Journal Pre-proof

Association of air pollution with dementia: A systematic review with meta-analysis including new cohort data from China

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PII: S0013-9351(22)02375-1

DOI: https://doi.org/10.1016/j.envres.2022.115048

Reference: YENRS 115048

To appear in: *Environmental Research*

Received Date: 4 September 2022

Revised Date: 25 November 2022

Accepted Date: 10 December 2022

Please cite this article as: Tang, J., Chen, A., He, F., Shipley, M., Nevill, A., Coe, H., Hu, Z., Zhang, T., Kan, H., Brunner, E., Tao, X., Chen, R., Association of air pollution with dementia: A systematic review with meta-analysis including new cohort data from China, *Environmental Research* (2023), doi: https://doi.org/10.1016/j.envres.2022.115048.

Credit Author Statement

Jie Tang: Conceptualization, Methodology, Formal analysis, Writing - original draft, Funding acquisition for DEMAIRPO - EU MSCA fellowship.

Anthony Chen: Anhui Cohort Data analysis, Writing, Review & editing.

Fan He: The ZJMPHS cohort study design, Project administration, Data collection, Writing, Review & editing, Funding acquisition for ZJMPHS.

Martin Shipley: Meta-analysis methods verification, Review & Editing,

Alan Nevill: Statistical methods verification, Writing - review & editing, Funding acquisition for DEMAIRPO – co-supervision.

Hugh Coe: Critical Review, Revisions, Funding acquisition for DEMAIRPO – co-supervision.

Zhi Hu: The Anhui cohort data collection and curation, Writing - review & editing.

Tao Zhang: The ZJMPHS data collection and curation, Formal analysis, review, Funding acquisition for ZJMPHS.

Haidong Kan: The Anhui cohort air pollution data collection and curation, Review & editing.

Eric Brunner: Critical Review, Revisions, Funding acquisition for DEMAIRPO – co-supervision.

Xuguang Tao: Literature Review, Writing, Revisions & Editing.

Ruoling Chen: Conceptualization, Methodology, Formal analysis, Visualization, Supervision, Writing, Revisions & editing, Funding acquisition for the presented project - PI. Funding acquisition for DEMAIRPO - EU MSCA fellowship, and for the Anhui cohort study.

Association of air pollution with dementia: a systematic review with meta-analysis including new cohort data from China

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Word Count: 296 in abstract, 6259 in text, 4 tables, 2 figures, 80 references, 5 Supplements (4 eTables, 1 eFigure)

ABSTRACT

It remains unclear whether a total exposure to air pollution (AP) is associated with an increased risk of dementia. Little is known on the association in low- and middle-income countries. Two cohort studies in China (in Anhui cohort 1402 older adults aged >=60 followed up for 10 years; in Zhejiang cohort 6115 older adults followed up for 5 years) were contacted to examine particulate matter - $PM_{2.5}$ associated with all dementia and air quality index (AQI) with Alzheimer's disease, respectively. A systematic literature review and meta-analysis was performed following worldwide literature searched until 20th May 2020 to identify 15 population-based cohort studies examining the association of AP with dementia (or any specific type of dementia) through PubMed, MEDLINE, PsycINFO, SocINDEX, CINHAL, and CNKI. The cohort studies in China showed a significantly increased relative risk (RR) of dementia in relation to AP exposure; in Anhui cohort the adjusted RR was 2.14 (95% CI 1.00-4.56) in people with $PM_{2.5}$ exposure at >= 64.5 $\mu g/m^3$ versus <63.5$\mu g/m^3$ and in Zhejiang cohort the adjusted RR was 2.28 (1.07-4.87) in AQI>90 versus<=80. The systematic review revealed that all 15 studies were undertaken in high income countries/regions, with inconsistent findings. While they had reasonably good overall quality of studies, seven studies did not adjust smoking in analysis and 13 did not account for depression. Pooling all eligible data demonstrated that dementia risk increased with the total AP exposure (1.13, 1.08-1.19). In air pollutant analysis, it significantly increased with $PM_{2.5}$ (1.06, 1.03-1.10 in 2nd tertile exposure; 1.13, 1.07-1.19 in 3rd tertile versus 1st tertile), PM_{10} (1.05, 0.86-1.29; 1.62, 0.60-4.36), carbon monoxide (1.69, 0.72-3.93; 1.52, 1.35-1.71), nitrogen dioxide (1.06, 1.03-1.09; 1.18, 1.10-1.28) and nitrogen oxides (1.09, 1.04-1.15; 1.26, 1.13-1.41), but not ozone. Controlling air pollution and targeting on specific pollutants would reduce dementia globally.

Keywords: Air Pollution; Particulate Matters; Carbon Monoxide; Nitrogen Oxide; Sulfur Dioxide; Dementia

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55 **HIGHLIGHTS**:

56 • Two cohort studies were conducted in China to investigate the high $PM_{2.5}$ and poor air
57 quality index associated with dementia risk, revealing significant association.
58 • Pooling data from all eligible studies published and new cohorts in China showed
59 dementia risk increased with overall AP exposure, $PM_{2.5}$, PM_{10}, CO, NO_2, NOx, but
60 not O_3.
61 • Controlling air pollution and targeting on specific pollutants would reduce dementia
62 globally.

63

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INTRODUCTION

Dementia is one of the world's most challenging public health problems. There are currently over 50 million people with dementia in the world, and the number of people affected is predicted to rise to 82 million in 2030 and to 152 million in 2050.[1] Dementia costs US$ 818 billion annually, and the costings will rise further.[2] There is no known cure for dementia, and thus more efforts are made to investigate the aetiology of dementia for prevention.

Ambient air pollution (AP) is an important global environmental concern.[3] AP includes a variety of air pollutants, such as particulate matter (e.g., $PM_{2.5}$, PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone (O_3). Exposure to AP, particularly $PM_{2.5}$, increases the risk of cardiovascular diseases,[4,5] diabetes,[6] anxiety[7] and depression.[8] It also showed a significant association with cognitive impairment across the life course.[9] Its association with an increased risk of dementia, however, remains unclear; some studies showed a positive association,[10-12] whilst others did not.[13,14] Recent two meta-analysis studies[15,16] tried to assess the association of AP with dementia, but their findings were not robust due to methodological issues. They missed some eligible papers according to their literature search criteria; e.g., one[15] did not include two eligible studies[17,18] and other[16] missed three studies[14,19,20] for systematically reviewing. Fu and Yung's meta-analysis study[16] also showed there might be potential publication bias towards the finding.[16] The evidence for the association of AP with dementia requires to be further assessed. Furthermore, little is known which air pollutants were most closely associated with dementia risk. Current knowledge of the association is derived from studies conducted in high income countries or regions (HICs), and the data is lack from low- and middle-income countries (LMICs), where the levels of AP exposure and dementia risk are higher.[21]

In this study, we examined the data of cohort studies from China - the largest LMIC and performed a systematic literature review with meta-analysis to determine the impact of overall AP and individual air pollutant exposure on the risk of dementia.

METHODS

Participants were derived from two new cohort studies in China

Anhui Cohort Study. The methods of its sampled population, baseline interview and follow-up have been fully described in our previous publications.[22,23] Briefly, in 2001-2003 we recruited a random sample of 3336 permanent residents aged ≥ 60 years in Anhui province, China for a baseline health survey. Using a general health and risk factors record and the Geriatric Mental State (GMS) questionnaire we interviewed them. The GMS data were read by the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) to diagnose dementia, depression, and other mental disorders.[24] In one year after the baseline investigation (wave 2), 2007-2009 (wave 3) and 2010-2011 (wave 4), we re-interviewed 2608, 1757 and 944 surviving cohort participants respectively. In the interviews of waves 3 and 4, the 10/66 algorithm dementia research package was added.[25] The vital status of the cohort was followed up until December 2011. For those deceased, a standard WHO Verbal Autopsy tool was used to interview their family members, relatives, neighbors, or friends to identify mortality and causes of death, including dementia.[22]

Using a satellite-based model with a high spatiotemporal resolution,[26] we assessed daily $PM_{2.5}$ concentrations for each cohort member based on his home address. The earliest year predicted $PM_{2.5}$ concentrations was from 2005. We used an average $PM_{2.5}$ daily concentration of 2005 and 2006, which was in the middle time of the cohort, for air pollution exposure analysis. The exposure assessment in the model has been validated in previous studies.[26]

Of 3336 participants, 2978 were followed up by any interviews from waves 2, 3 or 4, and by mortality record. After excluding 223 participants who had baseline dementia, 2755 remained in the cohort for investigation on incident dementia. Considering the impact of educational level on GMS-AGECAT dementia diagnosis,[27] we included 1421 participants who had at least primary school education for analysis. After excluding 19 participants who did not have $PM_{2.5}$ exposure recorded due to house address, we analysed the data of 1402 cohort members, of which 109 developed dementia over the follow-up period of the cohort. We employed multivariate adjusted Cox regression models to examine the independent association of $PM_{2.5}$ exposure with incident dementia, and calculated hazard ratio (HR) and 95% confidence intervals (CIs), with different sets of confounders for adjustment.

Zhejiang cohort study. The details of the methods of studied population, baseline survey and follow-up have been recently reported in the journal.[28] We described it briefly in the manuscript's Supplement for "Methods of Zhejiang cohort study". In this paper we examined the risk of Alzheimer's Disease (AD) in the participants in 2019 in relation to the Air Quality Index (AQI) measured in 2013-2015 according to three levels of AQI.[29] A multi-level binary logistic regression model was used to calculate odds ratio (OR) and its 95% confidential intervals of AD in relation to AQI, with multiple adjustment, according to our previous data analysis.[28] In the late meta-analysis for individual air pollutants, we extracted the findings of six air pollutants (ie, $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3) from this cohort study,[28] (see Model 3 in eTable 2).

Worldwide systematic literature review and meta-analysis

Systematic literature search

We searched literature from PubMed, Embase, Web of Science, and CINAHL databases. The strategy for the database search was developed using the Population, Exposure and Outcome framework (PEO).[30] The search terms used were "*Pollution*" (air pollution;

137 environmental pollution; nitrogen dioxide; black carbon; ozone; particulate matter; vehicle
138 pollution; vehicle emissions; traffic pollution; traffic emissions; traffic-related pollution;
139 distance to road; distance from road) and "*Dementia*" (Alzheimer disease; dementia; mild
140 cognitive impairment; mild cognitive impairment; cognitive decline; amyloid) for all fields,
141 including MeSH terms, abstract, title or text words. The literatures were searched from the
142 inception of each database until 20th May 2020. The search for relevant articles included all
143 studies with no language restrictions. We read the title and abstract of the searched studies.
144 Citations and abstracts of unique research articles were screened, and full texts of relevant
145 articles were retrieved for assessment.

146 Studies were included in the systematic review if they were original research, which (1)
147 investigated an association between AP (measured an overall AP exposure or any individual
148 air pollutant) and dementia (all type, Alzheimer disease [AD], vascular dementia [VaD] or
149 others) in human beings, and (2) were designed as a cohort study for analysis. We included
150 studies of measuring AP level in any air pollutants exposure or using a proxy such as the
151 residential distance proximity to major roadways (REDPMR),[11,12,31] or air quality index (AQI)
152 as an overall AP exposure.[29] Articles would be excluded if they had (1) measured exposure
153 using AP mixed with others (e.g., traffic noise) which were not separately analysed in the
154 article, and (2) outcome variables as mild cognitive impairment (MCI), general cognitive
155 ability/decline or another cause of cognitive impairment (e.g., Parkinson's disease) only, but
156 not dementia diagnosed with validated methods.

157 Searching four electronic datasets for literature, we had 1401 hits. After eliminating
158 duplicates, 1168 remained. We reviewed their titles and abstracts and identified 34 relevant
159 papers. Reading through these papers we excluded 19 which had not met the inclusion criteria
160 and left 15 articles[10-14,17-20,31-36] for systematic review. The details of literature searched and
161 identified were seen in eFigure 1 in the supplement.

Literature review

Eligible articles were qualitatively reviewed and presented according to standard procedures as guided by Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA).[37] Two reviewers (JT & RC) independently extracted data and assessed the quality of these studies. Discrepancies were resolved through face-to-face discussion, and where the differences remained, a 3rd reviewer (XT) made the final judgement. Following our previous studies, [38-41] we developed a standard form to extract the following data from the eligible articles: first author, year of publication, study location, study design, participants' age range, sample size, data source and measurement of AP, criteria of dementia diagnosis and type of dementia, the number of dementia cases in outcome, data analyses, variables adjusted and findings. All adjusted analyses were included where available in the original text. The Newcastle-Ottawa Quality Assessment for Cohort Studies was used to review the quality of eligible articles. [42]

Meta-analysis

We took all eligible data from 15 published studies and two cohort studies in China for meta-analysis. We analysed the data from each studied population for all types of dementia first. If the study population did not provide data of all type of dementia, its sub-types of data would be used. Only reported relative risk (RR) (e.g., HR or OR) and 95% CI from confounders adjusted models were considered for including in the analysis. If the same studied population was used to examine different air pollutants associated with dementia in different papers,[10,11,14,18] we included them all in the meta-analysis. However, if two or more papers used the same or similar population data to produce the findings,[10,14,19] we would take the paper with the most statistical adjustment for meta-analysis.[10] Of the 15 studies, four[10,14,18,19] from Sweden used the same population data of the Betula study (of which three investigated the association

between NO_x exposure and dementia risk[10,14,19]), and three from Canada used the same datasets of Ontario population[11,20,22] (of which two examined the same measurements of AP exposure associated with dementia[33,34]). After excluding two Swedish papers using the same data to update the results[14, 19] and one Canadian paper measuring the same exposure,[34] 12 studies were left for the meta-analysis.[10-13,17,18,20,21,32,33,35,36] We examined the risk of dementia in relation to overall AP exposure, analysing the data of studies which measured REDPMR[11,12,31] or AQI as a comprehensive indicator of AP. If such a comprehensive AP indicator was not available in published papers [10,12,17,18,20,36] we would combine RRs from multiple air pollutants to get a surrogate comprehensive AP data (the details shown in Table 2). Afterwards, we examined the risk of dementia in relation to each individual air pollutant separately, where the data was available in the studied population.

Due to variances in the data analysis from each study and complex findings, we employed three approaches of meta-analysis to pool the data, and then the findings were for comparison. First, we pooled the data of RRs from the highest *versus* lowest AP exposure in each study if the study presented the findings from the categorised data, according to the method we used before.[38] If the paper provided the finding of continuous AP measurement only,[12,13,31,33-35] we included it in the pooled data analyses. Second, we used the data of RR from all different levels of AP exposure *versus* lowest AP exposure in each study (ie, used all RRs for pooling data) for including all data analysis.[39] This approach would use the average RR of dementia from each study. Third, using a scaling factor method in our previous meta-analysis study,[43] we converted the reported RR estimates onto a standard scale of effect, comparing the highest third with the lowest third of the distribution of each air pollutant, in essence giving an estimate per 2.18 SD units of the pollutant where 2.18 is the difference in the means of the top and bottom third of the standard normal distribution. The reported comparisons included continuous measures (per SD, unit on original or log 10 scale), equal

size groups (top versus bottom with group size 50%, 33%, or 25% for 2, 3 or 4 groups, respectively), and unequal size groups (top versus bottom; 2 groups, 3 groups defined by cut point). The scaling methods assume that air pollutants are log normally distributed and that the association with dementia risk is log linear. After scaled RR where needed, we pooled the RR of dementia in the converted RRs in the highest tertile (T3) and the 2nd tertile (T2) levels of AP respectively. This approach analysis helped us examine a relative "dose-response" relationship of each air pollutant exposure with the risk of dementia.

The fixed-effects model or random-effects model was employed according to a statistical test of the homogeneity assumption; if existed, a fixed-effects model was used; otherwise, a random-effects model. A forest plot was produced for each analysis and publication bias was evaluated using Egger's regression. We examined the association of AP with AD and VaD respectively, where the data were available. All analyses in this study were performed in the statistical software package STATA version 14.0.

RESULTS

New cohort studies in China

Anhui Cohort Study. Of 1402 participants, the average age at baseline was 71.6 years (SD 5.7) and 57.1% were men. Their characteristics are seen in eTable 1 in the supplement. Participants who developed dementia were more likely to be older, have low education, be widowed, and have low activities of daily life at baseline. There were no significant differences in sex, lifestyles, and co-morbidities between participants with and without development of dementia. Table 1 shows the number, rate, and adjusted HR of incident dementia among participants with different levels of $PM_{2.5}$ exposure. Compared to those with $PM_{2.5}$ mean daily exposure < 63.5 μg/m^3 in 2005-06, fully adjusted HR of dementia was 2.04 (95% CI, 0.96 to 4.32) in participants with $PM_{2.5}$ >= 63.5 and < 64.5 μg/m^3, and 2.14 (95%CI 1.00 to 4.56) in

$PM_{2.5}$ >= 64.5 μg/m^3. In a sensitivity analysis excluding participants with dementia at wave 2, there remained significant association of $PM_{2.5}$ exposure in 2005 and 2006 with incident dementia at waves 3 and 4 (Table 1).

Zhejiang cohort study: Of 6155 participants, 986 had AD. Compared to those without AD in the cohort they were more likely to be older (70.5 vs 67.6 years) and female gender (63.3% vs 41.3%). Differences in other characteristics between two groups are seen in eTable 2 footnote. After adjusted for age, sex, and socioeconomic status, ORs of AD in participants living in the middle and high levels of AQI (poorer air quality) *versus* the low level were 1.86 (95%CI 0.76 - 4.51) and 2.42 (95%CI 1.20 - 4.87) (Model 1 in eTable 2). They were not substantially changed after further adjustment for lifestyles, cardiovascular disease, and risk factors (Model 2 and Model 3 in eTable 2).

Systematic literature review

Fifteen articles identified for this review were published between August 2014 to May 2020. Their study characteristics are shown in eTable 3 in the supplement. All studies were undertaken in HICs/regions: five[10,14,18-20] from Sweden, four from Canada[11,33-35], two each from Taiwan[13,36] and USA,[18,32] one each from UK[12] and Italy.[31] Of them eight were prospective cohorts[10,14,18-20,31,32,35] and seven retrospective cohorts[11-13,17,33,34,36], with sample sizes from 1,567 to 9,817,806. The baseline ages of these cohort participants were over 48 years old. The cohorts were followed up between 4 and 16 years.

In measuring AP exposure, four studies[11,12,31,35] took REDPMR. The studies measuring air pollutants used three methods to estimate the annual or daily concentrations of air pollutants in the participants' location, including land use regression,[10,13,14,18-20,32-36] dispersion model[20,31] or Bayesian Maximum entropy model.[17] Ten studies measured $PM_{2.5}$ exposure[12,13,17,18,20,31-35], six NO_2 [11,12,31,33,35,36], four NO_x [10,18,20,31], five O_3 [11,12,13,33,31], one each for CO[36] and one PM_{10} [31].

Thirteen studies diagnosed all types of dementia; five[10,18-20,33] used Diagnostic and Statistical Manual of Mental Disorders IV (DSM –IV), and eight[11-13,31,32,34-36] used ICD codes (ICD-9 or ICD-10), of which one[31] diagnosed AD further, one diagnosed AD and other AD[35] and three[12,19,33] diagnosed AD and VaD respectively. One study did not include all type of dementia for analysis but diagnosed AD[13]. One other study[17] did not clarify all or sub-types of dementia and diagnosed dementia by cranial CAT scan and a series of laboratory tests in participants who had significant decline in global cognitive function tested by the Modified Mini-Mental State. In diagnosing AD, one studies[13] used the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer's Criteria (NINCDS-ADRDA), three used ICD-9-CM codes,[31,32,35] one used ICD-10 revision codes[12] and other two[10,19] made diagnosis from the senior gero-psychiatrist through clinical futures. In diagnosing VaD, one study used ICD-9-CM,[31] one used ICD-10 revision codes,[12] and one[19] used imaging evidence of cerebrovascular disease and additional clinical futures.

All studies adjusted for confounders in the analysis, which ranged from 5 to 14 co-variables, mostly including age, sex, socioeconomic status, lifestyles, body mass index and comorbidities at baseline (eTable 3). However, seven studies[11,13,33,31,32,35,36] did not adjust for smoking, and 13 studies did not adjust for depression. Examining the quality across all studies we found that the overall quality of these studies was reasonably good, with a mean score of 8.3 (eTable 4). One cohort study[34] had a reduced quality score of 8 points due to the representativeness of the exposed cohort.

Meta-analysis

Table 2 shows an overall AP exposure associated with increased risk of dementia. There were a total population of 12,603,739 participants with 475,937 cases of dementia diagnosed in the meta-analysis. The pooled data using the RR of the highest AP exposure in each studied

population showed a RR of 1.13 (95% CI, 1.08 to 1.19) in the risk of dementia (Figure 1). There was no significant publication bias ($P_{\text{Egger's test}}$ = 0.059). The average-data analysis approach showed a similar RR of dementia in AP exposure (RR=1.27, 95%CI 1.05 to 1.52) (eFigure 2)

Table 3 shows the pooled RRs of dementia in relation to different specific air pollutants exposure. Pooled data from the RR of dementia in the highest *versus* lowest exposure of air pollutants from each study revealed that the risk of dementia increased in participants exposed to $PM_{2.5}$ (RR=1.11, 95%CI 1.06 to 1.17), CO (RR=1.60, 95%CI 1.39 to 1.84) and NO_2 (RR=1.14, 95%CI 1.03 to 1.27), but not significantly in exposure to PM_{10} (RR=1.57, 95%CI 0.55 to 4.54), NO_x (RR=1.13, 95%CI 0.96 to 1.33) and O_3 (RR=1.01, 95%CI 0.95 to 1.07) (Table 3). The average-data analysis approach demonstrated similar findings (eTable 5): RR increased significantly in $PM_{2.5}$ (RR=1.12, 95%CI 1.05 to 1.19), CO (RR=1.36, 95%CI 1.08 to 1.70) and NO_2 (RR=1.09, 95%CI 1.00 to 1.17), non-significantly increased in PM_{10} (RR=1.42, 95%CI 0.63 to 3.21) and NO_x (RR=1.14, 95%CI 0.97 to 1.34), and no increased RR in O_3 (RR=1.01, 95%CI 0.95 to 1.08).

Table 4 shows the pooled data of a relative "dose-response" trend in each air pollutants associated with dementia risk. Compared to the lowest tertile (T1) of $PM_{2.5}$ exposure, RR of dementia in the 2nd tertile (T2) was 1.06 (95%CI 1.03 to 1.10) and in the 3rd tertile (T3) 1.13 (95%CI 1.07 to 1.19). The corresponding figures in PM_{10} were 1.05 (95%CI 0.86 to 1.29) and 1.62 (95%CI 0.60 to 4.36), in CO 1.69 (95%CI 0.72 to 3.93) and 1.52(95%CI 1.35 to 1.71), in NO_2 1.06 (95%CI 1.03 to 1.09) and 1.18 (95%CI 1.10 to 1.28), in NO_x 1.09 (95%CI 1.04 to 1.15) and 1.26 (95%CI 1.13 to 1.41), respectively. Such a trend relation was not seen in O_3 (Table 4).

In stratifying types of dementia for analysis, the pooled RR of AD in the highest *vs* lowest AP total exposure from six studies was 1.07 (95%CI 1.00 to 1.15) and VaD 1.10 (95%CI

311 0.95 to 1.28) from three studies (Figure 2). In each air pollutant analysis, no significant
312 association with AD or VaD was found. There were no significant RRs of AD or VaD in the
313 average-data analysis approach, and in the "dose-response" trend analysis, which were similar
314 to those in Figure 2.
315

316 **DISCUSSION**

317 Our study including the new data from China and world-wide literature systematic
318 review provides a novel insight into the impact of different air pollutants on the risk of
319 dementia. The meta-analysis demonstrated a significant increase in the risk of dementia by
320 around 13% in relation to overall AP exposure. The association of AP with dementia risk was
321 relatively "dose-respondent" in exposure to $PM_{2.5}$, PM_{10}, NO_2 and NO_x. CO exposure was
322 significantly associated with increased risk of dementia, but O_3 exposure was not.

323 Over the past few years, there has been an increasing growth of interesting in examining
324 the impact of air pollution on dementia. Growing research from animal and laboratory studies[44]
325 have shown a significant, positive association between exposure to AP and dementia. In an
326 experimental study of rats exposed to diesel exhaust by inhalation over 4 weeks or a single
327 intratracheal administration of diesel exhaust particles, Levesque et al[45] found that the diesel
328 exhaust caused a microglial activation and up-regulation of oxidative stress, pattern recognition
329 receptor, neurotoxic cytokines, and chemokines in the brain of the rat, all of which may be
330 particularly relevant to the development of dementia. Power et al[46] examined the association
331 between brain MRI findings and particulate matters exposures approximately 5 to 20 years
332 prior to MRI in Americans and found that a higher level of long-term PM exposure was
333 associated with smaller deep-gray volumes within the brain, which may be relevant to the
334 aetiology of dementia.

However, the association of AP exposure with incident dementia in the population is not well studied and established. Firstly, the number of studies was limited, and all studies were from HICs. In our 2016 systematic literature examining the impacts of AP on cognitive impairment including dementia, [9] we identified only one population-based study published to examine the association with dementia, and our 2018 literature review showed several studies published to examine the association with dementia.[47] In 2019, Peters et al[48] carried out a systematic review, including 13 published articles to suggest that increased risk of dementia could be related to overall AP exposure. However, without a meta-analysis of the data in the literature review, [48] the publication bias and the dose-response association of AP with dementia risk could not be assessed. Secondly, the findings from previously published studies showed conflicting results; some revealed positive association between AP exposure and risk of dementia,[18,20,31-33] but others did not.[12,17] Such variations in the findings may not be able to be dealt with via random effect models in pooling data. The variation in the impact of AP on dementia risk could be due to different populations which have different characteristics and influencing factors for the impact (e.g., dietary intakes[28]). These need further investigation. Thirdly, some of original studies did not include important confounders for adjustment in the analysis; for example, seven studies[11,13,31-33,35,36,] were unable to adjust for smoking, of which four did not adjust educational level neither,[11,31-33] while most studies did not adjust for depression. Thus, the data of previous studies may over-estimate the association of AP with risk of dementia.

Strengths and limitations

Our study has several strengths. First, as far as we know, our meta-analysis is the first to include systematically identified studies for reviewing overall AP and air pollutants associated with dementia risk, which also included new data from LMICs to evaluate the impact of AP on dementia risk. Second, the new cohort studies in China adjusted for many

important confounders for adjustment in the analysis (such as depression,[49] which was largely missed from other studies on the topic) so that the residual effect would be minimised. The findings have filled in the knowledge gap. Third, our meta-analysis employed three approaches to pool data since there were some complexities in the data pooled from published studies. All showed consistent findings of the association between overall AP exposure and dementia risk, and variations in the associations among air pollutants.

Our study has limitations. Firstly, the Anhui cohort study had AP measurement recorded in the middle period of the cohort follow-up and were recorded not entirely before all dementia development in the cohort, which made difficulties in referring the cause-result relation between AP and dementia. However, we analysed the data of dementia occurred after AP exposure measured, i.e., AP measured in 2015 and 2016 prior to our cohort wave 3 follow-up (Table 1) and the positive association remained significant. Secondly, it should be cautious to interpret the findings from the meta-analysis. There might be potential biases in the meta-analysis, which were linked to the heterogeneity of studies, as shown in random effect model uses (Figure 1 and Figure 2). Overall pollution effect combined the effects measured from different components from some studies (Table 2), while the components had themselves heterogeneous effect on dementia (as shown in Table 3). The heterogeneity among these studies which examined the same components should be investigated. However, we could not run subgroup meta-analysis for this due to limited number of studies. Thirdly, we reviewed the 15 studies and found that they used different methods to analyse the data for the association between AP and dementia. This made us difficulties in pooling the overall dose-response data to assess the AP threshold for dementia risk. However, we examined and pooled their "tertile" exposure data to identify a "dose-response" trend. This would help identify the causal-results relationship between AP exposure and dementia. Nevertheless, in future primary studies a standard method of the dose-response data analysis is required. Fourthly, although we tried to

explore the impact of AP on AD and VaD separately, limited data in the literature has prevented from obtaining significant findings in VaD (Figure 2). Thus, more studies are required to examine the association of AP exposure with increased AD or VaD.

As the studies included in our systematic review and meta-analysis were observational, we considered the causal relationship between AP and dementia using the Bradford Hill Criteria to provide evidence.[50]

How strong are the associations between AP and dementia?

The studies in the current review have shown variations in the strength in the associations between AP exposure and incident dementia and are often based on a different unit-increase in air pollutants exposure. While Carey et al[12] did not find a significant association between residential proximity to major roadways and incident dementia in UK population, Chen et al[11] and Cerza et al[31] found it in Canada and Italy populations, respectively. Nine cohort studies[12,13,17,18,20,32-35] examining the association between exposure $PM_{2.5}$ and incident dementia showed a HR range from 1.03 to 1.92, of which four [13, 18, 34, 35] were not statistically significant. Five cohort[12,33,31,35,36] studies examined association between NO_2 exposure and risk of dementia showed a HR range from 1.05 to 1.74, of which two studies [31, 35] were not significant and other one[36] only showed significance among exposure to the fourth quartile of NO_2. While two studies [20, 31] showed a significant linear association of NO_x exposure with incident dementia, other four studies[12,13,31, 33] examining the linear association between O_3 and incident dementia showed a HR range from 0.85 to 1.06, two[12,33] of which demonstrated adverse association. Despite of these, pooled data in our meta-analysis showed a significant association of overall AP with incident dementia, with HR around 1.13–1.28 from different approach analysis, and also similar figures for some air pollutants. Thus, the association between AP exposure and risk of dementia was small to modest.

How consistent are the reported studies?

There is a clear consistency among the studies examining the association of residential proximity to major roadways, $PM_{2.5,}$ NO_2 and CO with incident dementia, although they used different methodologies in conducting the studies. Of four studies[11,12,31,35] examining the association between residential proximity to major roadways and incident dementia, three reported positive association[11,31,35]. Of nine studies[12,13,17,18,20,32-35] examining the association between $PM_{2.5}$ exposure and incident dementia, five reported positive association[12,17,20,32,33]. Of five studies[12,33,31,35,36] examining the association between NO_2 exposure and incident dementia, three reported positive association [12,33,36]. These revealed that most findings were consistent.

How specific is the response to proposed agents?

Similar to other chronic non-communicable diseases (e.g., stroke), dementia is in no way specific to AP, that has been attribute to many different causes at different stages. Dementia has had other risk factors, such as smoking and depression.[49,51] AP and particulate pollutants are also associated with other health other outcomes, including cardiovascular diseases that could be mediators for the association between AP and dementia[20, 52]. Thus, the finding from the present study raises serious issues relating to confounding factors. All studies identified have taken great care to allow for some important confounders such as education, hypertension, but some studies missed other important co-variables, including smoking, depression, and dietary intakes such as fish and vegetable consumption[28,39,53]. Therefore, such factors need to take account of in future research.

Is there a temporal relationship between exposure and response?

The effect of AP on the risk of dementia is obviously a chronic process, which related to exposure duration and concentration. All studies identified are thus showing a temporal relationship. This is most apparent in the prospective cohort studies [10,14,18-20,31,35].

Is there an exposure-response relationship?

Due to the differences in AP distributions and data analysis methods in the studies reviewed, our meta-analysis could not estimate the linear association between AP and dementia. However, we converted all exposure measurements into three tertile groups, representing the "low", "middle" and "high" level exposure, and the pooled RRs of dementia in relation to them showed a relatively "dose-response" relationship between $PM_{2.5}$, NO_2 and NO_x exposure and incident dementia. It is worth noting that the dose-response relationship was not consistent in the individual study identified, which may relate to the effect threshold of each pollutant other than sample size in each level of air pollutants in each study.

Is the association biologically plausible?

AP include gas, particles, or material desorbed from the particle surface, are able to cross the blood-brain barrier, which have the potential to act to induce inflammatory responses, microglial activation, production of reactive oxygen species, and increased production and deposition of A β peptides[45, 54, 55]. For example, evidence from an experimental study showed that rats exposed to diesel exhaust by inhalation over 4 weeks or a single intratracheal administration of diesel exhaust particles caused microglial activation and up-regulation of oxidative stress, pattern recognition receptor, neurotoxic cytokines, and chemokines in the brain, all of which may be particularly relevant to the development of dementia[45]. Furthermore, animal studies found that the ultra-fine particle matter <0.1um (UFPM) penetration into the olfactory bulb, the frontal cortical, and subcortical areas of the brain [56,57], which may induce inflammatory, immune response, and contribute to the development of dementia. Furthermore, we have recently reported the proposal that episodic release of biologic microparticles from pollution-induced lung inflammation causes secondary inflammation in the blood-brain barrier and cerebral microbleeds, culminating over time in cognitive impairment [58].

The impact of $PM_{2.5}$ on cerebro-vascular risk factors and stroke may accelerate the development of dementia [20,34]. Evidence has been indicated that increased $PM_{2.5}$ damage to the

vascular endothelium, the dysregulation of the sympathetic nervous system; even moderate increases in $PM_{2.5}$ levels have been associated with impaired cerebrovascular hemodynamics, including increased cerebral resistance and reduced cerebral blood flow[52, 59], and pathologically it has been shown that much dementia is associated with vascular diseases[60].

Is the evidence coherent with knowledge of the natural history?

Dementia is known to have multiple causes, including low education, smoking, obesity, physical inactivity, low social contact, depression, hypertension, hearing impairment, and diabetes[51]. The components of PM are complicated that include metal, such as lead, and other tobacco smoke, which have confirmed to be associated with increased risk of dementia[61, 62]. Therefore, exposure to AP, particularly to $PM_{2.5}$, NO_2, NO_x and CO increase the risk of dementia does not conflict with the existing evidence.

Is there experimental evidence?

A detailed examination of experimental studies on the association between AP and dementia is beyond the scope of our syntactical review but can be seen in Kilian et al' s systematic review for more details[63]. Here we only discussed it in brief. The association between exposure to AP and dementia found by the studies reviewed is partly supported by studies examining brain imaging and biochemical assays in young age groups.

Calderón-Garcidueñas et al[55, 64-68] carried out a series of experiment comparing Mexico City residents to those living in less polluted areas of Mexico. MRI scans showed increased white-matter hyperintensities in Mexico City children and young adults compare to controls, and minor decrease in bilateral and parietal temporal lobe white matter volume, while necropsy tissue examination demonstrated white matter lesions and disruption of the blood-brain barrier based on sonula occludens-1 (ZO-1) staining of tight junctions[57, 69]. Blood, urine, and necropsy tissue sample from children and adults showed increased in multiple cytokines, inflammatory response marker, oxidative stress markers, and down-regulation of prion-related protein in

multiple brain tissues for those living in Mexico City[64, 65, 67,68]. Pujol et al[69] conducted a MRI study of children aged 8-12 and found that higher exposure to $PM_{2.5}$ elemental carbon and NO2 with lower functional integration and segregation, both indications of slower maturation. Although all these population-based experimental studies did not focus on the outcome on dementia, these studies indicate that PM exposure can affect amyloid processing and inflammation response in the human brain.

There are also a number of studies investigated the underlying cellular and molecular mechanisms by using in vivo and vitro models. For example, mice that exposure to high levels of ultra-fine PM for short durations (2-6 weeks) demonstrated significant increase in pro-inflammatory cytokines IL-1α and TNF-α, Glial responses, and activation of NF-κB and AP-1 transcriptional factors in brain tissue[70,71]. In an animal study[72], mice exposed to PM showed impaired spatial learning and memory, increase cytokine production and reduced hippocampal dendritic spine density compared to the control. All these animal studies have provided some evidence for the direct effect of AP exposure on inflammation, immune response, and hemodynamic changes, which established potential linking pathways between AP exposure and incident dementia.

Does the evidence accord by analogy with that from other fields?

Our previous studies demonstrated that AP exposure increased cognitive dysfunction and impairment in children and older adults[9,29]. Tzivian et al[73] analysed the cross-sectional association of long-term exposure to AP and traffic noise with overall mild cognitive impairment (MCI) and amnestic MCI (aMCI) and non-amnestic MCI (naMCI) in Germany. They found that most air pollutants and traffic noise were associated with overall MCI and aMCI. Previous studies[62,74] showed that cigarette tobacco smoke have a negative impact on cognitive impairment, and increased incidence of clinically diagnosed dementia. Mukadam N et al[75] analysed the 10/66 dementia research surveys of representative populations in India,

China, and six Latin America countries to calculate population attributable fractions (PAFs) for dementia and found that smoking accounted for 5.5% of dementia worldwide. Our previous studies also showed exposure to environmental tobacco smoke was associated with the increased risk of dementia.[76,77]

Implications

Our study could have important environmental and population health implications. As the world population is ageing, there are more people suffering from dementia. It will affect more individuals, their families and society. As its costs are currently US $1 trillion annually in the world,[78] the global economy would be worse without reducing dementia. Due to having no effective treatment for dementia, its prevention become the upmost of importance. The findings from our meta-analysis have identified a significant increase in dementia risk by around 13% in relation to AP exposure. The World Health Organisation has set an advisory Air Quality guideline of 10μg/m^3 $PM_{2.5}$ to reduce harm to health,[79] but at present 91% of the world's population resides in areas that exceed these recommendations.[80] If the number of people living in areas exceeding these recommendations could be reduced to 50% from 91% in the world, it is estimated that around 2.8 million of incident dementia cases would be saved. Our findings from this study suggested that strategies on controlling for global AP, such as reducing the emission of air pollutants, using electric cars, particularly in LMICs, might potentially contribute to preventing dementia and other diseases as well and global climate warming. The findings of different impacts of specific air pollutants on dementia have provided the evidence of policy making to target on specific air pollutants in their importance rank for controlling AP exposure to prevent dementia, which may have more benefits in terms of economic costings and feasibilities. To minimize dementia burden, strategies on AP prevention should be monitored by public, public health professional, physicians, and policy makers.

In conclusion, our study has provided some evidence for the association of AP exposure with increased risk of dementia globally. The association was significant for air pollutants from $PM_{2.5}$, PM_{10}, CO, NO_2 and NOx, but not from O_3. Overall AP exposure is a potential modifiable risk factor for dementia. Globally reducing AP would minimize dementia burden.

Acknowledgements: The authors thank the participants and all who were involved in the Anhui cohort study and the ZJMPHS cohort study.

The systematic literature review was registered in PROSPERO International prospective register of systematic reviews, UK NIHR (https://www.crd.york.ac.uk/prospero/) (register number CRD42020187555) in 2020.

Authors' contributors: RC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: RC and JT.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: JT and RC.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: JT, AC, FH, MS, AN and RC.

Obtained funding: RC and JT.

Administrative, technical, or material support: MS, AN and RC.

Supervision: RC.

Conflict of Interest Disclosures: None reported.

Finding/Support: The study was funded by an EU grant from Horizon 2020 MSCA – DEMAIRPO #799247. The baseline and follow-up data collection of the Anhui cohort study

were funded by the Royal Society of UK, and the BUPA Foundation (Grants Nos. 45NOV06, and TBF-M09-05). The ZJMPHS cohort study was funded by Zhejiang Provincial Public Welfare Technology Application Research Projects of China (LGF19H260003, LGF21H260002).

Role of the Funder/ Sponsor: The funders/ sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

570 **References**

571 [1]. Alzheimer's Disease International. Dementia statistics. London, UK: Alzheimer's Disease
572 International; 2020 [cited April 27, 2020]. Available from: https://bit.ly/2Qq4pR1.
573 [2]. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. World Alzheimer Report 2015.
574 The Global Impact of Dementia. London, UK: Alzheimer's Disease International; 2015.
575 [3]. World Health Organization. Ten threats to global health in 2019. WHO website:
576 https://www.who.int/news-room/feature-stories/ten-threats-to-global-health-in-2019
577 (accessed on 20th May 2020).
578 [4]. Shah AS, Langrish JP, Nair H, et al. Global association of air pollution and heart failure: a
579 systematic review and meta-analysis. *Lancet.* 2013; **382**(9897): 1039-48.
580 [5]. Shah AS, Lee KK, McAllister DA, et al. Short term exposure to air pollution and stroke:
581 systematic review and meta-analysis. *BMJ.* 2015; **350**: h1295.
582 [6]. Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. The 2016 global and national burden of
583 diabetes mellitus attributable to PM 2·5 air pollution. *The Lancet Planetary Health.* 2018; **2**(7):
584 e301-e12.
585 [7]. Massimiliano B, Silvia G, Alice C, et al. Is there a link between air pollution and mental
586 disorders? *Environ Int.* 2018; **118**:154-168.
587 [8]. Kioumourtzoglou MA, Power MC, Hart JE, et al. The Association Between Air Pollution
588 and Onset of Depression Among Middle-Aged and Older Women. *Am J Epidemiol.* 2017;
589 **185**(9): 801-9.
590 [9]. Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. Exposure to air pollution and cognitive
591 functioning across the life course – A systematic literature review. *Environmental Research.*
592 2016; **147**:383-398.

[10]. Oudin A, Forsberg B, Adolfsson AN, et al. Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study. *Environ Health Perspect.* 2016;**124**(3):306-312.

[11]. Chen H, Kwong JC, Copes R, et al. Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet.* 2017; **389**(10070):718-726.

[12]. Carey IM, Anderson HR, Atkinson RW, et al. Are noise and air pollution related to the incidence of dementia? A cohort study in London, England. *BMJ Open.* 2018;**8**(9): e022404-2018-022404.

[13]. Jung C, Lin Y, Hwang B. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: a population-based cohort study in Taiwan. *J Alzheimer's Dis.* 2015;**44**(2):573-584.

[14]. Andersson J, Oudin A, Sundström A, Forsberg B, Adolfsson R, Nordin M. Road traffic noise, air pollution, and risk of dementia–results from the Betula project. *Environ Res.* 2018; **166**: 334-339.

[15]. Tsai TL, Lin YT, Hwang BF, et al. Fine particulate matter is a potential determinant of Alzheimer's disease: A systemic review and meta-analysis. *Environment Research.* 2019; **177**: 108638.

[16]. Fu P, Yung KKL. Air Pollution and Alzheimer's Disease: A Systematic Review and Meta-Analysis. *J Alzheimers Dis*. 2020;**77**(2):701-14.

[17]. Cacciottolo M, Wang X, Driscoll I, et al. Particulate air pollutants, APOE alleles and their contributions to cognitive impairment in older women and to amyloidogenesis in experimental models. *Translational psychiatry.* 2017;**7**(1): e1022.

[18]. Oudin A, Segersson D, Adolfsson R, Forsberg B. Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. *PloS one.* 2018;**13**(6):e0198283.

[19]. Oudin A, Andersson J, Sundström A, et al. Traffic-related air pollution as a risk factor for dementia: no clear modifying effects of APOEε4 in the Betula Cohort. *J Alzheimers Dis*. 2019; **71**(3): 733-740.

[20]. Grande G, Ljungman PLS, Eneroth K, Bellander T, Rizzuto D. Association between cardiovascular disease and long-term exposure to air pollution with risk of dementia. *JAMA Neurol.* 2020; **77**(7): 801-809.

[21]. Brauer M, Freedman G, Frostad J. et al. Ambient air pollution exposure estimation for the global burden of disease 2013. *Environ Sci Techhnol.* 2016; **50**(1):79-88.

[22]. Chen R, Hu Z, Wei L, Wilson K. Socioeconomic status and survival among older adults with dementia and depression. *Br J Psychiatry.* 2014;**204**(6):436-440.

[23]. Chen A, Zhou W, Hou J, Nevill A, Ding YL, Wan YH, Jester R, Qin X, Hu Z, Chen R. Impact of older age adiposity on incident diabetes: a community-based cohort study in China. *Diabetes Metab J*.2022; **46**(5):733-746.

[24]. Copeland JR, Prince M, Wilson KC, Dewey ME, Payne J, Gurland B. The Geriatric Mental State Examination in the 21st century. *Int J Geriatr Psychiatry*. 2002;**17**(8):729-732.

[25]. Chen R, Hu Z, Chen RL, Ma Y, Zhang D, Wilson K. Determinants for undetected dementia and late-life depression. *Br J Psychiatry*. 2013;**203**(3):203-208.

[26]. Meng X, Liu C, Zhang L, Wang W, Liu Y. Estimating PM2.5 concentrations in Northeastern China with full spatiotemporal coverage, 2005–2016. *Remote Sensing of Environment.* 2021; **253:** 112203.

[27]. Chen R, Hu Z, Wei L, Ma Y, Liu Z, Copeland JR. Incident dementia in a defined older Chinese population. *Plos One.* 2011; **6**(9): e24817.

[28]. He F, Tang JJ, Zhang T, et al. Impact of air pollution exposure on the risk of Alzheimer's disease in China: A community-based cohort study. *Environ Res*. 2022; **205**: 112318. doi: 10.1016/j.envres.2021.112318.

[29]. He F, Tang JJ, Zhang T, et al. Impact of Air Pollution on Cognitive Impairment in Older People: A Cohort Study in Rural and Suburban China. *J Alzheimers Dis.* 2020;**77**(4):1671-1679.

[30]. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; **151**, 264-269.

[31]. Cerza F, Renzi M, Gariazzo C, et al. Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study. *Environmental Health.* 2019; **18**(1):72.

[32]. Kioumourtzoglou MA, Schwartz JD, Weisskopf MG, et al. Long-term PM2.5 exposure and neurological hospital admissions in the northeastern United States. *Environ Health Perspect*. 2016; **124**(1), 23-29.

[33]. Chen H, Kwong JC, Copes R, et al. Exposure to ambient air pollution and the incidence of dementia: a population-based cohort study. *Environ Int.* 2017; **108**:271-277.

[34]. Ilango SD, Chen H, Hystad P, et al. The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study. *International J of Epidemiology*. 2020; **49**(1): 36-44.

[35] Yuchi W, Sbihi H, Davies H, et al. Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study. *Environmental Health*. 2020; **19** (1):8.

[36]. Chang K, Chang M, Muo C, Wu T, Chen C, Kao C. Increased risk of dementia in patients exposed to nitrogen dioxide and carbon monoxide: a population-based retrospective cohort study. *PloS One.* 2014;**9**(8): e103078.

[37]. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015; **4**(1):1.

668 [38]. Isaac M Danat, Angela Clifford, Martin Partridge, et al. Impacts of overweight and
669 obesity in older age on the risk of dementia: a systematic literature review and meta-anlaysis.
670 *J Alzheimers. Dis.* 2019; **70**(s1): S87-S99.
671 [39]. Bakre AT, Chen R, Khutan R, Wei L, Smith T, Qin G, Danat IM, Zhou W, Schofield P,
672 Clifford A, Wang J, Verma A, Zhang C, Ni J. Association between fish consumption and risk
673 of dementia: a new study from China and a systematic literature review and meta-analysis.
674 *Public Health Nutr* 2018;**21**: 1921-32.
675 [40]. Chen R, Hu Z, Chen RL, Zhang D, Xu L, Wang J, Wei L. Socioeconomic deprivation
676 and survival after stroke in China: a systematic literature review and a new population-based
677 cohort study. *BMJ Open*. 2015;**5**: e005688.
678 [41]. Rizwan N, Tang J, Amena D, et al. Influence of periodontal disease on risk of dementia:
679 a systematic literature review and a meta-analysis. *Eur J Epidemiol*. 2020; **35**(9):821-833
680 [42]. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the
681 quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;**25**(9):603-5.
682 [43]. Hemingway H, Philipson P, Chen R, et al. Evaluating the quality of research into a single
683 prognostic biomarker: a systematic review and meta-analysis of 83 studies of C-reactive
684 protein in stable coronary artery disease. *PLOS Med.* 2010;**7**(6):e1000286.
685 [44]. Kilian J, Kitazawa M. The emerging risk of exposure to air pollution on cognitive decline
686 and Alzheimer's disease - Evidence from epidemiological and animal studies. *Biomed J.*
687 2018;**41**(3): 141-62.
688 [45]. Levesque S, Taetzsch T, Luu ME, et al. Diesel exhaust activates and primes microglia:
689 air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity. *Environ*
690 *Health Perspect.* 2011; **119**(8): 1149-1155.

691 [46]. Power MC, Lamichhane AP, Liao D, et al. The association of long-term exposure to
692 particulate matter air pollution with brain MRI findings: the ARIC study. *Environ Health*
693 *Perspect*. 2018; **126**(2): 027009.
694 [47]. Zhang WH, Tao FB, Tong SL, Hu Z, Chen R. Air pollution and cognitive impairment
695 and dementia in the elderly: a literature review. *Chin J Public Health.* 2018; **34**(5): 774-776.
696 [48]. Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air Pollution and Dementia: A
697 Systematic Review. *J Alzheimers Dis.* 2019;**70**(s1): S145-S163.
698 [49]. Chen R, Hu Z, Wei L, Qin X, McCracken C, Copeland JR. Severity of depression and
699 risk for subsequent dementia: cohort studies in China and the UK. *Br J Psychiatry*.
700 2008;**193**(5):373-377.
701 [50]. Hill SB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;
702 **58**: 295-300.
703 [51]. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and
704 care. *Lancet.* 2017; **390**: 2673-734.
705 [52]. Ljungman PLS, Andersson N, Stockfelt L, et al. Long-term exposure to particulate air
706 pollution, black carbon, and their source components in relation to ischemic heart disease and
707 stroke. *Environ Health Perspect*. 2019;**127**(10):107012.
708 [53]. Jiang X, Huang J, Song D, et al. Increased consumption of fruit and vegetables is
709 related to reduced risk of cognitive impairment and dementia: meta-analysis. *Front Aging*
710 *Neurosci*. 2017; **9**: 18.

711 [54]. Wang S, Zhang J, Zeng X, et al. Association of traffic related air pollution with
712 children's neurobehavioral functions in Quanzhou, China. Environ. Health Perspect. 2009;
713 **117**: 1612-1618.

714 [55]. Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, et al. Long-term air pollution
715 exposure is associated with neuroinflammation, an altered innate immune response,

716 disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of
717 amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol*. 2008;
718 **36**(2):289-310.

719 [56]. Cheng H, Saffari A, Sioutas C, et al. Nanoscale particulate matter from urban traffic
720 rapidly induces oxidative stress and inflammation in olfactory epithelium with concomitant
721 effects on brain. *Environ Health Perspect*. 2016; **124**, 1537-1546.

722 [57]. Forman HJ, Finch CE. A critical review of assays for hazardous components of air
723 pollution. *Free Radic Biol Med*. 2018; **117**, 202-217.

724 [58]. Seaton A, Tran L, Chen R, Maynard RL, Whalley LJ. Pollution, Particles, and
725 Dementia: A Hypothetical Causative Pathway. *Int J Environ Res Public Health*. 2020; **17**(3):
726 862.

727 [59]. Stafoggia M, Cesaroni G, Peters A, et al. Long-term exposure to ambient air pollution
728 and Incidence of cerebrovascular events: results from11 European cohorts within the
729 ESCAPE project. *Environ Health Perspect*. 2014;**122**(9):919-925.

730 [60]. Thal DR, Grinberg LT, Attems J. Vascular dementia: different forms of vessel disorders
731 contribute to the development of dementia in the elderly brain. *Exp. Gerontol*. 2012; **47**:
732 816–824.

733 [61]. Bakulski KM, Seo YA, Hickman RC, et al. Heavy Metals Exposure and Alzheimer's
734 Disease and Related Dementias. *J Alzheimers Dis*. 2020; **76**(4): 1215–1242.

735 [62]. Anstey KJ , von Sanden C , Salim A , O'Kearney R. Smoking as a Risk Factor for
736 Dementia and Cognitive Decline: A Meta-Analysis of Prospective Studies. *Am J Epidemiol*.
737 2007;**166**:367–378.

738 [63]. Kilian J, Kitazawa M. The emerging risk of exposure to air pollution on cognitive
739 decline and Alzheimer's disease-evidence from epidemiology and animal studies. *Biomedical*
740 *J*. 2018; **41**(3):141-162.

741 [64]. Calderon-Garcidueñas L, Macías-Parra M, Hoffmann HJ, et al. Immunotoxicity and
742 environment: immunodysregulation and systemic inflammation in children. *Toxicol Pathol*.
743 2009;**37**(2):161-9.

744 [65]. Calderon-Garcidueñas L, Franco-Lira M, Carlos Henríquez-Roldán C, et al. Urban air
745 pollution: influences on olfactory function and pathology in exposed children and young
746 adults. *Exp Toxicol Pathol*. 2010;**62**(1):91-102.

747 [66]. Calderón-Garcidueñas L, Franco-Lira M, Henríquez-Roldán C, et al.
748 Neuroinflammation, hyperphosphorilated tau, diffuse amyloid plaques and down-regulation
749 of the cellular prion protein in air pollution exposed children and adults. *J Alzheimer Dis.*
750 2012; **28**:93-107.

751 [67]. Calderón-Garcidueñas L, Mora-Tiscareño A, Styner M, et al. White matter,
752 hyperintensities, systemic inflammation, brain growth, and cognitive functions in children
753 exposed to air pollution. *J Alzheimer Dis*. 2012; **31**:183-91.

754 [68]. Calderon-Garcidueñas L, Reed W, Maronpot RR, et al. Brain inflammation and
755 Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol*.
756 2004; **32**:650e8.

757 [69]. Pujol J, Martı´nez-Vilavella G, Macia D, Fenoll R, Alvarez- Pedrerol M, Rivas R, et al.
758 Traffic pollution exposure is associated with altered brain connectivity in school children.
759 *NeuroImage*. 2016; **129**:175-84.

[70]. Kleinman MT, Araujo J, Nel A, et al. Inhaled ultrafine particulate matter affects CNS inflammatory processes and may act via MAP kinase signaling pathways. *Toxicol Lett*. 2008;**178**:127-30.

[71]. Campbell A, Oldham M, Becaria A, et al. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. *Neurotoxicology*. 2005; **26**: 133-40.

[72]. Fonken L, Xu X, Weil Z, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. *Mol Psychiatry.* 2011;**16**: 987-995.

[73]. Tzivian L, Dlugai M, Winkler A, et al. Long-term air pollution and traffic noise exposures and mild cognitive impairment in older adults: a cross-sectional analysis of Heinz Nixdorf recall study. *Environ Health Perspect*. 2016; **124**(9): 1361-8.

[74]. Collins N, Sachs-Ericsson N, Preacher KJ, et al. Smoking increases risk for cognitive decline among community-dwelling older Mexican Americans. *Am J Geriatr Psychiatry*. 2009; **17**(11):934-942.

[75]. Mukadam N, Sommerlad A, Huntley J, et al. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Global Health*. 2019; **7**(5): e596-e603.

[76]. Chen R, Wilson K, Chen Y, et al. Association between environmental tobacco smoke exposure and dementia syndromes. *Occup Environ Med*. 2013;**70**: 63-9.

[77]. Chen R. Association of environmental tobacco smoke with dementia and Alzheimer's disease among never smokers. *Alzheimer's & Dementia*. 2012; **8**: 590-5.

[78]. Patterson C. World Alzheimer report 2018. London: Alzheimer’s Disease International, 2018.

783 [79]. World Health Organization. Ambient (outdoor) air pollution. WHO website:
784 https://www.who.int/en/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-
785 health (accessed on 12th Aug 2022).

786 [80]. Zhang YL, Cao F. Fine particulate matter (PM2.5) in China at a city level. *Scientific*
787 *Reports*. 2015; **5**: 14884.

Table 1. Number, rate and hazard ratio (HR) of incident dementia in older people exposed to $PM_{2.5}$: the Anhui cohort study

$PM_{2.5}$ ($\mu g/m^3$) ǂ	Participants		Model 1		Model 2		Model 3	
	All	Dementia (n, %)*	HR (95% CI)[1]	**P**	HR (95% CI)[2]	**P**	HR (95% CI)[2]	**P**
Whole cohort								
< 63.5	177	12(6.78)	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
>= 63.5 and < 64.5	667	55(8.25)	1.68(0.85-3.32)	0.138	2.08(1.01-4.30)	0.047	2.04(0.96-4.32)	0.064
>= 64.5	558	42(7.53)	1.65(0.82-3.32)	0.162	2.09(1.00-4.39)	0.051	2.14(1.00-4.56)	0.050
Sensitivity analysis#								
< 63.5	170	5(2.94)	1.00 [Reference]		1.00 [Reference]		1.00 [Reference]	
>= 63.5 and < 64.5	641	29(4.52)	2.54(0.91-7.03)	0.074	2.60(0.90-7.52)	0.077	2.60(0.87-7.80)	0.088
>= 64.5	545	29(5.32)	2.78(0.99-7.79)	0.052	2.90(0.99-8.49)	0.052	3.08(1.02-9.26)	0.046

ǂ using China national mean of $PM_{2.5}$ (61 $\mu g/m^3$) [80] and the distribution of our Anhui cohort $PM_{2.5}$ data we took $PM_{2.5}$ < 63.5 $\mu g/m^3$ as a cut-off point for analysis, and then above it there were two groups of $PM_{2.5}$ < 64.5 $\mu g/m^3$ and >= 64.5 $\mu g/m^3$ which had approximate equal number of participants.

* Chi-square test p <0.001 for incident rate across three levels of $PM_{2.5}$ in the whole cohort and also in the sensitivity analysis cohort. # Exclude 46 participants who had dementia diagnosed at Wave 2.

Model 1: adjusted for age (cont.), sex, education level; income.
Model 2: adjusted for age (cont.), sex, education level, income, smoking, drinking alcohol, BMI (category), walking or group touring, marital status, living with.
Model 3: adjusted for age (cont.), sex, education level, income, smoking, drinking alcohol, BMI (category), walking or group touring, marital status, living with, hypertension, hypercholesterolemia, diabetes, heart disease, stroke, depression, and Instrumental Activities of Daily Living (ADL group).

Table 2. Air pollutants in each studied population for estimating the pooled RR of dementia

Study ID	Air pollutants								Comprehensive AP[#]	Pooled
	$PM_{2.5}$	PM_{10}	NO_2	NO_x	O_3	CO	SO_2	Coarse PM		RR
Chang et al [36]			√			√			Pooled	1.57(1.42-1.74)
Jung et al [13]	√				√				Pooled	1.05(1.00-1.10)[a]
Oudin et al [10, 18]	√			√					Pooled	1.43(1.16-1.75)
Kioumourtzoglou et al [32]	√								Single	1.08(1.05-1.11)
Cacciottolo et al [17]	√								Single	1.92(1.32-2.80)
Grande et al [20]	√			√					Pooled	1.32(0.98-1.77)
Cerza et al [31]	√	√	√	√	√			√	√ (Distance to road)	1.01(0.97-1.06)
Chen et al [11, 33]	√		√		√				√ (Distance to road)	1.07(1.06-1.08)
Carey et al [12]	√		√		√				√ (Distance to road)	1.03(0.99-1.07)
Yuchi et al [35]	√		√						√ (Distance to road)	1.14(1.08-1.20)
Anhui cohort study	√								Single	2.14(1.00-4.56)
Zhejiang cohort study	√	√	√		√	√	√		√ (Air quality index)	2.28(1.07-4.87)
Overall RR										***1.13(1.08-1.19)***
Publication bias for overall RR (Egger's test)										0.059

a, fixed effect

[#] Six studies [10, 13, 17, 18, 20, 36] did not provide the RR for overall AP exposure and thus used surrogate comprehensive AP exposure through multiple air pollutants to pool the data.

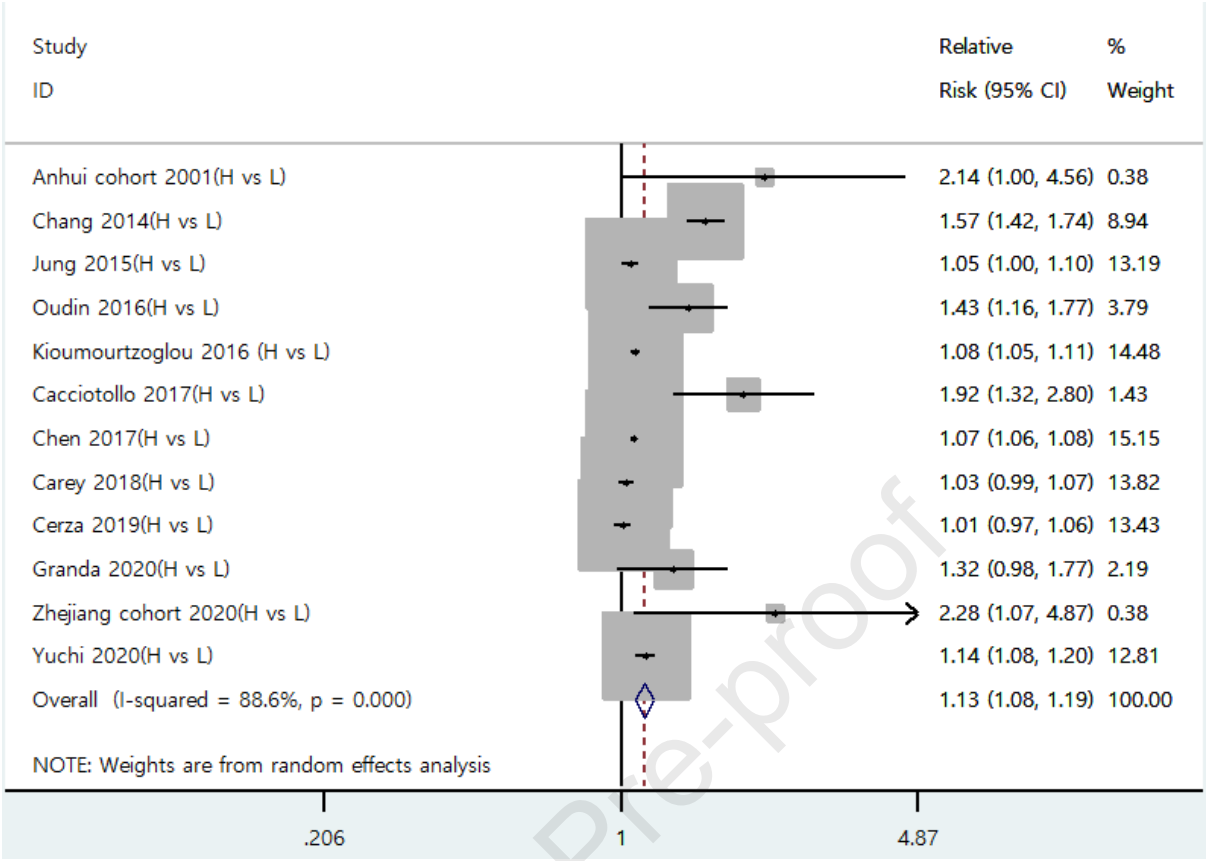

Figure 1. Forest plot for the RR of all dementia in air pollution exposure.

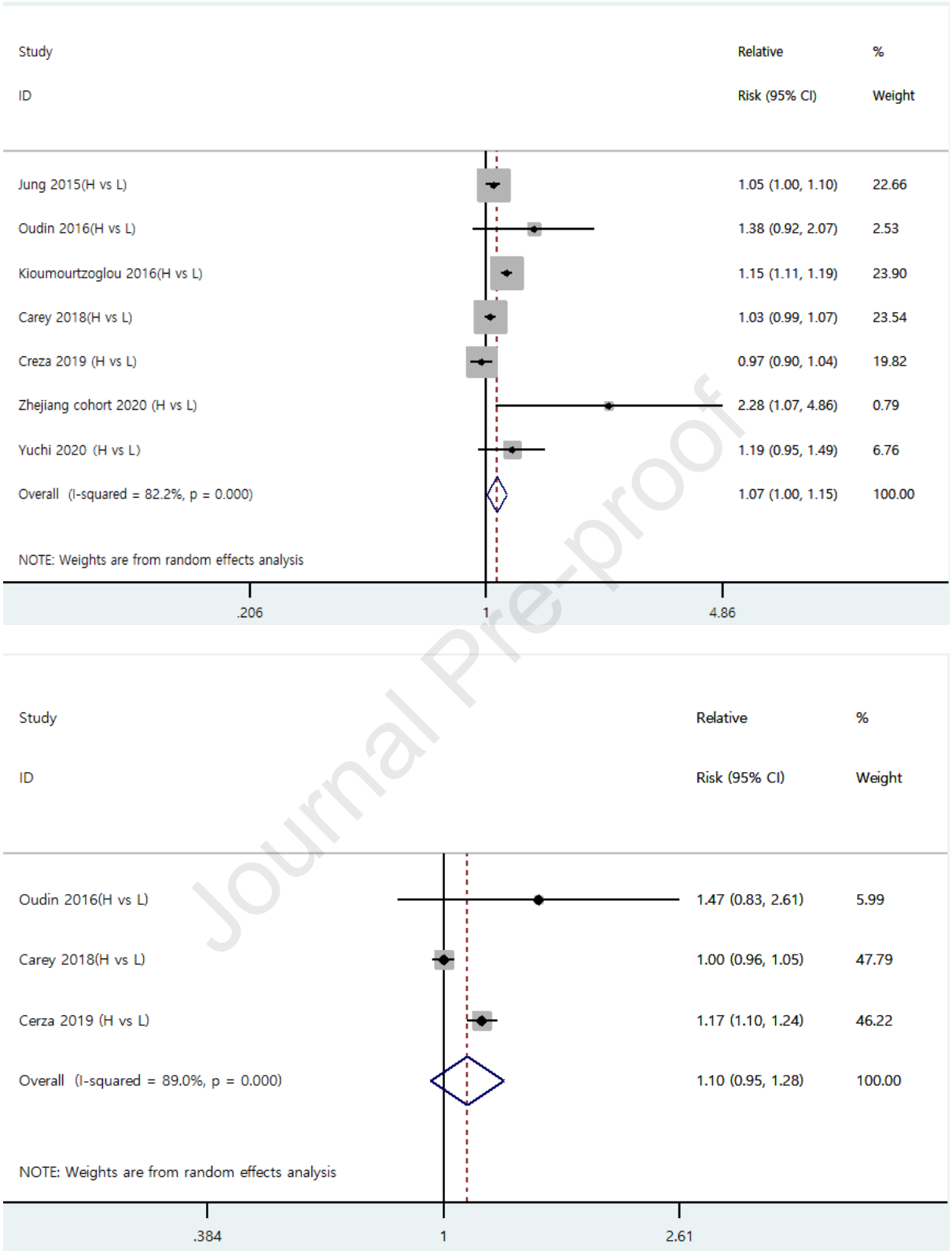

Figure 2. Forest plot for the RR of AD [up part] and VaD [low part] in air pollution

Table 3. RR in each studied population used for estimating the pooled RR of specific air pollutant and dementia

	Pooled RR of dementia for each air pollutant					
	$PM_{2.5}$ (n=11)	PM_{10} (n=2)	CO (n=2)	NO_2 (n=6)	NO_x (n=3)	O_3 (n=5)
Chang et al [36]			1.61(1.39-1.85)	1.54(1.34-1.77)		
Jung et al [13]	1.03(0.95-1.11)					1.06(1.00-1.12)
Oudin et al [10, 18]	1.34(1.04-1.74)[a]				1.60(1.02-2.10)	
Kioumourtzoglou et al [32]	1.08(1.05-1.11)					
Cacciottolo et al [17]	1.92(1.32-2.80)					
Grande et al [20]	1.54(1.33-1.78)				1.14(1.01-1.29)	
Cerza et al [31]	0.99(0.96-1.02)	1.00(0.98-1.03)		0.97(0.96-0.99)	1.01(1.00-1.02)	1.06(1.03-1.08)
Chen et al [11, 33]	1.04(1.03-1.05)			1.10(1.08-1.12)		0.98(0.96-1.00)
Carey et al [12]	1.06(0.99-1.13)			1.13(0.99-1.28)		0.87(0.76-1.01)
Yuchi et al [35]	0.99(0.89-1.10)			0.94(0.78-1.14)		
Anhui cohort	2.14(1.00-4.56)					
Zhejiang cohort	3.92(2.09-7.36)	3.00(1.22-7.41)	1.19(0.45-3.18)	0.95(0.28-3.19)		0.50(0.21-1.21)
Overall RR	***1.11(1.06-1.17)***	***1.57(0.55-4.54)***	***1.60(1.39-1.84)[a]***	***1.14(1.03-1.27)***	***1.13(0.96-1.33)***	***1.01(0.95-1.07)***

[a]fixed model.

Table 4. RR in each studied population used for estimating the "dose-response" trend for specific air pollutant associated with dementia risk

Study		Pooled RR of dementia for each air pollutant					
		$PM_{2.5}$ (n=11)	PM_{10} (n=2)	CO (n=3)	NO_2 (n=6)	NO_x (n=3)	O_3 (n=5)
Chang et al [36]	T2 *vs* T1 exposure			1.19(1.07-1.33)	1.05(0.95-1.16)		
	T3 *vs* T1 exposure			1.52(1.35-1.71)	1.38(1.23-1.55)		
Jung et al [13]	T2 *vs* T1 exposure	1.02(0.97-1.07)					1.08(1.00-1.17)
	T3 *vs* T1 exposure	1.05(0.93-1.17)					1.19(1.00-1.41)
Oudin et al [10, 18]	T2 *vs* T1 exposure	1.08(0.76-1.54)				1.31(1.01-1.70)[a]	
	T3 *vs* T1 exposure	1.32(1.07-1.63)				1.60(1.02-2.10)	
Kioumourtzoglou et al [32]	T2 *vs* T1 exposure	1.06(1.04-1.09)					
	T3 *vs* T1 exposure	1.10(1.07-1.13)					
Cacciottolo et al [17]	T2 *vs* T1 exposure	1.47(1.18-1.85)					
	T3 *vs* T1 exposure	2.46(1.47-4.14)					
Grande et al [20]	T2 *vs* T1 exposure	1.36(1.23-1.51)				1.12(1.01-1.25)	
	T3 *vs* T1 exposure	1.93(1.54-2.41)				1.34(1.02-1.75)	
Cerza et al [31]	T2 *vs* T1 exposure	1.03(1.00-1.05)	1.03(1.01-1.05)		1.07(1.03-1.11)	1.08(1.06-1.11)	1.02(0.98-1.07)
	T3 *vs* T1 exposure	1.06(1.01-1.10)	1.07(1.02-1.12)		1.25(1.13-1.39)	1.22(1.16-1.28)	1.05(0.96-1.14)
Chen et al [11, 33]	T2 *vs* T1 exposure	1.02(1.02-1.03)			1.04(1.03-1.05)		0.98(0.96-1.00)
	T3 *vs* T1 exposure	1.06(1.05-1.08)			1.14(1.11-1.17)		0.96(0.92-1.00)
Carey et al [12]	T2 *vs* T1 exposure	1.05(1.01-1.11)			1.11(1.03-1.20)		0.89(0.82-0.97)

	T3 *vs* T1 exposure	1.11(1.02-1.25)			1.26(1.07-1.51)		0.79(0.67-0.94)
Yuchi et al [35]	T2 *vs* T1 exposure	1.00(0.90-1.11)			0.98(0.83-1.16)		
	T3 *vs* T1 exposure	1.03(0.92-1.14)			1.05(1.01-1.09)		
Anhui cohort study	T2 *vs* T1 exposure	2.04(0.96-4.32)					
	T3 *vs* T1 exposure	2.14(1.00-4.56)					
Zhejiang cohort study*	T2 *vs* T1 exposure	1.50(0.90-2.50)	1.74(0.65-4.65)	2.86(1.32-6.20)	0.63(0.17-2.27)		0.38(0.20-0.74)
	T3 *vs* T1 exposure	3.92(2.09-7.36)	3.00(1.22-7.41)	1.19(0.45-3.18)	0.95(0.28-3.19)		0.50(0.21-1.21)
Overall RR in T2		***1.06(1.03-1.10)***	***1.05(0.86-1.29)***	***1.69(0.72-3.93)***	***1.06(1.03-1.09)***	***1.09(1.04-1.15)***	***0.99(0.97-1.01)[b]***
Overall RR in T3		***1.13(1.07-1.19)***	***1.62(0.60-4.36)***	***1.52(1.35-1.71)***	***1.18(1.10-1.28)***	***1.26(1.13-1.41)***	***0.97(0.94-1.01)[b]***

[a] fixed model, [b] fixed model.

*the cut-off points for three groups in each air pollutant exposure were the same as our recently published paper[28].

HIGHLIGHTS:

- Two cohort studies were conducted in China to investigate the high $PM_{2.5}$ and poor air quality index associated with dementia risk, revealing significant association.
- Pooling data from all eligible studies published and new cohorts in China showed dementia risk increased with overall AP exposure, $PM_{2.5}$, PM_{10}, CO, NO_2, NOx, but not O_3.
- Controlling air pollution and targeting on specific pollutants would reduce dementia globally.

Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: