Blood pressure change and cognition in childhood and early adulthood: a systematic review

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Abstract

Introduction: High blood pressure in midlife is an established risk factor for cognitive decline and dementia but less is known about the impact of raised blood pressure on cognition in childhood and early adulthood.

Method: We systematically reviewed and quantified the existing evidence base relating to blood pressure in early life and subsequent cognitive performance. Medline, Embase, PsycINFOo, Scopus, and Web of Science were searched from inception to July 2020. We included longitudinal cohort and case–control studies involving participants aged 0–40 years with a baseline and at least one follow-up blood pressure assessment alongside at least one measure of cognition, occurring at the same time as, or subsequent to blood pressure measures. Risk of bias was assessed independently by two reviewers. PROSPERO registration CRD42020214655.

Results: Of a total of 5638 records identified, three cohort and two case–control studies were included with ages ranging from 3 to early 30s. Repeated blood pressure measurements averaged over 25 years or cumulative blood pressure in the 25–30 years prior to assessment of cognitive function were associated with poorer cognitive performance in the two largest cohort studies. The smallest cohort study reported no evidence of an association and the results from the two case–control studies were contradictory. All studies were at risk of bias.

Conclusion: Overall, the evidence in this area is lacking and study quality is mixed. Our review highlights an urgent need for studies evaluating the potential for a relationship between raised blood pressure and poorer cognition in early life given the potential for possible risk reduction if such a relationship exists.

Keywords: cognition, dementia, early life, high blood pressure, hypertension

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Introduction

Over the last 40–50 years, a large literature has developed linking raised blood pressure to an increased risk of cognitive decline or dementia in later life. Leading examples of early work include data from Sweden showing those who developed dementia at age 79–85 had higher systolic and diastolic pressures at age 70[1] and from the Honolulu Asia Aging Study where systolic pressures of greater than 139 mmHg and or diastolic pressures over 89 mmHg in midlife were associated with over twofold increase in risk of incident dementia in those never treated for hypertension.[2] This inevitably prompted work to evaluate the impact of blood pressure lowering as a therapeutic strategy for dementia risk reduction, and in so doing, has highlighted the complexity of the relationships between blood pressure and cognition, relationships that we are still trying to unravel.[3–5]

Collating the evidence has shown that these relationships are stronger when the raised blood pressure is experienced in midlife (40–65 years) and that the evidence in later life is more mixed

– perhaps also more confounded.[3,6,7] Blood pressure also evolves across the life-course rising until midlife after which diastolic pressure begins to fall.[8] In addition, as the clinical trials of antihypertensives have shown, our understanding of what is an acceptable or goal blood pressure has changed over time.[9,10] Finally, blood pressure, of course, is also continuously present; unlike some of the other established dementia risk factors (e.g. smoking) we cannot remove it.

The gradual nature by which dementia pathology is accrued over decades,[11] the lifelong presence of blood pressure and evidence from the cardiovascular arena of in utero or early life exposures linked to later life risk[12,13] point us towards needing a lifelong understanding of the impact of the blood pressure cognition relationship.[14] We need to begin to help develop this understanding and to highlight research gaps in the current evidence base. Our aim was to systematically review the literature, focusing on the age group that has been largely omitted so far, those aged 0–40 years at the time of blood pressure measurement.

Methods

Standard systematic review methodology was used. Databases Medline, Embase, PsycINFO®, Scopus, and Web of Science were searched from inception to 01 July 2020 with search terms including 'cognition', 'neuropsychology', 'attention', 'memory', 'language', 'processing speed', 'executive function', 'visuo-spatial ability' and 'blood pressure', 'hypertension' (see online supplement, for example, search strategy for PsycINFO). The full search strategy was developed in consultation with a university research librarian. Title, abstract and full-text screening were carried out by two independent reviewers (K.L., R.P.) with any disagreement resolved by discussion. The reference lists of the publications examined at the full-text stage were also examined for additional articles. Data including the first author`s surname, publication year, country(ies) where sample was obtained, recruitment source, participant demographics, sample size at baseline and follow-up assessments, duration of follow-up, details of blood pressure measurement, blood pressure value or classification, cognitive or neuropsychological test administered and result, statistical analyses conducted, variables adjusted for, main outcomes, and relevant summary statistics were extracted into predesigned forms and checked by a third reviewer (Y.X.). Where multiple models with different adjustment for confounders were available, the most adjusted model was extracted. Studies were included if they were of longitudinal prospective design (including cohort and case–control studies) with a baseline, at least one follow-up assessment of blood pressure and at least one measure of cognition, using recognised quantitative cognitive or neuropsychological measures, occurring at the same time as, or after, follow-up assessment of blood pressure. Where there were multiple publications from the same population the reports with the longest follow-up and largest sample size with appropriate blood pressure and cognitive measures were selected. Animal studies were excluded as were human studies where baseline and at least one follow-up blood pressure assessment were not collected between birth and age 40. A wide age range was used to ensure that all potential data were captured. An upper age limit of 40 years was selected based on the widely used definition of midlife in dementia risk factor epidemiology as between 40 and 65 years. Studies on prenatal or pregnancy specific blood pressure were excluded as systematic reviews have already focused in these areas.[15,16] Randomised controlled trials of phase 0–2 inclusive, single case studies, systematic reviews, meta-analyses, editorials, commentaries, protocols, conference papers, or theses were excluded. Studies that included participants with conditions that could potentially influence the relationships under investigation, such as acute cardiovascular disease, immunological disorders, metabolic disorders, cancer, neurological and psychiatric conditions, head trauma, alcohol use disorders and substance disorders, were excluded. Also excluded were studies involving conditions or interventions known to have an effect on cognition (e.g. pre/postoperative cognitive functioning, anaesthetics, educational interventions, lead or chemical exposure). To evaluate the potential for aspects of the study design, assessment or follow-up to have exposed the study results to risk of bias this was assessed independently by two reviewers (K.L., R.P.) using key factors selected from the Critical Appraisal Skills Programme checklists for evaluating case–control and cohort studies.[17] The use of a focused research question, appropriate methodology, measurement of exposure and outcome, attrition, confounding and reporting were considered and a

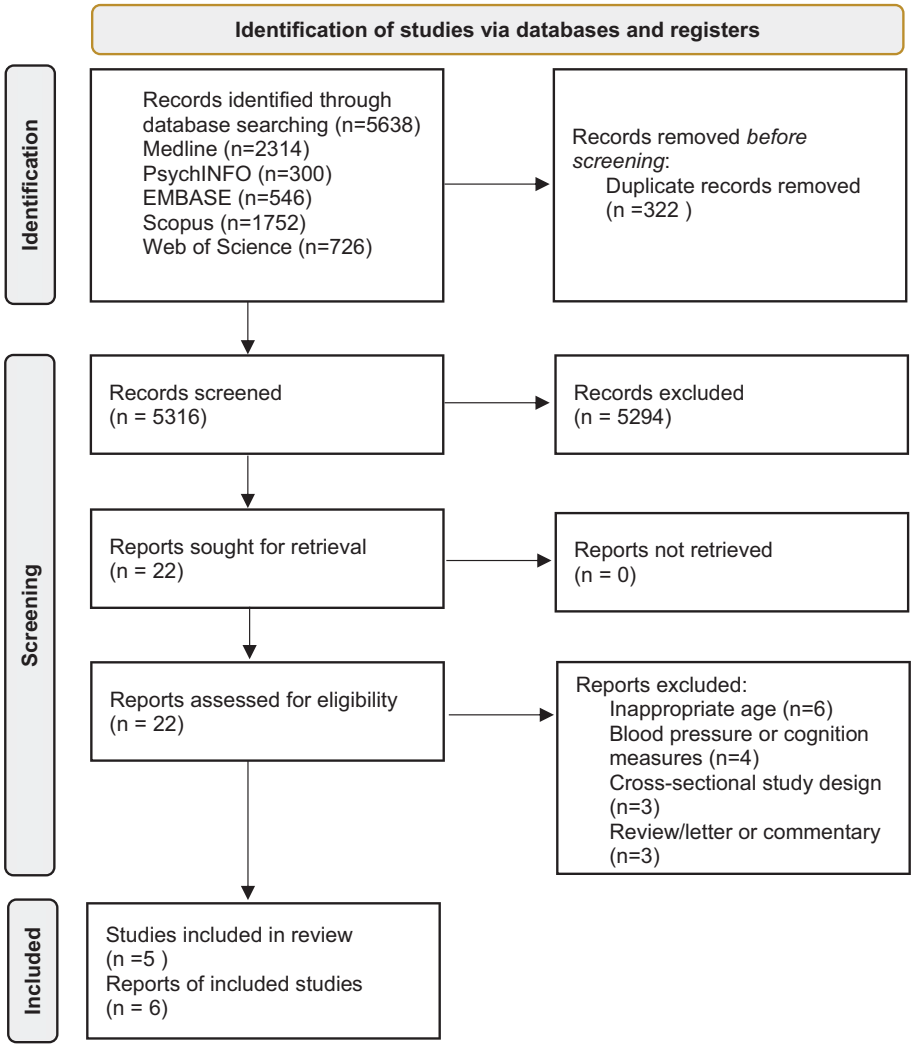

Figure 1. PRISMA flow chart.

categorical judgement made of low, moderate or high potential risk of bias. A formal scoring system was not used as this can lead to a loss of subtlety. Any disagreement between reviewers was resolved by discussion.

The principles of the PRISMA statement were followed and the protocol was registered with PROSPERO: registration CRD42020214655.

Results

Searches found 5638 records reduced to 5316 after duplicates were removed. Title and abstract screening removed a further 5294 with 22 articles assessed at full-text stage of which 16 were excluded as ineligible (Supplementary Text 2), leaving 6 included articles[18–23] reporting on 5 studies (2 articles[21,22] were from 1 study) (Figure 1).

Table 1 shows the characteristics of the included studies. The five studies were carried out in the United States,[18,19,21,22] Finland[23] and the Seychelles,[20] two were case–control studies comparing groups with hypertension (cases) to those without hypertension (matched controls)[18,19] with populations of 150[19] and 82,[18] respectively. The remaining three studies were cohort studies of 580,[20] 2026[23] and 3381[21,22] participants. There were no studies reporting on the very young (ages 0–2); however, the ages of those included ranged from 3[23] to those in their 30s.[18] Overall follow-up

Table 1. Characteristics of the included studies.

Study	Population age	Percentage female	Recruiting sites and criteria	Sample size	Follow-up	Blood pressure measures
Miller *et al.*[18]	Mean (SE) 31.68 years (1.78)	41%	USA Hypertension Clinic, University of Pittsburgh. Controls subjects were 'volunteer friends' of the patients (see prior publication Shapiro *et al.*[24]) Inclusion and exclusion criteria unspecified	82 (41 cases with hypertension, 41 controls without hypertension matched for age, race, and education)	Follow-up at 15 months Numbers available at follow-up 58 [24 normotensive (50% female); 34 hypertensive (53% female)]	Procedure not reported. Hypertension: DBP 90–105 mmHg. Baseline: • Male SBP/DBP Normotensive controls ($n = 12$) 125/74 Untreated hypertensives ($n = 6$) 148/85 Treated hypertensives ($n = 10$) 153/101 • Female SBP/DBP Normotensive controls ($n = 12$) 118/74 Untreated hypertensives ($n = 7$) 146/98 Treated hypertensives ($n = 11$) 156/97 Follow-up: • Male SBP/DBP Normotensive controls ($n = 12$) 126/74 Untreated hypertensives ($n = 6$) 149/90 Treated hypertensives ($n = 10$) 138/93 • Female SBP/DBP Normotensive controls ($n = 12$) 120/73 Untreated hypertensives ($n = 7$) 142/92 Treated hypertensives ($n = 11$) 140/93 Follow-up vs baseline: all comparisons nonsignificant except treated hypertensives: Male SBP $p < 0.001$, DBP $p < 0.01$; Female SBP $p < 0.001$

(Continued)

Table 1. (Continued)

Study	Population age	Percentage female	Recruiting sites and criteria	Sample size	Follow-up	Blood pressure measures
Lande *et al.*[19]	Range 10–18 years	31% at follow-up	USA Paediatric Hypertension Clinics, Emory University Control recruited from general paediatric clinics and primary care. Inclusion: Hypertensive, newly diagnosed children (10–18 years) with untreated hypertension; normotensive, healthy children (10–18 years). Exclusion: on medication for attention deficit/hyperactivity disorder, learning problem/disability, disorder of cognitive impairment, history of chelation treatment for elevated lead level, history of chronic renal, cardiovascular, gastrointestinal tract, hepatic, endocrine, or rheumatologic disease, pregnancy or breastfeeding, obstructive sleep apnea, secondary hypertension.	150 (75 cases with newly diagnosed hypertension, 75 controls without hypertension) Cases and controls were frequency matched for sex, obesity (BMI $\geqslant$ 95th percentile), maternal education	Follow-up at 1 year after baseline 121 (55 cases, 66 control) at follow-up. Cases received lifestyle modification alone or with antihypertension treatment during follow-up.	Clinic blood pressure was measured 3 times at 5-min intervals by an automated oscillometric device at the site Clinical Research Centre, and the blood pressure for that study visit was calculated as the average of the second and third reading. At baseline, each subject with a history of office hypertension had this confirmed with 24-h ambulatory blood pressure monitoring (ABPM). Presence of hypertension was confirmed if the mean waking SBP or waking DBP, mean sleeping blood pressure, or both were greater than or equal to the 95th percentile or if the mean ambulatory blood pressure was $<$ 95th percentile, but the participant had both a blood pressure load of more than 25% (ambulatory prehypertension) and left ventricular hypertrophy on echocardiogram. Controls were similarly classified using mean daytime and nighttime SBP and DBP $<$ 95th percentile and 24-h SBP and DBP load $<$ 25% on ABPM. Baseline: • Normotensive controls Daytime: SBP index 0.87 $\pm$ 0.05, DBP index 0.80 $\pm$ 0.06 Nighttime: SBP index 0.87 $\pm$ 0.06, DBP index 0.82 $\pm$ 0.07 24 h: SBP load 6.2 $\pm$ 6.2, DBP load 5.3 $\pm$ 4.8 • Hypertension cases Daytime: SBP index 1.02 $\pm$ 0.05, DBP index 0.91 $\pm$ 0.08 Nighttime: SBP index 1.02 $\pm$ 0.07, DBP index 0.95 $\pm$ 0.10 24 h: SBP load 57.6 $\pm$ 16.9, DBP load 28.0 $\pm$ 17.6 Follow-up: (Follow-up vs baseline p values, if significant) • Normotensive controls Daytime: SBP index 0.88 $\pm$ 0.06, DBP index 0.80 $\pm$ 0.06 Nighttime: SBP index 0.88 $\pm$ 0.06 ($p < 0.05$), DBP index 0.83 $\pm$ 0.08 24 h: SBP load 10.1 $\pm$ 10.1 ($p = 0.001$), DBP load 6.6 $\pm$ 6.0 • Hypertension cases Daytime: SBP index 0.96 $\pm$ 0.06 ($p < 0.001$), DBP index 0.85 $\pm$ 0.07 ($p < 0.001$) Nighttime: SBP index 0.98 $\pm$ 0.10 ($p < 0.05$), DBP index 0.91 $\pm$ 0.11 ($p < 0.05$) 24 h: SBP load 37.8 $\pm$ 26.3 ($p < 0.001$), DBP load 17.6 $\pm$ 13.2 ($p < 0.001$)

(Continued)

Table 1. (Continued)

Study	Population age	Percentage female	Recruiting sites and criteria	Sample size	Follow-up	Blood pressure measures
Lyngdoh *et al.*[20]	12 and 15 years	54%	Seychelles Inclusion: Participants recruited for cognitive assessment from the Seychelle's Child Development Study (SCDS) Exclusion: Lack of data on prenatal exposure to mercury from fish consumption, the presence of medical conditions that might affect development, withdrawal from the stud, problems with colour vision.	580 (with blood pressure at 12 and 15 years) Analyses used 407 participants with data on cognition at age 17	Follow-up at 17 years with cognitive tests	Blood pressure measurements obtained from school surveys Seychelles Ministry of Health and Ministry of Education (blood pressure was measured by trained school nurses in all students of all schools at ages 12 and 15 years. Readings were performed using a validated oscillometric automated device). Two seated blood pressure readings were taken 1 min apart at each visit and the average of the two values was computed at both 12 and 15 years of age. *z* scores of both SBP and DBP specific for age, sex, and height were generated using standard guidelines. Mean blood pressure at baseline: SBP 107.67 (SD 9.60), DBP 66.98 (6.99), MAP 88.55 (7.10). Follow-up blood pressure not reported.
Reis *et al.*[21] and Yaffe *et al.*[22]	Range 18–30 years	55%	USA Participants recruited from four US cities, Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; Oakland, California; the Coronary Artery Risk Development in Young Adults (CARDIA) Study Inclusion: Young adults between 18 and 30 years of age. Exclusion: Women who were pregnant at the time of the years 0, 7, 20 or 25 examinations.	Reis *et al.*[21]: 2932 participants with completed information in years 0, 7 and 25 and cognitive tests in year 25. 1753 available at follow-up with complete data on all health behaviours, factors and covariates. Yaffe *et al.*[22]: 3381 who completed the year 25 visit and had cardiovascular risk factor measurements from $\geqslant 2$ time points and $\geqslant 1$ cognitive assessments at year 25.	Follow-up at years 7 and 25 used in these analyses. Cognition tested at 25 years.	Blood pressure was measured on the right arm with a Hawksley random zero sphygmomanometer (WA Baum Company, Copaigue, NY) by trained and certified technicians using standardised methods after the participant had rested for 5 min at years 0 and 7. At year 25, a digital blood pressure monitor was used (Omron HEM-907XL; Online Fitness, Santa Monica, CA). Three measurements were obtained at 1-min intervals. The average of the second and third measurements was used in analyses. Blood pressure from Reis *et al.*[21] was calculated as the mean of measures collected at years 0, 7 and 25. Described in the context of the number of ideal cardiovascular components present, SBP/DBP 115.6/73.1 (one cardiovascular health component), 115.1/70.9 (two components), 111.4/69.1 (three components), 110.3/68.5 (four components), 107.7/67.1 (five components), 105.6/66.4 (six components), 103.4/64.4 (seven components) Blood pressure from Yaffe *et al.*[22] Baseline: SBP 109.9 (SD10.8), DBP 68.4 (9.4) Year 25: SBP 119.7 (16.2), DBP 74.8 (11.2) Time-weighted average: SBP 111.8 (9.3) DBP 71.2 (6.7)
Rovio *et al.*[23]	At baseline mean (SD) 10.8 (5.0) At cognitive testing 41.8 (5.0)	54%	Finland Randomly selected children and adolescents aged 3, 6, 9, 12, 15 and 18 from the population register at baseline.	2026 in these analyses (3596 in the whole study)	Follow-up visits approximately every 3 years, 1983-89, then in 2001, 2007, 2011. Cognition tested in 2011 at visit 6 at approximately 30 years.	Blood pressure stated as collected using standard procedure (details not supplied). Baseline: SBP 112.8 (SD 11.9), DBP 68.6 (9.4) Follow-up: SBP 118.9 (14.1), DBP 74.9 (10.5)

DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

times ranged from 1[19] to 25–30 years[21–23] with all studies including both male and female participants. Two of the studies did not report details of the procedure used for blood pressure measurement,[18,23] two studies provided comprehensive details[19,21,22] and another study leveraged data collected in school surveys.[20] All studies used some level of neuropsychological battery for cognitive testing.

Case–control studies

Both case–control studies assessed change in cognitive function. Miller *et al.* used analysis of variance to compare overall cognitive change over 15 months combining battery of sensory-perceptual, cognitive and psychomotor test performance and found that hypertensive cases with treated hypertension showed a significantly improved overall cognitive function *z* score, whereas in those who were untreated declined, and the controls (normotensive group) showed no change (Table 2).[18] In contrast, Lande *et al.*[19] with a year of follow-up used analysis of covariance adjusting for key confounders and reported both subjects with hypertension (regardless of the effectiveness of antihypertensive therapy) and normotensive controls significantly improved in scores of subtests of the Rey Auditory Verbal Learning Test (RAVLT), Grooved Pegboard Test and Delis–Kaplan Executive Function System Tower Test. However, the control group also significantly improved compared with the hypertensive group on the Wechsler Intelligence Scale for Children-Fourth Edition Spatial Span Forward.[19]

Cohort studies

The cohort studies reported on longitudinal blood pressure exposure but only assessed cognition at a single time point rather than measuring change. For the two studies with longer follow-up, the Coronary Artery Risk Development in Young Adults (CARDIA)[21,22] and the Young Finn's study,[23] blood pressure was collected repeatedly throughout follow-up and cognition collected after around 25–30 years of follow-up. For the CARDIA study, blood pressure averaged over 25-year follow-up was categorised as poor, intermediate and ideal.[21] Trend tests found a relationship between category of mean blood pressure and performance on the Digit Symbol Substitution Test (DSST) speed, a Stroop test interference score (calculated by subtracting score on subtest II from subtest III) and the delayed recall trial of the RAVLT such that those with higher pressures performed more poorly than those with lower pressures.[21] Additional analyses using cumulative blood pressure exposures reported similar results with poorer performance on the DSST speed, Stroop test interference score and RAVLT delayed recall associated with a greater area under the curve (AUC) of systolic blood pressure and poorer performance on the DSST speed and Stroop test interference score associated with greater AUC of diastolic blood pressure.[22] The Young Finn's study also reported on cumulative blood pressure exposure overall (from 6 to 24 years) and by age group, for childhood, adolescence and early adulthood. Overall, they reported that a significant increase in cumulative systolic blood pressure (per ~6 mmHg) associated with one standard deviation lower performance on a rapid visual processing test [i.e. the Paired Associate Learning test (PAL)], but no significant findings for spatial working memory or rapid visual information tests.[23] Results on the PAL were similar across the three age groups (6–12, 12–18 and 18–24 years old) and stronger for systolic rather than diastolic pressure but did not always reach statistical significance.[23] The smaller cohort study reported no consistent evidence for an association between blood pressure measured earlier in adolescence (12 and 15 years) and cognitive function assessed at age 17 or 19.[20]

Risk of bias

All of the studies were at some risk of bias (Table 3). In general, exposure and outcome measurement was adequate. Blood pressure measurement was reported by the authors as having been completed using standard methods and cognitive testing was by well-validated neuropsychological tests rather than cognitive screening tests. When considering the potential impact of blood pressure on cognition, however, the case–control studies were small and relatively short given the length of time that may be needed to see the impact of blood pressure on cognition, and the cohort studies, although larger and longer, were unable to measure cognitive change. In terms of statistical methods to determine significant cognitive change, the relevant longitudinal studies used adequate methods. When considering all the studies, a minority

Table 2. Cognitive testing and results.

Study	Cognitive assessment at follow-up	Primary analyses and adjustments	Results
Miller *et al.*[18]	*Sensory-Perceptual Tests* Visual Recognition Threshold Perception of Spaced Stimuli Critical Flicker Frequency Two-Flash Fusion Threshold *Cognitive Tests* Digit Symbol Substitution Test Block Design Memory for Designs Time Judgement (reproduction, estimation) *Psychomotor Function Tests* Lift and Jump Reaction Times Tapping Speed Transfer Coordination Speed Traverse Time Movement Reversal Time Handgrip Strength	Repeated measures ANOVA (analysis of variance) without adjustments comparing overall cognitive change over time in a *z* score combining the battery of sensory-perceptual, cognitive and psychomotor test performance as a function of antihypertensive treatment status (three groups: normotensives $n=24$, nontreated hypertensives $n=13$, treated hypertensives $n=21$)	Treated hypertensives showed overall improvement on the battery (mean *z* score = 0.1594), while the untreated group had a mean decrement in performance (mean *z* score = −0.3250), a difference that was significant at $p<0.05$. The normotensive controls were virtually unchanged overall (mean *z* score = −0.0261) and did not differ significantly from either of the hypertensive groups.
Lande *et al.*[19]	• Rey Auditory Verbal Learning Test RAVLT (List A Trial 1, List A Total, List A Short Delay Recall, List A Long Delay Recall). • CogState Groton Maze Learning Test GMLT (Total Error, Delayed Recall). • WASI, Wechsler Abbreviated Scales of Intelligence (Vocabulary, Matrix Reasoning, FSIQ, Full Scale IQ). • Grooved Pegboard Test (Time to completion dominant and nondominant hands). • Delis–Kaplan Executive Function System DKEFS Tower Test (Total Achievement). • Wechsler Intelligence Scale for Children WISC-IV (Digit Span Forward and Backward, Spatial Span Forward and Backward). • CogState Set Shifting (Set Shifting Total Error). • Connors' Continuous performance Test CPT-II (Omission Errors, Commission Errors, Variability, Detectability). • Parent BRIEF Behavior Rating Inventory of Executive Function (MI Behavior Regulation Index, BRI Behavior Regulation Index).	ANCOVA (analysis of covariance) models with changes in neurocognitive test scores as dependent variable and study group as independent variable With adjustment for corresponding baseline of the neurocognitive test score, age, sex, Sleep-Related Breathing Disorder Scale of the Paediatric Sleep Questionnaire score, maternal education (<high school, high school, college, >college), household income (<$25,000, $25,000–$75,000, >$75,000), African American race, baseline body mass index *z* score, change in body mass index *z* score from baseline to 1-year and baseline homeostatic model assessment value (glucose × insulin/405). Additional post hoc analyses by response to prescribed treatment using three groups: 1. Cases with hypertension whose blood pressure improved ($n=38$); 2. Cases with hypertension whose blood pressure did not improve ($n=17$); 3. Controls those who sustained normotension ($n=56$).	Of the 55 hypertensive subjects [defined using ambulatory blood pressure monitoring (ABPM)], 38 (69%) had successful treatment of their hypertension. The hypertension group improved in scores of subtests of the RAVLT (verbal learning and memory), Grooved Pegboard (manual dexterity) and DKEFS Tower Test (executive function) with moderate effect sizes (all $p<0.01$). The control group also improved in the same measures with similar effects sizes. There was no statistical difference in the change in scores between groups for these measures. In addition, the control group improved in scores for WISC-IV Spatial Span Forward with a moderate effect size $p<0.01$, whereas the hypertension group did not, and the between-group comparison showed that the change in scores for the control and hypertension groups for this measure were significantly different $p<0.05$. Some differences by improved hypertension but numbers and effect sizes small.

(Continued)

Table 2. (Continued)

Study	Cognitive assessment at follow-up	Primary analyses and adjustments	Results
Lyngdoh *et al.*[20]	At 17 years of age: • Cambridge Neurological Test Automated Battery (CANTAB); • DMS, delayed match to sample; IED, intra-extra dimensional shift; PAL, paired associate learning; PRM, pattern recognition memory; RTI, simple reaction time; • RVP, rapid visual information processing; • SRM, spatial recognition memory; SWM, spatial working memory; WJTA, Woodcock Johnson Tests of Achievement.	Multivariable regression analysis comparing association of blood pressure (SBP, DBP and MAP) at age 12–15 years (independent variable) with CANTAB and WJTA outcomes at 17 years and Finger Tapping and K-BIT at 19 years (dependent variables). *z* scores of blood pressure used to adjust for normal variation of sex, age and height in blood pressure measurements. Separate analyses conducted for males and females.	No consistent evidence of an association between blood pressure measured in early adolescence (12–15 years old) and cognitive outcomes measured in late adolescence (17 years old). Multivariate analyses adjusted for sex, socioeconomic status, birth weight, gestational age, alcohol intake, body mass index, blood glucose, total *n*-3 and *n*-6 polyunsaturated fatty acids found no relationships between blood pressure and performance on the CANTAB with the sole exception of male performance on the IED for the number of trials where higher SBP, DBP and MAP were associated with worse performance reported as at a significance level of $p < 0.05$. On adjusting for multiple testing, the few significant associations in the univariate and multivariate regressions were no longer significant.
Reis *et al.*[21] and Yaffe *et al.*[22]	• DSST, Digital Symbol Substitution Test; • Stroop test; • RAVLT, Rey Auditory Verbal Learning Test.	Reis *et al.*:[21] Categorised blood pressure by ideal (<120/<80), intermediate (120–139 or 80–89 or treated to goal blood pressure) and poor (⩾140 or ⩾90) Trend tests for performance on cognitive testing at year 25 by category of mean blood pressure exposure from years 0 to 25 Prese6nted multivariable adjusted*mean cognitive scores (DSST, RAVLT, Stroop) at year 25 by blood pressure categorised as ideal/intermediate/poor based on an average of blood pressure from baseline, years 7 and 25. *Adjusted variables: age, sex, race, educational attainment, alcohol use, study centre Yaffe *et al.*:[22] Linear regression to assess the independent associations of the areas under the curve (capturing both the duration and intensity of blood pressure) with cognitive function assessed at the year 25 visit, controlling for age at year 25, race/ethnicity, sex, and education, body mass index, diabetes mellitus, and smoking and baseline blood pressure level Adjusted for or excluding participants with incident cardiovascular events, including myocardial infarction, coronary revascularisation, stroke, peripheral artery disease and congestive heart failure Also looked at association of cognitive function with CVRF levels above and below American Heart Association guidelines: ideal SBP < 120 mmHg, DBP < 80 mmHg, fasting blood glucose < 100 mg.dL, total cholesterol < 200 mg/dL	Reis *et al.*[21]: Adjusted mean score on each test (95% confidence interval, CI) • DSST (p for trend < 0.001) • ideal 69.9 (69.3–70.6), intermediate 68.1 (67.3–68.9), poor 63.4 (59.8–67.1). • Stroop test (p for trend < 0.001) • Ideal 22.6 (22.1–23.1), intermediate 23.5 (22.9–24.1), poor 29.0 (26.3–31.6) • RAVLT (p for trend 0.008) • ideal 8.3 (8.2–8.4), intermediate 8.0 (7.8–8.2), poor 8.0 (7.3–8.7) Yaffe *et al.*[22]: Adjusted for age, sex, race and education, the cumulative effects of SBP remained negatively associated with cognitive function: *z* score change associated with each standard deviation increase in area under the curve: • RAVLT = −0.09, 95% CI, −0.15 to −0.03 • DSST = −0.12, 95% CI, −0.18 to −0.06 • Stroop = −0.11, 95% CI, −0.17 to −0.05 Cumulative levels of DBP were significantly associated with worse performance: • DSST = −0.07, 95% CI, −0.12 to −0.02 • Stroop = −0.09, 95% CI, −0.14 to −0.03 • but not RAVLT −0.05, 95% CI, −0.11 to 0.0. Additional adjustment for diabetes mellitus, smoking and body mass index led to similar results. Further adjustment for baseline blood pressure level did not appreciably change the association between areas under the curve effects and cognition. Finally, after adjustment for incident cardiovascular events, the associations between blood pressure areas under the curve and cognitive function remained statistically significant, but effect sizes were reduced. The associations were similar for models that excluded participants with incident cardiovascular events. Cumulative exposure above guideline associated with significantly worse cognitive function: SBP: • DSST −0.24; 95% CI, −0.41 to −0.07 ($p < 0.005$) • Stroop −0.24; 95% CI −0.42 to −0.05 ($p < 0.005$), • but not RAVLT −0.17; 95% CI, −0.35 to 0.0 DBP: • RAVLT −0.25; 95% CI −0.48 to -−0.03 ($p < 0.005$) • Stroop −0.29; 95% CI −0.53 to −0.06 ($p < 0.005$) but not DSST −0.22; 95% CI −0.44 to 0

(Continued)

Table 2. (Continued)

Study	Cognitive assessment at follow-up	Primary analyses and adjustments	Results
Rovio *et al.*[23]	Paired associate learning test (PAL) Spatial working memory test Reaction time Rapid visual information test	Principal component analysis to identify and normalise components accounting for majority of variation in cognitive domains. Estimated participant-specific curves for cardiovascular risk factors using mixed model regression with splines. The area under the curve calculated for childhood (6–12 years), adolescence (12–18 years), young adulthood (18–24 years) and early life (6–24 years). Age, sex, serum total-cholesterol, body mass index, smoking, baseline household income, antihypertensive or dyslipidaemia medication, diagnoses of cardiovascular disease and diabetes (type 1 and 2).	Association between cumulative burden of early-life vascular risk factors (6–24 years) and midlife visual and episodic memory and visuospatial learning (PAL). For SBP beta-0.064 (standard error 0.028) $p = 0.023$, i.e. a 0.064 standard deviation decrease in PAL performance for each standard deviation (~6 mmHg) increase in blood pressure in the cumulative exposure from 6 to 24 years. No clear patterns for other cognitive tests. PAL results analysed by childhood, adolescence and young adulthood and adjusted for age and sex are shown below in β coefficient (standard error) and p value: 6–12 years SBP −0.058 (0.023), $p = 0.013$; DBP −0.024 (0.027), $p = 0.382$ 12–18 years SBP −0.067 (0.026), $p = 0.011$; DBP −0.035 (0.027), $p = 0.185$ 18–24 years SBP −0.097 (0.030), $p = 0.001$; DBP −0.053 (0.025), $p = 0.035$

DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 3. Risk of bias.

Study	Miller *et al.*[18]	Lande *et al.*[19]	Lyngdoh *et al.*[20]	Reis *et al.*[21] and Yaffe *et al.*[22]	Rovio *et al.*[23]
Did they ask a clearly focused issue?	Yes, clear hypothesis presented.	Yes, clear hypothesis presented.	Yes, clear hypothesis presented.	Yes, clear hypotheses presented.	Yes, clear hypothesis presented.
Appropriate method?	Case–control study with longitudinal data. Used an ANOVA (analysis of variance) for primary analysis.	Case–control study with longitudinal data. Used an ANCOVA (analysis of covariance) for primary analysis.	Cohort study with longitudinal blood pressure data and a single measure of cognition at follow-up.	Cohort study with longitudinal blood pressure data and a single measure of cognition at follow-up.	Cohort study with longitudinal blood pressure data and a single measure of cognition at follow-up.
Selection bias?	Cases were recruited from the Hypertension Clinic of the University Health Centre, University of Pittsburgh and controls subjects were 'volunteer friends' of the patients. Controls were a convenience sample.	Cases were recruited from paediatric hypertension clinics and controls from general paediatric clinics and family medicine primary care practices, not population-based.	Recruited from longitudinal study representing approx. 50% of all births in 2-year period. Excluded participants with medical conditions that might affect development or withdrawal from study.	Population-based samples recruited from four US cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA) balanced within centre by age, sex, race and education.	Potential participants were selected based on the population register. However, participation was not uniform with participants more often female, older, came from families with higher income, and had better childhood academic performance and greater body mass index.
Measurement of exposure to minimise bias?	Measurement details not reported.	Standard methods to measure blood pressure. Unclear how index value was calculated. Different visit frequency depending on the methods used to lower blood pressure.	Standard methods were used to measure blood pressure but data were taken from a routine school surveillance programme.	Standard methods were used to measure blood pressure.	Article states that standard methods were used to measure blood pressure, but details were not reported.

(Continued)

Table 3. (Continued)

Study	Miller *et al.*[18]	Lande *et al.*[19]	Lyngdoh *et al.*[20]	Reis *et al.*[21] and Yaffe *et al.*[22]	Rovio *et al.*[23]
Measurement of outcome to minimise bias?	Study specifies that alternative forms of tests were used at the follow-up, for tasks that might show practice effects. Unclear whether assessment was blinded.	Standardised cognitive measures used, same measures used for both groups at both time points. Assessor blinding was not reported.	Standardised cognitive measures used. Different measures used across visits with various correlation among tests. No measure of change in cognition. Assessor blinding likely, as cognition was assessed by the study team whereas blood pressure measurements were part of the school screening programme.	Standardised cognitive measures used for all participants at year 25. Data collected by trained investigators. However, cognition only measured at follow-up.	Computerised cognitive testing was completed using the CANTAB online testing package. However, cognition only measured at follow-up. Assessor blinding was not reported.
Confounding factors identified?	Confounding factors not adjusted for. Although an analysis of variance revealed that there was no race or education effect on the type of treatment administered to the hypertensive subjects, it is unclear how race, education and other factors differed between groups and confounded the associations of our interest.	Key confounders were adjusted for.	Key confounders were adjusted for.	Key confounders were adjusted for.	Key confounders were adjusted for and age, sex and height specific *z* scores of systolic and diastolic blood pressure and mean arterial pressure were used.
Attrition reported and accounted for?	Study reports the number of participants from each group that dropped out. No analysis to compare differences between those who remained/left the study.	Study reports the number of participants from each group that dropped out. Analysis showed differences between those who remained/left the study.	Study reports the number of participants that dropped out, provided possible explanations and confirmed no significant differences in baseline characteristics between dropouts and remaining participants.	Attrition reported. Retention rates fell across examinations. Multiple imputation used to impute missing values and sensitivity analyses carried out using the complete case sample. Not clear how this applied to the cognitive assessment.	The cohort that was analysed was smaller than the original study; in addition, refusal to complete all cognitive testing was reported. Unclear if the potential impact of this was evaluated.
Results?	Analysis appropriate to study design. No reporting of effect sizes/least square means/ confidence intervals.	Ran additional analyses to examine the impact of missing data. Ran secondary subgroup analyses to compare subjects with successful and unsuccessful hypertension treatments, but numbers were small.	Analysis appropriate to study design, but only detailed univariate associations were reported in tables, and the adjusted results were presented in the supplementary. No reporting of effect sizes/least square means/confidence intervals.	Analysis appropriate to study design, results presented with uncertainty clearly represented.	Analysis appropriate to study design, results presented with uncertainty clearly represented.

Considered at low risk of bias
Considered at medium risk of bias
Considered at high risk of bias

used demographically corrected blood pressure measures and cognitive scores, and most adjusted for demographic variables within their samples. In this regard, only one study used age-, sex- and height-specific z scores of systolic and diastolic blood pressure and mean arterial pressure and found that the association between blood pressure and cognition did not differ by sex.[20] This is particularly relevant in diverse populations where the use of adjustment with the study population may mask important demographic differences.

Discussion

A systematic review of the evidence examining the relationships between raised blood pressure and cognitive function in early life is indicative. Studies tentatively indicate the potential for the relationship between higher blood pressure and poorer cognition earlier than midlife. Nevertheless, the evidence base is not yet strong enough to provide unequivocal evidence for, or even against, a link between higher early-life blood pressures and cognition.

Limitations in the current evidence base include a lack of data with relatively small number of studies, only two of which were able to report on change in cognition and neither of which reported a clear relationship between blood pressure and poorer cognition in their primary analyses. Furthermore, these two studies[18,19] are small case–control studies with follow-up durations of 12 and 15 months, attrition at follow-up (not controlled for statistically), assessment of the outcome measures is unblinded and there are small numbers in their analyses leaving them at risk of bias. The larger cohort studies[20–23] that have reported in this area were longer and were able to address cumulative blood pressure exposure with interestingly similar results across crucial age groups (e.g. between 6 and 12, 12 and 18 and 18 and 24)[23] but were unable to assess change in cognition meaning that it is impossible to fully understand whether general cognitive competence and other shared risk factors such as socioeconomic status may be driving the associations. The lack of studies in this area also precluded the use of meta-analysis to derive summary estimates and assessment of publication bias.

There are also some limitations in our methods. We used a combination of title and abstract screening, and although we searched the published evidence and the clinical trial registries, we did not include conference abstracts or theses and it is nevertheless possible that we missed relevant grey literature. We also chose to exclude additional reports in population subgroups; however, it should be noted that the CARDIA study in particular has multiple publications examining the relationships between various blood pressure and cardiovascular parameters and cognition.[21,22,25,26]

Future considerations

While the data to date give some indication that a relationship may be present, we still lack an understanding of when and how such relationships may develop. The sparsity of data and lack of longer-term assessment of cognition and blood pressure at each developmental age is important for several reasons. In particular, without repeat assessment over longer follow-up and a greater breadth of assessment from additional studies we will not be able to quantify whether, when or how relationships between blood pressure and cognition occur.

Careful assessment at different ages is particularly important as cognitive skills develop through childhood, adolescence and early adulthood and blood pressure also changes. While there is evidence from later life cohorts that shows the midlife period as a time when we are susceptible to the impact of raised blood pressure increasing risk of dementia in later life, we lack understanding of whether there are also developmental periods prior to age 40 during which we are susceptible. Assessing cognitive function using developmentally relevant testing with a focus on the skill sets most pertinent to the developmental age of the population will be important for future research. Furthermore, future, robust longitudinal studies in this area should use optimal statistical methods to measure cognitive change (e.g. mixed-effect models). The heterogeneity in cognitive outcomes also suggests that this field of research may require some level of harmonisation in the selection of cognitive domains. Furthermore, the use of normative data on the selected neuropsychological test scores at least at baseline may assist in determining whether the control group and the clinical group perform within expectations. This is important because poor performance is the number one factor associated with cognitive change.[27] Alongside this, evaluating the impact of raised blood pressure on cognition over time

requires disentangling the roles of blood pressure trajectory, absolute blood pressure level and expected blood pressure for each age group.

In addition, without repeated and larger studies in similar age populations with robust methods, we will continue to lack the statistical power to disentangle relationships driven by population characteristics or external factors. For example, there are major differences between sexes in terms of brain development and blood pressure.[28,29] Therefore, it would be advisable that this demographic characteristic be correctly represented and systematically analysed. Skilled adjustment and analysis is also needed to take account of other factors that may play a role including underlying issues such as socioeconomic status, race/ethnicity (when relevant, either to due to biological or to historical racial discrimination and related lack of quality in education and social opportunities), lifestyle (including aspects of this that may influence both blood pressure and cognition, e.g. body mass index or obesity) and experience of adversity especially during the childhood years and related mental health sequalae.

It remains a possibility that exposure to elevated blood pressure during childhood, adolescence and early adulthood either as a consequence of or in conjunction with other factors may have a negative impact on cognitive performance with the potential for a subsequent impact on academic and workplace performance.

Blood pressure lowering through lifestyle and pharmacological means is available and (for the latter at least) shows significant promise in protecting cognition in later life stages. Because blood pressure is lifelong, it is also important to develop our understanding of early-life blood pressure impact and trajectory. This review represents the first synthesis of data on the relationship between early-life blood pressure and cognition and highlights a need for additional data to further our understanding. It is too early to say whether we can identify an at-risk population, in childhood or early adulthood, and whether we can intervene to protect cognition earlier in the life-course.

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Author contributions

Kurt Lancaster: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.
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Supplemental material

Supplemental material for this article is available online.

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