UMEÅ UNIVERSITY

Air Pollution and Dementia in a Low Exposure Setting

– the Role of Noise, Olfaction, and the APOE gene

John Andersson

Department of Psychology
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“[N]eurodegenerative disorders such as Alzheimer’s may begin early in life with air pollutants playing a crucial role.”

Calderon-Garcidueñas et al., 2002, p. 373.

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Abstract

Previous research indicates an association between air pollution exposure, and risk of dementia. Still, a number of factors that may play a role in this association remain to be explored. In addition, while most studies on air pollution and brain health have taken place in highly exposed large urban areas, the studies included in this thesis are conducted in an area with relatively low levels of air pollution and road traffic noise.

The overall aim of this thesis is to investigate possible mechanisms - more specifically the role of noise, olfaction and the APOE-ε4 allele - in the association between air pollution and dementia, in a low exposure area. Because olfactory deficits have been linked to air pollution, and can be an early sign of dementia, an additional aim is to examine associations between exposure to air pollution and olfactory function.

Methods: Participants were drawn from the Betula project – a prospective cohort study – in Umeå, Sweden. Modelled data on concentrations of nitrogen oxides (NO_x), fine particle matter ($PM_{2.5}$) and levels of road traffic noise, were matched with participants residential address at baseline. $PM_{2.5}$ levels at the day of testing were obtained from a measuring station in the vicinity of the test location. Data on dementia diagnoses, APOE status, olfactory functions, and covariates, were drawn from the Betula project. Dementia assessment was primarily based on medical records, and conducted by a geropsychiatrist. Odor identification was assessed using the Scandinavian Odor Identification Test, and odor detection threshold by "sniffin' sticks". APOE genotype was determined by DNA analyses of blood samples.

Study I. Where there is pollution, there is also often noise. In addition, exposure to noise can increase the risk of dementia. The aim of study I was to investigate the individual and combined effect of noise and air pollution on risk of dementia. The results showed an association between NO_x and dementia. However, noise from road traffic did not contribute to this association.

Study II. Olfactory deficits can be an early sign of dementia and might also be caused by air pollution. Olfactory receptor cells in the nasal cavity are exposed to inhaled air, and the olfactory bulb is one of the areas of the brain most affected by air pollution. The APOE-ε4 allele is important to consider, as it is a risk factor for both dementia and declining olfactory functions. The aim of study II was to investigate the role of olfaction and the APOE-ε4 allele in the association between air pollution and dementia. Stratified analyses showed that associations between

$PM_{2.5}$ and dementia persisted only among APOE-ε4 carriers, and those with poor odor identification ability.

Study III. The olfactory system may be vulnerable to air pollution, and olfactory dysfunction is an early sign of dementia. In addition, the moderating effect of odor identification ability found in study II, could be explained by air pollution increasing the risk of olfactory functions and dementia independent of each other. Thus, the aim of study III was to investigate the associations between $PM_{2.5}$ (both long term exposure, and concentrations on the day of testing), and odor identification and detection. A *positive* association was observed between long term air pollution exposure and odor identification ability. No association was found between long term air pollution exposure and odor detection, or between short term exposure and either olfactory outcome.

Conclusion: Low levels of long-term exposure to air pollution increases the risk of dementia. APOE-ε4 carriers, and those with poor odor identification ability, seem particularly vulnerable. No residual confounding from road traffic noise was found, suggesting that air pollution is the main component in the association between traffic related exposures and dementia in low-exposure areas. The positive association between air pollution and odor identification might be explained by socioeconomic status, and the links between olfaction and semantic memory.

List of studies

I. Andersson, J., Oudin, A., Sundström, A., Forsberg, B., Adolfsson, R., Nordin, M. (2018). Road traffic noise, air pollution, and risk of dementia – results from the Betula project. *Environmental Research, 166,* 334-339. doi: 10.1016/j.envres.2018.06.008. Reprinted under terms of CC BY-NC-ND license.

II. Andersson, J., Sundström, A., Nordin, M., Segersson, D., Forsberg, B., Adolfsson, R., Oudin, A. (in press). PM2.5 and Dementia in a Low exposure Setting: The Influence of Odor Identification Ability and APOE. *Journal of Alzheimer's Disease*. doi: 10.3233/JAD-220469. ©2023. Reprinted with permission from IOS Press.

III. Andersson, J., Oudin, A., Nordin, S., Forsberg, B., Nordin, M. (2021). $PM_{2.5}$ exposure and olfactory functions. *International Journal of Environmental Health Research*. doi: 0.1080/09603123.2021. 1973969. ©2021. Reprinted with permission of Informa UK Limited, trading as Taylor & Taylor & Francis Group.

Abbreviations

Aβ	Amyloid Beta. A peptide that can form extracellular plaques in the brain. A biomarker for Alzheimer's Disease.
AD	Alzheimer's Disease
APOE	The gene coding for the protein Apolipoprotein E
APOE-ε4	An allele (gene variant) of the APOE gene. A risk factor for dementia.
CNS	Central Nervous System
CVD	Cardiovascular Disease
NFT	Neurofibrillary Tangle. Intracellular aggregates of hyper-phosphorylated tau protein. A biomarker for Alzheimer's Disease.
NO_x	Nitrogen Oxides
NO_2	Nitrogen Dioxide
PM	Particle Matter
$PM_{2.5}$	Particle matter with a diameter less than 2.5 μm, also called "*fine particle matter*"
SES	Socioeconomic Status
SOIT	The Scandinavian Odor Identification Test
VaD	Vascular Dementia
WHO	World Health Organization

Sammanfattning på svenska

Tidigare forskning har visat på ett samband mellan långvarig exponering för luftföroreningar och risken att utveckla demens. Det finns dock ett antal faktorer som kan spela en roll för detta samband som ännu inte har undersökts. Medan de flesta studier om luftföroreningar och hjärnans hälsa har gjorts i storstadsområden, har studierna som ingår i den här avhandlingen utförts i ett område med relativt låga halter av föroreningar och trafikbuller.

Således är avhandlingens syfte att undersöka tänkbara faktorer av betydelse för sambandet mellan luftföroreningar och demens. Mer specifikt undersöks betydelsen av buller, APOE-ε4 allelen och luktsinnets funktioner för sambandet mellan luftföroreningar och demens i ett lågexponerat område. Eftersom försämrat luktsinne kan ha ett samband med luftföroreningar och vara ett tidigt tecken på demens är ett ytterligare syfte att undersöka sambandet mellan luftföroreningar och luktfunktioner.

Metod: Deltagarna hämtades från Betulaprojektet, en prospektiv kohortstudie i Umeå. Med hjälp av matematiska modeller erhölls koncentrationer av kväveoxider (NO_x), fina partiklar ($PM_{2.5}$), och bullernivåer från vägtrafik i Umeå med omnejd över tid. Dessa data matchades sedan med deltagarnas bostadsadresser vid studiernas respektive startpunkter. $PM_{2.5}$-nivåerna på testdagen hämtades från en mätstation i närheten av testplatsen. Data gällande demensdiagnoser, APOE-status, luktfunktioner och kovariater hämtades från Betulaprojektet. Demensbedömningen baserades främst på medicinska journaler och utfördes av en geropsykiater. Förmåga att identifiera dofter bedömdes med ”the Scandinavian Odor Identification Test” och luktdetektionströskel bedömdes med hjälp av "Sniffin’ sticks". APOE-genotyp bestämdes genom DNA-analyser av blodprover.

Studie I. Utsläppskällor såsom vägtrafik genererar inte bara luftföroreningar utan även buller. Dessutom kan exponering för buller öka risken för demens. Syftet med studie I var att undersöka hur risken för demens påverkas av buller och luftföroreningar, både var och en för sig och i kombination. Resultaten visade ett samband mellan NO_x och demens, men trafikbuller bidrog dock inte till detta samband.

Studie II. Nedsatt luktsinne kan vara ett tidigt tecken på demens. Nedsatt luktsinne kan orsakas av luftföroreningar eftersom luktsinnets receptorceller i näshålan är exponerad för den luft vi andas in, och eftersom luktbulben är ett av de områden i hjärnan som påverkas mest av luftföroreningar. APOE-ε4-allelen är viktig att ta med i beräkningen eftersom den är en riskfaktor både för demens och

försämrade luktfunktioner. Syftet med studie II var att undersöka vilken roll luktsinnet och APOE-ε4-allelen har i sambandet mellan luftföroreningar och demens. Stratifierade analyser visade att sambandet mellan $PM_{2,5}$ och demens kvarstod endast hos bärare av APOE-ε4 allelen och hos dem med dålig förmåga att identifiera dofter.

Studie III. Luktsinnet kan påverkas av luftföroreningar och är ett tidigt tecken på demens. Därför skulle den modererande effekten av luktidentifieringsförmåga som observerades i studie II kunna förklaras av att föroreningar ökar risken för nedsatt luktsinne och demens oberoende av varandra. Syftet med studie III var därför att undersöka sambanden mellan $PM_{2,5}$ (både långtidsexponering och halter på testdagen) och identifikation och detektion av dofter. Ett positivt samband observerades mellan långvarig exponering för luftföroreningar och förmåga att identifiera dofter. Inget samband hittades mellan långvarig exponering för luftföroreningar och luktdetektion. Inte heller hittades några samband mellan kortvarig exponering och vare sig luktidentifikation eller luktdetektion.

Slutsats: Långvarig exponering för luftföroreningar, även vid relativt låga exponeringsnivåer, ökar risken för demens. Bärare av APOE-ε4 allelen och personer med sämre förmåga att identifiera dofter utgör särskilt utsatta grupper. Inget samband mellan trafikbuller och demens observerades vilket tyder på att föroreningar är den viktigaste komponenten i sambandet mellan trafikrelaterade exponeringar och demens i lågexponerade områden. Det positiva sambandet mellan luftföroreningar och luktidentifiering kan möjligtvis förklaras av socioekonomisk status och av kopplingen mellan semantiskt minne och förmågan att identifiera dofter.

Introduction

Exposure to air pollution can have a severe impact on human health by increasing the risk of e.g. cardiovascular diseases (CVD), pulmonary diseases, and cancer (Manisalidis et al. 2020). It has been estimated that 4.2 million deaths worldwide could be attributed to air pollution in the year 2019 (World Health Organization, 2022a). Furthermore, a body of research over the past decades has shown that exposure to traffic-related air pollutants may also have detrimental effects on brain health, showing associations with decreased cognitive functions (Clifford et al., 2016; Power et al., 2016) and increased risk of dementia (Peters et al., 2019; Power et al, 2016; Weuve et al, 2021a). It has been estimated that 2% of all dementia cases worldwide could be attributed to air pollution (Livingstone et al. 2020). This number may well rise, as the proportion of the global population living in urban environments, where levels of air pollution is higher compared to rural areas, is growing. In 2020, 33% of the world's population lived in cities with a population of more than 300,000 people, and this proportion is projected to reach 39% by 2035 (United Nations Habitat, 2020). Another factor to be considered is climate change, which is likely to lead to increased levels of e.g. ozone due to atmospheric changes and increased levels of particulate matter due to e.g. an increased number of large forest fires (World Meteorological Organization, 2022). This "climate penalty effect" is expected to be particularly prominent in Asia (World Meteorological Organization, 2022), but will also feature in parts of Europe (Guzman et al. 2022). Meanwhile, the world's population is aging (United Nations Department of Economic and Social Affairs, 2022). As a consequence of all these factors, investigating the potential links between air pollution and dementia becomes an issue of great importance.

Most research on air pollution and health have been conducted in large urban areas with high exposure levels, but air pollution can be harmful even at levels well below established environmental guidelines (Stafoggia et al. 2022). Results from seven European population-based cohort studies found an association between air pollution and non-accidental mortality, even at exposure levels below current air quality guidelines (Stafoggia et al. 2022). In Sweden, a country with comparably low levels of air pollution, about 7% of all deaths in 2019 could be attributed at least in part to air pollution, and the total health impact of air pollution for the same year was estimated to have cost at least 168 billion SEK (Gustafsson et al. 2022).

In 2021, the World Health Organization (WHO) updated its air quality guidelines (World Health Organization, 2021), significantly lowering the recommended maximum exposure. According to the WHO's newer guidelines, about 90% of the Swedish population are exposed to unacceptable levels of fine particles

(Gustafsson et al. 2022). A Swedish study (Segersson et al. 2021) showed that an association between exposure to fine particles and mortality can be seen even at small increases in particles, of e.g. 1 μg/m^3 or less. These findings highlight the relevance of investigating air pollution in low-exposure areas. One of only a few studies that investigated associations between air pollution and dementia in an area with low exposure was a study by Oudin and colleagues (2016), who found an association between air pollution and dementia in Umeå municipality in northern Sweden, drawing data from the same prospective cohort study as the studies presented in this thesis.

Although a number of studies suggest air pollution to be associated with an increased risk for dementia, a number of other factors that may play a role in the link between air pollution and dementia remain to be explored. For example, more research is needed about possible modifiers, mediators, and confounders. To address some of these knowledge gaps, this thesis investigates mechanistic associations between air pollution and dementia in a low-exposure setting. Specifically, it explores the potentially confounding and moderating factors of traffic noise, olfactory function, and a genetic risk-factor for dementia (the APOE-ε4 allele), leaving this thesis in the overlap between psychology and biology.

Air Pollution

WHO defines air pollution as the "*contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere*" (World Health Organization, 2022a). Major emission sources include industries, motorized traffic, forest fires, and burning of fuel (e.g. coal, wood, and oil) for energy and heating. Air pollution can contain a variety of gasses and particles, and the exact composition of this pollution differs greatly depending on its source. Examples of common gasses in air pollution are carbon oxides, ozone, and nitrogenous oxides (NO_x) (Almetwally et al., 2020). Combustion engine exhaust is the largest source of NO_x emissions, thus NO_x correlates with many other traffic-related pollutants and can be seen as a proxy for overall exposure to traffic-related air pollution. Traffic-related air pollution consists both of engine exhaust and particles from the wear and tear of tires and street material (Cassee et al. 2013).

Particulate matter (PM) is often categorized by size rather than chemical composition. In general, smaller particles tend to be more hazardous. Not only does a smaller size make it physically possible for these particles to reach body tissue, but these particles also tend to be more reactive because of their larger surface to volume ratio (Cassee et al. 2013). PM with a diameter greater than 2.5 μm and up to 10 μm (PM_{10}) is classified as coarse PM, and considered less hazardous because these larger particles tends to get stuck in the upper airways

(Forman & Finch, 2018). This does not mean these larger particles are safe to inhale. Using data from more than 200 cities throughout the world, Liu and colleagues (2022) found that PM_{10} exposure was associated with increased risk for cardiovascular and respiratory mortality, even when the statistical models were controlled for exposure to finer particles. PM with a diameter of 2.5 μm and smaller ($PM_{2.5}$) is classified as fine PM. $PM_{2.5}$ is considered more hazardous than coarse PM as it can reach the lungs, and has been associated with increased risk for e.g. CVD, Alzheimer's disease, and lung cancer (Forman & Finch, 2018).

Of course, particle size is not the sole determinant of toxicity. A particle's chemical and physical properties determine its ability to transfer to various tissue, how it is transported, and the type of damage it causes (Heusinkveld, 2016; Zoroddu et al. 2014). For example, exposure to specific ultrafine particles has been associated with the formation of reactive oxygen species and oxidative stress in the brain (Khalili et al. 2015; Zoroddu et al. 2014), as well as risk of dementia (Shi et al. 2021).

Airborne particles and the brain

Several pathways have been suggested for explaining how air pollutants can affect the brain. Using animal studies, Heusinkveld and colleagues (2016) found two direct ways in which pollutants can reach the brain, which in the end may affect cognitive functions. The first is the olfactory route. When we breathe in through the nose, environmental PM will end up in the olfactory epithelium in the nasal cavity. Though many of the particles will not proceed further, a number of them will be able to enter olfactory neurons. Through retrograde neuronal transport (i.e. from the axon towards the soma), the particles will eventually end up in the olfactory bulb (Heusinkveld et al., 2016). Most of the evidence for the olfactory route come from studies on animals, primarily rodents (see for example Oberdörster et al. 2004) or canines (Calderon-Garcidueñas et al., 2002). But there is also some evidence from human studies. For example, Calderon-Garcidueñas and colleagues (2004, 2008) performed *post mortem* examinations on people who had lived in either heavy polluted or less polluted areas of Mexico. They found that people who had lived in heavily polluted areas had an increased deterioration of the olfactory epithelium compared with those living in areas with low air pollution, as well as an upregulation of inflammatory markers in the olfactory bulb. The possible role of the olfactory system in transporting particles to the central nervous system (CNS), and the impact of said particles on the olfactory epithelium, olfactory nerve, and olfactory bulb also indicate that olfactory functions may be particularly vulnerable to air pollution exposure.

The second direct route goes trough the blood brain barrier. Inhaled particles will not all get stuck in the olfactory epithelium, but some will inevitably be transported to the lungs. If the particles are small enough, they can enter the bloodstream *via* the lungs. Depending on the particles' size and chemical properties, they may then break the blood brain barrier and enter the brain tissue (Heusinkveld et al. 2016).

In addition, an indirect pathway, the systemic route, has been proposed (see for example Block & Calderon-Garcidueñas, 2009). The systemic route refers to inflammations in other parts of the body that cause an immune response in the brain. In other words, it may not be necessary for air pollutants to physically reach the CNS in order to have an effect on inflammation in the brain. If a pollutant causes inflammation in other parts of the body, e.g. the lungs, levels of cytokines in the bloodstream rise. These cytokines could then enter the brain *via* the circulatory system, thus transferring inflammation to the brain. Furthermore, air pollution exposure has harmful effects on the cardiovascular system and increases the risk of CVD which in turn increases the risk of vascular dementia (Fiordelisi et al. 2017; Iadecola, 2013).

Dementia

Dementia is a degenerative and chronic condition that affects cognitive processes. The WHO defines dementia as "*an umbrella term for several diseases affecting memory, other cognitive abilities and behavior that interfere significantly with a person's ability to maintain their activities of daily living. Although age is the strongest known risk factor for dementia, it is not a normal part of ageing*" (World Health Organization, 2022b). In the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), dementia is characterized by a decline in cognitive abilities leading to a significant loss of function in a patient's social and/or professional life. In DSM-IV, all dementia subtypes have in common memory deficits and at least one of the following conditions: aphasia (loss of ability to understand or produce speech); apraxia (loss of motor ability despite intact motor function); agnosia (loss of ability to recognize or identify objects); deficits in executive functions (e.g. loss of ability to plan ahead) (American Psychiatric Association, 1994). In the latest edition of the DSM, DSM-V (American Psychiatric Association, 2013), the term "*dementia*" has been replaced with the term "*major neurocognitive disorder*". In this thesis, however, the word dementia will be used.

Dementia not only affects those who suffer from this disease, but also puts a strain on family and friends, emotionally and often financially, and it also has a high cost to society. In 2019, approximately 57.4 million people suffered from dementia, and this number is expected to exceed 150 million by 2050

(Collaborators, G. B. D. D. F., 2022). In 2016, Alzhelmer's disease (the most common type of dementia) alone was estimated to cost 820 million USD globally (Prince et al., 2016). Given the lack of effective medical treatment, much research in recent years has focused on reducing dementia incidence by identifying risk factors.

Many risk factors for dementia have been identified, and a 2020 report from the Lancet commission on dementia prevention, intervention, and care (Livingstone et al., 2020) broke these risk factors down into either non-modifiable or modifiable. Non-modifiable risk factors included sex (with women being at slightly greater risk than men) and various genetic risk factors, such as carrying the ε4 allele of the APOE gene. Modifiable risk factors included low education, hypertension, smoking, obesity, hearing impairment, physical inactivity, depression, diabetes, infrequent social contacts, excessive alcohol consumption, and traumatic brain injury; importantly, the Lancet commission report recommended that air pollution should be added to the list of modifiable risk factors for dementia. By reducing exposure to modifiable risk factors, it has been proposed that dementia onset could be delayed, or even prevented, at least in vulnerable sub-populations (Rasmussen & Langerman, 2019).

Dementia itself can also be broken down into a number of subtypes (primary, vascular, or secondary dementia) depending on the underlying causes (Almkvist, 2014). Primary dementias are caused by neurological diseases affecting cognitive functions. The most common, and well known, of the primary dementias is Alzheimer's disease (AD). Vascular dementia (VaD) is caused by neuronal death due to oxygen deprivation as a result of CVD, such as stroke or atherosclerosis. Secondary dementias are a side effect of events like physical trauma or infectious diseases. A person with dementia can show signs of multiple types of dementia pathology, resulting in what is called mixed dementia. This thesis focuses on AD and VaD because these are the most common types of dementia, and because plausible pathways between air pollution and dementia have been suggested for both AD (Heusinkveld et al., 2016) and VaD (Fiordelisi et al. 2017).

The APOE gene and dementia

An important risk factor for dementia is the APOE gene (Corder et al. 1993). The abbreviation APOE can refer both to apolipoprotein E and the gene coding for it. In this text, "*APOE*" will exclusively refer to the gene, whereas "*apolipoprotein E*" will refer to the protein.

Apolipoprotein E is a protein involved in transportation and metabolism of cholesterol in many parts of the human body. In the CNS, it is produced by glial cells, especially astrocytes, and released into the cerebrospinal fluid. The protein serves multiple functions in the CNS, many of which slow down AD pathology (such as promoting anti-inflammatory processes), thereby slowing down the formation of intracellular neurofibrillary tangles and increasing clearance of amyloid beta plaques (Flowers & Rebeck, 2020; for more details about AD pathology, see the next section). The APOE gene has three known alleles (ε2, ε3, and ε4) of which the ε4 allele is a risk factor for dementia (Corder et al. 1993). Compared with non-carriers, heterozygotic APOE-ε4 carriers (i.e. people with one APOE-ε4 allele) have a three-fold increase in risk for late onset AD, whereas homozygotes (people with two APOE-ε4 alleles) have an eight-fold increased risk (Corder et al. 1993). Furthermore, APOE-ε4 is associated with earlier onset of AD (by 10–20 years) (Corder et al. 1993). APOE-ε4 has also been associated with VaD (Rohn 2014; Yin et al. 2012) *via* higher levels of low-density lipoprotein cholesterol (Haan & Mayeda, 2010) which is a major risk factor for CVD (Wadhera et al. 2016), and *via* degeneration of capillaries in for example, the hippocampus (Montagne et al. 2020).

Alzheimer's disease

AD is the most common type of dementia, believed to be responsible for 60–80% of all dementia cases (Sosa-Ortiz et al., 2012). In AD, neuronal death leads to declining cognitive functions, especially functions relating to language and memory (Kalaria, 2002). AD is also characterized by psychiatric symptoms such as hallucinations and delusions, and behavioral changes such as increased agitation and aggression (Gottesman & Stern, 2019). The prevalence of AD differs geographically. Because age is the most important risk factor for AD, industrialized countries in which people have longer life expectancies tend to have higher incidences. The age-related increase in risk starts approximately at age 60 and rises rapidly from there. Epidemiological research suggests that 5–9% of those older than 60 suffer from AD (Lopez & Kuller, 2019). A UK study (Sampson et al. 2009) found that the incidence of AD in people over 90 years of age was 48% for men and 75% for women.

On a cellular level, AD pathology is characterized by extracellular plaques consisting of a peptide called amyloid beta (Aβ) and intracellular neurofibrillary tangles (NFT). Strong correlations between Aβ plaques and AD led the amyloid cascade hypothesis to dominate research in the field for a long time. This hypothesis states that Aβ plaques are the main cause of AD, as they interrupt interneuronal communication (Hardy & Higgins, 1992). However, it is not uncommon for persons with plenty of Aβ plaques to show few to no AD symptoms, and there are AD patients with hardly any Aβ plaques at all (Harrison

& Owen, 2015; Kametani & Hasegawa 2018). The second characteristic of AD is tau pathology, which gives rise to the formation of NFT. In every neuron there are microtubules that give structural support and help transport vesicles within the cell. The microtubules are stabilized by a type of protein called tau, but if the tau proteins are phosphorylated, they detach from the microtubule, which then disassembles. This process can be induced by the immune system as a means of causing neuronal death, and as various functions within the neuron deteriorate, phosphorylated tau aggregates, thus creating NFT (Wang & Mendelkow, 2016; Oliver & Reddy, 2019). The typical progression of tau pathology in the brain closely follows cognitive impairments in AD, and seems to show a higher association with AD progression than the formation of Aβ plaques (Kametani & Hasegawa, 2018).

Vascular dementia

VaD is responsible for about 15–20% of dementia cases (Korczyn et al. 2012; O'Brien & Thomas, 2015), making it the second-most common cause of dementia after AD. VaD arises as a result of cardiovascular dysfunction in cerebral blood vessels, which reduces the blood flow to certain areas of the brain, leading to neurons dying from oxygen deprivation (Almkvist 2014). As with other dementias, older age is a major risk factor for VaD (Korczyn et al. 2012). Given its association with CVD, mortality is higher in VaD than AD. Unlike AD, VaD is more common among men than women; a likely explanation is that men tend to be at higher risk for e.g. stroke (Bir et al., 2021). As a disease, VaD is more variable than AD, but one common symptom is deficits in cognitive functions based in the frontal lobe, leading to impairments in attention, ability to plan ahead, and processing speed (Kalaria, 2002). Even though more severe CVD, such as stroke, are major risk factors, most cases of VaD are due to smaller lesions caused by subcortical ischemic vascular disease arising from e.g. atherosclerosis or diabetes (Roman et al, 2002; O'Brien & Thomas, 2015). In addition, injured blood vessels also disturb the trophic signaling that is crucial for maintenance and repair of neurons (Iadecola 2013).

Mixed dementia

The term mixed dementia can be used to refer to dementia in which a patient shows signs of both AD and VaD (Fierini, 2020). It has been estimated that 20–40% of all dementia cases can be classified as mixed dementia (Zekry et al. 2002). AD and VaD share many common risk factors, and there are synergetic effects in which symptoms of one condition increases the risk for, or accelerates the progression of, the other (Emrani et al. 2020; Fierini 2020). In fact, Emrani et al. (2020) concluded that "*pure*" AD or VaD is rare compared to dementia cases where the two conditions co-exist. In light of these findings, a new view of dementia pathology is emerging, where most dementia cases are not classified as

either AD or VaD, but rather exist on a spectrum between the two (Emrani et al. 2020).

Air Pollution, Cognitive Decline, and Dementia

Numerous studies have investigated associations between air pollution and cognitive decline or dementia. These studies use a diversity of methods and measures, differing in regard to e.g. exposure measurements, cognitive outcomes, and means of dementia assessment. Still, the overall results indicate that long term exposure to air pollution increases the risk of dementia and cognitive decline.

A series of studies from Taiwan showed that dementia incidence was associated with exposure to various air pollutants such as carbon monoxide (CO) and nitrogen dioxide (NO_2) (Chang et al. 2014), ozone and $PM_{2.5}$ (Jung et al. 2015), and PM_{10} (Wu et al. 2015). Carey and colleagues (2018) conducted a study in London and found that dementia incidence was associated with NO_2 and $PM_{2.5}$, but not ozone. Another UK study (Parra et al. 2022), found an association between dementia incidence and both $PM_{2.5}$ and NO_x. A French study (Mortamais et al. 2021) found an association between dementia and $PM_{2.5}$, but not between dementia and NO_2 or black carbon (soot particles). In Scandinavia, Oudin and colleagues (2016) drew data from the Betula project and investigated associations between NO_x exposure and increased risk of dementia in the low-exposure area of Umeå, Sweden. Their results showed that those in the 3rd and 4th quartile of NO_x exposure (i.e., those experiencing higher levels of exposure) had higher risk of dementia than the least exposed quartile. The study by Oudin et al. (2016) is relevant to the studies presented in this thesis, as it was conducted in the same area, and drew data from the same prospective cohort study.

A project that has garnered a lot of attention is a Canadian effort (Chen et al. 2017a, 2017b) that followed all residents over 55 years old in the Canadian province of Ontario over a 12-year period, resulting in a study sample of more than two million people. The researchers found that both distance to the nearest major road (Chen et al. 2017b) and $PM_{2.5}$ and NO_x exposure (Chen et al, 2017a) were associated with increased risk of dementia and that 6% of dementia cases could be attributed to air pollution. Another large North American study by Shi and colleagues (2021) used a sample of over twelve million people, and found associations between dementia and exposure to both $PM_{2.5}$ and NO_2.

Air pollution has also been linked to impairments in a wide range of cognitive functions, from global cognitive abilities (such as mild cognitive impairment, a strong predictor of dementia) (Tzivian et al. 2016) to more specific cognitive domains (such as visuospatial ability) (Schikowski et al. 2015). A recent Korean

study (Park et al. 2022) found an association between air pollution and older adults having lower scores on the Mini-Mental State Examination. Reviews have highlighted the lack of longitudinal studies focusing on intrapersonal cognitive change (Power et al., 2016) and point out that the diversity of the studies makes a meta-analysis impossible and the evidence is inconsistent (Clifford et al., 2016). The aforementioned reviews agree that research (e.g. on underlying physiological mechanisms) clearly suggests that air pollution has an adverse effect on cognitive abilities. These effects seem to be present throughout an individual lifespan. Air pollution exposure in childhood, even *in utero*, has been associated with neurodevelopmental outcomes such as IQ level (Russ et al., 2021) and educational success (Clifford et al. 2016).

Air pollution and Alzheimer's disease – the role of the immune system

The immune system is of key importance for understanding the pathways through which exposure to particulate matter could cause dementia. This system plays an important role in maintaining brain health and protecting against AD, e.g. by facilitating removal of Aβ plaques with the help of microglial cells (Heppner et al. 2015). At the same time, the immune response can contribute to, and even be a driving factor behind, AD pathology (Heppner et al. 2015). When particles reach the brain, they can cause numerous small inflammations. If these inflammations become chronic, a number of things can happen. The function of the microglia cells can be impaired, reducing the ability to remove Aβ plaques (Heppner et al. 2015). Furthermore, the constant presence of pro-inflammatory cytokines can, first, promote an increase in Aβ deposition, tau phosphorylation and neurodegeneration, and second, stimulate astrocytes, which results in an even stronger inflammatory response (Meraz-Rios, 2013). Finally, the presence of particles in the brain has been associated with an imbalance between antioxidants and reactive oxygen species, leading to oxidative stress. A culprit in many neurodegenerative diseases, oxidative stress can be prompted by the immune system as yet another way to induce neuronal death (Meraz-Rios et al. 2013). According to Heusinkveld et al. (2016, p. 99), *"…oxidative stress induced by inhalation of PM could initiate neurotoxicity or enhance pre-existing (e.g. Aβ-induced) pathology and thus form a vicious cycle that promotes the initiation and progression of neurodegenerative diseases."* In short: PM can cause chronic inflammations in the brain, which in turn generates an immune response that leads to neuronal death, which in the end can cause dementia.

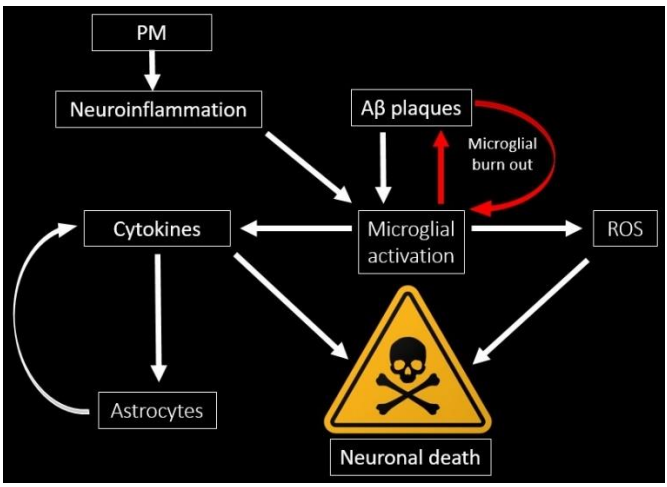

***Figure 1**. Suggested pathways linking particles in the brain to neuronal death. Red arrows indicate down regulation. "ROS" = "Reactive Oxygen Species"*

Calderon-Garcidueñas and colleagues (2002; 2004; 2008) performed *post mortem* examinations of the brains of dogs and humans and compared samples from individuals that had lived in highly polluted areas with those from cleaner areas. They found that humans and dogs from heavily polluted areas showed greater accumulations of both Aβ and inflammatory mediators in the brain tissue, even in children and young adults. In addition, an upregulation of inflammatory markers was found in the CNS, and was most prominent in the vagus nerve, olfactory bulb, basal ganglia and prefrontal cortex (Calderon-Garcidueñas et al., 2008). These studies relied on *post mortem* examinations, which can point to correlations not causes; still, their work indicated that particles can reach the brain and trigger an inflammatory response, which in turn may cause chronic brain inflammations with the potential to affect AD pathology.

Potential Mechanisms that link Air Pollution and Dementia

In order to gain a better understanding of the link between high air pollution and detrimental effects on the brain, it is important to further investigate factors that may act as moderators, mediators, or possible confounders. Presence of the APOE-ε4 allele, the relationship between high air pollution and noise, and the proposed olfactory route for particulate matter to enter the brain may all be important factors to investigate to gain a better understanding of the relationship between air pollution and dementia.

Olfactory functions, air pollution, and dementia

The human body uses the olfactory system to perceive the outside world by detecting, identifying, and discriminating among thousands of different chemical compounds (Firestein, 2001). Olfactory functions play an important role in ingestion (e.g. detecting and identifying food) and avoiding hazards (e.g. detecting smoke) (Croy et al, 2014; Stevenson et al. 2010). It has also been hypothesized that olfaction could play a role in social interactions, and could act as an emotional contagion (Stevenson et al. 2010).

Our ability to perceive odors depends on multiple olfactory functions, such as odor identification, detection, and discrimination. These functions differ with regards to which cognitive functions are involved, and to what extent. Hedner and colleagues (2010) investigated olfactory functions and their cognitive correlates, using a wide range of tests to assess executive functions, and semantic- and episodic memory. Their results showed that odor identification and discrimination were reliant on executive functions and semantic memory, whereas none of the investigated cognitive factors were associated with odor detection.

A review by Croy and colleagues (2014) found that though most people who experience olfactory deficits cope well, some experience depression and reduced quality of life. More recently, a number of studies have investigated the long-term consequences of olfactory dysfunction resulting from COVID-19. For example, Vaira and colleagues (2022), found that olfactory dysfunction due to COVID-19 was associated with lower quality of life, especially in aspects related to mental health. Impaired olfactory functions have been associated with frailty and general poor health in old age, and overall mortality (Van Regemorter et al. 2020; Schubert et al., 2017). The mechanisms behind these associations are not clear, but it is likely that olfactory deficits indicate underlying age-related pathology, or accelerated brain aging (Van Regemorter et al., 2020; Shubert et al. 20217).

Olfactory impairments have been linked to several neurological conditions (Barresi et al., 2012), and is an early marker for AD (Murphy 2019). It has been argued that dementia should not be seen as a disease, but rather as a continuum of pathological events, of which olfactory impairments are one, that start decades before onset of clinical dementia (Bathini et al. 2019). A study drawing data from the Betula project (Stanciu et al. 2014) demonstrated that impaired olfactory functions were associated with dementia over a 10-year follow-up period. A US study (Adams et al. 2017) showed that poor odor identification ability predicted dementia five years before diagnosis, with roughly the same accuracy as biomarkers in people already experiencing cognitive decline.

The olfactory receptor cells are situated in the roof of the nasal cavity, embedded in mucosa. The receptor cells send information *via* the olfactory nerve to the olfactory bulb in the forebrain. Animal studies have shown that due to stem cells in the olfactory epithelium, the olfactory bulb is highly plastic (Huart et al., 2018). This plasticity is important because olfactory receptor neurons are exposed to inhaled air (Huart et al., 2018). Studies conducted in Mexico City, a highly polluted area, showed associations between air pollution and olfactory bulb pathology (such as presence of Aβ and upregulation of mRNA involved in the inflammatory response) even in young children (Calderon-Garciduenas et al., 2010), and that APOE-ε4 accelerated this process (Calderon-Garciduenas et al., 2018). However, it is not clear to what extent this type of neuronal damage translates to diminished olfactory functions.

In a review, Ajmani et al. (2016a) concluded that air pollution seems to be associated with a decrease in multiple olfactory functions, although the authors pointed out that these results must be interpreted carefully because *"most studies have used proxies for pollution exposure in small samples of convenience"* (Ajmani et al. 2016a, p. 1638). Other studies using larger samples (Ajmani et al. 2016b; Ekström et al. 2022) have also found associations between air pollution and declining olfactory functions. Since air pollution can cause deficits in olfactory functions, which are dependent on cognitive functions, and because declining olfactory functions are associated with dementia, it is of great interest to investigate the role of olfaction in the associations between air pollution and dementia in more detail.

APOE, air pollution, and dementia

The APOE-ε4 allele is an important factor to consider in studies involving dementia and olfaction, as it is a known risk factor for dementia. In addition, the APOE-ε4 allele has also been linked to olfactory deficits independent of dementia (Olofsson et al. 2010). The APOE-ε4 allele may also play a role in the association between air pollution and dementia. It has been suggested that air pollution can cause inflammations in the CNS, which leads to an immune response, which in the end causes neuronal death (Heppner et al. 2015; Meraz-Rios, 2013). Because apolipoprotein E is involved in the down-regulation of inflammatory processes in the brain (Flowers & Rebeck, 2020), it is possible that carriers of the APOE-ε4 allele are more susceptible than non-carriers to the detrimental effects of air pollution on brain health

Though many studies on air pollution and dementia have controlled their analyses for APOE status, only a handful of epidemiological studies have focused on the possible moderating role of the APOE gene, and the results from these studies conflict with each other. For instance, a German study (Schikowski et al.

2015) found an association between exposure to traffic and its byproducts and declining visuospatial abilities only in APOE-ε4 carriers. A US study (Cacciottolo et al. 2017) found a stronger association between air pollution and dementia in APOE-ε4 carriers than in non-carriers. Another US study (Cleary et al. 2018) found that exposure to ozone led to a faster cognitive decline in APOE-ε4 carriers than in non-carriers. On the other hand, a large study (more than 500,000 individuals with a follow-up time of seven years) by Parra et al. (2022), that found an association between dementia and exposure to $PM_{2.5}$ and NO_2, did not find that APOE moderated any of these associations. In a study conducted in the same area in northern Sweden as the studies presented in this thesis, Oudin et al. (2019) found no evidence for a modifying effect by APOE-ε4 on the association between exposure to traffic related NO_x and incidence of dementia. Given the inconclusive findings, this area needs more consideration.

Noise, air pollution, and dementia

According to the European Environment Agency (2022), more than 100 million people are exposed to noise levels exceeding what the EU considers safe noise levels (long-term day-evening-night noise levels exceeding 55 dB), with road traffic being the largest source of noise pollution in Europe. The term "*noise*" can be simply defined an undesirable sound. It is harder to define what "*undesirable*" means in this context, since the experience of sound is dependent on both the physical properties of the sound (e.g. loudness, frequency, and duration), the individual's physiological and psychological state (past experiences, and social and cultural attitudes), and other external factors (e.g. the time of day) (Ouis et al. 2001).

Long exposure to ambient noise from e.g. road traffic has been associated with increased risk of dementia and decreasing cognitive abilities. For example, Weuve et al. (2021b) conducted a study in Chicago and found associations between noise and both global cognitive performance and AD. Tzivian and colleagues, using data from a German cohort, found noise to be associated with cognitive functions (Tzivian et al. 2017), risk of mild cognitive impairment (a condition that can be an early stage of dementia) (Tzivian et al. 2015), and AD (Tzivian et al. 2017). Tzivian and colleagues (2017) also found that the association between air pollution and cognition was stronger among those who were exposed to higher levels of noise, indicating a synergetic effect between noise and air pollution on cognitive functions.

The mechanisms linking noise to dementia are unclear. Because exposure to unwanted sounds is likely to cause annoyance and stress (Ouis et al. 2001), it has been suggested that long-term noise exposure can lead to a stress reaction *via* an overactivation of cortisol response, and thereby disturbed sleep (Eriksson &

Pershagen 2018), thereby increasing the risk of CVD such as ischemic heart disease (Kempen et al. 2018), which in turn can cause VaD and accelerate AD pathology (Attems & Jellinger, 2014). In addition, noise exposure may have a direct impact on the structure of the brain from an early age. For example, Beckwith and colleagues (2020) found that high levels of traffic noise exposure in early childhood was associated with reduced gray matter volume in early adolescence.

Experimental animal studies have shed some light on possible pathways linking noise exposure to dementia. For example, Jafari and colleagues (2018) showed that mice who had been exposed to high noise for eight hours a day for 30 days, had lower brain volume, cortical thickness, and neuronal density in the prefrontal cortex than a control group. Cui and colleagues (2015) found that noise exposure increased Aβ pathology and neuroinflammation in rats, suggesting that prolonged noise exposure might be able to influence both onset and development of AD. In another study on rats, Gai and colleagues (2017) found that chronic noise exposure led to an increased stress response, and increased tau phosphorylation in the hippocampus.

Of course, road traffic not only generates noise, but air pollution. Because both may contribute to the development of dementia, it is possible that the association between air pollution and dementia could be explained by confounding by noise. In their study in Ontario, Canada, Chen and colleagues (2017b) found associations between the distance from a person's residential address to the nearest major road, and risk of dementia. Interestingly, they noted that air pollution did not explain all of the observed association, and suggested that road traffic noise might account for this discrepancy. A recent review of noise exposure and dementia by Meng and colleagues (2022) highlighted the need for studies that considered the combined effects of multiple environmental exposures in future studies on air pollution and cognitive outcomes.

Aims

Associations between air pollution and dementia now seem well established. But as in all research, new findings inevitably lead to more questions. The overall aim of this thesis is to investigate possible mechanisms for the association between air pollution and dementia, in a low exposure area. Because olfactory deficits have been linked to air pollution, and can be an early sign of dementia, an additional aim is to examine associations between exposure to air pollution and olfactory function. More specifically, this thesis poses the following questions:

1. Can the association between air pollution and dementia be attributed to noise exposure (study I)?

2. What are the roles of olfactory functioning and the APOE-ε4 allele in the association between air pollution and dementia (study II)?

3. Is there an association between air pollution and olfactory functioning in a low-exposure setting (study III)?

Methods

Exposure Measures

All measures of long-term air pollution and noise exposure were based on modelled estimates. In these models, the study area was divided into a grid with an estimate of the exposure assigned to each square in the grid. The resolution (the size of each square) differed somewhat depending on the type of model used, and some models had a higher resolution (i.e. smaller grid size) in urban areas than in rural areas. By geocoding the participants' residential addresses at baseline, each participant was assigned to a square in the grid, and thus an individual exposure estimate.

Air pollution

In study I, estimated annual mean levels of traffic-related NO_x-exposure were used as exposure measurement. Measured data was collected from 36 measuring stations throughout Umeå during four week-long periods between November 2009 and June 2010. These data were combined with geographic information systems to build a land-use regression model, with a grid size of 50x50 meters, which provided estimates for areas in-between stations. The model was constructed using the protocol created by the European Study of Cohorts for Air Pollution Effects (ESCAPE; Beelen et al. 2013).

In studies II and III, the exposure measurement was annual mean levels of fine particle matter ($PM_{2.5}$) from both regional and local sources (see fig.2 for an overview of $PM_{2.5}$ levels over the study area). Estimates of $PM_{2.5}$ concentrations for the years 1990, 2000, and 2010 were obtained from a dispersion model calculated by the Swedish Meteorological and Hydrological Institute (SMHI), and has been described in detail elsewhere (Segersson et al. 2017). A dispersion model is a mathematical model that calculates levels of air pollution based on emission data, topography, road networks, and meteorological conditions (Jerett et al. 2005). The model used in studies II and III included a number of sources such as background (or regional) air pollution, both exhaust and non-exhaust (e.g. road wear) emissions from traffic, residential wood burning, industries, agriculture, and more (Segersson et al. 2017). The resolution of the model varied from 50 x 50 meters in urban areas to 3200 x 3200 meters in the most rural areas. Study III also investigated effects of $PM_{2.5}$ concentration on the day of testing. Daily mean $PM_{2.5}$ levels were calculated using hourly measurements, obtained through SMHI, from a measuring station approximately 1 km from the test site.

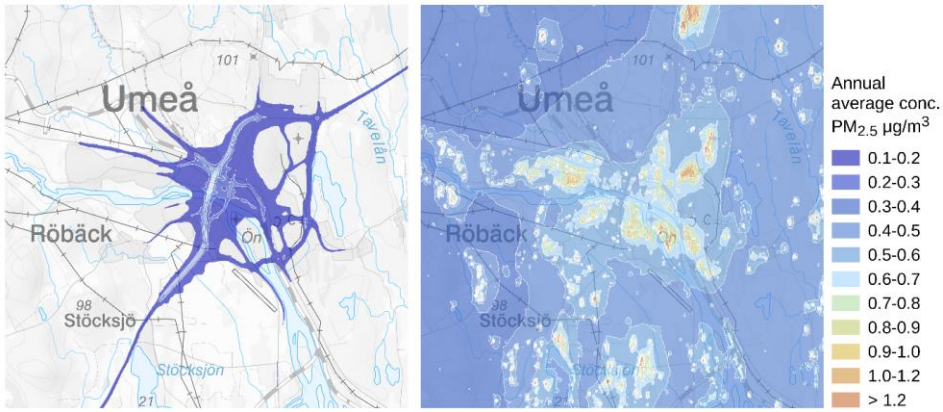

Figure 2. *Modelled annual average contribution to PM2.5 during 2011 from road traffic exhaust (left map) and small-scale residential wood burning (right map) by SMHI. (from Oudin et al. 2018; ©Lantmäteriet; reprinted under CC-BY license).*

The air pollution levels in the study area were relatively low. For example, in Study II and III, the mean annual $PM_{2.5}$ concentration at residential address at baseline was 6.8 µg/m³ (see fig. 3), which is 1.8 µg/m³ above the World Health Organization's definition of clean air (World Health Organization, 2021), and for context can be compared to, for example, a study in Taiwan (Jung et al. 2015) where mean annual $PM_{2.5}$ levels were 34 µg/m³, or about five times as high as in this study area.

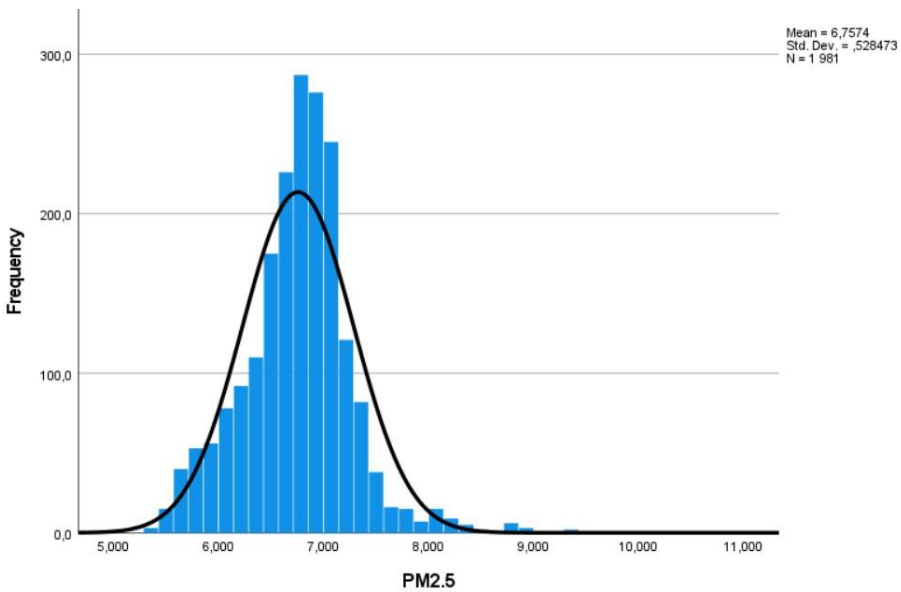

Figure 3. *Histogram showing the distribution of $PM_{2.5}$ levels for the sample used in Study III*

Road traffic noise

In addition to NO_x, study I also used noise as exposure variable. In study I, noise was defined as daily mean levels of A-weighted (dBA) equivalent sound levels (Leq 24h) from road traffic. Noise is the sum of many individual sounds over time. An equivalent sound level is the entire sound exposure over a certain time, translated into a hypothetical single constant signal with the same total energy. That a sound measurement is A-weighted means that it compensates for the fact that human hearing is more sensitive to higher frequencies, perceiving these frequencies as louder than a low-frequency sound with the same energy. Data were obtained from the Umeå Municipality Noise Survey for the year 2011 (Umeå Kommun, 2012). The model included traffic-related noise sources based on road traffic estimates from Umeå Municipality and the Swedish Transport Administration. The model combined these estimates with a topographical map including natural features (types of terrain) and man-made features (roads, buildings etc.). The model had a resolution ranging from 5 x 5 meters in urban areas to 25 x 25 meters in rural areas. In study I, noise estimates from 2011 was matched with participants' residential address at baseline (1993), assuming the local contrast in noise exposure for 2011 closely correlate with those in 1993.

Participants

The majority of data used in these studies were drawn from the Betula project (the exceptions being the exposure measurements and the data on educational level used in study II). The Betula project is a population-based prospective cohort study on memory, health, and aging in Umeå municipality in northern Sweden, and has been described in detail elsewhere (Nilsson et al. 2004, Nyberg et al. 2020). In short, the first test wave (T1) took place in 1988–1990, when a first sample (S1) was included in the study. Participants were randomly selected using the population registry, stratified by age and sex. S1 (n=1000) consisted of 10 age cohorts five years apart (35, 40, 45, … 75, 80 years of age) with 100 participants in each cohort. The male-female ratio was not equal, but representative of the ratio for the respective cohorts in the general population. Additional test waves (T2-T6) took place every five years, with the introduction of new samples (S2-S6) and follow-up for existing samples (see Table 1). Participants were excluded from further follow-up if they moved from Umeå municipality or chose to decline further participation.

At each test wave, participants were examined on two occasions about a week apart. The first occasion consisted of a health examination conducted by a nurse, including measurements of e.g. blood pressure, weight, vision, etc. In addition, blood and urine samples were collected. On the second occasion, participants underwent a large number of cognitive tests that probed episodic memory, semantic memory, short-term memory, visuospatial ability, and attention. In

between the two test occasions, participants were asked to fill out an extensive battery of self-assessment forms providing background information on e.g. socioeconomic status and general health.

***Table 1**. An overview of the Betula project, showing the number of participants of each sample (S) who underwent the initial health assessment in each test wave (T).*

	T1	**T2**	**T3**	**T4**	**T5**	**T6**
	1988-1991	1993-1995	1998-2001	2003-2005	2008-2010	2013-2014
S1	1000	875	729	591	403	249
S2		994	673			
S3		963	826	689	440	259
S4			553			
S5				558		
S6					357	66
Total	1000	2832	2781	1838	1200	574

Outcome Measures

In studies I and II, dementia status (AD and VaD) was used as outcome variable. In study III, olfactory functions were the outcome variables, more specifically odor detection threshold and odor identification ability.

Dementia

The diagnostic evaluation of participants in Betula has been described in detail by Nyberg and colleagues (2020). In short, assessment of dementia status, sub-diagnosis, and time of onset was conducted by a geropsychiatrist. The assessment was primarily based on medical records and diagnoses were made using clinical criteria-based systems, such as the DSM-IV classification core criteria for dementia. Biomarkers or *post mortem* findings were part of the diagnostic decision when available. Health and cognitive test data from the Betula project also helped inform the diagnostic assessment. Participants were referred to a geropsychiatrist for extended dementia evaluation if any of the following criteria were met during testing: 1) a score on the Mini-Mental State Examination < 24 or a drop by at least three points from the previous test wave; 2) the z-score of a composite cognitive measure, compared to the previous test, dropping from high ($z > 1.8$) to normal ($-1.8 < z < 1.8$) or low ($z < -1.8$), or from normal to low; 3) self-reports of memory dysfunction; 4) behavioral or cognitive deviations suggestive of cognitive impairment. A blinded diagnostic re-evaluation was conducted every five years by a geropsychiatrist in order to enhance the reliability of the diagnosis.

Olfactory functions

Odor identification ability was used as an outcome variable in studies II and III. A version (Bende & Nordin 1997) of the Scandinavian Odor Identification Test (SOIT) (Nordin et al. 1998) was included in the Betula project from T3 and onwards. The procedure is described in detail by Larsson and colleagues (2004). In short, the participants were presented with thirteen different odors, the majority of which were in the form of etherical oils. The odors, assumed to be well known to the study population, included e.g. vanilla, orange, and bitter almond. After each presentation, the participant was asked which of four alternatives was the correct odor. The test score is simply the number of correct answers (maximum score = 13). The order in which the odors were presented was randomized, but the odors and the corresponding response alternatives were the same for all participants. The etherical oils had an estimated shelf life of one year, after which a new set of oils was acquired. The version of SOIT used in the Betula project was constructed to avoid ceiling effects (i.e. to minimize the number of people scoring the maximum possible score). This effect was avoided by making response alternatives more similar to the stimuli, which had the effect of making the test slightly harder than the standard version.

Odor detection ability was used as an outcome variable in study III. An odor detection test was part of the Betula test battery in T5 and T6. In this test, odor detection thresholds were determined using "Sniffin' sticks" (Hummel et al. 1997), i.e. felt-tip pens filled with *n*-butanol in sixteen dilution steps numbered from 1 (strongest) to 16 (weakest). A new set of pens was acquired before each test wave. In each trial, the participant smelled a pair of pens, one after the other in randomized order. One of the pens contained the odorant whereas the other did not. The participant was then tasked with deciding which of the pens had the strongest smell. The procedure was repeated with the same pens until the participant either gave the wrong answer, or gave four consecutive correct answers. If the participant answered correctly on four out of four trials on a certain dilution step, it was determined that the participant had successfully detected the odor of that particular concentration. The 8th dilution step was the first odor presented to participants. If a participant passed this threshold, the next pair of pens included the 16th (weakest) dilution. If not, the 7th (i.e. slightly stronger) dilution step was presented. In either case, participants were thereafter presented with increasing concentrations until they reached a dilution step at which they could detect the odorant. The number of the weakest dilution step detected also became their score on the test. This means that a higher score indicates a lower odor threshold and thus a better ability to detect odors.

Covariates

The statistical models in the studies were adjusted for various sets of covariates (Table 2). All covariates are known risk factors for dementia. Using the dataset from study I, correlations between all covariates were investigated using Spearmans Rho (ρ). The correlation between sex and waste-hip ratio was $\rho = -0.58$ ($p < 0.01$), but no other correlation exceeded +/- 0.3.

APOE: APOE genotype was used a covariate in studies I and III, and as a moderating factor in study II. Participants in the Betula project provided blood samples, by which APOE genotype was determined (for details, see Sundström et al. 2004). APOE status was classified as either APOE-ε4 carrier (hetero- or homozygotic) or non-carrier.

Education: In study I, self-reported data on highest level of education attained was used, categorizing participants into three categories, namely compulsory, high school, or university education. In study II, data on highest education level was retrieved through Statistics Sweden and re-coded into the same three levels as in study I. In study III, education was based on self-reported number of years of education.

Smoking: Participants were classified as smokers, former smokers, or non-smokers based on their self-reported smoking habits.

Physical activity: Participants were categorized depending how they answered the question "*Over the last three months, did you do any sports, exercise or walking?"* with the following answering alternatives: "*Never*", "*Occasionally*", "*A few times a month*", "*Weekly*", or "*Daily*".

Alcohol: Based on self-reports of alcohol consumption, participants were classified as "*present consumers*", "*former consumers*", or "*non-consumers*".

BMI and WHR: Body Mass Index (BMI) and Waste Hip Ratio (WHR) were used to indicate if a participant was overweight. Following National Institutes of Health standards (Van Itallie, 1985), the cut-off value between "*normal weight*" and "*overweight*" was a BMI of 23.8 for women and 25.0 for men. For WHR, the cut-off was 0.8 for women and 1.0 for men.

Medical history: Self-reports of medical history were used to identify participants who at the time of the health evaluation, or in the five years prior to the health evaluation, had suffered from diabetes, stroke, hypertension, or heart disease.

CVDRF: In study II, a variable representing a history of cardiovascular diseases and risk factors (CVDRF) was created. A participant was considered to have a history of CVDRF if they, either at the time of the health evaluation or in the 5 years prior to the health evaluation, suffered from any of the following conditions: diabetes, hypertension, stroke, or heart disease.

Table 2. *A summary of the variables used in the different studies.*

	Study		
	I	**II**	**III**
Exposure			
NOx	x		
PM2.5		x	x
Noise	x		
Outcome			
AD	x	x	
VaD	x	x	
Odor identification			x
Odor detection			x
Covariates			
Age	x	x	x
Sex	x	x	x
Apoe	x	x	x
Education	x	x	x
Smoking	x		x
Physical activity	x		
Alcohol	x		
BMI	x		
WHR	x		
Diabetes	x	x	
Hypertension	x	x	
Stroke	x	x	
Heart disease		x	

Statistical analyses

In studies I and II, dementia incidence was the dependent variable and Cox proportional-hazards regression was used to calculate hazard ratios (HR). The HR is an estimate that tells us by which factor the risk of a specific event (in these cases, dementia onset) changes with each one-unit increase of the independent variable. A major advantage of Cox proportional-hazards regression is that it is not dependent on a predetermined end point. If a participant drops out before end of follow-up without experiencing the event, the participant is not removed from the analyses. Instead, the statistical model makes use of the information the participant provided up to that point (Walters, 2012). An occasion that marks the end point for a participant, other than the occurrence of the event, is called censoring (Walters, 2012). In these studies, censoring occurred when a participant died, was lost to follow-up (e.g. moved outside the catchment area of the Betula study, or dropped out of the study), or at the end of the study period – whichever occurred first.

In study III, where the dependent variables (olfactory functions) were continuous, two kinds of linear regression analyses were used. Linear regression was used in a cross-sectional analysis to investigate associations between daily mean $PM_{2.5}$ concentration and olfactory functions on the day of testing. In longitudinal analyses of long-term effects of $PM_{2.5}$ on olfaction, general linear models were used to specify repeated measures models, where individual measurements of the dependent variable were entered for each test wave. The same repeated measures approach was used when investigating the rate of change of olfactory functions over time, but instead of crude test scores, the difference in score between baseline assessment and the score at each subsequent test wave was used as the dependent variable.

The Empirical Studies

Study I: Road traffic noise, air pollution, and risk of dementia – results from the Betula project

Previous research using data from the Betula project (Oudin et al., 2016) found an association between traffic-related air pollution at residential address and dementia incidence. But where there is more traffic there is also more noise, and it is possible that traffic-related noise to some extent could contribute to these associations. Thus, the aim of study I was to investigate whether the individual and combined effect of noise and air pollution had an effect on the risk of dementia.

In study I, T2 (1993–1995) of the Betula project was used as baseline. At the time that the analyses were performed, the latest update of the dementia diagnoses available to us was from 2010, and therefore 2010 became the endpoint of this study. The study sample included all participants, aged 55 or older, who were tested at T2 (S1–S3), which gave us a total sample of n=1721, of which 302 participants had developed either AD (n=191) or VaD (n=111) at follow-up. In order to make the results comparable to Oudin et al. (2016), the three statistical models were adjusted for the same sets of covariates, and the NO_x estimates were divided into quartiles. The noise exposure was estimates of daily mean, A-weighted, equivalent sound levels (Leq 24h). The noise variable was transformed into a dichotomous variable, where Leq 24h levels < 55 dB (n=1619) were classified as "*low exposure*" and Leq levels ≥ 55 dB (n=102) were classified as "*high exposure*". The 55-dB cut-off was derived from the Swedish Environmental Protection Agency's (2017) level for good environmental sound quality.

The results showed an association between NO_x and dementia for the 3rd quartile of exposure (fully adjusted model: HR=1.48, 95% CI 1.03-2.12, compared to the lowest quartile of exposure), but not for the 4th quartile, as the lower confidence interval for the 4th quartile dropped under 1 (HR=1.41, 95% CI: 0.97-2.03). No associations were found between traffic-related noise and dementia incidence in any model, nor when the sample was stratified by dementia sub-type (AD and VaD).

Study II: Air Pollution and Dementia – the Influence of Odor Identification Ability and APOE

Olfactory deficits can be an early sign of dementia and might also be caused by air pollution. Therefore, the role of olfaction in the association between air pollution and dementia is of great interest. When investigating olfaction and air pollution, the APOE gene also needs to be considered. The APOE-ε4 allele is not only a risk factor for dementia, but also for declining olfactory functions independent of dementia (Olofsson et al. 2010). In addition, the hypothesized pathway through which airborne particles can negatively affect the brain goes *via* neuroinflammation, and apolipoprotein E is involved in regulating the inflammatory response in the brain. Thus, the aim of study II was to investigate the role of olfaction and the APOE-ε4 allele in the association between $PM_{2.5}$ and dementia.

The baseline sample of this study was all participants 55 years or older who participated at T3 (1998–2000). Of the 1846 participants, 348 developed either AD (n=211) or VaD (n=137) during the 21-year follow-up period. The results showed an association between $PM_{2.5}$ exposure and dementia incidence (HR: 1.24, 95% CI: 1.02–1.51, for each 1 $\mu g/m^3$ increase in the fully adjusted model).

Interaction effects were found between $PM_{2.5}$ and odor identification ability (HR=0.90, 95% CI: 0.82–0.99), as well as between $PM_{2.5}$ and APOE-ε4 status (HR=1.62, 95% CI: 1.09–2.40). As a consequence, the sample was stratified first by odor identification ability using the mean SOIT-score (6.68) as cutoff, thereby allowing us to compare high (n=945) and low (n=760) performers. The results showed that the association between $PM_{2.5}$ and dementia persisted only among the low performers (HR=1.32, 95% CI: 1.02–1.71). Thereafter, the sample was stratified based on APOE-ε4 status (carriers, n=482, *versus* non-carriers, n=1364) and found an association between $PM_{2.5}$ exposure and dementia only for APOE-ε4 carriers (HR=1.61, 95% CI: 1.15–2.24).

Study III: $PM_{2.5}$ exposure and olfactory functions

The olfactory receptor cells in the nasal cavity are exposed to air and therefore also air pollution. It has been suggested that PM can reach the brain *via* the olfactory nerve. In addition, research indicates that the olfactory bulb is one of the areas of the brain most detrimentally affected by air pollution (Calderon-Garcidueñas et al., 2004; 2008). The aim of study III was to investigate the associations between long-term $PM_{2.5}$ exposure and olfactory functions (odor detection and odor identification), and rate of change in these functions over time. In addition, the possible association between short-term $PM_{2.5}$ exposure (i.e. PM levels on the day of testing) and odor detection was investigated. Both

baseline and sample sizes varied in the different analyses, since the olfactory tests were not included in all test waves, and short-term exposure measurements were not available prior to T5 (see fig. 4).

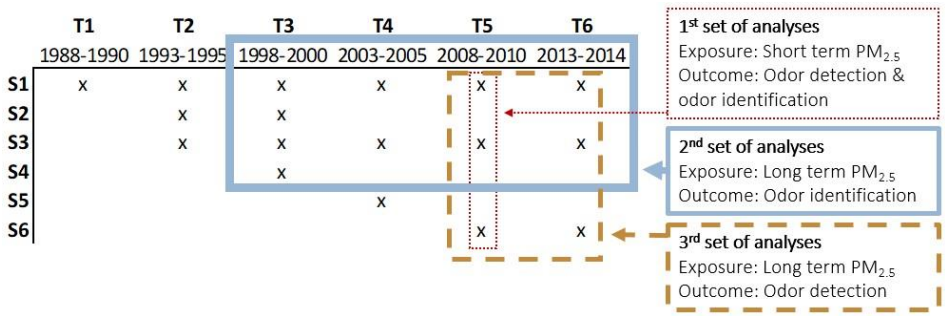

Figure 4. *Overview of the Betula project, showing the samples and test waves from which data were drawn for the various sets of analyses in study III.*

A first set of analyses investigated the association between short-term $PM_{2.5}$ exposure and olfactory function. The results revealed that there was no association and therefore subsequent analyses were not adjusted for $PM_{2.5}$ levels on the day of testing. The next set of analyses investigated long-term $PM_{2.5}$ exposure and odor identification ability, and found a positive association ($\beta=0.27$; $p<0.001$). This indicates that increased exposure to air pollution is associated with *better* ability to identify odors. When investigating odor identification ability, an interaction effect was found between $PM_{2.5}$ and age ($\beta=0.01$; $p<0.05$), as well as a weak correlation between $PM_{2.5}$ exposure and age ($r=0.10$, $p<0.01$). No interaction effect between $PM_{2.5}$ and APOE-ε4 status was found. When the sample was stratified by age, the association remained in the older group (age≥65, n=1315, $\beta=0.30$, $p<0.01$), but not the younger group (age<65, n=1206, $\beta=0.01$, $p>0.05$). No association was found between long-term $PM_{2.5}$ and any of the other outcome variables, i.e. odor detection, rate of change in odor detection, or the rate of change in odor identification.

***Table 3**. Estimated regression parameters (β) and 95% confidence intervals (95% CI) for test scores on odor identification and detection tests, and rate of change of these scores over time.*

	ODOR IDENTIFICATION				ODOR DETECTION			
	Test score		Rate of change		Test score		Rate of change	
Model	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Crude	0.15*	0.01, 0.29	-0.03	-0.23, 0.17	0.12	-0.20, 0.44	0.07	-0.40, 0.53
Age adj.	0.27***	0.13, 0.41	0.06	-0.12, 0.25	0.20	-0.10, 0.51	0.15	-0.30, 0.61
Fully adj.	0.20**	0.06, 0.34	0.03	-0.15, 0.21	0.12	-0.20, 0.44	0.11	-0.35, 0.56

***Note**: The fully adjusted model was adjusted for age, for sex, education, APOE-ε4 status, and smoking habits. All models using rate of change as outcome variable were also adjusted for baseline performance (*p<0.05, **p<0.01, ***p<0.001).*

Discussion

The aim of this thesis was to investigate possible mechanisms behind the association between air pollution and dementia in a low-exposure area. An additional aim was to examine associations between exposure to air pollution and olfactory functions. The results show that long-term exposure to air pollution, measured both as NO_x (study I) and $PM_{2.5}$, (study II), is related to dementia incidence, even at low levels. These findings are in line with other studies on pollution and dementia in the same area (Oudin et al. 2016, 2018; Åström et al. 2021). This thesis further investigates the possible influence of road traffic noise and the roles of olfactory functions and of APOE genotype. The main findings can be summarized as follows:

1. Noise from road traffic did not contribute to the association between NO_x and dementia (study I).

2. The association between air pollution and risk of dementia was stronger among APOE-ε4 carriers and those with below-average odor identification abilities (study II).

3. A *positive* association was observed between long-term $PM_{2.5}$ exposure and odor identification ability (i.e. increased concentrations of $PM_{2.5}$ was associated with *better* ability to identify odors). No associations were found between long-term $PM_{2.5}$ exposure and odor detection, rate of change in odor detection, or the rate of change in odor identification.

Road traffic noise, air pollution, and dementia (study I)

Areas with high levels of traffic-related air pollution are likely to be exposed to higher levels of road-traffic noise. Previous research has linked noise exposure to diminished cognitive functions (Thompson et al. 2022), and CVD (Kempen et al. 2018) which in turn is a known risk factor for VaD. Yet few studies on dementia or cognitive functions have considered both exposures in the same study (Tzivian et al., 2015). The results from study I showed that NO_x exposure was associated with increased risk of dementia, but no significant association was found with noise. Thus, these results indicate that air pollution should be considered the main component in the association between traffic-related exposure and dementia, at least in areas with low levels of noise exposure, as in the setting in this study.

A limitation of this study that needs to be considered when interpreting these results, is that estimates of noise exposure were acquired from a model for the year 2011, with the assumption that local contrasts in noise exposure had remained largely unchanged since 1993. Another limitation is the range of noise exposure, which in this setting was generally very low. Only 6% of the participants were exposed to noise levels high enough to be classified as poor outdoor environmental quality as defined by the Swedish EPA (i.e. Leq > 55 dB) (Swedish Environmental Protection Agency, 2017). Therefore, these findings should not be generalized to areas with higher noise exposure. One pathway through which traffic noise could increase dementia risk is *via* disturbed sleep. It is likely that the levels of night-time noise in our study area were too low to cause sleep disturbances severe enough to increase the risk of dementia. Unfortunately, data on night-time noise specifically were not available for this study. However, there have been studies conducted on night-time noise in areas with higher exposure. For example, Carey et al. (2018) examined the impact of night-time noise and air pollution on dementia risk in London, and found an independent association between night-time noise and air pollution, and night-time noise and dementia. But in a combined model, with both measures included simultaneously, the effect of noise diminished.

The role of olfactory functioning in the association between air pollution and dementia (studies II and III)

In study II, the sample was divided into two groups, high and low performers on the odor identification test. The results showed an association between air pollution and dementia only among the low performers, indicating that those with low olfactory functions are more vulnerable to the detrimental effects of air pollution. It may be that the olfactory deficit is caused by some underlying condition that also affects the olfactory system in a way that makes it easier for particles to reach the brain *via* the olfactory nerve, or for these particles to cause more damage when they reach the CNS. However, to my knowledge no such biological pathway has been identified. Another possibility is that the observed moderating effect of olfaction in study II may reflect a confounding effect by air pollution, causing olfactory deficits and increasing the risk of dementia independently of each other. Research has suggested that air pollution exposure is associated with both dementia incidence (Abolhasani et al. 2022) and decline in olfactory functions (Ajmani et al. 2016a). But as shown in study III, no detrimental effects of air pollution on olfaction were found in this setting.

The results of study III indicate that long-term exposure to $PM_{2.5}$ is associated with a *better* ability to identify odors. There is – to my knowledge – no biological mechanism that supports the notion that exposure to air pollution could cause improved olfaction. This somewhat surprising finding could of course be due to a

type 1 error, i.e. a chance result. But there are other possible explanations that need to be considered. When stratified by age, the positive association between air pollution and odor identification only remained in the older group, suggesting that age plays a role. One possible explanation relates to dropout and the survival effect, which always need to be considered when analyzing data from prospective cohort studies. Those in poor general health and those with poor cognitive abilities are more likely to drop out of the study. As a result, those who keep participating at older ages are no longer representative of their age group, as they are in better health, both physically and cognitively. In addition, the results show a slightly higher mean exposure for the older participants than the younger participants, which could indicate that older people are more likely to take up residence in urban areas, possibly (for example) to be closer to public services. If older participants tend to live in urban areas, and if they have on average better cognitive health, it is not unlikely that they are better at identifying odors despite being exposed to air pollution.

Another possible explanation relates to socioeconomic status (SES). In a recent US study, Christensen et al. (2022) argued that the complicated relationship between SES and exposure to air pollution (especially in cities and when only considering a single measure of air pollution) can lead to seemingly positive associations between air pollution and cognitive outcomes. In the case of study III, odor identification is related to semantic memory (see Hedner et al. 2010), which is in turn related to education level (see e.g., Lövden et al., 2004), and people with more education may be more likely to reside in urban (and thus more polluted) areas. Consequently, cognitively healthy older people living in urban areas might perform better on odor identification tests than those in more rural areas. If air pollution is unrelated to olfactory function in cognitive healthy adults, at least when exposed at low levels, then the observed positive association in study III could be expected. In addition, preliminary results from an ongoing study on air pollution and semantic memory, using data from the Betula Project, also suggest a positive association between $PM_{2.5}$ and semantic memory (Andersson et al. 2023, work in progress), lending support to the hypothesis that the observed positive association between air pollution and odor identification ability could in fact reflect performance of semantic memory.

It is important to note that due to the low exposure levels, these results cannot be generalized to areas with higher levels of air pollution. In a study that in many aspects resembles ours, Ekström et al. (2022) found an association between higher air pollution exposure and a decline in odor identification ability in a setting where the mean $PM_{2.5}$ exposure was roughly 25% higher than the mean exposure in study III. Furthermore, declining olfactory functions is an early marker of dementia that may occur at least up to a decade before onset of clinical dementia (Murphy et al. 2019; Stanciu et al. 2014). Research set in the highly

exposed area of Mexico City has shown associations between air pollution and neurodegeneration, even in children (Calderon-Garciduenas et al. 2018). Therefore, those with poor olfactory functions may already suffer from neurodegeneration that can progress to dementia. If such is the case, a higher incidence of dementia in those with poor olfactory function is to be expected. However, it is unclear if neuronal damage to the olfactory bulb also occurs in low exposure areas, and if so, to what extent this damage translates to diminished olfactory functions.

The role of the APOE-ε4 allele in the associations among air pollution, olfaction, and dementia (study II)

Study II also explored whether the observed association between air pollution and dementia is moderated by the APOE-ε4 allele. The results suggest an association between $PM_{2.5}$ and dementia only among carriers of the APOE-ε4 allele, and among those with below-average odor identification abilities. Previous research conducted in more polluted areas has shown stronger associations between air pollution and dementia in APOE-ε4 carriers than non-carriers (Cacciottolo et al. 2017; Cleary et al. 2018). Study II was set in a less-polluted setting, and found a statistically significant association between dementia and air pollution only in APOE-ε4 carriers. Because apolipoprotein E is involved in the down-regulation inflammatory responses in the central nervous system (Flowers & Rebeck, 2020), it is possible that the variant of Alipoprotein E resulting from the APOE-ε4 allele makes the brain less able to deal with the added strain of neuroinflammation that follows from air pollution, even at low levels of exposure.

It is important to note that the results from study II differ from a previous study on the Betula cohort (Oudin et al., 2019), which found that APOE-ε4 did *not* moderate the effects between air pollution and dementia. This discrepancy may be due to differences in methodology. For one thing, the follow-up period of study II was longer (up to 21 years) than in Oudin and colleagues' study (up to 15 years), and consequently, more people developed dementia over time (n=348) than in the study by Oudin and colleagues (n=275). Another difference is the measures of exposure. Oudin and colleagues (2019) used a land-use regression model to calculate NO_x levels from traffic-related sources, whereas study II used a dispersion model to calculate $PM_{2.5}$ levels from both local (e.g. road traffic) and regional sources.

The possible influence of APOE also needs to be considered in regard to the observed moderating effect of olfaction. The APOE-ε4 allele has been associated not only with dementia, but also with deficits in olfactory functions independent of dementia (Olofsson et al., 2010). Therefore, the moderating effect of olfaction found in study II could be a consequence of an overrepresentation of carriers of

the APOE-ε4 alleles among low performers on the odor identification test. However, the interaction between $PM_{2.5}$ and odor identification ability observed in study II remained the same when the model was adjusted for APOE status. This result indicates that odor identification ability and APOE status moderate the association between air pollution and dementia independently of each other.

Limitations and further directions

The studies presented in this thesis have many strengths. The data were drawn from a large, prospective cohort study, and the dementia diagnoses were based on medical records combined with additional information from health and cognitive testing. In addition, the modeled exposure data allowed for individual estimates of the exposures at participants' residential address, whereas many other studies in the field have used exposures on a neighborhood level. However, as with all research, the studies also have some noticeable limitations.

A setting with low exposure levels

Most studies in this field have been conducted in large urban areas with higher levels of air pollution exposure. Studies conducted in low exposure areas are less common, but nonetheless important in order to get a more complete picture of the association between air pollution and dementia. In study II, the annual mean $PM_{2.5}$ exposure at baseline was 6.77 $\mu g/m^3$; these levels in other studies have been e.g. 9.58 $\mu g/m^3$ in a nation-wide cohort study in the US (Shi et al. 2023), or 34 $\mu g/m^3$ in a Taiwanese study (Jung et al. 2015). The comparatively lower exposure levels in our setting can be viewed as a limitation because higher exposure levels should result in a higher number of cases attributed to air pollution, which would increase the likelihood of stronger association between air pollution and the outcome of interest. Even so, I would argue that the relatively low levels of exposure in this setting is in fact a major strength. One reason is that, if we are to get a better understanding of how the risk of dementia increases with increasing exposure to air pollution, then studies with varying levels of exposure are important. Furthermore, a setting with lower exposure can be very useful when trying to identify vulnerable subgroups, because the question "who are the first to suffer the consequences of increasing levels of exposure?" can then be asked and answered.

Exposure misclassification

As with all research on air pollution and health, the possibility of exposure misclassification needs to be addressed. It is important to note that the exposure measures used in this thesis provide estimates of exposure outside the residential address at baseline. But that is also all that the data can tell us. To get a more precise understanding of the impact of air pollutants on brain health, researchers

would need to get a better sense of exposure throughout the day. Workplace exposures to air pollution may contribute significantly to overall exposure, but this issue is something that these studies unfortunately have no information about. Someone living in a neighborhood with clean air may well spend his or her days working outdoors doing road construction on a highway. At the same time, the indoor home environment is also an important factor for which these studies lack information. Oudin and colleagues (2018) showed that living in areas where wood is commonly burned in stoves is associated with a higher risk for dementia, but *only* for those who themselves used a wood-burning stove. This observation highlights the importance of taking the indoor environment into account. It would also be beneficial to learn more about exposure at earlier places of residence, which is additionally something that these studies were unable to account for.

Identifying the composition of fine particulate matter

In studies II and III, $PM_{2.5}$ was used as measure of air pollution. Though this grade of particulate matter is commonly used to measure air pollution exposure, it does not give information on proportions of fractions with diameters less than 2.5 μm. It has been suggested, for instance, that ultrafine particles (those with a diameter of less than 0.1 μm) are particularly hazardous to our health, as their small size makes it physically possible for them to penetrate into body tissues. These particles also tend to be more reactive because of their larger surface-to-volume ratios (Cassee et al. 2013). Studies II and III also lack information regarding the chemical and physical properties of the particles. These properties determine how a particle is taken up by the body, a particle's ability to transfer to various tissue, how it is transported through the blood brain barrier, and the type of damage it may cause (Zoroddu et al., 2014; Heusinkveld, 2016). Some studies have investigated the effects of specific particles. For example, the inhalation of manganese dioxide has been associated with the formation of reactive oxygen species and oxidative stress in the brain (Zoroddu et al. 2014). In a large US study (n>18 million people), Shi and colleagues (2023) found an association between $PM_{2.5}$ exposure and dementia, and specifically that sulfate, black carbon, and organic matter were driving these associations. It seems clear that knowing more about the components of particle matter is important for gaining a deeper understanding of the links between airborne particles and brain health.

Exposure at different points over the life-span

Much of the research in this field has used outcomes that manifest themselves with older age, such as dementia or cognitive decline. This is also the case in this thesis, where studies I and II used dementia as the outcome variable, and the study samples only included those aged 55 years or older at baseline. As a result, the study populations in epidemiological studies on dementia tend to be older

adults, at which point it may be too late for any environmental interventions to be beneficial.

Meanwhile, research indicates that high exposure to air pollution early in life could affect cognitive functions in adult life (Russ et al. 2021), and maybe even the risk of dementia (Calderon-Garcidueñas et al. 2002). Research by Calderon-Garcidueñas et al. (2002, 2004, 2008) showed that exposure to air pollution can initiate accumulation of AD precursors via chronic brain inflammations at a young age, and this group concluded that "*neurodegenerative disorders such as Alzheimer's may begin early in life with air pollutants playing a crucial role*" (Calderon-Garcidueñas et al., 2002, p. 373).

It is critical that we learn at which age air pollution is most crucial for the later development of dementia, but this question will pose quite a challenge for epidemiological researchers, given that there are often many decades between air pollution exposure and dementia onset. Interestingly, Russ et al. (2021) used statistical models to estimate historical exposure levels in a Scottish cohort, going back to the 1930s, and showed an association between air pollution exposure *in utero* and slower increases in IQ in childhood and throughout adulthood. Grande et al. (2020) investigated air pollution and dementia in Stockholm and found a strong association between air pollution exposure and dementia if the exposure happened five years before dementia onset, but a weaker association if the exposure was 6–11 years before onset. The results from Grande et al. (2022) indicate that effects of air pollution may manifest themselves rather quickly, and that exposure later in life is also an important factor to consider. These studies demonstrate that air pollution may be associated with different outcomes in different stages of life.

Quasi-experimental study designs

The causal links between air pollution and brain health, as well as the role of possible mediators and moderators, remain unclear. Most studies on the association between air pollution and brain health have had an epidemiological approach and used observational research designs. However, observational studies cannot answer questions regarding causality. Though a number of animal experiments have been conducted, any experiments on human subjects are unfeasible for ethical and practical reasons. Therefore, the need of other study designs, such as quasi-experiments, has been highlighted (Dominici et al., 2014). One example of a quasi-experimental design looking at the association between air pollution and dementia is a recent US study in which the researchers found an association between improvements in air quality and a reduced risk for dementia in older women, which indicates that detrimental effects of air pollution on brain health may be reversible (Wang et al., 2022).

Socioeconomic status as a possible confounder

In studies I–III, it is speculated that some of the results may be influenced by SES, but we were not able to investigate this factor in greater detail. In this thesis, the exposure assessment is tied to a person's residential address. The neighborhood where a person lives may be linked to SES, which is a known risk factor for dementia (Livingstone et al. 2017). A suggested link between low SES and dementia is that people with lower SES might be more exposed to environmental risk factors such as air pollution (Hajat et al. 2015; Bodryzlova et al. 2022), because people with lower SES often reside in areas with higher levels of air pollution. Therefore, it is possible that SES is a possible confounder for the association between air pollution and dementia, and of course this aspect is something that needs to be investigated further.

Studies on SES and air pollution in Europe have not shown consistent results with studies done in other parts of the world (Hajat et al. 2015), and Sweden in particular seems to be a country where these associations are more complex (Stroh et al. 2005). Swedes with high SES may be more likely to take up residence in urban areas and city centers, i.e. areas with relatively high levels of air pollution. Therefore, if SES confounds the association between air pollution and dementia in the studies presented in this thesis, the true association between air pollution and dementia could be even stronger than these results show. That being said, all the studies in this thesis used statistical models adjusted for education. Of course, education in only one aspect of a multifaceted concept, even though education is often used as an indicator of SES (Geyer et al. 2006).

Conclusions and implications

This thesis further highlights the need to consider environmental exposures in studies on brain health, and cognitive functions. The overall results presented in this thesis indicate that even relatively low levels of long-term exposure to air pollution can increase the risk of dementia, and that there is no residual confounding effect from road traffic noise, at least not at the present low levels of noise. In addition, the APOE gene and odor identification ability were found to moderate the observed association between air pollution and dementia. Moreover, a positive association was found between air pollution and odor identification, which might be explained by SES and the links between odor identification and well-functioning semantic memory. Still, the causal links between air pollution, olfaction, and dementia remain unclear. There are likely several as-yet unidentified factors that could have moderating, mediating, or confounding effects on the association between air pollution and dementia. Therefore, more research is needed in order to further our understanding the mechanisms behind the detrimental effects of air pollution on the brain.

Moreover, it is important to more accurately identify those who are particularly vulnerable to these effects.

One way of interpreting these results, is that efforts need to be made to identify persons with poor olfactory functions and APOE-ε4 carriers, and encourage them to not reside in polluted areas. This approach is neither practical nor realistic. It is unlikely that these people would move from an urban area, solely based on a somewhat increased risk of dementia decades in the future. Instead, maybe these results should be seen yet as another argument for policy makers to reduce air pollution, even in areas with relatively clean air. A major source of $PM_{2.5}$ emissions is tire and road wear. Therefore, transitioning to electrical cars may not be enough to reduce the amount of health issues arising from air pollution. However, efforts to reduce road traffic in urban areas, would likely decrease the risk of dementia for these vulnerable sub populations, while simultaneously decrease the risk of e.g. cardiovascular and respiratory diseases for everyone.

Acknowledgements

"Generally speaking, people useless at everything else become academics."

— Steven Erikson, Dust of Dreams

When I first moved to Umeå back in the late 90's, we developed a longstanding tradition in my family. After spending the summers back home in Gästrikland, my parents would drive me back to Umeå for the start of the new semester. And every time - EVERY time - six hours in to a seven-hour drive, at the same stretch of road somewhere between Nordmaling and Hörnefors, my dad would draw a deep sigh, turn to me, and ask the same question: *"Couldn't you have found a school bench closer to home?"*. The answer to that question, as I've now come to realize, is *"I couldn't have found a* better *one."* As a workplace, the department of Psychology here in Umeå has been all that a doctoral student could wish for. Rarely have I gone to work and had the feeling was going to work, if that makes sense.

A colleague at the department once asked me who my supervisors were. I told him, and he asked "*Three of them? Why do you need so many supervisors?*" Well I guess some people just need more supervision… So, thank you, Anna Oudin, for your guidance through statistical methods and exposure modelling, and for dragging me along into various other projects, which have led me to travel strange and exotic places such as eastern Finland, southern Europe, northern America, and western Skåne. Thank you, Anna C Sundström, for sharing your knowledge in the field of aging and dementia, insights into all things Betula, invaluable feedback during the writing process of this thesis, and more than one lunch. And of course, my main supervisor Maria Nordin. Having a supervisor whose main fields of research include stress, health, and work-life balance, can be quite handy at times. Exposure to your patience, encouragement, and relentless optimism, have consistently shown statistically significant associations with a down-regulation of the activity in my hypothalamic-pituitary-adrenal axis, and subsequent decline in blood cortisol levels. I also want to thank Bertil Forsberg, Rolf Adolfsson, Steven Nordin, and David Segersson, for co-authorship and expertise.

Let's not forget the true heroes of this story: the participants of the Betula project. Thousands of them! All repeatedly volunteering their time and effort, getting nothing in return but a parking fee and an annual Christmas card. Mine is only one of more than thirty (!) PhD-theses made possible by their participation. Of course, my thoughts go out to Professor Lars-Göran Nilsson, founder of the Betula project, who sadly passed away recently, but rests assure the research he started is still very much alive.

Moving on. To anyone who, at any point during the months leading up to my thesis defense, had the misfortune of ending up next to me in the lunch room: I'm so sorry that happened to you. I thank you for your patience and support. Thank you, all past and present doctoral students, for listening to my endless ramblings and allowing me to listen to yours. Gustaf, Anna, and Frida, who all started at the same time as myself, and with whom I occupied doktorandstugan for two years: It's been a treat following your journeys, and having you tag along on mine. Johan and Mats: thanks for keeping me up to speed with the black- and death metal scene. Hats off the new guard! Thanks for AW's, pre-fika coffee breaks, post lunch walks, chatgroups, playlists, and in general providing a much-needed breath of fresh air to the PhD-student group. Go sports! Ingrid and the merry band of FONites: By Grabthar's hammer, our excursions into the fantastical and beyond have been a real lifesaver!

Friends, family, obviously. Goes without saying. People have asked how I've managed to write a thesis with three small children at home. Truth be told, kids do make things harder occasionally. But they also make things possible.

Finally. Most importantly. Camilla, tack för att du står ut med mig.

Epilogue

They rarely take the car for trips up north these days, not since the new railroad was built. It's less than five hours now, to see their grandchildren. As the train passes the station in Nordmaling, the man draws a deep sigh and turns to his spouse: "*But seriously, couldn't he have found a school bench closer to home?"*

Umeå, February, 2023.

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