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Association between air pollution and incidence of dementia: A systematic review and meta-analysis of cohort studies

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Abstract

Objective. To estimate risk of dementia in association with exposure to air pollutants.

Methods. Six databases were searched. Cohort studies that reported the hazard ratio (HR) of dementia in association with exposure to air pollutants in adults > 40y were included. For all meta-analyses, the random-effects model was used.

Results. A total of 16 and 13 studies were included in the systematic review and the meta-analysis, respectively. Risk of dementia increased by 4% per 1$\mu g/m^3$ increase in fine particulate matter level (HR, 1.04; 95%CI, [1.02, 1.06]), which was statistically significant. The risk of dementia increased by 3% per 10$\mu g/m^3$ increase in nitrogen oxides level (HR, 1.03; 95%CI, [0.98, 1.08]), and by 3% per 10$\mu g/m^3$ increase in nitrogen dioxide level (HR, 1.03; 95%CI, [1.00, 1.07]); however, the associations were not statistically significant

Conclusion. This meta-analysis indicates a significant association between exposure to fine particulate matter and incidence of dementia.

Keywords

Dementia; Alzheimer's Disease; Air Pollution; Fine Particulate Matter; $PM_{2.5}$; Nitrogen Oxides; Nitrogen Dioxide; Ozone; Systematic Review; Meta-Analysis

Summary for Lay Audience

Objective. To estimate risk of dementia in association with exposure to air pollutants.

Methods. Six databases were searched for long-term studies. Those reported the risk of dementia in association to exposure to air pollutants in adults who were older than 40 years of age were included, and analyses of similar studies were conducted

Results. A total of 13 studies were included in the analyses of similar studies. The risk of dementia increased by 4% per 1$\mu g/m^3$ increase in fine particles level, which was statistically significant. The risk of dementia increased by 3% per 10$\mu g/m^3$ increase in nitrogen oxides level, and by 3% per 10$\mu g/m^3$ increase in nitrogen dioxide level; however, the associations were not statistically significant

Conclusion. This analysis of similar studies indicates a significant association between exposure to fine particulate matter and incidence of dementia.

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Dedication

Dedicated to:

My Lovely Son, Bardiya

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1 Introduction

1.1 Dementia

Neurological disorders account for 10% of the global burden of disease and are the leading cause of disability-adjusted life years (DALYs). About 10% of DALYs from neurological disorders are due to dementia. While the trend of prevalence and incidence of dementia is stable or declining in high-income countries, low-income and middle-income countries are expecting a rise in the burden of dementia (1). The annual cost of dementia in the United States was estimated to be around 157 to 215 billion dollars (2). While the Canadian population is considerably smaller than the United States, the burden of dementia was reported to be 15 billion dollars in 2008, and is expected to reach 153 billion dollars in 2038 (3, 4).

Dementia is categorized as Alzheimer's disease (AD) and non-Alzheimer dementia (NAD) with AD being the most commonly diagnosed type of dementia. An important proportion of NAD is vascular dementia (VaD). The subtypes of dementia including AD are diagnosed clinically; however, neuropathological examination of the brain of 1,161 deceased individuals with dementia demonstrated that 41% of AD cases could be attributed to AD pathology alone and pathological features related to other types of dementia could be seen in those diagnosed with dementia. In addition, over two-thirds of cases of AD could be attributed to other neuropathologies that were common for the age of individuals (5). These findings infer that relying on the clinical diagnosis of dementia subtypes might be misleading, and it is better to evaluate all of them under the umbrella of dementia.

Numerous genetic, behavioural, and environmental factors are associated with dementia. The important risk factors for dementia are age, female sex, traumatic brain injury, current smoking, low educational level, and pre-existing metabolic disorders or cardiovascular diseases (CVD) (6, 7). Age is the most important risk factor for developing dementia and the prevalence increases from 2% to 3% at age 65 to more than 30% at age 90 or older (8-10). Along with the increasing population worldwide and improvement in public health, the elderly will constitute a large proportion of the population. It means that an increase in chronic and non-communicable diseases of the elderly, including dementia, should be expected. It is estimated that the number of people with dementia will rise from 44 million individuals in 2013 to 135 million in 2050 (11). Due to such an important effect on health and economy, the World Health Organization announced dementia as a public health priority (12). Therefore, understanding and preventing the causes of dementia would be beneficial to both healthcare systems and governments.

One of the environmental factors that is hypothesized to be associated with dementia is air pollution. Air pollution has become a global concern during the recent decades and its association with numerous medical conditions has been reported. During the last decade, the association of air pollutants with cognitive decline and dementia has been examined and there was a discrepancy among the reported associations.

1.2 Air pollution

Air pollution has been associated with adverse health outcomes (13). There is a large body of evidence that associates air pollution to CVD (14), respiratory diseases (15-17),

psychiatric disorders such as depression and suicide (17), and neurological disorders including decline in cognitive function and dementia (18, 19).

The pollutants can be of natural sources or human-activity-related sources. Natural sources include volcanic activities, wildfire, and dust, and are difficult to control. Sources related to human-activity are mainly from traffic, home cooking and heating, industrial combustion of fossil fuels, mining, and agriculture. Human-activity-related pollutants can be reduced with appropriate intervention. Some of the most important air pollutants are particulate matter (PM), especially PM of diameter less than 2.5μm ($PM_{2.5}$), nitrogen oxides (NO_X) including nitrogen dioxide (NO_2) and nitrogen monoxide (NO), and ozone (O_3). Some strategies to decrease traffic-related air pollution have shown beneficial effects on health (20). Therefore, the level of air pollutants should be kept low to prevent detrimental health outcomes. The World Health Organization (WHO) air quality guideline indicated that the annual and daily mean levels of $PM_{2.5}$ should not exceed 10μg/m^3 and 25μg/m^3, respectively. The guideline levels for the annual and daily mean levels of NO_2 are 40μg/m^3 and 200μg/m^3, respectively. The recommended threshold for mean levels of O_3 is 100μg/m^3/8 hour. Nonetheless, according to "Ambient (outdoor) air quality and health" report by WHO in 2016, about 91% of the world population were living in regions where the level of pollutants exceeded the WHO air quality guidelines. This report also estimated that about 4.2 million premature deaths worldwide were due to exposure to air pollution. Most of the deaths occurred in low-income and middle-income countries (21).

1.2.1 Particulate Matter

Particulate matter (PM) is a collective name for a group of particles with different sizes and various composition that can be liquid or solid. Particulate matter might be of natural or human-activity-related sources. The primary PM is produced directly from natural or human-activity-related sources. Secondary PM is a complex combination of different pollutants due to photochemical reactions in the atmosphere (22).

Particulate matter is produced in various sizes. The United States Environmental Protection Agency (EPA) has categorized PM according to the diameter of the particles, ranging from ultrafine, fine, and coarse PM.

Ultrafine PM has a dimeter of < 100nm and therefore, it is called $PM_{0.1}$. The main constituents of ultrafine PM are organic matters with inorganic ions and metals being its minor constituents. The fine PM ($PM_{2.5}$) has a diameter of < 2.5μm and its main constituents are inorganic ions, with metals and organic matter being its minor constituents. Coarse PM (PM_{10}) has a diameter between 2.5μm and 10μm with inorganic ions and metals being its main constituents (23). The importance of this categorization is that each particle might have a different fate and unique effect on the human body.

While PM_{10} is mainly trapped in the upper respiratory tract, $PM_{0.1}$ and $PM_{2.5}$ not only deposits in the lungs, but also enters the circulation and is taken up into cells and may cross the brain-blood barrier (24). In addition, $PM_{0.1}$ can directly enter the brain through olfactory nerve endings in the nose (25). The surface of $PM_{0.1}$ and $PM_{2.5}$ can also carry other hazardous chemicals and metals (26), and their entrance into the blood stream and brain may lead to cell damage. The entrance of PM in the brain cells can initiate inflammation,

neurotoxicity, neuronal damage, and cell loss (27). In addition, there is an association between exposure to PM and cardiovascular morbidity and mortality (28), which is a risk factor for dementia and can lead to cognitive impairment and contribute to the development of dementia and AD (29).

While the negative effect of pollution on cognition has been studied in children whose mothers were exposed to air pollution during pregnancy, the results have been discrepant. One component of PM is the polycyclic aromatic hydrocarbons (PAHs) that is shown to be associated with decreased verbal and overall IQ in 5-year-old children born to African-American and Dominican mothers in New York city who were exposed to PAHs during pregnancy (30). On the other hand, a meta-analysis of six European studies on the association between prenatal exposure to air pollutants and psychomotor development did not show any association with PM_{10} or $PM_{2.5}$ (31). Harris et al. studied the association of prenatal exposure to traffic-related air pollution, specifically $PM_{2.5}$, in 1109 mother-child pairs in Eastern Massachusetts and reported a limited association between exposure to $PM_{2.5}$ and childhood cognitive decline (32). This heterogeneity in suggested associations might be due to different levels of exposure to pollutants and potential unknown interactions between other pollutants affecting overall toxicity. In addition, PM is a mixture of various chemical elements and its composition might differ from region to region and from time to time according to other environmental factors.

The negative effect of exposure to air pollution is not limited to the prenatal period. Childhood exposure to air pollutants is also associated with cognitive decline. In a pilot study in Mexico City, Calderón-Garcidueñas et al. evaluated 134 consecutive autopsies of subjects with the mean age of 20 (range, 11mo to 30y) and reported progressive

development of AD in 99.25% of the autopsies. They also reported cognitive impairment in 66% of healthy individuals ≤ 30 years old who were exposed to more than standard levels of $PM_{2.5}$ and O_3 during their lifetime (33).

Numerous studies have shown the association between air pollution and cognitive decline in the elderly population. In a study of elderly women from the SALIA cohort (duration, 22 y) in Germany, Schikawski et al. reported a significant decrease in the semantic memory and visuo-construction subsets of cognitive function with increases in NO_x and PM. In addition, they reported a significant association of decline in cognitive function in the carriers of APOE ϵ4 allele (34). Gatto et al. investigated the association of air pollution with different domains of cognition in adults (mean age, 60.5 y) in Los Angeles and reported lower verbal learning in those exposed to $PM_{2.5}$ and lower logical memory in those exposed to NO_2 (35).

Alishire and Clarke studied the cognitive function of 780 Hispanic participants in the American Changing Lives Study and evaluated the association of the cognitive errors with exposure to $PM_{2.5}$ using the Short Portable Mental Status Questionnaire (SPMSQ). Their results showed that in comparison to exposure to the lower levels of $PM_{2.5}$, exposure to higher levels of $PM_{2.5}$ was associated with 1.5 times higher error rates in working memory and orientation domains of cognitive function (36).

Another study of 19,409 women from Nurses' Health Study Cognitive Cohort in the United States evaluated the association of PM with global cognition. This study indicated a decline in global cognition among those who were exposed to higher levels of $PM_{2.5}$ in comparison to those exposed to lower levels. In addition, there was a linear association between

increase in $PM_{2.5}$ levels and decline in global cognition in a two-year evaluation interval. They indicated that higher levels of PM was associated with faster cognition decline (37).

Lin et al. studied the association of $PM_{2.5}$ with overall and domain-specific disability according to the 12-item version of the World Health Organization Disability Assessment Schedule (WHODAS 2.0) among adults of six low-income and middle-income countries. Evaluation of the data from 45,625 participants of the Study on global AGEing and adult health (SAGE) from these countries showed an increase over baseline of 0.72 (95%CI, [0.22, 1.22]) in overall WHODAS score (maximum score: 48) and 0.10 (95%CI, [0.02, 0.18]) increase in cognitive domain per $10\mu g/m^3$ increase in $PM_{2.5}$ level. In addition, they indicated that women and older adults are more at risk of being affected by ambient PM (38).

Although cognitive decline might be the early manifestation of dementia, not everyone with cognitive decline will progress to dementia. Therefore, the risk of cognitive decline does not necessarily indicate the risk of dementia and longitudinal studies are required to evaluate the risk of dementia in association with air pollutants. In addition, similar as for other chronic conditions, time-to-event analysis and reporting the hazard ratio (HR) in cohort studies seems to be the appropriate measure of risk of dementia due to chronic exposure to high levels of PM.

The association between PM and dementia has been studied in several epidemiological cohorts. In a population-based cohort study in Taiwan, Jung et al. examined the association between $PM_{2.5}$ and AD by using the data from 95,690 individual from the longitudinal health insurance database (LHID2000). Their study reported a 3% increase in the hazard

of developing dementia per interquartile range (IQR) of $PM_{2.5}$ (13.21μg/m^3); however, the association was not statistically significant (HR, 1.03; 95%CI, [0.95, 1.11]) (39).

In 2017, Cacciottolo et al. evaluated the association between exposure to $PM_{2.5}$ and cognitive impairment in 3,647 women from The Women's Health Initiative Memory Study (WHIMS) in the United States. Their study showed higher risk of dementia in those exposed to higher levels of $PM_{2.5}$ (> 12μg/m^3) in comparison to those exposed to lower levels (HR, 1.92; 95%CI, [1.32, 2.80]). Moreover, they showed that the presence of APOE ε4 is associated with a higher HR of developing dementia (ε3/3: HR, 1.68; 95%CI, [0.97, 2.92]; ε3/4: HR, 1.91; 95%CI, [1.17, 3.14[; and ε4/4: HR, 3.95; 95%CI, [1.18,13.19]) (40).

Oudin et al. evaluated the association between $PM_{2.5}$ and dementia in 1,806 individuals from the Betula project in Sweden. They evaluated the HR for dementia (AD and VaD) for exposure to $PM_{2.5}$ due to residential wood burning as well as traffic exhaust. Their results indicated a significant association between $PM_{2.5}$ from residential wood burning and dementia for the group with high exposure levels compared to the group with lower exposure levels (HR, 1.74; 95%CI, [1.10, 2.75]). In addition, the association between $PM_{2.5}$ from traffic exhaust and dementia was statistically significant in those exposed to higher levels of $PM_{2.5}$ compared to those exposed to lower levels (HR, 1.41 95%CI, [0.97, 2.23]) (41).

In a study by Carey et al., 131,869 residents of the great London, the United Kingdom, who were registered with a general practice were evaluated for the association of several air pollutants including traffic-related $PM_{2.5}$ with dementia. The study indicated an 8% increase in HR of dementia (HR, 1.08; 95%CI, [1.01 to 1.16]), 13% increase in HR of AD

(HR, 1.13; 95%CI, [1.02 to 1.26]), an 8% increase in HR of VaD (HR, 1.08; 95%CI, [0.95 to 1.23]), and an 8% increase in HR of non-specific dementia (HR, 1.08; 95%CI, [0.97 to 1.19]) per interquartile change in the traffic-related $PM_{2.5}$ (0.58μg/m^3). These results indicated a stronger association between $PM_{2.5}$ and AD than any other subtype of dementia. In addition, the study did not report any association between night-time noise levels (HR, 1.01; 95%CI, [0.98, 1.03]; per IQR change of night-time noise level [+2.68 dB]) or distance to major roads (HR, 1.00; 95%CI, [0.95, 1.05]; per IQR change in distance from major roads [-310m]) and dementia when the regression model was adjusted for other pollutants ($PM_{2.5}$ and NO_2) (42). This finding might indicate that the main causal pathway to dementia is affected by air pollutants, and proximity to roads is a factor that increases the chance of exposure to traffic pollution.

Another study from Sweden, evaluated the exposure to $PM_{2.5}$ and risk of dementia in 2,927 individuals in the Kungsholmen district of Stockholm using the data from Swedish National Study on Aging and Care in Kungsholmen (SNAC-K). They reported a statistically significant risk of developing dementia during the five-year period preceding the exposure to $PM_{2.5}$ (HR, 1.54; 95%CI, [1.33, 1.78]; per IQR difference of $PM_{2.5}$ [0.88 μg/m^3]). There was also a statistically significant association between exposure to $PM_{2.5}$ and incidence of VaD (HR, 1.54; 95%CI, [1.33, 1.78]; per IQR difference of $PM_{2.5}$ [0.88 μg/m^3]). This study aimed to evaluate the mediatory role of CVD in development of dementia due to air pollution, and reported stroke as the most important intermediate condition that might mediate the effect of air pollution in developing dementia (43).

In a case-control study to evaluate the association of PM_{10} with AD and VaD, Wu et al. recruited 249 patients with AD, 125 patients with VaD, and 497 controls from three

teaching hospitals in northern Taiwan. Their study showed approximately four times higher odds of AD in those exposed to the highest tertile (> 49.23 μg/m^3) compared to the lowest tertile (< 44.95 μg /m^3) of PM_{10} level (OR, 4.17; 95%CI, [2.31, 7.54]). Moreover, the odds of VaD in the highest tertile was almost 3.5 times of the odds in the lowest tertile (OR, 3.61; 95%CI, [1.67, 7.81]) (44).

In a nested case-control study among the beneficiaries of Taiwan's National Health Insurance program (Taiwan's National Health Insurance Research Database [NHIRD]), Li et al. could not find any association between VaD and exposure to PM_{10} five years before developing dementia (OR, 0.99; 95%CI, [0.98, 1.00]; per 10μg/m^3 increase in PM_{10}) (45). These results are expected because PM_{10} is usually caught in macrophages and cells of upper and lower respiratory tract and might not be the main culprit in developing dementia.

1.2.1.1 Studies in Canada

The association between air pollution and dementia was studied in three provinces of Canada, namely, Ontario, British Columbia, and Quebec.

The first population-based study in Canada was conducted in 2017 by Chen et al. who used the data from Ontario Population Health and Environment Cohort (ONPHEC) to evaluate the association of air pollution with incidence of dementia among the Canadian-born residents of Ontario who were registered in the provincial healthcare plan (OHIP). Of approximately 2.06 million individuals followed from 2001 to 2013, there was a 3% increase in HR of dementia (HR, 1.03; 95%CI, [1.02, 1.04]; per IQR difference of $PM_{2.5}$ [4.8μg/m^3]). In addition, they attributed 2.4% (95%CI, [1.8%, 3.0%]) to $PM_{2.5}$ alone. When including cases due to NO_2 exposure, 6.1% (95%CI, [4.8%, 7.5%]) of dementia incidence

could be attributed to air pollution (46). This study suggests the potential importance of addressing air pollution in preventing a considerable fraction of dementia.

In a population-based retrospective cohort study, Ilango et al. evaluated the mediatory role of CVD in the association between incidence of dementia and air pollution in residents of Ontario, Canada, from 2001 to 2013. The study population included 34,391 Canadian-born Ontario residents who had resided in this province for at least five years. In order to assess the mediating role of CVD, the investigator considered a three-year exposure period followed by a five-year lag. During the five-year lag after exposure period, CVD could occur, but if the patients developed dementia, they would be excluded from the analysis. Their results indicated around 30% increase in HR of dementia per 10$\mu g/m^3$ increase in $PM_{2.5}$ levels; however, the result was not statistically significant (HR, 1.29; 95%CI, [0.99, 1.64]). On mediation analysis, almost 21% (on multiplicative model) and 4% (on additive model) of the association of $PM_{2.5}$ with the incidence of dementia was attributed to causal pathways related to CVD (47).

In British Columbia, Yuchi et al. evaluated the association between air pollutants and developing NAD and AD by evaluating 633,949 individuals from the ministry of health database, using a nested-case-control design to evaluate the association between air pollution and AD. Their study indicated a nonsignificant association between $PM_{2.5}$ and NAD (HR, 1.02; 95%CI, [0.98, 1.05]; per IQR difference of $PM_{2.5}$ [1.54$\mu g/m^3$]). In addition, they did not find association between noise and developing NAD, but reported an attenuating effect of greenness on the association between exposure to $PM_{2.5}$ and NAD. The analysis of nested-case control data indicated no statistically significant association

between AD and exposure to $PM_{2.5}$ (OR, 0.90; 95%CI, [0.76, 1.07]; per IQR increase of 1.54 $\mu g/m^3$] (48).

In a retrospective population-based cohort study, Smargiassi et al. investigated the association of ambient air pollution with the risk of developing dementia in an open cohort of 1,807,133 individuals who had resided in Quebec for the previous four years. Their results showed a 1.5% increase in HR of dementia per 3.90 $\mu g/m^3$ (IQR) increase in $PM_{2.5}$ level (HR, 1.02; 95%CI, [1.01, 1.03]). The increase in the HR of dementia was around 5% per 2.10$\mu g/m^3$ (IQR) increase in $PM_{2.5}$ level in the island of Montreal (HR, 1.05; 95%CI, [1.03, 1.07]). Distance from major roads was negatively associated with the incidence of dementia (HR, 0.95; 95%CI, [0.94–0.96]; per 150m distance from major roads[IQR]) (49).

1.2.1.2 First-Time Hospitalization With Dementia

In addition to association with total incidence of dementia, the association of air pollution with incidence of the first-time admission to hospital with the diagnosis of dementia has been evaluated in a few studies.

The association between long-term exposure to $PM_{2.5}$ and hospitalization for neurological disorders including dementia was evaluated in 50 cities of the northern United States. In this population-based cohort study, Kioumourtzoglou et al. evaluated 9.8 million fee-for-service Medicare enrollees who had exposure to $PM_{2.5}$ during 1999 through 2010. They excluded cases that developed dementia during the first two years of enrollment and included the remaining 7.9 million enrollees for their time-to-event analysis. The study indicated 15% (HR, 1.15; 95%CI, [1.10, 1.19]) and 7% (HR, 1.07; 95%CI, [1.04, 1.11]) increase in the HR of the first-time hospitalization with dementia and AD per 1$\mu g/m^3$

increase in $PM_{2.5}$ levels, respectively, with similar rates for men and women. In addition, they found 8% increase in HR of first-time hospitalization with Parkinson's disease per 1μg/m^3 increase in $PM_{2.5}$ levels (HR, 1.08; 95%CI, [1.04, 1.12]), potentially relating negative association of air pollution with the central nervous system diseases (50).

In a population-based cohort study in Rome, Italy, Cerza et al. evaluated the association between air pollution and first-time hospitalization with dementia. They evaluated 350,884 residents of Rome who had completed the population census in 2001 and followed them until 2013. The study reported no statistically significant association between exposure to $PM_{2.5}$ (HR, 0.99; 95%CI, [0.96, 1.02]; per 5μg/m^3 increase]) as well as PM_{10} (HR, 1.00; 95%CI, [0.98, 1.03]; per 10μg/m^3 increase]) with the first-time hospitalization with dementia. Moreover, such an association was not statistically significant for AD and senile dementia. On the other hand, first-time hospitalization with VaD was significantly associated with increase in levels of $PM_{2.5}$ (HR, 1.07; 95%CI, [1.01, 1.12]; per 10μg/m^3 increase]) and PM_{10} (HR, 1.06; 95%CI, [1.02, 1.10]; per 10μg/m^3 increase]). In addition, the association of dementia and its subtypes with distance from high-traffic road was only significant for AD (51).

Lee et al. evaluated the association between exposure to $PM_{2.5}$ and hospitalization with dementia in seven southern states of the United States. In this population-based study, they evaluated 13.3 million Medicare beneficiaries and followed the participants for 13 years. The study results indicated that for each 1μg/m^3 increase in $PM_{2.5}$, there was a 5% increase in HR of the first-time admission with dementia (HR, 1.049; 95%CI, [1.048, 1.051]), 6% increase in HR of the first-time admission with AD (HR, 1.60; 95%CI, [1.057, 1.062]), and

9% increase in HR of the first-time admission with VaD (HR, 1.086; 95%CI, [1.082, 1.090]) (52).

1.2.2 Nitrogen oxides

Nitrogen oxide species (NO_X) are composed of nitrogen dioxide (NO_2) and nitrogen monoxide (NO). This combination makes it hard to evaluate the association of NO_x with dementia because the combination of NO_2 and NO varies from region to region. Nitrogen dioxide is a traffic-related air pollutant that is generated primarily from vehicles and can cause detrimental effects on health. The levels of NO_2 have been increasing worldwide. One study showed that the levels of NO_2 in 1996 had increased by 2.7 times in 2012 (53).

Animal studies have shown that prenatal exposure to NO_2 is associated with problems in neuromuscular coordination and functional deficits in mice (54). Some studies on pregnant women who were exposed to air pollutants reported that the effect of NO_X on brain might be due to oxidative stress (55, 56). Evidence also suggests that NO_2 disrupts the blood-brain barrier and leads to neural inflammation in children (57, 58). These studies indicate that the detrimental effects of NO_X can start with intrauterine exposure to nitrogen oxides. It has been proposed that intrauterine exposure of human fetus to NO_X is associated with poor cognitive outcomes in early childhood.

In a study on 1,889 children whose mother had been exposed to NO_2 in the first trimester of pregnancy, NO_2 had inverse association with mental development although the association was not significant (β, -0.95; 95%CI, [-3.90, 1.89]) (59). Another study on 9,426 children of one to six years old from six European birth cohorts, namely, GENERATION R (The Netherlands), DUISBURG (Ger many), EDEN (France), GASPII

(Italy), RHEA (Greece), and INMA (Spain), showed that prenatal exposure to NO_2 is associated with decreased global psychomotor development (β, -0.65; 95%CI, [-1.25, -0.11]). Such an association was not seen with general cognition or language development. In addition, significant association was not found between cognitive decline and other air pollutants including, NOx, $PM_{2.5}$, and PM_{10} (31). In a population-based study in Spain, 438 mother-child pairs were recruited and children were evaluated around 15 months of age by the Bayley Scales of Infant Development. The results indicated that for 1μg/m^3 increase in exposures level of NO_2 during pregnancy, child's mental scale score of decreases by 0.29 points (90%CI, [-0.47, -0.11]); however, such an association was not statistically significant for motor scale score (β, -0.14, 90%CI, [-0.34, 0.06]) (60).

Early life exposure to NO_2 is reported to have negative association with child development. In a cohort study in Malaga Province, Spain, 210 children were followed for a year and their motor and cognitive development was evaluated at age five with McCarthy Scales of Children's Abilities (MSCA). Children with higher level of exposure (> 24.75μg/m^3) showed a decrease in domains of cognitive function including general cognition score (β, -4.19; 95%CI, [-14.02, 5.64]), quantitative (β, 6.71; 95%CI, [-17.91, 4.49]), working memory (β, -7.37; 95%CI, [-18.98, 4.24]), and gross motor (β, -8.61; 95%CI, [-18.96, 1.74]) areas. Nonetheless, none of these changes were statistically significant (61).

In a study in Amsterdam, Netherlands, 553 school-age children of nine to 11 years old were evaluated for the association of exposure to NO_2 and transportation noise with cognitive performance of children at school. The results indicated significant decline in memory span length at school (χ^2, 6.8; df, 1; p-value = 0.01). When the outcome was adjusted for transportation and aircraft noise, the association remained statistically significant (χ^2, 5.9;

df, 1; p-value = 0.015), indicating the association of exposure to NO_2 with memory span length was independent of surrounding noise (62).

The negative effect of NO_2 on cognition continues during adulthood and those exposed to air pollution later in life are not necessarily spared. In a cross-sectional study in the United States, 1,496 healthy men and postmenopausal women (mean age, 60.5 y) were evaluated for the association of air pollutants including NO_2 with cognitive function. There was no statistically significant difference between those exposed to higher levels of NO_2 (> 20ppb) and those exposed to lower levels of NO2 (< 10ppb) in global function or any of the six measured cognitive domains (executive function, verbal learning, logical memory, visual memory, semantic memory, and visual processing). However, there was a decrease in logical memory (β, -0.62; 95%CI, [-1.35, 0.11]), global function (β, -0.32; 95%CI, [-0.92, 0.28]), visual memory (β, -0.26; 95%CI, [-0.97, 0.45]), and semantic memory (β, -0.24; 95%CI, [-0.87, 0.39]) (35). The lack of significance in this study might be due to small sample size but inverse association of NO_2 with domains of cognitive function raises the possibility of association with further decline in cognitive function and progression to dementia in the future.

Several studies have investigated the association between NO_X and NO_2 with dementia and its subtypes with discrepant results.

In a study by Chang et al. in Taiwan, data of 29,545 individuals (mean age, 61.5 y) from the NHIRD were evaluated for the association between exposure to NO_2 and dementia from 2000 to 2010. Their results indicated 54% increase in HR in those exposed to the fourth quartile compared to those exposed to the first quartile of NO_2 levels (HR, 1.54;

95%CI, [1.34, 1.77]). The same increase in HR ratio was seen for male (HR, 1.52; 95%CI, [1.23, 1.88]) and female subgroups (HR, 1.56; 95%CI, [1.29, 1.87]) indicating no difference in the risk of dementia between sexes regarding exposure to NO_2 (63).

In a population-based cohort study in northern Sweden, Oudin et al. used data of 1,806 individuals from Betula project to evaluate the association between exposure to NO_X and development of AD and VaD. They followed patients for a maximum period of 15 years (1995-2010) and compared the highest level of exposure (> 26μg/m^3) to the lowest level of exposure (< 9μg/m^3) and reported 38% increase in HR of AD (HR, 1.56; 95%CI, [1.29, 1.87]) and 47% increase in HR of VaD (HR, 1.56; 95%CI, [1.29, 1.87]). However, such an association was not statistically significant for changes in HR per 10μg/m^3 increase in level of NO_X (AD: HR, 1.05; 95%CI, [0.97, 1.15]; and VaD: HR, 1.02; 95%CI, [0.92, 1.14]) (64). Using the same database, the authors later evaluated the role of APOE ϵ4 and did not find any evidence of modifying HR of dementia by this genotype (65). This might indicate that the association of NO_X with cognition and dementia is through another pathway that does not involve APOE ϵ4. Andersson et al. used the data from the same cohort and indicated no association between noise and dementia (66), suggesting that the association of NO_X with developing dementia is not modified by noise or in other words, may be due to air pollution itself rather than traffic-related noise.

In a study by Carey et al. in London, United Kingdom, exposure to NO_2 was associated with dementia, AD, and VaD; however, this association was not statistically significant for VaD (HR, 1.15; 95%CI, [0.96 to 1.39]; per IQR of 7.5μg/m^3). Their study indicated that per one IQR increase in NO_2 levels, HR ratio of dementia and AD increase by 16% (HR, 1.16; 95%CI, [1.05 to 1.28]) and 23% (HR, 1.23; 95%CI, [1.07 to 1.43]), respectively. In

addition, adjustment for night-time noise had slight modification on the association between dementia and NO_2 (42).

Another study in Sweden evaluated the mediator role of CVD in the causal association between NO_X and dementia. In this study, 2,927 individuals with mean age 71.4 years from Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) were selected. The HR of dementia increased by 14% per IQR difference (8.35μg/m^3) in mean exposure to NO_X during the last preceding five years at the residential address (HR, 1.14; 95%CI, [1.01 to 1.29]). Although HR of dementia increased with the presence of heart failure and ischemic heart disease, the mediation analysis did not show any mediatory role of CVD on the association of NO_X and dementia (OR, 1.11; 95%CI, [0.93, 1.32]) (43).

In a case-control study using NHIRD, Li et al. evaluated the association of NO_2 with VaD in Taiwan. Their results indicated higher odds of VaD in those exposed to higher levels of NO_2 in comparison to the lowest levels five years before the diagnosis of VaD (OR, 2.22; 95%CI, [1.35, 3.65]). On the other hand, there was no statistically significant association between NO_2 levels and dementia when the incremental levels of NO_2 were fitted (OR, 1.28; 95%CI, [0.98, 1.66]; per IQR of 4.69ppb)(45).

1.2.2.1 Studies in Canada

In a large population-based cohort study in Ontario, Canada, data of over two million individuals with the mean age of 66.8 years from Ontario Population Health and Environment Cohort (ONPHEC) were evaluated for the association between NO_2 and dementia. The study indicated a 10% increase in HR of dementia per IQR (4.8μg/m^3) increase in NO_2 levels (HR, 1.10; 95%CI, [1.08, 1.12]) (46). Another study in Montreal,

Quebec, Canada, evaluated the association of NO_2 with the incidence dementia by evaluating 1.8 million individuals over 65 years of age. The study indicated 1.5% increase in incidence of dementia per IQR (13.26ppb) change in NO_2 levels (HR, 1.015; 95%CI, [1.007, 1.023]); however, after including $PM_{2.5}$ levels in the model this became statistically insignificant (HR, 1.005; 95%CI, [0.994, 1.017])(49). The population-based cohort study on the association of NOx with NAD in Vancouver, British Columbia, Canada, did not indicate a significant association between incidence of NAD and exposure to NO_2 (HR, 1.02; 95%CI, [0.99, 1.06]; per IQR of 9.1ppb) or NO (HR, 1.00; 95%CI, [0.96, 1.04]; per IQR of 12ppb). They designed a nested-case-control study within their cohort to evaluate the association of air pollution with AD and reported a statistically significant lower odds of exposure to NO_2 in cases (OR, 0.84; 95%CI, [0.70, 0.99]; per IQR of 8.96) and no statistically significant association between NO and AD (OR, 0.91; 95%CI, [0.77, 1.11]; per IQR of 13.68) (48).

1.2.2.2 First-Time Hospitalization With Dementia

A population-based study by Cerza et al. in Rome, Italy reported on the association between NO_X and first-time hospitalization with dementia, and found a marginal increase in HR of dementia per 20µg/m^3 increase in levels of NO_X (HR, 1.01; 95%CI, [1.00, 1.02]). Such an increase in the incidence of the first-time hospitalization was seen with VaD (HR, 1.08; 95%CI, [1.06, 1.10]), but not with AD (HR, 0.96; 95%CI, [0.94, 0.98]). In addition, they reported a higher HR for dementia in women who were exposed to NO_X (HR, 1.10; 95%CI, [1.07, 1.12]) in comparison to men (HR, 1.06; 95%CI, [1.03, 1.09]). Regarding NO_2 levels, there was a statistically significant increase in incidence of first-time hospitalization with VaD (HR, 1.08; 95%CI, [1.06, 1.10]) and not with AD (HR, 0.91;

95%CI, [0.89, 0.94]) per 10μg/m^3 increase in levels of NO_2 (51). Some part of such an association with air pollution might be due to comorbidities such as CVD that are both associated with air pollution and are at risk for VaD.

1.2.3 Ozone

Ozone (O_3) is also an important pollutant, which is a strong oxidant. Animal and cellular studies have shown that inhaled O_3 has neurotoxic effects (67-69) and may interfere with the central nervous system and contribute to dementia pathology. The association between exposure to ambient O_3 and cognitive function decline is a recently described phenomenon, and therefore, few studies have reported on such an association.

In a cross-sectional study, Chen et al. conducted a secondary analysis on Neurobehavioral Evaluation System-2 (NES2) data of 1,764 adults with mean age of 37.5 (SD,10.9) years who participated in the Third National Health and Nutrition Examination Survey in 1988–1991. Their results showed that for every 10ppb increase in annual O_3 a consistent increase was seen in symbol-digit substitution test (SDST; measures coding ability; β, 0.16; 95%CI, [0.01, 0.23]) and in serial-digit learning test points (SDLT; measures attention and short-term memory; β, 0.56, 95%CI, [0.07, 1.05]), which was equivalent to 3.5 and 5.3 years age-related decline in cognitive function (70).

Another cross-sectional study in Los Angeles, California, evaluated the association of air pollution with six domain-specific cognitive functions and a measure of global cognitive function in 1,469 middle-aged and older adults (mean age, 60.5 y). Their results indicated that exposure to an annual mean O_3 of 49ppb was associated with decrease in scores of verbal learning (β, −0.20; 95%CI, [−0.63, 0.2]) and executive function (β, −0.66; 95%CI,

[−1.35, 0.03]); however, only the decrease in executive function seemed to be associated with exposure to higher levels of O_3. In addition, there was no association between exposure to O_3 and decline in global cognitive function (71).

In a retrospective population-based cohort study on participants of the national Alzheimer's Disease Center (ADC) program, the association between exposure to air pollution and cognitive decline was evaluated. The investigators followed 5,419 individuals for a maximum of 7.5 years and reported a correlation between exposure to O_3 and decline in cognitive function as there was a significant difference in MMSE score between those exposed to lowest (30.4ppb to 36.7ppb) and highest levels (40.0ppb to 47.5ppb) of O_3 (β, 0.3; 95%CI, [0.1, 0.5]). The authors concluded that exposure to higher levels of O_3 accelerates cognitive decline and the presence of APOE ϵ4 accelerates such a decline (72).

In a case-control study in Taiwan, exposure to higher levels of ozone was associated with almost twice higher odds of developing AD (OR, 2.0; 95%CI, [1.14, 3.50]) and VaD (OR, 2.09; 95%CI, [1.01, 4.33]) when the highest tertile (> 21.56ppb) of exposure was compared to the lowest tertile (< 20.20ppb). They did not find any evidence of modifying the association between exposure to O_3 and VaD by APOE ϵ4 (44). On the other hand, in the nested case-control study in Taiwan by Li et al., there was no statistically significant association between odds of exposure to O_3 within five-years before diagnosis and incidence of dementia (45).

A few cohort studies have evaluated the association between exposure to O_3 and HR of dementia. A population-based cohort study in Taiwan on 95,690 individuals (age ≥ 65 y) between 2001 to 2010 demonstrated a 6% increase in HR of AD per IQR (9.36ppb) increase

in O_3 levels over baseline (HR, 1.06; 95%CI, [1.00, 1.12]). When the change in O_3 (10.91 ppb) during follow-up period was used in the model, the HR of newly diagnosed AD was increased by 211% (HR, 3.12; 95%CI, [2.92, 3.33]) (39). Their results indicated that the increasing trend of O_3 concentration over the follow-up period was more strongly associated with incidence of AD than simply mean annual levels of exposure.

In a population-based cohort study in the United Kingdom, a decreasing trend in the incidence of dementia, AD, and VaD was seen with IQR change (+5.6μg/m^3) of O_3; however, the decrease in HR was statistically significant for dementia (HR, 0.84; 95%CI, [0.75, 0.94]) and AD (HR, 0.78; 95%CI, [0.66, 0.92]), but not for VaD (HR, 0.88; 95%CI, [0.71, 1.09]) (42).

1.2.3.1 Study in Canada

The only study in Canada that evaluated the association of O_3 with dementia is the population-based cohort study by Chen et al. that included over two million residents of Ontario. This study did not find any association between exposure to O_3 and incidence of dementia (HR, 0.98; 95%CI, [0.96–1.00]; per IQR of 6.3ppb) (46).

1.2.3.2 First-Time Hospitalization With Dementia

In the study by Cerza et al, the association between exposure to O_3 and the first-time admission to hospital with the diagnosis of dementia was evaluated. Their results indicated a 6% increase in HR of dementia per 10μg/m^3 increase in the mean annual exposure to O_3 (HR, 1.06; 95%CI, [1.03–1.08]). However, such an association was not found for AD (HR, 0.98; 95%CI, [0.95–1.02]) and VaD (HR, 1.02; 95%CI, [0.98–1.06]) (51).

The contradictory results regarding the association of O_3 with incidence of dementia indicate that there might be either a weak association between them or there are other factors that modify the association of O_3 with dementia by either attenuating or strengthening its effects.

1.2.4 Meta-analyses of the Association of Air Pollution and Incidence of Dementia

Although numerous systematic reviews have evaluated the association between air pollution and dementia, the meta-analyses on such an association had been scarce at the time of formulating this study. Shortcomings of pre-existing meta-analyses include heterogeneity of assessments and methodology, as well as a limited number of included studies.

In a systematic review and meta-analysis by Tsai et al. in 2019, the association of $PM_{2.5}$ with dementia was evaluated. They searched six databases and included four studies (39, 42, 46, 50) in their meta-analysis. Using a random-effects model, they reported that by a $10\mu g/m^3$ increase in $PM_{2.5}$, the incidence of dementia would increase by 326% (HR, 3.26; 95%CI, [1.20, 5.31]). In addition, there was a statistically significant association between exposure to $PM_{2.5}$ and incidence of dementia (HR, 4.82; 95%CI, [2.28, 7.36]) (73). The high pooled HR in this study might be due to using 10 units increase in levels of $PM_{2.5}$ that might be beyond what the original data meant to present. Moreover, converting the original HR to the new increment, i.e. $10\mu g/m^3$, might not be accurate and conversion to log and back to estimates might provide extraordinarily large values for the new estimate. In

addition, the small number of included studies makes the results prone to favour larger estimates in the included studies.

Another meta-analysis by Fu et al. (74) on the association between $PM_{2.5}$ exposure and neurological disorders in 2019 included five studies in their final model: three in meta-analysis for dementia (46, 50, 75) and three for AD (39, 50) with one of them being included in both models (50). The study reported an increased HR of dementia (HR, 1.16; 95%CI, [1.07, 1.26]) and AD (HR, 3.26; 95%CI, [0.84, 12.74]) per 10μg/m^3 increase $PM_{2.5}$ levels. In addition to the concerns raised regarding the previous meta-analysis, one of the included studies (75) had overlapping data with a previous study, but reported the adjusted HR of dementia for road proximity and therefore, should have been excluded from their meta-analysis.

Although no completed meta-analyses on the association of other air pollutants, namely, $PM_{2.5}$, NO_X, and O_3, with incidence of dementia or its subtypes in cohort studies, a few are ongoing at the time of writing this report. The recency of the issue, discrepant reports from around the world, and lack of an updated meta-analysis suggests that an updated systematic review and meta-analysis is needed in order to include recent studies with valid methods of synthesis in order to direct appropriate attention toward the important potential associations between air pollutants and incidence of dementia based on best available evidence.

1.3 Objectives

This study aimed to evaluate the association between exposure to three main outdoor air pollutants, i.e., $PM_{2.5}$, NO_X, and O_3, with incidence of dementia or its subtypes by

evaluating the cohort studies on individuals over 40 years old that have reported HR as their outcome. The aim of this systematic review and meta-analysis was to evaluate the association between air pollution with incidence of dementia or its subtypes amongst individuals over 40 years of age in population-based cohort studies.

The results of this study will be beneficial for scientists who want to conduct studies on the association of exposure to air pollution and dementia because this study informs them of the gaps and flaws of the previous studies and guides them to devise future studies. In addition, the public health authorities and government will be able to evaluate the current evidence and plan for future actions. Moreover, the citizens of the world will be aware of the importance of the issue and advocate the policies to decrease air pollution across the globe.

Chapter 2

2 Materials and Methods

This study aimed to evaluate the association of dementia with particulate matter 2.5 ($PM_{2.5}$), nitrogen oxides (NO_X), nitrogen dioxide (NO_2) and ozone (O_3) in a systematic review and meta-analysis. The protocol of the study was registered in PROSPERO with the registration number CRD42020219036.

2.1 PECO

In this study, the PECOS (population, exposure, controls, outcome, and study design) was defined as follows:

P: Adults over 40 years of age, from any country, whether urban or rural;

E: Exposure to higher levels of air pollutants, including any one or more of PM2.5, NO_x, NO_2, or O_3;

C: Exposure to lower levels of these air pollutants;

O: Incidence of dementia or its subtypes, as reported by hazard ratios (HR); and

S: Cohort studies (retrospective, prospective, population-based, and registry-based).

The search was not limited to any specific period, or by language.

2.2 Searching Databases and Data Extraction

2.2.1 Information sources

The search strategy was designed and executed in collaboration with medical librarians at Western University. The search was conducted twice (April 2020 and August 2020). The

first search was very broad and was performed to identify different types of air pollutants and study types. Based on the papers that met inclusion criteria during screening of the results from the first search, we conducted a second search to include more specific terms for the most commonly-studied pollutants, as well as to further focus the study design toward cohort studies only. Databases searched included PubMed (1809 - present), MEDLINE (1946 – present), EMBASE (1947 – present), PsycINFO (1806 – present), Scopus (1788 – present), and Web of Science (1900 – present). We also searched gray literature for unpublished work and dissertations. At the data extraction step, we also contacted some of the authors for additional information or incremental HR when the study had reported categorical comparisons between high exposure and low exposure. The final search was completed on August 15, 2020.

2.2.2 Search Strategy

The search strategy included the combination of terms for the outcome and terms for the exposure. PubMed was searched with the following terms:

("Alzheimer Disease"[Mesh] OR "Dementia"[Mesh] OR alzheimer* OR dementia) AND ("air pollution"[MeSH Terms] "Particulate Matter"[MeSH Terms] OR "Nitrogen Oxides"[MeSH Terms] OR "Nitrogen Dioxide"[MeSH Terms] OR "Nitrous Oxide"[MeSH Terms] OR "Ozone"[MeSH Terms] "Petroleum"[MeSH Terms] OR "Sulfur Oxides"[MeSH Terms] OR (air pollut*) OR (Particulate Matter*) OR (Nitrogen AND (Oxide* OR dioxide*)) OR (Nitrous AND Oxide*) OR (Ozone) OR (Sulfur AND Oxide*) OR smok* OR "Cooking"[Mesh] OR cooking* OR "environmental pollution"[MeSH Terms] OR "Environmental Pollutants"[Mesh Terms] OR "Environmental Exposure"[Mesh] OR

"traffic-related pollution"[MeSH Terms] OR "Vehicle Emissions"[Mesh Terms] OR traffic-related OR traffic* OR car* OR Vehicle* OR road* OR transport* OR road-proximity OR "Fossil Fuels"[Mesh] OR "Petroleum Pollution"[Mesh] OR gas OR gasoline* OR diesel* OR fossil* OR petroleum* OR fuel* OR environment* OR "PM2.5" or PM10 or NOx OR NO2) AND (pollut* OR exposur* OR emission*).

No filters were used to limit the study by language, study type, or year of publication. The search terms for other databases are provided in Appendix A.

2.2.3 Study Selection

After completing the search, the results were imported to a reference manager software (EndNote). Screening was performed by two independent reviewers. First, the duplicated studies were removed. The title and abstract of the studies were assessed and irrelevant papers were removed. Then the full texts of the remained papers were examined and included studies were subjected to data extraction and decision on inclusion in the meta-analysis.

2.2.4 Data Collection Process

Data from included studies were extracted onto an Excel spreadsheet. The pilot form was used in the first pass on three papers, and after reflection, other items were added or modified to make the final form. The final form was used by one author for extracting the data from the rest of the papers. A second investigator read the full texts and verified the data entry.

Some of the papers did not use increments of air pollutants in their estimation of HR. Instead, they compared the highest exposure with the lowest exposure. To have a better estimation of the HR, we contacted the authors to request more detailed estimates.

2.2.5 Data items

The following data were extracted from each included study: 1) study identifiers: Author surname, year of publication, type of cohort (prospective or retrospective), and name of the study or cohort if available; 2) characteristic of the studied population: country, state/province, and city, included population, age at baseline; 3) information on exposure: studied pollutants, method of pollutant measurement, exposure period, units of measurement, and the correlation coefficient between pollutants if more than one pollutant was studied; 4) information on those with a lower level of exposure; 5) information on the outcome: follow-up period, the incidence of dementia and its subtypes, age at the time of diagnosis, applied statistical tests, and hazard ratio according to the increment of pollutants.

2.3 Risk of Bias in Individual Studies

To ascertain the validity of the included studies, the risk of bias was assessed by “Tool to Assess Risk of Bias in Cohort Studies”. The tool is devised by the CLARITY Group at McMaster University and comprises eight questions, each of which addresses a different type of bias and has four possible answers: Definitely yes (low risk of bias); Probably yes, Probably no, and Definitely no (high risk of bias). According to the answers to each question, the studies were assigned to high, moderate, or low risk of bias. The risk of bias assessment was performed independently by two authors. The information was used to

prioritize the studies that could be included in the study or should be removed in sensitivity analysis.

2.4 Statistical Analysis

2.4.1 Summary Measures

The primary outcome measure was HR for incidence dementia and its subtypes, estimated by the Cox proportional hazard model or its derivatives. This study aimed to evaluate whether HR for dementia was associated with increasing pollutant levels. When enough information on the HR of dementia with an increase in levels of air pollutants was not available, we contacted the authors for additional estimations. The summary measure was the pooled HR for the incidence of dementia and its subtypes using the random-effects model.

2.4.2 Converting Units of Measurement and Making the Estimates Comparable Across Studies

To make the reported estimates by included studies comparable, we made some changes to the increments of air pollutants. $PM_{2.5}$ is mainly reported in $\mu g/m^3$ and hence, the same unit of measurement was used and if any study had reported the level of $PM_{2.5}$ in ppb, we would convert it to $\mu g/m^3$ (Table 1). To make the studies on $PM_{2.5}$ comparable, HR and 95% CI were estimated for a 1-unit increase in $PM_{2.5}$ level. For exposure to NO_X, exposure units were converted to $\mu g/m^3$ and HR and 95% CI were estimated for a 10-unit increase in NO_X level. For NO_2, the unit of exposure in $\mu g/m^3$ was converted to ppb and HR and 95% CI were estimated for a 10-unit increase in NO_2 level. The unit of O_3 measurement

was converted from pbb to μg/m^3 and HR estimate and 95% CI were calculated for 10-unit changes in O_3 level.

Table 1. Conversion of the Units of Measurement for Studied Air Pollutants

Pollutant	Levels in ppb	levels in μg/m^3
PM2.5	1	1
NO_x	1	1.91
NO_2	1	1.9125
O_3	1	1.9957

The formulae that were used to convert the reported estimates to new estimates based on the new increments were as follows:

- For converting the original HR to HR for the new increment of pollutants, the natural logarithm of the HR was calculated, multiplied by the new increment, and then divided by the original increment (HR_O, original HR; HR_N, New HR; I_O, old increment; and I_N, new increment):

$$ln(HR_N) = ln(HR_O) \times \frac{I_N}{I_O}$$

- For converting confidence levels to new confidence levels, the following formulae were used (LCL, lower confidence level; UCL, upper confidence level; O indicates the old value and N indicates new values for the new increment):

$$\beta = \frac{ln(HR_O)}{I_O}$$

$$SE = \frac{ln(LCL_O) - (\beta \times I_O)}{1.96 \times I_O}$$

$$95\%\ LCL_N = exp[(\beta \times I_N) - (1.96 \times SE \times I_N)]$$

$$95\%\ UCL_N = exp[(\beta \times I_N) + (1.96 \times SE \times I_N)]$$

2.4.3 Meta-analysis and Subgroup Analysis

The meta-analysis for computing pooled HR uses the inverse variance of each study estimate and therefore, the natural logarithm of HR estimate and standard error of each included study were introduced to RevMan (Review Manager [Computer program]. Version 5.4. The Cochrane Collaboration, 2020) for calculating the pooled HR estimates. The studies had included populations from different parts of the world, and they were clinically heterogeneous with regard to measuring exposure and reported outcome. Therefore, the random-effects model was used to estimate the pooled HR. The pooled HR for dementia was estimated separately for each pollutant.

The included studies had reported on different outcomes, namely, the incidence of dementia, first-time hospitalization with dementia, and subtypes of dementia such as Alzheimer's disease (AD), vascular dementia (VaD), and non-Alzheimer dementia (NAD). The main goal of this meta-analysis was to provide a pooled estimate of HR for studies that reported on the association between air pollution and dementia, irrespective of the subtype

of dementia and incidence of hospitalized or non-hospitalized cases of dementia. It is noteworthy that a recent study has shown that cases that were classified as AD demonstrated the neuropathological features of other types of dementia in autopsy examination (5) and therefore, relying on the clinical classification of subtypes of dementia might be misleading. Moreover, most of the studies had reported on the HR for dementia as well as for its subtypes which enabled subgroup analysis to evaluate the effect of each outcome on the pooled HR.

Whenever the study had reported on the HR for dementia, this estimate was used in the meta-analysis to estimate pooled HR. Whenever they had reported on only subtypes of dementia, that subtype was included in the analysis as a subgroup. In addition, studies that reported on the HR of the first-time hospitalization with dementia were included as a subgroup in the analysis. For each pollutant, HR estimates were calculated for dementia and its subgroups. Moreover, because the geographic region might affect the incidence of dementia, the subgroup analysis was performed according to the country/continent where the study was conducted.

We planned to perform a meta-analysis according to the decades that the exposure happened and evaluate the trend of changes in pollutants levels and incidence of dementia. Moreover, we planned to evaluate and compare the association of long-term exposure to air pollutants with incidence of dementia between males and females.

2.4.4 Assessing Heterogeneity Across Studies

The heterogeneity in effect size across the included studies was quantified by I^2 and reported for all the meta-analyses as well as subgroup analyses. I^2 was interpreted as a

continuous scale, with higher values inferring higher heterogeneity in effect size across studies. The advantage of I^2 to other statistics of assessing heterogeneity such as Q and τ^2 is that it is neither sensitive to the number of studies nor to the scale of measurement as it is the ratio of true heterogeneity to the total variation in observed effects (76).

2.4.5 Risk of bias across studies

For each study, the HR was plotted against its inverse standard error to create a funnel plot, which was inspected visually for each studied pollutant for visual evidence of potential publication bias. In addition, "*metabias*" package in Stata 16SE (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) was used to perform Egger's test to explore whether there is evidence of a small study-effect indicative of publication bias, , where a p-value < 0.10 would indicate small studies are missing from the available set of identified studies.

2.4.6 Additional Analyses

Sensitivity analyses were performed to evaluate robustness of the pooled estimate to the presence or absence of studies according to predefined variables. Since studies were heterogeneous regarding the included population and outcome of the study, studies with a small population were removed one-by-one from the meta-analysis and the effect on the pooled HR was examined. In addition, studies from certain parts of the world, for instance, Asia, were removed to examine the robustness of the pooled effect measure to potential geographic reporting differences. Because some studies had reported outcomes other than total incidence of dementia, they were also subjected to sensitivity analysis to examine the effect of differing definitions on the pooled estimates.

Chapter 3

3 Results

3.1 Study selection

The search was completed on August 14, 2020. Searching PubMed yielded 3,368 papers. Web of Science and Scopus database search resulted in 1,078 and 164 papers. Medline, Embase, and APA PsycInfo were accessed through Ovid Lippincott Williams & Wilkins Total Access Collection and yielded 1,008 papers. After removal of 1,174 duplicate papers, 4,462 papers were assessed for eligibility. Finally, a total of 16 papers were selected for full text review.

Of the studies collected for full-text review, two papers did not report the incidence of dementia for increments of NO_2 or $PM_{2.5}$ and were excluded from the meta-analysis. A study by Oudin et al. on the Betula Cohort in 2016 (64) was excluded from the meta-analysis because an update to the data was published by the same author in 2019 where the authors examined the role of APOE $\epsilon 4$ on the association estimate (65). The reasons for excluding the papers are described in the PRISMA flow diagram (Fig. 1).

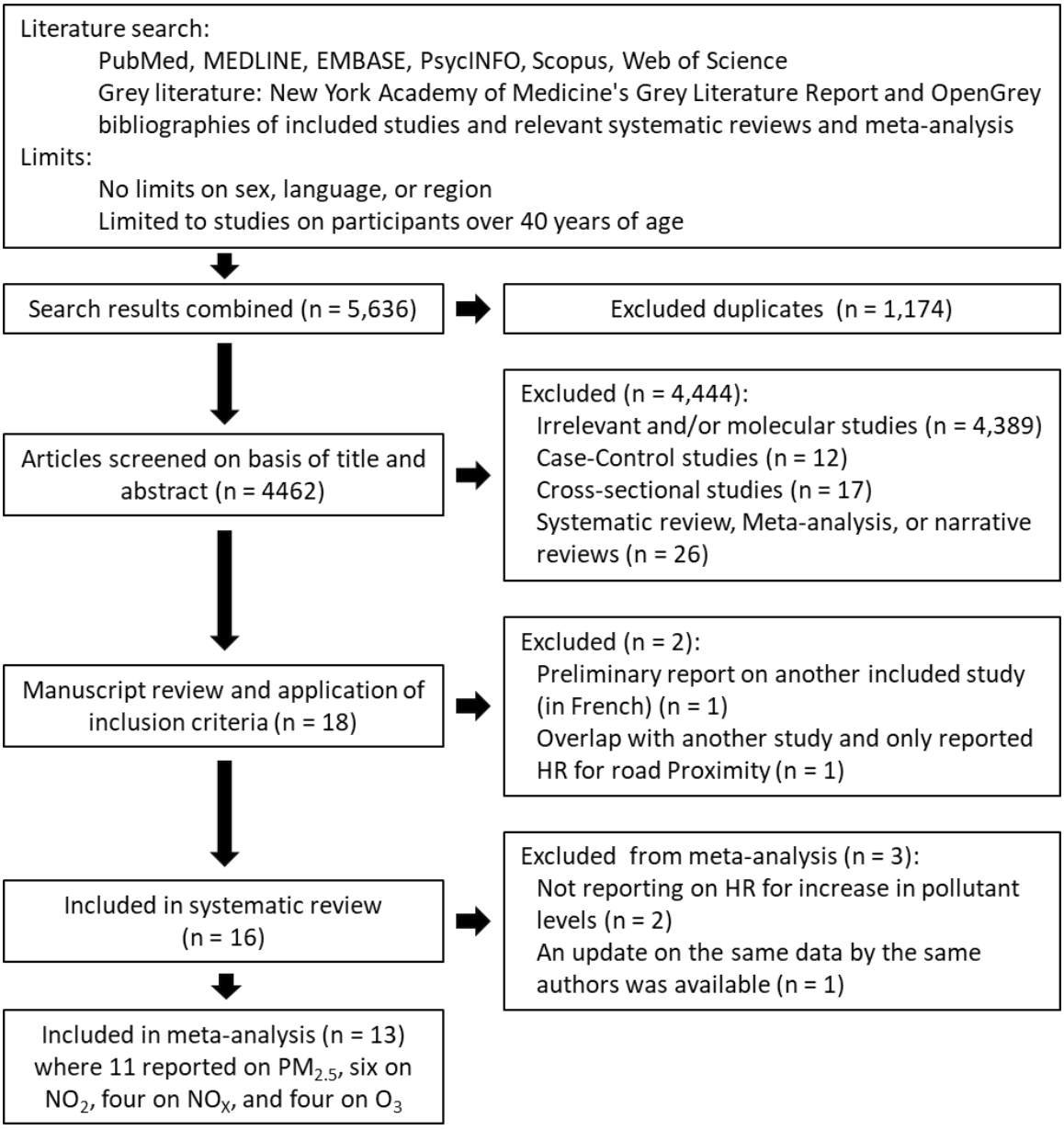

Figure 1. PRISMA Flow Chart of Review Process and Screening Papers

3.2 Study Characteristics

The characteristics of the included studies are presented in Tables 2 to 5. Finally, a total of 16 population-based cohort studies, all published in English, were included in this systematic review and 13 were included in the meta-analysis. During the data extraction,

some information from almost every study was not reported in papers or supplementary information. In total, authors from eight studies provided additional information for our analysis. Since the studies were population-based cohorts, access to the data was generally limited to the time of study, and authors could not add additional information.

The years of recruitment of included cohorts at baseline ranged from 1993 to 2005 and the endpoint of cohorts ranged from 2003 to 2013. The longest cohorts were from the Betula project, Umea, Sweden, that followed the population for 17 years (41, 64-66). The studies were conducted on the population of the following countries: Sweden (5 studies) (41, 43, 64-66), Canada (4 studies) (46-49), the United States (3 studies) (40, 50, 52), Taiwan (2 studies) (39, 63), the United Kingdom (51), and Italy (51).

3.2.1 Population

The total population in the included studies was 28,285,298. Included individuals were ≥ 45 years and free of dementia at baseline, for whom the data on exposure to air pollution was available. Both sexes were included in the included studies except the study by Cacciottolo et al. (40) that examined the association of $PM_{2.5}$ with cognitive impairment of women within the Women's Health Initiative Memory Study (WHIMS). The mean (SD) of age at baseline was not reported in some studies and contacting the authors did not yield additional information for most of them. Moreover, some studies reported age as a categorical variable and data on baseline age were presented as the frequency of individuals in the specific age groups (Table 2 and 3).

The latest endpoint in included studies was 2013 which seems reasonable due to the registry-based design of the cohorts and since such data need time to be collected, cleaned,

and become available to researchers. In addition, a lengthy time of acquisition and analyzing such data might cause several years of delay in reporting the results. Therefore, the studies that were published in 2020 could not provide information on the situation after 2013.

Table 2.Information on Included Studies [a]

Author, Year	Study Name	Region, Country	Baseline Age, y[b]	Baseline Date	Included papulation	Endpoint
Andersson et al. (2018) (66)	Betula Cohort	Sweden	68.5 (9.4) Range, 55-85;	1993	**the second test wave T2** (1993–1995), where sample 3 (S3) was introduced, and sample 1 (S1) was tested for the second time.	2010
Cacciottolo et al. (2017) (40)	WHIMS	US, 48 states	Range, 65-79	1995	Community-dwelling women of ε3/3, ε3/4, and ε4/4 alleles of **European ancestry** (primarily non-Hispanic whites) with complete PM2.5 exposure estimates	2010
Carey et al. (2018) (42)	CPRD	London, UK	62.1 (8.4); range, 50-79	2005	Individuals in 75 practices who had been registered for 1 year continuously with their practice.	2010
Cerza et al. (2019) (51)	NA	Rome, Italy	74.5 (6.9)	2001	All residents in Rome who were ≥ 65 years old and filled out the questionnaire of the population census from 2001.	2013
Chang et al. (2014) (77)	A subset of NHIRD	Taiwan	61.4 (8.5)	2000	Individuals ≥ 50 years or older for whom estimable air pollution data were available but did not present a history of head injury, stroke, dementia before 2000	2010

[a] Abbreviations: NA, Not available; CPRD, The Clinical Practice Research Datalink; NHIRD, the National Health Insurance Research Database; and WHIMS, The Women's Health Initiative Memory Study.

[b] Data are presented as mean (SD) and range if available.

Table 2. Information on Included Studies [a] (Continued)

Author, Year	Study Name	Region, Country	Baseline Age, y[b]	Baseline Date	Included papulation	Endpoint
Chen et al. (2017) (46)	ONPHEC	Ontario, Canada	66.8 (8.2); Range, 55-85	2001	Canadian-born individuals who resided in Ontario for> 5 years and were registered with provincial health insurance	2013
Grande et al. (2020) (43)	SNAC-K	Stockholm, Sweden	74.1 (10.7)	2001	Residents of the Kungsholmen district in central Stockholm from March 21, 2001, through August 30, 2004, and 60 ≥ years	2013
Ilango et al. (2020) (47)	NA	Ontario, Canada	60.19 (10.56)	1996	Canadian-born Ontario residents who participated in the **1996–97** cycle of the National Population Health Survey (NPHS) and **2000/01**, **2003** and **2005** cycles of the Canadian Community Health Survey (CCHS). if they lived in Ontario for at least 5 years and were ≥45 years or older at the date of survey (i.e. study baseline).	2013
Jung et al. (2015) (39)	LHID2000	Taiwan	NA	2001	Individuals from LHID2000 aged ≥65 years at the baseline	2010
Kioumourtzoglou et al. (2016) (50)	NA	US (50 cities) across the northeastern US)	75.6 (7.6)	1999	Fee-for-service Medicare enrollees (≥ 65 years old)	2010

[a] Abbreviations: NA, Not available; LHID2000, The longitudinal health insurance database 2000; ONPHEC, Ontario Population Health and Environment Cohort; and SNAC-K, Swedish National Study on Aging and Care in Kungsholmen.

[b] Data are presented as mean (SD) and range if available.

Table 2. Information on Included Studies [a] (Continued)

Author, Year	Study Name	Region, Country	Baseline Age, y[b]	Baseline Date	Included papulation	Endpoint
Lee et al. (2019) (52)	NA	Seven states of Southeastern US (AL, FL, GA, MS, NC, SC, and, TN)	70.4 (7.3)	2000	Beneficiaries of the Medicare fee-for-service (FFS) plan who were aged ≥ 65 y and resided in the southeastern part of the United States between 2000 and 2013.	2013
Oudin et al. (2016) (64)	Betula Cohort	Umea municipality, Sweden	Range, 55-85	1993	Participants who were > 55 years from samples S1, S2, and S3 gathered at **T2**	2010
Oudin et al. (2018) (41)	Betula Cohort	Umea municipality, Sweden	Range, 55-85	1993	**T**he second test wave **T2** (1993–1995), where sample 3 (S3) was introduced, and sample 1 (S1) was tested for the 2nd time.	2010
Oudin et al. (2019) (65)	Betula Cohort	Umea municipality, Sweden	69 (NA); Range, 55-85	1993	**T**he second test wave **T2** (1993–1995), where sample 3 (S3) was introduced, and sample 1 (S1) was tested for the 2nd time.	2010
Smargiassi et al. (2020) (49)	NA	Quebec, Canada	69.70 (6.76)	2000	Adults ≥ 65 years who lived in Quebec for the last four years (Open Cohort)	2012
Yuchi et al. (2020) (48)	NA	Metro Vancouver, BC	Range, 45-84	1994	All adults aged 45–84 years old who resided in Metro Vancouver, registered with MSP, and had lived in Metro Vancouver during the exposure period	2003

[a] Abbreviations: NA, Not available; CPRD, The Clinical Practice Research Datalink

[b] Data are presented as mean (SD) and range if available.

Table 3. Information on Included Studies [a]

Author, Year	Case Ascertainment/ Diagnosis Criteria	Follow-up Duration, y[b]	Follow-up Period	Statistical Models	Adjusted covariates	Age at Diagnosis[b]
Andersson et al. (2018) (66)	DSM-IV	NA	1993-2010	Cox proportional HR	adjusted for baseline age, education, physical activity, smoking, sex, BMI, WHR, alcohol, and ApoE4, for baseline medical history of DM, HTN, and stroke.	NA
Cacciottolo et al. (2017) (40)	DSM-IV; The standardized WHIMS outcome ascertainment protocols	9.9	1999-2010	Cox proportional HR	age, geographic region, education, income, employment status, lifestyle factors (smoking; alcohol use; physical activities) and clinical characteristics (use of hormone treatment, depression, BMI HCL, HTN, DM, and histories of CVD)	NA
Carey et al. (2018) (42)	ICD10 Read codes for dementia within QOF.	6.9	2005-2013	Cox proportional HR	Age, sex, ethnicity, smoking, alcohol, BMI and Index of Multiple Deprivation.	77.2 (6.2)
Cerza et al. (2019) (51)	ICD-9-CM	10.6	2001-2013	Cox proportional HR	Age, sex, education, place of birth, marital status, area-based socioeconomic position	77.1 (6.5)
Chang et al. (2014) (77)	ICD-9-CM	NA	2000-2010	Cox proportional HR	Age, sex, monthly income, DM, IHD, HTN, COPD, alcoholism and urbanization	61.4 (8.5)

[a] Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; HCL, hypercholesterolemia; HTN, hypertension; IHD, ischemic heart disease; NA, not available; WHR, waist-hip ratio; and WHIMS, the Women's Health Initiative Memory Study.

[b] Data are presented as mean (SD) if available unless stated otherwise

Table 3. Information on Included Studies [a] (Continued)

Author, Year	Case Ascertainment/ Diagnosis Criteria	Follow-up Duration, y[b]	Follow-up Period	Statistical Models	Adjusted covariates	Age at Diagnosis[b]
Chen et al. (2017) (46)	population-based health administrative databases with a validated algorithm	10 (3.3)	2001-2013	multilevel random-effects Cox proportional HR	Age, sex, and stratified region, neighborhood-level income, education, unemployment rate, Urban residency and a North/South indicator, pre-existing brain injury, stroke, DM, HTN, CAD, heart failure, and arrhythmia, and Indirectly adjusted for smoking, physical activity, obesity, and education (Model 5)	73.8 (6.9)
Grande et al. (2020) (43)	Dementia: DSM-IV AD: according to NINDS/ADRD criteria VaD: NINDS and ARN	6.01 (2.56)	2001-2013	Cox proportional HR	Age, sex, educational attainment, smoking, physical inactivity, SES, early retirement, BMI, depression, baseline MMSE score, and cardiovascular risk factors	Dementia: 83.1 (7.4)
Ilango et al. (2020) (47)	Patients' records in the registry	10.6(3.7)	2002-2013	Cox proportional HR and an Aalen additive hazards model	Age, sex, education, marital status, income quintile, smoking status, BMI, physical activity, rural residence and northern region; area level: recent immigrants, unemployment and education.	NA

[a] Abbreviations: ADRD, Alzheimer's Disease and Related Disorders Association; ARN, Association Internationale Pour la Recherché et l`Enseignement en Neurosciences; BMI, body mass index; CAD, coronary heart disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; IHD, ischemic heart disease; NINDS, the National Institute of Neurological and Communicative Diseases and Stroke; MMSE, Mini-Mental State Examination; and NA, not available.

[b] Data are presented as mean (SD) if available unless stated otherwise

Table 3. Information on Included Studies [a] (Continued)

Author, Year	Case Ascertainment/ Diagnosis Criteria	Follow-up Duration, y[b]	Follow-up Period	Statistical Models	Adjusted covariates	Age at Diagnosis[b]
Jung et al. (2015) (39)	MMSE, NINCDS-ADRDA criteria, ICD-9-CM, DSM-IV, Hachinski ischemic score	NA	2000-2010	Cox proportional HR	age, gender, income, DM, HTN, MI, stroke, asthma and COPD	NA
Kioumourtzoglou et al. (2016) (50)	ICD-9-CM	NA	1999–2010	Cox proportional HR and Anderson and Gill Extension	Age, sex, race, year of follow-up, any previous admission for CHF, COPD, MI, or DM and number of days spent in intensive and coronary care units, ZIP-code level median income as a proxy for SES.	NA
Lee et al. (2019) (52)	ICD-9_CM	Median, 6	2000-2013	Extended Cox Model (Andersen-Gill)	Age, sex, race, Medicaid eligibility, educational attainment at the Zip Code level, and U.S. state of address.	82.2
Oudin et al. (2016) (64)	DSM-IV	11.4	1993-2010	Cox proportional HR	Baseline age, education, physical activity, smoking, sex, BMI, WHR, alcohol, ApoE4, medical history of DM, HTN, and stroke.	NA

[a] Abbreviations: ADRDA, Alzheimer's Disease and Related Disorders Association; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; MI, myocardial infarction; MMSE, Mini-Mental State Examination; NINCDS, the National Institute of Neurological and Communicative Diseases and Stroke; NA, not available; SES, socioeconomic status.

[b] Data are presented as mean (SD) if available unless stated otherwise

Table 3. Information on Included Studies [a] (Continued)

Author, Year	Case Ascertainment/ Diagnosis Criteria	Follow-up Duration, y[b]	Follow-up Period	Statistical Models	Adjusted covariates	Age at Diagnosis[b]
Oudin et al. (2018) (41)	DSM-IV	11.4	1993-2010	Cox proportional HR	Age, Education, physical activity, smoking, sex, BMI, WHR, and alcohol consumption, APOE4	NA
Oudin et al. (2019) (65)	Registry files ICD-9 and ICD-10	7.3(4.3)	2000-2013	extended Cox proportional HR	stratified for sex, adjusted for calendar year, and indexes of social and material deprivation.	NA
Smargiassi et al. (2020) (49)	ICD-9 or ICD-10	NA	1999-2003	Cox proportional HR	Age, sex, comorbidities (TBI, DM, HTN, stroke, CAD, CHF, and arrhythmia), household income, education and ethnicity	Median, 76

[a] Abbreviation: BMI, body mass index; CAD, coronary heart disease; CHF, congestive heart failure; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; NA, not available; TBI, traumatic brain injury; WHR, waist-hip-ratio

[b] Data are presented as mean (SD) if available unless stated otherwise

3.2.2 Exposure

Among the included studies, four, three, and one exclusively reported on exposure to $PM_{2.5}$ (40, 41, 50, 52), NO_X (64-66), and NO_2 (63), respectively. Other studies reported on two or more exposures and few studies reported correlation coefficient between pollutants. Exposure was measured through various methods. For most of the studies, a land use regression (LUR) model was used to assign the concentration of the pollutants to the postal code of the residents. These measurements have their limitations and assigning the pollutant level to a specific area was not similar among studies. Some studies used information from satellites along with data from pollutant measuring stations to estimate the population exposure in each residential area (Table 4). While the exposure period was not clearly separated from the follow-up period in most of the studies, a study by Lee et al. on the association of $PM_{2.5}$ and dementia considered a five-year-lag before developing dementia as the exposure period (52). Additionally, Ilango et al. examined the mediating role of cardiovascular diseases (CVD) in developing dementia after exposure to No_2 and/or $PM_{2.5}$. They considered a three-year exposure before a five-year lag for developing dementia during which the CVD could develop (47).

3.2.3 Controls

In all included studies, the incidence of dementia was evaluated against those who had not developed dementia by Cox proportional hazard regression model or its derivatives (Table 3). Since almost everyone in the population was exposed to some degree to the air pollutants, some studies categorized the exposure according to the level of exposure. When the exposure level was used as a categorical variable in the regression models and the hazard ratio (HR) for unit(s) increase in air pollutants was not available, the authors

were contacted for an estimate of HR per increments of pollutants and four authors responded and sent the requested estimates The information on two studies that had reported the categorical levels of exposure (40, 63) could not be obtained and therefore, they were excluded from the meta-analysis. Overall, eight authors responded to our request for additional information about age at baseline, duration of follow-up, and exposure period.

Table 4. Information on Evaluated Pollutant, Exposure Measurement, and Exposure Period [a]

Author, Year	Pollutants	Measures of Exposure	Exposure period
Andersson et al. (2018) (66)	NOx	LUR model based on measurements during a four-week long period between November 2009 and June 2010.	1993-2010
Cacciottolo et al. (2017) (40)	$PM_{2.5}$	A spatiotemporal model that integrated AQS and the output of chemical transport models to at all WHIMS residential locations in 1999–2010.	1999-2010
Carey et al. (2018) (42)	NO2, $PM_{2.5}$ O3	Modelled annual concentrations for air pollutants were estimated using the KCL urban dispersion modelling system at a resolution of 20×20 m from 2004-2010	2004-2010
Cerza et al. (2019) (51)	$PM_{2.5}$ NO2 NO_X O3	LUR models. $PM_{2.5}$ was measured in 20 sites, and NOx was measured in 40 sites in three two-week periods during 2010. To estimate summer daily ozone (8 h) exposure FARM was used.	2001-2013
Chang et al. (2014) (77)	NO2	Data from 74 ambient air quality monitoring stations were used. Yearly average concentrations of pollutants were calculated from the baseline to the end of the study	2000-2010

[a] Abbreviations: AQS, air quality system; FARM, Flexible Air quality Regional Model; LUR, land use regression; and WHIMS, the Women's Health Initiative Memory Study

Table 4. Information on Evaluated Pollutant, Exposure Measurement, and Exposure Period [a] (continued)

Author, Year	Pollutants	Measures of Exposure	Exposure period
Chen et al. (2017) (46)	$PM_{2.5}$ NO2 O3	$PM_{2.5}$: information from satellite observations in combination with outputs from a global atmospheric chemistry transport model (GEOS-Chem CTM) producing an annual mean concentration of PM2.5 (1× 1 km) yearly between 1998 and 2012. NO2: a national LUR model using NO2 observations at fixed-site monitors from National Air Pollution Surveillance Network. O3: Environment and Climate Change Canada has produced a long-term annual mean warm-season exposure surface of O3 (21 ×21 km) covering Canada between 2002 and 2009.	1994-2013
Grande et al. (2020) (43)	$PM_{2.5}$ NO_X	Annual mean air pollution levels from local sources were calculated using emission inventories describing traffic and nontraffic sources for 1990, 1995, 2000, 2005, and 2011. Annual mean levels of $PM_{2.5}$ and NO_X for 1990 through 2011 were obtained from linear interpolation during the 4 years between each model simulation, and levels for 2012 and 2013 were set as of 2011.	5 years

[a] Abbreviation: LUR, land use regression

Table 4. Information on Evaluated Pollutant, Exposure Measurement, and Exposure Period [a] (continued)

Author, Year	Pollutants	Measures of Exposure	Exposure period
Ilango et al. (2020) (47)	NO_2 $PM_{2.5}$	used previously estimated mean measurements of NO_2 and $PM_{2.5}$ at a spatial resolution of about 1 x 1km for each year between 1993 and 2013. Calculated averages of pollutant measurements over the three years leading up to the time of baseline survey completion.	The 3-year average of pollutants with a 5-year lag before dementia. CVD could develop in the 5-year period
Jung et al. (2015) (39)	$PM_{2.5}$ O_3	Hourly PM_{10} and O_3 data available from 70 Taiwan EPA monitoring stations on Taiwan's main island from 2000 through 2010. The mean ratio between $PM_{2.5}$ and PM_{10} during 2006-2010 was used to estimate the concentrations of $PM_{2.5}$ from 2000 to 2006.	1999-2010
Kioumourtzoglou et al. (2016) (50)	$PM_{2.5}$	$PM_{2.5}$data obtained from the U.S. EPA and AQS database (U.S. EPA 2013). Annual $PM_{2.5}$ averages within each city were estimated from 1999 through 2010.	1999-2010
Lee et al. (2019) (52)	$PM_{2.5}$	The observations from a satellite with a 1-km resolution were calibrated to PM2.5 data from ground monitors	5 years before Dx

[a] Abbreviations: AQS, air quality system; CVD, cardiovascular diseases; Dx, diagnosis; and EPA, Environmental Protection Agency

Table 4. Information on Evaluated Pollutant, Exposure Measurement, and Exposure Period [a] (continued)

Author, Year	Pollutants	Measures of Exposure	Exposure period
Oudin et al. (2016) (64)	NO_X	LUR model for Umeå to estimate the annual average levels of nitrogen oxides (NO_X).	Annual mean NOx concentration (estimated for 2009–2010) was used as a marker for long-term exposure to air pollution
Oudin et al. (2018) (41)	$PM_{2.5}$	They used data on the annual mean concentration of $PM_{2.5}$ for 1990, 2000 and 2010, calculated by the Swedish Meteorological and Hydrological Institute (SMHI).	1993-2010 measured at 1990, 2000, 2010
Oudin et al. (2019) (65)	NO_X	A LUR model was used to estimate the concentration at the residence of each study person.	Annual mean NOx concentration (estimated for 2009–2010) was used as a marker for long-term exposure to air pollution
Smargiassi et al. (2020) (49)	$PM_{2.5}$ NO_2	NO_2: a national LUR model $PM_{2.5}$: satellite imagery	2000-2012
Yuchi et al. (2020) (48)	$PM_{2.5}$ NO_2 NO	LUR models specific to Metro Vancouver were applied to estimate exposure to pollutants. monthly predicted air pollution concentrations were averaged to obtain air pollutant concentrations over the entire exposure period.	1994-1998 (January 1994–December 1998)

[a] Abbreviation: LUR, land use regression.

3.2.4 Outcome

Case ascertainment was not consistent among the studies. All cohorts were retrospective and therefore, the main method of categorizing dementia or its subtypes as a diagnosis was through examining administrative database or electronic health record diagnosis. In this sense, most of the studies used different versions of the International Classification of Diseases (ICD) according to the year of the study and development of codes. Other studies used DSM-IV criteria to diagnose dementia, alone or in combination with other tools such as ICD, MMSE, Hachinski ischemic score, or other validated algorithms (Table 3).

The total incidence of dementia and its subtypes, namely, Alzheimer's disease (AD), vascular dementia (VaD), and non-Alzheimer dementia (NAD), was 2,381,422 (11.88%) in a total population of 28,285,298. Some studies reported the incidence of AD and/or VaD as the sole outcome or as a subgroup of dementia with a total of 848,702 cases of AD and 166,235 cases of VaD. Three studies reported the incidence of first-time hospitalization with dementia (50-52). The total incidence of the first first-time hospitalization with dementia was 1,634,610 (including 846,046 cases of AD and 165,420 cases of VaD) in a total population of 23,478,591. The total included population across all included studies was 28,285,298, and approximately 83% of the included population in this systematic review was from these three studies on the first-time hospitalization with dementia (Table 5).

It is noteworthy that four studies from Sweden (41, 64-66) used data from the Betula project, a population-based longitudinal study on memory, health, and ageing, and reported incidence of dementia and subtypes in association with exposure to different pollutants.

Hence, there might be overlap among included populations and reported cases of dementia and for calculating the total population and incidence of dementia and its subtypes, only the largest sample size and incidence of dementia were included.

Table 5. Population Included in Each Study and Number of Incidence Cases [a]

Author, Year	Included Population (n)	Male, n (%)	Outcome			
			Dementia	AD	Vad	NAD
Andersson et al. (2018) (66)	1721	985 (57%)	302[b]	191	111	-
Cacciottolo et al. (2017) (40)	3647	0	173	-	-	-
Carey et al. (2018) (42)	130,978	65,130 (49.7%)	2181	848	634	-
Cerza et al. (2019) (51)	350,884	145,994 (42%)	21,548	7,669	7,494	-
Chang et al. (2014) (77)	29,547	13606 (46%)	1,720	-	-	-
Chen et al. (2017) (46)	2,066,639	966,246 (46.8%)	257,816	-	-	-
Grande et al. (2020) (43)	2,927	1082 (37%)	364	218	70	146
Ilango et al. (2020) (47)	34,391	14,555 (42%)	2,559	-	-	-
Jung et al. (2015) (39)	95,690	-	-	1,399	-	-
Kioumourtzoglou et al. (2016) (50)	9,817,806	43.70%	203,463	266,725	-	-
Lee et al. (2019) (52)	13,309,901	5,871,658 (54.1%)	1,409,599	571,652	157,926	-
Oudin et al. (2016) (64)	1806	773 (43%)	-	191	111	-
Oudin et al. (2018) (41)	1,806	773 (43%)	-	191	111	-
Oudin et al. (2019) (65)	1,567	687 (44)	-	173	102	-
Smargiassi, 2020 (49)				-	-	-
Quebec	1,807,133	44.91%	199,826			
Island of Montreal	457,768	41.16%	51,815			
Yuchi et al. (2020) (48)	633,949	300,192 (47%)	-	-	-	13,170

[a] Abbreviations: AD, Alzheimer's disease; HR, hazard ratio; NAD, non-Alzheimer dementia; and VaD, vascular dementia.

[b] Alzheimer's disease and vascular dementia

[c] First-time Hospitalized with the diagnosis of dementia and its subtypes.

3.3 Risk of Bias Within Studies

Risk of bias was assessed in each study using the “Tool to Assess Risk of Bias in Cohort Studies” (78). According to our assessment, included studies had assigned the exposure to the residential address and the methods used for estimating exposure were not accurate. Therefore, all the studies bear some uncertainty in the assessment of exposure. Since the registry data was used to ascertain cases and assigning the codes might not be accurate, absence of the dementia at baseline and ascertainment of cases might not be free of error. This might also cause some misclassification of both cases and controls. In addition, each study adjusted for different variables at analysis level and some of the risk factors for the outcome were not adjusted for in the statistical analysis. The exact period and level of exposure that can cause dementia as well as the period between exposure and the clinical presentation of dementia is not fully known and the adequacy of the follow-up period would be uncertain. Hence, studies had an intermediate risk of bias in most of the assessed domains. (Table 6).

Table 6. The Assessment of the Risk of Bias Using Tool to Assess Risk of Bias in Cohort Studies [a]

	Domains of Bias [†]							
Authors, year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Andersson et al., 2018 (66)								
Cacciottolo et al., 2017 (40)								
Carey et al., 2018 (42)								
Cerza et al., 2019 (51)								
Chang et al., 2014 (77)								
Chen et al., 2017 (46)								
Grande et al., 2020 (43)								
Ilango et al., 2020 (47)								
Jung et al., 2015 (39)								
Kioumourtzoglou et al., 2016 (50)								
Lee et al., 2019 (52)								
Oudin et al., 2016 (64)								
Oudin et al. , 2018 (41)								
Oudin et al., 2019, (65)								
Smargiassi, 2020 (49)								
Yuchi et al., 2020 (48)								

[*] Each question has four choices: Definitely yes, low risk of bias; Green; Probably yes, high intermediate risk, yellow; Probably no, low intermediate risk, pink; and Definitely no, high risk of bias; red.

[†] Domains of bias; the Questions to be answered were:

1. Was selection of exposed and non-exposed cohorts drawn from the same population?
2. Can we be confident in the assessment of exposure?
3. Can we be confident that the outcome of interest was not present at start of study?
4. Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?
5. Can we be confident in the assessment of the presence or absence of prognostic factors?
6. Can we be confident in the assessment of outcome?
7. Was the follow up of cohorts adequate?
8. Were co-interventions similar between groups?

3.4 Results of Individual Studies

Results of the individual studies are presented in Tables 7 to 10. All the included studies had used the Cox proportional hazard model or its derivatives to produce HR estimates. In addition, the level of exposure was not the same among the included studies. Therefore, some studies dichotomized and compared the higher level of exposure with a lower level of exposure or categorized the exposure into tertiles or quartiles for comparing different levels of exposure. Since most of the studies had reported HR in association with an increase in a certain level of pollutants, e.g., interquartile range (IQR), we excluded studies that did not report HR for incremental changes in pollutants if the authors did not or could not provide the estimates when they were contacted. Therefore, studies by Chang et al. (63) and Cacciottolo et al. (40) were removed from the meta-analysis.

Table 7. Hazard Ratio and 95% Confidence Interval of Dementia and Its Subtypes Reported per Increment of PM2.5 in the Included Studies [a]

Author, year	Increment, μg/m^3	HR (95%CI)			
		Dementia	AD	VaD	NAD
Cacciottolo et al. (2017) (40)	[b]	1.92 (1.32, 2.80)	-	-	-
Carey et al. (2018) (42)	0.95[c]	1.07 (1.02, 1.12)	1.10 (1.02, 1.18)	1.06 (0.97, 1.16)	-
Chen et al. (2017) (46)	4.8	1.03 (1.02, 1.04)	-	-	-
Grande et al. (2020) (43)	0.88[c]	1.54 (1.33, 1.78)	-	1.66 (1.38, 1.99)	-
Ilango et al. (2020) (47)	10	1.29 (0.99, 1.64)	-	-	-
Jung et al. (2015) (39)	13.21[c]	-	1.03 (0.95, 1.11)	-	-
Oudin et al. (2018) (41)	1	1.14 (0.59, 2.23)[d]	-	-	-
Smargiassi et al. (2020) (49)	3.9[c]	1.02 (1.01, 1.03)	-	-	-
Yuchi et al. (2020) (48)	1.54[c]	-	-	-	1.02 (0.980, 1.050)
First-time Hospitalization					
Cerza et al. (2019) (51)	5	0.99 (0.96, 1.02)	0.91 (0.85, 0.97)	1.07 (1.01, 1.12)	-
Kioumourtzoglou et al. (2016) (50)	1	1.15 (1.10, 1.19)	1.07 (1.04, 1.11)	-	-
Lee et al. (2019) (52)	1	1.049 (1.048, 1.051)	1.06 (1.057, 1.062)	1.086 (1.082, 1.09)	-

[a] Abbreviations: HR, hazard ratio; AD, Alzheimer's disease; VaD, vascular dementia; and non-Alzheimer dementia.

[b] Higher level of exposure (>12 μg/m^3) compared to the lower level; the study was excluded from the meta-analysis.

[c] Per interquartile change in PM2.5.

[d] Alzheimer's disease and vascular dementia

Table 8. Hazard Ratio and 95% Confidence Interval of Dementia and Its Subtypes Reported per Increment of NO_x in the Included Studies [a]

Author, year	Increment, μg/m³	HR (95%CI)		
		Dementia	AD	VaD
Andersson et al. (2018) (66)	[b]	1.41 (0.97, 2.03)	-	-
Grande et al. (2020) (43)	8.35 [c]	1.14 (1.01, 1.29)	-	1.09 (0.98, 1.3)
Oudin et al. (2016) (64)	10	1.05 (0.98, 1.12)[d]	1.05 (0.97, 1.15)	1.02 (0.92, 1.14)
Oudin et al. (2019) (65)	10	1.03 (0.97, 1.1)	1.04 (0.96, 1.13)	-
First-time Hospitalization				
Cerza et al. (2019) (51)	20	1.01 (1, 1.02)	0.96 (0.94, 0.98)	1.08 (1.06, 1.1)

[a] Abbreviations: AD, Alzheimer's disease; HR, hazard ratio; and VaD, vascular dementia.

[b] Higher level of exposure (>26 μg/m³) compared to the lower level (<9 μg/m³); the HR (95% CI) for a 1-unit increase in NO_x level was provided by the author.

[c] Per Interquartile change.

[d] Alzheimer's disease and vascular dementia

Table 9. Hazard Ratio and 95% Confidence Interval of Dementia and its Subtypes Reported per Increments of NO_2 in the Included Studies [a]

Author, year	Increment	HR (95%CI)			
		Dementia	AD	VaD	NAD
Carey et al. (2018) (42)	7.47 μg/m^3 [b]	1.16 (1.05, 1.28)	1.23 (1.07, 1.43)	1.15 (0.96, 1.39)	-
Chang et al. (2014) (77)	[c]	1.54 (1.34, 1.77)	-	-	-
Chen et al. (2017) (46)	14.2 ppb	1.1 (1.08, 1.12)	-	-	-
Ilango et al. (2020) (47)	5 ppb	1.1 (0.99, 1.19)	-	-	-
Smargiassi et al. (2020) (49)	13.26 ppb[b]	1.015 (1.007, 1.023)	-	-	-
Yuchi et al. (2020) (48)	9.06 ppb[b]	-	-	-	1.02 (0.99, 1.06)
First-time Hospitalization					
Cerza et al. (2019) (51)	10 **μ**g/m^3	0.98 (0.96, 0.99)	0.91 (0.89, 0.94)	1.05 (1.03, 1.07)	-

[a] Abbreviations: HR, hazard ratio; AD, Alzheimer's disease; and VaD, vascular dementia.

[b] Per interquartile change in NO_2.

[c] Higher level of exposure (>26 **μ**g/m^3) compared to the lower level (<9 **μ**g/m^3).

[d] Alzheimer's disease and vascular dementia

Table 10. Hazard Ratio and 95% Confidence Interval of Dementia and its Subtypes Reported per Increment of O_3 in the Included Studies [a]

		HR (95%CI)		
Author, year	**Increment**	**Dementia**	**AD**	**VaD**
Carey et al. (2018) (42)	5.56 μg/m^3 [b]	0.84 (0.75, 0.94)	0.78 (0.66, 0.92)	0.88 (0.71, 1.09)
Chen et al. (2017) (46)	6.3 ppb	0.98 (0.96, 1.00)	-	-
Jung et al. (2015) (39)	9.63 ppb [b]	-	1.06 (1.00, 1.12)	-
First-time Hospitalization				
Cerza et al. (2019) (51)	10 **μ**g/m^3	1.06 (1.03, 1.08)	0.98 (0.95, 1.02)	1.02 (0.98, 1.06)

[a] Abbreviations: HR, hazard ratio; AD, Alzheimer's disease; and VaD, vascular dementia.

[b] Per interquartile change in O_3.

3.5 Synthesis of Results

3.5.1 Particulate Matter with Diameter < 2.5μ

The HR of dementia and/or its subtypes in association with $PM_{2.5}$ was reported in 12 studies. The study by Cacciottolo et al. (40) was excluded because it did not report the HR of dementia in association with a unit increase of $PM_{2.5}$. Dementia was the reported outcome in nine studies, four of which also reported on VaD as the outcome. In addition, AD was reported in five studies, and was the only reported outcome in one study (39). Moreover, a study by Yuchi et al. reported NAD as the only outcome (48). Three studies reported on first-time hospitalization with dementia (50-52) and because of their large sample size, they affected the pooled estimate significantly.

The pooled HR showed a statistically significant association between $PM_{2.5}$ and incidence of dementia, either first-time hospitalized or any case of dementia (HR, 1.04; 95%CI: [1.02, 1.06]; I^2 = 100%). The largest estimate was seen in the subgroup that reported on the incidence of first-time hospitalization with dementia (HR, 1.06; 95%CI: [1.01, 1.10]; I^2 = 99%), which was expected because they were larger registry-based studies and comprised almost 80% of the study population. Such an association was statistically significant for studies that reported on incidence of dementia (HR, 1.02; 95%CI: [1.01, 1.03]; I^2 = 95%).

The p-value for subgroup interaction was significant (p-value = 0.02), indicating that the effect sizes for these subgroups are statistically different from one another, and indicating that differences in effect size were found according to definition of dementia.

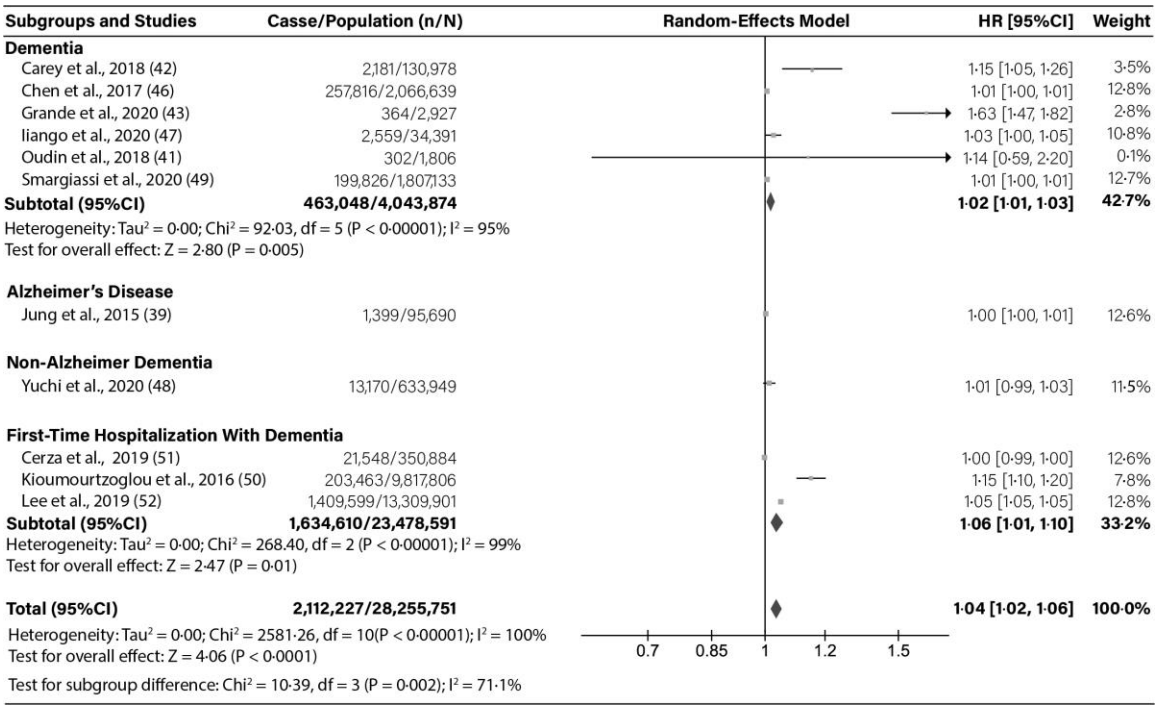

Figure 2. Subgroup analysis of hazard ratio per 1μg/m^3 increase in $PM_{2.5}$ level for all the studies that reported on the association of $PM_{2.5}$ with incidence of any type of dementia and the incidence of the first-time hospitalization with dementia

To further evaluate the effect of subtype of dementia on the pooled estimate, the studies that reported on AD, VaD, and NAD either as the main outcome or as a subgroup of dementia were included in the meta-analysis, while the studies that had reported only on dementia as the sole outcome were excluded. There was a significant association between exposure to $PM_{2.5}$ and incidence of subtypes of dementia (HR, 1.06; 95%CI: [1.03, 1.08]; I^2 = 99%); however, the association was statistically significant for VaD (HR, 1.15; 95%CI: [1.08, 1.23]; I^2 = 99%) but not for the incidence of AD (HR, 1.04; 95%CI: [1.00, 1.08]; I^2 = 99%) (Fig. 3).

The p-value for subgroup interaction was significant (p-value = 0.001), indicating that the effect sizes for these subgroups are statistically different from one another, and indicating that differences in effect size were found according to definition of dementia.

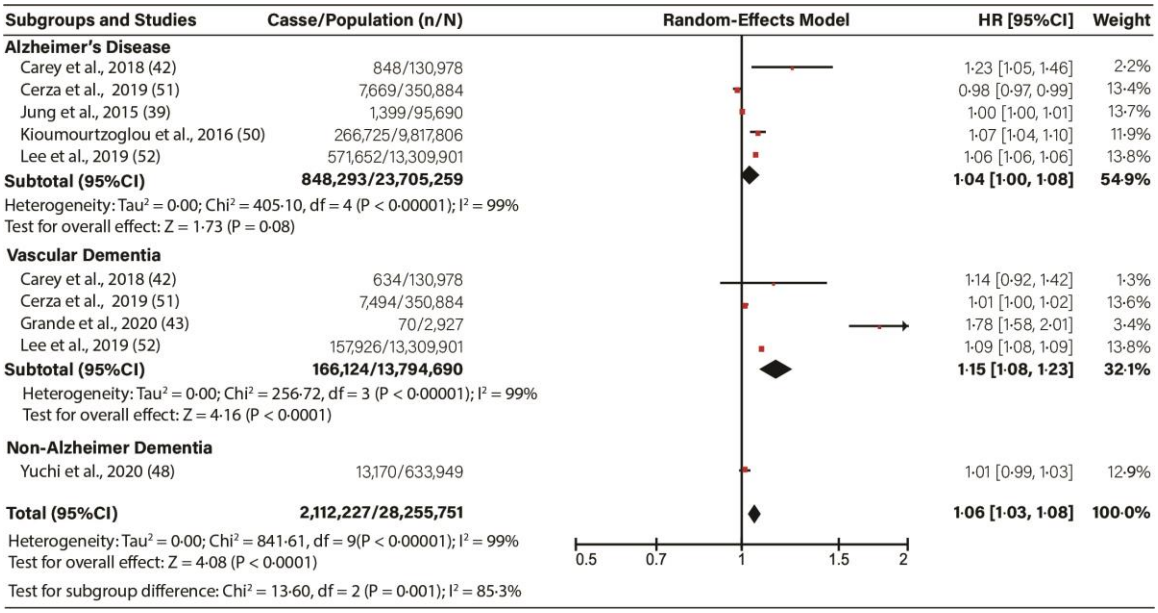

Figure 3. Subgroup analysis of hazard ratio per 1μg/m^3 increase in $PM_{2.5}$ for the studies that reported on the association of $PM_{2.5}$ with Alzheimer's disease, vascular dementia, and non-Alzheimer dementia

The pooled HR was also estimated for studies from North America (six studies) (46-50, 52), Europe (four studies) (41-43, 51), and Asia (one study) (39) to see if geographical region might have an effect on the estimates. Pooled estimates indicated a significant association between exposure to $PM_{2.5}$ and incidence of dementia in studies from North America (HR, 1.03; 95%CI: [1.01, 1.06]; I^2 = 100%). On the other hand, although the pooled estimate of the studies in Europe (United Kingdom, Italy, and Sweden) was large,

the confidence intervals were wide and the association was not statistically significant (HR, 1.22; 95%CI: [0.94, 1.58]; I^2 = 97%; Fig. 4).

The p-value for subgroup interaction was significant (p-value = 0.02), indicating that the effect sizes for these subgroups are statistically different from one another, and indicating that differences in effect size were found according to the continent where the study was performed.

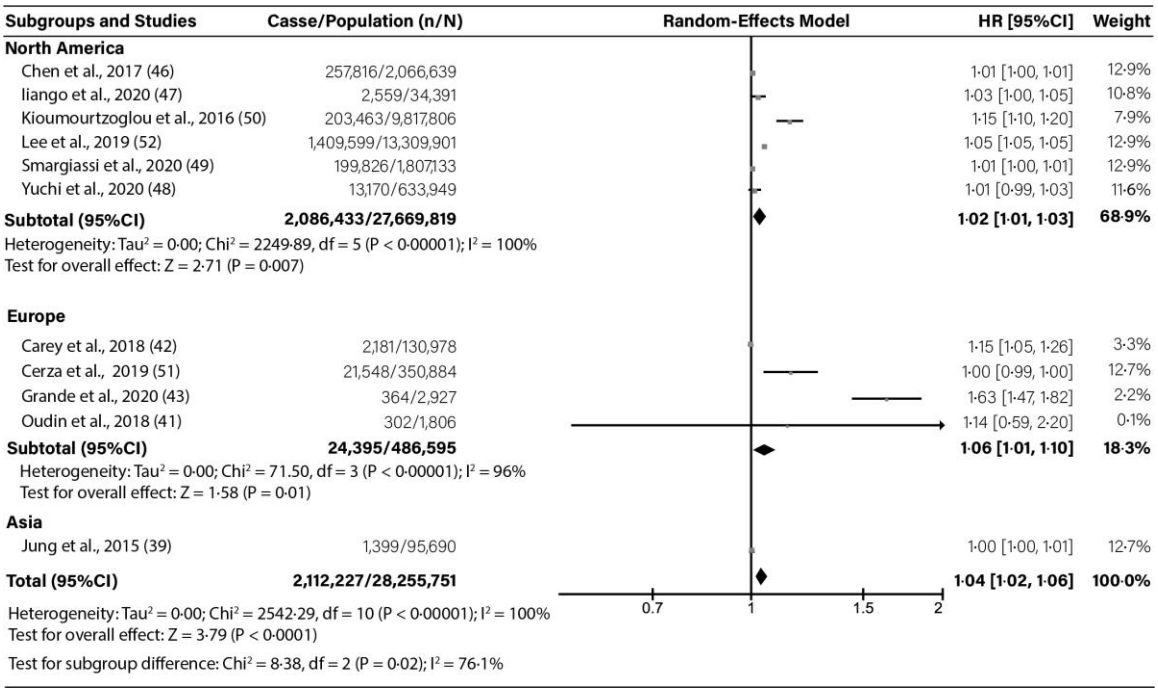

Figure 4. Subgroup analysis of hazard ratio per 1µg/m^3 increase in $PM_{2.5}$ for the studies from different continents that reported on the association of $PM_{2.5}$ with any type of dementia

3.5.2 Nitrogen Oxides

A total of four studies evaluated the association of exposure to NO_X with the incidence of dementia (43, 51, 65, 66); however, one of the studies was the update to a previous study

(64, 65) and we only included one of them in the meta-analysis. In addition, one study reported first-time hospitalization with dementia as its outcome and was included in the meta-analysis as a subgroup. The study by Andersson et al. (66) measured NO_X in $\mu g/m^3$ and compared the highest levels of exposure with the lowest levels of exposure, and the author provided the HR estimate for one-unit and 10-unit increase in NO_X level when he was contacted. The conversion of ppb to $\mu g/m^3$ is challenging because the exact proportion of nitric oxide and NO_2 should be known. Unfortunately, such information was not available and the conversion of ppb to $\mu g/m^3$ for Andersson et al. was not possible due to inaccurate data based on general knowledge about the coefficient of conversion that was already reported. Since none of the individual estimates indicated a significant association between NO_X and incidence dementia, the pooled estimate was also expected to show no statistically significant association (HR, 1.04; 95%CI: [0.98, 1.10]; I^2 = 57%) either when the study by Andersson et al. was added (Fig. 5) or when the study by Cerza et al. (51) that reported on the first-time Hospitalization was introduced as a subgroup (Fig. 6).

The p-value for subgroup interaction was non-significant (p-value = 0.13; Fig. 6), indicating that the effect sizes for these subgroups are not statistically different from one another, and indicating that differences in effect size were not found according to definition of dementia.

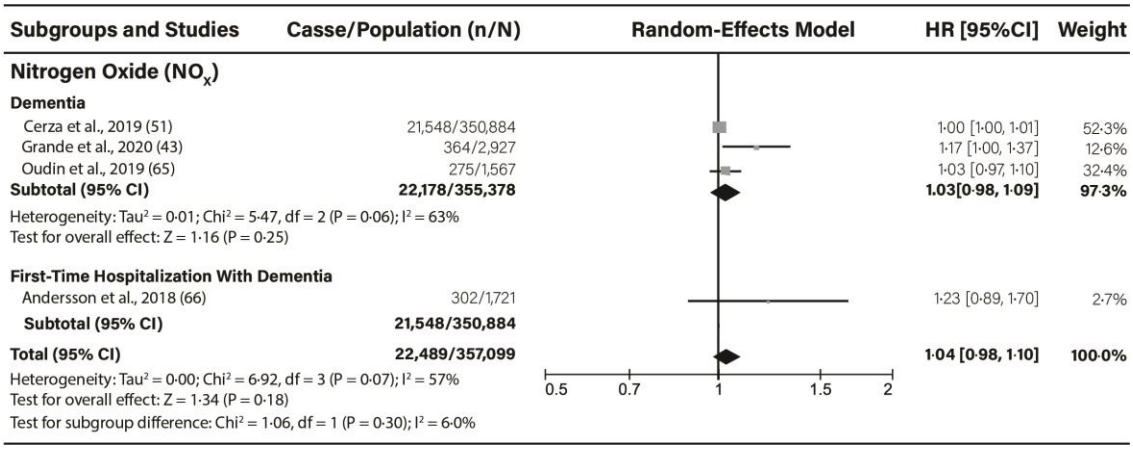

Figure 5. Pooled hazard ratio per 10 µg/m^3 increase in NOx for the studies that reported on the association of NOx with dementia

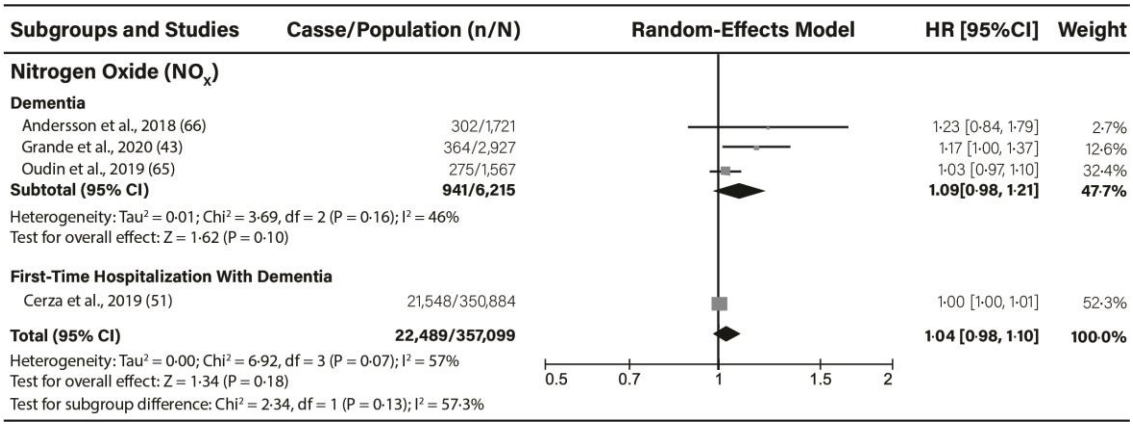

Figure 6. Pooled hazard ratio per 10µg/m^3 increase in NOx for the studies that reported on the association of NOx with dementia when study on the first-time hospitalization was introduced as a subgroup

3.5.3 Nitrogen Dioxide

A total of seven studies reported on exposure to NO_2 (42, 46-49, 51, 63). Six studies reported on dementia (42, 46, 47, 49, 51, 63) and one study on NAD (48). In addition, the study by Chang et al. did not provide the HR for a unit increase in NO_2 and was not included in the meta-analysis. (63). Moreover, only two studies reported on the incidence o AD and VaD as subtypes of dementia (42, 51). The pooled HR was estimated by including studies on the first-time hospitalization with dementia and a study that reported on the incidence of NAD as subgroups (Fig. 7). Although there was a significant association between the incidence of dementia and exposure to NO_2 (HR, 1.07; 95%CI: [1.02, 1.12]; I^2 = 96%), such an association did not exist when studies that reported on NAD and first-time hospitalization with dementia were included in the meta-analysis (HR, 1.04; 95%CI: [1.00, 1.08]; I^2 = 96%).

The p-value for subgroup interaction was significant (p-value < 0.001), indicating that the effect sizes for these subgroups are statistically different from one another, and indicating that differences in effect size were found according to definition of dementia.

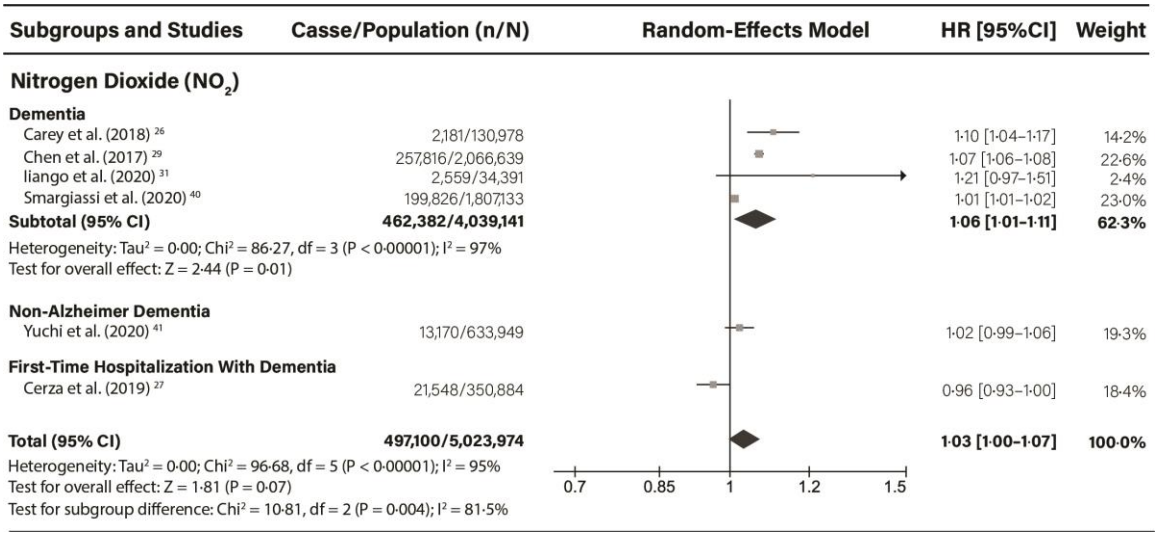

Figure 7. Subgroup analysis of hazard ratio per 10 µg/m^3 increase in NO_2 for the studies that reported on the association of NO_2 with incidence of dementia, first-time hospitalization with dementia, and non-Alzheimer dementia

3.5.4 Ozone

The HR for association between O_3 and dementia was reported in four studies (39, 42, 46, 51), one of which reported only on the association with AD (39). Only the study by Creza et al. reported a significant association between exposure to O_3 and incidence of first-time hospitalization with dementia (51). The pooled HR was estimated for all four studies where the study by Creza et al. on the first-time hospitalization with dementia and the study by Jung et al. on the incidence of AD (39) were introduced to the model as subgroups (Fig. 8). No statistically significant association was found between exposure to O_3 and dementia for two studies that reported on dementia (HR, 0.87; 95%CI: [0.70, 1.09]; I^2 = 54%) and for all included studies (HR, 1.01; 95%CI: [0.91, 1.11]; I^2 = 82%). The p-value for

subgroup interaction was non-significant (p-value = 0.12), indicating that the effect sizes for these subgroups are not statistically different from one another, and indicating that differences in effect size were not found according to definition dementia.

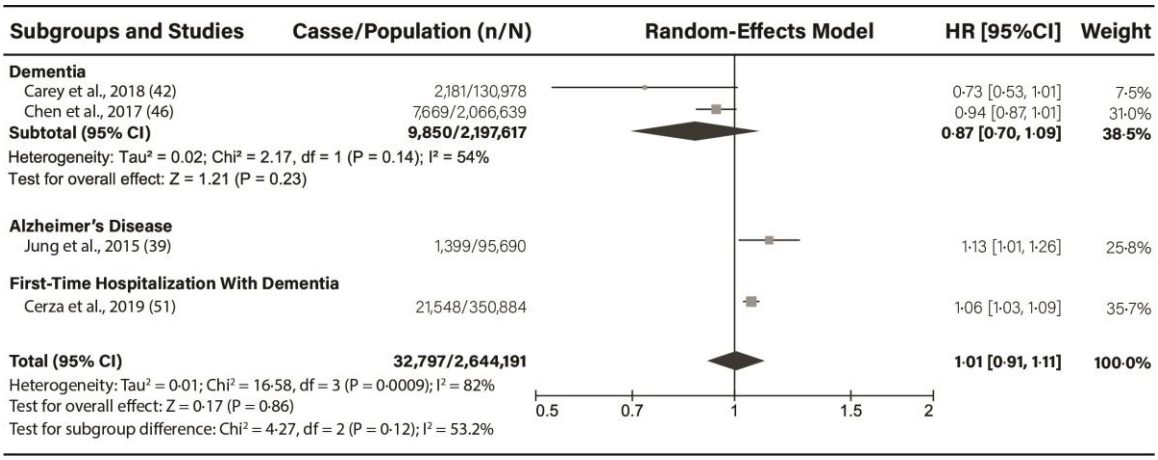

Figure 8. Subgroup analysis of hazard ratio per 10 µg/m^3 increase in O_3 for the studies that reported on the association of O_3 with incidence of dementia, first-time hospitalization with dementia, and Alzheimer's disease

Two studies reported on the incidence of AD and VaD as a subgroup of dementia (42, 51). The pooled estimate for these two subgroups did not yield any statistically significant association between exposure to O_3 and the incidence of AD (HR, 1.02; 95%CI: [0.88, 1.17] I^2 = 75%) or VaD (HR, 1.02; 95%CI: [0.98, 1.06]; I^2 = 0%) (Fig. 9).

The p-value for subgroup interaction was significant (p-value = 1.0), indicating that the effect sizes for these subgroups are not statistically different from one another, and indicating that differences in effect size were not found according to definition of dementia.

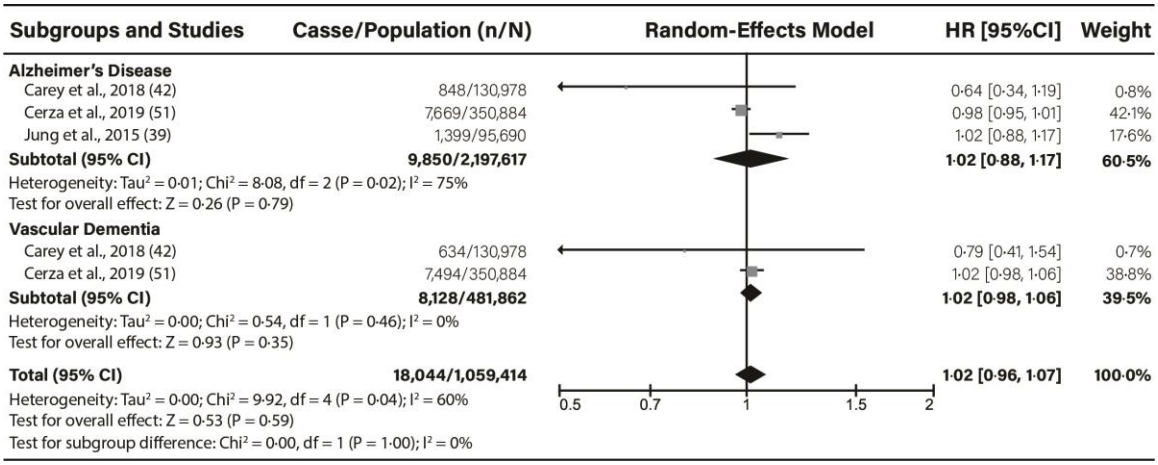

Figure 9. Subgroup analysis of hazard ratio per 10 µg/m^3 increase in O_3 for the studies that reported on the association of O_3 with incidence of Alzheimer's disease and vascular dementia

3.6 Heterogeneity Across Included Studies

Significant heterogeneity was found among studies that reported on the association between exposure to $PM_{2.5}$ and incidence of dementia (I^2 = 95%), studies that reported on the incidence of the first-time hospitalization with dementia (I^2 = 99%), and when all studies were included in the meta-analysis of the association between $PM_{2.5}$ and incidence of dementia (I^2 = 100%).

There was also evidence of heterogeneity across studies that evaluated the association of dementia and its subtypes with the exposure to NO_2 (I^2 = 96%) and O_3 (I^2 = 82%). There was also a moderate heterogeneity among studies that evaluated the association of dementia with exposure to NO_X (I^2 = 57%).

3.7 Risk of Bias Across Studies

To evaluate the publication bias, funnel plots were created and evaluated (Fig. 10-13). It is noteworthy that the funnel could not be forced on the plots because of the small number of included studies. The plot indicated asymmetry in all studied pollutants. While the graphs indicate potential asymmetry for the association of each pollutant with dementia, the small number of studies makes it difficult to rule in or rule out publication bias. Overall, it appears that small negative studies are missing from the funnel plot, indicating potential publication bias.

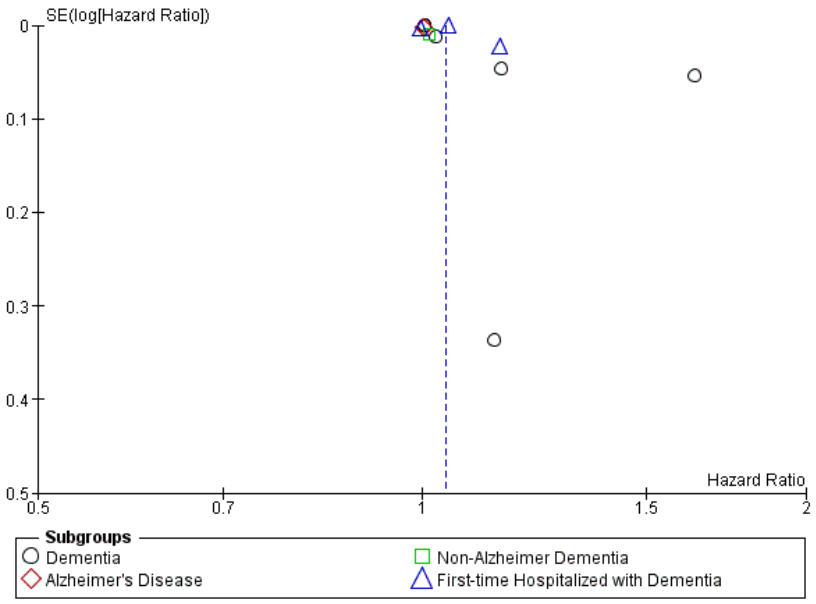

Figure 10. Funnel plot to evaluate publication bias in studies reporting on association of exposure to $PM_{2.5}$ with incidence of dementia and its subtypes

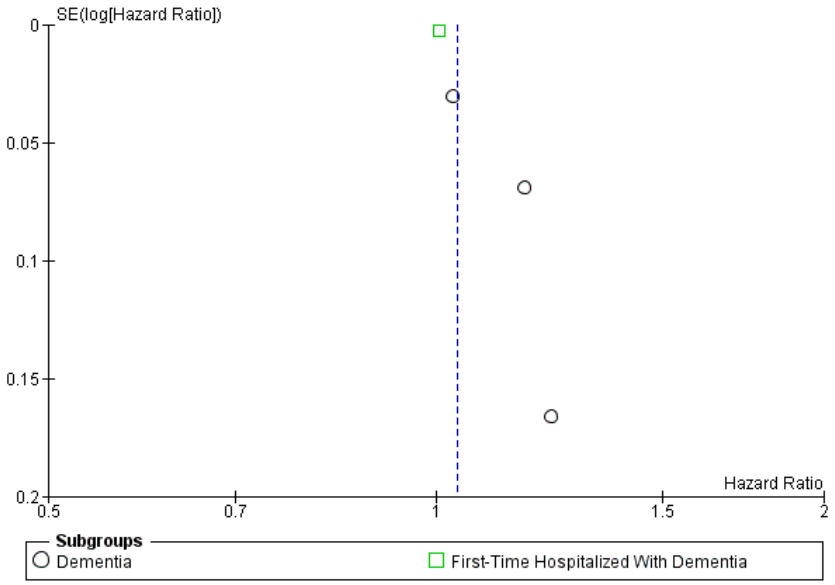

Figure 11. Funnel plot to evaluate publication bias in studies reporting on association of exposure to NO_X with incidence of dementia and its subtypes

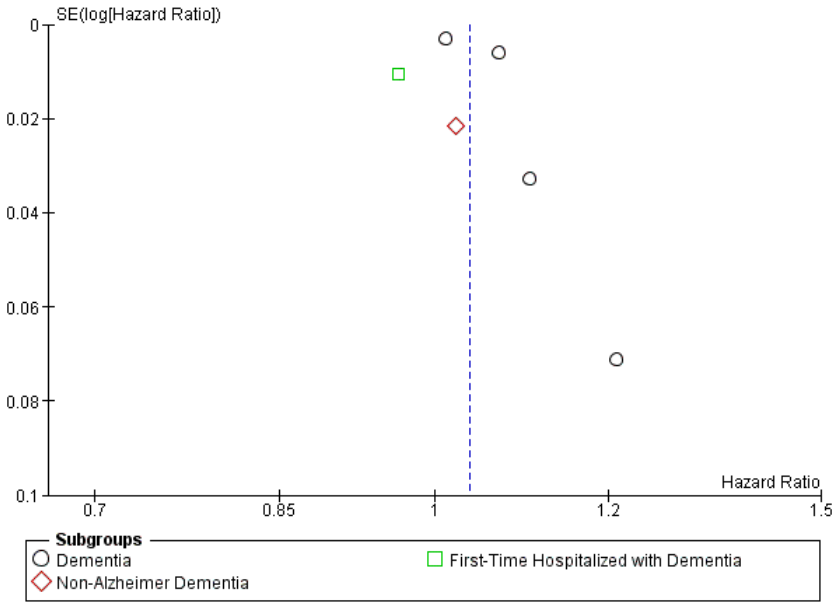

Figure 12. Funnel plot to evaluate publication bias in studies reporting on association of exposure to NO_2 with incidence of dementia and its subtypes

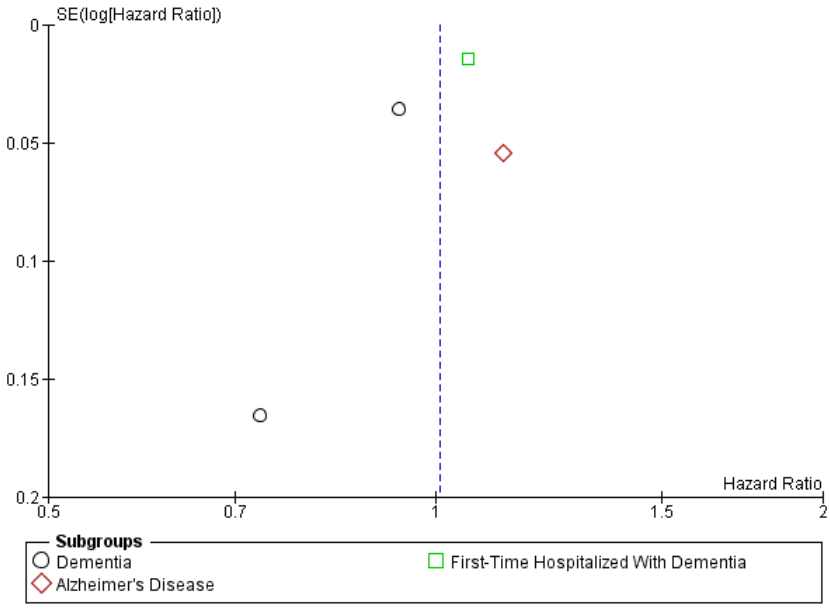

Figure 13. Funnel plot to evaluate publication bias in studies reporting on association of exposure to O_3 with incidence of dementia and its subtypes

In addition, the risk of publication bias was evaluated by Egger's regression test. The small-study effect was significant only for studies reporting on the association of exposure to NO_X with incidence of dementia. Publication bias estimates are limited by the small number of studies that were eligible for meta-analysis, suggesting that the Egger's test will be underpowered to rule out potential publication bias (Table 11).

Table 11. Egger's Test for small-study effect

Pollutant	Studies (n)	Bias Coefficient (95%CI)	t	P-value [a]
PM2.5	11	4.97 (-6.13, 16.07)	4.74	0.43
NOx	4	-14.77 (-27.1, -2.44)	-3.50	0.07
NO2	6	-16.24 (-80.18, 47.69)	-0.54	0.62
O3	4	17.03 (-32.21, 66.28)	1.01	0.42

[a] Significance level is set at $\alpha > 0.10$.

3.8 Sensitivity Analyses

The leave-one-out analysis was performed by excluding one study at the time and evaluating the effect on the subgroup pooled estimate compared to the overall pooled estimate.

3.8.1 Particulate Matter with Diameter < 2.5μ

The results of the sensitivity analysis for the association between exposure to $PM_{2.5}$ and the incidence of dementia is summarized in Table 12 (the model is presented in Fig 2).

In the leave-one-out analysis of the dementia subgroup, the pooled HR for the dementia subgroup ranged from 1.01 to 1.15 and the I^2 ranged from 67% to 96%. Additionally, the pooled estimate for the overall association of exposure to $PM_{2.5}$ ranged from 1.03 to 1.05 with and I^2 ranging from 99% to 100%. The leave-one-out analysis for the studies that reported on dementia as their outcome indicated that omitting the studies by Chen et al. (75) or Smargiassi et al. (49) would make the association between exposure to $PM_{2.5}$ and dementia stronger by increasing the HR of dementia from 1.02 to 1.15, but would not meaningfully affect the overall pooled estimate. Nonetheless, these two studies were the

largest in this subgroup and the main observed HR in this subgroup can be attributed to them. Removing studies with a small sample size (41, 43, 47) did not meaningfully affect the subgroup and total estimations.

Sensitivity analysis did show a significant change in the overall association when the study by either Jung et al. (39) or Yuchi et al. (48) was excluded from the model. On the other hand, removing any study that reported on the incidence of the first-hospitalization with dementia affected the subgroup estimate with pooled HR ranging from 1.02 to 1.10 and I^2 ranging from 94% to 100%; however, excluding any of these studies made the association in the subgroup statistically insignificant but did not meaningfully affect the overall estimate of the association with pooled HR ranging from 1.01 to 1.05 and I^2 ranging from 93% to 100%.

In addition, excluding studies from any continent did not affect the pooled HR estimate for the association between exposure to PM2.5 and incidence of dementia with HR ranging from 1.3 to 1.5 and I^2 ranging from 94% to 100% (data are not shown).

Table 12. The Results of the Sensitivity Analysis (Leave-One-Out Analysis) for the Association Between Exposure to $PM_{2.5}$ and Incidence of Dementia [a]

Excluded Study	Subgroup HR (95%CI)	Subgroup I^2	Total HR (95%CI)	Total I^2
Dementia				
All studies included	1.02 (1.01, 1.03)	95%	1.04 (1.02, 1.06)	100%
Carey et al. (2018) (42)	1.01 (1.00, 1.03)	95%	1.04 (1.02, 1.06)	100%
Chen et al. (2017) (46)	1.15 (1.06, 1.24)	96%	1.05 (1.03, 1.07)	99%
Grande et al. (2020) (43)	1.01 (1.00, 1.01)	67%	1.03 (1.01, 1.05)	100%
Ilango et al. (2020) (47)	1.02 (1.00, 1.03)	96%	1.04 (1.02, 1.07)	100%
Oudin et al. (2018) (41)	1.02 (1.01, 1.03)	94%	1.04 (1.02, 1.06)	100%
Smargiassi et al. (2020) (49)	1.15 (1.06, 1.24)	96%	1.05 (1.03, 1.07)	100%
AD				
Jung et al. (2015) (39)	-	-	1.05 (1.03, 1.07)	100%
NAD				
Yuchi et al. (2020) (48)	-	-	1.05 (1.02, 1.07)	100%
First-time Hospitalisation				
All studies included	1.06 (1.01, 1.10)	99%	1.04 (1.02, 1.06)	100%
Cerza et al. (2019) (51)	1.10 (1.00, 1.20)	94%	1.05 (1.03, 1.07)	100%
Kioumourtzoglou et al. (2016) (50)	1.02 (0.97, 1.07)	100%	1.03 (1.01, 1.06)	100%
Lee et al. (2019) (52)	1.07 (0.93, 1.23)	97%	1.01 (1.01, 1.02)	93%

[a] Abbreviations: HR, hazard ratio, AD, Alzheimer's disease; and NAD, non-Alzheimer dementia.

3.8.2 Nitrogen Oxides

The results of the sensitivity analysis for the association between exposure to NO_X and the incidence of dementia is summarized in Table 13 (the model is presented in Fig. 6). Excluding neither of the studies could make the overall association of NO_X and dementia statistically significant, although the pooled HR estimate ranged from 1.01 to 1.09 and I^2 ranged from 5% to 68%. When the study by Oudin et al. (65) was excluded, there was a statistically significant association between exposure to NO_X and incidence of dementia in this subgroup (HR, 1.18; 95%CI, [1.04, 1.33]). In addition, the subgroup and the total

heterogeneities were reduced (subgroup's I^2, 8%; and total I^2, 5%) when the study by Grande et al. (43) was excluded from the analysis.

Table 13. The Results of the Sensitivity Analysis (Leave-One-Out Analysis) for the Association Between Exposure to NO_X and Incidence of Dementia [a]

Excluded Study	Subgroup HR (95%CI)	Subgroup I^2	Total HR (95%CI)	TotalI^2
Dementia				
All studies included	1.09 (0.89, 1.70)	46%	1.04 (0.98, 1.10)	57%
Andersson et al. (2018) (66)	1.08 (0.96, 1.22)	65%	1.03 (0.98, 1.09)	63%
Grande et al. (2020) (43)	1.04 (0.96, 1.14)	8%	1.01 (0.99, 1.02)	5%
Oudin et al. (2019) (65)	1.18 (1.04, 1.33)	0%	1.09 (0.95, 1.24)	68%
First-time Hospitalization				
Cerza et al. (2019) (51)	-	-	1.09 (0.98, 1.21)	46%

[a] Abbreviations: HR, hazard ratio.

3.8.3 Nitrogen Dioxide

The results of the sensitivity analysis for the association between exposure to NO_2 and the incidence of dementia is summarized in Table 14 (the model is presented in Fig 7). One-by-one exclusion of the studies in the dementia subgroup did not change the total pooled HR (total HR range, 1.03 to 1.05; total I^2 range, 78% to 96%); however, the pooled HR of the dementia subgroup remained significant only when the study by Smargiassi et al. (49) was excluded. In addition, only excluding the study by Cerza et al. (51) on the incidence of the first-time hospitalization with dementia increased the overall pooled HR and made the association statistically significant.

Table 14. The Results of the Sensitivity Analysis (Leave-One-Out Analysis) for the Association Between Exposure to NO_2 and Incidence of Dementia [a]

Excluded Study	Subgroup HR (95%CI)	Subgroup I^2	Total HR (95%CI)	Total I^2
Dementia				
All studies included	1.07 (1.02, 1.12)	96%	1.04 (1.00, 1.08)	96%
Carey et al. (2018) (42)	1.06 (1.00, 1.12)	97%	1.03 (0.99, 1.07)	96%
Chen et al. (2017) (46)	1.08 (0.99, 1.19)	85%	1.03 (0.99, 1.07)	78%
Ilango et al. (2020) (47)	1.05 (1.00, 1.11)	98%	1.03 (0.99, 1.07)	96%
Smargiassi et al. (2020) (49)	1.9 (1.04, 1.14)	49%	1.05 (0.99, 1.12)	89%
NAD				
Yuchi et al. (2020) (48)	-	-	1.04 (1.00, 1.09)	96%
First-time Hospitalization				
Cerza et al. (2019) (51)	-	-	1.06 (1.01, 1.10)	95%

[a] Abbreviations: HR, hazard ratio; and NAD, non-Alzheimer dementia.

3.8.4 Ozone

Results of the sensitivity analysis for the association between exposure to O_3 and the incidence of dementia is summarized in Table 15 (the model is presented in Fig 8). Leave-one-out analysis of studies did not make the association between exposure to O_3 and the incidence of dementia statistically significant. The pooled HR ranged from 0.85 to 1.04, and I^2 ranged from 69% to 86%.

Table 15. The Results of the Sensitivity Analysis (Leave-One-Out Analysis) for the Association Between Exposure to O_3 and Incidence of Dementia [a]

Excluded Study	Total HR (95%CI)	Total I^2
All studies included	1.01 (0.91,1.11)	82%
Dementia		
Carey et al. (2018) (42)	1.03 (0.94, 1.13)	83%
Chen et al. (2017) (46)	1.04 (0.93, 1.17)	69%
AD		
Jung et al. (2015) (39)	0.85 (0.78, 1.10)	86%
First-time Hospitalisation		
Cerza et al. (2019) (51)	0.96 (0.81, 1.15)	82%

[a] Abbreviations: HR, hazard ratio; and AD, Alzheimer's disease.

3.9 Other Analyses

Association between levels of pollutants was reported by some studies (Table 16). Since the confidence intervals were not provided, it was not possible to perform meta-analysis on the reported Pearson's correlation coefficients. Reported estimates were heterogenous and association could not be implied from the reported values. Nonetheless, a positive association between $PM_{2.5}$ and NO_2 was reported by most of the studies while the association between $PM_{2.5}$ and O_3 ranged from -0.96 to 0.51 and the association between NO_2 and O_3 ranged from -0.99 to 0.66.

Table 16. Pearson's Correlation Coefficient Between Studied Pollutants [a]

Author, year	$PM_{2.5}$ & NO_2	$PM_{2.5}$ & O_3	NO_2 & O_3	NO_x & $PM_{2.5}$	NO_x & NO_2	NO_x & O_3
Chen et al. (2017) (46)	0.38 [b]	0.38 [b]	-0.22 [b]	-	-	-
Carey et al. (2018) (42)	0.98	-0.96	-0.99	-	-	-
Cerza et al. (2019) (51)	0.66	-0.03	0.66	0.61	0.71	-0.12
Jung et al. (2015) (39)	-	-	0.07[b]	-	-	-
Lee et al. (2019) (52)	-0.25	0.51	-0.59			
Smargiassi et al. (2020) (49)	0.75		-	-	-	-
Yuchi et al. (2020) (48)						
AD	0.24	-	-	-	-	-
NAD	0.52	-	-	-	-	-

[a] Abbreviations: AD, Alzheimer's disease; and NAD, non-Alzheimer's disease.

[b] correlation coefficients for the baseline levels.

While we intended to explore trends in the association between pollutants and dementia overtime, it was not possible to do so since it was not possible to separate those who were exposed before and after 2000 due to overlapping periods in the studies and the lack of patient-level data. In addition, meta-analysis based on sex was not feasible since sex was adjusted for in the original studies' regression models.

Chapter 4

4 Discussion

Existing evidence from cohort studies suggests that $PM_{2.5}$ is significantly associated with dementia. While other pollutants were not significantly associated with dementia, a clinically-relevant association could not be ruled out given the width of the confidence intervals. Meta-analysis showed that a $1\mu g/m^3$ increase in the level of $PM_{2.5}$ is associated with a 4% increase in risk of any type of dementia, with varied duration of follow-up across the studies. In addition, the increased risk was higher for VaD (15%) in comparison to AD (4%). Although the pooled estimate showed a 4% increase in risk of any type of dementia per $10\mu g/m^3$ increase in NO_X levels, the association was not statistically significant. There was a 7% increase in risk of dementia per $10\mu g/m^3$ increase in NO_2 when only studies that reported incidence of dementia as the outcome were included; however, a 4% increase in risk of any type of dementia was not statistically significant when NAD and the incidence of the first-time hospitalization with dementia were included in the analysis. Finally, there was no association between the incidence of dementia and O_3. The sensitivity analysis indicated that the pooled estimates were robust to exclusion of studies with small sample size. Nonetheless, there was a high heterogeneity of effects across all the studies and all the conducted analyses and leave-one-out analyses did not reduce the heterogeneity. The small number of studies made it difficult to assess for potential publication bias; however, visual inspection of funnel plots indicated that negative studies might have been missed while the tests for ruling out publication bias were underpowered due to a few available studies. Although studies that directly compared the highest to the lowest levels of

exposure could not be included in the meta-analyses, all of them individually reported a significant association between air pollution and dementia.

While not the focus of this meta-analysis, additional studies indicated that there was no association between noise and dementia. Studies on the association of incidence of dementia and road proximity were contradictory, and in one study the association was not statistically significant when the model was adjusted for air pollutants (42). The presence of APOE ϵ4 strengthened the association between exposure to PM2.5 and incidence of dementia (40), but such an association was not seen with exposure to NO_X (65).

The strength of this study was in the inclusion of the most important air pollutants according to best available knowledge from existing studies. In the first search, we looked for the most important air pollutants to design our study. Then we searched more specifically for the more frequently investigated air pollutants. In addition, due to the small number of studies and recency of the issue, there were only two meta-analyses on the association of $PM_{2.5}$ and incidence of dementia with few included studies, technical problems and no meta-analysis on the association of NO_X, NO_2, or O_3 with the incidence of dementia. By including the latest studies published in 2020, this study is the first systematic review and meta-analysis to include all air pollutants. Moreover, in order to have a precise estimate, study authors were contacted, and new estimates based on the original data were used to calculate pooled estimates.

This study has some limitations. Although air pollution has been associated with numerous health problems (14-17), the association of air pollutants with dementia has only recently attracted the attention of researchers, and therefore, there are few studies on this topic. In

addition, the effect of air pollution on neuronal cells might be evident only after long-term exposure, and given the nascent studies in the field, this makes drawing conclusions about causal associations difficult. Dementia is a condition of the elderly and numerous risk factors contribute to its pathology. Consequently, the incidence of dementia cannot be attributed to one cause, and our reported association should be treated conservatively.

There was high heterogeneity across studies that maybe due to different study designs, sample sizes, diagnosis methods, measurement of air pollutants, and different geographical areas. Although the studies were population-based cohort studies, the recorded data and diagnostic criteria were not the same. Some studies included almost everyone in the registry and some studies used a proportion of the databases. Such studies are expensive, which limits the design and analysis to the available budgets. In addition to the extremely high price of accessing these databases, the access period to the data is limited. Once the authors had the data and finished working with it, it was difficult for them to provide more information, especially when the studies were conducted years ago. For this reason, a number of authors could not provide additional information when we contacted them.

The levels of air pollutants were measured through different sources and various methods were used to assign the pollutants' levels to residential addresses and estimate the exposure level in each individual. Most of the studies reported the mean annual level, which might not be an accurate measure of air pollutants where some days of the year might have had higher level of pollutants, for instance, school seasons. Moreover, climate may have changed over the different periods of observation contributing to the variability among studies. Another potential problem arises from land-use regression models. These models may misclassify exposure because the exposure is not evaluated at the individual level, and

depending on the number and distribution of the pollution measurement stations and available information about potential confounders, the classification may be biased. Furthermore, such a model does not consider daily or seasonal movements of individuals and that they might be exposed to different levels of exposure during the day due to working in a different place than their residential area. Furthermore, indoor pollution due to using wood or fossil fuel for cooking or heating is not considered in these models. People living in rural areas and on farms might be exposed to other types of pollutants that might have a detrimental effect on cognitive function and be associated with dementia. Furthermore, according to previous studies, the effect of pollution on cognitive function may begin during childhood (33, 34) and continues through adulthood (35-38). Therefore, where the population lived before enrolment in the study may be an important factor that was not considered in most of the studies. This could be especially relevant for countries with large populations of immigrants.

At the analysis level, the exposure variables were not treated the same across studies. Some studies had dichotomized the exposure level, and some had divided the exposure level into tertiles or quartiles. In this case, it was not possible to provide pooled estimates, as they were not comparable. Even when the HR was provided for a certain unit increase in pollutant's level, they were not easily compared because they used various increments such as IQR changes that varied depending on the total exposure levels in the studies. Although the units were converted to a specific unit increase, this conversion may introduce imprecision. In addition, upscaling the measurement units, for instance, conversion of one-unit change to 10-unit change, might provide estimates that are beyond what the original data was intended to extrapolate. This was more evident when units of measurement were

converted from ppb to μg/m^3 or vice versa. In addition, NO_X is a mixture of NO_2 and nitrogen monoxide and to convert the measurement units, the exact concentration of each molecule in the examined sample should be known. Therefore, the converted estimate might not be precise.

In addition, the difference in adjustment for variables in the regression models posed challenges for our analysis. Although the studies had adjusted for risk factors of dementia, they did not adjust for the same variables, and this may impact on their reported estimates. Moreover, for most of the studies, the time between exposure and incidence of dementia was not clear. Even in studies that reported the mean exposure period before diagnosis of dementia, it was unclear when the pathology started and how long after the initiation of the molecular pathology dementia was diagnosed. While some evidence points to a strong association between CVD and dementia (79-81), and some evidence supports air pollution as a known risk factor for CVD morbidity and mortality (14), only one of the included studies evaluated the mediation role of CVD by providing three-year intervals for developing CVD before diagnosis of dementia (47). Although most of the studies had adjusted for CVD, they did not provide any information on the temporal association of air pollution with CVD incidence and dementia.

The outcome definitions differed across the included studies. Some reported on the incidence of dementia and some focused on subtypes of dementia, i.e., AD, VaD, and NAD. In addition, three studies reported on the incidence of first-time hospitalization with dementia (50-52), where the non-hospitalized individuals with dementia were not included. Therefore, these studies were introduced to the analyses as subgroups and the analyses focused on the total incidence of dementia irrespective of the reported subtypes because

the clinical diagnosis of these subtypes does not necessarily confirm the involved neuropathology (5). Moreover, using registry data has its limitations as the codes and information are not complete which makes the certainty of the absence of dementia at baseline and the precise diagnosis of the outcome less reliable, which might lead to selection bias and misclassification of the outcome in included studies

Most of the studies were performed in North America and Europe, where air quality regulation may be improved compared to other parts of the world. Low- and middle-income countries in Africa, Asia, as well as South and Central America may face altered risks due to differing regulations, shorter life expectancy, and proximity of living conditions to roads and other areas where pollutants are generated. In addition, indoor pollution from cooking and heating and/or lighting are important additional contributors to exposure to pollutants in low-income countries (82-90). Interestingly, one included study in this meta-analysis indicated an association between $PM_{2.5}$ from residential wood burning and incidence of dementia in Umea, Sweden. Although their results indicated a 55% increase in HR of dementia per 1$\mu g/m^3$ increase in $PM_{2.5}$ levels, the association was not statistically significant (41). Studies should be conducted in these areas to investigate the association of air pollution with dementia. In addition, future studies should implement the lessons from previous studies to design cohorts that not only include and adjust for important risk factors for dementia, but also consider the long-term effects of air pollution on health and the period between effect on the central nervous system and diagnosis of dementia. Given the interaction between and multitudes of exposure to each of these pollutants in combination, the association of air pollution with the incidence of dementia cannot be definitively attributed to increased levels of any one specific pollutant alone.

In addition, $PM_{2.5}$ is defined based on the diameter of the particle and it can deliver numerous toxic ingredients as well as viruses and bacteria into the human body (22, 91). Therefore, it is difficult to assign the observed association to a particle that might have various ingredients potentially differing from region to region. Additional studies may provide better insight on the role $PM_{2.5}$ plays on human health.

Notwithstanding the limitations, our study has some implications for public health and government authorities, researchers, and the public.

The world population is increasing, and advances in medical care and social wellbeing have improved life expectancy. This means that the elderly will constitute a large proportion of the population and therefore, conditions associated with ageing, such as dementia, will be more frequent. It is estimated that dementia cases will triple by 2050 (11), and this may translateinto a ‘tsunami of dementia’ in the near future. Detecting and understanding preventable risk factors may help to mitigate this growth. One of the plausible and preventable contributors to dementia is air pollution. According to the “Ambient (outdoor) air quality and health” report by WHO in 2016, more than 90% of the world population is living in regions with higher than recommended levels of air pollution (21). Thus, if there is a causal association between air pollution and dementia, a large proportion of the population are at increased risk of developing dementia in the future. The sheer magnitude underscores the importance of further research to understand this association and effective mitigation efforts.

While more studies are needed to evaluate the causal pathway between air pollution and dementia, current evidence points to a plausible association that is worthy of attention.

Since most of the pollution in the included studies concerned traffic-related air pollution, governments should improve regulations for air quality assessment and accelerate the transition from fossil fuels to sustainable energies such as electricity. In addition, public health authorities should consider programs to prevent dementia by reducing exposure to preventable risk factors for dementia including air pollutants. Such a plan mandates an interdisciplinary approach involving governmental, health, community, and funding sectors.

These findings are also important to regular citizens. By understanding the imposed risk of dementia through exposure to air pollution, individuals would consider using sustainable energies, living away from regions with a high level of pollutants, and advocate for global interventions to reduce air pollution.

The current study draws a scratch of a big picture that most of it are not completely understood yet. Further research is needed to improve our knowledge and understanding of the association between air pollution and dementia. Future prospective population-based studies should consider the limitations of previous studies such as measuring exposure more precisely with adequate follow-up over time to evaluate the effect of moving from one region to another. In addition, in countries with significant migration or immigration, the exposure before immigration should be considered. Dementia should be defined using standardized definitions, preferably with clinical assessment rather than by registry codes to prevent misclassification of the outcome. Moreover, prognostically relevant factors should be included in the analysis and if possible, the mediation role of other conditions such as CVD should be evaluated. In addition, the duration of exposure prior to developing dementia should be evaluated. Finally, sex should be included as a subgroup not just a

variable in the regression models so that difference between males and females can be evaluated. In conclusion, this meta-analysis of cohort studies indicates a significant association between exposure to $PM_{2.5}$ and incidence of dementia. However, there were few studies on other pollutants, and the high heterogeneity of effects across studies should be considered in interpreting the results.

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Appendices

Appendix A: Search Terms

	Alzheimer	**Pollution**
PubMed	("Alzheimer Disease"[Mesh] OR "Dementia"[Mesh] OR alzheimer* OR dementia)	("air pollution"[MeSH Terms] "Particulate Matter"[MeSH Terms] OR "Nitrogen Oxides"[MeSH Terms] OR "Nitrogen Dioxide"[MeSH Terms] OR "Nitrous Oxide"[MeSH Terms] OR "Ozone"[MeSH Terms] "Petroleum"[MeSH Terms] OR "Sulfur Oxides"[MeSH Terms] OR (air pollut*) OR (Particulate Matter*) OR (Nitrogen AND (Oxide* OR dioxide*)) OR (Nitrous AND Oxide*) OR (Ozone) OR (Sulfur AND Oxide*) OR smok* OR "Cooking"[Mesh] OR cooking* OR "environmental pollution"[MeSH Terms] OR "Environmental Pollutants"[Mesh Terms] OR "Environmental Exposure"[Mesh] OR "traffic-related pollution"[MeSH Terms] OR "Vehicle Emissions"[Mesh Terms] OR traffic-related OR traffic* OR car* OR Vehicle* OR road* OR transport* OR road-proximity OR "Fossil Fuels"[Mesh] OR "Petroleum Pollution"[Mesh] OR gas OR gasoline* OR diesel* OR fossil* OR petroleum* OR fuel* OR environment* OR "PM2.5" or PM10 or NOx OR NO2) AND (pollut* OR exposur* OR emission*)

	Alzheimer	**Pollution**
Scopus	(TITLE-ABS-KEY (alzheimer*) OR TITLE-ABS-KEY (dementia))	(TITLE-ABS-KEY (particulate AND matter*) OR TITLE-ABS-KEY (nitrogen AND oxide*) OR TITLE-ABS-KEY (nitrogen AND dioxide*) OR TITLE-ABS-KEY (nitrous AND oxide*) OR TITLE-ABS-KEY (ozone) OR TITLE-ABS-KEY (NO2) OR TITLE-ABS-KEY (NOx) OR TITLE-ABS-KEY (PM2.5) OR TITLE-ABS-KEY (smok*) OR TITLE-ABS-KEY (cooking) OR TITLE-ABS-KEY (PM10) OR TITLE-ABS-KEY (environment*) OR TITLE-ABS-KEY (traffic*) OR TITLE-ABS-KEY (car*) OR TITLE-ABS-KEY (vehicle*) OR TITLE-ABS-KEY (transport*) OR TITLE-ABS-KEY (road AND proximity) OR TITLE-ABS-KEY (road) TITLE-ABS-KEY (fuel*) OR TITLE-ABS-KEY (fossil*) OR TITLE-ABS-KEY (petroleum*) OR TITLE-ABS-KEY (gas) OR TITLE-ABS-KEY (gasoline*) OR TITLE-ABS-KEY (diesel)) AND (TITLE-ABS-KEY (pollut*) OR TITLE-ABS-KEY (expos*))
Web of Science	TS= (alzheimer* OR dementia)	TS=(particulate AND matter*) OR TS=(nitrogen AND oxide*) OR TS=(nitrogen AND dioxide*) OR TS=(NOx OR NO2 OR PM2.5 OR PM10 OR ozone OR O3 OR smoke* OR cooking OR environment* OR traffic* OR car* OR vehicle* OR transport OR road*) OR TS=(road AND proximity) OR TS=(fossil* OR fuel* OR petroleum* OR gasoline* OR diesel*) AND TS = (Pollut*)

	Alzheimer	Pollution
OVID MEDLINE, PSYCHINFO, and EMBASE	1. exp dementia/ or exp Alzheimer disease/ or alzheimer*.mp. 2. exp semantic dementia/ or exp frontotemporal dementia/ or exp "mixed depression and dementia"/ or exp Pick presenile dementia/ or exp frontal variant frontotemporal dementia/ or exp senile dementia/ or exp multiinfarct dementia/ or exp dementia/ or exp Cornell Scale for Depression in Dementia/ or dementia.mp. or exp presenile dementia/	3. exp particulate matter/ or exp air pollution/ or air pollut*.mp. or exp air pollutant/ 4. exp nitrogen dioxide/ or exp nitrogen oxide/ or nitrogen oxide*.mp. or exp ozone/ 5. nitrogen dioxide*.mp. 6. exp nitrous oxide/ or exp nitrous oxide emission/ or nitrous oxide*.mp. 7. ozone*.mp. 8. exp aerosol/ or exp airborne particle/ or particulate matter*.mp. 9. exp pollutant/ or exp pollution/ or pollut*.mp. 10. exp smoking/ or smok*.mp. or exp nicotine/ 11. environment*.mp. 12. exp traffic/ or exp traffic related pollution/ or traffic-related pollut*.mp. 13. exp motor vehicle/ or exp exhaust gas/ or vehicle emission*.mp. 14. (road* or road proximity or vehicle* or car* or transport*).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, tc, id, tm, mh] 15. exp petroleum derivative/ or petroleum*.mp. or exp petroleum/ 16. exp fossil fuel/ or fossil fuel*.mp. 17. gasoline.mp. or exp gasoline/ 18. exp diesel fuel/ or exp diesel engine/ or diesel*.mp. 19. exp fossil energy/ or fossil.mp. 20. 3 or 4 or 5 or 6 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 21. "PM10".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, tc, id, tm, mh] 22. "PM2.5".mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, tc, id, tm, mh] 23. NO2.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, tc, id, tm, mh] 24. NOx.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy, tc, id, tm, mh] 25. 20 or 21 or 22 or 23 or 24 26. 1 and 2 and 25 27. 9 and 26

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