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

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## 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  $\geq 60$  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 20<sup>th</sup> 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, CINAHL, 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  $\geq 64.5 \mu g/m^3$  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  $\leq 80$ . 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 2<sup>nd</sup> tertile exposure; 1.13, 1.07-1.19 in 3<sup>rd</sup> tertile versus 1<sup>st</sup> 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

## **HIGHLIGHTS:**

- Two cohort studies were conducted in China to investigate the high PM<sub>2.5</sub> 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<sub>2.5</sub>, PM<sub>10</sub>, CO, NO<sub>2</sub>, NO<sub>x</sub>, but not O<sub>3</sub>.
- Controlling air pollution and targeting on specific pollutants would reduce dementia globally.

## 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.<sup>1</sup> Dementia costs US\$ 818 billion annually, and the costings will rise further.<sup>2</sup> 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.<sup>3</sup> AP includes a variety of air pollutants, such as particulate matter (e.g., PM<sub>2.5</sub>, PM<sub>10</sub>), carbon monoxide (CO), nitrogen dioxide (NO<sub>2</sub>), and ozone (O<sub>3</sub>). Exposure to AP, particularly PM<sub>2.5</sub>, increases the risk of cardiovascular diseases,<sup>4,5</sup> diabetes,<sup>6</sup> anxiety<sup>7</sup> and depression.<sup>8</sup> It also showed a significant association with cognitive impairment across the life course.<sup>9</sup> Its association with an increased risk of dementia, however, remains unclear; some studies showed a positive association,<sup>10-12</sup> whilst others did not.<sup>13,14</sup> Recent two meta-analysis studies<sup>15,16</sup> 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<sup>15</sup> did not include two eligible studies<sup>17,18</sup> and other<sup>16</sup> missed three studies<sup>14,19,20</sup> for systematically reviewing. Fu and Yung's meta-analysis study<sup>16</sup> also showed there might be potential publication bias towards the finding.<sup>16</sup> 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.<sup>21</sup>

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.<sup>22,23</sup> Briefly, in 2001-2003 we recruited a random sample of 3336 permanent residents aged  $\geq 60$  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.<sup>24</sup> 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.<sup>25</sup> 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.<sup>22</sup>

Using a satellite-based model with a high spatiotemporal resolution,<sup>26</sup> we assessed daily PM<sub>2.5</sub> concentrations for each cohort member based on his home address. The earliest year predicted PM<sub>2.5</sub> concentrations was from 2005. We used an average PM<sub>2.5</sub> 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.<sup>26</sup>

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,<sup>27</sup> we included 1421 participants who had at least primary school education for analysis. After excluding 19 participants who did not have PM<sub>2.5</sub> 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<sub>2.5</sub> 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.<sup>28</sup> 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.<sup>29</sup> 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.<sup>28</sup> In the late meta-analysis for individual air pollutants, we extracted the findings of six air pollutants (ie, PM<sub>2.5</sub>, PM<sub>10</sub>, SO<sub>2</sub>, NO<sub>2</sub>, CO and O<sub>3</sub>) from this cohort study,<sup>28</sup> (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).<sup>30</sup> The search terms used were "*Pollution*" (air pollution;

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

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

Searching four electronic datasets for literature, we had 1401 hits. After eliminating duplicates, 1168 remained. We reviewed their titles and abstracts and identified 34 relevant papers. Reading through these papers we excluded 19 which had not met the inclusion criteria and left 15 articles<sup>10-14,17-20,31-36</sup> for systematic review. The details of literature searched and 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).<sup>37</sup> 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 3<sup>rd</sup> reviewer (XT) made the final judgement. Following our previous studies,<sup>38-41</sup> 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.<sup>42</sup>

## ***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,<sup>10,11,14,18</sup> 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,<sup>10,14,19</sup> we would take the paper with the most statistical adjustment for meta-analysis.<sup>10</sup> Of the 15 studies, four<sup>10,14,18,19</sup> from Sweden used the same population data of the Betula study (of which three investigated the association

between NO<sub>x</sub> exposure and dementia risk<sup>10,14,19</sup>), and three from Canada used the same datasets of Ontario population<sup>11,20,22</sup> (of which two examined the same measurements of AP exposure associated with dementia<sup>33,34</sup>). After excluding two Swedish papers using the same data to update the results<sup>14,19</sup> and one Canadian paper measuring the same exposure,<sup>34</sup> 12 studies were left for the meta-analysis.<sup>10-13,17,18,20,21,32,33,35,36</sup> We examined the risk of dementia in relation to overall AP exposure, analysing the data of studies which measured REDPMR<sup>11,12,31</sup> or AQI as a comprehensive indicator of AP. If such a comprehensive AP indicator was not available in published papers<sup>10,12,17,18,20,36</sup> 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.<sup>38</sup> If the paper provided the finding of continuous AP measurement only,<sup>12,13,31,33-35</sup> 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.<sup>39</sup> This approach would use the average RR of dementia from each study. Third, using a scaling factor method in our previous meta-analysis study,<sup>43</sup> 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 2<sup>nd</sup> 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<sub>2.5</sub> exposure. Compared to those with PM<sub>2.5</sub> mean daily exposure < 63.5 µg/m<sup>3</sup> in 2005-06, fully adjusted HR of dementia was 2.04 (95% CI, 0.96 to 4.32) in participants with PM<sub>2.5</sub> ≥ 63.5 and < 64.5 µg/m<sup>3</sup>, and 2.14 (95%CI 1.00 to 4.56) in

PM<sub>2.5</sub>  $\geq$  64.5  $\mu\text{g}/\text{m}^3$ . In a sensitivity analysis excluding participants with dementia at wave 2, there remained significant association of PM<sub>2.5</sub> 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<sup>10,14,18-20</sup> from Sweden, four from Canada<sup>11,33-35</sup>, two each from Taiwan<sup>13,36</sup> and USA,<sup>18,32</sup> one each from UK<sup>12</sup> and Italy.<sup>31</sup> Of them eight were prospective cohorts<sup>10,14,18-20,31,32,35</sup> and seven retrospective cohorts<sup>11-13,17,33,34,36</sup>, 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<sup>11,12,31,35</sup> 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,<sup>10,13,14,18-20,32-36</sup> dispersion model<sup>20,31</sup> or Bayesian Maximum entropy model.<sup>17</sup> Ten studies measured PM<sub>2.5</sub> exposure<sup>12,13,17,18,20,31-35</sup>, six NO<sub>2</sub><sup>11,12,31,33,35,36</sup>, four NO<sub>x</sub><sup>10,18,20,31</sup>, five O<sub>3</sub><sup>11,12,13,33,31</sup>, one each for CO<sup>36</sup> and one PM<sub>10</sub><sup>31</sup>.

Thirteen studies diagnosed all types of dementia; five<sup>10,18-20,33</sup> used Diagnostic and Statistical Manual of Mental Disorders IV (DSM –IV), and eight<sup>11-13,31,32,34-36</sup> used ICD codes (ICD-9 or ICD-10), of which one<sup>31</sup> diagnosed AD further, one diagnosed AD and other AD<sup>35</sup> and three<sup>12,19,33</sup> diagnosed AD and VaD respectively. One study did not include all type of dementia for analysis but diagnosed AD<sup>13</sup>. One other study<sup>17</sup> 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<sup>13</sup> 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,<sup>31,32,35</sup> one used ICD-10 revision codes<sup>12</sup> and other two<sup>10,19</sup> made diagnosis from the senior geropsychiatrist through clinical futures. In diagnosing VaD, one study used ICD-9-CM,<sup>31</sup> one used ICD-10 revision codes,<sup>12</sup> and one<sup>19</sup> 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<sup>11,13,33,31,32,35,36</sup> 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<sup>34</sup> 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<sub>2.5</sub> (RR=1.11, 95%CI 1.06 to 1.17), CO (RR=1.60, 95%CI 1.39 to 1.84) and NO<sub>2</sub> (RR=1.14, 95%CI 1.03 to 1.27), but not significantly in exposure to PM<sub>10</sub> (RR=1.57, 95%CI 0.55 to 4.54), NO<sub>x</sub> (RR=1.13, 95%CI 0.96 to 1.33) and O<sub>3</sub> (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<sub>2.5</sub> (RR=1.12, 95%CI 1.05 to 1.19), CO (RR=1.36, 95%CI 1.08 to 1.70) and NO<sub>2</sub> (RR=1.09, 95%CI 1.00 to 1.17), non-significantly increased in PM<sub>10</sub> (RR=1.42, 95%CI 0.63 to 3.21) and NO<sub>x</sub> (RR=1.14, 95%CI 0.97 to 1.34), and no increased RR in O<sub>3</sub> (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<sub>2.5</sub> exposure, RR of dementia in the 2<sup>nd</sup> tertile (T2) was 1.06 (95%CI 1.03 to 1.10) and in the 3<sup>rd</sup> tertile (T3) 1.13 (95%CI 1.07 to 1.19). The corresponding figures in PM<sub>10</sub> 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<sub>2</sub> 1.06 (95%CI 1.03 to 1.09) and 1.18 (95%CI 1.10 to 1.28), in NO<sub>x</sub> 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<sub>3</sub> (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

0.95 to 1.28) from three studies (Figure 2). In each air pollutant analysis, no significant association with AD or VaD was found. There were no significant RRs of AD or VaD in the average-data analysis approach, and in the “dose-response” trend analysis, which were similar to those in [Figure 2](#).

## **DISCUSSION**

Our study including the new data from China and world-wide literature systematic review provides a novel insight into the impact of different air pollutants on the risk of dementia. The meta-analysis demonstrated a significant increase in the risk of dementia by around 13% in relation to overall AP exposure. The association of AP with dementia risk was relatively “dose-respondent” in exposure to PM<sub>2.5</sub>, PM<sub>10</sub>, NO<sub>2</sub> and NO<sub>x</sub>. CO exposure was significantly associated with increased risk of dementia, but O<sub>3</sub> exposure was not.

Over the past few years, there has been an increasing growth of interest in examining the impact of air pollution on dementia. Growing research from animal and laboratory studies<sup>44</sup> have shown a significant, positive association between exposure to AP and dementia. In an experimental study of rats exposed to diesel exhaust by inhalation over 4 weeks or a single intratracheal administration of diesel exhaust particles, Levesque et al<sup>45</sup> found that the diesel exhaust caused a microglial activation and up-regulation of oxidative stress, pattern recognition receptor, neurotoxic cytokines, and chemokines in the brain of the rat, all of which may be particularly relevant to the development of dementia. Power et al<sup>46</sup> examined the association between brain MRI findings and particulate matters exposures approximately 5 to 20 years prior to MRI in Americans and found that a higher level of long-term PM exposure was associated with smaller deep-gray volumes within the brain, which may be relevant to the 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,<sup>9</sup> 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.<sup>47</sup> In 2019, Peters et al<sup>48</sup> 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,<sup>48</sup> 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,<sup>18,20,31-33</sup> but others did not.<sup>12,17</sup> 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<sup>28</sup>). These need further investigation. Thirdly, some of original studies did not include important confounders for adjustment in the analysis; for example, seven studies<sup>11,13,31-33,35,36</sup>, were unable to adjust for smoking, of which four did not adjust educational level neither,<sup>11,31-33</sup> 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,<sup>49</sup> 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.<sup>50</sup>

#### *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<sup>12</sup> did not find a significant association between residential proximity to major roadways and incident dementia in UK population, Chen et al<sup>11</sup> and Cerza et al<sup>31</sup> found it in Canada and Italy populations, respectively. Nine cohort studies<sup>12,13,17,18,20,32-35</sup> examining the association between exposure PM<sub>2.5</sub> and incident dementia showed a HR range from 1.03 to 1.92, of which four<sup>13, 18, 34, 35</sup> were not statistically significant. Five cohort<sup>12,33,31,35,36</sup> studies examined association between NO<sub>2</sub> exposure and risk of dementia showed a HR range from 1.05 to 1.74, of which two studies<sup>31, 35</sup> were not significant and other one<sup>36</sup> only showed significance among exposure to the fourth quartile of NO<sub>2</sub>. While two studies<sup>20,31</sup> showed a significant linear association of NO<sub>x</sub> exposure with incident dementia, other four studies<sup>12,13,31,33</sup> examining the linear association between O<sub>3</sub> and incident dementia showed a HR range from 0.85 to 1.06, two<sup>12,33</sup> 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<sub>2.5</sub>, NO<sub>2</sub> and CO with incident dementia, although they used different methodologies in conducting the studies. Of four studies<sup>11,12,31,35</sup> examining the association between residential proximity to major roadways and incident dementia, three reported positive association<sup>11,31,35</sup>. Of nine studies<sup>12,13,17,18,20,32-35</sup> examining the association between PM<sub>2.5</sub> exposure and incident dementia, five reported positive association<sup>12,17,20,32,33</sup>. Of five studies<sup>12,33,31,35,36</sup> examining the association between NO<sub>2</sub> exposure and incident dementia, three reported positive association<sup>12,33,36</sup>. 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.<sup>49,51</sup> 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<sup>20, 52</sup>. 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<sup>28,39,53</sup>. 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<sup>10,14,18-20,31,35</sup>.

*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<sub>2.5</sub>, NO<sub>2</sub> and NO<sub>x</sub> 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 $\beta$  peptides<sup>45, 54, 55</sup>. 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<sup>45</sup>. Furthermore, animal studies found that the ultra-fine particle matter <0.1 $\mu$ m (UFPM) penetration into the olfactory bulb, the frontal cortical, and subcortical areas of the brain<sup>56,57</sup>, 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<sup>58</sup>.

The impact of PM<sub>2.5</sub> on cerebro-vascular risk factors and stroke may accelerate the development of dementia<sup>20,34</sup>. Evidence has been indicated that increased PM<sub>2.5</sub> damage to the

vascular endothelium, the dysregulation of the sympathetic nervous system; even moderate increases in PM<sub>2.5</sub> levels have been associated with impaired cerebrovascular hemodynamics, including increased cerebral resistance and reduced cerebral blood flow<sup>52, 59</sup>, and pathologically it has been shown that much dementia is associated with vascular diseases<sup>60</sup>.

*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<sup>51</sup>. 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<sup>61, 62</sup>. Therefore, exposure to AP, particularly to PM<sub>2.5</sub>, NO<sub>2</sub>, NO<sub>x</sub> 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<sup>63</sup>. 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<sup>55, 64-68</sup> 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<sup>57, 69</sup>. 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<sup>64, 65, 67,68</sup>. Pujol et al<sup>69</sup> conducted a MRI study of children aged 8-12 and found that higher exposure to PM<sub>2.5</sub> elemental carbon and NO<sub>2</sub> 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-1 $\alpha$  and TNF- $\alpha$ , Glial responses, and activation of NF- $\kappa$ B and AP-1 transcriptional factors in brain tissue<sup>70,71</sup>. In an animal study<sup>72</sup>, 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<sup>9,29</sup>. Tzivian et al<sup>73</sup> analysed the cross-sectional association of long-term exposure to AP and traffic noise with overall mild cognitive impairment (MCI) and amnesic MCI (aMCI) and non-amnesic MCI (naMCI) in Germany. They found that most air pollutants and traffic noise were associated with overall MCI and aMCI. Previous studies<sup>62,74</sup> showed that cigarette tobacco smoke have a negative impact on cognitive impairment, and increased incidence of clinically diagnosed dementia. Mukadam N et al<sup>75</sup> 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.<sup>76,77</sup>

### ***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,<sup>78</sup> the global economy would be worse without reducing dementia. Due to having no effective treatment for dementia, its prevention become the utmost 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  $10\mu\text{g}/\text{m}^3$   $\text{PM}_{2.5}$  to reduce harm to health,<sup>79</sup> but at present 91% of the world's population resides in areas that exceed these recommendations.<sup>80</sup> 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<sub>2.5</sub>, PM<sub>10</sub>, CO, NO<sub>2</sub> and NO<sub>x</sub>, but not from O<sub>3</sub>. Overall AP exposure is a potential modifiable risk factor for dementia. Globally reducing AP would minimize dementia burden.

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**Table 1. Number, rate and hazard ratio (HR) of incident dementia in older people exposed to PM<sub>2.5</sub>: the Anhui cohort study**

PM <sub>2.5</sub> (µg/m <sup>3</sup> ) ‡	Participants		Model 1		Model 2		Model 3	
	All	Dementia (n, %)*	HR (95% CI) <sup>1</sup>	P	HR (95% CI) <sup>2</sup>	P	HR (95% CI) <sup>2</sup>	P
<b>Whole cohort</b>								
< 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
<b>Sensitivity analysis<sup>#</sup></b>								
< 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

‡ using China national mean of PM<sub>2.5</sub> (61 µg/m<sup>3</sup>)<sup>80</sup> and the distribution of our Anhui cohort PM<sub>2.5</sub> data we took PM<sub>2.5</sub> < 63.5 µg/m<sup>3</sup> as a cut-off point for analysis, and then above it there were two groups of PM<sub>2.5</sub> < 64.5 µg/m<sup>3</sup> and >= 64.5 µg/m<sup>3</sup> which had approximate equal number of participants.

\* Chi-square test p < 0.001 for incident rate across three levels of PM<sub>2.5</sub> 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.

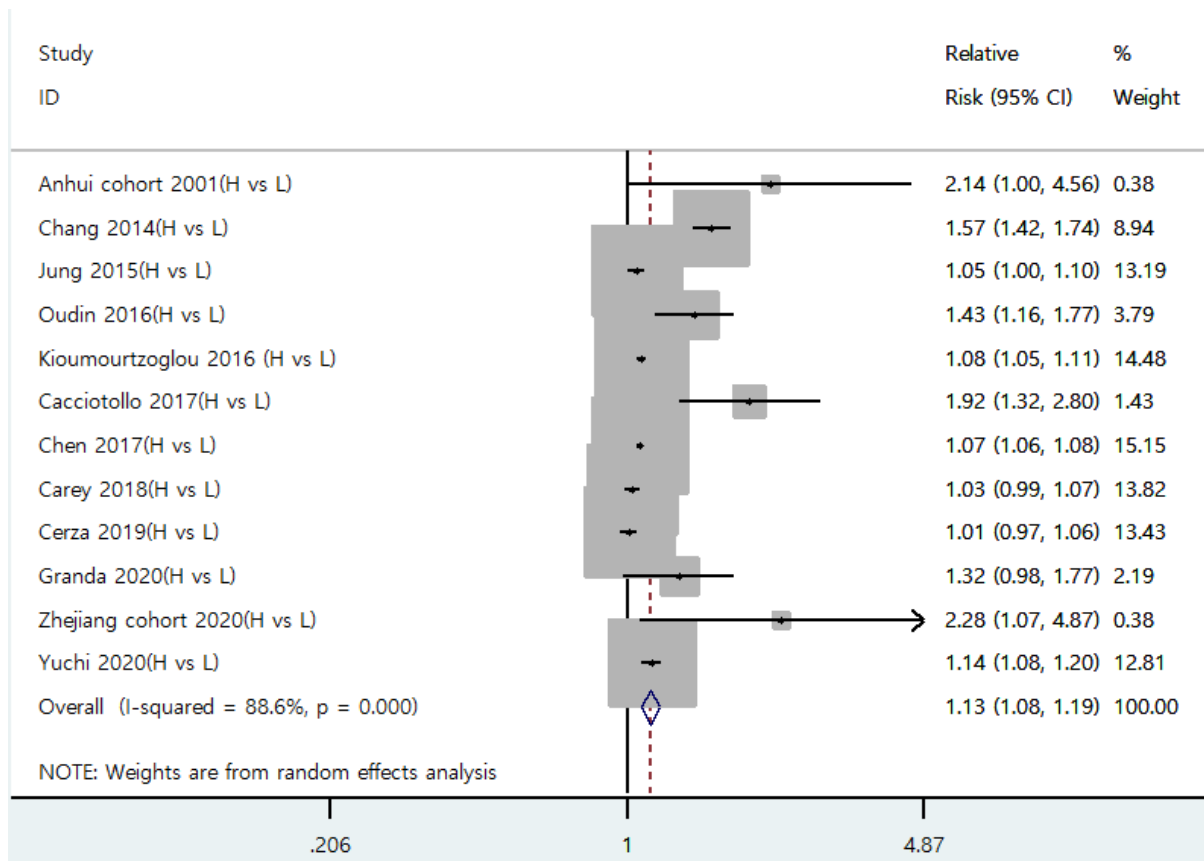
Model 3: adjusted for age (cont.), sex, education level, income, smoking, drinking alcohol, BMI (category), walking or group touring, marital status, living with, hypertension, hypercholesterolemia, diabetes, heart disease, stroke, depression, and Instrumental Activities of Daily Living (ADL group).

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

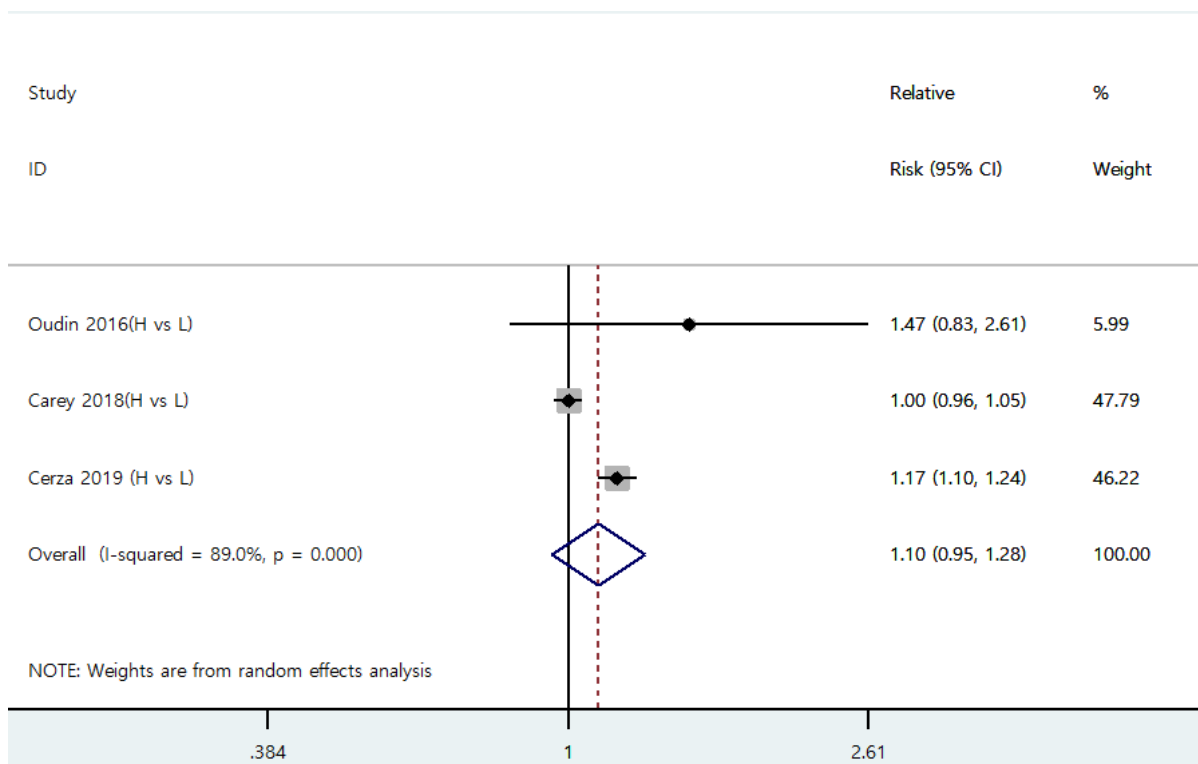
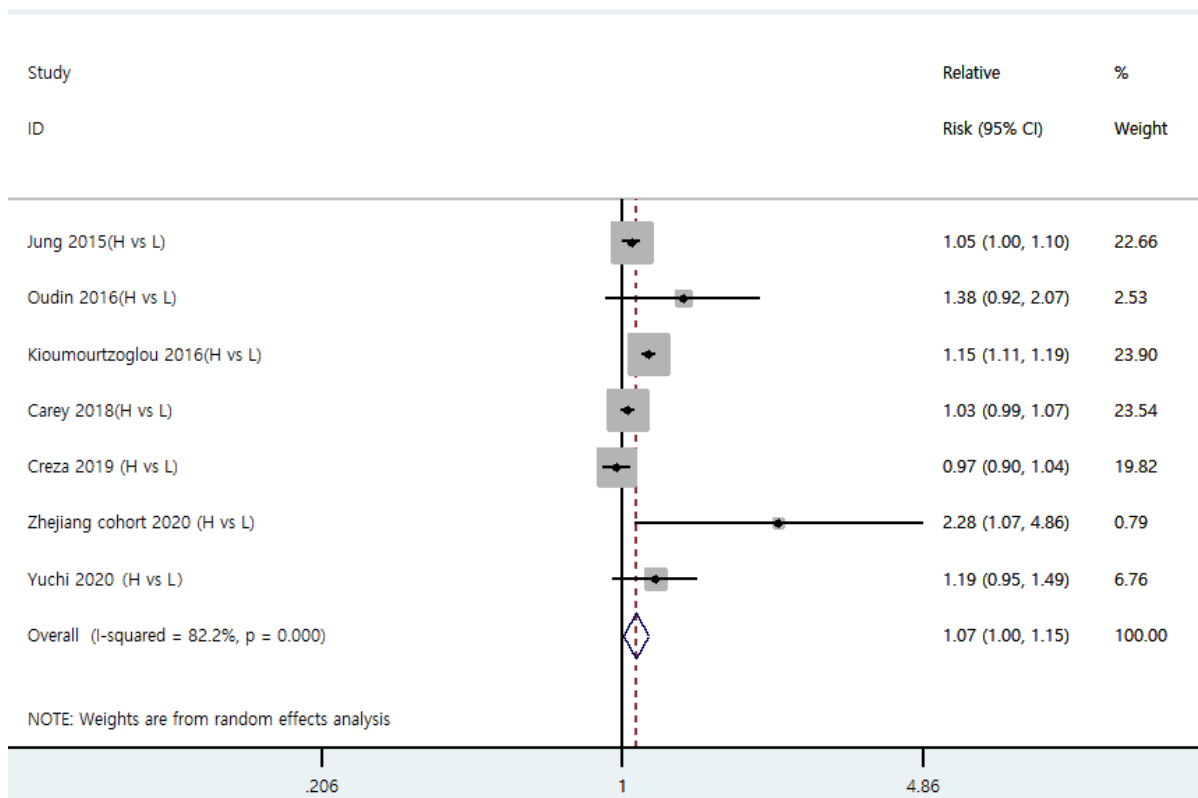
Study ID	Air pollutants								Comprehensive AP <sup>#</sup>	Pooled RR
	PM <sub>2.5</sub>	PM <sub>10</sub>	NO <sub>2</sub>	NO <sub>x</sub>	O <sub>3</sub>	CO	SO <sub>2</sub>	Coarse PM		
Chang et al [36]			√			√			Pooled	1.57(1.42-1.74)
Jung et al [13]	√					√			Pooled	1.05(1.00-1.10) <sup>a</sup>
Oudin 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)
<b>Overall RR</b>										<b>1.13(1.08-1.19)</b>
Publication bias for overall RR (Egger's test)										0.059

a, fixed effect

<sup>#</sup> 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 <sub>2.5</sub> (n=11)	PM <sub>10</sub> (n=2)	CO (n=2)	NO <sub>2</sub> (n=6)	NO <sub>x</sub> (n=3)	O <sub>3</sub> (n=5)
Chang et al <sup>[36]</sup>			1.61(1.39-1.85)	1.54(1.34-1.77)		
Jung et al <sup>[13]</sup>	1.03(0.95-1.11)					1.06(1.00-1.12)
Oudin et al <sup>[10, 18]</sup>	1.34(1.04-1.74) <sup>a</sup>				1.60(1.02-2.10)	
Kioumourtzoglou et al <sup>[32]</sup>	1.08(1.05-1.11)					
Cacciottolo et al <sup>[17]</sup>	1.92(1.32-2.80)					
Grande et al <sup>[20]</sup>	1.54(1.33-1.78)				1.14(1.01-1.29)	
Cerza et al <sup>[31]</sup>	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 <sup>[11, 33]</sup>	1.04(1.03-1.05)			1.10(1.08-1.12)		0.98(0.96-1.00)
Carey et al <sup>[12]</sup>	1.06(0.99-1.13)			1.13(0.99-1.28)		0.87(0.76-1.01)
Yuchi et al <sup>[35]</sup>	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	<b>1.11(1.06-1.17)</b>	<b>1.57(0.55-4.54)</b>	<b>1.60(1.39-1.84)<sup>a</sup></b>	<b>1.14(1.03-1.27)</b>	<b>1.13(0.96-1.33)</b>	<b>1.01(0.95-1.07)</b>

<sup>a</sup>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 <sub>2.5</sub> (n=11)	PM <sub>10</sub> (n=2)	CO (n=3)	NO <sub>2</sub> (n=6)	NO <sub>x</sub> (n=3)	O <sub>3</sub> (n=5)
Chang et al <sup>[36]</sup>	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 <sup>[13]</sup>	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 <sup>[10, 18]</sup>	T2 vs T1 exposure	1.08(0.76-1.54)				1.31(1.01-1.70) <sup>a</sup>	
	T3 vs T1 exposure	1.32(1.07-1.63)				1.60(1.02-2.10)	
Kioumourtzoglou et al <sup>[32]</sup>	T2 vs T1 exposure	1.06(1.04-1.09)					
	T3 vs T1 exposure	1.10(1.07-1.13)					
Cacciottolo et al <sup>[17]</sup>	T2 vs T1 exposure	1.47(1.18-1.85)					
	T3 vs T1 exposure	2.46(1.47-4.14)					
Grande et al <sup>[20]</sup>	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 <sup>[31]</sup>	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 <sup>[11, 33]</sup>	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 <sup>[12]</sup>	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 <sup>[35]</sup>	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		<b>1.06(1.03-1.10)</b>	<b>1.05(0.86-1.29)</b>	<b>1.69(0.72-3.93)</b>	<b>1.06(1.03-1.09)</b>	<b>1.09(1.04-1.15)</b>	<b>0.99(0.97-1.01)<sup>b</sup></b>
Overall RR in T3		<b>1.13(1.07-1.19)</b>	<b>1.62(0.60-4.36)</b>	<b>1.52(1.35-1.71)</b>	<b>1.18(1.10-1.28)</b>	<b>1.26(1.13-1.41)</b>	<b>0.97(0.94-1.01)<sup>b</sup></b>

<sup>a</sup> fixed model, <sup>b</sup> fixed model.

\*the cut-off points for three groups in each air pollutant exposure were the same as our recently published paper<sup>28</sup>.

## Supplementary Content

### Methods of Zhejiang cohort study

**eTable 1.** Characteristics of Anhui cohort participants

**eTable 2.** Association of AQI with Alzheimer's Disease in Zhejiang cohort participant

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**eTable 5. RR in each studied population used for estimating the pooled RR of specific air pollutant (average) and dementia**

**eFigure 1.** PRISMA 2009 flow diagram for the review on the association between air pollution and the risk of dementia

e Figure 2. Forest plot for the RR of all dementia in average air pollution exposure.

### *Methods of Zhejiang cohort study*

The methods of studied population, baseline survey and follow-up have been fully described in our previous papers.<sup>28,29</sup> Briefly, in 2014 the Zhejiang Major Public Health Surveillance (ZJMPHS) Program was set up to recruit a random sample of 9353 residents aged  $\geq 60$  years from six counties in Zhejiang province, China. The participants were interviewed by local community general practitioners in the community hospital or at home to record socio-demographic characteristics, lifestyles, disease histories, risk factors and dietary intakes. Each participant completed a Chinese version Mini-Mental State Examination (MMSE) to assess cognitive impairment (CoI). 1406 participants were identified to have CoI. In 2015 and 2016, 8598 surviving cohort members were re-interviewed using the same questionnaires as those at baseline.<sup>28</sup> In 2019, we re-examined 6115 surviving cohort members using the same questionnaires as those in the baseline. Additionally, the general practitioners or neurologists examined all participants with CoI to diagnose Alzheimer's Disease (AD) using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association-Alzheimer's Criteria (NINCDS-ADRDA). In total 986 participants were diagnosed with AD. We collected data of 2013-2015 atmospheric environmental monitoring from the Department of Ecology and Environment of Zhejiang Province and assigned the daily mean of air pollutants (including  $PM_{2.5}$  ( $\mu g/m^3$ ),  $PM_{10}$  ( $\mu g/m^3$ ),  $SO_2$  ( $\mu g/m^3$ ),  $NO_2$  ( $\mu g/m^3$ ),  $CO$  ( $mg/m^3$ ) and  $O_3$  ( $\mu g/m^3$ )) within the same county in which the ZJMPHS participants lived. Based on the level of the six air pollutants we calculated the Air Quality Index (AQI) for the participants<sup>1</sup>. We took the three years averaged concentration of AP and divided participants into three groups at low, middle, and high levels of AQI and air pollutant exposure for baseline data analysis according to our previous study.<sup>1,2</sup> We employed

multi-level binary logistic regression models to calculate odds ratio (OR) and its 95% confidential intervals of AD in relation to AP exposure.

**eTable 2. Characteristics of Anhui cohort participants**

Variable	All participants		Non-Dementia		Dementia		P
	N=1402 (%)		n= 1293 (%)		n=109 (%)		
<b>Age (years)</b>	71.55	5.74	71.38	5.68	73.46	6.19	<0.001
mean (SD)							
<b>Sex (n, %)</b>							
Men	801	57.1	747	57.8	54	49.5	0.095
Women	601	42.9	546	42.2	55	50.5	
<u>Socio-economic status</u>							
<b>Educational level</b>							
High secondary school +	678	48.4	645	49.9	33	30.3	<0.001
Secondary school	381	27.2	355	27.5	26	23.9	
Primary school	343	24.5	293	22.7	50	45.9	
<b>Income</b>							
Very satisfactory	239	17.0	214	16.6	25	22.9	0.400
Satisfactory	935	66.7	867	67.1	68	62.4	
Average	189	13.5	176	13.6	13	11.9	
Poor	39	2.8	36	2.8	3	2.8	
<u>Lifestyles</u>							
<b>Smoking over the last 2 years</b>							
No	964	68.8	892	69.0	72	66.1	0.526
Yes	438	31.2	401	31.0	37	33.9	
<b>Alcohol drinking in the last 2 years</b>							
No	1113	79.4	1023	79.1	90	82.6	0.392
Occasionally/often	289	20.6	270	20.9	19	17.4	
<b>BMI (kg/m<sup>2</sup>)<sup>@</sup></b>							
<20 kg/m <sup>2</sup>	159	11.3	141	10.9	18	16.5	0.228
20 < 23 kg/m <sup>2</sup>	431	30.7	395	30.5	36	33.0	
23 < 26 kg/m <sup>2</sup>	468	33.4	438	33.9	30	27.5	
≥ 26 kg/m <sup>2</sup>	344	24.5	319	24.7	25	22.9	
<b>Walking or group touring</b>							
Yes	1069	76.2	993	76.8	76	69.7	0.096
No	333	23.8	300	23.2	33	30.3	
<u>Social network and support</u>							
<b>Marital Status</b>							
Married	1155	82.4	1075	83.1	80	73.4	0.035
Widowed	233	16.6	206	15.9	27	24.8	
Divorced/never married	14	1.0	12	0.9	2	1.8	
<b>Living with</b>							
Someone	1317	93.9	1219	94.3	98	89.9	0.066
No-one	85	6.1	74	5.7	11	10.1	
<u>Cardiovascular risk factors</u>							
<b>Hypertension</b>							
No	569	40.6	528	40.8	41	37.6	0.511
Yes	833	59.4	765	59.2	68	62.4	
<b>Hypercholesterolemia</b>							
No	1203	85.8	1104	85.4	99	90.8	0.184
Yes	185	13.2	175	13.5	10	9.2	
Unknown*	14	1.0	14	1.1	0	0.0	
<u>Comorbidities</u>							
<b>Heart disease</b>							
No	1093	78.0	1013	78.3	1093	73.4	0.254
Yes	301	21.5	273	21.1	301	25.7	
Unknown*	8	0.6	7	0.5	8	0.9	
<b>Stroke</b>							
No	1354	96.6	1249	96.6	105	96.3	0.815

Yes	46	3.3	42	3.2	4	3.7	
Unknown*	2	0.1	2	0.2	0	0.0	
<b>Diabetes</b>							
No	1273	90.8	1173	90.7	100	91.7	0.758
Yes	127	9.1	118	9.1	9	8.3	
Unknown*	2	0.1	2	0.2	0	0.0	
<b>Depression (GMS-AGECAT)</b>							
Non-depression	1327	94.7	1225	94.7	102	93.6	0.159
Subcase	44	3.1	42	3.2	2	1.8	
Cases	31	2.2	26	2.0	5	4.6	
<b>Activity of daily living (score)†</b>							
0	1276	91.0	1184	91.6	92	84.4	0.042
1-4	76	5.4	66	5.1	10	9.2	
≥5	50	3.6	43	3.3	7	6.4	

\*P - value in the  $\chi^2$  test was calculated based on available data, not including these “missing” data. also, if applicable for small data, Fisher exact test was used for P value.

@ Most suitable cutting-off points for older age adiposity in Chinese<sup>23</sup>

† the higher score, the lower ADL.

**eTable 2. Association of AQI with Alzheimer’s Disease in Zhejiang cohort participants**

AQI (unit)	Participants			Model 1			Model 2			Model 3		
	All	AD#	(%)*	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Level 1 (<=80)	2899	344	11.9	1.00						1.00		
Level 2 (80-90)	909	145	16.0	1.86	0.76 - 4.51	0.172	1.71	0.66 - 4.44	0.272	1.71	0.65 - 4.48	0.276
Level 3 (>90)	2307	497	21.5	2.42	1.20 - 4.87	0.013	2.28	1.07 - 4.83	0.032	2.28	1.07 - 4.87	0.033

# 986 older people with AD versus those without AD were more likely to be illiterate, high income, smoking, but less likely to drink alcohol, be overweight, have environmental tobacco smoke (ETS) exposure, and suffer from hyperlipidemia and stroke at baseline. There were no significant differences in consumptions of fish and vegetables, doing exercise, having hypertension, diabetes, ischemic heart disease, Parkinson’s disease, depression and family history of dementia between participants with and without AD. The details shown in published paper.<sup>31</sup>

\*Chi - square test in AQI,  $p < 0.001$ .

Model 1: adjusted for age, sex, education and economic status.

Model 2: adjusted for age, sex, education, economic status, BMI (category), smoking, drinking, exercise, vegetable consumption, and fish/shrimp consumption.

Model 3: adjusted for age, sex, education, economic status, BMI (category), smoking, ETS, drinking, exercise, vegetable consumption, fish/shrimp consumption, hypertension, hyperlipidemia, diabetes, stroke, ischemic heart disease, Parkinson’s disease, depression and family history of dementia.

**eTable 3. Characteristics and findings of 14 cohort studies identified in the comprehensive systematic review**

First author (publication year); place of study	Study type; Duration (if applicable)	Total sample size (%female) Age range (mean age; <i>SD</i> ) Exclusion criteria	Air Pollution data source; modelling; Statistical comparison	Dementia type and diagnostic tool;	Controlled covariates	Findings
<b>Chang et al</b> (2014) <sup>[36]</sup> ; Taiwan	Retrospective cohort study (12 years)	29,547 (54%); ≥50 years; (61.4 ± 8.5 years).  Exclusion criteria: present with a history of head injury, stroke, and dementia before 2000.	Database of NO <sub>2</sub> and CO from Taiwan Environmental Protection Administration, 1998-2010.  Individual pollutant exposure from monitoring station in the residential district of the clinic were participants most frequently sought treat for upper respiratory infections.  Quartiles of exposure with Q1 being the lowest level.	Dementia, VaD or AD according to National Health Insurance Research Database (ICD - 9). N=1,720	Age, sex, monthly income, diabetes, hypertension, ischemic heart disease, COPD, alcoholism, and urbanization.	NO <sub>2</sub> : HR at Q2, Q3 and Q4 was 1.10 (0.96 - 1.26); 1.01 (0.87 - 1.17); and 1.54 (1.34 - 1.77)  CO: HR at Q2, Q3 and Q4 was 1.07 (0.92 - 1.25); 1.37 (1.19 - 1.58); 1.61 (1.39 - 1.85).  RR of dementia for highest vs lowest level of overall air pollution was 1.57 (1.42 - 1.74) <sup>a</sup> .
<b>Jung et al</b> (2015) <sup>[13]</sup> ; Taiwan	Retrospective cohort study (10 years)	95,690 (46%); ≥65 years (mean not given);  Exclusion criteria: had experienced AD prior to baseline	Ozone and PM <sub>2.5</sub> 1 year prior to baseline were obtained from Taiwan Environmental Protection Agency, 2000 - 2010  Exposure model: inverse distance weighting (IDW) model Increase in IQR of exposure	AD according to National Health Insurance Research Database (ICD - 9) N=1,399	Age, gender, income, diabetes mellitus, hypertensive disease, myocardial infarction, stroke, asthma and COPD	Ozone: HR for per 9.63 ppb increase was 1.06 (1.00, 1.12)  PM <sub>2.5</sub> : HR for per 13.21 μg/m <sup>3</sup> increase was 1.03 (0.95 - 1.11).  RR of AD for highest vs lowest level of overall air pollution was 1.05 (1.00 - 1.10) <sup>b</sup>
<b>Oudin et al</b> (2016) <sup>[10]</sup> ; Northern Sweden (Betula Study)	Prospective cohort study (15 years)	1806 (57%); ≥55 years (mean not given)  Exclusion criteria: Participants who had previously received a dementia diagnosis were excluded	Annual mean NO <sub>x</sub> levels at the residential address at baseline estimated by land - use regression model  Quartiles of exposure (Q1 4.8–9; Q2 9–17; Q3 17–26; Q4 ≥26 μg/m <sup>3</sup> )	AD and VaD evaluated by neuropsychiatrists according to DSM - IV and clinical information N=302(191 AD and 111 VaD)	Age, sex, education, physical activity, smoking status, alcohol consumption, BMI, WHR, APOE - ε4, baseline history of diabetes, stroke and hypertension	Dementia: HR at Q2, Q3 and Q4 was 1.13 (0.77 - 1.66); 1.49 (1.04 - 2.14); and 1.60 (1.02 - 2.10). Per 10 μg/m <sup>3</sup> : 1.05 (0.98 - 1.12).  RR of dementia for highest vs lowest level of overall air pollution was 1.43 (1.16 - 1.75) <sup>d</sup> .

						<p>Sensitivity analysis excluding those examined only once (after 5 years):</p> <p>AD: HR at Q2, Q3 and Q4 was 1.15 (0.72 - 1.86); 1.51 (0.96 - 2.37); and 1.38 (0.97 - 2.19). Per 10 µg/m<sup>3</sup>: 1.05 (0.97 - 1.15)</p> <p>VaD: HR at Q2, Q3 and Q4 was 1.15 (0.62 - 2.11); 1.46 (0.83 - 2.61); and 1.47 (0.83 - 2.61). per 10 µg/m<sup>3</sup>: 1.02 (0.92 - 1.14).</p>
<b>Andersson et al</b> (2018) <sup>[14]</sup> ; Sweden (Betula Study)	As above	<p>1721 (42%); 55 - 85 years (68.5 ±9.4 years)</p> <p>Exclusion criteria: participants who were diagnosed with any subtype of dementia other than VaD or AD were excluded.</p>	As above	As above	As above plus traffic noise	<p>Dementia: HR at Q2, Q3 and Q4 was 1.14 (0.78 - 1.67); 1.48 (1.03 - 2.12); and 1.41 (0.97 - 2.03)</p>
<b>Oudin et al</b> (2018) <sup>[18]</sup> ; Sweden (Betula Study)	As above	<p>1806 (57%). 55 - 85 (mean not given)</p> <p>Exclusion criteria: air pollution data not available</p>	<p>Annual mean concentrations of PM<sub>2.5</sub> from residential wood burning and from traffic exhaust obtained from Swedish Meteorological and Hydrological Institute</p> <p>Exposure model: wind model and a Gaussian air quality dispersion model</p> <p>Quartiles of exposure:</p> <p>Wood burning Q1 0.21 - 0.54; Q2 0.54 - 0.72; Q3 0.72 - 0.91; Q4 0.91 - 3.34 µg/m<sup>3</sup>.</p>	As above	Physical activity, smoking, sex, BMI, WHR, alcohol consumption and age	<p>Residential wood burning: HR at Q2, Q3 and Q4 was 0.88 (0.61 - 1.25); 0.87 (0.60 - 1.26); and 1.29 (0.91 - 1.83)</p> <p>Risk with increase of 1 µg/m<sup>3</sup> was 1.55 (1.00 - 2.41)</p> <p>Vehicle exhaust: HR at Q2, Q3 and Q4 was 1.02 (0.68 - 1.52); 1.66 (1.16 - 2.39); and 1.41 (0.97 - 2.04)</p> <p>HR with increase of 1 µg/m<sup>3</sup> was 1.14 (0.59 - 2.23)</p>

			Vehicle exhaust Q1 0.017 - 0.086; Q2 0.086 - 0.14; Q3 0.14 - 0.24; Q4 0.24 - 1.81 $\mu\text{g}/\text{m}^3$ .  Increase of 1 $\mu\text{g}/\text{m}^3$			
Oudin et al, (2019) <sup>[19]</sup> ; Sweden (Betula Study)	As above	1567 (56%); 55 - 85 years (mean not given)	Annual mean NO <sub>x</sub> levels at the residential address at baseline estimated by land - use regression model  Quartiles of exposure (Q1 4.8 – 9.0; Q2 9.0 – 17.0; Q3 17.0 – 26.0; Q4 $\geq$ 26 $\mu\text{g}/\text{m}^3$ )	AD and VaD evaluated by geropsychiatrists according to DSM - IV and clinical information N=275(173 AD and 102 VaD)	Age, sex, education, physical activity, smoking status, alcohol consumption, BMI, WHR.	Dementia: Risk at Q2, Q3 and Q4 was 1.11 (0.77 - 1.59); 1.52 (1.08 - 2.12); and 1.41 (1.01 - 1.98); linear 1.04 (0.96 - 1.13)  AD: Risk at Q2, Q3 and Q4 was 1.25 (0.79 - 1.98); 1.72 (1.12 - 2.65); and 1.53 (0.99 - 2.36); linear: 1.04 (0.96 - 1.13).
<b>Kioumourtzoglou et al (2016)</b> <sup>[32]</sup> ; USA	Prospective cohort study (11 years)	9.8 million fee-for-service Medicare enrollees aged $\geq$ 65 years (75.6 $\pm$ 7.6) from 50 cities across the northeastern United States	Annual PM <sub>2.5</sub> average within each city for the period of 1999-2000. Increase of 1 $\mu\text{g}/\text{m}^3$	AD and Dementia using codes from the ICD-9-CM; N=266725(AD) N=203463(Dementia)	Previous admission for CHF, COPD, MI, or diabetes and number of days spent in intensive and coronary care units; ZIP-code level median income for Social economic status, age, sex, race and follow-up years	HR for AD: 1.15(1.11-1.19); HR for dementia: 1.08(1.05-1.11)
<b>Cacciottolo et al (2017)</b> <sup>[17]</sup> ; USA, (WHIMS)	Retrospective cohort study (11 years)	3,647 (100%) 65 - 79 years (mean not given)  Exclude criteria: excluded participants with $\epsilon$ 2/2, $\epsilon$ 2/3 or $\epsilon$ 2/4 allele and participants with missing PM <sub>2.5</sub> data.	Average PM <sub>2.5</sub> at residential address estimated from spatiotemporal models 1999 – 2010  High (>12 $\mu\text{g}/\text{m}^3$ ) versus low exposure	All cause dementia obtained from annual screening with clinical data and 3MS. N=173	Age, geographic region, education, income, employment status, lifestyle factors (smoking; alcohol use; physical activities) and clinical characteristics (use of hormone treatment; depression; body mass index; hypercholesterolemia; hypertension, diabetes;	HR: PM <sub>2.5</sub> 1.92 (1.32 - 2.80)

					and histories of cardiovascular disease)	
<b>Chen et al (2017a)</b> <sup>[11]</sup> ; Ontario, Canada (ONPHEC)	Retrospective cohort study (16 years)	2,165,268 (53%); 55 - 85 years (66.8 ± 8.2 years)  Exclude criteria: participants who had diagnosis of dementia prior to baseline.	Residential proximity to major roadways or highways based on 6 - character postal - code addresses 5 years before cohort inception Less than 50m, 50–100m, 101–200m, 201–300m, >300m	Dementia obtained from Canadian Institute for Health Information, Ontario Health Insurance Plan database and Ontario Drug Benefits programme databases N=243,611	Age, sex, pre - existing comorbidities (traumatic brain injury, diabetes, hypertension, stroke, coronary heart disease, congestive heart failure, and arrhythmia), and neighbourhood, socioeconomic status	HR at <50m 1.07 (1.06 – 1.08); 50 - 100m 1.04 (1.02 – 1.05); 101 - 200m 1.02 (1.01 – 1.03); 201-300m 1.00 (0.99 – 1.01); >300m REF.
<b>Chen et al (2017b)</b> <sup>[33]</sup> ; Ontario, Canada (ONPHEC)	Retrospective cohort study (12 years)	2,066,639 (53%); 55 - 85 years (66.8 years)  Exclude criteria: participants who had diagnosed as dementia, Parkinson's disease, or multiple sclerosis at baseline	Annual mean concentration of PM <sub>2.5</sub> estimated from geographically weighted regression NO <sub>2</sub> exposure were estimated from land use regression model O <sub>3</sub> exposure estimated from optimal interpolation technique Increase in IQR of exposure (4.8µg/m <sup>3</sup> ; 14.2ppb; 6.3ppb respectively)	Dementia obtained from health administrative data. N=257,816	Age, sex, stratified region, pre - existing comorbidities (traumatic brain injury, diabetes, hypertension, stroke, coronary heart disease, congestive heart failure, and arrhythmia), neighbourhood socioeconomic status, area of residency	HR: PM <sub>2.5</sub> 1.04 (1.03 - 1.05) NO <sub>2</sub> 1.10 (1.08 - 1.12) O <sub>3</sub> 0.98 (0.96 - 1.00)
<b>Carey et al (2018)</b> <sup>[12]</sup> ; UK	Retrospective cohort study (Mean 7 years)	130,978 (50.3%); 50 - 79 years (mean not given)  Exclude criteria: participants with an existing diagnosis of dementia by 1 January 2005.	Annual concentrations in 2004 of NO <sub>2</sub> , PM <sub>2.5</sub> and O <sub>3</sub> based on interpolation from the closest 20×20 m point of the dispersion model; distance to nearest major road.  Increase in IQR of exposure (7.47 µg/m <sup>3</sup> , 0.95 µg/m <sup>3</sup> , 5.56 µg/m <sup>3</sup> , respectively); decrease in IQR of distance (310m)	AD, VaD and non - specified dementia obtained from primary care records. N=2181, (848 AD, and 747 VaD)	Age, sex, ethnicity, smoking, alcohol consumption, BMI, Index of Multiple Deprivation, comorbidities (ischaemic heart disease, stroke, diabetes, heart failure) and night - time traffic noise	HR for Dementia: NO <sub>2</sub> 1.15 (1.04 - 1.28); PM <sub>2.5</sub> 1.06 (1.01 - 1.13); O <sub>3</sub> 0.85 (0.76 - 0.96); Distance 1.00 (0.95 - 1.05) HR for AD: NO <sub>2</sub> 1.23 (1.07 - 1.43); PM <sub>2.5</sub> 1.10 (1.02 - 1.18); O <sub>3</sub> 0.78 (0.66 - 0.92); Distance 1.03 (0.99 - 1.07) HR for VaD: NO <sub>2</sub> 1.15 (0.96 - 1.39); PM <sub>2.5</sub> 1.06 (0.97 - 1.16); O <sub>3</sub>

						0.88 (0.71 - 1.09); Distance 1.00 (0.96 - 1.05)
<b>Ilango et al (2019)</b> <sup>[34]</sup> ; Ontario, Canada	Retrospective cohort study (12 years)	34,391 (58%), over 50 years (60.2±10.6);  Exclude criteria: participants who were diagnosed as dementia at baseline.	Annual mean concentration of PM <sub>2.5</sub> estimated from geographically weighted regression  NO <sub>2</sub> exposure were estimated from land use regression model. Increase in 10µg/m <sup>3</sup> and 5 - ppb, respectively for PM <sub>2.5</sub> and NO <sub>2</sub>	Dementia obtained from health administrative data. N=2,559	age, sex, education, marital status, income quintile, smoking status, BMI, physical activity, rural residence and Northern region and neighbourhood - level percentages of recent immigrants, income quintile, unemployment and less than high school education.	HR for dementia: NO <sub>2</sub> 1.10 (0.99 - 1.19); PM <sub>2.5</sub> 1.29 (0.99 - 1.64)
<b>Cerza et al (2019)</b> <sup>[31]</sup> ; Roma longitudinal study	Prospective cohort study (12 years)	350,844 (58.4%); 65 - 100 years (74.5±6.8) years.  Exclude criteria: participants who had diagnosed as dementia at baseline.	Annual mean PM <sub>2.5</sub> , PM <sub>10</sub> , NO <sub>2</sub> , NO <sub>x</sub> at each site estimated by land - use regression model.  Summer daily O <sub>3</sub> exposure estimated by the Flexible Air quality Regional Model.  Residential proximity to the nearest high - traffic road measured by ArcGIS software.  Increase in unit of exposure (PM <sub>10</sub> 10µg/m <sup>3</sup> , Coarse PM 5 µg/m <sup>3</sup> , PM <sub>2.5</sub> 5µg/m <sup>3</sup> , NO <sub>2</sub> 10ug/m <sup>3</sup> , NO <sub>x</sub> 20ug/m <sup>3</sup> , O <sub>3</sub> 10ug/m <sup>3</sup> 5.6ppb respectively); Less than 50m, 50–100m, 101–200m, 201–300m, >300m	AD, VaD and senile dementia according to the Hospital Discharge Registry (ICD - 9 - CM). N=21548 (VaD 7497, AD 7669)	age, education, place of birth, marital status, area - based socioeconomic position with baseline hazard function stratified by sex	Dementia: PM <sub>10</sub> 1.00 (0.98 - 1.03); Coarse PM 0.98 (0.96 - 1.02); PM <sub>2.5</sub> 1.00 (0.98 - 1.03); NO <sub>2</sub> 0.97(0.96 – 0.99); NO <sub>x</sub> 1.01 (1.00 - 1.02); O <sub>3</sub> 1.06 (1.03 - 1.08); Risk at <50m 1.01(0.97 - 1.06); 50 -100m 0.98 (0.93 - 1.02); 101 - 200m 0.99 (0.95 - 1.03); 201 - 300m 1.00 (0.95 - 1.04); >300m REF  VaD: PM <sub>10</sub> 1.06 (1.02 - 1.10); Coarse PM 1.06 (1.03 - 1.09); PM <sub>2.5</sub> 1.07 (1.01 - 1.12); NO <sub>2</sub> 1.05 (1.03 - 1.07); NO <sub>x</sub> 1.08 (1.06 - 1.10); O <sub>3</sub> 1.02 (0.986 - 1.06); Risk at <50m 1.17 (1.10 - 1.24); 50 -100m 1.11 (1.03 - 1.17); 101 - 200m 1.10(1.03 - 1.17); 201 - 300m 1.02 (0.94 -1.09); >300m REF.  AD: PM <sub>10</sub> 0.95 (0.91 - 0.99); Coarse PM 0.91 (0.87 - 0.94);

						PM <sub>2.5</sub> 0.91 (0.85 - 0.97); NO <sub>2</sub> 0.91 (0.89 - 0.94); NO <sub>x</sub> 0.96 (0.94 - 0.98); O <sub>3</sub> 0.98 (0.95 - 1.02); Risk at <50m 0.97 (0.90 - 1.04); 50 - 100m 0.96 (0.89 - 1.04); 101 - 200m 0.99 (0.92 - 1.05); 201 - 300m 1.00 (0.93-1.08); >300m REF.
<b>Grande et al (2020)</b> <sup>[20]</sup> ; Sweden	Prospective study (12 years, mean followed up 6.01 years)	2927 (63.0%); over 60 years (74.1±10.7). Exclude criteria: participants with missing data at baseline, only participate baseline assessment and have diagnosed as dementia as baseline	Annual mean of M <sub>2.5</sub> and NO <sub>x</sub> were estimated using Gaussian dispersion model.  Increase in 0.88 µg/m <sup>3</sup> and 8.35 µg/m <sup>3</sup> , respectively, for PM <sub>2.5</sub> and NO <sub>x</sub> .	Dementia diagnosis in according with DSM - IV. N= 364	Age, sex, educational attainment, smoking, physical inactivity, socioeconomic status, early retirement, BMI, depression, baseline Mini - Mental State Examination score, and cardiovascular risk factors.	HR for dementia: PM <sub>2.5</sub> 1.54 (1.33 - 1.78); NO <sub>x</sub> 1.14 (1.01 - 1.29). RR of dementia for highest vs lowest level of overall air pollution was 1.32 (0.98 - 1.77) <sup>d</sup>
<b>Yuchi et al (2020)</b> <sup>[35]</sup> ; Canada	Prospective study (4 year)	Comprised of 7.3 and 7.4 million person-years of observations. Include criteria: all adults aged 45–84 years old who resided in Metro Vancouver, or had lived in Metro Vancouver. Exclude criteria at baseline: Individuals who had a diagnosis of non-Alzheimer’s dementia (NAD), AD, Parkinson’s disease (PD) and multiple sclerosis at baseline were excluded	Residential proximity to highways or major road: major road =<50m or highway=<150m major road >50m or highway>150m;  Increase interquartile range of exposure: for NAD, PM <sub>2.5</sub> , 1.54 ug/m <sup>3</sup> ; Black carbon, 1.06 ug/m <sup>3</sup> ; NO <sub>2</sub> , 9.06ppb; NO, 13.47ppb. For AD, PM <sub>2.5</sub> , 1.54 ug/m <sup>3</sup> ; Black carbon, 1.09 ug/m <sup>3</sup> ; NO <sub>2</sub> , 8.96ppb; NO, 13.68ppb	NAD and AD were diagnosed according to ICD-9; Cases of NAD were 13170, and cases of AD were 1277	HR for NAD adjusted for age, sex, comorbidities, household income, education and ethnicity; OR for AD adjusted for comorbidities, household income, education and ethnicity.	HR for NAD: Major road <50m or highway<150m: 1.14 (1.07-1.20); PM <sub>2.5</sub> : 1.02 (0.98-1.05); Black carbon: 1.01 (0.98-1.04); NO: 1.00 (0.96-1.04); NO <sub>2</sub> : 1.02 (0.99-1.06);  OR for AD: Major road <50m or highway<150m: 1.19 (0.95-1.49); PM <sub>2.5</sub> : 0.90 (0.76-1.07); Black carbon: 0.91 (0.76-1.08); NO: 0.90 (0.77-1.11); NO <sub>2</sub> : 0.84 (0.70-0.99).

Abbreviations: AD Alzheimer's Disease; APOE - ε4 Apolipoprotein epsilon 4 allele; BMI Body Mass Index; CI Confidence Interval; CO Carbon Monoxide; COPD Chronic Obstructive Pulmonary Disease; HR Hazard Ratio; ICD - 9 International Classification of Disorders 9<sup>th</sup> Edition; NO Nitrogen Oxide; NO<sub>2</sub> Nitrogen dioxide; ONPHEC Ontario Population Health and Environment Cohort; PM<sub>2.5</sub> Small Particulate Matter measuring <2.5 micrometers; PM<sub>10</sub> Large Particulate Matter measuring ≤10 micrometers; SD Standard Deviation; VaD Vascular Dementia; WHIMS Women's Health Initiative Memory Study; WHR Waist Hip Ratio.

- a. RR was combined by RRs from highest versus lowest level of CO and NO<sub>2</sub> in reference [36].
- b. RR was combined by RRs from highest versus lowest level of PM<sub>2.5</sub> and O<sub>3</sub> in reference [13].
- c. RR was combined by RRs from highest versus lowest level of PM<sub>2.5</sub> and NO<sub>x</sub> in reference [10] and [18].
- d. RR was combined by RRs from highest versus lowest level of PM<sub>2.5</sub> and NO<sub>x</sub> in reference [20].

**eTable 4. Results of the quality assessment of the studies included in this systematic review and meta-analysis using the Newcastle - Ottawa Quality Assessment\***

First author; publication year	Selection				Comparability	Outcome/Exposure			Score (Assessed Standard)
	1	2	3	4	1	1	2	3	
Chang; 2014 <sup>[36]</sup>	*	*	*	*	**	*	*	*	9(Good)
Jung; 2015 <sup>[13]</sup>	*	*	*	*	**	*	*	*	9(Good)
Oudin; 2016 <sup>[10]</sup>	*	*	*	*	**	*	*	*	9(Good)
Andersson; 2018 <sup>[14]</sup>	*	*	*	*	**	*	*	*	9(Good)
Oudin; 2018 <sup>[18]</sup>	*	*	*	*	**	*	*	*	9(Good)
Oudin; 2019 <sup>[19]</sup>	*	*	*	*	**	*	*	*	9(Good)
Kioumourtzoglou 2016 <sup>[32]</sup>	*	*	*	*	**	*	*	*	9(Good)
Cacciotollo; 2017 <sup>[17]</sup>		*	*	*	**	*	*	*	8(Good)
Chen; 2017a <sup>[11]</sup>	*	*	*	*	**	*	*	*	9(Good)
Chen; 2017b <sup>[33]</sup>	*	*	*	*	**	*	*	*	9(Good)
Carey; 2018 <sup>[12]</sup>	*	*	*	*	**	*	*	*	9(Good)
Cerza; 2019 <sup>[31]</sup>	*	*	*	*	**	*	*	*	9(Good)
Ilango; 2019 <sup>[17]</sup>	*	*	*	*	**	*	*	*	9(Good)
Grande; 2020 <sup>[20]</sup>	*	*	*	*	**	*	*	*	9(Good)
Yuchi; 2020 <sup>[35]</sup>	*	*	*	*	**	*	*	*	9(Good)
Zhejiang Cohort study	*	*	*	*	**	*	*	*	9(Good)
Anhui Cohort study	*	*	*	*	**	*	*	*	9(Good)

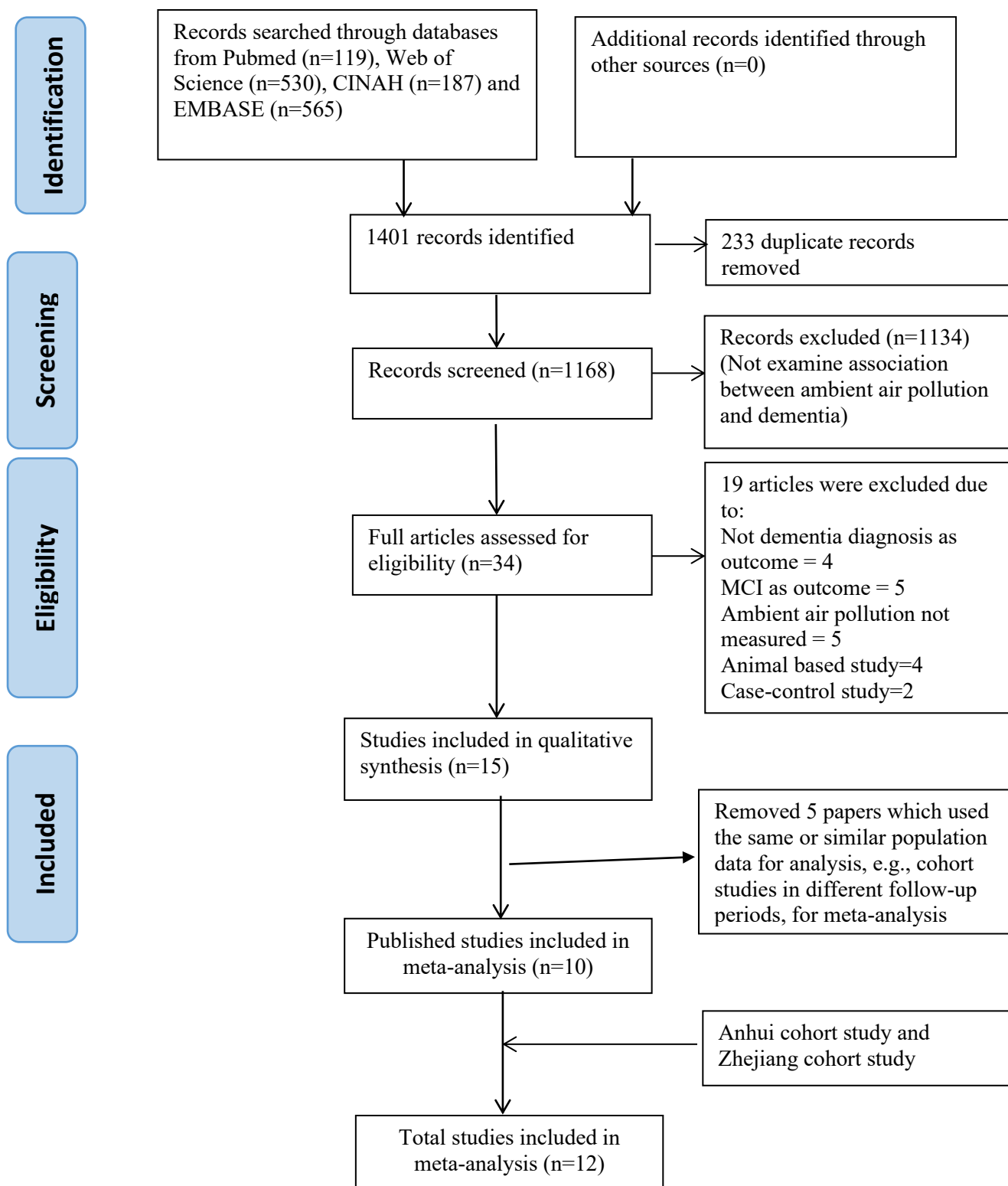
\* A star was assigned if there was a quality feature; scores of 1-9 were distributed (the comparability domain can score 1-2 stars). Studies with scores of 1 to 3 were defined as poor quality, 4 to 6 intermediate and 7 to 9 high.<sup>42</sup>

**eTable 5. RR in each studied population used for estimating the pooled RR of specific air pollutant (average) and dementia**

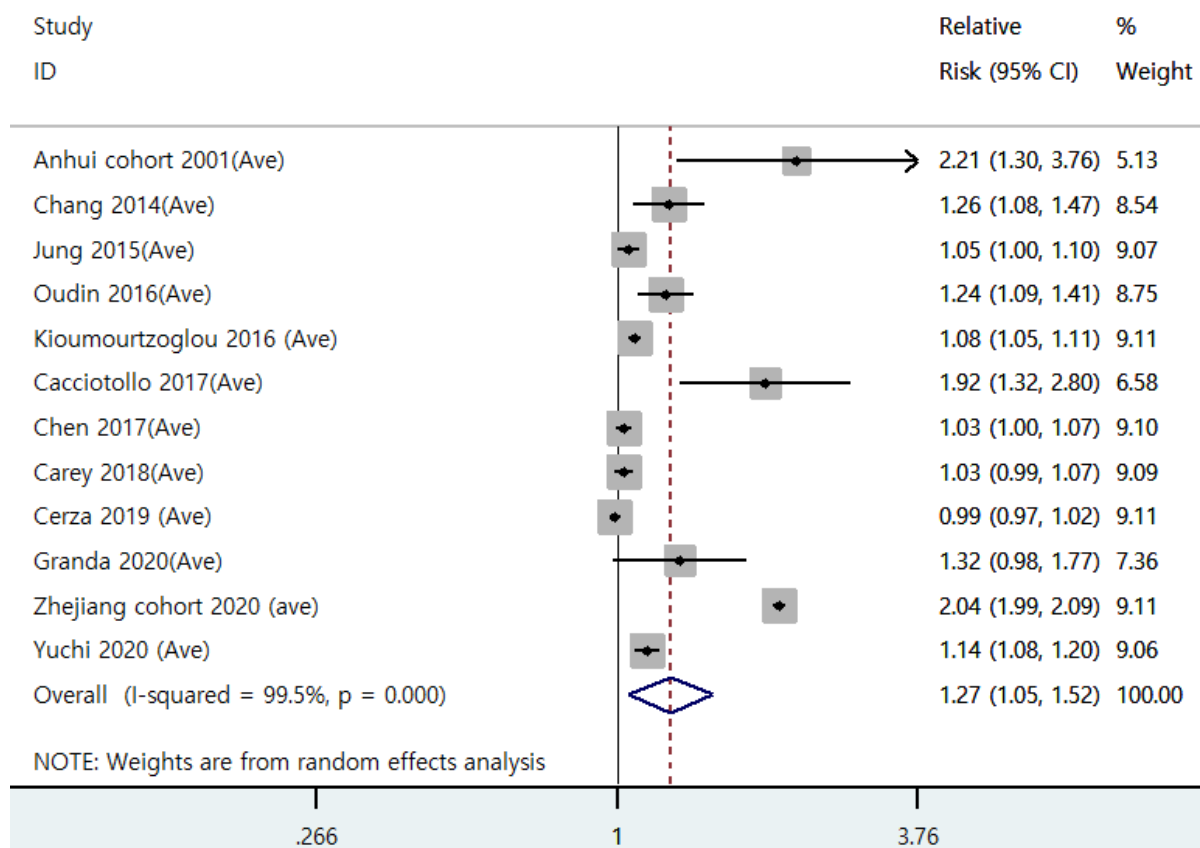
	Pooled RR of dementia for each air pollutant (average)					
	PM <sub>2.5</sub> (n=11)	PM <sub>10</sub> (n=2)	CO (n=2)	NO <sub>2</sub> (n=6)	NO <sub>x</sub> (n=3)	O <sub>3</sub> (n=5)
Chang et al <sup>[36]</sup>			1.33(1.06-1.68)	1.20(0.93-1.54)		
Jung et al <sup>[13]</sup>	1.03(0.95-1.11)					1.03(0.95-1.11)
Oudin et al <sup>[10, 18]</sup>	1.16(1.00-1.35) <sup>a</sup>				1.40(1.14-1.74)	
Kioumourtzoglou et al <sup>[32]</sup>	1.08(1.05-1.11)					
Cacciottolo et al <sup>[17]</sup>	1.92(1.32-2.80)					
Grande et al <sup>[20]</sup>	1.54(1.33-1.78)				1.14(1.01-1.29)	
Cerza et al <sup>[31]</sup>	1.07(1.01-1.12)	1.00(0.98-1.03)		0.97(0.96-0.99)	1.01(1.00-1.02)	1.03(0.99-1.13)
Chen et al <sup>[11, 33]</sup>	1.04(1.03-1.05)			1.10(1.08-1.12)		0.98(0.96-1.00)
Carey et al <sup>[12]</sup>	1.03(1.01-1.13)			1.13(0.99-1.28)		1.03(0.99-1.13)
Yuchi et al <sup>[35]</sup>	0.99(0.89-1.10)			0.94(0.78-1.14)		
Anhui cohort	2.21(1.30-3.77)					
Zhejiang cohort	1.50(0.90-2.50)	2.32(1.20-4.48)	1.95(0.83-6.20)	0.78(0.32-1.90)		0.42(0.25-0.71)
Overall RR	<b>1.12(1.05-1.19)</b>	<b>1.42(0.63-3.21)</b>	<b>1.37(1.08-1.70)<sup>a</sup></b>	<b>1.09(1.00-1.17)</b>	<b>1.14(0.97-1.34)</b>	<b>1.01(0.95-1.08)</b>

<sup>a</sup>fixed model.





**eFigure 1.** PRISMA 2009 flow diagram for the review on the association between air pollution and the risk of dementia



e Figure 2. Forest plot for the RR of all dementia in average air pollution exposure.