**Associations between long term exposure to air pollution and the
incidence of dementia and cognitive impairment in a Canadian
prospective cohort study**

By

Yanjiang Yu

M.Sc. Probability and Statistics, Carleton University

SCHOOL OF MATHEMATICS AND STATISTICS

Supervised by:

Drs. Shirley Mills and Paul Villeneuve

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ABSTRACT

The findings from a series of animal studies as well as human epidemiological studies suggest that long-term exposure to air pollution may adversely impact cognitive functioning and play a role in the development of dementia. Air pollutants that have drawn particular attention in these biological pathways have included nitrogen dioxide (NO₂), a marker of traffic-related pollution, and fine particulate matter (PM_{2.5}). To date, the epidemiological studies that have investigated associations between pollution and dementia have been cross-sectional in nature and were limited in the methods used to identify incident cases of dementia and measure cognitive decline. Few studies have been longitudinal in nature while also being able to control for the potential confounding influence of other risk factors.

The primary objective of this study was to investigate associations between long-term exposure to NO₂ and PM_{2.5} and the incidence of dementia, cognitive impairment with no dementia (CIND), and Alzheimer's disease (AD). In addition, we investigated whether these associations differed across selected individual-level characteristics of the study participants. These characteristics included: education level, diabetic, and obesity.

This thesis makes use of data previously collected from the Canadian Study of Health and Aging (CHSA). This was a cohort study that initially included 10,263 people who were 65 years of age or older at baseline. Participants were selected from study centres across Canada. These participants were followed from 1991 until the earliest of development of dementia, death, or December 31, 2004. Participants were screened for cognitive function at baseline and at two subsequent follow-intervals in 1991 and 1996. A series of neuropsychological measurements and information collected from proxy responses of those who died were used to identify those individuals with dementia. In contrast, those with either

CIND or Alzheimer's disease were identified strictly using the results from the neuropsychological tests administered in 1991, and 1996. At baseline, participants also completed questionnaires which collected information on other risk factors for dementia.

The analyses excluded those who were cognitively impaired at baseline or who were missing important covariates. Two sets of analyses were completed. The first was restricted to those who underwent neuropsychological assessments after baseline, while a second set of analyses incorporated information from decedents. The latter was used to identify additional incident dementias that could be ascertained through death certificates and interviews with relatives. The primary analyses presented in this thesis are based on 5249 subjects in which there were, respectively, 1001 and 526 incident cases of dementia and Alzheimer's disease identified during follow-up. Analyses were also undertaken on these 5249 subjects after excluding those with cognitive impairment at baseline to investigate associations with 1008 incident cases of CIND that were identified during follow-up. Finally, since additional cases of dementia could be identified for some participants using information obtained from death certificates, other analyses were performed on 6901 participants, of which a total of 1346 were determined to have developed dementia. The 5249 subjects that formed the basis of the first set of analyses, were a subset of the 6901 participants

Estimated concentrations of air pollution at the place of residence of the participants at baseline were derived using satellite imaging for PM_{2.5} and a Canadian national land-use regression surface for NO₂. Specifically, ground-level concentrations of PM_{2.5} at a 10 × 10 km resolution were estimated using remote sensing-derived estimates over the 9-year period between 1998 and 2006. These estimates were assigned to geographical coordinates of the centroid of participants' six character postal code of residence at baseline. The Cox

proportional hazards model was used to describe associations between these two air pollution measures and development of dementia, Alzheimer's disease, and cognitive impairment. The hazard ratios and 95% confidence intervals obtained from these models were adjusted for other risk factors of dementia including, age, sex, drinking, participation in physical activities, and use of non-steroidal anti-inflammatory drugs.

Among the subjects who formed the basis of the analyses, the mean concentrations for PM_{2.5} and NO₂ were 7.5 (s.d=3.2 µg/m³) and 12.7 (s.d=6.3 ppb), respectively. The analyses revealed that PM_{2.5} was somewhat positively associated with the development of dementia, Alzheimer's, and CIND. Specifically, the adjusted hazard ratios (HR) in relation to a 10 µg/m³ increase in PM_{2.5} for these three conditions were: 1.15 (95% CI=0.93-1.40), 1.32(95% CI=0.95-1.83) and 1.52 (95% CI=1.20-1.95), respectively. In contrast, NO₂ concentrations were not associated with any of these three outcomes as the hazard ratios were close to unity. The corresponding hazards ratios for a 5 ppb increase in NO₂ for dementia, AD, and CIND were 0.98 (95% CI=0.93-1.03), 1.00(95% CI=0.91-1.09) and 0.99 (95% CI=0.83-1.06), respectively. Our findings also suggest that the association between PM_{2.5} and our measures of dementia are stronger among those who are obese when compared to those who are not.

In conclusion, these analyses suggest that long-term exposure to fine particulate matter air pollution increases the risk of developing dementia. The strength of this association is similar in magnitude to more established health outcomes to which air pollution has been linked, such as cardiovascular disease. These findings should be interpreted cautiously due to some limitations of the study, which include the inability to track changes in exposure over time and a relatively small number of outcomes. Additional research is needed to investigate these associations in other study populations.

CHAPTER 1: INTRODUCTION

1.1 Dementia, Alzheimer's disease, and cognitive impairment

Dementia refers to a group of diseases that involve “a chronic deterioration of intellectual function and other cognitive skills severe enough to interfere with the ability to perform activities of daily living” (1). Dementia is an important health concern as it affects an estimated 8% of Canadians 65 years of age or older (2). It has been estimated that there are about 104,000 newly diagnosed cases of dementia in Canada each year (3). It is a progressive and irreversible condition that affects more than 500,000 Canadians and nearly 36 million people worldwide (4). The Canadian economic health burden including direct (medical) and indirect (lost earnings of dementia) total an estimated \$33 billion annually (5). Due to the aging of the Canadian population, the economic health burden associated with dementia and Alzheimer's Disease (AD) is expected to increase substantially. The Alzheimer's Society of Canada predicts that in 2031 dementia will affect 1.4 million Canadians and that by 2040, the total annual costs will be \$293 billion (6). The adaptation of preventive strategies to reduce the incidence of these neurodegenerative conditions can therefore yield considerable economic cost savings. Presently, there are few interventions to prevent, delay or halt cognitive decline.

Dementia includes Alzheimer's disease, which is the most common form of dementia, as well as vascular dementia, and other rarer conditions. AD has been defined as "a progressive, inexorable loss of cognitive function associated with an excessive number of senile plaques in the cerebral cortex and subcortical gray matter, which also contains β -amyloid and neurofibrillary tangles consisting of tau protein (1)." Findings from the Canadian Study of Health and Aging (CHSA) have estimated that Alzheimer's disease accounts for

approximately 69% of dementia cases among women and 53% among men (7). Age is the most important risk factor for AD since the prevalence of this disease among Canadians aged 65-74, 75-84, and 85+ has been estimated at 2.8%, 11.6% and 37.1%, respectively (7).

Cognitive impairment refers to a condition where an individual has difficulty remembering, concentrating, learning new things, or making decisions that may affect their everyday life. This impairment can range from mild to severe. Mild cognitive impairment (MCI) as well as cognitive impairment with no dementia (CIND) has been the focus of an increasing number of studies. Cognitive impairment is considered to be an intermediate state between cognitive changes that occur with aging and mild dementia, particularly of the Alzheimer type (8). Previous studies have shown that individuals who have MCI or CIND are at an increased risk of developing dementia and that the conversion rates vary between 3% and 15% per year depending on whether the individuals are in a community or clinical setting (9, 10). At this time, there is no specific pharmacological treatment available to prevent cognitive impairment (11).

1.2 Epidemiology of dementia, Alzheimer's disease and CIND

In this section, we provide a brief review of the risk factors for dementia, Alzheimer's disease and cognitive impairment. This background is important since many of these risk factors are also associated with air pollution and could therefore potentially bias associations between air pollution and the health outcomes in this study. This section has been divided into risk factors that are demographic, lifestyle-related, as well as other medical conditions.

1.2.1 Demographic Factors

Age

Age is well recognized as the most important risk factor for dementia, and although dementia is considered a disease of the elderly, it may still affect individuals who are less than 65 years of age (12). Data from the Canadian Study of Health and Aging provide compelling evidence of the dramatic changes in dementia prevalence with increasing age (2). This increase was evident in both sexes. Among women, an estimated 28 per 1,000 of those aged 65 to 74 had dementia and this estimate increased to 116 and 371 per 1,000 women aged 75 to 84, and aged 85 and over, respectively. Among men, the corresponding prevalence rates of dementia in the same age groupings were 19, 104 and 287 per 1,000.

Sex

The prevalence of Alzheimer's disease is higher in women compared to men, and previous work suggests that nearly two-thirds of individuals diagnosed with AD are women (13). An explanation for the increased prevalence is the longer life expectancy enjoyed by women (13). Most US based studies that have compared incidence rates of Alzheimer's disease have not found differences in age-specific comparisons of disease rates between men and women. In Canada, the Canadian Study of Health and Aging did not find sex to be a significant risk factor for Alzheimer's disease (14). However, prospective studies in Europe have identified female sex as a risk factor for the incidence of AD, but only after age 85 or 90 (15).

For cognitive impairment, the findings from studies that have compared rates between men and women have been inconsistent (16). While some studies have reported sex differences in CIND these differences have varied depending on the design of the study, age

distribution of the study population, and the diagnostic method (16). In general, women tend to have higher incidence at older ages, while men have higher incidence rates for non-amnesic mild cognitive impairment (17).

Education Level

Several prospective studies provide support for a reduced risk of Alzheimer's disease among individuals with higher educational attainment (18-22). Some of these studies found this association to exist for women only (20) or to be stronger for women (21).

1.2.2 Lifestyle Factors

Exercise

A number of biological mechanisms have been suggested whereby participation in physical activity can reduce the risk of developing dementia. These mechanisms include: a reduced risk of cardiovascular disease, improved cerebral perfusion, and the induction of cortical angiogenesis. A number of cohort studies have shown that regular exercise can substantially reduce the risk of developing cognitive impairment (23). In longitudinal analyses of the Canadian Study of Health and Aging data, regular physical activity, a modifiable lifestyle habit, was found to reduce the risk of AD by approximately 50% (24). This study also reported increased protection with higher levels of physical activity for AD and dementia of any type as well as for CIND. They found that inverse associations between physical activity and the risk of CIND, dementia or AD were strongest in women. Although the literature is not entirely consistent, this finding has been supported by other studies (14).

Diet

It has also been suggested that diet may play a role in the development of dementia. In particular, it has been hypothesized that a Mediterranean diet could reduce the risk of cognitive decline. The pathways implicated in this relationship include improved carbohydrate metabolism coupled with anti-oxidative and anti-inflammatory mechanisms (25). Two prospective cohort studies lend credence to this hypothesis (26). A US based study of 1393 adults with normal cognitive function at baseline observed a 28% reduction in cognitive impairment after 4.5 years of follow-up among those who had a high proportion of Mediterranean-style diet (27).

Non-steroidal anti-inflammatory drugs

Several studies have examined the association between non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin) and development of dementia. In previous analyses of the Canadian Study of Health and Aging, the regular use of NSAIDs was associated with a 35% reduction in the risk of AD (14). A meta-analysis that was based on three (3) case-control studies found that use of NSAIDs decreased the risk by half (28). At least two other longitudinal studies have supported these inverse associations (29, 30), though others have not (30, 31). Although it is encouraging that use of NSAIDs may help to protect against AD, suggesting this as a preventive action the recommendation of increased NSAIDs use is not straightforward given the concern about potential side effects, particularly gastrointestinal bleeding. Recently published meta-analyses of NSAIDs and Alzheimer's disease concluded that observational studies demonstrate an inverse association, however no such association was evident in the one randomised controlled trial that was conducted (32).

Alcohol

It is well established that alcohol has neurotoxic actions that are exerted with accelerated cerebral atrophy and reduced acetylcholine synthesis (33). Broe et al reported associations between alcohol drinking and poorer recall based on memory test performance (34). For the most part, prospective trials that have examined the relationship between alcohol consumption and dementia have revealed either a J-shaped or U-shaped pattern. The studies have shown that low consumption of alcohol is associated with a reduced risk of cognitive impairment, while increased risks of dementia are observed for those who drink higher amounts.

In the Canadian Study of Health and Aging, regular wine consumption was associated with a reduced risk of Alzheimer's disease (Odds Ratio=0.49; $p<0.05$) when compared to those who did not drink wine regularly. This inverse association was somewhat stronger among women (Odds Ratio=0.38). These findings are consistent with findings reported in a cohort study undertaken in France (35). Some have suggested that substances found in wine, apart from alcohol, may exert a positive effect on nerve cells (36). However, this was not confirmed in a prospective study in the Netherlands which reported reduced risks of dementia among those who drank in light to moderate amounts, but found no evidence of variation in risk by type of alcohol (36).

Vitamin D

Vitamin D deficiency increases with age due to reduced sun exposure and as many as 50% of the population have been shown to have this deficiency (37). This vitamin plays an important role in the synthesis of neurotrophic factors and neurotransmitters (38) and is also involved in the receptor regulation in memory-relevant parts of the brain (39). A series of cross-sectional studies that have looked at associations between Vitamin D and brain

disorders have yielded equivocal results (33). Grant's work highlighted that vitamin D was beneficial in reducing the risk of dementia such as vascular and metabolic diseases and that several mechanisms that lead to dementia can be impaired by vitamin D (40). More recently, in a follow-up study of 1658 adults free of dementia, vitamin D was found to reduce the risk of developing dementia during a 6-year follow-up interval (41).

1.2.3 Medical history

Diabetes

The link between diabetes and cognitive impairments is supported by a number of biochemical, imaging-related and histopathological findings (33). A systematic review of 14 cohort studies observed an increased incidence of dementia among those with diabetes, however there was no adjustment for other comorbid health conditions including stroke or hypertension (42). More recent prospective studies have accounted for some of these limitations and found diabetes was an independent risk factor for dementia (43-45). In addition, an increased duration of diabetes, lack of antidiabetic medication, and an increased number of hypoglycemic episodes have been linked to decreased cognition (46).

Hypertension

Hypertension can contribute to vascular-related cognitive impairment through a number of different mechanisms including arteriosclerosis, hypoperfusion, leukoaraiosis, and cerebral infarction (33). The negative impact that hypertension has on cognitive function was first hinted at in the 1960s in research involving psycho-motor speed among air traffic pilots and controllers (47). Since that time, hypertension has been linked with a variety of cognitive deficits including attention deficit, impaired memory, and reduced abstract reasoning (47). Among middle aged adults, hypertension has been linked with increased risk of dementia as

well as stroke (48).

Vaccines

Individuals' vaccination histories have been shown to be associated with dementia. In the Canadian Study of Health and Aging, past exposure to vaccines against diphtheria or tetanus, poliomyelitis, and influenza was found to reduce the risk of Alzheimer's disease (49). Specifically, after adjusting for age, sex and education, vaccines against diphtheria or tetanus and against poliomyelitis were significantly associated with 60% and 40% lower risks of AD, respectively. A lower risk was also suggested for influenza vaccine however this result did not achieve statistical significance.

Estrogen therapy

Previous work has suggested that estrogen therapy reduced the risk of AD. The CSHA did not see a protective effect (14) and other studies have yielded inconsistent findings (50, 51). A prospective US study found no association between estrogen use and cognitive decline related to aging, although few women in the study used estrogen for at least two years (52). On the other hand, another cohort study found that women who formerly used hormone therapy had a reduced risk of AD, as did current users whose treatment exceeded 10 years (53). More recently, findings from the Women's Health Initiative showed an increased risk of AD among women in the estrogen/progesterone arm of the study (54).

1.3 Air pollution

Air pollution is a known public health concern owing to decades of epidemiological and toxicological evidence that support a causal relationship with cardiorespiratory morbidity/mortality. Indeed, the recent Global Burden of Disease report (55) lists ambient

particulate air pollution as the 6th most important contributor to global disease burden, ahead of such factors as alcohol use and obesity. This report estimates that air pollution is responsible for an estimated 3% of cardiopulmonary deaths and 5% of lung cancer deaths. Overall, the authors of this report have estimated that air pollution is responsible for 0.8 million premature deaths and 6.4 million person-years of life lost each year.

Fine particulate matter air pollution (particles with a median aerodynamic diameter of $< 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$)) has been identified as an important pollutant affecting human health since it tends to penetrate more deeply into the lungs due to its smaller size. $\text{PM}_{2.5}$ has been shown to increase blood coagulation and viscosity, increase heart rate variability, and induce oxidative stress (56-58). Long-term exposure to $\text{PM}_{2.5}$ has been consistently associated with cardiorespiratory mortality (59) with linear dose-response relationships suggesting that adverse health effects occur even at the low levels now observed in Canada (60, 61). While the magnitude of the risk estimates reported in these studies tend to be low, the ubiquitous nature of air pollution results in a large overall population health impact.

More recently, increased attention has focused on studying associations between air pollution and disease incidence rather than on mortality. For example, recent evidence suggests that traffic-related air pollution may be associated with an increased incidence of diabetes (62, 63), hypertension (64), and lung cancer (65). Traffic-related pollution can be described using several measures such as distance to major road or highways, traffic volume, or total length of road within a certain buffer area.

Nitrogen dioxide (NO_2) is a gaseous pollutant that is often used as a surrogate measure of traffic-related pollution since it correlates highly with roadway characteristics. NO_2 tends

to be more highly spatially variable within urban areas than PM_{2.5} which includes regional components of air pollution. This thesis research evaluated associations between both these pollutants and three neurodegenerative disease outcomes (dementia, Alzheimer's disease, and CIND). To date, there has been no study that has examined the relationship between long-term exposure to air pollution and the development of dementia or AD. The emergence of remote-sensing technologies to create air pollution exposure surfaces has accelerated our ability to study these possible associations as the surfaces can be linked to place of residence.

1.4 Air Pollution and Dementia

A number of biological mechanisms have been proposed to explain how exposure to air pollution may adversely affect the central nervous system, thus contributing to the development of dementia.

First, particulate matter air pollution, such as that found in diesel engine emissions, is small enough to pass through blood barriers in the lung and enter the circulation system, ultimately translocating to other body tissues including the brain (66, 67). Experimental studies that simulated PM_{2.5} tailpipe emissions suggest the particles may breach the blood-brain barrier (68, 69). It has also been suggested that these particles can translocate directly to the brain via the olfactory nerve (70). The presence of these particles in the brain is associated with both neuro-inflammation and oxidative stress. Oxidative stress refers to a state of redox imbalance that is a consequence of a production of reactive oxygen species that exceeds the capacity of antioxidant defense mechanisms (71). Oxidative stress has been cited as an important biological mechanism whereby exposure to air pollution can increase the risk of cardiovascular and respiratory health outcomes. In a recent review paper (57), oxidative stress was found to modify the impact of PM_{2.5} for several health outcomes. Others have

hypothesized that the central nervous system is particularly susceptible to damage from oxidative stress as it consumes high levels of energy and physiological oxygen or because it has relatively weak antioxidant defense mechanisms (72-74). In their review, Migliore and Coppede (74) outlined how oxidative stress affects several neurodegenerative processes. Recent work has revealed evidence of increased oxidative stress products in senile plaques and neurofibrillary tangles(75) that are an indication of AD (72).

Second, traffic-related air pollution may affect the health of the central nervous system indirectly through its effects on cardiovascular health. Exposure to air pollution is associated with a number of cardiovascular endpoints including plasma viscosity, heart rate variability, hypertension, and atherosclerosis (56, 58, 76, 77). Several of these endpoints are associated with worse cognitive function (78-80).

Third, there is an interesting similarity between air pollution induced neuropathies and neurodegenerative disorders. Olfactory dysfunction, especially in ApoEε4 carriers, can be seen from childhood in individuals that grew up in highly polluted environments (81). Yet olfactory dysfunction is also among the first clinical signs of AD (82).

1.4.1 Animal Studies

A number of animal studies have investigated the possibility that exposure to air pollution may impact cognitive function or dementia. Gerlofs-Nijland et al (83) investigated whether specific regions of the brain are more susceptible to exposure to diesel-derived air pollution. They exposed rats to air pollution for 5 days a week for 4 weeks using a nose-only exposure chamber. They found that baseline levels of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-alpha) and interleukin-1 alpha (IL-1alpha) increased after

exposure to diesel engine exhaust and that the impacts varied by the region analyzed. They concluded that neuro-inflammation occurred in response to exposure to air pollution.

Levesque et al (84) also evaluated the effects of subchronic exposure to diesel exhaust ,specifically those effects related to neuro-inflammation and markers of early neuropathology. They exposed 344 rats to 5 different concentrations of diesel exhaust (992, 311, 100, 35 and 0 $\mu\text{g PM}/\text{m}^3$) by inhalation over 6 months. They found that diesel exposure resulted in elevated levels of TNF-alpha at high concentrations in all regions tested, with the exception of the cerebellum. The midbrain region was the most sensitive, where exposures as low as 100 $\mu\text{g PM}/\text{m}^3$) significantly increased brain TNF alpha levels. The authors concluded that the midbrain may be more sensitive to the neuro-inflammatory effects of subchronic air pollution exposure.

In post-mortem studies of canines, increased levels of inflammation, β -amyloid deposition, and oxidative damage to DNA, as well as evidence of blood-brain barrier disruption in subcortical and cortical structures, were found in otherwise healthy dogs who lived in areas of high air pollution when compared to those that inhabited less polluted rural areas (85). Postmortem examination of human samples also found that those who lived in highly polluted areas of Mexico City exhibited higher COX-2 expression in the olfactory bulb, the hippocampus, and the frontal cortex, and greater neuronal astrocytic accumulation of AB42 when compared to age-gender and education-matched subjects from cities with lower pollution levels (86).

1.4.2 Human Studies

There have been very few epidemiological studies that have investigated associations

between ambient air pollution and neurodegenerative disease. We have reviewed these studies below.

Ranft et al. (87) studied long-term residential exposure to traffic-related particulate matter air pollution and mild cognitive impairment (MCI) in a small cohort of 399 women (aged 68-79) who had lived at the same place for at least 20 years. MCI was determined using a series of neuropsychological tests. Exposure-response relationships were observed between these measures of traffic-related pollution and MCI after adjusting for factors such as age, educational attainment, physical activity, and other comorbid health conditions. However, this study was limited by a rather crude exposure assignment (i.e., assigned value of 2 for those who lived within 50 m of a busy street, 1 for 50-100m and 0 for >100 m). Furthermore, they administered their series of clinical tests at the end of the follow-up period, so no baseline measure of cognitive performance was available, and they were unable to restrict their study population to those with no cognitive impairment.

Just recently, Gatto et al, in a cross-sectional analyses of middle-age and older adults in Los Angeles, found that ambient exposure to NO₂ was associated with lower logical memory (88). Elsewhere, Power et al (89) examined the relationship between black carbon (BC), a marker of traffic-related pollution, and cognitive functioning among US male veterans who lived in Boston. In this study of 680 elderly men, estimates of BC were assigned to the residential addresses of the participants, while cognitive testing was done using the Mini-Mental State Examination (MMSE). Analyses were restricted to those that had an estimate of BC exposure before the cognitive test data obtained between 1996 and 2007. They found that exposure to BC was associated with decreased cognitive functioning. Specifically, for each doubling of BC, the odds of having a MMSE score of less than 25 was 1.3 times

higher (95% CI=1.1, 1.6). An important strength of this study was the highly spatially resolved measure of air pollution. However, this study was not capable of looking at development of disease as it did not screen out those with cognitive impairments at baseline. As a result, they were unable to investigate whether living in highly polluted areas produced deterioration in cognitive function over time.

A recently published study by Oudin and colleagues (90) examined the relationship between residential measures of air pollution and the risk of development dementia. The longitudinal nature of this study and its ability to control for the potential confounding influence of other risk factors were distinct strengths. The study followed 1806 participants over a 15-year period. Exposure to traffic-related air pollution was estimated using a land-use regression surface. They found that those in the highest exposure group had hazard ratios of 1.43 for dementia and 1.37 for Alzheimer's disease when compared to those in the lowest exposure group. Stronger associations were observed when the investigators excluded a younger sample of the cohort that had only been followed for 5 years.

To date, the only Canadian study to investigate associations between ambient air pollution and neurodegenerative disease was that by Finkelstein and Jerrett (91). They explored associations between the diagnosis and treatment of Parkinson's disease (PD) and markers of exposure to vehicle exhaust and industrial emissions of manganese (Mn) in a cohort of 110,000 residents of Toronto and Hamilton. Incident cases of PD were ascertained using a combination of physician billing and prescription drug databases. No association between PD and traffic-related air pollution among Toronto residents was found. However, they found an elevated odds ratio for a physician's diagnosis of PD disease (OR=1.03, 95% CI=1.00-1.07) per a 10 ng/m³ increase of Mn in Hamilton. While this study suggests that

exposure to air pollution may be weakly associated with PD, they were unable to study dementia or AD.

1.6 Summary of literature and rationale for study

The experimental studies conducted to date present a compelling argument that long-term exposure to air pollution may contribute to an increased risk of developing dementia and adversely impact cognitive functioning. There are several reasons why additional research is needed to address this important research gap. First and foremost, there have been very few epidemiological studies that have attempted to answer this question. Of those that have been undertaken, they are limited by small sample sizes, inability to control for other confounding variables, and inability to restrict the study population to exclude those with cognitive impairment. Apart from the study by Oudin (90), there have been no other studies that have examined these associations using a longitudinal study design, with rigorous neuropsychological tests needed to identify incident cases of dementia.

CHAPTER 2: RESEARCH OBJECTIVES

The primary objective of this thesis is to investigate associations between long-term exposure to air pollution and the development of dementia and cognitive impairment. The specific research questions are as follow.

1. Is long-term exposure to fine particulate matter (PM_{2.5}) and NO₂ associated with the development of dementia, Alzheimer's disease, and CIND?
2. Are associations between long-term exposure to PM_{2.5} and NO₂ and the development of dementia, Alzheimer's disease, and CIND modified by the following factors:
 - i. Education level
 - ii. Diabetes
 - iii. Obesity

CHAPTER 3: MATERIALS AND METHODS

3.1 Study Population

This study uses data previously collected from participants in the Canadian Study on Health and Aging (CSHA). The CSHA is a longitudinal population-based study of dementia that recruited a nationally representative sample of Canadians who were 65 years of age or older. A total of 9008 individuals who were living in the community participated and an additional 1255 adults who were living in institutions participated.

3.1.1 Study Design

The Canadian Study of Health and Aging went through ethical reviews via the boards at the central coordinating center and at each of the 18 participating research centers. This was a longitudinal study with baseline data collected in 1991 (CSHA-1), and additional data were collected in 1996 (CSHA-2) and 2001 (CSHA-3).

At baseline (CSHA-1), representative samples of the participants with age of more than 65 were selected from 39 urban areas and the rural areas surrounding them. Participants were not recruited in the Yukon or the Northwest Territories due to the small numbers of seniors living in those areas, as well as the logistical challenges in collecting data from them. For community subjects, the interviews took place at their homes and they were screened for cognitive impairment using instruments that were standardized and validated.

During the first two phases of the study (CSHA-1 and CSHA-2), participants who lived in the community were screened for cognitive problems and this screening was done using the Modified Mini-Mental State (3MS) test (92). Those participants who screened positive for

cognitive impairment (3MS score < 78) then underwent more detailed clinical and neuropsychological examinations (93, 94). The study also randomly selected approximately 500 individuals who tested negative to undertake the more detailed clinical examination. At the third phase (CSHA-3), the procedures used were modified slightly and incorporated a cut-point of <90 on the 3MS. This was done to allow for a more detailed study of earlier stages of cognitive impairment. During this phase, those who scored less than 90 underwent the neuropsychological test and those deemed to be impaired by a neuropsychologist received a clinical exam from a physician.

3.1.2 Diagnosis of dementia, Alzheimer's disease, and CIND

Diagnoses of dementia were made using clinical examinations. At all phases (1991, 1996, 2001), a registered nurse administered the 3MS and recorded vital signs, hearing, vision, height, and weight. In 1991 and 1996, a physician then interviewed the participants and conducted a physical and neurological exam. Lastly, a psychometrist administered a battery of neuropsychological tests to subjects with a 3MS test scores of at least 50 and these were subsequently interpreted by a neuropsychologist. Participants with a 3MS score of < 50 were deemed to be untestable by neuropsychological tests. In 2001, those who scored between 50 and 89 on the 3MS were first administered the battery of neuropsychological tests; those who were deemed to show the possibility of cognitive impairment or dementia were clinically examined. For all phases, the physician and neuropsychologist independently formed preliminary diagnoses, and then met in a consensus conference to arrive at a final diagnosis. The diagnosis was based on the DSM-III-R criteria (95) for cognitive impairment or dementia, and the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke for the Alzheimer's disease and Related Disorders Association) criteria for possible and probable Alzheimer's disease. CIND (cognitive impairment, no dementia) was a

diagnosis of exclusion; those with CIND did not meet criteria for dementia, nor were they without cognitive impairment (NCI)(96). On the basis of all the data collected, participants were classified with: no cognitive impairment (NCI), CIND, or dementia.

In addition to identifying incident cases of dementia using data collected from the clinical examinations, the investigators of the Canadian Study of Health and Aging developed methodology to identify additional cases of dementia among those who had died. Specifically, among those who died, information was sought from a relative/informant about their physical and cognitive status at the end of life, and the underlying cause of death and date of death was extracted from death certificates (97). This interview with the informant included questions about whether the person had previously been diagnosed with dementia, and questions about cognitive signs and symptoms. This information was then used to estimate the probability that the decedent had dementia at the time of their death. This approach was validated using a sample of participants who had died within 5 months after undergoing the CSHA clinical examination (98). The predictive algorithm performed well, with an estimated sensitivity and specificity of 82% and 93%, respectively. However, the data collected among decedents was unable to differentiate between dementia and Alzheimer's disease and therefore was only able to identify additional cases of dementia.

3.1.3 Other data collected from study participants

A self-administered questionnaire was used to collect information from participants on several known or suspected risk factors for dementia. If participants were initially screened as being cognitively impaired, a proxy informant was interviewed instead. The questionnaire collected information on a number of lifestyle risks including consumption of alcohol, including wine, spirits, and beer. Participants were also asked to provide information on

cigarette smoking behavior and patterns of exercise.

Socio-demographic information was also collected. The number of years of education, defined as complete years of schooling, was also collected from participants. Individuals were asked about whether they had any of a number of chronic health conditions. Participants were also asked to indicate what their main occupation was during their working history. These occupations were coded using Statistics Canada's standard occupational codes (3). These codes were used to categorize participants in the following categories: never formally employed, housewives, unclassified occupations, unskilled laborers, farmers, clerical, sales, service employees, and managers and professionals. Body mass index was calculated using measured height and weight.

Detailed place of residence data were also collected. In particular, the six character postal codes of the participants were recorded. The six-character postal code, in urban areas, represents one side of a block between two intersecting streets. It therefore has a high degree of spatial resolution. At baseline, those who were screened as cognitively normal were asked to supply the names of towns, counties, provinces and countries lived in during their lifetimes along with the dates they lived there. In addition, at the two follow-up intervals (1996 and 2001) residential data were obtained.

3.2 Assignment of Air Pollution Concentrations

3.2.1 Remote-sensing derived estimates of PM_{2.5}

While epidemiological studies have commonly used data from fixed-site monitoring networks to assign air pollution exposure estimates, this approach has important limitations. These networks provide limited geographical coverage as they exist only in urban areas, or

around specific sources of pollution. In recent years, the use of remote sensing to model air pollution surfaces has advanced considerably and is capable of overcoming many of the limitations of fixed-site monitoring. In this study, we used estimated concentrations of PM_{2.5} derived from satellite remote sensing during the period between 2001 and 2006 that were developed by van Donkelaar et al (99). Briefly, this exposure surface was generated using observations of total column aerosol optical depth (AOD) from NASA's MODIS and MSIR instruments onboard the Terra satellite. Aerosol optical depth measures light extinction by aerosol in the atmospheric column above the Earth's surface. The Terra satellite has a sun-synchronous orbit and circles the earth about 15 times each day. From these observations, ground-level PM_{2.5} is estimated from the total columnar aerosol depth by applying a conversion factor that accounts for spatial and temporally-varying relationships (i.e., $PM_{2.5} = \eta \times AOD$), where η is a function of factors that relate daily dry aerosol mass to satellite observations of ambient AOD. These factors include: ambient size, aerosol type, diurnal variation, relative humidity, and the vertical structure of aerosol extinction. The GEOS-Chem global transport model [geos-chem.org] was used to calculate the η for the time and location of each AOD observation. By following this approach, estimates of long-term average exposure to PM_{2.5} between 1998 and 2006 were created at a resolution of approximately 10×10 km. The methods used to generate these estimates have been previously validated using ground-based in-situ measurements that showed significant spatial agreement was achieved with North American measures ($r=0.77$, slope=1.07, $n=1057$) (99). These estimates of PM_{2.5} were linked to the latitude and longitude of the centroid of the 6 character postal code of the place of residence of the study participants. This approach to exposure assignment was recently applied to other Canadian cohorts to investigate associations between long-term exposure to air pollution and cardiovascular mortality (60) and diabetes (100). A map of this surface is provided below:

Figure 3.1: Global estimates of fine particulate matter air pollution in Canada between 2000 and 2006 from van Donkelaar et al

3.2.2 National Land-use regression surface for NO₂

These analyses also made use of a previously developed land-use regression model for NO₂. This model, developed by Hystad et al., was created using Canadian monitoring data captured in 2006 (101). The models were developed in two stages. First, ArcGIS was used to derive satellite-based estimates of NO₂ for each National Air Pollution Surveillance (NAPS) fixed-site monitoring station, as well as geographic variables such as road length, population density, and proximity to large emitters. There were a total of 134 monitoring stations for NO₂ across the country. The authors used a forward stepwise regression to develop land use regression models and retain variables that corresponded to hypothesized effect directions. Only variables significant at the 5% significance level were retained. In the second stage, they conducted comprehensive literature reviews to identify deterministic factors so as to capture local scale gradients in pollution concentrations that were associated with specific sources (i.e. highways, major roads, gas stations). They identified NO₂ concentrations near those sources in relation to local background levels and developed deterministic multipliers with distance decay rates. This enabled them to obtain background and regional concentration LUR estimates. The national land use regression model seemed to perform reasonably well as it was estimated that it explained 73% of the variability in fixed site monitor concentrations of NO₂.

3.3 Data cleaning and exclusions

As mentioned previously, in total, there were 10,263 participants of the Canadian Study of Aging. Since our primary research question was to evaluate the association between long-term exposure to air pollution (PM_{2.5} and NO₂) and the development of dementia, Alzheimer's disease, and cognitive impairment, we excluded those individuals who were identified as having a cognitive impairment at baseline. Based on the initial screening tests, there were 1132 people who were diagnosed with prevalent dementia at baseline. We also excluded an

additional 508 participants who were screened as being cognitively impaired on the basis of the 3MS administered in 1991 but were unable to undergo the clinical examination. An additional 1722 participants were excluded from analyses because they were missing data on one or more risk factors, leaving a remaining 6901 participants for analysis. However, nearly 1700 of these individuals died before being able to be evaluated during the second phase of the study, and therefore, for these individuals we were unable to identify whether they had developed Alzheimer's disease or cognitive impairment. The flow chart in the figure below depicts the exclusions applied to the cohort and the remaining number of participants left for analysis. In total, 1346 individuals were diagnosed with dementia during follow-up and this included 1001 identified from survivors and 345 identified among those who had died. Similarly, a total of 526 incident cases of Alzheimer's disease and 1008 incident cases of CIND were identified between 1991 and 2001.

Figure 3.2 Flowchart depicting the number of participants and exclusions for Dementia, Alzheimer's and CIND

3.4 Methods

3.4.1 Cox regression

The Cox proportional hazards model was used to describe the associations between residential-based measures of air pollution and the risk of developing dementia, Alzheimer's disease, and CIND. Given the central role that this model plays in addressing the objectives of this research, below we provide background information on it. The hazard function $h(t)$ is defined as

$$h(t) = \lim_{\Delta t \rightarrow 0} \frac{\Pr(t \leq T < t + \Delta t \mid T \geq t)}{\Delta t}$$

The model is applied in longitudinal studies in order to quantify the instantaneous risk of events that occur at time t . The probability that a certain event appears at exact time t is approximately zero when time is measured on a continuous scale. However, the probability that a certain event appears during a small interval from t to $t + \Delta t$ can be analyzed this is a conditional probability that assumes that the person has already survived to time t . Persons are not obviously at risk of the event at all, if they have died. Therefore, only those persons who are alive at the start of this interval $[t, t + \Delta t)$ contribute to the estimation of risk. These considerations lead to the numerator in the above equation, namely $\Pr(t \leq T < t + \Delta t \mid T \geq t)$.

However, it should be noted that this probability is a function of Δt which is non-decreasing. It follows that it is more likely that a certain event occurs in this interval if the interval is longer. So Δt is used as a divisor in the equation above. In addition, the risk for the appearance of an event at the exact time t is expected to be extremely small relative to the risk for appearance in an interval starting with t . This interval shrunk down by making Δt continuously smaller, up to a limiting value. Another simple formula expresses the hazard in

terms of p.d.f and survivor function: $h(t) = f(t)/S(t)$.

With this background of the hazard rate, the Cox regression model can be expressed as follows:

$$h_i(t) = \lambda_0(t) \exp(\beta_1 x_{i1} + \dots + \beta_k x_{ik})$$

An important assumption of this model is that the ratio of the hazards remains constant over follow-up. The model above does not include non-proportional hazards or time-dependent covariates; however the Cox model can be extended to include these features. A couple other points warrant mention. First, the function $\lambda_0(t)$ is left unspecified but cannot be negative. Second, the model includes a linear function of a set of k fixed covariates with exponential growth. The above two factors lead to the determination of the hazard for a person at the exact time t . In our regression analyses, the covariates would include not only air pollution concentrations but also other risk factors that could influence the strength of the association between air pollution and the cognitive outcomes under study. The function $\lambda_0(t)$ can also be considered as one for a person whose covariates are all zero; this is sometimes referred to as the baseline hazard function.

$$\log h_i(t) = \alpha(t) + \beta_1 x_{i1} + \dots + \beta_k x_{ik}$$

The logarithm of both sides can be taken and the Cox model can be re-specified under the scenario where $\alpha(t) = \log \lambda_0(t)$. The term $\alpha(t)$ can be replaced by other possible options in order to fit other models. For example, when $\alpha(t)$ is specified as α , the above equation simplifies to the simpler exponential model. Alternatively, $\alpha(t)$ can be specified as αt yielding the Gompertz model, and finally, when $\alpha(t)$ is specified as $\alpha \log t$, the Weibull model is obtained. In most epidemiological studies of air pollution, the Cox model is fit and the resulting coefficients are exponentiated to obtain an estimate of the hazard ratio. This in turn provides an estimate of the relative risk of disease in one group of individuals relative to another.

In this study, the start time is the date of entry into the study and the follow-up is extended to the earliest of date of diagnosis of dementia, AD, CIND, or death. In addition, we used the midpoint between the evaluation periods to determine the date of diagnosis of dementia or AD or CIND. This is halfway between CSHA1 and CSHA2, or halfway between CSHA2 and CSHA3.

3.4.2 Stepwise selection

Characterizing the associations between long-term exposure to air pollution and the risk of dementia must consider the possible confounding influence of other covariates. Confounders, by definition are other risk factors that are related to both health outcome and are associated with air pollution concentrations. The final regression models must therefore allow for the possibility of including other risk factors.

We applied stepwise regression to identify the series of risk factors that should be included in the final models. Stepwise regression is regarded as a semi-automated process. Stepwise regression operates by building a model through successively removing or adding variables on the basis of t-statistics of estimated coefficients. It is a useful technique to apply when a large number of possible independent variables need to be considered. It provides an objective and data-driven approach to control for the impacts of other variables on the association of primary interest – air pollution and measures of cognition.

One approach with the model building is to begin with all variables in the model and to proceed by removing one variable at a time (backward elimination) until a final series of covariates has been identified. Alternatively, one can start the model building approach with no variables in this model and add a variable at a time and continue to proceed forward (forward

selection). In stepwise regression, at each iteration, the t-statistic is calculated for each variable and from this the F-statistic is derived. This program automatically removes the variable which has the smallest F-to-remove statistic and enters the variable which has the largest F-to-enter statistic, according to certain control parameters which have been specified. In our case, the research question is concerned about the impact of air pollution on the development of dementia and so air pollution is an explanatory variable that must be forced, or locked, into the model.

3.4.3 Confounder and interaction

A confounder can influence the strength of the association between the independent variable and outcome under study. In this study, we are interested in estimating the association between air pollution and the development of dementia, after adjusting for the influence of the other risk factors for dementia.

The concept of interaction differs from that of confounding. Interaction implies that the strength of the association between our exposure of interest and our outcome will be different depending on the level of the interaction variable. For example, if an association was only evident for men, but not women, sex would be considered an interaction. In epidemiology, it is important to adjust our risk estimates for the possible influence of a confounder. Conversely, with interaction, it is important to describe how the association between exposure and disease is different across levels of the interacting variable.

To evaluate whether interaction is present, one can visually inspect the risk estimates obtained across different stratum. Risk estimates that are the same across strata are an indication that there is no interaction. Another method of determining whether or not there is interaction is

by including a first-order interaction term into the model and testing whether this term is statistically significant. In our study, we specifically evaluated interaction for education, obesity and sex.

3.4.4 Non-linear associations between air pollution and health

The Cox regression model as described in the earlier section described a log-linear relationship between the exposure of interest, and the outcome under study or, expressed alternatively, that an increase in exposure produces a linear increase in the hazard ratio. When air pollution concentrations are measured, they are described as a continuous variable and epidemiological studies typically will include these continuous measures in regression models.

Our analyses considered the possibility of nonlinear associations using two methods. First, we categorized exposures to NO₂ and PM_{2.5} through the use of quintiles and then modeled this variable as an independent variable within the Cox regression model. Graphs were constructed to determine whether hazards ratios associated with each quintile increased in a linear or non-linear fashion. The lowest exposure category was used as the reference category. Secondly, spline analyses were done by modeling a natural cubic spline within the fully adjusted Cox regression model. Plots of these exposure functions were made using the R software program. Sensitivity analyses were also done to explore the impact of changing the number of degrees of freedom, and we fitted splines with 2 and 4 degrees of freedom. .

CHAPTER 4: RESULTS

4.1 Descriptive statistics

The participants of the Canadian Study of Health and Aging that formed the basis of analyses lived in a number of regions across Canada. As depicted in Figure 4.1 most of these participants lived in Southern Ontario and Quebec. There were a total of 18 different study sites that were generally located near larger metropolitan areas.

Figure 4.1 Place of residence at the time of entry for the 6901 participants of the Canadian Study of health and Aging included in the air pollution analyses

The frequency distribution of several key characteristics of the participants that were included in the air pollution analyses are presented in Table 4.1. Overall, the mean concentration of PM_{2.5} among the 5249 subjects in the study was 7.5 µg/m³ (s.d.=3.2). The corresponding mean and standard deviation for NO₂ was 12.9 and 6.3 ppb, respectively. Higher concentrations of PM_{2.5} were observed among those who: took vitamins, had diabetes, and who exercised. Similar patterns were evident for NO₂. There were no statistically significant differences in concentrations of air pollution by age-group (p=0.47) or sex (p=0.35).

In Table 4.2, we present the hazard ratios describing the association between selected characteristics and the incidence of dementia, Alzheimer's disease, and CIND(hazard ratios are age and sex adjusted). Women had a higher risk than men of developing dementia (HR=1.14, 95% CI=1.00-1.30) and Alzheimer's disease (HR=1.30; 95% CI=1.04-1.56). In contrast, they had a lower risk of developing CIND (HR=0.86, 95% CI=0.74-1.00). The use of NSAIDs was associated with a reduced risk of dementia (HR=0.86, 95% CI=0.76-0.99), while conversely, increased risks of dementia, Alzheimer's disease, and CIND were observed among those who drank alcohol when compared to those who did not. Those who participated in exercise had reduced risks of dementia (HR=0.56; 95% CI=0.49-0.63), Alzheimer's disease (HR=0.58, 95% CI=0.47-0.71), and CIND (HR=0.63, 95% CI=0.55-0.74).

Table 4.1 Mean concentrations of NO₂ and PM_{2.5} for selected characteristics of the 5249 participants of the Canadian Study of Health and Aging who were included in the air pollution analyses

Characteristic		N	PM _{2.5}		NO ₂	
			mean±SD	p†	mean±SD	p
Sex	Men	2040	7.5±3.2	0.35	12.8±6.2	0.21
	Women	3209	7.6±3.2		13±6.3	
Age-group	64 – 69	1585	7.6±3.2	0.47	12.6±6.2	0.35
	70 – 74	1157	7.4±3.1		13.1±6.4	
	74 – 79	1430	7.5±3.2		12.9±6.1	
	80+	1077	7.6±3.3		13.1±6.4	
Years of education	0 – 9	2032	7.7±3.2	0.14	12±6.7	0.09
	10 – 19	3091	7.5±3.3		13.4±5.9	
	20+	104	7.6±3.1		13.8±5.6	
Hypertension	Yes	1726	7.4±3.2	0.54	12.8±6.3	0.91
	No	2803	7.4±3.1		12.8±6.1	
	Unknown	720	8.5±3.4		13.7±6.1	
Diabetes	Yes	452	7.7±3.3	<0.01	13.4±6.6	<0.01
	No	3861	7.4±3.2		12.7±6.1	
	Unknown	936	8.3±3.4		13.4±6.7	
Take vitamins	Yes	323	8.2±3.5	<0.01	14.3±5.4	<0.01
	No	4926	7.5±3.2		12.8±6.3	
NSAIDs(Nonsteroidal anti-inflammatory drugs)	Yes	2659	7.5±3.2	0.17	12.9±6.2	0.12
	No	1946	7.4±3.2		12.5±6.1	
	Unknown	644	8.3±3.2		13.5±6.6	
Obesity	Yes	2556	7.5±3.2	0.88	12.9±6.2	0.56
	No	2549	7.5±3.2		12.5±6.1	
	Unknown	144	7.8±3.3		13.2±6.1	
Drink Alcohol	Yes	1343	7.5±3.3	0.35	13.3±5.9	0.02
	No	3736	7.6±3.2		12.7±6.4	
	Unknown	170	8.1±3.3		13.4±6.8	
Exercise regularly	Yes	1720	7.8±3.3	<0.01	12.7±6.6	0.18
	No	3281	7.4±3.2		13±6.0	
	Unknown	248	8.0±3.3		13.1±6.9	
Full cohort		5249	7.5±3.2		12.9±6.3	

† The p-value tests for differences in the mean concentration of air pollution levels between the categories and is based on an independent two-sample t-test or ANOVA.

Table 4.2 Hazard Ratios of developing dementia, Alzheimer's disease, and CIND for selected characteristics of the 5249 participants of the Canadian Study of Health and Aging who were included in the air pollution analyses

Characteristic		Total*	Dementia (n=1001)	Alzheimer's disease (n=526)	CIND (n=1008)
			HR** (95% CI)	HR (95% CI)	HR (95% CI)
Taking Vitamins	No	4926	1.0	1.0	1.0
	Yes	323	0.60 (0.44-0.82)	0.53(0.31-0.90)	0.61(0.43-0.88)
Sex	Males	2040	1.0	1.0	1.0
	Female	3209	1.14 (1.00-1.30)	1.30 (1.04-1.56)	0.86 (0.74-1.00)
Diabetes	No	3861	1.0	1.0	1.0
	Yes	452	1.24 (0.80-1.68)	1.40 (0.91-2.16)	0.71 (0.56-0.90)
NSAIDS	No	1946	1.0	1.0	1.0
	Yes	2659	0.86 (0.76-0.99)	0.93 (0.81-1.05)	0.97 (0.84-1.13)
Hypertension	No	2803	1.0	1.0	1.0
	Yes	1726	1.12 (1.02-1.23)	1.41 (1.11-1.78)	0.98 (0.84-1.15)
Obesity	No	2556	1.0	1.0	1.0
	Yes	2549	1.38 (1.21-1.56)	1.54 (1.25-1.90)	1.10 (0.95-1.28)
Drink Alcohol	No	3736	1.0	1.0	1.0
	Yes	1343	1.28 (1.10-1.49)	1.52 (1.17-1.96)	1.21 (1.02-1.44)
Exercise	No	3281	1.0	1.0	1.0
	Yes	1720	0.56 (0.49-0.63)	0.58 (0.47-0.71)	0.63 (0.55-0.74)

*Due to missing data the summation may not be the same for each variable

** HR= Hazard ratio, and hazard ratios are age and sex adjusted.

4.2 Association between air pollution and cognition outcomes

The associations between residential measures of NO₂ and dementia, Alzheimer's disease, and CIND are presented in Table 4.3. Three series of hazard ratios are presented. The first was adjusted for age only, while the second was adjusted for sex, vitamin use, NSAIDs, hypertension, obesity, age, and exercise. The final set of hazard ratios was adjusted for covariates that were retained after running a stepwise regression model, and these varied slightly across the three cognitive outcome measures. All models consistently found no statistically significant association between residential measures of NO₂ and dementia, Alzheimer's disease, or CIND.

Table 4.3 Adjusted hazard ratios of dementia, Alzheimer's disease and CIND in relation to a5 ppb increase in NO₂, Canadian Study of Health and Aging

	D S* HR1 [1]	D S HR2 [2]	D S HR3 [3]	D** HR1	D HR2	D HR3
NO₂	0.96(0.90, 1.02)	0.99(0.93, 1.06)	0.99(0.93, 1.06)	0.99(0.98, 1.00)	0.98(0.93, 1.04)	0.98(0.93, 1.03)
Sex	0.80(0.69, 0.94)	0.79(0.67, 0.95)	0.80(0.68, 0.93)	0.88(0.78, 1.01)	0.85(0.73, 0.99)	0.87(0.76, 1.00)
Age	1.14(1.13, 1.15)	1.13(1.12, 1.15)	1.13(1.12, 1.15)	1.13(1.12, 1.15)	1.12(1.11, 1.14)	1.12(1.11, 1.14)
Taking Vitamins		0.71(0.49, 1.02)	0.71(0.49, 1.02)		0.72(0.52, 0.99)	0.72(0.52, 0.98)
Years of education		0.95(0.93, 0.97)	0.95(0.93, 0.97)		0.96(0.94, 0.98)	0.96(0.94, 0.98)
Exercise		0.81(0.69, 0.95)	0.81(0.69, 0.95)		0.71(0.62, 0.81)	0.71(0.62, 0.81)
MSAIDs		1.03(0.89, 1.21)			0.99(0.87, 1.13)	
Drink Alcohol		0.97(0.80, 1.17)			1.02(0.86, 1.20)	
Diabetes		0.85(0.66, 1.10)			0.75(0.61, 0.91)	0.73(0.60, 0.90)
Obesity		1.05(0.89, 1.25)			1.02(0.88, 1.18)	
Hypertension		1.04(0.88, 1.22)			0.93(0.81, 1.06)	
	AD*** HR1	AD HR2	AD HR3	CIND**** HR1	CIND HR2	CIND HR3
NO₂	0.99(0.97, 1.00)	1.00(0.91, 1.09)	1.00(0.91, 1.09)	0.98(0.97, 1.00)	1.00(0.93, 1.06)	0.99(0.93, 1.06)
Sex	1.30(1.04, 1.62)	1.11(0.88, 1.42)		0.68(0.59, 0.80)	0.64(0.54, 0.76)	0.66(0.56, 0.77)
Age	1.00(0.98, 1.02)	0.99(0.98, 1.01)		1.10(1.08, 1.11)	1.09(1.08, 1.10)	1.09(1.08, 1.10)
Taking Vitamins		0.57(0.33, 0.99)	0.57(0.33, 0.97)		0.72(0.50, 1.03)	0.71(0.50, 1.02)
Years of education		0.95(0.92, 0.98)	0.95(0.92, 0.97)		0.91(0.89, 0.93)	0.91(0.89, 0.93)
Exercise		0.60(0.49, 0.75)	0.60(0.48, 0.74)		0.77(0.65, 0.90)	0.77(0.65, 0.90)
MSAIDs		1.08(0.87, 1.34)			1.00(0.86, 1.16)	
Drink Alcohol		1.18(0.89, 1.55)			1.10(0.91, 1.32)	
Diabetes		1.46(0.95, 2.26)	1.48(0.96, 2.29)		0.82(0.65, 1.05)	0.82(0.65, 1.04)
Obesity		1.48(1.17, 1.86)	1.59(1.28, 1.96)		0.98(0.83, 1.16)	
Hypertension		1.47(1.16, 1.87)	1.47(1.16, 1.86)		0.94(0.80, 1.11)	

[1] Adjusted for age and sex at baseline.

[2] Adjusted for all the risk factors

[3] Adjustment factors were identified using stepwise regression.

*D_S is Dementia survival cohort **D is dementia ***AD is Alzheimer's disease

****CIND is cognitive impairment with no dementia

The hazard ratios describing the relationship between PM_{2.5} and incident dementia, Alzheimer's disease, and CIND are presented in Table 4.4 (Linearity of log hazard is analyses are presented in Appendix Figure A1-A3). Similar to the above results for NO₂, three sets of hazards ratios are presented with the last set being the one derived from stepwise regression techniques. Unlike NO₂, positive associations between PM_{2.5} and all three health outcomes were evident. A 10 µg/m³ increase in PM_{2.5} increased the risk of developing CIND by 52% (HR=1.52, 95% CI=1.19-1.94). An increased risk was also noted for Alzheimer's disease though it did not quite achieve statistical significance at the 5% level (HR=1.32, 95% CI=0.96-1.83).

Table 4.4 Adjusted hazard ratios of dementia, Alzheimer's disease and CIND in relation to a 10µg/m³ in PM_{2.5}, Canadian Study of

Health and Aging

	D_S* HR1 [1]	D_S HR2 [2]	D_S HR3 [3]	D** HR1	D HR2	D HR3
PM_{2.5}	1.03(0.81, 1.31)	1.15(0.90, 1.45)	1.16(0.91, 1.47)	1.03(0.97, 1.05)	1.15(0.93, 1.40)	1.14(0.93, 1.40)
Sex	0.80(0.69, 0.94)	0.79(0.66, 0.94)	0.79(0.68, 0.93)	0.88(0.77, 1.01)	0.85(0.73, 0.99)	0.87(0.76, 1.00)
Age	1.14(1.13, 1.15)	1.13(1.12, 1.15)	1.13(1.12, 1.15)	1.13(1.12, 1.15)	1.12(1.11, 1.14)	1.12(1.11, 1.14)
Taking Vitamins		0.70(0.48, 1.07)	0.70(0.48, 1.01)		0.71(0.51, 0.97)	0.70(0.51, 0.97)
Years of education		0.95(0.93, 0.97)	0.95(0.93, 0.97)		0.96(0.94, 0.98)	0.96(0.94, 0.98)
Exercise		0.81(0.70, 0.95)	0.81(0.71, 0.95)		0.71(0.62, 0.82)	0.71(0.62, 0.81)
MSAIDs		1.03(0.88, 1.20)			0.99(0.87, 1.13)	
Drink Alcohol		0.97(0.80, 1.18)			1.02(0.86, 1.20)	
Diabetes		0.86(0.67, 1.11)			0.75(0.61, 0.92)	0.74(0.60, 0.91)
Obesity		1.05(0.89, 1.25)			1.02(0.88, 1.18)	
Hypertension		1.03(0.88, 1.21)			0.927(0.81, 1.06)	
AD*** HR1	AD*** HR1	AD HR2	AD HR3	CIND*** HR1	CIND HR2	CIND HR3
PM_{2.5}	1.03(0.99, 1.06)	1.32(0.95, 1.83)	1.32(0.96, 1.83)	1.36(1.07, 1.74)	1.52(1.20, 1.95)	1.52(1.19, 1.94)
Sex	1.31(1.05, 1.63)	1.12(0.88, 1.42)		0.69(0.59, 0.80)	0.64(0.53, 0.76)	0.66(0.56, 0.77)
Age	1.00(0.98, 1.02)	0.99(0.98, 1.01)		1.10(1.08, 1.11)	1.09(1.08, 1.11)	1.09(1.08, 1.11)
Taking Vitamins		0.56(0.33, 0.97)	0.56(0.33, 0.97)		0.70(0.49, 1.01)	0.70(0.49, 1.01)
Years of education		0.95(0.92, 0.98)	0.95(0.92, 0.98)		0.91(0.89, 0.93)	0.91(0.89, 0.93)
Exercise		0.61(0.49, 0.75)	0.60(0.49, 0.75)		0.77(0.66, 0.90)	0.77(0.65, 0.90)
MSAIDs		1.08(0.87, 1.33)			0.98(0.84, 1.14)	
Drink Alcohol		1.18(0.89, 1.55)	1.21(0.92, 1.59)		1.10(0.91, 1.33)	
Diabetes		1.46(0.95, 2.27)	1.48(0.96, 2.29)		0.81(0.64, 1.03)	0.81(0.64, 1.03)
Obesity		1.47(1.17, 1.85)	1.52(1.22, 1.89)		0.99(0.83, 1.17)	
Hypertension		1.46(1.15, 1.86)	1.46(1.15, 1.85)		0.93(0.79, 1.09)	

[1] Adjusted for age and sex at baseline.

[2] Adjusted for all the risk factors

[3] Adjustment factors were identified using stepwise regression.

*D_S is Dementia survival cohort **D is dementia ***AD is Alzheimer's disease

****CIND is cognitive impairment with no dementia

In addition to modeling NO₂ and PM_{2.5} as continuous variables, we also examined their association with dementia, Alzheimer's disease, and CIND using quintiles. The corresponding results are provided in Figures 4.2 and 4.3. These figures again demonstrate the lack of an association with NO₂, which contrasts with the positive association noted for PM_{2.5}. Additional analyses are presented in Appendix tables A1-A6)

Figure 4.2 Adjusted hazard ratios of incident dementia, Alzheimer's disease and CIND by quintile of exposure to NO₂ (Observations numbers are in the bars) Adjusted for Age, Vitamin, Sex, Diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol and Exercise

Figure 4. Adjusted hazard ratios of incident dementia, Alzheimer's disease and CIND by quintile of exposure to PM_{2.5}(Observations numbers are in the bars) Adjusted for Age, Vitamin, Sex, Diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol and Exercise

4.4 Effect modification by obesity, education level, and diabetic status

A secondary research objective of my thesis was to investigate whether the associations between air pollution and dementia, Alzheimer's disease and CIND differed by obesity, diabetic status, and educational attainment. Table 4.5 presents the findings obtained by conducting a stratified analysis of these factors. The findings provide little suggestion of effect modification for the three factors that were examined, and no statistically significant associations were observed.

Table 4.5 Adjusted hazards ratios* of dementia, Alzheimer's disease, and CIND in relation to a 5 ppb increase in NO₂, by obesity, diabetic status, and educational attainment

Characteristic	Dementia		Alzheimer's		CIND	
	n	HR(95%CI)	n	HR(95%CI)	n	HR(95%CI)
Education < 10 y	622	0.98 (0.92-1.04)	256	1.03 (0.93-1.14)	407	0.96 (0.89-1.04)
Education ≥10 y	325	0.97 (0.88-1.07)	106	0.91 (0.76-1.08)	287	1.07 (0.93-1.21)
Missing variable	54		164		314	
Diabetic	109	0.90 (0.77-1.05)	22	1.07 (0.75-1.52)	78	0.84 (0.69-1.02)
Non-diabetic	838	0.98 (0.93-1.04)	340	1.01 (0.91-1.09)	616	0.99 (0.92-1.06)
Missing variable	54		164		314	
Obese (BMI≥30)	409	0.96 (0.89-1.04)	142	1.03 (0.90-1.18)	339	0.93 (0.85-1.03)
Non-obese (BMI<30)	538	0.98 (0.91-1.05)	220	0.99 (0.89-1.10)	355	1.00 (0.91-1.10)
Missing variable	54		164		314	

*Adjusted for Age, Vitamin, Sex, Diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, and Exercise

The adjusted hazard ratios in relation to a 10 µg/m³ increase in PM_{2.5} are presented in Table 4.6. Positive associations with PM_{2.5} were noted for all health outcomes. The stratified analyses by obesity suggested that those who had a body mass index of 30 or higher had stronger associations between concentrations of PM_{2.5} and the development of dementia, Alzheimer's disease, or CIND. For example, in relation to a 10 µg/m³ increase in PM_{2.5} the hazard ratio of developing dementia among those who had a BMI of at least 30 was 1.26 (95% CI=0.97, 1.65) whereas among those with a BMI of less than 30 it was 1.00 (95% CI=0.72, 2.37). The difference in the strength of association between those who were obese and non-obese was greatest among those who developed CIND. Here the hazard ratio was

1.46 (95% CI=1.02-2.08) among those with a BMI of at least 30, while it was 1.00 (95% CI=1.14, 2.24) among those with a BMI of less than 30.

Table 4.6 Adjusted hazards ratios* of dementia, Alzheimer's disease, and CIND in relation to a 10 µg/m³ increase PM_{2.5}, by obesity, diabetic status, and educational attainment

Characteristic	Dementia		Alzheimer's		CIND	
	n	HR	n	HR	n	HR
Education < 10 y	622	1.14 (0.89-1.47)	256	1.42 (0.97-2.10)	407	1.61 (1.20-2.16)
Education ≥10 y	325	1.24 (0.87-1.78)	106	1.20 (0.66-2.20)	287	1.55 (1.00-2.42)
Missing variable	54		164		314	
Diabetic	109	0.92 (0.51-1.70)	22	1.56 (0.37-6.42)	78	1.00 (0.45-2.24)
Non-diabetic	838	1.16 (0.93-1.44)	340	1.34 (0.96-1.87)	616	1.58 (1.23-2.05)
Missing variable	54		164		314	
Obese (BMI≥30)	409	1.26 (0.97-1.65)	142	1.36 (0.90-2.07)	339	1.46 (1.02-2.08)
Non-obese (BMI<30)	538	1.00 (0.72-1.37)	220	1.33 (0.79-2.24)	355	1.69 (1.14-2.24)
Missing variable	54		164		314	

*Adjusted for age at entry, sex, vitamin use, diabetes, NSAID use, hypertension, obesity, alcohol use, and exercise

4.5 Spline Analyses

Spline analyses were conducted to examine whether the associations between air pollution concentration and incident outcomes were non-linear. The findings from these analyses have been graphed in Figures 4.4 and 4.5. The plots of these splines were highly sensitive to the number of degrees of freedom that were chosen. The splines for NO₂ were nonlinear and suggestive of higher risks at the highest concentrations of NO₂. However, the confidence bounds were quite broad due to the small number of subjects with these exposure levels. The spline plots for PM_{2.5} were also suggestive of a non-linear association for all outcomes. The association was strongest for CIND.

Figure 4.4 NO_2 HR curve (solid red line) and 95% CI (blue dashed lines) for Dementia, Alzheimer's and CIND based on natural spline models with 3 degrees of freedom. Adjusted for Age, Vitamin, Sex, Diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, and exercise

Figure 4.5 $PM_{2.5}$ HR curve (solid red line) and 95% CI (blue dashed lines) for Dementia, Alzheimer's and CIND based on natural spline models with 3 degrees of freedom. Adjusted for Age, Vitamin, Sex, Diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, and exercise

CHAPTER 5 DISCUSSION

In this prospective study of Canadians, we observed that increased concentrations of PM_{2.5} were associated with an increased risk of developing dementia, Alzheimer's disease and cognitive impairment. We did not observe a statistically significant association with NO₂. Our study has distinct strengths when compared to previous studies in this area. In particular, it was a prospective study design, and therefore is able to overcome limitations of cross-sectional studies that measure exposure and disease at the same time. In addition, in our study, we were able to screen out individuals with existing cognitive impairment at baseline. This is an important consideration as individuals with cognitive impairment may choose to live in urban areas in order to receive care.

Another important strength of the study is that the CSHA collected detailed information on a number of risk factors for dementia. Many of these risk factors are thought to be related to air pollution levels, and therefore, they could bias the associations between air pollution and dementia. For example, work by Villeneuve et al (102) has shown that air pollution concentrations are associated with a number of lifestyle factors such as: smoking, socio-demographic status, educational level, and marital status. We were able to adjust for many of these factors over time.

This study made use of remote sensing estimates of ground-level PM_{2.5}. These remote sensing based estimates correlate highly with ground-level measures of air pollution. In particular work by van Donkelaar et al observed correlated in excess of 90% with ground-based monitoring data (99). We were able to assign measures of PM_{2.5} to virtually all participants in the Canadian Study of Health and Aging. Had we relied on fixed site monitors, we would have only been able to assign measures to those who lived near fixed site monitors which are typically in urban areas.

The air pollution concentrations that were used were based on satellite measures taken after the follow-up of the cohort had ended. This could introduce some degree of exposure misclassification. However, previous studies have found that the spatial variability in concentrations of PM_{2.5} in Canada have maintained similar patterns over time (103).

Namely, areas of higher concentrations of PM_{2.5} tend to remain consistently high relative to other areas over time. In addition, concentrations of ambient PM_{2.5} are far less variable than other pollutants in Canadian cities. For example, in Hamilton the 25th and 75th percentiles of PM_{2.5} obtained from a dense summer sampling campaign involving 43 monitors throughout the city were 6.10 and 6.95 µg/m³ (103). Levy et al also found that there was little variation in the median PM_{2.5} concentrations across 10 different areas in Montreal (104). Further, previous studies that have attempted to correct for historical changes in PM_{2.5} over time when looking at other chronic health conditions have found that these corrections produce only minor changes in the measures of association.

Another limitation of our work is that we approximated the time of diagnosis of dementia, and Alzheimer's disease using the midpoint of the two assessment intervals. However, this time interval was relatively small, within 5 years, and given the same procedures were applied to everyone in the cohort, this method of assigning date of diagnosis is unrelated to individuals' exposure to air pollution. For this reason, it is unlikely to introduce any bias with respect to estimating associations between air pollution, and dementia outcomes.

That we observed an association between measures of fine particulate matter air pollution and dementia, but not NO₂ requires some comment. First, many of the epidemiological and experimental evidence have highlight the relevance of particulate pollution, and less so for the gaseous pollutant NO₂. Our inability to detect an association with NO₂ might also be due to increased exposure misclassification for this pollutant. NO₂ varies substantially within an urban area and much more so than PM_{2.5}. As people tend to move around a given city, the use of a residentially based measure for NO₂ may not capture individual-level exposure as well as one for PM_{2.5}.

In our analyses, we attempted to better understand the shape of the exposure-response curves for both NO₂ and PM_{2.5} in relation to the three outcomes (AD, CIND, and dementia). The shapes of the spline were very sensitive to the number of degrees of freedom, and we had limited statistical power to evaluate departures from non-linearity. In our view, the most informative information provided in from the categorical analyses of pollution based on quintile approach. For NO₂, the associations were not statistically significant and tended to

show lower hazard ratios for CIND, AD, and dementia with increasing exposure. In contrast, associations for all three outcomes were positive for PM_{2.5} with strongest associations noted for AD and CIND.

Another key finding in our project was the stronger association observed between PM_{2.5} and dementia and CIND that was observed among those who were more obese. Weichenthal et al (105) recently highlighted that those who were more obese may be more susceptible to the health effects of air pollution due to differential impacts on oxidative stress. The stronger associations we observed between PM_{2.5} and dementia among those with a body mass index of ≥ 30 (HR=1.26, 95% CI=0.97-1.65) when compared to those with a BMI of less than 30 (HR=1.00, 95% CI=0.72-1.37) are consistent with this hypothesis. We also observed an even larger discrepancy between those who were obese and not for CIND (1.46, 95% CI=1.02-2.08 vs 1.69, 95% CI=1.14-2.24)

To our knowledge, there have been few studies that have looked at air pollution and dementia using a longitudinal approach. Recently, Oudin et al (90) examined the relationship between air pollution and dementia in a cohort of Swedish adults. The length of their follow-up interval was 15 years, and they examined associations using a land-use regression surface with a spatial resolution of 50 m x 50 m. The pollutant they examined was NO_x, and no data were modeled for PM_{2.5}. They found similar associations between NO_x and dementia and Alzheimer's. Those in the upper quartile of exposure had a hazard ratio of 1.43 for developing dementia when compared to those in the lowest, while the hazard ratio was 1.38 for AD. They did not examine CIND, and their study was limited in that the overall study population was only 1806 subjects, of whom 191 developed Alzheimer's disease. Nonetheless, their findings suggest that intra-urban variations in pollution levels are relevant in the development of dementia.

Our findings provide some evidence that exposure to fine particulate matter at low concentrations increases the risk of developing dementia. At present, the estimates of the health impacts from the Global Burden of Disease do not take into account increased risks that might occur at concentrations that are less than 5.8 $\mu\text{g}/\text{m}^3$. Moreover, their estimates of the health impacts from air pollution do not consider impacts on dementia or Alzheimer's

disease. If such association are indeed real, the impacts provided by the Global Burden of Disease would underestimate impacts considerably.

CHAPTER 6: CONCLUSION

Survival analysis was used to examine the effects of exposure to air pollutants such as NO₂ and PM_{2.5} on risk of developing dementia, Alzheimer's and CIND in Canada from 1991 to 2001. Step-wise selection and spline plot were used to build more advanced model. The relationship of air pollutants and certain group of people such as people who are obese was also explored.

This study has found positive associations between fine particulate matter (PM_{2.5}) and dementia Alzheimer's and CIND. These associations are most pronounced for Alzheimer's disease and CIND, and our analyses suggest those who are more obese may be more susceptible to these effects. In contrast, our analysis did not reveal an association between NO₂, a marker of traffic pollution, and the three outcomes under study dementia, Alzheimer's and CIND. While this study has several distinct strengths, it is limited by a relatively small number of outcomes identified, particularly among individuals who live in high areas of air pollution. Future works that overcome this limitation, perhaps by using a case-control study design, and also by examining intra-urban variations in air pollution is needed.

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Appendix

Table A1 Hazard ratios of incident dementia by quintile of exposure to NO₂ with 5249 participants

NO ₂ Quintile	Number in quintile	Dementia	HR1 (95%CI) ^[1]	HR2 (95%CI) ^[2]
(0 , 6.71]	1049	216	1.0	1.0
(6.71 , 10.90]	1050	204	0.96(0.79-1.17)	1.01(0.83-1.23)
(10.90 , 14.20]	1050	202	0.88(0.73-1.08)	1.00(0.82-1.22)
(14.20 , 18.90]	1049	190	0.77(0.63-0.95)	0.89(0.72-1.10)
(18.90 , 38.50]	1051	189	0.85(0.70-1.04)	0.93(0.76-1.14)

[1] Adjusted for age and sex at entry

[2] Adjusted for: age, vitamin use, sex, diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, Education and Exercise.

Table A2 Hazard ratios of incident Alzheimer's disease by quintile of exposure to NO₂ with 5249 participants

NO ₂ Quintile	Number in quintile	Alzheimer's Cases	HR1 (95%CI) ^[1]	HR2 (95%CI) ^[2]
(0 , 6.71]	1049	116	1.0	1.0
(6.71 , 10.90]	1050	102	0.86(0.63-1.17)	0.95(0.69-1.30)
(10.90 , 14.20]	1050	109	0.81(0.59-1.11)	0.96(0.69-1.32)
(14.20 , 18.90]	1049	100	0.66(0.47-0.92)	0.81(0.58-1.15)
(18.90 , 38.50]	1051	99	0.83(0.60-1.14)	0.97(0.70-1.34)

[1] Adjusted for age and sex at entry

[2] Adjusted for: age, vitamin use, sex, diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, Education and Exercise.

Table A3 Hazard ratios of incident CIND by quintile of exposure to NO₂ with 5028 participants

NO ₂ Quintile	Number in quintile	CIND	HR1 (95%CI) ^[1]	HR2 (95%CI) ^[2]
(0 , 6.48]	1006	227	1.0	1.0
(6.48 , 10.70]	1006	219	0.84(0.68-1.05)	0.93(0.75-1.17)
(10.70 , 14.00]	1005	174	0.63(0.50-0.80)	0.79(0.62-1.00)
(14.00 , 18.70]	1005	181	0.65(0.51-0.82)	0.78(0.61-0.99)
(18.70 , 37.40]	1006	207	0.83(0.66-1.05)	0.97(0.77-1.23)

[1] Adjusted for age and sex at entry

[2] Adjusted for: age, vitamin use, sex, diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, Education and Exercise.

Table A4 Hazard ratios of incident dementia by quintile of exposure to PM_{2.5} with 5249 participants

PM _{2.5} Quintile	Number in quintile	Dementia	HR1 (95%CI) ^[1]	HR2 (95%CI) ^[2]
(0 , 4.40]	1049	221	1.0	1.0
(4.40 , 5.69]	1050	172	0.86(0.71-1.01)	0.85(0.69-1.03)
(5.69 , 7.90]	1050	260	1.03(0.83-1.22)	0.99(0.80-1.22)
(7.90 , 11.10]	1049	167	1.18(0.97-1.43)	1.14(0.94-1.38)
(11.10 , 15.80]	1051	181	1.06(0.87-1.33)	1.01(0.83-1.24)

[1] Adjusted for age and sex at entry

[2] Adjusted for: age, vitamin use, sex, diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, Education and Exercise.

Table A5 Hazard ratios of incident Alzheimer's disease by quintile of exposure to PM_{2.5} with 5249 participants

PM _{2.5} Quintile	Number in quintile	Alzheimer's	HR1 (95%CI) ^[1]	HR2 (95%CI) ^[2]
(0 , 4.40]	1049	97	1.0	1.0
(4.40 , 5.69]	1050	86	0.98(0.70-1.3)	0.99(0.71-1.39)
(5.69 , 7.90]	1050	145	1.25(0.88-1.7)	1.27(0.90-1.81)
(7.90 , 11.10]	1049	86	1.36(0.98-1.8)	1.35(0.98-1.87)
(11.10 , 15.8]	1051	112	1.32(0.95-1.8)	1.29(0.93-1.80)

[1] Adjusted for age and sex at entry

[2] Adjusted for: age, vitamin use, sex, diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, Education and Exercise.

Table A6 Hazard ratios of incident CIND by quintile of exposure to PM_{2.5} with 5028 participants

PM _{2.5} Quintile	Number in quintile	CIND	HR1 (95%CI) ^[1]	HR2 (95%CI) ^[2]
(0 , 4.30]	1006	202	1.0	1.0
(4.30 , 5.80]	1006	216	0.89(0.71-1.12)	0.84(0.67-1.05)
(5.80 , 7.90]	1005	202	1.01(0.79-1.30)	1.01(0.79-1.30)
(7.90 , 10.60]	1005	178	1.02(0.80-1.29)	0.96(0.76-1.22)
(10.60 , 15.80]	1006	210	1.35(1.07-1.70)	1.32(1.05-1.66)

[1] Adjusted for age and sex at entry

[2] Adjusted for: age, vitamin use, sex, diabetes, NSAIDs, Hypertension, Obesity, Drinking Alcohol, Education and Exercise.

Figure A1 *Linearity of log hazard of Dementia for PM2.5*

It seems the assumption of linearity of log hazard for PM2.5 is correct

Figure A2 *Linearity of log hazard of Alzheimer's for PM2.5*

It seems the assumption of linearity of log hazard for PM2.5 is correct

Figure A3 *Linearity of log hazard of CIND for PM2.5*

It seems the assumption of linearity of log hazard for PM2.5 is correct