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Air pollution and plasma amyloid beta in a cohort of older adults: Evidence from the Ginkgo Evaluation of Memory study

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Abstract

Air pollution has been linked to Alzheimer's disease and related dementias (ADRD), but the mechanisms connecting air pollution to ADRD have not been firmly established. Air pollution may cause oxidative stress and neuroinflammation and contribute to the deposition of amyloid beta (Aβ) in the brain. We examined the association between fine particulate matter<2.5 μm in diameter ($PM_{2.5}$), particulate matter<10 μm in diameter (PM_{10}), nitrogen dioxide (NO_2), and plasma based measures of Aβ1–40, Aβ1–42 and Aβ1–42/Aβ1–40 using data from 3044 dementia-free participants of the Ginkgo Evaluation of Memory Study (GEMS). Air pollution exposures were estimated at residential addresses that incorporated address histories dating back to 1980, resulting in one-, five-, 10- and 20- year exposure averages. Aβ was measured at baseline (2000–

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CRediT authorship contribution statement

Anjum Hajat: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Christina Park:** Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Claire Adam:** Methodology, Writing – review & editing. **Annette L. Fitzpatrick:** Conceptualization, Funding acquisition, Writing – review & editing. **Sindana D. Ilango:** Writing – review & editing. **Cindy Leary:** Validation, Visualization, Writing – review & editing. **Tanya Libby:** Validation, Visualization, Writing – review & editing. **Oscar Lopez:** Writing – review & editing. **Erin O. Semmens:** Conceptualization, Funding acquisition, Writing – review & editing. **Joel D. Kaufman:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107800.

2002) and then again at the end of the study (2007–2008) allowing for linear regression models to assess cross-sectional associations and linear random effects models to evaluate repeated measures. After adjustment for socio-demographic and behavioral covariates, we found small positive associations between each air pollutant and Aβ1–40 but no association with Aβ1–42 or the ratio measures in cross sectional analysis. In repeat measures analysis, we found larger positive associations between each air pollutant and all three outcomes. We observed a 4.43% (95% CI 3.26%, 5.60%) higher Aβ1–40 level, 9.73% (6.20%, 13.38%) higher Aβ1–42 and 1.57% (95% CI: 0.94%, 2.20%) higher Aβ1–42/Aβ1–40 ratio associated with a 2 μg/m^3 higher 20-year average $PM_{2.5}$. Associations with other air pollutants were similar. Our study contributes to the broader evidence base on air pollution and ADRD biomarkers by evaluating longer air pollution exposure averaging periods to better mimic disease progression and provides a modifiable target for ADRD prevention.

Keywords

Air pollution; Alzheimer's disease; Dementia; Biomarkers; Amyloid beta; Aging

1. Introduction

The global population is rapidly aging. Globally, the percentage of people age 65 and older is expected to increase from 8% in 2010 to 16% by 2050 (Nichols et al., 2022). With the aging population, cases of dementia are also anticipated to rise, resulting in an estimated 152.8 million cases, a tripling, by 2050 (Nichols et al., 2022). Treatments for Alzheimer's Disease and related dementias (ADRD) remain elusive, but several modifiable risk factors have been identified. In addition to lifestyle factors such as exercise and diet (Bhatti et al., 2019; Kivimäki and Singh-Manoux, 2018), environmental hazards such as air pollution have also been linked to ADRD (Weuve et al., 2021).

The mechanism by which air pollution causes dementia has not yet been firmly established. Several animal studies suggest that air pollution through its impacts on the central nervous system (CNS) causes neuroinflammation and oxidative stress, which are critical to the development of ADRD (Bhatt et al., 2015; Patten et al., 2021; Sahu et al., 2021). In addition, by altering the activity of key enzymes, air pollution may increase deposition of amyloid beta (Aβ) in the brain, a hallmark of Alzheimer's disease (AD) (Patten et al., 2021). Animal studies have found that long-term exposure to traffic-related air pollution (TRAP) resulted in more Aβ plaques in animals exposed to TRAP compared to those exposed to filtered air (Patten et al., 2021; Sahu et al., 2021).

Although the utility of treatments that reduce Aβ plaques as a means to improve cognitive function have been debated (Ackley et al., 2021), understanding the mechanism by which air pollution impacts brain health remains an important endeavor. Aβ1–40, a peptide with a chain of 40 amino acids, has proinflammatory and atherosclerotic properties and has been associated with cardiovascular disease and diabetes (Peters et al., 2017; Roeben et al., 2016; Stamatelopoulos et al., 2018); studying Aβ1–40 and air pollution can also shed light on

other disease processes. Aβ1–42, on the other hand, is a key component of Aβ plaques found in the brain (Gouras et al., 2015; Wang et al., 2017).

Unlike Aβ plaques in the brain, the presence of Aβ in plasma is expected. Plasma Aβ biomarkers are dynamic over time, can be impacted by various factors (Lopez et al., 2020) and have different trajectories for cognitively intact individuals compared to those that go on to develop dementia. For the cognitively intact, plasma Aβ levels increase with age (Song et al., 2011; Wang et al., 2020) while for those who transition from intact to MCI to AD, a decline in plasma Aβ biomarkers is seen over time (Bateman et al., 2012; Wang et al., 2020). Aβ from the brain can be transported to the blood via the blood brain barrier (and vice versa) (Chen et al., 2017; Wang et al., 2020). In disease-free individuals, soluble Aβ found in the brain could clear into the blood resulting in higher plasma levels, while in diseased persons, the soluble Aβ turns into insoluble Aβ plaques in the brain, which the body is unable to clear, resulting in lower plasma levels.

Given that higher air pollution has been shown to result in worse outcomes (greater cognitive decline and more dementia) (Semmens et al., 2022; Weuve et al., 2021), we would expect that higher air pollution levels would be associated with *lower* plasma Aβ levels among those who go on to develop dementia but *higher* among those who remain disease free. Higher plasma Aβ levels may signify air pollution's role in accelerating plasma Aβ levels that could then result in worse cognitive health.

Only a few studies have explored the association between air pollution and Aβ in humans, some using positron emission tomography (PET) scans or magnetic resonance imaging (MRI) to identify Aβ (Alemany et al., 2021; Iaccarino et al., 2021; Lee et al., 2020), others using cerebrospinal fluid (CSF) (Alemany et al., 2021; Calderón-Garcidueñas et al., 2018, 2016) or autopsy data (Caldeón-Garcidueñas et al., 2012; Calderón-Garcidueñas et al., 2008; Shaffer et al., 2021). Overall the research finds a positive association between air pollution and Aβ; studies using imaging data show a more consistent association. These approaches, although effective at identifying Aβ, have disadvantages in terms of ease, cost and participant burden relative to blood biomarkers of AD. To our knowledge, no study has examined the effect of air pollution on plasma-based Aβ biomarkers.

Researchers continue to search for highly sensitive approaches to measuring Aβ in the blood (Hansson, 2021) in hopes of developing a diagnostic test to more easily identify ADRD. Once identified, these approaches will allow for a better understanding of the mechanisms underlying demonstrated associations between air pollution and dementia. In this study we examined the associations between air pollution and plasma based biomarkers of Aβ both cross-sectionally and in repeated measures in a cohort of dementia-free older adults.

2. Materials and methods

This study consisted of 3,069 adults aged 75 years or older who were free of dementia at baseline and enrolled in the Ginkgo Evaluation of Memory Study (GEMS), a randomized double-blind controlled trial originally designed to evaluate the efficacy of *Ginkgo biloba* on AD and dementia (DeKosky et al., 2008, 2006). Participants were recruited from

four US study sites (Winston-Salem, North Carolina; Hagerstown, Maryland; Sacramento, California; and Pittsburgh, Pennsylvania) between 2000 and 2002 (Fitzpatrick et al., 2006) and followed through 2008. Participants were censored upon death, the development of ADRD or loss to follow-up. This study was approved by the Institutional Review Board at the University of Washington and all institutions affiliated with the trial.

2.1. Exposure ascertainment

Primary exposures of interest were long-term residential concentrations of fine particulate matter<2.5 μm in diameter ($PM_{2.5}$), particulate matter<10 μm in diameter (PM_{10}) and nitrogen dioxide (NO_2) estimated at participant residential addresses. Address histories dating back to 1980 (20 years prior to study entry) were reconstructed using data from LexisNexis (LN), a data analytics corporation that applies a proprietary algorithm to publicly available real estate, driver's license, voting and court records to identify residential history. LN has been used by a few previous epidemiologic studies to create residential histories (Hurley et al., 2017; Semmens et al., 2022; Woolpert et al., 2021). For individuals missing historical residential address data, we used air pollution estimates from last known residential address. More information on the reconstruction of residential histories can be found in the supplement of Semmens et al., 2022.

A previously-described spatiotemporal model was then applied to individual addresses to predict air pollution concentrations at participant's address (Kim et al., 2017; Young et al., 2016). Briefly, the model uses inputs from EPA monitoring data and over 300 geographic covariates to predict air pollution. External validation statistics show good performance of the air pollution prediction models, with R^2 ranging from 0.84 to 0.91 for $PM_{2.5}$ and 0.78 to 0.88 for NO_2 (Kim et al., 2017; Young et al., 2016). Several exposure metrics reflecting different averaging periods were created to better understand when during the life course exposure to air pollution was most strongly associated with Aβ and to better reflect the development of ADRD. Exposure to $PM_{2.5}$ was estimated by averaging one, five, ten, and 20 years of modeled $PM_{2.5}$ prior to the date of blood draw. Estimates of PM_{10} and NO_2 were based only on one-, five- and ten-year exposure metrics because data were not available to create a 20-year prediction.

2.2. Outcome ascertainment

Primary outcomes of interest were levels of plasma Aβ1–40, Aβ1–42 and Aβ1–42/Aβ1–40 ratio. The ratio of Aβ1–42/Aβ1–40, both in plasma and CSF, has been found to improve diagnosis of AD relative to Aβ1–42 alone (Dumurgier et al., 2015) and is used frequently in research. Aβ levels were measured from stored blood samples collected in 2000–2002 and 2007–2008 using a sandwich ELISA initially developed by Eli Lilly and implemented at the University of Vermont Laboratory for Clinical Biochemistry. Interassay coefficients of variation ranged from 3.1% to 7.9% for Aβ1–40 and 12.0% to 20.0% for Aβ1–42 (Shah et al., 2012).

2.3. Covariates

Covariates included basic socio-demographic characteristics: continuous age, sex (male or female), race (white or person of color), education (high school or less, some college,

college graduate or postgraduate), and study site (Winston-Salem, NC; Sacramento, CA; Hagerstown, MD; and Pittsburgh, PA). Although the GEMS clinical trial was negative, treatment assignment (*Ginkgo biloba* vs placebo) was included to account for potential differences between the two arms of the original study. Cystatin C (from plasma collected at the same time as Aβ) was an additional covariate given its role in binding to soluble Aβ and inhibiting Aβ deposition in the brain (Levy, 2008).

A neighborhood deprivation index (NDI) was created for all GEMS participants because of the lack of data on individual income and to account for its potential role as a confounder between air pollution and Aβ. Annual NDI values for each participant were based on the census tract of residence and were created from decennial Census data from 1980, 1990, 2000 and American Community Survey (ACS) 2005–2009. Previous research used over 30 Census variables to conduct a principal components analysis (PCA) to identify the variables that most strongly represented the latent construct of neighborhood disadvantage (Christine et al., 2015). Seven variables were identified from the PCA (% of adults age 25 or older with at least a high school education; % of adults age 25 or older with at least a Bachelor's degree; % of persons age 16 and older with executive, managerial, or professional occupation; median value of owner occupied housing units; median household income; % of households with income of at least $50,000; and % of households with interest, dividend, or net rental income) and weighted according to factor loadings (see supplementary material for more information).

Covariates to account for behavioral factors were smoking status (current, former, never), pack-years smoking, percentage of life exposed to secondhand smoke (created by dividing the number of years exposed to secondhand smoke by age at baseline), alcohol consumption (yes/no), and physical activity. We created a physical activity score based on responses to questions from the GEMS questionnaires that are adapted from components of the validated Physical Activity Scale for the Elderly (PASE) questionnaire (Washburn et al., 1999) designed to assess physical activity in adults aged 65 years and older. The total physical activity score was calculated from answers to questions about the frequency of engaging in seven activities: gardening and yard work, walking, volunteering, assisting family or friends, hunting, fishing or camping, babysitting and shopping. Response options were "never or less than once a month", "once a month", "few (2–3) times a month", "once a week", "few (2–3) times a week" and "every day". Responses were assigned a score of 0–5 and then summed to a total score ranging from 0 to 35 (potential maximum total score) with higher scores indicating greater physical activity. Missing values were imputed by taking the average of the non-missing responses within each participant if at least 3 of the questions had complete data. In the present study, we used physical activity data collected one year after baseline (nearest the blood sample collection in 2000–2002) and carried forward to missing measurements at the 2007–2008 visit in participants with non-missing data.

Apolipoprotein E (APOE ε4) carrier status (yes/no), hypertension (defined as anti-hypertensive medication use or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and recorded one year after baseline) and body mass index (BMI) created from measured height and weight were also included as covariates. Mild cognitive impairment (MCI) was defined using guidelines from the International Working group on

mild cognitive impairment (Snitz et al., 2009) and provided for descriptive purposes as was participant's average score on the Modified Mini-Mental State Examination (3MSE).

2.4. Statistical analyses

Descriptive statistics were calculated for all variables. Due to the skewed nature of Aβ, a one percent Winsorization was performed, i.e., values less than or equal to the first percentile of the distribution were set to the minimum value. For Aβ1–40 these values corresponded to 56.75 and 28.73 pg/mL in 2000–02 or 2007–08 respectively and for Aβ1–42 they were 0.75 and 0.77 pg/mL respectively. Winsorized values were then log transformed (Fig. 1). To create Aβ1–42/Aβ1–40 ratio, we first log-transformed the numerator and denominator before dividing the values. Given the continuous nature of the outcomes, cross-sectional associations were examined using ordinary least squares regression. Repeated measures analyses were evaluated using linear random effects models with a random intercept for participant. Results were reported as percent differences with their corresponding 95% confidence intervals (CIs).

A staged modeling approach was used to assess the impact of adding increasingly more covariates. Model 1 included basic socio-demographic characteristics (continuous age, sex, race, education, study site, treatment assignment, Cystatin C and NDI). Model 2 included Model 1 covariates plus smoking history, alcohol consumption, pack-years smoking, percentage of life exposed to secondhand smoke and physical activity. Model 3 included Model 2 covariates plus APOE ε4, and Model 4 included Model 3 covariates plus hypertension and BMI. As these variables are potentially on the causal pathway between air pollution and Aβ, they were included at the last stage. We considered model 3 as the primary model of interest. Age, Cystatin C, NDI, BMI and hypertension were treated as time-varying in the random effects models.

Data in 2000–02 were carried forward for two individuals missing data on non-time-varying covariates in 2007–08. Most covariates had ≤ 8% missing data with the exception of APOE ε4 which had about 20% missingness. We implemented multiple imputation using chained equations (MICE) to handle missing continuous and categorical covariates. Separate MICE procedures were implemented for each combination of air pollution metric and Aβ outcome at baseline and repeat measures. Logistic or multinomial regression models were specified to impute missing categorical variables. Predictive mean matching was used to impute missing continuous variables. All covariates were included as predictors in the imputation models, but we also included time-varying 3MSE scores as they are potentially informative variables. Ten imputed datasets were constructed using 50 iterations per imputation. Final models were evaluated on all ten imputed datasets and parameter estimates and standard errors were pooled according to Rubin's rules (Rubin, 2004).

In addition to our main analysis, we conducted a secondary analysis to explore the association between air pollution and Aβ outcomes among those with and without MCI. This analysis assessed whether or not plasma Aβ biomarkers show different trajectories for cognitively intact individuals versus those exhibiting some cognitive impairment irrespective of if they go on to develop ADRD. We ran stratified models for both cross-sectional and

repeated measures analysis using only Model 3 covariates and the longer-term averaging periods for air pollutants.

Two sensitivity analyses are also presented. First, to explore the impact of our approach to handling outliers we constructed models using a) the original distribution of values and b) excluding those that were less than or equal to the first percentile. Second, to account for potential selection bias among participants who remained in the study until the end of follow-up (those with repeated Aβ measurements), we ran separate OLS models with baseline and follow-up Aβ as the outcome among only those participants with repeated Aβ measurements (i.e., we did not include those who only had baseline values of Aβ).

Analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC). MICE was performed using PROC MI/PROC MIANALYZE in SAS, and plots were generated using R version 4.0.4 (R Foundation for Statistical Computing). All statistical tests were two-sided and considered significant at p-value < 0.05.

3. Results

We excluded 25 individuals who did not have data on at least one baseline Aβ measurement; 23 of these individuals were also missing address data so did not have air pollution exposure estimates. Our final analytic cohort consisted of 3,044 participants, among whom 1,669 participants had Aβ1–40 or Aβ1–42 measurements from blood samples drawn between 2007 and 2008. Specifically, 1375 censored participants did not have a blood sample available for testing at follow-up, of these 379 died, 469 developed ADRD, and 527 were lost to follow-up. Exact sample sizes vary depending on the specific outcome (Supplemental Fig. 1). Baseline Aβ1–40 ranged from 56.75 pg/mL to 473.95 pg/mL and Aβ1–42 from 0.75 pg/mL to 140.23 pg/mL (Fig. 1). At baseline, average age was 78.6 years, participants were mostly non-Hispanic White (95%), were 46% female, and 64% had at least a college degree (Table 1). Seventeen percent were considered to have mild cognitive impairment at baseline and the average score on the 3MSE for all participants was 93.4 out of 100. Distributions of air pollutants showed higher levels of $PM_{2.5}$ and NO_2 at the Pittsburgh site, higher concentrations for longer averaging periods (e.g., 20 year vs one year averages) and declines in air pollution between baseline and follow-up (Fig. 2). Model results are reported per interquartile range (IQR) increase which corresponded to 2 μg/m^3 for $PM_{2.5}$, 3 μg/ m^3 for PM_{10} and 6 ppb for NO_2. IQR for each air pollutant was obtained by taking the mean IQR across all averaging periods at baseline.

Characteristics that are updated at follow-up visit include age, neighborhood deprivation index, body mass index, hypertension, Cystatin C, mild cognitive impairment status and Mini-Mental State Exam Score.

Number and percent missing are presented for the following characteristics that were missing data at baseline and follow-up visits, respectively: alcohol consumption, n = 48 (2%) and n = 26 (2%); smoking history, n = 58 (2%) and n = 32 (2%); pack-years smoking, n = 230 (8%) and n = 132 (8%); percentage of life exposed to SHS, n = 63 (2%) and n = 33 (2%); neighborhood deprivation index, n = 15 (<1%) and n = 10 (<1%); body mass index, n

= 13 (<1%) and n = 4 (<1%); hypertension, n = 2 (<1%) and n = 11 (<1%); physical activity score, n = 185 (6%) and n = 21 (1%); Cystatin C, n = 3 (<1%) and n = 2 (<1%); APOE ε4 carrier status, n = 624 (20%) and n = 305 (18%); and Mini-Mental State Exam score, n = 0 (0%) and n = 18 (1%).

In cross-sectional analysis using baseline Aβ measurements, we observed small positive associations between Aβ1–40 and each air pollutant in Model 3, our primary model. A 2 μg/m^3 higher one-year $PM_{2.5}$ level was associated with a 1.69% higher Aβ1–40 concentration (95% CI: 0.52%,2.87%). The estimates were attenuated and much closer to zero for longer $PM_{2.5}$ averaging periods. All PM_{10} averaging periods showed a similar association with Aβ1–40, where a 3 μg/m^3 higher PM_{10} was associated with 2% (95% CI: 0.82%, 3.19%), 2.19% (95% CI: 0.92%, 3.48%) and 1.89% (95% CI: 0.74%, 3.05%) higher Aβ1–40 for the one-, five- and ten-year averages respectively. Associations between the one, five and ten-year NO_2 metrics and Aβ1–40 were similar in magnitude but had slightly worse precision. For the other two outcomes, Aβ1–42 and the ratio measure, Model 3 showed null associations between our three air pollutants at differing averaging periods (Fig. 3a – 3c and Supplemental Table 1).

The repeated measures analysis showed stronger magnitudes of effect for all pollutant-outcome combinations in Model 3 (Fig. 3d – 3f and Supplemental Table 2). We observed a 4.43% (95% CI 3.26%, 5.60%), 5.01% (95% CI 3.93%, 6.10%) and 7.20% (95% CI 5.45%, 8.97%) higher Aβ1–40 level associated with an IQR higher 20-year average $PM_{2.5}$, ten-year PM_{10} and ten-year NO_2 respectively. Aβ1–42 had even higher magnitudes of association with each of the air pollutants: 20-year $PM_{2.5}$ was associated with 9.73% (6.20%, 13.38%) higher Aβ1–42; ten-year PM_{10} was associated with 7.34% (95% CI 4.19%, 10.60%) higher Aβ1–42; and ten-year NO_2 was associated with 13.28% (95% CI: 7.95%, 18.86%) higher Aβ1–42. The Aβ1–42/Aβ1–40 ratio showed the smallest associations with all three pollutants: 1.57% (95% CI: 0.94%, 2.20%) with 20-year $PM_{2.5}$, 1.13% (95% CI: 0.56%, 1.71%) with ten-year PM_{10} and 2.09% (95% CI: 1.16%, 3.03%) with ten-year NO_2.

Our MCI-stratified models showed little difference between those with and without MCI both in cross-sectional (Supplemental Table 3) and repeated measures analysis (Supplemental Table 4). For example, a 2 μg/m^3 higher 20-year average $PM_{2.5}$ was associated with a 3.55% higher Aβ1–40 among those with MCI and 4.37% higher Aβ1–40 among those without MCI. Slightly larger differences between those with and without MCI were seen in the Aβ1–42 results, however, the confidence limits were wide and overlapping.

In sensitivity analyses, we explored alternative methods to ensure normality of the outcome residuals, specifically trimming (i.e., excluding) the extreme outliers and making no change to the distribution. This did not change the results in any substantive way but did result in a slight attenuation of parameter estimates when outliers were excluded specifically in the repeat measures analysis (Supplemental Table 5 for cross sectional analysis and Supplemental Table 6 for repeat measures analysis).

Furthermore, we investigated the potential impact of selection bias by examining only those participants who contributed samples to both baseline and the 2007 – 2008 visit (i.e., those

who were not censored or lost to follow-up). We found stronger associations for both $PM_{2.5}$ and NO_2 with all outcomes measured at follow-up relative to baseline (Supplemental Table 7). There was little change in PM_{10} results. This suggests that findings from our repeated measures analysis were driven by participants who remained in the study until the end of follow-up.

4. Discussion

Our study examined the association between air pollutants and biomarkers of Aβ in plasma samples of dementia-free older adults. Findings suggest strong positive associations in the repeat measures analysis for all pollutant-outcome combinations, confirming our initial hypothesis, but largely null associations (with the exception of Aβ1–40) in the cross-sectional ones. Our study contributes to the broader evidence base on air pollution and ADRD biomarkers by evaluating longer air pollution exposure averaging periods relative to many existing studies (Alemany et al., 2021; Calderón-Garcidueñas et al., 2018, 2016; Iaccarino et al., 2021; Lee et al., 2020) and improved exposure assessment relative to others (Calderón-Garcidueñas et al., 2018; Iaccarino et al., 2021; Lee et al., 2020). Given that ADRD develops over the course of many years, evaluating air pollution at longer averaging periods more closely mimics disease development (Jack et al., 2013).

There are several potential reasons that our repeated measures analysis produced stronger associations compared to the cross-sectional results. First, we have more power to detect an effect in the repeated measures analysis given its larger sample size. In addition, those in our repeated measures analysis may have less misclassification of exposure because we are more certain about residential histories during follow up and the several years prior to GEMS enrollment (e.g., approximately 1998–2008 for the 10 year averaging period) relative to residential histories prior to GEMS enrollment (approximately 1990–2000 for the 10 year averaging period). Furthermore, exposure assessment further back in time relies on historical models which are based on less monitoring data and are thus more prone to measurement error. Both improved power and less exposure measurement error could be producing estimates with larger magnitudes in the repeat measures analysis.

We opted to perform a repeat measures analysis as opposed to one that evaluates change in Aβ over time because plasma biomarker data fluctuates significantly, with some disease-free participants seeing decreases in Aβ over the period of follow up. Given the dynamic nature of plasma Aβ (described above), this is to be expected. Furthermore, given the loss to follow up in our sample the repeat measures approach allows us to have a more generalizable sample with more power.

In terms of our MCI stratified results, we did not observe lower Aβ levels among those with MCI. It has been well documented that some with MCI revert back to normal cognition over time (Canevelli et al., 2016); one study estimates an over 50% reversion rate from MCI to normal (Overton et al., 2019). Alternatively, those with stable MCI may not be far enough along in their disease progression to show declines in Aβ. Furthermore, the number of people with MCI in our study was relatively small and our analysis may have been underpowered to see an effect.

Our findings are not directly comparable to existing research as ours was the first to examine plasma Aβ; other studies examined Aβ via PET scans, CSF and autopsy data. Studies in cognitively normal or mildly impaired populations found five-year average PM_{10} (Lee et al., 2020) and annual average NO_2 (Alemany et al., 2021) to be associated with higher odds of Aβ positivity measured via PET scan (i.e., those with indication of Aβ deposits in their brain). Although these studies were cross-sectional in nature, for these mildly impaired groups the association with air pollution was in the expected direction and corroborates our findings.

Another study found that biennial $PM_{2.5}$ concentrations were associated with higher odds of Aβ positivity, also measured with PET scans, in a population composed of participants with either MCI or dementia (Iaccarino et al., 2021). One might expect to see different associations with air pollution between the two groups; air pollution would be associated with higher odds of Aβ positivity in the MCI group, but lower Aβ positivity in those with dementia (Jansen et al., 2015; Ossenkoppele et al., 2015). To better evaluate the Iaccarino et al. findings, stratification by dementia and MCI would be needed.

Limited research has explored the association between air pollution and Aβ measured in CSF. One recent study found no association between several air pollutants and Aβ ratio (Alemany et al., 2021), but others have seen lower concentrations of Aβ1–42 among children living in more polluted areas (Calderón-Garcidueñas et al., 2018, 2016). Substantial research finds that those with AD have lower concentrations of Aβ1–42 in CSF compared to those with MCI and normal cognition (Ma et al., 2022; Skillbäck et al., 2015; Toledo et al., 2015). Thus future air pollution studies should stratify by disease stage in order to better evaluate the relation between air pollution and CSF Aβ.

It is difficult to compare our results to autopsy studies (Calderón-Garcidueas et al., 2012; Shaffer et al., 2021) because the GEMS population at the end of follow-up is likely a mix of those who have ADRD pathology and those who do not and because we do not know who went on to develop ADRD after the GEMS study ended.

Many studies of dementia do not find Aβ1–40 to be highly predictive of dementia status (Song et al., 2011; Wang et al., 2020). In our study the strong associations with Aβ1–40, which as noted above has inflammatory and atherosclerotic properties (Peters et al., 2017; Roeben et al., 2016; Stamatelopoulos et al., 2018), could reflect the well-established relation between air pollution and cardiovascular disease (Brook et al., 2010; Cosselman et al., 2015). These results help validate our findings and suggest that future research on air pollution and dementia should explore Aβ1–40 as it may be playing an important role in vascular dementia.

Our study has several strengths. GEMS provides a large sample size of standardized data, thorough adjustment for potential confounders, and state-of-the-art exposure assessment approaches at the individual residential address level. In terms of limitations, we recognize that our study uses an older biomarker assay. In recent years the scientific community has made significant advances in identifying Aβ in plasma (Hansson, 2021; Nakamura et al., 2018); we hope to utilize new biomarker technology for future air pollution studies.

Furthermore, GEMS is a cohort of primarily White participants who were more educated relative to the US population. At the end of GEMS follow up we were left with a healthier and more resilient population. These features limit our ability to generalize to the broader population. Lastly, we did not adjust for multiple comparisons, which could increase the possibility that findings are due to chance alone, because we set out to test a priori hypotheses about the importance of evaluating longer air pollution averaging periods and because the multiple averaging periods (5-, 10- and 20 year) are nested exposures so may not be considered separate exposures.

A better understanding of the relationship between air pollution and plasma biomarkers of ADRD will help shed light on the mechanisms by which air pollution may be impacting cognitive health. Air pollution is modifiable through policy and regulation thus providing another realistic target for ADRD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The authors do not have permission to share data.

References

Ackley SF, Zimmerman SC, Brenowitz WD, Tchetgen Tchetgen EJ, Gold AL, Manly JJ, Mayeda ER, Filshtein TJ, Power MC, Elahi FM, Brickman AM, Glymour MM, 2021. Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. BMJ 372. 10.1136/bmj.n156.

Alemany S, Crous-Bou M, Vilor-Tejedor N,Mila-Alomá M, Suárez-Calvet M,Salvadó G, Cirach M, Arenaza-Urquijo EM, Sanchez-Benavides G, Grau-Rivera O, Minguillon C, Fauria K, Kollmorgen G, Domingo Gispert J,Gascón M,Nieuwenhuijsen M, Zetterberg H, Blennow K, Sunyer J, Luis Molinuevo J, 2021. Associations between air pollution and biomarkers of Alzheimer's disease in cognitively unimpaired individuals. Environ. Int 157, 106864. 10.1016/j.envint.2021.106864. [PubMed: 34537521]

Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC, Network DIA, 2012. Clinical and biomarker

changes in dominantly inherited Alzheimer's disease. N. Engl. J. Med 367, 795–804. 10.1056/NEJMoa1202753. [PubMed: 22784036]

Bhatt DP, Puig KL, Gorr MW, Wold LE, Combs CK, 2015. A pilot study to assess effects of long-term inhalation of airborne particulate matter on early Alzheimer-like changes in the mouse brain. PLoS One 10. 10.1371/journal.pone.0127102.

Bhatti GK, Reddy AP, Reddy PH, Bhatti JS, 2019. Lifestyle Modifications and Nutritional Interventions in Aging-Associated Cognitive Decline and Alzheimer's Disease. Front. Aging Neurosci 11, 369. 10.3389/fnagi.2019.00369. [PubMed: 31998117]

Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Whitsel L, Kaufman JD, 2010. Particulate Matter Air Pollution and Cardiovascular Disease. Circulation 121, 2331–2378. 10.1161/CIR.0b013e3181dbece1. [PubMed: 20458016]

Calderon-Garcidueas L, Kavanaugh M, Block M, D'Angiulli A, Delgado-Chávez R, Torres-Jardon R, Gonźalez-Maciel A, Reynoso-Robles R, Osnaya N, Villarreal-Calderon R, Guo R, Hua Z, Zhu H, Perry G, Diaz P, 2012. Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. J. Alzheimer's Dis 28 10.3233/JAD-2011-110722.

Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B,Herritt L, Villarreal-Calderón R, Osnaya N, Stone I, García R, Brooks DM, González-Maciel A, Reynoso-Robles R, Delgado-Chávez R, Reed W, 2008. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β−42 and α-synuclein in children and young adults. Toxicol. Pathol 36, 289–310. 10.1177/0192623307313011. [PubMed: 18349428]

Calderón-Garcidueñas L, Avila-Ramírez J, Calderán-Garcidueñas A, González-Heredia T, Acuña-Ayala H, Chao C-K, Thompson C, Ruiz-Ramos R, Cortés-González V, Martínez-Martínez L, García-Pérez MA, Reis J, Mukherjee PS, Torres-Jardón R, Lachmann I, 2016. Cerebrospinal Fluid Biomarkers in Highly Exposed PM2.5 Urbanites: The Risk of Alzheimer's and Parkinson's Diseases in Young Mexico City Residents. J. Alzheimers. Dis 54, 597–613. 10.3233/JAD-160472. [PubMed: 27567860]

Calderón-Garcidueñas L, Mukherjee PS, Waniek K, Holzer M, Chao C-K, Thompson C, Ruiz-Ramos R, Calderón-Garcidueñas A, Franco-Lira M, Reynoso-Robles R, Gónzalez-Maciel A, Lachmann I, 2018. Non-Phosphorylated Tau in Cerebrospinal Fluid is a Marker of Alzheimer's Disease Continuum in Young Urbanites Exposed to Air Pollution. J. Alzheimers. Dis 66, 1437–1451. 10.3233/JAD-180853. [PubMed: 30412505]

Canevelli M, Grande G, Lacorte E, Quarchioni E, Cesari M, Mariani C, Bruno G, Vanacore N, 2016. Spontaneous Reversion of Mild Cognitive Impairment to Normal Cognition: A Systematic Review of Literature and Meta-Analysis. J. Am. Med. Dir. Assoc 17, 943–948. 10.1016/j.jamda.2016.06.020. [PubMed: 27502450]

Chen GF, Xu TH, Yan Y, Zhou YR, Jiang Y, Melcher K, Xu HE, 2017. Amyloid beta: Structure, biology and structure-based therapeutic development. Acta Pharmacol. Sin 38 10.1038/aps.2017.28.

Christine PJ, Auchincloss AH, Bertoni AG, Carnethon MR, Sanchez BN,Moore K, Adar SD, Horwich TB, Watson KE, Diez Roux AV, 2015. Longitudinal Associations Between Neighborhood Physical and Social Environments and Incident Type 2 Diabetes Mellitus: The Multi-Ethnic Study of Atherosclerosis (MESA). JAMA Intern Med 175, 1311–1320. 10.1001/jamainternmed.2015.2691. [PubMed: 26121402]

Cosselman KE, Navas-Acien A, Kaufman JD, 2015. Environmental factors in cardiovascular disease. Nat. Rev. Cardiol 12, 627–642. 10.1038/nrcardio.2015.152. [PubMed: 26461967]

DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL,Burke G, Fried L, Kuller LH, Robbins J, Tracy R, Woolard N, Dunn L, Kronmal R, Nahin R, Furberg C, 2006. 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 27, 238–253. 10.1016/j.cct.2006.02.007. [PubMed: 16627007]

DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA,Lopez OL, Burke G, Carlson MC, Fried LP, Kuller LH, Robbins JA, Tracy RP, Woolard NF, Dunn L, Snitz BE, Nahin

RL, Furberg CD, 2008. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA 300, 2253–2262. 10.1001/jama.2008.683. [PubMed: 19017911]

Dumurgier J, Schraen S, Gabelle A, Vercruysse O, Bombois S, Laplanche J-L,Peoc'h K, Sablonnière B, Kastanenka KV, Delaby C, Pasquier F, Touchon J, Hugon J, Paquet C, Lehmann S, 2015. Cerebrospinal fluid amyloid-β 42/40 ratio in clinical setting of memory centers: a multicentric study. Alzheimers. Res. Ther 7, 30. 10.1186/s13195-015-0114-5. [PubMed: 26034513]

Fitzpatrick AL, Fried LP, Williamson J, Crowley P, Posey D, Kwong L, Bonk J, Moyer R, Chabot J, Kidoguchi L, Furberg CD, DeKosky ST, GEM Study Investigators, 2006. Recruitment of the elderly into a pharmacologic prevention trial: the Ginkgo Evaluation of Memory Study experience. Contemp. Clin. Trials 27, 541–53. 10.1016/j.cct.2006.06.007. [PubMed: 16949348]

Gouras GK, Olsson TT, Hansson O, 2015. β-amyloid Peptides and Amyloid Plaques in Alzheimer's Disease. Neurotherapeutics 12. 10.1007/s13311-014-0313-y.

Hansson O, 2021. Biomarkers for neurodegenerative diseases. Nat. Med 27, 954–963. 10.1038/s41591-021-01382-x. [PubMed: 34083813]

Hurley S, Hertz A, Nelson DO, Layefsky M, Von Behren J, Bernstein L,Deapen D, Reynolds P, 2017. 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 10.1093/aje/kww108.

Iaccarino L, La Joie R, Lesman-Segev OH, Lee E, Hanna L, Allen IE, Hillner BE,Siegel BA, Whitmer RA, Carrillo MC, Gatsonis C, Rabinovici GD, 2021. Association between Ambient Air Pollution and Amyloid Positron Emission Tomography Positivity in Older Adults with Cognitive Impairment. JAMA Neurol 78, 197–207. 10.1001/jamaneurol.2020.3962. [PubMed: 33252608]

Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS,Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ, 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet. Neurol 12, 207–216. 10.1016/S1474-4422(12)70291-0. [PubMed: 23332364]

Jansen WJ, Ossenkoppele R, Knol DL, Tijms BM, Scheltens P, Verhey FRJ,Visser PJ, Amyloid Biomarker Study Group, Aalten P, Aarsland D, Alcolea D, Alexander M, Almdahl IS, Arnold SE, Baldeiras I, Barthel H, van Berckel BNM, Bibeau K, Blennow K, Brooks DJ, van Buchem MA, Camus V, Cavedo E, Chen K, Chetelat G, Cohen AD, Drzezga A, Engelborghs S, Fagan AM, Fladby T, Fleisher AS, van der Flier WM, Ford L, Förster S, Fortea J, Foskett N, Frederiksen KS, Freund-Levi Y, Frisoni GB, Froelich L, Gabryelewicz T, Gill KD, Gkatzima O, Gómez-Tortosa E, Gordon MF, Grimmer T, Hampel H, Hausner L, Hellwig S, Herukka S-K, Hildebrandt H, Ishihara L, Ivanoiu A, Jagust WJ, Johannsen P, Kandimalla R, Kapaki E, Klimkowicz-Mrowiec A, Klunk WE, Köhler S, Koglin N, Kornhuber J, Kramberger MG, Van Laere K, Landau SM, Lee DY, de Leon M, Lisetti V, Lleó A, Madsen K, Maier W, Marcusson J, Mattsson N, de Mendonça A, Meulenbroek O, Meyer PT, Mintun MA, Mok V, Molinuevo JL, Møllergård HM, Morris JC, Mroczko B, Van der Mussele S, Na DL, Newberg A, Nordberg A, Nordlund A, Novak GP, Paraskevas GP, Parnetti L, Perera G, Peters O, Popp J, Prabhakar S,Rabinovici GD, Ramakers IHGB, Rami L, Resende de Oliveira C, Rinne JO, Rodrigue KM, Rodríguez-Rodríguez E, Roe CM, Rot U, Rowe CC, Rüther E, Sabri O, Sanchez-Juan P, Santana I, Sarazin M, Schröder J, Schütte C, Seo SW, Soetewey F, Soininen H, Spiru L, Struyfs H, Teunissen CE, Tsolaki M, Vandenberghe R, Verbeek MM, Villemagne VL, Vos SJB, van Waalwijk van Doorn LJC, Waldemar G, Wallin A, Wallin ÅK, Wiltfang J, Wolk DA, Zboch M, Zetterberg H, 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 313, 1924–38. 10.1001/jama.2015.4668. [PubMed: 25988462]

Kim S-Y, Olives C, Sheppard L, Sampson PD, Larson TV, Keller JP, Kaufman JD, 2017. 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 125, 38–46. 10.1289/EHP131. [PubMed: 27340825]

Kivimäki M, Singh-Manoux A, 2018. Prevention of dementia by targeting risk factors. Lancet (London, England) 10.1016/S0140-6736(18)30578-6.

Lee JH, Byun MS, Yi D, Ko K, Jeon SY, Sohn BK, Lee JY, Lee Y, Joung H, Lee DY, 2020. Long-Term Exposure to PM10 and in vivo Alzheimer's Disease Pathologies. J. Alzheimer's Dis 78 10.3233/JAD-200694.

Levy E, 2008. Cystatin C: a potential target for Alzheimer's treatment. Expert Rev.Neurother 8, 687–689. 10.1586/14737175.8.5.687. [PubMed: 18457524]

Lopez OL, Klunk WE, Mathis CA, Snitz BE, Chang Y, Tracy RP, Kuller LH,2020. Relationship of amyloid-β1–42 in blood and brain amyloid: Ginkgo Evaluation of Memory Study. Brain Commun 2 10.1093/braincomms/fcz038.

Ma Y, Brettschneider J, Collingwood JF, 2022. A Systematic Review and Meta-Analysis of Cerebrospinal Fluid Amyloid and Tau Levels Identifies Mild Cognitive Impairment Patients Progressing to Alzheimer's Disease. Biomedicines 10. 10.3390/biomedicines10071713.

Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, Fowler C,Li QX, Martins R, Rowe C, Tomita T, Matsuzaki K, Ishii K, Ishii K, Arahata Y, Iwamoto S, Ito K, Tanaka K, Masters CL, Yanagisawa K, 2018. High performance plasma amyloid-β biomarkers for Alzheimer's disease. Nature 554. 10.1038/nature25456.

Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F,Abdoli A, Abualhasan A, Abu-Gharbieh E, Akram TT, Al Hamad H, Alahdab F, Alanezi FM, Alipour V, Almustanyir S, Amu H, Ansari I, Arabloo J, Ashraf T, Astell-Burt T, Ayano G, Ayuso-Mateos JL, Baig AA, Barnett A, Barrow A, Baune BT, Béjot Y, Bezabhe WMM, Bezabih YM, Bhagavathula AS, Bhaskar S, Bhattacharyya K, Bijani A, Biswas A, Bolla SR, Boloor A, Brayne C, Brenner H, Burkart K, Burns RA, Cámera LA, Cao C, Carvalho F, Castro-de-Araujo LFS, Catalá-López F, Cerin E, Chavan PP, Cherbuin N, Chu D-T, Costa VM, Couto RAS, Dadras O, Dai X, Dandona L, Dandona R, De la Cruz-Góngora V, Dhamnetiya D, Dias da Silva D, Diaz D, Douiri A, Edvardsson D, Ekholuenetale M, El Sayed I, El-Jaafary SI, Eskandari K, Eskandarieh S, Esmaeilnejad S, Fares J, Faro A, Farooque U, Feigin VL, Feng X, Fereshtehnejad S-M, Fernandes E, Ferrara P, Filip I, Fillit H, Fischer F, Gaidhane S, Galluzzo L, Ghashghaee A, Ghith N, Gialluisi A, Gilani SA, Glavan I-R, Gnedovskaya EV, Golechha M, Gupta R, Gupta VB, Gupta VK, Haider MR, Hall BJ, Hamidi S, Hanif A, Hankey GJ, Haque S, Hartono RK, Hasaballah AI, Hasan MT, Hassan A, Hay SI, Hayat K, Hegazy MI, Heidari G, Heidari-Soureshjani R, Herteliu C, Househ M, Hussain R, Hwang B-F, Iacoviello L, Iavicoli I, Ilesanmi OS, Ilic IM, Ilic MD, Irvani SSN, Iso H, Iwagami M, Jabbarinejad R, Jacob L, Jain V, Jayapal SK, Jayawardena R, Jha RP, Jonas JB, Joseph N, Kalani R, Kandel A, Kandel H, Karch A, Kasa AS, Kassie GM, Keshavarz P, Khan MAB, Khatib MN, Khoja TAM, Khubchandani J, Kim MS, Kim YJ, Kisa A, Kisa S, Kivimäki M, Koroshetz WJ, Koyanagi A, Kumar GA, Kumar M, Lak HM, Leonardi M, Li B, Lim SS, Liu X, Liu Y, Logroscino G, Lorkowski S, Lucchetti G, Lutzky Saute R, Magnani FG, Malik AA, Massano J, Mehndiratta MM, Menezes RG, Meretoja A, Mohajer B, Mohamed Ibrahim N, Mohammad Y, Mohammed A, Mokdad AH, Mondello S, Moni MAA, Moniruzzaman M, Mossie TB, Nagel G, Naveed M, Nayak VC, Neupane Kandel S, Nguyen TH, Oancea B, Otstavnov N, Otstavnov SS, Owolabi MO, Panda-Jonas S, Pashazadeh Kan F, Pasovic M, Patel UK, Pathak M, Peres MFP, Perianayagam A, Peterson CB, Phillips MR, Pinheiro M, Piradov MA, Pond CD, Potashman MH, Pottoo FH, Prada SI, Radfar A, Raggi A, Rahim F, Rahman M, Ram P, Ranasinghe P, Rawaf DL, Rawaf S, Rezaei N, Rezapour A, Robinson SR, Romoli M, Roshandel G, Sahathevan R, Sahebkar A, Sahraian MA, Sathian B, Sattin D, Sawhney M, Saylan M, Schiavolin S, Seylani A, Sha F, Shaikh MA, Shaji KS, Shannawaz M, Shetty JK, Shigematsu M, Shin JI, Shiri R, Silva DAS, Silva JP, Silva R, Singh JA, Skryabin VY, Skryabina AA, Smith AE, Soshnikov S, Spurlock EE, Stein DJ, Sun J, Tabarés-Seisdedos R, Thakur B, Timalsina B, Tovani-Palone MR, Tran BX, Tsegaye GW, Valadan Tahbaz S, Valdez PR, Venketasubramanian N, Vlassov V, Vu GT, Vu LG, Wang Y-P, Wimo A, Winkler AS, Yadav L, Yahyazadeh Jabbari SH, Yamagishi K, Yang L, Yano Y, Yonemoto N, Yu C, Yunusa I, Zadey S, Zastrozhin MS, Zastrozhina A, Zhang Z-J, Murray CJL, Vos T, 2022. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Heal 7 10.1016/S2468-2667(21)00249-8 e105–e125.

Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BNM, Scheltens P, Visser PJ, Amyloid PET Study Group, Verfaillie SCJ, Zwan MD, Adriaanse SM, Lammertsma AA, Barkhof F, Jagust WJ, Miller BL, Rosen HJ, Landau SM, Villemagne VL, Rowe CC, Lee DY, Na DL, Seo SW, Sarazin M, Roe CM, Sabri O, Barthel H, Koglin N, Hodges J,Leyton CE, Vandenberghe R, van Laere K, Drzezga A, Forster S, Grimmer T, Sánchez-Juan P, Carril JM, Mok V, Camus V, Klunk WE, Cohen AD, Meyer PT, Hellwig S, Newberg A, Frederiksen KS, Fleisher AS, Mintun MA, Wolk DA, Nordberg A, Rinne JO, Chételat G, Lleo

A, Blesa R, Fortea J, Madsen K, Rodrigue KM, Brooks DJ, 2015. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA 313, 1939–49. 10.1001/jama.2015.4669. [PubMed: 25988463]

Overton M, Pihlsgård M, Elmståhl S, 2019. Diagnostic Stability of Mild Cognitive Impairment, and Predictors of Reversion to Normal Cognitive Functioning. Dement. Geriatr. Cogn. Disord 48, 317–329. 10.1159/000506255. [PubMed: 32224608]

Patten KT, Valenzuela AE, Wallis C, Berg EL, Silverman JL, Bein KJ, Wexler AS, Lein PJ, 2021. The effects of chronic exposure to ambient traffic-related air pollution on alzheimer's disease phenotypes in wildtype and genetically predisposed male and female rats. Environ. Health Perspect 129 10.1289/EHP8905.

Peters KE, Davis WA, Taddei K, Martins RN, Masters CL, Davis TME, Bruce DG, 2017. Plasma Amyloid-β Peptides in Type 2 Diabetes: A Matched Case-Control Study. J. Alzheimer's Dis 56, 1127–1133. 10.3233/JAD-161050. [PubMed: 28106562]

Roeben B, Maetzler W, Vanmechelen E, Schulte C, Heinzel S, Stellos K, Godau J,Huber H, Brockmann K, Wurster I, Gaenslen A, Grüner E, Niebler R, Eschweiler GW, Berg D, 2016. Association of Plasma Aβ40 Peptides, but Not Aβ42, with Coronary Artery Disease and Diabetes Mellitus. J. Alzheimer's Dis 52, 161–169. 10.3233/JAD-150575. [PubMed: 27003209]

Rubin DB, 2004. Multiple imputation for nonresponse in surveys John Wiley & Sons Ltd.

Sahu B, Mackos AR, Floden AM, Wold LE, Combs CK, 2021. Particulate Matter Exposure Exacerbates Amyloid-β Plaque Deposition and Gliosis in APP/PS1 Mice. J. Alzheimer's Dis 80 10.3233/JAD-200919.

Semmens EO, Leary CS, Fitzpatrick AL, Ilango SD, Park C, Adam CE, DeKosky ST, Lopez O, Hajat A, Kaufman JD, 2022. Air pollution and dementia in older adults in the Ginkgo Evaluation of Memory Study. Alzheimers. Dement 10.1002/alz.12654.

Shaffer RM, Li G, Adar SD, Dirk Keene C, Latimer CS, Crane PK, Larson EB, Kaufman JD, Carone M, Sheppard L, 2021. Fine Particulate Matter and Markers of Alzheimer's Disease Neuropathology at Autopsy in a Community-Based Cohort. J. Alzheimers. Dis 79, 1761–1773. 10.3233/JAD-201005. [PubMed: 33459717]

Shah NS, Vidal JS, Masaki K, Petrovitch H, Ross GW, Tilley C, Demattos RB, Tracy RP, White LR, Launer LJ, 2012. Midlife blood pressure, plasma β-amyloid, and the risk for alzheimer disease: The honolulu asia aging study. Hypertension 59. 10.1161/HYPERTENSIONAHA.111.178962.

Skillbäck T, Farahmand BY, Rosén C, Mattsson N, Nägga K, Kilander L, Religa D, Wimo A, Winblad B, Schott JM, Blennow K, Eriksdotter M,Zetterberg H, 2015. Cerebrospinal fluid tau and amyloid-β1–42 in patients with dementia. Brain 138, 2716–2731. 10.1093/brain/awv181. [PubMed: 26133663]

Snitz BE, Saxton J, Lopez OL, Ives DG, Dunn LO, Rapp SR, Carlson MC, Fitzpatrick AL, Dekosky ST, GEM study Investigators, 2009. Identifying mild cognitive impairment at baseline in the Ginkgo Evaluation of Memory (GEM) study. Aging Ment. Health 13, 171–182. 10.1080/13607860802380656. [PubMed: 19347684]

Song F, Poljak A, Valenzuela M, Mayeux R, Smythe GA, Sachdev PS, 2011. Meta-analysis of plasma amyloid-β levels in Alzheimer's disease. J. Alzheimers. Dis 26, 365–375. 10.3233/JAD-2011-101977. [PubMed: 21709378]

Stamatelopoulos K, Pol CJ, Ayers C, Georgiopoulos G, Gatsiou A, Brilakis ES, Khera A, Drosatos K, de Lemos JA, Stellos K, 2018. Amyloid-Beta (1–40) Peptide and Subclinical Cardiovascular Disease. J. Am. Coll. Cardiol 72, 1060–1061. 10.1016/j.jacc.2018.06.027. [PubMed: 30139434]

Toledo JB, Zetterberg H, van Harten AC, Glodzik L, Martinez-Lage P, Bocchio-Chiavetto L, Rami L, Hansson O, Sperling R, Engelborghs S, Osorio RS, Vanderstichele H, Vandijck M, Hampel H, Teipl S, Moghekar A, Albert M, Hu WT, Monge Argilés JA, Gorostidi A, Teunissen CE, De Deyn PP, Hyman BT, Molinuevo JL, Frisoni GB, Linazasoro G, de Leon MJ, van der Flier WM, Scheltens P, Blennow K, Shaw LM, Trojanowski JQ, Alzheimer's Disease Neuroimaging Initiative, 2015. Alzheimer's disease cerebrospinal fluid biomarker in cognitively normal subjects. Brain 138, 2701–2715. 10.1093/brain/awv199. [PubMed: 26220940]

Wang J, Gu BJ, Masters CL, Wang YJ, 2017. A systemic view of Alzheimer disease - Insights from amyloid-β metabolism beyond the brain. Nat. Rev. Neurol 13 10.1038/nrneurol.2017.111.

Wang X, Sun Y, Li T, Cai Y, Han Y, 2020. Amyloid-β as a Blood Biomarker for Alzheimer's Disease: A Review of Recent Literature. J. Alzheimers. Dis 73, 819–832. 10.3233/JAD-190714. [PubMed: 31868667]

Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA, 1999. The physical activity scale for the elderly (PASE): evidence for validity. J. Clin. Epidemiol 52, 643–651. 10.1016/s0895-4356(99)00049-9. [PubMed: 10391658]

Weuve J, Bennett EE, Ranker L, Gianattasio KZ, Pedde M, Adar SD, Yanosky JD, Power MC, 2021. Exposure to air pollution in relation to risk of dementia and related outcomes: An updated systematic review of the epidemiological literature. Environ. Health Perspect 10.1289/EHP8716.

Woolpert KM, Ward KC, England CV, Lash TL, 2021. Validation of LexisNexis Accurint in the Georgia Cancer Registry's Cancer Recurrence and Information Surveillance Program. Epidemiology 32, 434–438. 10.1097/EDE.0000000000001327. [PubMed: 33591053]

Young MT, Bechle MJ, Sampson PD, Szpiro AA, Marshall JD, Sheppard L, Kaufman JD, 2016. Satellite-Based NO2 and Model Validation in a National Prediction Model Based on Universal Kriging and Land-Use Regression. Environ. Sci. Technol 50, 3686–3694. 10.1021/acs.est.5b05099. [PubMed: 26927327]

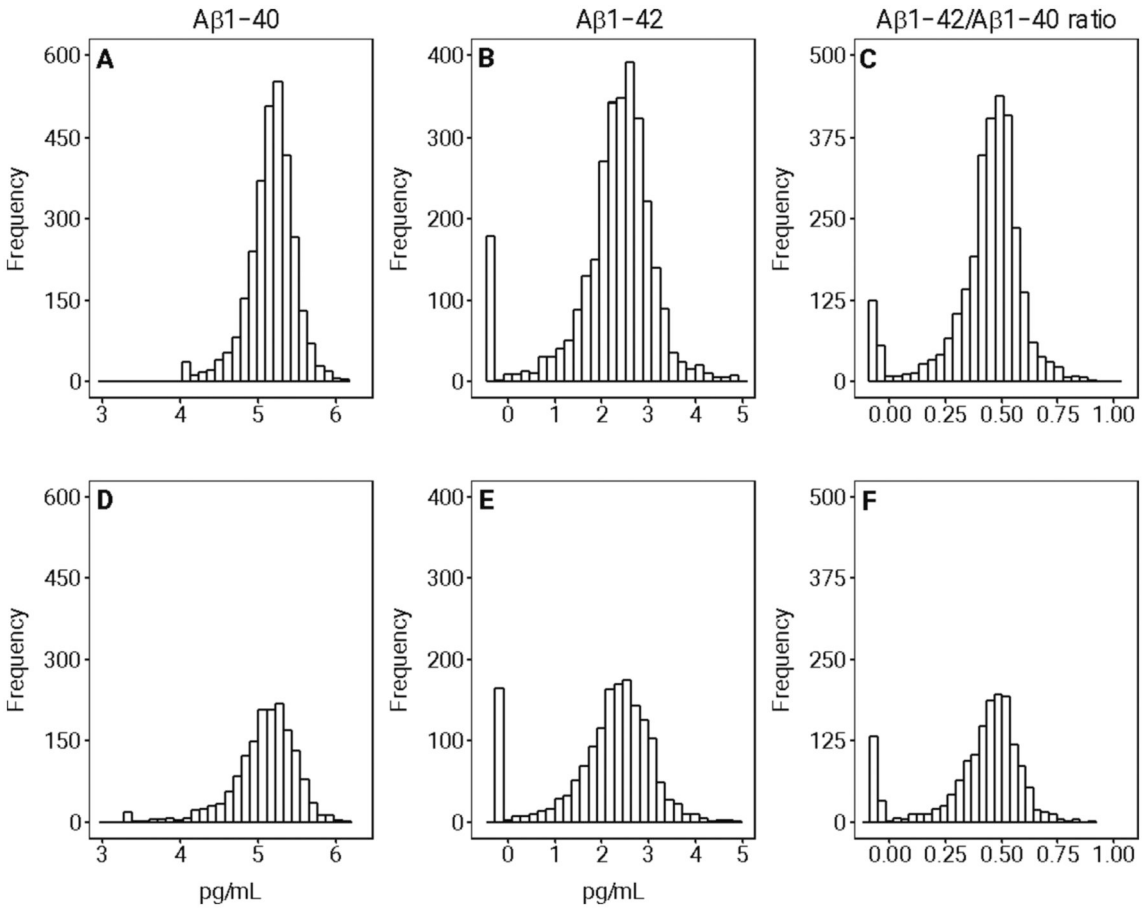

Fig. 1.

Histograms of log-transformed and winsorized Aβ1–40 (pg/mL), Aβ1–42 (pg/mL) and Aβ1–42/Aβ1–40 ratio values at 2000–02 **(A, B and C)** and 2007–08 **(D, E and F)**. Aβ values less than or equal to the first percentile of their distributions at 2000–02 and 2007–08 were removed and set to the minimum value (winsorized) and then log-transformed. The Aβ1–42/Aβ1–40 ratio was created by taking the log-transformation of both the numerator and denominator before division.

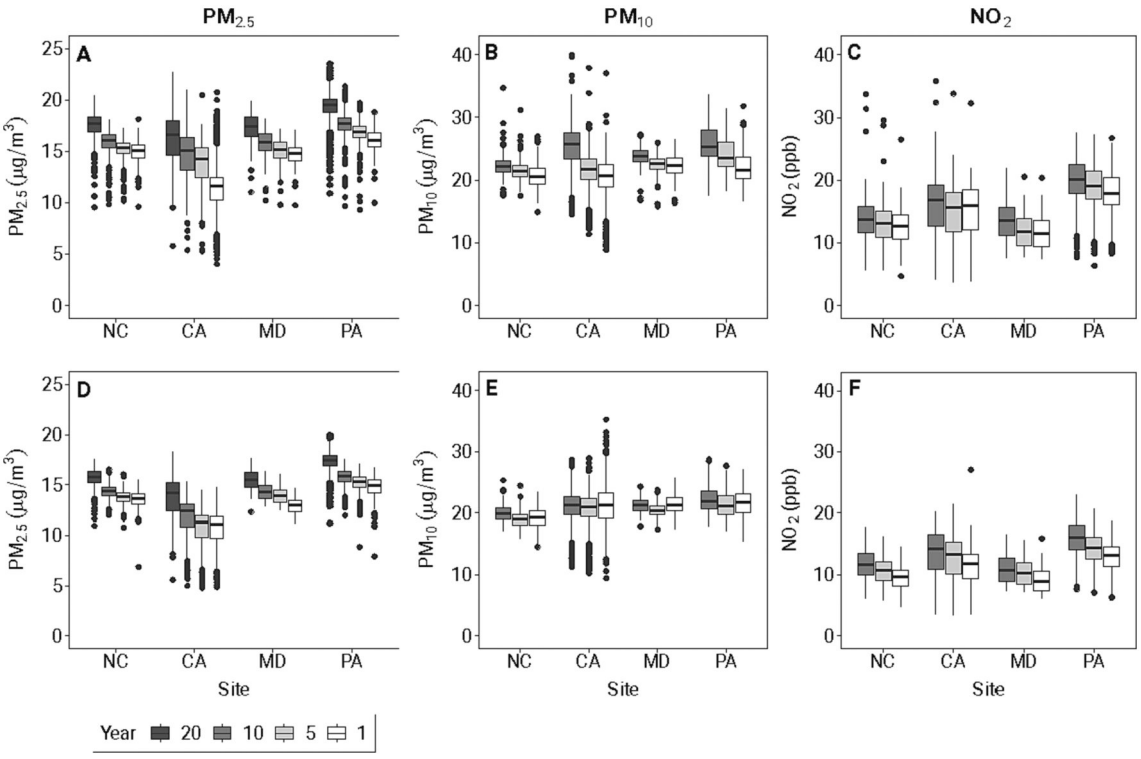

Fig. 2.

Distributions of $PM_{2.5}$, PM_{10} and NO_2 by study site and different exposure periods (1-, 5-, 10- and 20-year averages) prior to 2000–02 (*A*, *B* and *C*) and 2007–08 (*D*, *E* and *F*). Abbreviations: CA, California; MD, Maryland; NC, North Carolina; PA, Pennsylvania. Note: Data were not available for 20-year averages of PM_{10} and NO_2.

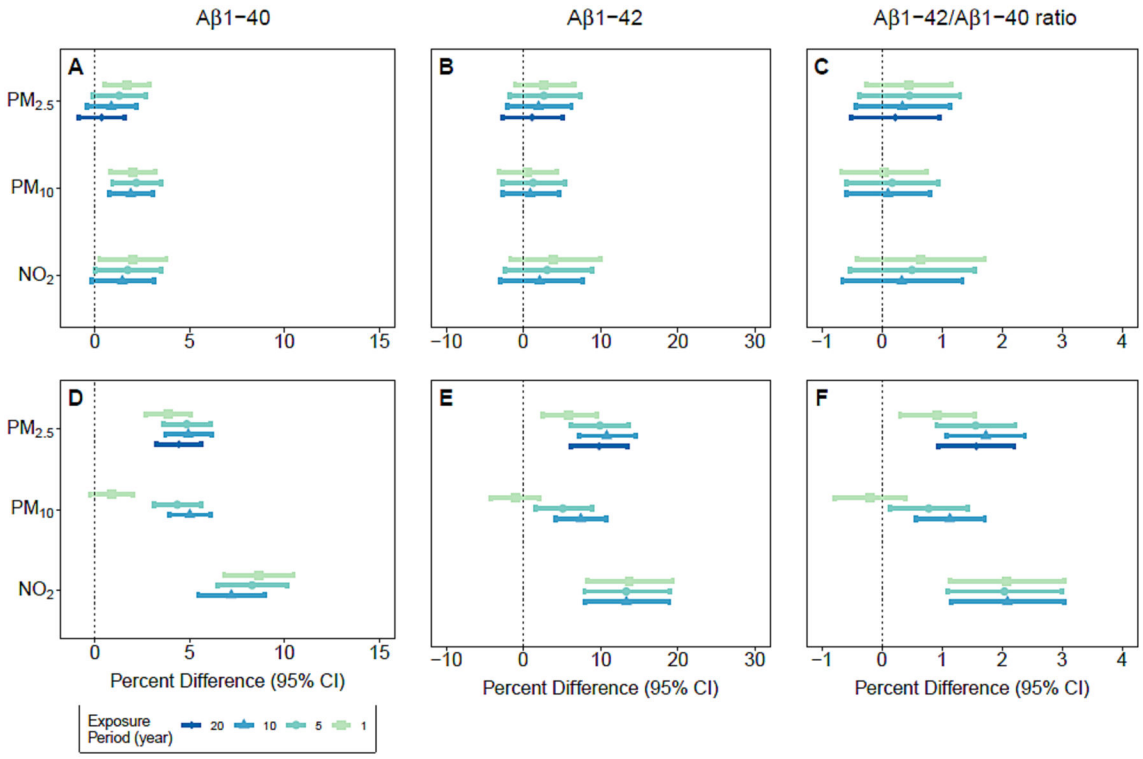

Fig. 3.

Adjusted percent differences and 95% confidence intervals (CIs) in baseline (*A*, *B* and *C*) and repeat (*D*, *E* and *F*) measures of Aβ1–40, Aβ1–42 and Aβ1–42/Aβ1–40 ratio per 1 interquartile range (IQR) unit higher $PM_{2.5}$ (IQR = 2 μg/m^3), PM_{10} (IQR = 3 μg/m^3) and NO_2 (IQR = 6 ppb) by different averaging periods for $PM_{2.5}$ (10 and 20 years) and PM_{10} and NO_2 (5 and 10 years for both) in Model 3. Model 3 adjusted for age, sex, race, education, study site, treatment assignment, Cystatin C, neighborhood deprivation index, smoking history, alcohol consumption, pack-years smoking, percentage of life exposed to secondhand smoke, physical activity and APOE ε4.

Table 1

Characteristics at baseline and follow-up of GEMS participants stratified by groups with Aβ measurements at 2000–02 (N = 3,044) and 2007–08 (N = 1,669).

Characteristic	2000–02	2007–08
	N = 3,044	**N = 1,669**
Age, years	78.6 (3.3)	84.5 (3.0)
Female sex, n (%)	1408 (46)	727 (44)
People of color, n (%)	139 (5)	68 (4)
Placebo assignment, n (%)	1511 (50)	847 (51)
Education, n (%)		
High school or less	335 (11)	168 (10)
Some college	763 (25)	415 (25)
College graduate	767 (25)	400 (24)
Postgraduate	1179 (39)	686 (41)
Study site, n (%)		
Winston-Salem, NC	724 (24)	384 (23)
Sacramento, CA	909 (30)	533 (32)
Hagerstown, MD	454 (15)	252 (15)
Pittsburgh, PA	957 (31)	500 (30)
Alcohol consumption, n (%)	1328 (44)	766 (47)
Smoking history, n (%)		
Never	1214 (41)	684 (42)
Former	1637 (55)	887 (54)
Current	135 (5)	66 (4)
Pack-years smoking	3.6 (0.0, 27.0)	2.4 (0.0, 24.8)
Percentage of life exposed to SHS	24 (1, 46)	24 (0, 45)
Neighborhood deprivation index		
1 year	0.04 (−2.26, 2.22)	−0.08 (−2.28, 1.87)
5 year	0.08 (−2.18, 2.18)	−0.06 (−2.27, 1.90)
10 year	0.10 (−2.20, 2.22)	0.01 (−2.20, 2.02)
20 year	0.14 (−1.93, 2.25)	0.12 (−2.10, 2.05)
Body mass index, kg/m^2	27.1 (4.3)	26.4 (4.1)
Hypertension, n (%)	2114 (69)	1319 (80)
Physical activity score	13.4 (4.8)	14.0 (4.5)
Cystatin C, mg/L	0.83 (0.21)	0.97 (0.32)
APOE ε4 carrier status, n (%)	574 (24)	299 (22)
Mild cognitive impairment status, n (%)	510 (17)	469 (28)
Modified Mini-Mental State Exam score	93.4 (4.7)	94.9 (4.9)

Continuous variables are presented as mean (SD) or median (interquartile range), where appropriate, and categorical variables are presented as n (%). Abbreviations: *APOE*, apolipoprotein E; *SHS*, secondhand smoke.