**Blood pressure and risk of dementia and its subtypes: a historical cohort study with long-term follow up in 2.6 million people**

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**ABSTRACT**

**Background:** Elevated blood pressure (BP) is prevalent, modifiable and has been hypothesized to lead to increased risk of dementia.

**Data:** 2,593,629 people from the United Kingdom Clinical Practice Research Database, aged ≥40 years or older with a BP measurement between 1992 to 2011 and no prior record of dementia.

**Methods:** We used Poisson regression models to study the association between BP and physician-diagnosed dementia. BP is believed to fall during the prodromal phase of dementia development, so we investigated associations by categories of time since BP measurement (<5 years, 5-10 years, >10 years), and by subtypes of dementia.

**Results:** During a median follow up of 8.2 years, we observed 65618 cases of dementia: 49161 Alzheimer’s, 13816 vascular dementia, and 2541 other subtypes. For each 10mmHg higher systolic BP, the future dementia risk was 9.2% (95% CI, 8.4%-10.0%) lower, but this association varied markedly by time since BP measurement. Short-term associations with dementia were inverse with a 15.8% (15.5%-17.0%) lower risk 0-5 years after BP measurement and a 5.8% (7.7%- 4.4%) lower risk 5-10 years after BP measurement. During the period >10 years after BP measurement, dementia risk was only 1.6% (0.1%-3.0%) lower, with a 4.3% (2.5%-6.0%) lower risk of Alzheimer’s disease, and a 7.0% (3.8%-10.2%) higher risk of vascular dementia.

**Conclusions:** Elevated BP is associated with decreased risk of dementia in the short-term, possibly due to reverse causation. Long-term associations of BP with dementia are less marked and differ by dementia subtype.

**INTRODUCTION**

It has been hypothesized that elevated blood pressure (BP) may lead to increased risk of dementia, a condition expected to affect over 65 million people by 2030.(1) It is therefore important to understand the association between BP and dementia, particularly given plausible links between the two conditions.(2)

Confusion exists regarding the associations between BP and dementia or its subtypes. For example, a recent article listed mid-life hypertension as one of seven potentially modifiable risk factors “with consistent evidence of an association with Alzheimer’s disease (AD)”, estimating mid-life hypertension to be responsible for 2% of AD cases.(3,4) In contrast, the World Alzheimer’s report and a meta-analysis by the Alzheimer’s Research Forum concluded that the association of midlife hypertension with dementia “has not yet been convincingly demonstrated, and the size of possible effects has probably been over-estimated”.(5,6) A complicating factor is that the association between BP and dementia risk appears to be different for vascular dementia and AD, and may vary depending on age-at-measurement and time since measurement, thereby hindering attempts to synthesise evidence across studies.(5,6) Additionally, such studies have often been small and used inconsistent criteria to define high BP.(5,6)

Accordingly, we analysed information from nearly 2.6 million people identified through general practice records in order to estimate the association of BP with risk of any dementia; and investigated how these associations vary with age and between the two major subtypes of dementia.

**METHODS**

We conducted a historical cohort study using routine United Kingdom primary care data from the Clinical Practice Research Datalink (CPRD). Patient information was recorded during routine general practice, including diagnoses, prescriptions, physiological measurements, diagnostic tests, lifestyle information, and secondary care referrals. The patients in CPRD represent around 7% of the UK population. Data collection began in 1987 and we used data up to December 2014.

The index BP measurement was defined as the first measurement amongst patients aged 40 years or older between Jan 1, 1992, and Dec 31, 2011, during a period at when data was deemed of research quality. The index date was defined as the date of index BP measurement or 12 months after patient registration, whichever occurred later. We excluded the first 12 months after patient registration to avoid including prevalent cases of dementia. General practices routinely record past medical history shortly after a patient’s new registration.(7) Repeat BP measurements taken after the index date, but before dementia diagnosis or censoring, were used to adjust for BP variability over time; see Statistical Analysis section and Appendix.

People with dementia recorded before their index date were excluded. Follow-up was until the practice’s final CPRD data record (i.e. of death or leaving the practice), or the first record of dementia, whichever occurred first. Validation of CPRD data quality has previously been done for many disorders, including dementia: in a study of AD, 84% of patient with a relevant read code were found to have probable or possible AD using a manual review of patient records.(8) We classified a patient as having dementia if any of the following terms were recorded during follow-up: dementia, Alzheimer, Lewy body disease, or Pick’s disease. Dementia recorded on a death certificate was also used to identify and classify patients with dementia. We classified dementia into vascular dementia, AD/unspecified dementia, or other dementia. We used read codes from a previous study of vascular dementia in CPRD which classified patients as having vascular dementia if a vascular aetiology was assigned to the dementia (Supplementary Table 1).(9)

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare Products Regulatory Agency (MHRA) and made available to journal reviewers. CPRD operates a consent policy whereby GP practices opt-in to providing de-identified data to CPRD, GPs are then required to inform individual patients of their right to opt-out of data collection. CPRD obtains ethical approval from National Health Service Research Ethics Committees to do so and to supply patient data for public health research, and is overseen by the MHRA

**Statistical analysis**

To relate BP to risk of dementia, we used Poisson regression models to estimate incidence rates and rate ratios. We adjusted for age (in 5-year bands), sex, and index date. We updated age at risk as people moved through the age categories. In sensitivity analyses, we further adjusted rate ratios for the following covariates at the time of BP measurement: body mass index; previous stroke; atrial fibrillation; chronic obstructive pulmonary disease or heart failure; prior use of anti-hypertensives or statins within 12 months; history of diabetes or evidence of prior diabetic medications; smoking status; and alcohol consumption. We primarily related systolic BP to dementia, but also considered diastolic BP.

Previous research suggests that BP may drop during the prodromal phase of dementia its risk associations may vary with age.(5,6) Therefore, we split follow up into three intervals (0-5 years, 5-10 years, 10+ years) and age-at-risk into three intervals (<70,70-84,85+) and fitted separate Poisson regression models in each of the resulting nine categories. Since BP is known to be highly variable over time, we corrected for regression dilution bias using serial measurements of BP (Supplementary Appendix; regression dilution ratio 0.42).

To assess the reliability of BP measurements, we conducted analyses relating systolic BP to stroke, for which strong positive associations are well known.(10) Studies which assess disorders that are strongly associated with increasing age can be prone to bias due the competing risk of death.(11) To assess the likely impact of such “joint-frailty” linking dementia risk and mortality risk, we conducted a simulation study to investigate the potential bias this might cause (Supplementary Appendix).

**RESULTS**

Of 6,622,747 individuals in CPRD aged at least 40 years between 1992 and 2010, a total of 2,593,629 patients had one or more BP measurements, at least 12 months of follow-up after date of general practice registration, and no prior history of dementia (Figure 1). The median age at baseline was 54 years, 54.1% were female and the median follow up was 8.2 years (interquartile range (IQR): 4.4-12.4) (**Table 1)**. The median systolic BP was 136 (IQR: 120-150) mmHg, and the median diastolic BP was 80 (IQR: 74-90) mmHg. Increasing BP was associated with increasing age and obesity.

During follow up, there were 65,518 incident cases of dementia (incidence rate: 2.9 per 1000 person years); of which 49,161 (75.0% of cases) were AD, 13,816 (21.1%) were vascular dementia, and 2,541 (3.9%) were other rare subtypes of dementia (**Table 2, Supplementary Table 1**). Dementia and its subtypes were very strongly associated with increasing age.

Age- and sex-adjusted standardized rates of dementia were lower amongst individuals with higher systolic BP (**Supplementary Figure 1**). However, dementia subtype, age-at-risk, and time since baseline BP measurement all influenced associations with dementia risk.

During the first 5 years following the index BP measurement, systolic BP was moderately inversely associated with dementia risk (rate ratio [RR] per 10mmHg higher long-term average systolic BP: 0.842, 95% CI 0.830-0.855), with similar associations across all age groups (**Figure 2A, Table 3**). Systolic BP was more strongly negatively associated with AD (RR:0.834, 0.821-0.848) than vascular dementia (RR:0.903, 0.872-0.935), (**Figure 2D & 2G, Table 3 left column)**.

During 5-10 years after BP measurement, the negative association of systolic BP with dementia was less marked (RR 0.942, 95% CI 0.927-0.956) than during the first 5 years (**Figure 2B, Table 3 middle column)**. Systolic BP was negatively associated with AD during this period (RR 0.937, 95% CI 0.921-0.954), but the inverse association with vascular dementia was non-significant (RR 0.979, 95% CI 0.948-1.011) (**Figures 2E & 2H)**.

When considering dementia risk more than 10 years after BP measurement, there was only a very weak association with systolic BP (RR 0.984, 0.970-0.999), but there was clear evidence that the association varied by age at index measurement (p for interaction with age <0.0001). There was a weak positive association with dementia amongst individuals aged <70 (RR:1.067, 95% CI 1.003-1.134), but this was not the case amongst older patients in whom more cases of dementia occur. The association amongst people aged 70-84 (RR:0.995, 0.975-1.015) was non-significant and amongst those aged or 85 or older it was negative (RR 0.951, 95% CI 0.931-0.979)(**Figure 2C,Table 3**). Differences in the association of systolic BP with dementia risk across age groups was less marked for AD, which was weakly inversely associated with systolic BP (RR:0.957, 0.940-0.975), with broadly similar associations across age groups (**Figure 2F,Table 3**). The association with vascular dementia was age-dependent (p for interaction <0.0001, **Figure 2I,Table 3**). There was a moderate positive association amongst people aged <70 (RR:1.269, 1.120-1.438); a weaker positive association in those aged 70-85+ (RR:1.095, 1.052-1.139); and no association in those aged 85 or older (RR:1.005, 0.956-1.057). Across all of our analyses, there was no clear evidence of a threshold between the association between BP and dementia (Figure 2).

We conducted a range of sensitivity analyses to assess the reliability of our findings. We found associations of diastolic BP with dementia followed very similar trends as associations with systolic BP (**Supplementary Table 2, Supplementary Figure2)**. Associations were similar upon restriction to patients not on anti-hypertensives at baseline (data not shown). We compared the associations of systolic BP with dementia at 10-12.5 years, 12.5-15 years, and >15 years since the index measurement. (**Supplementary Table 4**). We found that associations during these periods were broadly similar, suggesting a 10-year gap between BP measurement and assessment of dementia risk may be sufficient to exclude reverse-causality as a major cause of bias. We found a strong positive association of systolic BP with stroke (**Supplementary Figure 3,Supplementary Table 5)**, suggesting that BP measurements were reliable. In analyses focussing on midlife dementia, we restricted to more than 10 years since BP measurement and people aged under 65 (**Supplementary Table 6**). Associations of BP with AD or overall dementia were similar, although we noted that the positive association with vascular dementia was somewhat stronger. To assess the potential bias that could be caused by “joint-frailty” linking dementia risk and mortality risk, we conducted a simulation study (**Supplementary Appendix**). Any bias caused by joint frailty would likely be weak in patients aged under 70 years, and moderate in patients aged 70-85 years or over 85 years. In the simulation with the strongest joint-frailty, we estimated that with no real effect of systolic BP on dementia (i.e. RR=1), bias caused by joint frailty would result in observed RRs (per 10mmHg higher) of 0.96 in patients under 70, 0.93 in patients aged 70-85, and 0.92 in patients aged over 85.

**DISCUSSION**

We found that increased BP was moderately inversely associated with dementia during the first 10 years following the initial measurement, and weakly or not associated with dementia risk thereafter. A fall in BP is known to occur prior to clinical diagnosis of dementia,(12) hence the inverse associations during the first 10 years are probably due to reverse-causation, and the weaker associations observed beyond 10 years after measurement may be more reliable. The association between dementia is also known to vary by age, with a previous study reporting that BP measurements taken in midlife, but not later life, are associated with increased risk of dementia.(13) However, similar analyses in our dataset suggest midlife BP is at most weakly associated with dementia risk.

Specifically, we find that BP was not positively associated with the risk of AD amongst at any age, regardless of time since index BP measurement. Hence it seems implausible that lowering BP would reduce the risk of AD, which accounts for the bulk of dementia cases. A previous meta-analysis of BP with AD risk reported little or no association between BP and dementia risk.(5) Although others have reported positive associations, a large genetic study including over 17,000 AD patients and 34,000 age matched controls reported that people with genetic variants which increase BP were at lower risk of AD.(14) The weak inverse association in our study could reflect a causal association, for example via cerebral hypoperfusion in elderly people with low BP (15), but requires cautious interpretation; it could be an artefact resulting from a moderate co-dependency (or “joint frailty”) between dementia and death. Our findings do, however, suggest that claims that managing BP could reduce risk of AD may inappropriate.(3,4)

Consistent with previous studies, we report a positive long-term association between BP and risk of vascular dementia amongst people aged under 85.(9) Vascular dementia is common following stroke, and so one explanation for this association is via increased stroke risk in people with higher BP. A previous study in CPRD estimated this pathway to be responsible for roughly one-third of excess cases of vascular dementia seen in patients with high BP.(9)

Thus, BP reduction may decrease risk of vascular dementia, but have a limited effect on overall dementia risk.(3) Several randomised trials have studied the effect of anti-hypertensive therapies on dementia risk, but their findings are inconclusive. Syst-Eur trial reported a significant reduction in dementia risk with anti-hypertensives in elderly patients, but was an exploratory analysis and so should be treated with caution.(16) Several other trials did not demonstrate a significant reduction.(17,18)

Our study is the largest to investigate the association between BP and dementia, and included over 65,000 dementia cases amongst 2.6 million people. Previous studies have been hampered by selective reporting, inconsistent cut-offs for hypertension, varying age ranges, and varying definitions of dementia.(5,6) The large sample allowed us to investigate how this relationship varies according to age, latency periods, and subtype of dementia. We also demonstrated the lack of any clear threshold in the relationship between BP and dementia. Repeat BP measurements allowed us to adjust for regression dilution bias thereby avoiding under-estimation of associations with dementia.

Our study has limitations. Cases of dementia were identified using routine clinical records, in which some people may have transferred out of practice prior to its clinical diagnosis. Patients with low blood pressure were transferred out of practice slightly more often, so we would expect that our analyses may tend to slightly over-estimate positive associations of BP with dementia, or under-estimate negative associations. Only 39% of potentially eligible people had both an eligible blood pressure measurement and 12 months of prior data. This could have led to some selection bias, although it is unclear why the association of blood pressure with dementia would differ amongst patients not meeting these inclusion criteria. Our analysis spanned over 20 calendar years, during which increased awareness of dementia led to more frequent dementia diagnoses. However, because BP was not strongly related to calendar year of measurement, inclusion of data across several decades is unlikely to importantly bias our results.

We could only adjust for a small set of potential confounders. But the three most common risk factors strongly associated with dementia are age and socio-economic status-which we adjusted for-and variation in the APOE gene, which is unrelated to BP.(19) Residual confounding could explain our weak inverse association between BP with AD, but it cannot explain inverse associations observed in a recent large genetic study, which should be free from confounding by design.(14) Associations could be biased by the competing risk of death if patients at high risk of death and dementia die earlier when they have high BP. However, the likely size such bias is modest, particularly amongst patients diagnosed with dementia at a younger age. Incorrect diagnoses could have altered associations with dementia subtypes. We grouped none specific read codes for dementia with AD, and the clinical diagnosis of AD is prone to error even when diagnosed by specialists.(20) Some misclassification of dementia subtypes is therefore likely and would dilute differences in the associations between vascular dementia and AD. Conversely, selective diagnosis of vascular dementia in patients with high BP or a prior stroke may have exaggerated differences. Although it could be informative to understand how associations with underlying pathologies differ, misclassification does not alter associations of BP with overall dementia, nor associations with the real-world diagnoses of subtypes.

**Conclusions**

Elevated BP is associated with decreased risk of dementia in the short-term, possibly due to reverse causation. Long-term associations of BP with dementia are less marked, with moderate positive associations for vascular dementia and a weaker inverse association for AD.

Acknowledgements

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**Table 1**: Baseline characteristics of study participants by baseline systolic blood pressure

|  |  |  |  |
| --- | --- | --- | --- |
| Patient characteristic | Baseline systolic blood pressure | | |
|  | <120 mmHg  Median (IQR) or n(%) | 120-139mmHg  Median (IQR) or n(%) | >= 140mmHg  Median (IQR) or n(%) |
| N | 405466 | 971985 | 1216175 |
| Follow up duration (years) | 7.6 (4.1 to 11.7) | 8.0 (4.4 to 12.2) | 8.6 (4.5 to 12.7) |
| **Basic characteristics** |  |  |  |
| Age (years) | 46.0 (41.5 to 54.0) | 50.0 (43.0 to 60.8) | 61.0 (51.0 to 72.0) |
| Female | 264760 (65.3%) | 509126 (52.4%) | 630034 (51.8%) |
| Current smoker | 108198 (27.1%) | 239831 (25.1%) | 264999 (22.4%) |
| Current alcohol user | 311792 (83.7%) | 753550 (84.6%) | 898127 (82.1%) |
| BMI (kg/m2) | 24.4 (22.1 to 27.3) | 26.0 (23.4 to 29.2) | 26.9 (24.1 to 30.4) |
| Diastolic blood pressure (mmHg) | 70.0 (65.0 to 75.0) | 80.0 (74.0 to 83.0) | 88.0 (80.0 to 94.0) |
| **Previous medication and medical history** |  |  |  |
| Antihypertensives | 38035 (9.4%) | 132066 (13.6%) | 310533 (25.5%) |
| Statin | 14290 (3.5%) | 44436 (4.6%) | 57685 (4.7%) |
| Stroke | 8787 (2.2%) | 33603 (3.5%) | 92306 (7.9%) |
| Atrial fibrillation | 7347 (1.8%) | 18599 (1.9%) | 32938 (2.7%) |
| Heart failure | 6355 (1.6%) | 12656 (1.3%) | 24817 (2.0%) |
| MI | 10748 (2.7%) | 25589 (2.6%) | 38116 (3.1%) |
| COPD | 6515 (1.6%) | 17435 (1.8%) | 32726 (2.7%) |

BMI = body mass index, COPD = chronic obstructive pulmonary disease, IQR = interquartile range, MI = myocardial infarction

**Table 2:** Incidence rates of dementia and selected subtypes by sex and age-at-risk

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Age at risk | Incidence rate per 1000 person years (N) | | | | |
| All dementia |  | Subtypes of dementia | | |
|  | Alzheimer’s disease | Vascular dementia | Other/Unspecified dementia |
| **Male** |  |  |  |  |  |
| <50 | 0.02 (53) |  | 0.02 (38) | 0.00 (2) | 0.01 (13) |
| 50-60 | 0.16 (459) |  | 0.11 (316) | 0.02 (70) | 0.02 (73) |
| 60-70 | 0.85 (2174) |  | 0.58 (1480) | 0.19 (474) | 0.09 (220) |
| 70-80 | 5.02 (8624) |  | 3.42 (5869) | 1.28 (2204) | 0.32 (551) |
| 80+ | 16.17 (12052) |  | 11.57 (8627) | 4.01 (2991) | 0.58 (434) |
| **Female** |  |  |  |  |  |
| <50 | 0.02 (71) |  | 0.02 (57) | 0.00 (5) | 0.00 (9) |
| 50-60 | 0.14 (461) |  | 0.11 (371) | 0.02 (51) | 0.01 (39) |
| 60-70 | 0.80 (2239) |  | 0.63 (1745) | 0.13 (361) | 0.05 (133) |
| 70-80 | 5.62 (12012) |  | 4.35 (9295) | 1.07 (2285) | 0.20 (432) |
| 80+ | 20.00 (27373) |  | 15.61 (21363) | 3.93 (5373) | 0.47 (637) |
| Overall | 2.91 (65518) |  | 2.18 (49161) | 0.61 (13816) | 0.11 (2541) |

**Table 3**:Age and sex adjusted risk ratios per 10mmHg higher long-term average systolic blood pressure for dementia, Alzheimer’s disease and vascular dementia stratified by age-at-risk and time since baseline systolic blood pressure measurement

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age-at-risk | 0-5 years since measurement | | 5-10 years since measurement | | 10+ years since measurement | |
|  |  | Events | Rate ratio (95% CI) | Events | Rate ratio (95% CI) | Events | Rate ratio (95% CI) |
| All dementia | |  |  |  |  |  |  |
|  | <70 | 2245 | 0.849 (0.807-0.893) | 1762 | 0.934 (0.882-0.988) | 1450 | 1.067 (1.003-1.134) |
|  | 70-85 | 13674 | 0.846 (0.830-0.863) | 12445 | 0.949 (0.930-0.968) | 12125 | 0.995 (0.975-1.015) |
|  | 85+ | 7651 | 0.835 (0.815-0.856) | 6602 | 0.929 (0.905-0.954) | 7564 | 0.955 (0.931-0.979) |
|  | Overall | 23570 | 0.842 (0.830-0.855) | 20809 | 0.942 (0.927-0.956) | 21139 | 0.984 (0.970-0.999) |
| Alzheimer’s disease | | |  |  |  |  |  |
|  | <70 | 1703 | 0.846 (0.799-0.897) | 1308 | 0.891 (0.834-0.953) | 996 | 0.981 (0.909-1.058) |
|  | 70-85 | 10785 | 0.842 (0.824-0.860) | 9035 | 0.953 (0.931-0.975) | 8497 | 0.965 (0.942-0.988) |
|  | 85+ | 6310 | 0.821 (0.799-0.843) | 5037 | 0.918 (0.891-0.946) | 5490 | 0.942 (0.914-0.970) |
|  | Overall | 18798 | 0.834 (0.821-0.848) | 15380 | 0.937 (0.921-0.954) | 14983 | 0.957 (0.940-0.975) |
| Vascular dementia | | |  |  |  |  |  |
|  | <70 | 348 | 0.986 (0.870-1.116) | 301 | 1.147 (1.009-1.303) | 314 | 1.269 (1.120-1.438) |
|  | 70-85 | 2492 | 0.886 (0.847-0.927) | 2872 | 0.965 (0.926-1.006) | 3015 | 1.095 (1.052-1.139) |
|  | 85+ | 1210 | 0.922 (0.867-0.980) | 1415 | 0.977 (0.923-1.034) | 1849 | 1.005 (0.956-1.057) |
|  | Overall | 4050 | 0.903 (0.872-0.935) | 4588 | 0.979 (0.948-1.011) | 5178 | 1.070 (1.038-1.102) |

Figure legends:

**Figure 1**: Flow chart showing creation of the database for analysis from the entire CPRD cohort

**Figure 2:** Age and sex standardized rates by long-term average systolic blood pressure and time since baseline blood for: A-C) dementia; D-F) Alzheimer’s disease; G-I) Vascular dementia.

Error bars represent 95% confidence intervals