**Supplementary files**

**Supplementary figure e-1 Flow chart for blood pressure**

**Supplementary Figure e-2 Flow chart for cholesterol**

**Supplementary Figure e-3 Flow chart for body mass index**

**Supplementary table e-1 Study results for Blood Pressure (BP) (full details)**

**Supplementary table e-2 Risk of bias blood pressure**

**Supplementary table e-3 Risk of bias cholesterol**

**Supplementary table e-4 Risk of bias body mass index**

**Supplementary text e-1 Search strategy**

**Figure e-1 Flow chart for blood pressure**

Full-text articles excluded, (2 did not exclude prevalent cases, 42 did not have data on trajectories, 2 did not have suitable data on cognitive function)

(n =46)

Two time points only 10

Records excluded
(n =1620)

Studies with more than 2 time points
(n =5)

(6 articles)

Records identified through database searching
(n = 1787)

Full-text articles assessed for eligibility
(n =52)

Records screened
(n =1672)

Records after duplicates removed
(n =1672)

**Figure e-2 Flow chart for cholesterol**

Full-text articles excluded (3 did not exclude prevalent cases, 14 did not have data on trajectories),

(n =17)

Studies with more than 2 time points
(n = 3)

Records identified through database searching
(n = 2439)

Full-text articles assessed for eligibility
(n = 20)

Records excluded
(n =1968)

Records screened
(n =1988)

Records after duplicates removed
(n =1988)

**Figure e-3 Flow chart for body mass index**

Studies with more than 2 time points
(n =4)

Records identified through database searching
(n = 6235)

Full-text articles assessed for eligibility
(n =35)

Records excluded
(n =4845)

Records screened
(n =4880)

Records after duplicates removed
(n =4880)

Full-text articles excluded, (1 did not exclude prevalent cases, 30 did not have data on trajectories)

(n =31)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study **Supplementary table e-1 Study results for Blood Pressure (BP) (full details)**name  | Number of visits | Mean base-line BP | Methods of analysis | Depend-ent var-iables | Methods of cognitive assess-ment | Overall result | Co-variates |
| Adult Changes in Thought study, Li et al 2007 | 5 for the graph4 for numerical analysis.  | not provided  | Logistic regression was used to evaluate the impact of BP at 2, 4 and 6 years prior to final visit on incident dementia. Models were constructed separately for three age groups (65-74, 75-84, >=85 years At study entry). Also plotted mean SBP by age and dementia status at each year of FU. | All cause dement-ia | Cognitive Abilities Screening Instrument (CASI), if CASI<86 then diagnostic exam DSMIV, NINCDS ADRDA | Graphical results Li et al graph suggests that for those aged <75: participants who went on to develop dementia had high SBP up to 2 years prior to diagnosis but that SBP fell more sharply in this group over the final 2 years. In the >=75s SBP fell in both groups over FU and there was no obvious difference in SBP level. Numerical results: For all cause dementiaAt final visit 65-74 years <140mmHg reference 1.0; 65-74 years 140-159mmHg OR0.98 95% CI(0.56:1.72); 65-74 years >=160mmHg OR2.42 (1.33:4.40); >=75 years <140mmHg reference 1.0; >=75 years 140-159mmHg OR1.22 (0.84:1.79); >=75 years >=160mmHg OR0.92 (0.56:1.52)2 years before final visit65-74 years <140mmHg reference 1.0; 65-74 years 140-159mmHg OR0.82 (0.42:1.59); 65-74 years >=160mmHg OR2.74 (1.51:4.99); >=75 years <140mmHg reference 1.0; >=75 years 140-159mmHg OR1.39 (0.95:2.01); >=75 years >=160mmHg OR0.81 (0.51:1.30)4 years before final visit65-74 years <140mmHg reference 1.0; 65-74 years 140-159mmHg OR0.76 (0.37:1.56); 65-74 years >=160mmHg OR2.91 (1.58:5.39)>=75 years <140mmHg reference 1.0; >=75 years 140-159mmHg OR0.82 (0.54:1.25); >=75 years >=160mmHg OR0.89 (0.57:1.39)6 years before final visit65-74 years <140mmHg reference 1.0; 65-74 years 140-159mmHg OR0.91 (0.48:1.73); 65-74 years >=160mmHg OR1.33 (0.69:2.57)>=75 years <140mmHg reference 1.0; >=75 years 140-159mmHg OR1.12 (0.69:1.82); >=75 years >=160mmHg OR1.15 (0.67:1.95) | Age, sex, race,educat-ion pres-ence of *APOE4* allele  |
| Kung-sholmen project. (Qiu et al 2009)\* | 3 | not provided  | N/A graphical representation only. | All cause dement-ia | Dementia at time 4. DSMIIIR (data from medical records and death certificates) | Graphical results For all cause dementia: Qiu et al graph suggests a rise in SBP between time 1 and time 2 (~5mmHg). From time 2-3 SBP falls, the fall appears to be steeper in the group who go on to receive a diagnosis of dementia. From time 3-4 the group without dementia show no change to mean SBP, the group developing dementia show a steep fall in mean SBP (~10mHg).For DBP the groups are similar from time 1-3 showing no change in BP time 1-2 and a slight fall time 2-3. The groups diverge between times 3-4 with the incident dementia group showing a fall.  | Age, sex.  |
| Kung-Shol-men project(Qiu et al 2004)\* | 3 | not provided | Dementia as the dependent variable, linear mixed models taking account of repeated BP measures and examining dementia newly diagnosed at time 2 and dementia newly diagnosed at time 3.  | All cause dement-ia and AD | MMSE, DSMIIIR, specific criteria for AD | Numerical results Linear mixed models: SBP and DBP fell prior to dementia diagnosis. No participants had a diagnosis of dementia at baseline.For SBPIn those with dementia at time 2: Group\*time 2 interaction was Beta -13.0 (Standard Error (SE)2.0) P<0.001; Group\*time 3 interaction was Beta -18.0 (Standard Error (SE)3.1P<0.001In those with dementia at time 3: Group\*time 2 interaction was Beta 3.4 (Standard Error (SE)2.4) P=0.144; Group\*time 3 interaction was Beta -14.7 (Standard Error (SE)2.8) P<0.001. For DBPIn those with dementia at time 2: Group\*time 2 interaction was Beta -3.2 (Standard Error (SE)1.1) P=0.003; Group\*time 3 interaction was Beta -5.7 (Standard Error (SE)1.5) P<0.0001In those with dementia at time 3: Group\*time 2 interaction was Beta 0.2 (Standard Error (SE)1.3) P=0.904; Group\*time 3 interaction was Beta -5.7 (Standard Error (SE)1.4) P<0.0001. Results provided for BP and AD over two visits only.  | Age, sex, educat-ionvascular disease, baseline MMSE, antihypertensive use, disability*APOE4*, duration of first follow up |
| EPESE (Morris et al 2001) | 3  | 142/76mmHg | Graphical representation of BP trajectory split by those with and without incident AD.  | AD | Neurological exam, neuropsychological performance, NINCDS-ADRDA | Graphical results Age and sex adjusted mean BP levels were plotted for visits in 1973 through to 1988 with AD diagnosis made in 1986. The authors state that after adjustment for age there was no difference in blood pressure by incident AD/no incident AD over more than 15 years of observation. Data from 3 visits 13, 4.3 years and 1.5 years prior to diagnosis and 1.2 years post clinical exam. Similar pattern when analysis was restricted to the 288 with BP measures at each visit. No numerical statistical results are reported.  | Unclear for traject-ory analysis.  |
| HAAS (Stewart et al 2009) | 6 | 128/81mmHg | Random effects model with random intercept and slope to account for between participant heterogeneity and unequal time intervals between visits. Fitted with a 3 piece linear spline with 2 knots fixed at the mean sample age of 61 and 78 years. BP as the dependent variable, dementia, time and dementiaXtime as independent variable.Plotted BP over time for those with incident dementia (VaD and AD) and no dementia. | All cause dement-ia, AD, VaD | Dementia assessed at visits in 1991/3, 1994/6 1997/9. Cognitive screening; neuropsychological exam and diagnosis with imaging and clinical consensus: DSMIIIR, NINCDS-ADRDA, California Alzheimer's Disease Diagnostic and Treatment Centers criteria. | Graphical results Stewart et al graphs show SBP rising faster with age and falling more sharply in late-life BP in the group developing dementia (all-cause dementia and AD). For VaD also those who developed dementia show a higher SBP, a steeper rise with age and a steeper fall in late life that those without dementia. DBP shows similar pattern but with general fall rather than rise in pressure with ageing. Numerical resultsAdditional change in rate of change in SBP associated with all dementia mmHg/year (most adjusted model). P=0.002; Mean age 54-60 0.22 (-0.24:0.67) Mean age 61-78 0.29 (0.04:0.54); Mean age >78 -1.04 (-1.76:-0.32)Additional change in rate of change in DBP associated with all dementia mmHg/year.P=NS; Mean age 54-60 0.16 (-0.16:0.48) Mean age 61-78 0.01 (-0.12:0.14); Mean age >78 -0.18 (-0.54:0.18)Additional change in rate of change in SBP associated with AD mmHg/year. P=NS; Mean age 54-60 0.45 (-0.09:0.98) Mean age 61-78 0.03 (-0.25:0.31);Mean age >78 -0.76 (-1.55:0.03)Additional change in rate of change in DBP associated with AD mmHg/year.P=NS; Mean age 54-60 0.44 (0.07:0.81) Mean age 61-78 -0.09 (-0.24:0.06); Mean age >78 -0.06 (-0.48:0.36)Additional change in rate of change in SBP associated with VaD mmHg/year. P<0.001;Mean age 54-60 -0.29 (-1.54:0.96) Mean age 61-78 1.18 (0.77:1.59); Mean age >78 -3.75 (-5.61:-1.90)Additional change in rate of change in DBP associated with VaD mmHg/year.P=0.013; Mean age 54-60 -0.24 (-1.19:0.71) Mean age 61-78 0.47 (0.16:0.78); Mean age >78 -1.28 (-1.93:-0.64) | SBP all dementia model adjusted for age educat-ionvascular disease,disability Other analy-ses adjusted for age.  |
| Prospective population study of women in Gothenburg, Sweden (Joas et al 2012) | 6 | 131/82mmHg | Linear mixed models with random intercept and slope to account for intra-individual correlations across measurements and between person heterogeneity. Fitted with a 3 piece linear spline BP as the dependent variable, dementia, time and dementiaXtime as independent variable.Plotted BP over time for those with incident dementia (VaD and AD) and no dementia. | All cause dementia and AD | DSMIIIR, NINCDS ADRDA | Graphical results Joas et al graphs show rising SBP over time with a steeper rise and sharper fall in those who develop dementia. In those without antihypertensive treatment, those with and without later dementia have a similar trajectory although those with later dementia high a higher SBP over time and a sharper fall in late life. Those with antihypertensive treatment and later dementia start with lower SBP values, have a faster rise on SBP, a very much sharper fall in late life and an earlier onset of fall in BP ~69 rather than ~77 years. Numerical results:Difference in rate of change mmHg,For SBP and all dementia;1968-1992 0.19 (-0.01:0.38) P=0.061992-2000 -0.79 (-1.53:-0.04) P=0.04; >2000 -1.64 (-3.43:0.16) P=0.07For SBP and AD; 1968-1992 0.20 (-0.01:0.42) P=0.06 1992-2000 -1.16 (-1.96:-0.36) P<0.01; >2000 -2.03 (-3.60:-0.46)P=0.01 | Age, educat-ionCardio-vascular disease, diabetessmokingcho-lesterol, stress, stroke, BMI |

**Supplementary table e-2 Risk of bias blood pressure**

|  |  |  |  |
| --- | --- | --- | --- |
| Study name  | Exposure bias | Outcome bias | Follow up bias |
| Adult Changes in Thought study, Li et al 2007 | Moderate. BP taken by trained staff using a standard procedure. Participants were required to have at least 2 blood pressure recordings, and be treated with antihypertensive at least one visit but no information is provided on blood pressure variability across visits or on missing data. | Low. Standard assessment and diagnostic tools were used and assessment was at regular intervals. | Moderate. Not clear how many visits participants contributed or what impact attrition after short follow up may have had.  |
| Kungsholmen project. (Qiu et al 2009) | Moderate. BP taken by trained staff using a standard procedure.  | High. Standard diagnostic tool but included information collected from medical records and death certificates, i.e. diagnoses not systematically assessed.  | Moderate. Not clear how many participants were included in the graphs and how attrition may have impacted on the results. |
| East Boston Established Populations of Epidemiologic Studies of the Elderly (EPESE), (Morris et al 2001) | Moderate. Standard measures  | Low. AD assessed using standard diagnostic criteria. | Moderate. Not clear how data on the 288 with follow up at all four visits was analysed.  |
| Kungsholmen project. (Qiu et al 2004) | Moderate. BP taken by trained staff using a standard procedure.  | Low. Standard diagnostic tool and included only those with clinical exam | Moderate, not clear how many are in each analysis.  |
| The Honolulu Asia Aging Study (Stewart et al 2009) | Moderate. BP taken using a standard procedure. | Low. Used standard assessment and diagnostic criteria administered by trained staff | Moderate, role of attrition unclear, sample is 60% of original |
| Prospective population study of women in Gothenburg, Sweden (Joas et al 2012) | Moderate. BP taken using a standard procedure. | Low. Used standard assessment and diagnostic criteria administered by trained staff | Moderate, role of attrition unclear  |

**Supplementary table e-3 Risk of bias cholesterol**

|  |  |  |  |
| --- | --- | --- | --- |
| Study name  | Exposure bias | Outcome bias | Follow up bias |
| The Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE) cohort (Toro et al 2014) | Low. Some exclusion due to lack of genotyping (participant refusal) | Moderate. Standard criteria but only MCI and AD used as outcomes.  | Moderate. Discrepancy in reported cohort numbers.  |
| Honolulu Asia Aging Study (Stewart et al 2007) | Low. Some exclusion due to selection of only those who were dementia free at the 1991-3 visit.  | Low. Standard criteria. | Possible. No adjustment for attrition but did run sensitivity analyses to assess the impact of missing data finding no substantial differences.  |
| Prospective population study of women. (Mielke et al 2010) | Low. Unclear how many cholesterol values are available at each visit despite the inclusion of all participants in the analyses.  | Moderate. Standard criteria, however also included data from hospital records and death certificates which may be subject to bias.  | Low. Data was available for all participants due to use of hospital records and death certificates.  |

**Supplementary table e-4 Risk of bias body mass index**

|  |  |  |  |
| --- | --- | --- | --- |
| Study name  | Exposure bias | Outcome bias | Follow up bias |
| Honolulu Asia Aging Study (HAAS) (Stewart et al 2005) | Low. Used standard measures. | Low. Used standard diagnostic tools. | Moderate, presence of attrition but follow up long enough to detect incident dementia. Plus comparison of those who left compared to those who remain in the study was carried out.  |
| Indianapolis Dementia Project (Ibadan) (Gao et al 2011) | Low. Had multiple measures. The shorter cohort may be at risk of greater bias due to shorter follow up.  | Low. Used standard diagnostic tools. | Moderate, presence of attrition but follow up long enough to detect incident dementia.  |
| Prospective population study of women in Gothenburg (Gustafson et al 2012) | Low. Standard measures and protocol used.  | Low. Used standard diagnostic tools  | Low. Attrition was present but used models to account for missing data. |
| The Whitehall II Study. (Singh-Manoux et al 2018) | Moderate. Standard measures and protocol used at each clinic assessment, however, BMI per year estimated via modelling. | High, data from health databases and accuracy of date of dementia ascertainment uncertain. | Low. Used health records with universal coverage to assess outcome.  |

**Supplementary text e-1 Search strategy**

**Search terms**

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1999 to 26 April 2018

Search Strategy:

--------------------------------------------------------------------------------

1 (trajector\* or life-course or time course or life course or "follow up" or time factors).af.

2 (dementia or alzheimer\* or cognit\* or cognition disorders).af.

3 (blood pressure or BP or systolic or diastolic or sbp or dbp or pulse pressure).af.

4 1 and 2 and 3

5 limit 4 to english language

6 limit 5 to human

9 limit to adulthood <18+ years> [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher; records were retained] (869)

For cholesterol

(cholesterol or ldl or hdl or lipoprotein\* or triglyceride\*). af.

For Body Mass Index (BMI)

(obesity or "body mass index" or bmi or "waist hip ratio" or whr or "waist hip circumference" or whc or overweight or underweight).af.

Search strategy advice from Dr Andrew Booth, Reader in evidence based information practice and director of information. School of Health and Related Research. University of Sheffield , UK. Qualifications of searchers: Dr R Peters, BSc, MSc, PhD, Dr J Peters FFPHM, BTech, MPH, PhD.