded as '<5'. Lower cognitive function scores indicated better cognitive performance for all cognitive tests used in this study (mean correct response time, pairs matching, fluid intelligence and prospective memory)

Characteristics of participants included in the two subsets of our study, one with follow up cognitive measures and the other who attended the first imaging visit, are presented in Table 7.2. 11, 455 participants were included in both the cognitive function and neuroimaging cohorts. In our cognition cohort, participants with a history of infection were slightly older (supplementary figure 1), more likely to be female (57.9%) and to

have a greater proportion of comorbidities compared to those without a history of infection. In terms of infection site, 1,681 (10.1%) participants in the cognition cohort had other LRTIs, 674 (4.0%) had UTIs, 532 (3.2%) had skin and soft tissue infections, 45 (0.3%) had pneumonia, 23 (0.1%) had sepsis and 6 (0.0%) had multiple infection diagnoses on the same date from different infection sites. For clinical setting of infections, 2770 (93.2%) had GP recorded infections and 201 (6.8%) had a hospital recorded infection.

Table 7.2. Baseline characteristics of participants included in the study with data on cognitive function measures and neuroimaging outcomes, stratified by history of common infections

Characteristics	**Cohort with cognitive function measures (N=16,728)**		**Cohort with neuroimaging measures (N=14,712)**	
	No Infection (N=13,757)	**Any Infection (N=2,971)**	**No Infection (N=12,277)**	**Any Infection (N=2,435)**
Age at baseline assessment (mean)	55.42 (7.50)	56.35 (7.43)	54.70 (7.45)	55.46 (7.49)
Age at baseline assessment (median)	56.00 (49.00-61.00)	57.00 (51.00-62.00)	55.00 (49.00-61.00)	56.00 (49.00-61.00)
Age category (years)				
40-44	1,415 (10.3%)	235 (7.9%)	1,442 (11.7%)	238 (9.8%)
45-49	2,054 (14.9%)	404 (13.6%)	1,963 (16.0%)	373 (15.3%)
50-54	2,410 (17.5%)	477 (16.1%)	2,365 (19.3%)	416 (17.1%)
55-59	3,056 (22.2%)	665 (22.4%)	2,716 (22.1%)	551 (22.6%)
60-64	3,279 (23.8%)	769 (25.9%)	2,648 (21.6%)	583 (23.9%)
65+	1,543 (11.2%)	421 (14.2%)	1,143 (9.3%)	274 (11.3%)
Women	6,856 (49.8%)	1,720 (57.9%)	6,318 (51.5%)	1,463 (60.1%)
Ethnicity				
White European	13,417 (97.5%)	2,906 (97.8%)	11,910 (97.0%)	2,365 (97.1%)
South Asian	90 (0.7%)	20 (0.7%)	110 (0.9%)	25 (1.0%)

African Caribbean	59 (0.4%)	17 (0.6%)	61 (0.5%)	15 (0.6%)
Mixed or other	155 (1.1%)	22 (0.7%)	158 (1.3%)	27 (1.1%)
Missing	36 (0.3%)	6 (0.2%)	38 (0.3%)	<5
Diabetes category				
No Diabetes	12,229 (88.9%)	2,533 (85.3%)	11,062 (90.1%)	2,141 (87.9%)
Pre-diabetes	276 (2.0%)	94 (3.2%)	220 (1.8%)	59 (2.4%)
Undiagnosed diabetes	891 (6.5%)	213 (7.2%)	721 (5.9%)	163 (6.7%)
Controlled diabetes	267 (1.9%)	95 (3.2%)	205 (1.7%)	51 (2.1%)
Uncontrolled diabetes	94 (0.7%)	36 (1.2%)	69 (0.6%)	21 (0.9%)
Educational attainment (years in education)	16.72 (4.3)	16.20 (4.5)	16.85 (4.3)	16.20 (4.5)
Baseline BMI (mean)	26.58 (4.2)	27.45 (4.9)	26.42 (4.1)	27.10 (4.6)
Townsend deprivation score (mean)	-2.16 (2.5)	-2.12 (2.5)	-2.09 (2.6)	-2.01 (2.6)
Baseline number of days/week moderate physical activity >10 mins	3.00 (2.00-5.00)	3.00 (2.00-5.00)	3.00 (2.00-5.00)	3.00 (2.00-5.00)
Smoking status				
Never Smoker	9,994 (72.6%)	2,066 (69.5%)	8,989 (73.2%)	1,681 (69.0%)
Ex-Smoker	2,931 (21.3%)	719 (24.2%)	2,548 (20.8%)	590 (24.2%)
Current smoker	820 (6.0%)	181 (6.1%)	729 (5.9%)	160 (6.6%)
Missing	12 (0.1%)	5 (0.2%)	11 (0.1%)	<5
Baseline alcohol intake frequency				
Rarely or never	1,752 (12.7%)	440 (14.8%)	1,510 (12.3%)	350 (14.4%)
1-8 times per month	5,036 (36.6%)	1,123 (37.8%)	4,497 (36.6%)	902 (37.0%)
16 times per month- every day	6,968 (50.7%)	1,406 (47.3%)	6,266 (51.0%)	1,181 (48.5%)
Missing	<5	<5	<5	<5
Comorbidities				
Anxiety and depression	1,494 (10.9%)	474 (16.0%)	1,262 (10.3%)	398 (16.3%)

Severe mental illness	149 (1.1%)	38 (1.3%)	126 (1.0%)	29 (1.2%)
Inflammatory bowel disease	519 (3.8%)	189 (6.4%)	462 (3.8%)	149 (6.1%)
Multiple Sclerosis	34 (0.2%)	17 (0.6%)	30 (0.2%)	11 (0.5%)
Rheumatoid Arthritis	112 (0.8%)	43 (1.4%)	94 (0.8%)	32 (1.3%)
Psoriasis	362 (2.6%)	98 (3.3%)	319 (2.6%)	83 (3.4%)
Asthma	1,511 (11.0%)	588 (19.8%)	1,380 (11.2%)	455 (18.7%)
Chronic kidney disease	112 (0.8%)	29 (1.0%)	100 (0.8%)	19 (0.8%)
Chronic liver disease	359 (2.6%)	120 (4.0%)	249 (2.0%)	79 (3.2%)
Chronic obstructive pulmonary disease	44 (0.3%)	70 (2.4%)	28 (0.2%)	47 (1.9%)
Heart failure	143 (1.0%)	65 (2.2%)	113 (0.9%)	36 (1.5%)
Hypertension	2,020 (14.7%)	593 (20.0%)	1,574 (12.8%)	408 (16.8%)
Obstructive sleep apnoea	86 (0.6%)	40 (1.3%)	77 (0.6%)	20 (0.8%)
Stroke	88 (0.6%)	28 (0.9%)	58 (0.5%)	22 (0.9%)
Traumatic brain injury	88 (0.6%)	30 (1.0%)	67 (0.5%)	25 (1.0%)

For data protection, table cells containing fewer than 5 participants were recorded as '<5'.

Figure 7.2 and Table 7.3 show no evidence for differences in cognitive performance change over follow up in participants with a history of any infections compared to those without infections for the mean correct response time (estimated difference in slope [infections versus no infections] = 0.40 milliseconds, 95% CI: -0.17 - 0.96 per year), visual memory (estimated difference in slope 0.00036 log errors per year, 95% CI: (-0.0034 - 0.0041), fluid intelligence (estimated difference in slope 0.0066, 95% CI: -0.010-0.023) and prospective memory tests (OR 0.88, 95% CI: 0.68-1.14). No association was found between the site and clinical setting of infections with cognitive decline for any of the tests, with the exception of visual memory. The log of the visual memory errors increased by 0.011 (95% CI: 0.0037-0.018) per year in participants with

a history of UTIs compared to those with no prior infection. Results for the association of sepsis and pneumonia with cognitive decline were not presented due to a small number of participants diagnosed with these infections (23 and 45 participants, respectively).

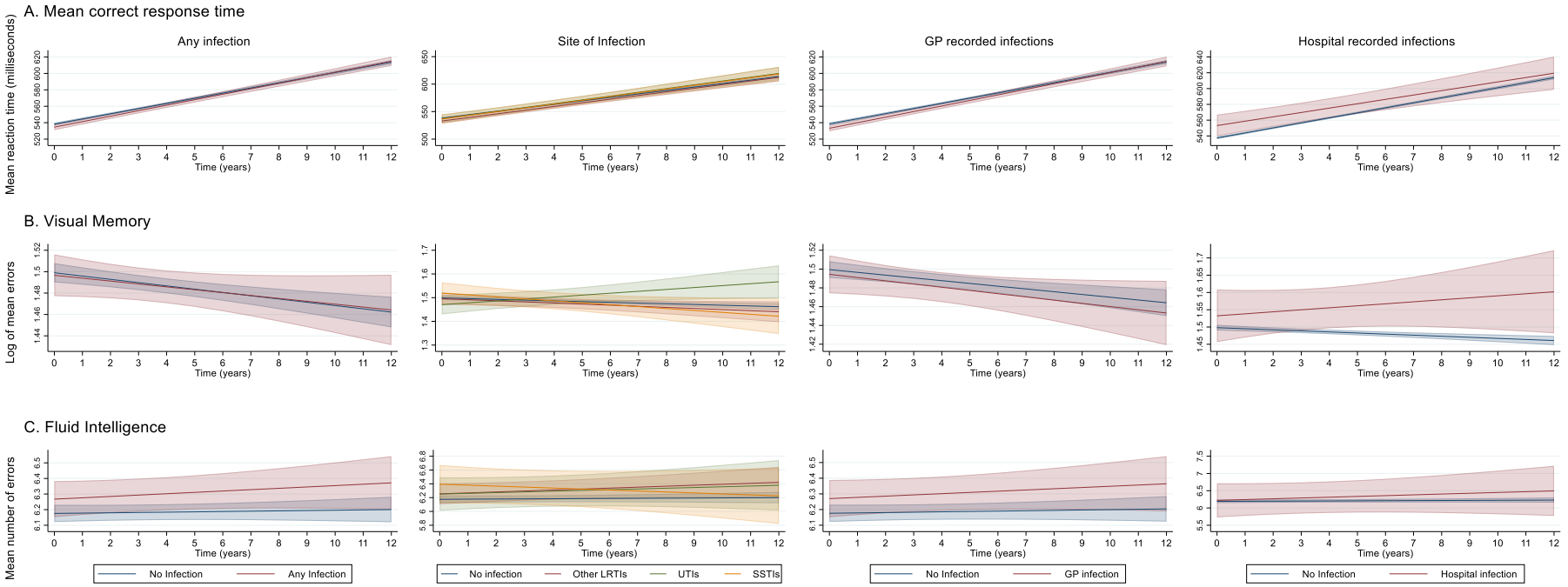


Figure 7.2. Association of presence, site and setting (GP and hospital) with changes in cognitive performance over follow up
Linear mixed models with random intercept and slope used to illustrate fitted changes in cognitive function over time for the mean correct response time, visual memory (log transformed) and fluid intelligence test. **A.** Mean correct response time models adjusted for age, sex, time, baseline test score, interaction term with time x infection status, ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. **B.** Visual memory models adjusted for age, sex, time, baseline test score, interaction term with time x infection status, ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. **C.** Fluid intelligence models adjusted for age, sex, time, baseline test score, interaction term with time x infection status and years in education.

Table 7.3. Association of site and clinical setting of common infections with cognitive decline

	Minimally adjusted			**Fully adjusted model**		
	No. of participants	**β (95% CI)**	**P value**	**No. of participants**	**β (95% CI)**	**P value**
Mean correct response time (Difference in slope compared with no infection)						
Site of infection						
No infection	13,707	Reference		13,275	Reference	
Any infection	2,956	0.47 (-0.09 to 1.03)	0.10	2,809	0.40 (-0.17 to 0.96)	0.17
LRTIs	1,682	0.50 (-0.21 to 1.22)	0.17	1,598	0.34 (-0.39 to 1.07)	0.37
UTIs	672	0.39 (-0.70 to 1.47)	0.49	636	0.57 (-0.54 to 1.68)	0.31
SSTI	529	0.63 (-0.58 to 1.84)	0.31	507	0.53 (-0.70 to 1.75)	0.40
Clinical setting of infection						
No infection	13,906	Reference		13,463	Reference	
GP infection	2,757	0.56 (-0.02 to 1.13)	0.06	2,621	0.50 (-0.09 to 1.08)	0.10
No infection	16,464	Reference		15,896	Reference	
Hospital recorded infections	199	-0.62 (-2.50 to 1.27)	0.52	188	-0.83 (-2.76 to 1.09)	0.40
Visual memory (Difference in slope compared with no infection)						
Site of infection						
No infection	11,873	Reference		11,481	Reference	
Any infection	2,562	0.00 (-0.00 to 0.00)	0.73	2,436	0.00036 (-0.0034 to 0.0041)	0.85
LRTIs	1,461	-0.0016 (-0.0063 to 0.00)	0.52	1,387	-0.0015 (-0.0064 to 0.0033)	0.53
UTIs	579	0.011 (0.0040 to 0.018)	0.002	548	0.011 (0.0037 to 0.018)	0.003
SSTI	459	-0.0040 (-0.012 to 0.0040)	0.33	441	-0.0051 (-0.013 to 0.0030)	0.22
Clinical setting of infection						
No infection	12,041	Reference		11,639	Reference	
GP infection	2,394	-0.00029 (-0.0041 to 0.0035)	0.88	2,278	-0.00049 (-0.0044 to 0.0034)	0.80
No infection	14,267	Reference		13,759	Reference	
Hospital recorded infections	168	0.010 (-0.0024 to 0.022)	0.11	158	0.0089 (-0.0039 to 0.022)	0.17

Fluid intelligence (Difference in slope compared with no infection)						
Site of infection						
No infection	4,685	Reference		4,673	Reference	
Any infection	1,070	0.0063 (-0.010 to 0.023)	0.46	1,066	0.0066 (-0.010 to 0.023)	0.44
LRTIs	619	0.012 (-0.0091 to 0.033)	0.27	616	0.011 (-0.0092 to 0.033)	0.27
UTIs	245	0.0083 (-0.025 to 0.041)	0.62	244	0.0086 (-0.024 to 0.042)	0.61
SSTI	184	-0.018 (-0.055 to 0.019)	0.34	184	-0.0162 (-0.053 to 0.021)	0.39
Clinical setting						
No infection	4,743	Reference		4,731	Reference	
GP infection	1,012	0.0051 (-0.012 to 0.022)	0.56	1,008	0.0055 (-0.012 to 0.023)	0.53
No infection	5,697	Reference		5,681	Reference	
Hospital recorded infections	58	0.021 (-0.044 to 0.085)	0.53	58	0.020 (-0.044 to 0.084)	0.55
Prospective memory	**No. of participants**	**OR (95% CI)**	**P value**	**No. of participants**	**OR (95% CI)**	**P value**
Site of infection						
No infection	4,174	Reference		4,083	Reference	
Any infection	926	0.83 (0.65 to 1.06)	0.14	894	0.88 (0.68 to 1.14)	0.33
LRTIs	549	072 (0.54 to 0.97)	0.03	532	0.76 (0.56 to 1.03)	0.07
UTIs	204	0.82 (0.51 to 1.33)	0.42	198	0.88 (0.53 to 1.46)	0.63
SSTI	154	1.58 (0.77 to 3.26)	0.21	147	1.74 (0.80 to 3.75)	0.16
Clinical setting						
No infection	4,221	Reference		4,127	Reference	
GP infection	879	0.82 (0.64 to 1.06)	0.13	850	0.88 (0.68 to 1.14)	0.33
No infection	5,053	Reference		4,933	Reference	
Hospital infection	47	1.07 (0.38 to 2.99)	0.90	44	0.95 (0.34 to 2.69)	0.93
Linear Mixed models results with random intercept and random slope. The associations of site of infection, GP infection and hospital infection were not assessed in the same model but rather in three separate models. For analyses on site of infections, participants with pneumonia, sepsis or multiple infections recorded on the same date where not included. For mean correct response time, visual memory (log transformed) and fluid intelligence tests, minimally adjusted: age, sex, time, baseline test score and time x						

infection status interaction term which represents the rate of decline by presence of infection with the difference in slope compared to that of no infection (reference group). For mean correct response time, fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models additionally adjusted for ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the fluid intelligence test, fully adjusted models additionally included years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. Minimally adjusted models for this test include age and sex and fully adjusted models additionally adjusted for physical activity in the fully adjusted models. Bold values indicate that the change in cognitive performance varies significantly over follow up in participants with infection compared to those without infection.

Table 7.4 shows that the increase over time in the log of visual memory errors was slightly steeper by 0.0064 (95% CI 0.0019 to 0.011) per year, for every additional infection. No association was found between the number of infections beyond the first and cognitive decline in all other cognitive tests.

Table 7.4. Association of frequency of common infections with cognitive decline

	Minimally adjusted			**Fully adjusted model**		
	No. of participants	**β (95% CI)**	**P value**	**No. of participants**	**β (95% CI)**	**P value**
Mean correct response time (Difference in slope compared with no infection)						
No infection	14,494	Reference		14,006	Reference	
First infection	2,169	0.26 (-0.37 to 0.89)	0.42	2,078	0.13 (-0.51 to 0.77)	0.68
Second or more infections (continuous)	817	-0.22 (-0.91 to 0.46)	0.52	760	-0.25 (-0.96 to 0.47)	0.50
Visual memory (Difference in slope compared with no infection)						
No infection	12,575	Reference		12,136	Reference	
First infection	1,860	0.00 (-0.00 to 0.0052)	0.63	1,781	0.00089 (-0.0034 to 0.0051)	0.68
Second or more infections +(continuous)	728	0.0059 (0.0018 to 0.010)	0.005	679	0.0064 (0.0019 to 0.011)	0.005
Fluid intelligence (Difference in slope compared with no infection)						
No infection	4,975	Reference		4,961	Reference	
First infection	780	0.0048 (-0.014 to 0.024)	0.61	778	0.0052 (-0.014 to 0.024)	0.59
Second or more infections +(continuous)	297	-0.014 (-0.039 to 0.012)	0.31	295	-0.014 (-0.040 to 0.011)	0.27
Prospective memory						
	No. of participants	**OR (95% CI)**	**P value**	**No. of participants**	**OR (95% CI)**	**P value**
No infection	4,424	Reference		4,322	Reference	
First infection	676	0.78 (0.59 to 1.02)	0.07	655	0.79 (0.60 to 1.05)	0.10
Second or more infections +(continuous)	256	0.88 (0.67 to 1.16)	0.36	245	0.89 (0.66 to 1.21)	0.47

Linear Mixed models results with random intercept and random slope. For mean correct response time, visual memory (log transformed) and fluid intelligence tests, minimally adjusted: age, sex, time, baseline test score and time x infection status interaction term which represents the rate of decline by presence of infection with the difference in slope compared to that of no infection (reference group). Bold values for continuous measures indicate that the change in cognitive performance per year for every one unit increase in the number of infections after the first infection. For mean correct response time, fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes, anxiety and

depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models additionally adjusted for ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the fluid intelligence test, fully adjusted models additionally included years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. Minimally adjusted models for this test include age and sex and fully adjusted models additionally adjusted for physical activity in the fully adjusted models.

Figure 7.3 depicts the association between the timing of infections in the 5 years prior to baseline and cognitive decline in fully adjusted models. We found no association between common infections in each year prior to baseline and cognitive decline according to any of the cognitive tests.

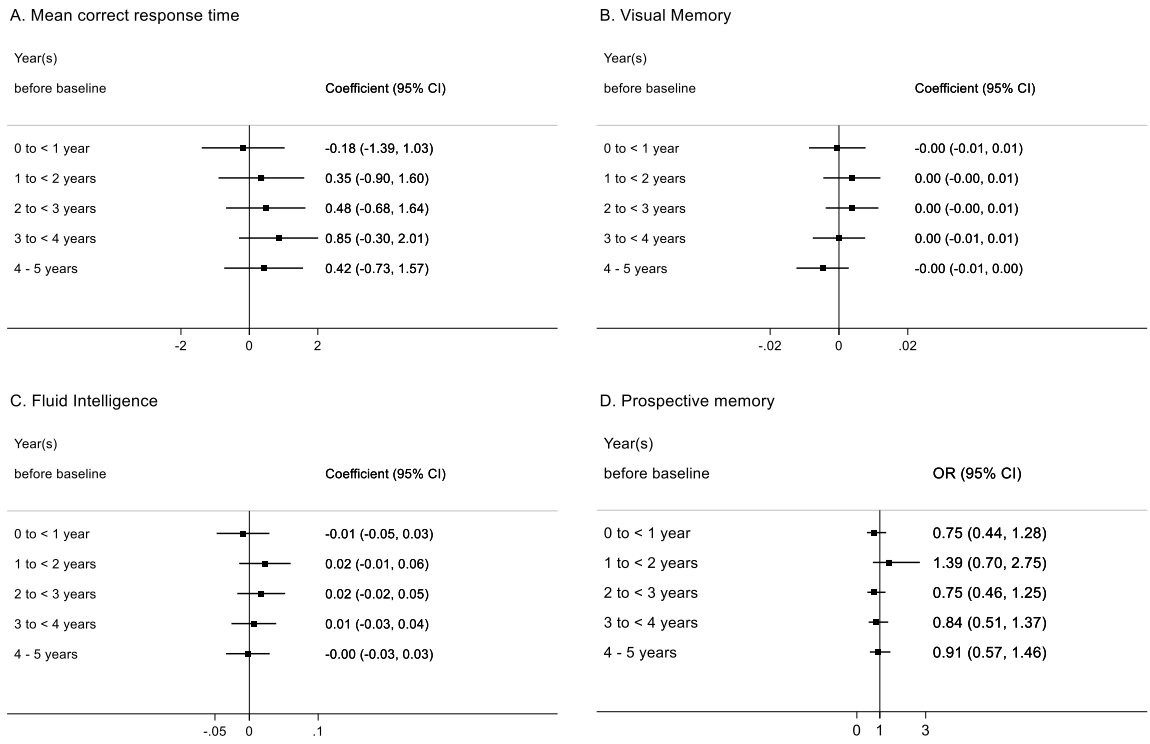


Figure 7.3. Association of common infections and cognitive decline, stratified by timing of common infections in the five years prior to baseline

Linear Mixed models results with random intercept and random slope. For mean correct response time, visual memory (log transformed) and fluid intelligence tests, minimally adjusted: age, sex, time, baseline test score and time x infection status interaction term which represents the rate of cognitive decline by presence of infection with the difference in slope of infection compared to that of no infection (reference group). For mean correct response time, fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes category, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models additionally adjusted for ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes status, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the verbal-numerical reasoning test, fully adjusted models additionally included years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. Minimally adjusted models for this test include age and sex and fully adjusted models additionally adjusted for physical activity in the fully adjusted models.

Association between infections and neuroimaging outcomes

Figure 7.4 shows that a history of any common infections and LRTIs excluding pneumonia was associated with a 5% higher WMH volume compared to no prior infection in minimally adjusted models. In fully adjusted analyses, the difference reduced to a 2% higher WMH volume for those with infections, however, the association was no longer statistically significant. No association was found between the presence or site of infections with hippocampal volume in minimally or fully adjusted models.

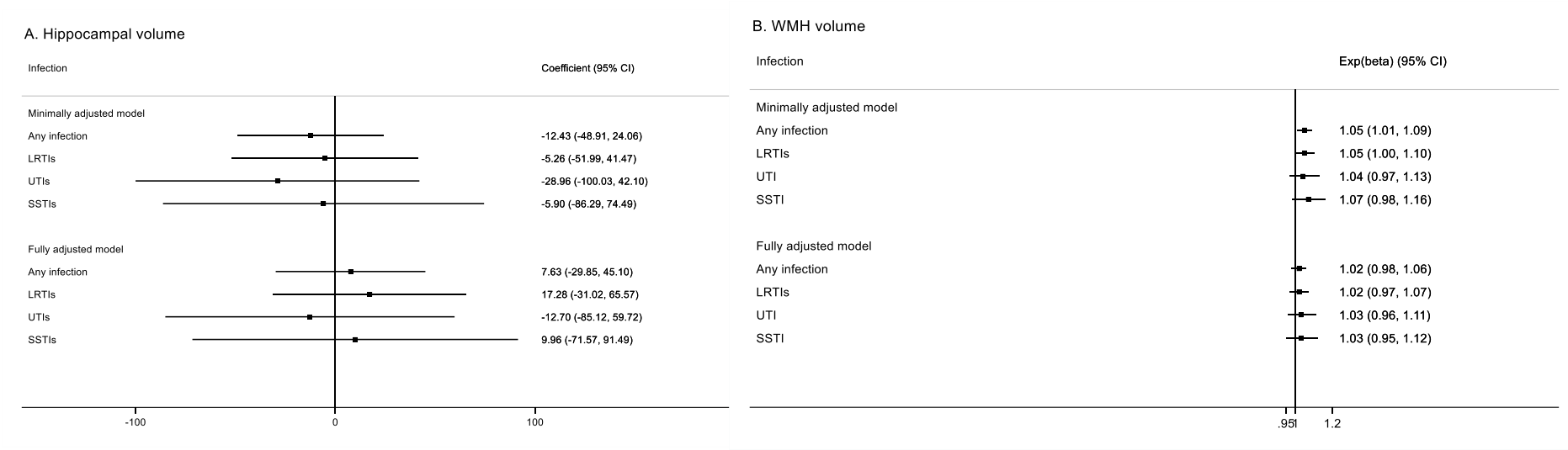


Figure 7.4. Association of presence and site of common infections with hippocampal volume and WMH volume
WMH; White matter hyperintensities. **A.** represents the association between common infections and hippocampal volume. Minimally adjusted models for adjusted for age and sex. Fully adjusted models additionally adjusted for ethnicity, BMI, smoking, physical activity, alcohol consumption, years in education, diabetes, chronic obstructive pulmonary disease, asthma and hypertension (n=14,239). **B.** represents the association of common infections with WMH volume. Minimally adjusted models for B adjusted for age and sex and fully adjusted models additionally adjusted for BMI, smoking and hypertension (14,357).

Additional secondary analyses and sensitivity analyses

In further additional secondary analyses, we found evidence of an interaction by diabetes for mean correct response time (p for interaction=0.015). Participants with diabetes and infections performed better on mean correct response time compared to participants with diabetes and no infection. In stratified results, there was no association between common infections and cognitive decline in any of the cognitive tests in people with and without diabetes (supplementary table 4). We found no difference by sex and age in the association between infections and cognitive decline for any of the cognitive measures (supplementary tables 5 and 6). Our sensitivity analyses did not materially change our conclusions (supplementary tables 7 – 11).

Discussion

To our knowledge, this is the largest longitudinal study to date examining the association of common infections occurring in midlife with subclinical markers of dementia risk (cognitive decline, hippocampal volume and WMH volume). We did not find an association between common infections and cognitive decline for any of the cognitive measures, with the exception of visual memory. We found small associations between UTIs and an increasing number of infections with worsening of performance on the visual memory test over follow up. Regarding neuroimaging measures, common infections were not associated with lower hippocampal volume or higher WMH volume.

Previous studies

Evidence from previous studies has yielded mixed findings. A US case-control study of 4,802 intensive care unit survivors (ICU) with a mean age of 65.9 years did not find an association between sepsis and cognitive decline.[256] ICU stay and sepsis are associated

with mortality risk as such the competing risk of mortality in ICU survivors with sepsis may have weakened the associations in this study.[257,258] Two prospective US studies with a mean/median age of 76.9 years or 77 (IQR, 70-83) found that pneumonia or severe sepsis hospitalisation was associated with increased odds of moderate to severe cognitive impairment.[105,106]

Differences in our findings compared to previous studies may be due to heterogeneity in populations studied including their ages, clinical setting, site of infection, cognitive measures and domains assessed, and study design. Participants in our study were younger (mean age 55.6 and median age and 56.00 [IQR, 50.00-61.00]) than those in previous studies. Therefore, given that age is the single greatest risk factor for dementia, with the risk doubling every 5 years after the age of 65, differences in age groups could be explain discrepancies between our findings and those of previous studies.[67] We found no association between hospitalised infections with cognitive decline, however, these findings could have been due to the nature of the population studied, the aforementioned limitations of the cognitive measures, and also a reduced power to detect an association as only a small subset of 201 (6.8%) participants with infections had hospitalised infections. The numbers of participants with hospitalised infections in previous studies ranged from 827 to 1529 participants. Previous studies only assessed sepsis or pneumonia as individual exposures; however, our study had insufficient statistical power to study the association of these infections with cognitive decline individually. Given that exposed participants in our study were predominantly diagnosed with more mild infections (GP recorded infections and other LRTIs), this may explain the lack of association observed and discrepancies with previous studies as it is hypothesised that more severe systemic infections may be more likely to trigger the

release of pro-inflammatory cytokines and induce systemic inflammation (or other pathways) which may lead to cognitive decline or dementia. [259]

The only study to investigate the association of common infections other than pneumonia or sepsis with cognitive decline was a Danish cohort study of 161,696 individuals which found an association between infections resulting in hospitalisation including respiratory, urological and skin infections with lower general cognitive scores using a Danish intelligence test.[260] However, the generalisability of these findings is limited by the selective population of young adult male recruits (mean age of 19.4 years old) and the fact that cognitive function was assessed at one time point during the study meant that changes in cognition over time were not assessed.

Regarding neuroimaging measures, two case-control studies found lower hippocampal volume in hospitalised individuals with sepsis compared to healthy controls. Studies were limited either by their small study size and one study had inadequately matched controls. Differences in study design and statistical method limited comparability of these studies with our findings.[261,262] Previous studies reveal the presence of white matter lesions in septic shock patients who developed acute brain dysfunction, however, studies examining the association of common, predominantly bacterial infections, other than sepsis with WMH or hippocampal volume are scarce.[263]

An explanation for our findings of no association between infections, cognitive decline, hippocampal or WMH volume could be that these neuroimaging or cognitive measures may have lacked sufficient sensitivity to detect subtle brain changes following infection in the prodromal phases. Our finding of a small association between UTIs and increasing

numbers of infections with cognitive decline and evidence of effect modification by diabetes on the visual memory test needs to be interpreted with caution. Given the number of analyses on multiple cognitive tests assessed in this study, it is possible that these findings may have occurred by chance, thus caution must be applied when interpreting these results.

Strengths and Limitations

Strengths of this study include the large size of the study population and the use of repeated cognitive assessments over follow up assessing four individual domains of cognition. The extensive information on sociodemographic and lifestyle factors and comorbidities linked to primary and secondary care electronic health records allowed for the adjustment of multiple confounding variables. Further we explored medically recorded common infections by infection site, severity, timing and dose response as well as conducting extensive secondary and sensitivity analyses.

However, there are a number of important limitations to consider. First, selection bias was likely given that participants with poorer cognitive ability and fewer years in education were more likely to have no follow up cognitive measures in our study. This selective attrition would likely underestimate any associations of infections with cognitive decline thus biasing our estimates towards the null. Second, our findings may also have been influenced by a potential practice effect in which participants' performance on the same cognitive tests improved during follow up due to familiarity with the test.[264] Although both infected and uninfected groups would have been expected to have a similar benefit of practice, these practice effects may dilute any differences between the two groups therefore potentially masking any association of

infections on cognitive decline.[191,264] Third, cognitive tests were non-standardised and there were differences in how the tests were conducted at baseline and during follow-up with the pairs matching and fluid intelligence tests completed online or at the assessment centre. However, for the present study, we only included tests completed at the assessment centre. Visual memory test results had poor correlation between the baseline and the first repeat assessment (r=0.16) which will likely have led to non-differential measurement error biasing effect estimates towards the null.[191] Fourth, although we assessed a wide range of covariates as potential confounders, as with all observational studies we cannot rule out the possibility of residual confounding through unmeasured confounders e.g. frailty. Fifth, we restricted our analyses to only infections diagnosed within 5 years prior to baseline, therefore, infections occurring prior to this period were not included in our primary analyses which may underestimate our associations and bias our effect estimates towards the null. However, sensitivity analyses excluding participants diagnosed with infections during follow-up did not materially change our conclusions. Sixth, participants in our study had a mean age of approximately 55 years old which may limit the generalisability of our findings to older adults, who are at a greater risk of cognitive decline and dementia. Lastly, our study population was healthier than the general population and had more years in education compared to those excluded during follow-up. This may have delayed cognitive decline during follow up, thus reducing the ability to detect a significant association between infections and cognitive decline.

Future studies

Our findings highlight the need for further studies to assess the potential effects of common infections on cognition at different life stages and in more representative

populations, including ethnic and other diversity with sufficient sample sizes to test different types of infection. These need careful attention to loss to follow up as well as incorporating the impacts of mortality. We excluded participants with evidence of cognitive impairment or dementia before their baseline assessment. Given cognitive decline following infection hospitalisation has been suggested to be accelerated in individuals with dementia[251], it is important for further studies to explore trajectories of cognitive decline in people with pre-existing cognitive impairment or dementia following infection**.** Neuroimaging measures were assessed at one time point in our study and future studies could investigate the longitudinal changes in hippocampal and WMH volume over time in individuals with and without infections.

Conclusion

In summary, our findings extend the scarce literature on infections, cognitive decline and neuroimaging measures into a younger age group than the majority of previous studies. We found no evidence of accelerated cognitive decline in people across the age groups of 40-69 (at UK Biobank recruitment) with a history of common infections occurring in midlife compared to those without infections in all cognitive tests except for visual memory in the UK Biobank cohort. A small association was found between UTIs and second and subsequent infections with cognitive decline on the visual memory test. Our findings on visual memory should be interpreted with caution and further studies are needed to confirm our results. Further studies are needed to confirm our findings.

Conflicts of interest

The authors declare no conflicts of interest.

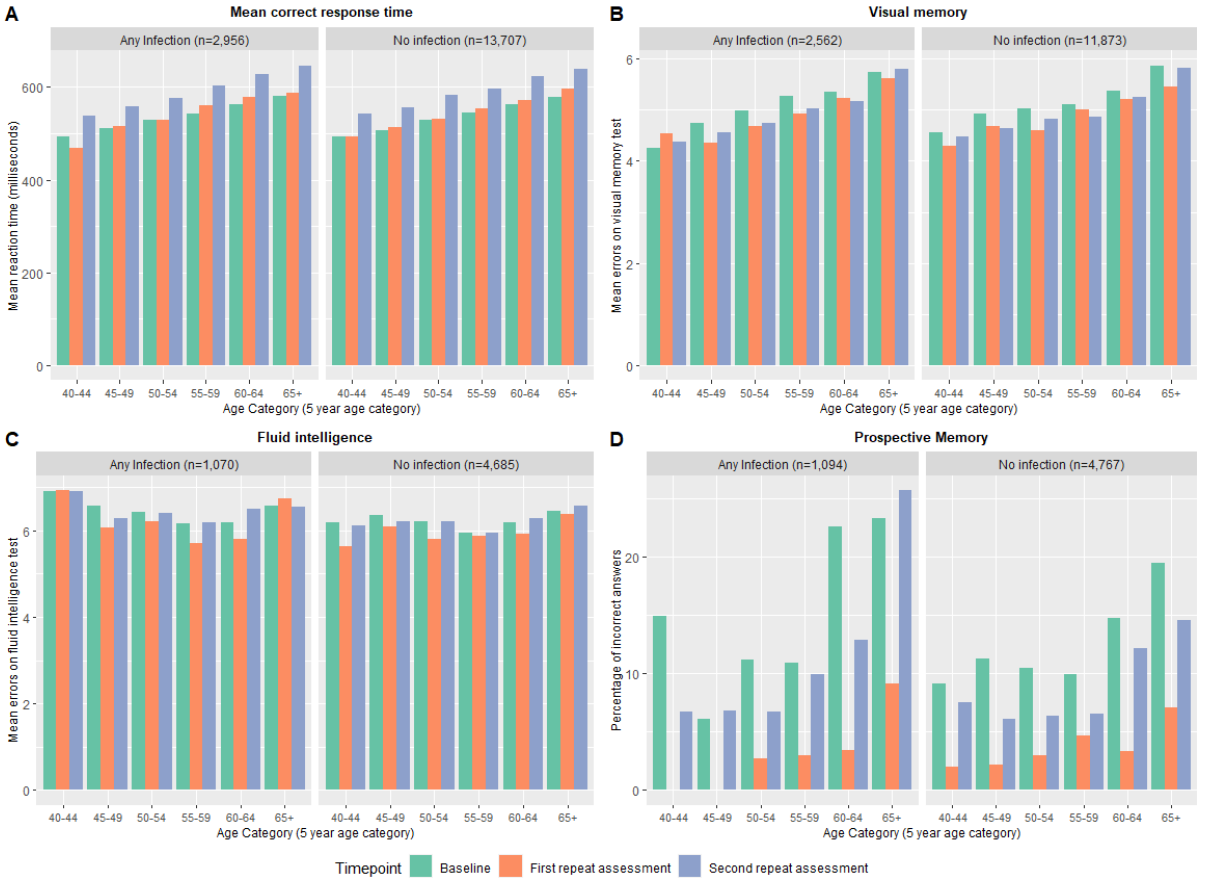
Funding

RM is supported by an Alzheimer's Society PhD studentship 379 (AS-PhD-17-013). CWG is supported by a Wellcome Intermediate Clinical Fellowship, Wellcome Trust (201440_Z_16_Z) and KB holds a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society. VG is jointly funded by a grant from Diabetes UK and the British Heart

7.3 Description of cognitive function scores over time stratified by age and infection status

Age is the greatest risk factor for dementia. Figure 7.5 illustrates the mean scores or proportions of each cognitive measure stratified by 5-year age intervals and infection status. Overall, compared to the baseline assessment, participants generally performed better on the first repeat assessment for the visual memory, fluid intelligence and prospective memory tests. Performance generally worsened for all tests on the second repeat assessment compared to the first repeat assessment and performance worsened with age. This figure is suggestive of a potential practice effect in which participants' performance on the same cognitive tests improved during follow up due to familiarity with the test. This practice effect could have therefore masked the potential effect of common infections on cognitive decline which may have biased effect estimates towards the null.

Figure 7.5. Cognitive function scores stratified by age category and infection status



Age-specific mean cognitive function scores at baseline, first repeat assessment and second repeat assessment in participants with and without a history of common infections for the reaction time, visual memory (log) and fluid intelligence test stratified by age (40-44, 45-49, 50-54, 55-59, 60-64, 65+). For all tests higher scores represent worse performance.

7.4 Additional analyses on common infections and total brain volume

Whole brain atrophy is a commonly studied neuroimaging marker in the diagnosis and progression of Alzheimer's disease.[55] Whole brain atrophy rate is associated with increased risk of cognitive decline and progression to dementia.[265] Given the link between total brain volume, cognitive decline and dementia, I carried out additional analyses investigating the association between infections and total brain volume.

I used the same neuroimaging cohort as in research paper 4 consisting of 14,712 participants, all of whom had a measurement of total brain volume during the first UK Biobank imaging visit. Total brain volume was measured using T1 structural brain MRI of the sum of grey and white matter, normalised for head size (data field - 25009).[266] I used linear regression models to estimate the association of the presence and site of infections (assessed in the 5 years before baseline) with total brain volume (assessed at one timepoint at the first UK Biobank imaging visit). I applied the same approach to confounder adjustment as in research paper 4.

Table 7.5. shows that infections were associated with an increase in total brain volume in all models, including the fully adjusted models. When stratified by site of infections, I saw that this positive association was being driven by other LRTIs (excluding pneumonia). This finding of an increase in total brain volume in participants with infection compared to those without prior infection was unexpected. As a result, I explored these findings in further exploratory analyses. In Table 7.5, I also present the association of infections and total brain volume stratified by clinical setting. In this analysis, I found that the association of common infections and total brain volume was being driven by GP recorded infections.

Table 7.5. Association between the presence and site of common infections and total brain volume (mm^3)

	Crude model		Age and sex adjusted model		Fully adjusted model	
	β Coefficient (95% Confidence Interval)	P Value	β Coefficient (95% Confidence Interval)	P Value	β (95% Confidence Interval)	P Value
Presence and site of infection						
No infection	Reference					
Any infection	3541.05 (920.60 to 6161.50)	0.008	3541.05 (920.60 to 6161.50)	0.008	4102.27 (1473.94 to 6730.59)	0.0020
Other LRTI	252.76 (-3787.61 to 4293.12)	0.90	4831.38 (1476.78 to 8185.98)	0.0048	5428.49 (2064.84 to 8792.15)	0.0016
UTI	3870.04 (-2216.56 to 9956.65)	0.21	1104.81 (-3996.91 to 6206.54)	0.67	1255.89 (-3845.01 to 6356.78)	0.63
SSTI	797.98 (-6157.83 to 7753.78)	0.82	2808.83 (-2962.22 to 8579.87)	0.34	3949.22 (-1844.25 to 9742.69)	0.18
Setting of infection						
No infection	Reference					
GP infection	2262.53 (-982.33 to 5507.39)	0.17	4278.11 (1577.54 to 6978.68)	0.0019	4802.81 (2095.04 to 7510.57)	0.00051
No infection	Reference					
Hospital infection	-11881.07 (-22737.73 to -1024.40)	0.032	-5746.52 (-14756.55 to 3263.51)	0.21	-4968.69 (-13989.71 to 4052.32)	0.28

Estimates for any infection, or site of infection indicate differences relative to the group with no infections. Fully adjusted models adjusted for age, sex, BMI and smoking.

Given that infections that were more likely to be mild such as primary care infections and other LRTIs, appeared to be driving the association between infections and increasing total brain volume, I explored the possibility of health seeking behaviour playing a role in the association observed. I defined consultation frequency using the number of clinical events recorded in the linked GP records dataset. Data on the type of consultation and role of staff member attending was not included in this dataset thus all clinical events including face to face consultations, telephone consultations and administrative consultations were included. Multiple clinical events on a given date where recorded as a single consultation. However, findings in table 7.6. which stratified analyses by number of consultations, suggests that consultation frequency is unlikely to be driving the positive association between infections and total brain volume.

Table 7.6. Association between the presence and site of common infections and total brain volume, stratified by consultation frequency

	Crude model		Age and sex adjusted model		Fully adjusted model	
	β Coefficient (95% Confidence Interval)	P Value	β Coefficient (95% Confidence Interval)	P Value	β (95% Confidence Interval)	P Value
No infection	Reference					
Any infection						
Less than 15	4178.58 (-3885.31 to 12242.47)	0.31	5669.57 (-1121.36 to 12460.51)	0.10	6177.81 (-631.44 to 12987.06)	0.075
15 to 30	5927.60 (251.10 to 11604.10)	0.041	1850.63 (-2885.10 to 6586.36)	0.44	2451.30 (-2285.10 to 7187.71)	0.31
30+	4841.73 (247.05 to 9436.41)	0.039	3754.71 (-32.16 to 7541.57)	0.052	3829.14 (42.19 to 7616.08)	0.048
Estimates for any infection, or site of infection indicate differences relative to the group with no infections. Fully adjusted models adjusted for age, sex, BMI and smoking.						

I performed further exploratory analyses by stratifying the association between infections and total brain volume by age as shown in table 7.7. Infections were associated with a higher total brain volume in the 50-54 and 55-59 age groups though stratum-specific confidence intervals overlapped and there were differences in sample size for each age groups. Finally, I performed further analyses to investigate the suitability of these measures in detecting neuropathological changes. In table 7.8, I compare the association of infections with baseline cognitive function measures. These findings show no evidence of an association between reaction time, visual memory, fluid intelligence and prospective memory with total brain volume. These findings question the suitability of total brain volume in investigating the association between common midlife infections and whole brain atrophy.

Table 7.7 Association between common infections and total brain volume, stratified by age category

		Crude model		Sex adjusted model		Fully adjusted model		
	No. of participants	β Coefficient (95% Confidence Interval)	P Value	β Coefficient (95% Confidence Interval)	P Value	No. of participants	β (95% Confidence Interval)	P Value
40-44 years								
No infection	1,442	Reference		Reference		1,438	Reference	
Any infection	238	1874.57 (-6503.55 to 10252.70)	0.66	-1909.88 (-10075.63 to 6255.87)	0.65	233	-1715.16 (-9951.86 to 6521.54)	0.68
45-49 years								
No infection	1,963	Reference		Reference		1,959	Reference	
Any infection	373	4850.73 (-1851.60 to 11553.05)	0.16	2891.30 (-3713.73 to 9496.32)	0.39	373	4002.33 (-2599.59 to 10604.25)	0.23
50-54 years								
No infection	2,365	Reference		Reference		2,360	Reference	
Any infection	416	9890.51 (3461.33 to 16319.69)	0.0026	7923.69 (1571.09 to 14276.29)	0.015	415	8738.68 (2377.75 to 15099.60)	0.0071
55-59 years								
No infection	2,716	Reference		Reference		2,707	Reference	
Any infection	551	9759.07 (4120.81 to 15397.33)	0.00070	8858.97 (3243.64 to 14474.29)	0.0020	548	9430.09 (3793.95 to 15066.23)	0.0010
60-64 years								
No infection	2,648	Reference		Reference		2,642	Reference	
Any infection	583	2869.54 (-2684.29 to 8423.37)	0.31	1225.14 (-4305.77 to 6756.05)	0.66	581	1530.65 (-4016.34 to 7077.65)	0.59
65+ years								
No infection	1,143	Reference		Reference		1,140	Reference	
Any infection	274	-3405.86 (-11112.7 to 4300.97)	0.39	-4163.23 (-11856.61to 3530.15)	0.29	274	-3457.75 (-11193.77 to 4278.27)	0.38
Estimates for any infection, or site of infection indicate differences relative to the group with no infections. Fully adjusted models adjusted for age, sex, BMI and smoking.								

Table 7.8. Association between baseline cognitive function tests and total brain volume

	Total Number	Age and sex adjusted	
		β Coefficient (95% Confidence Interval)	**P Value**
Reaction time	11,439	-10.93 (-22.51 to 0.65)	0.064
Pairs Matching	10,572	-1613.99 (-3909.35 to 681.37)	0.17
Fluid intelligence	4,171	469.53 (-435.40 to 1374.47)	0.31
Prospective memory			
Correct	3,659	Reference	
Incorrect	532	-3506.75 (-9013.97 to 2000.46)	0.21

Previously, whole brain atrophy rate rather than baseline whole brain volume has been suggested to predict the progression from mild cognitive impairment to Alzheimer's disease.[267] Therefore, baseline total brain volume may be not be a suitable measure to assess neuropathological changes in the preclinical phase of dementia in those with and without infections.

Given that brain volume declines with advancing age, with the rate of decline suggested to be increasing markedly over the age of 70, it is possible that mid-life may not be the most appropriate age to measure associations between infections and total brain volume.[268,269] Studies investigating this association are lacking but future work is needed to investigate this relationship at different life-stages.

Findings from the present study may have been influenced by unmeasured confounders such as frailty and the apolipoprotein E4 gene. Further studies on common infections and total brain volume are warranted to understand these unexpected findings. Specifically, longitudinal studies with repeated measures of whole brain imaging to enable atrophy measures could also provide a better understanding of the association between infections and neuroimaging markers.

7.5 Summary

- In this chapter I investigated the association of mid-life common infections with cognitive decline and neuroimaging measures using data from the UK Biobank cohort study linked to primary and secondary care records
- In a subset of 16,728 participants (median age 56.0 years [IQR 50.0-61.0]; 51.3% women) with baseline and one or two follow up cognitive function measures, there was no association between the presence, site, setting and frequency of infections and cognitive decline for mean correct response time, visual memory and fluid intelligence tests.
- UTIs were associated with a slight increase of 0.011 (95% CI: 0.004-0.018) per year in the log visual memory errors compared to those without infections. Log visual memory errors also slightly increased per year for each additional infection (β 0.0064, 95% CI: 0.0019-0.011). Though these findings should be interpreted with caution and need to be confirmed in future studies.
- In a subset of 14,712 participants (median age 55.0 [IQR 49.0-63.0]; 52.9% women) with neuroimaging measures at the first imaging visit, no association was found between infections and hippocampal or white matter hyperintensity volume in fully adjusted models.

- Further studies with longitudinal measures of whole brain volume are warranted to understanding the unexpected findings between infections and total brain volume

Chapter 8: Discussion

8.1 Introduction

This thesis explored the association of common infections with incident dementia, cognitive decline and neuroimaging measures using linked routinely collected primary and secondary care EHRs and data from a prospective cohort study, the UK Biobank study. In this chapter, I summarise the key findings of this thesis, discuss causality within the framework of the Bradford Hill criteria for the findings on incident dementia, place the findings of this thesis in context with previous literature and outline the strengths and limitations of the approaches used. I conclude by discussing the clinical implications of this research and recommendations for future research.

8.2 Summary of key findings

8.2.1 Research aim 1: to summarise evidence from literature investigating the association between common clinically symptomatic bacterial infections and incident cognitive decline and dementia in longitudinal studies.

In Chapter 3, nine longitudinal studies conducted in the United States and Taiwan of adults aged 18 years and older were included in the systematic review with seven studies assessing dementia as an outcome and 2 investigating cognitive decline. All seven dementia studies found that sepsis, pneumonia, UTIs and cellulitis were associated with an increased risk of dementia (HR 1.10; 95% CI 1.02–1.19) to (OR 2.60; 95% CI 1.84–3.66) while the two studies assessing cognitive decline did not find an association following sepsis or pneumonia. These studies were rated very low in terms of their overall quality of evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment tool. The overall quality of evidence was assessed for six studies which investigated sepsis and dementia and 3 studies reporting on pneumonia and dementia. Studies were rated either "serious" or "very serious" for the inconsistency, indirectness, risk of bias or imprecision domains. However, for the risk of bias assessment, which was conducted using the Cochrane collaboration approach, the association of infections on dementia risk remained consistent in the three studies that had no domains at high risk of bias.[163,244,270] Studies

included in the review predominantly assessed hospitalised infections, the majority of which were pneumonia or sepsis with only one study included UTIs or cellulitis. There were few studies on infections and cognitive decline and these studies faced methodological limitations which included inadequate confounder adjustment, poor comparability of comparator groups, and small sample sizes which limited the ability to draw accurate conclusions of the study results. This study was the first systematic review to my knowledge to investigate the longitudinal association of common infections with incident dementia or cognitive impairment. Overall, studies included in the review suggested common infections were associated with an increased risk of dementia, however, evidence was limited with a lack of studies investigating the association of infections other than pneumonia or sepsis in clinical settings other than secondary care (hospital). Although findings from studies with no domains at high risk of bias also found an association between common infections and an increased risk of dementia, there is a clear need for further large scale, high quality robust research to clarify the association between common infections, cognitive decline and dementia.

8.2.2 Research aim 2: to investigate the association of common infections and incident dementia using UK primary care electronic health records linked to Hospital Episode Statistics (HES).

In Chapter 5, using routinely collected UK primary and secondary care EHRs (CPRD and HES), I found that the common acute infections that were predominantly bacterial associated with an increased risk of incident dementia (HR 1.53, 95% CI: 1.50–1.55) in a historical cohort study of almost one million adults aged 65 years and older. The study period was between 2004 and 2018 with a median follow-up of 5.2 years (IQR 2.3–9.0) and mean age of 71.7 (sd 7.9) years. In terms of type of infection, I found that the more severe infections, pneumonia and sepsis, were associated with a greater risk of dementia compared to the less severe infections. Given that the studies included in the systematic review of chapter 3 predominantly assessed hospitalised infections, I explored the association of infections on dementia by clinical setting in chapter 5. In this study, infections resulting in hospital admission were associated with a greater risk of dementia while a weak association was found for infections treated in primary care (general practice). I also examined this association and found that the risk of dementia

was highest between 3 months to 1 year following infection diagnosis though the associated persisted for more than 9 years. Another novel finding in this study was that the association of common infections and dementia risk was higher in individuals with diabetes. In terms of frequency of infections, I found that the risk of dementia increased with an increasing number of infections, although the magnitude of this trend was small. Lastly, evidence of cognitive impairment was a secondary outcome of this study in which, and in this analysis, I also found that common infections were associated 29% increased risk of cognitive impairment. This association was weaker than that of common infections and dementia.

8.2.3 Research aim 3: to investigate the association of common infections with the risk of dementia using data from the UK Biobank study and linked primary and secondary care electronic health records.

In Chapter 6, I assessed the association of common infections occurring in mid-life with dementia risk in a historical cohort study (UK Biobank study) of over 500,000 adults aged between 40-69 years at recruitment linked to routinely collected primary and secondary health care records. A total of 176,207 participants were included in this study, with a mean age of 56.6 (sd 8.1) and median follow up of 8.9 years (8.3-9.7). No association was found between common infections overall and dementia (HR 1.10, 95%CI: 0.95-1.27) or site of infection and dementia. In analyses stratified by clinical setting, hospital recorded infections were associated with an increased risk of dementia (HR 1.60, 95% CI: 1.19-2.16) and no association was found for GP recorded infections and dementia (HR 1.05, 95% CI: 0.92-1.21)

8.2.4 Research aim 4: to investigate the association between common infections and cognitive decline using data from the UK Biobank study and linked primary and secondary care electronic health records.

This historical cohort study using data from the UK Biobank study linked to primary and secondary care EHRs, included a subset of 16,728 participants with cognitive function measures at baseline and at least one follow-up cognitive function measure. The mean age for this cohort was 55.6 (sd 7.5) and the mean time interval between baseline and

the first or second repeat cognitive function assessment was 4.0 years (sd 0.78) and 8.3 years (sd 1.6), respectively. Another subset of 14,712 participants who attended the first neuroimaging test and had neuroimaging measures on hippocampal volume, white matter hyperintensity volume and total brain volume were included.

In this study, I found no association between the presence, site and setting of common infections and cognitive decline for the mean correct response time, fluid intelligence and prospective memory tests. In analyses stratified by type of infection, UTIs were associated with a slight increase of 0.011 (95% CI: 0.0037-0.018) per year in the log visual memory errors compared to those with no prior infection. In terms of frequency of infections, a slight increase in the log of visual memory errors per year was also found for every additional infection (β 0.0064, 95% CI: 0.0019-0.011). Regarding the neuroimaging measures, no association was found between infections and dementia in fully adjusted analyses.

8.3 Association of common infections with incident dementia within the framework of the Bradford Hill criteria

Given that this thesis investigated a potential causal association between common infections and dementia, in this section I discussed causality within the framework of the Bradford Hill criteria.[271]

8.3.1 Strength of association

According to the Bradford Hill criteria larger associations were more likely to be causally related than small associations. The strength of association of common infections and dementia varied according to site, clinical setting, timing of infections and dementia subtype. In the CPRD and HES study, stronger associations were found for more severe infections such as infections leading to hospitalisation HR 1.76 (95% CI, 1.29-2.39), sepsis HR 2.08 (95% CI, 1.89–2.29) and pneumonia HR 1.88 (95% CI, 1.77–1.99]. In the UK Biobank dementia study, a stronger association was also found for hospital recorded infections 1.76 (95% CI, 1.29-2.39) and vascular dementia 1.72 (95%

CI, 1.16-2.54) while no associations were found for the presence or type of common infection.

The HRs presented above of up to 2 may not be considered high in terms of the Bradford hill criteria. One of the examples used by Hill to illustrate the strength of association criteria was the link between cigarette smokers and death rate from cancer. Cigarette smokers had a nine to ten times higher death rate from lung cancer than non-smokers, and the rate in heavy smokers was ten to twenty times that of non-smokers.[271] However, it should be acknowledged that a weaker association does not necessarily reflect the absence of causality.

8.3.2 Consistency

While the association of the presence or site of common infections with incident dementia differed in the CPRD and HES study compared to the UK Biobank in the fully adjusted analyses, the 95% confidence interval overlapped and included a hazard ratio of 1.21 which is consistent with both studies. The findings of the two studies were consistent in terms of the association of hospital recorded infections and dementia risk. Moreover, a consistent association was also found for the association of common infections and vascular dementia in both studies. Owing to the small number of events for the more severe infections, sepsis and pneumonia, in the UK Biobank study I was unable to examine whether the association of these infections with dementia would have been consistent with the CPRD and HES study. Given that the CPRD and HES study showed that infections more likely to be severe were associated with a greater risk of dementia, the fact that fewer participants in the UK Biobank study were diagnosed with these infections could have also contributed to the lack of association observed. Another explanation for the differences in findings could be that the UK Biobank population is healthier than the general population and had a small number of dementia events (n=1,201).

In terms of existing literature, hospital treated infections in the UK Biobank were associated with an increased risk of dementia consistent with the findings in Chapter 6.[162] Also in agreement with chapter 6, previous studies using UK EHRs have found no association was found between GP recorded infections and dementia.[159,241] A consistent

association has been found across geographical settings with US, Taiwanese and German longitudinal studies finding an association between sepsis,[161,163,242,244,270,272,273] pneumonia,[242-244] UTIs,[244] and cellulitis,[244] with an increased risk of dementia. In contrast to these findings, a Swedish cohort study did not find an association between sepsis and dementia, though the selective population of intensive care unit patients limits comparability with the studies in this thesis.[160]

A UK study investigating post-stroke dementia following common infections using the same data sources of this thesis, CPRD and HES, found consistent findings with research paper 3. These similar findings include stronger associations for hospital recorded infections, LRTIs, UTIs and increasing numbers of infections with early post-stroke dementia.[158] No association was found between infection type and late post-stroke dementia though these findings are difficult to interpret with the findings of this thesis due to the highly selective population of only stroke survivors.

8.3.3 Specificity of association

To fulfil the criteria for specificity, the association between infections and dementia would be specific only to dementia and not for other conditions. However, as is the case for many exposure and outcome associations, infections are associated with a range of different outcomes other than dementia.

There are further challenges in terms of whether a single risk factor is associated with dementia risk. Dementia has a complex, multifactorial aetiology which is likely to involve an interplay of genetic, environmental, health and behavioural factors.[274] As a result, there are challenges in disentangling the pathophysiological effects of these risk factors with non-modifiable risk factors such as age as well as the independent effects of infections on dementia risk. It is unlikely that a single modifiable risk factor will prevent the risk of dementia as it is likely that tackling multiple risk factors will be necessary to lower the risk of dementia.

An alternative and more relevant interpretation of specificity of association could be considered in terms of whether specific infections are associated with dementia risk. The findings of the CPRD and HES study show that the effect of infections on dementia

risk was present across a range of infection types and sites which are likely to reflect different organisms.

8.3.4 Temporality

In the systematic review of chapter 3, I specifically included only longitudinal studies in which infection diagnosis preceded cognitive decline or dementia in order to assess temporality. For all the studies of this thesis, I conducted longitudinal studies in which I excluded individuals with evidence of dementia or cognitive impairment prior to infection diagnosis.

However, it is important to acknowledge that people living with dementia are more susceptible to common infections and this presents challenges in determine the temporality in those with undiagnosed dementia. Further, dementia has a long pre-clinical phase which may precede the onset of infection, therefore, to minimise reverse causality, follow up time should be sufficient enough for dementia to develop. Studies included in the systematic review of chapter 3 had a mean or median follow up which ranged from 2.5 to 9.0 years. Therefore, the possibility of reverse causality cannot be ruled out.

Although the CPRD and HES study in chapter 5 had a median follow up of 5.2 years (IQR 2.3–9.0), individuals were followed up for up to 14 years. To further investigate the temporality of the association of common infections and dementia, I performed analyses stratifying by timing of infections. I found that the association of common infections and dementia incidence was strongest between 3 months to 1 year following an infection diagnosis HR 1.86 (95% CI, 1.80–1.92). This stronger association observed for dementia diagnosed shortly after infection was likely to reflect undiagnosed dementia. The risk of dementia attenuated over time but persisted for more than 9 years after infection diagnosis as a result it is unlikely that reverse causality accounts for all of the observed effect. Reverse causality was less likely in the UK Biobank dementia study compared to the CPRD and HES study as all participants had to give consent to take part in the study, making significant impairment unlikely. However, reverse causality remains a possible explanation in both studies.

8.3.5 Biological gradient (Dose-response)

In the CPRD and HES study, I found evidence of a dose-response relationship between an increasing number of infections and risk of dementia (likelihood ratio test for trend p<0.0001), however although highly significant, the magnitude of this association is small HR 1.02 (95% CI 1.01–1.02). Two studies investigating this relationship in literature have also reported association between an increasing number of common infections with dementia.[158,244] In addition, the finding that more severe infections are more likely to be associated with dementia than less severe infections could reflect a dose response relationship with more severe infections representing a large 'infectious dose'. Severity of infection could also reflect a greater inflammation 'dose' as inflammation is a key mechanism proposed to be driving the association between infections and dementia.

8.3.6 Plausibility

Although the underlying biological pathways by which infections may increase the risk of dementia are unknown, systemic inflammation has been proposed as a plausible potential mechanism. Infections trigger the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-6 which induce systemic inflammatory responses associated with cognitive decline and dementia. Cytokines and systemic inflammatory markers have been associated with an increased risk of dementia and smaller brain volumes, including hippocampal volume.[123,275,276] The blood-brain barrier is an important interface between the blood and brain that prevents the entry of microorganisms into the central nervous system. However, the blood-brain barrier becomes more permeable with age, increasing susceptibility to infection and leading to profound consequences to the central nervous system.[124,277] Another plausible mechanism underlying the associations seen could be potentiating vascular damage. Respiratory tract infections and other common infections have been shown to trigger acute cardiovascular events including myocardial infarction and stroke and cause subclinical vascular damage and inflammation.[225] Potentiating vascular damage could also explain why for both CPRD and HES and UK Biobank studies, a greater risk of infections with vascular dementia risk was found compared to the association of infections on risk of Alzheimer's disease.

8.3.7 Coherence

The association of common infections on incident dementia is compatible with evidence from cohort studies of infections and inflammatory markers in individuals with cognitive decline or dementia. It is also coherent with animal models of inflammatory markers and cognitive dysfunction.

In a prospective cohort study of individuals with Alzheimer's disease, tumour necrosis factor-α (TNF-α) levels were associated with a 4-fold increase in the rate of cognitive decline over time. Increased levels of TNF-α remained associated with cognitive decline and long term cognitive impairment independent of age, delirium and other confounders.[122] Systemic infection and elevated levels of another pro-inflammatory cytokine, interleukin-1β, has been associated with cognitive decline in individuals with Alzheimer's disease.[278] Systemic infection has been found to exacerbate brain cytokine levels (including IL-1β, IL-6, TNF-α, IL-8 and IL-15) and markers of cerebrovascular dysfunction in Alzheimer's disease, vascular dementia and healthy controls. [279]

In animal models, intracerebral lipopolysaccharide resulted in systemic inflammation which resulted in marked microglial IL-1β expression and other cytotoxic inflammatory mediators that exacerbate neurodegeneration and lead to disease progression.[280,281] Animal models induced with sepsis, found that sepsis triggered systemic inflammation and subsequently amyloid-β accumulation and cognitive dysfunction.[282,283]

8.3.8 Experiment

Evidence on the association of infections and incident dementia has been conducted in observational studies. However, to provide stronger evidence of a causal link between infections and dementia risk, intervention studies focusing on whether strategies to reduce infections or systemic inflammation lower the risk incident dementia are needed. These further intervention studies are explained further in section 8.6.

8.3.9 Analogy

Besides the common infections studied in this thesis, other common clinically symptomatic infections such as periodontitis have been associated with an increased

risk of dementia in a growing number of longitudinal studies.[284-286] Viral infections such as herpesvirus infections have been widely studied in literature for their potential association with dementia, though longitudinal population-based studies are warranted.[148] Acute infections including LRTIs and UTIs have been associated with vascular outcomes such as acute myocardial infarction and stroke.[129,287-289] This further supports the role of infections, through inflammatory processes, in contributing to chronic conditions.

8.3.10 Summary

In summary, using the Bradford Hill criteria for causality, there is evidence to support a causal relationship between common infections and dementia for the strength of association, consistency, temporality, biological gradient, plausibility, coherence and analogy criteria. There is no evidence for a causal link for the specificity criterion though given dementia's multifactorial aetiology a lack of specificity may not necessarily reflect the absence of causality. Currently, experimental evidence is lacking and therefore to further elucidate the causal relationship of common infections and dementia and to strengthen to evidence in support of causality, future intervention studies are required which can determine whether strategies which reduce infections also lower the risk of dementia.

8.4 Explanation of findings on infections and cognitive decline in context with previous studies

The findings of the UK Biobank cognitive decline study (chapter 7) differ from the other three studies of this thesis which investigated associations between common infections and incidence of dementia. The UK Biobank cognitive decline study assessed mid-life infections while the CPRD and HES study assessed late life infections. This difference in the age at which infections were studied may explain the contrasting findings for cognitive impairment in this study, compared with the findings for the CPRD and HES dementia study. Therefore, common infections may not contribute to cognitive decline or structural brain changes during mid or early late life.

Other reasons for these differences could include heterogeneity in study population, infection subtype, selection bias and differences in neuropsychological assessment tools used. The study population of the UK Biobank subset with cognitive function measures had a mean and median age 55.6 years (sd 7.5) and 56.0 (IQR, 50.0-61.0), respectively, which was younger than that of the incident dementia studies. In comparison with studies in literature that found an association between severe sepsis or pneumonia with moderate or severe cognitive impairment, the mean or median ages of these studies were 76.9 years or 77 (IQR, 70-83). These differences in age could explain the lack of association in the UK Biobank study given that older adults aged 65 years and older are at a greater risk of cognitive decline and dementia. Thus, the results on cognitive decline in chapter 7 may not be generalisable to older adults. Previous studies in literature have focused on more severe infections such as sepsis or pneumonia infections which may be more likely to induce a stronger systemic inflammation response and consequently cognitive dysfunction than more mild infection. Additionally, previous studies only included individuals with hospitalised infections n=827 and n=1520, respectively, whereas the UK Biobank cognitive decline study included both GP and hospital recorded infections with only 201 participants with hospital infections.[105,106] Therefore, subgroup analyses on hospitalised infections may not have been sufficiently powered to detect an association between hospital recorded infections and cognitive decline. The previous studies mentioned were not included in the systematic review of this thesis as they did not fit the criteria for inclusion in terms of having a comparator group with no infection. This difference in study design suggests these findings may not be directly comparable to the results of the UK Biobank study and could also explain the differences in findings. Studies included in the systematic review of chapter 3 showed no association between sepsis or pneumonia hospitalisation. These studies were limited by either use of inappropriate comparator group, inadequate adjustment for confounders and small sample size. Selection bias may explain why the findings of the UK Biobank cognitive decline study differ with other previous studies on cognitive impairment. Selection bias is described in more detail in section 8.5. Lastly, previous studies used different neuropsychological tests compared to the UK Biobank study. Differences in tests and cognitive domains assessed may contribute to the differences in findings. Moreover, it is unclear whether the UK Biobank cognitive tests were sensitive enough to detect small changes in cognition. However, it is important to also

acknowledge that it is possible that there is no true association between infections and cognitive decline.

8.5 Strengths and limitations

In previous chapters, I discussed the strengths and limitations of each study and of the data sources used in the previous chapters, however, in this section I will emphasise some of the important strengths and limitations of these chapters and will discuss those relevant to the thesis as a whole.

8.5.1 Sample size

The CPRD and HES study of chapter 5 had a large study population of almost one million individuals which was a key strength that improved the precision of the effect estimates of the study findings. As highlighted in the systematic review in chapter 3, three of the seven studies assessing dementia as an outcome were considered at high risk of bias in terms of study size. At the time of publication, the study in chapter 5 was the largest study conducted, to my knowledge, investigating the association of common infections and incident dementia. While sample size was a strength of chapter 5, it was a limitation of chapters 6 and 7 which examined the association of common infections with dementia, cognitive decline and neuroimaging measures. Although there are over 500,000 participants in the UK Biobank study, this study included only individuals with follow up cognitive measures (n=16,728) and neuroimaging measures at the first imaging visit (n=14,712). As a result of limitations associated with this data source such as selection bias and the fact that the UK Biobank population is younger and healthier than the general population, the number of participants who were diagnosed with infections, developed dementia or were invited for repeat cognitive assessments or were lost to follow up, reduced the sample size for the dementia and cognitive decline studies. This reduction in sample size affected the precision of effect estimates and ability to adjust for a larger set of confounders.

8.5.2 Use of multiple data sources

Throughout this thesis, I used multiple different sources of data to address each research question of this thesis. Triangulating data from multiple sources is important

in obtaining more reliable conclusions of research questions and contributes to the causal inference of findings.[290] This enabled me to reduce misclassification when ascertaining exposures, outcomes and covariates. Additionally, using numerous data sources enabled me to 1) perform multiple sensitivity and secondary analyses, 2) stratify analyses by important confounders such as age and sex, 3) investigate effect modification by diabetes, 4) detect small associations and 5) control for a wide range of confounders, particularly in chapter 5. The use of multiple EHRs also allowed for a more complete follow up though the completeness of these records varied over time due changes in recording over time.

8.5.3. Use of multiple cognitive function tests and neuroimaging data

A key strength of the UK Biobank study is the use of multiple cognitive function tests, assessing different domains of cognitive function, measured at baseline and multiple follow up time points. The UK Biobank is thus one of the largest data sources in the UK with a range of cognitive function measures. Additionally, the UK Biobank dataset contains extensive data on a wealth of neuroimaging measures and is the largest, most comprehensive imaging study in the world. This allowed me to explore the association of infections with specific cognitive and neuroimaging outcomes that are not well recorded or measured in other datasets such as CPRD and HES.

8.5.4 Generalisability

Another strength of this work is the use of population based CPRD data which is generalisable to real world populations in the UK. CPRD is representative of the UK population in terms of age, sex and ethnicity.[164,169] Though, CPRD GOLD may not geographically representative of the UK population.[168]

8.5.5 Selection bias

Selection bias was a key issue in studies which used data from the UK Biobank, chapter 6 and 7, and warrants further elaboration in this section. There were several ways in which selection bias occurred in these studies.

First, the UK Biobank had a low response rate as only 5.5% of those invited participated in the study. This resulted in selection bias as UK Biobank participants were older, more

likely to be female, less deprived, less likely to be obese and had fewer self-reported conditions than those who did not participant in the study. Second, selection bias occurred as only a subset of participants were invited via email for repeat cognitive assessments or imaging assessment. 91% and 92% participants were thus excluded from the cognitive or neuroimaging cohorts (chapter 7), respectively, as they did not have any follow up cognitive measures or did not attend the first UK Biobank imaging visit. This substantial decline in participants resulted in small sample sizes in subgroup analyses of chapters 6 and 7 in terms of exposures which affected the precision of effect estimates and confounder adjustment. More importantly, participants who were not included in the final analytic sample for the UK Biobank cognitive decline study (chapter 7) were younger, healthier (had less comorbidities), had more years in education and performed better at baseline cognitive function tests. As a result of this selection attrition, associations between common infections and cognitive decline were likely underestimated and effect estimates were likely to be biased towards the null. The overall UK Biobank cohort and cognitive or neuroimaging subsets are highly selective which limits the external validity. As a result, the findings of this thesis cannot be translated to a wider population without first considering its limitations.

Finally, selection bias may have been possible in regard to the exposure. Individuals with more severe infections such as pneumonia or sepsis, may not have been able to attend to baseline assessment as a result the study population may have been more likely to consist of participants who had a history of more mild infections. This may have thus biased associations towards the null as more severe infections may be associated with a greater systemic inflammation response. However, given that infections were captured within 5 years of baseline assessment, participants are likely to have recovered from the acute infections before the baseline assessment.

8.5.6 Misclassification of exposure, outcomes and covariates

Misclassification is a key limitation of EHRs. In these datasets, ascertainment of variables relies on selecting accurate diagnostic codes recorded by GPs for a given condition. However, these codes can vary across studies and it is possible to select incorrect diagnostic codes or to miss relevant codes. Additionally, errors during data entry by the GP are also possible. To minimise errors in creating code lists, I used

multiple resources to create the code lists which included using relevant pre-existing code lists, the BNF and guidance from clinicians. Further, a wide range of diagnoses in CPRD have been validated, including dementia.[181,183]

The UK Biobank prescription dataset had missing codes for some data providers thus it is possible that prescription data for some antibiotics were missing which may have resulted in misclassification of UTIs and SSTIs. Misclassification of exposure would have likely underestimated the association between infections, cognitive decline and neuroimaging measures thus biasing effect estimates towards the null. Misclassification of infections was also possible given that participants with mild infections may have been less likely to visit their GP and thus receive an infection diagnosis. This misclassification bias was probably non-differential according to dementia status and would likely bias effect estimates towards the null. Additionally, infections in primary care are frequently diagnosed without microbiological data to confirm diagnosis increasing likelihood for misclassification. To address this, in this thesis individuals were defined as having UTIs or SSTIs if they were prescribed antibiotics on the same date as infection diagnosis which increased the specificity of the definition of these infections. However, the observed associations may have been underestimated as antibiotics were included in the definition of infections which meant that any mitigating effect of antibiotic therapy would have been included in the observed associations. An overdiagnosis of infections may have also occurred in individuals experiencing delirium. Patients presenting with delirium are often diagnosed with limited evidence of infection which is likely to lead to misclassification. In the UK biobank studies, infections were defined 5 years prior to baseline which increased the likelihood of misclassification as participants diagnosed with infections during follow up were not defined as having infections. This incomplete ascertainment of exposure may underestimate associations and bias effect estimates towards the null. However, I explored this potential bias in the UK Biobank cognitive decline study by performing a sensitivity analysis excluding participants diagnosed with infections during follow-up and this analysis did not materially change the findings of this study.

There is potential for misclassification in the ascertainment of dementia in EHRs. In primary care, dementia has been recognised to be frequently underdiagnosed [59 60],

although the recording of dementia has been changing with time as recent evidence now suggests that around two thirds of people living with dementia have a received a diagnosis.[61] The use of both CPRD and HES data improved dementia ascertainment. Linking CPRD to HES may have introduced ascertainment bias as certain groups such as ethnic minorities and those with less severe dementia are less likely to be receive a hospital dementia diagnosis.[291] However, the recording of dementia in HES has been increasing since 2008 and the sensitivity and specificity for each person's complete hospital records has been estimated to be around 78% and 92%, respectively. [291] In CPRD, positive predictive values (PPVs) of dementia have been reported at around 80 - 90%.[182] Dementia sub-type diagnoses have also been validated in routinely collected health-care datasets with PPVs ranging from 57%-100% for Alzheimer's disease and 19%-91% for vascular dementia.[292] In a subset of the UK Biobank population recruited in Edinburgh, PPVs for Alzheimer's disease were 74.1% and 68.2% respectively in primary care and hospital admissions while PPVs for vascular dementia were 43.8% in both data sources.[237] However, these diagnoses are reliant on clinical judgement rather than objective diagnostic tests and evidence suggest diagnoses in clinical practice may be inconsistent neuropathological data.[237,293] Under-recording of dementia diagnoses during follow up in the CPRD and HES study (chapter 5) and UK Biobank dementia study (chapter 6) could have underestimated the association of infections and incident dementia and biased effect estimates towards the null. However, inclusion of individuals with undiagnosed dementia, could have biased effect estimates away from the null. Individuals with undiagnosed dementia may be more likely to receive a dementia diagnosis when they encounter health care services, for example, if diagnosed with an infection. Dementia is associated with morbidity including increased susceptibility to infections and increased rates of hospitalisation compared to people without dementia.[294,295] This therefore increases the likelihood of receiving a dementia diagnosis in individuals with undiagnosed dementia. In chapter 5, I found that the risk of dementia was highest between 3 months and 1 year after an infection, and this association was likely reflective of undiagnosed dementia. Lastly, incentives to increase the recording of dementia such as the QOF in 2004 and the National Dementia Strategy in 2009 increased the likelihood of a dementia diagnosis recording.[63,64] To account for this, follow up began from 2004 onwards for the CPRD and HES study and dementia

was captured after the UK Biobank baseline assessment which was between 2006 and 2009. In addition to this, I adjusted for calendar period.

Finally, there was potential for misclassification of covariates in all studies as confounders were assessed prior to baseline. Confounders occurring during follow up were thus not included in any of the studies increasing the likelihood for misclassification.

8.5.7 Confounding

Unmeasured confounding was a limitation of the studies in this thesis. Although I limited confounding by linking data to primary and secondary care datasets to improve the ascertainment of variables, there are still potential confounders I was unable to adjust for in these studies. The UK Biobank dataset allowed me to adjust for confounders which are not well captured in CPRD such as education and physical activity, however, residual confounding remained as I was unable to adjust for other potential confounders such as genetic factors specifically the APOE4 gene which has been linked to an increased risk of infections and dementia (section 8.6). Although this variable is available in the UK Biobank dataset, there were issues regarding downloading and extracting genetic data onto LSHTM servers and owing to the time constraints of this project I was unable to utilise genetic data from the UK Biobank study.

For studies using UK Biobank data, I was unable to adjust for all potential confounders as I had done in the CPRD and HES study due to small sample sizes in sub-group analyses. Initially, I selected confounders based on pre-existing literature, however, given the small sample sizes in the subgroup analyses and the instability of the linear mixed models, I was unable to adjust for all potential confounders. I therefore used a change-in-estimate approach whereby I selected confounders based on whether they changed the effect estimate of the exposure by approximately 10%. Change-in-estimate is a common variable selection approach recommended in epidemiology textbooks though I recognise that there are limitations to this approach.[296] An example of a limitation is where there is a high disease frequency and rate ratios or odds ratios are used, the change in effect estimate may be partly attributed to non-collapsibility of the

effect measure and not confounding.[297] However, logistic regression was used for only one cognitive measure (the prospective memory test) and frequency of infections and cognitive decline in this study low.

8.5.8 Practice effects

For the cognitive tests used in chapter 7, there was evidence of a practice effect for the verbal memory, fluid intelligence and prospective memory tests. Practice effects occur when participants' cognitive test performance improves due to familiarity with the test as a result of having performed the same test previously. Evidence from longitudinal neuropsychological studies suggests that these practice effects have been shown to persist years after testing.[264] Other UK Biobank studies have reported practice effects in the same cognitive tests used in this study.[253] These practice effects may have masked the potential effect of common infections on cognitive decline and thus underestimated the rate of cognitive decline.

8.5.9 Infection definition

Another key limitation of this thesis is that infections were limited to common infections specifically pneumonia, other LRTIs, UTIs, SSTIs and sepsis. This limited the ability to further explore the association of a much wider range of infection types, such as viral, fungal or CNS infections on dementia or cognitive decline. Including a wider range of infections may have increased the evidence to support a potential causal relationship between infections and dementia and may have provided a better understanding on the underlying mechanisms responsible. However, I focused on infections that frequently occur in the general population and were likely to increase the potential for public health intervention for example through infection prevention and control strategies and vaccination trials. In addition to this, the association of bacterial and viral pathogens and chronic infections such as herpes simplex viruses and periodontitis with cognitive impairment and dementia has been widely studied in

literature while studies on common acute infections and dementia are scarce.[148,150,154,286]

8.5.10 Temporality of infection

Another important limitation was the inconsistent assessment of the temporality of infections in relation to subsequent cognitive impairment and dementia for the CPRD and HES study and the UK Biobank studies. In the CPRD and HES study infections were ascertained during following up with infection included as a time-updated variable. In this study, prior to infection, individuals contributed person-time to the unexposed group (no infection) but once diagnosed with an infection they contributed person-time to the exposed group (infection). However, in the UK Biobank studies, infections were identified in the 5 years up to the baseline assessment visit. The rationale for this design was because cognitive function tests were assessed at baseline and follow up, therefore, to ensure infections preceded cognitive decline, infections were ascertained before participants undertook the baseline cognitive function tests. A 5-year exposure ascertainment period was chosen due to issues with the completeness of historical linked primary care data in the UK Biobank study as discussed in chapter 4. The same exposure ascertainment window was selected for the two UK Biobank studies (chapter 6 and chapter 7), to enable comparison between these two studies. However, this choice has limited comparison between the UK Biobank and CPRD and HES dementia studies. Therefore, this key difference in study design between the dementia studies could have accounted for the differences in study findings. In addition, since infection ascertainment in the CPRD and HES study was not restricted to 5 years, there was a longer period to capture information on frequency and timing of infections compared to the UK Biobank studies which may also explain some of the differences in findings.

8.6 Directions for future research

Findings of this thesis highlight the need for further studies to 1) better understand the underlying biological mechanisms linking common infections and dementia, 2) improve the methodology of future studies, 3) improve understanding of the associations between infections, cognitive decline and dementia across different geographical settings, infection sub-types and populations with differing comorbidities.
Over the last few decades, bacterial, viral and fungal microorganisms have been associated with dementia, particularly Alzheimer's disease, in numerous studies.[150,154] However, the microorganisms responsible for this association remain unclear thus more research is needed to identify the exact pathogen(s) implicated. These microorganisms could then become a potential target for vaccination trials or anti-microbial therapies. To better understand the mechanisms that link infections and dementia, further longitudinal studies with neuroimaging measures assessed at multiple time points are needed to establish whether infections are associated with biomarkers related to dementia. In particular, studies investigating the more severe infections such as pneumonia, sepsis or hospitalised infections. These studies could explore the association between infections and cerebrospinal fluid biomarkers of Alzheimer's disease, namely amyloid and tau, or cerebrovascular abnormalities associated with vascular dementia, or neurodegenerative structural imaging biomarkers, such as hippocampal atrophy. These biomarkers have been associated with diabetes therefore the effect of infections on these biomarkers in people with and without diabetes could be explored in future studies.[298]

Findings of the UK Biobank cognitive decline study highlight the need for further studies to investigate the effect of common infections on cognition at different life stages (early life, midlife and late life) in more representative populations. These studies will need to have sufficient sample sizes to explore associations of different types of infections and other stratified analyses e.g. by age and sex. In terms of the neuropsychological tests, there is a need to validate whether the UK Biobank cognition tests are able to detect early stages of cognitive decline and thus subtle changes in cognition over time. A lack of follow up measures on cognition was a major issue in the UK Biobank study thus further work will need to pay careful attention to loss of follow up and to increasing the number of participants offered repeat assessments. A major challenge of dementia

incidence studies is follow-up time. Because of the long preclinical phase of dementia and possibility of reverse causality, large-scale studies with a long follow up period are needed to provide further evidence on the temporality of this association. The studies of this thesis focused on the incidence of dementia or cognitive decline, however, existing literature suggests common infections, particularly respiratory, UTIs and sepsis, frequently occur in individuals with dementia.[294,299] Therefore, further studies are needed to investigate the trajectories of cognitive decline in individuals with dementia following infection.

Residual confounding is a key drawback of observational studies and of particular in the association of infections and dementia risk given the wide range of potential confounders. Future studies could employ the use of negative controls for example chronic diseases of ageing such as hip fracture to detect residual confounding and improve causal inference.[300]

Infections occur more frequently in older adults as the immune system deteriorates with age.[301] Frailty also develops with increasing age and is associated with a weakened inflammatory response and a poor recovery after infections. Frailty is also associated with adverse outcomes including cognitive impairment and dementia.[302-305] Considering this, future studies could explore whether frailty modifies the association between common infections and dementia. In addition, further studies could explore immunosuppression as a potential effect modifier. Reduced immunity is associated with increased susceptibility to infections and conditions associated with immunosuppression (e.g. due to immunosuppressive therapy) such as kidney transplantation have been linked with dementia risk.[306] It is possible that immunosuppression could be on the causal pathway of infections and dementia with the association of infections on dementia risk higher among immunosuppressed individuals. Furthermore, given that diabetes was an effect modifier for the association between infections and dementia in the CPRD and HES study, reduced immunity could be driving this association and this highlights the importance of future work to explore immunosuppression as a potential effect modifier in this association. Another potential effect modifier could be inflammatory conditions. Systemic inflammation has been identified as a mechanism by which infections may increase dementia risk, and in turn

markers of systemic inflammation are also associated with dementia incidence as such it is possible that inflammatory conditions may be on the causal pathway of infections and dementia. Further work could investigate whether inflammatory conditions modify the effect of infections and dementia. Similarly, systemic inflammation is a potential mechanism linking infections, delirium and dementia, however, this relationship remains poorly understood. Delirium is not well captured in EHRs as such it was not possible to explore assess delirium in this thesis. However, more work is needed to better understand the independent associations between infections and dementia, to explore whether delirium lies on the causal pathway between infections and dementia, potentially modifying this association, and to explore the role of systemic inflammation in this relationship.

The association of infections with cognitive decline or dementia may be affected by the apolipoprotein (*APOE*) gene. The *APOE ε*4 allele is a genetic risk factor for Alzheimer's disease and has been associated with infections including sepsis progression[307-310] In a recent prospective French study of 1037 individuals, those with herpes simplex virus who were carriers of the *APOE ε*4 allele were associated with an increased risk of Alzheimer's disease.[311] Another recent US cohort study of 569 individuals found that *APOE ε*4 may modify the association between infection burden and poor cognition.[312] Therefore, there is a need to explore whether *APOE ε*4 modifies any association between common infections and dementia or cognitive decline.

An infection that was not explored in this thesis but warrants further exploration in future studies is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 (Coronavirus disease 2019) which has resulted in more than 237 million confirmed cases and over 4.8 million deaths has highlighted not only the burden of infections on society, individuals and health care systems but also the impact of complications from infections.[313] One such complication is neurological deficits. Increasing studies have found that individuals infected with COVID-19 experience global cognitive impairment as well as impairment on multiple individual cognitive domains including memory, attention and executive function and verbal fluency. [314] A direction for future studies could be to investigate whether COVID-19 is associated with long term cognitive impairment. These studies could assess the trajectory of cognitive

deficits following COVID-19 over time and the underlying biological mechanisms. In context with the findings of this thesis, future work could focus on the association between COVID-19 infection and risk of dementia with consideration for the severity of infection, including whether the infection resulted in hospital admission. Given that the neuropathological processes of dementia may take decades to develop, these studies will take years to complete.

As explained in the background in chapter 1, the burden of dementia is rising, particularly in low to middle income countries. Research on common infections and dementia has been conducted in a few high-income countries; US, Taiwan, the United Kingdom, Germany and Sweden. More research is needed in other countries, particularly in low- and middle-income countries where currently over 60% of the world's population living dementia reside and in 2050 it is estimated that this number will rise to over 70% owing to global population growth and ageing.[315,316] The potential for dementia risk reduction interventions may therefore be higher in these countries. Despite this, only 10% of dementia related research is conducted in these countries. Moreover, the prevalence and type of infections or pathogens may differ in different geographical locations, and any future interventions on lowering infection and dementia risk may need to account for cultural or environmental differences. In order to compare studies conducted across different countries and continents, consistency in dementia and infection definition will be required.

8.7 Implications for clinical practice

Findings of the CPRD and HES study suggest that infections could be a potentially modifiable risk factor for dementia, especially in some high-risk groups such as people with diabetes. To provide further evidence on whether the association between infections and dementia causal, future studies could use mendelian randomisation to examine the relationship between genetic susceptibility to infections and dementia risk. To translate these findings into clinical practice, there is also a need for intervention trials, which could involve utilising long term follow up of vaccination trials, or observational studies aimed at investigating whether infection prevention interventions are effective at reducing the risk of dementia. These studies could also involve strategies

focusing on the early recognition and treatment of infections in people with diabetes and other high-risk groups. Knowledge of the efficacy, timing and target population groups of these interventions would then inform clinical practice.
These findings could have implications in identifying those at high risk of developing infections and public health strategies to address infections to delay the onset of dementia. Strategies for preventing infections may include the early recognition and treatment of infections, and strategies to increase vaccine uptake.

Additionally, given that in the CPRD and HES study there was evidence suggesting that diabetes modifies the effect of infections on dementia, future studies should explore this link further and this could lead to strategies to improve the recognition and treatment of infections in people with diabetes. These strategies in those with diabetes could be early identification of infections in people with diabetes or improvements in antibiotic prescribing to ensure better management of infections. This is especially important given the global rise in the number of people living with diabetes.

8.8 Conclusions

In conclusion, this thesis extends existing literature on the longitudinal association of common infections, dementia and cognitive decline. The findings suggest that common infections occurring during late life are associated with an increased risk of dementia in adults aged 65 years and older. People who have had infections that are likely to be severe such as sepsis, pneumonia or hospitalised infections were at a greater risk of dementia while the association of milder infections such as those treated in community general practice was weaker. The risk of infections on dementia was somewhat stronger in individuals with diabetes. In a healthier, younger cohort study of adults recruited between 40-69 years of age, midlife infections leading to hospital admission were associated with incident dementia though no association was found between the presence and site of midlife infections with dementia in this cohort. No association was found between midlife common infections and cognitive decline in all cognitive tests, with the exception of the visual memory test. To translate these findings into clinical practice, further studies are warranted to determine whether strategies to lower the risk of infections are associated with a reduced risk of dementia. In terms of cognitive

decline, future studies with sufficient sample sizes for infection types and hospital infections using cognitive measures with sufficient sensitivity to detect subtle changes in cognition in middle age, are needed to confirm the findings of this thesis.

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10. Appendix

Appendix 10.1 Supplementary information for chapter 3

In this section, I provide the supplementary information for chapter 3. This supplementary information relates to research paper 1 and 2. For research paper 1, the systematic review protocol, I include the protocol for the systematic review that was registered on the PROSPERO database and the search strategy of the review for one of the electronic databases used. For research paper 2, the systematic review, I include the supplementary material for this paper which includes the search strategy across all databases searched, extracted data items, Reasons for up- or downgrading on the GRADE quality assessment, changes to protocol, risk of bias, GRADE quality assessment and the exploration of heterogeneity.

Citation

Rutendo Muzambi, Charlotte Warren-Gash, Liam Smeeth, Krishnan Bhaskaran, Carol Brayne. Common bacterial infections and incident cognitive decline or dementia: a systematic review. PROSPERO 2018 CRD42018119294 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018119294

Review question

1. Are common bacterial infections associated with an increased risk of cognitive impairment or dementia?

2. What are the main gaps in literature and recommendations for future research on this topic?

Searches

A search strategy will be conducted for published studies and grey literature. Published studies will be searched in the following electronic databases: MEDLINE (Ovid interface) EMBASE (Ovid interface), Web of Science, Scopus, Global health, Cochrane Library, PsycINFO and CINAHL. Grey Literature will be searched on relevant databases including OpenGrey and the British Library of electronic theses databases (ETHOS). In addition, reference lists of included papers will be manually searched to identify any other relevant papers. There will be no restrictions based on the geographical settings, date of publication or language of the studies.

Types of study to be included

The review will comprise of longitudinal studies only. These will include retrospective and prospective cohort studies, randomised controlled trials and case control studies.

Condition or domain being studied

Incident dementia (all subtypes).

Incident cognitive impairment.

Common bacterial infections.

Participants/population

Eligible for inclusion will be human studies of adults aged 18 years and over with a clinical diagnosis of a common bacterial illness.

Since the review will focus on bacterial illness, studies only focussing on specific bacterial pathogens without a diagnosis of an actual bacterial illness will be excluded. Additionally, animal studies will be excluded.

Intervention(s), exposure(s)

The primary exposures are common bacterial infections (sepsis, urinary tract infections, lower respiratory tract infections and skin and soft tissue infections).

Comparator(s)/control

No exposure or person time without common bacterial infections.

Context

Studies conducted in any setting (e.g. primary or secondary care, community) will be potentially eligible for inclusion.

Main outcome(s)

All types of dementia.

Cognitive Impairment.

Measures of effect

Timing: Diagnosis of common bacterial infections must precede cognitive impairment and dementia.

Effect measures: measures of association (relative risks, hazard ratios, odds ratio) for incidence of cognitive impairment or dementia with common bacterial infections.

Additional outcome(s)
None.

Measures of effect
Not applicable.

Data extraction (selection and coding)
Data will be extracted by two researchers who will independently screen all titles and abstracts based on the inclusion criteria. The researchers will then independently screen full text articles and decide on whether the inclusion criteria has been met. If there are any discrepancies between reviewers' results, the full article will be retrieved, and the differences will be resolved by discussion. If necessary, a third reviewer will be consulted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be used as a template for reporting study inclusion.

Information will be extracted on: study identification (authors, name of study, year of publication); population characteristics (age, sex); study characteristics (study design, setting, country, sample size, duration of follow up); exposure (type of bacterial infection) outcomes (criteria for defining cognitive impairment and dementia). If any information is missing, study authors will be contacted directly for further details.

Risk of bias (quality) assessment
Risk of bias assessment will be assessed according to the Cochrane Collaboration risk of bias approach. Risk of bias for each component will be classified as 'high risk', 'low risk' or 'unclear risk'. In addition, the quality of evidence will be assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria.

Strategy for data synthesis
A narrative synthesis will be conducted. If there is an adequate number of studies with sufficient homogeneity in terms of participants, exposures and outcomes, a meta-analysis will be performed. Heterogeneity will be assessed using the I^2 statistic and a fixed or random effects model will be selected based on the level of heterogeneity.

Analysis of subgroups or subsets
Subgroup analyses will be performed if a sufficient number of studies are obtained. These analyses will assess the incidence of cognitive impairment or dementia separately according to the type of common bacterial infection and compare high risk of bias to low risk of bias studies.

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Type and method of review
Epidemiologic, Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date
07 January 2019

Anticipated completion date
06 January 2020

Funding sources/sponsors
Rutendo Muzambi is supported by an Alzheimer's Society PhD Studentship (379 (AS-PHD-17-013))

Conflicts of interest
None known

Language
English

Country
England

Published protocol
https://bmjopen.bmj.com/content/9/9/e030874

Stage of review
Review Completed published

Details of final report/publication(s) or preprints if available
Common Bacterial Infections and Risk of Dementia or Cognitive Decline: A Systematic Review.

Muzambi R; Bhaskaran K; Brayne C; Davidson JA; Smeeth L; Warren-Gash C 2020 Journal of Alzheimer's disease : JAD
https://content.iospress.com/articles/journal-of-alzheimers-disease/jad200303

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Bacterial Infections; Cognitive Dysfunction; Dementia; Humans; Risk Factors

Date of registration in PROSPERO
20 December 2018

Date of first submission
11 December 2018

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note

Regarding our exposure, we intend to capture studies focussing on common bacterial infections causing illness rather than studies only focussing on specific bacterial pathogens. Upon further discussion prior to performing the review, we decided to include sepsis as an exposure too as it fits this definition. Excluding sepsis from the systematic review might mean that we miss relevant studies that could provide further evidence on the association of common bacterial infections with cognitive decline or dementia.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

20 December 2018
21 June 2019
23 February 2021

Appendix 1. Medline (OVID) search strategy

1. Pneumonia/ or pneumonia, bacterial/
2. Pneumonia.ti,ab
3. Lower respiratory tract infection*.ti,ab
4. (LRTI or LRTIS).ti,ab.
5. Exp urinary tract infections/
6. (Urinary adj5 infection*).ti,ab.
7. (UTI or UTIS).ti,ab
8. exp Cystitis/
9. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.
10. exp cellulitis/
11. (Skin and soft tissue infection).mp.
12. Exp sepsis/
13. (septic* or sepsis or septic?emia or systemic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Exp dementia/
16. Exp prion diseases/
17. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab
18. (Dement* or Alzheimer*).ti,ab
19. (Lewy*adj2 bod*).ti,ab.
20. Cognitive dysfunction/
21. (Mild cognitive impairment or MCI).ti,ab
22. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.
23. Cognitive function.ti,ab.
24. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. cohort studies/ or longitudinal study/ or follow-up study/ or prospective study/ or retrospective study/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
26. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
27. Incidence/ or incidence.ti,ab,kw.
28. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.
29. 25 or 26 or 27 or 28
30. 14 and 24 and 29

Supplementary material for research paper 2

Common bacterial infections and risk of dementia or cognitive decline: a systematic review

Authors: Rutendo Muzambi[a], Krishnan Bhaskaran[a], Carol Brayne[b], Jennifer A Davidson[a] Liam Smeeth[a], Charlotte Warren-Gash[a]

SUPPLEMENTARY APPENDIX 1: SEARCH STRATEGY

a) MEDLINE (OVID) search strategy

1. Pneumonia/ or pneumonia, bacterial/
2. Pneumonia.ti,ab
3. Lower respiratory tract infection*.ti,ab
4. (LRTI or LRTIS).ti,ab.
5. Exp urinary tract infections/
6. (Urinary adj5 infection*).ti,ab.
7. (UTI or UTIS).ti,ab
8. exp Cystitis/
9. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.
10. exp cellulitis/
11. (Skin and soft tissue infection).mp.
12. exp sepsis/
13. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Exp dementia/

16. Exp prion diseases/

17. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab

18. (Dement* or Alzheimer*).ti,ab

19. (Lewy*adj2 bod*).ti,ab.

20. Cognitive dysfunction/

21. (Mild cognitive impairment or MCI).ti,ab

22. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.

23. Cognitive function.ti,ab.

24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. cohort studies/ or longitudinal study/ or follow-up study/ or prospective study/ or retrospective study/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

26. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

27. Incidence/ or incidence.ti,ab,kw.

28. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

29. 25 or 26 or 27 or 28

30. 14 and 24 and 29

b) Embase (OVID) search strategy

1. Bacterial pneumonia/ or Pneumonia/

2. Pneumonia.ti,ab

3. Lower respiratory tract infection*.ti,ab

4. (LRTI or LRTIS).ti,ab.

5. Exp Urinary tract infections/

6. exp Bacteriuria/

7. exp Pyuria/

8. (Urinary adj5 infection*).ti,ab.

9. (UTI or UTIS).ti,ab

10. Exp cystitis/

11. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.

12. exp cellulitis/

13. (Skin and soft tissue infection).mp.

14. exp sepsis/

15. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.

16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. Exp dementia

18. Exp Creutzfeldt-jakob disease

19. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab

20. Dement*.ti,ab.

21. Exp mild cognitive impairment/

22. (Mild cognitive impairment or MCI)ti,ab

23. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.

24. Cognitive function.ti,ab.

25. Alzheimer*.ti,ab

26. (Lewy*adj2 bod*).ti,ab.

27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. cohort analysis/ or longitudinal study/ or follow-up/ or prospective study/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

29. Case control study/ or Control Group/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

30. Incidence/ or incidence.ti,ab,kw.

31. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

32. 28 or 29 or 30 or 31

33. 16 and 27 and 32

c) Global health (OVID) search strategy

1. Pneumonia/ or bacterial pneumonia/

2. Pneumonia.ti,ab

3. Lower respiratory tract infection*.ti,ab

4. Lower respiratory tract infections/

5. (LRTI or LRTIS).ti,ab.

6. Exp Urinary tract infections/

7. Exp Bacteriuria/

8. (Urinary adj5 infection*).ti,ab.

9. (UTI or UTIS).ti,ab

10. Exp cystitis/

11. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.

12. exp cellulitis/

13. (Skin and soft tissue infection).mp.

14. Exp sepsis/

15. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.

16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. Exp dementia/

18. Exp creutzfeldt-jakob disease/or exp prion diseases/

19. (Dement* or Alzheimer*).ti,ab

20. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab

21. (Mild cognitive impairment or MCI).ti,ab.

22. Cognitive function.ti,ab.

23. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.

24. (Lewy*adj2 bod*).ti,ab.

25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

26. cohort studies/ or longitudinal studies/ or follow up/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

27. Case-Control Studies/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

28. Incidence/ or incidence.ti,ab,kw.

29. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

30. 26 or 27 or 28 or 29

31. 16 and 25 and 30

d) PsychINFO (OVID) search strategy

1. Pneumonia/
2. Pneumonia.ti,ab
3. Lower respiratory tract infection*.ti,ab
4. (LRTI or LRTIS).ti,ab.
5. (Urinary adj5 infection*).ti,ab.
6. (UTI or UTIS).ti,ab
7. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.
8. (Skin and soft tissue infection).mp.
9. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Exp dementia
12. Exp kluver bucy syndrome/
13. Exp huntingtons disease/
14. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab
15. (Dement* or Alzheimer*).ti,ab
16. cognitive impairment/
17. (Mild cognitive impairment or MCI)ti,ab
18. Cognitive function.ti,ab.
19. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.

20. (Lewy*adj2 bod*).ti,ab.

21. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. cohort analysis/ or longitudinal studies/ or followup studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

23. ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

24. Incidence/ or incidence.ti,ab,kw.

25. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

26. 22 or 23 or 24 or 25

27. 10 and 21 and 26

e) CINAHL Plus search strategy

S1. (MH "pneumonia, bacterial")

S2. (MH "Pneumonia")

S3. TI "pneumonia" or AB "pneumonia"

S4. TI "lower respiratory tract infection*" or AB "lower respiratory tract infection"

S5. TI LRTI or AB LRTI or TI LRTIs or AB LRTIs

S6. (MH "urinary tract infections+")

S7. TI "urinary tract infection*" or AB "urinary tract infection*"

S8. TI "UTI" or AB "UTI" or TI "UTIs" or AB "UTIs"

S9. (MH "cystitis+")

S10. TI "cystitis" or AB "cystitis"

S11. TI "bacteriuria" or AB "bacteriuria"

S12. TI "pyuria" or AB "pyuria"

S13. (MH "pyelonephritis")

S14. TI “pyelonephritis” or AB “pyelonephritis”

S15. (MH “cellulitis+”)

S16. TI “cellulitis” or AB “cellulitis”

S17. (TI “skin and soft tissue infection” or AB “skin and soft tissue infection”

S18. TI "septic*" or AB "septic*" or TI sepsis or AB sepsis or TI septic#emia or AB septic#emia or TI "systematic inflammatory response syndrome" or AB "systematic inflammatory response syndrome" or TI "blood stream infection" or AB "blood stream infection" or TI py#emia or AB py#emia

S19. (MH "Sepsis+") OR (MH "Systemic Inflammatory Response Syndrome+") OR (MH "Shock, Septic+")

S20. S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19

S21. (MH “Dementia+”) or (MH “Frontotemporal Dementia+”) or (MH “Dementia, Vascular+” or (MH “Dementia, Multi-Infarct+” or (MH “Lewy Body Disease”) or (MH “Dementia, senile+”) or (MH “Dementia, presenile+”)

S22. (MH”Creutzfeldt-Jakob syndrome+) or (MH “prion diseases+”)

S23. (MH “Alzheimer’s Disease”)

S24. (MH “Huntington’s Disease”)

S25. (MH “Pick Disease of the Brain”)

S26. TI “Dement*” or AB “Dement*”

S27. TI “Alzheimer*” or AB “Alzheimer*”

S28. TI “huntington*” or AB “huntington*” or TI “kluver-bucy” or AB “kluver-bucy” or TI “Creutzfeldt-Jakob” or AB “Creutzfeldt-Jakob” or TI “primary progressive aphasia” or AB “primary progressive aphasia”

S29. TI “Mild cognitive impairment” or AB “Mild cognitive impairment” or TI “MCI” or AB “MCI”

S30. TI “Cognitive function” or AB “cognitive function”

S31. TI ((cognit* or memory or cerebr* or mental*) N3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)) OR AB ((cognit* or memory or cerebr* or mental*) N3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*))

S32. TI “Lewy*bod*” or AB “Lewy* bod*”

S33. S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32

S34. (MH “Prospective studies”)

S35. (MH “Retrospective studies”)

S36. TI “cohort” or AB “cohort” or TI “longitudinal” or AB “longitudinal” or TI “prospective” or AB “prospective” or TI “retrospective” or AB “retrospective”

S37. (MH “Case Control Studies”)

S38. (MH “Control Group”)

S39. (MH “Matched-Pair Analysis”)

S40. TI “case* control* or AB “case* control*” or TI “case comparison*” or AB “case comparison*” or TI “control group*” or AB “control group*”

S41. (MH “incidence”)

S42. Incidence

S43. TI “Hazard Ratio” or AB “Hazard Ratio” or TI HR or AB HR or TI “odds ratio” or AB “odds Ratio” or TI “relative risk” or AB “relative risk” or TI RR or AB RR

S44. S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43

S45. S20 and S33 and S44

f) Cochrane Library search strategy

1. MESH Descriptor: [bacterial infections] this term only
2. Bacterial infection:ti,ab,kw
3. Pneumonia:ti,ab,kw
4. MeSH descriptor [Pneumonia] this term only
5. MeSH descriptor [Pneumonia, bacterial] explode all trees
6. (Lower respiratory tract infection*):ti,ab,kw
7. (LRTI or LRTIS):ti,ab,kw
8. MeSH descriptor: [Urinary tract infections] explode all trees
9. (Urinary tract infections):ti,ab,kw
10. (UTI or UTIS):ti,ab,kw
11. MeSH descriptor: [Bacteriuria] explode all trees
12. MeSH descriptor: [Pyuria] explode all trees
13. (Bacteriuria or pyuria or pyelonephritis or cystitis or cellulitis):ti,ab,kw
14. MeSH descriptor: [cystitis] explode all trees
15. MeSH descriptor: [cellulitis] explode all trees
16. Skin and soft tissue infection:ti,ab,kw
17. MeSH descriptor: [sepsis] explode all trees
18. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab,kw
19. #1 or #2 or #3 or #4 or #5 or #6 or #7 or# 8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
20. MeSH descriptor: [dementia] explode all trees
21. MeSH descriptor: [Alzheimer disease] explode all trees
22. (Dement*):ti,ab,kw

23. (Alzheimer*):ti,ab,kw

24. MeSH descriptor: [Dementia, multi-infarct] explode all trees

25. MeSH descriptor: [prion diseases] explode all trees

26. MeSH descriptor: [pick disease of the brain] explode all trees

27. (Mild cognitive impairment or MCI):ti,ab,kw

28. (Cognitive function):ti,ab,kw

29. MeSH descriptor: [cognitive dysfunction] explode all trees

30. (Lewy* bod*):ti,ab,kw

31. #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30

32. MeSH descriptor: [cohort studies] explode all trees

33. MeSH descriptor: [longitudinal] explode all trees

34. (cohort or longitudinal or prospective or retrospective):ti,ab,kw

35. MeSH descriptor: [case-control groups] explode all trees

36. MeSH descriptor: [matched-pair analysis] explode all trees

37. MeSH descriptor: [control groups] explode all trees

38. Case-Control Studies/ or ((case* control*) or (case comparison*) or control group*).ti,ab,kw

39. MeSH descriptor: [incidence] explode all trees

40. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

41. #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40

42. #19 and #31 and #40

g) Web of Science search strategy

1. TS=(pneumonia or “lower respiratory tract infection” or LRTI OR LRTIs or “urinary tract infection*” or UTI or UTIs or bacteriuria or pyuria or pyelonephritis or cystitis or “skin and

soft tissue infection” or "septic*" or sepsis or septic?emia or "systematic inflammatory response syndrome" or "blood stream infection" or py?emia)

2. TS=(dement* or Alzheimer* or “lewy* bod*” or “primary progressive aphasia” or huntington* or “kluver-bucy” or “prion disease” or “Creutzfeldt-jakob disease” or “mild cognitive impairment” or MCI or “cognitive function”) OR TS=((cognit* or memory or cerebr* or mental*) NEAR/3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*))

3. TS=(cohort study or longitudinal or “follow up” or prospective or retrospective or “case control” or “case comparison” or “control group” or incidence or “hazard ratio” or HR or “odds ratio” or “relative risk” or RR)

4 #1 and #2 and #3

h) Scopus search strategy

((TITLE-ABS (pneumonia OR "lower respiratory tract infection*" OR lrti OR lrtis OR "urinary tract infection*" OR uti OR utis OR bacteriuria OR pyuria OR pyelonephritis OR cystitis OR "skin and soft tissue infection" OR cellulitis OR sepsis OR "septic*" OR "sepsis" OR septic?emia OR "systematic inflammatory response syndrome" OR "blood stream infection" OR py?emia))) AND (((TITLE-ABS (dement* OR alzheimer* OR "lewy* bod*" OR "primary progressive aphasia" OR "huntington*" OR "kluver-bucy" OR "creutzfeldt-jakob" OR "mild cognitive impairment" OR mci OR "cognitive function"))) OR ((TITLE-ABS (cognit* OR memory OR cerebr* OR mental*) W/3 (declin* OR impair* OR los* OR deteriorat* OR degenerat* OR complain* OR disturb* OR disorder*))

)) AND ((TITLE-ABS (cohort OR longitudinal OR "follow up" OR prospective OR retrospective OR "case control" OR "control group" OR "incidence" OR "hazard ratio" OR hr OR "odds ratio" OR "relative risk" OR rr)))

i) Open Grey search strategy

1. “Bacteria* infection*” and dement*
2. “Bacteria* infection*” and Alzheimer*
3. “Bacteria* infection” and cognit*
4. Pneumonia and dement*
5. Pneumonia and Alzheimer*
6. Pneumonia and cognit*
7. “Lower respiratory tract infection*” and dement*
8. “Lower respiratory tract infection*” and Alzheimer*
9. “Lower respiratory tract infection*” and cognit*
10. “Urinary tract infection” and dement*
11. “Urinary tract infection” and Alzheimer*
12. “Urinary tract infection” and cognit*
13. cystitis and dement*
14. cystitis and Alzheimer*
15. Cystitis and cognit*
16. Bacteriuria and dement*
17. Bacteriuria and Alzheimer*
18. Bacteriuria and cognit*
19. Pyelonephritis and dement*
20. Pyelonephritis and Alzheimer*

21. Pyelonephritis and cognit*
22. cellulitis and dement*
23. cellulitis and Alzheimer*
24. cellulitis and cognit*
25. “skin and soft tissue infection” and dement*
26. “skin and soft tissue infection” and Alzheimer*
27. “skin and soft tissue infection” and cognit*
28. Sepsis and dement*
29. Sepsis and Alzheimer*
30. Sepsis and Cognit*
31. Septic* and dement*
32. Septic* and Alzheimer*
33. Septic* and cognit*

J) British Library of Electronic Theses (EThOS) search strategy

1. Bacterial infection and dementia
2. Bacterial infection and Alzheimer
3. Bacterial infection and cognition
4. Pneumonia and dementia
5. Pneumonia and Alzheimer
6. Pneumonia and cognition

7. Lower respiratory tract infection and dementia
8. Lower respiratory tract infection and Alzheimer
9. Lower respiratory tract infection and cognition
10. Urinary tract infection and dementia
11. Urinary tract infection and Alzheimer
12. Urinary tract infection and cognition
13. Cystitis and dementia
14. Cystitis and Alzheimer
15. Cystitis and cognition
16. Bacteriuria and dementia
17. Bacteriuria and Alzheimer
18. Bacteriuria and cognition
19. Pyelonephritis and dement*
20. Pyelonephritis and Alzheimer*
21. Pyelonephritis and cognit*
22. cellulitis and dementia
23. cellulitis and Alzheimer
24. cellulitis and cognition
25. skin and soft tissue infection and dementia
26. “skin and soft tissue infection” and Alzheimer*
27. “skin and soft tissue infection” and cognit*
28. Sepsis and dementia
29. Sepsis and alzheimer
30. Sepsis and cognition
31. Septicemia and dementia

32. Septicemia and Alzheimer

33. Septicemia and cognition

34. Septicaemia and dementia

35. Septicaemia and Alzheimer

36. Septicaemia and cognition

SUPPLEMENTARY APPENDIX 2: EXTRACTED DATA ITEMS

Population: age (mean, median or range), sex, inclusion and exclusion criteria.

Exposure: definition of exposure, type of bacterial infection, cause of sepsis, number of exposed.

Comparators: identification and definition of comparator, number of comparators.

Outcomes: definition of outcome and identification of cognitive decline and dementia, number of participants with the outcome.

Study characteristics: authors, name of study, year of publication, study design, type of longitudinal study, healthcare setting, country, sample size, duration of follow-up.

SUPPLEMENTARY APPENDIX 3: GRADE QUALITY ASSESSMENT REASONS TO UP- OR DOWNGRADE

1. Risk of bias:

- Not serious if >50% of studies have no domain which is at high risk of bias.
- Serious if studies are judged to be between 'not serious' and 'very serious'.
- Very serious if studies which have two or more domains at high risk of bias represent more than 50% of the total studies and contribute more than 50% to any meta-analyses.

2. Inconsistency:

- Not serious if have 0, serious if have 1, and very serious if have two or more of the following:
- Heterogeneity is moderate (I^2 ~30-60%), or above.
- Wide variance of point estimates across different studies.
- Minimal overlap of confidence intervals.

3. Indirectness:

Not serious if have 0, serious if have 1, and very serious if have two of the following:

- An indirect comparison (for example study A compares to a group without any infection and study B compares to a group without a specific infection category).
- Studies differ in terms of population (e.g. hospitalized patients only vs primary care patients)
- Studies differ in terms of exposure definition (e.g. for example use different methods to ascertain common bacterial infections).

- Studies differ in terms of outcome measures (e.g. for example restricted to certain time-frames, or have a different definition of dementia or cognitive impairment).

4. Imprecision

Low power and wide confidence intervals

- Serious imprecision: Wide confidence intervals
- Very serious imprecision: Very wide confidence intervals

5. Upgrading

Upgrading reasons include

Large effect:

- None: most effect estimates <2
- Strong association: effect estimates >2 or <0.5 (based on direct evidence, with no plausible confounders)
- Very strong association: effect estimates >4 or <0.2 (based on direct evidence with no serious problems with risk of bias or precision, i.e. with (sufficiently narrow confidence intervals).

Plausible confounding

- Would dilute the demonstrated effect: e.g. If, for instance, only sicker patients are exposed, yet they still fare better, it is likely that the actual exposure effect is even larger than the data suggest (confounding by indication).
- Would suggest spurious effect: When confounding is expected to increase the effect but no effect was observed.

6. Quality

Very low, low, moderate or high

SUPPLEMENTARY APPENDIX 4: CHANGES TO PROTOCOL

- In our protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO), we had not included sepsis as one of the bacterial infections that we would be including in the present review. However, as sepsis is a common infection that fits our exposure definition. As such, excluding sepsis from the systematic review may result in the omission of relevant studies.

RISK OF BIAS

Supplementary table 1. Risk of bias judgement and justification

	1. Confounding	**2. Selection of participants**		**3. Misclassification of variables**										**4. Bias due to missing data**		**5. Reverse Causation**	**6. Generalizability**	**7. Study Power**
	Age and other confounders	Participation bias	Selection of control/comparator group	**Exposure**				**Outcome**				**Covariates**		Differential loss to follow up	Exclusion of individuals with missing data			
				Differential			Non-differential	Differential				Differential	Non-differential					
				Recall bias	Observer bias	Ascertainment bias		Recall bias	Observer bias	Ascertainment bias	Non-differential							
Shah et al, 2013 [224]	Low. Adjusted for age and sex and other confounders	Moderate: Non-random sample and comparisons show those enrolled were younger than those not included. Refusal rates were higher among women than men.	Low. Comparators selected from the same population as cases	Unclear. Participants asked about hospitalizations but medical records were then checked and pneumonia identified using ICD-9 CM codes	Low. Pneumonia defined prior dementia.	Low. Pneumonia defined before dementia.	Unclear. Participants self-report hospitalizations thus misclassification is possible. However, medical records checked and pneumonia hospitalizations defined using ICD-10 codes.	Low. Dementia defined using multiple diagnostic tests.	Low. Dementia defined using multiple diagnostic tests, diagnosis of dementia unlikely to be influenced by infections	Low. Ascertainment of dementia unlikely to be influenced by pneumonia status	Low. Dementia assigned in multiple diagnostic tests.	Low. Capture of covariates unlikely to differ by exposure status.	Low. Covariates ascertained using ICD-9 diagnostic codes.	Unclear. Loss to follow up not described.	Low. Less than 5% of data missing on covariates and less than 5% data missing on 3MS test.	Low. Pneumonia defined before dementia.	Hospitalized patients in the US	High. No power calculation described and small study.
Guerra et al, 2012 [252]	Low. Adjusted for age and other covariates	Low. Random sample of all Medicare beneficiaries	Low. Comparators selected from the same population as cases	Low. Severe sepsis defined using ICD-9 CM codes	Low. Sepsis defined prior to dementia.	Low. Sepsis defined before dementia.	Low. All members assessed for critical illnesses, including severe sepsis, at baseline.	Low. Dementia defined using ICD-9-CM codes.	Low. Dementia defined using medical records, diagnosis of dementia unlikely to be influenced by infections	Low. Sepsis unlikely to be associated with health-seeking behavior and influence dementia	Low. Dementia diagnosed using ICD-9-CM codes	Low. Capture unlikely to differ by exposure status	Low. Covariates ascertained using ICD-9 diagnostic codes.	Low. Automated follow up.	Unclear. Missing data not described.	Low. Severe sepsis defined prior to dementia.	Hospitalized adults in the US eligible for Medicare	Low. Large study with narrow confidence intervals.

										ascertainment								
Mawanda et al, 2016 [292]	Low. Adjusted for age, sex and other covariates.	Low. Automated participation (veterans' health administration databases)	Low. Comparators selected from the same population as cases	Low. Exposure status ascertained using ICD-9 diagnostic codes.	Low: Exposure defined using ICD-9 codes. Exposure defined before outcome	Low: Exposure defined before outcome	Low: Infections defined using ICD-9 codes and PPV estimated at 70% for pneumonia and cellulitis.	Low. Dementia defined using ICD-9 codes.	Low. Dementia defined using medical records, diagnosis of dementia unlikely to be influenced by infections	Low. Bacterial infections unlikely to be associated with health-seeking behavior and influence dementia ascertainment	Low. Medical diagnosis of dementia. PPV of medical conditions estimate at 98.3%.	Low. Capture unlikely to differ by exposure status	Low. Covariates ascertained using medical records.	Low. Automated follow up.	Moderate. 22% with missing data on demographic variables excluded from study. Missing data on other variables in study population not described	Low. Exposure defined before outcome.	US male veterans	Low: Large study with narrow confidence intervals.
Chou et al, 2017 [152]	Low. Age and sex matched, adjusted for other confounders.	Low. Automated participation (longitudinal health insurance database)	Low. Comparators selected from the same population as cases but not selected randomly.	Low. Exposure defined using hospital diagnostic codes for septicemia	Low. Septicemia defined before outcome.	Low. Septicemia defined before dementia.	Low. Septicemia defined using ICD-9-CM codes	Low. Dementia defined using ICD-9 codes.	Low. Dementia defined using medical records, diagnosis of dementia unlikely to be influenced by infections	Low. Septicemia unlikely to be associated with health-seeking behavior and influence dementia ascertainment	Low. Medical diagnosis of dementia.	Low. Capture unlikely to differ by exposure status	Low. Covariates ascertained using ICD-9 diagnostic codes.	Low. Automated follow up.	Unclear. Missing data not described.	Low. Septicemia defined before outcome and those with dementia at baseline excluded.	Hospitalized adults in Taiwan	Low. Large study with narrow confidence intervals.

Chou et al. 2018. [5]	High. Age and sex matched, but matching not described and adjustment for other confounders not mentioned.	Low. Automated participation (longitudinal health insurance database)	Unclear. Selection of comparator group unclear	Ascertainment of exposure unclear.	Ascertainment of exposure unclear.	Ascertainment of exposure unclear.	Ascertainment of exposure unclear.	Ascertainment of outcome unclear.	Ascertainment of outcome unclear.	Ascertainment of outcome unclear.	Ascertainment of outcome unclear.	Ascertainment of outcome unclear.	Ascertainment of outcome unclear.	Low. Automated follow up.	Unclear. Missing data not described.	Low. Septicemia defined before outcome and those with dementia at baseline excluded.	Hospitalized adults in Taiwan	Low. Large study with narrow confidence intervals.
Tate et al, 2014. [6]	Low. Adjusted for age and sex and other confounders	Low. Participants form a randomized double-blind clinical trial	Low. Comparators selected from the same population as cases	Low. Exposure status defined by hospital medical records (ICD-9 codes and text field searches)	Low. Pneumonia defined before dementia.	Low. Pneumonia defined before dementia.	Low. Pneumonia defined using medical records	Low. Dementia defined using ICD-9 codes.	Low. Dementia defined using medical records, diagnosis of dementia unlikely to be influenced by infections	Low. Pneumonia unlikely to be associated with health-seeking behavior and influence dementia ascertainment	Low. Participants screened for dementia every 6 months.	Low. Capture unlikely to differ by exposure status	High. Covariates self-reported	Unclear. Loss to follow up not described.	Unclear. Missing data not described.	Low. Exposure defined before outcome. Those with dementia at baseline excluded.	Hospitalized adults in the US	High. No power calculation described, small study and wide confidence intervals.
Kao et al. 2015. [7]	Low. Age and sex matched and adjusted for other confounders	Low. Automated participation (longitudinal health insurance database)	Low. Controls selected from the same population as the cases. Random sampling used.	Low. Exposure defined using hospital diagnostic codes for septicemia	Low. Exposure defined before dementia.	Low. Sepsis defined before dementia.	Low. Sepsis defined using ICD-9-CM codes	Low. Dementia defined using ICD-9 codes.	Low. Dementia defined using medical records, diagnosis of dementia unlikely to be influenced by infections	Low. Sepsis unlikely to be associated with health-seeking behavior and influence dementia ascertainment	Low. Medical diagnosis of dementia.	Low. Capture of covariates unlikely to differ by exposure status.	Unclear. Ascertainment of covariates not reported.	Low.	Unclear. Missing data not described.	Low. Septicemia defined 5 years prior to dementia diagnosis.	Hospitalized adults in Taiwan	High. Small study with large confidence intervals.

Davydow et al, 2013. [8]	High. No adjustment for age or other covariates	Moderate with no comparison of characteristics of those excluded.	Low. Comparators selected from the same population as cases	Low. Pneumonia was diagnosed using ICD-9-CM principal diagnostic codes	Low. Pneumonia defined before cognitive impairment.	Low. Pneumonia hospitalizations ascertained before cognitive impairment	Low. Pneumonia hospitalizations defined using ICD-9-CM codes.	Low. Cognitive impairment assessed using Telephone Interview for Cognitive Status (TICS)	Low. Cognitive impairment defined using validated cognition test. Diagnosis of cognitive impairment unlikely to be influenced by infections	Low. Ascertainment of cognitive impairment unlikely to be influenced by pneumonia status	Low. Active data collection at follow up and validated diagnostic method.	N/A. Analyses not adjusted for covariates	N/A. Analyses not adjusted for covariates	Unclear. Loss to follow up not described.	Unclear. Missing data not described.	Unclear	Synthetic cohorts of pneumonia with stroke/myocardial infarction. May not be generalize to any population of interest.	High. No power calculation and small study
Sakusic 2018. [9]	Low. Age and sex matched and adjusted for other confounders.	Moderate. No comparison of characteristics of those excluded.	Low. Controls selected from the same population as the cases. Random sampling used.	Unclear. Sepsis ascertainment not clear.	Low. Individuals with cognitive impairment excluded at baseline	Low. Exposure defined before outcome.	Unclear. Ascertainment of exposure is uncertain.	Low. Cognitive impairment defined using electronic medical records.	Unclear. Ascertainment of sepsis is unclear therefore it is unclear if diagnosis of cognitive impairment likely to be influenced by sepsis	Low. Sepsis unlikely to be associated with health-seeking behavior and influence cognitive impairment ascertainment	Low. Electronic search algorithm validated. Sensitivity and specificity 97% and 99%.	Low. Capture of covariates unlikely to differ by exposure status.	Low. Covariates ascertained using medical records.	Low.	Unclear. Missing data not described.	Low. Sepsis defined prior to cognitive impairment.	ICU adult survivors in the US	High. No power calculation and small study

GRADE QUALITY ASSESSMENT

We planned to carry out a GRADE assessment on each infection and outcome, however, we could not assess the study quality when only one study was available. This was due to difficulties in assessing inconsistency and indirectness with a single study. As a result, study quality was assessed only for the studies investigating the association of sepsis or pneumonia with incident dementia.

Supplementary table 2. GRADE assessment of quality of evidence for dementia outcome

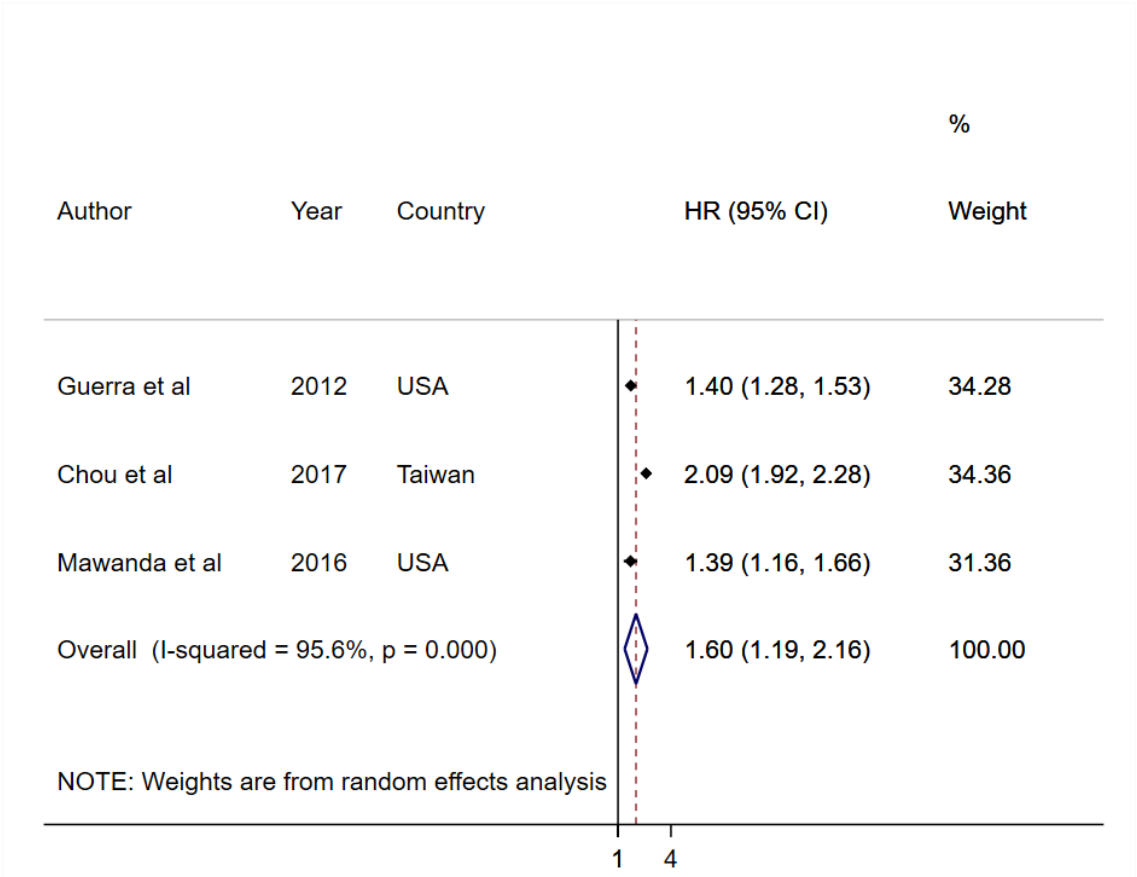
		Downgrade				Upgrade	
Exposure	Study design and no. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision		Quality
Sepsis	5 cohort studies and 1 case control study	serious	very serious	serious	serious	None	⊕◯◯◯ very low
Pneumonia	3 cohort studies	serious	very serious	serious	very serious	None	⊕◯◯◯ very low

EXPLORATION OF HETEROGENEITY

We explored heterogeneity on the association of sepsis with incident dementia by excluding studies from Taiwan.

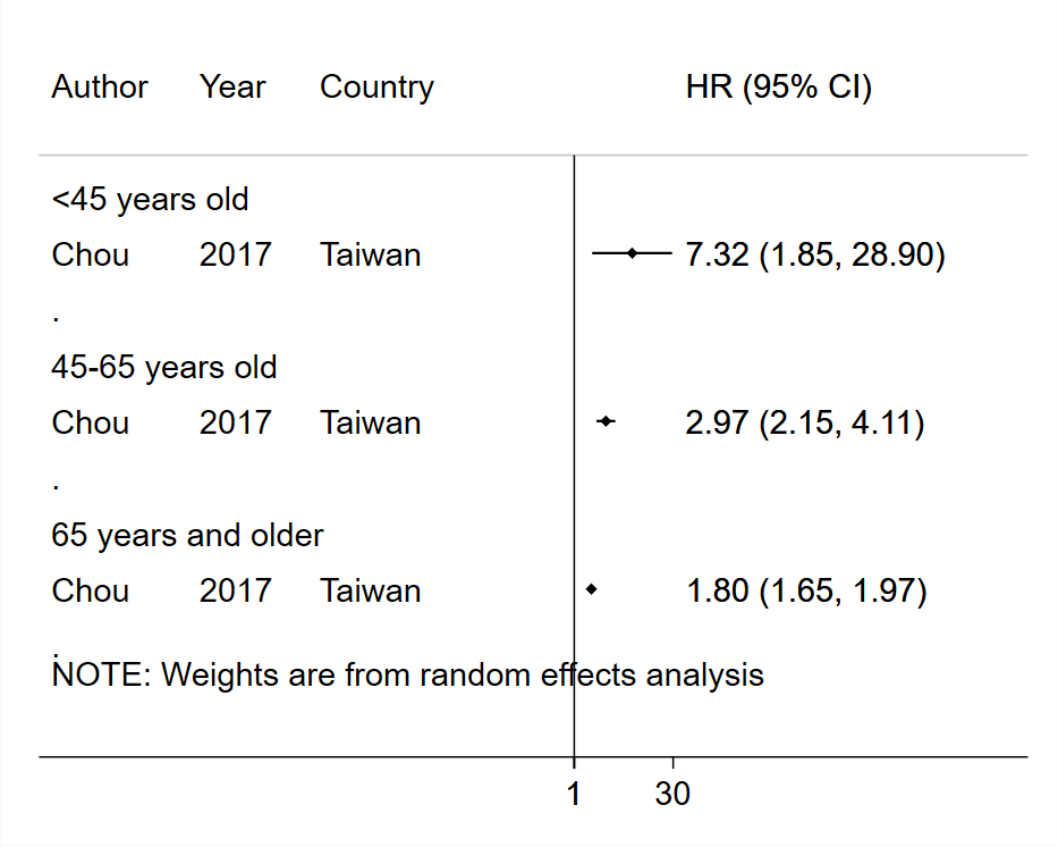
Supplementary Figure 1. The effect of sepsis on dementia, by country (United States)

Supplementary Figure 2. The effect of sepsis on dementia after removing studies with a domain at high risk of bias

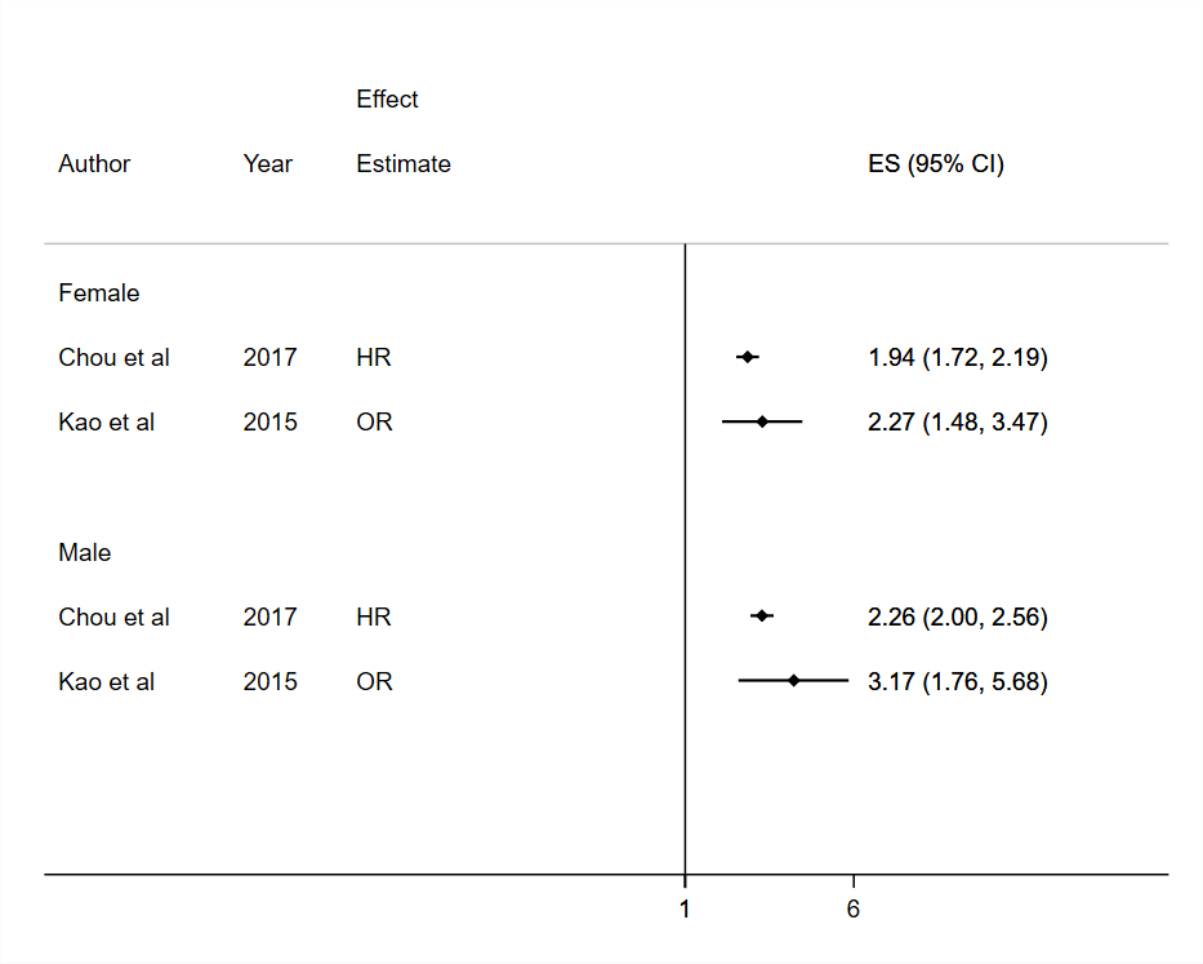

Author
Year
Country
HR (95% CI)
%
Weight
Guerra et al
2012
USA
1.40 (1.28, 1.53)
34.28
Chou et al
2017
Taiwan
2.09 (1.92, 2.28)
34.36
Mawanda et al
2016
USA
1.39 (1.16, 1.66)
31.36
Overall (I-squared = 95.6%, p = 0.000)
1.60 (1.19, 2.16)
100.00
NOTE: Weights are from random effects analysis
1
4

SUB GROUP ANALYSES

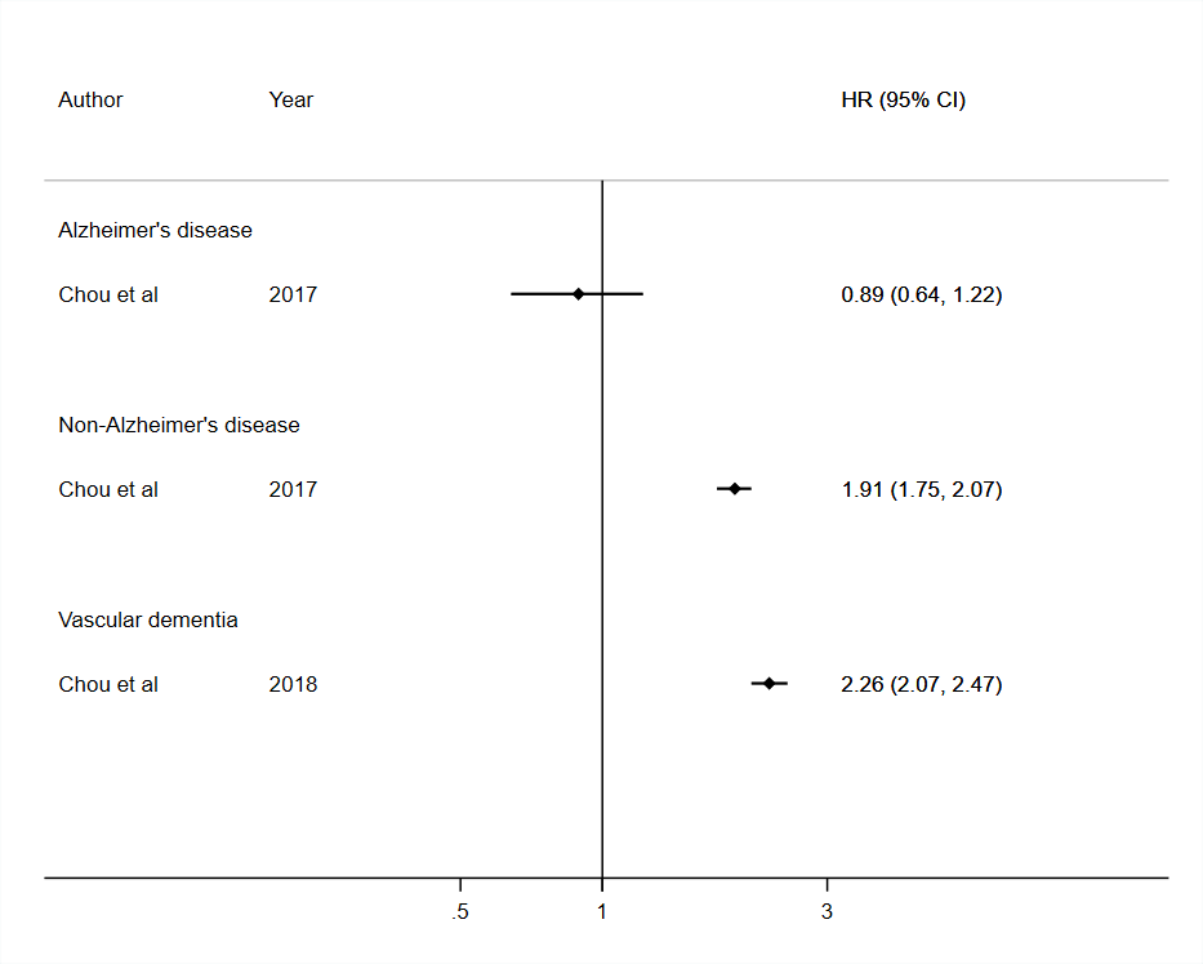
Supplementary Figure 3. The effect of sepsis on dementia, by age



Supplementary Figure 4. The effect of sepsis on dementia, by sex



Supplementary Figure 5. The effect of sepsis on dementia, by dementia subtype



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Appendix 10.2 Supplementary information for chapter 5

This appendix focuses on the supplementary information for research paper 3 in chapter 5. This supplementary information includes the ISAC protocol, LSHTM ethics approval, search strategy, directed acyclic graph of potential confounders and effect modifiers, variable definition and the supplementary tables and figures of the research paper.

Medicines & Healthcare products Regulatory Agency

CPRD

INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC) PROTOCOL APPLICATION FORM
PART 1: APPLICATION FORM

IMPORTANT

Both parts of this application must be completed in accordance with the guidance note 'Completion of the ISAC Protocol Application Form', which can be found on the CPRD website cprd.com/research-applications

FOR ISAC USE ONLY	
Protocol No. -	**Submission date -**

GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title (Max. 255 characters)

The effect of common infections on the risk of dementia in individuals with and without diabetes: a cohort study using UK primary and secondary care data

2. Research Area (place **'X'** in all boxes that apply)

Drug Safety		Economics	
Drug Utilisation		Pharmacoeconomics	
Drug Effectiveness		Pharmacoepidemiology	
Disease Epidemiology	X	Methodological	
Health Services Delivery			

3. Chief Investigator

Title:	Dr
Full name:	Charlotte Warren-Gash
Job title:	Associate Professor of Epidemiology/ Wellcome Intermediate Clinical Fellow
Affiliation/organisation:	London School of Hygiene and Tropical Medicine
Email address:	Charlotte.warren-gash1@lshtm.ac.uk
CV Number (if applicable):	815_16

4. Corresponding Applicant

Title:	Ms
Full name:	Rutendo Muzambi
Job title:	PhD Student
Affiliation/organisation:	London School of Hygiene and Tropical Medicine
Email address:	Rutendo.muzambi@lshtm.ac.uk
CV Number (if applicable):	298_19

5. List of all investigators/collaborators

Title:	Ms
Full name:	Rutendo Muzambi
Job title:	PhD Student
Affiliation/organisation:	London School of Hygiene and Tropical Medicine
Email address:	Rutendo.muzambi@lshtm.ac.uk
CV Number (if applicable):	298_19
Will this person be analysing the data? (Y/N)	Y

Title:	Professor
Full name:	Liam Smeeth
Job title:	Professor of Clinical Epidemiology
Affiliation/organisation:	London School of Hygiene and Tropical Medicine
Email address:	Liam.smeeth@lshtm.ac.uk
CV Number (if applicable):	045_15CEPSL
Will this person be analysing the data? (Y/N)	N

Title:	Professor
Full name:	Krishnan Bhaskaran
Job title:	Professor in statistical epidemiology and Sir Henry Dale fellow
Affiliation/organisation:	London School of Hygiene and Tropical Medicine
Email address:	Krishnan.bhaskaran@lshtm.ac.uk
CV Number (if applicable):	156_15CESL
Will this person be analysing the data? (Y/N)	N

Title:	Professor
Full name:	Carol Brayne
Job title:	Director of the Cambridge Institute of Public Health
Affiliation/organisation:	Cambridge University
Email address:	Cb105@medschl.cam.ac.uk
CV Number (if applicable):	414_16
Will this person be analysing the data? (Y/N)	N

Title:	Professor
Full name:	Nish Chaturvedi
Job title:	Professor of Clinical Epidemiology
Affiliation/organisation:	University College London
Email address:	n.chaturvedi@ucl.ac.uk
CV Number (if applicable):	220_17
Will this person be analysing the data? (Y/N)	N

6. Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

Name:	**Protocol Number/s:**
Dr Charlotte Warren-Gash	17_176R, 18_134R, 19_096
Professor Liam Smeeth	12_027RA, 12_065, 15_257, 16_174, 16_113A, 18_207, 18_278
Professor Krishnan Bhaskaran	12_090, 10_097, 12_044, 12_027, 16_174, 16_113A

List below the member(s) of the research team who have statistical expertise.

Name(s):
Professor Krishnan Bhaskaran

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

Name(s):
Professor Krishnan Bhaskaran
Professor Liam Smeeth

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

Name(s):
Ms Rutendo Muzambi
Professor Liam Smeeth

ACCESS TO THE DATA

7. Sponsor of the study

Institution/Organisation:	London School of Hygiene and Tropical Medicine
Address:	Keppel Street, London, WC1E 7HT

8. Funding source for the study

Same as Sponsor?	Yes		No	X
Institution/Organisation:	Alzheimer's Society			
Address:	Alzheimer's Society, 43-44 Crutched Friars, *London*, EC3N 2AE			

9. Institution conducting the research

Same as Sponsor?	Yes	X	No	
Institution/Organisation:	London School of Hygiene and Tropical Medicine			
Address:	Keppel Street, London, WC1E 7HT			

10. Data Access Arrangements

Indicate with an '**X**' the method that will be used to access the data for this study:

Study-specific Dataset Agreement	

Institutional Multi-study Licence	X
Institution Name	London School of Hygiene and Tropical Medicine
Institution Address	Keppel Street, London, WC1E 7HT

Will the dataset be extracted by CPRD?

Yes		No	X

If yes, provide the reference number:

11. Data Processor(s):

Processing	X
Accessing	X
Storing	X
Processing area (UK/EEA/Worldwide)	UK
Organisation name	London School of Hygiene and Tropical Medicine
Organisation address	Keppel Street, London, WC1E 7HT

[Add more processors as necessary by copy and pasting a new table for each processor]

INFORMATION ON DATA

12. Primary care data (place 'X' in all boxes that apply)

CPRD GOLD	X	CPRD Aurum	

13. Please select any linked data or data products being requested

Patient Level Data (place '**X**' in all boxes that apply)

ONS Death Registration Data		CPRD Mother Baby Link	
HES Admitted Patient Care	X	Pregnancy Register	
HES Outpatient		NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data	
HES Accident and Emergency		NCRAS Cancer Patient Experience Survey (CPES) data	
HES Diagnostic Imaging Dataset		NCRAS Systemic Anti-Cancer Treatment (SACT) data	
HES PROMS (Patient Reported Outcomes Measure)		NCRAS National Radiotherapy Dataset (RTDS) data	
		Mental Health Services Data Set (MHDS)	

Area Level Data (place '**X**' in all boxes that apply)

Practice level (UK)		**Patient level (England only)**	
Practice Level Index of Multiple Deprivation (Standard)	X	Patient Level Index of Multiple Deprivation	X
Practice Level Index of Multiple Deprivation (Non-standard)		Patient Level Townsend Score	
Practice Level Index of Multiple Deprivation Domains (Non-standard)			
Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland) (Standard)			
2011 Rural-Urban Classification at LSOA level (Non-standard)			

Reference number (where applicable):

14. Are you requesting linkage to a dataset not listed above?

Yes		No	**X**

If yes, provide the reference number:

15. Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?

Yes		No	**X**

If yes, provide further details:

VALIDATION/VERIFICATION

16. Does this protocol describe an observational study using purely CPRD data?

Yes	**X**	No	

17. Does this protocol involve requesting any additional information from GPs, or contact with patients?

Yes		No	**X**

If yes, provide the reference number:

PART 2: PROTOCOL INFORMATION

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*' and justification provided**
A. Study Title (Max. 255 characters) The effect of common infections on the risk of dementia in individuals with and without diabetes: A cohort study using UK primary and secondary care data
B. Lay Summary (Max. 250 words) Dementia is a major public health burden posing a devastating impact on individuals, caregivers and healthcare services. In the UK, it was estimated that around 850,000 people were living with dementia in 2015 and this number is projected to rise to over 1 million by 2025. Due to the rising ageing population and lack of medications that can cure or prevent dementia, it has become increasingly important to identify factors that can reduce the risk of dementia. Over, the last few decades, there has been growing interest on the role of infections on the risk of dementia. However, it remains unclear whether people with common infections such as pneumonia and urinary tract infections, have a higher chance of developing dementia. Additionally, common infections frequently occur in people with diabetes, and in turn diabetes is associated with dementia. Therefore, we aim to carry out a study where we will follow individuals over time using anonymous data from primary care and hospital health records to investigate whether people with common infections are at an increased risk of developing dementia and whether this risk differs in people with and without diabetes. Infections and diabetes are potentially preventable and therefore a better understanding of how these conditions affect the risk of dementia could lead to important public health interventions. These interventions may include strategies to increase the uptake of vaccines to prevent infections, and early recognition and treatment of infections in people with diabetes to reduce the risk of developing dementia.
C. Technical Summary (Max. 300 words) Dementia poses a significant burden on disability and dependence worldwide. Due to the increasing ageing population and absence of pharmacological therapies that can delay the onset or progression of dementia, dementia risk reduction has become a public health priority. Recent evidence suggests that the incidence of dementia is declining in Europe and the USA, and this change has been partly attributed to modifiable risk factors. Common infections have been identified as potential risk factors for dementia. In turn, common infections are more prevalent in diabetes, which is a strong risk factor for dementia. We hypothesise that individuals diagnosed with common infections (lower respiratory tract, urinary tract, skin and soft tissue infections and sepsis) will have an increased risk of dementia, and that this risk will increase in individuals with diabetes compared to those without diabetes. To test this hypothesis, we will carry out a cohort study of older adults aged 65 years and over using prospectively collected CPRD data linked to hospital episode statistics. We will exclude individuals with prevalent dementia and cognitive impairment at baseline. We will assess the age-specific incidence rates of dementia in individuals with and without common infections. Then, we will use Cox regression models to investigate the effect of the type, timing and frequency of infections on the incidence of dementia, adjusting for confounding factors. We will then investigate the presence of effect modification by diabetes on the association between common infections and incident dementia. Finally, we will investigate whether there is an association between common infections and evidence of cognitive impairment. To the test the robustness of our findings, we will carry out a range of sensitivity analyses. Improved understanding of the interrelationship between infections and diabetes with incident dementia will help to inform dementia risk reduction interventions.
D. Outcomes to be Measured <u>Primary Outcomes</u> (1) Incidence of dementia (all types) (2) Incident dementia (type-specific Alzheimer's disease, vascular, mixed, other). <u>Secondary Outcome</u> (1) Evidence of cognitive impairment

Objectives, Specific Aims and Rationale

Objective

The objective of this study is to investigate the effect of common infections (lower respiratory tract, urinary tract and skin and soft tissue infections and sepsis) on the incidence of dementia in adults aged 65 years and older and whether this risk varies in individuals with and without diabetes, using CPRD data linked to HES.

Specific aims

1. To describe the age-specific incidence rates of dementia in adults aged 65 years and older with and without common infections.
2. To investigate whether the presence, frequency, timing and type of common infections affect the risk of dementia.
3. To investigate whether diabetes modifies any association between common infections and incident dementia.
4. To investigate whether the presence or type of common infections are associated with evidence of cognitive impairment (secondary outcome).

Rationale

Identifying modifiable risk factors for dementia has become increasingly important given the increasing burden of dementia. As a result, dementia risk reduction is a public and global health priority. If diabetes and common infections interact to increase the risk of developing dementia, these potentially preventable conditions could be a target to reduce the risk of dementia.

E. Study Background

Dementia is a major public health challenge. With the global prevalence projected to rise from 47.5 million in 2015 to 135.5 million by 2050, the burden of dementia on individuals, caregivers and healthcare services is set to rise markedly [290]. Currently, there are no pharmacological therapies that can delay the onset or progression of dementia and as the ageing population continues to rise, dementia risk reduction has become a public health priority [296].

Recently, a large multi-area, population-based study from the UK reported a 20% decrease in the age-specific incidence of dementia in adults aged 65 years and older [3]. Other population based studies from Europe and the US have reported a declining trend in the age-specific incidence of dementia among older adults, [4-9] with improvements in education and vascular risk factors partly accounting for this change [297]. Therefore, identification of risk factors for dementia could play an important role in risk reduction. Although the single biggest predictor of dementia is age[298], a non-modifiable risk factor, population-based cohort studies have shown that addressing modifiable risk factors can reduce the risk of dementia by a third [12-14]. These risk factors include smoking, hypertension, education, socioeconomic status and diabetes.

Over the last few decades, there has been a large body of evidence to suggest that infections play a role in the risk of dementia. Pathological evidence has demonstrated the prevalence of bacterial, viral and fungal infections in individuals with Alzheimer's disease [15-17]. However, due to the cross-sectional nature of these studies, the ability to assess temporality or to make any inferences about causality is limited. Acute infections are well known to precipitate short term changes in cognition. However, the association of these infections with long term cognitive impairment is less established. Findings from a US prospective study of older adults showed that individuals hospitalised with sepsis, an acute life threatening infection, were likely to develop moderate to severe cognitive impairment [93]. In turn, cognitive impairment is a strong predictor for dementia [19].

Common infections such as pneumonia and urinary tract infections, have been shown to be prevalent in individuals with dementia [20, 21]. Few longitudinal studies have investigated the role of these infections on the incidence of dementia. Two of these studies were insufficiently powered and focused only on patients hospitalised with pneumonia, limiting their ability to capture patients with less severe infections [225] [224]. A large scale retrospective study of US veterans (N=417,172) found that the incidence of dementia was increased by the following infections: pneumonia (HR 1.10 95% CI 1.02-1.19), urinary tract infections (HR 1.13 95% CI 1.08-1.18), cellulitis (HR 1.14 95% CI 1.09-1.20) and sepsis [226]. However, the generalisability of the findings was restricted to males and military veterans, and as with the two aforementioned studies, the study was conducted in the US, limiting generalisability to other countries. Recently, a large-scale population-based study of over 60,000 individuals using a Taiwanese longitudinal health insurance database showed that individuals with a history of sepsis were at a greater risk of developing dementia compared to those without sepsis. However, the majority of these studies did not investigate a range of common infections within the same study and none of these studies examined the effects of multiple episodes of infection on the incidence of dementia. Additionally, although a longitudinal study using UK primary care data found that episodes of infection were associated with an increased likelihood of a diagnosis of dementia in elderly adults aged 84 years or older [305], no studies in the UK have specifically investigated the association between types and frequency of common infections with incident dementia.

Infections frequently occur in people with diabetes [306]. In a recent systematic review of cohort and case control studies, diabetes was associated with an increased incidence of infections including respiratory, genitourinary and skin infections [127]. Additionally, two studies using data from UK electronic health records showed that individuals with diabetes were at an increased risk of infections compared to the general population [28] [29]. Diabetes is a well-known risk factor for dementia. In a recent systematic review and meta-analysis of 14 prospective studies from 2.3 million people, diabetes was associated with a 60% increased risk of dementia overall [30]. These findings were consistent with two previous meta-analyses of longitudinal studies [308] [130]. Given the co-occurrence of infections and diabetes, and their association with dementia, it is possible that diabetes could modify the effect of common infections on the risk of dementia.

To our knowledge, no studies have investigated the potential interaction between diabetes and infections on the incidence of dementia. Diabetes and infections are both major health conditions that pose a significant impact on public health services. As both conditions are potentially preventable, understanding their association with dementia could have public health implications in targeting populations at an increased risk of dementia and early treatment of infections and diabetes could reduce the risk and burden of dementia.
Therefore, our aim is to investigate the effect of common infections on the risk of dementia and to investigate whether this effect varies in individuals with and without diabetes, using a large dataset of primary care records

linked to hospital episode statistics (HES), representative of the UK population. We will also investigate the association between common infections and evidence of cognitive impairment.

Study Type

Descriptive

Hypothesis-testing

F. Study Design

Historical cohort study using CPRD data and linked HES data

G. Feasibility counts

- There were 1,009, 629 individuals aged 65 years and older in CPRD with linked HES data between 2004 and 2018 with at least 12 months research standard follow up and no prior history of dementia. 16.4% had any common infection.
- 11.4% had a lower respiratory tract infection, 0.7% had sepsis, 3.1% had a urinary tract infection and 4.2% had a skin and soft tissue infection. The median follow-up time was 12.7 years. 82% had more than 5 years of follow up.
- 4.7% (n=47589) developed dementia.
- The incidence of dementia in adults aged 65 years and older in the UK has been estimated to be around 209,600 new cases of dementia per year [3]. As dementia is underdiagnosed in primary care, it is likely that the incidence of dementia will be lower in CPRD.

H. Sample size considerations

We used the results of our feasibility counts to carry out our sample size calculations. Here we calculated the minimum effect estimate for common infections on the risk of dementia. Our estimates are conservative as we estimated that 16.4% of our study population had a first ever common infection and 4.7% of our total population developed dementia.

From our feasibility counts, we estimated that we would have 5 people unexposed to infections for every person with an infection. Hence, we will have an 80% power at a 5% significance level to detect a minimum hazard ratio of 1.02.

I. Planned use of linked data (if applicable):

We plan to use primary care data from CPRD linked to Hospital Episode Statistics. Although dementia cases are likely to be diagnosed in primary care settings, using HES will help to identify additional cases and improve the accuracy of information available on timing of dementia diagnosis. We will also identify infections using linked HES data: a recent UK study comparing incidence of community acquired pneumonia in primary and secondary care data among adults aged 65 years and older found that the incidence estimates of community acquired pneumonia were 28% lower in primary care data alone compared to linked data [33].

We also plan to use patient-level IMD and practice-level IMD as a measure of socioeconomic deprivation, which is a potential confounding factor. Our primary analysis will include only individuals with linked data, and therefore we plan to use patient-level IMD for this analysis. We will consider practice-level IMD for the sensitivity analysis which includes individuals without linked data.

J. Definition of the Study population

We will include all adults aged 65 years and older present in CPRD (Gold) with linked HES data, who were registered in CPRD between 1st January 2004 and 31 December 2018. We will include individuals with at least 12 months of research standard follow up in CPRD. Therefore, follow up will begin at the latest of 01/01/2004, 65th birthday or 12 months after research standard follow up.

We will follow individuals to the earliest of: incident dementia diagnosis, date of death, transfer out date, the practice's last data collection date or end of study period.

Exclusion

We will exclude individuals with a history of dementia and cognitive impairment. To account for delirium, which is an acute complication of common infections, we will exclude the first 3 months after infection.

K. Selection of comparison group(s) or controls

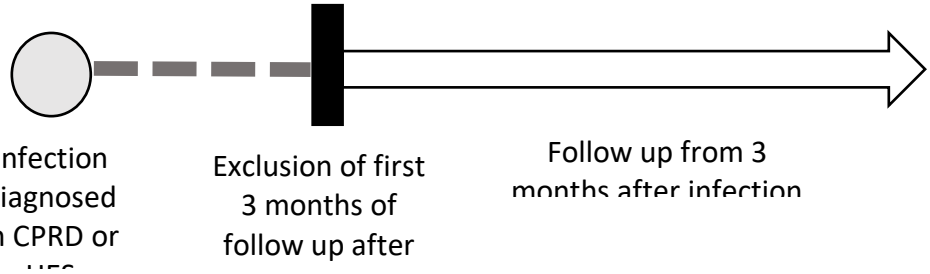
The comparison group will comprise of adults aged 65 and over unexposed to common infections during the study period.

L. Exposures, Outcomes and Covariates

Exposure

Common infections

We will identify Read codes and ICD-10 codes of common infections in both CPRD and HES data.
Common infections can result in short term reversible changes in cognition, delirium, as a result it is possible that individuals diagnosed with dementia shortly after infection could have been experiencing delirium and were misdiagnosed as having dementia. Therefore, the reduce the risk of misclassifying delirium as dementia, we will exclude the first 3 months of follow up after an infection.



Our exposure will reflect an ever diagnosis of infection. This will mean that individuals can move from the unexposed group to exposed but once diagnosed with infection they cannot move to the unexposed group.

Exposure will be defined as one of the following:

1. A clinical code for lower respiratory tract infections
2. A clinical code for sepsis
3. A clinical code for urinary tract infections and a prescription for antibiotics
4. A clinical code for soft tissue infections and a prescription for antibiotics

We will group all common infections (lower respiratory tract, urinary tract, skin and soft tissue infections and sepsis) into one category 'any infection' in order to determine the overall association of common infections with incident dementia. Then we will group infections according to subtype of infection. Each subtype of infection will be further subdivided according to the frequency of infections.

Primary Outcome

Dementia

Our primary outcome will be defined as first ever dementia diagnosis. Incident dementia will be identified using Read codes for dementia (any dementia subtype) and ICD-10 codes in HES data. We will exclude those with a prior history of dementia, evidence of cognitive impairment and cases in which dementia occurs before infection.

Secondary Outcome

Evidence of cognitive impairment

Our secondary outcome will be defined as first ever evidence of cognitive impairment. We will identify cognitive impairment using Read codes and ICD-10 codes in CPRD and HES. We will exclude individuals with a prior history of cognitive impairment and dementia.

Covariates

- Age (65-69, 70-74, 75-79,80-84, 85-89, 90+ using data from CPRD)
- Sex (male and female using data from CPRD)
- Ethnicity (White, black, South Asian and other using data from CPRD or HES)
- Calendar year (2004-2008, 2009-2013, 2014-2018)
- Socioeconomic deprivation (using Index of Multiple Deprivation Quintiles)
- BMI, kg/m^2 (underweight, <18.5, normal weight 18.5-25, overweight/obese $\geq$25 using additional files in CPRD)

- Smoking (Non-smoker, ex-smoker and current smoker using additional files in CPRD)
- Alcohol consumption (non-drinker, current drinker, heavy drinker, light drinker, moderate drinker and ex drinker, using additional files in CPRD)
- Frequency of health service usage (Information relating to health service usage will be obtained from the number of GP consultations and hospitalisations using CPRD and HES)

We will identify read codes relating to the following conditions in clinical, test and therapy files using CPRD and HES:

- Cardiovascular disease: atrial fibrillation, angina, previous myocardial infarction, hypertension, ischemic heart disease, congestive heart failure
- Comorbid conditions: traumatic brain injury, stroke, atherosclerosis, chronic kidney disease, peripheral vascular disease, retinopathy, neuropathy, chronic liver disease, asthma, chronic obstructive pulmonary disease, epilepsy, Parkinson's disease, obstructive sleep apnoea and HIV
- Psychiatric comorbidity: cognitive impairment, post-traumatic stress disorder, major depression, schizophrenia, bipolar disorder and anxiety disorder
- Glycaemic control using HbA1c (<6%, 6-6.5%, 6.5-7%, 8-10% and >10%)

M. Data/ Statistical Analysis

Aim 1
We will describe the age specific incidence rates of dementia in individuals with and without common infections by calculating the number of events and person time at risk of dementia. Age will be stratified into the following groups: 65-69, 70-74, 75-79,80-84, 85-89, 90+.

Aim 2
We acknowledge that the competing risk of mortality is possible when estimating the risk of dementia, particularly in an elderly multimorbid population, and that failure to account for this may lead to biased effect estimates if a competing risk analysis approach is not used. However, when addressing aetiological research questions, Cox regression is an appropriate method of analysis [34, 35]. Therefore, as we aim to investigate the causal relationship between common infections and dementia, we will use Cox regression analysis to estimate the incidence of dementia in those exposed and unexposed to any common infection. Current age will be fitted as the underlying time scale. Our final model will adjust for all the confounders listed previously.
We will then stratify by:

- type of infections (sepsis, lower respiratory tract, urinary tract, skin and soft tissue infections) and this will also include the severity of infections (e.g. hospitalised infections vs non-hospitalised infections or severe sepsis)
- time after infection diagnosis (e.g. 3-12 months, 3-24 months, 3-36 months etc)
- frequency of infections (e.g. 0 1, 2, $\geq$3).

We will consider infections that occur within 28 days of each other as a single episode of infection.

Aim 3
We will investigate the presence of effect modification by fitting an interaction term of diabetes to our Cox regression model and then carrying out likelihood ratio tests.

Aim 4
We will use Cox regression models to estimate the risk for our secondary outcome of cognitive impairment in those exposed and unexposed to common infections.

Sensitivity analyses

1. We will stratify by dementia subtype in order to explore the incidence of dementia according to subtypes of dementia (Alzheimer's disease and vascular dementia).
2. We will stratify by sex to compare the incidence of dementia in men and women.
3. We will repeat our primary analyses to include individuals in CPRD without HES linked data.
4. We will exclude individuals with read codes for dementia that is causally linked with other diseases such as 'HIV associated dementia' and we will instead perform sensitivity analyses only for dementia that is not specifically caused by a particular disease.
5. To more reliably assess whether infections are associated with evidence of cognitive impairment and we will exclude individuals with recodes for symptoms of cognitive impairment and instead only include those with less ambiguous read codes of cognitive impairment such as 'mild cognitive impairment'.
6. We will repeat our primary analyses defining all types of common infections using clinical codes and an antibiotic prescription.
7. We will repeat our primary analyses stratifying according to the time period before death.

N. Plan for addressing confounding
Our final model will include all potential confounders specified in section K.

O. Plans for addressing missing data
We will describe the pattern of missing data present and choose a suitable method for accounting for missing data accordingly. We expect to find missing data on smoking and ethnicity. However, since these data are less likely to be missing at random, we will most likely use a complete case analysis to carry this out.

P. Patient or user group involvement (if applicable)
This study is funded by the Alzheimer's Society. Through the Alzheimer's society, we have been assigned a group of three lay volunteers who will act as research monitors for the present study. We will seek the research monitors views on the design and conduct of our study as well as the dissemination of our results.

Q. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

We will disseminate our findings at relevant conferences, events, meetings and we plan to submit our results for publication in a peer reviewed journal. We will work with the Alzheimer's Society to present our findings to members of the public.

Conflict of interest statement: There are no competing interests to declare.

R. Limitations of the study design, data sources, and analytic methods

Misclassification of dementia

There are a number of ways dementia could be misclassified. First, dementia is known to be frequently underdiagnosed in primary care with studies suggesting that over 50% of dementia cases are not detected in primary care [51] [37], although this has been changing with time across this period as recent evidence now suggests that around two thirds of people with dementia have a diagnosis in primary care[53]. Nevertheless, misclassification and underestimation of dementia incidence is possible. However, the positive predictive values of dementia in CPRD are over 80% and we will link CPRD to HES data which will enable us to capture more dementia cases, although this will likely introduce other biases as certain groups such as ethnic minorities and those with milder dementia are less likely to be receive a hospital dementia diagnosis [39]. Therefore, misclassification in HES is also possible although the recording of dementia in HES has been increasing since 2008 and the sensitivity and specificity for each person's complete hospital records has been estimated to be around 78% and 92%, respectively [39]. Second, dementia has a long pre-clinical phase and therefore it is possible that individuals classified as not having dementia in CPRD could already be experiencing cognitive decline or already have dementia. In turn, these individuals may be more susceptible to having infections. To address this, we will present the hazard ratios for incident dementia in different time periods after infection. Additionally, in the period before death, older individuals could be at risk of serious cognitive decline which could also increase their likelihood of a dementia diagnosis. As a result, we will explore the proximity of dementia diagnosis to death. Lastly, common infections are known to be associated with delirium, a serious neuropsychiatric syndrome characterised by acute cognitive dysfunction and inattention. It is therefore possible that delirium may be misclassified as dementia. To reduce this, we will exclude all dementia cases occurring within 3 months after an infection. Additionally, we acknowledge that dementia diagnosed shortly after infection, even after delirium has resolved, is less likely to be causally linked to infection due to the long pre-clinical phase of dementia.

Misclassification of cognitive impairment

Read codes for cognitive impairment have not been validated in CPRD and thus misclassification is possible. Read codes related to cognitive impairment may have been assigned without a diagnostic test and it is possible that individuals who were older and of a lower educational background may have been misclassified as having evidence of cognitive impairment. Additionally, individuals in CPRD are unlikely to have had their cognition tested at multiple time points, as a result, without a comparison of previous cognitive ability, misclassification of cognitive impairment is possible. Furthermore, codes relating to symptoms of cognitive impairment may be inaccurate and may not specifically relate to clinical cognitive impairment. To minimise this, we will perform sensitivity analyses for codes that indicate a diagnosis of cognitive impairment rather than symptoms of cognitive impairment.

Misclassification of common infections

There are a number of ways in which misclassification of infections is possible during this study. Firstly, in primary care settings, infections are often diagnosed without microbiological data to confirm diagnosis. Secondly, people with less serious infections might be less likely to visit the GP which might also lead to an underestimation of people with infections. Lastly, it is possible that people who will be unexposed to infections during the study period were exposed to common infections before the study which might affect their risk for dementia.

Detection bias

People with diabetes are more likely to visit health services compared to those without, thus potentially increasing their chances of a dementia diagnosis. Diabetes is also a known risk factor for dementia and as such it is possible that people with diabetes might be screened more frequently for dementia which might also increase their chances of a dementia diagnosis. Recently, dementia risk has been included in the NHS health checks programme and diabetes has been identified as a risk factor for dementia. This might also increase the likelihood of people with diabetes to receive a dementia diagnosis.

Missing data

Missing data on confounding variables such as ethnicity, smoking and education are likely. We will describe the pattern of our missing data (whether our data is missing completely at random, missing at random or missing not at random) and choose an appropriate method for dealing with the missing data.

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List of Appendices

1. **Provisional code lists for outcomes (CPRD)**

a) Dementia
b) Cognitive impairment

2. **Provisional code lists for exposures (CPRD)**

c) Lower respiratory tract infections
d) Sepsis
e) Urinary tract infections and antibiotics
f) Skin and soft tissue infections and antibiotics

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL		***by e-mail***	
PROTOCOL NO:	19_129R		
PROTOCOL TITLE:	The effect of common infections on the risk of dementia in individuals with and without diabetes: a cohort study using UK primary and secondary care data		
APPLICANT:	Dr Charlotte Warren-Gash London School of Hygiene and Tropical Medicine Charlotte.warren-gash1@lshtm.ac.uk		
APPROVED ☒	**APPROVED WITH COMMENTS (resubmission not required)** ☐	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐
INSTRUCTIONS: ***Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.*** **REVIEWER COMMENTS:** **APPLICANT FEEDBACK:**			
DATE OF ISAC FEEDBACK:	25/06/19		
DATE OF APPLICANT FEEDBACK:			

For protocols approved from 01 April 2014 onwards, applicants are required to include the ISAC protocol in their journal submission with a statement in the manuscript indicating that it had been approved by the ISAC (with the reference number) and made available to the journal reviewers. If the protocol was subject to any amendments, the last amended version should be the one submitted.

Guidance on resubmitting applications, or making amendments to approved protocols, can be found on the CPRD website at https://cprd.com/research-applications.

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Observational / Interventions Research Ethics Committee

Ms Rutendo Muzambi
LSHTM

25 July 2019

Dear Rutendo,

Study Title: The effect of common infections on the risk of dementia in individuals with and without diabetes: a cohort study using UK primary and secondary care data

LSHTM Ethics Ref: 17752

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Investigator CV	Krishnan Bhaskaran SCHOOL CV TEMPLATE v3.2 4jan2019	04/01/2019	1
Protocol / Proposal	ISAC Protocol 19_129_	20/06/2019	2
Local Approval	19_129R_ISAC Approval	25/06/2019	Approval
Investigator CV	Short cv_CWG_16-07-2019 (1)	16/07/2019	1
Investigator CV	CV RM 18.06.19	18/07/2019	1
Investigator CV	Liam Smeeth 2 page CV 2019	19/07/2019	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor Jimmy Whitworth
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Supplementary material for research paper 3

Supplementary Appendix 1: Search strategy

a) MEDLINE (OVID) search strategy

1. Pneumonia/ or pneumonia, bacterial/
2. Pneumonia.ti,ab
3. Lower respiratory tract infection*.ti,ab
4. (LRTI or LRTIS).ti,ab.
5. Exp urinary tract infections/
6. (Urinary adj5 infection*).ti,ab.
7. (UTI or UTIS).ti,ab
8. exp Cystitis/
9. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.
10. exp cellulitis/
11. (Skin and soft tissue infection).mp.
12. exp sepsis/
13. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Exp dementia/
16. Exp prion diseases/
17. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab
18. (Dement* or Alzheimer*).ti,ab
19. (Lewy*adj2 bod*).ti,ab.
20. Cognitive dysfunction/
21. (Mild cognitive impairment or MCI).ti,ab
22. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.
23. Cognitive function.ti,ab.
24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. cohort studies/ or longitudinal study/ or follow-up study/ or prospective study/ or retrospective study/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

26. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

27. Incidence/ or incidence.ti,ab,kw.

28. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

29. 25 or 26 or 27 or 28

30. 14 and 24 and 29

b) Embase (OVID) search strategy

1. Bacterial pneumonia/ or Pneumonia/
2. Pneumonia.ti,ab
3. Lower respiratory tract infection*.ti,ab
4. (LRTI or LRTIS).ti,ab.
5. Exp Urinary tract infections/
6. exp Bacteriuria/
7. exp Pyuria/
8. (Urinary adj5 infection*).ti,ab.
9. (UTI or UTIS).ti,ab
10. Exp cystitis/
11. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.
12. exp cellulitis/
13. (Skin and soft tissue infection).mp.
14. exp sepsis/
15. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. Exp dementia
18. Exp Creutzfeldt-jakob disease
19. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab
20. Dement*.ti,ab.
21. Exp mild cognitive impairment/
22. (Mild cognitive impairment or MCI)ti,ab
23. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.
24. Cognitive function.ti,ab.
25. Alzheimer*.ti,ab
26. (Lewy*adj2 bod*).ti,ab.
27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. cohort analysis/ or longitudinal study/ or follow-up/ or prospective study/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

29. Case control study/ or Control Group/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

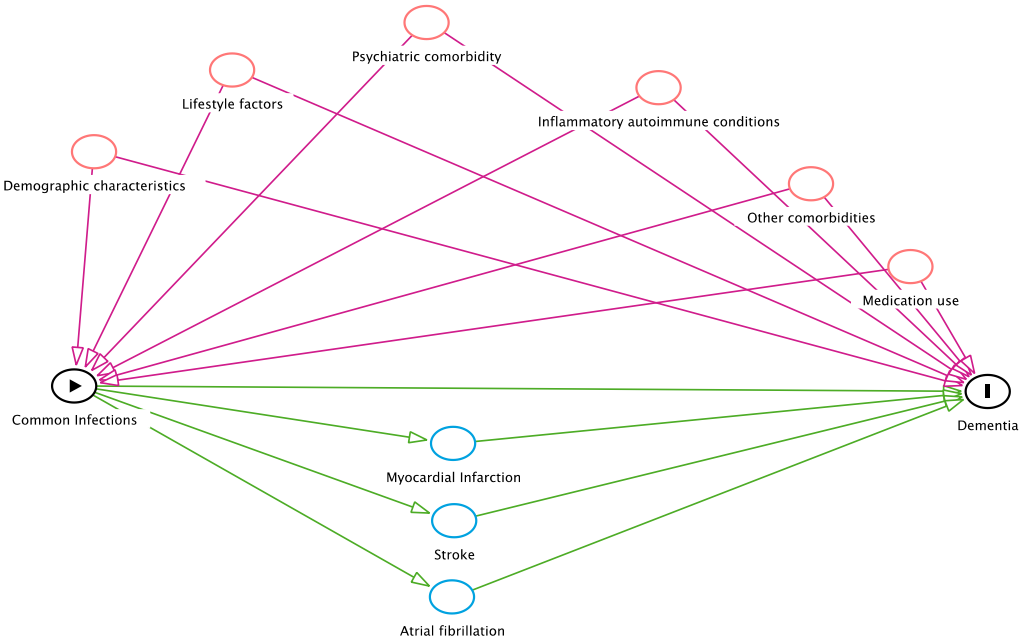
30. Incidence/ or incidence.ti,ab,kw.

31. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

32. 28 or 29 or 30 or 31

33. 16 and 27 and 32

Supplementary Appendix 2: Directed acyclic graphic depicting the possible confounders and effect modifiers in the association between common infections and dementia.



Legend:

exposure | outcome | ancestor of outcome | ancestor of exposure and outcome | biasing path | causal path

Supplementary Appendix 3: Variable definitions

Infections

First ever infection

Infections were identified using primary care data from the Clinical Practice Research Datalink (CPRD) and secondary care data from Hospital Episode Statistics (HES). In order to confirm a diagnosis of infections and capture more serious infections, urinary tract infections (UTIs) and skin and soft tissue infections (SSTIs) were defined using a Read code and a prescription for antibiotics on the same date as a diagnosis of infection. Sepsis, pneumonia and other lower respiratory tract infections (LRTIs) were not defined using a prescription for antibiotics as these infections can also be caused by viruses. Infections identified in HES were not linked with a prescription for antibiotics as medication data is not available in HES and hospitalised infections are likely to be more serious than those diagnosed in the community.

To avoid misclassification of dementia, we excluded the first 3 months after an infection. That is, when an individual was diagnosed with an infection, they exited the study for 3 months and re-entered after the 3-month exit period.

Type and clinical setting of infection

For instances in which an individual was diagnosed with two different types of infections on the same date, a hierarchical approach was used based on the infection type and data source. If two different infections were diagnosed on the same date in CPRD and HES, the infection recorded in HES was used as the primary diagnosis. Then, if sepsis was diagnosed on the same date as another infection, sepsis was the primary diagnosis. If pneumonia and other lower respiratory tract infections were diagnosed on the same date, then the pneumonia diagnosis was taken. If two infections were diagnosed in hospital and GP records, the infection diagnosed in hospital was taken.

Frequency of infections

Individuals who were diagnosed with subsequent infections during the 3-month exit period remained out of the study 3 months from subsequent infection diagnosis.

Covariates

Socioeconomic deprivation

We linked CPRD to patient-level Index of Multiple Deprivation 2015 (IMD 2015). The IMD 2015 is a measure of relative deprivation for small areas across England based on seven domains which can be divided into groups ranking from least to most deprived.(1) Socioeconomic deprivation was defined using patient-level Index of Multiple Deprivation (IMD) which includes only English GP practices. Socioeconomic deprivation was categorised into quintiles; 1 least deprived and 5 most deprived.(1)

Ethnicity

Ethnicity was categorised as follows: White, South Asian, Black and Mixed/Other. Using CPRD, we used the most commonly recorded ethnicity, then we used the most recent ethnicity where several ethnicities were recorded. When ethnicity in CPRD was missing, we then used ethnicity recorded in HES. The algorithm we used for ethnicity in CPRD and HES has been previously described.(2)

BMI and smoking status

We derived BMI at entry into the study from the CPRD additional details file and defined using methods previously described.(3) We excluded records when an individual was under 16 years, during pregnancy or records under 20kg. BMI was calculated using weight records with height recorded on the same date. However, if a height record on the same date as weight record was not available, we used an older height record. If not available, we used a future height record. The following cut-off points by the World Health Organisation (WHO) were used to define BMI; underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), obese (30.0>). Smoking status was defined in CPRD, using Read codes and data from the additional details file. Smoking and BMI status were assigned using the nearest record in the period of -1 year to +1 month from start of follow up, if available (best). If not available, the second option was to use the nearest record in the period +1month to +1 year after start of follow up. If not available, the third option was to take the nearest record before -1 year from start of follow up and if not available the least best option was to take any nearest record after +1 year from start of follow up.

Depression and anxiety

Depression and anxiety were also defined in CPRD and HES. In CPRD, we included individuals with:

1) a diagnostic or symptomatic Read code for depression or anxiety and

2) a prescription for antidepressants or medications indicated for treatment of anxiety in the British National Formulary (BNF) within 90 days of clinical code.

Depression and anxiety were defined as above due to the changes in diagnosing depression in the UK primary care given that in 2006 GPs switched from using diagnostic to symptomatic codes (4). Additionally, from 2004 antidepressants were no longer routinely prescribed for mild depression, therefore to increase the likelihood of capturing those with more severe depression, we defined depression with a clinical code and prescription for antidepressants (5). Given that depression and anxiety have overlapping clinical codes and medication, we combined the variables for depression and anxiety together. In HES, we used ICD-10 codes alone as individuals diagnosed in hospital are more likely to be severe than those in diagnosed in primary care.

Diabetes

We defined diabetes using diagnoses for diabetes mellitus (type 1, type 2 and unspecified) and codes for diabetes complications. To define diabetes, we used Read codes in CPRD and ICD-10 codes in HES. Codes for gestational diabetes, secondary diabetes such as “diabetes mellitus induced by steroids” and diabetes care codes were excluded.

Polypharmacy

We defined polypharmacy as the concurrent use of 5 or more medications using BNF chapters. We excluded vaccines and devices that do not administer medication. Medication use was captured in the 12 months prior to baseline.

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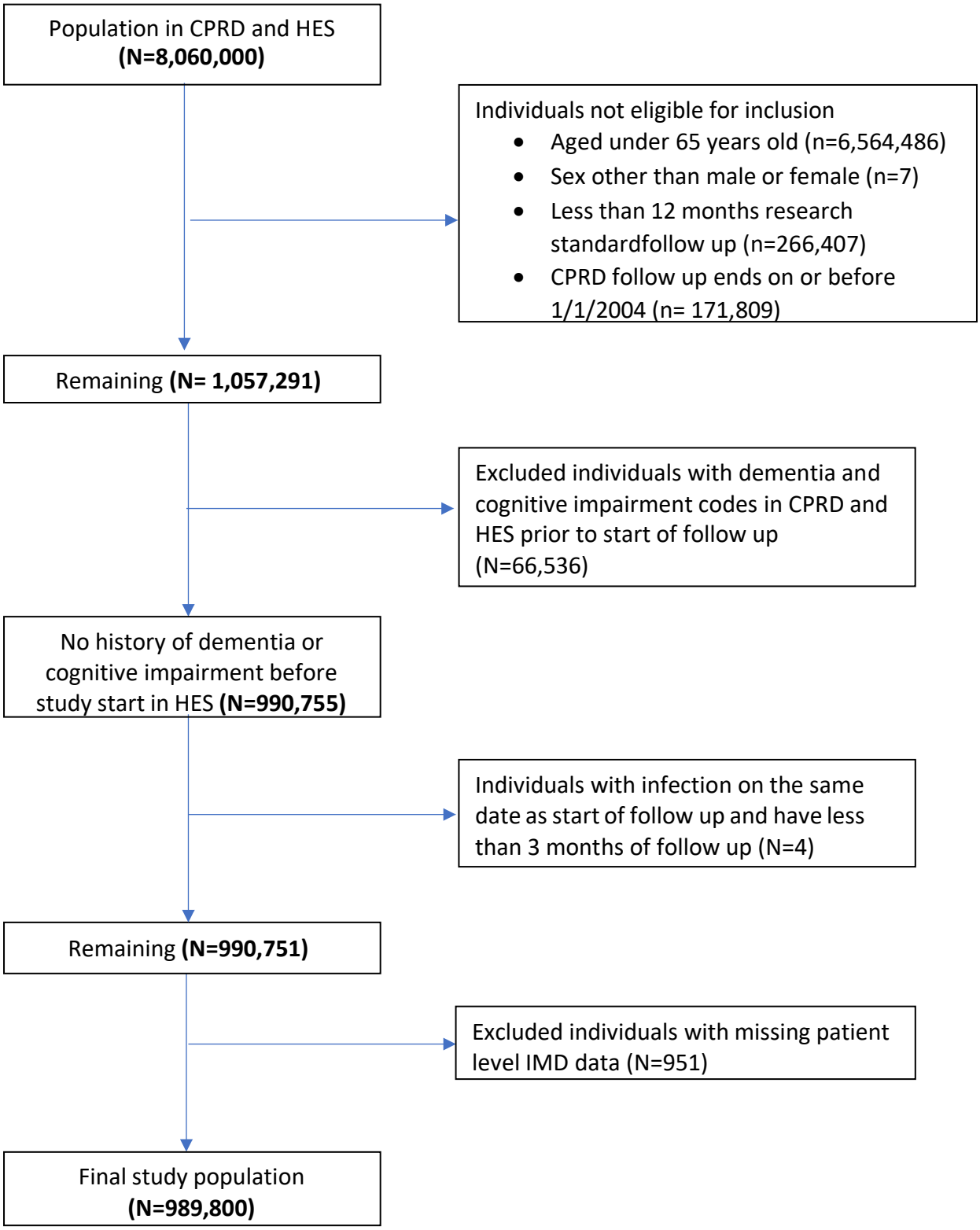
Supplementary Table 1: Sensitivity analyses

Sensitivity analysis	Justification
Primary analyses repeated excluding individuals with secondary dementia causally related to other conditions.	Infections are unlikely to be causally associated with this type of dementia
Primary analyses repeated defining all infections in CPRD with a diagnostic code and prescription for antibiotics	To improve the accuracy of our infection definition
Primary analysis repeated excluding individuals diagnosed with infections from two different sites (e.g. skin and soft tissue infections and pneumonia) on the same date	To avoid any potential biases introduced from including these infections.
We excluded codes relating to symptoms of cognitive impairment from analysis of infections and cognitive impairment	To improve the accuracy of our definition of cognitive impairment

Supplementary Figures

Supplementary Figure 1: Flowchart of study population



Supplementary Table 2. Age-specific incidence rates of dementia during person-time with and without prior common infections.

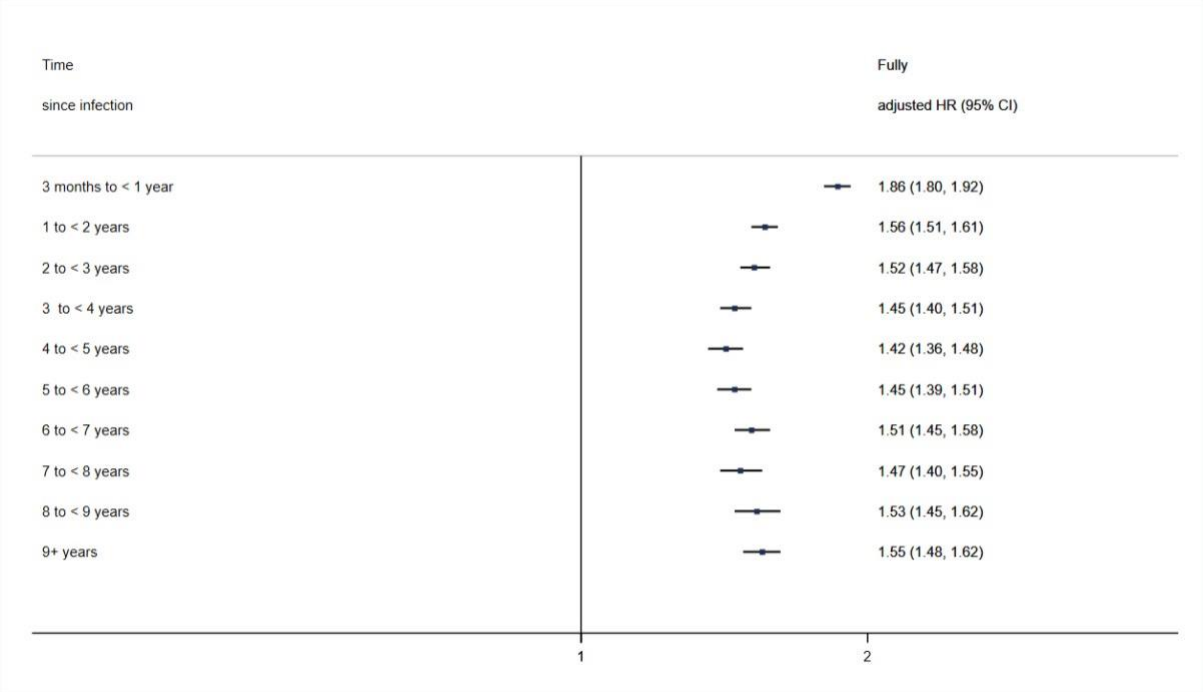
Age group (years)	Person-years	Total number of incident dementia diagnoses	Rate (per 1000-person years)	Lower (95% CI)	Upper (95% CI)
No infections					
65-69	1395965	1263	0.90	0.86	0.96
70-74	935486	2523	2.70	2.59	2.80
75-79	693243	4684	6.76	6.57	6.95
80-84	481002	6697	13.92	13.59	14.26
85-89	258807	6079	23.49	22.91	24.09
90+	130528	4068	31.17	30.22	32.14
Total	3895032	25314	6.50	6.42	6.58
Any infections					
65-69	260196	544	2.09	1.92	2.27
70-74	426037	2104	4.94	4.73	5.15
75-79	408733	4681	11.45	11.13	11.79
80-84	331452	7749	23.38	22.86	23.91
85-89	212080	8865	41.80	40.94	42.68
90+	116458	7545	64.79	63.34	66.27
Total	1754956	31488	17.94	17.75	18.14

Supplementary Table 3. Crude rate and hazard ratios for the association of common infections and dementia, additionally adjusted for potential mediators and BMI

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Fully adjusted HR	**Additionally adjusted for potential mediators HR	***Additionally adjusted for BMI HR
No infection	25314	3895032	6.50 (6.42-6.58)	1.00	1.00	1.00
Any Infection	31488	1754956	17.94 (17.75-18.14)	1.53 (1.50-1.55)	1.65 (1.62-1.68)	1.53 (1.50-1.56)
Sepsis	427	16814	25.40 (23.10-27.92)	2.08 (1.89-2.29)	2.32 (2.11-2.56)	2.07 (1.87-2.29)
Pneumonia	1247	47836	26.07 (24.66-27.56)	1.88 (1.77-1.99)	2.11 (2.00-2.24)	1.88 (1.77-2.00)
Other LRTI	13429	910432	14.75 (14.50-15.00)	1.34 (1.31-1.37)	1.46 (1.42-1.49)	1.35 (1.32-1.38)
UTI	10513	481341	21.84 (21.43-22.26)	1.73 (1.69-1.78)	1.86 (1.82-1.91)	1.73 (1.68-1.77)
SSTI	5535	291603	18.98 (18.49-19.49)	1.54 (1.49-1.58)	1.67 (1.62-1.72)	1.57 (1.52-1.62)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
*Age as underlying time scale. * Adjusted for age, sex, patient level IMD, calendar period, ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy. **Additionally adjusted for atrial fibrillation, myocardial infarction and stroke. ***Fully adjusted model additionally adjusted for BMI

Supplementary Figure 2. Forest plot depicting adjusted hazard ratios of the association between common infections and dementia, stratified according to time since infection (non-overlapping time periods)



HR, hazard ratio. Adjusted for age, sex, patient level IMD, calendar period, ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 4. Crude rate and hazard ratios for the association of common infections and dementia in people with and without diabetes

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
Individuals without diabetes						
No infection	22610	3523440	6·42 (6·33-6·50)	1·00	1·00	1·00
Any Infection	27141	1543709	17·58 (17·37-17·79)	1·75 (1·72-1·78)	1·61 (1·58-1·64)	1·50 (1·47-1·53)
Individuals with diabetes						
No infection	2704	371592	7·28 (7·01-7·56)	1·00	1·00	1·00
Any Infection	4347	211247	20·58 (19·98-21·20)	1·94 (1·85-2·04)	1·74 (1·66-1·83)	1·70 (1·61-1·79)

HR, hazard ratio; Age as the underlying time scale. ** Adjusted for age, sex, ethnicity, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy. Likelihood ratio test for interaction comparing models with and without interaction term between infections and diabetes, p=0.00014.

Supplementary Table 5. Crude rate and hazard ratios for the association of common infections and cognitive impairment, stratified by type of infection

Infection	Total number of incident cognitive impairment events	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	34730	3855389	9·01 (8·91-9·10)	1·00	1·00	1·00
Any Infection	32608	1679805	19·41 (19·20-19·62)	1·57 (1·55-1·60)	1·45 (1·42-1·47)	1·29 (1·27-1·32)
Sepsis	340	15763	21·57 (19·39-23·99)	1·74 (1·56-1·93)	1·57 (1·41-1·75)	1·39 (1·25-1·55)
Pneumonia	1110	44972	24·68 (23·27-26·18)	1·83 (1·72-1·94)	1·65 (1·56-1·75)	1·45 (1·36-1·54)
Other LRTI	15527	875906	17·73 (17·45-18·01)	1·50 (1·47-1·53)	1·38 (1·35-1·41)	1·22 (1·20-1·25)
UTI	9627	457755	21·03 (20·61-21·46)	1·63 (1·60-1·67)	1·51 (1·48-1·55)	1·36 (1·33-1·40)
SSTI	5787	279042	20·74 (20·21-21·28)	1·61 (1·56-1·65)	1·48 (1·43-1·52)	1·34 (1·30-1·38)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTI, skin and soft tissue infection
*Age as the underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 6: Crude rate and hazard ratios for the association of common infections and dementia, stratified by dementia subtype

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
Alzheimer's Disease						
No infection	7137	3895032	1.83 (1.79-1.88)	1.00	1.00	1.00
Any Infection	6424	1754956	3.66 (3.57-3.75)	1.33 (1.29-1.38)	1.12 (1.08-1.16)	1.09 (1.05-1.13)
Sepsis	54	16814	3.21 (2.46-4.19)	1.16 (0.89-1.52)	0.99 (0.75-1.29)	0.98 (0.75-1.28)
Pneumonia	203	47836	4.24 (3.70-4.87)	1.40 (1.21-1.61)	1.19 (1.04-1.37)	1.15 (1.00-1.33)
Other LRTI	2956	910432	3.25 (3.13-3.37)	1.25 (1.20-1.30)	1.07 (1.02-1.12)	1.03 (0.99-1.08)
UTI	2050	481341	4.26 (4.08-4.45)	1.47 (1.40-1.55)	1.21 (1.15-1.27)	1.17 (1.11-1.23)
SSTI	1126	291603	3.86 (3.64-4.09)	1.34 (1.26-1.43)	1.13 (1.06-1.21)	1.09 (1.02-1.17)
Vascular Dementia						
No infection	5040	3895032	1.29 (1.26-1.33)	1.00	1.00	1.00
Any Infection	7132	1754956	4.06 (3.97-4.16)	2.06 (1.98-2.13)	1.88 (1.81-1.95)	1.69 (1.62-1.76)
Sepsis	119	16814	7.08 (5.91-8.47)	3.54 (2.96-4.25)	3.16 (2.63-3.79)	2.74 (2.28-3.29)
Pneumonia	295	47836	6.17 (5.50-6.91)	2.79 (2.48-3.13)	2.46 (2.19-2.77)	2.08 (1.85-2.35)
Other LRTI	3136	910432	3.44 (3.33-3.57)	1.85 (1.77-1.94)	1.68 (1.60-1.75)	1.50 (1.43-1.58)
UTI	2262	481341	4.70 (4.51-4.90)	2.24 (2.14-2.36)	2.11 (2.01-2.22)	1.89 (1.79-1.99)
SSTI	1242	291603	4.26 (4.03-4.50)	2.05 (1.92-2.18)	1.87 (1.76-1.99)	1.69 (1.59-1.80)
Unspecified Dementia						
No infection	12210	3895032	3.13 (3.08-3.19)	1.00	1.00	1.00
Any Infection	16956	1754956	9.66 (9.52-9.81)	1.92 (1.88-1.97)	1.84 (1.80-1.89)	1.72 (1.67-1.76)
Sepsis	247	16814	14.69 (12.97-16.64)	2.86 (2.52-3.24)	2.79 (2.46-3.17)	2.51 (2.21-2.85)
Pneumonia	716	47836	14.97 (13.91-16.11)	2.55 (2.36-2.75)	2.46 (2.28-2.65)	2.22 (2.05-2.39)
Other LRTI	6909	910432	7.59 (7.41-7.77)	1.64 (1.59-1.69)	1.57 (1.53-1.62)	1.46 (1.41-1.51)
UTI	5861	481341	12.18 (11.87-12.49)	2.25 (2.18-2.33)	2.14 (2.07-2.21)	1.99 (1.92-2.05)
SSTI	3009	291603	10.32(9.96-10.69)	1.93 (1.85-2.00)	1.86 (1.79-1.94)	1.74 (1.67-1.81)

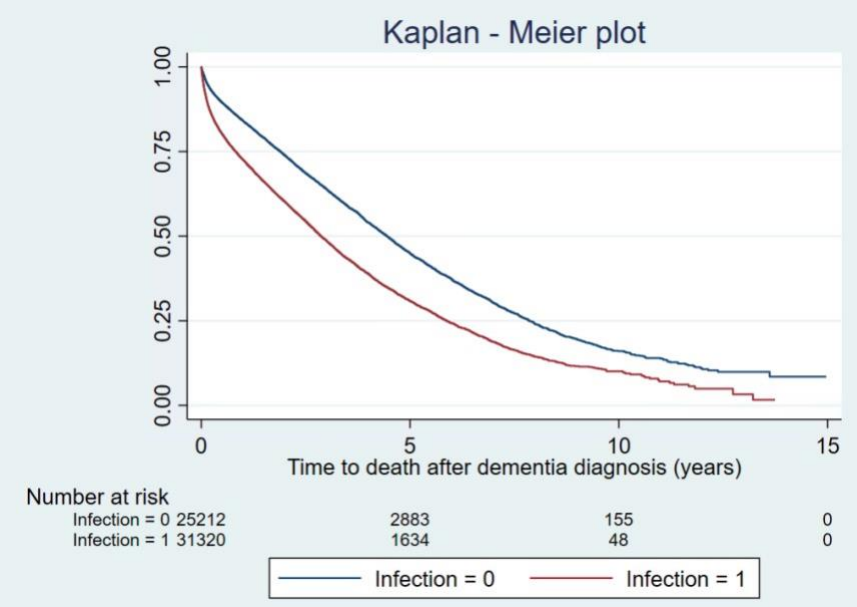
HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy

Supplementary Table 7: Crude rate and hazard ratios for the association of common infections and dementia, stratified by sex

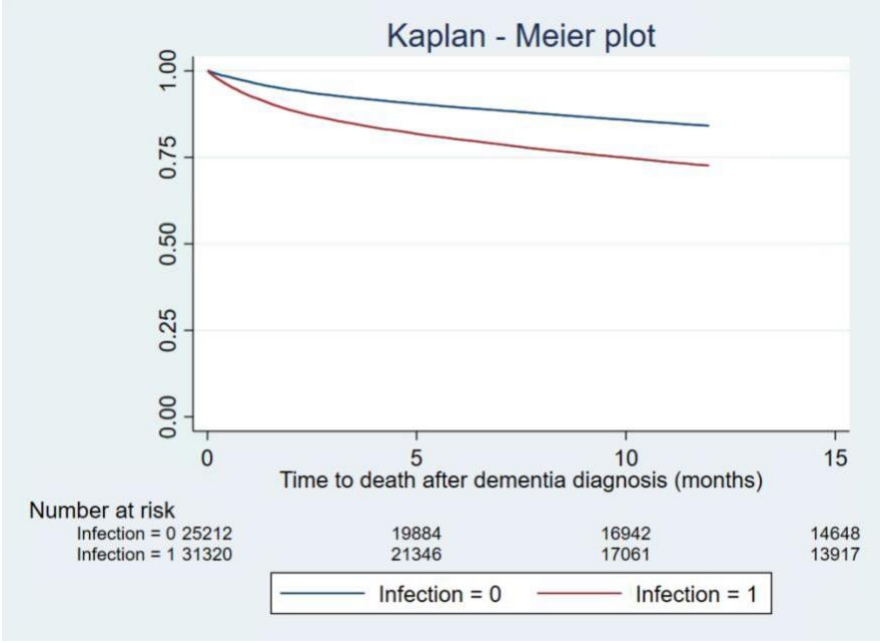
Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
Female						
No infection	15427	2043935	7.55 (7.43-7.67)	1.00	1.00	1.00
Any infection	20658	1065696	19.38 (19.12-19.65)	1.75 (1.71-1.79)	1.61 (1.58-1.65)	1.51 (1.48-1.55)
Sepsis	219	7641	28.66 (25.11-32.72)	2.51 (2.20-2.87)	2.30 (2.01-2.63)	2.11 (1.84-2.42)
Pneumonia	650	21756	29.88 (27.67-32.26)	2.20 (2.03-2.38)	1.99 (1.84-2.16)	1.81 (1.67-1.96)
Other LRTI	7979	495893	16.09 (15.74-16.45)	1.55 (1.51-1.59)	1.42 (1.38-1.46)	1.33 (1.29-1.37)
UTI	8124	373232	21.77 (21.30-22.25)	1.94 (1.89-1.99)	1.80 (1.75-1.85)	1.68 (1.64-1.73)
SSTI	3469	162895	21.30 (20.60-22.02)	1.73 (1.66-1.79)	1.59 (1.53-1.65)	1.51 (1.45-1.57)
Male						
No infection	9887	1851097	5.34 (5.24-5.45)	1.00	1.00	1.00
Any infection	10830	689261	15.71 (15.42-16.01)	1.83 (1.78-1.88)	1.69 (1.64-1.74)	1.56 (1.51-1.60)
Sepsis	208	9173	22.67 (19.79-25.98)	2.53 (2.21-2.91)	2.30 (2.01-2.64)	2.08 (1.81-2.39)
Pneumonia	597	26080	22.89 (21.13-24.80)	2.42 (2.23-2.63)	2.20 (2.03-2.39)	1.98 (1.82-2.15)
Other LRTI	5450	414539	13.15 (12.80-13.50)	1.61 (1.56-1.67)	1.49 (1.44-1.54)	1.37 (1.33-1.42)
UTI	2389	108109	22.10 (21.23-23.00)	2.25 (2.15-2.36)	2.09 (2.00-2.19)	1.90 (1.81-1.99)
SSTI	2066	128708	16.05 (15.37-16.76)	1.88 (1.79-1.97)	1.73 (1.64-1.81)	1.58 (1.51-1.66)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Figure 3: Kaplan-Meier survival curve depicting the time to death after a dementia diagnosis in years



Supplementary Figure 4: Kaplan-Meier survival curve depicting the time to death 12 months after dementia diagnosis



Supplementary Table 8: Crude rate and hazard ratios for the association of common infections and dementia, stratified by age

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
65-79						
No infection	8470	3024694	2.80 (2.74-2.86)	1.00	1.00	1.00
Any Infection	7329	1094966	6.69 (6.54-6.85)	1.72 (1.67-1.78)	1.60 (1.55-1.66)	1.43 (1.38-1.48)
80-89						
No infection	12776	739810	17.27 (16.97-17.57)	1.00	1.00	1.00
Any infection	16614	543532	30.57 (30.11-31.04)	1.72 (1.68-1.76)	1.57 (1.53-1.60)	1.49 (1.46-1.53)
90 years and older						
No infection	4068	130528	31.17 (30.22-32.14)	1.00	1.00	1.00
Any infection	7545	116458	64.79 (63.34-66.27)	2.07 (1.99-2.15)	1.89 (1.82-1.97)	1.76 (1.69-1.84)

*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 9: Crude rate and hazard ratios for the association of common infections and dementia, stratified by age (<90 and 90> years)

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
<90 years old						
No infection	21246	3764504	5.64 (5.57-5.72)	1.00	1.00	1.00
Any Infection	23943	1638498	14.61 (14.43-14.80)	1.72 (1.69-1.75)	1.58 (1.55-1.61)	1.47 (1.44-1.50)
90 years and older						
No infection	4068	130528	31.17 (30.22-32.14)	1.00	1.00	1.00
Any infection	7545	116458	64.79 (63.34-66.27)	2.07 (1.99-2.15)	1.89 (1.82-1.97)	1.76 (1.69-1.84)

*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 10: Crude rate and hazard ratios for the association of common infections and dementia, with interaction between age and non-proportional covariates (sex, ethnicity, patient-level IMD, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, chronic kidney disease, hypertension, traumatic brain injury, benzodiazepines and polypharmacy)

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	25314	3895032	6.50 (6.42-6.58)	1.00	1.00	1.00
Any Infection	31488	1754956	17.94 (17.75-18.14)	1.78 (1.75-1.81)	1.64 (1.61-1.66)	1.52 (1.49-1.55)

*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease , diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 11: Crude rate and hazard ratios for the association of common infections and dementia, excluding dementia related to other diseases

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	24387	3890864	6.27 (6.19-6.35)	1.00	1.00	1.00
Any Infection	30512	1751183	17.42 (17.23-17.62)	1.78 (1.75-1.81)	1.63 (1.61-1.66)	1.52 (1.50-1.55)
Sepsis	420	16789	25.02 (22.74-27.53)	2.52 (2.29-2.78)	2.32 (2.10-2.55)	2.11 (1.91-2.32)
Pneumonia	1214	47753	25.42 (24.03-26.89)	2.28 (2.15-2.41)	2.08 (1.96-2.20)	1.87 (1.77-1.99)
Other LRTI	13001	908633	14.31 (14.06-14.56)	1.57 (1.54-1.60)	1.44 (1.41-1.47)	1.34 (1.31-1.37)
UTI	10173	480182	21.19 (20.78-21.60)	2.03 (1.99-2.08)	1.85 (1.81-1.90)	1.71 (1.67-1.76)
SSTI	5377	290917	18.48 (18.00-18.98)	1.78 (1.73-1.84)	1.64 (1.59-1.69)	1.53 (1.48-1.58)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 12: Crude rate and hazard ratios for the association of common infections and dementia, according to definition of infections

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
All infections in CPRD treated with antibiotics						
No infection	27548	4003253	6.88 (6.80-6.96)	1.00	1.00	1.00
Any infection	29503	1653011	17.85 (17.65-18.05)	1.71 (1.69-1.74)	1.57 (1.55-1.60)	1.47 (1.44-1.50)
Sepsis	372	13620	27.31 (24.67-30.23)	2.53 (2.28-2.80)	2.32 (2.09-2.57)	2.13 (1.92-2.36)
Pneumonia	1109	41212	26.91 (25.37-28.54)	2.23 (2.10-2.37)	2.03 (1.91-2.16)	1.84 (1.73-1.95)
Other LRTIs	11635	818240	14.22 (13.96-14.48)	1.48 (1.45-1.52)	1.36 (1.33-1.39)	1.27 (1.24-1.30)
UTI	10511	481330	21.84 (21.42-22.26)	1.96 (1.91-2.00)	1.79 (1.75-1.84)	1.67 (1.63-1.71)
SSTI	5535	291627	18.98 (18.49-19.49)	1.71 (1.66-1.76)	1.58 (1.53-1.63)	1.48 (1.44-1.52)
Excluding multiple infection diagnoses						
No infection	25314	3875552	6.53 (6.45-6.61)	1.00	1.00	1.00
Any infection	31151	1748025	17.82 (17.62-18.02)	1.75 (1.72-1.78)	1.61 (1.58-1.64)	1.50 (1.47-1.53)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 13: Crude rate and hazard ratios for the association of common infections and cognitive impairment, excluding codes related to symptoms of cognitive impairment

Infection	Total number of incident cognitive impairment diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	5297	3102598	1.71 (1.66-1.75)	1.00	1.00	1.00
Any Infection	7243	1471353	4.92 (4.81-5.04)	1.93 (1.86-2.00)	1.74 (1.68-1.81)	1.62 (1.56-1.68)
Sepsis	97	14809	6.55 (5.37-7.99)	2.40 (1.96-2.93)	2.04 (1.67-2.50)	1.86 (1.52-2.27)
Pneumonia	316	41986	7.53 (6.74-8.40)	2.43 (2.17-2.72)	2.08 (1.85-2.33)	1.87 (1.67-2.10)
Other LRTI	3191	821156	3.89 (3.75-4.02)	1.50 (1.44-1.57)	1.33 (1.27-1.39)	1.21 (1.16-1.27)
UTI	2240	425612	5.26 (5.05-5.49)	1.82 (1.73-1.91)	1.68 (1.60-1.77)	1.57 (1.49-1.65)
SSTI	1332	258961	5.14 (4.87-5.43)	1.78 (1.68-1.89)	1.58 (1.49-1.68)	1.48 (1.40-1.58)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Appendix 10.3 Supplementary information for chapter 6

This appendix includes the supplementary information which comprises of primary care code lists for dementia and medication use (systemic corticosteroids, benzodiazepines and proton pump inhibitors). The rest of the codelists used in this chapter are the same as those in chapter 7 and can be accessed at https://doi.org/10.17037/DATA.00002573.

Dementia primary care code list

Read code	Read v2/CTV3	Description
1JA2.	Read v2	suspected dementia
4L49.	Read v2	prion protein markers for creutzfeldt-jakob disease
A411.	Read v2	jakob-creutzfeldt disease
A4110	Read v2	sporadic creutzfeldt-jakob disease
A413.	Read v2	progressive multifocal leucoencephalopathy
E00..	Read v2	senile dementia
E000.	Read v2	uncomplicated senile dementia
E001.	Read v2	presenile dementia
E0010	Read v2	uncomplicated presenile dementia
E0011	Read v2	presenile dementia with delirium
E0012	Read v2	presenile dementia with paranoia
E0013	Read v2	presenile dementia with depression
E001z	Read v2	presenile dementia nos
E002.	Read v2	senile dementia with depressive or paranoid features
E0020	Read v2	senile dementia with paranoia
E0021	Read v2	senile dementia with depression
E002z	Read v2	senile dementia with depressive or paranoid features nos
E003.	Read v2	senile dementia with delirium
E004.	Read v2	arteriosclerotic dementia
E0040	Read v2	uncomplicated arteriosclerotic dementia
E0041	Read v2	arteriosclerotic dementia with delirium
E0042	Read v2	arteriosclerotic dementia with paranoia
E0043	Read v2	arteriosclerotic dementia with depression
E004z	Read v2	arteriosclerotic dementia nos
E00y.	Read v2	presbyophrenic psychosis
E00z.	Read v2	senile or presenile psychoses nos
E011.	CTV3	korsakov's alcoholic psychosis
E0110	Read v2	korsakov's alcoholic psychosis
E0111	Read v2	korsakov's alcoholic psychosis with peripheral neuritis
E012.	Read v2	other alcoholic dementia
E0120	Read v2	chronic alcoholic brain syndrome
E02y1	Read v2	drug-induced dementia
E041.	Read v2	dementia in conditions ec
Eu00.	Read v2	[x]dementia in alzheimer's disease
Eu000	Read v2	[x]dementia in alzheimer's disease with early onset
Eu001	Read v2	[x]dementia in alzheimer's disease with late onset
Eu002	Read v2	[x]dementia in alzheimer's dis, atypical or mixed type
Eu00z	Read v2	[x]dementia in alzheimer's disease, unspecified
Eu01.	Read v2	[x]vascular dementia
Eu010	Read v2	[x]vascular dementia of acute onset
Eu011	Read v2	[x]multi-infarct dementia
Eu012	Read v2	[x]subcortical vascular dementia
Eu013	Read v2	[x]mixed cortical and subcortical vascular dementia
Eu01y	Read v2	[x]other vascular dementia
Eu01z	Read v2	[x]vascular dementia, unspecified
Eu02.	Read v2	[x]dementia in other diseases classified elsewhere
Eu020	Read v2	[x]dementia in pick's disease
Eu021	Read v2	[x]dementia in creutzfeldt-jakob disease
Eu022	Read v2	[x]dementia in huntington's disease
Eu023	Read v2	[x]dementia in parkinson's disease
Eu024	Read v2	[x]dementia in human immunodef virus [hiv] disease
Eu025	Read v2	[x]lewy body dementia
Eu02y	Read v2	[x]dementia in other specified diseases classif elsewhere

Eu02z	Read v2	[x] unspecified dementia
Eu03.	Read v2	[x]korsakov's psychosis, nonalcoholic
Eu041	Read v2	[x]delirium superimposed on dementia
Eu106	Read v2	[x]korsakov's psychosis, alcohol induced
Eu107	Read v2	[x]alcoholic dementia nos
F102.	Read v2	cerebral degeneration in lipidoses ec
F1020	Read v2	cerebral degeneration in gaucher's disease
F102z	Read v2	cerebral degeneration in lipidosis nos
F103.	Read v2	cerebral degeneration in diseases ec
F103z	Read v2	cerebral degeneration in disease nos
F11..	Read v2	other cerebral degenerations
F110.	Read v2	alzheimer's disease
F1100	Read v2	alzheimer's disease with early onset
F1101	Read v2	alzheimer's disease with late onset
F111.	Read v2	pick's disease
F112.	Read v2	senile degeneration of brain
F116.	Read v2	lewy body disease
F118.	Read v2	frontotemporal degeneration
F11x.	Read v2	cerebral degeneration in other disease ec
F11x0	Read v2	cerebral degeneration due to alcoholism
F11x2	Read v2	cerebral degeneration due to cerebrovascular disease
F11x4	Read v2	cerebral degeneration due to neoplastic disease
F11x5	Read v2	cerebral degeneration due to myxoedema
F11x6	Read v2	cerebral degeneration due to vitamin b12 deficiency
F11x7	Read v2	cerebral degeneration due to jakob - creutzfeldt disease
F11x8	Read v2	cerebral degeneration due to progressive multifocal leucoencephalopathy
F11x9	Read v2	cerebral degeneration in parkinson's disease
F11xz	Read v2	cerebral degeneration other disease nos
F11y.	Read v2	other cerebral degeneration
F11yz	Read v2	other cerebral degeneration nos
F11z.	Read v2	cerebral degeneration nos
F134.	Read v2	huntington's chorea
F21y2	Read v2	binswanger's encephalopathy
Fyu30	Read v2	[x]other alzheimer's disease
X002w	CTV3	senile dementia
X002x	CTV3	[x]dementia in alzheimer's disease with early onset
X0030	CTV3	[x]dementia in alzheimer's disease with late onset
X0037	CTV3	frontotemporal degeneration
X003A	CTV3	lewy body disease
X003P	CTV3	[x]dementia in human immunodef virus [hiv] disease
X003R	CTV3	[x]vascular dementia of acute onset
X003T	CTV3	[x]subcortical vascular dementia

10.3.2 Benzodiazepine therapy code list

Product name	BNF code	Read v2 code	dm+d code
temazepam 10mg tablets	15.01.04.01.00		
lormetazepam 500microgram tablets	04.01.01.00.00		
lorazepam 1mg tablets	04.01.02.00.00		
temazepam capsules 10mg	04.01.01.00.00		
chlordiazepoxide tablets 5mg	04.01.02.00.00		
temazepam 20mg tablets	15.01.04.01.00		
nitrazepam 5mg tablets	04.01.01.00.00		
temazepam tablets 10mg	0401010T0AAAMAM		
chlordiazepoxide 5mg capsules	04.01.02.00.00		
lormetazepam 1mg tablets	04.01.01.00.00		
temazepam tabs 10mg		d1a9.	321152004
lorazepam tab 1mg		d2a1.	321294008
temazepam tab 10mg		d1a9.	321152004
temazepam cap 10mg		d1a1.	1.42655E+17
temazepam tab 10		d1a9.	321152004
nitrazepam tab 5		d182.	321127001
nitrazepam tabs 5mg		d182.	321127001
nitrazepam 5mg tablets		d182.	321127001
loprazolam-p42 1mg tablet	0401010N0AAAAAA		
chlordiazepoxide caps 5mg		d241.	321247000
chlordiazepoxide tab 5mg		d246.	9.8235E+16
temazepam 10mg tablets		d1a9.	321152004
lorazepam tabs 1mg		d2a1.	321294008
temazepam cap 10		d1a1.	1.42655E+17
loprazolam 1mg tablets	04.01.01.00.00		
temazepam caps 10 mg		d1a1.	1.42655E+17
chlordiazepoxide 5mg tablets	04.01.02.00.00		
temazepam tablets 10 mg	0401010T0AAAMAM		
temazepam capsules 20mg	04.01.01.00.00		
temazepam tabs 20mg	0401010T0AAANAN		
temazepam tabs 10mg	0401010T0AAAMAM		
clonazepam 500microgram tablets	04.08.01.15.00		
chlordiazepoxide capsules 5mg	0401020E0AAADAD		
chlordiazepoxide capsules 10mg	040102		
lormetazepam tabs 1mg		d172.	321123002
loprazolam tablets 1mg	0401010N0AAAAAA		
chlordiazepoxide tabs 25mg	040102		
temazepam capsules 10 mg		d1a1.	1.42655E+17

nitrazepam tablets 10mg	04.01.01.00.00		
temazepam tabs 20 mg		d1aa.	321153009
temazepam 10mg tab		d1a9.	321152004
nitrazepam tablets 5 mg	0401010R0AAACAC		
chlordiazepoxide 10mg capsules	04.01.02.00.00		
lormetazepam tabs 1mg	0401010P0AAACAC		
nitrazepam tablets 5mg	0401010R0AAACAC		
loprazolam tab 1		d161.	321120004
chlordiazepoxide tablets 10mg	04.01.02.00.00		
temazepam tabs 10 mg		d1a9.	321152004
temazepam-p42 10mg tablet	0401010T0AAAMAM		
nitrazepam tabs 5mg	0401010R0AAACAC		
temazepam tab 20mg		d1aa.	321153009
loprazolam tablets 1 mg		d161.	321120004
clonazepam tab 500mcg		dn4y.	322897008
clonazepam 500microgram tablets		dn4y.	322897008
clonazepam tabs 500 micrograms		dn4y.	322897008
clonazepam tabs 0.5mg		dn4y.	322897008
temazepam 10mg/5ml oral solution sugar free	04.01.01.00.00		
chlordiazepoxide 10mg tablets	04.01.02.00.00		
chlordiazepoxide cap 10mg		d242.	321248005
chlordiazepoxide 10mg capsules		d242.	321248005
nitrazepam tabs 5 mg		d182.	321127001
clonazepam 2mg tablets	04.08.01.15.00		
temazepam tablets 20mg		d1aa.	321153009
temazepam 20mg caps			2.99275E+17
lorazepam tablets 1mg		d2a1.	321294008
temazepam capsules 15mg	04.01.01.00.00		
chlordiazepoxide tablets 10mg	040102		
temazepam cap 20mg		d1a3.	1.42665E+17
temazepam tabs 20mg		d1aa.	321153009
temazepam 20mg tablets		d1aa.	321153009
nitrazepam tab 5mg		d182.	321127001
chlordiazepoxide caps 10mg	040102		
chlordiazepoxide caps 5mg	0401020E0AAADAD		
temazepam tablets 10mg		d1a9.	321152004
temazepam capsules 10mg			2.99275E+17
temazepam 10mg tabs		d1a9.	321152004
nitrazepam capsules 5mg	04.01.01.00.00		
temazepam tablets 20 mg	0401010T0AAANAN		
temazepam cap 15mg		d1a2.	1.42675E+17

chlordiazepoxide tablets 25mg	040102		
temazepam tabs 10 mg			2.99275E+17
temazepam tablets 10 mg		d1a9.	321152004
chlordiazepoxide tabs 10mg	040102		
lormetazepam tab 1mg		d172.	321123002
lormetazepam 1mg tablets		d172.	321123002
temazepam cap 20		d1a3.	1.42665E+17
lorazepam tablets 1 mg		d2a1.	321294008
temazepam capsules 30mg	15.01.04.01.00		
chlordiazepoxide caps 10mg		d242.	321248005
nitrazepam tab 5mg			2.99275E+17
lorazepam 1mg tablets		d2a1.	321294008
temazepam 10mg tablets			2.99275E+17
lormetazepam tablets 500micrograms	0401010P0AAABAB		
lormetazepam tablets 1mg	0401010P0AAACAC		
clonazepam tablets 500micrograms	0408010F0AAABAB		
alprazolam 250microgram tablets	04.01.02.00.00		
chlordiazepoxide-p42 10mg capsule	040102		
loprazolam tabs 1mg	0401010N0AAAAAA		
temazepam tablets 20mg	0401010T0AAANAN		
nitrazepam-p42 5mg tablet	0401010R0AAACAC		
lorazepam 1mg tabs		d2a1.	321294008
chlordiazepoxide hydrochloride capsules 5 mg		d241.	321247000
lorazepam tablets 1mg	0401020P0AAABAB		
nitrazepam tablets 5 mg		d182.	321127001
temazepam capsules 10 mg			2.99275E+17
loprazolam tabs 1mg		d161.	321120004
temazepam-p42 10mg tabs	0401010T0AAAMAM		
chlordiazepoxide tabs 5mg	040102		
temazepam 10mg capsules		d1a1.	1.42655E+17
lorazepam 2.5mg tablets	04.01.02.00.00		
chlordiazepoxide cap 5mg		d241.	321247000
temazepam gelthix gel-filled capsules 20mg [pharmacia]	15.01.04.01.00		
lormetazepam 500microgram tablets		d171.	321122007

lormetazepam tab 500mcg		d171.	321122007
lormetazepam tabs 0.5mg		d171.	321122007
chlordiazepoxide hydrochloride tablets 10 mg		d244.	321250002
loprazolam tab 1mg		d161.	321120004
temazepam cap 10mg			2.99275E+17
chlordiazepoxide tabs 10mg		d247.	9.8275E+16
temazepam gelthix gel-filled capsules 10mg [pharmacia]	15.01.04.01.00		
lormetazepam tablets 0.5mg		d171.	321122007
flurazepam 15mg capsules	04.01.01.00.00		
loprazolam tablets 1mg			2.99275E+17
lorazepam tablets 1mg			2.99275E+17
lormetazepam tablets 500 micrograms		d171.	321122007
clonazepam tabs 500micrograms	0408010F0AAABAB		
nitrazepam cap 5mg		d181.	1.29255E+17
nitrazepam tab 10mg		d183.	1.29285E+17
temazepam tab 10mg			321152004
temazepam 10mg caps		d1a1.	1.42655E+17
temazepam tab 10mg			2.99275E+17
clonazepam tabs 2mg		dn4z.	322898003
lorazepam tab 1		d2a1.	321294008
nitrazepam tabs 5 mg			2.99275E+17
loprazolam 1mg tablets		d161.	321120004
loprazolam tabs 1 mg			2.99275E+17
temazepam capsules 10 mg		d1a9.	321152004
temazepam 10mg/5ml oral solution sugar free		d1ao.	321167000
temazepam eli 10		d1ao.	321167000
chlordiazepoxide-p42 5mg tablet	040102		
lormetazepam cap 1mg			1.21635E+17
chlordiazepoxide tablets 5mg	040102		
chlordiazepoxide capsules 5mg		d241.	321247000
chlordiazepoxide tablets 25mg	04.01.02.00.00		
lormetazepam tablets 1mg		d172.	321123002
lorazepam-p42 1mg tablet	0401020P0AAABAB		
temazepam capsules 20 mg		d1a3.	1.42665E+17
lorazepam tabs 1mg	0401020P0AAABAB		
temazepam tab 20		d1aa.	321153009

chlordiazepoxide hydrochloride tablets 25mg	04.01.02.00.00		
temazepam capsules 15 mg			2.99275E+17
clonazepam tablets 500 micrograms	0408010F0AAABAB		
temazepam tabs			2.99275E+17
*temazepam, cap, 20.00mg			2.99275E+17
lormetazepam tab 500mcg			2.99275E+17
temazepam_tab 10mg		d1a9.	321152004
temazepam-p42 20mg tablet	0401010T0AAANAN		
nitrazepam 5mg tablets			2.99275E+17
temazepam 10mg		d1a9.	321152004
temazepam-p42 10mg tab	0401010T0AAAMAM		
temazepam-p42 10mg capsule	040101		
temazepam 10 mg caps	040101		
temazepam caps 10mg		d1a1.	1.42655E+17
loprazolam tablets 1mg		d161.	321120004
lorazepam tablets 1 mg	0401020P0AAABAB		
chlordiazepoxide hydrochloride tablets 5 mg			2.99275E+17
chlordiazepoxide hydrochloride capsules 5 mg			2.99275E+17
chlordiazepoxide tab 25		d248.	9.8285E+16
chlordiazepoxide 25mg tablets		d248.	9.8285E+16
lormetazepam capsules 1mg	04.01.01.00.00		
temazepam capsules 15 mg		d1a2.	1.42675E+17
lormetazepam tab 1		d172.	321123002
chlordiazepoxide 5mg capsules		d241.	321247000
temazepam sf elixir 10mg/5ml		d1ao.	321167000
clonazepam 2mg tablets		dn4z.	322898003
clonazepam tablets 500 micrograms		dn4y.	322897008
clonazepam tablets 500 micrograms			2.99275E+17
temazepam elixir 10 mg/5ml		d1ao.	321167000
chlordiazepoxide 5mg		d241.	321247000
lormetazepam tabs 500micrograms	0401010P0AAABAB		
nitrazepam tablets 5mg			2.99275E+17
temazepam tablets 20 mg		d1aa.	321153009

temazepam capsules 20 mg		d1aa.	321153009
clonazepam tab 2mg		dn4z.	322898003
temazepam 20mg caps		d1a3.	1.42665E+17
temazepam 10mg tab	0401010T0AAAMAM		
lorazepam tabs 2.5mg		d2a2.	321295009
chlordiazepoxide tablets 10mg [ddsa]	04.01.02.00.00		
temazepam 10mg tablets (actavis uk ltd)	15.01.04.01.00		
nitrazepam 2.5mg/5ml oral suspension	04.01.01.00.00		
temazepam gel-filled capsules 10mg	15.01.04.01.00		
clonazepam tablets 0.5mg	0408010F0AAABAB		
temazepam			2.99275E+17
chlordiazepoxide capsules 10mg		d242.	321248005
chlordiazepoxide hcl tabs 10mg		d244.	321250002
clonazepam 250micrograms/5ml oral solution		dn4..	8.39571E+15
clonazepam oral soln 250micrograms/5ml		dn4..	8.39571E+15
temazepam 10mg tablets (genus pharmaceuticals ltd)	15.01.04.01.00		
nitrazepam tablets 5mg		d182.	321127001
midazolam 10mg/5ml solution for injection ampoules	15.01.04.01.00		
nitrazepam 5mg tablets (actavis uk ltd)	04.01.01.00.00		
alprazolam tabs 250micrograms		d22y.	321241004
alprazolam tabs 500micrograms		d22z.	321242006
chlordiazepoxide hcl tabs 5mg		d243.	321249002
alprazolam 500microgram tablets	04.01.02.00.00		
clonazepam tablets 500 micrograms	0408010F0AAABAB		
clonazepam 2mg tablets (a a h pharmaceuticals ltd)	04.08.01.15.00		
midazolam 10mg/2ml solution for injection ampoules	15.01.04.01.00		
clonazepam 1mg/1ml solution for injection ampoules and diluent	04.08.02.00.00		
temazepam 10mg tablets (mylan ltd)	15.01.04.01.00		

midazolam 5mg/5ml solution for injection ampoules	15.01.04.01.00		
loprazolam tablets 1 mg	0401010N0AAAAAA		
midazolam 10mg/ml oromucosal solution	04.08.02.00.00		
alprazolam 250microgram tablets		d22y.	321241004
chlordiazepoxide hydrochloride tablets 10 mg	040102		
clonazepam tabs 2mg	0408010F0AAACAC		
clonazepam tablets 2 mg	0408010F0AAACAC		
temazepam 10mg tablets (teva uk ltd)	04.01.01.00.00		
midazolam 5mg/5ml solution for injection ampoules (amco)	15.01.04.01.00		
midazolam 2mg/2ml solution for injection ampoules	15.01.04.01.00		
chlordiazepoxide hydrochloride capsules 10 mg	040102		
lorazepam 1mg tablets (genus pharmaceuticals ltd)	04.01.02.00.00		
midazolam injection 5mg/ml	15.01.04.01.00		
lorazepam 1mg tablets (a a h pharmaceuticals ltd)	04.01.02.00.00		
midazolam inj 10mg/2ml		o57z.	334018006
midazolam inj 10mg/5ml		o57y.	334017001
midazolam 10mg/2ml solution for injection ampoules (hameln pharmaceuticals ltd)	15.01.04.01.00		
lormetazepam tablets 1 mg	0401010P0AAACAC		
nitrazepam suspension 2.5 mg/5 ml	0401010R0AAAAAA		
lorazepam 4mg/1ml solution for injection ampoules	04.01.02.00.00		
lorazepam 1mg tablets (arrow generics ltd)	15.01.04.01.00		
chlordiazepoxide hydrochloride tablets 5 mg	040102		
lorazepam 2.5mg tablets (sandoz ltd)	04.01.02.00.00		
lorazepam 1mg/5ml oral solution	04.01.02.00.00		
temazepam sugar-free oral solution 10 mg/5 ml	0401010T0AAAEAE		
temazepam 10mg tablets	04010100	d1a9.	
nitrazepam 5mg tablets	04010100	d182.	

clonazepam 500microgram tablets (a a h pharmaceuticals ltd)	04.08.01.15.00		
lorazepam 1mg tablets	04010201	d2a1.	
temazepam 20mg tablets	04010100	d1aa.	
clonazepam 500microgram tablets	04080100	dn4y.	
buccolam 5mg/1ml oromucosal solution pre-filled oral syringes (shire pharmaceuticals ltd)	04.08.02.00.00		
midazolam 10mg/2ml solution for injection ampoules (amco)	15.01.04.01.00		
midazolam 10mg/2ml oromucosal solution pre-filled oral syringes	04.08.02.00.00		
chlordiazepoxide 5mg capsules (a a h pharmaceuticals ltd)	04.01.02.00.00		
midazolam 10mg/2ml solution for injection ampoules	15010401	o57z.	
lorazepam 1mg/5ml oral suspension	04.01.02.00.00		
buccolam 10mg/2ml oromucosal solution pre-filled oral syringes (shire pharmaceuticals ltd)	04.08.02.00.00		
temazepam 10mg tablets (sandoz ltd)	04.01.01.00.00		
chlordiazepoxide hydrochloride capsules 5 mg	0401020E0AAADAD		
midazolam 10mg/5ml solution for injection ampoules	15010401	o57y.	
buccolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes (shire pharmaceuticals ltd)	15.01.04.01.00		
temazepam 20mg tablets (actavis uk ltd)	15.01.04.01.00		
chlordiazepoxide 5mg capsules	04010201	d241.	
chlordiazepoxide 5mg tablets		d243.	321249002
clonazepam 500micrograms/5ml oral solution sugar free	04.08.01.15.00		
lorazepam 500micrograms/5ml oral suspension	15.01.04.01.00		
buccolam 2.5mg/0.5ml oromucosal solution pre-filled oral ...	04080200	o573.	

midazolam 5mg/5ml solution for injection ampoules	15010401	o57..	
epistatus 10mg/1ml oromucosal solution (special products ...	04080200	o57..	
temazepam 20mg tablets (teva uk ltd)	15.01.04.01.00		
lorazepam 1mg tablets	15010401	d2a1.	
midazolam 5mg/1ml oromucosal solution pre-filled oral syringes	04.08.02.00.00		
midazolam 7.5mg/1.5ml oromucosal solution pre-filled oral syringes	04.08.02.00.00		
midazolam 50mg/10ml solution for injection ampoules	15.01.04.01.00		
midazolam 10mg/1ml oromucosal solution pre-filled oral syringes	15.01.04.01.00		
temazepam 10mg/5ml oral solution sugar free (focus pharmaceuticals ltd)	15.01.04.01.00		
midazolam pre-filled syringe buccal solution 5mg/0.5ml	15.01.04.01.00		
lormetazepam 1mg tablets	04010100	d172.	
epistatus buccal solution 10mg/ml [spec prod]	04.08.02.00.00		
clonazepam 500microgram tablets (almus pharmaceuticals ltd)	04.08.01.15.00		
chlordiazepoxide 10mg capsules	04010201	d242.	
temazepam elixir 10 mg/5 ml	0401010T0AAAEAE		
lorazepam 1mg tablets	04010200	d2a1.	
clonazepam 2mg tablets	04080100	dn4z.	
temazepam 10mg tablets (a a h pharmaceuticals ltd)	15.01.04.01.00		
temazepam 10mg/5ml oral solution sugar free (sandoz ltd)	15.01.04.01.00		
epistatus pre-filled syringe buccal solution 10mg/1ml [spec prod]	04.08.02.00.00		
epistatus 10mg/1ml oromucosal solution pre-filled oral sy...	04080200	o57..	
clonazepam 250micrograms/5ml oral solution	04.08.01.15.00		

buccolam 5mg/1ml oromucosal solution pre-filled oral syringes (shire pharmaceuticals ltd)		o575.	1.95305E+16
buccolam 10mg/2ml oromucosal solution pre-filled oral syr...	04080200	o576.	
chlordiazepoxide 5mg tablets	04010201	d243.	
lorazepam 1mg tablets (sandoz ltd)	04.01.02.00.00		
clonazepam 500microgram tablets (alliance healthcare (distribution) ltd)	04.08.01.15.00		
midazolam 10mg/2ml solution for injection ampoules (wockhardt uk ltd)	15.01.04.01.00		
clonazepam 500micrograms/5ml oral solution sugar free	04080100	dn4w.	
temazepam 20mg tablets (sandoz ltd)	15.01.04.01.00		
temazepam 10mg/5ml oral solution sugar free	04010100	d1ao.	
midazolam 2mg/2ml solution for injection ampoules	15010401	o57..	
midazolam 10mg/2ml solution for injection ampoules		o57z.	334018006
buccolam 10mg/2ml oromucosal solution pre-filled oral syr...		o576.	3.25188E+16
midazolam pre-filled syringe buccal solution 2.5mg/0.25ml	15.01.04.01.00		
lorazepam 1mg tablets (actavis uk ltd)	04.01.02.00.00		
midazolam 10mg/2ml solution for injection ampoules (accord healthcare ltd)	15.01.04.01.00		
clonazepam 500micrograms/5ml oral solution sugar free (rosemont pharmaceuticals ltd)	04.08.01.15.00		
midazolam injection 10 mg/2 ml ampoule	1501041T0AAAAAA		
tapclob 5mg/5ml oral suspension (martindale pharmaceuticals ltd)	04.01.02.00.00		
midazolam injection 5 mg/ml 10 ml ampoule	15010401		
lorazepam 2.5mg tablets		d2a2.	321295009

midazolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes	15.01.04.01.00		
alprazolam tablets 500 micrograms	040102		
nitrazepam 2.5mg/5ml oral suspension	04010100	d184.	
midazolam 10mg/5ml solution for injection ampoules (amco)	15.01.04.01.00		

Proton pump inhibitors therapy code list

Product name	BNF code	Read v2 code	dm+d code
losec 20mg gastro-resistant capsules (astrazeneca uk ltd)	01.03.05.00.00		
omeprazole 20mg gastro-resistant capsules	01.03.05.00.00		
pantoprazole 40mg gastro-resistant tablets	01.03.05.00.00		
rabeprazole 20mg gastro-resistant tablets	01.03.05.00.00		
rabeprazole 10mg gastro-resistant tablets	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules	01.03.05.00.00		
lansoprazole caps 30mg		a6c2.	317309001
omeprazole 10mg gastro-resistant capsules	01.03.05.00.00		
lansoprazole 30mg gastro-resistant capsules	01.03.05.00.00		
omeprazole 40mg gastro-resistant capsules	01.03.05.00.00		
omeprazole caps 20mg		a6b1.	317291008
omeprazole 10mg cap			2.99275E+17
omeprazole 20mg			2.99275E+17
omeprazole cap 20mg			2.99275E+17
esomeprazole 20mg gastro-resistant tablets	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules		a6c3.	317310006
omeprazole cap 20mg		a6b1.	317291008
omeprazole 20mg gastro-resistant capsules		a6b1.	317291008
lansoprazole caps 15mg		a6c3.	317310006
lansoprazole cap 30mg		a6c2.	317309001
omeprazole 20mg gastro-resistant tablets	01.03.05.00.00		
rabeprazole 20mg gastro-resistant tablets		a6f2.	317325006
rabeprazole sodium tabs 20mg		a6f2.	317325006
lansoprazole cap 30		a6c2.	317309001
lansoprazole 30mg gastro-resistant capsules		a6c2.	317309001
lansoprazole gastro resistant capsules 15mg	0103050L0AAABAB		
omeprazole-p42 20mg capsule	0103050P0AAAGAG		
omeprazole capsules 20mg		a6b1.	317291008
omeprazole 10mg dispersible gastro-resistant tablets	01.03.05.00.00		
lansoprazole 30mg capsules			2.99275E+17

omeprazole 10mg capsules			2.99275E+17
omeprazole tablets (gastro-resistant) 20 mg		a6bv.	407847009
lansoprazole capsules (gastro-resistant) 30 mg		a6c2.	317309001
lansoprazole gastro resistant caps 30mg	0103050L0AAAAAA		
omeprazole capsules 20mg	0103050P0AAAGAG		
lansoprazole gastro resistant capsules 30mg	0103050L0AAAAAA		
omeprazole cap 10		a6b7.	317297007
omeprazole 10mg gastro-resistant capsules		a6b7.	317297007
omeprazole cap 20		a6b1.	317291008
omeprazole caps 10mg		a6b7.	317297007
omeprazole capsules (gastro-resistant) 20 mg	0103050P0AAAGAG		
lansoprazole cap 15mg		a6c3.	317310006
pantoprazole tab 40		a6e1.	317318004
omeprazole caps 20mg	0103050P0AAAGAG		
omeprazole 20mg capsules			2.99275E+17
lansoprazole gastro resistant caps 15mg	0103050L0AAABAB		
rabeprazole sodium e/c tablets 20 mg		a6f2.	317325006
omeprazole capsules 20 mg		a6b1.	317291008
omeprazole capsules 10 mg		a6b7.	317297007
rabeprazole tabs 20mg		a6f2.	317325006
rabeprazole 20 mg tabs e/c -		a6f2.	317325006
omeprazole caps 20 mg -		a6b1.	317291008
lansoprazole caps 30 mg -		a6c2.	317309001
lansoprazole caps 30 mg			2.99275E+17
losec 40mg gastro-resistant capsules (astrazeneca uk ltd)	01.03.05.00.00		
omeprazole 10mg gastro-resistant tablets	01.03.05.00.00		
omeprazole capsules (gastro-resistant) 10 mg	0103050P0AAAFAF		
omeprazole 20mg caps		a6b1.	317291008
losec mups 20mg gastro-resistant tablets (astrazeneca uk ltd)	01.03.05.00.00		
nexium 20mg gastro-resistant tablets (astrazeneca uk ltd)	01.03.05.00.00		
pantoprazole 20mg gastro-resistant tablets	01.03.05.00.00		
rabeprazole sodium tablets 20mg		a6f2.	317325006

omeprazole cap 10mg		a6b7.	317297007
omeprazole caps 10 mg			2.99275E+17
omeprazole capsules 10mg	0103050P0AAAFAF		
lansoprazole 30mg gastro-resistant granules sachets	01.03.05.00.00		
omeprazole caps 20 mg		a6b1.	317291008
losec 20mgx28 caps		a6b3.	9.23011E+14
lansoprazole capsules (gastro-resistant) 15 mg		a6c3.	317310006
lansoprazole cap 15		a6c3.	317310006
omeprazole capsules 40mg	0103050P0AAAEAE		
omeprazole 20mg dispersible gastro-resistant tablets	01.03.05.00.00		
lansoprazole 15mg capsules			2.99275E+17
losec 10mg gastro-resistant capsules (astrazeneca uk ltd)	01.03.05.00.00		
omeprazole caps 10mg	0103050P0AAAFAF		
pantoprazole gastro resistant tablets 20mg	010305		
pantoprazole enteric coated tablets 40mg		a6e1.	317318004
lansoprazole 30mg capsules		a6c2.	317309001
omeprazole 20mg capsules		a6b1.	317291008
omeprazole disp tab 10mg		a6bx.	398942003
losec caps 20mg	0103050P0BBAAAA		
lansoprazole caps 15 mg		a6c3.	317310006
omeprazole caps 10 mg		a6b7.	317297007
*omeprazole 10mg		a6b7.	317297007
lansoprazole capsules (gastro-resistant) 15 mg	0103050L0AAABAB		
lansoprazole capsules (gastro-resistant) 30 mg	0103050L0AAAAAA		
lansoprazole 15mg capsules		a6c3.	317310006
omeprazole disp tab 20mg		a6by.	398905005
omeprazole cap (20mg)			2.99275E+17
losec cap (20mg)			2.99275E+17
omeprazole capsules (gastro-resistant) 20 mg		a6b1.	317291008
lansoprazole capsules 15mg		a6c3.	317310006
lansoprazole capsules 30mg		a6c2.	317309001
omeprazole 20mg		a6b1.	317291008
lansoprazole 30mg		a6c2.	317309001
losec cap 10		a6b6.	6.4411E+13
losec cap 20mg		a6b3.	9.23011E+14

pantoprazole ec tab 20mg		a6e5.	317322009
pantoprazole 20mg gastro-resistant tablets		a6e5.	317322009
nexium 20mg gastro-resistant tablets (astrazeneca uk ltd)		a6h1.	1.54111E+14
nexium tabs 20mg		a6h1.	1.54111E+14
omeprazole capsules 10mg		a6b7.	317297007
pantoprazole 40mg e/c tablets			2.99275E+17
rabeprazole tabs 10mg		a6f1.	317324005
rabeprazole 10mg gastro-resistant tablets		a6f1.	317324005
esomeprazole 40mg gastro-resistant tablets	01.03.05.00.00		
omeprazole 10mg caps		a6b7.	317297007
omeprazole cap 40mg		a6b5.	317295004
omeprazole caps 20 mg			2.99275E+17
rabeprazole sodium tablets 20mg	0103050T0AAABAB		
rabeprazole sodium tabs 20mg	0103050T0AAABAB		
pantoprazole tab 40mg		a6e1.	317318004
omeprazole capsules 20mg			2.99275E+17
omeprazole capsules 10 mg			2.99275E+17
pantoprazole enteric coated tablets 20mg		a6e5.	317322009
lansoprazole			2.99275E+17
omeprazole			2.99275E+17
omeprazole caps 40mg		a6b5.	317295004
omeprazole 40mg gastro-resistant capsules		a6b5.	317295004
losec caps 20mg		a6b3.	9.23011E+14
omeprazole 10mg capsules		a6b7.	317297007
omeprazole 40mg capsules			2.99275E+17
pantoprazole gastro-resistant tablets 20 mg		a6e5.	317322009
pantoprazole ec tab 40mg			2.99275E+17
lansoprazole caps 15mg			2.99275E+17
omeprazole 10mg tablet	010305		
pantoprazole enteric coated 20mg		a6e5.	317322009
pantoprazole enteric coated 40mg			2.99275E+17
rabeprazole sodium 20mg		a6f2.	317325006
pantoprazole ec tab 40mg		a6e1.	317318004
pantoprazole 40mg gastro-resistant tablets		a6e1.	317318004

rabeprazole tablets 10mg	0103050T0AAAAAA		
rabeprazole tablets 20mg	0103050T0AAABAB		
omeprazole tabs 20mg		a6by.	398905005
losec cap 20		a6b3.	9.23011E+14
esomeprazole 20mg gastro-resistant tablets		a6hz.	317335000
omeprazole tabs 10mg	010305		
losec capsules 20mg	0103050P0BBAAAA		
omeprazole capsules 10 mgs	0103050P0AAAFAF		
omeprazole 20 mg cap	0103050P0AAAGAG		
pantoprazole tablets 40mg	0103050R0AAAAAA		
omeprazole capsules (gastro-resistant) 40 mg	0103050P0AAAEAE		
lansoprazole 15mg capsules 15mg	0103050L0AAABAB		
rabeprazole sodium tabs 10mg		a6f1.	317324005
lansoprazole cap e/c 30mg			2.99275E+17
lansoprazole cap e/c15mg			2.99275E+17
pantoprazole tab e/c 40mg			2.99275E+17
lansoprazole cap e/c 15mg			2.99275E+17
rabeprazole ec tab 10mg		a6f1.	317324005
omeprazole caps(ec grans) 20mg		a6b1.	317291008
rabeprazole sodium tab 20		a6f2.	317325006
losec 20mg gastro-resistant capsules (astrazeneca uk ltd)		a6b3.	9.23011E+14
losec cap 40		a6b4.	9.35511E+14
lansoprazole capsules (gastro-resistant) 30 mg		a6c2.	317309001
omeprazole 40mg gastro-resistant tablets	01.03.05.00.00		
omeprazole 40mg capsules		a6b5.	317295004
losec mups tablets 20 mg			2.99275E+17
omeprazole caps 40mg	0103050P0AAAEAE		
omeprazole cap 40		a6b5.	317295004
losec caps 10mg		a6b6.	6.4411E+13
lansoprazole grans for susp 30mg		a6c5.	317312003
rabeprazole sodium tabs 10mg	0103050T0AAAAAA		
omeprazole 10mg dispersible gastro-resistant tablets		a6bx.	398942003
omeprazole 40mg capsules		a6bA.	317300002
omeprazole mups 20 mgm. tab.	0103050P0AAAGAG		

omeprazole capsules (gastro-resistant) 10 mg		a6b7.	317297007
losec capsules 20 mg	0103050P0BBAAAA		
omeprazole capsules 40mg		a6b5.	317295004
losec caps 20mg			2.99275E+17
omeprazole mups 10 mgm. tab.	010305		
omeprazole		a6by.	398905005
omeprazole capsules 20 mg			2.99275E+17
losec caps 20 mg		a6b3.	9.23011E+14
losec cap 10mg		a6b6.	6.4411E+13
losec 10mg gastro-resistant capsules (astrazeneca uk ltd)		a6b6.	6.4411E+13
lansoprazole caps 30 mg		a6c2.	317309001
omeprazole 20 mg capsules			2.99275E+17
omeprazole 20mg dispersible gastro-resistant tablets		a6by.	398905005
lansoprazole capsules30mg-p42 0	0103050L0AAAAAA		
rabeprazole sodium 20mg e/c tablets		a6f2.	317325006
omeprazole cap e/c 20mg			2.99275E+17
lansoprazole cap 30mg			2.99275E+17
lansoprazole capsules 30 mg		a6c2.	317309001
omeprazole capsules 40 mg		a6b5.	317295004
losec cap 40mg		a6b4.	9.35511E+14
lansoprazole tab 30		a6c2.	317309001
pantoprazole gastro-resistant tablets 40 mg		a6e1.	317318004
losec capsules 10mg	0103050P0BBACAF		
pantoprazole gastro resistant tabs 40mg	0103050R0AAAAAA		
omeprazole capsules10mg-p42 0	0103050P0AAAFAF		
omeprazole caps 40mg			2.99275E+17
rabeprazole sodium tablets 10mg	0103050T0AAAAAA		
omeprazole 40mg			2.99275E+17
omeprazole caps.20mg			2.99275E+17
omeprazole 20 mg caps	0103050P0AAAGAG		
rabeprazole sodium tab 10		a6f1.	317324005
omeprazole 10mg caps	0103050P0AAAFAF		
esomeprazole tablets 20 mg		a6hz.	317335000
pantoprazole gastro resistant tablets 40mg	0103050R0AAAAAA		
lansoprazole capsules 15mg	0103050L0AAABAB		

losec mups 10mg gastro-resistant tablets (astrazeneca uk ltd)	01.03.05.00.00		
omeprazole tablets (gastro-resistant) 20 mg	010305		
rabeprazole sodium e/c tablets 10 mg	0103050T0AAAAAA		
rabeprazole sodium e/c tablets 20 mg	0103050T0AAABAB		
omeprazole capsules 40mg			2.99275E+17
omeprazole cap e/c 40mg			2.99275E+17
pantoprazole tablets e/c 20mg-p42 0	010305		
omeprazole capsules 20 mg	0103050P0AAAGAG		
nexium tablets 20 mg	010305		
pantoprazole tabs e/c 20 mg		a6e5.	317322009
losec caps 10mg	0103050P0BBACAF		
losec 20mg		a6b3.	9.23011E+14
omeprazole 40mg dispersible gastro-resistant tablets	01.03.05.00.00		
omeprazole_cap e/c 20mg			1.111E+12
losec caps 20 mg			2.99275E+17
esomeprazole tabs 20mg		a6hz.	317335000
rabeprazole sodium 20mg e/c tablets			2.99275E+17
omeprazole capsules 10 mg	0103050P0AAAFAF		
omeprazole tabs 20mg	010305		
omeprazole 20mg caps			2.99275E+17
omeprazole 20mg tabs		a6b1.	317291008
pantoprazole e/c tablets 40 mg			2.99275E+17
rabeprazole na 20mg e/c tabs		a6f2.	317325006
omeprazole caps 20mg			2.99275E+17
losec capsules 20mg			2.99275E+17
pantoprazole 40mg tablets	0103050R0AAAAAA		
pantoprazole 20mg tablets	010305		
*omeprazole 10 mg caps supply 28			2.99275E+17
*omeprazole 10 mg caps supply			2.99275E+17
lansoprazole caps 15 mg			2.99275E+17
omeprazole capsules 20mg -		a6b1.	317291008
lansoprazole cap e/c 15mg		a6c3.	317310006
losec capsules 20 mg			2.99275E+17
omeprazole tablets 10mg		a6bu.	407846000

losec mups 40mg gastro-resistant tablets (astrazeneca uk ltd)	01.03.05.00.00		
pantoprazole tabs e/c 40 mg			2.99275E+17
omeprazole 20mg tablets			2.99275E+17
pantoprazole 20mg e/c tablets		a6e5.	317322009
lansoprazole 15mg	0103050L0AAABAB		
lansoprazole 30mg orodispersible tablets	01.03.05.00.00		
omeprazole caps(ec grans) 10mg		a6b7.	317297007
omeprazole gastro-res cap 20mg		a6b1.	317291008
omeprazole caps(ec grans) 40mg		a6b5.	317295004
lansoprazole caps(ec grans) 15mg		a6c3.	317310006
esomeprazole tabs 40mg	010305		
omeprazole gastro-res cap 10mg		a6b7.	317297007
lansoprazole caps(ec grans) 30mg		a6c2.	317309001
lansoprazole 15mg capsules	0103050L0AAABAB		
omeprazole gr tab 20mg		a6bv.	407847009
lansoprazole 15mg orodispersible tablets	01.03.05.00.00		
omeprazole capsules of enteric coated granules 20mg		a6b1.	317291008
omeprazole tablets 20mg		a6bx.	398942003
pantoprazole e/c tablets 40 mg		a6e1.	317318004
rabeprazole gr tab 20mg		a6f2.	317325006
lansoprazole 15mg orodispersible tablets		a6c7.	4.05341E+15
lansoprazole orodisp g-r tab 15mg		a6c7.	4.05341E+15
lansoprazole gr susp 30mg		a6c5.	317312003
lansoprazole orodisp g-r tab 30mg		a6c8.	4.05351E+15
lansoprazole 30mg orodispersible tablets		a6c8.	4.05351E+15
lansoprazole 30mg gastro-resistant granules sachets		a6c5.	317312003
pantoprazole ec tabs 20mg		a6e5.	317322009
lansoprazole capsules of enteric coated granules 30mg		a6c2.	317309001
omeprazole gastro-res cap 40mg		a6b5.	317295004
rabeprazole gr tab 10mg		a6f1.	317324005

lansoprazole 30mg gastro-resistant capsules (actavis uk ltd)	01.03.05.00.00		
esomeprazole gr tab 20mg		a6hz.	317335000
lansoprazole orodispersible gastro-resistant tablet 15mg		a6c7.	4.05341E+15
esomeprazole tablets 40mg	010305		
lansoprazole orodispersible tabs 15mg	010305		
pantoprazole e/c tablets 20 mg	010305		
lansoprazole 15mg gastro-resistant capsules (niche generics ltd)	01.03.05.00.00		
esomeprazole tabs 20mg	010305		
omeprazole gastro-resistant capsules 20mg		a6b1.	317291008
omeprazole tablets 20mg	010305		
omeprazole 10mg gastro-resistant tablets (almus pharmaceuticals ltd)	01.03.05.00.00		
nexium 40mg gastro-resistant tablets (astrazeneca uk ltd)	01.03.05.00.00		
omeprazole 10mg gastro-resistant tablets		a6bu.	407846000
omeprazole tablets 10mg	010305		
mepradec 20mg gastro-resistant capsules (discovery pharmaceuticals)	01.03.05.00.00		
rabeprazole ec tab 20mg		a6f2.	317325006
omeprazole tablets 10 mgm	010305		
esomeprazole gr tab 40mg		a6hy.	317334001
esomeprazole 40mg gastro-resistant tablets		a6hy.	317334001
nexium tabs 40mg		a6h2.	2.40211E+14
esomeprazole tabs 40mg		a6hy.	317334001
esomeprazole gastro-resistant capsules 20 mg	010305		
esomeprazole tablets 20mg	010305		
pantoprazole gastro resistant tabs 20mg	010305		
lansoprazole capsules of enteric coated granules 15mg		a6c3.	317310006
nexium 40mg gastro-resistant tablets (astrazeneca uk ltd)		a6h2.	2.40211E+14
lansoprazole orodispersible tabs 30mg	010305		

lansoprazole orodispersible tablets (gastro-resistant) 30 mg	010305		
lansoprazole orodispersible tablets 30mg	010305		
rabeprazole sodium e/c tablets 20mg			2.99275E+17
lansoprazole orodispersible gastro-resistant tablet 30mg		a6c8.	4.05351E+15
esomeprazole tablets 20mg		a6hz.	317335000
lansoprazole granules for suspension 30mg		a6c5.	317312003
lansoprazole 30mg gastro-resistant capsules (mylan ltd)	01.03.05.00.00		
esomeprazole tablets 20 mg	010305		
esomeprazole tab 20mg	010305		
omeprazole tabs 40mg	010305		
omeprazole 20 mg tablets			2.99275E+17
omeprazole 20 mg capsules		a6b1.	317291008
esomeprazole 40 mg tablets			2.99275E+17
lansoprazole 15mg caps	0103050L0AAABAB		
lansoprazole orodispersible tablets 15mg	010305		
esomeprazole gastro-resistant tablets 40 mg	010305		
esomeprazole 20mg tabs	010305		
omeprazole capsules of enteric coated granules 10mg		a6b7.	317297007
omeprazole 20mg gastro-resistant capsules (dexcel-pharma ltd)	01.03.05.00.00		
nexium tabs 20mg	010305		
nexium tabs 40mg	010305		
esomeprazole tablets 40mg		a6hy.	317334001
esomeprazole 40mg tab	010305		
omeprazole 20mg gastro-resistant tablets		a6bv.	407847009
esomeprazole 20mg	010305		
esomeprazole 20 mg tablets			2.99275E+17
lansoprazole 30 mg capsules			2.99275E+17
omeprazole 20mg gastro-resistant capsules (mylan ltd)	01.03.05.00.00		
esomeprazole 20mg tab	010305		

omeprazole disp tab 40mg		a6bz.	398787005
omeprazole 20mg gastro-resistant capsules (almus pharmaceuticals ltd)	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules (actavis uk ltd)	01.03.05.00.00		
rabeprazole sodium e/c tablets 10 mg		a6f1.	317324005
rabeprazole sodium tablets 10mg		a6f1.	317324005
omeprazole tabs 40mg		a6bw.	407848004
lansoprazole 30 mg oro-dispersible tablets			2.99275E+17
omeprazole 10 mg capsules			2.99275E+17
losec 40mg gastro-resistant capsules (astrazeneca uk ltd)		a6b4.	9.35511E+14
losec 40 mg capsules			2.99275E+17
omeprazole 40 mg capsules			2.99275E+17
esomeprazole gastro-resistant tablets 20 mg		a6hz.	317335000
lansoprazole orodispersible tablets (gastro-resistant) 15 mg	010305		
mepradec gastro-res cap 10mg		a6bO.	1.08205E+16
mepradec 10mg gastro-resistant capsules (discovery pharmaceuticals)		a6bO.	1.08205E+16
omeprazole 20mg gastro-resistant tablets (actavis uk ltd)	01.03.05.00.00		
pantoprazole e/c tablets 40 mg	0103050R0AAAAAA		
omeprazole tabs 20mg		a6bv.	407847009
omeprazole 20mg gastro-resistant capsules (teva uk ltd)	01.03.05.00.00		
lansoprazole 30mg gastro-resistant capsules (ivax pharmaceuticals uk ltd)	01.03.05.00.00		
lansoprazole capsules (gastro-resistant) 30mg		a6c2.	317309001
omeprazole capsules (gastro-resistant) 20mg		a6b1.	317291008
nexium tablets 20mg		a6h1.	1.54111E+14
omeprazole gr tab 10mg		a6bu.	407846000
pantoprazole e/c tablets 20 mg		a6e5.	317322009
lansoprazole 15mg capsule	0103050L0AAABAB		

losec caps 40mg		a6b4.	9.35511E+14
lansoprazole suspension strawberry sach 30mg	0103050L0AAADAD		
lansoprazole 30mg gastro-resistant capsules (consilient health ltd)	01.03.05.00.00		
omeprazole capsules of enteric coated granules 10mg	0103050P0AAAFAF		
lansoprazole capsules 15 mg		a6c3.	317310006
rabeprazole sodium tablets 10 mg		a6f1.	317324005
pantoprazole tablets 40 mg		a6e1.	317318004
omeprazole tabs 10mg		a6bu.	407846000
esomeprazole tablets 40 mg		a6hy.	317334001
lansoprazole oro-dispersible tablets 15mg	010305		
losec 10mg caps	0103050P0BBACAF		
mepradec 10mg gastro-resistant capsules (discovery pharmaceuticals)	01.03.05.00.00		
lansoprazole oro-dispersible tabs 30mg	010305		
rabeprazole 10mg tab	0103050T0AAAAAA		
rabeprazole 20mg tab	0103050T0AAABAB		
omeprazole tablets 40mg	010305		
omeprazole multiple unit pellet system dispersible tablets 20mg	010305		
lansoprazole 15mg gastro-resistant capsules (sandoz ltd)	01.03.05.00.00		
lansoprazole 15 mg	0103050L0AAABAB		
pantoprazole tablets 20mg	010305		
esomeprazole gastro-resistant tablets 20 mg	010305		
lansoprazole 30mg gastro-resistant capsules (a a h pharmaceuticals ltd)	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules (arrow generics ltd)	01.03.05.00.00		
omeprazole 40mg gastro-resistant tablets (sandoz ltd)	01.03.05.00.00		
omeprazole gastro-resistant capsules 10mg		a6b7.	317297007
rabeprazole enteric coated tablets 10mg		a6f1.	317324005
lansoprazole tablets 15mg		a6c7.	4.05341E+15

nexium tablets 40mg		a6h2.	2.40211E+14
pantoprazole e/c tablets 20mg		a6e5.	317322009
omeprazole 20mg gastro-resistant tablets (almus pharmaceuticals ltd)	01.03.05.00.00		
omeprazole 40mg gastro-resistant capsules (mylan ltd)	01.03.05.00.00		
lansoprazole 30mg gastro-resistant capsules (teva uk ltd)	01.03.05.00.00		
omeprazole 20mg capsule	0103050P0AAAGAG		
rabeprazole tablets 10mg		a6f1.	317324005
mepradec 20mg gastro-resistant capsules (discovery pharmaceuticals)		a6bP.	1.08201E+16
lansoprazole 30mg gastro-resistant capsules (arrow generics ltd)	01.03.05.00.00		
lansoprazole oro-dispersible tabs 30mgs	010305		
omeprazole gastro-resistant capsules 40mg [dexcel]	01.03.05.00.00		
losec capsules 20 mg		a6b3.	9.23011E+14
losec capsules 20mg		a6b3.	9.23011E+14
omeprazole 10mg gastro-resistant capsules (actavis uk ltd)	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules (teva uk ltd)	01.03.05.00.00		
omeprazole tablets 20 mg	010305		
lansoprazole capsules 15 mg	0103050L0AAABAB		
omeprazole 40mg gastro-resistant tablets (almus pharmaceuticals ltd)	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules (mylan ltd)	01.03.05.00.00		
omeprazole 20mg tab	010305		
lansoprazole capsules of enteric coated granules 30mg	0103050L0AAAAAA		
lansoprazole capsules of enteric coated granules 15mg	0103050L0AAABAB		
omeprazole multiple unit pellet system dispersible tablets 40mg	010305		

omeprazole tablets 20mg tablets	010305		
omeprazole tablets 10 mg	010305		
omeprazole tablets 20mg		a6bv.	407847009
esomeprazole tablets 40 mg	010305		
omeprazole 40mg dispersible gastro-resistant tablets		a6bz.	398787005
omeprazole 10mg gastro-resistant capsules (almus pharmaceuticals ltd)	01.03.05.00.00		
omeprazole tabs tabs 10mg	010305		
esomeprazole tablets 40mgs	010305		
lansoprazole 15mg gastro-resistant capsules (zentiva)	01.03.05.00.00		
omeprazole tablets (gastro-resistant) 40 mg	010305		
esomeprazole gastro-resistant tablets 40mg		a6hy.	317334001
omeprazole 20mg gastro-resistant tablets (ivax pharmaceuticals uk ltd)	01.03.05.00.00		
esomeprazole tablets 40mg			2.99275E+17
omeprazole capsules of enteric coated granules 40mg		a6b5.	317295004
pantoprazole gastro-resistant tablets 40 mg		a6e1.	317318004
esomeprazole			2.99275E+17
lansoprazole oro-dispersible tablets 30mg	010305		
omeprazole caplets 20mg [neolab]	01.03.05.00.00		
pantoprazole e/c tablets 40mg		a6e1.	317318004
lansoprazole tabs 15mg	010305		
nexium 20 mgm tablets	010305		
esomeprazole gastro-resistant tablets 40 mg		a6hy.	317334001
nexium 40 mgm tablets	010305		
rabeprazole ec tabs 20mg		a6f2.	317325006
omeprazole 20mg/5ml oral suspension	01.03.05.00.00		
omeprazole 10mg gastro-resistant capsules (zentiva)	01.03.05.00.00		
omeprazole 10mg gastro-resistant capsules (dexcel-pharma ltd)	01.03.05.00.00		

pantoprazole tablets 40 mg	0103050R0AAAAAA		
rabeprazole enteric coated tablets 20mg		a6f2.	317325006
omeprazole capsules 40 mg	0103050P0AAAEAE		
omeprazole 20mg tablet	010305		
rabeprazole sodium 20 mg enteric coated tablets			2.99275E+17
rabeprazole tablets 20mg		a6f2.	317325006
lansoprazole capsules 30 mg	0103050L0AAAAAA		
lansoprazole 30mg	0103050L0AAAAAA		
omeprazole gastro-resistant tablets 20mg	010305		
nexium 20mg tablets	010305		
rabeprazole sodium e/c tablets 10mg		a6f1.	317324005
lansoprazole oro-disdpersible tablets 30mg	010305		
omeprazole capsules of enteric coated granules 20mg	0103050P0AAAGAG		
omeprazole gr tab 40mg		a6bw.	407848004
omeprazole tablets 40 mg	010305		
omeprazole 20mg gastro-resistant capsules (actavis uk ltd)	01.03.05.00.00		
omeprazole multiple unit pellet system dispersible tabs 20mg	010305		
omeprazole multiple unit pellet system dispersible tabs 40mg	010305		
omeprazole 20mg	0103050P0AAAGAG		
nexium tablets 40mg	010305		
lansoprazole 15 mg capsules			2.99275E+17
lansoprazole fast tablets 30mg	010305		
nexium 20 mg tablets	010305		
omeprazole 40mg gastro-resistant tablets		a6bw.	407848004
omeprazole 10mg gastro-resistant capsules (dr reddy's laboratories (uk) ltd)	01.03.05.00.00		
lansoprazole orodispersible tablets (gastro-resistant) 30 mg		a6c8.	4.05351E+15
esomeprazole 40mg			2.99275E+17
lansoprazole oro-dispersible tabs 15mg	010305		
omeprazole capsules (gastro-resistant) 40mg		a6b5.	317295004

lansoprazole 30mg gastro-resistant capsules (niche generics ltd)	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules (sovereign medical ltd)	01.03.05.00.00		
mepradec gastro-res cap 20mg		a6bP.	1.08201E+16
omeprazole 20mg gastro-resistant capsules (zentiva)	01.03.05.00.00		
lansoprazole 30mg gastro-resistant capsules (sovereign medical ltd)	01.03.05.00.00		
omeprazole oral susp 20mg/5ml		a6b..	8.67071E+15
omeprazole 20mg gastro-resistant tablets (dexcel-pharma ltd)	01.03.05.00.00		
lansoprazole 15mg gastro-resistant capsules (a a h pharmaceuticals ltd)	01.03.05.00.00		
lansoprazole capsules (gastro-resistant) 15 mg		a6c3.	317310006

Systemic corticosteroids code list

Product name	BNF code	Read v2 code	dm+d code
depo-medrone 80mg/2ml suspension for injection vials (pfizer ltd)	10.01.02.02.00		
prednisolone 5mg gastro-resistant tablets	06.03.02.00.00		
depo-medrone injection 40mg/ml [pharmacia]	10.01.02.02.00		
depo-medrone with lidocaine injection 40mg/ml + 10mg/ml [pharmacia]	10.01.02.02.00		
depo-medrone with lidocaine suspension for injection 1ml vials (pfizer ltd)	06.03.02.00.00		
prednisolone tab 5mg		fe62.	325427002
hydrocortisone 10mg tablets	06.03.02.00.00		
triamcinolone acetonide injection suspension 40mg/1ml	10.01.02.02.00		
prednisolone 5mg tablets	06.03.02.00.00		
prednisolone tablets 5 mg		fe62.	325427002
depo-medrone with lidocaine suspension for injection 2ml vials (pfizer ltd)	10.01.02.02.00		
triamcinolone hexacetonide injection 20mg/ml	10.01.02.02.00		
prednisolone 1mg tablets	06.03.02.00.00		
prednisolone 2.5mg gastro-resistant tablets	06.03.02.00.00		
prednisolone tabs 5mg		fe62.	325427002
depo-medrone (1ml) inj 40		j431.	6.5615E+16
depo-medrone (1ml) inj 40mg/ml		j431.	6.5615E+16
depo-medrone 40mg/1ml suspension for injection vials (pfizer ltd)	10.01.02.02.00		
hydrocortisone 2.5mg muco-adhesive buccal tablets sugar free	12.03.01.00.00		
methylprednisolone/l inj 40			1.12465E+17
prednisolone 25mg tablets	06.03.02.00.00		
depo-medrone (2ml) inj 40mg/ml		j431.	6.5615E+16
hydrocortistab inj 25mg/ml		j423.	3.01751E+15
methylprednisolone acetate injection 40mg/ml	06.03.02.00.00		
triamcinolone acetonide injection 40mg/ml	06.03.02.00.00		
depo-medrone inj 40mg/ml		j431.	6.5615E+16
prednisolone tablets 5 mg	0603020T0AAACAC		
triamcinolone acetonide 10mg/1ml suspension for injection ampoules	10.01.02.02.00		
depo-medrone with li inj		j436.	6.5635E+16
depo-medrone with lidocaine (1ml) inj		j436.	6.5635E+16
hydrocortistab 25mg/1ml suspension for injection ampoules (amco)	10.01.02.02.00		

prednisolone soluble tablet 5mg [sovereign]	06.03.02.00.00		
depo-medrone 40mg/ml inj 40		j431.	6.5615E+16
prednisolone tab 5		fe62.	325427002
depo-medrone inj 40			0
methylprednisolone acetate with lidocaine injection 40mg/ml + 10mg/ml	10.01.02.02.00		
triamcinolone hexacetonide inj 20mg		j47z.	1.99635E+17
prednisolone e/c tablets 5 mg	0603020T0AAAGAG		
prednisolone e/c tab 5mg		fe6i.	325443009
prednisolone ec tab 5mg		fe6i.	325443009
dexamethasone 2mg tablets	06.03.02.00.00		
depo-medrone with lidocaine inj		j436.	6.5635E+16
prednisolone 2.5mg tablets	06.03.02.00.00		
beclometasone disc 200micrograms	03.02.00.00.00		
depo-medrone with lidocaine (1ml) inj 40mg		j436.	6.5635E+16
prednisolone tab 25mg		fe6z.	325450008
depo-medrone + lidocaine inj 40mg/ml + 10mg/ml		j436.	6.5635E+16
prednisone 5mg tablets	10.01.02.01.00		
deltastab 25mg/1ml suspension for injection ampoules (amco)	06.03.02.00.00		
depo-medrone with lidocaine injection -		j436.	6.5635E+16
depo-medrone with lidocaine injection 40mg/ml + 10mg/ml		j436.	6.5635E+16
depo-medrone + lidocaine inj		j436.	6.5635E+16
hydrocortisone-p42 10mg tablet	0603020J0AAADAD		
hydrocortisone tabs 10mg	0603020J0AAADAD		
hydrocortistab injection 25 mg/ml		j423.	3.01751E+15
prednisolone tablets 5mg	0603020T0AAACAC		
prednisolone ec tablets 5mg	0603020T0AAAGAG		
beclometasone disc 400micrograms	03.02.00.00.00		
beclometasone disc 100micrograms	03.02.00.00.00		
depo-medrone with lidocaine inj			6.5635E+16
depo-medrone with lidocaine (1ml) inj 40mg/ml		j436.	6.5635E+16
methylprednisolone/lignocaine hcl (2ml) inj 40			1.12465E+17
depo-medrone + lidocaine inj 40mg/ml+10mg/ml		j436.	6.5635E+16
prednisolone sodium phosphate sol tab 5mg		fe6j.	325444003
prednisolone 5mg soluble tablets		fe6j.	325444003
hydrocortone 10mg tablets (auden mckenzie (pharma division) ltd)	06.03.01.02.00		
depo-medrone with lidocaine (2ml) inj		j436.	6.5635E+16
depo-medrone 80mg/2ml injection			2.99275E+17
hydrocort.acetate 1%			400668006
prednisolone tabs 1mg	0603020T0AAAAAA		

prednisolone ec tabs 5mg	0603020T0AAAGAG		
hydrocortisone 1% 100gm			2.99275E+17
prednisolone suppos 5mg			2.99275E+17
triamcinolone acetonide ia / im inj 40mg/ml		j46z.	1.44905E+17
hydrocortistab injection 25mg/ml [1ml vial(s)]		j423.	3.01751E+15
methylprednisolone acetate 80mg/2ml suspension for injection vials	06.03.02.00.00		
prednisolone ec tabs 2.5mg	0603020T0AAAFAF		
prednisolone e/c tab 5		fe6i.	325443009
methylprednisolone sodium succinate 40mg powder and solvent for solution for injection vials	06.03.02.00.00		
prednisolone soluble tablets 5mg	0603020V0AAABAB		
prednisolone soluble tab 5		fe6j.	325444003
prednisolone tabs 25mg		fe6z.	325450008
prednisolone tabs 5mg	0603020T0AAACAC		
methylprednisolone inj 40mg/ml			7.0945E+16
depo-medrone (2ml) inj 40		j431.	6.5615E+16
depo-medrone with lidocai			2.99275E+17
prednisolone tab 5mg			2.99275E+17
hydrocortisone tabs 10 mg		fe41.	325373001
hydrocortisone 10mg tablets		fe41.	325373001
hydrocortisone tabs 20 mg		fe42.	325374007
betamethasone 500microgram tablets	06.03.02.00.00		
prednisolone 5mg tablets		fe62.	325427002
hydrocortistab 25mg/1ml inj		j423.	3.01751E+15
depo-medrone injection 40 mg/1 ml vial		j431.	6.23611E+14
prednisolone supps 5mg	0105000N0AAAAAA		
hydrocortisone acetate 25mg/1ml suspension for injection ampoules	10.01.02.02.00		
prednisolone soluble tabs 5mg	0603020V0AAABAB		
prednisolone soluble tab 5mg		fe6j.	325444003
betamethasone valerate mousse 0.12 % (= 0.1 % betamethasone)	1304000F0AABFBF		
triamcinolone acetonide im injection 80mg/2ml	10.01.02.02.00		
prednisolone tablets tab 5mg-p42 0	0603020T0AAACAC		
depomedrone with lidocaine vial 2ml inj 40mg/ml	1001022K0BBAFAF		
methylprednisolone/lignocaine hcl (1ml) inj 40mg/ml			7.0765E+16
dexamethasone 500microgram tablets	06.03.02.00.00		
prednisolone ec tabs 5 mg		fe6i.	325443009
hydrocortisone inj 25mg		j421.	329978005
depo-medrone injection 40 mg/ml		j431.	6.5615E+16
prednisolone tablets 5mg		fe62.	325427002
prednisolone 5mg gastro-resistant tablets		fe6i.	325443009

prednisolone tabs, enteric-coated 5 mg		fe6i.	325443009
depo-medrone inj 40mg/ml			2.99275E+17
prednisolone enteric coated tablets 5mg			2.99275E+17
prednisolone enteric coated tablets 2.5mg			2.99275E+17
prednisolone sodium phosphate soluble tablet 5mg	06.03.02.00.00		
dexamethasone inj 4mg		j41y.	1.09225E+17
betamethasone valerate lot 0.1%	1304000F0AABCBC		
dexamethasone tab 2		fe32.	325356003
hydrocortisone na succinate injection 100mg/vial	06.03.01.02.00		
prednisolone 1mg tablets		fe61.	325426006
prednisolone tab 1mg		fe61.	325426006
prednisone tab 10mg			6.5105E+16
prednisolone tabs 1mg		fe61.	325426006
hydrocortisone 20mg tablets	06.03.01.02.00		
prednisolone enteric coated tablets 5mg	06.03.02.00.00		
methylprednisolone 100mg tablets	06.03.02.00.00		
triamcinolone acetonide intra-articular / intramuscular injection 40mg/ml	06.03.02.00.00		
prednisolone e/c tab 2.5		fe6h.	325442004
triamcinolone injection 40 mg / 1ml ampoule			2.99275E+17
methylprednisolone acetate 40mg/1ml suspension for injection vials	06.03.02.00.00		
prednisolone tab 25mg			2.99275E+17
hydrocortone tablets 10mg	0603020J0BCAAAD		
depomedrone vial 1ml inj 40mg/ml	1001022K0BBAAAA		
hydrocortone tablets 20mg	0603020J0BCABAE		
hydrocort tab 10mg			2.99275E+17
hydrocortisone 10mg			2.99275E+17
hydrocortisone tabs 10mg		fe41.	325373001
prednisone tab 1mg		fe71.	418349006
prednisolone tab 2.5mg		fe6w.	1.37755E+17
prednisolone tabs 25mg	0603020T0AAARAR		
prednisolone e/c tablets 5 mg		fe6i.	325443009
prednisone tabs 5mg	0603020X0AAABAB		
hydrocortisone tablets 20 mg	0603020J0AAAEAE		
hydrocortisone tablets 10mg	0603020J0AAADAD		
hydrocortisone acetate inj 25mg/ml		j421.	329978005
prednisolone ec tab 2.5mg		fe6h.	325442004
hydrocortisone acetate (1ml) inj 25mg/ml		j421.	329978005
depo-medrone 40mg/1ml injection			2.99275E+17
prednisolone tablets 1mg	0603020T0AAAAAA		
prednisone tabs 5mg		fe72.	373994007
prednisolone ec tablets 2.5mg	0603020T0AAAFAF		
prednisolone 2.5mg gastro-resistant tablets		fe6h.	325442004

prednisolone tablets 1mg		fe61.	325426006
prednisolone enteric coated tablets 5mg		fe6i.	325443009
hydrocortone tablets 10mg		fe44.	1.97211E+14
hydrocortistab 25mg/1ml		j423.	3.01751E+15
prednisolone sod. ph dro 0.5			1.55385E+17
prednisolone tabs 1 mg			2.99275E+17
prednisolone tabs, enteric-coated 5 mg			2.99275E+17
methylprednisolone/lignocaine hcl (1ml) 40 mg/ml inj			7.0765E+16
beclomethasone dipropionate disc 200micrograms		c61s.	1.61605E+17
beclometasone 200micrograms disc		c61s.	1.61605E+17
beclometasone dipropionate disc 200micrograms		c61s.	1.61605E+17
beclomethasone dipropionate disc 200mcg		c61s.	1.61605E+17
prednisolone tab 25		fe6z.	325450008
deltastab (1ml) inj 25mg/ml		j441.	3.55311E+14
hydrocortisone tabs 10 mg			2.99275E+17
depo-medrone c. lidocaine injection		j436.	6.5635E+16
prednisolone tablets 25mg		fe6z.	325450008
betamethasone 500microgram soluble tablets sugar free	06.03.02.00.00		
hydrocortisone ung 1% 15g			2.99275E+17
prednisolone 5mg e/c tablets			2.99275E+17
triamcinolone acetonide 40mg/1ml suspension for injection vials	10.01.02.02.00		
prednisolone enteric coated tablets 5 mg		fe6i.	325443009
medrone 100mg tablets (pfizer ltd)	06.03.02.00.00		
beclomethasone dipro 200		c61s.	1.61605E+17
triamcinolone acetonide inj 10mg		j46x.	5.6825E+16
deltastab injection 25mg/ml		j441.	3.55311E+14
prednisolone enteric coated tablets 2.5mg		fe6h.	325442004
prednislone soluble tablets 5 mg			2.99275E+17
prednisolone tablets 1mg soluble			2.99275E+17
methylprednisolone 40mg/1ml / lidocaine 10mg/1ml (1%) suspension for injection vials	06.03.02.00.00		
prednisone 1mg tablets	06.03.02.00.00		
betamethasone tabs 500micrograms	0603020B0AAABAB		
deflazacort 6mg tablets	06.03.02.00.00		
prednisolone e/c tablets 2.5 mg		fe6h.	325442004
depo-medrone injection 40mg/ml [1ml vial(s)]		j431.	6.5615E+16
hydrocortisone tab 10		fe41.	325373001
efcortelan soluble injection 50mg/ml [glaxo]	06.03.01.02.00		
prednisolone ec tabs 5mg		fe6i.	325443009
deflazacort 1mg tablets	06.03.02.00.00		

depo-medrone 120mg/3ml suspension for injection vials (pfizer ltd)	06.03.02.00.00		
prednisolone e/c tab 2.5mg		fe6h.	325442004
prednisone 1mg tablets		fe71.	418349006
betamethasone 4mg/1ml solution for injection ampoules	06.03.02.00.00		
prednisolone 25mg/1ml suspension for injection ampoules	06.03.02.00.00		
hydrocortisone acetate injection 25mg/ml (1ml amp)		j421.	329978005
prednisolone tab 1		fe61.	325426006
prednisolone tabs, enteric-coated 2.5 mg		fe6h.	325442004
hydrocortisone injection 100 mg/vial		fe46.	7.3735E+16
depo-medrone injection 40mg/ml [1ml vial(s)]			2.99275E+17
prednisolone 5mg tabs		fe62.	325427002
prednisolone tablets 1 mg		fe61.	325426006
prednisolone 2.5mg e/c tabs		fe6h.	325442004
prednisolone 5mg e/c tabs		fe6i.	325443009
prednisolone 2.5mg		fe6h.	325442004
prednisolone 5mg		fe62.	325427002
depo-medrone with lidocaine injection 40mg/ml +		j436.	6.5635E+16
triamcinolone acetonide syringe 2ml inj 40mg/ml	0603020Z0AAABAB		
triamcinolone acetonide prefilled syringe 40 mg/1 ml			2.99275E+17
hydrocortistab 25mg/1ml injection			2.99275E+17
prednisolone e/c 5mg tabs		fe6i.	325443009
prednisolone ec 1mg tablets		fe61.	325426006
prednisolone ec 5mg		fe6i.	325443009
cortisyl tablets 25mg [aventis]	06.03.01.02.00		
prednisolone tablets 25mg	0603020T0AAARAR		
methylprednisolone acetate with lidocaine injection 40mg/ml			1.50805E+17
triamcinolone inj 10mg			1.59165E+17
betamethasone valerate mousse 100g 0.12%	1304000F0AABFBF		
prednisolone ec tab 5mg			2.99275E+17
methylprednisolone acetate + lidocaine inj 40mg/ml + 10mg/ml			1.50805E+17
hydrocortisone tablets 20mg	0603020J0AAAEAE		
hydrocortisone lozenges 2.5 mg		lb4z.	1.81735E+17
depo-medrone with lidocaine injection		j436.	6.5635E+16
depo-medrone with lidocaine 40mg/ml+10mg/ml injection (pharmacia ltd)		j436.	6.5635E+16
deltastab (1ml) inj 25mg		j441.	3.55311E+14
deltastab im inj 25mg/ml		j441.	3.55311E+14
entocort cr 3mg capsules (astrazeneca uk ltd)	01.05.02.00.00		
prednisolone 5mg e/c tabs		fe6i.	325443009
prednisolone tabs 5 mg		fe62.	325427002

methylprednisolone acetate 120mg/3ml suspension for injection vials	06.03.02.00.00		
depo-medrone (1ml) inj 40mg		j431.	6.5615E+16
methylprednisolone/lignocaine hcl (2ml) inj 40mg			1.12465E+17
prednisolone tabs 5 mg			2.99275E+17
hydrocort loz 2.5mg			2.99275E+17
hydrocortisone na succinate loz 2.5mg		lb4z.	1.81735E+17
hydrocortisone acetate injection 25mg/ml			2.99275E+17
methylprednisolone acetate vial 2ml inj 40mg/ml	1001022K0AAABAB		
depo-medrone injection 40mg/ml			2.99275E+17
prednisolone + cinchocaine supp 1.3mg + 1mg			2.25275E+17
prednisolone 5mg tablets			2.99275E+17
depo-medrone with lidocaine (2ml) inj 40mg/ml		j436.	6.5635E+16
hydrocortistab (1ml) inj 25mg/ml		j423.	3.01751E+15
prednisolone 2.5mg e/c tablets			2.99275E+17
prednisolone 1mg tablets			2.99275E+17
prednisolone tablets 25 mg	0603020T0AAARAR		
depomedrone with lidocaine vial 1ml inj 40mg/ml	1001022K0BBAGAG		
prednisolone e/c tablets 2.5 mg	0603020T0AAAFAF		
prednisolone ec 5mg tablet	0603020T0AAAGAG		
hydrocortisone tab 10mg		fe41.	325373001
triamcinolone acetonide inj 40mg/ml		j46z.	1.44905E+17
entocort cr mr cap 3mg		aa92.	3.76581E+15
prednisolone enteric coated 5mg		fe6i.	325443009
betamethasone soluble tablets 500micrograms	0603020C0AAABAB		
depo-medrone with li inj 40		j436.	6.5635E+16
hydrocortisone pelle loz 2.5			1.14505E+17
triamcinolone acetonide vial 1ml inj 40mg/ml			
depo-medrone with lidocaine injection, 2 ml vial		j436.	6.5635E+16
hydrocortisone tab 20mg		fe42.	325374007
hydrocortistab (1ml) inj 25		j423.	3.01751E+15
prednisolone		fe6i.	325443009
hydrocortisone acetate injection 25mg/ml [1ml vial(s)]		j421.	329978005
dexamethasone /framy ear 0.05			1.09345E+17
depo-medrone with lidocaine injection 40mg/ml + 10mg/ml			2.99275E+17
hydrocortisone oromucosal tablets 2.5mg	1203010M0AAAAAA		
triamcinolone ace 50mg/5ml inj			2.99275E+17
methylprednisolone tabs 100mg		fe5m.	325410005
prednisolone e/c tab 1			1.36045E+17
beclometh diprop disk 200mcg & diskhaler		c61s.	1.61605E+17

beclometh diprop disk 200mcg refill		c61s.	1.61605E+17
triamcinolone acetonide syringe 1ml inj 40mg/ml	0603020Z0AAAAAA		
triamcinolone acetonide 40mg/ml ia/im		j46z.	1.44905E+17
triamcinolone acetonide inj 40		j46z.	1.44905E+17
depo-medrone with lidocaine injection -			2.99275E+17
triamcinolone acetonide ia / id 10mg/ml		j46x.	5.6825E+16
hydrocortisone inj 100mg			1.01845E+17
prednisolone 5mg ec tabs		fe6i.	325443009
prednisolone enteric coated tablets 5 mg		fe6i.	325443009
depo-medrone + lidocaine injection 40 mg/ml			2.99275E+17
prednisolone 5mg tabs e/c		fe6i.	325443009
prednisone tab 5mg		fe72.	373994007
prednisolone tab 15mg			1.09785E+17
hydrocortistab injection 25 mg/ml (1 ml amp)		j423.	3.01751E+15
prednisolone tab e/c 5mg		fe62.	325427002
triamcinolone hexacetonide vial 1ml inj 20mg/ml	1001022Y0AAABAB		
prednisolone tab 50			1.09845E+17
hydrocortisone 25mg/1ml inj.		j421.	329978005
hydrocortistab injection 25mg/ml		j423.	3.01751E+15
prednisolone e/c 5mg		fe6i.	325443009
prednisolone 15 mg tab			1.09785E+17
prednisone		fe72.	373994007
prednisilone			2.99275E+17
prednisolone		fe62.	325427002
triamcinolone inj 80mg		fe8y.	1.44915E+17
prednisolone ec 5mg	0603020T0AAAGAG		
prednisolone p42 25mg tablet	0603020T0AAARAR		
prednisolone tablets 1 mg	0603020T0AAAAAA		
prednisolone tab e/c 5mg			2.99275E+17
depo-medrone + lidocaine inj 40mg/ml+10mg/ml[1m		j436.	6.5635E+16
prednisolone tablets 25mg			2.99275E+17
prednisolone 25mg tablets			2.99275E+17
prednisolone tabs 5mg			2.99275E+17
entocort cr caps 3mg	0105000B0BBAAAA		
depo-medrone with lidocaine injection 40mg/ml + 10mg/ml			6.5635E+16
depo-medrone 40mg/1ml inj			2.99275E+17
methylprednisolone/lignocaine hcl (2ml) inj 40mg/ml			1.12465E+17
budenofalk mr cap 3mg		aa93.	3.80781E+15
budenofalk 3mg gastro-resistant capsules (dr. falk pharma uk ltd)		aa93.	3.80781E+15
prednisolone ec 5mg tablets	0603020T0AAAGAG		
prednisone tablets 5mg	0603020X0AAABAB		
methylprednisolone injection 40 mg/ml			2.99275E+17

depo-medrone c. lidocaine injection 40/10mg/1ml			2.99275E+17
hydrocortone 10mg tablets (auden mckenzie (pharma division) ltd)		fe44.	1.97211E+14
hydrocortone tabs 10mg		fe44.	1.97211E+14
hydrocortisone na succinate lozenge 2.5mg	12.03.01.00.00		
depo-medrone with lidocaine inj			2.99275E+17
dexamethasone tab 500mcg		fe31.	325355004
prednisolone-p42 1mg tabs	0603020T0AAAAAA		
prednisolone-p42 5mg supp	0105000N0AAAAAA		
prednisolone-p42 1mg tablet	0603020T0AAAAAA		
depo-medrone 40mg/ml (3ml) inj 40		j431.	6.5615E+16
betamethasone lot 0.05%			1.80655E+17
betamethasone .05 % lot			1.80655E+17
deflazacort tabs 6mg		fe91.	325472005
deflazacort tab 6mg		fe91.	325472005
deflazacort 6mg tablets		fe91.	325472005
depo-medrone + lidocaine inj 40mg/ml + 10mg/ml			6.5635E+16
hydrocortisone na phosphate inj 100mg/ml		fe4d.	1.16915E+17
triamcinolone aceton inj 40		j46z.	1.44905E+17
prednisolone tab 2.5		fe6w.	1.37755E+17
hydrocortistab 25mg/1ml inj.		j423.	3.01751E+15
hydrocortistab inj 25mg/1ml		j423.	3.01751E+15
depo-medrone + lidocaine inj 80mg/2ml + 20mg/2ml		j435.	7.69111E+14
triamcinolone acetonide vial 5ml inj 10mg/ml	10010202		
depo-medrone injection 40mg/ml [1ml vial(s)]		j431.	6.23611E+14
hydrocortisone oromucosal tablets 2.5mg		lb4z.	331164004
triamcinolone acetonide 50mg/5ml suspension for injection vials	10.01.02.02.00		
depo-medrone injection 40mg/ml			6.5615E+16
methylprednisolone 80mg/2ml / lidocaine 20mg/2ml (1%) suspension for injection vials	10.01.02.02.00		
depo-medrone inj 80mg/2ml		fe5c.	7.77311E+14
depo-medrone + lidocaine inj 40mg/1ml + 10mg/1ml		j436.	4.70611E+14
methylprednisolone acetate inj 40mg/ml		j43z.	1.25255E+17
dexamethasone tablets 2mg	0603020G0AAADAD		
beclometasone disc 400micrograms		c61B.	1.61615E+17
beclometasone 400microgram disc		c61B.	1.61615E+17
depo-medrone inj 40mg/1ml		j431.	6.23611E+14
prednisolone tablets 25 mg		fe6z.	325450008
triamcinolone acetonide 80mg/2ml suspension for injection pre-filled syringes	10.01.02.02.00		

hydrocortisone na phosphate injection 100mg/ml	06.03.01.02.00		
prednisolone 50mg tablets	06.03.02.00.00		
betamethasone sodium phosphate sol tab 500micrograms		fe1x.	325344004
betamethasone 500microgram soluble tablets sugar free		fe1x.	325344004
betamethasone tabs 500micrograms		fe1y.	325345003
hydrocortisone tabs 20mg	0603020J0AAAEAE		
depo-medrone inj 120mg/3ml		j434.	3.23181E+15
prednisolone 2.5mg gastro-resistant tablets (actavis uk ltd)	06.03.02.00.00		
prednisolone non tariff ec tabs 5mg	0603020T0AAAGAG		
prednisolone 25mg tablets		fe6z.	325450008
methylprednisolone acetate injection 120 mg/3 ml vial		fe5..	1.30054E+16
methylprednisolone acetate + lidocaine inj 40mg/1ml+10mg/1ml			325398000
depo-medrone 40mg/ml injection (pharmacia ltd)		j431.	6.5615E+16
dexamethasone tablets 500micrograms	0603020G0AAABAB		
dexamethasone tabs 2mg		fe32.	325356003
prednisolone 5mg gastro-resistant tablets (actavis uk ltd)	06.03.02.00.00		
prednisolone enteric coated tablets 5mg [biorex]	06.03.02.00.00		
dexamethasone tablets 2 mg	0603020G0AAADAD		
triamcinolone acetonide ia / im inj 80mg/2ml		fe8y.	325467001
triamcinolone acetonide ia / im inj 40mg/1ml		j46z.	2.43245E+17
hydrocortisone sodium succinate vial with diluent inj 100mg	0603020M0AAAAAA		
methylprednisolone tabs 100mg	0603020S0AAADAD		
methylprednisolone acetate inj 40mg/1ml		j43w.	325422008
triamcinolone acetonide ia / id 10mg/ml		j46y.	2.3135E+16
hydrocortisone sf oromucosal tabs 2.5mg	1203010M0AAAAAA		
beclometasone disc 200micrograms		c61s.	1.61605E+17
methylprednisolone tablets 100mg	0603020S0AAADAD		
beclometasone dipropionate disc 400micrograms [blister(s) re		c61B.	1.61615E+17
methylprednisolone acetat + lidocain inj 80mg/2ml + 20mg/2ml			325397005
prednisolone e/c tablets 5mg		fe6i.	325443009
betamethasone sodium phosphate soluble tablets 500 micrograms	0603020C0AAABAB		
methylprednisolone acetate inj 80mg/2ml		j43z.	325423003

deltastab inj 25mg/ml		j441.	3.55311E+14
prednisolone e/c tablets 5 mg		fe6i.	325443009
dexamethasone tabs 0.5mg		fe31.	325355004
methylprednisolone 4mg tablets	06.03.02.00.00		
depo-medrone inj 40mg/ml			6.5615E+16
dexamethasone 2mg/5ml oral solution sugar free	06.03.02.00.00		
dexamethasone tabs 500micrograms	0603020G0AAABAB		
hydrocortisone acetate inj 25mg/1ml		j421.	329978005
beclometasone refill disks 400 micrograms/dose	0302		
prednisolone 5mg tablets (almus pharmaceuticals ltd)	06.03.02.00.00		
beclometasone dipropionate disc 400micrograms		c61B.	1.61615E+17
hydrocortisone tablets 10mg		fe41.	325373001
prednisolone soluble tablet 5mg			3.92511E+14
prednisolone tablets 5mg			8.5511E+13
prednisolone 5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	06.03.02.00.00		
dexamethasone 4mg/1ml solution for injection ampoules	06.03.02.00.00		
betamethasone soluble tabs 500micrograms	0603020C0AAABAB		
depo-medrone injection 120 mg/3 ml vial	1001022K0BBAEAE		
prednisolone enteric coated tablets 5mg	0603020T0AAAGAG		
depo-medrone injection 40mg/ml		fe5c.	7.77311E+14
depo-medrone with lidocaine injection 40mg/ml + 10mg/ml [1ml			2.99275E+17
prednisolone sodium phosphate soluble tablet 5mg		fe6j.	325444003
hydrocortisone sodium phosphate 100mg/1ml solution for injection ampoules	06.03.01.02.00		
methylprednisolone acetate injection 40mg/1ml vial			2.99275E+17
prednisolone 1mg tablet	0603020T0AAAAAA		
hydrocortisone(as sodium succinate) lozenges sugar free 2.5 mg	1203010M0AAAAAA		
methylprednisolone acetate vial 3ml inj 40mg/ml	1001022K0AAAEAE		
methylprednisolone acetate vial 1ml inj 40mg/ml	1001022K0AAAAAA		
depo-medrone injection 40mg/ml		j431.	6.5615E+16
prednisolone 2.5mg gastro-resistant tablets (a a h pharmaceuticals ltd)	06.03.02.00.00		
dexamethasone 2mg tablets		fe32.	325356003
prednisolone 2.5 mg enteric coated tablets			2.99275E+17

triamcinolone hexacetonide inj 20mg/ml		j47z.	1.99635E+17
hydrocortisone na succinate inj 100mg/vial		fe46.	7.3735E+16
methylprednisolone acetate injection 40mg/ml			1.25255E+17
depo-medrone injection 40mg/ml [2ml vial(s)]		j431.	6.5615E+16
prednisolone 5mg tablets (actavis uk ltd)	06.03.02.00.00		
depo-medrone injection 40mg/ml		j431.	6.23611E+14
beclometasone dipropionate disc 200micrograms [blister(s) re		c61s.	1.61605E+17
hydrocortisone na phosphate 100mg/ml injection		fe4d.	1.16915E+17
methylprednisolone tabs 2mg		fe5n.	325411009
methylprednisolone 16mg tablets	01.05.02.00.00		
beclometasone dipropionate with device 15 disks each with 8 blisters disks 200mcg/dose	0302		
budenofalk 3mg gastro-resistant capsules (dr. falk pharma uk ltd)	01.05.02.00.00		
prednisolone 1mg tablets (a a h pharmaceuticals ltd)	06.03.02.00.00		
triamcinolone hexacetonide injection 5mg/ml	10.01.02.02.00		
dexamethasone sodium phosphate injection 4mg/ml	10.01.02.02.00		
methylprednisolone acetate & lignocaine 80 mg + 20 mg / 2 ml			2.99275E+17
triamcinolone acetonide suspension for injection 10 mg/ml 5 ml vial	10010202		
triamcinolone acetonide suspension for injection 40 mg/ml 1 ml vial			
hydrocortisone na succinate 100mg/vial injection		fe46.	7.3735E+16
hydrocortisone sf oromucosal tablets 2.5mg	1203010M0AAAAAA		
triamcinolone acetonide injection 10 mg/ml	1001022U0AAAAAA		
hydrocortistab injection 25mg/1ml		j423.	3.01751E+15
hydrocortisone 20mg tablets		fe42.	325374007
hydrocortisone tabs 20mg		fe42.	325374007
triamcinolone acetonide intra-articular / intradermal injection 10mg/ml	10.01.02.02.00		
depo-medrone injection 40mg/1ml		j431.	6.23611E+14
methylprednisolone 40mg/1ml / lidocaine 10mg/1ml (1%) suspension for injection vials			325398000
triamcinolone acetonide intra-articular / intramuscular inje			2.99275E+17
dexamethasone 500microgram tablets		fe31.	325355004

prednisolone enteric coated tablets 5mg		fe62.	325427002
beclometasone disc 200micrograms			2.99275E+17
beclometasone disc 400micrograms			2.99275E+17
hydrocortistab injection 25mg/ml			2.99275E+17
betamethasone sodium phosphate soluble tablet 500micrograms		fe1x.	325344004
depo-medrone with lidocaine injection, 2 ml vial		j435.	7.69111E+14
prednisolone 25mg tablets (zentiva)	06.03.02.00.00		
prednisolone tablets 5 mg		fe62.	325427002
prednisolone 5mg e/c tablets		fe6i.	325443009
hydrocortone 20mg tablets (auden mckenzie (pharma division) ltd)	06.03.02.00.00		
budenofalk caps 3mg		aa93.	3.80781E+15
deflazacort tabs 1mg		fe95.	325476008
deflazacort 1mg tablets		fe95.	325476008
hydrocortisone na succinate lozenge 2.5mg		lb4z.	1.81735E+17
beclometasone dipropionate refill 15 disks each with 8 blisters disks 200mcg/dose	0302		
prednisolone 5 mgms ec tablet	0603020T0AAAGAG		
entocort cr 3mg capsules (tillotts pharma ltd)		aa92.	3.76581E+15
triamcinolone acetonide amp 1ml inj 10mg/ml	10010202		
methylprednisolone acetate with lidocaine 40mg/ml + 10mg/ml injection			1.50805E+17
methylprednisolone 40mg/1ml / lidocaine 10mg/1ml (1%) suspen			325398000
hydrocortistab inj susp 25mg/1ml		j423.	3.01751E+15
prednisolone 5mg tablets (a a h pharmaceuticals ltd)	06.03.02.00.00		
methylprednisolone acetate inj 120mg/3ml		j43y.	325399008
methylprednisolone and lidocaine injection 40 mg/ml + 10 mg/			325397005
depo-medrone 40mg/1ml suspension for injection vials (pfizer ltd)		j431.	6.23611E+14
beclometasone disc 200micrograms			1.61605E+17
beclometasone 200micrograms disc			1.61605E+17
methylprednisolone acetate injection 80mg/2ml vial		j43z.	325423003
methylprednisolone acetate 80mg/2ml suspension for injection vials		j43z.	325423003
hydrocortisone + benzyl benzoate & soothing agents supp			1.64735E+17

triamcinolone acetonide ia / id 10mg/1ml		j46x.	330002005
beclometasone gr mr tablets 5mg		aaBz.	1.18804E+16
beclometasone 5mg gastro-resistant modified-release tablets		aaBz.	1.18804E+16
hydrocortistab injection suspension 25mg/1ml			2.99275E+17
dexamethasone elixir 0.5mg/5ml	06.03.02.00.00		
depo-medrone 80mg/2ml suspension for injection vials (pfizer ltd)		fe5c.	7.77311E+14

Appendix 10.4 Supplementary information for chapter 7

This appendix comprises of the supplementary information for chapter 7. This includes supplementary information includes the UK biobank protocol, LSHTM ethical approval and supplementary methods and results for research paper 4.

UK Biobank Protocol

A1. Project Title

The effect of common infections on cognitive decline, brain structure and incident dementia in the UK Biobank study

A2. Research question and aim(s)

Research question: Are common infections associated with cognitive decline, hippocampal volume, white matter hyperintensities and incident dementia?

Aims:

(a) To investigate whether the presence of common infections is associated with worsening cognitive decline.
(b) To investigate the association of common infections with hippocampal volume and white matter hyperintensities volume.
(c) To investigate whether the presence of common infections is associated with incident dementia.

A3. The background and scientific rationale of the proposed research project in general

Dementia is a major public health burden. Currently, there are no effective treatments and as the global burden of dementia is forecast to rise rapidly, due to the ageing population, there is an urgent need to develop effective approaches to risk reduction. Recent evidence suggests that the age-specific incidence of dementia is declining in Europe and the USA, and this change has been attributed to changes in modifiable risk factors.[1-6] Thus, it is therefore important to identify other potentially preventable risk factors for dementia.

Infections have been proposed to play a role in the aetiology of dementia for decades. In our recently published systematic review of longitudinal studies, predominantly from Taiwan and the United States, individuals with common infections were at a greater risk of developing dementia compared to those without infections.[313] Common infections such as pneumonia, urinary tract infections and sepsis are well known to precipitate serious, reversible changes in cognition manifested as delirium. In turn, delirium and cognitive decline are major risk factors of dementia.[8-10] However, it remains unclear whether infections increase the risk of long-term changes in cognition. Findings from a US prospective study of older adults showed that individuals hospitalised with sepsis were associated with moderate to severe cognitive impairment.[93] However, other studies have found conflicting findings and face a number of important methodological limitations such as small sample sizes and inadequate adjustment for confounding. In addition, studies investigating the effect of type, frequency and timing of infections on multiple domains of cognitive impairment are scarce.

People with diabetes have impaired immune defence mechanisms and as a result they are at a greater risk of serious infections compared to people without diabetes, as evidenced by a large body of literature including a systematic review of 345 cohort and case control studies and a UK study of 102,493 individuals using primary care electronic health records.[12, 13] Diabetes is a well-known risk factor for cognitive decline and dementia.[14-16] In a recent systematic review and meta-analysis comprising 2.3 million individuals from 14 prospective

studies, diabetes was associated with a 60% increased risk of all cause dementia and a 40% increased risk of non-vascular dementia.[17] Numerous neuropsychological studies have consistently found that people with diabetes perform worse on multiple domains of cognitive function tests, including speed processing and mental flexibility, compared to the general population.[18-20]

Diabetes has also been associated with neuropathological markers of cognitive dysfunction, such as hippocampal atrophy and white matter hyperintensities in neuroimaging studies.[21, 22] In turn, these structural brain measures are associated with cognitive decline and dementia. [314] Moreover, sepsis survivors and individuals with major infections have been linked with abnormalities in brain structure and lower brain volumes [315 316] However, the association of infections on structural brain measures remains unclear and requires further study.

We aim to investigate the effect of the of common infections on cognitive decline using cognitive function tests and structural brain imaging data from the UK Biobank study linked to primary and secondary care records. In our secondary analyses, we will investigate the effect of type, frequency, clinical setting and timing of infections on cognitive decline. We will also investigate the association of common infections on cognitive decline in people with and without diabetes and the effect of infections on hippocampal volume, white matter hyperintensities and dementia.

A4. The expected value of the research

Infections and diabetes are potentially modifiable conditions with an increasing public health burden. Our study may provide a better understanding of the interrelationship between infections and diabetes with cognitive decline and the cognitive domains affected. Further, if infections and diabetes are associated with cognitive decline this may help inform intervention trials and public health strategies to reduce the risk of cognitive decline and dementia. Strategies could involve identifying populations most at risk of both infections and cognitive impairment, early recognition and treatment of infections, and approaches to increase vaccine uptake. Strategies among people with diabetes could include interventions to improve diabetes self-management and early identification of infections in people with diabetes.

A5. Please provide a lay summary of your research project in plain English, stating the aims, scientific rationale, project duration and public health impact:

As we age, changes occur in the brain that are expected as part of the normal aging process. This includes changes in memory, attention and how quickly the brain processes information. Cognitive decline occurs when these changes are beyond that expected of an individual based on their age and educational background. Having cognitive decline increases the risk of dementia, and cognitive decline often occurs years before dementia develops. Over the last few decades, increasing evidence suggests that preventable risk factors, such as education and heart disease, may increase the chances of developing cognitive decline and dementia. With this in mind, it is important to identify other potentially preventable risk factors. One such potentially modifiable risk factor could be infections.

Common infections, such as sepsis and urinary tract infections, often trigger reversible short-term changes in brain function. However, it is unclear whether these infections may also lead to long term changes in cognition. A number of studies suggest that individuals hospitalised with common infections are at an increased risk of developing cognitive changes that persist in the long term. However, evidence of this association remains unclear.

People with diabetes have a greater chance of developing cognitive decline compared to the general population. Studies have also shown they perform worse in tests that measure cognitive abilities. A decline in cognitive abilities may affect how individuals are able to self-manage their diabetes and may result in worsening of diabetes. People with diabetes are also known to have a higher risk of dementia.

Overall, we aim to investigate whether common infections (sepsis, lower respiratory tract-, urinary tract- and skin and soft tissue infections) are associated with differences in brain function, using data from the UK Biobank study. First, we will investigate whether the presence of common infections is associated with cognitive decline. Second, we will investigate whether common infections are associated with changes in brain structure. Third, we will investigate whether infections are associated with dementia.

Infections and diabetes are potentially modifiable and may therefore present a potential target to delay or prevent the onset of cognitive decline and dementia. Understanding how infections and diabetes work to affect brain function can help to develop effective strategies in reducing the burden of cognitive decline and dementia.

A6. Study population

We will include adults aged 40-69 years of age at recruitment for the UK Biobank study between 2006 and 2010. Specifically, we will only include individuals with linked primary care data (approximately 45% of UK Biobank cohort) and at least 12 months follow up in primary care records prior to baseline assessment. For our analyses on cognitive decline, we will only include individuals with valid measures of cognitive function completed at baseline and one or two follow-up visits (either the first repeat assessment date in 2012-13 and/or the imaging visit from 2014 onwards). We will exclude individuals with dementia and cognitive impairment at baseline. For our analyses focusing on infections and neuroimaging measures, we will only include individuals with baseline neuroimaging data.

A7. Study design

Historical cohort study using UK biobank data with linked primary and secondary care data

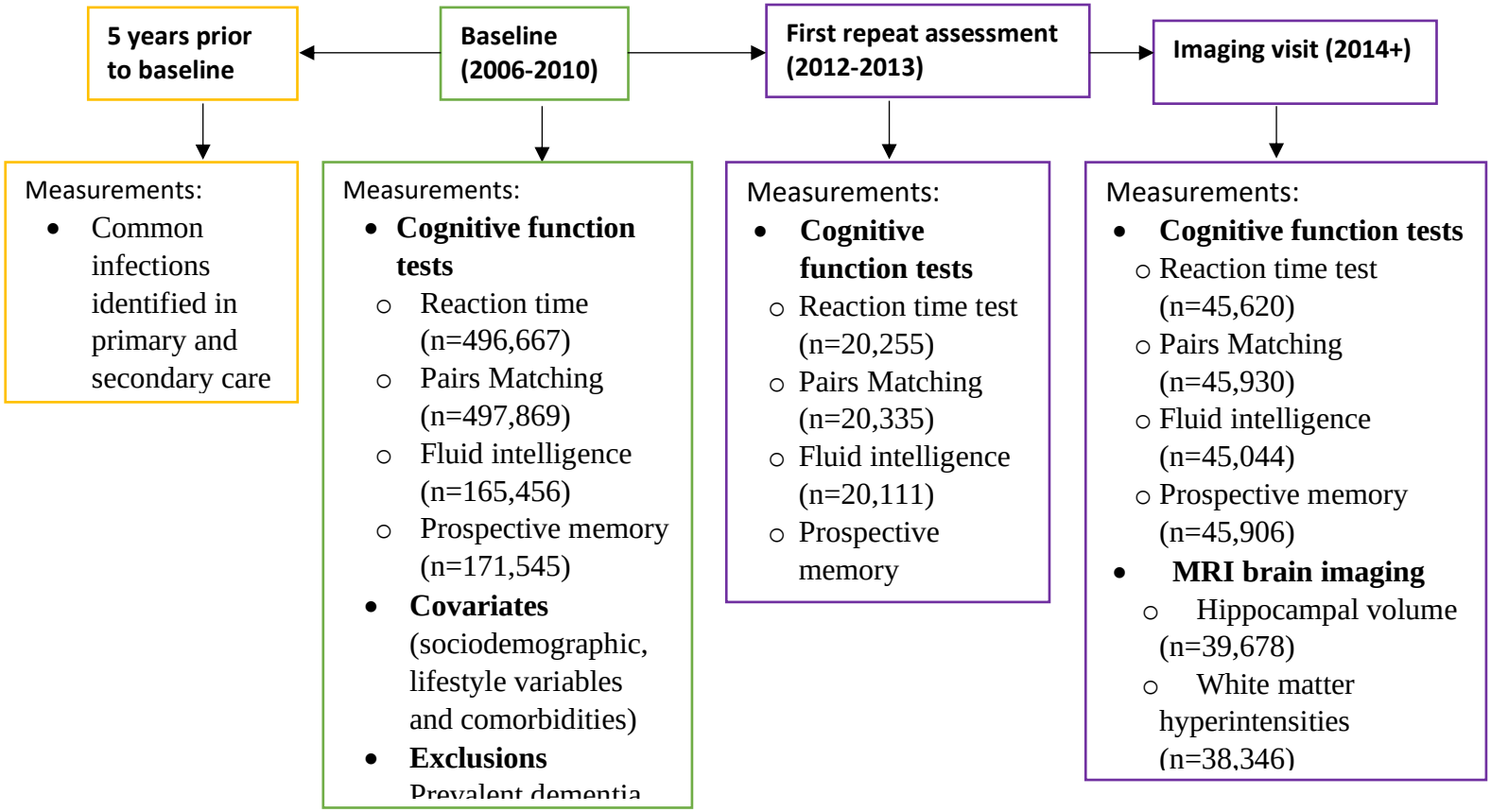


Fig 1. Study design and population

Source: https://biobank.ndph.ox.ac.uk/showcase/ Accessed October 2020

A8. Outcome

Cognitive decline

Our primary outcome is cognitive decline. We will measure changes in cognitive function from baseline to follow up. We will include the following cognitive function tests which were all assessed at the baseline visit and follow up time points: reaction time, pairs matching, fluid intelligence and prospective memory.

Reaction time
The reaction time test was designed to assess speed processing and was measured using a computer version of the game 'snap'. Participants were shown two cards on a touch screen and were instructed to press a button as quickly as possible when the symbols on the cards matched. We will assess the outcome measure for reaction time using the mean time (milliseconds) taken to correctly identify matches.

Pairs matching
The pairs matching test assessed for visual memory. For this test, participants were shown 6 pairs of cards with symbols for 5 seconds and were instructed to memorise the position of as many matching pairs of cards, in the fewest tries, as possible. The outcome measure will be the total number of incorrect matches in participants who completed the test.

Fluid intelligence
Fluid intelligence assessed verbal and numeric reasoning. For this test, participants were given two minutes to answer as many questions as possible. The questions required logic and reasoning ability. An example of a verbal reasoning question was "If Truda's mother's brother is Tim's sister's father, what relation is Truda to Tim?". An example of a numeric reason question was: "If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from eighty-five." Participants were given a number of possible responses to select from. The total number of correct answers to the 13 questions will be the outcome measure.

Prospective memory
The prospective memory test assessed participants' ability to remember to perform an action in the future. Before participants completed the other tests, they were first instructed the following: "At the end of the games we will show you four coloured shapes and ask you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead". Participants were scored 1 for correct at first attempt and 0 for incorrect at first attempt.

Fluid intelligence and prospective memory tests were included when the baseline assessment tests had already been initiated, as a result the sample sizes for the tests at baseline is smaller than that of the reaction time and pairs matching tests.[26]

Neuroimaging measures
Structural brain MRI measures, white matter hyperintensities and hippocampal volume, were measured at the imaging visit from 2014 onwards. We will use T1 and T2 weighted FLAIR imaging technique measuring the total volume of white matter hyperintensities.

Dementia

Incident dementia will be defined using Read and ICD-10 codes from linked primary and secondary care records and mortality data. Dementia will be defined using a broad definition which will include Alzheimer's disease and vascular dementia. Individuals who self-reported as having dementia at the baseline nurse interview and those with a history of dementia in their linked primary and secondary records will be excluded from the study. Our prevalent dementia codes will include administrative codes such as 'dementia care plan' as well as diagnostic codes.

A9. Exposure

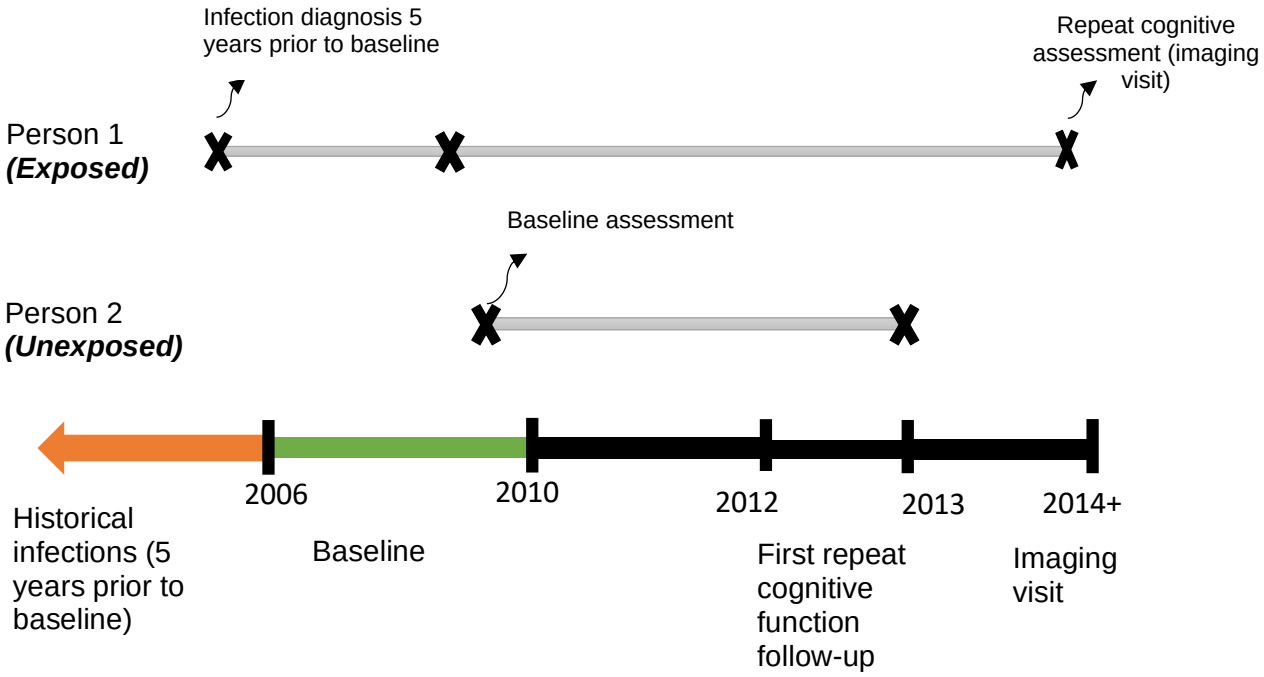


Fig 2. Definition of exposure status

We will identify common infections using linked primary and secondary care records. These infections will comprise sepsis, pneumonia, other lower respiratory tract infections, urinary tract infections and skin and soft tissue infections. We will group all common infections into one category 'any infection' in order to determine the overall association of common infections with cognitive decline. Then we will group infections according to subtype of infection for our secondary analyses.

Infections will be identified in the 5 years prior to baseline. If individuals are diagnosed with more than one infection during this period, the earliest record of infection is taken. Participants diagnosed with infections during follow up will be classified as unexposed.

Individuals will be defined as having sepsis, lower respiratory tract infections or pneumonia if they have a clinical diagnostic code for these infections. Individuals will be diagnosed as having urinary tract infections or skin and soft tissue infections if they have both a clinical diagnostic code and a prescription for antibiotics on the same date.

A10. Covariates

Based on existing literature we will consider the following potential confounders. Information on demographic, lifestyle factors and comorbidities will be identified using data from the baseline assessment questionnaires and linked primary and secondary care data. Demographic variables will include age, sex, ethnicity (white, south Asian, black, mixed or other), education and socioeconomic background which will be obtained from the initial interview assessment at baseline. Socioeconomic status will be measured using the Townsend Deprivation Index, based on postal codes, and measured using quintiles ranging from least deprived to most deprived. Potential lifestyle factors will include body mass index, smoking (never smoker, former smoker or current smoker), alcohol intake frequency (daily or almost daily, three or four times a week, once or twice a week one to three times a month, special occasions only, never) and physical activity (number of days spent doing moderate or physical activity). Diabetes status will be ascertained using HbA1c and medication history at baseline. Other comorbidities include hypertension, stroke, myocardial infarction, chronic kidney disease, chronic liver disease, traumatic brain injury, asthma, chronic obstructive pulmonary disease, severe mental illness, depression, anxiety, inflammatory autoimmune conditions, psychiatric comorbidity and inflammatory disease, and medication use. APOE status will be ascertained using genetic data.

A11. Statistical analyses

First, we will perform descriptive analyses to describe the characteristics (sociodemographic, lifestyle factors and comorbidities) of participants excluded from the study from recruitment to repeat assessments, using numbers and percentages for categorical data and mean and median values and interquartile range for continuous data. We will also perform further descriptive analyses to investigate the characteristics of participants diagnosed with infections and dementia. Second, we will describe the age-specific mean cognitive function scores at baseline and follow up assessment in participants with and without common infections. We will stratify age into the following age groups: 40-44, 45-49, 50-54, 55-59, 60-64, 65+.

Third, for cognitive function tests with continuous outcomes (reaction time, pairs matching and fluid intelligence), we will use linear mixed models with random intercept and random slope. For binary outcome measures (prospective memory), we will use multiple logistic regression models in individuals with correct recall at baseline, and we will adjust for time elapsed since baseline measurement. To select the confounders appropriate for inclusion, we will use a directed acyclic graph. We will then use a backwards deletion approach to identify screen potential confounders. Fourth, we will investigate the association between type (sepsis, pneumonia, other lower respiratory tract infections, urinary tract infections and skin and soft tissue infections), frequency, clinical setting (GP vs Hospital recorded infections) and timing (time since infection diagnosis) of infections. We will explore whether the effect of infections on cognition differs by glycaemic status and test the presence of effect modification by fitting an interaction term.

Fifth, we will perform cross-sectional analyses, based on the time point of the imaging visit, using multiple linear regression models to estimate the association between common infections and each structural brain MRI marker (hippocampal volume and white matter hyperintensities).

Lastly, we will use Cox regression models to estimate the association between common infections and incident dementia. We will test for the Cox proportional hazards assumption using log-log plots and Schoenfeld residuals.

We will consider the following sensitivity and additional secondary analyses in which we will:

1. Repeat main analyses excluding individuals with less than 5 years of follow up prior to baseline assessment given that infections will be captured in the 5 years prior to baseline
2. Repeat our main analyses excluding participants diagnosed with infections during follow up
3. Explore effect modification of the association between common infections and cognitive decline by Apolipoprotein (APOE) genotype
4. Stratify by sex to compare the effect of infections on cognitive decline in men and women.
5. Stratify by dementia subtype in order to explore the incidence of dementia according to subtypes of dementia (Alzheimer's disease and vascular dementia).
6. Investigate the longitudinal association of common infections with hippocampal volume and white matter hyperintensities

A12. Plans for confounding

Our final model will use a parsimonious model approach to include confounders specified in section A9.

A13. Missing data

We expect missing data on all four cognitive function tests and covariates such as ethnicity, BMI and education. We will describe the pattern of our missing data (whether our data is missing completely at random, missing at random or missing not at random) and choose an appropriate method for dealing with the missing data.

A14. Feasibility counts

- Approximately 181,631 participants aged 40 years and older in the UK Biobank study with linked primary and secondary care data with at least 12 months follow up prior to baseline assessment and no history of dementia or cognitive impairment. Of these participants, 161,490 had at least 5 years of follow up prior to baseline assessment.
- From our preliminary analysis, we found that 17,127 participants had at least one follow-up measurement for the pairs matching test, 17,040 individuals for the reaction time test and 5,934 for the fluid intelligence test. 5,256 participants had a correct answer for the prospective memory test and at least one follow up measurement.
- In our preliminary analysis of GP recorded infections, 3,817 participants were diagnosed with any infection, 2,903 had lower respiratory tract infections (pneumonia

=34, other lower respiratory tract infections =2,869), 424 had urinary tract infections, 371 has skin and soft tissue infections and 119 participants had sepsis.

A15. Sample size calculation

Based on our feasibility counts described above, we estimated the number of participants with follow cognitive function data and individuals with and without any infection (A.14). Using data from a previous UK Biobank study, the overall raw mean score of the cognitive function tests were as follows: 6.98 (sd 2.09) for fluid intelligence 4.90 (sd 3.11) for pairs matching and 552.23 (sd 212.01) for reaction time.[26] We estimate that at 90% power and 5% significance level, a minimum detectable difference of 0.2, 0.19 and 12.65 in mean score will be detected between individuals with and without infections for the fluid intelligence, pairs matching and reaction time tests, respectively.

A16. Strengths and limitations

Strengths of this study include the large size of the UK biobank study population, multiple measures of cognitive function, assessment of cognitive function at multiple timepoints, extensive data on many covariates and the linkage to primary and secondary care records.

However, there are a number of limitations. First, as individuals were recruited into the UK Biobank study aged 40-69, our findings may not be generalisable to older adults. However, trajectories of cognitive decline are recognised to be underway years before onset of dementia thus a better understanding of the timing of cognitive decline following infection could inform dementia risk reduction strategies.[302] Second, loss of follow up is an issue in the UK Biobank cohort, particularly regarding cognitive measures. There is potential for bias if participants with more severe infections or poorer cognitive ability may be more likely to be lost at follow up for cognitive function tests and imaging visits [318] Further, only participants who had an email address were able to take the cognition tests at follow up, which may mean that the characteristics of those at baseline and follow up may differ. Moreover, there are differences in the way in which cognitive function tests were carried out at baseline and at follow up. At baseline, all cognition tests were performed using a touch screen interface, whereas at follow up, a mouse interface was used. This may contribute to variability in cognitive performance over time. Fourth, cognitive function tests were brief, non-standardised and lacked external validity.[26] However, a recent prospective study using UK Biobank data demonstrated an association between the baseline cognitive function tests and incident dementia, validating their use in dementia-related research.[28] Finally, participants in the UK Biobank are generally healthier than the general population. However, this is not a limitation when investigating exposure and outcomes associations and the findings may still be widely generalisable.[29]

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Observational / Interventions Research Ethics Committee

Ms Rutendo Muzambi
LSHTM

15 March 2021

Dear Ms Rutendo Muzambi

Study Title: The effect of common infections on cognitive decline, brain structure and incident dementia in the UK Biobank study

LSHTM Ethics Ref: 22721

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Consent form	UKBB_Consent_form	01/01/2006	20061124
Investigator CV	Liam Smeeth 2 page CV 2019 (1)	01/01/2019	1
Investigator CV	Krishnan Bhaskaran SCHOOL CV TEMPLATE v3.2 4jan2019 (1)	04/01/2019	3.2
Investigator CV	Short cv_CWG_19-02-2020	19/02/2020	1
Investigator CV	Academic CV 01.2020	31/12/2020	1
Protocol / Proposal	UK Biobank Protocol Infections and cognition v2	22/01/2021	2
Covering Letter	Cover Letter UK Biobank LSHTM ethics	25/01/2021	v1
Covering Letter	Cover Letter UK Biobank LSHTM ethics 120321	12/03/2021	v1
Local Approval	7661_Approval_Provision_of_data_120321	12/03/2021	v2

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

[redacted]

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Improving health worldwide

Supplementary material for research paper 4

Are common infections associated with cognitive decline and neuroimaging outcomes? A historical cohort study using data from the UK Biobank study linked to primary and secondary care electronic health records

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Contents

Supplementary Methods

UK Biobank study population

9, 238,453 million individuals aged registered with the National Health Service who lived within 40 km of one of the 22 UK Biobank assessment centres in England, Scotland and Wales were invited to take part in the UKB study via postal invitations. Of these individuals, the response rate was low with 503, 317 (5.5%) participating in the baseline assessment which took place between 2006 and 2010.[1] During the baseline assessment visit, participants signed consent to the study, completed a web-based touch screen questionnaire that assessed medical history, lifestyle and behavioural factors, and sociodemographic factors. Participants attended a nurse interview, completed cognitive tests, underwent physical examinations and provided biological samples (blood, urine and saliva collections).[2]

UK biobank data was linked to routinely available national databases including hospital admission, death registry and primary care records. Approximately 230,000 participants (45%) of the total UK Biobank population provided written consent for linkage of the primary care records. [188] Data was collected from GP practices in England, Scotland and Wales using EMIS, Vision and TPP GP computer system suppliers. Diagnoses were recorded using Read v2 or Clinical Terms Version 3 (CTV3) coding classification. Prescription data from these practices was coded using Read v2, British National Formulary or Dictionary of Medicines and Devices (dm+d) coding classifications.

Our study included participants with linked primary and secondary care data. We excluded participants who had less than 12 months registration with a GP practice to avoid incorporating historical diagnoses when defining our exposure.

Cognitive function measures

Participants undertook a brief 15-minute cognitive test battery to assess cognitive function using a touchscreen computer. Participants were given instructions for the test on the screen and completed the assessment without supervision. These tests included reaction time (mean correct response time), visual memory, fluid intelligence and prospective memory. The tests are described in detail by Lyall et al, 2016.[180]

The reaction time test rounds 0-4 were regarded as "training" so were excluded in the present study and reaction times under 50 milliseconds and over 2000 milliseconds were also excluded as outlined on the UKB data showcase for reaction time. [320]

Neuroimaging measures

Structural MRI scans included in the UK Biobank protocol were T1, T2 fluid attenuation inversion recovery (FLAIR) and susceptibility-weighted MRI, diffusion MRI and resting and task functional MRI. To ascertain the volume of white matter hyperintensities, we used T1 and T2 FLAIR images. T1 scans, which allow precise volumetric measures of cortical, subcortical and whole brain regions, were also used to determine the volume of the left and right hippocampus separately. These subcortical structures were modelled using FMRIB's Integrated Registration and Segmentation Tool (FIRST).[6,7]

Follow up cognitive function and neuroimaging data

Between August 2012 and June 2013, a subset of approximately 20,000 participants who lived within a 35km radius of the Stockport coordinating centre were invited via email to attend a repeat assessment of the UK Biobank baseline measures. Repeat assessments were conducted on cognitive function measures as well as other information including that pertaining to health and lifestyle information, and physical measurements. [321] The second repeat follow-up targeting the same regions which also assessed cognitive function began in

2014. In 2014, participants completed the fluid intelligence or pairs matching tests online or at the assessment centre. In our study, we only included participants who conducted the tests at the assessment centre.

From April 2014, participants were re-invited via email (postal invitations were sent in 2020) to undergo magnetic resonance imaging including brain imaging. Imaging examinations took place at assessment centres in Stockport, Newcastle-upon-Tyne, Reading and Bristol. These centres were chosen in order to limit travel times for the majority of participants. [7] Quality assurance across all imaging centres was managed through a centralised training and monitoring team. A six-week training programme was attended by all staff members prior to the opening of centres and monthly training was provided by the MR physicist. Across all centres, a standardised training programme for all radiographers, standard operating procedures and other quality assurance and control measures were employed. Identical protocols, scanner models, software, types of coils and adjustment and tuning methods were used in each centre to ensure fully harmonised imaging data.[7]

All participants included in our study had completed baseline cognitive function assessment and at least one follow up assessment for the same test. For each test, some participants attended only one follow up assessment and some attended both follow up assessments.[4,9]

The fluid intelligence and prospective memory were added part way through the baseline assessment and only used at ten assessment centres as such baseline data on these tests were missing for the majority of participants. Other tests such as the numeric memory test were not included in the present study as they were removed during the baseline assessment and not included in the first repeat assessment. [180] Fluid intelligence and reaction time had an adequate test retest reliability of 0.65 and 0.54, respectively, while the visual memory test had a poor test retest reliability of 0.16 between the baseline and the first repeat assessment. [180] The poor reliability is likely to bias any effect estimates to the null. For the second repeat assessment, participants completed web-based questionnaires for the fluid intelligence and visual memory test remotely online at home. As such the testing conditions differed from baseline and first repeat assessment for these tests. [322]

Covariates

Socioeconomic deprivation

The Townsend deprivation index at recruitment (data field 189), which was used as a proxy for socioeconomic status.[323] The Townsend deprivation score was assigned to each participant using postcodes and is calculated from unemployment, non-car ownership, non-home ownership and household overcrowding data.[221] Positive scores (greater than zero) represent higher than average deprivation and negative scores (below zero) represent less deprivation/relative affluence.

Education attainment (years in full time education)

Baseline qualifications were used to ascertain the years in education of the participants. We used the International Standard Classification of Education ISCED 1997 (ISCED 1997) and applied the classification to the UK's educational qualifications. [219,220] Participants who responded with "prefer not to answer" were coded as missing.

Supplementary Table S1. Years of schooling using UK Biobank qualifications and ISCED 1997

UK Biobank coding	UK Biobank qualifications (data field 6138)	ISCED 1997 level	Years of schooling
-7	None of the above	1	7
-3	Prefer not to answer	-	-
1	College or University degree	5	20
2	A levels/AS levels or equivalent	3	13
3	O levels/GCSEs or equivalent	2	10
4	CSEs or equivalent	2	10
5	NVQ or HND or HNC or equivalent	5	19
6	Other professional qualifications eg: nursing, teaching	4	15

Missing data

3.6% (n=595) of the cognition cohort study population had missing data on ethnicity (n=42), BMI (n=40), years in education (n=65), alcohol consumption (n=3), smoking (n=17) physical activity (n=447), Townsend deprivation index (n=10). In total, 3.2% (n=469) of the neuroimaging cohort had missing data on ethnicity (n=41), BMI (n=28), years in education (n=53), alcohol consumption (n=6), smoking (n=15), physical activity (n=359) and Townsend deprivation index (n=8). Due to the small proportion of missing data in both cohorts and the fact that not all covariates were used in all analyses, we used a complete case analysis.

Statistical analyses

Linear Mixed models

We estimated the association between common infections and cognitive changes over follow up using linear mixed models with random intercept and slope effects, estimated by restricted maximum likelihood and using an unstructured covariance matrix. Linear mixed models were chosen as they account for the correlation of repeated measures over time, use all available data over follow up and can handle missing data.

Using Q-Q plots, we found that the distribution of residuals for the reaction time test was right skewed. When we log transformed the reaction time variable, the distribution of residuals still appeared right skewed, though more normally distributed than the raw reaction time variable. We then inverse transformed the raw mean reaction variable and the residuals appeared normally distributed. However, models with inverse or log transformed variable either failed to provide standard errors or failed to converge when adding covariates into the model. As a result, we ran our main analysis using the raw mean reaction time variable and then a sensitivity analysis. In this sensitivity analysis, we repeated our main analysis using the inverse transformed reaction time but specified a model using a simple covariance structure matrix (independent instead of unstructured). The drawback of this model is that it assumes that observations on the same person over time are independent are not correlated.

Additional sensitivity analyses

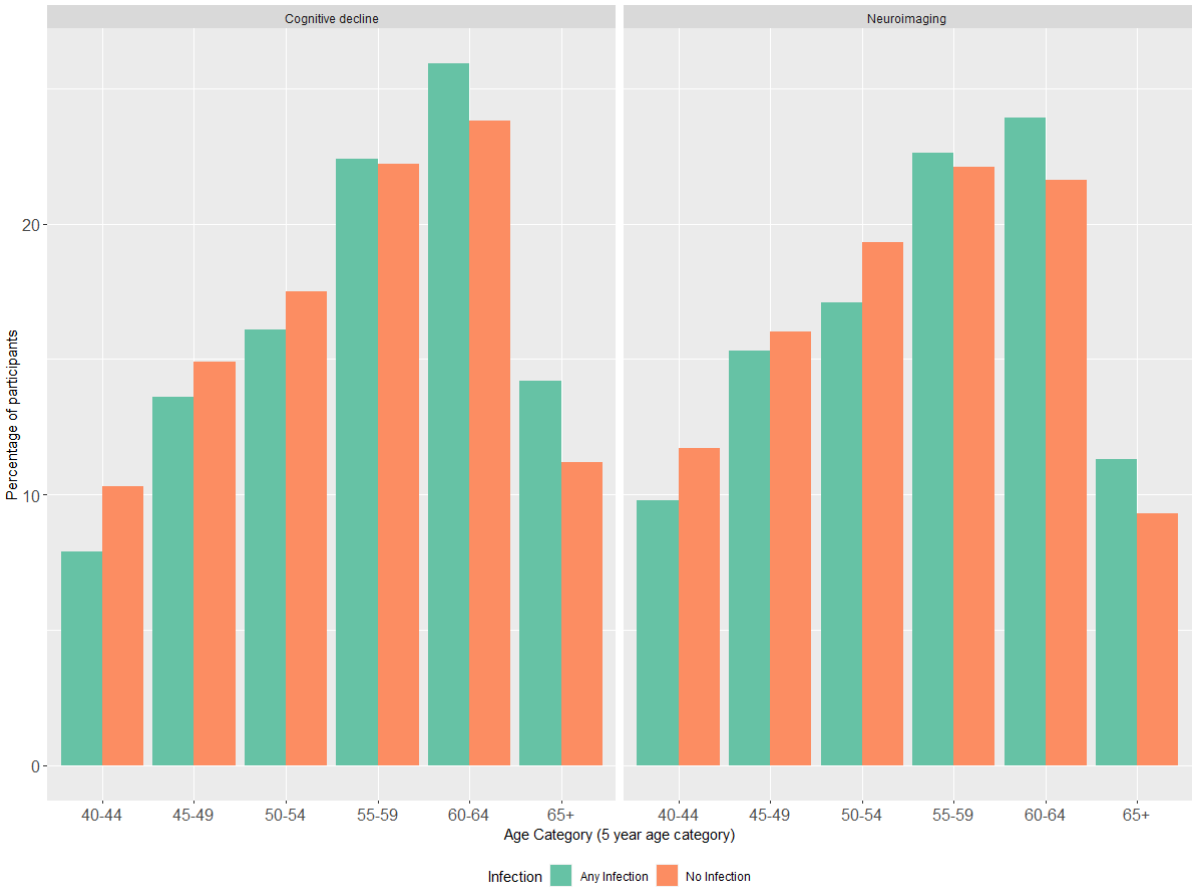
Supplementary Table 2: Additional sensitivity analyses and justification

Sensitivity analysis	**Justification**
Repeat main analyses excluding participants diagnosed with infections during follow up	To reduce misclassifying exposure (common infections)
Repeated our main analyses excluding participants whose current registration date with a GP practice was less than 5 years.	Given that infections were defined within 5 years prior to baseline, this analysis ensured that all participants had at least 5 years of follow up in which to capture infection diagnoses.
Repeated our analyses on hippocampal volume separately for the left and right hippocampus.	Previous studies suggest infections may have differing associations with the left and right hippocampus. [15]

Supplementary table 3: Infection profile of participants included and excluded from the study (cognition cohort)

Characteristic	Included cohort (N=2,971)	Cohort with no follow up cognitive measures (N=31,381)
Infection site		
Other Lower respiratory tract infections	1,691 (56.9%)	19,073 (60.8%)
UTI	674 (22.7%)	6,089 (19.4%)
SSTI	532 (17.9%)	5,260 (16.8%)
Pneumonia	45 (1.5%)	658 (2.1%)
Sepsis	23 (0.8%)	255 (0.8%)
Multiple infections diagnosed at different sites on the same date	6 (0.2%)	46 (0.1%)
Infection clinical setting		
GP infections	2,770 (93.2%)	28,246 (90.0%)
Hospital infections	201 (6.8%)	3,135 (10.0%)
Frequency of infections		
Number of infections, mean (sd)	1.48 (1.13)	1.60 (1.31)
Infection numbers (category)		
1 infection	2,154 (72.5%)	21,522 (68.6%)
2 infections	536 (18.0%)	5,799 (18.5%)
3+ infections	281 (9.5%)	4,060 (12.9%)
Mortality due to any common infection	5 (0.2%)	323 (1.0%)

Supplementary Figure 1. Percentage of participants with and without infections stratified by age in the cognitive decline and neuroimaging cohort



Supplementary table 4: Association of common infections on cognitive decline, stratified by diabetes status

	No. of Participants	Fully adjusted model β (95% CI)	P value (Likelihood test for interaction)
Mean correct response time (Difference in slope compared with no infection)			
Diabetes			0.015
No infection	338	Reference	
Any infection	177	-2.79 (-6.41 to 0.83)	
No diabetes			
No infection	12,937	Reference	
Any infection	2,692	0.48 (-0.096 to 1.05)	
Visual memory (Difference in slope compared with no infection)			
Diabetes			1.00
No infection	288	Reference	
Any infection	102	-0.018 (-0.039 to 0.0024)	
No diabetes			
No infection	11,193	Reference	
Any infection	2,334	0.00090 (-0.0029 to 0.0047)	
Fluid intelligence (Difference in slope compared with no infection)			
Diabetes			0.91
No infection	142	Reference	
Any infection	49	-0.0033 (-0.097 to 0.090)	
No diabetes			
No infection	4,531	Reference	
Any infection	1,017	0.0072 (-0.0098 to 0.024)	
Prospective memory			
Diabetes			0.68
No infection	114	Reference	
Any infection	37	0.78 (0.25 to 2.44)	
No diabetes			
No infection	3,969	Reference	
Any infection	857	0.89 (0.69 to 1.16)	

Linear Mixed models results with random intercept and random slope. For mean correct response time, visual memory (log transformed) and fluid intelligence tests. An interaction term was added between infection, time and diabetes. For mean correct response time, fully adjusted models adjusted for age, sex, time, baseline test score, interaction term with time x infection status, ethnicity, BMI, years in education, physical activity, alcohol consumption, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models adjusted for age, sex, time, baseline test score, interaction term with time x infection status, ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the fluid intelligence test, fully adjusted models included age, sex, time, baseline test score, interaction term with time x infection status, years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. An interaction term was added between infection, time and diabetes. Fully adjusted models for this test included age, sex and physical activity in the fully adjusted models. Likelihood ratio tests comparing models with and without interaction terms with diabetes.

Supplementary table 5: Association of common infections with cognitive decline, stratified by sex

	Minimally adjusted			**Fully adjusted model**		
	No. of participants	B (95% CI)	P value	No. of participants	B (95% CI)	P value
Mean correct response time (Difference in slope compared with no infection)						
Male						
No infection	6,879	Reference		6,687	Reference	
Any infection	1,246	0.08 (-0.74 to 0.91)	0.84	1,200	0.013 (-0.82 to 0.85)	0.98
Female						
No infection	6,828	Reference		6,588	Reference	
Any infection	1,710	0.74 (-0.02 to 1.50)	0.06	1,609	0.68 (-0.10 to 1.45)	0.09
Visual memory (Difference in slope compared with no infection)						
Male						
No infection	5,929	Reference		5,755	Reference	
Any infection	1,079	-0.0034 (-0.0091 to 0.0023)	0.24	1,038	-0.0045 (-0.010 to 0.0013)	0.13
Female						
No infection	5,944	Reference		5,726	Reference	
Any infection	1,483	0.0041 (-0.00076 to 0.0089)	0.10	1,398	0.0044 (-0.00053 to 0.0093)	0.08
Fluid Intelligence (Difference in slope compared with no infection)						
Male						
No infection	2,395	Reference		2,387	Reference	
Any infection	472	0.012 (-0.013 to 0.038)	0.34	470	0.014 (-0.012 to 0.039)	0.30
Female						
No infection	2,290	Reference		2,286	Reference	
Any infection	598	0.00078 (-0.021 to 0.023)	0.95	596	0.00056 (-0.022 to 0.023)	0.96
	No. of participants	**OR (95% CI)**	**P value**	**No. of participants**	**OR (95% CI)**	**P value**
Prospective memory						
Male						
No infection	2,141	Reference		2,103	Reference	
Any infection	408	0.88 (0.61 to 1.26)	0.49	399	0.91 (0.63 to 1.32)	0.62
Female						
No infection	2,033	Reference		1,980	Reference	

Any infection	518	0.79 (0.57 to 1.11)	0.18	495	0.86 (0.61 to 1.22)	0.39
Linear Mixed models results with random intercept and random slope. For mean correct response time, visual memory (log transformed) and fluid intelligence tests. minimally adjusted: age, sex, time, baseline test score, interaction term with time x infection status allows the calculation of the rate of decline by presence of infection with no infection as the reference group. For mean correct response time, fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes category, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models additionally adjusted for ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes status, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the fluid intelligence test, fully adjusted models additionally included years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. Minimally adjusted models for this test include age and sex and fully adjusted models additionally adjusted for physical activity in the fully adjusted models.						

Supplementary table 6: Association of common infections with cognitive decline, stratified by age

	Minimally adjusted			**Fully adjusted model**		
	No. of participants	B (95% CI)	P value	No. of participants	B (95% CI)	P value
Mean correct response time (Difference in slope compared with no infection)						
Age (40-49 years)						
No infection	3,455	Reference		3,372	Reference	
Any infection	638	-0.25 (-1.21 to 0.71)	0.60	614	-0.20 (-1.18 to 0.78)	0.69
Age (50-59 years)						
No infection	5,448	Reference		5,285	Reference	
Any infection	1,139	0.55 (-0.34 to 1.45)	0.23	1,091	0.40 (-0.52 to 1.31)	0.40
Age (60+ years)						
No infection	4,804	Reference		4,618	Reference	
Any infection	1,179	0.65 (-0.37 to 1.68)	0.21	1,104	0.59 (-0.45 to 1.63)	0.27
Visual memory (Difference in slope compared with no infection)						
Age (40-49 years)						
No infection	2,867	Reference		2,786	Reference	
Any infection	518	0.00 (-0.00 to 0.01)	0.52	496	0.00 (-0.01 to 0.01)	0.65
Age (50-59 years)						
No infection	4,738	Reference		4,591	Reference	
Any infection	988	0.00 (-0.01 to 0.01)	0.94	948	-0.00 (-0.01 to 0.01)	0.87
Age (60+ years)						
No infection	4,268	Reference		4,104	Reference	
Any infection	1,056	-0.00 (-0.01 to 0.01)	0.96	992	0.00 (-0.01 to 0.01)	0.89
Fluid Intelligence (Difference in slope compared with no infection)						
Age (40-49 years)						
No infection	1,145	Reference		1,141	Reference	
Any infection	237	-0.01 (-0.04 to 0.03)	0.75	235	-0.01 (-0.04 to 0.03)	0.70
Age (50-59 years)						

No infection	1,844	Reference		1,841	Reference	
Any infection	415	0.00 (-0.02 to 0.03)	0.85	414	0.00 (-0.02 to 0.03)	0.74
Age (60+ years)						
No infection	1,696	Reference		1,691	Reference	
Any infection	418	0.02 (-0.01 to 0.04)	0.29	417	0.01 (-0.01 to 0.04)	0.30
		OR (95% CI)	**P value**		**OR (95% CI)**	**P value**
Prospective memory						
Age (40-49 years)						
No infection	1,036	Reference		1,020	Reference	
Any infection	219	0.96 (0.52 to 1.78)	0.90	216	0.97 (0.52 to 1.79)	0.91
Age (50-59 years)						
No infection	1,677	Reference		1,636	Reference	
Any infection	372	1.15 (0.73 to 1.81)	0.55	362	1.12 (0.71 to 1.78)	0.63
Age (60+ years)						
No infection	1,461	Reference		1,427	Reference	
Any infection	335	1.38 (0.97 to 1.97)	0.08	316	1.26 (0.86 to 1.84)	0.23

Linear Mixed models results with random intercept and random slope. For reaction time, visual memory (log transformed) and fluid intelligence tests. minimally adjusted: age, sex, time, baseline test score, interaction term with time x infection status allows the calculation of the rate of decline by presence of infection with no infection as the reference group. For reaction time, fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes category, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models additionally adjusted for ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes status, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the fluid intelligence test, fully adjusted models additionally included years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. Minimally adjusted models for this test include age and sex and fully adjusted models additionally adjusted for physical activity in the fully adjusted models.

Supplementary table 7: Association of common infections with cognitive decline using inverse transformed reaction time with an independent covariance structure

		Minimally adjusted			**Fully adjusted model**	
	No. of participants	**β (95% CI)**	**P value**	**No. of participants**	**β (95% CI)**	**P value**
Inverse transformed mean correct response time (Difference in slope compared with no infection)						
Site of infection						
No infection	13,707	Reference		13,275	Reference	
Any infection	2,956	-9.34e-07 (-2.48e-06 to 6.13e-07)	0.24	2,809	-7.63e-07 (-2.34e-06 to 8.15e-07)	0.34
Linear Mixed models results with random intercept and random slope and an independent covariance structure. Minimally adjusted model included: age, sex, time, baseline test score, interaction term with time x infection status allows the calculation of the rate of decline by presence of infection with no infection as the reference group. Fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes category, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure.						

Supplementary table 8: Association of common infections with cognitive decline, with at least 5 years registration in GP records

		Minimally adjusted			**Fully adjusted model**	
	No. of participants	**β (95% CI)**	**P value**	**No. of participants**	**β (95% CI)**	**P value**
Mean correct response time (Difference in slope compared with no infection)						
No infection	11,562	Reference		11,202	Reference	
Any infection	2,740	0.40 (-0.18 to 0.99)	0.18	2,604	0.32 (-0.28 to 0.91)	0.29
Visual memory (Difference in slope compared with no infection)						
No infection	10,023	Reference		9,703	Reference	
Any infection	2,378	0.00044 (-0.0034 to 0.0043)	0.82	2,261	-0.00016 (-0.0041 to 0.0038)	0.94
Fluid intelligence (Difference in slope compared with no infection)						
No infection	4,033	Reference		4,022	Reference	
Any infection	1,005	0.0046 (-0.013 to 0.022)	0.61	1,002	0.0052 (-0.012 to 0.023)	0.56
	No. of participants	**OR (95% CI)**	**P value**	**No. of participants**	**OR (95% CI)**	**P value**
Prospective memory						
No infection	3,592	Reference		3,515	Reference	
Any infection	872	0.83 (0.64 to 1.07)	0.15	843	0.86 (0.66 to 1.12)	0.27

Linear Mixed models results with random intercept and random slope For reaction time, visual memory (log transformed) and fluid intelligence tests, minimally adjusted: age, sex, time, baseline test score and time x infection status interaction term which represents the rate of decline by presence of infection with the difference in slope compared to that of no infection (reference group). For reaction time, fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes category, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models additionally adjusted for ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes status, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the fluid intelligence test, fully adjusted models additionally included years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. Minimally adjusted models for this test include age and sex and fully adjusted models additionally adjusted for physical activity in the fully adjusted models.

Supplementary table 9: Association of common infections with cognitive decline, excluding follow up infections

		Minimally adjusted			**Fully adjusted model**	
	No. of participants	**β (95% CI)**	**P value**	**No. of participants**	**β (95% CI)**	**P value**
Mean correct response time (Difference in slope compared with no infection)						
No infection	10,336	Reference		10,026	Reference	
Any infection	2,956	0.58 (0.0085 to 1.15)	0.05	2,809	0.49 (-0.092 to 1.06)	0.10
Visual memory (Difference in slope compared with no infection)						
No infection	8,919	Reference		8,638	Reference	
Any infection	2,562	0.00071 (-0.0031 to 0.0045)	0.71	2,436	0.00028 (-0.0036 to 0.0041)	0.89
Fluid intelligence (Difference in slope compared with no infection)						
No infection	3,633	Reference		3,622	Reference	
Any infection	1,070	0.0061 (-0.011 to 0.023)	0.48	1,066	0.0064 (-0.011 to 0.024)	0.47
	No. of participants	**OR (95% CI)**	**P value**	**No. of participants**	**OR (95% CI)**	**P value**
Prospective memory (Difference in slope compared with no infection)						
No infection	3,258	Reference		3,188	Reference	
Any infection	926	0.74 (0.57 to 0.96)	0.02	894	0.78 (0.60 to 1.02)	0.07

Linear Mixed models results with random intercept and random slope. For reaction time, visual memory (log transformed) and fluid intelligence tests, minimally adjusted: age, sex, time, baseline test score and time x infection status interaction term which represents the rate of decline by presence of infection with the difference in slope compared to that of no infection (reference group). For reaction time, fully adjusted models additionally adjusted for ethnicity, BMI, years in education, physical activity, alcohol consumption, diabetes category, anxiety and depression, COPD, multiple sclerosis, hypertension and heart failure. For the visual memory test, fully adjusted models additionally adjusted for ethnicity, BMI, smoking status, socioeconomic deprivation, physical activity, alcohol frequency, years in education, diabetes status, anxiety and depression, COPD, hypertension, inflammatory bowel disease, rheumatoid arthritis, obstructive sleep apnoea, and multiple sclerosis. For the fluid intelligence test, fully adjusted models additionally included years in education. For the prospective memory test logistic regression was performed and the estimates reported are odds ratios. Minimally adjusted models for this test include age and sex and fully adjusted models additionally adjusted for physical activity in the fully adjusted models.

Supplementary table 10: Association of common infections with hippocampal volume and white matter hyperintensities volume excluding follow up infections

	Minimally adjusted model			Fully adjusted model		
	No. of participants	**β Coefficient (95% Confidence Interval)**	**P Value**	**No. of participants**	**B Coefficient (95% Confidence Interval)**	**P Value**
Total hippocampal volume (mm^3)						
No infection	12,275			11,911		
Any infection	2,435	-12.43 (-48.91 to 24.06)	0.50	2,328	7.63 (-29.85 to 45.10)	0.69
White matter hyperintensities (Exp B)						
No infection	12,011			11,982		
Any infection	2,386	1.05 (1.01 to 1.09)	0.02	2,375	1.02 (0.98 to 1.06)	0.35
Estimates for any infection and site of infection. Fully adjusted models for hippocampal volume adjusted for age, sex, smoking, alcohol consumption, years in education, diabetes category, chronic obstructive pulmonary disease, asthma, chronic kidney disease, chronic liver disease, hypertension, heart failure and psoriasis (n= 14,239). Fully adjusted models for log of volume of white matter hyperintensities included age, sex, BMI, anxiety and depression, chronic kidney disease, chronic liver disease, heart failure and psoriasis (n=14,357).						

Supplementary table 11: Association of common infections with left and right hippocampal volume

		Minimally adjusted model			Fully adjusted model	
	No. of participants	**β Coefficient (95% Confidence Interval)**	**P Value**	**No. of participants**	**β (95% Confidence Interval)**	**P Value**
		Left hippocampal volume (mm^3)				
No infection	12,275	Reference		11,911	Reference	
Any infection	2,435	-8.00 (-28.02 to 12.01)	0.43	2,328	3.76 (-16.80 to 24.32)	0.72
Other LRTI	1,372	-10.83 (-36.46 to 14.80)	0.41	1,306	2.97 (-23.53 to 29.46)	0.83
UTI	569	-20.45 (-59.42 to 18.53)	0.30	544	-12.92 (-52.65 to 26.80)	0.52
SSTI	431	16.15 (-27.94 to 60.24)	0.47	417	26.28 (-18.44 to 71.00)	0.25
		Right hippocampal volume (mm^3)				
No infection	12,275	Reference		11,911	Reference	
Any infection	2,435	-4.42 (-25.06 to 16.22)	0.67	2,328	3.87 (17.38 to 25.11)	0.72
Other LRTI	1,372	5.56 (-20.87 to 32.00)	0.68	1,306	14.31 (-13.07 to 41.69)	0.31
UTI	569	-8.52 (-48.72 to 31.69)	0.68	544	0.22 (-40.83 to 41.27)	0.99
SSTI	431	-22.05 (-67.53 to 23.43)	0.34	417	-16.32 (-62.54 to 29.90)	0.49
Estimates for any infection and site of infection. Fully adjusted models for left and right hippocampal volume adjusted for age, sex, smoking, alcohol consumption, years in education, diabetes category, chronic obstructive pulmonary disease, asthma, chronic kidney disease, chronic liver disease, hypertension, heart failure and psoriasis (n= 14,239)						

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