An assessment of the mediating role of hypertension in the effect of long-term air pollution exposure on dementia

Tanya E. Libby [a,*], Sindana D. Ilango [a], Cindy S. Leary [b], Erin O. Semmens [b], Claire E. Adam [b], Annette L. Fitzpatrick [a,c], Joel D. Kaufman [a,d,e], Anjum Hajat [a]

Background: Growing evidence links air pollution exposure to the risk of dementia. We hypothesized that hypertension may partially mediate this effect.

Methods: We previously documented an association between air pollution and dementia in the Ginkgo Evaluation of Memory Study, a randomized, placebo-controlled trial of 3069 adults ≥75 years across four US sites who were evaluated for dementia every 6 months from 2000–2008. We utilized a two-stage regression approach for causal mediation analysis to decompose the total effect of air pollution on dementia into its natural direct and indirect effect through prevalent hypertension. Exposure to air pollution in the 10 or 20 years before enrollment was assigned using estimates from fine-scale spatial-temporal models for $PM_{2.5}$, PM_{10}, and NO_2. We used Poisson regression models for hypertension and Cox proportional hazard models for time-to-incident all-cause dementia, adjusting for a priori confounders.

Results: Participants were free of mild cognitive impairment at baseline (n = 2564 included in analyses); 69% had prevalent hypertension at baseline. During follow-up, 12% developed all-cause dementia (Alzheimer's disease [AD] = 212; vascular dementia with or without AD [VaD/AD mixed] = 97). We did not find an adverse effect of any air pollutant on hypertension. Hypertension was associated with VaD/AD mixed (HR, 1.92 [95% CI = 1.14, 3.24]) but not AD. We did not observe mediation through hypertension for the effect of any pollutant on dementia outcomes.

Conclusions: The lack of mediated effect may be due to other mechanistic pathways and the minimal effect of air pollution on hypertension in this cohort of older adults.

[a]Department of Epidemiology, University of Washington, Seattle, Washington; [b]Center for Population Health Research, School of Public and Community Health Sciences, University of Montana, Missoula, Montana; [c]Department of Family Medicine, University of Washington, Seattle, Washington; [d]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington; [e]Department of Medicine, University of Washington, Seattle, Washington

Introduction

Dementia is a growing public health concern expected to affect over 130 million people worldwide by 2050.[1] In the absence of effective treatments, identification of modifiable risk factors is critical.[2] Recent reviews of the epidemiologic literature demonstrate substantial evidence for the deleterious effect of ambient air pollution exposure, including fine particulate matter, on the risk of dementia.[3–8] The exact mechanisms through which air pollution affects dementia outcomes remain unclear. Potential intermediates on the pathway include cardiovascular disease, stroke, and hypertension.[3] A better understanding of the causal pathway between air pollution and dementia can provide insights into the pathophysiology of the disease and inform clinical decision-making and prevention strategies.

Air pollution is hypothesized to affect blood pressure (BP) and hypertension through several mechanisms. Inhalation of particulate matter (PM) can lead to an imbalance in the autonomic nervous system and an increase in BP in a matter of minutes.[9] Prolonged exposure can induce oxidative stress, systemic inflammation, and vasoconstriction, and lead to endothelial injury and arterial remodeling.[9,10] While studies have consistently shown an adverse effect of particular matter (PM_{10}) and

What this study adds

While air pollution exposure has been associated with increased blood pressure, and hypertension is an established risk factor for dementia, our study is among the first to examine the mediating role of hypertension in the effect of air pollution on dementia. We did not find evidence that hypertension mediates the effect of long-term air pollution exposure on the risk of dementia. Our findings highlight the importance of accounting for the use of antihypertensive medications and provide insights for future research.

fine particulate matter ($PM_{2.5}$) on BP in the short term,[10] the evidence for longer-term air pollution exposure on hypertension has been somewhat mixed.[10–14] A meta-analysis, which included 57 studies published through August 2020, found that long-term exposure to $PM_{2.5}$, PM_{10}, and SO_2, but not NO_2 or NO_X, was associated with hypertension (prevalent or incident) in pooled analyses, though there was high heterogeneity in effect estimates among studies.[12] When limited to cohort studies, only $PM_{2.5}$ remained statistically associated with hypertension. Heterogeneity was attributed to study region, study quality, and variability in exposure and outcome assessment.[12] Differences in the prevalence of antihypertensive medication use and the methods for accounting for medication use in analyses likely impacted the observed effects.[15]

Hypertension is an important risk factor for both vascular dementia (VaD) and Alzheimer's disease (AD) dementia.[16] Mid-life and late-life hypertension have been associated with increased risk of dementia.[17,18] Potential mechanisms include acute cerebral ischemia, disruption of the blood-brain barrier, neuroinflammation, and accelerated brain atrophy.[19] In addition to direct neurological impacts, hypertension can increase the risk of cardiovascular disease, which is also a risk factor for dementia. In the multi-ethnic study of artherosclerosis (MESA), higher baseline systolic and diastolic BP was associated with worse cognitive function measured 10 years later.[20] A meta-analysis of 12 clinical trials found the use of antihypertensive medication was associated with a modest but significant decrease in risk of dementia and cognitive decline.[21] Given the high prevalence of hypertension, effective screening and control of hypertension could lead to important population-level reductions in dementia globally.

Few studies have quantified the mediating role of cardiovascular disease events,[22,23] stroke,[22] and diabetes[24] in the association between air pollution and dementia, and only one has evaluated the role of hypertension,[25] despite previously established mechanistic links. Identifying modifiable intermediaries, such as BP, can help target public health resources to control hypertension and possibly dementia outcomes. The objective of our study was to examine the mediating role of hypertension in the association between long-term air pollution exposure ($PM_{2.5}$, PM_{10}, and NO_2) and dementia risk in a cohort of 3069 older adults over up to 8 years of follow-up.[26]

Methods

Study design and participants

We used data from the Ginkgo Evaluation of Memory Study (GEMS), a randomized double-blind, placebo-controlled trial that evaluated *Gingko biloba* for the prevention of dementia. Detailed study procedures are published elsewhere.[26,27] Briefly, adults (n = 3069) ≥75 years were recruited from 2000 to 2002 across four clinical sites in the United States—Sacramento, CA; Hagerstown, MD; Winston-Salem, NC; and Pittsburg, PA. Individuals with prevalent dementia or other neurodegenerative diseases at baseline and those taking medications for dementia or cognitive enhancement were excluded. We recently documented an association between long-term air pollution exposure and the risk of dementia in this cohort,[26] and hypothesize that hypertension may partially mediate the effect of air pollution on dementia.

Dementia ascertainment

Participants were evaluated for dementia every 6 months from enrollment until the end of follow-up in 2008. At each visit,

participants completed three cognitive screening examinations: the Modified Mini-Mental State Examination (3MSE),[28] the cognitive subscale of the Alzheimer Disease Assessment Scale,[29] and the Clinical Dementia Rating.[30] Participants who did not pass two of the three examinations were administered a full neuropsychological battery consisting of 12 tests in six cognitive domains and were referred for neurological examinations and MRI if dementia was suspected.[31] Starting in 2004, all participants were administered the full neuropsychological battery annually. A dementia adjudication panel confirmed the diagnosis and categorized each dementia case as either AD, vascular dementia (VaD) with no AD, VaD with AD, or other dementia etiology. The dementia diagnostic criteria are detailed in the published trial protocol.[31] Due to the small number of participants with incident VaD with no AD, we combined these participants with VaD/AD mixed-type dementia for analysis, as was done previously.[26]

Mediator definition

For our main analysis, prevalent hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or the use of an antihypertensive medication based on medical record review or self-report. The average of two measurements taken at the study entry were used to define SBP and DBP. These cut points were selected to align with recommended BP targets at the time of the trial, but the eAppendix; http://links.lww.com/EE/A272 thoroughly evaluates other cutoffs commonly used and alternative hypertension definitions.[32,33]

We used prevalent hypertension at the first study visit rather than time-varying BP measurements to maximize the lag period between the mediator and outcome assessment.[24] In MESA, elevated BP in mid-life rather than changes over the mid- to late-life transition were predictors of cognitive performance.[20]

Air pollution assessment

Our primary exposures of interest were mean $PM_{2.5}$ in the 20 years before enrollment (1980–1999) and mean PM_{10} and NO_2 in the 10 years before enrollment (1990–1999) since, in general, we observed stronger associations between longer averaging periods (10 or 20 years vs. 1 or 5 years) and dementia.[26] Long-term air pollution exposure was based on participant residential addresses. Historical residential addresses for the 20 years before the study entry were reconstructed using data from the LexisNexis credit-reporting database.[26,34] LexisNexis uses public information (e.g., voter registration and mortgage records) and a propriety algorithm to obtain address history.[35] As detailed in the online supplement to Semmens et al[26] (see also eAppendix1; http://links.lww.com/EE/A272), our team developed a set of specific rules that were used to construct likely sequential address histories based on residency dates from LexisNexis and participant addresses recorded at each study visit. Addresses were geocoded using ArcGIS10.6.1 and exposure to air pollution was assigned as previously described.[26] Briefly, annual average $PM_{2.5}$ and PM_{10} concentrations were estimated using a validated spatiotemporal model.[36,37] NO_2 was estimated using a validated national prediction model.[38] Exposures were time-weighted based on the amount of time we believe the participant lived at each address (eAppendix1; http://links.lww.com/EE/A272).

Statistical analysis

Our analysis was restricted to those without mild cognitive impairment (MCI) at baseline. Relevant descriptive statistics were used to summarize baseline participant characteristics. We

calculated the mean duration of study follow-up and the median and interquartile range (IQR) of exposure to each pollutant over the 10 or 20 years before enrollment.

For our mediation analysis, we first evaluated the direct effects of air pollution on hypertension and hypertension on dementia separately. We used Poisson regression models to calculate risk ratios (RRs) for the association between air pollution and binary hypertension; RRs are more readily interpretable than odds ratios from logistic regression.[39] We used Cox proportional hazard models for time-to-incident dementia. Hazard ratios (HRs) over the follow-up period and RRs were calculated for each IQR increase in pollutant. Follow-up time began at age at randomization and ended at age halfway between the clinical examination at which the dementia diagnosis was made and the last clinical examination at which the patient was dementia-free.[31] Participants were censored at the date of death or last contact. We ran separate models for all-cause dementia, AD, and VaD/AD mixed.

To control for confounding, all models were adjusted for enrollment site and enrollment year, and for *Ginkgo biloba* treatment arm as a precision variable. We additionally adjusted for *a priori* confounding factors identified based on literature review[8,40] and recorded at study entry: age, sex (male or female), education level, history of smoking (ever or never), pack-years (quartiles), secondhand smoke exposure (percent of life exposed) and 20-year average neighborhood deprivation index (continuous), which was constructed at the census tract level using residential history information between 1980 and 1999,[26] since research demonstrates the neighborhood social environment is an important confounder of air pollution and health.[41] In models for hypertension, we adjusted for alcoholic drinks per week, as alcohol consumption is a risk factor for hypertension[42] and may be associated with neighborhood and therefore air pollution exposure. In sensitivity analyses, we adjusted for physical activity score (scale: 0–35) based on participants reported frequency of engaging in the following activities: gardening and yard work, walking, volunteering, assisting family or friends, hunting, fishing or camping, babysitting, and shopping.[43]

We used a two-stage regression approach for causal mediation analysis to decompose the total effect of air pollution on dementia into its natural direct and indirect effects through hypertension.[44,45] The natural indirect effect represents the change we would observe on a given dementia outcome if we could change each person's hypertension status to the value it would naturally take if there was an air pollution intervention where air pollution was set to a specific level. Here, we assume that air pollution is set to zero.[46] Using the product method, we calculated the indirect effect of hypertension (yes/no) on each air pollutant and dementia outcome as:

$$NIE = e^{\beta_1}$$

Where β_1 represents the coefficient for air pollution exposure from the mediator model and γ_1 represents the coefficient for hypertension from the outcome model. The product method gives mediated effects for proportional hazards models when the outcome is rare[45] (<10% of our study population developed AD or VaD/mixed[47]). We calculated 95% confidence intervals (CIs) for the indirect and direct effects via bootstrapping with 500 resamples. All statistical analyses were performed with R Studio version 1.3.

Sensitivity analyses

We assessed whether results were robust to alternate definitions[48] of hypertension. First, we used lower cut points to align with updated American Heart Association treatment guidelines for "elevated" BP: SBP ≥130 or DBP ≥80.[49] Second, we removed antihypertensive use from the definition and instead stratified by medication use because these medications may attenuate the

risk of dementia.[50] Third, because antihypertensives lower BP and may mask the impact of air pollution on hypertension, we explored the addition of a fixed BP (10 or 15 mmHg) for participants on antihypertensives and then applied the respective BP cut points to define hypertensive cases.[15] In MESA, results were sensitive to this method.[48] Finally, we assessed SBP and DBP as continuous variables, both with and without the adjustment for medication use described above. In mediation analysis, these continuous outcomes were modeled using linear regression.

In sensitivity analyses, we assessed how robust the estimates were to violations of four key assumptions of this causal mediation analysis: namely, that there is no unmeasured confounding of the exposure-outcome, exposure-mediator, or mediator-outcome relationships; and that no confounder of the mediator-outcome relationship is affected by the exposure. We assessed whether any mediator-outcome confounders (e.g., physical activity) were affected by the exposure using logistic regression and scatter plots. Finally, we assessed the sensitivity of our findings to inclusion of participants with MCI at baseline.

Results

Of the 3069 participants enrolled in GEMS, we excluded 23 due to missing information on air pollution exposure and 482 with MCI at baseline. Characteristics of the 2564 participants included in our analytic sample are summarized in Table 1. The mean age at study entry was 78.4 years and 54.4% were male. Median 20-year exposure to $PM_{2.5}$ was 18.41 (IQR = 2.44) µg/m³. Median 10-year exposure to PM_{10} was 24.78 (IQR = 4.44) µg/m³ and NO_2 was 16.62 (IQR = 6.67) ppb. At enrollment, 57% of participants were taking antihypertensive medication and 69% had prevalent hypertension. Participants were followed for an average of 5.7 years and 324 (12.6%) developed dementia.

We did not find an adverse effect of any air pollutant on hypertension (Table 2). Hypertension was associated with VaD/AD mixed dementia (HR, 1.92; 95% CI = 1.14, 3.24) but not AD (HR, 0.88; 95% CI = 0.66, 1.19) (Table 3). We did not observe mediation through hypertension for the effect of either pollutant on dementia outcomes (Figure 1, eTable 1; http://links.lww.com/EE/A272). The percent mediated ranged from 0.0% (95% CI = −0.99, 1.05) for NO_2 and AD to 0.30% (95% CI = −1.40, 1.54) for $PM_{2.5}$ and VaD/AD mixed dementia (eTable 1; http://links.lww.com/EE/A272).

Results did not change when hypertension was operationalized with different cut points (e.g., SBP≥130, DBP ≥80), without the inclusion of antihypertensive medication, or categorized after the addition of fixed BP (10 or 15 mmHg) for participants on antihypertensives (eTables 2 and 3; http://links.lww.com/EE/A272). There was no adverse effect of any air pollutant on continuous SBP or DBP (eTable 4; http://links.lww.com/EE/A272) and results did not appreciably change when stratifying by use of an antihypertensive (eTable 4; http://links.lww.com/EE/A272). The inclusion of participants with MCI at baseline did not change our overall findings.

Discussion

The present study was the first, to our knowledge, to use BP measurements and medical records to examine the mediating role of hypertension in the effect of air pollution on dementia. We found hypertension was more strongly associated with vascular/mixed dementia than AD or all-cause dementia, which is consistent with known biological mechanisms for vascular pathologies. Vascular dementia is a progressive disease caused by decreased blood circulation to the brain, which may be associated with detected and undiagnosed stroke.[51] Risk factors include cardiovascular disease, metabolic syndrome, and hypertension.[51] Uncontrolled hypertension can cause vascular injury

Table 1.

Baseline characteristics of included study participants from the Ginkgo Evaluation of Memory Study (GEMS), n = 2,564

Characteristic	N (%)[a]
Enrollment site	
Sacramento, CA	781 (30.5)
Hagerstown, MD	386 (15.1)
Winston-Salem, NC	579 (22.6)
Pittsburgh, PA	818 (31.9)
Demographics at baseline	
Age, years (mean [SD])	78.4 (3.2)
Sex	
Female	1170 (45.6)
Male	1394 (54.4)
Race and ethnicity	
White	2480 (96.7)
People of color	84 (3.3)
Education	
High school or less	930 (36.3)
Some college	628 (24.5)
College graduate	425 (16.6)
Postgraduate	581 (22.7)
Neighborhood deprivation index (mean [SD])	−0.09 (2.99)
Blood pressure (BP) at baseline	
Systolic BP (mmHg) (mean [SD])	132.7 (17.9)
Diastolic BP (mmHg) (mean [SD])	69.0 (9.7)
Antihypertensive medication use	1452 (56.6)
Hypertension[b]	1767 (68.9)
Smoking status	
Never	1017 (40.4)
Former	1391 (55.2)
Current	110 (4.4)
Pack-years smoking	
0	1030 (43.4)
>0 to 24	692 (29.1)
>24	653 (27.5)
Percent of life exposed to secondhand smoke	
≤1.14	615 (24.6)
>1.14 to ≤24.39	616 (24.6)
>24.39 to ≤46.43	637 (25.4)
>46.43	636 (25.4)
Alcoholic drinks/week (mean [SD])	3.7 (6.6)
BMI, kg/m^{3} (mean [SD])	27.2 (4.2)
Physical activity score,[c] out of 35 (mean [SD])	13.5 (4.6)
Outcome & follow-up	
All-cause dementia	324 (12.6)
Alzheimer's disease (AD)	212 (8.3)
Vascular/AD mixed dementia	97 (3.8)
Follow-up, years (mean [SD])	5.7 (1.5)

[a]Unless otherwise specified.

[b]Defined as systolic BP ≥140, diastolic BP ≥90, or use of antihypertensive.

[c]Score based on participants reported frequency of engaging in the following activities: gardening and yard work, walking, volunteering, assisting family or friends, hunting, fishing or camping, babysitting, and shopping.

Table 2.

Association between air pollutants and prevalent hypertension at baseline

Exposure	Hypertension (yes/no)[a] RR (95% CI)
NO$_2$ (per 6.6 ppb)	1.02 (0.92, 1.11)
PM$_{2.5}$ (per 2.4 µg/m^{3})	1.01 (0.91, 1.10)
PM$_{10}$ (per 4.4 µg/m^{3})	1.00 (0.93, 1.09)

RRs are reported per IQR increase in pollutant.

[a]Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg, or use of an antihypertensive. Poisson models adjusted for age at study entry, year of enrollment, enrollment site, treatment arm, sex, education, 20-year average neighborhood deprivation index (NDI), smoking status, pack-years, secondhand smoke exposure, and number of alcoholic drinks per week.

CI indicates confidence interval; RR, risk ratio.

Table 3.

Association between hypertension and time-to-dementia subtype

| Outcome	HR (95% CI)
All-cause dementia	1.10 (0.86, 1.41)
Vascular/mixed dementia	1.92 (1.14, 3.24)
Alzheimer's disease	0.88 (0.66, 1.19)

Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg, or use of an antihypertensive. Cox models adjusted for age at study entry, year of enrollment, enrollment site, treatment arm, sex, education, 20-year average neighborhood deprivation index (NDI), smoking status, and secondhand smoke exposure.

CI indicates confidence interval; HR, hazard ratio.

and damage to the white matter of the brain, and BP treatment has been shown to slow this progression.[52] Our findings support current hypertension treatment recommendations.[33]

We found a minimal effect of air pollution on hypertension in our study population, despite previously documented associations, mechanistic links, and biological plausibility.[10,12,40,53] This may be due to the older age of the cohort and the high prevalence of hypertension at baseline. Air pollution may affect BP earlier in life than was possible to measure in this cohort of adults ≥75 years. In a meta-analysis, Cai et al[10] found that the age of study participants was negatively associated with effect sizes for the association between long-term exposure to NO$_2$ and PM$_{2.5}$ and hypertension.[10] BP is known to decrease in the very elderly,[54] which could have obscured effects of earlier life air pollution exposure on hypertension risk at study entry. The use of antihypertensives was common in our study population (over half of participants were using antihypertensives at baseline) and medication-induced decreases in BP may mask the effect of air pollution.

We did not find evidence that hypertension mediated the effect of air pollution on dementia outcomes for any pollutant studied, owing at least in part to the lack of an observed effect of air pollution on hypertension. These findings are consistent with a recent study that evaluated whether hypertension mediated the effect of PM$_{2.5}$ on dementia using survey data from a population-based cohort of US retirees.[25] Pathways other than hypertension (such as inflammation, oxidative stress, or disruption of the blood-brain barrier) may explain the effect of air pollution on dementia. Several recent studies have aimed to quantify the potential mediating role of diabetes, stroke, and cardiovascular disease. Findings from the Sacramento Area Latino Study on Aging (SALSA) suggest that 20% of the traffic-related air pollution-dementia pathway is mediated through type 2 diabetes.[24] An examination of the mediating role of atrial fibrillation, ischemic heart disease, heart failure, and stroke among a cohort enrolled in the Swedish National Study on Aging and Care found stroke to be an intermediate condition in 49% of air pollution-related dementia cases.[22] Ilango et al[23] conducted a causal mediation analysis using data from the Canadian Health Survey and found 9% and 21% of the pathway from NO$_2$ and PM$_{2.5}$, respectively, was attributed to cardiovascular disease on the multiplicative scale (defined as hospital admissions or medical procedures for coronary heart disease, stroke, arrhythmia, and congestive heart failure).

Several other explanations should be considered for the lack of observed mediation through hypertension. First, the association between air pollution and dementia may be more strongly mediated through mid-life rather than later-life hypertension. Abell et al[18] found an increased risk of dementia for those with SBP ≥130 at age 50 years, but not at age 60 or 70. This is consistent with the findings from MESA that mid-life hypertension, rather than changes over the mid- to late-life transition, predicts cognitive performance.[20] There is evidence to suggest that the increasing duration of hypertension predicts lower cognitive performance,[55] however, duration and age at onset of hypertension
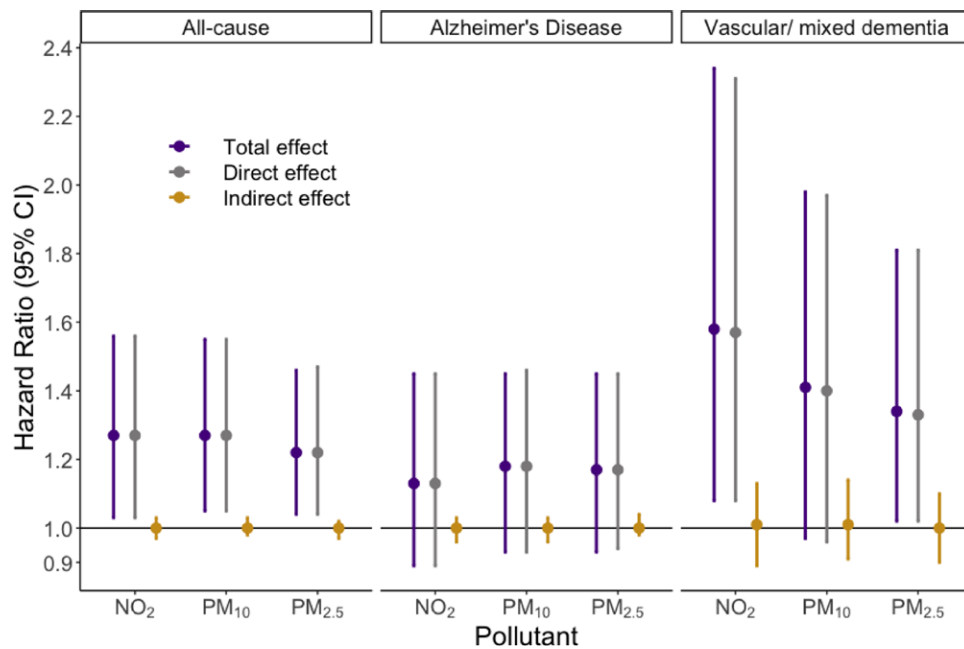
Figure 1. Mediation analysis results: total, direct, and indirect effects through hypertension of each pollutant on time-to-incident dementia.

were not known in our study. Therefore, we chose to examine prevalent hypertension, assuming that the development of hypertension after study enrollment (i.e., after age 75) would not present the same increased risk of dementia as hypertension earlier in life[18] and that any effect of air pollution exposure on hypertension risk would have occurred before study enrollment. Enrollment of participants earlier in life may have improved our ability to detect an effect.

Recruiting an older population is efficient when the design benefits from a high incidence of dementia over a short period of follow-up, as was the case in the GEMS cohort. However, if the biological period of interest occurs long before disease onset, which may be the case for possible mediators, then recruitment of a much younger population may be needed. This would allow for examining incident hypertension and duration of hypertension while better ensuring temporality between exposure and mediator. Nevertheless, the long follow-up duration required may be infeasible or prohibitively expensive.

It is possible that long-term air pollution exposure has a minimal effect on the risk of hypertension. Among participants in MESA, no association was seen between air pollution and hypertension after controlling for time-varying age and calendar time, likely due to decreases in air pollution and BP over time.[48] Fuks et al[40] separately examined the effect in individuals taking and not taking antihypertensive medication and found partially differing results. PM was weakly associated with BP only in medicated participants, and traffic load was associated with BP in nonmedicated participants.[40] We saw similarly inconsistent results by medication use in our study. This highlights the importance and challenge of accounting for medication use, which could both confound the mediator-outcome relationship and mask the exposure-mediator relationship. Participants ≥75 years of age who are not using an antihypertensive medication may represent a less susceptible group. Further, the effect of medication on downstream outcomes of interest also remains inconclusive. In the Systolic Blood Pressure Intervention Trial (SPRINT), the risk of MCI and cardiovascular disease was lower comparing intensive BP treatment (goal of <120 mmHg) vs. standard (goal <140 mmHg) treatment, but no association was seen for dementia[56] or for specific cognitive domains, though the study may have been underpowered for these outcomes.[57]

The present study expands upon recent work examining the mediating role of hypertension by using a more objective measure of hypertension (based on BP measurements and medical record review), rather than self- or proxy-report.[25] Additional strengths of the present study include a well-characterized clinical trial population with detailed information on potential confounders and comprehensive prospective assessment for dementia, the primary endpoint of the trial. Regular screening visits enhanced the precision of diagnosis dates, and the use of brain MRI and an expert adjudication panel to determine subtypes ensured highly accurate dementia classification. Reconstruction of historical addresses allowed for residential mobility and more precise air pollution exposure estimates during the critical window for dementia development.[58]

There are several limitations to our study. While GEMS included four geographically diverse sites in the United States, most study participants identified as white. Thus, the findings may not be generalizable to other groups. Misclassification of hypertension may have occurred, as individuals' BP can fluctuate throughout the day, though we used the average of two BP measurements to mitigate this concern. Because the onset of hypertension is not known, it is possible that hypertension onset proceeded exposure assessment leading to measurement error. We would expect any exposure and mediator misclassification to be nondifferential with respect to the outcome. On average, nondifferential misclassification of exposure in a cohort study biases estimates towards the null. We excluded participants with missing covariate data (<5% for all included variables) but expect minimal impact on results as missingness was not associated with the exposure or outcome and the use of multiple imputation did not impact estimates of the main effect.[26] Finally, individuals experiencing cognitive decline or those suffering from complications of high BP are more prone to nonparticipation in research studies and may be more susceptible to attrition. This would lead to an attenuation of the association with air pollution and could have contributed to our null mediation findings.

Our results corroborate existing evidence for the deleterious effect of hypertension on the risk of vascular dementia. However, we did not find evidence that hypertension mediates the air pollution-dementia relationship, perhaps due to the complex role of BP-lowering medications and the age of the cohort.

Future work could address the mediating role of mid-life hypertension in cohorts that start at younger ages; the use of well-defined population registries, updated historical air pollution models, and statistical modeling may overcome the otherwise prohibitive follow-up duration required. Further exploration of the pathways underlying the effect of air pollution on dementia is needed to effectively identify high-risk populations and target prevention strategies.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

References

1. International AD, Wimo A, Ali GC, et al. *World Alzheimer Report 2015: The global impact of dementia: An analysis of prevalence, incidence, cost and trends*. Published online September 21, 2015. Available at: https://www.alzint.org/resource/world-alzheimer-report-2015/. Accessed 23 March 2023.

2. Shah H, Albanese E, Duggan C, et al. Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurol*. 2016;15:1285–1294.

3. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. *Lancet*. 2020;396:413–446.

4. Weuve J, Bennett EE, Ranker L, et al. Exposure to air pollution in relation to risk of dementia and related outcomes: an updated systematic review of the epidemiological literature. *Environ Health Perspect*. 2021;129:96001.

5. Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: a systematic review of epidemiologic research. *Neurotoxicology*. 2016;56:235–253.

6. Dhiman V, Trushna T, Raj D, Tiwari RR. Is air pollution associated with increased risk of dementia? a meta-analysis of epidemiological research. *Neurol India*. 2022;70:1004–1019.

7. Cheng S, Jin Y, Dou Y, et al. Long-term particulate matter 2.5 exposure and dementia: a systematic review and meta-analysis. *Public Health*. 2022;212:33–41.

8. Wilker EH, Osman M, Weisskopf MG. Ambient air pollution and clinical dementia: systematic review and meta-analysis. *BMJ*. 2023;381:e071620.

9. Brook RD, Rajagopalan S. Particulate matter, air pollution, and blood pressure. *J Am Soc Hypertens*. 2009;3:332–350.

10. Cai Y, Zhang B, Ke W, et al. Associations of short-term and long-term exposure to ambient air pollutants with hypertension. *Hypertension*. 2016;68:62–70.

11. Liang R, Zhang B, Zhao X, Ruan Y, Lian H, Fan Z. Effect of exposure to PM2.5 on blood pressure: a systematic review and meta-analysis. *J Hypertens*. 2014;32:2130–40; discussion 2141.

12. Qin P, Luo X, Zeng Y, et al. Long-term association of ambient air pollution and hypertension in adults and in children: a systematic review and meta-analysis. *Sci Total Environ*. 2021;796:148620.

13. Li N, Chen G, Liu F, et al. Associations between long-term exposure to air pollution and blood pressure and effect modifications by behavioral factors. *Environ Res*. 2020;182:109109.

14. Zhang Z, Guo C, Lau AKH, et al. Long-term exposure to fine particulate matter, blood pressure, and incident hypertension in Taiwanese adults. *Environ Health Perspect*. 2018;126:017008.

15. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat Med*. 2005;24:2911–2935.

16. Nagai M, Hoshide S, Kario K. Hypertension and dementia. *Am J Hypertens*. 2010;23:116–124.

17. Walker KA, Sharrett AR, Wu A, et al. Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA*. 2019;322:535–545.

18. Abell JG, Kivimäki M, Dugravot A, et al. Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension. *Eur Heart J*. 2018;39:3119–3125.

19. Canavan M, O'Donnell MJ. Hypertension and cognitive impairment: a review of mechanisms and key concepts. *Front Neurol*. 2022;13:821135.

20. Hughes TM, Craft S, Baker LD, et al. Changes in metabolic risk factors over 10 years and their associations with late-life cognitive performance: the Multi-Ethnic Study of Atherosclerosis. *Alzheimers Dement (Amst)*. 2017;8:18–25.

21. Hughes D, Judge C, Murphy R, et al. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA*. 2020;323:1934–1944.

22. Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association between cardiovascular disease and long-term exposure to air pollution with the risk of dementia. *JAMA Neurol*. 2020;77:801–809.

23. Ilango SD, Chen H, Hystad P, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. *Int J Epidemiol*. 2020;49:36–44.

24. Paul KC, Haan M, Yu Y, et al. Traffic-related air pollution and incident dementia: direct and indirect pathways through metabolic dysfunction. *J Alzheimers Dis*. 2020;76:1477–1491.

25. Zhang B, Langa KM, Weuve J, et al. Hypertension and stroke as mediators of air pollution exposure and incident dementia. *JAMA Netw Open*. 2023;6:e2333470.

26. Semmens EO, Leary CS, Fitzpatrick AL, et al. Air pollution and dementia in older adults in the ginkgo evaluation of memory study. *Alzheimers Dement*. 2023;19:549–559.

27. DeKosky ST, Fitzpatrick A, Ives DG, et al; GEMS Investigators. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. *Contemp Clin Trials*. 2006;27:238–253.

28. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48:314–318.

29. Mohs RC. The Alzheimer's disease assessment scale. *Int Psychogeriatr*. 1996;8:195–203.

30. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412–2414.

31. DeKosky ST, Williamson JD, Fitzpatrick AL, et al; Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA*. 2008;300:2253–2262.

32. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. National Institutes of Health; 2004:104. Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/jnc7full.pdf

33. Arnold MJ. Blood pressure targets in adults with hypertension: guidelines from the AAFP. *Am Fam Physician*. 2022;106:721–722. Available at: https://www.aafp.org/pubs/afp/issues/2022/1200/practice-guidelines-hypertension.html. Accessed 1 August 2023.

34. Leary CS, Hajat A, Fitzpatrick AL, et al. Evaluating the importance of historical address histories in an air pollution and dementia study. *Alzheimers Dement*. 2021;17:e053407.

35. Hurley S, Hertz A, Nelson DO, et al. Tracing a path to the past: exploring the use of commercial credit reporting data to construct residential histories for epidemiologic studies of environmental exposures. *Am J Epidemiol*. 2017;185:238–246.

36. Kim SY, Olives C, Sheppard L, et al. Historical prediction modeling approach for estimating long-term concentrations of PM2.5 in cohort studies before the 1999 implementation of widespread monitoring. *Environ Health Perspect*. 2017;125:38–46.

37. Kirwa K, Szpiro AA, Sheppard L, et al. Fine-scale air pollution models for epidemiologic research: insights from approaches developed in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). *Curr Environ Health Rep*. 2021;8:113–126.

38. Young MT, Bechle MJ, Sampson PD, et al. Satellite-based NO_2 and model validation in a national prediction model based on universal kriging and land-use regression. *Environ Sci Technol*. 2016;50:3686–3694.

39. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159:702–706.

40. Fuks KB, Weinmayr G, Foraster M, et al. Arterial blood pressure and long-term exposure to traffic-related air pollution: an analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Environ Health Perspect*. 2014;122:896–905.

41. Hajat A, Hsia C, O'Neill MS. Socioeconomic disparities and air pollution exposure: a global review. *Curr Environ Health Rep*. 2015;2:440–450.

42. Husain K, Ansari RA, Ferder L. Alcohol-induced hypertension: mechanism and prevention. *World J Cardiol*. 2014;6:245–252.

43. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. *J Clin Epidemiol*. 1999;52:643–651.

44. VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health*. 2016;37:17–32.

45. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology*. 2011;22:582–585.

46. Lange T, Starkopf L. Commentary: mediation analyses in the real world. *Epidemiology*. 2016;27:677–681.

47. Lapointe-Shaw L, Bouck Z, Howell NA, et al. Mediation analysis with a time-to-event outcome: a review of use and reporting in healthcare research. *BMC Med Res Methodol*. 2018;18:118.

48. Adar SD, Chen YH, D'Souza JC, et al. Longitudinal analysis of long-term air pollution levels and blood pressure: a cautionary tale from the Multi-Ethnic study of atherosclerosis. *Environ Health Perspect*. 2018;126:107003.

49. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. *J Am Coll Cardiol*. 2018;71:e127–e248.

50. Thunell J, Chen Y, Joyce G, et al. Drug therapies for chronic conditions and risk of Alzheimer's disease and related dementias: a scoping review. *Alzheimers Dement*. 2021;17:41–48.

51. Venkat P, Chopp M, Chen J. Models and mechanisms of vascular dementia. *Exp Neurol*. 2015;272:97–108.

52. Verhaaren BFJ, Vernooij MW, de Boer R, et al. High blood pressure and cerebral white matter lesion progression in the general population. *Hypertension*. 2013;61:1354–1359.

53. Yang BY, Qian Z, Howard SW, et al. Global association between ambient air pollution and blood pressure: a systematic review and meta-analysis. *Environ Pollut*. 2018;235:576–588.

54. Pinto E. Blood pressure and ageing. *Postgrad Med J*. 2007;83:109–114.

55. Power MC, Tchetgen Tchetgen EJ, Sparrow D, Schwartz J, Weisskopf MG. Blood pressure and cognition: factors that may account for their inconsistent association. *Epidemiology*. 2013;24:886–893.

56. Williamson JD, Pajewski NM, Auchus AP, et al; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia. *JAMA*. 2019;321:553–561.

57. Rapp SR, Gaussoin SA, Sachs BC, et al; SPRINT Research Group. Intensive versus standard blood pressure control and domain-specific cognitive function in SPRINT: a sub analysis of a randomized controlled trial. *Lancet Neurol*. 2020;19:899–907.

58. Delgado-Saborit JM, Guercio V, Gowers AM, Shaddick G, Fox NC, Love S. A critical review of the epidemiological evidence of effects of air pollution on dementia, cognitive function and cognitive decline in adult population. *Sci Total Environ*. 2021;757:143734.