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AMBIENT AIR POLLUTION AND TRANSPORTATION NOISE: HOW THEY AFFECT MENTAL HEALTH IN OLDER ADULTS

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Ambient Air Pollution and Transportation Noise: How They Affect Mental Health in Older Adults

Thesis for Doctoral Degree (Ph.D.)

By

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In memory of my mother

纪念我的母亲

Remember me, though I have to say goodbye

请记住我 虽然再见必须说

Remember me, don't let it make you cry

请记住我 眼泪不要坠落

For even if I'm far away, I hold you in my heart

我虽然要离你远去 你住在我心底

I sing a secret song to you each night we are apart

在每个分离的夜里 为你唱一首歌

Remember me, though I have to travel far

请记住我 虽然我要去远方

Remember me each time you hear a sad guitar

请记住我 当听见吉他的悲伤

Know that I'm with you the only way that I can be

这就是我跟你在一起 唯一的凭据

Until you're in my arms again, remember me

直到我再次拥抱你 请记住我

Lyrics from "Remember Me"

by Robert Lopez and Kristen Anderson-Lopez

歌曲《记住我》

Popular science summary

Mental health in an aging world

In recent decades, the aging of the population has led to a rapid demographic shift in many countries, with individuals over 65 years of age comprising 10% of the global population. Mental health issues among older adults are very common. With the aging process, cognitive function tends to decline, often resulting in memory problems, difficulties communicating, and personality changes that can gradually lead to a loss of independence; all of which are early signs of dementia. Additionally, older adults are a vulnerable population who may experience depression due to a variety of factors, including coexisting medical conditions, unhealthy lifestyles, or social isolation. These mental health issues not only reduce older adults' quality of life but also place a burden on families and society as a whole.

What is environmental pollution?

With the continuous acceleration of urbanization, people are inevitably exposed to high levels of environmental pollution, especially air pollution and noise pollution. More than 90% of the global population is exposed to air pollution, and more than 100 million European residents are exposed to high levels of transportation noise. Air pollution mainly includes particles suspended in the air and toxic gases. In this thesis, particulate matters were grouped by size: $PM_{2.5}$ (diameter ≤2.5μm) and PM_{10} (diameter ≤10μm). Nitrogen oxides (NO_x) are a family of the most common toxic gases, which are mainly produced during the incomplete combustion process of the engine. These suspended particles and gases may be inhaled into the body and cause negative health outcomes. Railway, road traffic, and aircraft are the major sources of urban transportation noise. These transportation noises may also increase the stress response in the human body and result in health issues. However, the impact of long-term exposure to environmental pollution on mental health among older adults remains unclear.

Our study population and data source

This doctoral thesis examined long-term exposure to air pollution in relation to cognitive function and depression among older adults, as well as the effects of transportation noise on cognitive decline and impairment. All the data used in this thesis were from the Swedish National study on Aging and Care-Kungsholmen (SNAC-K). A total of 3363 older adults living in Kungsholmen, the central area of Stockholm, participated in the SNAC-K baseline assessment between 2001 and 2004. Later, we conducted follow-up assessments at regular intervals to observe participants' neuropsychological and mental states. We collected data on long-term exposure to air pollution and transportation noise based on participants' home addresses at baseline and during follow-ups.

How does environmental pollution influence mental health in late life?

Our findings suggest that long-term exposure to low-to-medium levels of $PM_{2.5}$ was associated with faster cognitive decline, particularly in those >80 years and those with cerebrovascular diseases. In addition, long-term exposure to air pollution was also associated with cognitive impairment. Notably, among older adults who are cognitively impaired, long-term exposure to air pollution was linked to an increased risk of developing dementia. Long-term exposure to air pollution was also related to an elevated risk of depression in older adults, but high social activities may offset this risk. We also found that railway noise was associated with an accelerated rate of cognitive decline over time. Long-term exposure to railway and aircraft noise was also associated with cognitive impairment onset, but we did not find an association between road traffic noise and cognitive outcomes in older adults.

Why do our findings matter?

Our ultimate goal is to achieve healthy aging for older adults, as people in late life are very susceptible to chronic diseases. A better understanding of modifiable environmental risk factors for mental disorders can help public health authorities reduce the disease burden by generating policies and regulations to control the levels of environmental pollution in residential areas for older adults. Moreover, promoting beneficial lifestyles or mitigating cardiovascular burdens on mental health could help individuals counteract the risk of environmental pollution to mental health among older adults.

老龄化世界的心理认知健康

在过去几十年里，许多国家的人口结构逐渐呈现老龄化趋势。10%的世界人口已经超过了 65 岁及以上。瑞典的老年人口比例也在不断增加。然而，老年人的心理认知健康问题非常常见。随着年龄的增长，人们的认知功能通常会逐年下降。许多老年人开始出现记忆力减退、表达困难或性格变化等问题，逐渐失去自理能力，这些都是失智症的早期症状。此外，老年人也是抑郁症的高风险人群。引起老年抑郁症的因素有多种，例如共发基础疾病、不健康的生活方式以及社交缺失等。这些心理认知健康问题不仅会影响老年人的生活质量，还会给家庭和社会带来巨大疾病负担。

什么是环境污染？

随着城市化进程的不断加速，人们难以避免地接触到环境污染，尤其是空气和噪声污染。对于城市居民来说，这些污染主要来自于交通运输。据统计，超过 90%的全球人口暴露在污染的空气中，而且超过 1 亿欧洲居民暴露在高水平的交通噪声中。空气污染主要包括悬浮颗粒物(PM)和有毒气体，其中根据颗粒大小通常分为 $PM_{2.5}$（直径≤2.5 微米）和 PM_{10}（直径≤10 微米）。氮氧化物（NO_x）是其中最常见的有毒气体，它主要产生于发动机的不完全燃烧过程。这些悬浮颗粒物和有毒气体可能被吸入体内，对健康造成危害。城市中的交通噪声主要来自于轨道、道路和航空交通。这些交通噪声可能会增加人体应激反应从而造成健康问题。然而，在老年人群中，长期的环境污染暴露对心理认知健康的影响仍有待于研究。

研究人群和数据来源

本篇博士论文探讨了空气污染对老年人认知功能和抑郁症的影响，以及交通噪声对认知功能下降和认知损伤的影响。所有相关数据均来源于瑞典国家老龄化与护理研究-国王岛人群（SNAC-K）。国王岛位于斯德哥尔摩市中心，共有 3363 位老年人在 2001 至 2004 年间参加了 SNAC-K 基线调查。随后，研究人员每隔几年对他们进行随访调查，以观察他们的心理认知状态。我们根据 SNAC-K 参与者在基线和随访期间的居住地址信息，收集了他们长期暴露于空气和交通噪声污染的数据。

环境污染对老年人群的心理认知有什么影响？

我们的研究结果表明，长期暴露于中低水平 $PM_{2.5}$ 与认知功能快速下降存在一定关联，尤其在 80 岁以上和患有心脏病的人群中更为明显。老年人长期暴露于悬浮颗粒物和氮氧化物都与认知功能障碍的风险增长相关。值得注意的是，对于已经患有认知障碍的老年人，长期暴露于空气污染会增加他们发展为失智症的风险。长期暴露在较高水平悬浮颗粒物和氮氧化物的环境中还会增加老年人抑郁症的风险，但积极的进行社交活动可能可以抵消空气污染带来的风险。此外，长期暴露在高水平的轨道交通造成的噪声会加速老年人认知功能下降的速度，轨道和航空交通也与新发认知功能障碍相关，但我们并没有发现道路交通与老年认知结局的关联。

为什么我们的发现很重要？

我们的最终目标是让人们健康老去，而老年人很容易患上慢性病。 更好地了解心理认知障碍的可改变环境风险因素可以帮助公共卫生部门通过制定政策和法规来控制老年人居住区的环境污染水平，从而减轻疾病负担。此外，倡导有益的生活方式或减轻心血管对心理健康的负担可以帮助老年人减轻环境污染对心理认知造成的风险。

Abstract

Whether environmental factors are associated with mental health issues among older adults remains unclear. This doctoral thesis aimed to determine the extent to which air pollution and transportation noise affect mental health in older adults. We used data from the Swedish National study on Aging and Care-Kungsholmen (SNAC-K).

Study I $PM_{2.5}$ was not linearly associated with faster cognitive decline over 12 years of follow-up. A significantly increased risk of faster cognitive decline was observed for low levels of $PM_{2.5}$ (<8.6μg/m^3) among the oldest-old group (OR 1.81; 95% CI: 1.02–3.22). The existence of cerebrovascular diseases further enlarged the risk.

Study II During follow-up, 15% of cognitively intact participants developed CIND, and 19% of cognitively impaired participants developed dementia. We observed 75%, 8%, and 18% increased risk of CIND onset corresponding to $PM_{2.5}$, PM_{10} (both per 1μg/m^3), and NO_x (per 10μg/m^3), respectively. Similarly, a higher hazard of progression from CIND to dementia was observed for exposure to higher levels of air pollution.

Study III Out of a total of 2812 participants, 137 initially depression-free participants were diagnosed with depression during follow-up. Exposure to higher levels of $PM_{2.5}$ and PM_{10} (per 1μg/m^3) and NO_x (per 10μg/m^3) were associated with 53% (HR 1.53; 95% CI: 1.22–1.93), 7% (HR 1.07; 95% CI: 0.98–1.18), and 26% (HR 1.26; 95% CI: 1.01–1.58) increased risk of depression, accordingly. Importantly, the hazardous effects of air pollution were attenuated among participants with high social activity.

Study IV A higher level of aircraft noise was associated with a faster annual rate of cognitive decline (β -0.007; 95% CI -0.012 to -0.001) over 16 years of follow-up. Higher levels of railway and aircraft noise exposure were associated with a 25% (HR 1.25; 95% CI 1.01–1.55) and 16% (HR 1.16; 95% CI: 0.91–1.49) higher hazard of developing CIND. However, no association was found between road traffic noise and cognitive outcomes.

Conclusions Long-term exposure to air pollution was associated with an increased risk of faster cognitive decline, cognitive impairment, and its progression to dementia, as well as depression incidence in older adults. Aircraft noise may be associated with worsening global cognition and cognitive impairment. Railway noise was associated with an increased risk of cognitive impairment. No evidence supported the relationship between road traffic noise and cognitive outcomes. These findings suggest air pollution and transportation noise may be risk factors impacting the mental well-being of older adults.

Keywords: air pollution, particulate matter, nitrogen oxides, transportation noise pollution, cognitive impairment, dementia, cognitive decline, depression.

List of scientific papers

I. Grande G*, **Wu J***, Ljungman PL, Stafoggia M, Bellander T, Rizzuto D. Long-term exposure to $PM_{2.5}$ and cognitive decline: a longitudinal population-based study. *Journal of Alzheimer's Disease*. 2021 Jan 1; 80(2):591–9.

II. **Wu J**, Grande G, Stafoggia M, Ljungman P, Laukka EJ, Eneroth K, Bellander T, Rizzuto D. Air pollution as a risk factor for Cognitive Impairment no Dementia (CIND) and its progression to dementia: A longitudinal study. *Environment International*. 2022 Feb 1; 160:107067.

III. **Wu J**, Grande G, Triolo F, Pyko A, Laukka EJ, Sjöberg L, Ljungman P, Eneroth K, Bellander T, Rizzuto D. Air pollution and depression in older adults: Results from a Swedish population-based cohort study. *Manuscript submitted*.

IV. **Wu J**, Grande G, Pyko A, Laukka EJ, Pershagen G, Ögren M, Bellander T, Rizzuto D. Long-term Exposure to Transportation Noise in Relation to Global Cognition Decline and Cognitive Impairment: Results from a Swedish Longitudinal Cohort. *Manuscript submitted*.

**Equal contribution*

Other scientific papers related to the topic of this doctoral thesis

I. **Wu J**, Xiong Y, Xia X, Orsini N, Qiu C, Kivipelto M, Rizzuto D, Wang R. Can dementia risk be reduced by following the American Heart Association's Life's Simple 7? A systematic review and dose-response meta-analysis. *Ageing Research Reviews*. 2022 Nov; 9:101788.

II. Imahori Y, Vetrano D, Ljungman P, Laukka EJ, **Wu J**, Grande G, Rizzuto D, Fratiglioni L, Qiu C. Association of ischemic heart disease with long-term risk of cognitive decline and dementia: a cohort study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. 2023

Contents

List of abbreviations

$\mu g/m^3$	One-millionth of a gram per cubic meter
AD	Alzheimer's disease
APOE ε4	Apolipoprotein E-4
CI	Confidence interval
CIND	Cognitive Impairment No Dementia
CO	Carbon monoxide
COVID-19	COronaVIrus Disease of 2019
CPRS	Comprehensive Psychopathological Rating Scale
CSHA	Canadian Study of Health and Aging
dB	Decibel
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EPA	Environmental Protection Agency
EU	European Union
GDP	Gross domestic product
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
ICD	International Classification of Diseases
ICE	Internal combustion engine
IPW	Inverse probability weighting
IQR	Interquartile range
$L_{Aeq,24h}$	A weighted, equivalent continuous sound pressure level for 24 hours
L_{den}	Day-evening-night weighted wound pressure level
L_{night}	Equivalent continuous sound pressure level during nighttime
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
MYHAT	Monongahela-Youghiogheny Healthy Aging Team
NDVI	Normalized difference vegetation index
NO	Nitric oxide
NO_2	Nitrogen dioxide
NOx	Nitrogen oxides
NPR	Swedish National Patient Register
O_3	Ozone
OR	Odds ratio
PM_{10}	Particulate matter with a diameter of 10 micrometers or less
$PM_{2.5}$	Particulate matter with a diameter of 2.5 micrometers or less
ppb	Parts per billion
ppm	Parts per million
SALSA	Sacramento Area Latino Study on Aging
SD	Standard deviation
SDGs	Sustainable Development Goals
SES	Socioeconomic status
SNAC-K	Swedish National study on Aging and Care in Kungsholmen
SO_2	Sulfur dioxide
US	United States
VOC	Volatile organic compounds
WHO	World Health Organization
β	Coefficient for global cognition scores

1 Introduction

1.1 Living longer: opportunities or challenges?

People are living longer than ever. The global population's average life expectancy has increased exponentially since the beginning of the 20th century and is now over 70 years.(1) According to World Bank statistics, in 2019 about 10% of the world's population was aged ≥65 years, and this share is projected to more than double by 2050.(2) Unfortunately, due to the global coronavirus (COVID-19) pandemic, estimated life expectancy at 65 years of age for 2020 was reduced in the US and Eastern Europe.(3,4)

The swift trend toward an aging population over the last half-century presents immense societal challenges both in Sweden and around the world.(5) Sweden is known for having one of the largest proportions of older people in the world.(2) Notably, the segment of the Swedish population aged ≥85 years is growing at the fastest rate.(2) However, the lifetime accumulation of chronic conditions and physical limitations results in a greater demand for formal or informal care and medical resources in people's elderhood, which places a greater burden on families and societies, especially given the growth of the aging population.

1.2 Mental Disorders in older age

1.2.1 Cognitive decline, cognitive impairment, and dementia

Along with global aging, the number of people suffering from Alzheimer's Disease (AD) and related dementia will dramatically increase, with burdensome consequences at both individual and societal levels. The World Health Organization (WHO) in 2018 reported that over 50 million people lived with dementia globally, and there was a net annual increase of about 10 million cases.(6) The number of prevalent dementia cases is projected to reach 82 million in 2030 and 152 million in 2050.(6) In Sweden, the dementia prevalence was high, affecting about 25% of people >75 years of age.(7) The costs of health services for individuals with dementia are high and are increasing further, reaching nearly 818 billion US dollars in 2015, which is equal to about 1.1% of the global gross domestic product (GDP).(8) Individuals with dementia have an up to 6-fold higher mortality rate compared to those without dementia, and the mean survival time was about 6 years after a clinical dementia diagnosis.(9) Distressingly, to date, disease-modifying treatment for dementia is limited and a very small number of medications have reached satisfactory results.

Over the past few decades, many efforts have been made to identify modifiable risk factors for dementia and major indicators that can aid in early diagnosis of the condition.(10,11) This is also justified by the fact that the pathophysiological changes of dementia start several years (or even decades) before its clinical manifestation.(12)

However, the progression of cognitive impairment may not always follow a linear pattern. Indeed, population-based studies have reported that about 29%–55% of cognitively impaired cases revert to normal cognition.(13,14) Therefore, the long prodromal phase is considered the critical window for disease-modifying prevention and intervention. While it is crucial to track cognitive patterns to identify clinically meaningful individual cognitive decline, there is still an ongoing debate regarding how to operationalize clinical concepts that can effectively describe the various pre-diagnostic phases of dementia.

The definition of cognitive impairment no dementia (CIND) was first proposed by Graham et al. in 1997, and was validated using data from the Canadian Study of Health and Aging (CSHA).(10) CIND describes individuals with the presence of cognitive deficits who do not meet a clinical diagnosis of dementia. CIND can significantly predict half of the cases that would progress to dementia within 5 years.(15) The definition of CIND usually involves cognitive deficits in cognitive domains that not only focus on memory but also language, executive function, perceptual speed, and visuospatial ability. So that the ability of CIND could elaborately identify subtle changes in cognition has gained popularity in epidemiological research.

1.2.2 Depression in late life

Depression is a widespread mental health condition across all stages of life. In 2017, WHO ranked it as the third leading cause of the burden of disease, affecting more than 264 million people globally.(16,17) Depression affects about 1%–4% of the population >60 years of age and about 4.6%–9.3% of the population >75 years of age.(18,19) In addition, depression was associated with 73% higher direct costs in older adults than those without depression.(20)

Even though depression is common in older adults, underdiagnosed and untreated mental conditions are not rare. Late-life depression is linked to higher risks of morbidity and suicidality, as well as decreased cognitive, social, and physical functioning, which can ultimately contribute to higher mortality rates.(21–23) Due to these devastating consequences, depression is definitively an important public health problem.

Depression was usually diagnosed with the presence of specific symptoms that last at least two weeks, including low mood or irritability; decreased interest or pleasure in most daily activities; dramatic weight gain or loss; change in sleep patterns; fatigue; restlessness or slowed movements; emotions of shame or inadequacy; concentration problems; and suicidality.(24) However, older adults with depression usually present different symptoms compared to younger adults. For instance, late-life depression cases are prone to showing cognitive shifts, physical symptoms, and apathy but rarely endorse affective symptoms.(25)

1.3 The theoretical framework of social determinants on mental health

Identifying factors that may cause disease is always prioritized in public health prevention. Social determinants refer to factors that are not related to medical conditions but can largely impact the ways in which people are born, reside, are employed, and age, and the systems that shape the circumstances of their everyday lives.(26) These are all in turn closely related to health outcomes and well-being in the population throughout the life course.(26) Social, environmental, and behavioral factors have previously been conceptualized as the upstream determinants of mental health.(27) Importantly, major social determinants of mental disorders were in line with many of the Sustainable Development Goals (SDGs) proposed by the United Nations in 2015 (**Figure 1**) to overcome the challenges of poverty, hunger, inequality, and climate change. These determinants include domains of both social and cultural factors, demographics, economics, neighborhood, and environmental events.(28)

As the population continues to age and the number of people affected by mental disorders inevitably increases, it becomes crucial to identify modifiable risk factors for mental well-being at an early stage to prevent the onset of these conditions. Recently, much attention has been paid to identifying modifiable environmental risk factors of mental health, as they inform higher-order changes at the group or policy level. A growing body of evidence identified nine modifiable risk factors for dementia, including lack of education, smoking, diabetes, physical inactivity, low social contact, hypertension, hearing impairment, obesity, and depression.(29) Similarly, many risk factors linked to late-life depression have been identified, such as genetic vulnerability, stressful events, and inflammation biomarkers.(30–33) In 2020, air pollution was added as an important risk factor for dementia by the Lancet Commission on dementia prevention, intervention, and care.(11) A growing body of evidence also supports the harmful effect of environmental factors (e.g., low greenspace accessibility and air pollution) on depression.(34,35)

Overall, based on the framework of social determinants on mental health, this doctoral thesis has a specific focus on discussing ambient air pollution and transportation noise in relation to mental health among older adults.

Figure 1 A framework of social and cultural determinants of mental disorders and the UN's SDG adapted from *Lund et al. 2018.*(28)

1.4 Environmental pollution at a glance

1.4.1 Ambient air pollution

Air pollution is the biggest environmental health hazard globally, causing approximately 4.2 million deaths around the world every year.(36) Long-term exposure to air pollution also exacerbates a variety of diseases and previous evidence has linked it to respiratory, cerebrovascular, and cardiovascular diseases, and lung cancer.(37–39) Susceptible populations include children, older adults, people with lower socioeconomic status, and people with pre-existing chronic diseases.(40)

The key contributor to air pollution is the combustion of fossil fuel; primarily stemming from road traffic, households, and energy production. In general, air pollution is a mixture of substances, including solid particles and gases. Particulate matter (PM) describes

small solid particles and fluid globules that are suspended in the air. Particle pollution is often categorized according to its size. Inhalable particle describes PM with a diameter of 10 micrometers or less (PM_{10}) and fine inhalable particle describes PM with a diameter of 2.5 micrometers or less ($PM_{2.5}$). The most common ambient gaseous air pollutants are nitrogen oxides (NO_x), sulfur dioxide (SO_2), ozone (O_3), and carbon monoxide (CO). In atmospheric chemistry, 'nitrogen oxides' are a general term for nitric oxide (NO) and nitrogen dioxide (NO_2), because the conversion between these two substances is rapid in the stratosphere and troposphere. When the temperature rises inside the internal combustion engine (ICE) of a vehicle or a power plant boiler, NO_x is generated during the incineration of a mixture of fuel and oxygen in the air. Also, a secondary pollutant from photochemical smog—ozone—is formed when NO_x and other air pollutants react with volatile organic compounds (VOC) while exposed to sunlight. SO_2 is today mostly controlled by removing sulfur from fuels before burning, which is also called 'fuel-gas desulfurization'. CO is usually a temporary pollutant in urban environments, originating chiefly from ICE exhaust and incomplete burning of other fuels, for instance, wood, coal, and diesel. CO also participates in the chain of chemical reactions that form photochemical smog.

Table 1 World Health Organization's (WHO) air quality guidelines, the US Environmental Protection Agency (EPA) standards, and The European Union's (EU) standards for outdoor air pollution in 2005.

Lengths	World Health Organization's guidelines					US Environmental Protection Agency standards						European Union standards					
	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	CO
1 year	10 *	20 *	40 *	-	-	12 *	-	53 **	-	-	-	25 *	40 *	40 *	-	-	-
10 minutes	-	-	-	500 *	-	-	-	-	-	-	-	-	-	-	-	-	-
1 hour	-	-	-	-	-	-	-	-	75 **	-	35 ***	-	-	200 *	350 *	-	-
3 hours	-	-	-	-	-	-	-	-	0.5 ***	-	-	-	-	-	-	-	-
8 hours	-	-	-	-	100 *	-	-	-	-	0.07 ***	9 ***	-	-	-	-	120 *	10 *
24 hours	25 *	50 *	200 *	20 *	-	35 *	150 *	100 **	-	-	-	-	50 *	-	125 *	-	-

*Unit indicators: *μg/m³: micrograms (one-millionth of a gram) per cubic meter of air; **ppb: parts per billion; ***ppm: parts per million. Unit conversion: 1ppb =0.001ppm. $PM_{2.5}$: particulate matter with a diameter of 2.5 micrometers or less; PM_{10}: particulate matter with a diameter of 10 micrometers or less; NO_2: nitrogen dioxide; SO_2: sulfur dioxide; O_3: ozone.*

With technological development and the implementation of clean air actions, the European Environment Agency reported that air quality has improved substantially over

the last few decades.(41) However, emerging evidence has linked an increasing range of air pollution at ever-lower concentrations with adverse health outcomes, which was especially observed for PM.(42) Of note, there is no suggested safe limit PM or ozone levels for human health.(42) In 2005, WHO, in accordance with the available scientific evidence, established guidelines on ambient air pollution levels that have been widely adopted by policymakers around the world to make management decisions and create goal lines to reduce and control air pollution. **Table 1** shows WHO guidelines in comparison to US and the European Union (EU) standards. With the increasing knowledge of the harmful effect of air pollution on health, together with the goals to achieve sustainable development for climate change, a new guideline was introduced by WHO in 2021.(43) According to the updated guidelines, almost all of the world's population (about 99%) live in places that do not comply with the air quality standard.

1.4.2 Noise pollution

Another overlooked environmental pollution is noise—which is always accompanied by air pollution and impacts millions of people on a daily basis, especially the urban-dwelling population. Noise is an unwanted sound that is pervasive in everyday life. Road traffic is also the main contributor to transportation noise, together with railway and aircraft noise in certain areas. The European Environmental Agency reported that there are more than 100 million Europeans exposed to environmental noise exceeding WHO recommended levels.(44) Decibel (dB) is the unit of measured sound pressure and is presented on a logarithmic scale. **Table 2** shows the detailed WHO environmental noise guidelines for the European Region alongside the strength of their recommendation.(45)

Table 2 Environmental noise guidelines for the European Region.

Noise sources	Exposure time	Guideline levels	Strength
Road traffic noise	Average	53 dB L_{den}	Strong
	Night	45 dB L_{night}	Strong
Railway noise	Average	54 dB L_{den}	Strong
	Night	44 dB L_{night}	Strong
Aircraft noise	Average	45 dB L_{den}	Strong
	Night	40 dB L_{night}	Strong
Wind turbine noise	Average	45 dB L_{den}	Conditional
Leisure time	Average	70 dB $L_{Aeq,24h}$	Conditional

dB: decibels; L_{den}: Day-evening-night-weighted sound pressure level; L_{night}: Equivalent continuous sound pressure level during nighttime. L_{Aeq}24h: A-weighted, equivalent continuous sound pressure level for 24 hours. A-weighting: a frequency-dependent correction that is applied to a measured or calculated sound of moderate intensity to mimic the varying sensitivity of the ear to sound for different frequencies.

Noise has both auditory and extra-auditory effects on health. Tinnitus and hearing loss are known auditory effects, which can be triggered by an acute one-time exposure to an extreme sound, such as gunfire, or by chronic long-term exposure to sound exceeding L_A 75–85dB. The most explored non-auditory outcomes for higher levels of noise exposure are perceived annoyance and disturbance, reduced cognitive performance in children, insomnia, and metabolic disease.(46–48)

1.5 Environmental pollution and mental health

1.5.1 Air pollution and cognitive function

An increasing body of evidence suggests that long-term exposure to air pollution raises the possibility of developing neurological disorders such as Alzheimer's disease and related dementia types. In a recent critical review by Juana and colleagues, a total of 69 recently published studies were included, showing that higher levels of air pollution exposure were consistently associated with an increased risk of dementia.(49) However, the results reporting air pollution in relation to cognitive decline and impairment are, overall, mixed and inconclusive.(49) The association between long-term exposure to PMs and cognitive impairment was studied most often. An almost tripled risk of cognitive impairment for a 1μg/m^3 increase in $PM_{2.5}$ was reported using data from The Monongahela-Youghiogheny Healthy Aging Team (MYHAT).(50) Findings from the Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes showed exposure to high levels of $PM_{2.5}$ (>12μg/m^3) was associated with an 81% increased hazard of faster cognitive decrease compared to those who are exposed to low levels of $PM_{2.5}$ (≤12μg/m^3).(51) Results from Chinese surveys also revealed a similar association for PMs.(52–55) However, other studies did not observe the relationship between long-term exposure to $PM_{2.5}$ and cognitive impairment.(56,57) The association between NO_x and impaired cognitive function, on the other hand, has not been studied in longitudinal settings.(49)

Whether air pollution could influence the progression from cognitive impairment to dementia has not yet been explored. Only one very recent Italian study using data from 53 MCI cases reported a potential non-linearly increased risk of dementia for exposure to high levels of PM_{10}, but the link was not statistically significant due to a lack of statistical power.(58)

Higher levels of long-term exposure to air pollution were also linked to a faster decline in global cognition. The Nurses' Health Study Cognitive Cohort demonstrated that every 10μg/m^3 increment in $PM_{2.5}$ corresponded to a 0.018 standard-unit of decline in global cognitive score.(59) Another study from the US integrated two longitudinal cohorts in the northern Manhattan area of New York City, showing PM and NO_2 were associated with significantly faster global cognitive decline, but these findings were only evident in one of the cohorts with a larger sample size but not the other.(60) A faster decrease in

Mini-Mental State Examination (MMSE) over the follow-up period was found for higher exposure to $PM_{2.5}$ but not for NO_2.(61) More specifically, the rate of decrease in the domain of memory has been explored for long-term exposure to air pollution, but no significant association was observed.(62,63)

1.5.2 Air pollution and depression

To date, many epidemiological studies have been carried out to study the association between air pollution and depression, and the association remains controversial.(35) A meta-analysis pooled 22 eligible studies from 10 countries, showing long-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 were associated with 12%, 4%, and 5% increased risk for depression in the general population, respectively, but none of these associations achieved statistical significance.(35) However, most of the included studies were cross-sectional and few focused on late-life depression.(35) Some large ecological studies in Germany,(64) Canada,(65) and China(66) found that exposure to high levels of air pollution was linked to a high tendency of hospital admission for depression. Recently, longitudinal studies found that long-term exposure to $PM_{2.5}$ was associated with an increased risk of late-life depression,(67–71) and increased depression symptoms;(72) but some did not observe such associations.(73,74) Also, most of the studies did not control for other important environmental factors; for instance, transportation noise and greenspace.(67–69,71,75) These factors have been closely associated with air pollution exposure as well as mental well-being. The discrepancy of the results was not only due to the study design and lack of adjustment to the environmental confounding factors, but also to the short-term follow-ups and differences in air pollution assessments.

1.5.3 Transportation noise and cognitive function

Previous research on transportation noise and cognitive performance was mostly in school children, while exposure to transportation noise pollution in relation to cognitive decline and cognitive impairment in older adults has rarely been examined and existing evidence mostly comes from cross-sectional studies.(76) Ecological studies have shown that living close to an airport with high noise from aircraft was related to a high rate of psychiatric hospital admission.(77,78) Among the small number of longitudinal studies that explored transportation noise pollution and cognition in older adults, noise from aircraft and railways has not yet been studied. Only one longitudinal study investigated the association between overall community noise and the rate of change in global cognition among older adults, and they did not find a significant association.(79) Cross-sectional studies also showed similar nonsignificant results.(80,81) Moreover, general environmental noise was cross-sectionally associated with an increased risk of mild cognitive impairment.(79,82) Results from longitudinal analyses showed road traffic noise was marginally associated with cognitive impairment or dementia incidence.(83) Taken together with the evidence related to noise and cognitive outcomes, studies

using longitudinal data and source-specific noise information are urgently needed to address this research gap.

1.6 The biological mechanisms

The causal direct effect of air pollution and noise on brain functioning is biologically plausible. Data from animal models indicate that environmental stressors including air and noise pollutions entail both direct and indirect biological pathways of adverse health outcomes.(84,85) Concerning air pollution exposure, the size and composition of the particles are important aspects in determining whether they are inhalable and where they are deposited in the respiratory tract. Fine particles may enter the olfactory bulb and travel directly into the brain, leading to several pathological processes and the deposition of amyloid plaques,(84,86) suggesting that air pollution may contribute to Alzheimer-like dementia development.(86) Air pollution also has a well-established association with cardio- and cerebrovascular diseases,(87) and higher cardiovascular morbidity is strongly linked to an increased risk of mental disorders.(19,88) Therefore, the hypothesis regarding the role of cardio- and cerebrovascular pathways is grounded in the association of air pollution and mental disorders. In addition, air pollution may induce pro-inflammatory irritation that acts on the lining of the nasal epithelium and deep into the lungs. These reactions may cause the release of cytokines that indirectly act on the brain. Thus, based on the biological hypotheses, several potential effect modifiers and/or mediators have been explored in some epidemiological studies, including *Apolipoprotein E-4 (APOE ε4),*(89–91) cardiovascular disease,(92,93) cerebrovascular diseases, smoking, and metabolic dysfunction.(94)

Additionally, environmental stressors, such as air pollution and noise may activate the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system and respond to these stress reactions, for instance, by chronically releasing glucocorticoid stress hormones (i.e., cortisol and catecholamines), leading to the subsequent induction of inflammation and oxidative stress.(95) As the brain is very sensitive to stress, high levels of stress hormones may affect mental health and chronic stress can cause biochemical and structural alteration in the brain. The physiological stress response systems could also be overloaded when the HPA axis is chronically activated and/or impaired.(95) On the other hand, consistent results showed that a lack of social activity increased the risk of depression due to an increased stress response,(96,97) and active social engagement was protective against depression.(98) Environmental stressors may also act synergistically through the same mechanism. Thus, it is possible to assume that ample social activities may potentially mitigate the effect of environmental stressors on depression, but no previous study has tested this hypothesis.

1.7 Knowledge gaps

To sum up, existing evidence has not yielded consistent results on the association between long-term air pollution and transportation noise exposures and mental health outcomes among older adults. Most results were from cross-sectional studies, used screening instruments instead of clinical diagnosis, with short follow-up times in longitudinal settings, or with residual confounding from other environmental exposure. There is no previous study that investigated the role of long-term environmental exposures on the conversion of cognitive impairment to dementia. In addition, factors that might play a role in such associations are not well studied. Thus, the research gaps need to be filled by longitudinal studies with long follow-up times, comprehensive evaluations of the outcomes, and sufficient information on various confounders.

1.8 Hypotheses

Based on the knowledge, we formulated the following hypotheses (**Figure 2**): 1) long-term exposure to environmental pollution (air pollution and transportation noise) has adverse effects on cognitive decline, cognitive impairment, and depression among urban-dwelling older adults; 2) long-term exposure to air pollution might accelerate the progression from cognitive impairment to dementia; 3) cardio- and/or cerebrovascular diseases play important roles in these associations through pathological changes; 4) a favorable lifestyle may counteract the potential risk triggered by environmental pollution.

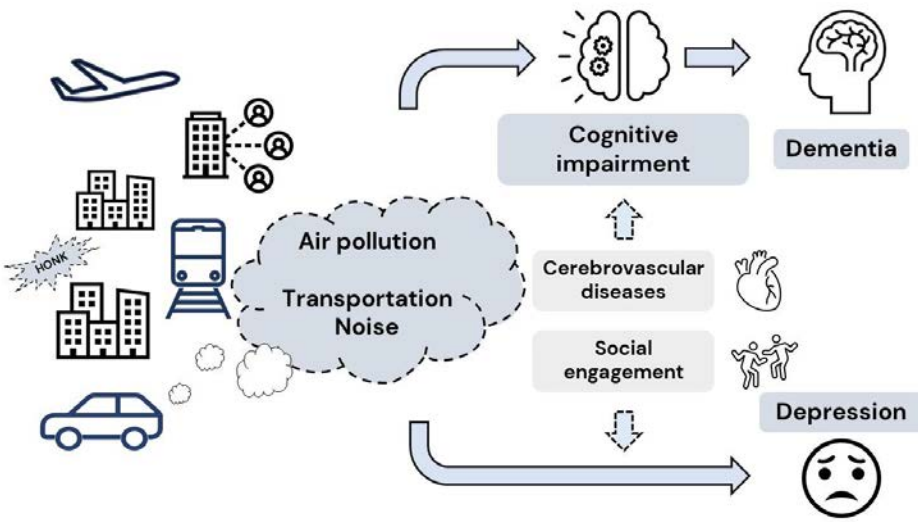

Figure 2 The illustration of the hypotheses pertaining to long-term exposure to air pollution and transportation noise in relation to mental health among older adults.

2 Research aims

2.1 Overall aim

The overarching aim of the current thesis is to understand the extent to which long-term exposure to air pollution and transportation noise could affect mental health among older people.

2.2 Specific aims

Study I To determine the impact of exposure to air pollution on cognitive performance in older adults and assess the role of cerebrovascular diseases in these associations.

Study II To evaluate the relationship between exposure to air pollution and cognitive impairment among older adults, and the role of air pollution on the progression from cognitive impairment to dementia.

Study III To understand the association between air pollution and depression in older adults and whether social engagement played a positive role in these associations.

Study IV To assess whether long-term exposure to transportation noise from aircraft, road traffic, and railways may affect global cognition and cognitive impairment in older adults.

3 Materials and methods

3.1 Study population

This doctoral thesis used data from an ongoing longitudinal population-based cohort: the Swedish National study on Aging and Care in Kungsholmen (SNAC-K). Individuals aged 60 years and above who lived in the Kungsholmen district of Stockholm were randomly selected based on eleven age cohorts. A total of 4590 eligible individuals were invited to participate in the study. During the baseline period of 2001 to 2004, overall, 3363 individuals were recruited to the cohort (response rate: 73.3%). We scheduled two types of follow-up schemes for the SNAC-K participants (**Figure 3**): every six years for the young-old cohorts (60, 66, and 72 years) and every three years for the old-old cohorts (78, 81, 84, 87, 90, 93, 96, and ≥99 years).

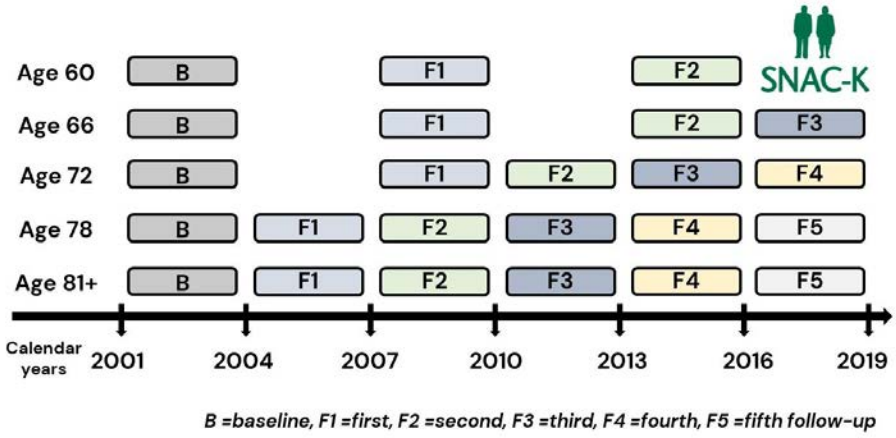

Figure 3 The study population and assessment waves of the SNAC-K study.

3.2 Analytical samples

Figure 4 presents the flowchart of study samples in each of the four studies. In *Study I,* we included 2253 dementia-free participants to examine the change in cognitive performance during follow-up (2001-2016). In *Study II & Study IV*, a total of 2594 dementia-free participants were included at baseline. Those individuals were included in *Study IV* to assess the rate of change in global cognition during the year 2001-2019. After this, two study sub-cohorts were formed for assessing different outcomes: 1) 1987 cognitively intact cohort for incident CIND (*Study II* during 2001-2013 & *Study IV* during 2001-2019); and 2) 607 CIND cohort for incident dementia (*Study II* during 2001–2013). In *Study III*, 2812 depression-free participants were included for assessing incident depression during 2001–2013.

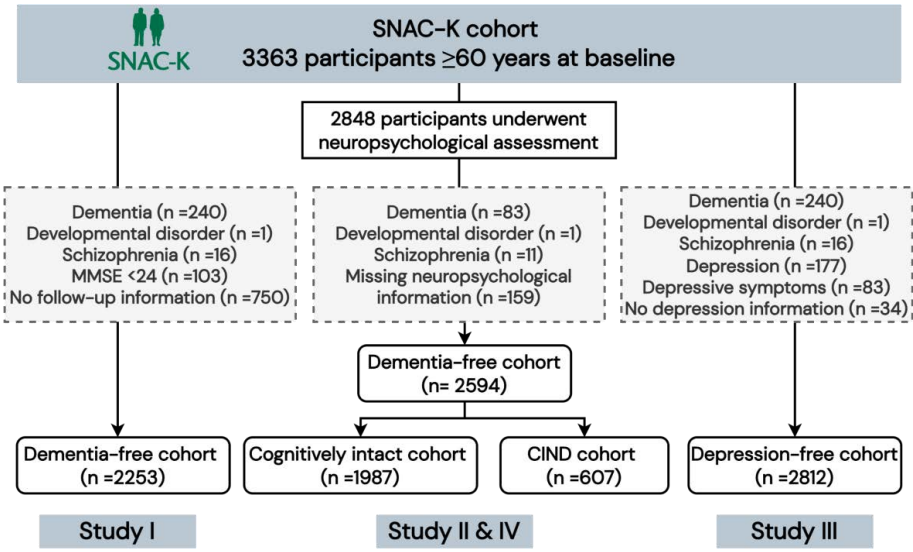

Figure 4 Flowchart of the analytical samples included in Studies I–IV at baseline.

The gray boxes were excluded from the analyses according to the exclusion and inclusion criteria corresponding to the study's aims.

3.3 Data collection

All participants underwent examinations lasting an average of six hours at baseline and four hours during follow-up by trained staff via face-to-face interviews based on a standard examination protocol. Information related to demographics (age, sex, education, current/previous occupation, marital status), lifestyle (smoking habit, alcohol consumption, physical activity, social activity), and physical functioning were collected by a nurse. Clinical examinations (medication use, medical history, MMSE, comprehensive psychopathological rating scale, and clinical dementia rating scale) were performed by a physician. Extensive cognitive assessments (psychological test battery assessment) were performed by a psychologist. Peripheral blood samples were collected from all participants for laboratory testing. Medical conditions were additionally derived by linking the Swedish National Patient Register (NPR) with the International Classification of Diseases (ICD) codes, 10th edition. Information on death was collected from the Swedish Cause of Death Register. Data on medication use were based on current medication intake and were classified using the World Health Organization Anatomical Therapeutic Chemical classification system.(99) We gathered the residency history of the participants via the Swedish Tax Agency. Through linkage to residential addresses, environmental pollution data were collected from 1990–2015. Information on neighborhood household average salary within areas with about 1000–2000 residents was collected from Statistics Sweden (https://www.scb.se).

3.4 Assessments of environmental exposure

3.4.1 Ambient air pollution

Residential air pollution levels were obtained by spatiotemporal dispersion models according to data from local emission inventories and meteorological measurements.(100) Concentrations of $PM_{2.5}$, PM_{10}, and NO_x were measured in five-year intervals from 1990–2011 from local inventories. The annual average levels of air pollution were derived from a Gaussian dispersion model with a 35–500 meters side squares' quadtree receptor grid where the vicinity of roads has the highest resolution and rural areas have the coarsest resolution. An additional concentration component was added, with a street canyon model for streets considering buildings on one or both sides.(101) A linear interpolation was used to estimate the annual levels of air pollution between 5-year intervals. The total levels were obtained by adding the annual average long-range contributions, according to a regional background station outside the model domain with continuous measurements. The modeled and measured annual mean levels of air pollution were compared by linear regressions at three traffic monitoring stations and one urban background station in Stockholm City resulting in r^2 values of 0.96 for $PM_{2.5}$, 0.93 for PM_{10}, and 0.99 for NO_x. Because of the stable trend in air pollution levels, the levels for the years 2012 and 2013 were considered the same as for 2011 (**Figure 5**).

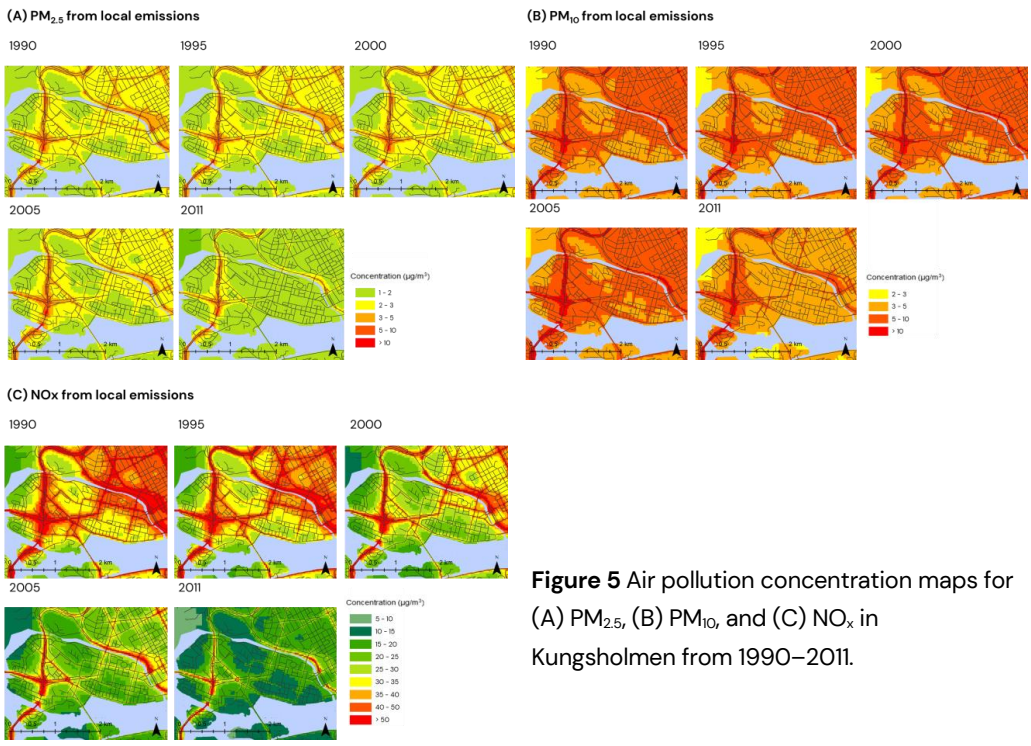

Figure 5 Air pollution concentration maps for (A) $PM_{2.5}$, (B) PM_{10}, and (C) NO_x in Kungsholmen from 1990–2011.

The yearly average levels of NO_2 were calculated from annual mean NO_x concentrations with the Romberg method:(102)

$$NO_2 = NO_X \times \left(\frac{30}{36 + NO_X} + 0.173\right)$$

The regression parameters have been adjusted based on measured concentrations of NO_x and NO_2.

The choice of the main exposure windows was based on specific study aims, consideration of the temporality of the exposure and outcomes, as well as on data availability. *Study I* considered the long-term effect of $PM_{2.5}$ prior to cognitive decline so we calculated 10-year average levels before baseline. *Study II* and *Study III* used the three-year moving average levels of all the aforementioned air pollutants before the event as the main exposure when considering any change in air pollution during follow-ups. *Study IV* used the 10-year average exposure to $PM_{2.5}$ and NO_2 before baseline, and the levels were dichotomized into high ($PM_{2.5}$ ≥8.7 and NO_2 ≥20.8μg/m^3) versus low ($PM_{2.5}$ <8.7 and NO_2 <20.8μg/m^3) according to the population means.

3.4.2 Transportation noise

A modified version of the Nordic prediction method was used to model residential road traffic and railway noise levels, including factors of average daily traffic flow, speed, the distribution of light and heavy traffic, type of road for major road conjunctions, and screening by terrain and buildings.(103,104) Levels of railway noise were measured within a 500-meter radius area around all railway tracks in Stockholm, including trams and subway lines, and ground absorption was taken into consideration. The noise maps were collected from Swedavia for the aircraft noise levels. The Integrated Noise model 7.0 was used to estimate the levels with categories of 1dB. During the study period, the L_{Aeq}, which represents the equivalent continuous A-weighted sound pressure level for the most exposed façade, was calculated for day-evening-night (L_{den}) at every residential address. Penalty levels of 5dB and 10dB were used for the noise in the evening and night, accordingly. Due to the imprecise estimations of the noise at lower levels, we set exposure levels to 40dB L_{den} for estimations lower than 40dB L_{den}. Road and railway noise levels were estimated in 5-year intervals from 1990–2015. We considered the values of 2016–2019 the same as 2015 because of the stable trend of noise levels.

Study III used a three-year time-weighted average road traffic noise before baseline assessment to align with the similar exposure period of air pollution. *Study IV* included 10-year time-weighted average levels before baseline, and three-year time-weighted moving average levels before the event for transportation noise from all sources in the analyses. The exposure levels were then categorized into three groups based on population tertiles and dichotomized into increased and not-increased levels with a cut-off point of 45dB L_{den} for railway and aircraft noise, and 50dB L_{den} for road traffic noise to count the number of noise sources.

3.5 Assessment of cognitive outcomes

3.5.1 Mini-Mental State Examination

The MMSE was used to assess participants' cognitive function at each study examination from 2001–2016 in *Study I*. The assessment is a short 30-point questionnaire comprising a range of cognitive abilities including memory, orientation, attention, language, and visuospatial abilities.

3.5.1.1 Definition of fast and slow decliner

The rate of change in MMSE scores from 2001–2016 was assessed via a linear mixed-effect model. The random slope and intercept were considered for each individual at baseline and during follow-ups. The estimated slope values were categorized by quartiles and then dichotomized into two groups: the *slow/non-decliners*, individuals in the lower three quartiles of decline (reference group); and the *fast decliners*, individuals in the upper quartile of decline.

3.5.2 Neuropsychological test battery

A comprehensive neuropsychological test battery was performed to assess domain-specific cognitive abilities at each wave of assessment, including domains of episodic memory (free recall and recognition tests), semantic memory (SRB:1 test), language (letter and category fluency), executive function (Tail-Making Tests part B), visuospatial ability (mental rotations), and perceptual speed (digit cancellation and pattern comparison). A summary of each test is shown in **Table 3.** The operationalization of the cognitive outcomes for *Study II* and *Study IV* are presented below. The choice of domains for each cognitive outcome was based on previous structural equation models and took into consideration the missingness of the domains.(105)

3.5.2.1 Cognitive impairment no dementia (CIND)

CIND was defined as any impairment in the domains of episodic memory (free recall), language (letter and category fluency), visuospatial ability (mental rotations), perceptual speed (digital cancellation and pattern comparison), or executive function (Trail Making Test Part B), but with the absence of a dementia diagnosis.(10) We first standardized each test score into a z-score according to the baseline mean and standard deviation (SD) of the full population. When the cognitive domain consisted of two tests, an average of the z-scores of the tests was calculated. The impairment of the cognitive domain was defined as a 1.5 SD lower z-score than the age-specific means at baseline. We applied the same procedure of standardization for follow-ups.

Table 3 Summary of the neuropsychological test battery.

Neuropsychological tests	Cognitive domains	Description	Range score	Diagnosis
Free recall	Episodic memory	A word list of 16 unrelated nouns was presented every five seconds. A two-minute recollection task was offered immediately after the word list. The number of correctly remembered words was recorded.	0–16	CIND & Global cognition
Recognition		The participants were asked to recognize the words previously presented. The total number of correct answers was recorded.	0–16	Global cognition
SRB:1	Semantic memory	The participants were asked to find one out of 5 synonyms for 30 words in 7 minutes. The total number correct was used.	0–30	Global cognition
Letter Fluency	Language	The participants were asked to generate as many words as possible, beginning with both letters "F" and "A" within 60 seconds for each task. The number of correct words was recorded for each letter.	>0	CIND & Global cognition
Category Fluency		The participants were asked to say as many different animals and professions as possible within 60 seconds. The number of correct words was recorded for each category.	>0	CIND & Global cognition
Digit cancellation	Perceptual speed	Consisted of 11 rows of random digits ranging from 1–9. Participants were asked to cross out every 4 they encountered. The score used for this task was the number of correctly crossed 4s within 30 seconds.	0–43	CIND & Global cognition
Pattern comparison		Consisted of pairs of basic line constructs and the participant had to mark, within 30 seconds, whether the pair was the 'same' or 'different'. The average number of correct answers was calculated from two trials.	0–30	CIND & Global cognition
Trail Making Test Part B (TMT-B)	Executive function	The participants were asked to connect circles with numbers and letters in both numeric and alphabetic order, alternating between the two categories (1-A-2-B, etc.). The number of correct answers (maximum of 12) was recorded.	0–12	CIND
Mental rotations	Visuospatial ability	Participants were presented with 10 pictures and asked which of three figures equaled the target figure, although the pictures were displayed from a different angle. The total number of correctly identified figures was recorded.	0–10	CIND

3.5.2.2 Global cognition score

Global cognition was determined with cognitive domains of episodic memory (free recall and recognition), semantic memory (SRB:1: vocabulary), perceptual speed (digit cancellation and pattern comparison), and language (letter and category fluency). A previous confirmatory structural equation model for global cognition was built for the selection of the tests.(105) Each of the seven test raw scores was standardized into z-scores using the mean and SDs of the baseline domain score. Global cognition score was the sum of the z-scores for the participants with data on at least half of the domains. The same procedure was applied for follow-ups.

3.6 Diagnoses of dementia

Dementia diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). A standard three-step procedure was applied for the diagnosis. First, the examining physician provided a primary diagnosis. Second, the clinical records of the participants were reviewed by a second physician who was also involved in data collection. Third, the discrepancy between the two previous diagnoses was solved by an external neurologist, who provided the final diagnosis. The dementia cases who died between follow-up evaluations were identified from the Swedish National Cause of Death Register and clinical medical records.

3.7 Diagnoses of depression

The presence and severity of various psychiatric symptoms were collected via a semi-structured measurement—the comprehensive psychopathological rating scale (CPRS).(106) The symptoms collected from CPRS were used together with a previously described algorithm to ascertain the presence of depression based on DSM-IV diagnostic criteria.(107) Major depression was defined as the presence of at least five symptoms with at least one of the two core symptoms (low mood or lack of interest) and minor depression was defined as the presence of two to four symptoms. In *Study III* the presence of either minor or major depression diagnosed between 2001–2013 was considered the outcome of interest.

3.8 Assessments of covariates

Demographics. *Age* was dichotomized into young-old (<78 years) and old-old (≥78 years) groups. The highest-held *education* levels were classified as elementary, high school, or university and above. *Socioeconomic status (SES)* was assessed by the longest-held occupation and described as blue-collar, white-collar, or entrepreneur. *Early retirement* was defined as retirement before age 65.

Lifestyles. *Smoking habits* were reported as never smoker, former smoker, or current smoker. *Alcohol intake* was assessed by the frequency and quantity of alcoholic drinks on a drinking occasion. A standard drink was equivalent to about 12g of alcohol. Alcohol consumption was categorized into three groups considering sex differences: no or occasional, light to moderate (men: 1–14 drinks/week [12–168g of alcohol]; women: 1–7 drinks/week [12–84g of alcohol]), and heavy (men: >14 drinks/week [>168g of alcohol]; women: >7 drinks/week [>84g of alcohol]).(108) *Physical activity* was measured by the intensity and frequency of physical exercise over the last 12 months. Inactive physical activity was defined as less than two occasions of light-to-intense exercise per week. A moderate level of physical activity was described as light exercise several times per week or everyday (e.g., walking along roads or in parks, walking in the woods, short bicycle ride, light aerobics, and golf). A high level of physical activity was defined as several times per week or everyday participation in moderate-to-intense exercise (i.e., jogging, long power walks, heavy-duty gardening, long bicycle rides, high-intensity aerobics, long-distance ice skating, swimming, ball sports but not golf, or other similar activity). Physical activity was then dichotomized into active (moderate or high) and inactive. *Social engagement* refers to the participation in social activities such as going to movies/theater/concerts, restaurants/bars/cafes, museum/art galleries, dancing, bingo, traveling, joining church meetings, watching sports events, study circles or courses, voluntary work, and other social meetings.(108) Participation in at least two of these activities per week in the last 12 months was defined as active social engagement.

Medical conditions. *Cerebrovascular diseases* were identified with the following ICD-10 codes: G45 (transient ischemic attack), G46 (vascular syndromes), I60–64 (hemorrhagic and ischemic stroke), I67 and I69 (cerebrovascular diseases).(109) Hearing loss due to deafness and hearing impairment were defined with the ICD-10 codes: H80 (otosclerosis), H90 (conductive and sensorineural hearing loss), H911 (presbycusis), H913 (deaf-mutism, not elsewhere classified), H919 (hearing loss, unspecified), Q16 (congenital malformations of the ear causing impairment of hearing), Z453 (adjustment and management of implanted hearing device), Z461 (fitting and adjustment of a hearing aid), Z962 (presence of otological and audiological implants), Z974 (presence of external hearing-aid).(109)

Other environmental factors. *Greenspace* was assessed by the Normalized Difference Vegetation Index (NDVI) with data obtained from Landsat 5 TM and Landsat 8 composite images during the summer months (May 1 to September 30) of corresponding years.(110) The annual average NDVI value at a 100m radius was used as the measure of greenspace. In *Study III*, three-year average levels of greenspace before baseline were calculated. In *Study IV*, the 10-year average level of NDVI before baseline was derived and dichotomized into high (≥0.25) and low (<0.25). *Water coverage* at a 100m radius was assessed from Geographical Information Systems software and land

use data from the Swedish Mapping, Cadastral, and Land registration authority. 10-year average levels of water space were calculated and dichotomized into any water space and no water space.

3.9 Statistical analyses

Overall, the main analytical models used in the doctoral projects are logistic regression models, cause-specific Cox proportional hazard models, and linear mixed-effect models. The summary of study methods is shown in **Table 4**. Logistic regression provides estimates of the probability of a binary outcome taking place. The odds ratio (OR) derived from logistic regression represents the odds of exposure among cases compared to the odds of exposure among non-cases. The Cox proportional hazard model is commonly used to assess to what extent specific factors may affect the rate of the outcome occurrence at a particular time point. The Cox model is semi-parametric, as it assumes the baseline hazard is proportionally distributed. Schoenfeld residuals were used to test the proportional hazard assumption in *Studies II, III, & IV,* and no violations of proportionality were found. For the continuous outcome with repeated measurements for the same individual, the correlation between and within individuals should be considered. A linear mixed-effect model has both fixed and random effects for non-independent measurements. Also, it could consider the unbalanced longitudinal data when there are different numbers of repeated assessments; or when there is the same number of assessments, but they were not measured at the same timepoints for each participant.

Additionally, some more specific approaches were used as sensitivity analyses to account for attrition, including inverse probability weighting (IPW),(111) to consider drop-out (due to moving or refusal), as well as Fine and Gray competing risk models,(112) to account for competing risk due to death. Detailed information on the sensitivity analyses can be found in the individual studies.

All analyses were performed with Stata SE version 16 or 17 (StataCorp LLC, TX, USA). A two-tailed test *P*–value <0.05 was considered statistically significant.

Study I. We used logistic regression to estimate the ORs and 95% confidence intervals (CIs) for fast cognitive decline (fast decliner versus no decliner) with 10-year average levels of $PM_{2.5}$. All analyses were conducted among total and age-specific study samples (≤80 years versus >80 years). The non-linear association was assessed by piecewise linear spline and restricted cubic splines with three knots at the 10^{th}, 50^{th}, and 90^{th} percentiles of the distribution with a reference of 8.6μg/m^3 (median level). The modifying effect of cerebrovascular diseases occurring between 2001–2016 was assessed by adding a multiplicative interaction term into the model.

Study II. Cox proportional hazard models were used to estimate the cause-specific hazard ratios (HRs) and 95% CIs of incident CIND in the cognitively intact cohort and incident dementia in the CIND cohort for air pollution exposure (a three-year moving average before the event). The estimations were reported as a 1μg/m^3 increase of $PM_{2.5}$ and PM_{10}, and a 10μg/m^3 increase of NO_x. Time at risk was calculated from baseline to the last assessment, death, or diagnosis of the outcome of interest (CIND or dementia). Models were adjusted for age, sex, SES, education, smoking, physical activity, neighborhood household mean income, early retirement, and the number of cognitive test occasions. Similarly, the concentration-response curve of air pollution and CIND incidence were modeled using restricted cubic splines with three knots.

Study III. We used Cox proportional hazards models to estimate cause-specific HRs (95% CIs) for depression incidence corresponding to a 1μg/m^3 increase of $PM_{2.5}$ and PM_{10} and a 10μg/m^3 increase of NO_x. The at-risk time for participants was considered from baseline until the first depression episode, the last assessment before attrition (due to moving or refusal to participate), death, or end of follow-up; whichever occurred first. We built three models by additively adjusting for covariates: age (timescale), sex, education, neighborhood household mean income, and SES (model 1); smoking, alcohol consumption, number of medications (model 2); and 3-year average greenspace and 3-year average road traffic noise levels (model 3). The potential temporal trends of exposure and birth cohort effect were considered in all models by adjusting for the year of baseline assessment and by stratifying the baseline hazard according to birth years (in groups of five years). The nonlinear association was assessed by restricted cubic splines with three knots using mean levels of air pollution as reference values. The interaction between social activity (active versus inactive) and air pollution on the depression incidence was assessed by adding multiplicative interaction terms into the models.

Study IV. The longitudinal change in global cognition over 16 years in correspondence to a 10dB L_{den} increment of transportation noise was assessed with linear mixed-effect models. For each participant, random intercept and random slope of follow-up time were included for the random effects with an unstructured covariance matrix. Cox models were used to assess the associations between exposure to long-term transportation noise and CIND incidence. Follow-up time was counted from baseline assessment to CIND onset, the end of the follow-up, death, or last follow-up before attrition; whichever came first. Nonlinear associations were assessed using restricted cubic splines with three knots. The main model adjustment included age, sex, education, baseline year, birth year (in groups of five years), SES, smoking, physical activity, number of medications, neighborhood household mean income, hearing loss, 10-year average levels of $PM_{2.5}$, NO_2, greenspace, and water space.

Table 4 Overview of the study methods.

	Study I	Study II	Study III	Study IV
Short Title	$PM_{2.5}$ and cognitive decline	Air pollution, CIND, and dementia	Air pollution and depression	Noise pollution and cognition
Design	Longitudinal cohort design			
Population	Swedish National study on Aging and Care in Kungsholmen (SNAC-K) (N =3363)			
Study Period	2001–2016	2001–2013	2001–2013	2001–2019
Sample Size	Dementia-free (n =2253)	Cognitively intact (n =1987) CIND (n =607)	Depression-free (n =2812)	Dementia-free (n =2594)
Main Exposure	$PM_{2.5}$	$PM_{2.5}$, PM_{10}, NO_x	$PM_{2.5}$, PM_{10}, NO_x	Aircraft, road traffic, railway noise
Main Exposure Windows	10-year average before the baseline	Three-year moving average before event	Three-year moving average before event	10-year average before the baseline & three-year moving average before event
Main Outcome	Faster cognitive decline (MMSE)	CIND (cognitive test battery) and dementia (DSM-IV)	Minor and major depression (DSM-IV)	Global cogitation score and CIND (cognitive test battery)
Covariates	Age, sex, education, smoking, SES, early retirement, physical activity	Age, sex, SES, education, smoking, physical activity, early retirement, neighborhood household mean income, number of cognitive test occasions	Age, sex, education, neighborhood household mean income, baseline year, birth year, SES, smoking, alcohol consumption, number of medications, greenspace, road traffic noise	Age, sex, education, baseline year, and birth year, SES, smoking, physical activity, number of medications, neighborhood household mean income, hearing loss, $PM_{2.5}$, NO_2, greenspace, water space
Interactions	Cerebrovascular diseases	-	Social engagement	Age, sex, physical activity, smoking habits, $PM_{2.5}$, NO_2, NDVI, water space
Main Analyses	Linear mixed effect model and logistic regression	Cox proportional hazard model	Cox proportional hazard model	Linear mixed effect model and Cox proportional hazard model

CIND, cognitive impairment no dementia; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; MMSE, Mini-Mental State Examination; NDVI, Normalized Difference Vegetation Index; NOx, nitrogen oxides; NO_2, nitrogen dioxide; PM, particulate matter; SES, socioeconomic status.

3.10 Ethical considerations

The SNAC-K study followed general principles of research ethics. The ethical permission of the SNAC-K cohort was proved by the Ethics Committee at Karolinska Institutet and the Regional Ethical Review Board in Stockholm at all phases of each study wave (Dnrs: KI 01-114, 04-929/3, Ö26-2007, 2009/595-32, 2010/447-31/2, 2013/828-31/3 & 2016/730-31/1).

All participants took part in the research voluntarily and were informed about the research in a comprehensible manner. Written informed consent has been obtained at all phases of the project, following the Declaration of Helsinki. In case of severe cognitive impairment, a proxy of consent was obtained from relatives or guardians. Eligible subjects were informed that they can discontinue participation at any stage of the examination. The physical examination and questionnaire interview took place in a friendly and comfortable environment with sufficient time to fulfill the examination tasks. If the participants expressed discomfort or concerns regarding the examination, the interview was terminated and eventually rescheduled. Participants were also asked to receive the results of their medical examinations if any diseases were detected. In such a fashion, participants were referred to their general practitioners or other physicians. A detailed report of laboratory test results was provided in case of any requisition.

Data collection and management followed standard protocol. All collected personal information was desensitized by removing all personally identifiable information to keep data confidential and anonymous. Data generated by the research were securely and appropriately stored in accordance with relevant legislation.

4 Results

4.1 Characteristics of the study sample

The SNAC-K participants lived in a wealthy urban area in Stockholm, Sweden. In general, the participants recruited at baseline (n =3363) were more likely to be female (65%), with education levels at high school and above (82%), and most were white-collar workers (66%).

The average age of the study samples was 72.1 (SD: 9.9) years for the dementia-free cohort in *Study I*, 71.6 (SD: 9.8) years for the cognitively intact cohort in *Studies II & IV*, 74.2 (SD: 9.9) years for CIND cohort in *Study II*, and 73.1 (SD: 10.5) years for the depression-free cohort in *Study III*.

4.2 Environmental pollution over time

We observed a stable trend of the yearly average levels of PM and a significant decreasing trend in NO_x over the last two decades from 1990–2011 (**Figure 6**). Transportation noise levels were stable from 1990–2018, and road traffic noise was the highest among all sources.

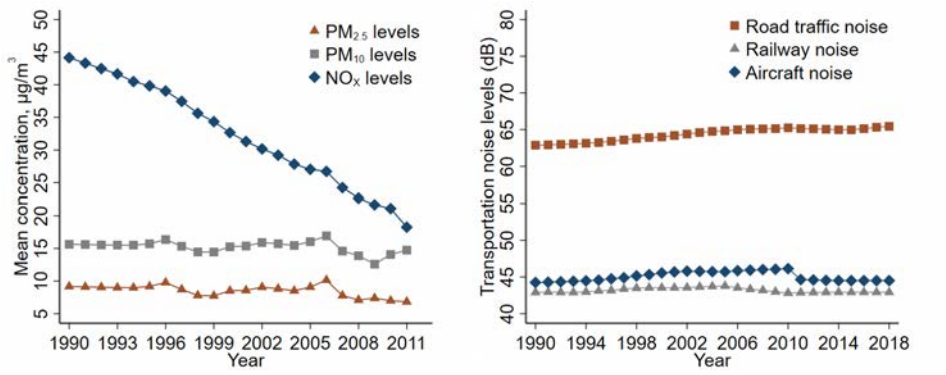

Figure 6 Annual average levels of air pollution (1990–2011) and transportation noise (1990–2018) for SNAC-K participants.

4.3 Air pollution and fast cognitive decline (Study I)

4.3.1 Piece-wise linear $PM_{2.5}$ and fast cognitive decline

A total of 564 fast cognitive decliners were identified. We did not observe a linear association between $PM_{2.5}$ and fast cognitive decline among the whole study sample (*P* =0.43). However, for participants aged ≥80 years, we observed an 81% (OR 1.81; 95% CI: 1.02–3.22) increased risk of faster cognitive decline, corresponding to per interquartile range (IQR, 0.6μg/m^3) increase in $PM_{2.5}$ at low-to-median levels (<8.6μg/m^3) while no further increased risk was observed above the level of 8.6μg/m^3 (**Figure 7**).

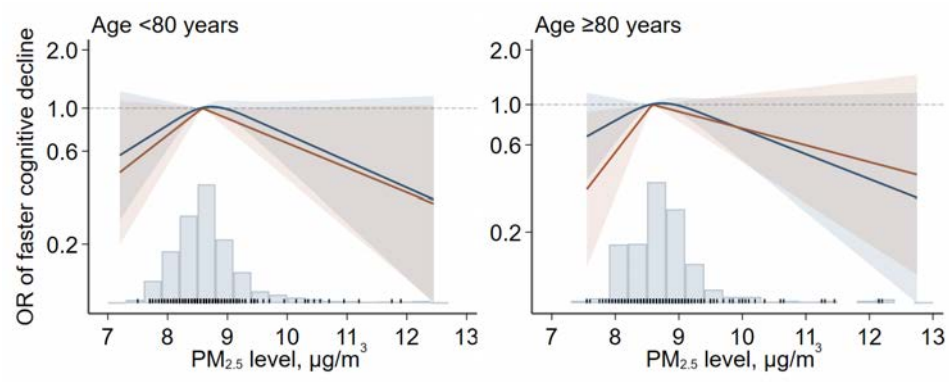

Figure 7 The association between $PM_{2.5}$ and fast cognitive decline by age groups.

$PM_{2.5}$ was modeled by restricted cubic splines with 95% CI (blue line and blue shade) and piece-wise spline (red line and red shade). The knot was set at the median level of $PM_{2.5}$ (8.6μg/m^3). The blue bars present the distribution of exposure levels in the two age groups. The spikes represent the fast decliners. Models are adjusted for age, sex, education, socioeconomic status, early retirement, smoking, and physical activity.

4.3.2 The role of cerebrovascular diseases

There was a significant interaction between $PM_{2.5}$ and cerebrovascular diseases for the risk of fast cognitive decline at exposure levels of $PM_{2.5}$ ≤8.6μg/m^3 for the overall study sample and by age groups (**Table 5**). Low-to-median levels of $PM_{2.5}$ were associated with the highest risk of fast cognitive decline in the old-old group who had cerebrovascular diseases (OR 1.97; 95% CI: 1.07–3.61). However, we did not observe the association between $PM_{2.5}$ and fast cognitive decline with cerebrovascular diseases at exposure levels above 8.6μg/m^3.

Table 5 The association between $PM_{2.5}$ and fast cognitive decline, by cerebrovascular diseases and age groups (N =2253).

Cerebrovascular diseases	Odds ratio (95% CI) of fast cognitive decline	
	$PM_{2.5}$ ≤8.6 μg/m^3	**$PM_{2.5}$ >8.6μg/m^3**
Overall		
No	1.46 (1.06–2.01)	0.87 (0.76–1.01)
Yes	1.57 (1.13–2.16)	0.83 (0.65–1.06)
P for interaction	*<0.001*	*0.395*
Age <80 years		
No	1.31 (0.90–1.91)	0.79 (0.62–1.00)
Yes	1.41 (0.97–2.05)	0.89 (0.66–1.19)
P for interaction	*<0.001*	*0.829*
Age ≥80 years		
No	1.85 (1.06–3.37)	0.93 (0.75–1.14)
Yes	1.97 (1.07–3.61)	0.74 (0.50–1.10)
P for interaction	*<0.001*	*0.215*

Odds ratio corresponds to an interquartile range (0.6μg/m^3) increase in 10-year average levels of $PM_{2.5}$. Models are adjusted for age, sex, education, smoking, socioeconomic status, early retirement, and physical activity.

4.4 Air pollution and cognitive impairment and its progression to dementia (Study II)

4.4.1 Air pollution and cognitive impairment

Out of 1987 cognitively intact participants, 301 developed CIND over the course of the 12-year follow-ups. CIND cases tended to be older, female, and had lower education and SES levels, compared to those who remained cognitively intact. Increased hazard of CIND was observed for per 1μg/m^3 increase of $PM_{2.5}$ (HR 1.75; 95% CI: 1.54–1.99) and PM_{10} (HR 1.08; 95% CI: 1.03–1.14) and per 10μg/m^3 increase of NO_x (HR 1.18; 95% CI: 1.04–1.33) (**Table 6**).

Table 6 Long-term exposure to air pollution in relation to CIND, and its progression to dementia.

Three-year moving average before event	Intact cohort (N =1987)	CIND cohort (N =607)
	Hazard ratio of CIND (95% CI)	Hazard ratio of dementia (95% CI)
$PM_{2.5}$ (per 1μg/m^3 increment)	1.75 (1.54–1.99)	1.90 (1.48–2.43)
PM_{10} (per 1μg/m^3 increment)	1.08 (1.03–1.14)	1.14 (1.03–1.26)
NO_x (per 10μg/m^3 increment)	1.18 (1.04–1.33)	1.34 (1.07–1.69)

Models are adjusted for age, sex, socioeconomic status, education, smoking, physical activity, early retirement, neighborhood household mean income, and number of cognitive test occasions.

4.4.2 Air pollution and the progression of CIND to dementia

Among the 607 CIND cases at baseline, we identified 118 incident dementia cases during the 12-year follow-up. We found a 90% (HR 1.90; 95% CI: 1.48–2.43), 14% (HR 1.14; 95% CI: 1.03–1.26), and 34% (HR 1.34; 95% CI: 1.07–1.69) increased hazard of progression from CIND to dementia for 1μg/m^3 increase of $PM_{2.5}$ and PM_{10}, as well as for 10μg/m^3 increase of NO_x, respectively (**Table 6**).

4.4.3 The concentration-response relationship between air pollution and CIND

Figure 8 shows the significant nonlinear association between air pollution and CIND risk. A nearly linear association was observed from low-to-mean levels of air pollution for CIND incidence. A flattening in HR was observed from mean-to-high levels of PM concentration, while a similar shape was also seen for NO_x, but with a wide confidence interval.

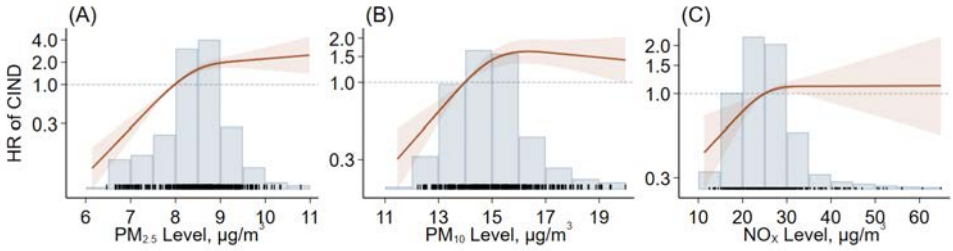

Figure 8 Concentration-response curves of long-term exposure to air pollution and hazard of CIND.

Air pollution was included as a time-varying covariate and modeled by restricted cubic splines with 95% CI (red line and red shade) for $PM_{2.5}$ (panel A), PM_{10} (panel B), and NO_X (panel C), respectively. The black spikes represent CIND cases. The blue bars present the distribution of air pollution levels. Models are adjusted for age, sex, education, smoking, socioeconomic status, early retirement, physical activity, neighborhood household mean income, and number of cognitive test occasions. The reference group is considered to be 8μg/m³ of $PM_{2.5}$, 14μg/m³ of PM_{10}, and 25μg/m³ of NO_x in the entire population (mean level).

4.5 Air pollution and depression (Study III)

4.5.1 Long-term exposure to air pollution and depression

Of 2812 depression-free participants at baseline, 137 participants developed incident depression during the 12-year follow-up. People who had depression were older, more likely to be female, had lower SES and education levels, and were prescribed more medications. An elevated hazard of depression has been observed by long-term exposure to air pollution (**Table 7**). We found that a 1μg/m^3 increase in $PM_{2.5}$ and PM_{10} was correspondence to a 53% (HR 1.53; 95% CI: 1.22–1.93) and 7% (HR 1.07; 95% CI: 0.98–1.18) increased hazard of depression for the fully adjusted model, accordingly. There was also a 26% increased hazard of depression associated with every 10μg/m^3 increase in NO_x (HR 1.26; 95% CI: 1.01–1.58).

Table 7 The association between exposure to long-term air pollution and depression incidence (N =2812).

Three-year moving average before event	Hazard ratio of depression (95% CI)		
	Model 1	Model 2	Model 3
$PM_{2.5}$ (per 1μg/m^3 increment)	1.49 (1.22–1.82)	1.51 (1.22–1.86)	1.53 (1.22–1.93)
PM_{10} (per 1μg/m^3 increment)	1.06 (0.98–1.15)	1.07 (0.99–1.17)	1.07 (0.98–1.18)
NOx (per 10μg/m^3 increment)	1.20 (1.00–1.44)	1.24 (1.02–1.50)	1.26 (1.01–1.58)

Model 1 is adjusted for age (timescale), sex, education, neighborhood household mean income, baseline year, and birth year (strata in five years group); model 2: model 1 + socioeconomic status, smoking, alcohol consumption, and number of medications; model 3: model 2 + three-year average levels of greenspace and road traffic noise before baseline.

4.5.2 The concentration-response relationship between air pollution and depression

With increasing in air pollution from low-to-mean levels, the hazard ratio of depression increased in a roughly linear fashion (**Figure 9**). The significant increase in depression hazard was attenuated from mean-to-high levels of $PM_{2.5}$. But a plateau of the depression hazard appeared from mean-to-high concentrations of PM_{10} and NO_x.

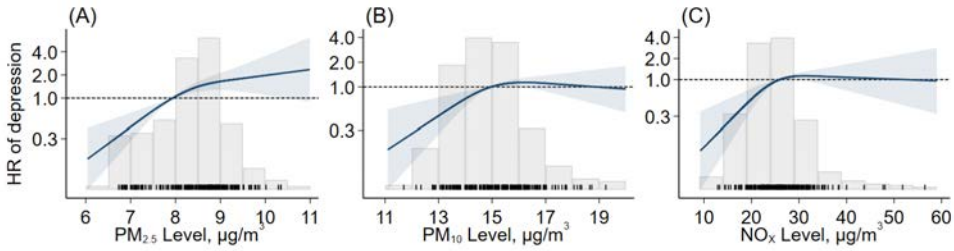

Figure 9 Concentration-response curve for the association between air pollution and depression.

Air pollution was included as a time-varying covariate and modeled by restricted cubic splines with three knots with 95% CI (blue lines and blue shade) for $PM_{2.5}$ (panel A), PM_{10} (panel B), and NO_x (panel C), respectively. The black spikes represent depression cases. The gray bars present the distribution of air pollution levels. Models are adjusted for age (timescale), sex, education, neighborhood household mean income, baseline year, birth year (strata in five years group), socioeconomic status, smoking, alcohol consumption, number of medications, three-year average levels of greenspace, and road traffic noise before baseline. The reference level is considered to be 8μg/m³ of $PM_{2.5}$, 15μg/m³ of PM_{10}, and 26μg/m³ of NO_x in the entire population (mean level).

4.5.3 The role of social engagement

Figure 10 shows the effect modification of social activities on long-term air pollution and depression risk. About two-thirds of incident depression cases had a socially inactive lifestyle at baseline. Social activities had significant interaction with $PM_{2.5}$ (P =0.02). While the modifying effect of social activity was not found for PM_{10} and NO_x (both P >0.05). Among participants with active social engagement, long-term exposure to $PM_{2.5}$ showed a lower risk of depression (HR 1.04; 95% CI: 0.70–1.55) in comparison to those who had inactive social engagement (HR 1.69; 95% CI: 1.29–2.21).

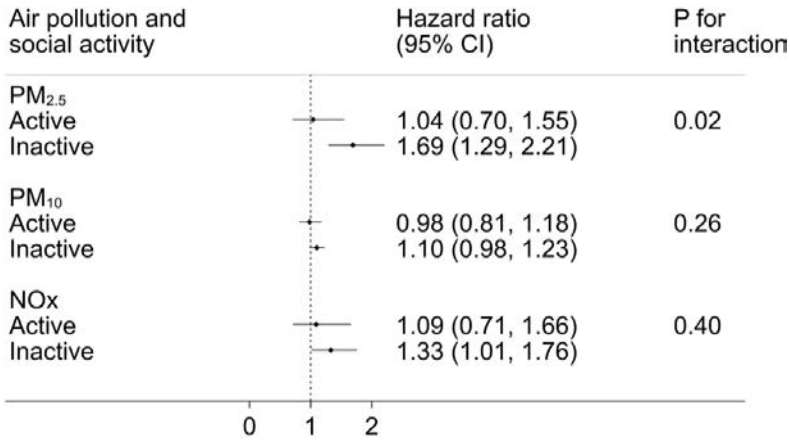

Figure 10 The modifying effect of social engagement on the relationship between air pollution and depression (N =2812).

Hazard ratios of depression correspond to per 1μg/m³ increase of $PM_{2.5}$ and PM_{10} and per 10μg/m³ increase of NO_x. Models are adjusted for age (timescale), sex, education, neighborhood household mean income, baseline year, birth year (strata in five years group), socioeconomic status, smoking, alcohol consumption, number of medications, three-year average levels of greenspace, and road traffic noise before baseline.

4.6 Transportation noise and cognition (Study IV)

4.6.1 Transportation noise and change in global cognition

About 43%, 93%, and 32% of the dementia-free cohort participants were exposed to increased levels of aircraft, road traffic, and railway noise, respectively. **Table 8** demonstrates the baseline differences and rate of change in global cognition score over a 16-year follow-up per 10dB L_{den} increase in transportation noise. The baseline global cognition score did not differ with the increase in transportation noise. During follow-up, we found a faster rate of decline in global cognition for exposure to higher aircraft noise levels (β -0.007, 95% CI: -0.012 to -0.001), but not for road traffic and railway noise.

Table 8 The associations between long-term exposure to transportation noise (per 10dB L_{den}) and the change of global cognition score (N =2594).

10-year average before baseline	β-coefficients for global cognition score (95% CI)		
	Model 1	Model 2	Model 3
Aircraft noise			
Baseline	-0.050 (-0.103, 0.003)	0.006 (-0.052, 0.063)	0.014 (-0.054, 0.081)
Annual change	-0.007 (-0.013, -0.002)	-0.007 (-0.012, -0.001)	-0.007 (-0.012, -0.001)
Road traffic noise			
Baseline	-0.017 (-0.047, 0.014)	-0.018 (-0.049, 0.012)	-0.012 (-0.052, 0.028)
Annual change	-0.001 (-0.004, 0.002)	-0.001 (-0.004, 0.002)	-0.001 (-0.004, 0.002)
Railway noise			
Baseline	-0.009 (-0.051, 0.033)	-0.031 (-0.073, 0.011)	-0.040 (-0.089, 0.008)
Annual change	0.001 (-0.003, 0.005)	0.002 (-0.002, 0.006)	0.002 (-0.002, 0.007)

Model 1 is adjusted for age, sex, education, birth year (in five years group), and year of baseline assessment; model 2: model 1 + socioeconomic status, smoking, physical activity, neighborhood mean income, number of medications, and hearing loss; model 3: model 2 + other environmental factors (10-year average levels of $PM_{2.5}$, NO_2, water space, and greenspace), and other transportation noise sources.

4.6.2 Transportation noise and cognitive impairment

During the 16 years of follow-up, 422 out of 1987 cognitively intact participants developed CIND. We observed a 5% (HR 1.05; 95% CI: 0.78–1.42) and 13% (HR 1.13; 95% CI: 0.92–1.39) increased risk of CIND for a 10dB L_{den} increment of the 10-year average of aircraft noise and railway noise, respectively (**Table 9**, model 3). No increased risk of CIND was found for exposure to higher levels of road traffic noise (HR 1.00; 95% CI: 0.84 –1.21). Slightly stronger effect estimations were observed when using the exposure window of the three-year moving average during follow-up. A 16% (HR 1.16; 95% CI: 0.91–1.49) and 25% (HR 1.25; 95% CI: 1.01–1.55) increased risk of CIND were observed for three-year moving average levels of aircraft and railway noise.

Table 9 The association between transportation noise and CIND incidence (N=1987).

Transportation noise	Hazard ratio of CIND (95% CI)		
	Model 1	Model 2	Model 3
10-year average before baseline			
Aircraft noise	1.24 (0.97–1.60)	1.05 (0.79–1.41)	1.05 (0.78–1.42)
Road traffic noise	1.01 (0.88–1.16)	0.99 (0.86–1.14)	1.00 (0.84–1.21)
Railway noise	1.12 (0.92–1.36)	1.12 (0.92–1.37)	1.13 (0.92–1.39)
Three-year moving average during follow-up			
Aircraft noise	1.31 (1.06–1.62)	1.16 (0.91–1.47)	1.16 (0.91–1.49)
Road traffic noise	1.05 (0.90–1.23)	1.01 (0.86–1.19)	1.01 (0.84–1.23)
Railway noise	1.25 (1.02–1.54)	1.24 (1.01–1.53)	1.25 (1.01–1.55)

Hazard ratio was reported for a 10-dB L_{den} increase in transportation noise and was derived from the multipollutant model. Model 1 is adjusted for age (timescale), sex, education, baseline year, and birth year (strata in five years group); model 2: model 1 + socioeconomic status, smoking, physical activity, number of medications, neighborhood household mean income, and hearing loss; model 3: model 2 + other environmental factors (10-year average levels of $PM_{2.5}$, NO_2, water space, and greenspace).

4.6.3 The dose-response relationship between transportation noise and CIND

Figure 11 shows the dose-response curve of the hazard of CIND with an increase in transportation noise. No departure from linearity was detected. A continuous increase in HR of CIND was observed for road traffic and railway noise (panels B and C). However, for aircraft (panel A), only a slight increase in CIND hazard was shown from 40dB L_{den} to mean levels.

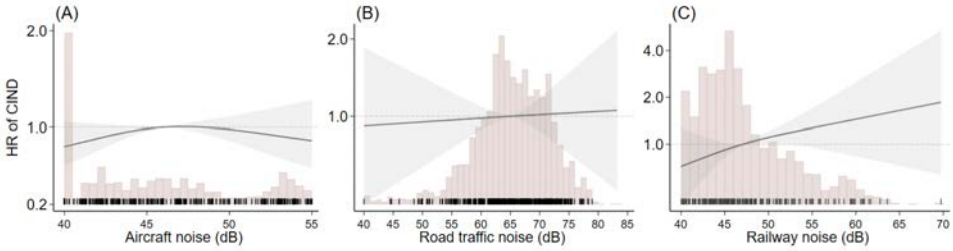

Figure 11 The nonlinear association between transportation noise and CIND.

Hazard ratios were estimated from Cox proportional hazard models according to transportation noise levels. Transportation noise by sources was included as a time-varying covariate and modeled by restricted cubic splines with 3 knots with 95% CI (gray lines and gray shades) for aircraft noise (panel A), road traffic noise (panel B), and railway noise (panel C). Black spikes represent CIND cases. The pink bars present the distribution of transportation noise levels. Models are adjusted for age (timescale), sex, education, baseline year, and birth year (strata in five years group), socioeconomic status, smoking, physical activity, number of medications, neighborhood household mean income, hearing loss, 10-year average levels of $PM_{2.5}$ and NO_2, greenspace, and water space before baseline. The reference groups were mean levels of the study population; namely 46dB L_{den} for aircraft, 65dB L_{den} for road traffic, and 47dB L_{den} for the railway. The analysis on railway noise was restricted in participants with exposure higher than 40dB L_{den}.

4.6.4 The number of transportation noise sources and CIND

About 68% of the CIND cases were exposed to two or more transportation noise sources. We found an increased risk of CIND (HR 1.14; 95% CI: 0.97–1.36) by one source increase in traffic noise (**Table 10**) and exposure to two or more traffic noise sources was associated with a 16% increased risk of CIND (HR 1.16; 95% CI: 0.93–1.46) compared to exposure to less than two noise source. But these results were not statistically significant.

Table 10 The association between the number of noise sources and CIND incidence (N =1987).

Number of sources	Cases/person-years	Hazard ratio of CIND (95% CI)	*P*-values
Four groups			
0 traffic noise source	32/1036.61	Reference	
1 traffic noise source	105/4799.66	1.21 (0.72–2.05)	0.472
2 traffic noise sources	270/11202.43	1.36 (0.82–2.27)	0.233
3 traffic noise sources	15/505.17	1.55 (0.75–3.21)	0.235
per traffic noise source increase	422/17543.87	1.14 (0.97–1.36)	0.121
Two groups			
0–1 traffic noise source	137/5836.27	Reference	
2–3 traffic noise sources	285/11707.60	1.16 (0.93–1.46)	0.191

The models are adjusted for age (timescale), sex, education, baseline year, and birth year (strata in five years group), socioeconomic status, smoking, physical activity, number of medications, neighborhood household mean income, hearing loss, 10-year average levels of $PM_{2.5}$ and NO_2, greenspace, and water space before baseline.

5 Discussion

5.1 Summary of main findings

In this doctoral thesis, using data from a Swedish longitudinal cohort with a long follow-up time, we investigated the extent to which air pollution and transportation noise influence mental health among older adults. The main findings of the doctoral thesis are summarized as follows:

I. Long-term exposure to $PM_{2.5}$ was associated with an increased risk of faster cognitive decline only among the oldest-old group at low-to-mean levels. These associations were more pronounced in the presence of cerebrovascular diseases (*Study I*).
II. Long-term exposure to air pollution was not only linked to an increased risk of cognitive impairment but also the conversion from cognitive impairment to dementia among older adults (*Study II*).
III. Long-term exposure to air pollution was associated with an increased hazard of depression in late life. Active social engagement could counteract the harmful effect of air pollution on depression risk (*Study III*).
IV. Aircraft noise was associated with a faster rate of deterioration of global cognition among older adults, while such an association was not observed for road traffic and railway noise. Long-term exposure to railway noise and aircraft noise was marginally associated with the increased hazard of cognitive impairment but not with road traffic noise (*Study IV*).

5.2 Interpretation of the main findings

5.2.1 Air pollution and cognition

Study I and *Study II* revealed the association between air pollution and negative cognitive outcomes among older adults, while the results were more evident for exposure to low-to-medium/mean levels of air pollution. These findings are consistent with some previous results,(50,52,53,59–61) but some prior studies did not find significant results (**Appendix Table 1**).(54–56,62,63) There are some potential explanations for the diverging results. The different concentrations of air pollution exposure may have different effects when there is a non-monotonic dose-response relationship. Air pollution levels in Kungsholmen are low compared to European and WHO air quality standards. However, several studies from high-exposure areas have also reported similar associations,(52–54) but the effect size was smaller, which was in line with our nonlinear concentration-response curve showing that mean-to-high levels of air pollution tend to have an attenuated effect. These levels may not be directly comparable but may provide some insights for interpretation.(113) As SNAC-K

participants were healthier and wealthier compared to other study samples, the attenuation of the effect could also be due to the 'healthy survivor' effect or the beneficial lifestyle that interfered with the harmful effect of air pollution on cognitive outcomes. The association was more pronounced when using a neuropsychological test battery in *Study II* rather than the MMSE, which was used for cognitive assessment in *Study I because* the screening instrument may be less sensitive in capturing subtle changes in cognition. Likewise, the MYHAT study assessed cognitive impairment with a clinical dementia rating,(50) instead of screening tools in other studies.(55,56) Their findings showed the strongest association between $PM_{2.5}$ and cognitive impairment.(50)

The body of evidence was stronger regarding the association between air pollution and the incidence of dementia.(114) *Study II* provided novel results on the association between air pollution and the progression from cognitive impairment to dementia. People with cognitive impairment have a higher risk of developing dementia. Understanding the modifiable risk factors for cognitively impaired people is of great importance for public health, as it may provide evidence aiding in the future generation of secondary prevention interventions for the cognitive aging continuum from normal cognition to dementia.

Also, people of more advanced age and with cerebrovascular diseases may be more susceptible to the harmful effect of air pollution on cognitive decline in *Study I*. Given a consistent link between air pollution and cardio/cerebrovascular diseases, especially among older adults in the literature,(115) our results may provide some understanding of how long-term exposure to air pollution may synergistically act on the shared pathway between brain-heart connections, and further accelerate the progression of cognitive decline.

5.2.2 Air pollution and depression

The relationship between long-term air pollution and depression risk was mostly addressed in the general population.(35) Our findings of an association between increased levels of air pollution and depression incidence were in accordance with two longitudinal Korean studies,(67,70) while two US studies only showed a tendency towards the association but were not statistically significant (**Appendix Table 2)**.(68,69) The heterogeneous results may be due to differences in diagnostic criteria for depression, follow-up times, or residual confounding. The screening instrument or tools used only for research purposes may be not sensitive to the clinical definition of depression and inappropriate selection of the cut-off points often leads to an underestimation of rates of depression.(107,116,117) Because low-income and marginalized communities are often disproportionately affected by air pollution and other environmental hazards in North American countries,(118) these communities may also have a higher prevalence of depression and other mental health disorders.(28) Lack

of follow-up time may also lead to a similar underestimation of cases. Other environmental factors, including transportation noise and greenspace were not considered in other studies, which may result in differences in the estimations. Exploring the association between air pollution and depression can help us better understand the health impacts of air pollution and may inform strategies for reducing its harmful effects on mental well-being in older adults.

Importantly, we were the first to evaluate the interaction between social activity and air pollution on depression risk. Our results suggest that the harmful effect of air pollution on depression was more profound in people with low levels of social activity. Some studies have shown insufficient social activity was associated with an increased risk of physical conditions, such as fatigue, sleep deprivation, and depression in older adults.(119) Social isolation may also activate the HPA and stimulate the release of stress hormones through the neuroendocrine stress response.(120) In contrast, we may assume that the environmental stimuli on stress response may be offset by active social engagement. Therefore, these results could be valuable in terms of mitigating the negative effect of air pollution on depression risk.

5.2.3 Transportation noise and cognition

Studies assessing the effect of transportation noise on cognitive outcomes were mostly cross-sectional and limited longitudinal studies reported mixed results (**Appendix Table 3**).(76) Our findings in *Study IV* contribute to evidence exploring source-specific transportation noise exposure in relation to cognitive decline and cognitive impairment, while most studies only modeled overall environmental noise. In opposite to the significant association we found between increased levels of aircraft noise and a faster decrease in global cognition score, Weuve and colleagues used data from the Chicago Health and Aging Project in which a sample of 5227 participants showed residential noise was not associated with cognition among either of the age groups.(121) Key limitations such as the short duration of follow-up and noise estimates from only daytime measurements may have precluded the authors from observing similar results. Our results also revealed that railway and aircraft noise was independent in relation to increased risk of cognitive impairment, which was supported by previous cross-sectional studies in the US(121) and Germany.(122) They showed consistent results that environmental noise was associated with about a 40% increased likelihood of cognitive impairment. In contrast with our null findings of associations between road traffic noise and either of the cognitive outcomes, results from the Sacramento Area Latino Study on Aging (SALSA) study (N =1612) with 10 years follow-up suggested long-term exposure to road traffic noise was marginally associated with an increased hazard of developing dementia or CIND after adjusting for air pollution.(123) Only high-speed light- and heavy-duty cars were taken into consideration in their road traffic noise models, which resulted in a higher 24-hour (69 ± 8.9dB) average road traffic exposure in the SALSA

population compared to exposure levels in our study population (64 ± 7dB L_{den}).(123) Moreover, despite the SALSA and SNAC-K study populations both located in urban residences, the SALSA population tended to be frailer and more socially disadvantaged than SNAC-K participants, both of which factors have been shown to be linked to poor cognitive outcomes. Consequently, given the methodological limitations and differences within and between studies, it is not possible to conclusively rule out the association between transportation noise and cognitive outcomes.

5.3 Methodological considerations

5.3.1 Study design

The longitudinal cohort and ecological cohort designs are the most often used study designs for assessing the effect of long-term (cumulative) environmental exposure on chronic health outcomes. To assure sufficient variation in cumulative exposure, individuals from geographic locations with different exposure gradients are acquired. Ecological studies usually use data from a large range of geographical areas. However, when maximizing the geographical contrasts of exposure, the effect estimations may be confounded by area-specific characteristics. Also, administrative data are not informative when it comes to detailed personal characteristics, such as demographics (e.g., age, sex, socioeconomic status, education levels) and individual lifestyles (e.g., smoking status, alcohol drinking, physical activity). Crude adjustments of area-specific factors may lead to biased results when individual characteristics are not considered. In contrast, a longitudinal cohort design usually involves the collection of detailed individual data over time, which could capture not only temporal contrasts but also less-biased estimations by adjusting for detailed potential confounders. Regarding outcome assessments, ecological studies usually obtain data from registries or medical claims. These data sources often lead to underdiagnoses or delayed diagnoses of the diseases in question.(124,125) More misclassification issues will be discussed in the information bias session below.

This doctoral thesis used data from a large longitudinal cohort with detailed individual information regarding demographics, lifestyle, disease history, and several environmental factors, which enabled us to control for potential confounding factors that were identified in existing literature.

5.3.2 Random errors

When studying the whole population is not realistic, researchers usually randomly draw a group of representative study subjects to make inferences on the entire population for certain research questions; for example, the association between environmental factors and mental health outcomes in older adults. However, random errors, such as sampling and measurement errors may be present and affect the reliability of the findings.

Sampling errors can result in type I error (rejecting the null hypothesis when it is true) or type II error (accepting the null hypothesis when it is false). The extent of sampling errors is usually quantified by the p-values and confidence intervals, while confidence intervals are considered more informative than p-values because they not only provide statistical significance but also a range of effects that may be reflective of the true population effect. These errors cannot be eliminated but can be controlled and kept at an acceptable level by increasing the sample size or through the application of efficient statistical methods and an appropriate study design. Measurement errors may occur because of imprecision related to devices, tools, measurements of exposure (e.g., air pollution and noise) and outcome (e.g., cognition), or other covariates. These errors may be solved by using the average values of several repeated measurements.

5.3.3 Systematic errors

Systematic errors contain three major components in longitudinal cohort studies, namely selection bias, information bias, and confounding. These issues are essential for epidemiological studies in deriving causal inferences.

5.3.3.1 Selection bias

In longitudinal cohort study with long follow-up time, selection bias may be introduced as a result of factors that influence the continued participation of subjects, such as loss to follow-up over time or death. If the rate of loss to follow-up differs when comparing exposed and unexposed groups, the rate of loss to follow-up also differs when comparing people who developed the disease and people who did not, as the association between exposure and health outcome would be biased. However, information on outcomes may not be obtained for dropouts. There are some established statistical methods to consider when addressing this bias, such as the inverse probability of selection weights and quantitative bias analysis.

Differential weighting can be applied for unequal probabilities of selection. IPW assigns weights to each participant that remains in the model.(126,127) If the characteristics of observation are similar to those who dropped out, then that observation will be given a larger weight, based on the characteristics that exist in the data for each observation. Given that, a *pseudo*-population is generated, which can better represent the characteristics of the whole cohort, including dropouts. The potential selection bias due to loss of follow-up will be reduced or even removed in the *pseudo*-population.(127)

A competing risk event is an alternative event that precludes the observation of the primary outcome of interest. In an aging population with notably high morbidities, the competing risk of death is especially high. The cause-specific hazard function and the subdistribution hazard function are recommended for analyzing competing risk survival data.(128) The cause-specific hazard function was usually employed when addressing

research questions on etiology and causal effects.(128) The subdistribution hazard function was more relevant for research questions estimating incidence or predicting disease prognosis in the presence of competing risks.(128) Overall, the estimations from the competing risk analyses can provide insights on the strengths of the associations between the risk factors and outcomes after considering competing risk events.

In the thesis studies, we first described the characteristics of dropouts (due to refusal or moving residences) and those that remained in the study. The exposure levels of the dropouts were very similar to those who remained in the study. Further, we applied IPW and considered competing risks in *Studies II, III*, and *IV* when the methods were applicable. We observed similar results compared to the main analyses, indicating the main findings were robust and selection bias was less likely to occur in our results.

5.3.3.2 Information bias

Information bias may happen when the information obtained from participants in the study is inaccurate. Consequently, the information collected regarding exposure and/or outcomes is misclassified. The information bias can be either differential or nondifferential, depending on whether the rate of misclassification differs in different study groups. Nondifferential misclassification arises from inaccuracies in how data is collected from any study group in either cases and non-cases, or exposed and non-exposed participants. This type of misclassification usually tends to dilute the true association and the relative risk tends to shift toward the null. On the contrary, differential misclassification leads to wrongly classified groups which often under- or overestimate the true association. For instance, unexposed cases are misclassified as being exposed more often than unexposed non-cases are misclassified as being exposed. In general, to avoid misclassification, the trained staff in the SNAC-K cohort objectively assessed the participants following standard protocols at baseline and follow-up examinations.

Exposure. The potential misclassification of the exposure may occur when the modeled exposure levels are not reflective of the true levels. Our assessment of the exposure was within high spatial resolutions of the residential addresses instead of the postal codes that were used in previous studies. Also, the exposure levels were validated with monitoring data, which showed high correlations. Moreover, we have detailed information on the residential changes during follow-ups. The misclassification issue may also occur when the modeled exposure windows were not aligned with the etiologic exposure windows, particularly when the disease has a long pre-clinical accumulation of disease pathology. Therefore, years to decades before disease onset are the most relevant exposure period.(129) Some studies used exposure periods one to two years before the baseline assessment as a proxy for chronic exposures.(91,94,130,131) Most studies had to estimate air pollution exposures based on very recent data or a single-

year exposure, and assume that the recent exposure levels are representative of those in the past to account for the effect of exposure earlier in life.(132,133) This assumption is very strong; particularly when the outcome and the relevant exposure window have long time intervals and in studies that fail to consider residential changes. To minimize potential misclassification of exposure levels, we considered several exposure windows, such as 10-, 5-, and 3-year average levels before baseline, as well as the moving average during follow-up assessments. Also, a study showed that retired Swedish older adults tend to spend more time at home or move around their accommodations.(134) Thus, the effect estimations of environmental exposure would more likely be in a nondifferential fashion.

Outcome. The potential misclassification of the cognitive outcomes and depression seemed more likely to be nondifferential in our studies, because environmental pollution is independently assessed from mental health outcomes and vice versa. As previously mentioned, data from the register or medical records may lead to underdiagnosis or delayed diagnosis of the outcomes, which has been evaluated in Sweden.(125) High positive and negative predictive values were observed in the Swedish patient register, but there was about 5 years of delayed entry for dementia cases.(125) Using such administrative data may cause an underestimation of the effect of environmental pollution. However, the ascertainment of dementia in the present doctoral thesis was made according to clinical DSM-IV diagnostic criteria at each wave of assessment. Information on dementia cases that occurred between two follow-up periods was derived from the patient register and death register, enabling us to capture dementia cases as exhaustively as possible. Cognition status was assessed using the MMSE and comprehensive neuropsychological test battery. MMSE is a widely used cognitive assessment tool in both clinical routine and research settings, but it has limitations on determining cognition in high- and low-education groups, referred to as 'ceiling' and 'floor' effects. MMSE also lacks tests on assessing cognitive components of executive function and processing speed, which may lead to less sensitive detection of subtle changes in the early stage of cognitive impairment, especially in highly educated populations like SNAC-K. However, instead of using predefined cut-offs to dichotomize the MMSE score, we took advantage of linear mixed-effect models to assess the longitudinal change in MMSE considering not only the fixed effect but also the random intercept and slope over time for each individual. Taken together, if the ceiling effect would have occurred, we could have had an underestimation or not detected the effect of air pollution on faster cognitive decline. On the contrary, the neuropsychological battery is a more robust instrument with a set of tests that are not influenced by education levels. For the depression diagnoses, we considered inclusively both minor and major depression cases based on DSM-IV criteria. Therefore, the definitions of the outcomes in this doctoral study are less likely to be misclassified and, if there is a misclassification, it is most likely to be nondifferential or an underestimation.

5.3.3.3 Confounding

Confounding refers to a factor that is an established risk factor for the outcome and associated with exposure, but is not a consequence of exposure. In the four doctoral studies, confounding factors were predefined according to the existing literature. We dealt with the potential confounding issues by including these factors in the model adjustment or stratification. However, residual confounding may occur because of unmeasured or unknown confounding factors. Some data were not available at the time we conducted the study, such as neighborhood socioeconomic factors and other environmental risk factors (e.g., green- or water space, and transportation noise), so we did not consider some of these factors in *Study I* and *Study II*. We also conducted additional sensitivity analyses for *Study I* and *Study II*. No significantly different results were observed. These factors were thoroughly considered in *Study III* and *Study IV*. However, we did not have information on individual indoor exposure levels related to air pollution and noise.

5.3.4 Generalizability

The final goal of epidemiological research is to apply the research findings to other circumstances. Considering the above-mentioned biases and errors, we believe our studies have generally high internal validity. Given the unique characteristics of the SNAC-K study participants—who reside in an urban area of central Stockholm, have high education levels, are relatively healthy and wealthy, and have low levels of environmental pollution; especially air pollution—the findings from the thesis may shed some light on populations with similar characteristics. Nevertheless, these findings have limited generalizability across heterogeneous populations; for instance, those with low social economic status, or places with very high levels of environmental pollution.

6 Conclusions

Based on the findings from the four constituent studies, we draw the following conclusions regarding the overall research aim of the doctoral project.

First, long-term exposure to air pollution was a risk factor for the full cognitive spectrum, including faster cognitive decline, cognitive impairment, and the progression from impaired cognitive function to dementia in older adults. Specifically, the oldest-old group with cerebrovascular diseases was the most vulnerable group, even at a low level of air pollution exposure. Second, long-term exposure to air pollution may also be a risk factor for depression in late life. However, active social engagement could counteract the hazardous effect of air pollution on developing depression. Third, transportation noise from aircraft and railways was also found to increase the risk of cognitive outcomes. No evidence supported the relationship between road traffic noise and cognitive outcomes. An increase in the number of transportation noise sources led to a higher risk of cognitive impairment.

To sum up, the findings of this doctoral project reveal that long-term exposure to air pollution and transportation noise is associated with negative mental health outcomes among older adults.

7 Points of perspective

7.1 Public health implications

The remarkable increase in the global aging population requires public health authorities to implement actions for a good and healthy aging life. Preventing or delaying age-related mental disorders has been identified as a global public health priority, as these diseases posed enormous economic and societal burdens for individuals, families, and communities. Our findings have important implications for reducing the burden of negative cognitive outcomes as well as promoting cognitive health in older adults, which was in line with Sustainable Development Goal 3 (good health and well-being) and Goal 11 (sustainable cities and communities).

Achieving these goals requires us to understand the extent to which environmental risk factors—such as air pollution and transportation noise—can have negative effects on mental well-being. If our observed associations are causal, our findings highlight the importance of future policies and interventions aiming at reducing environmental pollution levels in residential areas; for instance, urban planning measures, adding barriers beside the major roads, and regulations on transportation emissions. Such interventions could have significant public health benefits, potentially reducing the burden of mental disorders in older populations and improving overall cognitive health and quality of life. Also, individuals can benefit from the knowledge of the negative impact of environmental pollution on mental health, so that they may develop personal prevention approaches to attain better mental health, such as wearing facial masks, avoiding routes in heavily polluted areas, etc.

Moreover, identifying people who are more vulnerable to environmental risk factors is of great importance for disease prevention. Our findings suggested the presence of cardiovascular diseases and perceived cognitive impairment may enlarge the risk of cognitive decline and dementia corresponding to environmental pollution exposure, respectively. These may provide evidence for future tailored interventions or resource allocation that can address specific needs or the distribution of protective equipment to those who are at higher risk of exposure, such as the installation of air purifiers and improved ventilation.

Our results also suggested that more social engagement could potentially counteract the harmful effects of air pollution on depression. Thus, promoting healthy lifestyles that are beneficial for mental health may be another potential approach to reduce the risk of mental disorders due to environmental pollution.

7.2 Future directions

The present doctoral thesis, together with the existing literature, provides evidence regarding the extent to which environmental pollution is harmful to mental health in older adults. However, our main research findings need to be verified by future studies, and there are several research lines that can be advanced to fill the remaining research gaps.

Research on assessing the impact of environmental factors on mental health should be further extended. Although our line of research revealed the impact of environmental factors, including air pollution and transportation noise, in relation to mental disorders, to what extent other environmental factors—for instance, greenspace, water space, and built environments—could influence mental health in late life remains unclear. These environmental factors may be closely related to each other and act synergistically on mental health issues. The interaction between environmental pollution on mental health disorders, therefore, warrants further investigation.

Due to the unique characteristics of the SNAC-K population, our findings may not be generalizable to populations with low socioeconomic status or those exposed to very high levels of environmental pollution. Hence, studies in these settings relying on longitudinal data would be valuable.

Furthermore, the biological mechanisms underlying these observed associations merit further study. For instance, as we mentioned before, environmental pollution may elevate stress hormones or induce dysregulation of cardiovascular function, which further increases the risk of mental disorders. These pathway analyses are warranted to disentangle potential mechanisms. Also, the link between environmental pollution and negative cognitive outcomes was only reported according to clinical manifestations. Longitudinal brain imaging data could provide more insights into structural changes in the brain corresponding to high levels of environmental pollution.

Finally, previous research has identified many favorable cardiovascular factors for improving and maintaining cardiovascular health. Also, there is a clear brain-heart connection in dementia development. Thus, studies may focus on determining whether the association between environmental pollution and mental disorders could be mitigated through beneficial cardiovascular factors, such as the recently proposed "Life's Essential 8" ideal cardiovascular health by the American Heart Association.

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10 Appendices

Appendix Table 1 Longitudinal studies on long-term exposure to PM and NO_x in relation to cognitive function in older adults.

Study	Follow-up	N	Outcomes	Exposure length	Air pollution	Results β/RR (95% CI)
Cognitive decline						
NHS, US, 2012 **(59)**	4 years	19409	Global cognition	~10 years	$PM_{2.5}$ (per 10μg/m^3)	-0.018 (-0.035, -0.002)
WHICAP, US, 2020 **(60)** [a]	6 years	5330	Global cognition	1 year	$PM_{2.5}$ (per 4.81μg/m^3)	-0.066 (-0.085, -0.048)
					PM_{10} (per 9.90μg/m^3)	-0.030 (-0.046, -0.014)
					NO_2 (per 12.32μg/m^3)	-0.062 (-0.082, -0.041)
NOMAS US, 2020 **(60)** [b]	5 years	1093	Global cognition	1 year	$PM_{2.5}$ (per 1.34μg/m^3)	-0.015 (-0.065, 0.034)
					PM_{10} (per 5.37μg/m^3)	-0.019 (-0.059, 0.022)
					NO_2 (per 3.16ppb)	-0.004 (-0.040, 0.032)
3-City, France, 2022 **(61)**	12 years	6380	MMSE	5 years	$PM_{2.5}$ (per 1.5μg/m^3)	-0.006 (-0.011, -0.001)
					NO_2 (per 8.1μg/m^3)	-0.004 (-0.009, 0.002)
Betula, Sweden, 2017 **(63)**	15 years	2516	Episodic memory	1 year	NOx (per 1μg/m^3)	0.005 (-0.018, 0.027)
Whitehall II, UK, 2014 **(62)**	5 years	2867	Memory	5 years	$PM_{2.5}$ (per 1.1μg/m^3)	-0.033 (-0.080, 0.015)
					PM_{10} (per 1.8μg/m^3)	-0.023 (-0.071, 0.025)

Appendix Table 1 *Continued.*

Study	Follow-up	N	Outcomes	Exposure length	Air pollution	Results β/RR (95% CI)
Cognitive impairment						
REGARDS, US, 2015 **(56)**	~4 years	15,976 Urban	SIS ≤4	1 year	$PM_{2.5}$ (per 10μg/m^3)	OR 1.06 (0.77–1.48)
WHIMS, US, 2017 **(51)**	~9.6 years	3647 women	Δ3MS <8	3 years	$PM_{2.5}$ (>12 vs ≤12 μg/m^3)	HR 1.81 (1.42–2.32)
TLSA, China, 2019 **(52)**	-	2241	SPMSQ <3	3 years	PM_{10} (per 10μg/m^3)	OR 1.12 (1.04–1.20)
ZJMPHS, China, 2020 **(53)**	2 years	7311	CMMSE Illiteracy: 17/18; primary school: 20/21; above primary school; 24/25	1 year	$PM_{2.5}$ (per 1μg/m^3) PM_{10} (per 1μg/m^3)	OR 1.04 (1.01–1.08) OR 1.03 (1.001–1.06)
CLHLS, China, 2020 **(54)**	12 years	1324	MMSE <18	3 years	$PM_{2.5}$ (per 10μg/m^3)	HR 1.03 (1.01–1.06)
TIGER, China, 2020 **(55)**	4 years	360	MoCA-T <24	11 years	$PM_{2.5}$ T1 (<29μg/m^3) T2 (29–30μg/m^3) T3 (>30μg/m^3) PM_{10} T1 (<49.6μg/m^3) T2 (49.6–51.2μg/m^3) T3 (> 51.2μg/m^3)	Reference HR 2.23 (0.76–6.55) HR 4.56 (1.51–13.82) Reference HR 0.95 (0.42–2.14) HR 1.03 (0.43–2.47)
MYHAT study, US, 2021 **(50)**	5 years	1572	CDR =0.5	5 years	$PM_{2.5}$ (per 1μg/m^3)	HR 3.42 (2.81–4.16)

Note: CDR, Clinical Dementia Rating; CLHLS, Chinese Longitudinal Healthy Longevity Study; MoCA-T, Montreal Cognitive Assessment-Taiwanese version; MYHAT, Monongahela-Youghiogheny Healthy Aging Team; MMSE, Mini-Mental State Examination; NHS, Nurses' Health Study; NOMAS, Northern Manhattan Study; REGARDS, REasons for Geographic And Racial Differences in Stroke; SIS, Six-Item Screener; SPMSQ, Short Portable Mental Status Questionnaire; TLSA, Taiwan Longitudinal Study on Aging; TIGER, Taiwan Initiative for Geriatric Epidemiological Research; WHICAP, the Washington Heights Inwood Community Aging Project; WHIMS-ECHO, Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes; ZJMPHS, Zhe-jiang Major Public Health Surveillance.

Appendix Table 2 Summary of studies on long-term exposure to air pollution and depression in older adults.

Study	Design	N	Outcomes	Exposure length	Air pollution	Results
NHID, Korea, 2016 **(67)**	Longitudinal	27,270	ICD-10 (F32)	3 years	$PM_{2.5}$ (per 10μg/m^3)	HR 1.59 (1.02–2.49)
NHS, USA, 2017 **(68)**	Longitudinal	41,844 Women	Doctors' diagnosis or antidepressant prescription	5 years	$PM_{2.5}$ (per 10μg/m^3)	OR 0.97 (0.83–1.14)
NSHAP, USA,2017 **(69)**	Longitudinal	4008	CES-D-11 (≥9)	4 years	$PM_{2.5}$ (per 5μg/m^3)	OR 1.14 (0.97–1.34)
KSHS, Korea, 2019 **(70)**	Longitudinal	123045	CES-D or doctors' diagnosis or antidepressant prescription	1 year	$PM_{2.5}$ (per 10μg/m^3)	HR 1.01 (0.83–1.22)
					PM_{10} (per 10μg/m^3)	HR 1.11 (1.06–1.16)
SALIA, Germany, 2020 **(71)**	Cross-sectional	821 Women	Self-reported or CESD-R	1 year	$PM_{2.5}$ (per 1.8μg/m^3)	OR 1.62 (1.06–2.46)
					PM_{10} (per 2.2μg/m^3)	OR 1.25 (0.94–1.67)
					NO_x (per 23.4μg/m^3)	OR 1.37 (0.94–1.99)

Note: CES-D, Center for Epidemiologic Studies Depression Scale; HR, hazard ratio; ICD, international classification of diseases; KSHS, Kangbuk Samsung Health study; NHID, National Health Insurance Database; NHS, Nurses' Health Study; NSHAP, National Social Life, Health, and Aging Project; OR, odds ratio; SALIA, Study on The Influence of Air Pollution on Lung Function, Inflammation and Aging.

Appendix Table 3 Summary of studies on long-term exposure to noise and cognition in older adults.

Study	Design	N	Outcomes	Noise source	Results
HNRS, Germany, 2016 **(81)**	Cross-sectional	4050	Global cognition	General	β 0.02 (-0.04, 0.07)
HNRS, Germany, 2016 **(82)**	Cross-sectional	4086	MCI	General	OR 1.40 (1.03, 1.91)
ALFA, Spain, 2020 **(80)**	Cross-sectional	958	Global Cognition	General	β 0.11 (SE: 0.29)
SALSA, US, 2020 **(83)**	Longitudinal	1612	CIND or dementia	Roadway	HR 1.2 (0.97, 1.6)
CHAP, US, 2021 **(79)**[a]	Cross-sectional	5227	MCI AD	General	OR 1.36 (1.15, 1.62) OR 1.29 (1.08, 1.55)
CHAP, US, 2021 **(79)**[b]	Longitudinal	5227	Global Cognition	General	Baseline: β -0.04 (-0.11, 0.04) Change: NS

Note: AD, Alzheimer's dementia; ALFA, ALzheimer and FAmilies; CHAP, Chicago Health and Aging Project; CIND, cognitive impairment no dementia; HNRS, Heinz Nixdorf Recall's study; HR, hazard ratio; MCI, mild cognitive impairment; OR, odds ratio; SALSA, Sacramento Area Latino Study on Aging.

Appendix Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991–2022.

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly—Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and

utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia—Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study.

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta. Drug use among the very old living in ordinary households- Aspects on well-being, cognitive and functional ability.

Rehnman Jenny. The role of gender in face recognition. (Stockholm University)

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.

Meinow Bettina. Capturing health in the elderly population – complex health problems, mortality, and the allocation of home help services. (Stockholm University)

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

2009

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.

Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

2011

Schön Pär. Gender matter. Differences and changes in disability and health among our

oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

Lovén Johanna. Mechanism of women's own-gender bias and sex differences in memory for faces.

2013

Hooshmand Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical

variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

2015

Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

Svärd Joakim. Emotional facial processing in younger and older adults.

Wang Rui. Cardiovascular risk factors, brain structure, and cognitive decline in old age.

Pantzar Alexandra. Cognitive performance in old-age depression.

2016

Kelfve Susanne. Gotta survey somebody: methodological challenges in population surveys of older people.

Heap Josephine. Living conditions in old age: Coexisting disadvantages across life domains.

Håkansson Krister. The role of socio-emotional factors for cognitive health in later life.

Shakersain Behnaz. Impact of nutritional status and diet on cognitive decline and survival.

Bellander Martin. Plasticity of memory functioning: genetic predictors and brain changes.

2017

Ferencz Beata. Genetic and lifestyle influences on memory, brain structure, and dementia.

Köhncke Ylva. Lifestyle, cognitive aging, and brain correlates.

Santoni Giola. How well are we aging? Capturing the complexity of health trajectories of older adults.

Becker Nina. Inter-individual differences in associative memory: Structural and functional brain correlates and genetic modulators.

2018

Nilsen Charlotta. Do psychosocial working conditions contribute to healthy and active aging? Studies of mortality, late-life health, and leisure.

Darin-Mattsson Alexander. Set for life? Socioeconomic conditions, occupational complexity, and later life health.

Marseglia Anna. The Impact of diabetes on cognitive aging and dementia.

Heiland Emerald. Cardiovascular risk factor profiles in the development and progression of physical limitation in old age: A population-based study.

Sjöberg Linnea. Using a life-course approach to better understand depression in older age.

Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

2019

Seblova Dominika. Causal effects of education on cognition – How do we generate evidence?

Berggren Rasmus. Cognitive development and educational attainment across the life span.

Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.

Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.

Pan Kuan-Yu. Impact of psychosocial working conditions on health in older age.

Avelar Pereira Bárbara. Multimodal imaging: Functional, structural, and molecular brain correlates of cognitive aging

Morin Lucas. Too much, too late? Drug prescribing for older people near the end of life.

de Boer Lieke. Dopamine, decision-making, and aging: Neural and behavioural correlates.

Ek Stina. Predictors and consequences of injurious falls among older adults: A holistic Approach.

Ding Mozhu. The role of atrial fibrillation in cognitive aging: a population-based study

2020

Dintica Cristina Silvia. Oral health & olfactory function: what can they tell us about cognitive ageing?

Payton Nicola Maria. Understanding preclinical dementia: early detection of dementia through cognitive and biological markers.

Li Xin. The relation among aging, dopamine-regulating genes, and neurocognition.

Grande Giulia. Development of dementia in older adults: the body-mind connection.

2021

Shang Ying. How can older adults combat diabetes to achieve a longer and healthier life?

Sif Eyjólfsdóttir Harpa. Unequal tracks? Studies on work, retirement and health.

Sundberg Louise. Better all the time? Trends in health and longevity among older adults in Sweden.

2022

Saadeh Marguerita. Enjoying life and living healthier: impact of behavioral and psychosocial factors on physical function in old age.

Naseer Mahwish. Why do older adults seek emergency care? The impact of contextual factors, care, health, and social relations.

Guo Jie. Unraveling the relationship between body mass index and cardiometabolic disease, dementia, and survival in old age.