A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP8716.

Exposure to Air Pollution in Relation to Risk of Dementia and Related Outcomes: An Updated Systematic Review of the Epidemiological Literature

Jennifer Weuve,[1] Erin E. Bennett,[2] Lynsie Ranker,[1] Kan Z. Gianattasio,[2] Meredith Pedde,[3] Sara D. Adar,[3] Jeff D. Yanosky,[4] and Melinda C. Power[2]

[1]Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA
[2]Department of Epidemiology, The George Washington University Milken Institute School of Public Health, Washington, DC, USA
[3]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan, USA
[4]Department of Public Health Sciences, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA

Background: Dementia is a devastating neurologic condition that is common in older adults. We previously reviewed the epidemiological evidence examining the hypothesis that long-term exposure to air pollution affects dementia risk. Since then, the evidence base has expanded rapidly.

Objectives: With this update, we collectively review new and previously identified epidemiological studies on air pollution and late-life cognitive health, highlighting new developments and critically discussing the merits of the evidence.

Methods: Using a registered protocol (PROSPERO 2020 CRD42020152943), we updated our literature review to capture studies published through 31 December 2020, extracted data, and conducted a bias assessment.

Results: We identified 66 papers (49 new) for inclusion in this review. Cognitive level remained the most commonly considered outcome, and particulate matter (PM) remained the most commonly considered air pollutant. Since our prior review, exposure estimation methods in this research have improved, and more papers have looked at cognitive change, neuroimaging, and incident cognitive impairment/dementia, though methodological concerns remain common. Many studies continue to rely on administrative records to ascertain dementia, have high potential for selection bias, and adjust for putative mediating factors in primary models. A subset of 35 studies met strict quality criteria. Although high-quality studies of fine particulate matter with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) and cognitive decline generally supported an adverse association, other findings related to $PM_{2.5}$ and findings related to particulate matter with aerodynamic diameter $\leq$10 μm (PM_{10}, NO_2, and NO_x) were inconclusive, and too few papers reported findings with ozone to comment on the likely direction of association. Notably, only a few findings on dementia were included for consideration on the basis of quality criteria.

Discussion: Strong conclusions remain elusive, although the weight of the evidence suggests an adverse association between $PM_{2.5}$ and cognitive decline. However, we note a continued need to confront methodological challenges in this line of research. https://doi.org/10.1289/EHP8716

Introduction

Dementia erodes the affected person's independence, imposes emotional and financial burdens on care partners, and levies enormous costs to social safety nets (Alzheimer's Association 2018; El-Hayek et al. 2019). An estimated 5.8 million older Americans have Alzheimer's disease and related dementias (ADRD) (Hebert et al. 2013), and pre-COVID-19 forecasts predict 13.8 million ADRD cases by 2050 due to the changing age structure of the U.S. population (Hebert et al. 2013). This trend will echo globally (Prince et al. 2015). Efforts to develop drugs to treat Alzheimer's dementia (AD) have a >99% failure rate (Cummings et al. 2014). As such, efforts to identify and intervene on modifiable factors that prevent or delay the onset of dementia are critical to addressing the dementia epidemic (Alzheimer's Association 2015; Brookmeyer et al. 1998, 2018; Wu et al. 2016). However, interventions that rely on changes in individual behavior (e.g., physical activity, diabetes management) are notoriously challenging to apply broadly, and their success may require fundamental changes to social and economic norms. In contrast, many environmental exposures can be modified in the absence of individual behavioral change, yielding significant improvements in health. For example, regulations and technological innovation have demonstrably reduced air pollution exposures (Brauer et al. 2016; Samet 2011), and past reductions in air pollution exposure have contributed to increased life expectancy (Clancy et al. 2002; Correia et al. 2013; Dominici et al. 2007; Hedley et al. 2002; Laden et al. 2006; Peters et al. 2009; Pope et al. 2009, 2013).

We previously reviewed the epidemiological evidence examining the hypothesis that long-term exposure to air pollution affects risk of ADRD (Power et al. 2016). This review encompassed investigations of ADRD, along with its related cognitive precursors and manifestations (lower and worsening cognitive performance), and neuroimaging indices of dementia-related pathology. At the time, most studies observed that higher exposure to air pollution was associated with at least one adverse dementia-related outcome, yet air pollution is only now starting to enter clinical and advocacy discussions of risk factors for late-life cognitive impairment (Alzheimer's Association 2020; Livingston et al. 2020; Mayo Clinic 2020). Since our previous review, studies have continued to amass. Other systematic reviews have emerged as well, with most concluding that air pollution is likely associated with dementia or related outcomes (Babadjouni et al. 2017; Cipriani et al. 2018; de Prado Bert et al. 2018; Killin et al. 2016; Peters et al. 2019). Those reviews differed from ours in scope; some focused on a subset of outcomes (e.g., dementia, cognitive decline, or MRI-based outcomes) (de Prado Bert et al. 2018; Peters et al. 2019), and others extended to additional neurodegenerative conditions (Oliveira et al. 2020). They also differed in terms of purpose; whereas most other reviews aimed to comprehensively summarize all findings, we

Address correspondence to Melinda C. Power, George Washington University, Milken Institute School of Public Health, 950 New Hampshire Ave. NW, Washington, DC 20052 USA. Email: power@gwu.edu

Supplemental Material is available online (https://doi.org/10.1289/EHP8716).

M.C.P., J.W., and S.A. report grants from the National Institute on Aging (NIA) and National Institute of Environmental Health Sciences (NIEHS), including funding to examine the association between air pollution exposure and late-life cognitive health and related outcomes. These funds to M.C.P. provided salary support for E.E.B. and K.Z.G.. J.W. also reports consultancies with the Alzheimer's Association and the Health Effects Institute. S.A. also reports a consultancy with the Health Effects Institute. All other authors declare they have no actual or potential competing financial interests.

Received 25 November 2020; Revised 4 August 2021; Accepted 5 August 2021; Published 24 September 2021.

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to 508 standards due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehponline@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

sought to systematically identify those studies with the strongest designs for testing these hypotheses, given the numerous methodological challenges in conducting this research. This work builds on our previous review of epidemiological studies linking air pollution to ADRD, along with its cognitive and neuroimaging correlates by updating our search and integrating the new and previously reviewed evidence. We highlight new developments and critically discuss the merits and limitations of the evidence, focusing on those papers with the most methodological strengths.

Methods

We registered the original (PROSPERO 2015 CRD42015016805) and updated (PROSPERO 2020 CRD42020152943) systematic review protocols with PROSPERO. Under the updated protocol, we repeated our original literature searches (Supplemental Material, Appendix A) to capture articles added to PubMed and EMBASE between 11 August 2015 and 31 December 2020, and we conducted additional searches of PubMed and EMBASE from inception through 31 December 2020 to improve identification of manuscripts reporting on associations with neuroimaging outcomes (Supplemental Material, Appendix B).

We used eligibility criteria identical to those in the original review (Power et al. 2016). Briefly, eligible articles quantified the association between long-term, outdoor air pollution exposures and dementia-related outcomes in samples of adults (ages 18 y or older) who were not selected on the basis of having a specific disease other than cognitive impairment or dementia. Eligible outdoor air pollution exposures included 1-y or longer averages of ozone (O_3), sulfur dioxide (SO_2), oxides of nitrogen (NO_x, NO_2), and particulate matter (PM, any size fraction), including fine PM, [PM with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$)], and coarse PM [PM with an aerodynamic diameter 2.5–10 μm ($PM_{2.5–10}$)], or common surrogates for PM or traffic-related air pollution, including distance to road, soot, or black carbon. Eligible dementia-related outcomes included cognitive test scores; longitudinal change in cognitive test scores; cognitive impairment, dementia, or dementia subtypes; and neuroimaging findings associated with dementia or change in these neuroimaging findings. We excluded conference abstracts and non-peer-reviewed publications and considered only a single report from each data source unless the exposure–outcome pairs were distinct. In situations when multiple papers reported the effect estimate for an identical exposure–outcome pair in the identical study population, we retained results from the earliest paper. If effect estimates for an identical exposure–outcome pair were reported from different subsets of the same source population, we retained the estimates based on the larger sample size or longer follow-up. Papers focusing on effect modification or additional covariate adjustment were excluded if a paper reporting on the main effect was also available.

One author (E.E.B.) conducted the literature search update, manually excluded duplicate records, and reviewed the reference lists of review articles identified through our literature search for additional relevant citations. Two authors (M.C.P. and E.E.B.) independently reviewed titles and abstracts for all new unique citations to determine eligibility for full-text review. M.C.P. and J.W. reviewed the final list of eligible articles to identify any missing, eligible articles known to these authors. L.R., E.E.B., M.C.P., and J.W. reviewed articles identified for full-text review for eligibility and abstracted prespecified information from each eligible article (Supplemental Material, Appendix C). L.R., E.E.B., or S.A. and M.C.P. or J.W. independently assessed each new, eligible article for risk of bias, and M.P., S.A., and J.Y. additionally assessed each article for risk of bias related to exposure assessment, using criteria developed for the prior review. We selected these criteria to reflect common challenges in epidemiological studies of air pollution and dementia-related outcomes (Power et al. 2016). Bias determinations for all studies were reviewed at a consensus conference, and disagreements at each stage were resolved by discussion. Results from the updated literature search and bias assessment were combined with the results from the original literature search (Power et al. 2016) for the purpose of describing the state of the literature and discussing methodological strengths and limitations.

Next, we evaluated the state of the evidence and identified higher-quality studies. We collapsed our bias review criteria into five domains: exposure assessment and variability, outcome assessment, confounding and statistical adjustments, cohort formation and loss to follow-up, and generalizability. The central purpose of this review is to highlight and synthesize findings from those studies that had the strongest designs for evaluating the relationships of interest. Highlighting these studies is important, because informative research in this area is notoriously challenging to conduct, and evidence from studies with considerable methodological limitations may inadvertently sway conclusions about the general direction and strength of associations of interest. Therefore, we tabulated findings from all studies that exhibited strengths in three or more of the five domains above.

Among those studies deemed to have strengths in three or more methodologic domains, we intended to meta-analyze findings when five or more population-specific estimates were available for any given exposure–outcome pair and could be aligned in terms of a difference in comparable outcome (e.g., cognitive level ascertained using Mini-Mental State Examination (MMSE), scored out of 30, and parameterized dichotomously with a cutoff of <24) per standard exposure contrast (e.g., per 10 $\mu g/m^3$ $PM_{2.5}$). Ultimately, this criterion was not met for any exposure–outcome pair. As an alternative and more comprehensive approach to summarizing the quantitative findings, we tabulated all the primary exposure–outcome effect estimates from these papers (see Supplemental Tables). We also generated forest plots of these results when estimates of a specific exposure–outcome association were available from at least five populations (see Supplemental Figures). Where possible, we transformed all associations shown in this report between pollutant exposures and outcomes of interest to common exposure and outcome contrasts. We used per 10 $\mu g/m^3$ as a common exposure contrast for NO_2, NO_x, PM_{10}, $PM_{2.5}$, and $PM_{2.5–10}$ and used 10 ppb for O_3. Differences in cognitive level outcomes were expressed in standard deviation units, and differences in rates of cognitive score change were expressed in change in standard deviation (SD) units per 2 years, where possible. Because most studies reported results from several association models, these supplemental tables and figures show results from the most fully adjusted models that were not adjusted for putative mediators. When a study reported associations between both continuous and categorized exposure levels and a given outcome, we extracted only the former. Additionally, when multiple exposure windows were considered, we extracted the exposure window with the largest effect size; in most studies, exposure window choice did not substantially affect effect estimates.

From this subset of papers exhibiting strengths in three or more methodological domains, we synthesized the findings by air pollutant and dementia-related outcome, focusing on the direction, magnitude, and precision of associations, and without reliance on null hypothesis significance testing to issue summary judgments (Amrhein et al. 2019; McShane et al. 2019). We implemented two strategies to avoid giving undue weight to studies that reported results on a large number of cognitive measures. When a study reported results specific to multiple separate

cognitive tests, we considered the findings collectively, rather than as independent associations. This approach was taken because performance across cognitive tests, particularly those administered in the context of dementia-oriented studies, is correlated—that is, individuals who perform well on one test will, on average, perform well on others. In situations when associations were reported for composite scores as well as associations for the separate test scores that contributed to the composite scores, we focused on unique information to draw conclusions.

Results

We conducted our updated literature search in two phases and report each separately given overlap in identified studies (Figure S1). We initially identified 366 unique records through 31 July 2020, and after including two additional papers known to the authors, we selected 94 for full-text review after title and abstract review. We excluded 50 articles that did not meet our eligibility criteria and 6 articles that were previously included in our original review (Supplemental Material, Appendix D). Altogether, 38 new articles met our eligibility criteria (Cacciottolo et al. 2017; Carey et al. 2018; Casanova et al. 2016; Cerza et al. 2019; Chen et al. 2017a, 2017b; Cleary et al. 2018; Colicino et al. 2014; Crous-Bou et al. 2020; Cullen et al. 2018; Erickson et al. 2020; Gale et al. 2020; Grande et al. 2020; Hedges et al. 2019; Hedges et al. 2020; Ilango et al. 2020; Kim et al. 2019; Kulick et al. 2017, 2020; Lee et al. 2019; Li et al. 2019; Lo et al. 2019; Nußbaum et al. 2020; Oudin et al. 2017; Oudin et al. 2018; Paul et al. 2020; Petkus et al. 2020; Power et al. 2018a; Salinas-Rodríguez et al. 2018; Shin et al. 2019; Tallon et al. 2017; Tzivian et al. 2016; Wang et al. 2020; Wilker et al. 2016a; Wu et al. 2015; Wurth et al. 2018; Younan et al. 2020a; Yuchi et al. 2020). We further identified 78 unique records from 1 August 2020 through 31 December 2020 and selected 34 for full-text review. After excluding 21 articles, 13 new articles met our eligibility criteria (Ailshire and Walsemann 2021; Chen et al. 2017c, 2020; Dimakakou et al. 2020; He et al. 2020; Iaccarino et al. 2021; Petkus et al. 2021; Ran et al. 2021; Rocha et al. 2020; Shi et al. 2020; Smargiassi et al. 2020; Yao et al. 2021; Younan et al. 2020b). After combining the results of these new searches with results of the 18 articles previously reviewed (Ailshire and Crimmins 2014; Ailshire and Clarke 2015; Chang et al. 2014; Chen and Schwartz 2009; Chen et al. 2015; Gatto et al. 2014; Jung et al. 2015; Kioumourtzoglou et al. 2016; Loop et al. 2013; Oudin et al. 2016; Power et al. 2011, 2016; Ranft et al. 2009; Schikowski et al. 2015; Tonne et al. 2014; Wellenius et al. 2012a; Weuve et al. 2012; Wilker et al. 2015; Zeng et al. 2010) and further excluding 3 papers reporting effect estimates for the same population that were also reported in other included studies (Cacciottolo et al. 2017; Kioumourtzoglou et al. 2016; Lee et al. 2019), we considered a total of 66 articles (Table 1).

Study Characteristics

Geographic settings. The geographic areas from which participants were recruited ranged from specific metropolitan areas (Carey et al. 2018; Cerza et al. 2019; Chen et al. 2020; Colicino et al. 2014; Crous-Bou et al. 2020; Gatto et al. 2014; Grande et al. 2020; Kulick et al. 2017, 2020; Paul et al. 2020; Power et al. 2011; Rocha et al. 2020; Smargiassi et al. 2020; Tonne et al. 2014; Wellenius et al. 2012a; Wurth et al. 2018; Yuchi et al. 2020) to broader regions (Chen et al. 2017a, 2017b; He et al. 2020; Ilango et al. 2020; Kim et al. 2019; Nußbaum et al. 2020; Oudin et al. 2016, 2017, 2018; Power et al. 2018a; Ran et al. 2021; Ranft et al. 2009; Schikowski et al. 2015; Smargiassi et al. 2020; Tzivian et al. 2016; Wilker et al. 2015, 2016a; Wu et al. 2015; Yao et al. 2021) to entire countries (Ailshire and Walsemann 2021; Ailshire and Crimmins 2014; Ailshire and Clarke 2015; Casanova et al. 2016; Chang et al. 2014; Chen and Schwartz 2009; Chen et al. 2015, 2017c; Cleary et al. 2018; Cullen et al. 2018; Dimakakou et al. 2020; Erickson et al. 2020; Gale et al. 2020; Hedges et al. 2019, 2020; Iaccarino et al. 2021; Jung et al. 2015; Li et al. 2019; Lo et al. 2019; Loop et al. 2013; Petkus et al. 2020, 2021; Salinas-Rodríguez et al. 2018; Shi et al. 2020; Shin et al. 2019; Tallon et al. 2017; Wang et al. 2020; Weuve et al. 2012; Younan et al. 2020a, 2020b; Zeng et al. 2010). Since our last review, the geographic scope expanded to include studies in Canada (Chen et al. 2017a, 2017b; Ilango et al. 2020; Smargiassi et al. 2020; Yuchi et al. 2020), Italy (Cerza et al. 2019), Mexico (Salinas-Rodríguez et al. 2018), South Korea (Kim et al. 2019; Shin et al. 2019), Spain (Crous-Bou et al. 2020), and Brazil (Rocha et al. 2020). However, most newly identified studies were set in the United States (Ailshire and Walsemann 2021; Casanova et al. 2016; Chen et al. 2017c; Cleary et al. 2018; Colicino et al. 2014; Iaccarino et al. 2021; Kulick et al. 2017, 2020; Paul et al. 2020; Petkus et al. 2020, 2021; Power et al. 2018a; Shi et al. 2020; Tallon et al. 2017; Wilker et al. 2016a; Wurth et al. 2018; Younan et al. 2020a, 2020b) or in Europe (Carey et al. 2018; Cerza et al. 2019; Crous-Bou et al. 2020; Cullen et al. 2018; Dimakakou et al. 2020; Erickson et al. 2020; Gale et al. 2020; Grande et al. 2020; Hedges et al. 2019, 2020; Nußbaum et al. 2020; Oudin et al. 2017, 2018; Tzivian et al. 2016).

Dementia-related outcomes: scope and methods. Cognitive level (i.e., cognitive test scores at a single time point) remained the most commonly considered outcome (Table 1), with 15 of the newly identified studies reporting on this outcome (Chen et al. 2020; Crous-Bou et al. 2020; Cullen et al. 2018; Kim et al. 2019; Kulick et al. 2020; Lo et al. 2019; Nußbaum et al. 2020; Rocha et al. 2020; Salinas-Rodríguez et al. 2018; Shin et al. 2019; Tallon et al. 2017; Tzivian et al. 2016; Wurth et al. 2018; Yao et al. 2021; Younan et al. 2020a). In both previously included and newly identified studies, methods for defining cognitive level varied. Fifteen studies used domain-specific cognitive tests (Chen and Schwartz 2009; Chen et al. 2020; Crous-Bou et al. 2020; Cullen et al. 2018; Gatto et al. 2014; Kulick et al. 2020; Power et al. 2011; Ranft et al. 2009; Rocha et al. 2020; Salinas-Rodríguez et al. 2018; Tonne et al. 2014; Tzivian et al. 2016; Wellenius et al. 2012a; Wurth et al. 2018; Younan et al. 2020a), 14 used tests of global cognition (Ailshire and Crimmins 2014; Ailshire and Clarke 2015; Chen et al. 2020; Crous-Bou et al. 2020; Kim et al. 2019; Lo et al. 2019; Power et al. 2011; Ranft et al. 2009; Schikowski et al. 2015; Shin et al. 2019; Tallon et al. 2017; Wellenius et al. 2012a; Yao et al. 2021; Zeng et al. 2010), and 6 combined scores from domain-specific cognitive tests to create a global cognitive score (Crous-Bou et al. 2020; Gatto et al. 2014; Kulick et al. 2020; Power et al. 2011; Rocha et al. 2020; Tzivian et al. 2016). Additionally, eight studies dichotomized cognitive scores to classify persons as having "low" or impaired cognitive function (Chen et al. 2020; Kim et al. 2019; Lo et al. 2019; Power et al. 2011; Shin et al. 2019; Wellenius et al. 2012a; Yao et al. 2021; Zeng et al. 2010).

Newer studies were more likely to evaluate cognitive change, neuroimaging, or incident cognitive impairment/dementia. Of the 10 studies considering longitudinal change in cognitive function, 8 were newer studies (Cleary et al. 2018; Colicino et al. 2014; Cullen et al. 2018; Kulick et al. 2020; Oudin et al. 2017; Petkus et al. 2020, 2021; Younan et al. 2020a). Likewise, of the 22 studies considering incident cognitive impairment or dementia, 18 emerged in our updated literature search (Ailshire and Walsemann 2021; Carey et al. 2018; Cerza et al. 2019; Chen et al.

Table 1. Summary of study characteristics for eligible studies on air pollution and late-life cognitive health identified through 31 December 2020.

			Exposures considered								Outcomes considered							
Study Focus	Citation/cohort	*n*/Location	PM_{10}	$PM_{2.5–10}$	$PM_{2.5}$	Traffic-related air pollution[a]	Wood-burning PM	NO_2 or NO_x	Ozone	API	Cognitive test scores	Prevalent cognitive impairment	Change in cognitive test scores	Dementia (medical records or claims)	Dementia (study assessment)	Other incident cognitive impairment	Neuroimaging	New to the review
Cognitive Level	(Ailshire and Crimmins 2014)/HRS	13,996/USA	—	—	Yes	—	—	—	—	—	Yes	—	—	—	—	—	—	—
Cognitive Level	(Ailshire and Clarke 2015)/ACL Survey	780/USA	—	—	Yes	—	—	—	—	—	Yes	—	—	—	—	—	—	—
Cognitive Level	(Chen et al. 2020)/TIGER	360/Taipei and Keelung, Taiwan	Yes	Yes	Yes	—	—	Yes	—	—	Yes	Yes	—	—	—	—	—	Yes
Cognitive Level	(Chen and Schwartz 2009)/NHANES III	1,764/USA	Yes	—	—	—	—	—	Yes	—	Yes	—	—	—	—	—	—	—
Cognitive Level	(Gatto et al. 2014)/WISH, BVAIT, and ELITE	1,496/Los Angeles Basin, USA	—	—	Yes	—	—	Yes	Yes	—	Yes	—	—	—	—	—	—	—
Cognitive Level	(Kim et al. 2019)/ Volunteer community-based sample in South Korea	1,484/four regions of South Korea	Yes	Yes	—	—	—	Yes	—	—	Yes	Yes	—	—	—	—	—	Yes
Cognitive Level	(Lo et al. 2019)/TLSA	6,546/Taiwan	Yes	—	—	—	—	—	Yes	—	—	Yes	—	—	—	—	—	Yes
Cognitive Level	(Power et al. 2011)/NAS	680/Greater Boston, USA	—	—	—	Yes	—	—	—	—	Yes	Yes	—	—	—	—	—	—
Cognitive Level	(Ranft et al. 2009)/SALIA	399/Ruhr and adjacent area, Germany	Yes	—	—	Yes	—	—	—	—	Yes	—	—	—	—	—	—	—
Cognitive Level	(Rocha et al. 2020)/ ELSA-Brasil	3,050/Sao Paolo, Brazil	—	—	—	Yes	—	—	—	—	Yes	—	—	—	—	—	—	Yes
Cognitive Level	(Salinas-Rodríguez et al. 2018)/ENSANUT-2012	7,986/Mexico	—	—	Yes	—	—	—	—	—	Yes	—	—	—	—	—	—	Yes
Cognitive Level	(Schikowski et al. 2015)/ SALIA	789/Ruhr and adjacent area, Germany	Yes	—	Yes	Yes	—	Yes	—	—	Yes	—	—	—	—	—	—	—
Cognitive Level	(Shin et al. 2019)/KFACS	2,896/South Korea	Yes	—	Yes	—	—	Yes	Yes	—	Yes	Yes	—	—	—	—	—	Yes
Cognitive Level	(Tallon et al. 2017)/ NSHAP	3,377/USA	—	—	Yes	—	—	Yes	—	—	Yes	—	—	—	—	—	—	Yes
Cognitive Level	(Tzivian et al. 2016)/ Heinz Nixdorf RECALL	4,050/Ruhr area, Germany	Yes	Yes	Yes	Yes	—	Yes	—	—	Yes	—	—	—	—	—	—	Yes
Cognitive Level	(Wellenius et al. 2012a)/ MOBILIZE Boston	765/Boston, USA	—	—	—	Yes	—	—	—	—	Yes	Yes	—	—	—	—	—	—
Cognitive Level	(Wurth et al. 2018)/ BPRHS	1497/Boston, USA	—	—	Yes	Yes	—	—	—	—	Yes	—	—	—	—	—	—	Yes
Cognitive Level	(Yao et al. 2021)/CLHLS	11,187/China	—	—	—	Yes	—	—	—	—	Yes	Yes	—	—	—	—	—	Yes
Cognitive Level	(Younan et al. 2020a)/ WHIMS-MRI and WHISCA	998/USA	—	—	Yes	—	—	—	—	—	Yes	—	Yes	—	—	—	Yes	Yes
Cognitive Level	(Zeng et al. 2010)/CLHLS	15,973/China	—	—	—	—	—	—	—	Yes	—	Yes	—	—	—	—	—	—
Neuroimaging Level and Cognitive Level	(Crous-Bou et al. 2020)/ ALFA	958 (cognitive level); 228 (neuroimaging)/ Barcelona, Spain	Yes	Yes	Yes	Yes	—	Yes	—	—	Yes	—	—	—	—	—	Yes	Yes

Table 1. (*Continued.*)

			Exposures considered								Outcomes considered							
Study Focus	Citation/cohort	*n*/Location	PM_{10}	$PM_{2.5–10}$	$PM_{2.5}$	Traffic-related air pollution[a]	Wood-burning PM	NO_2 or NO_x	Ozone	API	Cognitive test scores	Prevalent cognitive impairment	Change in cognitive test scores	Dementia (medical records or claims)	Dementia (study assessment)	Other incident cognitive impairment	Neuroimaging	New to the review
Neuroimaging Level and Cognitive Level	(Nußbaum et al. 2020)/ 1000BRAINS	615/Ruhr area, Germany	Yes	—	Yes	Yes	—	Yes	—	—	Yes	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Casanova et al. 2016)/ WHIMS-MRI	1,365/USA	—	—	Yes	—	—	—	—	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Chen et al. 2015)/ WHIMS-MRI	1,403/USA	—	—	Yes	—	—	—	—	—	—	—	—	—	—	—	Yes	—
Neuroimaging Level	(Erickson et al. 2020)/UK Biobank	18,292/UK	Yes	Yes	Yes	—	—	Yes	—	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Gale et al. 2020)/UK Biobank	18,288/UK	Yes	Yes	Yes	—	—	Yes	—	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Hedges et al. 2019)/UK Biobank	18,278/UK	Yes	Yes	Yes	—	—	Yes	—	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Hedges et al. 2020)/UK Biobank	18,278/UK	Yes	Yes	Yes	—	—	Yes	—	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Iaccarino et al. 2021)/ IDEAS	18,178/USA	—	—	Yes	—	—	—	Yes	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Kulick et al. 2017)/ NOMAS	1,075/New York, USA	—	—	Yes	Yes	—	Yes	Yes	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Power et al. 2018a)/ ARIC	1,753/4 regions of the USA	Yes	—	Yes	—	—	—	—	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Wilker et al. 2015)/FOS	929[b]/New England, USA	—	—	Yes	Yes	—	—	—	—	—	—	—	—	—	—	Yes	—
Neuroimaging Level	(Wilker et al. 2016a)/ MADRC	236/New England and New York, USA	—	—	Yes	Yes	—	—	—	—	—	—	—	—	—	—	Yes	Yes
Neuroimaging Level	(Younan et al. 2020b)/ WHIMS-MRI	1,365 (cross-sectional); 712 (longitudinal)/ USA	—	—	Yes	—	—	—	—	—	—	—	—	—	—	—	Yes	Yes
Cognitive Level and Cognitive Change	(Cullen et al. 2018)/UK Biobank	86,759 (cross-sectional analysis); 2,913 (follow-up sample)/UK	Yes	Yes	Yes	—	—	Yes	—	—	Yes	—	Yes	—	—	—	—	Yes
Cognitive Level and Cognitive Change	(Kulick et al. 2020)/ WHICAP and NOMAS	5,330 (WHICAP); 1,093 (NOMAS)/northern Manhattan, New York, USA	Yes	—	Yes	Yes	—	Yes	—	—	Yes	—	Yes	—	—	—	—	Yes
Cognitive Level and Cognitive Change	(Tonne et al. 2014)/ Whitehall II	2,867/Greater London, UK	Yes	—	Yes	Yes	—	—	—	—	Yes	—	Yes	—	—	—	—	—
Cognitive Change	(Cleary et al. 2018)/ National AD Centers Database	5,116/USA	—	—	Yes	—	—	—	Yes	—	—	—	Yes	—	—	—	—	Yes
Cognitive Change	(Colicino et al. 2014)/ NAS	387/Greater Boston, USA	—	—	—	Yes	—	—	—	—	—	—	Yes	—	—	—	—	Yes

Table 1. (*Continued.*)

			Exposures considered								Outcomes considered							
Study Focus	Citation/cohort	*n*/Location	PM_{10}	$PM_{2.5–10}$	$PM_{2.5}$	Traffic-related air pollution[a]	Wood-burning PM	NO_2 or NO_x	Ozone	API	Cognitive test scores	Prevalent cognitive impairment	Change in cognitive test scores	Dementia (medical records or claims)	Dementia (study assessment)	Other incident cognitive impairment	Neuroimaging	New to the review
Cognitive Change	(Oudin et al. 2017)/Betula	1,469/Umeå, Sweden	—	—	—	—	—	Yes	—	—	—	—	Yes	—	—	—	—	Yes
Cognitive Change	(Petkus et al. 2020)/ WHISCA	2,202/USA	—	—	Yes	—	—	—	—	—	—	—	Yes	—	—	—	—	Yes
Cognitive Change	(Petkus et al. 2021)/ WHIMS-ECHO	1,583/USA	—	—	Yes	—	—	Yes	—	—	—	—	Yes	—	—	—	—	Yes
Cognitive Change	(Weuve et al. 2012)/NHS	19,409/USA	Yes	Yes	Yes	—	—	—	—	—	—	—	Yes	—	—	—	—	—
Prevalent Dementia	(Dimakakou et al. 2020)/ UK Biobank	502,504/UK	—	—	Yes	—	—	—	—	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Ailshire and Walsemann 2021)/HRS	9,970 (year 2004); 9,185 (year 2014)/USA	—	—	Yes	—	—	—	—	—	—	—	—	—	—	Yes	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Carey et al. 2018)/CPRD	130,978/Greater London, UK	—	—	Yes	Yes	—	Yes	Yes	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Cerza et al. 2019)/ Rome Longitudinal Cohort	350,844/Rome, Italy	Yes	Yes	Yes	Yes	—	Yes	Yes	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Chang et al. 2014)/ NHIRD Taiwan	29,547/Taiwan	—	—	—	—	—	Yes	—	—	—	—	—	Yes	—	—	—	—
Incident Dementia or Other Incident Cognitive Impairment	(Chen et al. 2017a)/ Ontario Population Health and Environment Cohort	2,066,639/Ontario, Canada	—	—	Yes	—	—	Yes	Yes	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Chen et al. 2017b)/ Ontario Population Health and Environment Cohort	2,165,268/Ontario, Canada	—	—	—	Yes	—	—	—	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Grande et al. 2020)/ SNAC-K	2,927/Kungsholmen district, Stockholm, Sweden	—	—	Yes	—	—	Yes	—	—	—	—	—	Yes	Yes	—	—	Yes

Table 1. (*Continued.*)

			Exposures considered								Outcomes considered							
Study Focus	Citation/cohort	*n*/Location	PM_{10}	$PM_{2.5–10}$	$PM_{2.5}$	Traffic-related air pollution[a]	Wood-burning PM	NO_2 or NO_x	Ozone	API	Cognitive test scores	Prevalent cognitive impairment	Change in cognitive test scores	Dementia (medical records or claims)	Dementia (study assessment)	Other incident cognitive impairment	Neuroimaging	New to the review
Incident Dementia or Other Incident Cognitive Impairment	(He et al. 2020)/ZJMPHS	7,311/Zhejiang province, China	Yes	—	Yes	—	—	Yes	Yes	Yes	—	—	—	—	—	Yes	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Ilango et al. 2020)/NPHS and CCHS participants	34,391/Ontario, Canada	—	—	Yes	—	—	Yes	—	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Jung et al. 2015)/NHIRD Taiwan	95,690/Taiwan	—	—	Yes	—	—	—	Yes	—	—	—	—	Yes	—	—	—	—
Incident Dementia or Other Incident Cognitive Impairment	(Li et al. 2019)/NHIRD Taiwan	4,155/Taiwan	Yes	—	—	—	—	Yes	Yes	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Loop et al. 2013)/ REGARDS	20,150/USA	—	—	Yes	—	—	—	—	—	—	—	—	—	—	Yes	—	—
Incident Dementia or Other Incident Cognitive Impairment	(Oudin et al. 2016)/Betula	1,806/Umeå, Sweden	—	—	—	—	—	Yes	—	—	—	—	—	Yes	Yes	—	—	—
Incident Dementia or Other Incident Cognitive Impairment	(Oudin et al. 2018)/Betula	1,806/Umeå, Sweden	—	—	—	Yes	Yes	—	—	—	—	—	—	Yes	Yes	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Paul et al. 2020)/SALSA	1,564/Sacramento Valley, California, USA	—	—	—	Yes	—	—	—	—	—	—	—	—	Yes	Yes	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Ran et al. 2021)/Chinese EHS	59,349/Hong Kong, China	—	—	Yes	—	—	—	—	—	—	—	—	Yes	—	—	—	Yes

Table 1. (*Continued.*)

			Exposures considered								Outcomes considered							
Study Focus	Citation/cohort	*n*/Location	PM_{10}	$PM_{2.5–10}$	$PM_{2.5}$	Traffic-related air pollution[a]	Wood-burning PM	NO_2 or NO_x	Ozone	API	Cognitive test scores	Prevalent cognitive impairment	Change in cognitive test scores	Dementia (medical records or claims)	Dementia (study assessment)	Other incident cognitive impairment	Neuroimaging	New to the review
Incident Dementia or Other Incident Cognitive Impairment	(Shi et al. 2020)/Medicare fee-for-service beneficiaries	63,038,019/USA	—	—	Yes	—	—	—	—	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Smargiassi et al. 2020)/QICDSS	1,807,133 (Québec); 457,768 (Montreal)/Québec/Montreal, Canada	—	—	Yes	Yes	—	Yes	—	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Wang et al. 2020)/CLHLS	13,324/China	—	—	Yes	—	—	—	—	—	—	—	—	—	—	Yes	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Wu et al. 2015)/Case-control	871/northern Taiwan	Yes	—	—	—	—	—	Yes	—	—	—	—	—	Yes	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment	(Yuchi et al. 2020)/MSP registry	633,949 (NAD analysis); 13,498 (AD analysis)/Metro Vancouver, Canada	—	—	Yes	Yes	—	Yes	—	—	—	—	—	Yes	—	—	—	Yes
Incident Dementia or Other Incident Cognitive Impairment and Neuroimaging Level	(Chen et al. 2017c)/WHIMS	1,403 (neuroimaging); 7,447 (incident dementia or cognitive impairment)/USA	—	—	Yes	Yes	—	—	—	—	—	—	—	—	Yes	Yes	Yes	Yes

Note: ACL, Americans' Changing Lives; AD, Alzheimer's disease; ALFA, Alzheimer's and Family; API, air pollution index; ARIC, Atherosclerosis Risk in Communities; BPRHS, Boston Puerto Rican Health Study; BVAIT, B-Vitamin Atherosclerosis Intervention Trial; CCHS, Canadian Community Health Survey; CLHLS, Chinese Longitudinal Healthy Longevity Survey; CPRD, Clinical Practice Research Datalink; EHS, Elderly Health Service; ELITE, Early Versus Late Intervention Trial; ELSA-Brasil, Brazilian Longitudinal Study on Adult Health; ENSANUT-2012, Spanish acronym for National Survey of Health and Nutrition in Mexico in 2012; FOS, Framingham Offspring Study; Heinz Nixdorf RECALL, Heinz Nixdorf Risk factors, Evaluation of Coronary Calcium and Lifestyle study; HRS, Health and Retirement Study; ICD-9, International Classification of Diseases, Ninth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IDEAS, Imaging Dementia – Evidence for Amyloid Scanning; KFACS, Korean Frailty and Aging Cohort Study; MADRC, Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort; MOBILIZE, Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly; MSP, Medical Service Plan; NAD, non-Alzheimer's dementia; NAS, Normative Aging Study; NHANES III, Third National Health and Nutrition Examination Survey; NHIRD, National Health Insurance Research Database; NHS, Nurses' Health Study; , nitrogen dioxide; NO_x, nitrogen oxides; NOMAS, Northern Manhattan Study; NPHS, National Population Health Survey; NSHAP, National Social Health and Aging Study; PM, particulate matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter $\leq$10 μm; $PM_{2.5–10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 micrometers; QICDSS, Quebec Integrated Chronic Disease Surveillance System; REGARDS, Reasons for Geographic and Racial Differences in Stroke; SALIA, Study on the Influence of Air Pollution on Lung Function, Inflammation, and Aging; SALSA, Sacramento Area Latino Study on Aging; SNAC-K, Swedish National Study of Aging and Care in Kungsholmen; TIGER, Taiwan Institute for Geriatric Epidemiological Research; TLSA, Taiwanese Longitudinal Study on Aging; USA, United States of America; WHICAP, Washington Heights-Inwood Community Aging Project; WHIMS-ECHO, Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; WHIMS-MRI, Women's Health Initiative Memory Study Magnetic Resonance Imaging Study; WHISCA, Women's Health Initiative Study of Cognitive Aging; WISH, Women's Isoflavone Soy Health; ZJMPHS, Zhejiang Major Public Health Surveillance.

[a]Includes measures of distance to road, traffic intensity, black carbon, traffic-sourced particulate matter, and TRAP-NO_x. Though NO_2 and are often considered as traffic-related air pollution, we consider them separately.

[b]Sample size varies by analysis. $n = 929$ represents the largest reported sample size for primary analyses.

2017a, 2017b, 2017c; Grande et al. 2020; He et al. 2020; Ilango et al. 2020; Li et al. 2019; Oudin et al. 2018; Paul et al. 2020; Ran et al. 2021; Shi et al. 2020; Smargiassi et al. 2020; Wang et al. 2020; Wu et al. 2015; Yuchi et al. 2020). Of the 17 studies on incident dementia, 6 assessed dementia using in-person examinations (Chen et al. 2017c; Grande et al. 2020; Oudin et al. 2016, 2018; Paul et al. 2020; Wu et al. 2015), sometimes supplemented with medical records (Grande et al. 2020; Oudin et al. 2016, 2018); the remainder relied on administrative data to identify dementia cases (Carey et al. 2018; Cerza et al. 2019; Chang et al. 2014; Chen et al. 2017a, 2017b; Ilango et al. 2020; Jung et al. 2015; Li et al. 2019; Ran et al. 2021; Shi et al. 2020; Smargiassi et al. 2020; Yuchi et al. 2020). One additional study considered prevalent dementia defined using diagnostic codes in hospital records (Dimakakou et al. 2020). Finally, of the 16 articles examining neuroimaging outcomes (Casanova et al. 2016; Chen et al. 2015, 2017c; Crous-Bou et al. 2020; Erickson et al. 2020; Gale et al. 2020; Hedges et al. 2019, 2020; Iaccarino et al. 2021; Kulick et al. 2017; Nußbaum et al. 2020; Power et al. 2018a; Wilker et al. 2015, 2016a; Younan et al. 2020a, 2020b) (Table 1), 14 were identified in our updated search (Casanova et al. 2016; Chen et al. 2017c; Crous-Bou et al. 2020; Erickson et al. 2020; Gale et al. 2020; Hedges et al. 2019, 2020; Iaccarino et al. 2021; Kulick et al. 2017; Nußbaum et al. 2020; Power et al. 2018a; Wilker et al. 2016a; Younan et al. 2020a, 2020b). Most considered brain volumes or related measures indicative of atrophy (Casanova et al. 2016; Chen et al. 2015, 2017c; Crous-Bou et al. 2020; Erickson et al. 2020; Gale et al. 2020; Hedges et al. 2019, 2020; Kulick et al. 2020; Nußbaum et al. 2020; Power et al. 2018a; Wilker et al. 2015; Wilker et al. 2016a; Younan et al. 2020a, 2020b), and five also considered white matter hyperintensity volumes or other markers of cerebrovascular injury (Chen et al. 2017c; Kulick et al. 2017; Power et al. 2018a; Wilker et al. 2015, 2016b). One study analyzed associations with PET amyloid positivity (Iaccarino et al. 2021).

Air pollutant exposures: scope and methods. PM remained the most commonly considered air pollutant exposure, although a growing number of studies also considered NO_2 or NO_x, measures of traffic-related air pollution, and O_3 (Table 1).

In studies in the previous review, investigators often relied on air pollution estimates linked to participants at the level of the participants' communities (Chang et al. 2014; Chen and Schwartz 2009; Zeng et al. 2010), postcodes (Jung et al. 2015; Tonne et al. 2014), or census tracts or census blocks (Ailshire and Crimmins 2014; Ailshire and Clarke 2015) rather than participants' residential addresses (Chen et al. 2015; Gatto et al. 2014; Loop et al. 2013; Oudin et al. 2016; Power et al. 2011; Ranft et al. 2009; Schikowski et al. 2015; Wellenius et al. 2012a; Weuve et al. 2012; Wilker et al. 2015). Although more of the newly identified studies relied on participants' residential addresses (Casanova et al. 2016; Cerza et al. 2019; Chen et al. 2017c, 2020; Colicino et al. 2014; Crous-Bou et al. 2020; Cullen et al. 2018; Erickson et al. 2020; Gale et al. 2020; Grande et al. 2020; Hedges et al. 2019, 2020; Kim et al. 2019; Kulick et al. 2017, 2020; Nußbaum et al. 2020; Oudin et al. 2017, 2018; Paul et al. 2020; Petkus et al. 2020, 2021; Power et al. 2018a; Ran et al. 2021; Rocha et al. 2020; Tallon et al. 2017; Tzivian et al. 2016; Wang et al. 2020; Wilker et al. 2016a; Wu et al. 2015; Yao et al. 2021; Younan et al. 2020a, 2020b), many still assigned exposures based on participants' counties or cities (He et al. 2020; Li et al. 2019; Lo et al. 2019; Wurth et al. 2018), full or partial postal codes (Carey et al. 2018; Chen et al. 2017a, 2017b; Cleary et al. 2018; Iaccarino et al. 2021; Shi et al. 2020; Smargiassi et al. 2020; Yuchi et al. 2020), or census tracts (Ailshire and Walsemann 2021; Chen et al. 2017c; Salinas-Rodríguez et al. 2018). One study defined exposure based on both residential and workplace addresses (Rocha et al. 2020). In another study, participants were asked to estimate the distance of their homes to the nearest busy road (Yao et al. 2021). Three additional new papers did not contain sufficient information to determine how air pollution exposures were linked to participants (Dimakakou et al. 2020; Ilango et al. 2020; Shin et al. 2019).

In general, newer studies also used more refined approaches to estimate pollution concentrations. In our prior review, approximately half of the studies used the following as surrogates for ambient pollutant concentrations at a person's home: pollutant concentrations from a single monitoring station (Chang et al. 2014; Ranft et al. 2009) or several (Ailshire and Crimmins 2014; Ailshire and Clarke 2015; Chen and Schwartz 2009; Gatto et al. 2014; Jung et al. 2015) monitoring stations nearest to a participant's residential location, city/county air pollution index values (Zeng et al. 2010), or distance to road or traffic load measures (Ranft et al. 2009; Schikowski et al. 2015; Wellenius et al. 2012a; Wilker et al. 2015). In contrast, the majority (Ailshire and Walsemann 2021; Carey et al. 2018; Casanova et al. 2016; Cerza et al. 2019; Chen et al. 2017a, 2017c, 2020; Cleary et al. 2018; Colicino et al. 2014; Cullen et al. 2018; Dimakakou et al. 2020; Erickson et al. 2020; Gale et al. 2020; Grande et al. 2020; Hedges et al. 2019, 2020; Iaccarino et al. 2021; Ilango et al. 2020; Kim et al. 2019; Kulick et al. 2017, 2020; Li et al. 2019; Nußbaum et al. 2020; Oudin et al. 2017, 2018; Paul et al. 2020; Petkus et al. 2020, 2021; Power et al. 2018a; Ran et al. 2021; Salinas-Rodríguez et al. 2018; Shi et al. 2020; Smargiassi et al. 2020; Tallon et al. 2017; Tzivian et al. 2016; Wang et al. 2020; Wilker et al. 2016a; Wu et al. 2015; Younan et al. 2020a, 2020b; Yuchi et al. 2020) of the newer studies used models that predicted ambient concentrations at or around each participant's home address (even if the spatial granularity of the models could not be fully exploited due to imprecise information on participant location). These spatial prediction models varied in their specific approach: Models used in 2 of the papers from the prior review (Loop et al. 2013; Wilker et al. 2015) and 10 of the new papers (Chen et al. 2017a; Cullen et al. 2018; Ilango et al. 2020; Kulick et al. 2020; Ran et al. 2021; Salinas-Rodríguez et al. 2018; Shi et al. 2020; Smargiassi et al. 2020; Wang et al. 2020; Wilker et al. 2016a) incorporated data on aerosols in the atmosphere from satellite measurements; models used in 6 of the older papers (Oudin et al. 2016; Power et al. 2011; Schikowski et al. 2015; Wellenius et al. 2012a; Weuve et al. 2012; Wilker et al. 2015) and 27 of the new papers (Cerza et al. 2019; Chen et al. 2017a, 2017c; Colicino et al. 2014; Crous-Bou et al. 2020; Cullen et al. 2018; Dimakakou et al. 2020; Erickson et al. 2020; Gale et al. 2020; Hedges et al. 2019, 2020; Ilango et al. 2020; Kim et al. 2019; Kulick et al. 2017, 2020; Nußbaum et al. 2020; Oudin et al. 2017; Petkus et al. 2021; Power et al. 2018a; Salinas-Rodríguez et al. 2018; Shi et al. 2020; Smargiassi et al. 2020; Tallon et al. 2017; Tzivian et al. 2016; Wang et al. 2020; Wilker et al. 2016a; Yuchi et al. 2020) incorporated characteristics of place, such as land use and local emission sources; and models used in 1 paper from the prior review (Tonne et al. 2014) and 22 of the new papers (Ailshire and Walsemann 2021; Carey et al. 2018; Casanova et al. 2016; Cerza et al. 2019; Chen et al. 2017a; 2017c; Cleary et al. 2018; Grande et al. 2020; Iaccarino et al. 2021; Ilango et al. 2020; Kulick et al. 2017; Nußbaum et al. 2020; Oudin et al. 2018; Paul et al. 2020; Petkus et al. 2020, 2021; Shi et al. 2020; Smargiassi et al. 2020; Tallon et al. 2017; Wang et al. 2020; Younan et al. 2020a, 2020b) included predictions from a chemical transport or dispersion model. Overall, across both older and newer papers, the spatial resolution of the exposure models ranged from address-specific predictions (resolved down to tens of

meters) to 1,296 km^2, with reported validation $R^{2\prime}$s ranging from approximately 0.4 to 0.9. In general, models of traffic-related pollutants performed best, and models of $PM_{2.5–10}$ performed worst. The explanatory power of the $PM_{2.5}$ model in the Manchester region in the United Kingdom was notably low ($R^2 = 0.2$) (Eeftens et al. 2012).

Between more specific participant location information and better spatial resolution of the prediction models, the overall spatial resolution of model-based exposure estimation approaches used in the literature has improved since our last review. Of studies modeling $PM_{2.5}$, 5 older (Chen et al. 2015; Schikowski et al. 2015; Tonne et al. 2014; Weuve et al. 2012; Wilker et al. 2015) and 24 newer studies (Casanova et al. 2016; Cerza et al. 2019; Chen et al. 2017c, 2020; Crous-Bou et al. 2020; Cullen et al. 2018; Erickson et al. 2020; Gale et al. 2020; Grande et al. 2020; Hedges et al. 2019, 2020; Kulick et al. 2017, 2020; Nußbaum et al. 2020; Oudin et al. 2018; Petkus et al. 2020, 2021; Power et al. 2018a; Ran et al. 2021; Tzivian et al. 2016; Wang et al. 2020; Wilker et al. 2016a; Younan et al. 2020a, 2020b) used approaches with overall spatial resolutions of 1 km^2 or less. Of NO_2 or NO_x studies, 2 older (Oudin et al. 2016; Schikowski et al. 2015) and 15 newer studies (Cerza et al. 2019; Chen et al. 2020; Crous-Bou et al. 2020; Cullen et al. 2018; Gale et al. 2020; Grande et al. 2020; Hedges et al. 2019, 2020; Kim et al. 2019; Kulick et al. 2017, 2020; Nußbaum et al. 2020; Oudin et al. 2017; Petkus et al. 2021; Tzivian et al. 2016) had overall resolutions of 1 km^2 or less. Three newer studies (Cerza et al. 2019; Kulick et al. 2017; Wu et al. 2015) had overall resolutions of 1 km^2 or less for O_3. For markers of traffic, excluding NO_2 and NO_x, all older studies (Power et al. 2011; Ranft et al. 2009; Schikowski et al. 2015; Wellenius et al. 2012a; Wilker et al. 2015) and 10 newer studies (Cerza et al. 2019; Chen et al. 2017c; Colicino et al. 2014; Crous-Bou et al. 2020; Kulick et al. 2017, 2020; Nußbaum et al. 2020; Oudin et al. 2018; Tzivian et al. 2016; Wilker et al. 2016a) used measures with spatial resolution less than 1 km^2. All other papers had coarser or unspecified resolution.

Quality Assessment Review

Although newer studies had better overall spatial resolution for exposure estimates, and there has been an increase in the number of studies evaluating cognitive change and incident dementia, methodological challenges remain in this literature. In fact, the overall quality of published research has declined since our initial literature search, with a smaller proportion of newly identified studies, vs. studies identified in our prior review, having strengths in three or more methodological domains (Table 2). Many limitations were study-specific, but three major limitations remained pervasive: *a*) use of claims or medical records to identify dementia; *b*) lack of information on cohort attrition, or, in MRI studies, predictors of participation, along with the associated potential for selection bias; and *c*) inclusion of potential mediators in primary covariate sets.

Although not rising to the level of a limitation in our risk of bias analysis, most studies continued to average exposures over periods less than 5 years. These short periods were unlikely to capture the etiologically relevant time period of exposure, especially when dementia was the outcome. Instead, these studies relied on the assumption that shorter averaging periods reflect exposures in the etiologically relevant window. Because wide-scale air pollution monitoring was less common before 2000 in the United States, and there is a similar lack of monitor data elsewhere, this is an inherent challenge to measuring distant exposures with historical data but is likely to improve over time.

Summary of Study Findings

Here we focus on the results from the subset of studies that had strengths in three or more methodological domains, as identified through our quality assessment (Table 2). Results from these studies are summarized in Tables S1 to S4 and Figures S2 to S7, except for results from (Zeng et al. 2010), which did not include exposure contrasts for air quality index (AQI) corresponding to the estimated effects.

NO_2 and NO_x. Collectively, results on NO_2 and NO_x were mixed. Some studies suggested adverse associations with cognitive level and cognitive change, but some reported effect sizes were small and imprecise, and other studies reported beneficial associations or a set of inconsistent associations (Tables S1 and S2; Figure S2). Associations with incident cognitive impairment and dementia were mixed (Table S3). The three papers that evaluated neuroimaging outcomes all reported adverse associations of NO_x exposure with measures of brain volume. Results from these same studies with respect NO_2, and with respect to either NO_x or NO_2 in relation to cerebrovascular outcomes, were small in magnitude, in mixed directions, and fairly imprecise. (Table S4).

O_3. Findings on O_3 were reported in only five studies. These findings, none of which pertained to cognitive decline, were not consistent.

PM. As a whole, the findings of papers considering $PM_{2.5}$ were supportive of adverse associations, although the consistency of evidence varied by outcome (Tables S1–S4; Figures S3–S6). Half of the studies of $PM_{2.5}$ and cognitive level (reporting results specific to 12 cohorts) suggested an adverse association. Associations were clearly adverse in six of those cohorts [Health and Retirement Study (HRS), Heinz-Nixdorf RECALL, National Social Health and Aging Study (NSHAP), ENSANUT (National Survey of Health and Nutrition in Mexico), Washington Heights-Inwood Community Aging Project (WHICAP), Korean Frailty and Aging Cohort Study (KFACS)]. In the Whitehall II cohort, results were mixed but on balance tended to favor an adverse association. Results from the 1000BRAINS study and Women's Health Initiative Memory Study Magnetic Resonance Imaging Study/Women's Health Initiative Study of Cognitive Aging (WHIMS-MRI/WHISCA) were mixed, and results of the remaining three cohorts (SALIA, NOMAS, ALFA) had mixed results that, on balance, suggested benefit of higher $PM_{2.5}$ levels (Table S1; Figure S3). All studies of $PM_{2.5}$ and cognitive decline reported effect estimates, with varying degrees of precision, that were supportive of an adverse association, but considerably fewer cohorts were represented with respect to this outcome ($n = 5$, reporting on results specific to five cohorts) (Table S2; Figure S4). In contrast, studies of incident cognitive impairment or dementia ($n = 4$ with one reporting separate results from the same underlying cohort specific to periods 10 years apart) reported less consistent associations (Table S3). Among the seven studies reporting on associations between $PM_{2.5}$ and brain volumes, findings tended to indicate smaller volumes with higher exposure, but these associations were often small in magnitude and estimated with substantial imprecision (Table S4; Figure S5). One study identified an association of $PM_{2.5}$with longitudinally assessed increase in gray matter atrophy (Younan et al. 2020b). Findings across the four studies reporting associations between $PM_{2.5}$ and cerebrovascular imaging (Table S4; Figure S6) measures were inconsistent and imprecise, although interestingly, findings related to white matter hyperintensity volume consistently indicated a protective effect.

Results from the 13 papers (reporting estimates on 13 cohorts) that examined associations with PM_{10} did not strongly support the presence of an association (Tables S1–S4; Figure S7). The collection of results from nine papers (reporting results on nine

Table 2. Summary of quality assessment for eligible studies on air pollution and late-life cognitive health identified through 31 December 2020.

		Study strengths[a]						
Study focus	Citation/cohort	Exposure assessment and variability	Outcome assessment	No substantial issues with confounding/ inappropriate adjustment	No substantial issues with cohort formation/loss to follow-up	Generalizability	New to the review	Noted study limitations[b]
Cognitive level	(Ailshire and Crimmins 2014)/HRS	—	Yes	Yes	Yes	Yes	—	No individual-level exposure assessment, restricted to regions near regulatory monitors.
Cognitive level	(Ailshire And Clarke 2015)/ACL Survey	—	—	—	Yes	Yes	—	No individual-level exposure assessment, restricted to regions near regulatory monitors; insensitive test of cognition will likely only pick up highly impaired; crude age and education adjustment.
Cognitive level	(Chen et al. 2020)/TIGER	—	—	—	—	Yes	Yes	Limited exposure variability; reporting on outcome definition is unclear; inappropriate adjustment for a potential intermediate; no information on correlates of attrition.
Cognitive level	(Chen and Schwartz 2009)/NHANES III	—	Yes	—	Yes	Yes	—	No individual-level exposure assessment, restricted to regions near regulatory monitors; adjusted for age in 10-year bands, different adjustment for socioeconomic status across exposures, specifically some models of PM_{10} not adjusted for both race/ethnicity and socioeconomic status.
Cognitive level	(Gatto et al. 2014)/WISH, BVAIT, and ELITE	—	Yes	Yes	—	—	—	Only modest capture of local exposure gradients; cohort was extremely healthy for age due to inclusion/exclusion criteria of original randomized controlled trials.
Cognitive level	(Kim et al. 2019)/ Voluntary community-based sample	Yes	—	—	—	Yes	Yes	Outcome was below threshold on dementia screening test after excluding persons with dementia or mild cognitive impairment; crude age adjustment, inappropriate adjustment for intermediates, reported only stratified analysis without justification.
Cognitive level	(Lo et al. 2019)/TLSA	—	—	—	—	Yes	Yes	No individual-level exposure assessment or information on exposure distribution; insensitive test of cognition will likely only pick up highly impaired; inappropriate adjustment for IADLs; lack of information on loss to follow-up despite use of repeated measures for cross-sectional analysis.
Cognitive level	(Power et al. 2011)/NAS	Yes	Yes	—	Yes	Yes	—	Inappropriate adjustment for intermediates.
Cognitive level	(Ranft et al. 2009)/SALIA	—	Yes	—	Yes	Yes	—	Relatively little exposure variability in recent exposure for rural participants, modest capture of local exposure gradients; crude adjustment for age and socioeconomic status, inappropriate adjustment for co-morbidities.
Cognitive level	(Rocha et al. 2020)/ELSA-Brasil	Yes	Yes	Yes	—	Yes	Yes	Excluded substantial proportion of sample for missing exposure data.
Cognitive level	(Salinas-Rodríguez et al. 2018)/ENSANUT-2012	—	Yes	Yes	Yes	Yes	Yes	No individual-level exposure assessment, limited capture of local air pollution exposure gradients.
Cognitive level	(Schikowski et al. 2015)/ SALIA	—	Yes	Yes	Yes	Yes	—	Relatively little variation in PM across study participants.
Cognitive level	(Shin et al. 2019)/KFACS	—	Yes	—	Yes	Yes	Yes	Limited exposure variation, exposure estimation poorly documented, no individual-level exposure assessment; inappropriate adjustment for comorbidities.
Cognitive level	(Tallon et al. 2017)/ NSHAP	—	Yes	Yes	Yes	Yes	Yes	Excluded one-third of participants from analyses with NO_2 exposure, spatial resolution is limited, especially for NO_2.
Cognitive level	(Tzivian et al. 2016)/Heinz Nixdorf RECALL	—	Yes	Yes	Yes	Yes	Yes	Limited exposure variability.
Cognitive level	(Wellenius et al. 2012a)/ MOBILIZE Boston	Yes	Yes	Yes	—	Yes	—	Lack of information on loss to follow-up despite use of repeated measures for cross-sectional analysis.

Table 2. (*Continued.*)

Study focus	Citation/cohort	Study strengths[a]						Noted study limitations[b]
		Exposure assessment and variability	Outcome assessment	No substantial issues with confounding/ inappropriate adjustment	No substantial issues with cohort formation/loss to follow-up	Generalizability	New to the review	
Cognitive level	(Wurth et al. 2018)/ BPRHS	—	Yes	—	—	Yes	Yes	Limited exposure variation, no individual-level exposure assessment; no adjustment for calendar time (necessary because a single monitor was used to assess exposure based on individual's cognitive test date); lack of information on loss to follow-up despite use of repeated measures for cross-sectional analysis.
Cognitive level	(Yao et al. 2021)/CLHLS	—	Yes	Yes	—	Yes	Yes	Use self-report for assessment of distance to road; excluded 23% due to missing MMSE data.
Cognitive level	(Younan et al. 2020a)/ WHIMS-MRI and WHISCA	Yes	Yes	—	Yes	—	Yes	Inappropriate adjustment for intermediates; MRI sample appears extremely healthy based on sample characteristics.
Cognitive level	(Zeng et al. 2010)/CLHLS	—	Yes	Yes	Yes	Yes	—	API is a crude measure combining multiple air pollutants with variable correlation, measured at the community level.
Neuroimaging level and cognitive level	(Crous-Bou et al. 2020)/ ALFA	—	Yes	Yes	Yes	—	Yes	Did not report exposure contrast associated with reported effect estimate; enriched in participants who are APOE E4 positive, have a family history of dementia.
Neuroimaging level and cognitive level	(Nußbaum et al. 2020)/ 1000BRAINS	—	Yes	Yes	Yes	Yes	Yes	Limited exposure variability.
Neuroimaging level	(Casanova et al. 2016)/ WHIMS-MRI	Yes	Yes	—	—	—	Yes	Adjustment for intermediates in presented models; no comparison of MRI subcohort to full cohort; MRI sample appears extremely healthy based on sample characteristics.
Neuroimaging level	(Chen et al. 2015)/ WHIMS-MRI	—	Yes	Yes	—	—	—	~11% of the cohort were missing >40% of $PM_{2.5}$ data for the exposure assessment period and point estimates are attenuated, but remain statistically significant when excluding this group; no comparison of MRI subcohort to full cohort; MRI sample appears extremely healthy based on sample characteristics.
Neuroimaging level	(Erickson et al. 2020)/UK Biobank	Yes	Yes	—	—	—	Yes	Inappropriate adjustment for intermediates or consequences of exposure or outcome; no comparison of MRI subcohort to full cohort; sample is much healthier than general UK population.
Neuroimaging level	(Gale et al. 2020)/UK Biobank	Yes	—	—	—	—	Yes	Unclear if volumes standardized by intracranial volume, no information on MRI processing pipeline, left/right separated without confirmation of effect modification; inappropriate adjustment for intermediates or consequences of exposure or outcome, a proxy of exposure; no comparison of MRI subcohort to full cohort; sample is much healthier than general UK population.
Neuroimaging level	(Hedges et al. 2019)/UK Biobank	Yes	—	—	—	—	Yes	Unclear if volumes standardized by intracranial volume, no information on MRI processing pipeline, left/right separated without confirmation of effect modification; inappropriate adjustment for intermediates or consequences of exposure or outcome, a proxy of exposure; no comparison of MRI subcohort to full cohort; sample is much healthier than general UK population.

Table 2. (*Continued.*)

		Study strengths[a]						
Study focus	Citation/cohort	Exposure assessment and variability	Outcome assessment	No substantial issues with confounding/ inappropriate adjustment	No substantial issues with cohort formation/loss to follow-up	Generalizability	New to the review	Noted study limitations[b]
Neuroimaging level	(Hedges et al. 2020)/UK Biobank	Yes	—	—	—	—	Yes	Unclear if volumes standardized by intracranial volume, no information on MRI processing pipeline, left/right separated without confirmation of effect modification; inappropriate adjustment for intermediates or consequences of exposure or outcome, a proxy of exposure; no comparison of MRI subcohort to full cohort; sample is much healthier than general UK population.
Neuroimaging level	(Iaccarino et al. 2021)/ IDEAS	—	Yes	—	—	—	Yes	No individual-level exposure assessment; inappropriate adjustment for intermediates; selection based on cognitive status could cause collider bias; highly selected clinical sample of people with uncertain cognitive impairment etiology who access tertiary care.
Neuroimaging level	(Kulick et al. 2017)/ NOMAS	Yes	Yes	Yes	—	Yes	Yes	No comparison of MRI subcohort to full cohort.
Neuroimaging level	(Power et al. 2018a)/ARIC	—	Yes	Yes	—	Yes	Yes	Limited exposure variation for site-specific analyses, selection based on cognitive status could cause collider bias.
Neuroimaging level	(Wilker et al. 2015)/FOS	Yes	Yes	Yes	—	Yes	—	No comparison of MRI subcohort to full cohort.
Neuroimaging level	(Wilker et al. 2016a)/ MADRC	Yes	Yes	Yes	—	—	Yes	Highly selected clinical sample.
Neuroimaging level	(Younan et al. 2020b)/ WHIMS-MRI	Yes	Yes	Yes	Yes	—	Yes	MRI sample appears extremely healthy based on sample characteristics.
Cognitive level and cognitive change	(Cullen et al. 2018)/UK Biobank	Yes	—	Yes	—	—	Yes	Time period elapsed and limited number of assessments may limit ability to detect change given age of sample; not representative of sampling frame and low participation rate; sample is much healthier than general UK population.
Cognitive level and cognitive change	(Kulick et al. 2020)/ WHICAP and NOMAS	—	Yes	Yes	—	Yes	Yes	Low exposure variability within NOMAS participants; no comparison of MRI subcohort to full cohort.
Cognitive level and cognitive change	(Tonne et al. 2014)/ Whitehall II	—	Yes	—	Yes	Yes	—	Relatively little variation in total PM_{10} and total $PM_{2.5}$ across study participants, no individual-level exposure assessment; did not report whether they adjusted for time-by-covariate interactions in analyses of cognitive change.
Cognitive change	(Cleary et al. 2018)/ National AD Centers Database	—	Yes	—	—	—	Yes	No individual-level exposure, low spatial resolution of model, use of tertiles for exposure; did not specify if including cross-product terms to adjust for confounding of decline; highly selected clinical sample and required development of cognitive impairment during follow-up; enriched in participants who are APOE E4 positive, have a family history of dementia, or have rare dementias.
Cognitive change	(Colicino et al. 2014)/NAS	Yes	Yes	—	—	Yes	Yes	Inappropriate adjustment for potential intermediates; no discussion of extent or correlates of attrition during follow-up.
Cognitive change	(Oudin et al. 2017)/Betula	—	Yes	Yes	Yes	Yes	Yes	Exposures were predicted for 2009–2010, but outcome follow-up spanned 1993–2010.
Cognitive change	(Petkus et al. 2020)/ WHISCA	Yes	Yes	—	—	Yes	Yes	Inappropriate adjustment for intermediates; no discussion of extent or correlates of attrition during follow-up.

Table 2. (*Continued.*)

		Study strengths[a]						
Study focus	Citation/cohort	Exposure assessment and variability	Outcome assessment	No substantial issues with confounding/ inappropriate adjustment	No substantial issues with cohort formation/loss to follow-up	Generalizability	New to the review	Noted study limitations[b]
Cognitive change	(Petkus et al. 2021)/ WHIMS-ECHO	Yes	Yes	—	—	Yes	Yes	Inappropriate adjustment for intermediates; recruitment required survival to age 80, no discussion of extent or correlates of attrition during follow-up.
Cognitive change	(Weuve et al. 2012)/NHS	Yes	Yes	Yes	—	Yes	—	No discussion of correlates of attrition during follow-up.
Prevalent dementia	(Dimakakou et al. 2020)/ UK Biobank	—	—	—	—	—	Yes	No information on exposure distribution, no information on how exposure was linked to participants; reliance on medical records; inappropriate adjustment for potential consequences of disease, no adjustment for individual-level SES; sample is much healthier than general UK population, inclusion of young participants not at risk of dementia; not representative of sampling frame and low participation rate.
Incident dementia or other incident cognitive impairment	(Ailshire and Walsemann 2021)/HRS	—	Yes	Yes	—	Yes	Yes	No individual-level exposure assessment; no information on proportion of persons lost to follow-up or correlates of attrition
Incident dementia or other incident cognitive impairment	(Carey et al. 2018)/CPRD	—	—	—	—	Yes	Yes	Limited exposure variation, no individual-level exposure assessment; reliance on medical records/claims data; no adjustment for individual-level education; no discussion of extent or correlates of attrition during follow-up.
Incident dementia or other incident cognitive impairment	(Cerza et al. 2019)/Rome Longitudinal Cohort	—	—	Yes	Yes	Yes	Yes	Exposures were predicted for 2009–2010, but outcome follow-up started in 2001; reliance on hospital admissions for identifying dementia.
Incident dementia or other incident cognitive impairment	(Chang et al. 2014)/ NHIRD Taiwan	—	—	—	—	—	—	No individual-level exposure estimates, exposure averaging period depended on date of censoring; use of ICD-9-CM codes for identification of dementia, youngest participants not at risk of dementia given <65 years of age for duration of follow-up; no adjustment for education, inappropriate adjustment for multiple potential mediating health conditions in all presented models; no information on attrition or its correlates; inclusion criteria required respiratory tract infection, which may have resulted in selection of sicker or more susceptible persons.
Incident dementia or other incident cognitive impairment	(Chen et al. 2017a)/ Ontario Population Health and Environment Cohort	—	—	—	—	Yes	Yes	No individual-level exposure assessment, poor resolution for ozone; reliance on medical records/claims data; crude adjustment for SES; no discussion of extent or correlates of attrition during follow-up.
Incident dementia or other incident cognitive impairment	(Chen et al. 2017b)/ Ontario Population Health and Environment Cohort	—	—	—	—	Yes	Yes	Proximity to major roadways based on postcode centroid; reliance on medical records/claims data; crude adjustment for SES, adjustment for mediators in primary analyses; no discussion of extent or correlates of attrition during follow-up.

Table 2. (*Continued.*)

Study focus	Citation/cohort	Study strengths[a]						Noted study limitations[b]
		Exposure assessment and variability	Outcome assessment	No substantial issues with confounding/ inappropriate adjustment	No substantial issues with cohort formation/loss to follow-up	Generalizability	New to the review	
Incident dementia or other incident cognitive impairment	(Grande et al. 2020)/ SNAC-K	—	—	—	Yes	Yes	Yes	Limited exposure variability; partial reliance on medical records for identification of dementia without information on frequency of identification through this method; inappropriate adjustment for intermediates.
Incident dementia or other incident cognitive impairment	(He et al. 2020)/ZJMPHS	—	Yes	Yes	Yes	Yes	Yes	No individual-level exposure assessment, spatial resolution is limited.
Incident dementia or other incident cognitive impairment	(Ilango et al. 2020)/NPHS and CCHS participants	—	—	Yes	—	Yes	Yes	Lacking information on how air pollution linked to participant location; reliance on medical records/claims data; no discussion of extent or correlates of attrition during follow-up.
Incident dementia or other incident cognitive impairment	(Jung et al. 2015)/NHIRD Taiwan	—	—	—	—	Yes	—	No individual-level exposure estimates; use of ICD-9-CM codes for identification of dementia; no adjustment for education or socioeconomic status; no information on attrition or its correlates.
Incident dementia or other incident cognitive impairment	(Li et al. 2019)/NHIRD Taiwan	—	—	—	—	Yes	Yes	No individual-level exposure assessment; use of ICD-9-CM codes for identification of dementia; crude adjustment for SES; case-control design assumes no informative attrition.
Incident dementia or other incident cognitive impairment	(Loop et al. 2013)/ REGARDS	—	Yes	Yes	—	Yes	—	No individual-level exposure estimates; no information on correlates of attrition and requirement of completion of two cognitive assessments for inclusion in analysis.
Incident dementia or other incident cognitive impairment	(Oudin et al. 2016)/Betula	—	—	Yes	Yes	Yes	—	Exposures were predicted for 2009–2010, but outcome follow-up spanned 1993–2010, results using back-extrapolated exposure predictions were reported to be similar, but data not shown; partial reliance on medical records for identification of dementia.
Incident dementia or other incident cognitive impairment	(Oudin et al. 2018)/Betula	Yes	—	Yes	—	Yes	Yes	Partial reliance on medical records for identification of dementia; did not address loss to follow-up as a potential source of bias.
Incident dementia or other incident cognitive impairment	(Paul et al. 2020)/SALSA	Yes	Yes	Yes	Yes	Yes	Yes	Nothing of note.
Incident dementia or other incident cognitive impairment	(Ran et al. 2021)/Chinese EHS	—	—	Yes	—	—	Yes	Limited exposure variability; reliance on medical records; no information on correlates of attrition; fee charged for participant enrollment.
Incident dementia or other incident cognitive impairment	(Shi et al. 2020)/Medicare fee-for-service beneficiaries	—	—	—	Yes	Yes	Yes	No individual-level exposure assessment; reliance on claims data; crude adjustment for SES

Table 2. (*Continued.*)

Study focus	Citation/cohort	Study strengths[a]						Noted study limitations[b]
		Exposure assessment and variability	Outcome assessment	No substantial issues with confounding/ inappropriate adjustment	No substantial issues with cohort formation/loss to follow-up	Generalizability	New to the review	
Incident dementia or other incident cognitive impairment	(Smargiassi et al. 2020)/ QICDSS	—	—	—	—	Yes	Yes	No individual-level exposure assessment, distance to road based on postcode centroid; reliance on medical records/ claims data; no adjustment for individual-level SES; no information on correlates of attrition.
Incident dementia or other incident cognitive impairment	(Wang et al. 2020)/CLHLS	Yes	—	—	—	Yes	Yes	No information on timing of follow-up assessment; inappropriate adjustment for intermediates; no discussion of selective survival to enrollment or correlates of attrition despite large loss to follow-up.
Incident dementia or other incident cognitive impairment	(Wu et al. 2015)/Case–control	—	Yes	—	—	Yes	Yes	Inadequate documentation of exposure model validation, used tertiles of exposure; large differences in age across cases and controls may result in positivity violations; unclear whether case-control selection related to exposure.
Incident dementia or other incident cognitive impairment	(Yuchi et al. 2020)/MSP Registry	—	—	—	—	Yes	Yes	No individual-level exposure assessment; reliance on medical records/claims data; crude adjustment for SES, inappropriate adjustment for potential mediators; no information on attrition or its correlates.
Incident dementia or other incident cognitive impairment and neuroimaging level	(Chen et al. 2017c)/ WHIMS	—	Yes	Yes	—	—	Yes	No individual-level exposure assessment for diesel; no comparison of MRI subcohort to full cohort, no discussion of extent of or correlates of attrition; MRI appears extremely healthy based on sample characteristics.

Note: ACL, Americans' Changing Lives; AD, Alzheimer's disease; ALFA, Alzheimer's and Family; ARIC, Atherosclerosis Risk in Communities; BPRHS, Boston Puerto Rican Health Study; BVAIT, B-Vitamin Atherosclerosis Intervention Trial; CCHS, Canadian Community Health Survey; CLHLS, Chinese Longitudinal Healthy Longevity Survey; CPRD, Clinical Practice Research Datalink; EHS, Elderly Health Service; ELITE, Early versus Late Intervention Trial; ELSA-Brasil, Brazilian Longitudinal Study on Adult Health; ENSANUT-2012, National Survey of Health and Nutrition in Mexico in 2012; FOS, Framingham Offspring Study; Heinz Nixdorf RECALL, Heinz Nixdorf Risk factors, Evaluation of Coronary Calcium and Lifestyle study; HRS, Health and Retirement Study; IADL, instrumental activities of daily living; ICD-9, International Classification of Diseases, Ninth Revision; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IDEAS, Imaging Dementia – Evidence for Amyloid Scanning; KFACS, Korean Frailty and Aging Cohort Study; MADRC, Massachusetts Alzheimer's Disease Research Center Longitudinal Cohort; MMSE, Mini-Mental State Examination; MOBILIZE, Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly; MRI, magnetic resonance imaging; MSP, Medical Service Plan; NAD, non-Alzheimer's dementia; NAS, Normative Aging Study; NHANES III, Third National Health and Nutrition Examination Survey; NHIRD, National Health Insurance Research Database; NHS, Nurses' Health Study; NO_2 nitrogen dioxides; NO_x, nitrogen oxides; NOMAS, Northern Manhattan Study; NPHS, National Population Health Survey; NSHAP, National Social Health and Aging Study; PM, particulate matter; $PM_{2.5}$, particulate matter with an aerodynamic diameter $\leq$2.5 micrometers; PM_{10}, particulate matter with an aerodynamic diameter $\leq$10 micrometers; $PM_{2.5–10}$, particulate matter with an aerodynamic diameter between 2.5 and 10 micrometers; QICDSS, Québec Integrated Chronic Disease Surveillance System; REGARDS, REasons for Geographic and Racial Differences in Stroke; SALIA, Study on the Influence of Air Pollution on Lung Function, Inflammation, and Aging; SALSA, Sacramento Area Latino Study on Aging; SES, socioeconomic status; SNAC-K, Swedish National Study of Aging and Care in Kungsholmen; TIGER, Taiwan Institute for Geriatric Epidemiological Research; TLSA, Taiwanese Longitudinal Study on Aging; WHICAP, Washington Heights-Inwood Community Aging Project; WHIMS-ECHO, Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; WHIMS-MRI, Women's Health Initiative Memory Study Magnetic Resonance Imaging Study; WHISCA, Women's Health Initiative Study of Cognitive Aging; WISH, Women's Isoflavone Soy Health; ZJMPHS, Zhejiang Major Public Health Surveillance.

[a]Studies that received a check mark for the study strength category were not found to have any substantial limitations in those categories. Substantial limitations in categories without a check mark are explained in the column farthest to the right.

[b]Study bias assessment pertains only to exposure-outcome associations that were unique to the sample population.

cohorts) on cognitive performance was not consistent, with adverse associations that were limited in count and magnitude. The three papers (reporting results on four cohorts) examining cognitive change suggested a possible adverse relation (Table S2), but their estimates were generally imprecise. Although associations with neuroimaging outcomes were suggestive of an adverse effect of PM_{10}, this evidence was restricted to three papers (Table S4). The two papers examining PM_{10} and dementia or impairment generated inconsistent results (Table S3).

Only four papers reported associations pertaining to $PM_{2.5–10}$, and these results were inconsistent. Although associations with cognitive decline (Weuve et al. 2012) and neuroimaging brain volume indices (Crous-Bou et al. 2020) were adverse, associations with cognitive function were mixed (Crous-Bou et al. 2020; Tzivian et al. 2016), and the single study of incident dementia reported a protective association with this outcome (Cerza et al. 2019).

Markers and measures of traffic-related air pollution (excluding total NO_2 and NO_x). Eleven papers (studying 11 cohorts) reported on measures of traffic-related air pollution and cognitive function with mixed results (Table S5). Results from three papers (reporting on four cohorts) on cognitive decline (Table S6), and the five studies of neuroimaging outcomes (Table S8) similarly did not support an adverse association with greater exposure to traffic. Two of the three studies of incident cognitive impairment/dementia (Table S7) reported adverse associations with higher exposure.

AQI. The single study of AQI found little association with incident cognitive impairment (He et al. 2020).

Discussion

Epidemiological evidence on the relation of air pollution exposure to dementia risk continues to amass rapidly. Here we summarized the findings of the 35 of 66 papers with strengths in three or more methodologic domains that reported on associations with NO_2/NO_x, O_3, PM, or traffic-related air pollution. On balance, results on $PM_{2.5}$ exposure and cognitive level were mixed. Although they were slightly more likely to suggest an adverse association than a null or beneficial effect, the margin was narrow. Studies of $PM_{2.5}$ and cognitive decline generally supported an adverse association, whereas there was suggestive but less abundant support for links of $PM_{2.5}$ with brain volumes. Findings related to PM_{10}, NO_2, NO_x, and of traffic-related exposures were mixed, and findings on other air pollutants, including $PM_{2.5–10}$ and O_3, were too sparse to discern a likely direction of effect, if any.

We note several new developments in the literature since our last review in 2016. The literature has expanded to include a substantial number of studies considering cognitive change, incident dementia or cognitive impairment, and dementia-related neuroimaging markers. Such studies offer different windows into dementia etiology, including whether specific air pollutants act on distinct etiologies. Moreover, triangulation across studies considering different dementia-related outcomes allows higher confidence in overall conclusions. Since the last review, overall spatial resolution for estimated air pollutant exposures has improved. This finer level of detail helps to distinguish the exposure profiles of individuals within the same region or city, thus reducing error in exposure measurement aside from that introduced by exposure modeling assumptions and increasing statistical precision. Newer studies have also begun to consider community noise as either a confounder or effect modifier. To date, studies with data on noise and air pollution have not found noise to be a substantial source of confounding (Andersson et al. 2018; Carey et al. 2018; Tzivian et al. 2016). However, there was some suggestion that it may be an effect modifier (Tzivian et al. 2017).

Recommendations for Further Strengthening the Evidence Base

Dementia ascertainment. As in our prior review, most studies of air pollution and incident dementia relied on administrative claims or medical records to identify persons living with dementia. One advantage of this approach is that it permits large studies inclusive of populations often underrepresented in research, and with greater sample size comes enhanced precision of effect estimates. However, use of this data to identify persons with dementia likely introduces systematic bias to the estimated effects of air pollution, resulting from misclassification of dementia status.

Administrative data, including insurance claims and medical records, are not created for research purposes. Many dementia claims reflect rule-out diagnoses; as such, a claim may not represent a true diagnosis. For example, the positive predictive value of a dementia claim in U.S. Medicare claims is only 56% (Taylor et al. 2009). However, an even bigger issue with use of claims and medical records data to ascertain dementia status is underdiagnosis of dementia due to missed or delayed diagnosis, which is extremely common, often exceeding 50% (Lang et al. 2017). If the resulting misclassification of dementia status were nondifferential, the result would generally be bias toward the null. Of particular consequence to estimating the effects of air pollution on dementia incidence, misclassification of dementia status in administrative data does not appear to be random. Rates of dementia underdiagnosis differ by race/ethnicity (Gianattasio et al. 2019) as well as health status and other sociodemographic factors (Power et al. 2020). This differential misclassification has been shown to lead to biased measures of association of other factors with dementia, even after adjustment for key covariates (Power et al. 2020).

In many settings, it is plausible that the same factors that predict the discordance between true dementia status and diagnostic status also correlate with air pollution exposure (Hajat et al. 2015; Miranda et al. 2011). For example, areas with high levels of air pollution could have greater rates of dementia overdiagnosis because air pollution, a risk factor for chronic disease, increases interactions with the medical system. Conversely, it could be that areas or subgroups with high air pollution exposure may have greater rates of dementia underdiagnosis or delayed diagnosis. If other air pollution–related health effects are more pressing or revenue-generating, the existence of dementia may never enter the medical record or generate a claim. It could also be that who is diagnosed (or misdiagnosed) and how much delay is involved are determined by spatially patterned factors, such as quality of and access to medical care and the level of stigma associated with a diagnosis of dementia.

There is little if any evidence about how much dementia misclassification in administrative records varies by level of exposure to air pollution, but the potential for bias from differential misclassification seems high. Although the pattern and severity of dementia misclassification in administrative data may vary by setting and over time, misclassification is common enough to warrant attention when these data are used in studies of air pollution, even in settings that provide universal health care for older adults or expansive socialized health care (McGuinness et al. 2019; Power et al. 2020; Rizzuto et al. 2018; Solomon et al. 2014; Taylor et al. 2009; Wilkinson et al. 2018). Unfortunately, adjusting for determinants of misclassification does not mitigate this bias and can instead induce bias (Greenland and Robins 1985).

Some new studies used an outcome definition of hospitalization with a dementia diagnosis. This measure likely captures newly onset cases as well as established cases that require hospitalization because they are sufficiently severe or involve acute comorbid conditions. Thus, estimates from these studies may mismeasure dementia onset and reflect the effects of air pollution on acute comorbid conditions (Phelan et al. 2012) or even the exacerbation of dementia symptoms. This latter possibility is of interest but was not an explicit focus of our review.

No study in our review that relied on administrative records for dementia ascertainment reported on the validity of their dementia ascertainment approach against *research-quality dementia adjudication* (i.e., in-person, study-based ascertainment that does not rely on interfacing with clinical services in the community), nor did any such study test the sensitivity of its findings to assumptions about the accuracy of these records. In the absence of such evaluations or evidence that diagnostic accuracy is not related to exposure status, confidence in studies that use records-based ascertainment remains limited. Thus, to the extent possible, we recommend that the performance of dementia classification using administrative data be evaluated against that of criterion-standard dementia diagnoses, with added investigation of whether performance differs by air pollution exposure status. Fortunately, a raft of validation studies in multiple settings on other outcomes such as stroke and heart failure—a body of work that has shaped research on these outcomes—offers a framework for moving in this direction.

Neuroimaging. The number of studies reporting on neuroimaging outcomes has grown substantially; however, it remains difficult to synthesize these reports. Some neuroimaging studies focused on markers of atrophy report on both broad (e.g., total brain volume) and selected regions of interest (e.g., thalamic volume), whereas others focused on a single, preselected region of the brain. Although there is value and potential mechanistic insight in considering regions known to atrophy preferentially with specific dementia-related disease processes, these results should be interpreted in the context of estimated associations with broader regions. For example, if we see an association between air pollution and atrophy of the thalamus, without more expansive investigation and reporting, it is unclear whether this is selective atrophy of the thalamus or simply a reflection of global atrophy. This logic also applies to measures of small vessel disease—e.g., white matter hyperintensities, lacunes, small subcortical infarcts, cerebral microbleeds, and perivascular spaces (Wardlaw et al. 2013). Examination of the set of markers thought to indicate a common underlying etiology is therefore more valuable than piecemeal examination of any specific marker.

Similarly, studies are beginning to evaluate neuroimaging findings as mediators of an association between air pollution and cognition (Younan et al. 2020a). Such analyses must be interpreted in the context of the broader literature. First, the currently available neuroimaging markers are crude measures of underlying pathological processes. As such, it may be difficult to detect substantial mediation between air pollution and cognitive symptoms by neuroimaging markers using the markers available to existing epidemiological studies. The field continues to evolve, and new developments may provide better options. Second, the choice of a particular marker to assess as a mediator of a particular air pollution–cognitive test performance association appears largely based on prior cohort-specific results, rather than on *a priori* hypotheses or biological plausibility informed by the broader literature. Without first establishing that the main effect of an air pollutant exposure appears across studies, reproducibility of mediation results is likely to be poor. Furthermore, it can be challenging to establish the temporal order of exposure, neuroimaging mediator, and cognition. Although it is of interest to understand the etiological underpinnings of associations between air pollution and cognition, using mediation analyses to explore questions about etiology requires strong rationale, rigor, and replication in diverse settings.

Attention to potential for selection bias. As in the prior review, reporting related to selection bias continues to be scarce. It is well established that cognitive status predicts study participation (Weuve et al. 2015), and it is reasonable to assume that higher air pollution exposures may be associated with study participation given their established adverse health effects, including increased mortality risk (Christidis et al. 2019; Dockery et al. 1993; Pope et al. 2019; Stockfelt et al. 2015; Weuve et al. 2016). If both high air pollution and low or declining cognitive status were to reduce participation, the ensuing bias would likely result in an underestimate of the effect of air pollution on cognitive decline.

These concerns are especially pertinent to brain imaging studies, and the expected direction of bias may differ in these settings. For example, imaging subcohorts of the Framingham Offspring Study and the Women's Health Initiative Memory Study comprised 51% and 61%, respectively, of eligible participants from the primary cohorts (Debette et al. 2010; Jaramillo et al. 2007). The selection patterns may be further affected by the incentives, barriers, and contraindications to participating in a brain imaging protocol, which requires participants to travel to the site housing the instrument. Alternatively, individuals may be motivated on the basis of family history or perceived personal risk. For example, investigators for the established cohort study, Monongahela–Youghiogheny Healthy Aging Team, asked study participants at their second assessment if they would be interested in undergoing a brain MRI protocol. Among those who were interested, mild cognitive impairment and dementia were less prevalent, but carriership of the *APOE4* allele (a common risk gene for dementia) was more prevalent than among those not interested (Ganguli et al. 2015). Similarly, in studies involving PET imaging and cerebrospinal fluid measurement of amyloid and tau, APOE4 carriership was far more prevalent than in the general population of older adults (Li et al. 2017a; Morris et al. 2019). Thus, the direction of an ensuing bias may be difficult to predict without information on participants and nonparticipants. Imaging cohorts are also sometimes purposefully selected based on cognitive status (Iaccarino et al. 2021; Power et al. 2018a), which may lead to collider bias.

Most studies in this review had characteristics that made them vulnerable to selection bias, such as advanced participant age at entry, long duration of follow-up and/or substantial losses of participants over follow-up, or a study protocol that placed considerable logistical burdens on participants (e.g., neuroimaging). Some studies quantified participation and reported indices such as the percentage of participants who remained alive and continued through the entire follow-up, or the percentage of participants who engaged in neuroimaging protocols. Far fewer studies reported correlates of participation, which is useful to gauge the risk of substantial bias from selective participation. A few studies, including an imaging study, explicitly attempted to adjust for selection bias using statistical methods including restriction to younger ages, inverse probability of selection weights, multiple imputation, or quantitative bias analysis and related simulations (Kulick et al. 2020; Paul et al. 2020; Power et al. 2018a; Weuve et al. 2015; Younan et al. 2020b). We recommend reporting details of the selection process, including persons contacted, refused, and lost to follow-up, as well as correlates of participation. Furthermore, where evidence suggests selection bias may be substantial, we recommend use of established statistical approaches to mitigate this bias.

Exposure. The overall spatial resolution of exposure estimates has improved substantially in more recent work, but a number of other exposure-related considerations warrant increased attention.

Existing studies used a wide variety of exposure estimation approaches; however, reporting on these approaches and models often lacked key details necessary to assess the likely degree of exposure misclassification. Studies should report the spatial resolution of their participant location information; this reporting is especially important for studies assigning exposures based on areas such as participants' postal codes. In addition, we recommend that epidemiological studies present all validation statistics from exposure prediction models and that statistics be based on exposure averaging periods and spatial domains that are relevant to the study at hand. We further recommend that reports provide information on both the absolute errors of the model and correlation with observed values as well as the source of these observed values (e.g., regulatory monitoring only or supplemented with research-based monitoring campaigns).

Many studies continue to consider 1- to 3-year average exposures near the time of outcome assessment as explicit or implicit proxies for exposure over longer or more historical periods (Power et al. 2016). Yet dementia-related changes to the brain (Jack et al. 2013) and even subtle declines in cognitive function (Knopman et al. 2018; Li et al. 2017b) are detectable decades before dementia diagnosis (Jack et al. 2013). As such, the etiologically relevant time period for exposure is likely in the more distant past for outcomes such as dementia or late-life cognitive decline, and slightly more recently for outcomes that capture earlier stages of the disease process (e.g., neuroimaging outcomes). Certainly, spatial contrasts in pollutant concentrations are largely stable over time, thus preserving ranks in concentration and meaning that recent exposure exposures often positively correlate with longer-term and historical exposures (Colmer et al. 2020). Nonetheless, with changes to air pollution concentrations globally over the past few decades, this correlation will weaken with longer time elapsed from the relevant to the measured exposures. The practice of using relatively recent exposures in the study of dementia-related outcomes is understandably driven by practical constraints due to a paucity of measurements in the 1990s and earlier. Fortunately, with air pollution models incorporating more time periods—e.g., models developed starting from the 2000s could conceivably extend through the 2020s—and as studies of aging continue to recruit individuals who are newly entering middle and older age, opportunities will abound to investigate exposures spanning much longer periods and even to delve into which period(s) might be most relevant. Thus, we encourage future studies that examine longer lags and longer averaging periods and attempt to identify the etiologically relevant period for these exposures. It is also worth considering the concentration–response function of these associations, given evidence from the literature of nonlinear health effects of air pollution (Burnett et al. 2014).

Statistical adjustment. Finally, there are a number of considerations related to modeling the effect of air pollution on dementia-related outcomes. There remains a common practice of adjusting for potential mediators, particularly cardiovascular risk factors and outcomes, in at least one set of analyses. Some studies designated these factors as potential mediators and compared estimates with and without adjustment for them. The assumption, occasionally made explicit, is that attenuation of the effect estimate with adjustment is evidence for mediation by cardiovascular risk factors and outcomes, and lack of attenuation indicates no mediation (e.g., Chen et al. 2015, 2017c; Ilango et al. 2020; Tzivian et al. 2016; Wilker et al. 2015). Drawing such conclusions, however, requires strong assumptions. For example, it is challenging to establish the temporal order of air pollution and cardiovascular risk factors relative to dementia-related outcomes, especially because midlife vascular risk factors appear important to dementia risk and most studies of air pollution rely on recent measures of exposure and mediators. In addition, most studies that adopted the "add-one-in" approach to mediation analysis did not evaluate the extent to which their analyses violated the key assumptions involved in using this method for inferring mediation (Kaufman et al. 2004; Valeri and Vanderweele 2013).

Another key issue is that air pollution levels have been dropping over time in many areas of the world, and dementia incidence, as well, appears to have declined in North America and Europe in recent decades (Satizabal et al. 2016; Wolters et al. 2020). Inasmuch as trends in dementia diagnosis or incidence over time may be unrelated to air pollution, time trends may be an important source of confounding to consider. This is especially true if outcome assessment occurs over a long period and time-varying exposures are used in the analysis. Studies with recruitment from multiple sites should consider potential confounding and heterogeneity of effect by place because sociodemographics and health are often tightly linked to place. Place can be difficult to adjust for using typical covariates, and site-adjustment or site-specific analyses may be warranted. (Burnett et al. 2014; Carroll and Stefanski 1995; Holloman et al. 2004; Park et al. 2014; Szpiro et al. 2011; Szpiro and Paciorek 2013; Zeger et al. 2000)

Limitations of this review. This systematic review was not without its own limitations. First, we personally have contributed to this literature and needed to review our own papers (Colicino et al. 2014; Power et al. 2011, 2018a; Weuve et al. 2012). Each paper underwent detailed evaluation by at least one reviewer who was not an author on that paper, and the final quality assessment judgments were agreed on by the whole team. This arrangement was not ideal, however, given the potential for bias about our own work, along with potential status differentials among members of our review team. However, excluding these papers' findings from consideration did not materially change any of the conclusions about the pollutant–outcome associations, except with respect to associations for which findings were already sparse.

We also acknowledge that risk of bias lies on a continuum, thus some elements of this review involve a degree of subjectivity. We built our quality assessment strategy using our combined expertise and experience in air pollution and dementia epidemiology. In doing so, we prioritized the methodological challenges faced in these realms (Weuve et al. 2015), which may differ in relevance from challenges in other lines of inquiry (Savitz et al. 2019). We also set criteria to identify and synthesize findings from studies with strengths across three or more core methodologic domains. We note that the use of three strengths as a cut point is arbitrary, and our designation gave equal weight to all domains, which might not be ideal (Savitz et al. 2019). Nonetheless, we felt that it was important to highlight the findings of research with stronger methodological features and found that some conclusions changed with more lenient cutoffs. Using studies of $PM_{2.5}$ and incident dementia or impairment as an example, the collective findings from the four studies that had the most methodological strengths do not strongly support an adverse association. The findings from these four studies stand in contrast to the findings from the 10 other studies with higher risks of bias, which collectively *do* support an adverse association. It remains possible that studies with noted limitations may still provide some insights into air pollution's relationship to dementia; however, the differences in

take-home messages between studies with more vs. less risk of bias highlight the need to carefully consider potential biases when interpreting this literature.

Future Directions and Gaps in the Literature

In addition to addressing the methodologic challenges raised above, there is benefit in expanding the scope of studies on air pollution and dementia risk. For example, only one study quantified the association of air pollution exposure with accumulation of brain pathologies that define Alzheimer's disease [amyloid beta plaque or neurofibrillary tangles (NFTs) made of hyperphosphorylated tau] (Iaccarino et al. 2021). As inquiries move in this direction—through the use of PET imaging, cerebrospinal fluid, blood, or autopsy—it is important to note that mixed dementia is the most common type of dementia and that a diverse set of neuropathologies may contribute to the clinical syndrome that we diagnose as dementia (Boyle et al. 2018; Brenowitz et al. 2017; Power et al. 2018b). These other neuropathologies (e.g., hippocampal sclerosis, Lewy bodies, etc.) should be assessed as well. There is also a clear need for mechanistic studies using experimental models, which would provide biological rationale for future work on mechanisms. Such studies would improve our understanding of the mechanisms by which air pollution exposure increases risk of cognitive impairment and dementia.

Similarly, monitoring change in brain morphology (e.g., Younan et al. 2020b) or markers of cerebrovascular disease would provide stronger evidence of a causal link than MRI results at a single time point. Such research may be particularly warranted because studies on $PM_{2.5}$ exposure and white matter hyperintensity volume reported protective associations. One author suggested that if $PM_{2.5}$ is associated with loss of white matter, there would be less white matter remaining to be susceptible to white matter hyperintensity formation, possibly explaining the unexpected direction of these associations (Wilker et al. 2016a). Longitudinal MRI studies may help determine whether these protective effects spuriously arise from this mechanism, or whether another mechanism is at play. (Carey et al. 2018; Oudin et al. 2018; Power et al. 2018a; Tonne et al. 2014)

Our review focused on air pollution's effects on dementia-related outcomes overall (i.e., "main effects"), rather than effects of combinations of exposures or in subgroups of individuals. Yet heterogeneity in the estimated effects of PM and other pollutants could stem, in part, from the presence of other pollutants or coexposures because a person is typically exposed to mixtures of pollutants rather than a single pollutant. Yet little is known about the extent to which exposures to two or more air pollutants magnify each other's effects on dementia risk, especially if they operate on different etiological levers. Wurth et al. initiated an exploration into mixtures and PM constituents by fitting two-pollutant models and also evaluating metal constituents within $PM_{2.5}$ (Wurth et al. 2018), but mixtures and PM constituents remain sparsely studied dimensions of air pollution and dementia risk. Similarly, little is known about the extent to which the constituents of PM or sources of PM explain the heterogeneity in the observed associations with dementia related end points within (Power et al. 2018a) or across studies. Addressing the importance of PM sources or heterogeneity in PM composition is a key outstanding research question both to inform public health interventions and ability to help indicate neurotoxic constituents of PM. Four studies in our review evaluated traffic-specific PM (Carey et al. 2018; Chen et al. 2017c; Oudin et al. 2018; Tonne et al. 2014), one of which also evaluated PM from wood smoke (Oudin et al. 2018). Also of potential interest are other coexposures, such as noise. As with studies encompassing longer exposure periods, we anticipate that the future holds more availability of both measured and modeled exposures of PM components and PM from different emission sources.

Of course, some caution is and will be warranted in comparing associations across pollutants in both single and multipollutant models because different pollutants are measured with differing levels of error. For example, total $PM_{2.5}$ is a more regional pollutant and is typically measured with less error than other pollutants such as O_3 and NO_x, which are more influenced by local sources. This can distort the relative apparent strength of associations, especially when pollutants are correlated.

It may also be informative to probe variation in air pollution's effects on cognitive health by socioeconomic status, as a few newer studies have done (Ailshire and Walsemann 2021; Chen et al. 2020; Yao et al. 2021). Some other health effects of air pollution appear to vary by socioeconomic status (Forastiere et al. 2007; Laurent et al. 2007; Martins et al. 2004; Yi et al. 2010), and socioeconomic factors may be tied to cognitive reserve (Stern et al. 2018), which posits that early and midlife advantage may confer protection from cognitive symptoms typically associated with an underlying dementia process until the process reaches a more severe state (Stern 2012).

Conclusions

In spite of substantial improvements in air quality, low levels of exposure remain associated with poor health outcomes (Di et al. 2017; U.S. EPA 2009, 2016; Wellenius et al. 2012b). If causally related, further reductions in air pollution levels across the globe may offer another path by which to address the dementia epidemic—one that does not rely on changing individual behavior. In updating our prior review of the state of the evidence linking long-term exposure to air pollution to dementia and related outcomes, we documented advances and continuing gaps in the evidence that has accrued in the last 5 years. This newly accrued evidence, in combination with the evidence that preceded it, suggests that exposure to air pollution may influence late-life cognitive health. Nonetheless, there remains substantial heterogeneity of findings across studies, and many studies have considerable limitations that could have altered their effect estimates, precluding strong conclusions for most pollutants. Overall, the evidence was strongest, in terms of volume and consistency, with respect to $PM_{2.5}$ and cognitive decline. This distinction is notable in light of a recent judgment of the U.S. Environmental Protection Agency. In its recent Integrated Science Assessment of $PM_{2.5}$, it concluded that long-term exposure to $PM_{2.5}$ was "likely to be causal" in relation to "nervous system effects" (U.S. EPA 2019).

With our review, we found a growing body of evidence. The newer evidence includes advances in exposure estimation and more studies on cognitive decline and incident dementia, although the overall quality of the evidence has not improved. Although no study is immune from limitations or the potential for bias, well-designed studies will be instrumental in allowing strong conclusions as future studies aim to fill the current gaps in the literature. These improvements will provide confidence that the resulting research, joined with the existing evidence base, can meaningfully inform future public health and environmental policy decisions.

Acknowledgments

The authors thank S. Powers, S. Durape, and C. Christopher for their assistance.

This work was funded by R01ES029509 to MCP from the NIEHS and NIA, R01ES028694, 1RF1AG05527, 2R01AG030153,

and 2R01AG051125 to SA from the NIEHS and NIA, and R01AG065359 and R01AG067497 to JW from the NIA.

References

Ailshire JA, Clarke P. 2015. Fine particulate matter air pollution and cognitive function among U.S. older adults. J Gerontol B Psychol Sci Soc Sci 70(2):322–328, PMID: 24906394, https://doi.org/10.1093/geronb/gbu064.

Ailshire JA, Crimmins EM. 2014. Fine particulate matter air pollution and cognitive function among older us adults. Am J Epidemiol 180(4):359–366, PMID: 24966214, https://doi.org/10.1093/aje/kwu155.

Ailshire J, Walsemann KM. 2021. Education differences in the adverse impact of $PM_{2.5}$ on incident cognitive impairment among U.S. older adults. J Alzheimers Dis 79(2):615–625, PMID: 33337363, https://doi.org/10.3233/JAD-200765.

Alzheimer's Association. 2018. 2018 Alzheimer's disease facts and figures. Alzheimers Dement. 14:367–429, https://doi.org/10.1016/j.jalz.2018.02.001.

Alzheimer's Association. 2020. Causes and Risk Factors. https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors#:~:text=The%20risk%20of%20developing%20Alzheimer's,blood%20pressure%20and%20high%20cholesterol. [accessed 15 June 2020].

Alzheimer's Association. 2015. Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars. https://www.alz.org/media/Documents/changing-the-trajectory-r.pdf [accessed 18 December 2018.

Amrhein V, Greenland S, McShane B. 2019. Scientists rise up against statistical significance. Nature 567:305–307, https://doi.org/10.1038/d41586-019-00857-9.

Andersson J, Oudin A, Sundström A, Forsberg B, Adolfsson R, Nordin M. 2018. Road traffic noise, air pollution, and risk of dementia–results from the Betula project. Environ Res 166:334–339, PMID: 29909174, https://doi.org/10.1016/j.envres.2018.06.008.

Babadjouni RM, Hodis DM, Radwanski R, Durazo R, Patel A, Liu Q, et al. 2017. Clinical effects of air pollution on the central nervous system; a review. J Clin Neurosci 43:16–24, PMID: 28528896, https://doi.org/10.1016/j.jocn.2017.04.028.

Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. 2018. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol 83(1):74–83.

Brauer M, Freedman G, Frostad J, van Donkelaar A, Martin RV, Dentener F, et al. 2016. Ambient air pollution exposure estimation for the global burden of disease 2013. Environ Sci Technol 50(1):79–88, PMID: 26595236, https://doi.org/10.1021/acs.est.5b03709.

Brenowitz WD, Keene CD, Hawes SE, Hubbard RA, Longstreth W Jr., Woltjer RL, et al. 2017. Alzheimer's disease neuropathologic change, Lewy body disease, and vascular brain injury in clinic-and community-based samples. Neurobiol Aging 53:83–92, PMID: 28236716.

Brookmeyer R, Abdalla N, Kawas CH, Corrada MM. 2018. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. Alzheimers Dement 14(2):121–129, PMID: 29233480, https://doi.org/10.1016/j.jalz.2017.10.009.

Brookmeyer R, Gray S, Kawas C. 1998. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health 88(9):1337–1342, PMID: 9736873, https://doi.org/10.2105/ajph.88.9.1337.

Burnett RT, Pope CA 3rd, Ezzati M, Olives C, Lim SS, Mehta S, et al. 2014. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. Environ Health Perspect 122(4):397–403, PMID: 24518036.

Cacciottolo M, Wang X, Driscoll I, Woodward N, Saffari A, Reyes J, et al. 2017. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. Transl Psychiatry 7(1):e1022, PMID: 28140404, https://doi.org/10.1038/tp.2016.280.

Carey IM, Anderson HR, Atkinson RW, Beevers SD, Cook DG, Strachan DP, et al. 2018. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. BMJ Open 8(9):e022404.

Carroll RR, Stefanski LA. 1995. *Measurement Error in Nonlinear Models*. London: Chapman & Hall.

Casanova R, Wang X, Reyes J, Akita Y, Serre ML, Vizuete W, et al. 2016. A voxel-based morphometry study reveals local brain structural alterations associated with ambient fine particles in older women. Front Hum Neurosci 10:495, PMID: 27790103.

Cerza F, Renzi M, Gariazzo C, Davoli M, Michelozzi P, Forastiere F, et al. 2019. Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study. Environ Health 18(1):72, PMID: 31399053, https://doi.org/10.1186/s12940-019-0511-5.

Chang KH, Chang MY, Muo CH, Wu TN, Chen CY, Kao CH. 2014. Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: a population-based retrospective cohort study. PLoS One 9(8):e103078, PMID: 25115939, https://doi.org/10.1371/journal.pone.0103078.

Chen H, Kwong JC, Copes R, Hystad P, van Donkelaar A, Tu K, et al. 2017a. Exposure to ambient air pollution and the incidence of dementia: a population-based cohort study. Environ Int 108:271–277, PMID: 28917207, https://doi.org/10.1016/j.envint.2017.08.020.

Chen H, Kwong JC, Copes R, Tu K, Villeneuve PJ, van Donkelaar A, et al. 2017b. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. Lancet 389(10070):718–726, PMID: 28063597, https://doi.org/10.1016/S0140-6736(16)32399-6.

Chen JC, Wang X, Serre M, Cen S, Franklin M, Espeland M. 2017c. Particulate air pollutants, brain structure, and neurocognitive disorders in older women. Res Rep Health Eff Inst 193:1–65, PMID: 31898881.

Chen JC, Schwartz J. 2009. Neurobehavioral effects of ambient air pollution on cognitive performance in US adults. Neurotoxicology 30(2):231–239.

Chen JC, Wang X, Wellenius GA, Serre ML, Driscoll I, Casanova R, et al. 2015. Ambient air pollution and neurotoxicity on brain structure: evidence from Women's Health Initiative Memory Study. Ann Neurol 78(3):466–476.

Chen JH, Kuo TY, Yu HL, Wu C, Yeh SL, Chiou JM, et al. 2020. Long-term exposure to air pollutants and cognitive function in Taiwanese community-dwelling older adults: a four-year cohort study. J Alzheimers Dis 78(4):1585–1600, PMID: 33164930, https://doi.org/10.3233/JAD-200614.

Christidis T, Erickson AC, Pappin AJ, Crouse DL, Pinault LL, Weichenthal SA, et al. 2019. Low concentrations of fine particle air pollution and mortality in the Canadian community health survey cohort. Environ Health 18(1):84, PMID: 31601202, https://doi.org/10.1186/s12940-019-0518-y.

Cipriani G, Danti S, Carlesi C, Borin G. 2018. Danger in the air: air pollution and cognitive dysfunction. Am J Alzheimers Dis Other Demen 33(6):333–341, PMID: 29874918, https://doi.org/10.1177/1533317518777859.

Clancy L, Goodman P, Sinclair H, Dockery DW. 2002. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. Lancet 360(9341):1210–1214.

Cleary EG, Cifuentes M, Grinstein G, Brugge D, Shea TB. 2018. Association of low-level ozone with cognitive decline in older adults. J Alzheimers Dis 61(1):67–78, PMID: 29103040, https://doi.org/10.3233/JAD-170658.

Clinic M. 2020. Alzheimer's disease: symptoms & causes. https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/symptoms-causes/syc-20350447 [accessed 15 June 2020].

Colicino E, Power MC, Cox DG, Weisskopf MG, Hou L, Alexeeff SE, et al. 2014. Mitochondrial haplogroups modify the effect of black carbon on age-related cognitive impairment. Environ Health 13(1):42, PMID: 24884505, https://doi.org/10.1186/1476-069X-13-42.

Colmer J, Hardman I, Shimshack J, Voorheis J. 2020. Disparities in $PM_{2.5}$ air pollution in the United States. Science 369(6503):575–578, PMID: 32732425, https://doi.org/10.1126/science.aaz9353.

Correia AW, Pope CA 3rd, Dockery DW, Wang Y, Ezzati M, Dominici F. 2013. Effect of air pollution control on life expectancy in the United States: an analysis of 545 U.S. counties for the period from 2000 to 2007. Epidemiology 24(1):23–31, PMID: 23211349, https://doi.org/10.1097/EDE.0b013e3182770237.

Crous-Bou M, Gascon M, Gispert JD, Cirach M, Sánchez-Benavides G, Falcon C, et al. 2020. Impact of urban environmental exposures on cognitive performance and brain structure of healthy individuals at risk for Alzheimer's dementia. Environ Int 138:105546, PMID: 32151419, https://doi.org/10.1016/j.envint.2020.105546.

Cullen B, Newby D, Lee D, Lyall DM, Nevado-Holgado AJ, Evans JJ, et al. 2018. Cross-sectional and longitudinal analyses of outdoor air pollution exposure and cognitive function in UK Biobank. Sci Rep 8(1):12089, PMID: 30108252, https://doi.org/10.1038/s41598-018-30568-6.

Cummings JL, Morstorf T, Zhong K. 2014. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 6(4):37, PMID: 25024750, https://doi.org/10.1186/alzrt269.

de Prado Bert P, Mercader EMH, Pujol J, Sunyer J, Mortamais M. 2018. The effects of air pollution on the brain: a review of studies interfacing environmental epidemiology and neuroimaging. Curr Environ Health Rep 5(3):351–364, PMID: 30008171, https://doi.org/10.1007/s40572-018-0209-9.

Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, et al. 2010. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. Stroke 41(4):600–606, PMID: 20167919, https://doi.org/10.1161/STROKEAHA.109.570044.

Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. 2017. Air pollution and mortality in the Medicare population. N Engl J Med 376(26):2513–2522, PMID: 28657878, https://doi.org/10.1056/NEJMoa1702747.

Dimakakou E, Johnston HJ, Streftaris G, Cherrie JW. 2020. Is environmental and occupational particulate air pollution exposure related to type-2 diabetes

and dementia? A cross-sectional analysis of the UK Biobank. Int J Environ Res Public Health 17(24):9581, PMID: 33371391, https://doi.org/10.3390/ijerph17249581.
Dockery DW, Pope CA 3rd, Xu X, Spengler JD, Ware JH, Fay ME, et al. 1993. An association between air pollution and mortality in six U.S. cities. N Engl J Med 329(24):1753–1759, PMID: 8179653, https://doi.org/10.1056/NEJM199312093292401.
Dominici F, Peng RD, Zeger SL, White RH, Samet JM. 2007. Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? Am J Epidemiol 166(8):880–888, PMID: 17728271, https://doi.org/10.1093/aje/kwm222.
Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, et al. 2012. Development of land use regression models for PM2.5, PM2.5 absorbance, PM10 and PMcoarse in 20 European study areas; results of the Escape Project. Environ Sci Technol 46(20):11195–11205, PMID: 22963366, https://doi.org/10.1021/es301948k.
El-Hayek YH, Wiley RE, Khoury CP, Daya RP, Ballard C, Evans AR, et al. 2019. Tip of the iceberg: assessing the global socioeconomic costs of Alzheimer's disease and related dementias and strategic implications for stakeholders. J Alzheimers Dis 70(2):323–341, PMID: 31256142, https://doi.org/10.3233/JAD-190426.
Erickson LD, Gale SD, Anderson JE, Brown BL, Hedges DW. 2020. Association between exposure to air pollution and total gray matter and total white matter volumes in adults: a cross-sectional study. Brain Sci 10(3):164, PMID: 32182984, https://doi.org/10.3390/brainsci10030164.
Forastiere F, Stafoggia M, Tasco C, Picciotto S, Agabiti N, Cesaroni G, et al. 2007. Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. Am J Ind Med 50(3):208–216, PMID: 16847936.
Gale SD, Erickson LD, Anderson JE, Brown BL, Hedges DW. 2020. Association between exposure to air pollution and prefrontal cortical volume in adults: a cross-sectional study from the UK Biobank. Environ Res 185:109365, PMID: 32222630, https://doi.org/10.1016/j.envres.2020.109365.
Ganguli M, Lee C-W, Hughes T, Snitz BE, Jakubcak J, Duara R, et al. 2015. Who wants a free brain scan? Assessing and correcting for recruitment biases in a population-based sMRI pilot study. Brain Imaging Behav 9(2):204–212, PMID: 24573773, https://doi.org/10.1007/s11682-014-9297-9.
Gatto NM, Henderson VW, Hodis HN, St John JA, Lurmann F, Chen JC, et al. 2014. Components of air pollution and cognitive function in middle-aged and older adults in Los Angeles. Neurotoxicology 40:1–7, PMID: 24148924, https://doi.org/10.1016/j.neuro.2013.09.004.
Gianattasio KZ, Prather C, Glymour MM, Ciarleglio A, Power MC. 2019. Racial disparities and temporal trends in dementia misdiagnosis risk in the United States. Alzheimer's Dement: Translational Res Clin Intervent 5(1):891–898, PMID: 31890853.
Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. 2020. Association between cardiovascular disease and long-term exposure to air pollution with the risk of dementia. JAMA Neurol 77(7):801–809, PMID: 32227140, https://doi.org/10.1001/jamaneurol.2019.4914.
Greenland S, Robins JM. 1985. Confounding and misclassification. Am J Epidemiol 122(3):495–506, PMID: 4025298, https://doi.org/10.1093/oxfordjournals.aje.a114131.
Hajat A, Hsia C, O'Neill MS. 2015. Socioeconomic disparities and air pollution exposure: a global review. Curr Environ Health Rep 2(4):440–450, PMID: 26381684, https://doi.org/10.1007/s40572-015-0069-5.
He F, Tang JJ, Zhang T, Lin J, Li F, Gu X, et al. 2020. Impact of air pollution on cognitive impairment in older people: a cohort study in rural and suburban China. J Alzheimers Dis 77(4):1671–1679, PMID: 32925056, https://doi.org/10.3233/JAD-200587.
Hebert LE, Weuve J, Scherr PA, Evans DA. 2013. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology 80(19):1778–1783, PMID: 23390181, https://doi.org/10.1212/WNL.0b013e31828726f5.
Hedges DW, Erickson LD, Gale SD, Anderson JE, Brown BL. 2020. Association between exposure to air pollution and thalamus volume in adults: a cross-sectional study. PLoS One 15(3):e0230829, PMID: 32226035, https://doi.org/10.1371/journal.pone.0230829.
Hedges DW, Erickson LD, Kunzelman J, Brown BL, Gale SD. 2019. Association between exposure to air pollution and hippocampal volume in adults in the UK Biobank. Neurotoxicology 74:108–120, PMID: 31220475, https://doi.org/10.1016/j.neuro.2019.06.005.
Hedley AJ, Wong CM, Thach TQ, Ma S, Lam TH, Anderson HR. 2002. Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. Lancet 360(9346):1646–1652.
Holloman CH, Bortnick SM, Morara M, Strauss WJ, Calder CA. 2004. A Bayesian hierarchical approach for relating PM2.5 exposure to cardiovascular mortality in North Carolina. Environ Health Perspect 112(13):1282–1288, PMID: 15345340, https://doi.org/10.1289/ehp.6980.
Iaccarino L, La Joie R, Lesman-Segev OH, Lee E, Hanna L, Allen IE, et al. 2021. Association between ambient air pollution and amyloid positron emission tomography positivity in older adults with cognitive impairment. JAMA Neurol 78(2):197–207, PMID: 33252608, https://doi.org/10.1001/jamaneurol.2020.3962.
Ilango SD, Chen H, Hystad P, van Donkelaar A, Kwong JC, Tu K, et al. 2020. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. Int J Epidemiol 49(1):36–44.
Jack CR Jr., Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 12(2):207–216.
Jaramillo SA, Felton D, Andrews L, Desiderio L, Hallarn RK, Jackson SD, et al. 2007. Enrollment in a brain magnetic resonance study: results from the Women's Health Initiative Memory Study Magnetic Resonance Imaging Study (WHIMS-MRI). Acad Radiol 14(5):603–612, PMID: 17434074.
Jung CR, Lin YT, Hwang BF. 2015. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. J Alzheimers Dis 44(2):573–584, PMID: 25310992, https://doi.org/10.3233/JAD-140855.
Kaufman JS, MacLehose RF, Kaufman S. 2004. A further critique of the analytic strategy of adjusting for covariates to identify biologic mediation. Epidemiol Perspect Innov 1(1):4, PMID: 15507130, https://doi.org/10.1186/1742-5573-1-4.
Killin LO, Starr JM, Shiue IJ, Russ TC. 2016. Environmental risk factors for dementia: a systematic review. BMC Geriatr 16(1):175, PMID: 27729011, https://doi.org/10.1186/s12877-016-0342-y.
Kim H, Noh J, Noh Y, Oh SS, Koh SB, Kim C. 2019. Gender difference in the effects of outdoor air pollution on cognitive function among elderly in Korea. Front Public Health 7:375, PMID: 31921740, https://doi.org/10.3389/fpubh.2019.00375.
Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, Melly SJ, Wang Y, Dominici F, et al. 2016. Long-term PM2.5 exposure and neurological hospital admissions in the northeastern United States. Environ Health Perspect 124(1):23–29, PMID: 25978701, https://doi.org/10.1289/ehp.1408973.
Knopman DS, Gottesman RF, Sharrett AR, Tapia AL, Davis Thomas S, Windham BG, et al. 2018. Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: the Atherosclerosis Risk in Communities Study. Alzheimer's Dement 14(11):1406–1415, PMID: 29763593, https://doi.org/10.1016/j.jalz.2018.03.011.
Kulick ER, Wellenius GA, Boehme AK, Joyce NR, Schupf N, Kaufman JD, et al. 2020. Long-term exposure to air pollution and trajectories of cognitive decline among older adults. Neurology 94(17):e1782–e1792, PMID: 32269113, https://doi.org/10.1212/WNL.0000000000009314.
Kulick ER, Wellenius GA, Kaufman JD, DeRosa JT, Kinney PL, Cheung YK, et al. 2017. Long-term exposure to ambient air pollution and subclinical cerebrovascular disease in NOMAS (the Northern Manhattan Study). Stroke 48(7):1966–1968, PMID: 28455324, https://doi.org/10.1161/STROKEAHA.117.016672.
Laden F, Schwartz J, Speizer FE, Dockery DW. 2006. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 173(6):667–672, PMID: 16424447, https://doi.org/10.1164/rccm.200503-443OC.
Lang L, Clifford A, Wei L, Zhang D, Leung D, Augustine G, et al. 2017. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. BMJ Open 7(2):e011146, PMID: 28159845, https://doi.org/10.1136/bmjopen-2016-011146.
Laurent O, Bard D, Filleul L, Segala C. 2007. Effect of socioeconomic status on the relationship between atmospheric pollution and mortality. J Epidemiol Community Health 61(8):665–675, PMID: 17630363, https://doi.org/10.1136/jech.2006.053611.
Lee M, Schwartz J, Wang Y, Dominici F, Zanobetti A. 2019. Long-term effect of fine particulate matter on hospitalization with dementia. Environ Pollut 254(Pt A):112926, PMID: 31404729, https://doi.org/10.1016/j.envpol.2019.07.094.
Li C, Loewenstein DA, Duara R, Cabrerizo M, Barker W, Adjouadi M, et al. 2017a. The relationship of brain amyloid load and APOE status to regional cortical thinning and cognition in the ADNI Cohort. J Alzheimers Dis 59(4):1269–1282, PMID: 28731444, https://doi.org/10.3233/JAD-170286.
Li G, Larson EB, Shofer JB, Crane PK, Gibbons LE, McCormick W, et al. 2017b. Cognitive trajectory changes over 20 years before dementia diagnosis: a large cohort study. J Am Geriatr Soc 65(12):2627–2633, PMID: 28940184, https://doi.org/10.1111/jgs.15077.
Li CY, Li CH, Martini S, Hou WH. 2019. Association between air pollution and risk of vascular dementia: a multipollutant analysis in Taiwan. Environ Int 133(Pt B):105233. PMID: 31678904, https://doi.org/10.1016/j.envint.2019.105233.
Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396(10248):413–446, PMID: 32738937, https://doi.org/10.1016/S0140-6736(20)30367-6.
Lo YC, Lu YC, Chang YH, Kao S, Huang HB. 2019. Air pollution exposure and cognitive function in Taiwanese older adults: a repeated measurement study. Int J

Environ Res Public Health 16(16):2976, PMID: 31430886, https://doi.org/10.3390/ijerph16162976.
Loop MS, Kent ST, Al-Hamdan MZ, Crosson WL, Estes SM, Estes MG, et al. 2013. Fine particulate matter and incident cognitive impairment in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. PLoS One 8(9):e75001, PMID: 24086422, https://doi.org/10.1371/journal.pone.0075001.
Martins MC, Fatigati FL, Véspoli TC, Martins LC, Pereira LA, Martins MA, et al. 2004. Influence of socioeconomic conditions on air pollution adverse health effects in elderly people: an analysis of six regions in São Paulo, Brazil. J Epidemiol Community Health 58(1):41–46, PMID: 14684725, https://doi.org/10.1136/jech.58.1.41.
McGuinness LA, Warren-Gash C, Moorhouse LR, Thomas SL. 2019. The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: a systematic review. Pharmacoepidemiol Drug Saf 28(2):244–255, PMID: 30667114, https://doi.org/10.1002/pds.4669.
McShane BB, Gal D, Gelman A, Robert C, Tackett JL. 2019. Abandon statistical significance. Am Stat 73(supp1):235–245.
Miranda ML, Edwards SE, Keating MH, Paul CJ. 2011. Making the environmental justice grade: the relative burden of air pollution exposure in the United States. Int J Environ Res Public Health 8(6):1755–1771, PMID: 21776200, https://doi.org/10.3390/ijerph8061755.
Morris JC, Schindler SE, McCue LM, Moulder KL, Benzinger TL, Cruchaga C, et al. 2019. Assessment of racial disparities in biomarkers for Alzheimer disease. JAMA Neurol 76(3):264–273, PMID: 30615028, https://doi.org/10.1001/jamaneurol.2018.4249.
Nußbaum R, Lucht S, Jockwitz C, Moebus S, Engel M, Jöckel KH, et al. 2020. Associations of air pollution and noise with local brain structure in a cohort of older adults. Environ Health Perspect 128(6):067012, PMID: 32539589, https://doi.org/10.1289/EHP5859.
Oliveira M, Padrão A, Ramalho A, Lobo M, Teodoro AC, Gonçalves H, et al. 2020. Geospatial analysis of environmental atmospheric risk factors in neurodegenerative diseases: a systematic review. Int J Environ Res Public Health 17(22):8414, PMID: 33202965, https://doi.org/10.3390/ijerph17228414.
Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. 2016. Traffic-related air pollution and dementia incidence in northern Sweden: a longitudinal study. Environ Health Perspect 124(3):306–312, PMID: 26305859, https://doi.org/10.1289/ehp.1408322.
Oudin A, Forsberg B, Lind N, Nordin S, Aström DO, Sundström A, et al. 2017. Is long-term exposure to air pollution associated with episodic memory? A longitudinal study from Northern Sweden. Sci Rep 7(1):12789, PMID: 28986549, https://doi.org/10.1038/s41598-017-13048-1.
Oudin A, Segersson D, Adolfsson R, Forsberg B. 2018. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. PLoS One 13(6):e0198283, PMID: 29897947, https://doi.org/10.1371/journal.pone.0198283.
Park ES, Hopke PK, Oh M-S, Symanski E, Han D, Spiegelman CH. 2014. Assessment of source-specific health effects associated with an unknown number of major sources of multiple air pollutants: a unified Bayesian approach. Biostatistics 15(3):484–497, PMID: 24622036, https://doi.org/10.1093/biostatistics/kxu004.
Paul KC, Haan M, Yu Y, Inoue K, Mayeda ER, Dang K, et al. 2020. Traffic-related air pollution and incident dementia: direct and indirect pathways through metabolic dysfunction. J Alzheimers Dis 76(4):1477–1491, PMID: 32651321, https://doi.org/10.3233/JAD-200320.
Peters A, Breitner S, Cyrys J, Stölzel M, Pitz M, Wölke G, et al. 2009. The influence of improved air quality on mortality risks in Erfurt, Germany. Res Rep Health Eff Inst 137:5–77, PMID: 19554968.
Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. 2019. Air pollution and dementia: a systematic review. J Alzheimers Dis 70(suppl 1):S145–S163, PMID: 30775976, https://doi.org/10.3233/JAD-180631.
Petkus AJ, Younan D, Wang X, Beavers DP, Espeland MA, Gatz M, et al. 2021. Air pollution and the dynamic association between depressive symptoms and memory in oldest-old women. J Am Geriatr Soc 69(2):474–484, PMID: 33205418, https://doi.org/10.1111/jgs.16889.
Petkus AJ, Younan D, Widaman K, Gatz M, Manson JE, Wang X, et al. 2020. Exposure to fine particulate matter and temporal dynamics of episodic memory and depressive symptoms in older women. Environ Int 135:105196, PMID: 31881430, https://doi.org/10.1016/j.envint.2019.105196.
Phelan EA, Borson S, Grothaus L, Balch S, Larson EB. 2012. Association of incident dementia with hospitalizations. JAMA 307(2):165–172.
Pope CA 3rd, Ezzati M, Dockery DW. 2009. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360(4):376–386, PMID: 19164188, https://doi.org/10.1056/NEJMsa0805646.
Pope CA 3rd, Ezzati M, Dockery DW. 2013. Fine particulate air pollution and life expectancies in the United States: the role of influential observations. J Air Waste Manag Assoc 63(2):129–132, PMID: 23472296.
Pope CA 3rd, Lefler JS, Ezzati M, Higbee JD, Marshall JD, Kim SY, et al. 2019. Mortality risk and fine particulate air pollution in a large, representative cohort of U.S. adults. Environ Health Perspect 127(7):077007, PMID: 31339350, https://doi.org/10.1289/EHP4438.
Power MC, Adar SD, Yanosky JD, Weuve J. 2016. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: a systematic review of epidemiologic research. Neurotoxicology 56:235–253, PMID: 27328897, https://doi.org/10.1016/j.neuro.2016.06.004.
Power MC, Gianattasio KZ, Ciarleglio A. 2020. Implications of the use of algorithmic diagnoses or Medicare claims to ascertain dementia. Neuroepidemiology 54(6):462–471, PMID: 33075766, https://doi.org/10.1159/000510753.
Power MC, Lamichhane AP, Liao D, Xu X, Jack CR, Gottesman RF, et al. 2018a. The association of long-term exposure to particulate matter air pollution with brain MRI findings: the ARIC Study. Environ Health Perspect 126(2):027009, PMID: 29467108, https://doi.org/10.1289/EHP2152.
Power MC, Mormino E, Soldan A, James BD, Yu L, Armstrong NM, et al. 2018b. Combined neuropathological pathways account for age-related risk of dementia. Ann Neurol 84(1):10–22, PMID: 29944741, https://doi.org/10.1002/ana.25246.
Power MC, Weisskopf MG, Alexeeff SE, Coull BA, Spiro A 3rd, Schwartz J. 2011. Traffic-related air pollution and cognitive function in a cohort of older men. Environ Health Perspect 119(5):682–687, PMID: 21172758, https://doi.org/10.1289/ehp.1002767.
Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M, et al. 2015. World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost, & Trends. London, UK: Alzheimer's Disease International
Ran J, Schooling CM, Han L, Sun S, Zhao S, Zhang X, et al. 2021. Long-term exposure to fine particulate matter and dementia incidence: a cohort study in Hong Kong. Environ Pollut 271:116303, PMID: 33370610, https://doi.org/10.1016/j.envpol.2020.116303.
Ranft U, Schikowski T, Sugiri D, Krutmann J, Krämer U. 2009. Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly. Environ Res 109(8):1004–1011, PMID: 19733348, https://doi.org/10.1016/j.envres.2009.08.003.
Rizzuto D, Feldman AL, Karlsson IK, Dahl Aslan AK, Gatz M, Pedersen NL. 2018. Detection of dementia cases in two Swedish health registers: a validation study. J Alzheimers Dis 61(4):1301–1310, PMID: 29376854, https://doi.org/10.3233/JAD-170572.
Rocha D, Suemoto CK, Souza Santos I, Lotufo PA, Benseñor I, Gouveia N. 2020. Vehicular traffic density and cognitive performance in the ELSA-Brasil study. Environ Res 191:110208, PMID: 32941838, https://doi.org/10.1016/j.envres.2020.110208.
Salinas-Rodríguez A, Fernández-Nino JA, Manrique-Espinoza B, Moreno-Banda GL, Sosa-Ortiz AL, Qian ZM, et al. 2018. Exposure to ambient PM2.5 concentrations and cognitive function among older Mexican adults. Environ Int 117:1–9, https://doi.org/10.1016/j.envint.2018.04.033.
Samet JM. 2011. The clean air act and health—a clearer view from 2011. N Engl J Med 365(3):198–201.
Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. 2016. Incidence of dementia over three decades in the Framingham Heart Study. N Engl J Med 374(6):523–532.
Savitz DA, Wellenius GA, Trikalinos TA. 2019. The problem with mechanistic risk of bias assessments in evidence synthesis of observational studies and a practical alternative: assessing the impact of specific sources of potential bias. Am J Epidemiol 188(9):1581–1585, PMID: 31145434, https://doi.org/10.1093/aje/kwz131.
Schikowski T, Vossoughi M, Vierkötter A, Schulte T, Teichert T, Sugiri D, et al. 2015. Association of air pollution with cognitive functions and its modification by APOE gene variants in elderly women. Environ Res 142:10–16, PMID: 26092807, https://doi.org/10.1016/j.envres.2015.06.009.
Shi L, Wu X, Yazdi MD, Braun D, Awad YA, Wei Y, et al. 2020. Long-term effects of $PM_{2.5}$ on neurological disorders in the American Medicare population: a longitudinal cohort study. The Lancet Planetary Health 4(12):e557–e565, PMID: 33091388, https://doi.org/10.1016/S2542-5196(20)30227-8.
Shin J, Han SH, Choi J. 2019. Exposure to ambient air pollution and cognitive impairment in community-dwelling older adults: the Korean Frailty and Aging cohort study. Int J Environ Res Public Health 16(19):3767, PMID: 31591354, https://doi.org/10.3390/ijerph16193767.
Smargiassi A, Sidi EAL, Robert LE, Plante C, Haddad M, Gamache P, et al. 2020. Exposure to ambient air pollutants and the onset of dementia in Quebec, Canada. Environ Res 190:109870, PMID: 32739624, https://doi.org/10.1016/j.envres.2020.109870.
Solomon A, Ngandu T, Soininen H, Hallikainen MM, Kivipelto M, Laatikainen T. 2014. Validity of dementia and Alzheimer's disease diagnoses in Finnish national registers. Alzheimers Dement 10(3):303–309, PMID: 23849592, https://doi.org/10.1016/j.jalz.2013.03.004.
Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, et al. 2018. Whitepaper: defining and investigating cognitive reserve, brain

reserve, and brain maintenance. Alzheimers Dement 16(9):1305–1311, PMID: 30222945, https://doi.org/10.1016/j.jalz.2018.07.219.
Stern Y. 2012. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 11(11):1006–1012.
Stockfelt L, Andersson EM, Molnár P, Rosengren A, Wilhelmsen L, Sallsten G, et al. 2015. Long term effects of residential NO(x) exposure on total and cause-specific mortality and incidence of myocardial infarction in a Swedish cohort. Environ Res 142:197–206, PMID: 26163761, https://doi.org/10.1016/j.envres.2015.06.045.
Szpiro AA, Paciorek CJ. 2013. Measurement error in two-stage analyses, with application to air pollution epidemiology. Environmetrics 24(8):501–517, PMID: 24764691, https://doi.org/10.1002/env.2233.
Szpiro AA, Sheppard L, Lumley T. 2011. Efficient measurement error correction with spatially misaligned data. Biostatistics 12(4):610–623, PMID: 21252080, https://doi.org/10.1093/biostatistics/kxq083.
Tallon LA, Manjourides J, Pun VC, Salhi C, Suh H. 2017. Cognitive impacts of ambient air pollution in the National Social Health and Aging Project (NSHAP) cohort. Environ Int 104:102–109, PMID: 28392067, https://doi.org/10.1016/j.envint.2017.03.019.
Taylor DH Jr., Østbye T, Langa KM, Weir D, Plassman BL. 2009. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. J Alzheimers Dis 17(4):807–815. [19542620], https://doi.org/10.3233/JAD-2009-1099.
Tonne C, Elbaz A, Beevers S, Singh-Manoux A. 2014. Traffic-related air pollution in relation to cognitive function in older adults. Epidemiology 25(5):674–681, PMID: 25036434, https://doi.org/10.1097/EDE.0000000000000144.
Tzivian L, Dlugaj M, Winkler A, Hennig F, Fuks K, Sugiri D, et al. 2016. Long-term air pollution and traffic noise exposures and cognitive function: a cross-sectional analysis of the Heinz Nixdorf Recall study. J Toxicol Environ Health A 79(22–23):1057–1069, PMID: 27924705, https://doi.org/10.1080/15287394.2016.1219570.
Tzivian L, Jokisch M, Winkler A, Weimar C, Hennig F, Sugiri D, et al. 2017. Associations of long-term exposure to air pollution and road traffic noise with cognitive function-an analysis of effect measure modification. Environ Int 103:30–38, PMID: 28363096, https://doi.org/10.1016/j.envint.2017.03.018.
U.S. EPA (U.S. Environmental Protection Agency). 2009. Integrated science assessment for particulate matter. EPA/600/R-15/068. Washington, DC: U.S. Environmental Protection Agency
U.S. EPA. 2016. Integrated science assessment (ISA) for oxides of nitrogen – health criteria (final report, 2016). EPA/600/R-15/068. Washington, DC: U.S. Environmental Protection Agency
U.S. EPA. 2019. Integrated science assessment (ISA) for particulate matter (final report, 2019). EPA/600/R-19/188. Washington, DC: U.S. Environmental Protection Agency
Valeri L, Vanderweele TJ. 2013. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. Psychol Methods 18(2):137–150, PMID: 23379553, https://doi.org/10.1037/a0031034.
Wang J, Li T, Lv Y, Kraus VB, Zhang Y, Mao C, et al. 2020. Fine particulate matter and poor cognitive function among chinese older adults: evidence from a community-based, 12-year prospective cohort study. Environ Health Perspect 128(6):067013, PMID: 32551881, https://doi.org/10.1289/EHP5304.
Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. 2013. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12(8):822–838.
Wellenius GA, Boyle LD, Coull BA, Milberg WP, Gryparis A, Schwartz J, et al. 2012a. Residential proximity to nearest major roadway and cognitive function in community-dwelling seniors: results from the MOBILIZE Boston study. J Am Geriatr Soc 60(11):2075–2080, PMID: 23126566, https://doi.org/10.1111/j.1532-5415.2012.04195.x.
Wellenius GA, Burger MR, Coull BA, Schwartz J, Suh HH, Koutrakis P, et al. 2012b. Ambient air pollution and the risk of acute ischemic stroke. Arch Intern Med 172(3):229–234, PMID: 22332153, https://doi.org/10.1001/archinternmed.2011.732.
Weuve J, Kaufman JD, Szpiro AA, Curl C, Puett RC, Beck T, et al. 2016. Exposure to traffic-related air pollution in relation to progression in physical disability among older adults. Environ Health Perspect 124(7):1000–1008, PMID: 27022889, https://doi.org/10.1289/ehp.1510089.
Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiébaut R, et al. 2015. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. Alzheimers Dement 11(9):1098–1109, PMID: 26397878, https://doi.org/10.1016/j.jalz.2015.06.1885.
Weuve J, Puett RC, Schwartz J, Yanosky JD, Laden F, Grodstein F. 2012. Exposure to particulate air pollution and cognitive decline in older women. Arch Intern Med 172(3):219–227, PMID: 22332151.
Wilker EH, Martinez-Ramirez S, Kloog I, Schwartz J, Mostofsky E, Koutrakis P, et al. 2016a. Fine particulate matter, residential proximity to major roads, and markers of small vessel disease in a memory study population. J Alzheimers Dis 53(4):1315–1323, PMID: 27372639, https://doi.org/10.3233/JAD-151143.
Wilker EH, Mittleman MA, Kloog I, Schwartz J, Koutrakis P, Blacker D. 2016b. Exposure to ambient air pollution and repeated measures of executive function. Alzheimer's Dement 12:P600–P600, https://doi.org/10.1016/j.jalz.2016.06.1184.
Wilker EH, Preis SR, Beiser AS, Wolf PA, Au R, Kloog I, et al. 2015. Long-term exposure to fine particulate matter, residential proximity to major roads and measures of brain structure. Stroke 46(5):1161–1166, PMID: 25908455, https://doi.org/10.1161/STROKEAHA.114.008348.
Wilkinson T, Ly A, Schnier C, Rannikmäe K, Bush K, Brayne C, et al. 2018. Identifying dementia cases with routinely collected health data: a systematic review. Alzheimers Dement 14(8):1038–1051, PMID: 29621480, https://doi.org/10.1016/j.jalz.2018.02.016.
Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. 2020. Twenty-seven-year time trends in dementia incidence in Europe and the United States: the Alzheimer Cohorts Consortium. Neurology 95(5):e519–e531, PMID: 32611641, https://doi.org/10.1212/WNL.0000000000010022.
Wu Y-C, Lin Y-C, Yu H-L, Chen J-H, Chen T-F, Sun Y, et al. 2015. Association between air pollutants and dementia risk in the elderly. Alzheimers Dement (Amst) 1(2):220–228. PMID: 27239507, https://doi.org/10.1016/j.dadm.2014.11.015.
Wu YT, Fratiglioni L, Matthews FE, Lobo A, Breteler MM, Skoog I, et al. 2016. Dementia in western Europe: epidemiological evidence and implications for policy making. Lancet Neurol 15(1):116–124, PMID: 26300044, https://doi.org/10.1016/S1474-4422(15)00092-7.
Wurth R, Kioumourtzoglou MA, Tucker KL, Griffith J, Manjourides J, Suh H. 2018. Fine particle sources and cognitive function in an older Puerto Rican cohort in greater Boston. Environ Epidemiol 2(3):e022, PMID: 30506018, https://doi.org/10.1097/EE9.0000000000000022.
Yao Y, Jin X, Cao K, Zhao M, Zhu T, Zhang J, et al. 2021. Residential proximity to major roadways and cognitive function among Chinese adults 65 years and older. Sci Total Environ 766:142607, PMID: 32551881, https://doi.org/10.1016/j.scitotenv.2020.142607.
Yi O, Kim H, Ha E. 2010. Does area level socioeconomic status modify the effects of PM(10) on preterm delivery? Environ Res 110(1):55–61, PMID: 19878932, https://doi.org/10.1016/j.envres.2009.10.004.
Younan D, Petkus AJ, Widaman KF, Wang X, Casanova R, Espeland MA, et al. 2020a. Particulate matter and episodic memory decline mediated by early neuroanatomic biomarkers of Alzheimer's disease. Brain 143(1):289–302, PMID: 31746986, https://doi.org/10.1093/brain/awz348.
Younan D, Wang X, Casanova R, Barnard R, Gaussoin SA, Saldana S, et al. 2020b. $Pm_{2.5}$ associated with gray matter atrophy reflecting increased Alzheimer's risk in older women. Neurology 96(8):e1190–e1201, PMID: 33208540, https://doi.org/10.1212/WNL.0000000000011149.
Yuchi W, Sbihi H, Davies H, Tamburic L, Brauer M. 2020. Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study. Environ Health 19(1):8, PMID: 31964412, https://doi.org/10.1186/s12940-020-0565-4.
Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, et al. 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect 108(5):419–426.
Zeng Y, Gu D, Purser J, Hoenig H, Christakis N. 2010. Associations of environmental factors with elderly health and mortality in China. Am J Public Health 100(2):298–305.