BJPsych | The British Journal of Psychiatry (2020) 216, 16–28. doi: 10.1192/bjp.2019.156

Review

Trajectory of blood pressure, body mass index, cholesterol and incident dementia: systematic review

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Background

The global ageing population and the long prodromal period for the development of cognitive decline and dementia brings a need to understand the antecedents of both successful and impaired cognitive ageing. It is increasingly apparent that the trajectory of risk-factor change, as well as the level of the risk factor, may be associated with an increased or decreased risk of cognitive decline or dementia.

Aims

Our aim was to summarise the published evidence and to generate hypotheses related to risk-factor trajectories and risk of incident cognitive decline or dementia.

Method

We collated data from longitudinal observational studies relating to trajectory of blood pressure, obesity and cholesterol and later cognitive decline or dementia using standard systematic review methodology. The databases MEDLINE, Embase and PsycINFO were searched from inception to 26 April 2018.

Results

Thirteen articles were retained for inclusion. Analytical methods varied. Our summary of the current evidence base suggests that first body mass index and then blood pressure rises and then falls more steeply in those who go on to develop dementia. The evidence for cholesterol was less consistent.

Conclusion

Based on our review we present the hypothesis that weight falls around 10 years and blood pressure around 5 years before diagnosis. Confirmatory work is required. However, characterisation of risk according to combinations and patterns of risk factors may ultimately be integrated into the assessments used to identify those at risk of receiving a diagnosis of cognitive decline or dementia in late life.

Declaration of interest

None.

Keywords

Dementia; trajectories; blood pressure; obesity; cholesterol.

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Over recent years it has become clear that the diagnosis of clinical dementia occurs at the end of a prodromal period which extends over several decades. Furthermore, numerous lifestyle and clinical risk factors occurring during the adult life course can act to influence the risk of developing dementia in older age. Exposure to such risk factors may similarly occur over many decades.[1,2] A life-course perspective is essential.[3] The patterns of the risk factors change over the life course (e.g. increasing or decreasing exposure). Subclinical pathology may influence risk factors (directly or indirectly) over the life course, e.g. reduced homeostatic control mechanisms, loss of appetite and weight loss. Methodologically, the combined risk of mixed populations and shorter-term studies of older adults may bring confounding, e.g. those with recent weight loss or gain alongside those sustaining a stable weight.

To be able to stratify by risk and to target at-risk groups we need to understand the relationship between risk-factor levels (e.g. higher or lower blood pressure), their trajectory and change over the life course, from early and mid- to late life, and the risk of incident cognitive decline or dementia. An increasing number of studies have adopted this approach for three of the core risk factors: blood pressure, cholesterol and obesity. When present in midlife all three risk factors have been associated with an increased risk of late-life cognitive decline and dementia (see comprehensive reviews by Alzheimer's Disease International and the *Lancet*).[1,2] Data on exposure to high blood pressure, obesity and cholesterol in late life are more mixed.[1,2] This raises questions relating to the need to understand trajectories of exposure to risk factors over the life course, for these three risk factors in particular. To begin to generate hypotheses relating to the pattern of risk-factor trajectory change and risk of cognitive decline and dementia, we systematically review and summarise the existing longitudinal observational studies reporting on trajectories of change in blood pressure, cholesterol and obesity from midlife (~40 to ~65 years), and subsequent late-life cognitive decline or dementia.

Methods

To ensure a robust and thorough overview of the literature we used systematic review techniques to search, select, extract and evaluate data from the published literature.

The databases MEDLINE, Embase and PsycINFO were searched from inception to 26 April 2018. Details of the search strategies are given in Supplementary Text 1 available at https://doi.org/10.1192/bjp.2019.156. Reference lists were also screened for other published papers. There were two analysts (R.P. and J.P.). The lead analyst (R.P.) carried out the literature searches. All identified abstracts, or titles where abstracts were unavailable, were independently read by both analysts and a list of papers potentially meeting the inclusion criteria was compiled by each analyst. The lists were then compared and any differences resolved by discussion. Once a list of full-text publications was agreed these were also read and assessed for relevance independently by both analysts. Any differences were again resolved by discussion.

Inclusion criteria

The inclusion criteria were as follows:

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(a) longitudinal observational studies where the independent variable relating to one of the three risk factors (blood pressure, cholesterol and obesity) has been assessed in terms of trajectory or change over time;
(b) repeated risk-factor data from at least three different time points;
(c) follow-up longer than one year;
(d) some indication, or clear implication, that participants were free of cognitive decline or dementia at baseline assessment;
(e) use of formal assessment of cognitive function to report on cognitive change or cognitive decline; and/or
(f) report of incident dementia outcomes (from medical records or where studies used standard diagnostic criteria).

Exclusion criteria

The exclusion criteria were as follows:

(a) non-English publications (in the absence of resources available for translation);
(b) paediatric or teenage populations;
(c) use of single aggregate measures of exposure that allow no assessment of change (e.g. an average value derived from several visits).

Data analysis

Data from the relevant identified full-text articles were extracted onto a standard extraction sheet and included information on study design, participant sample size, age, proportion of sample who were female, mean follow-up or details of study visits, the number of visits used to examine the trajectory of the risk factor, methods of analysis, measure of risk factor, measure of outcome, covariates used and results. Where a single study had generated more than one publication reporting on trajectories, the most recent was selected unless the results were representing different end-points or different analyses in which case both were extracted for completeness.

To assess the quality of each paper in terms of its validity a formal scoring scheme was not used as these hold poor discriminant ability when assessing quality. Instead, each paper was assessed against the key questions adapted from the Critical Appraisal Skills Programme cohort checklist (https://casp-uk.net/casp-tools-checklists/) and, in particular, included assessment of bias in evaluation of exposure, outcome assessment and follow-up and the results of this assessment were tabulated. Data are presented in extraction tables. The study characteristics and results presented in the tables are standardised as much as possible given their varied representation in the source publications. We included articles where no specific trajectory-based analysis was described but where articles described graphical or numerical analyses that provide potential description of trajectories relating to dependent cognitive variables. In the absence of data allowing meta-analysis, narrative synthesis and an illustrative figure has been used to summarise the results. The search strategy, assessment of bias and other review methods were defined *a priori* and the protocol was registered with PROSPERO: CRD42018091350. This work used published data therefore ethical approval was not required.

Results

Identification of eligible studies

Blood pressure

Searches identified 1672 unique records, of which 52 were assessed at the full-text stage and 6 publications (5 studies) were retained (see the flow chart in Supplementary Fig. 1). Exclusion at this stage was because of the potential for the inclusion of prevalent cases ($n = 2$), a lack of data on trajectory of blood pressure and cognitive outcomes ($n = 42$) and a lack of appropriate cognitive measures ($n = 2$).

Cholesterol

Searches identified 1988 unique records, of which 20 were assessed at the full-text stage and 3 publications (3 studies) were retained (see the flow chart in Supplementary Fig. 2). Exclusion at this stage was because of the potential for the inclusion of prevalent cases ($n = 3$) and a lack of data on trajectory of cholesterol and cognitive outcomes ($n = 14$).

Obesity

Searches identified 4880 unique records, of which 35 were assessed at the full-text stage and 4 publications (4 studies) were retained (see the flow chart in Supplementary Fig. 3). Exclusion at this stage was because of the potential for the inclusion of prevalent cases ($n = 1$) and a lack of data on trajectory of obesity and cognitive outcomes ($n = 30$). To allow comparable reporting across studies, body mass index (BMI) was selected as representing the most commonly reported measure of obesity.

Characteristics of the included studies

For the full study characteristics, see Table 1.

Blood pressure

Studies were recruited from North American, Japanese American and European populations.[4–9] Two studies began in midlife,[4,9] the remainder began in later life.[5–8] Follow-up ranged from approximately 6 years[5–7] to over 30 years.[4,9]

Cholesterol

Studies were recruited from Japanese American and European populations.[10–12] Two studies began in midlife[10,11] and one in later life.[12] Follow-up ranged from approximately 10 years[12] to approximately 30 years.[10,11]

Obesity

Studies were recruited from North American, Japanese American and European populations.[13–16] Three studies began in midlife[14–16] and one in later life.[13] Follow-up ranged from approximately 6 years[13] to approximately 25–30 years.[14–16]

Trajectories of risk factors and cognitive and/or dementia outcomes

In the absence of suitable data for meta-analysis, narrative synthesis is used to describe the overall results. In general, studies found that the levels of each risk factor rose with increasing age up to late midlife, for cholesterol, and to early/mid-late life for BMI and blood pressure, after which levels fell. For blood pressure and BMI, those who went on to develop dementia or cognitive decline generally showed higher baseline levels of each risk factor, a steeper rise and faster fall. The data were less specific for cholesterol. Figure 1 is an illustrative drawing to represent the general trajectories for each risk factor.

Blood pressure

Table 2 gives the results for blood pressure as the independent variable. Four studies reported on incident all-cause dementia: the Kungsholmen Project, the Honolulu-Asia Aging Study (HAAS),

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

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Table 1 Study characteristics

Risk factor	Study name	Analytical sample, *n*	Age at baseline, mean (s.d.), unless otherwise specified	% female	FU length where available; in years, mean (s.d.), unless otherwise specified	Number and timing of visits
BP	Adult Changes in Thought study[5]	2342	74.4 (6.0) (normal BP) 75.2 (5.8) (borderline BP) 76.5 (6.2) (high BP)	55.9% (normal SBP) 59.6% (borderline SBP) 67.4% (high SBP)	Not available	Biennial visits Data included from final visit and visits 2, 4 and 6 years prior to final visit
	Kungsholmen project[8]	422	In those who developed incident dementia: 86.2 (4) In those without incident dementia: 86.1 (3.8)	In those who developed incident dementia: 83.1% In those without incident dementia: 76.0%	9 years (s.d. 1 year) (range 6.3–10.5) (Mean 2.3 years (0.9) between time 3 and time 4)	Visits were in: 1987/9 (time 1), 1991/3 (time 2), 1994/6 (time 3), 1997/8 (time 4))
	EPESE[6]	634 had baseline BP 426 had 6-year FU 288 had BP at all 4 time points	For the baseline sample at the time of first evaluation for AD In those with SBP < 130: 70.8 In those with SBP ≥160: ≥73.7	For the baseline sample In those with SBP < 130: 64.8% In those with SBP 130–139: 65.7% In those with SBP 140–150: 64.8% In those with SBP 150–159: 54.0% In those with SBP ≥160: 64.4%	>6 years	First assessment for AD (1982/3). FU visits at ~3 years (1985/6) ~6 years (1988)
	Kungsholmen project[7]	947	Those without dementia at FU: 80.1 (4.4) Those who developed dementia over times 1–2 (~3 years): 82.9 (4.9) Those who developed dementia over times 2–3 (~3 years): 81.9 (4.0)	Those without dementia at FU: 74.5% Those who developed dementia over times 1–2: 86% Those who developed dementia over times 2–3: 77.1%	First FU: 3.5 (1.7:5.2) years Second FU: 3.0 (0.1:4.8) years	Visits were in: 1987/9 (time 1), 1991/3 (time 2), 1994/6 (time 3)
	HAAS[9]	1890	83 (3.8) at FU	0%	Estimated maximum FU: ~32 years	Visits were in: 1965/8, 1967–70, 1971/4, 1991/3, 1994/6, 1997/9
	Prospective population study of women in Gothenburg, Sweden[4]	707	45	100%	Estimated: 32–37 years	Visits were in: 1968/9, 1974/5, 1980/1, 1992/3, 2000/1, 2005/6
Cholesterol	ILSE cohort[12]	222	Control: 74.0 (1.0) Those who developed MCI: 74.3 (1.1) Those who developed AD: 74.8 (1.0)	Controls: 47.5, Those who developed MCI: 47.6 Those who developed AD: 40.9	Estimated maximum FU: ~22 years	Visits were in: 1993–5, 1997–2000, 2005–8
	HAAS[11]	1027	80.2 (4.2) at FU in 1994–6	0	Estimated maximum FU: ~29 years	Visits were in: 1965–8, 1970–2, 1971–4, 1980–2, 1991–3 and dementia assessment in 1994–6
	Prospective population study of women[10]	1462	Cohorts recruited aged 60, 54, 50, 46, 38 at baseline	100	Estimated maximum FU: ~32 years	Visits were in: 1968–9, 1974–5, 1980–1, 1992–3, 2000–1

(*Continued*)

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

Table 1 (*Continued*)

Risk factor	Study name	Analytical sample, *n*	Age at baseline, mean (s.d.), unless otherwise specified	% female	FU length where available; in years, mean (s.d.), unless otherwise specified	Number and timing of visits
BMI	HAAS[16]	1890	At baseline 46–68, 83 (3.8) at FU	0	Estimated maximum FU: ~22 years	Exam 1: 1965–1968, Exam 6: 1997–1999
	Indianapolis Dementia Project (Ibadan)[13]	1331	In those who developed dementia: 84 (7) years In those who developed MCI: 83.4 (6) years In those who developed neither: 82 (5) years	In those who developed dementia: 72% In those who developed MCI: 63% In those who developed neither: 73%	Mean FU In those who developed dementia: 6.1 years In those who developed MCI: 6.2 years In those who developed neither: 6.5 years	~ every 3 years Two cohorts The first had visits in 1992, 1995, 1998, 2001, 2004 and 2007 The second had visits in 2001, 2004 and 2007
	Prospective population study of women in Gothenburg[14]	531	5 cohorts from 1908 (60 years), 1914 (54 years), 1918 (50 years), 1922 (46 years), 1930 (38 years)	100	Estimated maximum FU: ~37 years	Not available
	The Whitehall II Study[15]	2303	In those who developed dementia: 50.5 (4.5) In those that did not develop dementia: 49.2 (4.9) years	In those who developed dementia: 43.8% In those that did not develop dementia: 43.8%	In those who developed dementia: 24.5 (3.5) years In those that did not develop dementia: 28.6 (1.1) years	Not available

AD, Alzheimer's disease; BMI, body mass index; BP, blood pressure in millimetres of mercury (mmHg); EPESE, East Boston Established Populations of Epidemiologic Studies of the Elderly; FU, follow up; HAAS, Honolulu Asia Aging Study; ILSE, Interdisciplinary Longitudinal Study on Adult Development and Aging; MCI, mild cognitive impairment; s.d., standard deviation; SBP, systolic blood pressure.

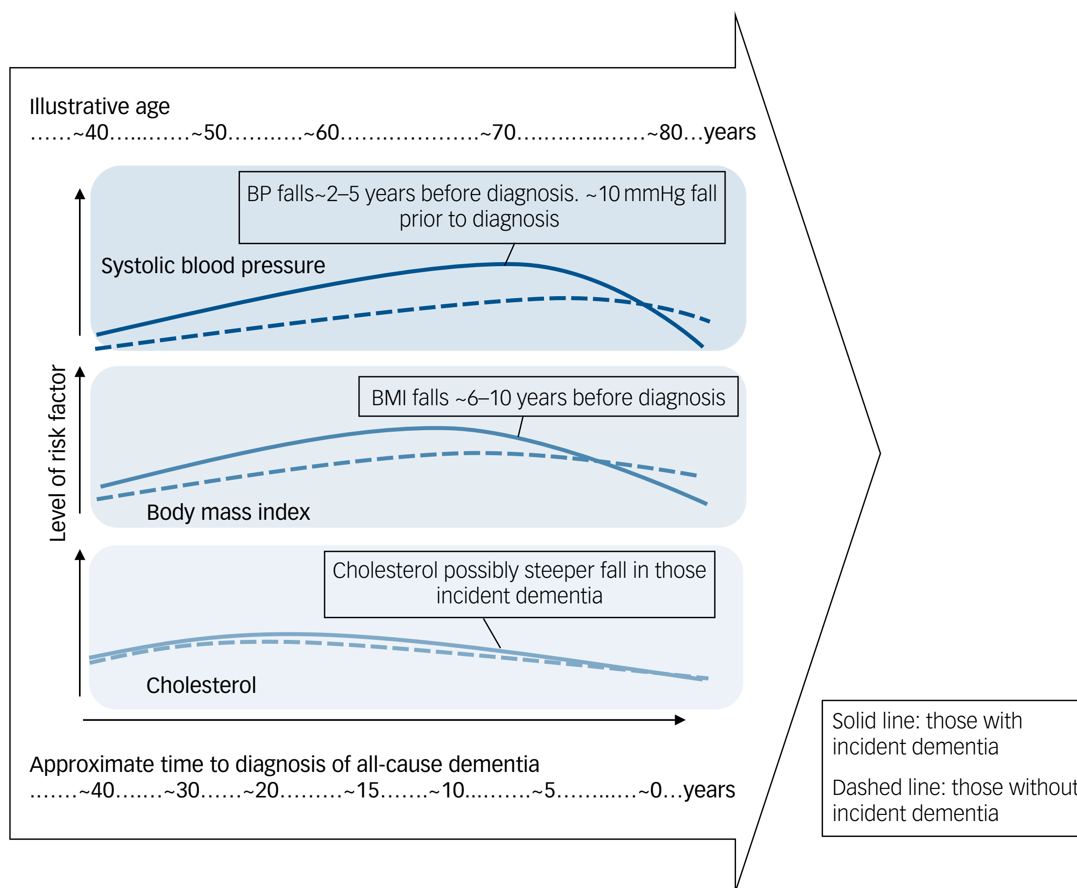


Fig. 1 Illustrative representation of trajectories.

BP, blood pressure; BMI, body mass index.

the Prospective Population Study of Women in Gothenburg (PPSW) and the Adult Changes in Thought (ACT) study.[4,5,7–9] Data from the Kungsholmen Project in Sweden were reported in two publications from 2004 and 2009, with the latter reporting longer follow-up. The Kungsholmen analyses consistently showed steeper blood pressure fall in those that went on to develop all-cause dementia in the 2–3 years before diagnosis, with a similar pattern for both systolic and diastolic pressure.[5,8] The HAAS reported a steeper rise in systolic blood pressure with age followed by a steeper fall after ~78 years in those who went on to develop dementia.[9] Patterns for diastolic pressure were similar but less strong.[9] The PPSW study showed a similar pattern overall but also found that those taking antihypertensive treatment had a steeper rise in systolic blood pressure with a sharper and earlier fall (~69 rather than ~77 years) compared with those without treatment.[4] The ACT study found that participants aged <75 who went on to develop dementia had higher systolic blood pressure and that this fell more sharply in the final 2 years before diagnosis, when compared with those without all-cause dementia. For those aged 75 or older, there was no blood pressure difference between those who did or did not develop dementia.[5]

Three studies reported results for incident Alzheimer's disease: HAAS,[9] PPSW[4] and the East Boston Established Populations of Epidemiologic Studies of the Elderly (EPESE).[6] The HAAS found a sharper fall in those who went on to develop all-cause and vascular dementia, with the strongest relationship occurring for Alzheimer's disease and vascular dementia.[9] The PPSW reported a similar pattern for Alzheimer's disease to that seen in all-cause dementia;[4] in contrast, the EPESE study found no relationship between blood pressure trajectory and incident Alzheimer's disease.[6]

Cholesterol

Table 3 gives the results for cholesterol as the independent variable. Two studies reported on incident all-cause dementia: the HAAS and the PPSW.[10,11] The HAAS also reported on Alzheimer's disease and vascular dementia. One study, the Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE), reported on Alzheimer's disease and mild cognitive impairment (MCI).[12] The PPSW and ILSE both reported cholesterol levels as rising and then falling from mid- to late life, with slightly higher baseline cholesterol levels and slightly steeper falls in the group who went on to develop dementia, Alzheimer's disease and MCI, with the highest values occurring around age 60. The HAAS, in contrast, reported total cholesterol as consistently lower in those men who went on to develop dementia;[11] however, their graphical representation suggests the possibility of a steeper fall in those who developed all-cause dementia with a similar pattern for Alzheimer's disease and vascular dementia.[11] They conclude that cholesterol levels declined at least 15 years before diagnosis.

Obesity (BMI)

Table 4 gives the results for BMI as the independent variable. Four studies reported incident dementia: the HAAS, PPSW, the Indianapolis-Ibadan Dementia Project (Ibadan) and the Whitehall II Study.[13–16] Stewart *et al* (HAAS) also reported on Alzheimer's

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

Table 2 Study results for blood pressure

Study name	Number of visits	Methods of analysis	Overall result
Adult Changes in Thought study[5]	5 for the graph 4 for numerical analysis	Logistic regression evaluated the impact of BP on incident dementia at 2, 4 and 6 years prior to final visit; 3 groups (65-74, 75-84, ≥85 years). Also plotted mean SBP by age and dementia status at each year of FU.	Graphical results The 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 SBP fell more sharply in this group over the final 2 years. In the ≥75s SBP fell in both groups and there was no obvious difference in SBP level. Numerical results: For all-cause dementia *At final visit*: 65–74 years, <140 mmHg, reference 1.0; 65–74 years, 140–159 mmHg, OR 0.98, 95% CI (0.56–1.72); 65–74 years, ≥160 mmHg, OR 2.42 (1.33–4.40); ≥75 years, <140 mmHg, reference 1.0; ≥75 years, 140–159 mmHg, OR 1.22 (0.84–1.79); ≥75 years, ≥160 mmHg, OR 0.92 (0.56–1.52) *2 and 4 years before final visit*: see Supplementary Table 1[a] *6 years before final visit*: 65–74 years, <140 mmHg, reference 1.0; 65–74 years, 140–159 mmHg, OR 0.91 (0.48–1.73); 65–74 years, ≥160 mmHg, OR 1.33 (0.69–2.57); ≥75 years, <140 mmHg, reference 1.0; ≥75 years, 140–159 mmHg, OR 1.12 (0.69–1.82); ≥75 years ≥160 mmHg, OR 1.15 (0.67:1.95)
Kungsholmen project[8,a]	3	N/A – graphical representation only	Graphical results *All-cause dementia:* the Qiu *et al* graph suggests a rise in SBP between time 1 and time 2 (~5 mmHg). From times 2–3, SBP falls and the fall appears to be steeper in the group who go on to receive a diagnosis of dementia. From times 3–4, the group without dementia show no change to mean SBP but the group developing dementia show a steep fall in mean SBP (~10 mmHg). *DBP:* see Supplementary Table 1[a]
Kungsholmen project[7,a]	3	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	Numerical results *Linear mixed models*: SBP and DBP fell prior to dementia diagnosis. No participants had a diagnosis of dementia at baseline. *SBP*: see Supplementary Table 1[a] *DBP*: see Supplementary Table 1[a] Results provided for BP and AD over 2 visits only.
EPESE[6]	3	Graphical representation of BP trajectory split by those with and without incident AD	Graphical results Age and sex adjusted mean BP levels were plotted for visits from 1973 to 1988 with AD diagnosis made in 1986. After adjustment for age there was no difference in BP by incident AD/no incident AD over more than 15 years of observation. Data from three 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.
HAAS[9]	6	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 dementia × time as independent variables; plotted BP over time for those with incident dementia (VaD and AD) and no dementia	Graphical results The graphs show SBP rising faster and falling more sharply in late-life BP in the group developing dementia (all-cause dementia and AD). For VaD those who developed dementia show a higher SBP, a steeper rise with age and a steeper fall in late life than those without dementia. DBP shows similar pattern but with general fall rather than rise in pressure with ageing. Numerical results *Additional 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 to −0.32) *Additional change in rate of change in DBP associated with all dementia mmHg/year*: see Supplementary Table 1[a] *Additional change in rate of change in SBP associated with AD mmHg/year and DBP with AD and DBP with VaD and SBP with VaD mmHg/year:* see Supplementary Table 1[a]

(*Continued*)

Table 2 (*Continued*)

Study name	Number of visits	Methods of analysis	Overall result
Prospective population study of women in Gothenburg, Sweden[4]	6	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 dementia × time as independent variables; plotted BP over time for those with incident dementia (VaD and AD) and no dementia	Graphical results 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 in 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) *SBP and all dementia:* 1968–1992, 0.19 (−0.01–0.38), $P = 0.06$; 1992–2000, −0.79 (−1.53 to —0.04) $P = 0.04$; after 2000, −1.64 (−3.43–0.16) $P = 0.07$ *SBP and AD*: see Supplementary Table 1[a]

AD, Alzheimer's disease; BP, blood pressure in millimetres of mercury (mmHg); DBP, diastolic blood pressure; EPESE, East Boston Established Populations of Epi-demiologic Studies of the Elderly; HAAS, Honolulu Asia Ageing Study; OR, odds ratio; SBP, systolic blood pressure; VaD, vascular dementia; CI, confidence interval.
a. Qiu *et al*, 2004 and Qiu *et al*, 2009 both report on data from the Kungsholmen longitudinal study. As Qiu *et al*, 2004 reports numerical results and Qiu *et al*, 2009 reports graphical results, both are represented in this table.
a. For the full version of this table, see Supplementary Table 1.

disease and vascular dementia[16] and Gao *et al* (Ibadan) on incident MCI.[13] The Ibadan study and Whitehall studies found steeper declines in BMI in those that went on to develop dementia. For the Ibadan study the decline started around 10 years before diagnosis and became statistically significant by 6 years, whereas for the Whitehall II study the decline started approximately 8 years before diagnosis.[13,15] Similar patterns were seen in the Ibadan study for MCI. In the HAAS, Japanese American men with incident dementia also had a higher midlife BMI and a sharper fall in late life than those who did not develop dementia. This was particularly pronounced for vascular dementia but less clear for Alzheimer's disease.[16] Swedish women also showed a similarly greater increase in BMI from mid- to late life and sharper fall in those who developed dementia, with age 70 selected as the pivotal point.[14]

Risk of bias

Overall the risk of bias in the included studies was low to moderate and most studies recruited from population samples and assessed all risk-factor exposures, using standard measurement methods. Outcome measures were also based on standard criteria with a generally low risk of bias although the criteria used for identification of all-cause dementia, Alzheimer's disease, vascular dementia and MCI varied. Studies reported follow-up times of sufficient length to assess incident dementia. However, in some cases it was unclear how many visits each participant had contributed and how many participants were included in each analysis or within the graphical representation of the trajectories analysis. For details of the risk of bias assessment, see Supplementary Tables 2–4. As in any review, sources of bias may be associated with variation in study design, together with visit frequency and choice of analysis methods. To reduce the potential risk of bias incurred by the selection of studies with a minimum of three time points, a sensitivity analysis was carried out to examine the results of similar longitudinal studies reporting only two time points for the assessment of trajectory. All abstracts were re-reviewed and a further 16 articles extracted. No clear pattern was seen in the studies using only two time points. There was also no indication that excluding these articles could have contributed to bias in our results.

Discussion

Several well-established longitudinal studies have reported on the relationships between the trajectory of change over time in levels of blood pressure, cholesterol and obesity (assessed using BMI) and incident all-cause dementia, with some additionally reporting on Alzheimer's disease, vascular dementia and MCI. The pattern of results from the studies is similar, with those who went on to develop all-cause dementia showing a greater increase followed by a sharper decrease in blood pressure and/or BMI before a positive diagnosis. The pattern for cholesterol was less clear but still suggested a fall in cholesterol level in later life that may be greater in those who developed dementia.

The results for Alzheimer's disease, vascular dementia and MCI were similar but with fewer data points.

The results are congruent with emerging literature showing an association between steeper falls in blood pressure in late life and increased risk of infarcts[17] and an established literature showing associations for low blood pressure and low weight in older age with an increased risk of dementia or cognitive decline.[18–20] It also suggests that these at-risk individuals are those who had higher blood pressure, weight and higher cholesterol in midlife and that it is the trajectory of change rather than the current blood pressure or weight that is potentially most useful in

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

Table 3 Study results for cholesterol

Study name	Trajectory measured over how many visits?	Cholesterol baseline where available, mean (s.d.)	Methods of analysis	Dependent variables	Methods of cognitive assessment	Overall result	Covariates
The Interdisciplinary Longitudinal Study on Adult Development and Aging cohort[12]	3	Controls: 233 (38) mg/dL; MCI: 247 (43.8) mg/dL; Alzheimer's disease: 246.1 (40.7) mgd/L	ANOVA, with repeated measures for time comparing diagnostic groups	Alzheimer's disease and mild cognitive impairment	MCI diagnosed according to the Ageing-Associated Cognitive Decline criteria, Alzheimer's disease diagnosed using NINCDS-ADRDA and vascular dementia using NINDS-AIREN	Numerical results; TC declined in follow-up in those diagnosed with Alzheimer's disease and MCI, Units given below are mean (s.d.) mg/dL. For controls: Time 0: 233 (38), Time 1: 232.6 (36.2), Time 2: 228.4 (38.9). For MCI: Time 0: 247 (43.8), Time 1: 242.9 (37.5), Time 2: 221.3 (42.8). For Alzheimer's disease: Time 0: 246.1 (40.7), Time 1: 242.8 (37.4), Time 3: 219.5 (47.1). ANOVA effect of time $P < 0.0001$, interaction diagnosis × time $P < 0.005$, diagnosis alone $P = 0.4$.	Not clear
Honolulu Asia Aging Study[11]	5 (TC measured in 1965–8, 1970–2, 1971–4, 1980–2, 1991–3; visits in 1970–2 and 1971–4 were merged for analyses)	229 (41) mg/dL	Individual trajectories of change in TC levels estimated from linear random effects models; included dementia, time, time × time and time × time × time to examine nonlinear relationships	All-cause dementia, Alzheimer's disease, vascular dementia	Dementia diagnosed using DSM-III-R (1980), Alzheimer's disease using NINCDS-ADRDA	Graphical results: graph shows steeper decline in cholesterol in those who develop all-cause dementia, Alzheimer's disease and vascular dementia. Numerical results: in those who developed dementia, TC was lower at all previous time points. (Additional analyses of change in cholesterol before dementia incidence as the dependent variable showed statistically significant relationships between dementia × time, stronger relationships between dementia × [time × time] and even stronger relationships between dementia × [time × time × time] and cholesterol level).	Age, education, blood pressure, weight, heart disease, stroke, diabetes, physical impairment, depression, lipid lowering drugs

(*Continued*)

Table 3 (*Continued*)

Study name	Trajectory measured over how many visits?	Cholesterol baseline where available, mean (s.d.)	Methods of analysis	Dependent variables	Methods of cognitive assessment	Overall result	Covariates
Prospective Population Study of Women[10]	5	Controls: 6.8 (1.1) mmol/L; dementia: 7.2 (1.0) mmol/L	Cox proportional hazards regression with quartile of change in cholesterol as a time-dependent variable at each examination	All-cause dementia and Alzheimer's disease	Dementia diagnosed using DSM-III-R, Alzheimer's disease using NINCDS-ADRDA plus captured diagnoses from hospital records and death certificates where participants had died or refused follow-up	Numerical results: units given below are mean (s.d.) g/dL. Cholesterol in those who developed dementia: 1968: 7.2 (1.0), 1974: 7.2 (1.2), 1980: 7.3 (1.2), 1992: 6.4(1.2), 2000: 6.2 (1.3). For those without dementia: 1968: 6.8 (1.1), 1974: 6.9 (1.2), 1980: 7.0 (1.2), 1992: 6.3 (1.0), 2000: 6.1 (1.0). A time-dependent decrease in cholesterol over follow-up was associated with an increased risk of dementia. Quartiles of change include one increasing cholesterol quartile, one decreasing cholesterol quartile and two middle reference quartiles. For dementia: increasing quartile: HR 1.3, 95% CI 0.48–2.69; decreasing quartile: HR 2.37, 95% CI 1.22–4.58. For Alzheimer's disease: increasing quartile: HR 1.73, 95% CI 0.71–4.20; decreasing quartile: HR 1.03, 95% CI 0.35–3.04.	Age cohort, education, diastolic blood pressure as a time-dependent variable, BMI, smoking

MCI, mild cognitive impairment; ANOVA, analysis of variance; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; NINDS-AIREN, National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences; TC, total cholesterol; HR, hazard ratio; BMI, body mass index.

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

Table 4 Study results for body mass index

Study name	Trajectory measured over how many visits?	BMI baseline (s.d.)	Methods of analysis	Dependent variables	Methods of cognitive assessment	Overall result	Covariates
Honolulu Asia Aging Study[16]	6	23.9 (2.7)	Random effects model with weight as the dependent variable, dementia and dementia × time as independent variables	All-cause dementia, Alzheimer's disease, vascular dementia	Dementia diagnosed using DSM-III-R, Alzheimer's disease using NINCDS-ADRDA	Graphical results:[16] those with incident dementia had higher midlife (exams 1–3) BMI than those who did not develop dementia, and lower and faster falling BMI in late life (exams 4–6). Numerical results: results of statistical models are given for exams 1–4 (mid- to late life); and exam 4–5 (late life). All-cause dementia: beta 0.04, 95% CI −0.06 to 0.14; and beta −0.35, 95% CI −0.52 to −0.18. Alzheimer's disease: beta −0.01, 95% CI −0.13 to 0.10; and beta −0.30, 95% CI −0.52 to −0.08. Vascular dementia: beta 0.27, 95% CI 0.05 to 0.50; and beta −0.60, 95% CI −1.07 to −0.13.	Age, education, vascular factors, depression, impaired physical function
Indianapolis-Ibadan Dementia Project[13]	Not clear	29.8 (5.7) for women, 28.3 (4.8) for men	Mixed effect models with random intercept and random slope for time run in those who developed incident dementia, those who developed incident MCI and those who developed neither	All-cause dementia and MCI	Community screening instrument for dementia. Detailed assessment included neuropsychological battery and diagnosis by expert consensus using DSM-III (1980) for dementia and criteria comparable to those advocated by the Mayo clinic for MCI	Graphical results:[13] steeper decline in those who developed dementia/MCI compared with those who did not; however, mean values for all groups declined over time. Graphically, decline appears to start around 10 years before diagnosis, however, it was not statistically significant at 12 or 9 years prior. By 6 years before diagnosis, those with dementia had a statistically significantly lower BMI ($P = 0.03$). For MCI: a similar pattern ($P = 0.006$). Differences more pronounced closest to diagnosis. No effect of baseline BMI although there were no underweight participants in the study at baseline.	Age, gender, smoking

(*Continued*)

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press

Table 4 (*Continued*)

Study name	Trajectory measured over how many visits?	BMI baseline (s.d.)	Methods of analysis	Dependent variables	Methods of cognitive assessment	Overall result	Covariates
Prospective Population Study of Women in Gothenburg[14]	6	In those who developed dementia, 24.1 (3.7); in those who did not develop dementia 24.1 (3.8)	Mixed model regression with linear splines, with knot at 70 years	All-cause dementia	Dementia diagnosed with DSM III-R	Graphical results:[14] increase in BMI for both groups until 70 years, then it falls. Those who went on to develop dementia had greater increase in BMI until 70 years. Numerical results: multivariate adjusted mixed model with a knot at 70 years. Dementia: follow-up at 70 years: beta −0.045, 95% CI −0.068 to −0.022; for follow-up after 70 years: beta −0.002, 95% CI −0.054 to 0.050.	Age at menopause, cardiovascular disease, diabetes, smoking, systolic blood pressure, triglycerides, cancer, glucose, cholesterol, socioeconomic status and education
The Whitehall II Study[15]	6	At 50 years in those who developed dementia 26.1 (4.2) and 25.2 (3.6) in those that did not go on to develop dementia. The corresponding values at age 60 were 26.4 (4.4) and 26.1 (4.1) and at age 70, 26.3 (4.6) and 26.7 (4.4)	Case control. Modelled backwards from the year of dementia, death or March 31 2015. BMI in each of the preceding 28 years (0 to −28) was estimated from mixed effects models with the intercept and slope as random effects and a backwards timescale. Dementia and its interaction with time and time × time were added to the model to test for differences in BMI trajectories between cases and controls	All-cause dementia	Comprehensive tracing of health records using the Mental Health Services data set, the national mortality register and the national hospital episode statistics database	Numerical results: in those that developed dementia, BMI was higher in midlife and showed accelerated decline in years before dementia. BMI was significantly higher in cases from year −28 ($P = 0.001$) to year −16 ($P = 0.05$), starting from year −8. BMI was lower in cases than controls. Similar pattern when comparing cases ($n = 329$) to matched controls ($n = 1974$) or to all others in the cohort ($n = 329 + 9979$)	Age, gender, education and their interactions with time and time × time and 5 year birth cohort

BMI, body mass index; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; MCI, mild cognitive impairment.

identifying those who are more likely to receive a subsequent diagnosis of cognitive decline or dementia. Causality is less clear. Although raised blood pressure, BMI and cholesterol have been associated with an increased risk of later dementia,[2] we cannot infer any causal relationships between risk-factor trajectories and dementia. In fact, the reverse may be the case since dementia is known to have a decades-long prodromal period. Dementia pathology, particularly Alzheimer's disease pathology, has been observed 20 years before diagnosis.[21] A further possibility is that some as-yet-unmeasured factor may have a causal relationship with both risk-factor change and dementia pathology. Such pathology may have a direct impact on regulation of biomarkers like blood pressure but may also have indirect effects, for example behaviour change may occur around 15–20 years before diagnosis, with increasing apathy and changes in social engagement, smell, appetite and an increased need for caregiving and support with medical and lifestyle factors as the disease progresses.[22] This in turn may also be associated with weight loss and fall in blood pressure.[22]

Our review has several strengths: it is the first such review to take a life-course approach and to collate longitudinal observational studies reporting on trajectories of exposure to risk factors. In doing so it may allow us to more confidently identify populations in the prodromal stages of developing dementia and to plan future studies to examine the impact of potential interventions. The lack of a detailed knowledge of risk-factor behaviour over the life course not only hampers our ability to develop targeted clinical and public health guidelines and interventions but also limits our ability to contextualise reports of changing dementia prevalence.[23] Furthermore, it restricts our ability to make the necessary healthcare, economic and societal predictions for future burden of disease. This review has advanced our knowledge and understanding of available evidence in this area.

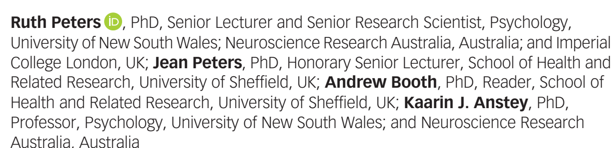
Limitations inevitably include the limited quantity and quality of included studies, the inevitable variation in study populations, length of follow-up, risk of attrition, the use of varied statistical techniques in the published articles precluding meta-analysis, the varied reporting of study results and the lack of granular or detailed data allowing a more sophisticated understanding of exposure to risk-factor trajectories. In particular, a lack of comparable cognitive testing across studies with different frequencies of assessment and the use of generic screening instruments rather than sophisticated neuropsychological batteries may mean that the identification and classification of cognitive decline or dementia may differ. This may have resulted in similarly labelled groups exhibiting more or less severe decline than others, further reducing our ability to compare risk-factor trajectories before diagnosis. Furthermore, due to less data on specific dementia types and the likelihood of mixed pathology in the majority of individuals with later-onset dementia, we are unable to unpick the relative contributions that different pathology types might make to risk-factor trajectory or to the relationship between trajectory and cognition. The evidence in this area could also be further strengthened by the evaluation of trajectories in other long-term longitudinal observational studies and exploration of populations by subgroups such as gender, ethnic group or presence of *APOE E4*.[24,25]

These data suggest that BMI falls first, around 10 years prior to diagnosis of dementia, followed by blood pressure which falls around 5 years prior. Future analyses should examine sequential and simultaneous changes in multiple risk-factor trajectories from mid to late life and how this relates to long-term risk of dementia. An understanding of the patterns and trajectories of change in those who do and do not develop dementia will add to our understanding of the role of risk factors across the life course and may facilitate early identification of those most at risk, particularly where repeated measures are common, for example, in general practice. Characterisation of risk of dementia according to combinations and patterns of risk factors may ultimately be required as part of a battery of assessments to identify those at increased risk of dementia in late life.

Current issues, opportunities and implications for research

The global ageing population brings an associated need to understand the antecedents of successful ageing. An understanding of the life-course trajectory for factors that influence cognitive ageing is needed, not least to support the identification and testing of potential interventions that may reduce risk and/or ways to promote healthy brain ageing. It may also go some way towards disentangling the varied associations reported for risk-factor exposure and cognitive function in later life. For example, where some studies report associations between high and some between low blood pressure and cognitive impairment in later life.[19]

Fully exploring this area requires sophisticated analysis with a minimum of three, but preferably more, repeated measures over follow-up from mid- to late life. Although the current evidence base is limited, the many multi-visit repeated measures longitudinal cohort studies in existence mean that there remains considerable potential for further exploration and evaluation. In examining the patterns and trajectories of the established risk factors for cognitive decline and dementia, this review provides the first overview of an emerging area. By necessity, the review takes a focus on three risk factors, however future work could feasibly include greater numbers of risk factors and the interaction between them and may eventually lead to personalised risk assessments and targeted interventions early in the asymptomatic, prodromal phase of cognitive decline and dementia.



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First received 26 Dec 2018, final revision 9 May 2019, accepted 24 May 2019

Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2019.156.

Funding

No funding was received directly for this work. All authors receive funding from various sources. R.P. was funded by the Australian National Health and Medical Research Council (NHMRC) National Institute for Dementia Research, Dementia Collaborative Research Centre at the time the work took place. K.J.A. is funded by NHMRC fellowship 1102694. We acknowledge support from the NHMRC Centre of Excellence in Cognitive Health and the Australian Research Council Centre of Excellence in Population Ageing.

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100 words

100 words on positive reward prediction error

Pavan Mallikarjun

Reward prediction errors are involved in the most basic form of error-driven reinforcement learning that is based on reward outcome. Reward prediction errors occur when there is a difference between predicted and received rewards. In positive prediction error, the received reward exceeds the anticipated reward, whereas in negative prediction error, the received reward is less than the predicted reward. Positive prediction errors are signalled by a phasic increase in dopamine activity in the midbrain neurons that is suggested to code the economic utility of the rewards. The striatum, amygdala and frontal cortex are also involved in mediating positive prediction errors.

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The British Journal of Psychiatry (2020) 216, 28. doi: 10.1192/bjp.2019.236

https://doi.org/10.1192/bjp.2019.156 Published online by Cambridge University Press