Blood cholesterol and risk of dementia in more than 1·8 million people over two decades: a retrospective cohort study

Masao Iwagami, Nawab Qizilbash, John Gregson, Ian Douglas, Michelle Johnson, Neil Pearce, Stephen Evans, Stuart Pocock

Summary

Background Uncertainty remains concerning the association of blood cholesterol with the risk of subsequent dementia. Using data from people with lipid measurements in the UK Clinical Practice Research Datalink (CPRD), we examined the association between blood lipid levels and dementia (both vascular and non-vascular, including Alzheimer's disease) by age at first measurement of blood lipids and duration of follow-up.

Methods We studied a cohort from the UK CPRD of people aged 40 years or older with a first total cholesterol recording between Jan 1, 1992, and Dec 31, 2009. Follow-up was until the first record of dementia, the last data collection date, patient death or transfer out of the practice, or Jan 5, 2015, whichever was earliest. We excluded individuals with a record of dementia before the total cholesterol measurement. We used Poisson regression to examine the association between baseline total cholesterol, LDL cholesterol and HDL cholesterol, and triglycerides and incident dementia diagnosis. Analyses were stratified by age at first measurement (<65 years or ≥65 years) and duration of follow-up (<10 years or ≥10 years). Our primary focus was LDL cholesterol. We adjusted for age, sex, calendar year, country within the UK, socioeconomic status, ethnicity, smoking, alcohol, body-mass index, comorbidities, and prescriptions.

Findings 1 853 954 people had a first total cholesterol recording (dementia diagnosis in 49 416 [2·7%] people), including 953 635 [51·4%] people with LDL cholesterol values for analysis (dementia diagnosis in 21 602 [2·3%] people). Overall, we found a modest positive association between LDL cholesterol and dementia, with an adjusted rate ratio (RR) of 1·05 (95% CI 1·03–1·06) per SD increase in LDL cholesterol (1·01 mmol/L or 39 mg/dL increase). Adjusted RRs per 1-SD increase in LDL cholesterol in people younger than 65 years at baseline (n=636 262) were 1·10 (95% 1·04–1·15) for dementia diagnosed in the first 10 years after measurement and 1·17 (1·08–1·27) for dementia diagnosed more than 10 years after measurement. Associations for LDL cholesterol in people aged 65 years or older at baseline (n=317 373) were weaker compared with people younger than 65 years (RR 1·03 [95% CI 1·01–1·05] for dementia diagnosed during the first 10 years of follow-up and 1·07 [1·03–1·13] for dementia diagnosed after 10 years). We observed a weaker association between total cholesterol and dementia incidence and no consistent associations for HDL cholesterol and triglycerides.

Interpretation LDL cholesterol measured in mid-life (<65 years) is modestly associated with dementia risk more than 10 years later. LDL cholesterol should be added to the list of modifiable risk factors for dementia.

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Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK (M Iwagami MD, N Qizilbash MRCP, J Gregson PhD, Prof I Douglas PhD, Prof N Pearce PhD, Prof S Evans MSc, Prof S Pocock PhD); **Department of Health Services Research, University of Tsukuba, Tsukuba, Japan** (M Iwagami); **OXON Epidemiology, London, UK** (N Qizilbash, M Johnson MSc); **OXON Epidemiology, Madrid, Spain** (N Qizilbash, M Johnson)

Correspondence to: Dr Nawab Qizilbash, OXON Epidemiology, 28036 Madrid, Spain **n.qizilbash@oxonepi.com**

Introduction

According to the 2016 Global Burden of Disease study, the number of people with dementia was estimated to be 43·8 million, more than doubling from 20·2 million in 1990.[1] Prevention is particularly important to reduce the increasing global burden of dementia, since there is currently no cure for the disease. According to the *Lancet* Commission on Dementia Prevention, Intervention, and Care, 40% of dementia cases are attributable to so-called potentially modifiable risk factors, including lower levels of education, hypertension, obesity, hearing loss, smoking, depression, physical inactivity, social isolation, diabetes, alcohol consumption, traumatic brain injury, and air pollution.[2] Notably, dyslipidaemia was not included in the list of potentially modifiable risk factors.

Evidence for the association between blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) and the risk of dementia has been inconsistent. The association between total cholesterol and risk of dementia appears to vary with age at measurement (mid-life [<65 years] or later life [≥65 years]) and follow-up duration.[3–8] Some studies reported no association or an inverse association with total cholesterol levels measured in later life, whereas those studies that showed a positive association examined the effect of mid-life total cholesterol levels with longer follow-up.

Research in context

Evidence before this study

The association between dyslipidaemia and dementia has been much debated. We searched PubMed on Jan 5, 2020, using the search terms ("dementia" OR "cognitive decline") AND ("lipid" OR "cholesterol" OR "triglycerides"), without restricting language or start and end dates of the search, and did manual searches of reference lists of previous studies. We identified several systematic and narrative reviews on this topic. Previous observational studies that examined the effect of midlife total cholesterol levels on dementia over longer follow-up durations were more likely to report a positive association than were studies measuring total cholesterol levels in later life and with shorter follow-up. However, these studies were small, with limited precision, and involved different study populations, methods to capture dementia, cutoff levels for total cholesterol, and methods to control for confounding. There are fewer and less conclusive data on the associations between LDL cholesterol and HDL cholesterol and triglycerides, and dementia.

Added value of this study

This study provides robust evidence of a positive association between risk of future dementia and LDL cholesterol measured at least 10 years before dementia diagnosis in people of middle age (<65 years). A weaker association between total cholesterol and dementia was found, suggesting that this association is largely driven by LDL cholesterol. We found no consistent evidence for an association between HDL cholesterol or triglycerides and dementia. As this is the largest single study to date to our knowledge, including a large number of participants with long-term follow-up to minimise reverse causation (ie, dementia causing changes in LDL cholesterol and total cholesterol levels during the preclinical period), our findings clarify the inconsistent results of previous smaller studies, particularly for LDL cholesterol.

Implications of all the available evidence

LDL cholesterol should be included in the list of so-called potentially modifiable risk factors (which also includes lower level of education, hypertension, obesity, hearing loss, smoking, depression, physical inactivity, social isolation, diabetes, alcohol consumption, traumatic brain injury, and air pollution, according to the 2020 *Lancet* Commission on Dementia Prevention, Intervention, and Care). Although randomised trials of statins have failed to show benefit in dementia incidence or cognitive dysfunction, such trials are limited by short duration of follow-up, few dementia events, and an inability to exclude such small risks. Middle age might be the best time to lower LDL cholesterol levels to reduce the risk of future dementia. Confirming this benefit might require follow-up beyond 10 years, with reliable measures to capture dementia, in large, randomised trials or comparative observational studies of interventions to lower LDL cholesterol.

However, synthesis of previous observational studies has been hampered by different study populations, different cutoff points of total cholesterol for categorisation, and varying methods for capturing dementia cases and controlling for confounding. There is even less information, and greater uncertainty, surrounding the association between LDL cholesterol, HDL cholesterol, and triglycerides and dementia risk.[3–8] Therefore, a sufficiently large study that overcomes these variations might better determine if there is an association between blood cholesterols (total cholesterol, LDL cholesterol, and HDL cholesterol) and triglycerides and dementia risk by age at measurement and duration of follow-up.

Using data from people with lipid measurements in the UK Clinical Practice Research Datalink (CPRD), we examined the association between blood lipid levels and dementia incidence (both vascular and non-vascular) by age at first measurement of blood lipids (<65 years *vs* ≥65 years) and duration of follow-up (<10 years *vs* ≥10 years).

Our focus was LDL cholesterol, as this is a major component of total cholesterol. Analyses were stratified, in keeping with other studies, by duration of follow-up, with a focus on 10 years or more since lipid measurement, to minimise reverse causality arising from a change in lipid levels during the prodromal phase of dementia, and age at first measurement of blood lipids, as people younger than 65 years are less prone to selection bias caused by the loss of older people who tend to die earlier.[9]

Methods

Data source and participants

For this retrospective cohort study, we used data from the CPRD GOLD, a database of anonymised electronic health records collected from general practitioners (GPs) in the UK.[10] As of Jan 5, 2015, more than 650 GPs have contributed data that met quality control standards to the CPRD, representing almost 7% of the UK population. The CPRD contains the following information: patient demographics, coded diagnoses (based on Read codes), prescriptions, laboratory test results, including total cholesterol, HDL cholesterol, and triglycerides, and referrals to secondary care. Dementia, among many other clinical diagnoses, has been validated in the CPRD, with a positive predictive value of over 80%.[11,12]

Participants were recruited from GPs satisfying the CPRD quality standards. Inclusion criteria included having at least 1 year of historical data, being aged 40 years or older, and having at least one total cholesterol measurement between Jan 1, 1992, and Dec 31, 2009. Participants with a history of dementia were excluded. Participants with total cholesterol values <1·75 mmol/L

or >20 mmol/L were also excluded because of probable recording errors (figure 1).[13]

We identified people with measurements of HDL cholesterol and triglycerides on the day of the first total cholesterol recording. Among people with both measurements available, we estimated LDL cholesterol based on the Friedewald formula.[14] Participants with a triglyceride level of ≥4·52 mmol/L (because the Friedewald formula might not be valid[14]) and participants with unrealistic values of LDL cholesterol (<0·75 mmol/L or >8 mmol/L)[13] were excluded.

This study uses data from the CPRD GOLD database obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone. This study was approved by the Medicines and Healthcare products Regulatory Agency's Independent Scientific Advisory Committee (protocol number 15_148R). The protocol is available online.

Outcome and follow-up

The primary outcome was the first diagnosis of dementia, based on diagnostic codes suggestive of dementia as recorded in CPRD (appendix pp 1–3).[11,12] Patients were followed up from the date of their first total cholesterol measurement (referred to as the index date). Follow-up was until the first record of dementia, the general practice's latest collection date of CPRD data, the end of the patient's record collection (because of death or leaving the practice), or Jan 5, 2015, whichever occurred first.

Covariates

We considered the following variables as potential confounding factors: age, sex, calendar year, country (England, Northern Ireland, Scotland, or Wales), practice-level socioeconomic status, ethnicity (White, South Asian, Black, or mixed or other ethnicity), smoking and alcohol status, body-mass index (BMI), history of myocardial infarction, stroke, atrial fibrillation, heart failure, or chronic obstructive pulmonary disease (COPD), and prescriptions of anti-hypertensive, anti-diabetic, or lipid-lowering drugs (statins, fibrates, nicotinic acids, or bile acid resins). Practice-level socioeconomic status was based on the postcodes of GPs and was assigned by quintiles according to the 2010 Office for National Statistics estimates of the Index of Multiple Deprivation. People with no record of ethnicity were grouped with White people, as was done in previous studies in UK primary care.[15] Smoking and alcohol status and BMI were assigned using data recorded at the timepoint closest to the index date, using existing algorithms.[16] We defined each comorbidity (myocardial infarction, stroke, atrial fibrillation, heart failure, and COPD) as being present if a relevant diagnostic code of that comorbidity was recorded at least once before a patient's index date. Prescriptions of anti-hypertensive, anti-diabetic, and lipid-lowering drugs were defined in the year before the index date.

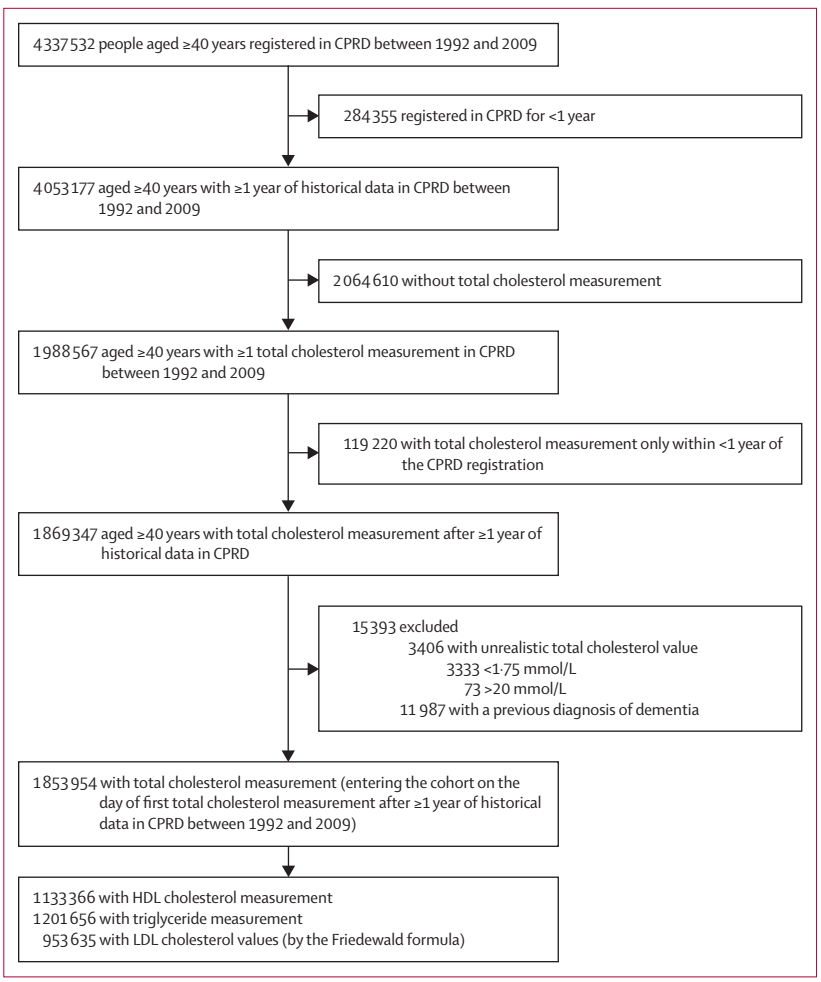

Figure 1: **Flow chart of creation of the dataset for analysis from the entire CPRD**
CPRD=Clinical Practice Research Datalink.

Statistical analysis

We used Poisson regression to estimate incidence rates and rate ratios of dementia across categories of blood lipids. We first adjusted for age at risk (in 5-year bands, time-updated[17]) and sex, and then adjusted for additional covariates at baseline, namely calendar year (in 5-year bands, time-updated[17]), country, practice-level socioeconomic status, ethnicity, smoking and alcohol status, BMI, comorbidities, and prescriptions. We adjusted for duration of follow-up using the log of the duration of follow-up as an offset variable. In fully adjusted models we used a complete case analysis as relatively few participants had missing data on smoking, alcohol, or BMI (<10% of the study participants). We reported rate ratio (RR) per 1-SD increase in each lipid fraction,[18] and according to five categories commonly used for blood lipids.[19]

We investigated the associations stratified by age at first measurement (<65 years *vs* ≥65 years) and by duration of follow-up (<10 years *vs* ≥10 years). We first separated patients into two groups according to age at

For the **online protocol summary** see http://www.encepp.eu/encepp/viewResource.htm?id=23960

See **Online** for appendix

first lipid measurement in the CPRD (<65 years *vs* ≥65 years). Within each age group, we divided each person's follow-up period into the following two intervals: 0–10 years since measurement and more than 10 years since measurement. Patients followed up for less than 10 years only featured in the analysis of 0–10 years since measurement. Patients followed up for more than 10 years featured in both analyses—their first 10 years of follow-up contributed to the analysis of 0–10 years and the remainder of their follow-up contributed to the more than 10 years analysis. A priori, we focused on people younger than 65 years at first measurement, who had long-term follow-up (≥10 years). Analyses of patients younger than 65 years are less prone to selection bias caused by loss to follow-up in older patients, who are often more frail and who tend to die earlier. Additionally, we focused on long-term associations to reduce reverse causality arising from a drop in lipid levels during the prodromal phase of dementia before a clinical diagnosis.[20] Although our population was based on the availability of total cholesterol recordings, our primary focus was LDL cholesterol. We also differentiated between vascular and non-vascular dementia diagnoses by considering patients to have vascular dementia if a vascular cause was suggested in the diagnostic codes.[21] For vascular dementia, we censored patients who were diagnosed with non-vascular dementia on the day of diagnosis, and for non-vascular dementia, we censored patients diagnosed with vascular dementia. Furthermore, among patients with non-vascular dementia, we differentiated between Alzheimer's disease and other or unspecified dementia (appendix pp 1–3).

We did several sensitivity analyses. First, we repeated analyses excluding users of lipid-lowering drugs at baseline, as we found substantial confounding due to lipid-lowering drugs (mostly statins), which lower LDL cholesterol levels and were associated with higher levels of other conditions, such as smoking and recorded cardiovascular diseases. Second, we repeated analyses after using multiple imputation to account for missing data for smoking, alcohol, or BMI. Third, we used Cox regression models to confirm our results of Poisson regression models. Fourth, in the LDL cholesterol cohort, we included people with LDL cholesterol greater than 8 mmol/L, as this might indicate familial hypercholesterolaemia instead of an unrealistic value. Fifth, we did analyses stratified by sex and by timing of cohort entry (1992–2000 *vs* 2001–09) to examine potential effect modification by these factors. Sixth, we considered the role of the apolipoprotein E epsilon 4 (*APOEε4*) allele, which is associated with both increased LDL cholesterol and increased risk of dementia.[2] We used a simulation study to estimate the expected size of the association between LDL cholesterol and dementia that would be induced by the *APOEε4* allele in the absence of any direct impact of LDL cholesterol on dementia risk (see appendix pp 35–36 for further details).

We used STATA (version 16) for statistical analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 1992, and Dec 31, 2009, 1 853 954 people with a first total cholesterol measurement were eligible for the study. We excluded 3406 people with first total cholesterol records less than 1·75 mmol/L (n=3333) and more than 20 mmol/L (n=73) due to being probable recording errors[13] and 11 987 people with a history of dementia (figure 1).

Among the remaining 1 853 954 people with total cholesterol measurements, HDL cholesterol and triglycerides were available on the day of first total cholesterol recordings in 1 133 366 people and 1 201 656 people, respectively, with 976 970 having both measurements available, enabling estimation of LDL cholesterol based on the Friedewald formula.[14] After excluding 21 452 people with a triglyceride level of 4·52 mmol/L or greater (because the Friedewald formula might not be valid[14]) and 1883 people with unrealistic values of LDL cholesterol (<0·75 mmol/L [n=1404] or >8 mmol/L [n=479]),[13] 953 635 people remained with LDL cholesterol values for analysis.

In the total cholesterol cohort, the median baseline age was 59 years (IQR 50–69), 905 830 (48·9%) of 1 853 954 were male, and median follow-up was 7·4 years (IQR 4·6–10·4, maximum 23 years). The distribution of duration of follow-up by year of cohort entry is shown in the appendix (p 4). There were 49 416 (2·7%) diagnoses of dementia (including 13 564 vascular and 35 852 non-vascular) at an overall incidence of 3·5 cases per 1000 person-years. Incidences by age, sex, and calendar year are shown in the appendix (p 5). Among patients who had a diagnosis of dementia, the mean age at diagnosis was 79·7 years (SD 7·7) in men and 82·1 years (7·5) in women. Mean levels of blood lipids were 5·62 mmol/L (SD 1·19) for total cholesterol, 3·42 mmol/L (1·01) for LDL cholesterol, and 1·45 mmol/L (0·42) for HDL cholesterol. The median level of triglycerides was 1·40 mmol/L (IQR 1·00–2·03).

Lower levels of LDL cholesterol were found more often in male participants, people with a greater number of comorbidities, and people prescribed lipid-lowering and anti-hypertensive drugs (table 1). Baseline characteristics by categories of total cholesterol, HDL cholesterol, and triglycerides are shown in the appendix (pp 6–11).

LDL cholesterol was not associated with increased dementia risk in age-adjusted and sex-adjusted models (RR per 1-SD higher LDL cholesterol levels 0·99, 95% CI 0·97–1·00; table 2; figure 2). However, after adjustment for further potential confounders in fully adjusted models, higher levels of LDL cholesterol were associated with increased dementia risk (adjusted RR 1·05, 95% CI 1·03–1·06).

	Overall (n=953 635)	By LDL cholesterol category				
		<2·59 mmol/L or <100 mg/dL (n=199 037)	2·60–3·36 mmol/L or 100–129 mg/dL (n=274 033)	3·37–4·14 mmol/L or 130–159 mg/dL (n=262 589)	4·15–4·92 mmol/L or 160–189 mg/dL (n=146 901)	>4·92 mmol/L or ≥190 mg dL (n=71 075)
Age (years)	58 (49–68)	59 (48–71)	57 (48–68)	58 (49–67)	59 (50–68)	60 (52–68)
Sex						
Male	458 953 (48·1%)	100 682 (50·6%)	133 359 (48·7%)	128 031 (48·8%)	68 165 (46·4%)	28 716 (40·4%)
Female	494 682 (51·9%)	98 355 (49·4%)	140 674 (51·3%)	134 558 (51·2%)	78 736 (53·6%)	42 359 (59·6%)
Cohort entry year	2005 (2003–2007)	2005 (2004–2007)	2005 (2003–2007)	2005 (2003–2007)	2005 (2003–2007)	2004 (2002–2007)
Country						
England	769 936 (80·7%)	155 960 (78·4%)	219 781 (80·2%)	213 821 (81·4%)	121 027 (82·4%)	59 347 (83·5%)
Northern Ireland	38 361 (4·0%)	8828 (4·4%)	11 893 (4·3%)	10 150 (3·9%)	5297 (3·6%)	2193 (3·1%)
Scotland	55 384 (5·8%)	12 833 (6·4%)	16 288 (5·9%)	14 888 (5·7%)	7779 (5·3%)	3596 (5·1%)
Wales	89 954 (9·4%)	21 416 (10·8%)	26 071 (9·5%)	23 730 (9·0%)	12 798 (8·7%)	5939 (8·4%)
Socioeconomic status (practice level)						
1 (least deprived)	191 372 (20·1%)	38 073 (19·1%)	55 893 (20·4%)	53 671 (20·4%)	29 689 (20·2%)	14 046 (19·8%)
2	193 101 (20·2%)	40 141 (20·2%)	56 004 (20·4%)	53 384 (20·3%)	29 615 (20·2%)	13 957 (19·6%)
3	197 122 (20·7%)	40 505 (20·4%)	55 667 (20·3%)	54 621 (20·8%)	30 956 (21·1%)	15 373 (21·6%)
4	198 692 (20·8%)	43 187 (21·7%)	57 060 (20·8%)	53 753 (20·5%)	30 269 (20·6%)	14 423 (20·3%)
5 (most deprived)	173 348 (18·2%)	37 131 (18·7%)	49 409 (18·0%)	47 160 (18·0%)	26 372 (18·0%)	13 276 (18·7%)
Ethnicity						
White or missing	925 120 (97·0%)	190 990 (96·0%)	264 857 (96·7%)	255 574 (97·3%)	143 715 (97·8%)	69 984 (98·5%)
South Asian	13 633 (1·4%)	4098 (2·1%)	4446 (1·6%)	3272 (1·2%)	1384 (0·9%)	433 (0·6%)
Black	8009 (0·8%)	2170 (1·1%)	2610 (1·0%)	1942 (0·7%)	953 (0·6%)	334 (0·5%)
Mixed or other	6873 (0·7%)	1779 (0·9%)	2120 (0·8%)	1801 (0·7%)	849 (0·6%)	324 (0·5%)
Smoking status						
Non-smoker	426 707 (44·7%)	83 802 (42·1%)	125 230 (45·7%)	120 067 (45·7%)	66 260 (45·1%)	31,348 (44·1%)
Ex-smoker	337 394 (35·4%)	76 267 (38·3%)	95 947 (35·0%)	90 769 (34·6%)	50 529 (34·4%)	23 882 (33·6%)
Current smoker	185 854 (19·5%)	38 167 (19·2%)	51 774 (18·9%)	50 781 (19·3%)	29 551 (20·1%)	15 581 (21·9%)
Missing	3680 (0·4%)	801 (0·4%)	1082 (0·4%)	972 (0·4%)	561 (0·4%)	264 (0·4%)
Alcohol status						
Non-drinker	115 187 (12·1%)	26 779 (13·5%)	32 649 (11·9%)	30 372 (11·6%)	16 955 (11·5%)	8432 (11·9%)
Ex-drinker	30,485 (3·2%)	7798 (3·9%)	8522 (3·1%)	7727 (2·9%)	4251 (2·9%)	2187 (3·1%)
Current drinker	752 172 (78·9%)	152 900 (76·8%)	216 615 (79·0%)	209 127 (79·6%)	117 197 (79·8%)	56 333 (79·3%)
Missing	55 791 (5·9%)	11 560 (5·8%)	16 247 (5·9%)	15 363 (5·9%)	8498 (5·8%)	4123 (5·8%)
Body-mass index (kg/m²)						
<18	32 564 (3·4%)	10 245 (5·1%)	10 267 (3·7%)	7417 (2·8%)	3241 (2·2%)	1394 (2·0%)
18–25	260 460 (27·3%)	58 133 (29·2%)	76 866 (28·0%)	69 526 (26·5%)	37 519 (25·5%)	18 416 (25·9%)
>25–30	356 022 (37·3%)	67 462 (33·9%)	98 931 (36·1%)	100 738 (38·4%)	59 233 (40·3%)	29 658 (41·7%)
>30	254 017 (26·6%)	52 305 (26·3%)	73 342 (26·8%)	71 086 (27·1%)	39 280 (26·7%)	18 004 (25·3%)
Missing	50 572 (5·3%)	10 892 (5·5%)	14 627 (5·3%)	13 822 (5·3%)	7628 (5·2%)	3603 (5·1%)
Medical history						
Myocardial infarction	37 317 (3·9%)	18 475 (9·3%)	9258 (3·4%)	5605 (2·1%)	2634 (1·8%)	1345 (1·9%)
Stroke	35 476 (3·7%)	13 664 (6·9%)	9400 (3·4%)	7059 (2·7%)	3614 (2·5%)	1739 (2·4%)
Heart failure	17 128 (1·8%)	6765 (3·4%)	4753 (1·7%)	3277 (1·2%)	1605 (1·1%)	728 (1·0%)
Atrial fibrillation	34 674 (3·6%)	11 885 (6·0%)	10 195 (3·7%)	7535 (2·8%)	3575 (2·4%)	1484 (2·1%)
Chronic obstructive pulmonary disease	29 034 (3·0%)	8702 (4·4%)	8318 (3·0%)	6975 (2·7%)	3498 (2·4%)	1541 (2·2%)
Anti-hypertensives	328,599 (34·5%)	90 974 (45·7%)	91 552 (33·4%)	80 793 (30·8%)	44 275 (30·1%)	21 005 (29·6%)
Anti-diabetics	78 730 (8·3%)	31 400 (15·8%)	22 236 (8·1%)	15 204 (5·8%)	6981 (4·8%)	2909 (4·1%)
Lipid-lowering drugs*	123 320 (12·9%)	69 197 (34·8%)	31 300 (11·4%)	13 887 (5·3%)	5791 (3·9%)	3145 (4·4%)

Data are median (IQR) or n (%). *Among lipid-lowering drug users, 97·0% were on statins, and others were on fibrates, nicotinic acids, or bile acid resins.

Table 1: **Baseline characteristics of patients with LDL cholesterol values overall and by category**

	Overall (n=953 635)	People with first measurement at age <65 years (n=636 262)		People with first measurement at age ≥65 years (n=317 373)	
		Follow-up <10 years (n=636 262)	Follow-up ≥10 years (n=147 393)	Follow-up <10 years (n=317 373)	Follow-up ≥10 years (n=62 249)
Number of outcomes, n	21 062	1686	577	17 372	1967
Age and sex adjusted RR (95% CI)	0·99 (0·97–1·00)	1·00 (0·95–1·04)	1·11 (1·03–1·21)	0·97 (0·96–0·99)	1·04 (0·99–1·08)
Fully adjusted RR (95% CI)*	1·05 (1·03–1·06)	1·10 (1·04–1·15)	1·17 (1·08–1·27)	1·03 (1·01–1·05)	1·07 (1·03–1·13)

Data are adjusted RRs (95% CI) per SD increase of LDL cholesterol, unless otherwise indicated. SD in the overall population (n=953 635) was 1·01 mmol/L for LDL cholesterol. BMI=body-mass index. RR=rate ratio. *Adjusted for age at risk (in 5-year bands, time-updated), sex, calendar year (in 5-year bands, time-updated), country, practice-level socioeconomic status, ethnicity, smoking and alcohol status, BMI, history of myocardial infarction, stroke, atrial fibrillation, heart failure, and chronic obstructive pulmonary disease, and prescriptions of anti-hypertensive, anti-diabetic, and lipid-lowering drugs at baseline. As a complete case analysis, we excluded patients with missing data on smoking, alcohol, or BMI (accounting for <10% of the study participants).

Table 2: **RRs per SD increase of LDL cholesterol for dementia diagnosis by age at measurement and follow-up length**

Associations between blood lipid levels and dementia varied depending on age at first measurement and duration of follow-up (table 2; figure 3). The fully adjusted RRs per 1-SD increase in LDL cholesterol (1·01 mmol/L or 39 mg/dL increase) in people younger than 65 years at baseline (n=636 262) were 1·10 (95% CI 1·04–1·15) for dementia diagnosed in the first 10 years after measurement and 1·17 (1·08–1·27) for dementia diagnosed more than 10 years after measurement. Associations for LDL cholesterol in people 65 years or older at baseline (n=317 373) were weaker compared with people younger than 65 years (1·03 [1·01–1·05] for dementia diagnosed during the first 10 years of follow-up and 1·07 [1·03–1·13] after 10 years). In people with LDL cholesterol measurement who were younger than 65 years and had follow-up for 10 or more years, according to the commonly used five categories of LDL cholesterol (<2·59 mmol/L, 2·60–3·36 mmol/L, 3·37–4·14 mmol/L, 4·15–4·92 mmol/L, and >4·92 mmol/L [<100 mg/dL, 100–129 mg/dL, 130–159 mg/dL, 160–189 mg/dL, and ≥190 mg/dL]), the fully adjusted RR comparing the highest and the lowest category was 1·59 (95% CI 1·13–2·22; figure 3).

Overall, associations of LDL cholesterol with vascular or non-vascular dementia were similar (fully adjusted RRs per 1-SD increase were 1·03 (95% CI 1·00–1·06) and 1·05 (95% CI 1·04–1·07), respectively; appendix p 12). However, in analyses that further separated non-vascular dementia, the adjusted RRs were 1·11 (1·08–1·14) for Alzheimer's disease and 1·01 (0·99–1·04) for other or unspecified dementia (appendix p 13). In people with LDL cholesterol measurement aged younger than 65 years and with follow-up for 10 or more years, the adjusted RRs were 1·30 (1·14–1·48) for Alzheimer's disease and 1·13 (0·98–1·30) for other or unspecified dementia.

The association between total cholesterol and dementia was weaker than the association for LDL cholesterol but followed a similar pattern (fully adjusted RR per 1-SD increase 1·02, 95% CI 1·01–1·03), with the strongest association observed in people younger than 65 years with more than 10 years after first total cholesterol measurement (1·08, 95% CI 1·03–1·12; appendix pp 14–16). For HDL

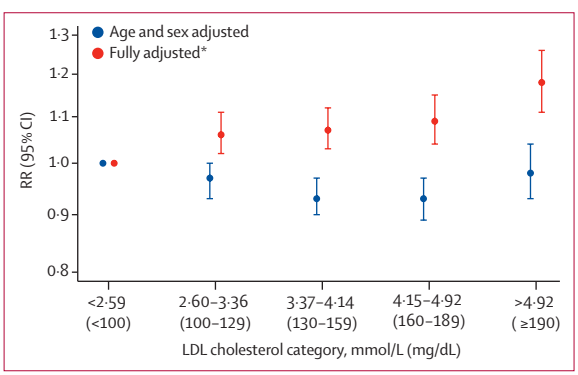

Figure 2: **RRs for dementia diagnosis by categories of LDL cholesterol (n=953 635)**
RR=rate ratio. BMI=body-mass index. *Predefined covariates included age at risk (in 5-year bands, time-updated), sex, calendar year (in 5-year bands, time-updated), country, practice-level socioeconomic status, ethnicity, smoking and alcohol status, BMI, history of myocardial infarction, stroke, atrial fibrillation, heart failure, or chronic obstructive pulmonary disease, and prescriptions of anti-hypertensive, anti-diabetic, or lipid-lowering drugs at baseline. As a complete case analysis, we excluded patients with missing data on smoking, alcohol, or BMI (accounting for <10% of the study participants).

cholesterol, the fully adjusted RR per 1-SD increase was 1·00 (0·98–1·01), with no associations irrespective of age or duration of follow-up (appendix pp 14, 17–18). For triglycerides, we found some suggestion of a U-shaped association (appendix p 19), but the overall association was weak (adjusted RR per 1-SD increase 0·97, 95% CI 0·96–0·99), as were all associations irrespective of age and duration of follow-up (appendix pp 14, 20).

In sensitivity analyses, findings were similar after exclusion of lipid-lowering drug users at baseline (appendix pp 21–29), using imputation to include patients with missing data at baseline (appendix p 30), using Cox regression models (appendix p 31), or including people with LDL cholesterol greater than 8 mmol/L (appendix p 32). The association between LDL cholesterol and dementia was similar in men and women (appendix p 33), and in people who entered the cohort in 1992–2000 versus 2001–09 (appendix p 34). In a simulation study for the *APOEε4* allele, we estimated that in the absence of any causal relationship between

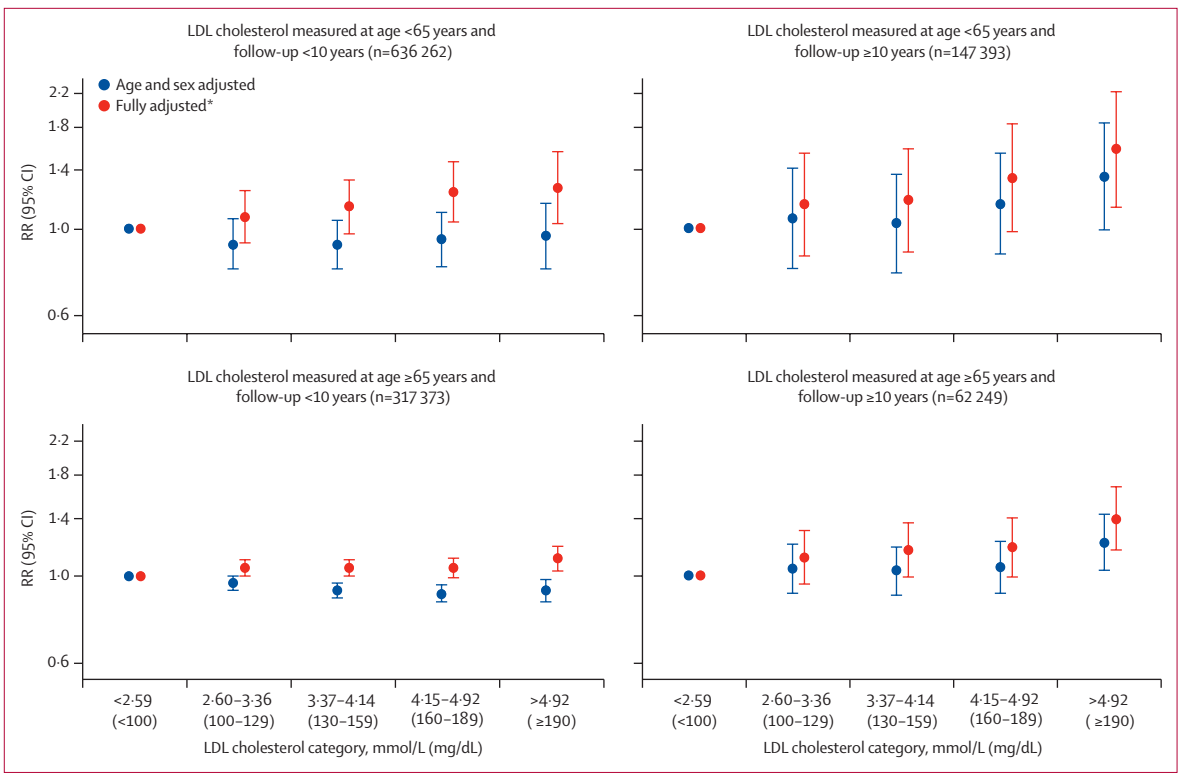

Figure 3: **RRs for dementia diagnosis by categories of LDL cholesterol according to age at measurement and follow-up duration**
RR=rate ratio. BMI=body-mass index. *Predefined covariates included age at risk (in 5-year bands, time-updated), sex, calendar year (in 5-year bands, time-updated), country, practice-level socioeconomic status, ethnicity, smoking and alcohol status, BMI, history of myocardial infarction, stroke, atrial fibrillation, heart failure, or chronic obstructive pulmonary disease, and prescriptions of anti-hypertensive, anti-diabetic, or lipid-lowering drugs at baseline. As a complete case analysis, we excluded patients with missing data on smoking, alcohol, or BMI (accounting for <10% of the study participants).

LDL cholesterol and dementia risk, confounding by the *APOEε4* allele would induce a RR for dementia of 1·09 per 1-SD increase in LDL cholesterol (appendix pp 35-36). Therefore, confounding caused by the *APOEε4* allele is unlikely to entirely explain the observed relationship between LDL cholesterol and dementia risk in people younger than 65 years with 10 or more years of follow-up.

Discussion

In this cohort study, with over 1·8 million people with total cholesterol measurements and almost 1 million people with LDL cholesterol measurements followed up over more than two decades, we observed modest positive associations between total cholesterol and LDL cholesterol and dementia risk. These associations were not fully explained by age, sex, and available baseline covariates. The associations were stronger for total cholesterol and LDL cholesterol measurements in mid-life (<65 years) and with longer follow-up (≥10 years). The association was stronger for LDL cholesterol than for total cholesterol, suggesting that the association between total cholesterol and dementia is in part driven by LDL cholesterol. There was almost no association between HDL cholesterol or triglycerides and dementia. Mid-life lipid levels are more likely to reflect individuals' exposure to dyslipidaemia over their life course, compared with late-life lipid levels, as lipid levels might fall in later life.[20] This bias is expected to be less pronounced in our analyses of patients younger than 65 years by excluding diagnoses in the first 10 years of follow-up.

Our findings are consistent with previous small studies that aimed to minimise the effect of reverse causation by including sufficient events after 10 years of follow-up, such as the Three Cities cohort (n=9294), which showed a significant association between total cholesterol and LDL cholesterol and dementia when using a 13-year,[18] but not a 7-year, follow-up.[22] Our findings suggest that short-term follow-up after lipid measurement, or measurement in later life, might result in an absent or inverse association between total cholesterol or LDL cholesterol and dementia. Unlike many previous studies, we also explored by simulation how the *APOEε4* allele can affect associations between dementia and LDL cholesterol, finding that it could not entirely explain the association observed in our study. In our study, the relationship between either HDL cholesterol or triglycerides and dementia was weak, with narrow CIs, suggesting an absence of any clinically meaningful association between these lipids and dementia risk. A 2021 Danish study found that people with the top 1% of triglyceride concentrations had a higher risk of

non-Alzheimer's related dementia,[23] but that more modestly elevated (51st to 99th percentiles) triglyceride levels were not significantly associated with either Alzheimer's dementia or non-Alzheimer's dementia.

The mechanism of how, over a prolonged period starting in mid-life, LDL cholesterol might cause Alzheimer's disease (the major dementia subtype) remains speculative.[24] Lipids in the brain might influence the function of cleavage enzymes such as β-secretase and γ-secretase, resulting in insoluble Aβ protein production, leading to Alzheimer's disease. Several genes, such as *APOE*, have important roles in brain cholesterol transport and are associated with Alzheimer's disease. As the blood–brain barrier prevents direct transport of lipids between plasma and the CNS, plasma levels might not reflect lipid levels in the brain over a short period of time; longer periods might be required for dementia to become clinically evident. The role of LDL cholesterol in cerebrovascular disease and vascular dementia remains uncertain.

Our study has several strengths. To our knowledge, this is the largest study to date of the association between blood lipids and dementia, with over 1·8 million people with total cholesterol and nearly 1 million people with LDL cholesterol followed up for up to 23 years. This statistical power allows precise risks of dementia to be investigated by categories of age at first measurement (<65 years and ≥65 years) and follow-up duration (<10 years and ≥10 years). Although the prodromal period of dementia might be longer than that of other diseases, we reduced reverse causality bias (ie, the onset of dementia leading to lower LDL cholesterol and total cholesterol levels[20]) by analysing cases over 10 years after the initial lipid measurement. Our results are not explained by confounding from available covariates including age, sex, BMI, smoking, several comorbidities, and lipid-lowering and anti-hypertensive agents.

However, our study has several limitations. Selection bias might exist, as lipid measurements were not taken routinely until 2009 for all individuals aged 40–74 years without a previous diagnosis of cardiovascular disease or risk factors.[25] We found that among 4 million people registered for at least 1 year in the CPRD between 1992 and 2009, only approximately half had undergone total cholesterol measurements (figure 1). Therefore, our estimated associations might not be representative of the general UK population if the association between total cholesterol and LDL cholesterol and dementia are different in patients not selected into our cohort. An association between LDL cholesterol and all-cause mortality could also cause selection bias, since many patients only enter the cohort when they are older. However, we expect any such bias to be modest, as LDL cholesterol is only weakly associated with all-cause mortality.[26,27] A further issue is the definition and classification of dementia. Dementia diagnosis in the CPRD has a positive predictive value of over 80%,[11,12] but a sensitivity of around 50%,[28] which might have changed over time. However, non-differential underdiagnosis of dementia would not change the association we found. The use of primary care records for the timing and diagnosis of dementia is more accurate and unbiased than using death certificates or hospital admissions because, in the UK, dementia is usually diagnosed first in primary care or at hospital outpatient clinics. Contact with GPs (and other physicians) might occur more often in people with higher LDL cholesterol levels, potentially leading to increased reporting of dementia, which might inflate the excess risk in those with high LDL cholesterol levels. Additionally, mild cognitive impairment was not examined in the current study, since it might not be accurately recorded by non-specialist primary physicians in the CPRD. Although we adjusted for many known risk factors for dementia,[2] we cannot exclude the possibility of unmeasured confounding factors. We could not obtain information on educational background, but adjusted for practice-level socioeconomic status, which is correlated with education. Although we adjusted for baseline use of lipid-lowering drugs and did sensitivity analyses excluding users of lipid-lowering drugs at baseline, we did not have data on dosing or compliance with statin use during follow-up. We investigated the role of the *APOEε4* allele via a simulation study but could not precisely adjust for this because genetic information was not available for our study population. We assessed associations of LDL cholesterol and total cholesterol measured at a single timepoint with dementia risk, which are weaker than associations for long-term average levels of these risk factors because of regression dilution bias.[29] Furthermore, random variations among different laboratories in the measurements of blood lipids could dilute the association between lipid levels and dementia diagnosis (meaning that the true association might be even larger).

Blood lipids are modifiable by lifestyle changes or lipid-lowering drugs. Randomised trials have found no evidence that statins prevent cognitive decline or dementia, but such trials are severely limited by the duration of follow-up (<5 years).[30] There is some evidence from randomised trials and comparative non-randomised studies that statins in younger people, those in earlier stages of dementia, and those with the *APOEε4* allele might modify cognitive function,[31–33] which could translate to a meaningful benefit at the population level for an irreversible disease that is a major cause of disability and mortality worldwide. The data to support an association between LDL cholesterol levels and dementia are as strong as the evidence for the association between blood pressure, which is on the list of modifiable risk factors for dementia, and dementia.[2]

In conclusion, LDL cholesterol levels in mid-life (<65 years) are modestly associated with dementia risk after at least 10 years of follow-up. LDL cholesterol should be added to the list of modifiable risk factors for dementia.

Contributors

SP and NQ were responsible for study conception, design, supervision, funding, analysis and interpretation of data, and drafting of the

manuscript. MI and JG had full access to and verified all the data in the study and were responsible for data acquisition, analysis, and interpretation and drafting of the manuscript. ID, MJ, NP, and SE substantially contributed to interpretation of data and drafting of the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

NQ is the owner of OXON Epidemiology, which conducts secondary data and field observational studies funded by the biopharmacuetical indusrty. MJ was an employee of OXON Epidemiology. All other authors declare no competing interests.

Data sharing

The data for this study were obtained from the UK CPRD. CPRD data governance does not allow us to distribute patient data to other parties. Researchers can apply for data access. This study was approved by the Medicines and Healthcare products Regulatory Agency's Independent Scientific Advisory Committee (protocol number 15_148R). The final study protocol was made available to reviewers. We registered our protocol in the European Union Electronic Register of Post-Authorisation Studies on May 12, 2018 (protocol number EUPAS23959). There were no deviations from our original protocol, except for some modified and sensitivity analyses requested during the review process of the current manuscript.

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