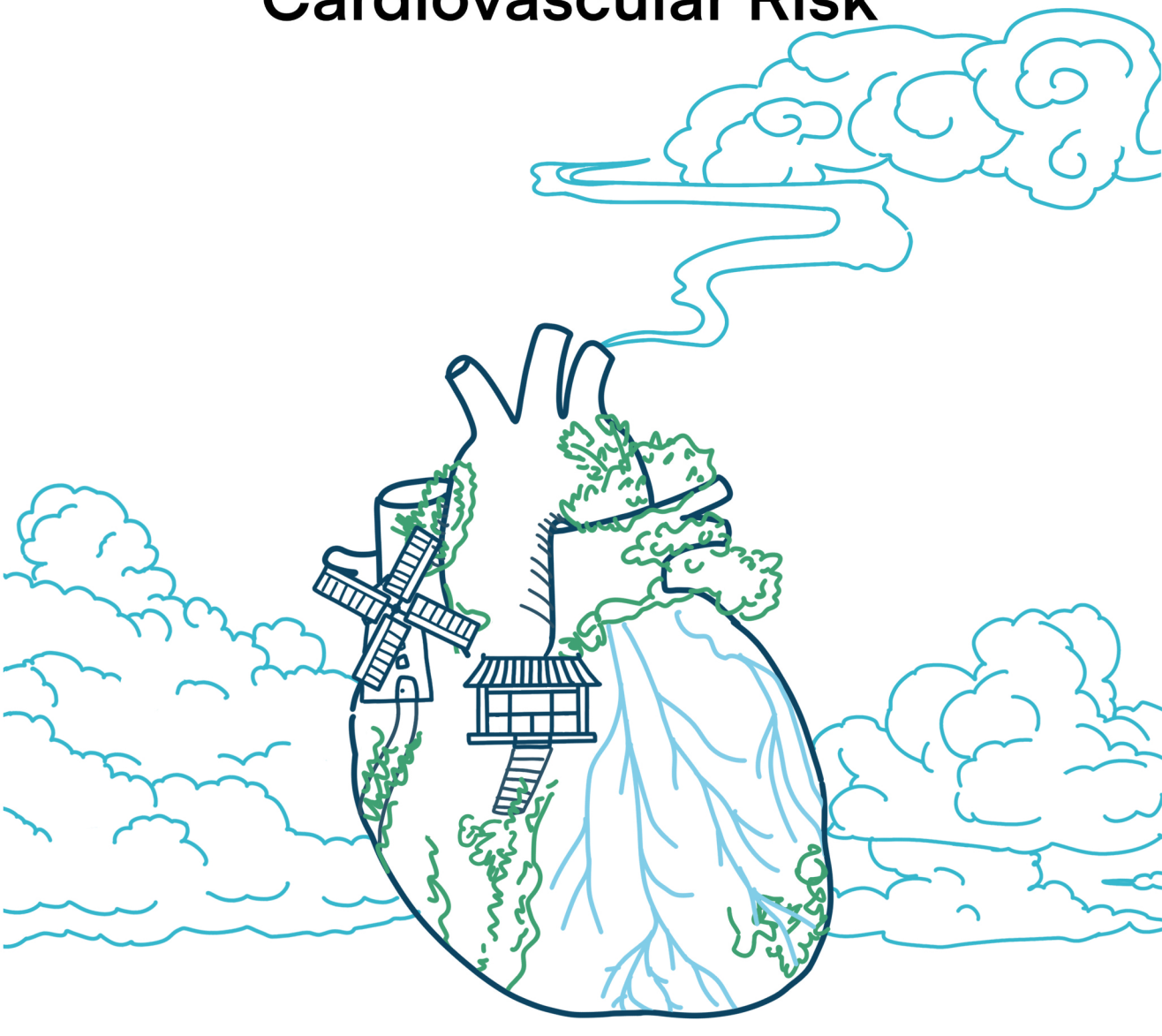
Built Environment and Cardiovascular Risk



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PhD thesis. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, the Netherlands.

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Built environment and cardiovascular risk

Gebouwde omgeving en cardiovasculair risico

(met een samenvatting in het Nederlands)

建成环境与心血管疾病风险

(附中文简介)

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Contents

CHAPTER 1

General introduction

Epidemiology of cardiovascular disease

Cardiovascular diseases (CVD) remain the leading cause of the global burden of disease and this is expected to rise substantially in the next few decades [1]. The prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019, which makes CVD the leading cause of global mortality and a major contributor to disability [2]. Globally, CVD caused 18.6 million deaths and 34.4 million years lived with disability in 2019 [2]. CVD deaths represent about one-third of all global deaths [3]. In order to meet the United Nations' Sustainable Development Goals 3 and achieve a one-third reduction in premature mortality from noncommunicable diseases by 2030 [4], it is essential to obtain knowledge on modifiable determinants of CVD and develop subsequent prevention strategies.

Determinants of cardiovascular risk

CVDs are a group of disorders of the heart and blood vessels. Among those, ischemic heart disease (IHD) and stroke contribute most to the disease burden. Specifically, 85% of CVD deaths were due to heart attack (acute event resulting from IHD) and stroke [2,3]. Atherosclerosis is a critical mechanism underlying many CVDs [5]. Endothelial dysfunction and inflammation contribute to the formation of fibrofatty lesions in the artery wall, which progress to plaque [5]. The resulting narrow and stiffness of arteries reduce blood flow and oxygen supply to tissues [5].

There are clinical risk factors such as obesity, hypertension, diabetes mellitus, dyslipidemia, and psychological disorders. The clinical risk factors are influenced by behavioural risk factors like physical activity, sedentary behaviour, diet, smoking, and sleep. These remain the top risk factors for global burden of CVD and mortality [2,6].

Socio-ecological models suggest that the above mentioned risk factors are further driven by "upstream" determinants, that is the contextual characteristics in social, policy, and built environment [7–9]. The built environment is defined as the characteristics of manmade entities of the communities in which we live, work and play, including neighbourhoods, home, office, and transportation infrastructures [10]. Its by-products,

like air pollution, noise levels, and ambient temperature, are often included [11]. Nowadays, the paradigm in CVD research has shifted from individual risk factors to these upstream determinants [12]. They are good entry points for population-level intervention [12]. The current thesis focuses on the built environment.

Gaps in current evidence

Previous literature reviews found preliminary evidence on the associations between neighbourhood built environment, behavioural risk factors, clinical risk factors, and CVD outcome (**Figure 1**) [11,13]. However, there are still a lot of gaps in the current evidence. First, time and place, or people's daily mobility were not well considered when investigating the association between built environment exposure and CVD [11]. Second, the empirical evidence on the mechanisms or pathways underlying the association between the built environment and CVD are not well established [11]. Third, the interaction or confounding effects of built environment attributes in relation to CVD are not well understood [11]. Lastly, the prospective design is critical and merited in establishing causality between the built environment and CVD [11].

Moreover, the cardiovascular risk is a continuum. Although CVD burden mostly comes from adults rather than children [2], it has been shown that the clustering of cardiometabolic risk factors is stable from childhood to adulthood [14–16]. The risk factors include body mass index, blood pressure, glucose, triglyceride, high-density lipoprotein cholesterol and so on. Therefore, out of early prevention, it is interesting to investigate the association between built environment attributes and cardiovascular risk among children.

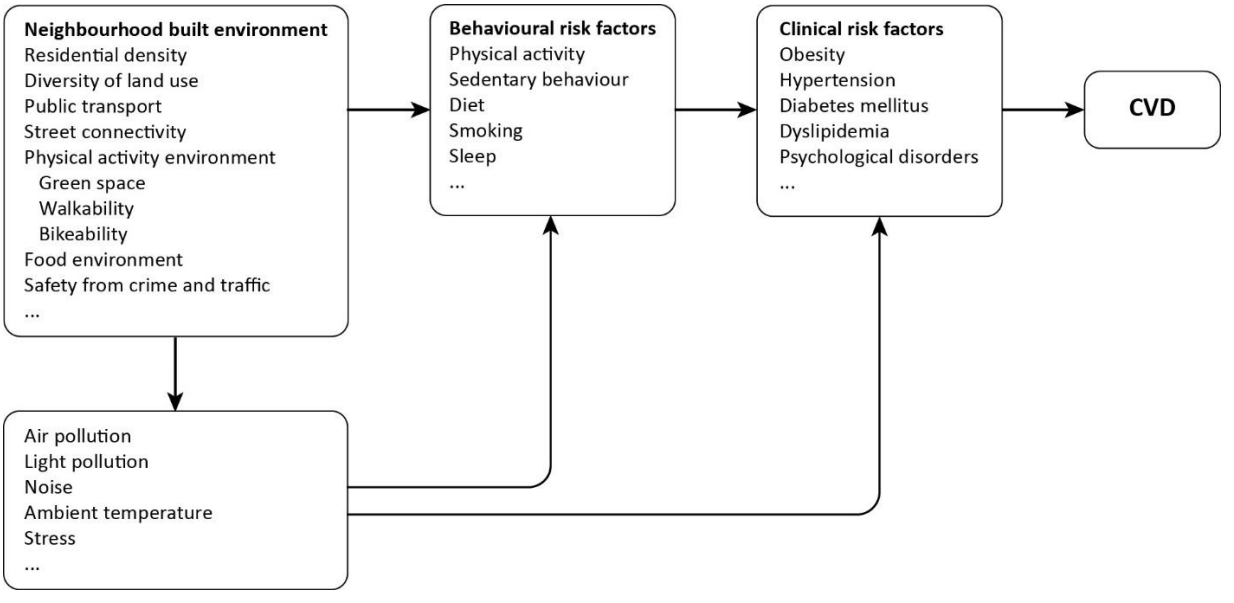

Figure 1. A simplified framework of the impact of neighbourhood built environment on CVD via behavioural risk factors and clinical risk factors [11,13].

Thesis objectives

The objective of this thesis is to gain insight into the current evidence of the association between the built environment and cardiovascular risk, and to originally investigate the underlying mechanisms and long-term associations, while taking into account the identified research gaps.

Setting

The studies described in this thesis were embedded within Exposome-NL [17]. Exposome-NL is a Dutch consortium of over fifty scientists from different disciplines, universities and medical centres [17]. Together the scientists are systematically sequencing the environmental factors influencing health [17].

One original study included in this thesis was conducted as a cross-sectional survey in Guangzhou, China. Guangzhou is the capital city of Guangdong Province in south China.

Other original studies included in this thesis were conducted in The Netherlands and used data from the Geoscience and Health Cohort Consortium (GECCO) [18–20]. GECCO is

a Dutch infrastructure to support researchers to study the relation between environmental characteristics and health. The environmental data are centralized and operationalized to enrich more than 25 ongoing cohort studies within GECCO. Three cohort studies that are affiliated with GECCO were included in this thesis. Apart from cohorts in the GECCO, the register data from the Statistics Netherlands (CBS) were also used, that included all registered residents in The Netherlands [21]. The environmental exposure data at the home address-level were linked to individuals.

Thesis outline

Chapter 2 summarizes the evidence on the association between built environment and CVD. Chapter 3 to 6 zoom in specific built environment characteristics and address the identified research gaps, respectively. Chapter 3 describes the spatial disparities in the availability of green space in the Netherlands. Chapter 4 investigates the mutual confounding effect of air pollution and green space in relation to cardiometabolic risk among children. Chapter 5 identifies trajectory groups of neighbourhood walkability in the Dutch population over thirteen years and compares their subsequent risk of CVD for eleven years. Chapter 6 provides empirical evidence on the pathways underlying the association between green space exposure and blood pressure. In this chapter, people's mobility was considered by combining exposure from residence and workplace.

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CHAPTER 2

The built environment and cardiovascular disease: an umbrella review and meta-meta-analysis

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Air pollution

Strong evidence
PM2.5 & stroke, SO_2 & AF, CO & AF, NO_2 & IHD events

Highly suggestive evidence
PM2.5 for MI, IHD mortality, CeVD mortality, CVD mortality, CVD events, stroke events. PM10 for AF.
NO_2 for CVD mortality, ICH mortality, CHD mortality

Meta-meta-analyses per 10 μg/m^3 increase
PM2.5 & IHD mortality: 1.64 (1.62 to 1.66)
PM2.5 & CVD mortality: 1.06 (1.04 to 1.08)
NO2 & CeVD mortality: 1.01 (0.98 to 1.05)

Ambient temperature

Suggestive evidence
Temperature for CVD mortality
Heat for CVD mortality, combined CVD mortality
Cold for CVD mortality, CeVD mortality, ICH morbidity, combined CVD mortality

Highly suggestive evidence
Meta-meta analysis per 1 °C increase
Heat & CVD mortality: 1.013 (1.010 to 1.015)

Current evidence on built environment and CVD

MEDLINE, EMBASE, CINAHL, Scopus, CDSR, JBI, and PROSPERO till April 16th, 2021

3304 Records after duplicates removed

51 Studies included in qualitative synthesis

4 meta-meta-analysis Studies included in quantitative synthesis

Gaps found in light pollution, food & physical activity environment, urbanisation

Strong evidence
Aircraft traffic noise increase the risk of CVD mortality

Residential noise

Suggestive evidence
Greenspace lower the risk of CVD mortality

Green space

Abstract

Aim

To provide a comprehensive overview of the current evidence on objectively measured neighbourhood built environment exposures in relation to cardiovascular disease (CVD) events in adults.

Review methods

We searched seven databases for systematic reviews on associations between objectively measured long-term built environmental exposures, covering at least one domain (i.e., outdoor air pollution, food environment, physical activity environment like greenspace and walkability, urbanisation, light pollution, residential noise, and ambient temperature), and CVD events in adults. Two authors extracted summary data and assessed the risk of bias independently. Robustness of evidence was rated based on statistical heterogeneity, small-study effect and excess significance bias. Meta-meta analyses were conducted to combine the meta-analysis results from reviews with comparable exposure and outcome within each domain.

Results

From the 3,304 initial hits, 51 systematic reviews were included, covering five domains and including 179 pooled estimates. There was strong evidence of the associations between increased air pollutants (especially PM2.5 exposure) and increased residential noise with greater risk of CVD. Highly suggestive evidence was found for an association between increased ambient temperature and greater risk of CVD. Systematic reviews on physical activity environment, food environment, light pollution and urbanisation in relation to CVD were scarce or lacking.

Conclusions

Air pollutants, increased noise levels, temperature, and greenspace were associated with CVD outcomes. Standardizing design and exposure assessments may foster the

synthesis of evidence. Other crucial research gaps concern the lack of prospective study designs, and lack of evidence from LMIC's.

Systematic review registration: PROSPERO CRD42021246580.

Lay summary

This study is a review of published systematic reviews on the relation between the neighbourhood built environment and cardiovascular disease (CVD) in adults.

- There was strong evidence of a relation between increased air pollutants and a greater risk of CVD. There was also strong evidence of a relation between increased residential noise and a greater risk of CVD. There was highly suggestive evidence of a rerlation between increased ambient temperature and a greater risk of CVD.

- Systematic reviews that examined other aspects of the built environment, such as the physical activity environment, food environment, light pollution and urbanisation were scarce or lacking.

Introduction

Cardiovascular diseases (CVD) are the leading cause of the global disease burden. [1] Worldwide CVD cases have doubled in the past 20 years. In 2019, 523 million cases led to 18.6 million deaths and 34.4 million years lived with disability. [2] The burden of CVD is not only an individual health issue, but also a societal burden that strains healthcare and economic systems. The World Heart Federation estimates that the global cost of CVD will rise from roughly $863 billion in 2010, to $1,044 billion in 2030. [3] Therefore, it is important to deepen our understanding of the determinants of CVD in individuals and populations and develop sustainable strategies for reduction and prevention.

Lifestyle behaviours, like physical inactivity and unhealthy diet, are important risk factors of CVD. [1,2,4] Ecological models suggest that these behavioural risk factors are driven by contextual characteristics in the social, policy and built environments, also known as "upstream determinants". [5-7] The paradigm in CVD research has shifted, with the focus moving to these upstream determinants as promising entry points for population-level action to prevent CVD. [8] The majority of the world's population resides and spends most of its time in highly organised built environments. The built environment is a subset of the exposome, which is the sum of all environmental drivers of health and disease throughout life. [9] The built environment is defined as all aspects of a person's surroundings that are man-made or modified, such as buildings, parks, facilities and infrastructure. [10] Its direct effects, like air pollution, noise levels, and ambient temperature, are often included. [11]

The mechanisms by which the built environment might affect CVD are not well established. Conceptually, there are two main pathways proposed. [12] The first pathway is between active built environmental exposure and behavioural risk factors. [12] For active exposure, one needs to actively use of the environment to be exposed. Attributes such as walkability, which is comprised of individual elements like sidewalks, connected streets and proximity to key destinations, can facilitate a more active lifestyle. [13,14] Access to and availability of certain food resources may either improve or diminish diet

quality, depending on whether these food resources are greengrocers or fast-food outlets, for example. [15] The second pathway is between passive built environmental exposure and CVD. This includes exposures that occur when one is simply present in the environment, such as air pollution, residential noise and ambient temperature. [12] Exposure to increased levels of air pollution can promote systemic inflammation and oxidative stress. As a result, a variety of pathological processes, such as increased thrombosis, hypercoagulability and endothelial dysfunction, could eventually lead to CVD. [16,17] Noise and ambient temperature may cause typical physiological responses including hypertension, vasoconstriction and tachycardia that may lead to CVD. [18,19]

The two aforementioned pathways are not mutually exclusive, which increases complexity of research in this field. [11] Many environmental aspects may be interrelated. For example, the benefits of living in a dense, walkable environment might be diminished by increased exposure to traffic-related air pollution. [20] Attributes may also operate at multiple scales or contexts, from neighbourhoods to entire regions, or from rural to urban areas. Consequently, the same built environmental aspects may have different effects from different perspectives or contexts. Urbanisation, a context indicator of the urban development level, serves as a container of above mentioned built environmental aspects. It is worthwhile to study urbanisation as a proxy of a built environment and its confounding or interaction effect with other aspects. Furthermore, 55% of the world's population lives in urban areas, a proportion that is expected to increase to 68% by 2050. [21] It is therefore relevant to understand what this means in terms of CVD risk.

Over the past two decades, a significant number of systematic reviews have examined the relationship between the built environment and CVD. However, these studies often address single (sub)domains of exposures, or the built environment was not the primary focus of the reviews. It is difficult for readers to assess and synthesise the piecemeal published evidence. As such, we aimed to provide a comprehensive overview of the current evidence, identify crucial research gaps and determine the implications for public health, clinical medicine, policy and regulation. To accomplish this, we conducted

an umbrella review of systematic reviews and meta-analyses to investigate associations between the built environment and CVD events in adults. This review may also serve as a reference point for those who are new to the field.

Methods

The current umbrella review was conducted according to the protocol published in the International Prospective Register of Systematic Reviews (PROSPERO; ID CRD42021246580) and adheres to the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA) (see **Appendix 1** for PRISMA checklist).

Literature search

We searched seven databases on April 16th, 2021: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE), Cumulative Index for Nursing and Allied Health Literature (CINAHL), Scopus, the Cochrane Database of Systematic Reviews (CDSR), the Joanna Biggs Institute (JBI) Database of Systematic Reviews and Implementation Reports, and PROSPERO. We built a search algorithm using search terms based on definitions and synonyms of the built environment, its attributes and definitions of CVD events. A detailed search strategy for each database is presented in **Appendix 2**. We also screened the reference lists of the included reviews to identify additional eligible reviews.

Inclusion and exclusion criteria

We included systematic reviews of primary studies of the general population if they: (1) reported on objectively measured long-term neighbourhood environmental exposures, covered at least one domain, including air pollution (e.g., particulate matter (PM), carbon monoxide (CO), nitrogen oxides (NO and NO_2), sulfur dioxide (SO_2) and ozone (O_3)), food environment (e.g., neighbourhood fast-food outlet density), physical activity environment (e.g., greenspace and walkability), urbanisation, light pollution (light at night), residential noise from road-, rail-, and/or air-traffic, and ambient temperature; (2) reported associations between these factors and CVD events (i.e., prevalence, incidence or mortality of coronary heart disease (CHD), stroke, transient ischemic attack (TIA), peripheral arterial disease (PAD), atrial fibrillation (AF), aortic disease, heart failure (HF)- but not congenital heart disease) in adults (i.e., ≥18 years); (3) used a systematic literature search, i.e., a reproducible search strategy with search strings

corresponding to databases; and (4) were published between January 1st, 2000 and April 16th 2021 in English. In the domain of temperature, the studies of short-term and long-term were mixed and meta-analysed in systematic reviews. Therefore, the criteria of long-term exposure was not applied too strictly for temperature.

We excluded reviews if they: (1) only focused on specific populations such as children, pregnant women, CVD patients or patients whose CVD risk may be influenced by other conditions (e.g., cancer, diabetes and chronic renal failure); (2) were published as conference abstracts, case reports, editorials and letters to editors; (3) reviewed studies on the indoor built environment (e.g., home environment), occupational environment (e.g., workplace environment), or subjective assessments of environmental characteristics (e.g., perceptions of neighbourhood safety), or only examined acute (short-term) exposure.

Study selection and data extraction

After removing duplicate records, two authors (ML and PM) screened all titles and abstracts independently. Then, these authors screened the full texts of potentially eligible articles separately and cross-checked a sample of each other's work. Screening was done using Rayyan software, a non-commercial, web-based application. [22] The two authors resolved any disagreements with discussion or, if no consensus could be reached, with discussion with other authors (TML, EJT, IV, JL). Two authors (ML and PM) conducted the data extraction and verified each other's work. For each eligible review, they extracted the following information: first author, year of publication, study design, study population, countries in which primary data were collected, exposure domain and type of environmental exposures, measures of the exposures, type and measure of the outcome studied, and summary of the (stratified) results. In the event that an included review was based on a meta-analysis, the following information was also extracted (where available): the pooled effect estimates and 95% confidence intervals (CIs), the effect size (ES) in the study with the largest study sample, the between-study heterogeneity using I^2-statistic, the results of the Egger's regression asymmetry test and excess statistical significance test, and the 95% prediction interval (PI).

Overlap of primary studies assessment

We assessed the overlap of primary studies across included reviews by a measure of Corrected Covered Area (CCA). [23] The first occurrence of a primary study in included reviews was defined as the index study. We created a cross-table of index studies and reviews for each built environmental domain (**Appendix 4**). The CCA-score was categorised into: limited overlap (score: 0-5), moderate overlap (score: 6-10), high overlap (score: 11-15) and very high overlap (score: >15) [23].

Risk of bias assessment

We assessed the risk of bias in included systematic reviews using the validated Risk of Bias in Systematic Reviews (ROBIS) tool. [24] Any disagreements in the assessment were resolved with discussion.

Statistical analysis

For the syntheses of quantitative research, we used statistical methods in accordance with the most up-to-date recommendations. [25-28] Specifically, to rate the robustness of evidence for each review that reported pooled results from a meta-analysis, we considered the following statistics:

- Statistical heterogeneity. The extent of statistical heterogeneity was evaluated using the I^2-statistic. When the I^2-statistic exceeded 50%, heterogeneity was considered large. We also evaluated heterogeneity using the 95% PI. This measure assesses the uncertainty of expected outcomes in new studies of the same association. [29]
- Small-study effect. The small-study effect refers to the observation that studies that include smaller sample sizes tend to yield larger ES than studies with larger study samples. The potential reasons for this include publication bias, reporting bias and real heterogeneity. The Egger's regression asymmetry test was used to assess whether or not a small-study effect was present. A *P* value <0.10 with a more conservative effect in larger studies was considered evidence of small-study effect. [30]

- Excess significance bias. This measure was used to evaluate whether there is evidence of an excessive number of studies with statistically significant results in the meta-analysis. It may result from reporting bias and data dredging. [31] The excess statistical significance test was used, with a *P* value <0.10 considered to be evidence of excess significance bias.

When these statistics were not available, a re-estimate based on the ES of primary studies in the included review was conducted. In line with up-to-date recommendations, the level of robustness for each pooled result was based on the following criteria [28]:

- Strong evidence: *P* value $<10^{-6}$ of the pooled estimate of meta-analysis, >1000 individuals of the total number of participants in the primary studies that were included in the review, *P* value <0.05 of the largest study in the meta-analysis, I^2-statistic <50%, no evidence of small-study effects, no evidence of excess significance bias, the null value does not fall in the 95% PI.
- Highly suggestive evidence: *P* value $<10^{-6}$ of the meta-analysis, >1000 individuals in the review, *P* value <0.05 of the largest study in the meta-analysis.
- Suggestive evidence: *P* value $<10^{-3}$ of the meta-analysis, >1000 individuals in the review.
- Weak evidence: *P* value <0.05 of the meta-analysis.

Within each category, *all* criteria had to be met.

We conducted meta-meta-analyses to combine the results from meta-analyses with comparable exposure and outcome. [27] We selected meta-analyses with comparable study populations, exposure and outcome assessment methods, and measure of association (relative risk or hazard ratio). By matching meta-analyses, we extracted the unique primary ES included in the pooled analyses. After the removal of duplicates, random-effect meta-analyses were conducted with restricted maximum likelihood approach for the estimation of variance components. The Wald method was used for estimating 95% confidence intervals. Heterogeneity was investigated with the I^2-

statistic. The Egger's regression asymmetry test was conducted to examine the small-study effect and excess statistical significance was tested for. To account for variability of covariate adjustment, we conducted sensitivity analyses by only including primary ES with similar covariate adjustment sets. All statistical analyses were conducted with the metaphor package in R software. [32,33]

Results

Literature search results

The literature search identified 3,304 unique publications (**Figure 1**). After screening all titles and abstracts, we excluded a total of 3,164 studies. After reading the full texts, we included a total of 51 eligible. Additional details are presented in the PRISMA article selection process flow chart. A full list of included reviews is presented in **Appendix 3**.

Characteristics of included reviews

The characteristics and a summary of the results of all 51 included systematic reviews are presented in **Table 1**. The number of relevant primary studies included in the reviews ranged from 2 to 67. Most reviews (n=43) were not restricted to specific countries or regions in the search, but most evidence was obtained in Europe (n=43), East and South Asia (n=38) and North America (n=37); relatively few studies were based in South America (n=10), Middle East (n=8), Oceania (n=8) and Africa (n=6). A variety of designs were used in primary studies, including ecological studies, cohort studies, cross-sectional studies, case-control studies, case-crossover studies, small-area studies, panel studies and time-series studies. Over one-third of the reviews (n=20) included only longitudinal studies.

Thirty-three reviews studied the domain of air pollution, four studied physical activity environment, one studied urbanisation, ten studied residential noise and eight studied ambient temperature. There were no systematic reviews found in the domains of food environment and light pollution. Most reviews (n=46) conducted one or multiple meta-analyses. Seven reviews only conducted narrative syntheses of the primary studies. In total, the meta-analyses summarised 180 pooled estimates of the association between specific built environmental factors and CVD events. The CCA-score for each domain was below 1, indicating only limited overlap of primary studies (**Appendix 4**).

Domain-specific results

Air pollution

Overall, long-term increased air pollution was associated with a higher risk of CVD events, based on a total of 105 meta-analyses. Among them, three reviews contained pooled results classified as strong evidence. [34-36] Four air pollutants were associated with a higher risk of CVD events (**Table 2**). Chen et al. found that both a 10 μg/m^3 higher ambient SO_2 (HR: 1.005; 95% CI: 1.004 to 1.007) and CO concentration (HR: 1.017; 95% CI: 1.013 to 1.022) were associated with an increased incidence of AF. [35] Furthermore, Yang et al. found that a 10 μg/m^3 higher ambient NO_2 concentration was associated with an increased risk of ischemic heart disease (IHD) events (RR: 1.05; 95% CI: 1.04 to 1.06). [36] Alexeeff et al. found that a 10 μg/m3 higher $PM_{2.5}$ concentration was associated with an increased risk of incident stroke (RR: 1.13; 95% CI: 1.11 to 1.15). [34] Among these three reviews that provide strong evidence, Chen et al. and Yang et al. had a low risk of bias, while Alexeeff et al. had a high risk of bias for study eligibility criteria, identification and selection (**Table 2**).

Thirteen specific pooled results were supported by highly suggestive evidence (**Table 3**). Associations were found between a higher ambient $PM_{2.5}$ concentration and higher risk of myocardial infarction (MI), IHD mortality, cerebrovascular disease (CeVD) mortality, CVD mortality and stroke events. Associations were also found between a higher ambient PM_{10} concentration and higher risk of AF, and for NO_2 with CVD, ICH and CHD mortalities. All evidence was limited by small study effects, excess significance bias or high heterogeneity. Only the studies by Alexeeff et al. and Zou et al. had a high risk of bias. [34,37] Furthermore, 32 pooled estimates were found to be non-significant (**Table 3**); most of these included a small number of studies (i.e., 2 to 4 studies).

We identified three specific exposure and outcome analyses suitable for meta-meta-analyses (studies presented in bold in **Table 3**). Firstly, a meta-meta-analysis of 29 unique primary studies from Alexeeff et al. and Chen et al. [34,38] showed that a 10 μg/m^3 increase in $PM_{2.5}$ was associated with increased IHD mortality (RR: 1.21; 95% CI: 1.10 to 1.33; I^2: 98.16%) (**Figure 2**) with a large degree of heterogeneity across studies (high I^2-statistic, and larger 95% PI than the 95% CI) (**Table 4**). As a sensitivity analysis, we conducted the meta-meta-analysis excluding studies that did not adjust for smoking,

which decreased the degree of heterogeneity, but did not affect the results (**Table 4 and Figure S1**). Secondly, a meta-meta-analysis of 26 unique primary studies from Yang et al. and Chen et al. [36,38] showed that each 10 μg/m^3 increase in $PM_{2.5}$ was associated with increased CVD mortality (RR: 1.11; 95% CI: 1.09 to 1.14; I^2: 74.23%) (**Figure 3**) with a large degree of heterogeneity across these 26 studies (**Table 4**). Excluding studies that did not adjust for any lifestyle behaviour did not result in any substantial change in effect estimates (**Table 4 and Figure S2**). Lastly, a meta-meta-analysis of 14 unique primary studies from Stieb et al. and Atkinson et al. [39,40] showed a non-significant association of NO_2 with CeVD mortality (HR: 1.03; 95% CI: 1.00 to 1.06; I^2: 45.64%) (**Figure 4**). There was no evident small study effect or excess significance bias in these three meta-analyses.

Five narrative reviews were found on air pollution with consistent results to other reviews (**Table 1)**. [41-45]

Physical activity environment

Three reviews studied associations in the physical activity environment domain including eight meta-analyses. All reviews in this domain studied greenspace exposure. Two associations related to greenspace were supported by suggestive evidence (**Table 3**). Gascon et al. found an inverse association for 10% higher greenspace exposure and CVD mortality; however, their review was at high risk of bias for study identification. [46] Six pooled estimates were not statistically significant. Among these, Yuan et al. reviewed the association between greenspace and IHD mortality [47] and Twohig-Bennett et al. reviewed the association between greenspace and IHD incidence with no obvious risk of bias [48], though they comprised a small number of studies (i.e., 2 to 3 studies).

Urbanisation

One review was identified in the urbanisation domain. [49] Angkurawaranon et al. reviewed studies focusing on Southeast Asian populations and included four meta-analyses. Two associations were supported by weak evidence. One pooled estimate showed that urban exposure was associated with higher odds of CHD (OR: 2.48; 95% CI:

1.20 to 5.11), while the other showed lower odds of RHD (OR: 0.31; 95% CI: 0.13 to 0.76). The other two pooled estimates for stroke and non-specific heart disease were non-significant. The eligibility criteria were not clearly reported in this review, resulting in an unclear risk of bias (**Table 3**).

Residential noise

In the residential noise domain, nine reviews were identified, including 30 meta-analyses (**Table 3**). Cai et al. found strong evidence of an association between 10 dB higher aircraft traffic noise and increased CVD mortality (HR: 1.17; 95% CI: 1.10 to 1.25), though this review had a high risk of bias in study eligibility criteria, identification and selection. [50] Two associations were supported by suggestive evidence. Babisch et al. found an association between 10 dB higher road traffic noise exposure and higher risk of CHD. [51] Vienneau et al. found a similar association between traffic noise exposure and higher risk of IHD. [52] Seventeen pooled estimates were non-significant. Among these, Weihofen et al. reviewed seven studies and found a marginal association between 10 dB higher aircraft traffic noise exposure and higher risk of stroke (RR: 1.013; 95% CI: 0.998 to 1.028). This review did not suffer from obvious risks of bias, heterogeneity, small study effect or excess significance bias. [53]

One systematic review covered multiple domains: air pollution, greenspace, walkability and noise. Using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, Rugel et al. found sufficient evidence of an association between increased noise and higher risk of CVD. [54]

Ambient temperature

In the ambient temperature domain, eight reviews were included. These reviews included 37 meta-analyses (**Table 3**). Associations between both higher and lower temperature in relation to higher risk of CVD were supported by suggestive evidence (three reviews); six associations were supported by weak evidence; 22 pooled estimates were non-significant. All results suffered from a high risk of bias. Two narrative reviews were found in this domain with inconsistent results.

In this domain, we identified one specific exposure and outcome analysis that was suitable for a meta-meta-analysis. Bunker et al. and Moghadamnia et al. meta-analysed the RR of CVD mortality per 1ºC change in temperature. [55,56] The meta-meta-analysis of 62 unique primary studies showed a significant association between increasing temperature and CVD mortality (RR: 1.04; 95% CI: 1.03 to 1.04; I^2: 98.63%) (**Figure 5**). Both a small study effect and excess significance bias were evident in this analysis. As sensitivity analyses, we conducted the meta-meta-analysis excluding studies that did not adjust for any confounders (**Appendix 7, Figure S3**), did not adjust for air pollution (**Appendix 7, Figure S4**) and adjusted only for air pollution (**Appendix 7, Figure S5**). These analyses did not substantially change the results of the main analyses.

Discussion

Principal findings

Our umbrella review found strong evidence of an association between increased air pollution, including increased ambient $PM_{2.5}$, SO_2, CO and NO_2 exposure, and CVD outcomes. There was also consistent evidence of associations between increased noise levels and CVD outcomes, including strong evidence for air traffic noise and CVD mortality. An association between increased ambient temperature and CVD mortality was supported by highly suggestive evidence. Review evidence in other domains, including physical activity environment, food environment, light pollution and urbanisation in relation to CVD are scarce or lacking. However, the limited available evidence is suggestive of a protective effect of greenspace exposure in terms of CVD mortality.

Strengths and limitations

To the best of our knowledge, this is the first umbrella review to comprehensively summarise the relationship between aspects of the built environment and CVD. Following a pre-specified protocol, we conducted a wide-ranging search across seven databases. The included reviews underwent extensive critical appraisal using a validated risk of bias assessment method. Both methodological quality and statistical evidence were evaluated to determine the robustness of evidence. Finally, meta-meta-analyses were performed where possible to combine all available quantitative evidence.

To contextualise the findings, certain limitations of our umbrella review need to be addressed. Firstly, the search strategy was limited to reviews published in the English language. Therefore, we may have omitted key studies published in other languages. Secondly, we included systematic reviews published between 1 January 2000 and 16 April 2021. The most recently published evidence has not yet been taken up in systematic reviews and is, therefore, not included here. Lastly, many included reviews (and studies to date) report on cross-sectional analyses, which inhibits identification of causality.

Evidence in relation to other studies

Our results were generally consistent with the WHO 2021 global air quality guidelines, as well as earlier umbrella reviews investigating air pollution and CVD outcomes. [57-61] Positive associations are consistently found for a variety of pollutants, as well as CVD outcomes. However, the association between $PM_{2.5}$ and CVD was the most widely investigated. NO_2 exposure was, thus far, not encompassed in the scope of the WHO guidelines because of the absence of clear quantitative evidence. Our results contribute strong evidence of an association between higher NO_2 exposure and a higher risk of IHD, and highly suggestive evidence of an association between higher NO_2 exposure and a higher risk of CVD mortality. While earlier work demonstrated strong evidence of a positive association between $PM_{2.5}$ and stroke only in Europe [61], our results show that this holds true when non-European countries are included.

This umbrella review indicates that studies of greenspace were heterogeneous in design and exposure assessment, which partly explains the limited combined evidence of an association between greenspace exposure and CVD. For example, greenspace assessment methods included the Normalised Different Vegetation Index (NDVI), percentage of greenspace coverage and distance to nearest greenspace. While the first two may be good indicators of the amount of greenspace in certain areas, they do not reflect access to those greenspaces. For distance to nearest greenspace, the opposite may be true. Therefore, studies of greenspace using different assessment methods are not directly comparable. [62,63] This same issue of limited combined evidence may also hold for other domains like physical activity, food environment, light pollution, and urbanisation, although our results did not provide information to support this.

Our findings about traffic noise and CVD events are in line with those from two WHO reports. [64,65] The WHO environmental noise guidelines for the European Region (2015) included a systematic review (included in the current review). [65] According to an adapted GRADE assessment, high-quality evidence was found on road traffic noise and IHD, and moderate-quality evidence was found for aircraft noise and stroke mortality, and for road traffic noise, IHD mortality and stroke events. Our study updated the

evidence base with strong evidence of an association between air traffic noise and CVD mortality. Furthermore, we observed that the existing evidence on rail traffic noise is still limited.

The 2019 Global Burden of Disease study estimated that global age-standardised CVD DALYs attributable to high temperature was 25.59 per 100,000 people. [66] The heat-related disease burden was the highest for stroke and was greater in regions with a lower socio-demographic Index (SDI). However, the observational evidence on specific outcomes and regional differences, as reported in the current review, was insufficient. The effect estimate found in the current meta-meta analysis might be small (**Figure 5**), but increasing temperature has a potentially large and increasing population reach.

Mutual confounding and interaction

Many aspects of the built environment may be interconnected, potentially leading to confounding and/or interaction effects. However, most existing reviews and meta-analyses focus on single (sub)domains of exposure. We only found one systematic review that covered multiple domains. This study observed sufficient evidence of an association between higher noise exposure and increased CVD morbidity, after adjusting for traffic-related air pollution. [54] A meta-analysis by Vienneau and colleagues observed an association between higher noise levels and increased IHD which remained robust after including studies that adjusted for air pollution exposure. [52] Despite the substantial amount of studies on the effects of air pollution and temperature on CVD, there is limited research available on their mutual confounding or interaction effects. One systematic review found that long-term air pollution exposure and colder temperatures are independently associated with an increased risk of CVD. [67] Additionally, another US cohort study found that the association between higher $PM_{2.5}$ and CVD was stronger in areas with higher green space, lower O_3 levels, and lower temperatures. [68] Furthermore, as a proxy for context, urbanisation may also have significant confounding or interaction effects with various aspects of the built environment. For example, a Dutch cohort study indicated associations between fast-food restaurant density and CVD in urban areas but not in rural areas. [69]

Possible mechanisms and explanations

Several potential mechanisms have been theorised that may explain the associations found in this study. Exposure to air pollutants may promote systemic inflammation and oxidative stress in the lungs, which eventually increases systemic inflammation and oxidative stress. [17] As a result, a variety of pathological processes could take place that eventually lead to CVD, such as increased thrombosis, hypercoagulability, endothelial dysfunction, atherosclerosis progression, insulin resistance and dyslipidemia. [16,17] Pollutants can also induce oxidative stress and inflammation in the central nervous system, especially in the hypothalamus, leading to an imbalance in the cardiac autonomic nervous system. [17] Moreover, smaller size pollutants can directly enter the circulation and damage the cardiovascular system and organs. [17] These mechanisms are better understood for PM exposure than for other pollutants. CO typically hampers oxygenation of tissues via carboxyhemoglobin production, which has a more significant influence on the myocardium than peripheral tissues. [70] These mechanisms may explain the more evident associations found for AF. AF is an early CVD endpoint that can lead to other CVD outcomes in the long term. For residential noise exposure, both direct and indirect pathways have been theorised. [18] The direct pathway is induced by the instant interaction between the acoustic nerve and the central nervous system. The indirect pathway relates to cognitive perception and subsequent cortical activation and emotional response. Both pathways can cause physiological stress responses, and in the long term, pathophysiologic alterations and CVD. The adverse effect of residential noise has been reported independent of sleep quality and self-reported noise sensitivity. But noise can indeed disturb sleep and subsequently cause reduced immune function and a pro-inflammatory state. [21] Changes in temperature can cause typical physiological responses that might lead to MI, including tachycardia and increased blood viscosity. [19] Both cold and heat exposure may increase sympathetic activation, which could lead to high blood pressure. [19] Lastly, it is hypothesised that greenspace improves air quality. By reducing the concentration of air pollutants, greenspace may reduce the impact of air pollution on CVD. [62] Additionally, greenspaces may facilitate physical activity, thereby promoting cardiovascular health. [62]

Gaps in current knowledge and suggestions for future research

Future primary studies should investigate the effects of PM_{10}, SO_2, CO, NO and $PM_{0.1}$, especially long-term exposure. As we observed evidence of early-onset CVD (e.g. AF), more studies of other CVD outcomes that occur later (e.g., IHD) are warranted. Research is needed on light pollution. Despite there being multiple primary studies on the food environment, they differ in definition of food environment and vary with regard to buffer size. As such, these studies cannot be meta-analysed. Standard design and exposure assessments should be developed and implemented to foster synthesis of evidence. More studies are also needed for residential noise and ambient temperature, especially from low-to-middle-income countries (LMICs). Future primary studies should preferably use prospective study designs in the domains of physical activity environment, urbanisation and residential noise to increase causal inference power. Furthermore, primary studies on interactions or interrelationships of built environmental aspects in relation to CVD are also warranted.

As for systematic reviews, future work should provide evidence on O_3 that is of higher quality. Review evidence on the physical activity environment, food environment and urbanisation was limited. There are primary studies on these domains, but future reviews to harmonise research data (e.g., in terms of the heterogeneity in the definition and measurement of exposures) and synthesise evidence are required. For example, in terms of greenspace, accessibility and composition may be crucial to determining its effects. [71] Furthermore, more high quality review evidence is needed on residential noise and ambient temperature, especially for LMICs. It is highly recommended that future systematic reviews on the built environment adhere to the PRISMA reporting guidelines and pre-register a protocol in a dedicated registry such as PROSPERO to guarantee transparency, prevent overlap in topics and promote methodological quality. Furthermore, the use of quality assessment should become common practice, using standardised, validated tools, as recommended by sources such as PRISMA and Cochrane. [72,73] We also observed that most primary studies and reviews focus on one single built environment aspect. However, these aspects co-exist and act together.

Accounting for multiple elements of the built environment may provide a better understanding of the relative contribution of each aspect to CVD risk. Systematic reviews should also consider comparing single-exposure to multi-exposure models to examine potential confounding effects between built environment exposures.

Implications for public health

There was strong evidence of a detrimental effect of air pollution on CVD. Therefore, it is important that governments and individuals take measures to reduce outdoor air pollution. The WHO has developed the 2021 long-term air quality guideline levels with interim targets. [60] Each country should establish air quality standards with adapted interim targets, specified measurement and statistical procedures to reduce CVD events attributable to air pollution. Another strategy could be the development of a framework for clinical recommendations and individual exposure mitigation strategies. The American Heart Association has stated such individual strategies to prevent air pollution, like using portable air cleaners, high efficiency heating ventilation and air conditioning systems, N95 Respirator, etc. [74]

We found suggestive evidence of a protective effect of greenspace on CVD. This supports the call for urban planners, city designers, project developers and policymakers to take greenspace into account. [75] There was also clear evidence of increased residential noise being associated with a higher CVD risk. The WHO developed guidelines pertaining to noise levels for the European Regions in 2015. [65] However, these recommendations may not be directly applicable to other regions. One general public health approach is to address the major sources of pollution (i.e. combustion, traffic, industry and power generation). Another approach is to develop healthy building guidelines (e.g. including advanced insulation) to reduce the exposure to outdoor air pollution, light pollution, residential noise and extreme temperatures.

Conclusion

This umbrella review provides a comprehensive overview of the observational evidence on the built environment and CVD. We found strong evidence of associations between increased air pollution, especially $PM_{2.5}$, and increased residential noise with higher risk of CVD. The present meta-meta-analysis produced highly suggestive evidence of an association between temperature and CVD. Evidence on physical activity environment, food environment, light pollution and urbanisation is scarce or lacking. Our identification of several knowledge gaps and methodological limitations in the current literature may improve and inform future research and contribute to a better understanding of the effect of the built environment on CVD.

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Conflict of interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: ML had financial support from China Scholarships Council; all other authors had financial support from NWO Gravitation grant Exposome-NL; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions: ML, PM and JL designed the study and developed the review question. ML and PM performed the literature search and were the primary reviewers. TML, EJT, IV, and JL acted as additional reviewers where required. EJT, DEG, JWB, IV, and JL supervised the study. ML and PM drafted the manuscript. All authors reviewed and revised the protocol and manuscript. JL acts as guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figures

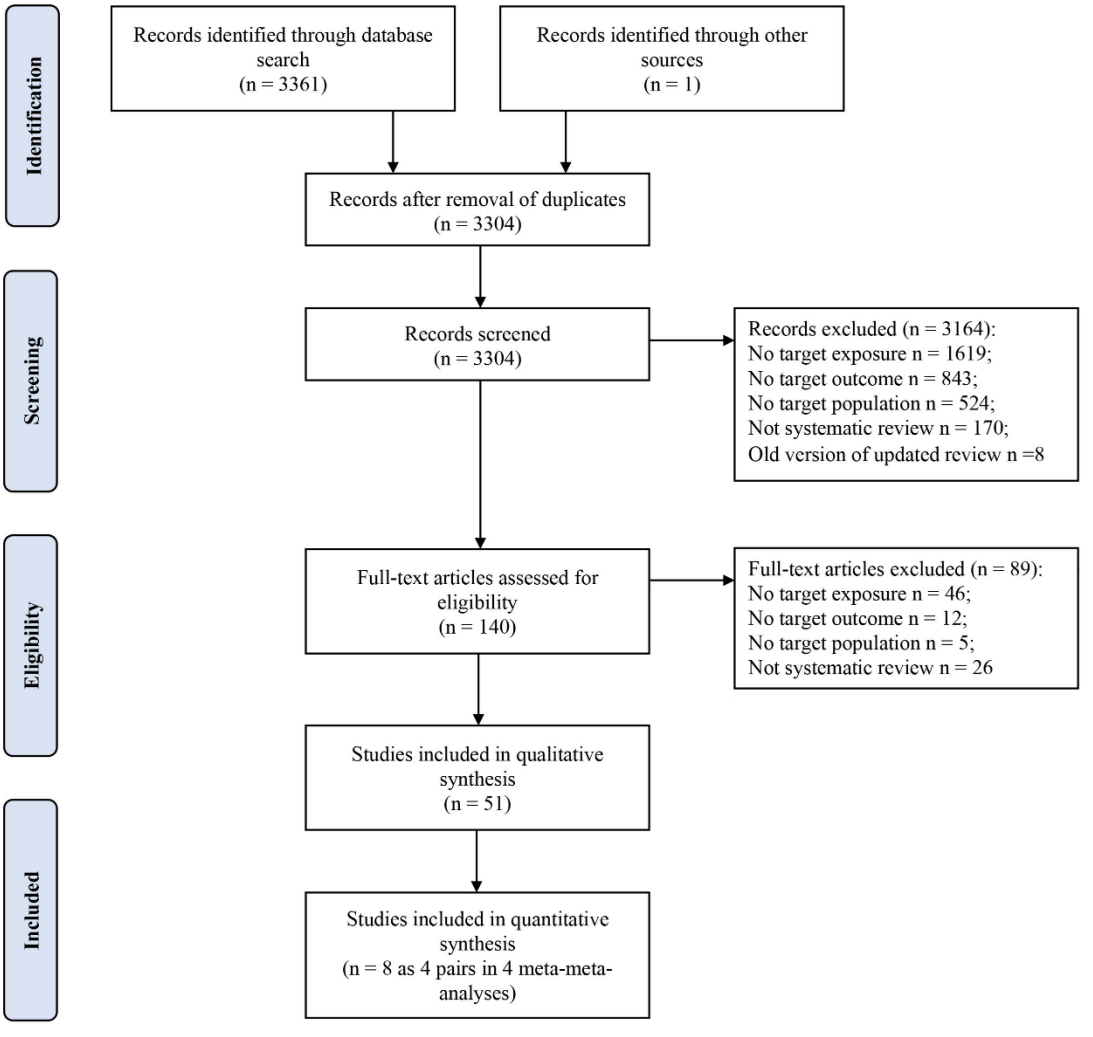

Figure 1. Flowchart of study selection

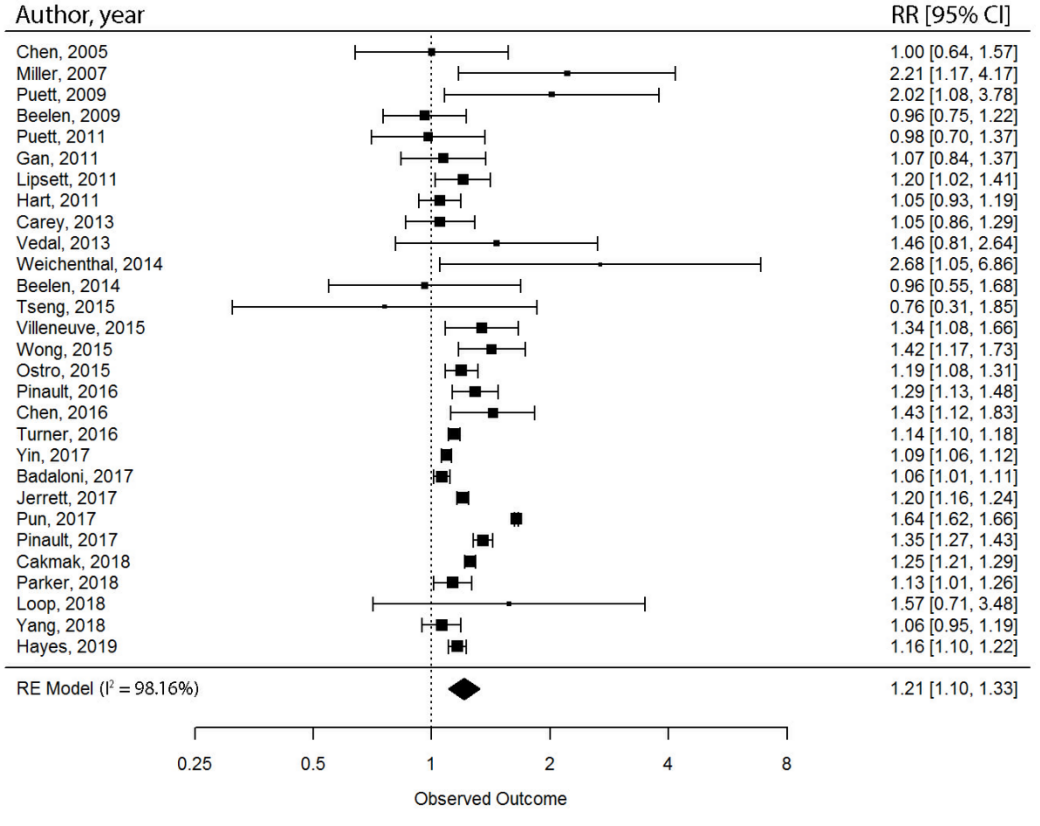

Figure 2. Meta-meta-analysis of the relative risk of ischemic heart disease mortality per 10 µg/m^3 in long-term fine particulate matter <2.5 µm in diameter exposure. A bibliography of included studies is presented in Appendix 3.

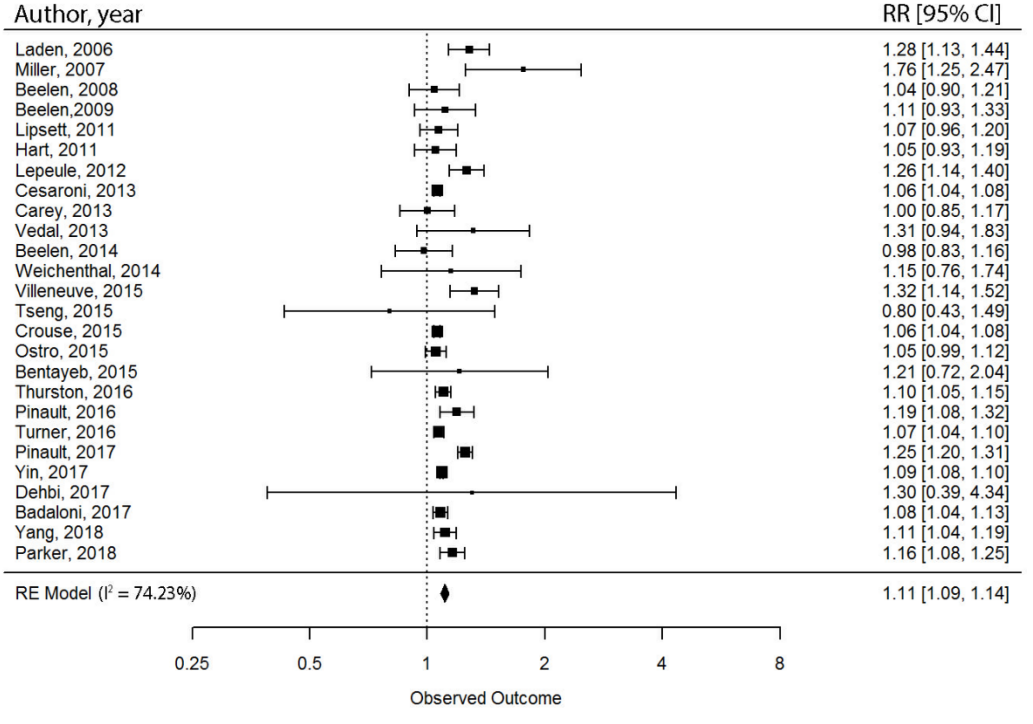

Figure 3. Meta-meta-analysis of the relative risk of cardiovascular disease mortality per 10 µg/m^3 in long-term fine particulate matter <2.5 µm in diameter exposure. A bibliography of included studies is presented in Appendix 3.

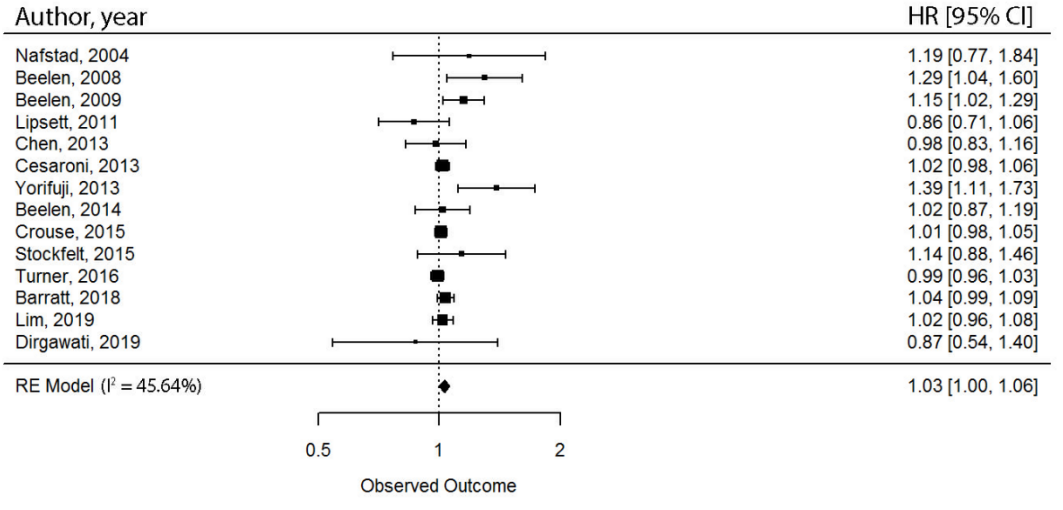

Figure 4. Meta-meta-analysis of the hazard ratio of cerebrovascular disease mortality per 10 parts per billion increase in NO_2 exposure. A bibliography of included studies is presented in Appendix 3.

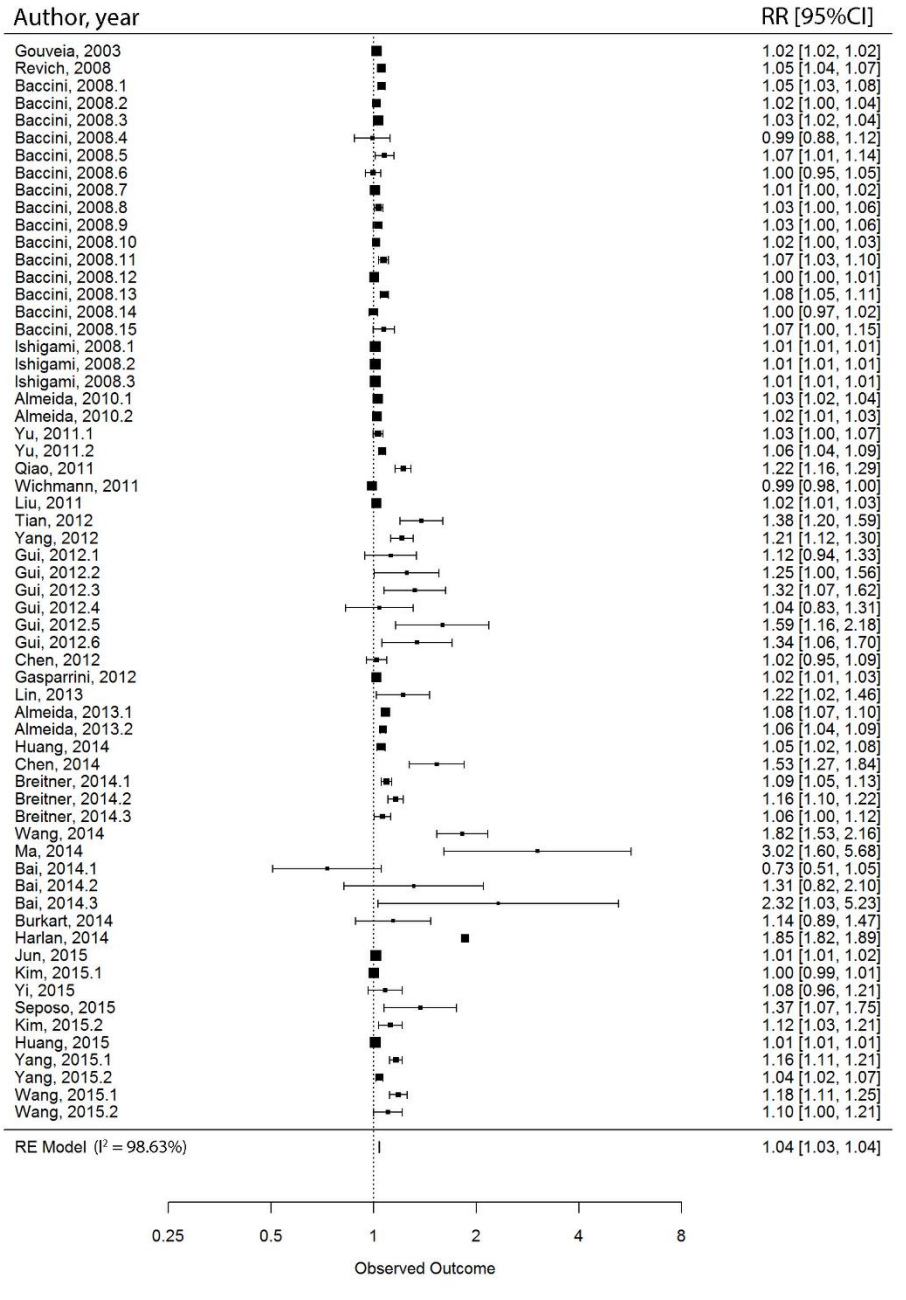

Figure 5. Meta-meta-analysis of the relative risk of cardiovascular disease mortality per 1 ºC change of temperature (heat). A bibliography of included studies is presented in Appendix 3.

Tables

Table 1. Summary of included systematic reviews (n=51)

First author and year by domain[1]	Population, year coverage, and country/region	Study design[2]	Exposures[3]	Summary of results[4]	Percentage of results in expected direction	Quality assessment (ROBIS)
Air pollution						
Alexeeff et al. 2021	General population, till 2019.12.31, country not restricted: Europe, Canada, US, UK, Australia, China, South Korea, Israel	42 CS	PM2.5	Per 10 μg/m^3 increase in long-term exposure, the pooled RRs and 95% CIs were **1.23 (1.15 to 1.31)** for IHD mortality, 1.08 (0.99 to 1.18) for incident acute MI, **1.24 (1.13 to 1.36)** for CeVD mortality, and **1.13 (1.11 to 1.15)** for incident stroke.	83%	High risk of bias
Atkinson et al. 2016	General population, till 2015.10, country not restricted: US, UK, China (Taiwan), France	Total 22 studies, relevant 8 studies: 8 CS	O_3	HRs expressed per 10 ppb increase in O_3. For long-term annual O_3 concentrations, the standardized effect estimates (HRs and 95% CIs) were 1.01 (0.99 to 1.03) for CVD mortality, 1.02 (1.00 to 1.04) for IHD mortality, and 1.01 (0.97 to 1.05) for stroke mortality. For long-term annual O_3 concentrations, the random-effects summary estimates (HR and 95% CI) were 0.98 (0.93 to 1.04) for CVD mortality, 1.00 (0.92 to 1.09) for IHD mortality. For the warm season/peak O_3, random-effects summary estimates were 1.01 (1.00 to 1.02).	42%	High risk of bias
Atkinson et al. 2018	General population, 1996-2016.10 (Medline, EMBASE), 1970-2016.10 (Web of Science), 1966-2016.10 (Pubmed), country not	Total 48 studies, relevant 22 studies: 22 CS	NO_2 (annual or multi-year averages)	Per 10 μg/m^3 increase in long-term exposure, the pooled HRs and 95% CIs were **1.03 (1.02 to 1.05)** for CVD mortality, **1.05 (1.03 to 1.06)** for CHD mortality, and 1.01 (0.98 to 1.03) for	91%	High risk of bias

	restricted: Europe, North America, China (mainland and Taiwan), Japan			CeVD mortality.		
Chen et al. 2008	Adults, 1950.01.01-2007.12.31, country not restricted: US, Norway, France, Netherlands, Canada, Germany	Total 32 studies, relevant 17 studies: 14 CS, 3 CCS	O_3, SO_2, NO/NO_2, black smoke, PM10, PM2.5, CO, benzene, and polycyclic aromatic hydrocarbons	RR per 10 μg/m^3 increase. For PM2.5 the pooled RRs and 95% CIs were **1.14 (1.09 to 1.18)** for CVD mortality and **1.16 (0.96 to 1.40)** for CHD mortality. For other particulate and gaseous pollutants, the paucity of data precludes drawing conclusions.	79%	High risk of bias
Chen et al. 2020	General population, till 2018.10.09, country not restricted: Europe, Canada, UK, US, Israel, New Zealand, South Korea, Japan, China (mainland, Taiwan, Hong Kong)	67 CS	PM2.5 and PM10	Per 10 μg/m^3 increase in long-term PM2.5 exposure, the pooled RRs and 95% CIs were **1.11 (1.09 to 1.14)** for CVD mortality, **1.16 (1.10 to 1.21)** for IHD mortality, and **1.11 (1.04 to 1.18)** for stroke mortality. The estimates of PM10 were 1.04 (0.99 to 1.10) for CVD mortality, **1.06 (1.01 to 1.10)** for IHD mortality, and 1.01 (0.83 to 1.21) for stroke mortality. The certainty of evidence was high for PM2.5 and CVD mortality, and was moderate for PM10 and CVD mortality, as measured by GRADE framework.	81%	Low risk of bias
Chen et al. 2021	General population, till 2019.10, country not restricted: South Korea, UK, Denmark, Sweden, Canada	Total 18 studies, relevant 6 studies: 6 CS	PM2.5, PM10, NO_2, SO_2, O_3, and CO	Per 10 μg/m^3 increase in long-term exposure, the pooled HRs and 95% CIs of AF were **1.116 (1.031 to 1.207)** for PM2.5, **1.034 (1.032 to 1.035)** for PM10, **1.017 (1.001 to 1.033)** for NO_2, **1.005 (1.004 to 1.007)** for SO_2, **1.017 (1.013 to 1.022)** for CO, and 1.007 (0.927 to 1.094) for O_3.	83%	Low risk of bias
Faustini et al. 2014	General population, 2004.01-2013.01, country not restricted: identified	Total 23 studies, relevant 17	NO_2	RR per 10 μg/m^3 increase. The pooled RRs and 95% CIs for CVD mortality were **1.13 (1.09 to 1.18)** for NO2 and **1.20**	94%	High risk of bias

	countries: Japan, China, Canada, US, UK, Italy, Germany, Sweden, the Netherlands, Norway	studies: 2 CCS, 15 CS		**(1.09 to 1.31)** for PM2.5.		
Hak-Kan et al. 2013	Chinese population, till 2012.30.06, 80 major Chinese cities in Mainland China, Hong Kong and Taiwan	Total 48 studies, relevant 3 studies: 3CS	PM10, NO_2, SO_2 and O_3	RR per 10 μg/m^3 increase. In one cohort study examining PM10 and NO_2, the corresponding RRs and 95% CIs were **1.0155 (1.0151 to 1.0160)** and **1.0246 (1.0231 to 1.0263)** for CVD mortality, and **1.0149 (1.0145 to 1.0153)** and **1.0244 (1.0227 to 1.0262)** for CeVD mortality. In another cohort study examining SO_2 and CVD, the corresponding RR was **1.032 (1.023 to 1.040)**.	100%	High risk of bias
Hoek et al. 2013	Not specified (adults), till 2013.01, country not restricted: identified countries: US, Germany, the Netherlands, Switzerland, Canada, China, New-Zealand, Japan, Italy, France, Denmark	Total 67 studies, relevant 34 studies: 34 CS	Long-term exposure to fine particulate matter (PM2.5, PM10, NO_2, elemental carbon and coarse particles)	RR per 10 μg/m^3 increase. For PM2.5 the pooled RR and 95% CI was **1.11 (1.05 to 1.16)** for CVD mortality. There was no consistent evidence that long-term exposure to coarse PM or elemental carbon is associated with CVD mortality. Several studies found positive associations between NO_2 exposure and fatal MI, but not non-fatal MI. The evidence for an association between air pollution and CeVD mortality was inconsistent.	88%	High risk of bias
Huang et al. 2021	General population, till 2002.02.29, country not restricted: US, Canada, Norway, Netherlands, UK, Italy, Denmark, France, Spain, Japan, China, South Korea, Australia, Sweden, Norway, Germany, Austria, Switzerland, France, Italy, Spain, Greece,	32 CS	NO_2	Per 10 ppb increase in annual NO_2 concentration, the pooled HR and 95% CI was **1.11 (1.07 to 1.16)** for cardiovascular mortality.	71%	High risk of bias

	Finland					
Jadambaa et al. 2015	Mongolian population (adults and children), until 2014.04, Mongolia	Total 59 studies, relevant 2 studies: 2 CSS	NO_2 and PM2.5	Two studies found an increased risk of CVD with increased exposure to NO_2 and PM2.5.	100%	Unclear
Jaganathan et al. 2019	General population, 1948.01.01-2018.03.06, country restricted to low- and middle-income countries, Mexico (Mexico City), Brazil (São José dos Campos, Cuiabá and Várzea Grande), China, India (Varanasi)	Total 17 studies, relevant 12 studies: 8 LS, 2 CSS, 1 CCR, 1 CS	PM2.5 (annual average or average measure of more than 3 days)	Eight out of nine studies (91%) reported significant effects on CVD mortality. Per 10 $\mu g/m^3$ increase in long-term exposure, the effect estimates of CVD mortality ranged from 0.24% to 6.11%. All four studies reported significant effects of long-term exposure on CVD hospitalization. Few studies have evaluated this association in LMICs. No studies were found in North and Sub-Saharan Africa	92%	Low risk of bias
Kan et al. 2005	General population, 1990-2002, China and worldwide	Total 26 studies, relevant 7 studies: 7 CS	Effects of particulate air pollution. PM10 was selected as the indicator particulate matter.	RR per 10 $\mu g/m^3$ increase. For PM10 the pooled RRs and 95% CIs were **1.0095 (1.0060 to 1.0130)** for CHA, **1.013 (1.007 to 1.019)** for CHA based on four European studies, and **1.008 (1.004 to 1.011**) for CHA based on three US and Canadian studies.	100%	High risk of bias
Karimi et al. 2019	Iran population, 1980.01-2018.01, country restricted to Iran	Total 38 studies, relevant 28 studies: 27 CSS, 1 ES	O_3, PM2.5, PM10, NO_2, NOx, SO_2, CO measured by environmental protection organization and air quality control center	Per 10 $\mu g/m^3$ increase in all air pollutants, the pooled increased risk (95% CI) in CVD mortality was **0.5% (0.4% to 0.6%)**. The estimate for PM2.5 and PM10 was **0.7% (0.4% to 1%)**.	NA	Unclear
Liu et al. 2018	General population, adults, 1974.01-2017.07, country not restricted: US, UK, Italy, Canada, China (mainland and Hong Kong), Europe, New Zealand, Japan	16 CS	PM2.5 and PM10	Per 10 $\mu g/m^3$ increase in long-term exposure, the pooled HRs and 95% CIs of CVD mortality were **1.12 (1.08 to 1.16)** for PM2.5, 1.02 (0.89 to 1.16) for PM10, and **1.10 (1.06 to 1.14)** for combined. In subgroup analyses, there is no	88%	Low risk of bias

				difference in the association stratified by categories of WHO PM levels or smoking status. The estimates of PM2.5 were **1.19 (1.11 to 1.27)** for studies with ≥11 years of follow-up, higher than those <11 years: **1.07 (1.04 to 1.11)**.		
Lu et al. 2015	Chinese population (adults only), 1990-2013, Mainland China, Hong Kong and Taiwan	Total 59 studies, relevant 2 studies: 2 CS	PM10 and PM2.5	RR per 10 μg/m3 increase. For the annual average concentration of PM10, the RR and 95% CI was **1.23 (1.19 to 1.26)** for CVD mortality in one study, and **1.55 (1.51 to 1.60)** for CVD mortality in another study.	100%	High risk of bias
Luben et al. 2017	Adults, till 2017.06.15, country not restricted: US, China (mainland and Taiwan), the Netherlands, Canada, South Korea, Spain, Italy	Total 24 studies, relevant, 3 studies: 2 CS, 1 LS	Ambient black carbon	There are generally modest, positive associations of long-term exposure to black carbon and elemental carbon with cardiovascular hospital admissions and mortality.	100%	High risk of bias
Niu et al. 2021	General population, till 2020.02.01, country not restricted: China, European, England, Japan (Shizuoka), US (California), Ghana, India, Mexico, Russia, South Africa	Total 68 studies, relevant 13 studies: 13 CS	PM2.5, PM10, and NO_2	Per 10 μg/m3 increase in long-term exposure, the pooled HRs and 95% CIs of stroke incidence were 1.081 (0.971 to 1.023) for PM2.5, 1.033 (0.907 to 1.175) for PM10, and 1.005 (0.977 to 1.034) for NO_2; the HRs and 95%CI of stroke mortality were 1.047 (0.995 to 1.101) for NO_2.	82%	High risk of bias
Prueitt et al. 2014	General population, 2006.01.01-2013.11.04, country not restricted: US, UK, Canada (Toronto), China (Liaoning)	Total 25 studies, relevant 11 studies: 8 CS, 2 CSS, 1 ES	O_3	For long-term O_3 exposure and CVD morbidity, studies were rare and reports were inconsistent. For CVD mortality, of 10 high quality studies, 5 reported positive association, the other 5 reported null or negative association.	17%	High risk of bias
Scheers et al. 2015	General population, till 2015.07.20, country not restricted: Japan, China, UK,	Total 20 studies, relevant 20	PM10 or PM2.5	HR per 10 $\mu g/m^3$ increase. For PM10, the pooled HRs and 95% CIs were **1.061 (1.018 to 1.105)** for overall stroke events,	50%	High risk of bias

	the Netherlands, Switzerland, Greece, US, Canada, Finland, Norway, Sweden, Denmark, Germany, Austria, Italy, Greece, France	studies: 14 CS, 6 ES		and 1.080 (0.992 to 1.177) for stroke mortality. For PM2.5, the pooled HRs and 95% CIs were **1.064 (1.021 to 1.109)** for overall stroke events, and **1.125 (1.007 to 1.256)** for stroke mortality.		
Shin et al. 2014	Not specified (adults), from 1990, country not restricted: US, UK	Total 20 studies, relevant 4 studies: 4 CS	PM2.5	RR per 10 μg/m^3 increase. In the frequentist meta-analysis, the pooled RR and 95% CI for long-term exposure to PM2.5 was 1.06 (1.00 to 1.13) for non-fatal strokes. The Bayesian meta-analysis found a posterior mean 1.08 (0.96 to 1.26) from a normal prior, and **1.05 (1.02 to 1.10)** from a gamma prior.	100%	High risk of bias
Stieb et al. 2021	General population, till 2020.02.25, country not restricted: Canada, US, UK, Europe, China (mainland, HK and Taipei), Australia, South Korea (Seoul), Japan (Shizuoka)	49 CS	NO_2	Per 10 ppb increase in long-term exposure, the pooled HRs and 95% CIs were 1.139 (0.997 to 1.301) for CVD mortality, **1.128 (1.076 to 1.182)** for IHD mortality, and 1.167 (0.936 to 1.456) for CeVD mortality. After excluding studies with probably high or high risk of bias, the pooled HRs and 95% CIs were **1.058 (1.026 to 1.091)** for CVD mortality, **1.111 (1.079 to 1.144)** for IHD mortality, and 1.014 (0.997 to 1.032) for CeVD mortality.	74%	Low risk of bias
Wang et al. 2020	Older adults aged ≥55 years, till 2020.01, country not restricted: US (Steubenville, Eastern Massachusetts, Boston), Germany (Erfurt), Finland (Helsinki), the Netherlands (Amsterdam), UK (Scotland: Aberdeen), China (Beijing, Taipei)	Total 19 studies, relevant 10 studies: 10 LS	Concentration of PM2.5	Per 10 mg/m^3 increase in long-term exposure, the pooled estimates and 95% CIs of HRV were -0.92% (-2.14% to 0.31%) for SDNN, **-1.96% (-3.48% to -0.44%)** for RMSSD in time-domain measurements, **-2.78% (-4.02% to -1.55%)** for LF, and -1.61% (-4.02% to 0.80%) for HF in frequency-domain measurements.	68%	High risk of bias
Yang et al. 2019	General population, till	35 CS	PM2.5, PM10, O_3, and	Per 10 μg/m^3 increase in long-term	87%	High risk of

	2018.04.25, country not restricted: Europe, UK, Canada, US, South Korea, China, Ghana, India, Mexico, Russia, South Africa, Japan		NO_2	PM2.5 exposure, the pooled RRs and 95% CIs were **1.11 (1.07 to 1.15)** for CVD events, **1.12 (1.05 to 1.19)** for stroke incidence, **1.12 (1.08 to 1.16)** for stroke events, **1.19 (1.09 to 1.30)** for IHD incidence, and **1.14 (1.08 to 1.21)** for IHD events. The estimates of CVD mortality were **1.11 (1.07 to 1.15)** for PM2.5, **1.09 (1.02 to 1.16)** for PM10, **1.23 (1.15 to 1.31)** for NO2, and **1.03 (1.02 to 1.05)** for O3. The estimates of NO2 and IHD events was **1.05 (1.04 to 1.06)**. No significant associations were found between PM10 and CVD, stroke, and IHD incidence.		bias
Yuan et al. 2019	General population, 1980-2018.12, country not restricted: Europe, US, China (Hong Kong), Ghana, India, Mexico, Russia, South Africa, UK, Sweden (Gothenburg), Italy	16 CS	PM2.5	Per 5 μg/m^3 increase in long-term exposure, the pooled HRs and 95% CIs were **1.11 (1.05 to 1.17)** for stroke incidence and **1.11 (1.05 to 1.17)** for stroke mortality. In subgroup analysis, the estimates of stroke incidence were **1.09 (1.05 to 1.14)** for North America (5 CS), **1.07 (1.05 to 1.10)** for Europe (4 CS), and 2.31 (0.49 to 10.95) for Asia (2 CS). The associations were insignificant in both sex and significant in both ischemic and hemorrhagic stroke. The estimates of stroke incidence were **1.08 (1.03 to 1.13)** for never smokers, **1.11 (1.01 to 1.22)** for former smokers, and 1.08 (0.94 to 1.25) for current smokers.	95%	Low risk of bias
Zhao et al. 2017	General population, 1990-2016, country not restricted: US, Israel, Japan, UK, China, Italy, Norway, Greece, Canada,	Total studies, 48 relevant studies: 48 25	PM10, PM2.5, SO_2, NO_2, CO, and O_3	HR per 10 μg/m^3 increase. For CHD mortality, the pooled HRs and 95% CI was **1.12 (1.04 to 1.20)** for PM10, **1.17 (1.12 to 1.22)** for PM2.5, 1.03 (1.00 to	NA	High risk of bias

	Denmark, France, South Korea, Iran, Germany, Finland, Sweden, Spain, Netherlands	CS, 23 LS		1.07) for SO_2, **1.04 (1.01 to 1.06)** for NO_2, 1.04 (0.98 to 1.10) for CO, and **1.06 (1.01 to 1.11)** for O_3 (10 mg/m^3 increase). For CHD incidence, the pooled HRs and 95% CIs were 1.01 (1.00 to 1.02) for PM10, 1.02 (1.00 to 1.03) for PM2.5, 1.01 (1.00 to 1.02) for SO_2, **1.04 (1.03 to 1.06)** for NO_2, 1.01 (0.97 to 1.04) for O_3, and 1.03 (1.00 to 1.05) for CO (10 mg/m^3 increase).		
Zhao et al. 2021	General population, time and country not restricted: China, Norway, UK, Netherlands, China (HK), Canada (Ontario)	7 CS	PM2.5 acquired through satellite-based model (5 studies) and outdoor-automated monitoring stations (2 studies)	Per 1.4-10 μg/m^3 increase in long-term PM2.5 exposure, the pooled HRs and 95% CIs of hemorrhagic stroke were **1.16 (1.03 to 1.30)** for total, 1.41 (0.92 to 2.15) for current smoker, and 1.04 (0.74 to 1.46) for never and former smoker.	71%	Low risk of bias
Zhu et al. 2021	General population, till 2020.08.02, country not restricted: Canada, Denmark, Netherlands, China, US, South Korea, Israel, UK (London)	12 CS	PM2.5	Per 10 μg/m^3 increase in long-term PM2.5 exposure, the pooled HRs and 95% CIs were **1.10 (1.02 to 1.18)** for MI incidence and **1.07 (1.04 to 1.09)** for post-MI mortality.	75%	Unclear
Zou et al. 2021	General population, till 2019.09, country not restricted: US, South Korea, UK, Canada, Sweden, Israel, Italy, Netherlands, Switzerland, Finland	27 CS	PM2.5 and PM10	Per 10 μg/m^3 increase in long-term exposure, the pooled RRs and 95% CIs of MI were **1.18 (1.11 to 1.26)** for PM2.5 and 1.03 (1.00 to 1.05) for PM10.	91%	Unclear
Physical activity environment						
Gascon et al. 2016	Adults, till 2014.11.14, country not restricted: US, UK, New-Zealand, Lithuania, Canada,	Total 12 studies, relevant 8 studies; 4 ES, 2 CS, 1 CSS	Residential natural outdoor environments, particularly green and blue spaces	For each 10% increase of greenness the RR and 95% CI was 0.993 (0.985 to 1.001) for CVD mortality. For high vs low categories of greenness, the RR and 95% CI was **0.96 (0.94 to 0.97)** for CVD mortality.	75%	Unclear
Twohig-Bennett	General population, till	Total 143	Greenspace measured by	Comparing higher to lower Greenspace	86%	High risk of

et al. 2018	2017.01, country not restricted: US, UK, Lithuania	studies, relevant 4 studies: 3 CS, 1 ES	residential NVDI, distance to nearest greenspace, and proportion of city area covered by green land	exposure, the pooled ORs and 95% CIs were 0.82 (0.61 to 1.11) for stroke (3 studies), **0.84 (0.76 to 0.93)** for CVD mortality (2 studies), and 0.92 (0.78 to 1.07) for CHD (2 studies).		bias
Yuan et al. 2020	Older adults (mostly ≥ 60 years), 2000.01.01-2020.07.01, country not restricted: Japan, Canada, US, Finland, China, Rome, Australia, Netherlands, Lithuania, Brazil, Israel, South Korea, Iran, UK,	Total 22 studies, relevant 17 studies:12 CS, 5 CSS	Greenspace measured by NDVI (mostly), percent of Greenspace coverage, distance to the nearest green space, park visitation and length of stay, and loss of trees from emerald ash bore disease	Of 8 studies in total CVD, 7 found beneficial effects of green space, the other study showed a lower risk of CVD with higher percentage of tree canopy, but not total green space. Evidence for stroke and MI was less consistent. Only cohort studies measuring NDVI and mortality were included in meta-analysis. Per 0.1 unit increase in NDVI, the pooled HRs and 95% CIs were 0.99 (0.89 to 1.09) for CVD mortality, 0.96 (0.88 to 1.05) for IHD mortality, and **0.77 (0.59 to 1.00)** for stroke mortality.	67%	Low risk of bias
Urbanization						
Angkurawaranon et al. 2014	Southeast Asian populations, until 2013.04, SE Asia countries: Brunei Darussalam, Cambodia, Indonesia, Laos PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor Leste, and Vietnam	Total 37 studies, relevant 7 studies: 7 CSS	Urban exposure	For urban exposure, the pooled ORs and 95% CIs were 1.01 (0.56 to 1.82) for stroke, 1.19 (0.35 to 4.07) for non-specific heart disease in the elderly, **2.48 (1.20 to 5.11)** for CHD, and **0.31 (0.13 to 0.76)** for RHD.	56%	Unclear
Residential noise[5]						
Babisch et al. 2014	Not specified (adults), time and country not restricted: identified countries: UK, Netherlands, Canada, Denmark, Germany, Sweden, Japan	5 CS, 4 CCS, 5CSS	Road traffic noise. L Aeq16hr, L Aeq24hr, L DEN, LDay, LNight	Relative risk per increase of the traffic noise level of 10 dB. For road traffic noise, the pooled OR and 95% CI was **1.08 (1.04 to 1.13)** for CHD.	71%	High risk of bias

Banerjee et al. 2014	Adult population, 1980-2010, country not restricted: Netherlands, UK, Germany, Serbia, Sweden, Austria, Italy, Lithuania, Portugal, Switzerland, France, Slovakia, Hungary	14 CSS	Transportation noise exposure	(No information on unit) For traffic noise (all sources) the pooled RRs and 95% CIs were 1.04 (0.96 to 1.12) for CVD, 1.01 (0.89 to 1.14) for MI, 1.08 (0.80 to 1.36) for AP, and 1.00 (0.73 to 1.26) for IHD. The estimates for air traffic noise exposure were 1.00 (0.91 to 1.09) for CVD, 1.04 (0.80 to 1.28) for AP, 1.02 (0.89 to 1.14) for MI, and 0.96 (0.80 to 1.12) for IHD. The pooled RR for road traffic noise was 1.03 (0.97 to 1.09) for CVD, 1.23 (0.38 to 2.09) for AP, 0.85 (-0.58 to 2.29) for MI, and 1.35 (0.78 to 1.92) for IHD.	73%	High risk of bias
Cai et al. 2021	Adults, general population, 2000.01.01-2020.10.05, country not restricted: Denmark (Copenhagen and Aarhus), France (Paris, Lyon, Toulouse), Switzerland, Sweden (Gothenburg), Spain (Barcelona), Netherlands, UK (London), Canada (Vancouver)	Total 12 studies, relevant 10 studies: 8 CS, 1 CSS, 2 ES	Residential traffic noise from road, rail and aircraft, measured or modelled: mostly Lden, LAeq24hr, LAeq16hr, LDN, Lday, Lnight	For road traffic, per 10 dB increase in Lden, the pooled HRs and 95% CIs were 1.01 (0.98 to 1.05) for CVD mortality, 1.03 (0.99 to 1.08) for IHD mortality, and 1.05 (0.97 to 1.14) for stroke mortality. For aircraft traffic, the estimates based on 3 studies were **1.17 (1.10 to 1.25)** for CVD mortality, 1.03 (0.82 to 1.29) for IHD mortality, and 1.06 (0.93 to 1.20) for stroke mortality. For rail traffic, the estimates were 0.98 (0.94 to 1.01) for CVD mortality (1 study) and 1.02 (0.91 to 1.14) for IHD mortality (2 studies).	68%	Unclear
Dzhambov et al. 2016	Adults, till 2015.11.24, country not restricted: Netherlands, UK, Denmark, Germany, France, Switzerland, US, Canada, Sweden, Greece, Italy	7 CS, 2 CSS, ES 4	Traffic noise	RR per 10dB noise increase. For road traffic noise the pooled RR and 95% CI was 1.03 (0.87 to 1.22). For air traffic noise the pooled RR was 1.05 (1.00 to 1.10).	72%	High risk of bias
Khosravipour et al. 2020	General population, time and country not restricted: till	7 CS, 5 CCS, 1 CSS	Road traffic noise	Comparing highest to lowest category of noise exposure (results from categorical	57%	Low risk of bias

	2019.11.29, UK, Germany, Sweden, Lithuania, Denmark, Netherlands			analysis), the pooled RR and 95% CI of MI were 1.03 (0.93 to 1.13). Per 10-dB increment (results from exposure-response analysis and transformed from categorical analysis), the pooled estimate was 1.02 (1.00 to 1.05). In subgroup analysis, pooled estimates were significant for CCS and CSS, but not for CS. Estimates for the exposure-response analyses were 1.03 (1.00 to 1.05) after excluding two conference papers, and **1.02 (1.01 to 1.03)** after further excluding the studies with only results from categorical analysis.		
van Kempen et al. 2002	Adults, 1970-1999, country not restricted: Iran, Belgium, Germany, Canada, India, Finland, Italy, Netherlands, Russia, US, Poland, Japan, Israel, China, France, South Africa, China (Taiwan), UK.	Total 43 studies, relevant 10 studies: 6 CSS, 2CCS, 2 CS	Community noise exposure (road and air traffic) assessed by calculations, personal dosimeter or sound level meter	RR per 5 dB(A) noise increase. For road traffic noise the pooled RRs and 95% CIs were **1.09 (1.05 to 1.13)** for IHD, 0.99 (0.84 to 1.16) for AP, and 1.03 (0.99 to 1.09) for MI. For air traffic noise the pooled RR was 1.03 (0.90 to 1.18) for AP.	25%	High risk of bias
van Kempen, et al. 2018	European, 2000-2014.10, European countries	Total 61 studies, relevant 32 studies: 14 CSS, 5 ES, 8 CS, 5 CCS	Noise from road, rail and air traffic, and wind turbines: LDEN	Road, rail, and air traffic noise in relation to prevalence, incidence, and mortality of IHD and stroke were analyzed respectively. Number of studies for each analysis is small. Per 10 dB increase in exposure, the pooled RR and 95% CI of IHD was **1.08 (1.01 to 1.15)** for road traffic. Estimates for other associations were of low quality or from less than 3 studies, and mostly insignificant.	NA	Low risk of bias
Vienneau et al. 2015	Not specified (general population), 1994.01-2014.01, country not restricted: Germany, UK, Netherlands,	3 CCS, 5 CS, 2 LS	Transportation noise exposure	RR per 10 dB increase in exposure. The pooled RR and 95% CI for IHD was **1.06 (1.03 to 1.09)**.	75%	High risk of bias

	Sweden, Switzerland, Denmark, Canada, US					
Weihofen et al. 2019	General population, till 2017.08.31, country not restricted: US, France (Paris, Lyon Saint, Toulouse), Canada (Vancouver), UK (London), Switzerland, Germany (Berlin, Frankfurt), Netherlands (Amsterdam), Sweden (Stockholm), Greece (Athen), Italy (Milan)	3 CSS, 1 ES, 4 CS, 1 CCS	Aircraft noise: LAeq, LDay, LNight, LDN, Lden, LDENAEI	Per 10 dB increase in Lden, the pooled RR and 95% CI of stroke was 1.013 (0.998 to 1.028) from 7 studies.	71%	Low risk of bias
Ambient temperature						
Bunker et al. 2016	Elderly (65+), 1975.01.01-2015.07.24, country not restricted: US, Bangladesh, China (mainland, Taiwan, and Hong Kong), Portugal, UK, Denmark, Australia, Russia, Italy, Hungary, Brazil, Vietnam, Sweden, Thailand, Norway, South Korea, Germany	Total 60 studies, relevant 47 studies; 47 LS	Ambient hot and cold temperature	Per 1°C temperature change, for heat, the pooled percentage changes and 95% CIs were **3.79 (3.40 to 4.18)** for CVD mortality, **1.62 (0.24 to 3.03)** for IHD mortality, **1.40 (0.06 to 2.75)** for CeVD mortality, 0.33 (-0.09 to 0.75) for IS, -0.66 (-2.13 to 0.84) for ICH, -0.17(-0.96 to 0.63) for CeVD, -0.16(-2.05 to 1.77) for MI, and 0.30(-0.12 to 0.81) for CVD. For cold, the estimates were **1.84 (0.85 to 2.84)** for CVD mortality, 0.45 (-0.01 to 0.91) for IHD mortality, **1.21 (0.66 to 1.77)** for CeVD mortality, 3.63 (-3.94 to 11.8) for IS, 1.49 (1.04 to 1.94) for ICH, -0.46 (-1.12 to 0.2) for CeVD, 0.66 (-0.14 to 1.48) for MI, -0.80 (-2.21 to 0.64) for AP, -0.67 (-2.15 to 0.83) for HF, and -0.28 (-1.39 to 0.84) for CVD.	73%	High risk of bias
Kofi Amegah et al. 2016	Sub-Saharan African populations, till 2014.12, Sub-Saharan Africa	Total 23 studies, relevant 5 studies: 4 LS,	Temperature	One study found that low temperature was associated with increased risk of CVD. Two studies found associations of low and high temperatures with CVD	56%	High risk of bias

		1 CSS		mortality. One study found no association between mean monthly temperature and CVD mortality. One study found 5 °C change in the monthly mean temperature to be associated with decreased risk of hospitalization for venous thromboembolism, stroke, and acute MI.		
Ma et al. 2020	Chinese population, 2010.01-2020.01, country restricted to China	Total 175 studies, relevant 19 studies: 19 LS	1. every 1 °C temperature increase/decrease beyond certain reference points 2. comparison between extreme temperatures and reference normal temperatures	Pooled RRs and 95% CIs of CVD were **1.089 (1.062 to 1.116)** and **1.171 (1.125 to 1.218)**, respectively, for hot and cold temperatures as compared to normal temperatures.	100%	High risk of bias
Moghadamnia et al. 2017	General population, 2000.01-2015.12.31, country not restricted: China (mainland, Taiwan, Hong Kong), Australia, Thailand, Philippines, South Korea, Germany, Spain	26 LS	Ambient temperature	RR per 1 ºC change of temperature. For CVD mortality the RRs and 95% CIs were 1.055 (1.050 to 1.060) for cold exposure and 1.013 (1.011 to 1.015) for heat exposure. Coefficient per 1 °C change in mean annual temperature. For CVD mortality the pooled estimates were 0.026 (-0.019 to 0.072) for cold exposure, and 0.008 (-0.015 to 0.031) for heat exposure.	96%	High risk of bias
Odame et al. 2018	Rural population, till 2018.04, country not restricted: Bangladesh (Matlab), Czech Republic, China (Naidong and Jiangzi in Tibet)	All 14 studies, relevant 3 studies: 3 LS	Daily mean temperature	Per 1 °C increase, the pooled RR and 95% CI of CVD mortality was **1.111 (1.045 to 1.181)**. The associations were significant in subgroup analyses of both developing and developed countries.	100%	High risk of bias
Turner et al. 2012	Not specified (general population), time and country not restricted: South Korea (Incheon), US, UK (London,	Total 21 studies, relevant 18 studies: 18 LS	Effects of ambient temperature. Maximum, minimum and mean daily temperature	RR per 1ºC increase in temperature. The pooled RRs and 95% CI were 0.999 (0.982 to 1.016) for CVD morbidities, 0.990 (0.887 to 1.105) for stroke, and	43%	High risk of bias

	Scotland), Europe, Australia (Brisbane), Thailand (Muang)			1.010 (0.930 to 1.097) for ACS/MI.		
Wang et al. 2016	Adults, till 2015.10.16, country not restricted: Japan, UK, Russia, Spain, China, Portugal, Italy, South Korea, China (Taiwan), Mozambique, US, France, Australia	7 CS, 13 LS, 1 CSS	Ambient temperature	OR per 1ºC increase in mean ambient temperature. The pooled ORs and 95% CIs were 0.97 (0.94 to 1.00) for ICH, 1.00 (0.99 to 1.01) for IS, and 1.00 (0.98 to 1.01) for SAH. The pooled estimates for ambient minimum and maximum temperature and IS were OR 0.99 (0.96 to 1.01) and 0.98 (0.94 to 1.02), respectively.	19%	Unclear
Zafeiratou et al. 2021	General population, 1990-2020, country not restricted: Serbia (Belgrade), China (Hong Kong), UK (London), US (New England), Finland (Helsinki), Switzerland, South Korea	Total 34 studies, relevant 6 studies: 4 ES, 2 CS	Mean annual temperature or variability; seasonal temperature or variability; annual temperature categories; mean annual degrees above/ below minimum mortality temperature	In temporal comparisons within the same area, increased cardiovascular mortality was associated with both increased or decreased temperature. Stronger association was found with cold rather than hot temperature. In geographical comparison in just one study, people living in areas with higher temperature were found a lower rate of IHD mortality, though no does-response.	5 studies on CVD mortality: 60%	High risk of bias
Multiple domains						
Rugel et al. 2020	Urban residents, 2003.01.01-2019.11, country not restricted: Netherlands, Sweden (Skåne), UK (London), Canada, Denmark (Copenhagen, Aarhus), Germany (Bochum, Essen, Mülheim/Ruhr), South Korea (Seoul, Ulsan, Cheonan), France, Spain, Norway, Greece, Italy (Rome, Verona), Switzerland, US (California), China (Shenyang, Anshan,	Total 51 studies, relevant 21 studies: 15 CS, 5 CSS, 1 ES	Traffic-related air pollution; Natural spaces, neighborhood walkability; Noise	Based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system for assessing the quality of the synthesized evidence base, evidence was sufficient for higher noise exposure with increased CVD. And evidence was sufficient for no association between traffic-related air pollution and CVD.	NA	High risk of bias

	Jinzhou, Taiwan)

[1] A bibliography of all included reviews is presented in Appendix 3.

[2] Ecological studies (ES), cohort studies (CS), cross-sectional studies (CSS), case-control studies (CCS), case-crossover studies (CCR), small-area studies (SAS), longitudinal study (LS, e.g. panel study, time-series).

[3] There were no systematic reviews found in the domains of food environment and light pollution.

[4] RR: relative risk; HR: hazard ratio; MI: myocardial infarction; AP: angina pectoris; CHA: cardiovascular hospital admission; ACS: acute coronary syndrome; CVD: cardiovascular disease; CHD: coronary heart disease; AF: atrial fibrillation; IHD: ischemic heart disease; CeVD: cerebrovascular disease; RHD: rheumatic heart disease; HRV: heart rate variability; SDNN: the standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; LF: low-frequency bands; HF: high-frequency bands; RE: risk estimate; events include both morbidity and mortality; ICH: intracerebral hemorrhage; IS: ischemic stroke; SAH; subarachnoid hemorrhage; HF: heart failure. The significant poled results were in bold.

[5] LAeq16hr: annual non-weighted 16 h average noise level during the day; LAeq24hr: the annual non-weighted day-night average noise level; LDEN: the annual weighted (day + 0 dB, evening + 5 dB, night + 10 dB) day-evening-night average noise level; LAeq: A-weighted average of an energy-equivalent continuous sound level over a period of time (A-weighting: in noise research typically the A filter is used which adjusts for deep and high frequencies, as these are perceived as less loud); LDay: LAeq for the day (usually 7:00 am – 7:00 pm) for all day periods of a year; LNight: LAeq for the night (usually from 11:00 pm – 7:00 am) for all night periods of a year; LDN: all 24 h LAeq periods of a year with additional 10 dB for nighttime noise annoyance (usually from 11:00 pm – 7:00 am); LDENAEI: see LDEN, but in addition weighted average exposure on municipal level.

Table 2. Robustness of evidence assessment and ROBIS quality assessment per review by domain[1]

Strong evidence by domain[2]	Robustness of evidence								ROBIS quality assessment (comments)				
	Level of comparison[3]	Random-effects summary ES (95% CI); P value	Sample size; N of included studies	ES (95% CI) in the largest study	I^2 (%)	Egger's test P value	Excess statistical significance test *P* value	95% prediction interval	Study eligibility criteria	Identification and selection of studies	Data collection, appraisal	Synthesis and findings	Overall
Air pollution													
Chen et al. 2021	RR per 10 µg/m3 increase in SO2 for AF	1.005 (1.004 to 1.007); <0.000001	>1000; 2 studies	1.005 (1.003 to 1.006)	0.0%	NA	0.53	1.004 to 1.007	Low risk	High risk (no additional methods to database search)	Low risk	Low risk	Low risk
Chen et al. 2021	RR per 10 µg/m3 increase in CO for AF	1.017 (1.013 to 1.022); <0.000001	>1000; 2 studies	1.017 (1.013 to 1.022)	0.0%	NA	0.53	1.013 to 1.022	Low risk	High risk (no additional methods to database search)	Low risk	Low risk	Low risk
Alexeeff et al. 2021	RR per 10 µg/m3 increase in PM2.5 for incident stroke	1.13 (1.11 to 1.15); <0.000001	>1000; 14 studies	1.12 (1.08 to 1.16)	0.0%	0.46	0.52	1.11 to 1.15	High risk	High risk	High risk	Low risk	High risk
Yang et al. 2019	RR per 10 µg/m3 increase in NO2 for IHD events (incidence and	1.05 (1.04 to 1.06); <0.000001	>1000; 4 studies	1.05 (1.03 to 1.06)	0.0%	0.68	0.27	1.04 to 1.07	Low risk	Unclear risk	Unclear risk	High risk	High risk

	mortality)												
Residential noise													
Cai et al. 2021	HR per 10 dB increase in aircraft traffic noise (Lden) for CVD mortality	1.17 (1.10 to 1.25); <0.000001	>1000; 3 studies	1.18 (1.10 to 1.26)	0.0%	0.82	0.77	1.10 to 1.25	Low risk	High risk (search strategy is simple and no MeSH terms used; language restricted to English; no information for two independent screeners)	Unclear risk	High risk	Unclear risk

[1] Here only presents results of strong evidence. For complete assessment, please refer to **Appendix 4**.

[2] A bibliography of above mentioned reviews is presented in Appendix 3.

[3] RR: relative risk; HR: hazard ratio; MI: myocardial infarction; AP: angina pectoris; CHA: cardiovascular hospital admission; ACS: acute coronary syndrome; CVD: cardiovascular disease; CHD: coronary heart disease; AF: atrial fibrillation; IHD: ischemic heart disease; CeVD: cerebrovascular disease; RHD: rheumatic heart disease; HRV: heart rate variability; SDNN: the standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; LF: low-frequency bands; HF: high-frequency bands; RE: risk estimate; events include both morbidity and mortality; ICH: intracerebral hemorrhage; IS: ischemic stroke; SAH; subarachnoid hemorrhage; HF: heart failure.

Table 3. Summary of evidence based on robustness and quality[1]

Robustness of evidence by domain[2]	Specific exposure and outcome[3]
Air pollution (positive association)	
Strong (n = 4)	**PM2.5 and stroke** (*, †, Alexeeff et al. 2021), **SO_2 and AF** (2 studies, Chen et al. 2021), **CO and AF** (2 studies, Chen et al. 2021), **NO_2 and IHD events** (4 studies, Yang et al. 2019)
Highly suggestive (n = 13)	**PM2.5 for MI** (†, ‡, Zou et al. 2021), **IHD mortality** (*, †, ⊥, #, Alexeeff et al. 2021) (#, Chen et al. 2020), **CeVD mortality** (*, †, #, Alexeeff et al. 2021), **CVD mortality** (‡, Yang et al. 2019) (‡, ⊥, #, Liu et al. 2018) (#, Chen et al. 2020), **CVD events** (‡, Yang et al. 2019), **stroke events** (‡, Yang et al. 2019) **PM10 ~~for~~ and AF** (4 studies, ‡, ⊥, Chen et al. 2021)

	NO_2 for CVD mortality (†, #, Huang et al. 2021), **ICH mortality** (‡, #, Stieb et al. 2021), **CHD mortality** (†, Atkinson et al. 2018)
Non-significant (n = 32)	**PM2.5 for CHD mortality** (†, #, Chen et al. 2008), **MI** (*, †, #, Alexeeff et al. 2021), **CVD** (#, Yang et al. 2019), **HRV** (*, †, Wang et al. 2020)
	PM10 for stroke (#, Yang et al. 2019), **stroke mortality** (#, Yang et al. 2019) (#, Chen et al. 2020), **stroke events** (#, Yang et al. 2019), **IHD** (2 studies, Yang et al. 2019), **IHD mortality** (4 studies, #, Yang et al. 2019), **IHD events** (6 studies, #, Yang et al. 2019), **CVD** (3 studies, #, Yang et al. 2019), **CVD mortality** (‡, ⊥, #, Liu et al. 2018) (#, Chen et al. 2020), **CVD events** (‡, #, Yang et al. 2019)
	NO_2 for stroke (4 studies, Yang et al. 2019), **stroke mortality** (2 studies, Yang et al. 2019), **stroke events** (6 studies, Yang et al. 2019), **CVD** (2 studies, Yang et al. 2019), **CeVD mortality** (13 studies, Stieb et al. 2021) (†, Atkinson et al. 2018)
	O_3 for AF (3 studies; Chen et al. 2021), **stroke** (2 studies, #, Yang et al. 2019), **stroke mortality** (3 studies, Yang et al. 2019) (†, Atkinson et al. 2016), **stroke events** (5 studies, #, Yang et al. 2019), **CVD mortality** (†, ‡, Atkinson et al. 2016), **CVD events** (‡, #, Yang et al. 2019), **IHD mortality** (†, ‡, Atkinson et al. 2016)
Physical activity environment (negative association)	
Suggestive (n = 2)	**Greenspace ~~for~~ and CVD mortality** (†, Gascon et al. 2016) (2 studies, Twohig-Bennett et al. 2018)
Non-significant (n = 6)	**Greenspace ~~for~~ and CVD mortality** (#, Yuan et al. 2020) (†, Gascon et al. 2016), **IHD mortality** (3 studies, Yuan et al. 2020), **stroke mortality** (4 studies, ‡, #, Yuan et al. 2020), **stroke** (‡, Twohig-Bennett et al. 2018), **CHD** (2 studies, Twohig-Bennett et al. 2018)
Urbanization (insufficient and mixed evidence)	
Weak (n = 2)	Positive association: **Urban exposure and CHD** (*, ‡, Angkurawaranona et al. 2014), Negative association: **Urban exposure and RHD** (*, Angkurawaranona et al. 2014)
Non-significant (n = 2)	**Urban exposure for stroke** (*, Angkurawaranona et al. 2014), **non-specific heart disease** (*, #, ⊥, Angkurawaranona et al. 2014)
Residential noise (positive association)	
Strong (n = 1)	**Aircraft traffic noise ~~for~~ and CVD mortality** (*, †, Cai et al. 2021)
Suggestive (n = 2)	**Road traffic noise ~~for~~ and CHD** (*, †, Babisch et al. 2014), **Traffic noise for IHD** (*, †, Vienneau et al. 2015)
Non-significant (n = 17)	**Traffic noise ~~for~~ and CVD** (†, Banerjee et al. 2014)
	Road traffic noise ~~for~~ and MI (†, Banerjee et al. 2014) (†, Khosravipour et al. 2020), **stroke** (†, #, Dzhambov et al. 2016), **AP** (†, Banerjee et al. 2014), **CVD mortality** (†, Cai et al. 2021), **IHD mortality** (†, Cai et al. 2021), **stroke mortality** (†, ‡, Cai et al. 2021)
	Aircraft traffic noise ~~for~~ and MI (†, Banerjee et al. 2014), **AP** (†, Banerjee et al. 2014), **IHD** (†, ‡, Banerjee et al. 2014), **stroke** (†, Dzhambov et al. 2016) (7 studies, Weihofen et al. 2019), **IHD mortality** (†, #, Cai et al. 2021), **stroke mortality** (†, Cai et al. 2021)
	Rail traffic noise and IHD mortality (†, #, Cai et al. 2021)
Ambient temperature (positive association)	
Suggestive (n = 8)	**Temperature ~~for~~ and CVD mortality** (†, Odame et al. 2018)
	Heat ~~for~~ and CVD mortality (†, ‡, #, Bunker et al. 2016) (†, ‡, ⊥, #, Moghadamnia et al. 2017), **combined CVD mortality** (†, ‡, #, Bunker et al. 2016)
	Cold ~~for~~ and CVD mortality (†, ‡, ⊥, #, Moghadamnia et al. 2017), **CeVD mortality** (†, Bunker et al. 2016), **ICH morbidity** (†, Bunker et al. 2016), **combined CVD mortality** (†, ‡, #, Bunker et al. 2016)
Non-significant (n = 22)	**Temperature ~~for~~ and CVD** (*, †, #, Turner et al. 2012), **stroke** (*, †, #, Turner et al. 2012), **ACS/MI** (*, †, #, Turner et al. 2012), **IS** (*, #, Wang et al. 2016), **SAH** (*, Wang et al. 2016)
	Heat ~~for~~ and IS (*, #, Wang et al. 2016) (†, ‡, ⊥, #, Bunker et al. 2016), **CeVD** (†, ‡, ⊥, #, Bunker et al. 2016), **CVD** (†, ‡, ⊥, #, Bunker et al. 2016), **MI** (†, ‡, #, Bunker et al. 2016), **ICH mortality** (†, #, Bunker et al. 2016), **combined CVD** (†, ⊥, #, Bunker et al. 2016)

Cold and CVD (†, ‡, Bunker et al. 2016), **combined CVD** (†, #, Bunker et al. 2016), **AP** (†, #, Bunker et al. 2016), **HF** (†, #, Bunker et al. 2016), **IHD mortality** (†, #, Bunker et al. 2016), **MI** (†, #, Bunker et al. 2016), **CeVD** (†, ‡, ⊥, #, Bunker et al. 2016), **combined CeVD** (†, ⊥, #, Bunker et al. 2016), **IS** (*, #, Wang et al. 2016) (†, #, Bunker et al. 2016)

[1] A bibliography of above mentioned reviews is presented in Appendix 3.

[2] There were 17 suggestive, 16 weak, and 23 unclear associations in the domain of air pollution; 10 unclear associations in residential noise; 6 weak and 1 unclear associations in ambient temperature. For complete summary, please refer to **Appendix 5 Table S1**.

[3] MI: myocardial infarction; AP: angina pectoris; CHA: cardiovascular hospital admission; ACS: acute coronary syndrome; CVD: cardiovascular disease; CHD: coronary heart disease; AF: atrial fibrillation; IHD: ischemic heart disease; CeVD: cerebrovascular disease; RHD: rheumatic heart disease; HRV: heart rate variability; SDNN: the standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; LF: low-frequency bands; HF: high-frequency bands; RE: risk estimate; events include both morbidity and mortality; ICH: intracerebral hemorrhage; IS: ischemic stroke; SAH; subarachnoid hemorrhage; HF: heart failure.

Note: * high risk or unclear risk in study eligibility criteria; † high risk or unclear risk in identification and selection; ‡ small study effect; ⊥ excess significance bias; # high heterogeneity

Table 4. Meta-meta-analyses and robustness of evidence assessment by domain

Included reviews[1]	Level of comparison[2]	Random-effects summary ES (95% CI); P value	Sample size; N of included studies	ES (95% CI) in the largest study	I^2 (%)	Egger's test P value	Excess statistical significance test *P* value	95% prediction interval	Robustness of evidence
Air pollution									
Alexeeff et al. 2021 Chen et al. 2020	RR per 10 µg/m3 increase in PM2.5 for IHD mortality	1.21 (1.10 to 1.33); <.0001	>1000; 29 studies	1.64 (1.62 to 1.66)	98.16%	0.36	0.21	0.7852 to 1.8617	Highly suggestive
Yang et al. 2019 Chen et al. 2020	RR per 10 µg/m3 increase in PM2.5 for CVD mortality	1.11 (1.09 to 1.14); <.0001	>1000; 26 studies	1.06 (1.04 to 1.08)	74.23%	0.08	0.37	1.0303 to 1.1959	Highly suggestive
Stieb et al. 2021 Atkinson et al. 2018	HR per 10 ppb increase in NO_2 for CeVD mortality	1.03 (1.00 to 1.06); 0.07	>1000; 14 studies	1.01 (0.98 to 1.05)	45.64%	0.09	0.41	0.9581 to 1.1044	Non-significant
Ambient temperature									
Bunker et al. 2016 Moghadamnia et al. 2017	RR per 1 ºC change of temperature (heat) for CVD mortality	1.04 (1.03 to 1.04); <.0001	>1000; 62 studies	1.013 (1.010 to 1.015)	98.63%	< 0.0001	< 0.01	1.0225 to 1.0538	Highly suggestive

[1] A bibliography of above mentioned reviews is presented in Appendix 3.

[2] RR: relative risk; HR: hazard ratio; CVD: cardiovascular disease; IHD: ischemic heart disease; CeVD: cerebrovascular disease.

CHAPTER 2 Appendices

Appendix 1. PRISMA 2020 checklist for reporting systematic reviews

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4 & Appendix 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data	9	Specify the methods used to collect data from reports, including	Page 5

collection process		how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5-6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5-6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and	Page 5-6

		extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5-6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 5-6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5-6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5-6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7 & Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7 & Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 7 & Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7-9 & Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7-9 & Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 7-9 & Appendix 5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of	Page 7-9 & Table 3 & Figure

		statistical heterogeneity. If comparing groups, describe the direction of the effect.	2-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7-9 & Appendix 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7-9 & Appendix 7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7-9 & Appendix 5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 7-9 & Appendix 5 & Table 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9
	23b	Discuss any limitations of the evidence included in the review.	Page 12
	23c	Discuss any limitations of the review processes used.	Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 11-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 4

	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 13
Competing interests	26	Declare any competing interests of review authors.	Page 13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 13

Appendix 2. Search strategy for all databases

A. MEDLINE/Pubmed

#1	“exposome”[MeSH] OR exposome [tiab] OR "city planning"[MeSH] OR "city plan*"[tiab] OR “urban plan*”[tiab] OR “town plan*”[tiab] OR “built environment”[MeSH] OR ((“environment*”[tiab]) AND (“built”[tiab] OR “living”[tiab] OR “lifestyle”[tiab] OR “obesogenic”[tiab] OR “neighbo*”[tiab] OR “urban”[tiab] OR “rural”[tiab] OR “city”[tiab] OR “factor*”[tiab]))
#2	“air pollution”[MeSH] OR “air pollutants”[MeSH] OR (“air”[tiab] AND (“pollut*”[tiab] OR “quality”[tiab])) OR “particulate matter”[MeSH] OR “particulate matter”[tiab] OR “PM 0.1”[tiab] OR “PM 2.5”[tiab] OR “PM 10”[tiab] OR “PM 20”[tiab]
#3	"carbon monoxide"[MeSH] OR “carbon monoxide*”[tiab] OR "nitrogen oxides"[MeSH] OR (“nitrogen”[tiab] AND (“oxide*”[tiab] OR “monoxide*”[tiab] OR “dioxide*”[tiab])) OR “nitric oxide*”[tiab] OR "sulfur dioxide"[MeSH] OR “sulfur dioxide*”[tiab] OR "ozone"[MeSH] OR “ozone*”[tiab]
#4	"fast foods"[MeSH] OR “fast food*”[tiab] OR "food supply"[MeSH] OR "food suppl*"[tiab] OR “food outlet*”[tiab] OR (“environment*”[tiab] AND (“food*”[tiab] OR “retail*”[tiab] OR “nutrition*”[tiab] OR “diet*”[tiab])) OR “food access*”[tiab] OR “food resource*”[tiab] OR “supermarkets”[MeSH] OR “grocery store*”[tiab] OR “supermarket*”[tiab] OR “convenience store*”[tiab] OR “restaurant*”[tiab]
#5	“physical activity environment*”[tiab] OR “sports facilit*”[tiab] OR “gym”[tiab] OR “gyms”[tiab] OR “sport field*”[tiab] OR “fitness facilit*”[tiab] OR “recreational facilit*”[tiab] OR “activity zone*”[tiab] OR “land-use mix*”[tiab] OR “residential densit*”[tiab] OR “urbanization”[MeSH] OR “urbanization”[tiab] OR “urbanisation”[tiab] OR “street connectivit*”[tiab]
#6	“greenness”[tiab] OR “green space*”[tiab] OR “blueness”[tiab] OR “blue space*”[tiab] OR “lakes”[MeSH] “lake*”[tiab] OR “canal*”[tiab] OR “rivers”[MeSH] OR “river*”[tiab] OR “sea”[tiab] OR “ocean*”[tiab] OR "open space*"[tiab] OR “park*”[tiab] OR “walkability”[tiab] OR “walk ability”[tiab] OR “hiking trail*”[tiab] OR “walking trail*”[tiab] OR “bikeability”[tiab] OR “bike ability”[tiab] OR “bike path*”[tiab] OR “cycle path*”[tiab] OR “driveability”[tiab] OR “night-time light*”[tiab] OR "Noise, Transportation "[MeSH] OR “noise*”[tiab] OR “environmental temperature*”[tiab] OR “ambient temperature*”[tiab] OR “air temperature*”[tiab] OR “heat”[tiab]
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	"cardiovascular diseases"[MeSH] OR "cardiovascular disease*"[tiab] OR “vascular disease*”[tiab] OR "cardiometabolic disease*"[tiab] OR "heart disease*"[tiab] OR

	"infarction*"[tiab] OR "ischemic heart disease*"[tiab] OR “transient ischemic attack”[tiab] OR “coronary artery disease*”[tiab] OR "coronary occlusion*"[tiab] OR "heart failure"[tiab] OR "stroke*"[tiab] OR “cerebrovascular disease*”[tiab] OR "cerebrovascular accident*"[tiab] OR "cerebrovascular event*"[tiab] OR “aortic disease*”[tiab] OR “aortic aneurysm*”[tiab] OR "arrhythmia*"[tiab] OR "angina pectoris*"[tiab] OR “hypertensive heart disease*”[tiab] OR “rheumatic heart disease*”[tiab] OR “pulmonary heart disease*”[tiab] OR “heart attack*”[tiab] OR “heart arrest*”[tiab]
#9	"mortality"[MeSH] OR “mortality”[tiab] OR “death”[MeSH] OR “death*”[tiab] OR “fatal”[tiab]
#10	(“Systematic Reviews as Topic”[MeSH] OR “Systematic review”[tiab] OR "Systematic Review"[Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR meta-analysis[tiab] OR meta-analyses[tiab] OR "Meta-Analysis "[Publication Type]) NOT ("Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Comment"[Publication Type])
#11	#7 AND (#8 OR (#8 AND #9)) AND #10
#12	#11 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR “adolescen*”[tiab] OR “child*”[tiab] OR “schoolchild*”[tiab] OR “infant*”[tiab] OR “girl*”[tiab] OR “boy”[tiab] OR “boys”[tiab] OR “teen*”[tiab] OR “teenager*”[tiab] OR “youth*”[tiab] OR “pediatr*”[tiab] OR “paediatr*”[tiab] OR “puber*”[tiab]) NOT ("Adult"[Mesh] OR “adult*”[tiab] OR “man”[tiab] OR “men”[tiab] OR “woman”[tiab] OR “women”[tiab]))
#13	#12 NOT (“animals”[MeSH] NOT “humans”[MeSH])
#14	#13 + Filters: English, from 2000 - 2021

B. EMBASE

#1	'exposome'/exp OR 'exposome':ti,ab,kw OR (('city'/de OR 'city':ti,ab,kw) AND ('planning'/de OR 'plan*':ti,ab,kw)) OR 'urban plan*':ti,ab,kw OR 'town plan*':ti,ab,kw OR 'built environment'/exp OR 'obesogenic environment'/exp OR (('environment*':ti,ab,kw) AND ('built':ti,ab,kw OR 'living':ti,ab,kw OR 'lifestyle':ti,ab,kw OR 'obesogenic':ti,ab,kw OR 'neighborhood'/exp OR 'neighbo*':ti,ab,kw OR 'urban':ti,ab,kw OR 'rural':ti,ab,kw OR 'city':ti,ab,kw OR 'factor*':ti,ab,kw))
#2	'air pollution'/exp OR 'air quality'/exp OR ('air':ti,ab,kw AND ('pollut*':ti,ab,kw OR 'quality':ti,ab,kw)) OR 'particulate matter'/exp OR 'particulate matter':ti,ab,kw OR 'pm

	0.1':ti,ab,kw OR 'pm 2.5':ti,ab,kw OR 'pm 10':ti,ab,kw OR 'pm 20':ti,ab,kw
#3	'carbon monoxide'/exp OR 'carbon monoxide*':ti,ab,kw OR 'nitrogen oxide'/exp OR (‘nitrogen’:ti,ab,kw AND (‘oxide*’:ti,ab,kw OR ‘monoxide*’:ti,ab,kw OR ‘dioxide*’:ti,ab,kw)) OR ‘nitric oxide*':ti,ab,kw OR 'nitrogen dioxide'/exp OR 'sulfur dioxide'/exp OR 'sulfur dioxide*':ti,ab,kw OR 'ozone'/exp OR 'ozone*':ti,ab,kw
#4	'fast food'/exp OR 'fast food*':ti,ab,kw OR 'catering service'/exp OR 'food suppl*':ti,ab,kw OR 'food outlet*':ti,ab,kw OR 'food environment'/exp OR ('environment*':ti,ab,kw AND ('food*':ti,ab,kw OR 'retail*':ti,ab,kw OR 'nutrition*':ti,ab,kw OR 'diet*':ti,ab,kw)) OR 'food access'/exp OR 'food access*':ti,ab,kw OR 'food resource*':ti,ab,kw OR 'grocery store'/exp OR ‘grocery store*’:ti,ab,kw OR 'supermarket*':ti,ab,kw OR ‘convenience store*’:ti,ab,kw OR 'restaurant'/exp OR 'restaurant*':ti,ab,kw
#5	‘physical activity environment*’:ti,ab,kw OR ‘sports facilit*’:ti,ab,kw OR ‘gym’:ti,ab,kw OR ‘gyms’:ti,ab,kw OR ‘sport field*’:ti,ab,kw OR ‘fitness facilit*’:ti,ab,kw OR ‘recreational facilit*’:ti,ab,kw OR ‘activity zone*’:ti,ab,kw OR ‘land-use mix*’:ti,ab,kw OR ‘residential densit*’:ti,ab,kw OR ‘urbanization’/exp OR ‘urbanization’:ti,ab,kw OR ‘urbanisation’:ti,ab,kw OR ‘street connectivit*’:ti,ab,kw
#6	'greenness'/exp OR 'green space'/exp OR 'greenness':ti,ab,kw OR 'green space*':ti,ab,kw OR 'blueness':ti,ab,kw OR 'blue space*':ti,ab,kw OR 'lake'/exp OR 'lake*':ti,ab,kw OR 'canal*':ti,ab,kw OR 'river'/exp OR ‘river*’:ti,ab,kw OR ‘sea’:ti,ab,kw OR ‘ocean*’:ti,ab,kw OR 'open space*':ti,ab,kw OR 'park'/exp OR 'park*':ti,ab,kw OR 'walkability'/exp OR 'walkability':ti,ab,kw OR 'walk ability':ti,ab,kw OR 'hiking trail*':ti,ab,kw OR 'walking trail*':ti,ab,kw OR 'bikeability'/exp OR 'bikeability':ti,ab,kw OR 'bike ability':ti,ab,kw OR 'bike path*':ti,ab,kw OR 'cycle path*':ti,ab,kw OR 'driveability':ti,ab,kw OR 'night-time light*':ti,ab,kw OR 'traffic noise'/exp OR 'noise*':ti,ab,kw OR 'environmental temperature'/exp OR 'environmental temperature*':ti,ab,kw OR 'ambient temperature*':ti,ab,kw OR 'air temperature'/exp OR 'air temperature*':ti,ab,kw OR 'heat'/exp OR 'heat':ti,ab,kw
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	‘cardiovascular disease’/exp OR ‘cardiovascular disease*’:ti,ab,kw OR ‘vascular disease*’:ti,ab,kw OR ‘cardiometabolic disease*’:ti,ab,kw OR ‘heart disease*’:ti,ab,kw OR ‘infarction*’:ti,ab,kw OR ‘ischemic heart disease*’:ti,ab,kw OR ‘transient ischemic attack’:ti,ab,kw OR ‘coronary artery disease*’:ti,ab,kw OR ‘coronary occlusion*’:ti,ab,kw OR ‘heart failure’:ti,ab,kw OR ‘stroke*’:ti,ab,kw OR ‘cerebrovascular disease*’:ti,ab,kw OR ‘cerebrovascular accident*’:ti,ab,kw OR

	'cerebrovascular event*':ti,ab,kw OR 'aortic disease*':ti,ab,kw OR 'aortic aneurysm*':ti,ab,kw OR 'arrhythmia*':ti,ab,kw OR 'angina pectoris*':ti,ab,kw OR 'hypertensive heart disease*':ti,ab,kw OR 'rheumatic heart disease*':ti,ab,kw OR 'pulmonary heart disease*':ti,ab,kw OR 'heart attack*':ti,ab,kw OR 'heart arrest*':ti,ab,kw
#9	'mortality'/exp OR 'mortality':ti,ab,kw OR 'death'/exp OR 'death*':ti,ab,kw OR 'fatal':ti,ab,kw
#10	('systematic review'/exp OR 'Systematic review':ti,ab,kw OR 'meta-analysis'/exp OR 'meta-analysis':ti,ab,kw OR 'meta-analyses':ti,ab,kw) NOT ('letter'/it OR 'editorial'/it OR 'note'/it)
#11	#7 AND (#8 OR (#8 AND #9 OR 'cardiovascular mortality'/exp)) AND #10
#12	#11 NOT (('juvenile'/exp OR 'juvenile*':ti,ab,kw OR 'adolescen*':ti,ab,kw OR 'child*':ti,ab,kw OR 'schoolchild*':ti,ab,kw OR 'infant*':ti,ab,kw OR 'girl*':ti,ab,kw OR 'boy':ti,ab,kw OR 'boys':ti,ab,kw OR 'teen*':ti,ab,kw OR 'teenager*':ti,ab,kw OR 'youth*':ti,ab,kw OR 'pediatr*':ti,ab,kw OR 'paediatr*':ti,ab,kw OR 'puber*':ti,ab,kw) NOT ('adult'/exp OR 'adult*':ti,ab,kw OR 'man':ti,ab,kw OR 'men':ti,ab,kw OR 'woman':ti,ab,kw OR 'women':ti,ab,kw))
#13	#12 NOT ('animal'/exp NOT 'human'/exp)
#14	#13 AND [english]/lim AND ([EMBASE]/lim OR [medline]/lim OR [pubmed-not-medline]/lim) AND [2000-2021]/py

C. CINAHL

#1	[mh "exposome"] OR "exposome":ti,ab,kw OR [mh "city planning"] OR "city plan*":ti,ab,kw OR "urban plan*":ti,ab,kw OR "town plan*":ti,ab,kw OR [mh "built environment"] OR ("environment*":ti,ab,kw AND ("built":ti,ab,kw OR "living":ti,ab,kw OR "lifestyle":ti,ab,kw OR "obesogenic":ti,ab,kw OR "neighbo*":ti,ab,kw OR "urban":ti,ab,kw OR "rural":ti,ab,kw OR "city":ti,ab,kw OR "factor*":ti,ab,kw))
#2	[mh "air pollution"] OR [mh "air pollutants"] OR ("air":ti,ab,kw AND ("pollut*":ti,ab,kw OR "quality":ti,ab,kw)) OR [mh "particulate matter"] OR "particulate matter*":ti,ab,kw OR "PM 0.1":ti,ab,kw OR "PM 2.5":ti,ab,kw OR "PM 10":ti,ab,kw OR "PM 20":ti,ab,kw
#3	[mh "carbon monoxide"] OR "carbon monoxide*":ti,ab,kw OR [mh "nitrogen oxides"] OR ("nitrogen":ti,ab,kw AND ("oxide*":ti,ab,kw OR "monoxide*":ti,ab,kw OR "dioxide*":ti,ab,kw)) OR "nitric oxide*":ti,ab,kw OR [mh "sulfur dioxide"] OR "sulfur dioxide*":ti,ab,kw OR [mh "ozone"] OR "ozone*":ti,ab,kw

#4	[mh “fast foods”] OR “fast food*”:ti,ab,kw OR [mh “food supply”] OR “food suppl*”:ti,ab,kw OR “food outlet*”:ti,ab,kw OR (“environment*”:ti,ab,kw AND (“food*”:ti,ab,kw OR “retail*”:ti,ab,kw OR “nutrition*”:ti,ab,kw OR “diet*”:ti,ab,kw)) OR “food access*”:ti,ab,kw OR “food resource*”:ti,ab,kw OR [mh “supermarkets”] OR “grocery store*”:ti,ab,kw OR “supermarket*”:ti,ab,kw OR “convenience store*”:ti,ab,kw OR “restaurant*”:ti,ab,kw
#5	“physical activity environment*”:ti,ab,kw OR “sports facilit*”:ti,ab,kw OR “gym”:ti,ab,kw OR “gyms”:ti,ab,kw OR “sport field*”:ti,ab,kw OR “fitness facilit*”:ti,ab,kw OR “recreational facilit*”:ti,ab,kw OR “activity zone*”:ti,ab,kw OR “land use mix*”:ti,ab,kw OR “residential densit*”:ti,ab,kw OR [mh “urbanization”] OR “urbanisation”:ti,ab,kw OR “street connectivit*”:ti,ab,kw
#6	“greenness”:ti,ab,kw OR “green space*”:ti,ab,kw OR “blueness”:ti,ab,kw OR “blue space”:ti,ab,kw OR [mh “lakes”] OR “lake*”:ti,ab,kw OR “canal*”:ti,ab,kw OR [mh “rivers”] OR “river*”:ti,ab,kw OR “sea”:ti,ab,kw OR “ocean”:ti,ab,kw OR “open space*”:ti,ab,kw OR “park*”:ti,ab,kw OR “walkability”:ti,ab,kw OR “bikability”:ti,ab,kw OR “bike ability”:ti,ab,kw OR “bike path*”:ti,ab,kw OR “cycle path*”:ti,ab,kw OR “drivability”:ti,ab,kw OR “drive ability”:ti,ab,kw OR “night time light*”:ti,ab,kw OR [mh “noise, transportation”] OR ([mh “noise”] NOT [mh “noise, occupational”]) OR “environmental temperature*”:ti,ab,kw OR “ambient temperature*”:ti,ab,kw OR “heat”:ti,ab,kw
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	[mh “cardiovascular diseases”] OR “cardiovascular disease*”:ti,ab,kw OR “vascular disease*”:ti,ab,kw OR “cardiometabolic disease*”:ti,ab,kw OR “heart disease*”:ti,ab,kw OR “infarction*”:ti,ab,kw OR “ischemic heart disease*”:ti,ab,kw OR “coronary artery disease*”:ti,ab,kw OR "coronary occlusion*":ti,ab,kw OR "heart failure":ti,ab,kw OR "stroke*":ti,ab,kw OR “cerebrovascular disease*”:ti,ab,kw OR "cerebrovascular accident*":ti,ab,kw OR "cerebrovascular event*":ti,ab,kw OR “aortic disease*”:ti,ab,kw OR “aortic aneurysm*”:ti,ab,kw OR "arrhythmia*":ti,ab,kw OR "angina pectoris*":ti,ab,kw OR “hypertensive heart disease*”:ti,ab,kw OR “rheumatic heart disease*”:ti,ab,kw OR “pulmonary heart disease*”:ti,ab,kw OR “heart attack*”:ti,ab,kw OR “heart arrest*”:ti,ab,kw
#9	[mh “mortality”] OR “mortality”:ti,ab,kw OR [mh “death”] OR “death*”:ti,ab,kw OR “fatal”:ti,ab,kw
#10	#7 AND (#8 OR (#8 AND #9)) in Cochrane Reviews

D. SCOPUS

(TITLE-ABS-KEY(“exposome” OR “city plan*” OR “urban plan*” OR “town plan*” OR (“environment*” AND (“built” OR “living” OR “lifestyle” OR “obesogenic” OR “neighbo*” OR “urban” OR “rural” OR “city” OR “factor*”)) OR (“air” AND (“pollut*” OR “quality”)) OR “particulate matter” OR “PM 0.1” OR “PM 2.5” OR “PM 10” OR “PM 20” OR “carbon monoxide*” OR “nitrogen oxide*” OR “nitric oxide*” OR “nitrogen monoxide*” OR “nitrogen dioxide*” OR “sulfur dioxide*” OR “ozone*” OR “fast food*” OR “food suppl*” OR “food outlet*” OR (“environment*” AND (“food*” OR “retail*” OR “nutrition*” OR “diet*”)) OR “food access*” OR “food resource*” OR “grocery store*” OR “supermarket*” OR “convenience store*” OR “restaurant*” OR “physical activity environment*” OR “sports facilit*” OR “gym” OR “gyms” OR “sport field*” OR “fitness facilit*” OR “recreational facilit*” OR “activity zone*” OR “land-use mix*” OR “residential densit*” OR “urbanization” OR “urbanisation” OR “street connectivit*” OR “Sports and Recreational Facilities” OR “greenness” OR “green space*” OR “blueness” OR “blue space*” OR “lake*” OR “canal*” OR “river*” OR "open space*" OR “park*” OR “walkability” OR “walk ability” OR “hiking trail*” OR “walking trail*” OR “bikeability” OR “bike ability” OR “bike path*” OR “cycle path*” OR “drive ability” OR “night-time light*” OR “noise*” OR “environmental temperature*” OR “ambient temperature*” OR “air temperature*” OR “heat”) AND

TITLE-ABS-KEY(("cardiovascular disease*" OR “vascular disease*” OR "cardiometabolic disease*" OR "heart disease*" OR "infarction*" OR "ischemic heart disease*" OR “transient ischemic attack” OR “coronary artery disease*” OR "coronary occlusion*" OR "heart failure" OR "stroke*" OR “cerebrovascular disease*” OR "cerebrovascular accident*" OR "cerebrovascular event*" OR “aortic disease*” OR “aortic aneurysm*” OR "arrhythmia*" OR "angina pectoris*" OR “hypertensive heart disease*” OR “rheumatic heart disease*” OR “pulmonary heart disease*” OR “heart attack*” OR “heart arrest*”) OR (("cardiovascular disease*" OR “vascular disease*” OR "cardiometabolic disease*" OR "heart disease*" OR "infarction*" OR "ischemic heart disease*" OR “transient ischemic attack” OR “coronary artery disease*” OR "coronary occlusion*" OR "heart failure" OR "stroke*" OR “cerebrovascular disease*” OR "cerebrovascular accident*" OR "cerebrovascular event*" OR “aortic disease*” OR “aortic aneurysm*” OR "arrhythmia*" OR "angina pectoris*" OR “hypertensive heart disease*” OR “rheumatic heart disea

se*” OR “pulmonary heart disease*” OR “heart attack*” OR “heart arrest*”) A ND (“mortality” OR “death” OR “fatal”)) OR “cardiovascular mortality”) AND

TITLE-ABS-KEY(“Systematic review” OR “meta-analysis”)) AND

PUBYEAR > 1999 AND (LIMIT-TO(DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English"))

E. Cochrane

#1	[mh “exposome”] OR “exposome”:ti,ab,kw OR [mh “city planning”] OR “city plan*”:ti,ab,kw OR “urban plan*”:ti,ab,kw OR “town plan*”:ti,ab,kw OR [mh “built environment”] OR (“environment*”:ti,ab,kw AND (“built”:ti,ab,kw OR “living”:ti,ab,kw OR “lifestyle”:ti,ab,kw OR “obesogenic”:ti,ab,kw OR “neighbo*”:ti,ab,kw OR “urban”:ti,ab,kw OR “rural”:ti,ab,kw OR “city”:ti,ab,kw OR “factor*”:ti,ab,kw))
#2	[mh “air pollution”] OR [mh “air pollutants”] OR (“air”:ti,ab,kw AND (“pollut*”:ti,ab,kw OR “quality”:ti,ab,kw)) OR [mh “particulate matter”] OR “particulate matter*”:ti,ab,kw OR “PM 0.1”:ti,ab,kw OR “PM 2.5”:ti,ab,kw OR “PM 10”:ti,ab,kw OR “PM 20”:ti,ab,kw
#3	[mh “carbon monoxide”] OR “carbon monoxide*”:ti,ab,kw OR [mh “nitrogen oxides”] OR (“nitrogen”:ti,ab,kw AND (“oxide*”:ti,ab,kw OR “monoxide*”:ti,ab,kw OR “dioxide*”:ti,ab,kw)) OR “nitric oxide*”:ti,ab,kw OR [mh “sulfur dioxide”] OR “sulfur dioxide*”:ti,ab,kw OR [mh “ozone”] OR “ozone*”:ti,ab,kw
#4	[mh “fast foods”] OR “fast food*”:ti,ab,kw OR [mh “food supply”] OR “food suppl*”:ti,ab,kw OR “food outlet*”:ti,ab,kw OR (“environment*”:ti,ab,kw AND (“food*”:ti,ab,kw OR “retail*”:ti,ab,kw OR “nutrition*”:ti,ab,kw OR “diet*”:ti,ab,kw)) OR “food access*”:ti,ab,kw OR “food resource*”:ti,ab,kw OR [mh “supermarkets”] OR “grocery store*”:ti,ab,kw OR “supermarket*”:ti,ab,kw OR “convenience store*”:ti,ab,kw OR “restaurant*”:ti,ab,kw
#5	“physical activity environment*”:ti,ab,kw OR “sports facilit*”:ti,ab,kw OR “gym”:ti,ab,kw OR “gyms”:ti,ab,kw OR “sport field*”:ti,ab,kw OR “fitness facilit*”:ti,ab,kw OR “recreational facilit*”:ti,ab,kw OR “activity zone*”:ti,ab,kw OR “land use mix*”:ti,ab,kw OR “residential densit*”:ti,ab,kw OR [mh “urbanization”] OR “urbanisation”:ti,ab,kw OR “street connectivit*”:ti,ab,kw
#6	“greenness”:ti,ab,kw OR “green space*”:ti,ab,kw OR “blueness”:ti,ab,kw OR “blue space”:ti,ab,kw OR [mh “lakes”] OR “lake*”:ti,ab,kw OR “canal*”:ti,ab,kw OR [mh

	“rivers”] OR “river*”:ti,ab,kw OR “sea”:ti,ab,kw OR “ocean”:ti,ab,kw OR “open space*”:ti,ab,kw OR “park*”:ti,ab,kw OR “walkability”:ti,ab,kw OR “bikability”:ti,ab,kw OR “bike ability”:ti,ab,kw OR “bike path*”:ti,ab,kw OR “cycle path*”:ti,ab,kw OR “drivability”:ti,ab,kw OR “drive ability”:ti,ab,kw OR “night time light*”:ti,ab,kw OR [mh “noise, transportation”] OR ([mh “noise”] NOT [mh “noise, occupational”]) OR “environmental temperature*”:ti,ab,kw OR “ambient temperature*”:ti,ab,kw OR “heat”:ti,ab,kw
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	[mh “cardiovascular diseases”] OR “cardiovascular disease*”:ti,ab,kw OR “vascular disease*”:ti,ab,kw OR “cardiometabolic disease*”:ti,ab,kw OR “heart disease*”:ti,ab,kw OR “infarction*”:ti,ab,kw OR “ischemic heart disease*”:ti,ab,kw OR “coronary artery disease*”:ti,ab,kw OR "coronary occlusion*":ti,ab,kw OR "heart failure":ti,ab,kw OR "stroke*":ti,ab,kw OR “cerebrovascular disease*”:ti,ab,kw OR "cerebrovascular accident*":ti,ab,kw OR "cerebrovascular event*":ti,ab,kw OR “aortic disease*”:ti,ab,kw OR “aortic aneurysm*”:ti,ab,kw OR "arrhythmia*":ti,ab,kw OR "angina pectoris*":ti,ab,kw OR “hypertensive heart disease*”:ti,ab,kw OR “rheumatic heart disease*”:ti,ab,kw OR “pulmonary heart disease*”:ti,ab,kw OR “heart attack*”:ti,ab,kw OR “heart arrest*”:ti,ab,kw
#9	[mh “mortality”] OR “mortality”:ti,ab,kw OR [mh “death”] OR “death*”:ti,ab,kw OR “fatal”:ti,ab,kw
#10	#7 AND (#8 OR (#8 AND #9)) in Cochrane Reviews

F. JBI

(“environment”) and ("cardiovascular disease*" OR ("cardiovascular disease*" AN D “mortality”))

G. Prospero

environment and ("cardiovascular disease*" OR ("cardiovascular disease*" AND mortality))

Appendix 3. List of included reviews

1. Amegah AK, Giovanni R, Jouni JKJ. Temperature-related morbidity and mortality in Sub-Saharan Africa: A systematic review of the empirical evidence. Environment International 2016; 91: 133-49.
2. Angkurawaranon C, Jiraporncharoen W, Chenthanakij B, Doyle P, Nitsch D. Urbanization and non-communicable disease in Southeast Asia: a review of current evidence. Public Health 2014; 128(10): 886-95.
3. Atkinson RW, Butland BK, Anderson HR, Maynard RL. Long-term Concentrations of Nitrogen Dioxide and Mortality: A Meta-analysis of Cohort Studies. Epidemiology 2018; 29(4): 460-72.
4. Babisch W. Updated exposure-response relationship between road traffic noise and coronary heart diseases: A meta-analysis. Noise and Health 2014; 16(68): 1-9.
5. Banerjee D. Association between transportation noise and cardiovascular disease: A meta-analysis of cross-sectional studies among adult populations from 1980 to 2010. Indian Journal of Public Health 2014; 58(2): 84-91.
6. Aditi B, Jan W, Alina V, et al. Effects of Air Temperature on Climate-Sensitive Mortality and Morbidity Outcomes in the Elderly; a Systematic Review and Meta-analysis of Epidemiological Evidence. EBioMedicine 2016; 6: 258-68.
7. Yutong C, Rema R, Kazem R. Long-term exposure to traffic noise and mortality: A systematic review and meta-analysis of epidemiological evidence between 2000 and 2020. Environmental Pollution 2021; 269: 116222.
8. Mark Goldberg. A Systematic Review of the Relation Between Long-term Exposure to Ambient Air Pollution and Chronic Diseases. Reviews on Environmental Health 2008; 23(4): 243-98.
9. Jie C, Gerard H. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environment International 2020; 143: 105974.
10. Chen M, Zhao J, Zhuo C, Zheng L. The Association Between Ambient Air Pollution and Atrial Fibrillation. Int Heart J 2021; 62(2): 290-7.
11. Stieb DM, Berjawi R, Emode M, et al. Systematic review and meta-analysis of cohort studies of long term outdoor nitrogen dioxide exposure and mortality. PLOS ONE 2021; 16(2): e0246451.
12. Dzhambov AM, Dimitrova DD, AM D, DD D. Exposure-response relationship between traffic noise and the risk of stroke: a systematic review with meta-

analysis. Arhiv za Higijenu Rada i Toksikologiju 2016; 67(2): 136-51.
13. van Kempen Elise EMM, Kruize H, Boshuizen Hendriek C, Ameling Caroline B, Staatsen Brigit AM, de Hollander Augustinus EM. The association between noise exposure and blood pressure and ischemic heart disease: a meta-analysis. Environmental Health Perspectives 2002; 110(3): 307-17.
14. Faustini A, Rapp R, Forastiere F. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. European Respiratory Journal 2014; 44(3): 744-53.
15. Mireia G, Margarita T-M, David M, et al. Residential green spaces and mortality: A systematic review. Environment International 2016; 86: 60-7.
16. Kan H-D, Chen B-h, Chen C-h, Wang B-y, Fu Q-Y. Establishment of exposure-response functions of air particulate matter and adverse health outcomes in China and worldwide. Biomedical and Environmental Sciences 2005; 18(3): 159.
17. Shin HH, Fann N, Burnett RT, Cohen A, Hubbell BJ. Outdoor fine particles and nonfatal strokes: systematic review and meta-analysis. Epidemiology 2014; 25(6): 835-42.
18. Hoek G, Krishnan RM, Beelen R, et al. Long-term air pollution exposure and cardio- respiratory mortality: a review. Environmental Health 2013; 12(1): 43.
19. Shiwen H, Haomin L, Mingrui W, et al. Long-term exposure to nitrogen dioxide and mortality: A systematic review and meta-analysis. Science of The Total Environment 2021; 776: 145968.
20. Jadambaa A, Spickett J, Badrakh B, Norman RE. The Impact of the Environment on Health in Mongolia:A Systematic Review. Asia Pacific Journal of Public Health 2015; 27(1): 45-75.
21. Jaganathan S, Jaacks LM, Magsumbol M, et al. Association of Long-Term Exposure to Fine Particulate Matter and Cardio-Metabolic Diseases in Low- and Middle-Income Countries: A Systematic Review. International Journal of Environmental Research and Public Health 2019; 16(14).
22. Behrooz K, Behnosh s, Sadegh S. Mortality and hospitalizations due to cardiovascular and respiratory diseases associated with air pollution in Iran: A systematic review and meta-analysis. Atmospheric Environment 2019; 198: 438-47.
23. Masoud K, Payam K. The association between road traffic noise and myocardial infarction: A systematic review and meta-analysis. Science of The Total Environment 2020; 731: 139226.

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25. Zhiguang L, Feng W, Wentao L, et al. Does utilizing WHO's interim targets further reduce the risk - meta-analysis on ambient particulate matter pollution and mortality of cardiovascular diseases? Environmental Pollution 2018; 242: 1299-307.
26. Turner LR, Barnett AG, Connell D, Tonga S. Review Article: Ambient Temperature and Cardiorespiratory Morbidity: A Systematic Review and Meta-analysis. Epidemiology 2012; 23(4): 594-606.
27. Feng L, Dongqun X, Yibin C, et al. Systematic review and meta-analysis of the adverse health effects of ambient PM2.5 and PM10 pollution in the Chinese population. Environmental Research 2015; 136: 196-204.
28. Ma Y, Zhang Y, Cheng B, et al. A review of the impact of outdoor and indoor environmental factors on human health in China. Environmental Science and Pollution Research 2020; 27(34): 42335-45.
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30. Niu Z, Liu F, Yu H, Wu S, Xiang H. Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: an updated systematic review and meta-analysis of more than 23 million participants. Environmental Health and Preventive Medicine 2021; 26(1): 15.
31. Odame EA, Li Y, Zheng S, Vaidyanathan A, Silver K. Assessing Heat-Related Mortality Risks among Rural Populations: A Systematic Review and Meta-Analysis of Epidemiological Evidence. International Journal of Environmental Research and Public Health 2018; 15(8).
32. Prueitt RL, Lynch HN, Zu K, Sax SN, Venditti FJ, Goodman JE. Weight-of-evidence evaluation of long-term ozone exposure and cardiovascular effects. Critical Reviews in Toxicology 2014; 44(9): 791-822.
33. Emily Jessica R, Michael B. Quiet, clean, green, and active: A Navigation Guide systematic review of the impacts of spatially correlated urban exposures on a range of physical health outcomes. Environmental Research 2020; 185: 109388.
34. Atkinson RW, Butland BK, Dimitroulopoulou C, et al. Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies. BMJ Open 2016; 6(2): e009493.

35. Scheers H, Jacobs L, Casas L, Nemery B, Nawrot TS. Long-Term Exposure to Particulate Matter Air Pollution Is a Risk Factor for Stroke. Stroke 2015; 46(11): 3058-66.
36. Alexeeff SE, Liao NS, Liu X, Eeden SKVD, Sidney S. Long-Term PM2.5 Exposure and Risks of Ischemic Heart Disease and Stroke Events: Review and Meta-Analysis. Journal of the American Heart Association 2021; 10(1): e016890.
37. Thomas JL, Jennifer LN, Steven JD, et al. A systematic review of cardiovascular emergency department visits, hospital admissions and mortality associated with ambient black carbon. Environment International 2017; 107: 154-62.
38. Twohig-Bennett C, Jones A. The health benefits of the great outdoors: A systematic review and meta-analysis of greenspace exposure and health outcomes. Environmental Research 2018; 166: 628-37.
39. Van Kempen E, Casas M, Pershagen G, Foraster M. WHO Environmental Noise Guidelines for the European Region: A Systematic Review on Environmental Noise and Cardiovascular and Metabolic Effects: A Summary. International Journal of Environmental Research and Public Health 2018; 15(2).
40. Vienneau D, Schindler C, Perez L, Probst-Hensch N, Röösli M. The relationship between transportation noise exposure and ischemic heart disease: A meta-analysis. Environmental Research 2015; 138: 372-80.
41. Fenghong W, Qingqing L, Mengqi S, et al. The relationship between exposure to PM2.5 and heart rate variability in older adults: A systematic review and meta-analysis. Chemosphere 2020; 261: 127635.
42. Wang X, Cao Y, Hong D, et al. Ambient Temperature and Stroke Occurrence: A Systematic Review and Meta-Analysis. International Journal of Environmental Research and Public Health 2016; 13(7).
43. Weihofen VM, Hegewald J, Euler U, Schlattmann P, Zeeb H, Seidler A. Aircraft Noise and the Risk of Stroke. Dtsch Arztebl Int 2019; 116(14): 237-44.
44. Yang H, Li S, Sun L, et al. Smog and risk of overall and type-specific cardiovascular diseases: A pooled analysis of 53 cohort studies with 21.09 million participants. Environmental Research 2019; 172: 375-83.
45. Yuan S, Wang J, Jiang Q, et al. Long-term exposure to PM2.5 and stroke: A systematic review and meta-analysis of cohort studies. Environmental Research 2019; 177: 108587.
46. Yuan Y, Huang F, Lin F, Zhu P, Zhu P. Green space exposure on mortality and cardiovascular outcomes in older adults: a systematic review and meta-analysis of observational studies. Aging Clin Exp Res 2021; 33(7): 1783-97.

47. Zafeiratou S, Samoli E, Dimakopoulou K, et al. A systematic review on the association between total and cardiopulmonary mortality/morbidity or cardiovascular risk factors with long-term exposure to increased or decreased ambient temperature. Science of The Total Environment 2021; 772: 145383.
48. Zhao K, Li J, Du C, Zhang Q, Guo Y, Yang M. Ambient fine particulate matter of diameter ≤ 2.5 μm and risk of hemorrhagic stroke: a systemic review and meta-analysis of cohort studies. Environ Sci Pollut Res Int 2021; 28(17): 20970-80.
49. Zhao Y, Cheng Z, Lu Y, et al. PM10 and PM2.5 particles as main air pollutants contributing to rising risks of coronary heart disease: a systematic review. Environmental Technology Reviews 2017; 6(1): 174-85.
50. Zhu W, Cai J, Hu Y, et al. Long-term exposure to fine particulate matter relates with incident myocardial infarction (MI) risks and post-MI mortality: A meta-analysis. Chemosphere 2021; 267: 128903.
51. Zou L, Zong Q, Fu W, et al. Long-Term Exposure to Ambient Air Pollution and Myocardial Infarction: A Systematic Review and Meta-Analysis. Frontiers in Medicine 2021; 8.

Appendix 4. Citation matrices of duplicated studies by each domain of built environment in umbrella review

The formula used to calculate the CCA is:

$$CCA = \frac{\mathrm{N} - \mathrm{r}}{\mathrm{r} \times \mathrm{c} - \mathrm{r}}$$

where N is the number of primary studies including double-counting, r is the number of index publications and c is the number of reviews. The CCA-score was categorised into: limited overlap (score: 0-5), moderate overlap (score: 6-10), high overlap (score: 11-15) and very high overlap (score: >15).[1]

Reference:

1 Pieper D, Antoine SL, Mathes T, Neugebauer EAM, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol* 2014; **67**: 368–75.

A. Citation matrix of Air pollution

See online: https://doi.org/10.1093/eurjpc/zwad241

B. Citation matrix of physical activity environment

Primary studies	Systematic reviews			
N = 32, r = 29, c = 4, CCA = 0.03448276	Gascon et al. 2016	Yuan et al. 2020	Rugel et al. 2020	Twohig-Bennett et al. 2018
Hu Z (2008)	1			
Lachowycz (2014)	1			
Mitchell (2011)	1			
Richardson (2010a)	1			
Richardson (2010b)	1			
Tamosiunas (2014)	1	1		1
Villeneuve (2012)	1			
James P (2016)		1		1
Wang D (2017)		1		
Orioli R (2019)		1		
Zijlema WL (2019)		1		
Klompmaker JO (2020)		1		
Donovan GH (2015)		1		
Massa KHC (2016)		1		
Yitshak-Sade M (2017)		1		
Jia X (2018)		1		
Klompmaker JO (2019)		1		
Seo S (2019)		1		
Wang K (2019)		1		
Aliyas Z (2019)		1		
Astell-Burt T (2019)		1		
Dalton AM (2020)		1		
Paul LA (2020)		1		
Vienneau D (2017)			1	
Chum A (2015)			1	
Vivanco-Hidalgo RM (2019)			1	
Domínguez-Berjón MF (2010)			1	
Wilker E (2014)				1
Bixby H (2015)				1

C. Citation matrix of urbanization

Primary studies	Systematic reviews
	Angkurawaranona et al. 2014
Fitzpatrick (2012)	1
Aung (1992)	1
Wada (2005)	1
Lim (1991)	1
Ishine (2006)	1
Wada (2005)	1

D. Citation matrix of residential noise

Primary studies	Systematic reviews									
N = 141, r = 86, c = 10, CCA = 0.07105943	van Kempen et al. 2002	Banerjee et al. 2014	Babisch, 2014	Vienneau et al. 2015	Dzhambov et al. 2016	van Kempen, et al. 2018	Weihofen et al. 2019	Khosravipour et al. 2020	Rugel et al. 2020	Cai et al. 2021
Knipschild P (1977)	1									
Knipschild P (1976a)	1									
van Brederode NE (1988)	1					1				
Babisch W (1992)	1	1				1				
Babisch W (1994)	1	1	1	1		1		1		
The Caerphilly and Speedwell Collaborative Group (1984)	1					1				
Babisch W (1988a)	1									
Babisch W (1988b)	1	1			1	1				
Babisch W (1993a)	1					1				
Babisch W (1993b)	1	1	1			1				
Babisch W (1999)	1			1		1				
Knipschild P (1976b)	1									
Altena K (1989)		1				1				
Franssen EA (2004)		1								
Belojevic G (2002)		1								
Bluhm G (2011)		1								
Lercher P (1992)		1								
Maschke C (2003a)		1				1				
Eiff AW (1981)		1								
Niemann H (2006)		1								
Greiser E (2007)		1								
TNO-PG-RIVM (1998)		1								
Selander J (2009)			1			1		1		

Beelen R (2009)			1	1	1	1			1	1
Eriksson C (2012)			1							
Gan WQ (2012)			1	1	1		1		1	1
Sørensen M (2012)			1						1	
Babisch W (2005a)			1	1		1		1		
Yoshida T (1997)			1							
Huss A (2010)				1	1	1				1
Sørensen M (2013)				1						
Hansell AL (2013)				1	1		1			1
Correia AW (2013)				1	1		1			
Floud S (2013)					1		1			
Halonen JI (2015)					1					1
Sørensen M (2014)					1				1	
Hoffmann B (2015)					1				1	
de Kluizenaar Y (2013)					1				1	
Sørensen M (2011)					1				1	
Evrard AS (2015)					1		1			
Lercher P (2008)						1				
Jarup L (2008)						1				
Babisch W (2008)						1				
Lekaviciute J (2007)						1				
Heimann D (2007)						1				
Maschke C (2005)						1				
Jarup L (2005)						1				
Babisch W (2005b)						1				
Grazuleviciene R (2004)						1				
Babisch W (2004)						1				
Maschke C (2003b)						1				
Babisch W (2003)						1				
Wiens D (1995)						1	1			
Pulles MPJ (1990)						1				
Babisch W (1990)						1				
Lercher P (2011)						1				
Frerichs RR (1980)							1			
Héritier H (2017)							1			
Seidler A (2016)							1			

Malinauskiene V (2011)								1		
Sorensen M (2012)								1		
Bodin T (2016)								1	1	
Carey IM (2016)								1	1	
Seidler A (2016)								1		
Roswall N (2017)								1	1	
Andersen ZJ (2018)								1		
Klompmaker JO (2019)								1		
Pyko A (2019)								1		
Hvidtfeldt UA (2019)									1	
Monrad M (2016)									1	
Roswall N (2017b)									1	
Sørensen M (2014a)									1	
Sørensen M (2017)									1	
Tonne C (2016)									1	
Vienneau D (2017)									1	
Cai Y (2018)									1	
Chum A (2015)									1	
Vivanco-Hidalgo RM (2019)									1	
Yang WT (2018)									1	
Domínguez-Berjón MF (2010)									1	
Andersson EM (2020)										1
Thacher JD (2020)										1
Klompmaker JO (2020)										1
Héritier H (2019)										1
Héritier H (2018)										1
Barcelo MA (2016)										1

E. Citation matrix of ambient temperature

Primary studies	Systematic reviews							
N = 136, r = 115, c = 8, CCA = 0.02608696	Turner et al. 2012	Kofi Amegah et al. 2016	Wang et al. 2016	Bunker at al. 2016	Moghadamnia et al. 2017	Odame et al. 2018	Ma et al. 2020	Zafeiratou et al. 2021
Schwartz J (2004)	1							
Hong YC (2003)	1			1				
Ebi KL (2004)	1		1					
Kovats RS (2004)	1							
Panagiotakos DB (2004)	1							
Misailidou M (2006)	1							
Ren C (2006a)	1							
Ren C (2006b)	1							
Dawson J (2008)	1		1					
Lin S (2009)	1			1				
Michelozzi P (2009)	1			1				
Green RS (2010)	1			1				
Ostro B (2010)	1							
Wichmann J (2011a)	1			1				
Pudpong N (2011)	1			1				
Wang XY (2009)	1		1					
Wolf K (2009)	1							
Bhaskaran K (2010)	1			1				
Kovats RS (2005)		1						
McMichael AJ (2008)		1						
Heunis JC (1995)		1						
Kynast-Wolf G (2010)		1						
Chang CL (2004)		1						
Goggins (2012)			1					
OYOSHI (1999)			1					
Tsementzis (1991)			1					

Sobel (1987)			1					
Shinkawa (1990)			1					
Nakaguchi (2008)			1					
Matsumoto (2010)			1					
Lejeune (1994)			1					
Lai (2014)			1					
Gomes (2015)			1					
Fang (2012)			1					
Chen (1995)			1					
Han (2015)			1	1				
Morabito (2011)			1	1				
Magalhães (2011)			1					
Lee (2008)			1					
Jimenez-Conde (2008)			1					
Feigin (2000)			1					
Abe (2008)			1					
Harlan SL (2014)				1				
Burkart K (2014)				1				
Huang J (2014)				1	1		1	
Almeida S (2013)				1				
Gasparrini A (2012)				1				
Liu L (2011)				1				
Wichmann J (2011b)				1				
Yu W (2011)				1	1			
Almeida SP (2010)				1				
Revich B (2008)				1				
Baccini M (2008)				1				
Ishigami A (2008)				1				
Gouveia N (2003)				1				
Xu W (2013)				1				
Analitis A (2008)				1				
Carder M (2005)				1				
Cagle A (2005)				1				
Giang PN (2014)				1				
Chan EYY (2013)				1				
Wichmann J (2013)				1				

Wichmann J (2012)				1				
Basu R (2012)				1				
Silva END (2012)				1				
Alessandrini E (2011)				1				
Hopstock LA (2011)				1				
Koken PJM (2003)				1				
Liu Y (2014)				1				
Vasconcelos J (2013)				1				
Hajat S (2002)				1				
Lin Y-K (2013b)					1			
Tian Z (2012)					1		1	
Qiao Z (2015)					1			
Goggins WB (2013)					1			
Kim J (2016)					1			
Yang J (2012)					1		1	
Guo Y (2012a)					1			
Yi W (2015)					1			
Seposo XT (2015)					1			
Chen R (2014)					1			
Guo Y (2012b)					1			
Kim H (2015)					1			
Huang Z (2015)					1			
Yang C (2015a)					1		1	
Breitner S (2014a)					1			
Wang C (2014)					1		1	
Ma W (2014)					1			
Yang J (2015c)					1			
Yu W (2011a)					1			
Chan EYY (2012)					1			
Wang X (2015)					1		1	
Bai L (2014a)					1	1		
Gomez-Acebo I (2013)					1			
Hashizume, M. (2009)						1		
Urban, A. (2014)						1		
Zhang YQ (2016a)							1	
Zhang Q (2018)							1	

Tian L (2016)							1	
Gao HL (2017)							1	
Ding Z (2016)							1	
Bai L (2014b)							1	
Guo YM (2011)							1	
Xiong J (2015)							1	
Deng C (2019)							1	
Sun X (2014)							1	
Zhang YS (2014)							1	
Ge YH (2018)							1	
Cui LJ (2019)							1	
Blagojević LM (2012)								1
Goggins WB (2015)								1
Rehill N (2015)								1
Yitshak-Sade M (2018)								1
Schreier N (2013)								1
Faeh D (2016)								1

Appendix 5. Robustness assessment and ROBIS quality assessment per review by domain

Online: https://doi.org/10.1093/eurjpc/zwad241

Appendix 6. Summary of evidence based on robustness and quality

Table S1. Summary of evidence based on robustness and quality

Robustness of evidence by domain[1]	Specific exposure and outcome[2]
Air pollution (positive association)	
Strong (n = 4)	$PM_{2.5}$ and stroke (high risk in study eligibility criteria, identification and selection, Alexeeff et al. 2021)
	SO_2 and AF (2 studies, Chen et al. 2021)
	CO and AF (2 studies, Chen et al. 2021)
	NO_2 and IHD events (4 studies, Yang et al. 2019)
Highly suggestive (n = 13)	$PM_{2.5}$ and MI (high risk in study identification and selection, small study effect, Zou et al. 2021)
	$PM_{2.5}$ and IHD mortality (high risk in study eligibility criteria, identification and selection, excess significance bias, high heterogeneity, **Alexeeff et al. 2021**) (high heterogeneity, **Chen et al. 2020**)
	$PM_{2.5}$ and CeVD mortality (high risk in study eligibility criteria, identification and selection, high heterogeneity, Alexeeff et al. 2021)
	$PM_{2.5}$ and CVD mortality (small study effect, **Yang et al. 2019**) (small study effect, excess significance bias, high heterogeneity, **Liu et al. 2018**) (high heterogeneity, **Chen et al. 2020**)
	$PM_{2.5}$ and CVD events (small study effect, Yang et al. 2019)
	$PM_{2.5}$ and stroke events (small study effect, Yang et al. 2019)
	PM_{10} and AF (4 studies, small study effect, excess significance bias, Chen et al. 2021)

	NO_2 and CVD mortality (high risk in study identification, high heterogeneity, Huang et al. 2021)
	NO_2 and ICH mortality (small study effect, high heterogeneity, Stieb et al. 2021)
	NO_2 and CHD mortality (high risk in study selection, Atkinson et al. 2018)
Suggestive (n = 17)	$PM_{2.5}$ and CVD mortality (high risk in study eligibility criteria, identification and selection, Hoek et al. 2013)
	$PM_{2.5}$ and post-MI mortality (high risk in study identification, Zhu et al. 2021)
	$PM_{2.5}$ and stroke (high heterogeneity, small study effect, Yuan et al. 2019) (7 studies, Yang et al. 2019)
	$PM_{2.5}$ and stroke mortality (small study effect, Yuan et al. 2019) (small study effect, Yang et al. 2019)
	$PM_{2.5}$ and IHD mortality (excess significance bias, Yang et al. 2019)
	$PM_{2.5}$ and IHD events (excess significance bias, Yang et al. 2019)
	$PM_{2.5}$ and HRV (high risk in study eligibility criteria, identification and selection, Wang et al. 2020)
	$PM_{2.5}$, PM_{10}, and CVD mortality (high risk in study identification, excess significance bias, Liu et al. 2018)
	NO_2 and CVD mortality (high risk in study identification and selection, high heterogeneity, small study effect, Faustini et al. 2014) (high heterogeneity, Stieb et al. 2021) (high heterogeneity, Yang et al. 2019) (high risk in study identification and selection, small study effect, Atkinson et al. 2018)
	NO_2 and CVD events (high heterogeneity, Yang et al. 2019)
	NO_2 and IHD mortality (2 studies, Yang et al. 2019)
	O_3 and CVD mortality (3 studies, Yang et al. 2019)
Weak (n = 16)	$PM_{2.5}$ and hemorrhagic stroke (high heterogeneity, Zhao et al. 2021)
	$PM_{2.5}$ and stroke mortality (high risk in study eligibility criteria and identification, Scheers et al. 2015) (high heterogeneity, Chen et al. 2020)
	$PM_{2.5}$ and stroke events (high risk in study eligibility criteria and identification, small study effect, Scheers et al. 2015)
	$PM_{2.5}$ and AF (high heterogeneity, Chen et al. 2021)
	$PM_{2.5}$ and MI (8 studies, Zhu et al. 2021)
	$PM_{2.5}$ and HRV (high risk in study eligibility criteria, identification and selection, small study effect, Wang et al. 2020)

	PM_{10} and MI (high risk in study identification and selection, small study effect, Zou et al. 2021)
	PM_{10} and stoke events (high risk in study eligibility criteria and identification, high heterogeneity, Scheers et al. 2015)
	PM_{10} and stroke mortality (high risk in study eligibility criteria and identification, Scheers et al. 2015)
	PM_{10} and IHD mortality (small study effect, high heterogeneity, Chen et al. 2020)
	PM_{10} and CVD mortality (small study effect, high heterogeneity, Yang et al. 2019)
	NO_2 and AF (small study effect, excess significance bias, Chen et al. 2021)
	NO_2 and IHD (2 studies, Yang et al. 2019)
	O_3 and IHD mortality (3 studies, Yang et al. 2019)
Non-significant (n = 32)	$PM_{2.5}$ and CHD mortality (high risk in study selection, high heterogeneity, Chen et al. 2008)
	$PM_{2.5}$ and MI (high risk in study eligibility criteria, identification and selection, high heterogeneity, Alexeeff et al. 2021)
	$PM_{2.5}$ and CVD (high heterogeneity, Yang et al. 2019)
	$PM_{2.5}$ and HRV (high risk in study eligibility criteria, identification and selection, Wang et al. 2020)
	PM_{10} and stroke (high heterogeneity, **Yang et al. 2019**)
	PM_{10} and stroke mortality (high heterogeneity, Yang et al. 2019) (high heterogeneity, Chen et al. 2020)
	PM_{10} and stroke events (high heterogeneity, Yang et al. 2019)
	PM_{10} and IHD (2 studies, Yang et al. 2019)
	PM_{10} and IHD mortality (4 studies, high heterogeneity, Yang et al. 2019)
	PM_{10} and IHD events (6 studies, high heterogeneity, Yang et al. 2019)
	PM_{10} and CVD (3 studies, high heterogeneity, Yang et al. 2019)
	PM_{10} and CVD mortality (small study effect, excess significance bias, high heterogeneity, **Liu et al. 2018**) (high heterogeneity, **Chen et al. 2020**)
	PM_{10} and CVD events (small study effect, high heterogeneity, Yang et al. 2019)
	NO_2 and stroke (4 studies, Yang et al. 2019)

	NO_2 and stroke mortality (2 studies, Yang et al. 2019)
	NO_2 and stroke events (6 studies, Yang et al. 2019)
	NO_2 and CVD (2 studies, Yang et al. 2019)
	NO_2 and CeVD mortality (13 studies, **Stieb et al. 2021**) (high risk in study identification and selection, **Atkinson et al. 2018**)
	O_3 and AF (3 studies; Chen et al. 2021)
	O_3 and stroke (2 studies, high heterogeneity, Yang et al. 2019)
	O_3 and stroke mortality (3 studies, **Yang et al. 2019**) (high risk in study identification and selection, **Atkinson et al. 2016**)
	O_3 and stroke events (5 studies, high heterogeneity, Yang et al. 2019)
	O_3 and CVD mortality (high risk in study identification and selection, small study effect, Atkinson et al. 2016)
	O_3 and CVD events (small study effect, high heterogeneity, Yang et al. 2019)
	O_3 and IHD mortality (high risk in study identification and selection, small study effect, Atkinson et al. 2016)
Physical activity environment (negative association)	
Suggestive (n = 2)	Greenspace and CVD mortality (high risk in study identification, **Gascon et al. 2016**) (2 studies, **Twohig-Bennett et al. 2018**)
Non-significant (n = 6)	Greenspace and CVD mortality (high heterogeneity, **Yuan et al. 2020**) (high risk in study identification, **Gascon et al. 2016**)
	Greenspace and IHD mortality (3 studies, Yuan et al. 2020)
	Greenspace and stroke mortality (4 studies, small study effect, high heterogeneity, Yuan et al. 2020)
	Greenspace and stroke (small study effect, Twohig-Bennett et al. 2018)
	Greenspace and CHD (2 studies, Twohig-Bennett et al. 2018)
Urbanization (insufficient and mixed evidence)	
Weak (n = 2)	Positive association: Urban exposure and CHD (unclear risk in study eligibility criteria, small study effect, Angkurawaranona et al. 2014)
	Negative association: Urban exposure and RHD (unclear risk in study eligibility criteria, Angkurawaranona et al. 2014)
Non-significant (n = 2)	Urban exposure and stroke (unclear risk in study eligibility criteria, Angkurawaranona et al. 2014)

	Urban exposure and non-specific heart disease (unclear risk in study eligibility criteria, high heterogeneity, excess significance bias, Angkurawaranona et al. 2014)
Residential noise (positive association)	
Strong (n = 1)	Aircraft traffic noise and CVD mortality (high risk in study eligibility criteria, identification and selection, Cai et al. 2021)
Suggestive (n = 2)	Road traffic noise and CHD (high risk in study eligibility criteria, identification and selection, Babisch et al. 2014)
	Traffic noise and IHD (high risk in study eligibility criteria and selection, Vienneau et al. 2015)
Non-significant (n = 17)	Traffic noise and CVD (high risk in study identification and selection, Banerjee et al. 2014)
	Road traffic noise and MI (high risk in study identification and selection, **Banerjee et al. 2014**) (high risk in study identification, **Khosravipour et al. 2020**)
	Road traffic noise and stroke (high risk in study identification, high heterogeneity, Dzhambov et al. 2016)
	Road traffic noise and AP (high risk in study identification and selection, Banerjee et al. 2014)
	Road traffic noise and CVD mortality (high risk in study identification and selection, Cai et al. 2021)
	Road traffic noise and IHD mortality (high risk in study identification and selection, Cai et al. 2021)
	Road traffic noise and stroke mortality (high risk in study identification and selection, small study effect, Cai et al. 2021)
	Aircraft traffic noise and MI (high risk in study identification and selection, Banerjee et al. 2014)
	Aircraft traffic noise and AP (high risk in study identification and selection, Banerjee et al. 2014)
	Aircraft traffic noise and IHD (high risk in study identification and selection, small study effect, Banerjee et al. 2014)
	Aircraft traffic noise and stroke (high risk in study identification, **Dzhambov et al. 2016**) (7 studies, **Weihofen et al. 2019**)
	Aircraft traffic noise and IHD mortality (high risk in study identification and selection, high heterogeneity, Cai et al. 2021)
	Aircraft traffic noise and stroke mortality (high risk in study identification and selection, Cai et al. 2021)
	Rail traffic noise and IHD mortality (high risk in study identification and selection, high heterogeneity, Cai et al. 2021)
Ambient temperature (positive association)	
Suggestive (n = 8)	Temperature and CVD mortality (high risk in study identification and selection, Odame et al. 2018)

	Heat and CVD mortality (high risk in study identification, small study effect, high heterogeneity, **Bunker et al. 2016**) (high risk in study identification and selection, small study effect, excess significance bias, high heterogeneity, **Moghadamnia et al. 2017**)
	Heat and combined CVD mortality (high risk in study identification, small study effect, high heterogeneity, Bunker et al. 2016)
	Cold and CVD mortality (high risk in study identification and selection, small study effect, excess significance bias, high heterogeneity, Moghadamnia et al. 2017)
	Cold and CeVD mortality (high risk in study identification, Bunker et al. 2016)
	Cold for ICH morbidity (high risk in study identification, Bunker et al. 2016)
	Cold and combined CVD mortality (high risk in study identification, small study effect, high heterogeneity, Bunker et al. 2016)
Weak (n = 6)	Heat and CVD (high risk in study eligibility criteria, identification and selection, small study effect, high heterogeneity, Ma et al. 2020)
	Cold and CVD (high risk in study eligibility criteria, identification and selection, high heterogeneity, Ma et al. 2020)
	Temperature for ICH (high risk in study eligibility criteria, small study effect, high heterogeneity, Wang et al. 2016)
	Heat and CeVD mortality (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Heat and IHD mortality (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Cold and CVD mortality (high risk in study identification, high heterogeneity, Bunker et al. 2016)
Non-significant (n = 22)	Temperature and CVD (high risk in study eligibility criteria and selection, high heterogeneity, Turner et al. 2012)
	Temperature and stroke (high risk in study eligibility criteria and selection, high heterogeneity, Turner et al. 2012)
	Temperature and ACS/MI (high risk in study eligibility criteria and selection, high heterogeneity, Turner et al. 2012)
	Temperature and IS (high risk in study eligibility criteria, high heterogeneity, Wang et al. 2016)
	Temperature and SAH (high risk in study eligibility criteria, Wang et al. 2016)
	Heat and IS (high risk in study eligibility criteria, high heterogeneity, **Wang et al. 2016**) (high risk in study identification, small study effect, excess significance bias, high heterogeneity, **Bunker et al. 2016**)
	Heat and CeVD (high risk in study identification, small study effect, excess significance bias, high heterogeneity, Bunker et al. 2016)

	Heat and CVD (high risk in study identification, small study effect, excess significance bias, high heterogeneity, Bunker et al. 2016)
	Heat and MI (high risk in study identification, small study effect, high heterogeneity, Bunker et al. 2016)
	Heat and ICH mortality (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Heat and combined CVD (high risk in study identification, excess significance bias, high heterogeneity, Bunker et al. 2016)
	Cold and CVD (high risk in study identification, small study effect, Bunker et al. 2016)
	Cold and combined CVD (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Cold and AP (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Cold and HF (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Cold and IHD mortality (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Cold and MI (high risk in study identification, high heterogeneity, Bunker et al. 2016)
	Cold and CeVD (high risk in study identification, small study effect, excess significance bias, high heterogeneity, Bunker et al. 2016)
	Cold and combined CeVD (high risk in study identification, excess significance bias, high heterogeneity, Bunker et al. 2016)
	Cold and IS (high risk in study eligibility criteria, high heterogeneity, **Wang et al. 2016**) (high risk in study identification, high heterogeneity, **Bunker et al. 2016**)

[1] There were 23 unclear associations in air pollution, 10 in residential noise, and 1 in ambient temperature.

[2] MI: myocardial infarction; AP: angina pectoris; CHA: cardiovascular hospital admission; ACS: acute coronary syndrome; CVD: cardiovascular disease; CHD: coronary heart disease; AF: atrial fibrillation; IHD: ischemic heart disease; CeVD: cerebrovascular disease; RHD: rheumatic heart disease; HRV: heart rate variability; SDNN: the standard deviation of NN intervals; RMSSD: root mean square of successive RR interval differences; LF: low-frequency bands; HF: high-frequency bands; RE: risk estimate; events include both morbidity and mortality; ICH: intracerebral hemorrhage; IS: ischemic stroke; SAH; subarachnoid hemorrhage; HF: heart failure.

Appendix 7. Results of sensitivity analyses

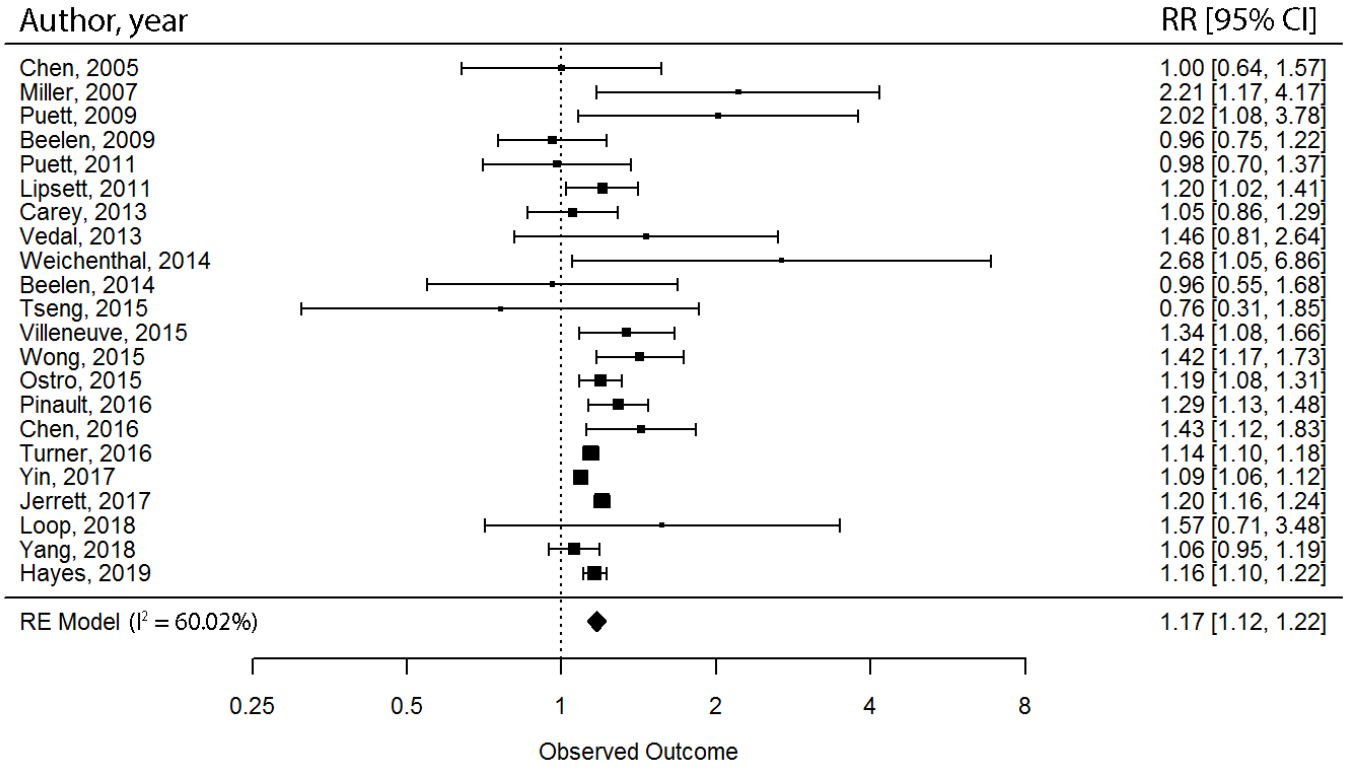

Figure S1. Meta-meta-analysis of the relative risk of ischemic heart disease mortality per 10 µg/m^3 in long-term fine particulate matter <2.5 µm in diameter exposure. Studies without adjustment for smoking were excluded.

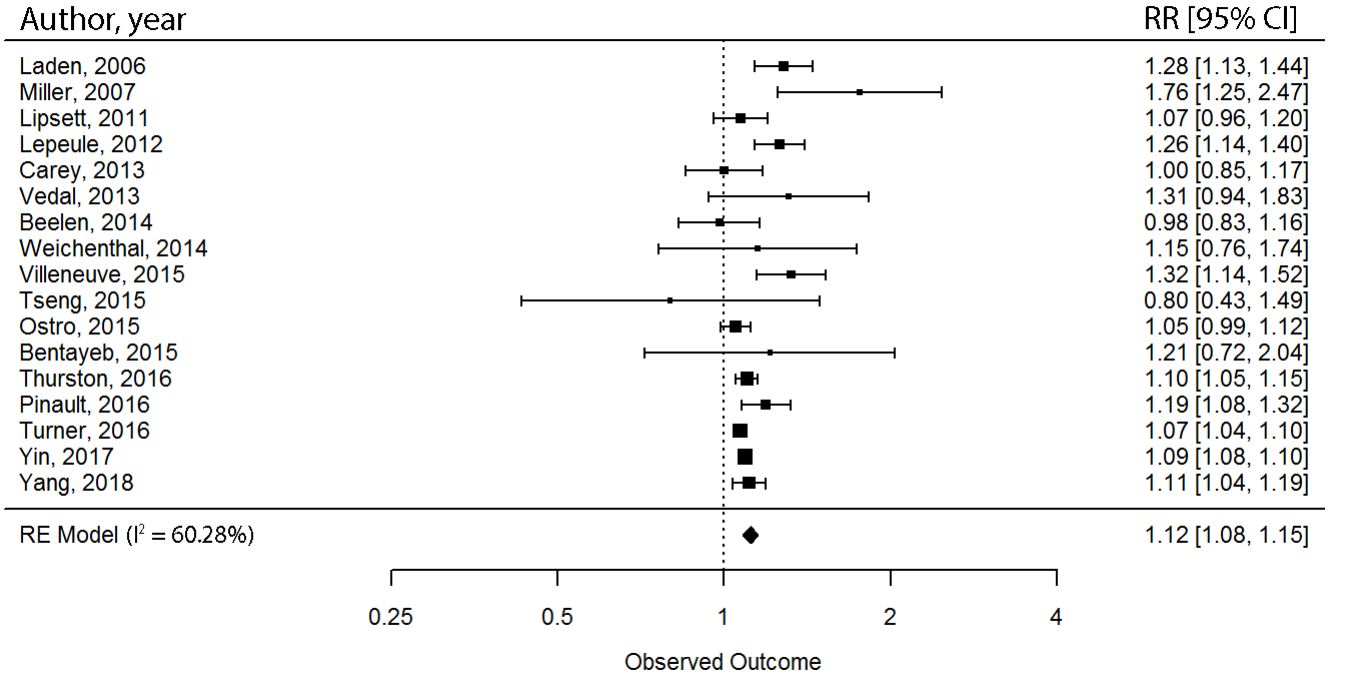

Figure S2. Meta-meta-analysis of the relative risk of cardiovascular disease mortality per 10 µg/m^3 in long-term fine particulate matter <2.5 µm in diameter exposure. Studies without adjustment for individual lifestyle were excluded.

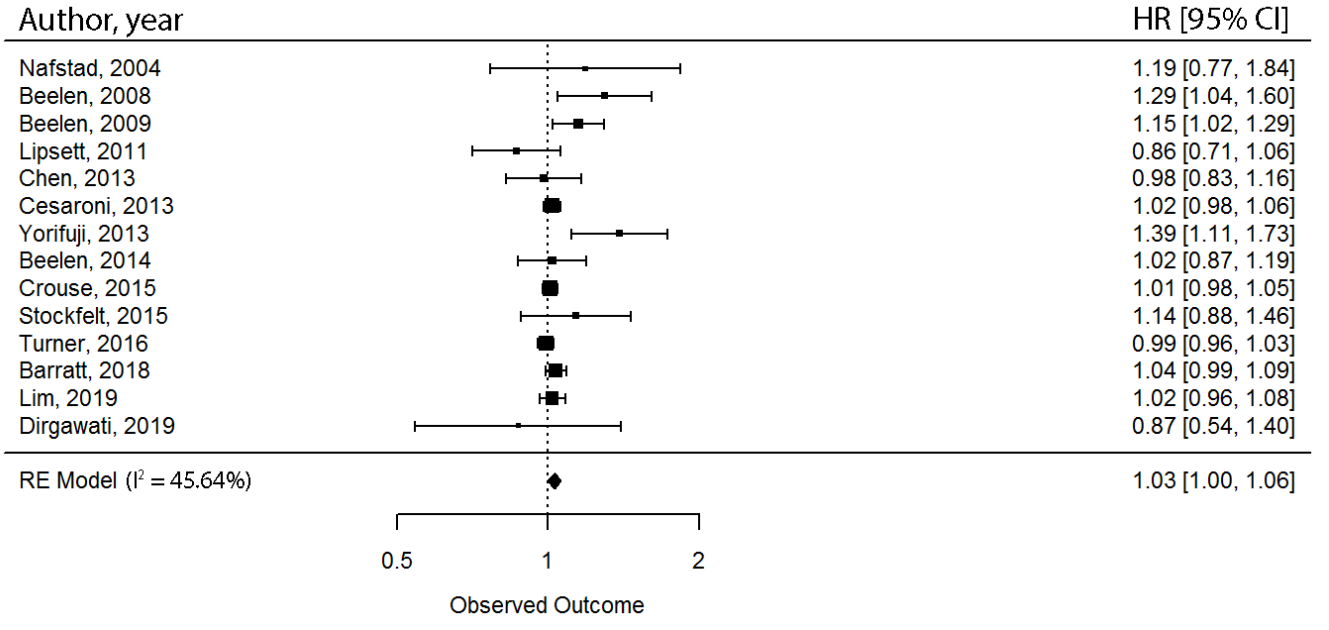

Figure S3. Meta-meta-analysis of the hazard ratio of cerebrovascular disease mortality per 10 parts per billion increase in NO^2 exposure.

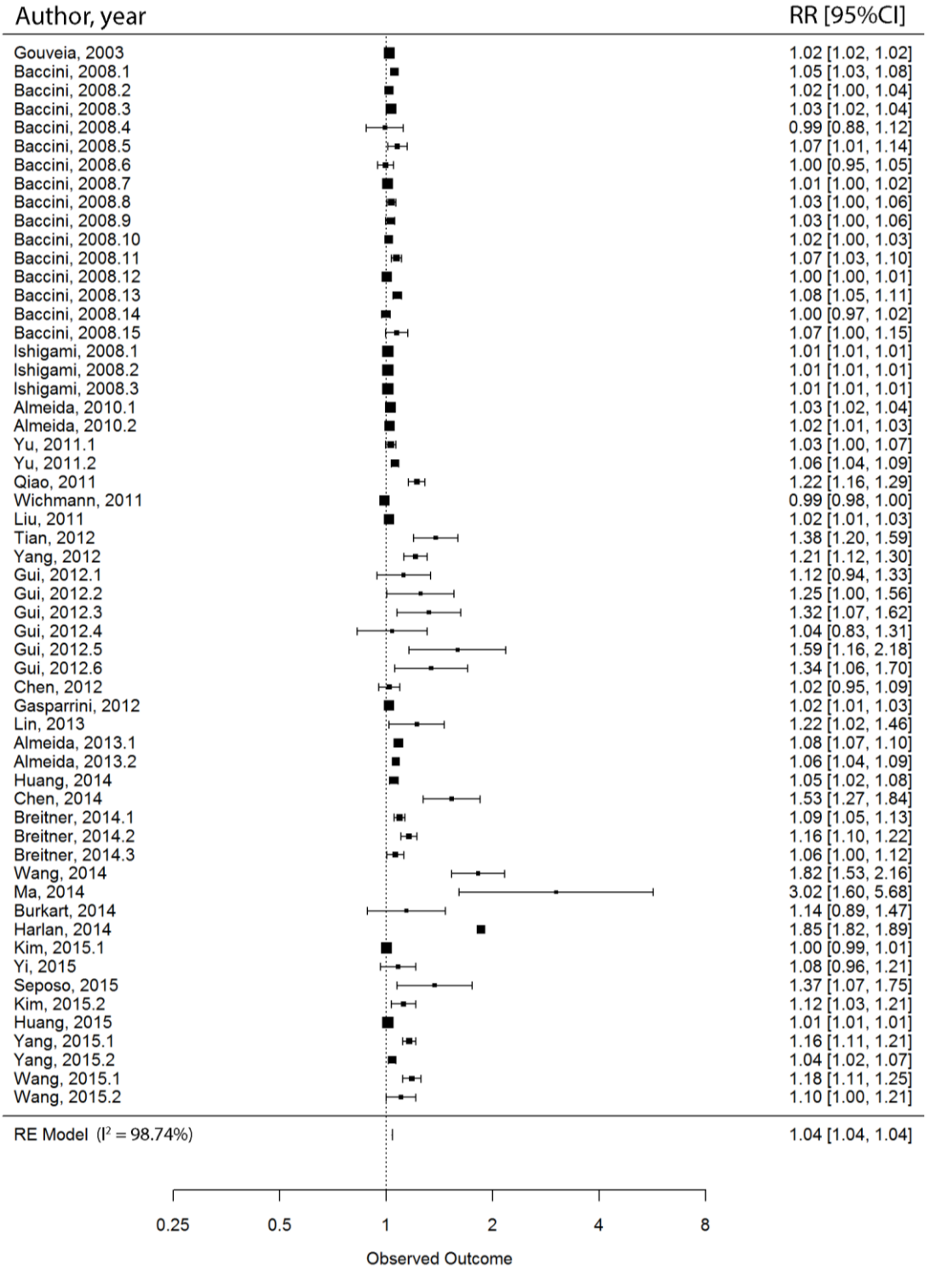
Author, year
RR [95%CI]
Gouveia, 2003 1.02 [1.02, 1.02]
Baccini, 2008.1 1.05 [1.03, 1.08]
Baccini, 2008.2 1.02 [1.00, 1.04]
Baccini, 2008.3 1.03 [1.02, 1.04]
Baccini, 2008.4 0.99 [0.88, 1.12]
Baccini, 2008.5 1.07 [1.01, 1.14]
Baccini, 2008.6 1.00 [0.95, 1.05]
Baccini, 2008.7 1.01 [1.00, 1.02]
Baccini, 2008.8 1.03 [1.00, 1.06]
Baccini, 2008.9 1.03 [1.00, 1.06]
Baccini, 2008.10 1.02 [1.00, 1.03]
Baccini, 2008.11 1.07 [1.03, 1.10]
Baccini, 2008.12 1.00 [1.00, 1.01]
Baccini, 2008.13 1.08 [1.05, 1.11]
Baccini, 2008.14 1.00 [0.97, 1.02]
Baccini, 2008.15 1.07 [1.00, 1.15]
Ishigami, 2008.1 1.01 [1.01, 1.01]
Ishigami, 2008.2 1.01 [1.01, 1.01]
Ishigami, 2008.3 1.01 [1.01, 1.01]
Almeida, 2010.1 1.03 [1.02, 1.04]
Almeida, 2010.2 1.02 [1.01, 1.03]
Yu, 2011.1 1.03 [1.00, 1.07]
Yu, 2011.2 1.06 [1.04, 1.09]
Qiao, 2011 1.22 [1.16, 1.29]
Wichmann, 2011 0.99 [0.98, 1.00]
Liu, 2011 1.02 [1.01, 1.03]
Tian, 2012 1.38 [1.20, 1.59]
Yang, 2012 1.21 [1.12, 1.30]
Gui, 2012.1 1.12 [0.94, 1.33]
Gui, 2012.2 1.25 [1.00, 1.56]
Gui, 2012.3 1.32 [1.07, 1.62]
Gui, 2012.4 1.04 [0.83, 1.31]
Gui, 2012.5 1.59 [1.16, 2.18]
Gui, 2012.6 1.34 [1.06, 1.70]
Chen, 2012 1.02 [0.95, 1.09]
Gasparrini, 2012 1.02 [1.01, 1.03]
Lin, 2013 1.22 [1.02, 1.46]
Almeida, 2013.1 1.08 [1.07, 1.10]
Almeida, 2013.2 1.06 [1.04, 1.09]
Huang, 2014 1.05 [1.02, 1.08]
Chen, 2014 1.53 [1.27, 1.84]
Breitner, 2014.1 1.09 [1.05, 1.13]
Breitner, 2014.2 1.16 [1.10, 1.22]
Breitner, 2014.3 1.06 [1.00, 1.12]
Wang, 2014 1.82 [1.53, 2.16]
Ma, 2014 3.02 [1.60, 5.68]
Burkart, 2014 1.14 [0.89, 1.47]
Harlan, 2014 1.85 [1.82, 1.89]
Kim, 2015.1 1.00 [0.99, 1.01]
Yi, 2015 1.08 [0.96, 1.21]
Seposo, 2015 1.37 [1.07, 1.75]
Kim, 2015.2 1.12 [1.03, 1.21]
Huang, 2015 1.01 [1.01, 1.01]
Yang, 2015.1 1.16 [1.11, 1.21]
Yang, 2015.2 1.04 [1.02, 1.07]
Wang, 2015.1 1.18 [1.11, 1.25]
Wang, 2015.2 1.10 [1.00, 1.21]
RE Model ($I^2 = 98.74\%$) 1.04 [1.04, 1.04]
0.25
0.5
1
2
4
8
Observed Outcome

Figure S4. Meta-meta-analysis of the relative risk of cardiovascular disease mortality per 1 ºC change of temperature (heat). Studies without adjustment were excluded.

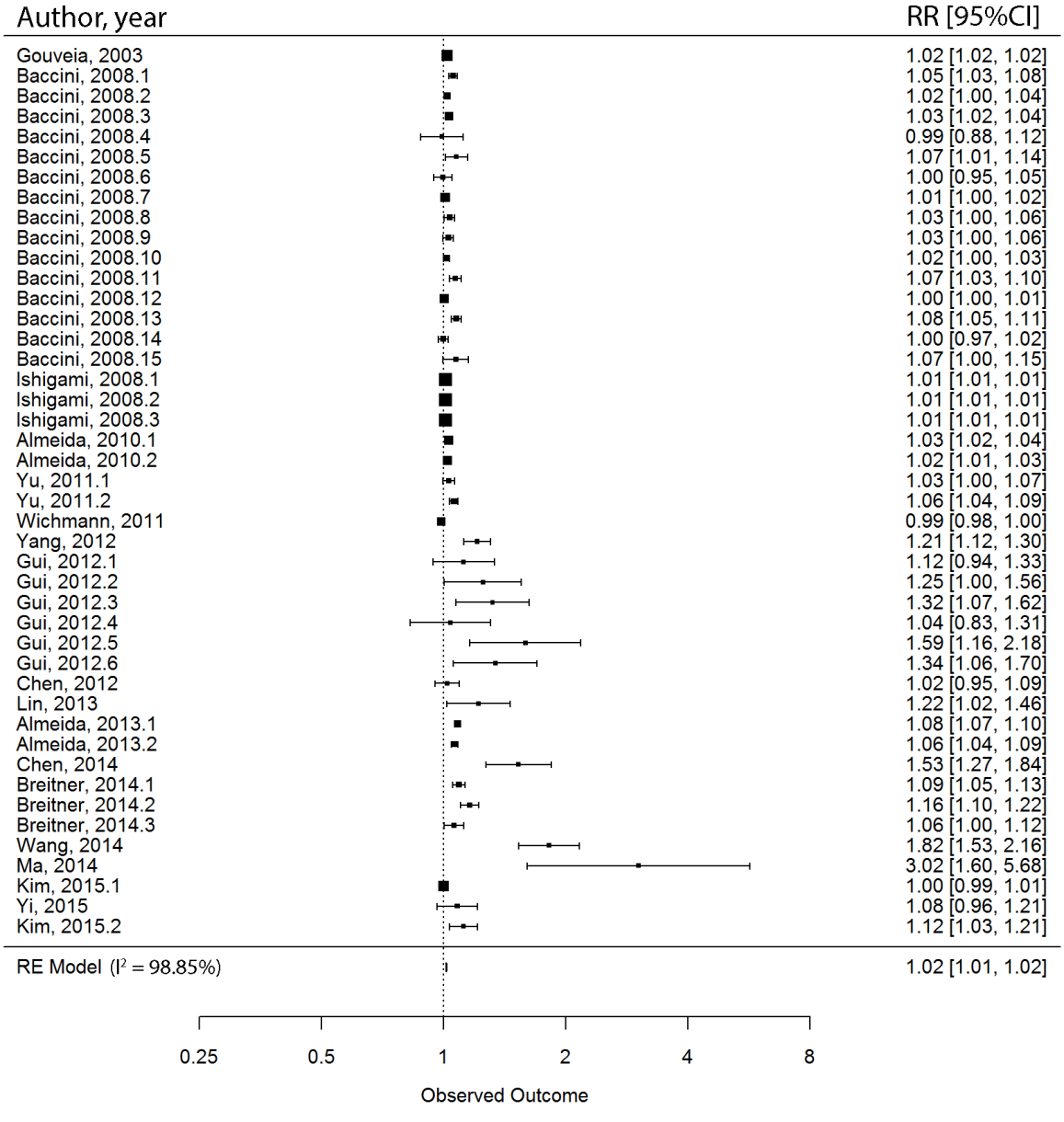

Figure S5. Meta-meta-analysis of the relative risk of cardiovascular disease mortality per 1 ºC change of temperature (heat). Studies without adjustment for air pollution were excluded.

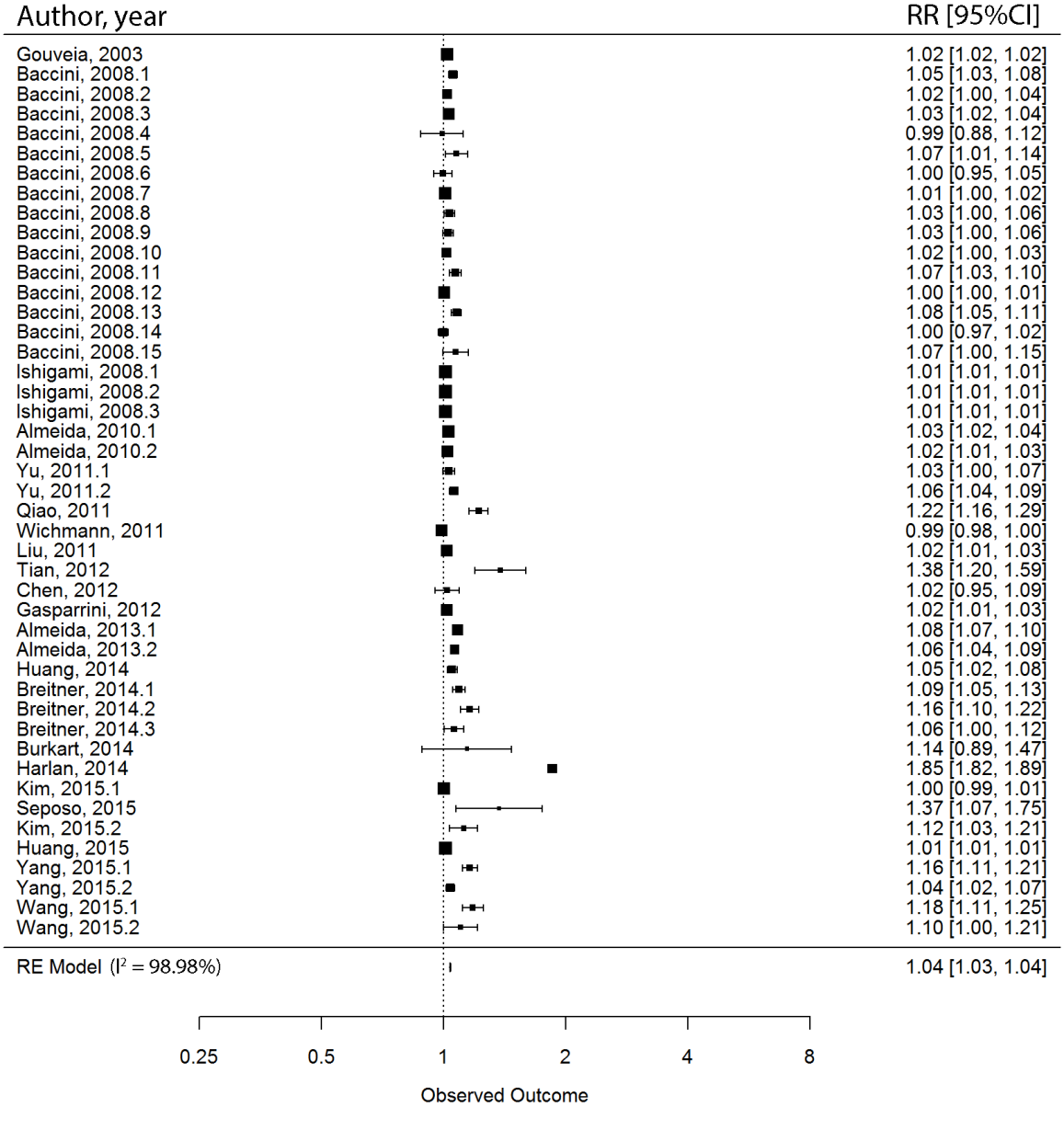

Figure S6. Meta-meta-analysis of the relative risk of cardiovascular disease mortality per 1 ºC change of temperature (heat). Studies with only adjustment for air pollution were excluded.

Table S2. Sensitivity analyses of meta-analyses

Included reviews	Level of comparison[1]	Sensitivity analysis	Random-effects summary ES (95% CI); P value	Sample size; N of included studies	ES (95% CI) in the largest study	I^2 (%)	Egger's test P value	Excess statistical significance test P value	95% prediction interval	Robustness of evidence
Air pollution										
Alexeeff et al. 2021 Chen et al. 2020	RR per 10 µg/m3 increase in $PM_{2.5}$ for IHD mortality	Studies without adjustment for smoking were excluded	1.17 (1.12 to 1.22); <0.0001	>1000; 22 studies	1.64 (1.62 to 1.66)	60.02%	0.07	0.04	1.0460 to 1.3073	Highly suggestive
Yang et al. 2019 Chen et al. 2020	RR per 10 µg/m3 increase in $PM_{2.5}$ for CVD mortality	Studies without adjustment for individual lifestyle were excluded	1.12 (1.08 to 1.15); <0.0001	>1000; 17 studies	1.09 (1.08 to 1.10)	60.28%	0.07	0.29	1.0322 to 1.2045	Highly suggestive
Ambient temperature										

Bunker et al. 2016 Moghadamnia et al. 2017	RR per 1 ºC change of temperature (heat) for CVD mortality	Studies without adjustment were excluded	1.04 (1.04 to 1.04); <0.0001	>1000; 57 studies	1.01 (1.01 to 1.01); <0.0001	98.74%	<0.0001	<0.01	1.0235 to 1.0550	Highly suggestive
table Bunker et al. 2016 Moghadamnia et al. 2017	RR per 1 ºC change of temperature (heat) for CVD mortality	Studies without adjustment for air pollution were excluded	1.02 (1.01 to 1.02); <0.0001	>1000; 44 studies	1.01 (1.01 to 1.01); <0.0001	91.85%	<0.0001	<0.01	1.0107 to 1.0215	Highly suggestive
Bunker et al. 2016 Moghadamnia et al. 2017	RR per 1 ºC change of temperature (heat) for CVD mortality	Studies with only adjustment for air pollution were excluded	1.04 (1.03 to 1.04); <0.0001	>1000; 45 studies	1.01 (1.01 to 1.01); <0.0001	98.98%	<0.0001	0.07	1.0224 to 1.0533	Highly suggestive

[1] RR: relative risk; HR: hazard ratio; CVD: cardiovascular disease; IHD: ischemic heart disease; CeVD: cerebrovascular disease.

CHAPTER 3

Socio-demographic and socio-economic differences in the availability of green space in the Netherlands

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Submitted

Summary

Background: We aimed to map the spatial distribution of green space in the Netherlands, and to first comprehensively assess socio-demographic and socio-economic differences in the availability of green space in the Netherlands.

Methods: Data was analyzed from all registered residents of the Netherlands aged one and above on January 1, 2017 (16,440,620 individuals). Socio-demographic and socio-economic information was derived from Statistics Netherlands (CBS). Data on green space density around home were assembled by the Institute for Public Health and the Environment at the address level. The distribution of exposure to green space was described by age groups, sex, ethnicity, household socioeconomic status (SES), and urbanicity degree, and stratified by green space type.

Results: The distribution of green space by all vegetation, trees, shrubs, low vegetation, grass field, and agriculture was mapped for the Netherlands in 2017. Small differences in green space density were found across age and sex groups. Ethnic Dutch (58.1%) and Indonesian (54.5%) had more green space coverage around residence than Turkish (50.0%) and Moroccan (50.0%). People with higher household SES had more green space coverage (48.0% to 52.0%), while in the highest level, the coverage decreased a little (51.7%). Higher urbanicity levels were monotonously associated with lower green space exposure. These differences particularly originated from differences in low vegetation. Observed differences between ethnic and SES groups originated mostly from differences in rural areas.

Conclusion: Environmental injustice was found among ethnic, SES, and urbanicity groups. The differences were mostly present in low vegetation and in rural areas.

Introduction

Green space exposure has been associated with multiple health benefits, including improved mental health, and lower risk of obesity, cardiometabolic diseases, and mortality [1–3]. Four potential pathways may have been linking green space exposure to health benefits [1]. First, green space may encourage an active lifestyle [1], which in turn is beneficial to people's overall health status [4]. Second, green space may reduce physiological stress and improve mental health [5]. Third, green space can reduce harm from exposure to air pollution, heat, and noise [1]. Last, green space releases certain chemical agents like phytoncides that may inhibit inflammation [6]. In the Netherlands, parts of agricultural land can be actively used by residents as walking and/or biking routes [7,8]. Therefore, agriculture was included as a type of green space in the current setting.

The environmental justice framework embraces the principle that all people regardless of *race*, color, national origin, or income are entitled to equal distribution of environmental amenities and no group should be disproportionately affected by environmental hazards [9]. Previous empirical research mainly focused on disparities in exposure to environmental hazards, such as air pollution [10], and less on environmental amenities, like green space [11].

Some previous studies investigated the environmental justice of green space exposure and yielded inconsistent findings in different settings. Dobb et al. analyzed 100 big cities around the world [12]. They found that there was less green space in cities that were characterized by a higher urbanization grade [12]. Generally, previous studies found that higher SES levels were associated with more green space, including evidence from Europe [13], the United States of America (USA) [11,14,15], Canada [16], and China [17–19]. Only the two studies from the USA were nationally representative [11,14]. Previous evidence was mostly derived from ecological studies that were on small area levels like neighbourhood, community, and census tract. On the contrary, Ju and colleagues found that cities or sub-cities with higher SES had less green space in Latin America [20]. A

previous nationwide study in the USA found urban-rural differences in green space exposure by poverty levels [11]. In this study, poverty levels were negatively associated with green space exposures in urban and suburban areas while these were positively associated in rural areas [11].

The ethnic differences in the availability of green space have been less extensively studied. The 2006-2010 USA nationwide study found that, on average, census tracts with higher percentages of African Americans and Hispanics included less green space [11]. The 2015-2019 USA nationwide study found that census tracts with higher percentages of non-Hispanic Whites and lower percentages of Hispanics included, on average more green space [14]. A weak positive association was observed between percentages of non-Hispanic Blacks and green space exposures in urban tracts but not in rural tracts [14]. A Canadian study that focused on urban environments found that minority ethnic populations (i.e., Latin American, African Canadian, and South Asian particularly individuals of Filipino ancestry) were exposed to less green space than the majority population (i.e., Whites) [16].

However, previous results are not generalizable to Western European countries, including the Netherlands, because of differences in ethnicity and socio-economic composition, built environment, lifestyle, and patterns of residence [21]. Previous studies in the Netherlands did not comprehensively include socio-demographic factors, socio-economic factors, and vegetation types, but predominately focused on green space exposures by income groups [22–25]. A comprehensive national assessment in the Netherlands is lacking.

The current study aims to address this research gap by (i) determining the spatial distribution of green space by mapping it on neighbourhood level in the Netherlands; and (ii) assessing whether green space exposure differs across socio-demographic and socio-economic subgroups at the individual level.

Method

Data source and linkage

A cohort of all registered residents of the Netherlands aged one and above on January 1, 2017 (n=17,074,889) was built from the National Population Register [26]. The register contains information on all legally residing citizens in the Netherlands, including date of birth, sex, current and previous residential address, and nationality [26]. SES information was integrated by Statistics Netherlands (CBS) and originated from the Population Statistics, the Integrated Income and Assets Survey, the Employment and Wages Statistics, and the Education Level File [27]. A detailed description of the data sources can be found elsewhere [28]. Area-level exposure data on green space and neighbourhood urbanicity were obtained from the Geoscience and Health Cohort Consortium (GECCO) [29,30]. These area-level exposure data were linked to individual-level data (age, sex, ethnicity, and household income) of all residents based on their residential address on January 1, 2017 in the secure environment of CBS. Linkage was successful for 96.3% of the addresses, and unsuccessful linkages were due to inconsistencies in addresses. The analytical sample included 16,440,620 residents. All data linkages and analyses were conducted in line with the policy from CBS and privacy legislation in the Netherlands. Ethical approval was not required for the present study.

Measures

Data on residential green space was assessed as green space density, which refers to the percentage of an area devoted to green space including trees, shrubs and low vegetation (grass field and agriculture) within a Euclidean buffer with radii of 500, 1000, and 2000 meters around residential addresses. The data were assembled by the National Institute for Public Health and the Environment (RIVM) at the address level in 10-meter raster in 2017. Low vegetation data from RIVM is based on satellite-derived altitude data. When only using data from RIVM, agriculture density can be underestimated because of seasonal change and fallow period. Therefore, the address-level agriculture density was separately derived from a second source, namely the land use map 2017 from CBS. For constructing the neighbourhood-level map for agriculture,

a third source, the polygon dataset of Basisregistratie Gewaspercelen, was used [31].

Based on age in years, individuals in the analytical sample were categorized into children (1 to <12 years), adolescents (12 to <18 years), adults (18 to <65 years), and older adults (≥65 years). The largest four ethnicity groups in the Netherlands were included, which are Dutch, Turkish, Moroccan, and Indonesian based on the register. Household SES was assessed by the household SES scores from CBS, which is based on household data concerning welfare (a combination of income and assets), highest level of education, and recent labour participation [32]. Household SES was categorized into quintiles. Urbanicity was defined by the number of addresses in a 1 km^2 circular buffer around the residential address. Urbanicity was categorized into non-urban (<500 addresses/km^2), limited urban (500-1000 addresses/km^2), moderately urban (1000-1500 addresses/km^2), strong urban (1500-2500 addresses/km^2), and very strong urban (≥2500 addresses/km^2). For the purpose of stratified analyses, urbanicity was also dichotomized into rural areas (<2000 addresses/km^2) and urban areas (≥2000 addresses/km^2).

Statistical analysis

First, the distribution of the analytical sample was described in terms of socio-demographic and socio-economic characteristics, including age groups, sex, ethnicity, household SES, and urbanicity degree. Second, the distribution maps of green space at the **neighbourhood level** in the Netherlands were created, for total green space, trees, shrubs, low vegetation, grass field, and agriculture, respectively. The neighbourhoods in the Netherlands (average area size: 3.1 km^2) are geographically delineated areas within municipalities and include, on average, approximately 630 households [29].

Third, the median (first quartile and third quartile) exposure of green space at the **individual level** was described by age groups, sex, ethnicity, quintiles of household SES, and urbanicity degree and stratified by green space type. In the main analyses, green space exposure in a 1000 meter Euclidean buffers was used. To assess the robustness of our findings, sensitivity analyses included green space exposure in smaller (500 m)

and larger (2000 m) Euclidean buffers. Fourth, multiple linear regression models were used to investigate the independent association of each factor with total green space density and green space by type. Age groups, sex, ethnicity, quintiles of household SES, and urbanicity degree were included as independent variables or covariates in the models. All data linkages and analyses were performed with strict authorized access in a secure environment of CBS, and in agreement with the privacy legislation in the Netherlands. All records and datasets were anonymized. All statistical analyses were conducted in R software.

Results

Table 1 presents socio-demographic and socio-economic characteristics of 16,440,620 included residents in 2017. Children, adolescents, adults, and older adults consisted 12.9%, 7.3%, 61.4%, and 18.5% of the population, respectively. The percentage of adults was larger in urban areas than in rural areas. The number of males and females was balanced. A higher proportion of native ethnic Dutch residents was observed in rural areas compared to urban areas (89.2% vs. 73.6%). The proportion of people with higher household SES was higher in rural areas than in urban areas. More residents lived in neighbourhoods with an urbanicity degree of 1500-2500 addresses/km^2 (26.0%) than neighbourhoods with other urbanicity levels.

Distribution of green space at the neighbourhood level

Figure 1 presents the distribution of green space at the neighbourhood level in the Netherlands in 2017. In general, residents living in the Netherlands had a high coverage of green space in their neighbourhoods. Most neighbourhoods in the north-eastern part of the Netherlands had more than eighty percent vegetation. Most neighbourhoods in cities had twenty to forty percent vegetation, except for the cities in middle-western areas like Amsterdam, Utrecht, Rotterdam, and The Hague. Neighbourhoods in centers of these big cities had less than twenty percent vegetation, while the peripheral neighbourhoods had more green space coverage.

A large proportion of the green space in the north-eastern and south-western parts of the Netherlands was agriculture (**Appendix Figure S1**). There was barely any agriculture in cities and in the coastland. There were more trees in neighbourhoods in the eastern part of the Netherlands (more rural areas) than in neighbourhoods in the western part of the country (more urban areas) (**Appendix Figure S2**). Neighbourhoods in cities in the west had less than twenty percent tree coverage, whereas this was higher in the east. On the contrary, there were more shrubs in the neighbourhoods in the western part of the Netherlands, especially in the coastland, than in the eastern part of the

country (**Appendix Figure S3**). The distribution of low vegetation was largely comparable to agriculture, except that the neighbourhoods in urban areas contained more low vegetation than agriculture (**Appendix Figure S4**). This can mainly be attributed to grass field, another component of low vegetation. Neighbourhoods in urban areas had 16% to 36% grass field coverage while neighbourhoods in rural areas barely had grass field (**Appendix Figure S5**). Neighbourhoods with the highest levels of grass field exposure were found in the coastland.

Distribution of green space at the individual level

Availability of green space by age and sex

There were hardly any differences in green space exposure across age and sex groups. This was regardless of green space type (**Appendix Figures S6 and S7**).

Availability of green space by ethnic group

The ethnic Dutch (58.1%) and Indonesian (54.5%) had more green space density around their residence than Turkish (50.0%) and Moroccan (50.0%). This difference mainly originated from the difference in exposure to low vegetation (**Figure 2**). When analyses were stratified by urbanicity (**Figure 3**), the differences in the availability of green space between ethnic groups remained in the rural areas (low vegetation: 49.0%, 44.5%, 40.9%, and 41.1% for ethnic Dutch, Indonesian, Turkish, and Moroccan, respectively). However, in urban areas, differences between ethnic groups were much smaller (low vegetation: 30.0%, 30.2%, 29.9%, and 30.2% for ethnic Dutch, Indonesian, Turkish and Moroccan, respectively).

Availability of green space by socio-economic status

Individuals with higher household SES gradually had more green space density around their residence (48.0%, 50.3%, 51.2%, and 52.0% from quintile 1 to quintile 4, respectively), while in the highest household SES level, the density was slightly lower again (51.7% for quintile 5). This difference mainly originated from low vegetation (**Figure 4**). When stratified by urbanicity (**Figure 5**), the differences in the availability of

green space between SES quintile groups remained in the rural areas (low vegetation: 45.3%, 47.8%, 48.7%, 49.8%, and 48.8% for quintile 1 to quintile 5, respectively). In urban areas, however, differences between SES groups were smaller (low vegetation: 29.8%, 30.3%, 30.5%, 30.2%, and 29.4% for quintile1 to quintile5, respectively).

Availability of green space by urbanicity degree

Residents living in areas with higher urbanicity degrees were exposed to lower levels of green space **Appendix Figure S8**). This was originated from exposures to both tree and low vegetation.

Detailed descriptive statistics on socio-demographic and socio-economic differences in green space density exposure in 1000-meter Euclidean buffers around residential addresses, are presented in **Appendix Table S1**. Furthermore, similar details, related to the sensitivity analyses in which green space density in 500-meter and 2000-meter Euclidean buffers, are presented in **Appendix Tables S2 and S3**. Results of the sensitivity analyses were largely in line with those of the main analyses.

The findings of the multiple linear regression analyses (**Table 2**) were generally in line with the patterns described above. The differences across socio-demographic and socio-economic groups were statistically significant, albeit these differences were small. After adjustment for several socio-demographic and socio-economic factors, the differences in total green space density across ethnic and SES groups slightly changed (**Table 2**).

Discussion

In this study, the distribution of green space by all vegetation, trees, shrubs, low vegetation, grass field, and agriculture was mapped for the Netherlands in 2017. This study also assessed socio-demographic and socio-economic differences in the availability of green space in the Netherlands. Hardly any differences in green space density were found across age or sex groups. Ethnic Dutch and Indonesian had more green space coverage around residence than Turkish and Moroccan. People with higher household SES gradually had slightly more green space coverage, while in the highest household SES level, the coverage decreased a little. Higher urbanicity levels were monotonously associated with lower green space exposure. These differences particularly originated from differences in the density of low vegetation, and observed differences between ethnic and SES groups originated mostly from differences in rural areas and less in urban areas. For the results from multiple linear regressions, it should be noted that although most estimates were statistically significant due to the large sample size, the interpretation of results should also take into account the practical significance.

The results regarding ethnic disparities in green space exposure indicated that the Dutch population was exposed to higher levels of green space density than the Turkish, Moroccan and Indonesian population, which are the three largest ethnic minority groups in the Netherlands. The current findings were in line with international research and showed that ethnic minority groups are exposed to less green space in comparison to the majority population. An individual-level study of urban Canadians found that minority ethnic populations (Latin American, African Canadian, and South Asian) were exposed to less green space than the majority population [16]. Two nationwide USA studies consistently found that census tracts with higher percentages of Hispanics were exposed to less green space [11,14]. The current study found urban-rural differences in green space exposure by ethnic groups. The ethnic disparities were more obvious in rural areas than in urban areas (**Figure 3**). The 2015-2019 USA nationwide study also found urban-rural differences. A weak positive association was observed between

percentages of non-Hispanic Blacks and green space exposures in urban tracts but not in rural tracts [14].

The difference in exposure to green space density across various SES groups was also examined by previous Dutch studies. Kruize et al. explored the distribution of several environmental aspects among socio-economic categories in Netherlands [22–24]. They found that people with higher income levels had more public green space exposure around residence [22]. The findings of the current study indicated that the positive association between SES and green space was not monotonous. The highest SES quintile had a slightly lower green space coverage compared to the fourth quintile. SES is defined in the current study as a combined measure of income, assets, education, and occupation. The results of the current study may be explained by the fact that people with lower SES and the highest SES were more likely to live in urban areas, and higher green space density was associated with a lower urbanicity degree. Van Velzen et al. assessed green space distribution around Dutch primary schools and found that schools in low SES neighbourhoods were exposed to lower levels of outdoor green space in comparison to high SES neighbourhoods [25]. In this study of Dutch primary schools, the percentage of non-Western migrants in the neighbourhood was associated with more outdoor green space, and no evidence was found for green space disparity across urbanicity levels [25]. Other international studies mostly supported that higher SES levels were associated with more green space [11,13–19]. Likewise, the current Dutch nationwide study and the 2015-2019 USA nationwide study both found urban-rural differences by SES groups [14].

Previous studies on socio-demographic and socio-economic differences in green space density in the Netherlands did not consider agricultural land as a component of green space exposure. For instance, Kruize et al. defined green space as parks, forests, recreational areas and nature [22–24], and Van Velzen et al. used a green space measure based on grass field, shrubs, and trees [25]. Agriculture, however, is an important component of green space in the Netherlands as shown in the current study. First, agriculture contributes to a large proportion of green space in the Netherlands. Second,

the identified ethnic and socio-economic differences in green space exposure originated from low vegetation, which consists of grass field and agriculture. Grass field was mostly present in urban areas and agriculture was mostly present in rural areas. In addition, stratified results showed that the identified differences were in rural areas, but not in urban areas. These findings indicate that the identified differences mostly originated from differences in the availability of agriculture, and suggest that it is important to consider agriculture in green space exposure measures in future research.

Green space exposure has been associated with multiple health benefits, including improved mental health, and lower risk of obesity, cardiometabolic diseases, and mortality [1–3]. One pathway through which green space exposure may influence health is increasing leisure time physical activity [1]. In the context of the Netherlands, parts of the agricultural land can also be actively used by residents. For instance, there are 159 recorded walking routes in agricultural areas named clog trail path (in Dutch: klompenpaden) [7]. Some of these areas are also popular among bikers, as there is an extensive cycle path network named cyclepath nodes (in Dutch: fiets knooppunt) of which many cross agricultural land [8]. Therefore, agriculture may have a positive health effect by encouraging an active lifestyle. However, this positive health effect might not be equal for all ethnic groups since cycling is much more common among the ethnic Dutch [33]. On the other hand, agriculture has been a large contributor to multiple air pollutants in the Netherlands, especially ammonia, nitrogen oxides, and particulate matter with diameters <10 μm [34]. Different from the decreasing effect of other types of green space on air pollution via deposition, agriculture increases air pollution and may have a detrimental effect on health. Since we have identified ethnic and SES differences in the availability of green space, consistent with previous studies, future studies on the health effects of green space should take ethnic and socioeconomic inequalities in green space exposure into account.

The current study has several strengths, including (1) nationwide registry data, (2) inclusion of various types of green space, including agricultural land, and (3) an extensive examination of socio-demographic and socio-economic differences in green

space exposure. There are also several limitations to consider when interpreting the current results. First, the cross-sectional design and unadjusted comparison preclude us from making causal inference. Second, the availability of green space was only measured as density. Other important measures like accessibility and utility of green space were not included in the present study. Third, only the exposure at the residence level was included. Green space exposures at the workplace or during commute could be described in future studies. Fourth, although the green space density data from 2017 are currently the most up-to-date and detailed data that are available for linkage, the results might be somewhat outdated. Since 2017, some newly built areas have been developed and some redesign of the landscape might have taken place. We have not been able to take these changes into account within our current analysis.

Conclusion

In conclusion, this is the first study that described multiple aspects of the socio-demographic and socio-economic differences in green space density in the Netherlands. Little differences in the availability of green space were found across age and sex groups. Ethnic Dutch and Indonesian had more green space coverage around residence than Turkish and Moroccan. People with a higher household SES had gradually more green space coverage, while in the highest SES level, the coverage was slightly lower again. Higher urbanicity levels were monotonously associated with lower green space exposure. The differences between ethnic groups and household SES groups originated from differences in the availability of low vegetation, and were mostly present in rural areas.

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Contributors:

M. Liu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Writing - original draft. **E.J. Timmermans:** Conceptualization; Project administration; Supervision; Writing - review & editing. **A. Wagtendonk:** Data curation; Methodology; Resources; Validation; Writing - review & editing. **P. Meijer:** Formal analyses, Writing – review & editing. **D.E. Grobbee:** Supervision; Validation; Writing - review & editing. **I. Vaartjes:** Conceptualization; Project administration; Supervision; Validation; Writing - review & editing.

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Table 1. Socio-demographic and socio-economic characteristics of all included Dutch residents in 2017 (n=16,440,620).

Characteristics	All, %	Rural areas (<2000 addresses/km^2), %	Urban areas (≥2000 addresses/km^2), %
Age groups			
Children (1 to <12 years)	12.9	13.1	12.4
Adolescents (12 to <18 years)	7.3	7.9	6.0
Adults (18 to <65 years)	61.4	59.8	64.6
Older adults (≥65 years)	18.5	19.2	17.0
Sex			
Males	49.7	49.9	49.2
Females	50.3	50.1	50.9
Ethnicity [1]			
Dutch	77.9	89.2	73.6
Turkish	2.3	1.3	5.3
Moroccan	2.2	1.2	5.2
Indonesian	2.1	1.9	3.1
Household SES [2]			
Quintile 1	19.4	14.9	29.1
Quintile 2	20.0	20.0	20.0
Quintile 3	20.3	21.9	16.8
Quintile 4	20.3	22.5	15.5
Quintile 5	20.1	20.8	18.7
Urbanicity degree (addresses/km^2)			
Non-urban (<500)	16.4	24.1	0
Limited urban (500-1000)	17.0	25.0	0
Moderately urban (1000-1500)	19.4	28.5	0
Strong urban (1500-2500)	26.0	22.4	33.6
Very strong urban (≥2500)	21.2	0	66.4

[1] A total of 15.5% of the population belongs to other ethnicity groups and is not shown here.

[2] Household socio-economic status (SES) score is developed by Statistics Netherlands based on standardized disposable income, taxable assets, highest education, and recent labour participation. A total of 1.8% of the population was missing in SES score.

Table 2. Linear relation between socio-demographic and socio-economic characteristics and green space density by types within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,440,620) [1].

Characteristics	β (95 % CI)				
	Total green space density	Tree density	Shrubs density	Low vegetation density	Agriculture density
Age groups					
Children (1 to <12 years)	Ref.	Ref.	Ref.	Ref.	Ref.
Adolescents (12 to <18 years)	**0.23 (0.21, 0.24)**	**0.16 (0.14, 0.18)**	**0.02 (0.02, 0.02)**	0.02 (-0.01, 0.03)	**0.38 (0.35, 0.41)**
Adults (18 to <65 years)	**-0.03 (-0.04, -0.02)**	**0.26 (0.25, 0.28)**	**0.002 (0.001, 0.004)**	**-0.38 (-0.40, -0.37)**	**0.10 (-0.12, -0.08)**
Older adults (≥65 years)	**0.69 (0.67, 0.70)**	**1.13 (1.12, 1.15)**	**0.08 (0.08, 0.08)**	**-0.78 (-0.79, -0.76)**	**-0.47 (-0.50, -0.45)**
Sex					
Males	Ref.	Ref.	Ref.	Ref.	Ref.
Females	**0.03 (0.02, 0.04)**	**0.01 (0.01, 0.02)**	**0.01 (0.01, 0.01)**	**-0.01 (-0.02, -0.002)**	**-0.04 (-0.05, -0.02)**
Ethnicity [2]					
Dutch	Ref.	Ref.	Ref.	Ref.	Ref.
Turkish	**-0.51 (-0.53, -0.48)**	**0.24 (0.22, 0.27)**	**-0.22 (-0.23, -0.22)**	**-0.06 (-0.09, -0.03)**	**-1.39 (-1.43, -1.34)**
Moroccan	**-0.04 (-0.06, -0.01)**	**0.17 (0.14, 0.19)**	**-0.08 (-0.08, -0.07)**	**0.40 (0.37, 0.43)**	**-0.98 (-1.03, -0.93)**
Indonesian	**0.61 (0.58, 0.63)**	**0.61 (0.58, 0.64)**	**0.09 (0.09, 0.09)**	**-0.24 (-0.27, -0.21)**	**-1.35 (-1.39, -1.30)**
Household SES [3]					
Quintile 1	Ref.	Ref.	Ref.	Ref.	Ref.
Quintile 2	**-0.07 (-0.08, -0.06)**	**-0.41 (-0.42, -0.39)**	**0.06 (0.06, 0.06)**	**0.37 (0.35, 0.38)**	**0.73 (0.71, 0.75)**

Quintile 3	**0.03 (0.02, 0.04)**	**-0.47 (-0.49, -0.46)**	**0.10 (0.10, 0.10)**	**0.51 (0.50, 0.53)**	**1.07 (1.05, 1.10)**
Quintile 4	**0.06 (0.05, 0.07)**	**-0.67 (-0.68, -0.65)**	**0.13 (0.13, 0.14)**	**0.74 (0.72, 0.75)**	**1.69 (1.67, 1.72)**
Quintile 5	**0.39 (0.38, 0.40)**	**-0.23 (-0.25, -0.22)**	**0.19 (0.18, 0.19)**	**0.24 (0.23, 0.26)**	**0.89 (0.87, 0.91)**
Urbanicity degree (addresses/km^2)					
Non-urban (<500)	Ref.	Ref.	Ref.	Ref.	Ref.
Limited urban (500-1000)	**-12.37 (-12.38, -12.35)**	**-3.10 (-4.01, -3.98)**	**-0.14 (-0.14, -0.14)**	**-15.18 (-15.20, -15.17)**	**-29.47 (-29.49, -29.45)**
Moderately urban (1000-1500)	**-19.19 (-19.21, -19.18)**	**-5.85 (-5.87, -5.84)**	**-0.31 (-0.31, -0.31)**	**-22.68 (-22.70, -22.67)**	**-44.74 (-44.76, -44.72)**
Strong urban (1500-2500)	**-24.87 (-24.88, -24.85)**	**-6.82 (-6.84, -6.81)**	**-0.44 (-0.45, -0.44)**	**-28.88 (-28.89, -28.87)**	**-56.39 (-56.41, -56.36)**
Very strong urban (≥2500)	**-30.10 (-31.01, -30.99)**	**-7.57 (-7.59, -7.56)**	**-0.77 (-0.77, -0.76)**	**-36.22 (-36.24, -36.21)**	**-64.07 (-64.09, -64.04)**

[1] The estimates presented in bold are statistically significant.

[2] A total of 15.5% of the population belongs to other ethnicity groups and is not shown here.

[3] Household socio-economic status (SES) score is developed by Statistics Netherlands based on standardized disposable income, taxable assets, highest level of education, and recent labor participation. A total of 1.8% of the population was missing in SES score. Quintile 1 is the lowest SES group.

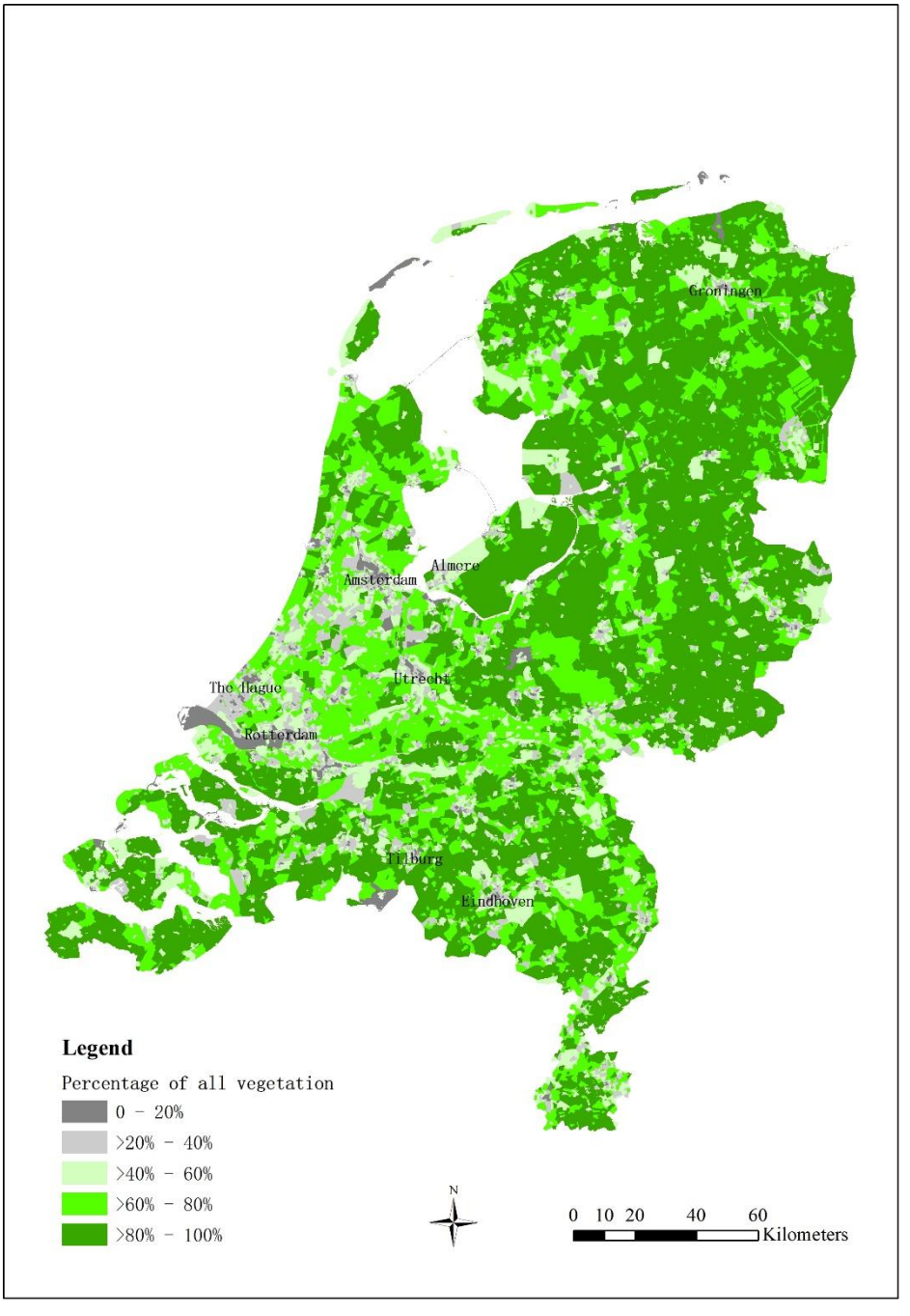

Figure 1. Distribution of green space (all vegetation including agriculture) at the neighbourhood level in the Netherlands, 2017.

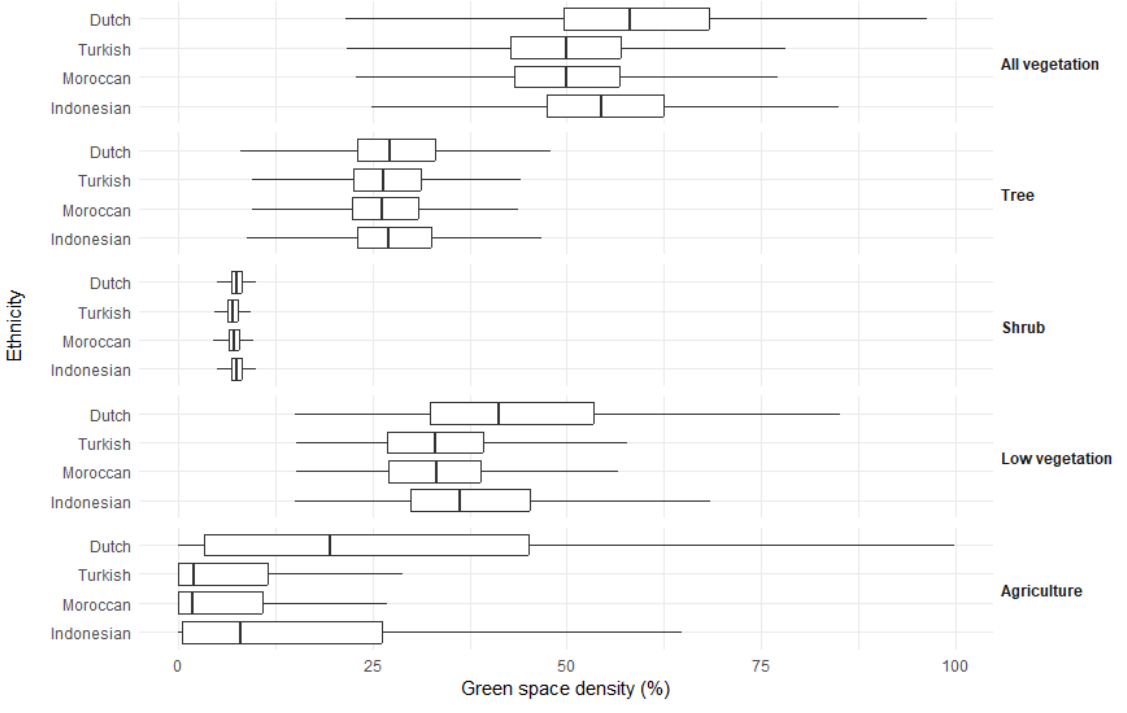

Figure 2. Boxplot of green space density by types and ethnicity within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=13,894,514).

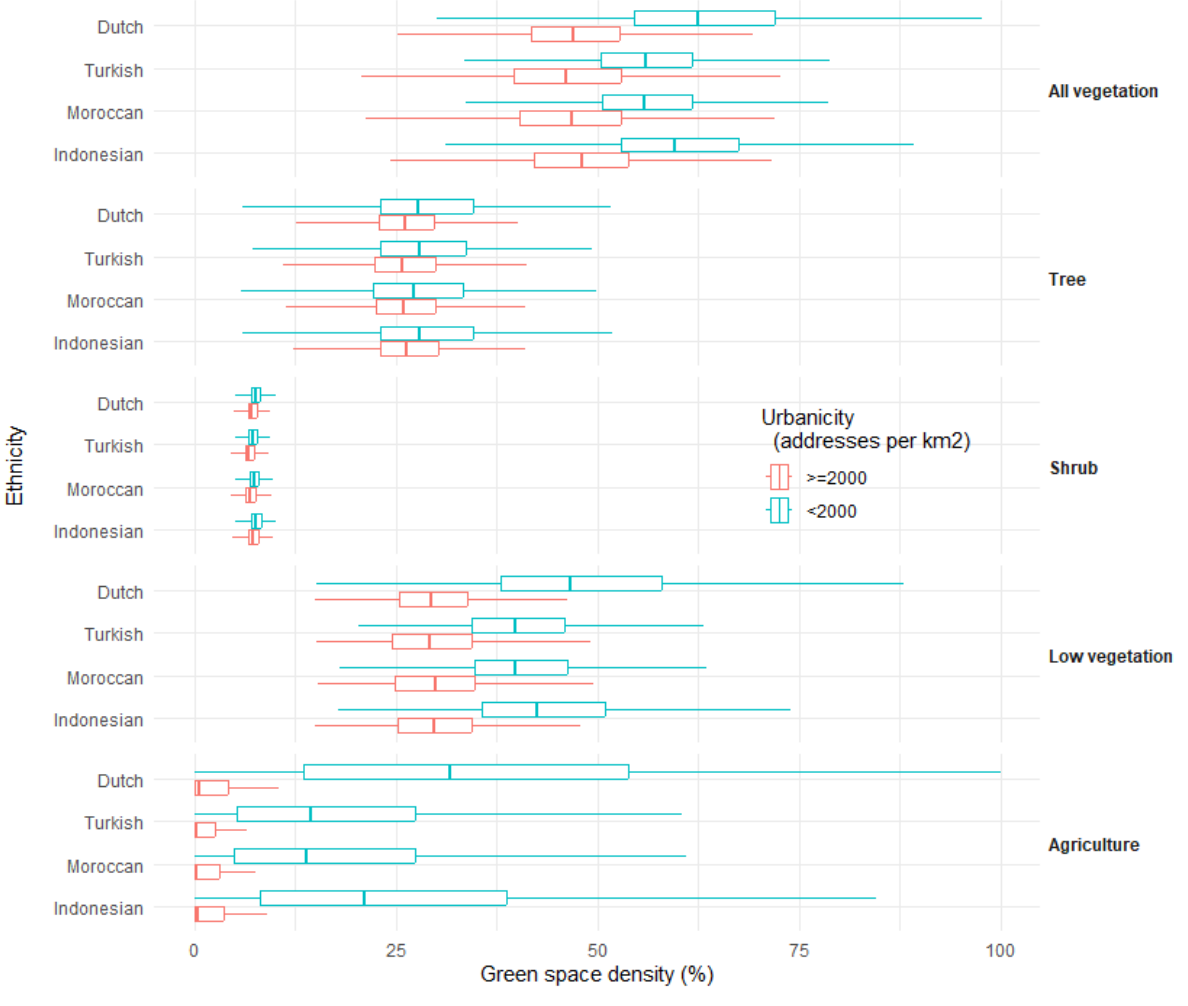

Figure 3. Boxplot of green space density by types and ethnicity within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands stratified by urbanicity degree (n=13,894,453).

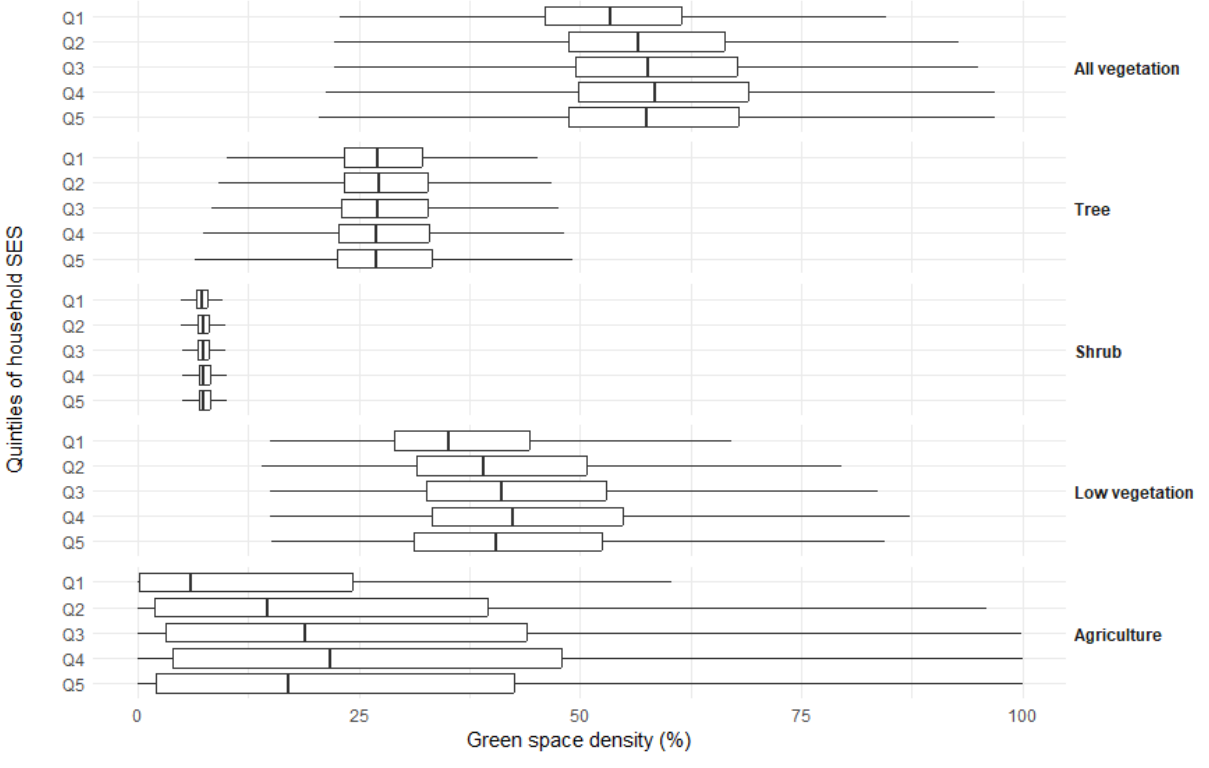

Figure 4. Boxplot of green space density by types and household socio-economic status (SES) score within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,145,371). Household SES score is developed by Statistics Netherlands based on standardized disposable income, taxable assets, highest level of education, and recent labour participation.

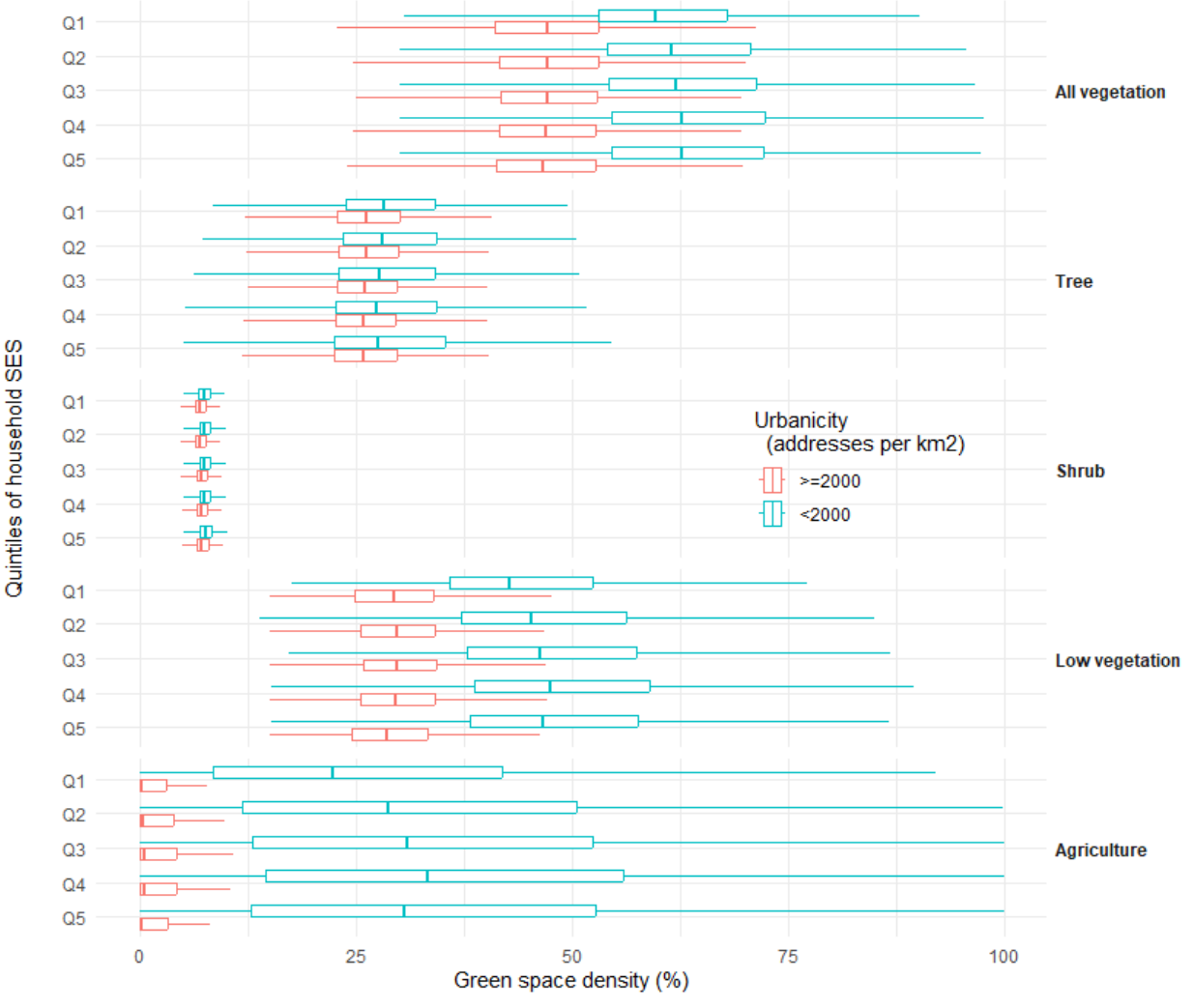

Figure 5. Boxplot of green space density by types and household socio-economic status (SES) score within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands stratified by urbanicity degree (n=16,145,294). Household SES score is developed by Statistics Netherlands based on standardized disposable income, taxable assets, highest level of education, and recent labour participation.

CHAPTER 3 Appendices

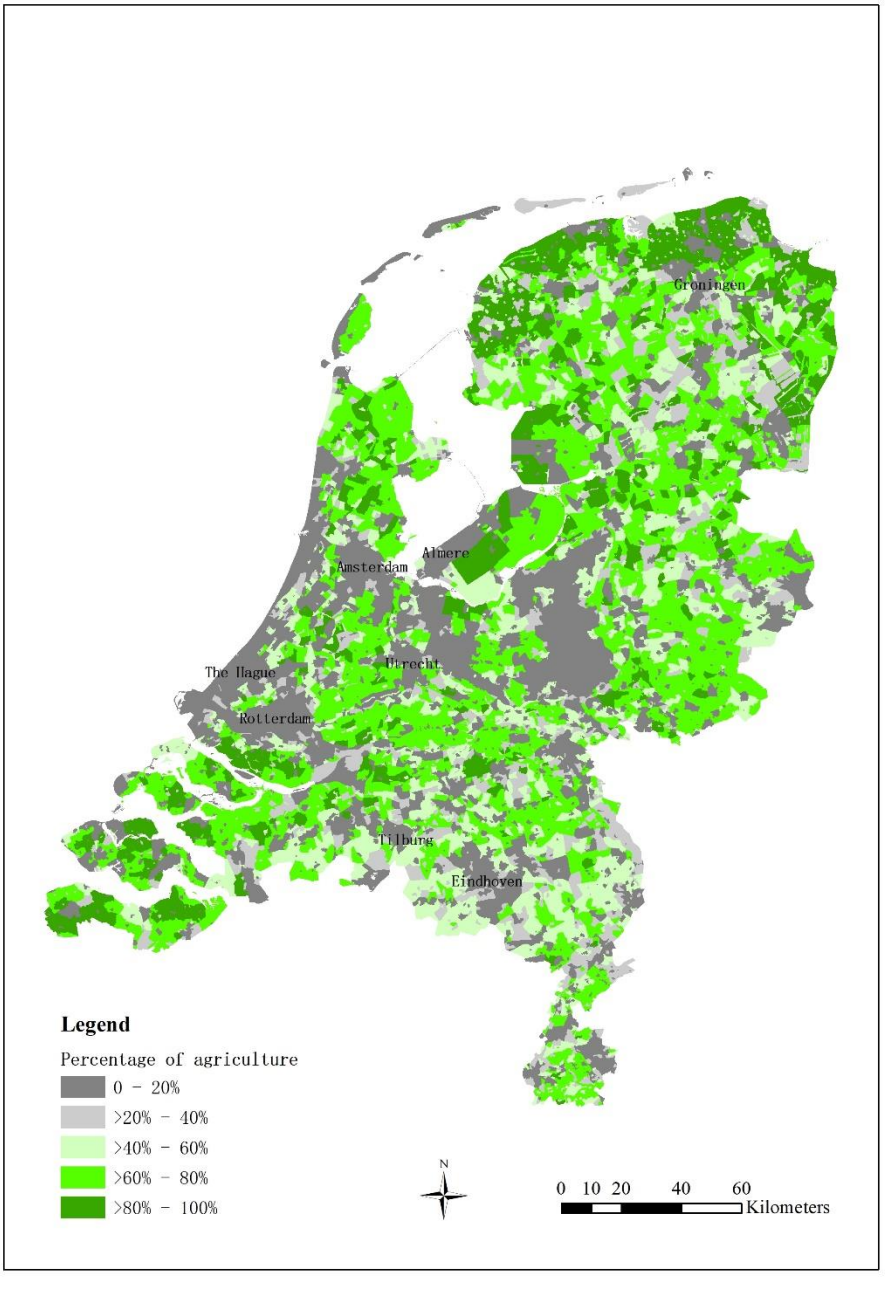

Figure S1. Distribution of agriculture at the neighbourhood level in the Netherlands, 2017.

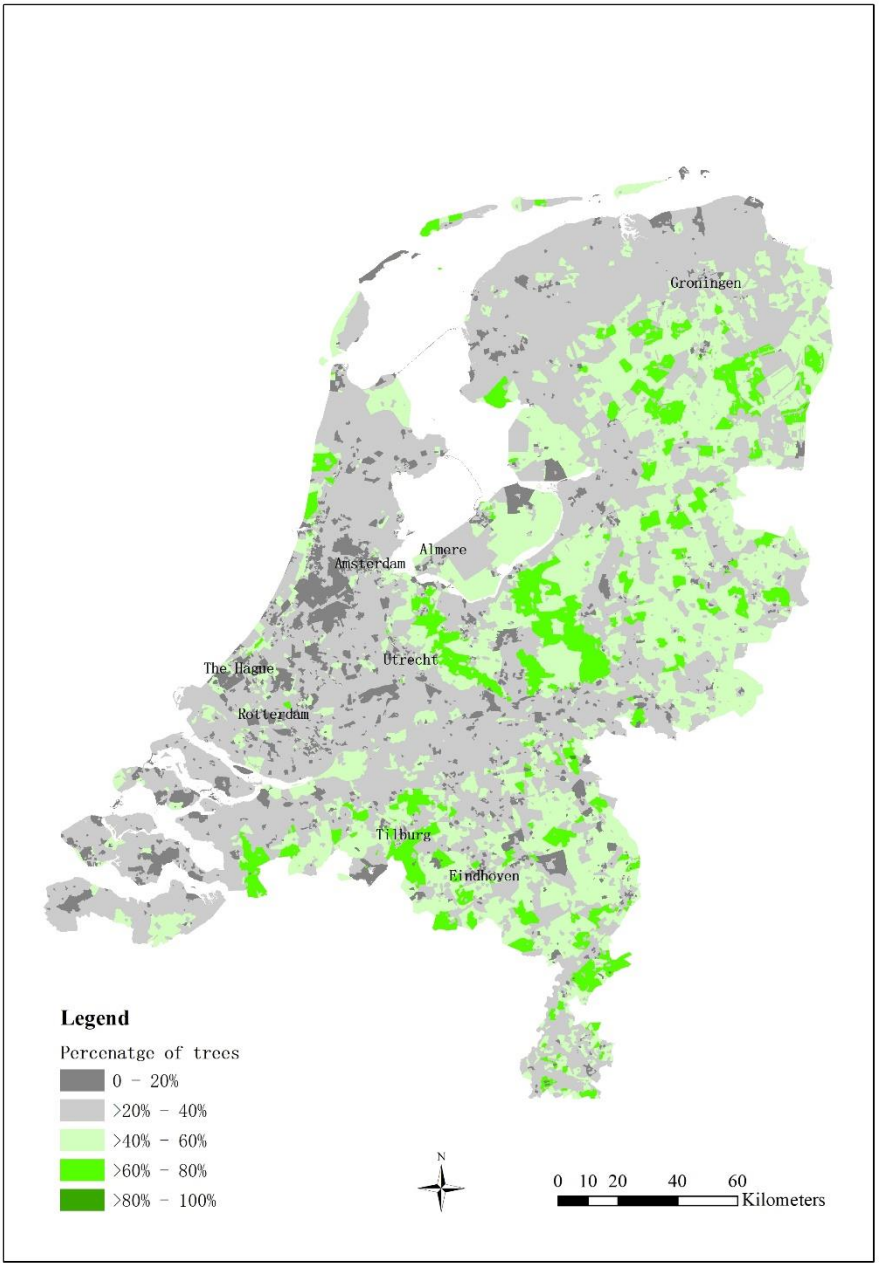

Figure S2. Distribution of trees at the neighborhood level in the Netherlands, 2017.

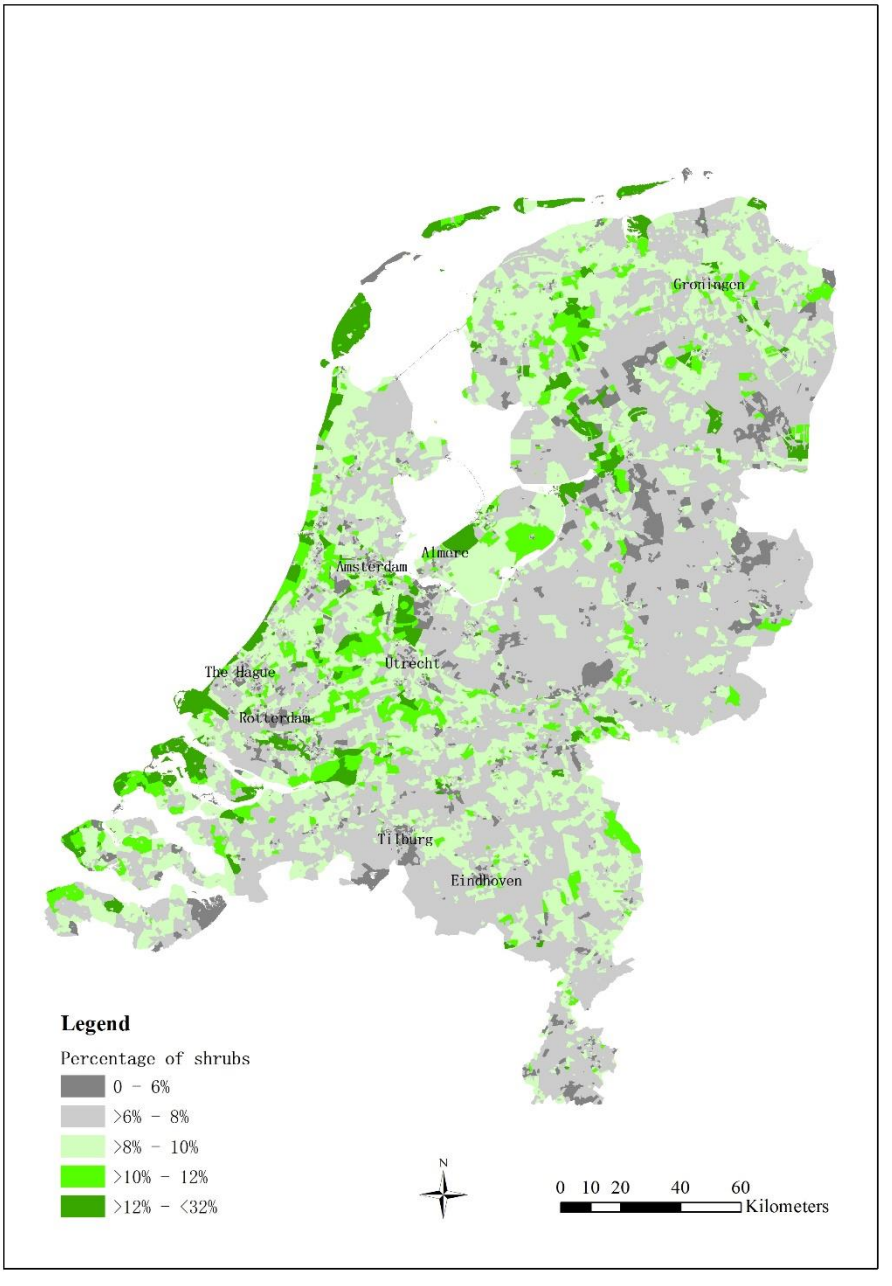

Figure S3. Distribution of shrubs at the neighborhood level in the Netherlands, 2017.

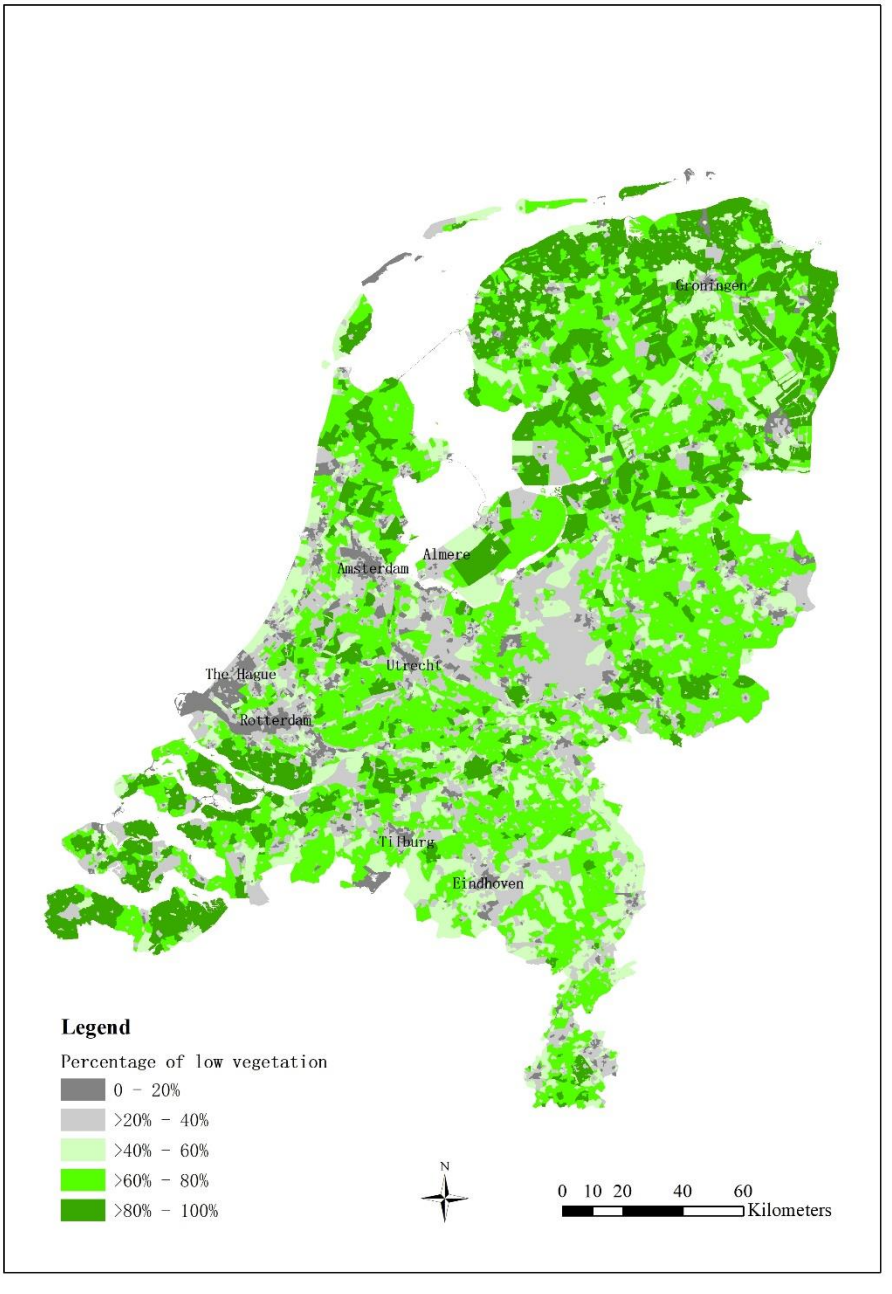

Figure S4. Distribution of low vegetation (any green space lower than 1 meter including grass and agriculture) at the neighborhood level in the Netherlands, 2017.

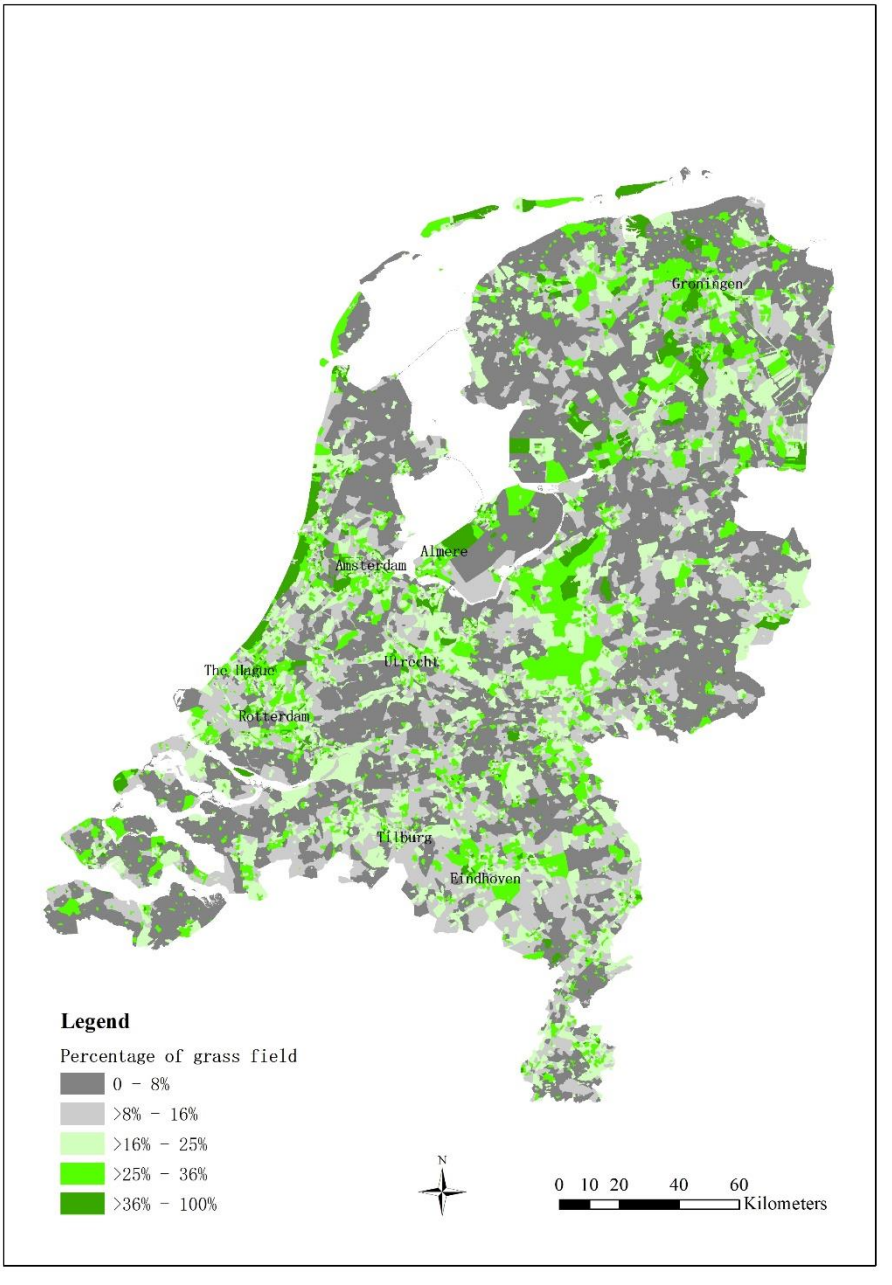

Figure S5. Distribution of grass field at the neighborhood level in the Netherlands, 2017.

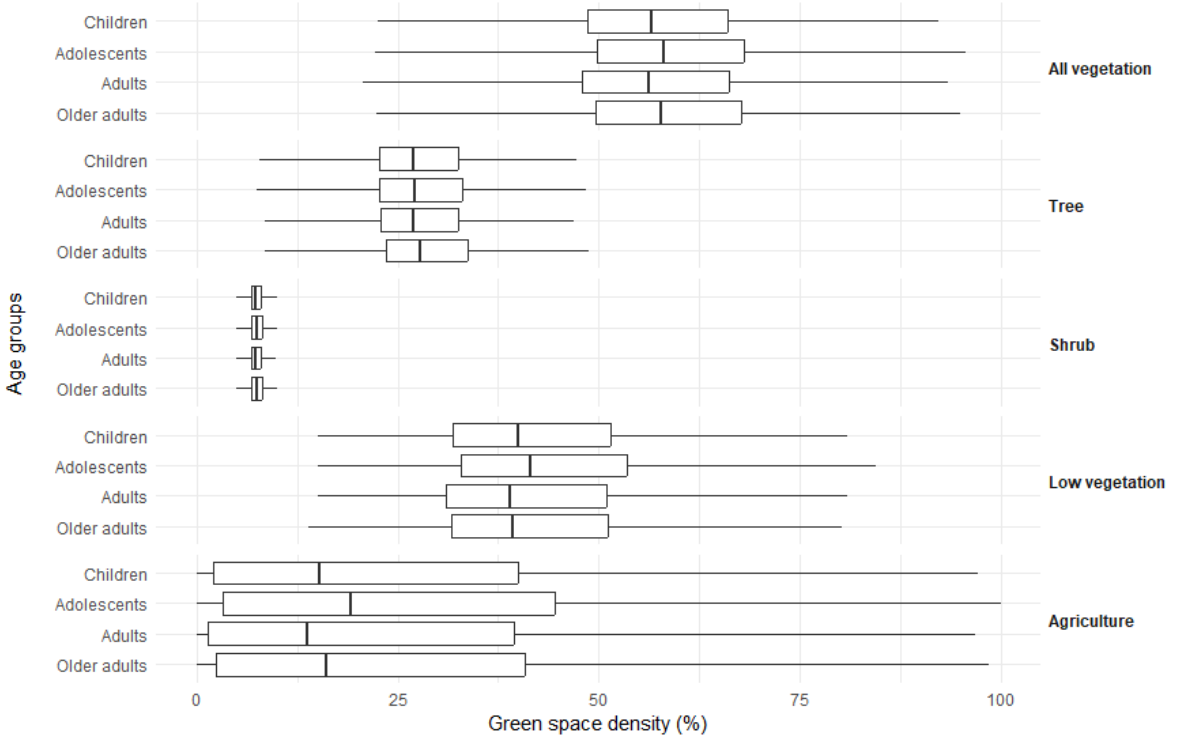

Figure S6. Boxplot of green space density by types and age groups within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,440,620). Children: 1 to <12 years. Adolescents: 12 to <18 years. Adults: 18 to <65 years. Older adults: ≥65 years.

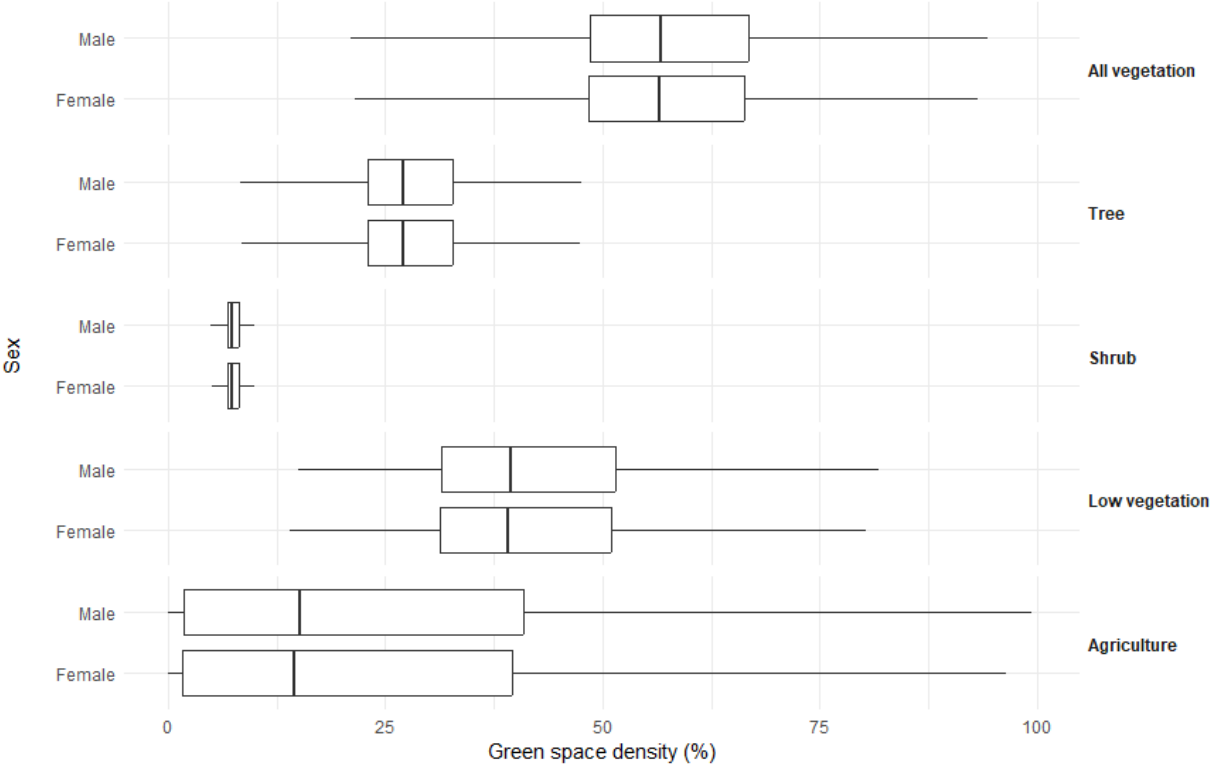

Figure S7. Boxplot of green space density by types and sex within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,440,620).

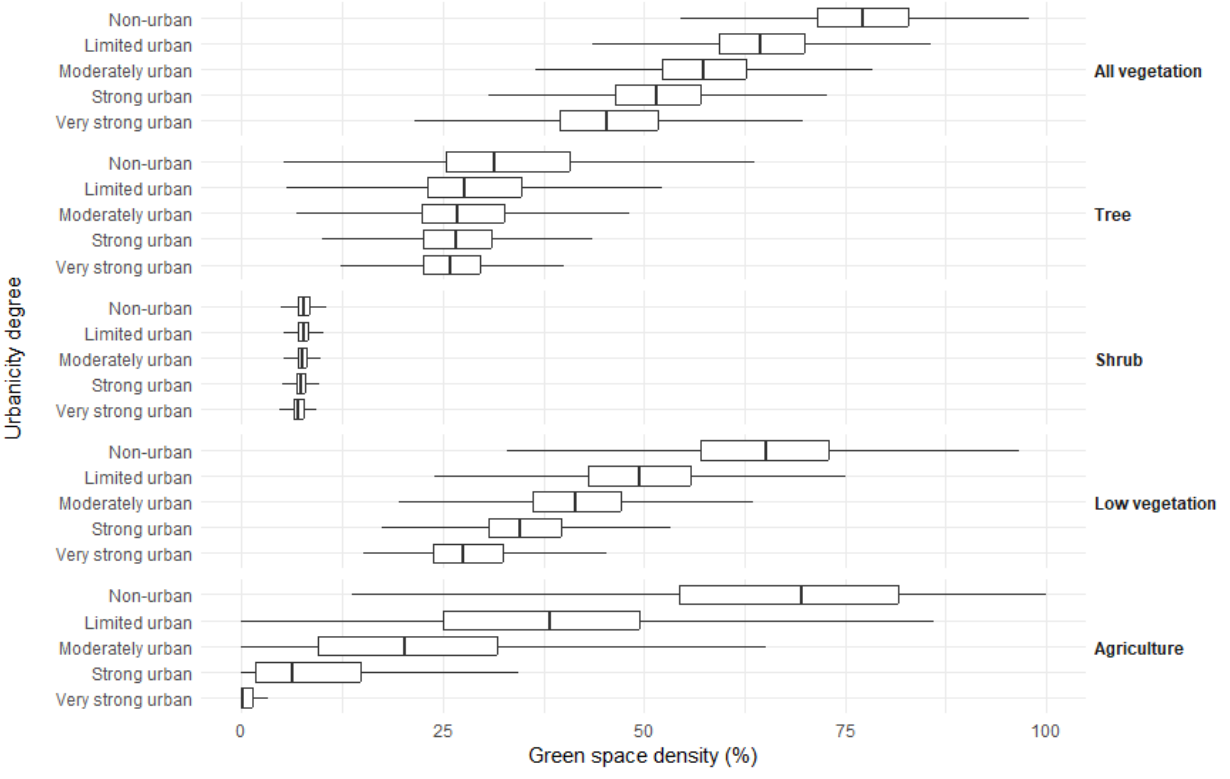

Figure S8. Boxplot of green space density by types and urbanicity degree within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,440,541). Non-urban: <500 addresses/km^2. Limited urban: 500-1000 addresses/km^2. Moderately urban: 1000-1500 addresses/km^2. Strong urban: 1500-2500 addresses/km^2. Very strong urban: ≥2500 addresses/km^2.

Table S1. Socio-demographic and socio-economic differences in the availability of green space within 1000-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,440,620)

Characteristics	%	Median (Quartile 1, Quartile 3) of density in percentage				
		Total green space density	Tree density	Shrubs density	Low vegetation density	Agriculture density
Age groups						
Children (1 to <12 years)	12.85	56.61 (48.64, 66.09)	26.90 (22.65, 32.49)	7.40 (6.83, 8.08)	39.93 (31.87, 51.49)	15.24 (2.01, 40.05)
Adolescents (12 to <18 years)	7.32	58.01 (49.70, 68.07)	27.09 (22.78, 33.02)	7.45 (6.88, 8.13)	41.41 (32.83, 53.48)	19.14 (3.26, 44.48)
Adults (18 to <65 years)	61.36	56.17 (47.94, 66.12)	26.95 (22.90, 32.51)	7.38 (6.82, 8.06)	38.90 (30.93, 50.89)	13.82 (1.36, 39.51)
Older adults (≥65 years)	18.47	57.70 (49.59, 67.72)	27.75 (23.63, 33.66)	7.42 (6.87, 8.11)	39.36 (31.72, 51.12)	16.11 (2.50, 40.87)
Sex						
Males	49.66	56.76 (48.50, 66.80)	27.10 (22.98, 32.79)	7.40 (6.83, 8.08)	39.46 (31.38, 51.52)	15.16 (1.79, 40.85)
Females	50.34	56.55 (48.44, 66.37)	27.11 (23.01, 32.74)	7.40 (6.84, 8.08)	39.13 (31.27, 50.91)	14.50 (1.69, 39.60)
Ethnicity [1]						
Dutch	77.88	58.07 (49.59, 68.31)	27.19 (23.05, 33.03)	7.44 (6.88, 8.11)	41.21 (32.33, 53.49)	19.49 (3.28, 45.06)
Turkish	2.32	49.99 (42.84, 56.96)	26.34 (22.53, 31.18)	6.94 (6.41, 7.61)	33.04 (26.94, 39.27)	2.01 (0.04, 11.60)
Moroccan	2.19	49.95 (43.19, 56.78)	26.28 (22.40, 30.96)	7.12 (6.48, 7.76)	33.23 (27.14, 38.95)	1.81 (0.04, 10.78)
Indonesian	2.12	54.53 (47.43, 62.48)	27.12 (23.06, 32.52)	7.43 (6.86, 8.13)	36.21 (29.82, 45.30)	8.02 (0.53, 26.28)
Household SES [2]						
Quintile 1	19.40	53.41 (45.99, 61.44)	27.13 (23.32, 32.09)	7.22 (6.67, 7.87)	35.15 (28.97, 44.22)	5.93 (0.22, 24.29)
Quintile 2	19.97	56.58 (48.65, 66.29)	27.28 (23.30, 32.72)	7.38 (6.82, 8.05)	39.05 (31.46, 50.71)	14.62 (1.87, 39.49)
Quintile 3	20.25	57.72 (49.52, 67.69)	27.13 (23.01, 32.83)	7.43 (6.87, 8.11)	41.06 (32.62, 53.02)	18.95 (3.20, 44.02)
Quintile 4	20.27	58.51 (49.86, 68.93)	26.94 (22.70, 32.90)	7.47 (6.91, 8.16)	42.44 (33.18, 54.81)	21.79 (3.94, 47.78)
Quintile 5	20.10	57.52 (48.70, 67.97)	26.91 (22.51, 33.19)	7.49 (6.92, 8.19)	40.43 (31.28, 52.52)	17.05 (2.07, 42.61)
Urbanicity degree (addresses/km^2)						
Non-urban (<500)	16.42	77.16 (71.45, 82.76)	31.43 (25.36, 40.71)	7.72 (7.06, 8.47)	65.14 (56.93, 72.88)	69.51 (54.41, 81.53)

Limited urban (500-1000)	16.98	64.43 (59.32, 69.83)	27.73 (23.07, 34.72)	7.62 (7.06, 8.30)	48.50 (43.06, 55.83)	38.24 (25.07, 49.45)
Moderately urban (1000-1500)	19.42	57.35 (52.19, 62.68)	26.74 (22.37, 32.70)	7.47 (6.97, 8.09)	41.43 (36.09, 47.09)	20.17 (9.51, 31.77)
Strong urban (1500-2500)	25.95	51.51 (46.43, 56.93)	26.55 (22.63, 31.04)	7.34 (6.82, 7.96)	34.60 (30.70, 39.73)	6.37 (1.66, 14.76)
Very strong urban (≥2500)	21.23	45.42 (39.58, 51.63)	25.89 (22.63, 29.58)	7.00 (6.48, 7.64)	27.47 (23.77, 32.39)	0.12 (0, 1.35)

[1] A total of 15.49% of the population belongs to other ethnicity groups and is not shown here.

[2] Household socio-economic status (SES) score is developed by Statistics Netherlands based on standardized disposable income, taxable assets, highest level of education, and recent labour participation. A total of 1.80% of the population was missing in SES score.

Table S2. Socio-demographic and socio-economic differences in the availability of green space within 500-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,440,620)

Characteristics	%	Median (Quartile 1, Quartile 3) of density in percentage				
		Total green space density	Tree density	Shrubs density	Low vegetation density	Agriculture density
Age groups						
Children (1 to <12 years)	12.85	50.39 (42.59, 59.60)	24.04 (19.52, 29.38)	7.21 (6.54, 7.96)	33.94 (27.50, 43.88)	4.37 (0.08, 25.06)
Adolescents (12 to <18 years)	7.32	51.64 (43.60, 61.69)	24.23 (19.68, 29.80)	7.30 (6.62, 8.04)	35.00 (28.16, 45.81)	6.68 (0.16, 30.00)
Adults (18 to <65 years)	61.36	50.19 (42.16, 59.79)	24.25 (19.89, 29.54)	7.21 (6.54, 7.95)	33.26 (26.80, 43.31)	3.58 (0.08, 24.75)
Older adults (≥65 years)	18.47	51.51 (43.66, 61.27)	25.13 (20.79, 30.62)	7.26 (6.61, 8.00)	33.32 (27.28, 43.07)	4.54 (0.08, 25.38)
Sex						
Males	49.66	50.67 (42.62, 60.42)	24.38 (19.98, 29.76)	7.23 (6.56, 7.97)	33.62 (27.12, 43.85)	4.29 (0.08, 26.02)
Females	50.34	50.47 (42.56, 59.97)	24.40 (20.02, 29.72)	7.23 (6.56, 7.97)	33.35 (27.03, 43.21)	3.82 (0.08, 24.59)
Ethnicity [1]						
Dutch	77.88	51.56 (43.44, 61.77)	24.41 (20.02, 29.84)	7.29 (6.63, 8.02)	34.63 (27.68, 45.60)	6.69 (0.16, 30.16)
Turkish	2.32	45.09 (37.93, 52.26)	23.99 (19.91, 28.98)	6.65 (6.02, 7.35)	29.38 (24.13, 34.44)	0.08 (0.00, 2.86)
Moroccan	2.19	45.41 (38.45, 52.23)	24.13 (19.98, 28.97)	6.77 (6.08, 7.47)	29.54 (34.35, 34.31)	0.08 (0.00, 2.31)
Indonesian	2.12	49.17 (41.81, 57.28)	24.63 (20.06, 29.82)	7.26 (6.58, 8.03)	31.51 (26.03, 38.80)	0.80 (0.00, 13.37)
Household SES [2]						
Quintile 1	19.40	47.95 (40.55, 55.67)	24.64 (20.55, 29.52)	6.96 (6.31, 7.66)	30.73 (25.36, 37.31)	0.40 (0.00, 10.27)
Quintile 2	19.97	50.28 (42.58, 59.41)	24.57 (20.36, 29.69)	7.18 (6.53, 7.90)	33.08 (27.04, 42.45)	3.66 (0.08, 23.48)
Quintile 3	20.25	51.18 (43.28, 60.93)	24.35 (19.99, 29.65)	7.26 (6.61, 7.99)	34.47 (27.83, 44.89)	6.21 (0.16, 28.72)
Quintile 4	20.27	52.02 (43.66, 62.64)	24.10 (19.60, 29.63)	7.34 (6.67, 8.08)	35.73 (28.30, 47.33)	8.44 (0.16, 33.90)
Quintile 5	20.10	51.74 (43.18, 62.47)	24.09 (19.34, 29.93)	7.42 (6.73, 8.17)	34.70 (27.29, 45.95)	6.04 (0.08, 29.92)
Urbanicity degree (addresses/km^2)						
Non-urban (<500)	16.42	71.18 (62.84, 79.63)	27.40 (21.89, 35.65)	7.60 (6.89, 8.40)	57.43 (47.69, 68.02)	55.86 (37.40, 77.19)

Limited urban (500-1000)	16.98	55.42 (48.83, 62.81)	23.91 (19.55, 29.87)	7.47 (6.86, 8.16)	39.98 (33.80, 47.12)	19.49 (7.64, 33.50)
Moderately urban (1000-1500)	19.42	50.39 (44.03, 57.14)	23.85 (19.19, 29.23)	7.30 (6.69, 8.01)	34.24 (29.16, 40.49)	6.44 (0.55, 18.23)
Strong urban (1500-2500)	25.95	46.26 (40.63, 52.55)	24.13 (19.77, 28.75)	7.12 (6.46, 7.84)	30.11 (26.18, 34.80)	0.40 (0.00, 5.33)
Very strong urban (≥2500)	21.23	41.94 (35.38, 49.49)	23.87 (20.08, 28.14)	6.81 (6.17, 7.50)	25.17 (21.05, 30.27)	0.00 (0.00, 0.16)

[1] A total of 7.84% of the population belongs to other ethnicity groups and is not shown here.

[2] Household socio-economic status (SES) score is developed by Statistics Netherlands based on standardized disposable income, taxable assets, highest level of education, and recent labour participation. A total of 1.80% of the population was missing in SES score.

Table S3. Socio-demographic and socio-economic differences in the availability of green space within 1500-meter Euclidean buffer zones around residential addresses in 2017 in the Netherlands (n=16,440,620)

Characteristics	%	Median (Quartile 1, Quartile 3) of density in percentage				
		Total green space density	Tree density	Shrubs density	Low vegetation density	Agriculture density
Age groups						
Children (1 to <12 years)	12.85	60.61 (52.48, 70.17)	28.88 (24.50, 34.64)	7.53 (6.99, 8.16)	44.37 (34.99, 56.07)	25.23 (6.94, 50.16)
Adolescents (12 to <18 years)	7.32	62.19 (53.68, 71.82)	29.15 (24.62, 35.36)	7.56 (7.02, 8.20)	45.95 (36.02, 57.82)	29.32 (9.15, 53.90)
Adults (18 to <65 years)	61.36	60.14 (51.71, 70.18)	28.89 (24.66, 34.66)	7.51 (6.98, 8.14)	43.30 (33.96, 55.48)	23.51 (5.59, 49.66)
Older adults (≥65 years)	18.47	62.05 (53.63, 71.81)	29.81 (25.29, 36.21)	7.54 (7.01, 8.20)	44.19 (35.09, 56.14)	26.64 (8.36, 51.88)
Sex						
Males	49.66	60.81 (52.32, 70.79)	29.07 (24.74, 35.01)	7.52 (6.98, 8.16)	43.98 (34.51, 56.09)	25.10 (6.56, 50.97)
Females	50.34	60.60 (52.28, 70.46)	29.07 (24.76, 34.96)	7.52 (6.99, 8.16)	43.66 (34.41, 55.63)	24.43 (6.42, 50.01)
Ethnicity [1]						
Dutch	77.88	62.45 (53.69, 72.21)	29.25 (24.82, 35.54)	7.55 (7.02, 8.19)	45.94 (35.80, 58.03)	29.98 (9.51, 54.82)
Turkish	2.32	53.27 (46.26, 59.53)	27.96 (24.23, 32.34)	7.12 (6.67, 7.74)	35.38 (28.94, 43.17)	6.79 (0.75, 20.30)
Moroccan	2.19	53.07 (46.25, 59.61)	27.56 (23.91, 32.13)	7.32 (6.75, 7.95)	35.60 (29.17, 42.94)	6.35 (0.71, 19.76)
Indonesian	2.12	58.08 (51.03, 66.13)	28.88 (24.71, 34.33)	7.56 (7.01, 8.21)	39.89 (32.67, 49.78)	16.28 (3.64, 36.32)
Household SES [2]						
Quintile 1	19.40	57.04 (49.59, 65.75)	28.88 (24.97, 33.82)	7.38 (6.87, 8.01)	38.62 (31.64, 49.32)	13.50 (2.33, 35.95)
Quintile 2	19.97	60.84 (52.60, 70.66)	29.25 (25.00, 34.98)	7.50 (6.98, 8.14)	43.80 (34.76, 55.81)	25.12 (7.06, 50.69)
Quintile 3	20.25	62.10 (53.61, 71.76)	29.16 (24.77, 35.19)	7.55 (7.02, 8.19)	45.82 (36.03, 57.75)	29.66 (9.47, 54.06)
Quintile 4	20.27	62.78 (53.90, 72.60)	29.02 (24.53, 35.39)	7.58 (7.04, 8.22)	47.02 (36.59, 58.95)	31.95 (10.39, 56.72)
Quintile 5	20.10	61.32 (52.41, 71.32)	28.96 (24.40, 35.71)	7.58 (7.04, 8.23)	44.56 (34.25, 56.35)	25.95 (6.63, 51.14)
Urbanicity degree (addresses/km^2)						
Non-urban (<500)	16.42	79.46 (74.41, 84.12)	34.05 (27.29, 43.78)	7.78 (7.14, 8.51)	67.97 (59.52, 74.94)	72.85 (58.67, 83.44)

Limited urban (500-1000)	16.98	69.81 (65.06, 74.33)	30.79 (25.26, 38.54)	7.70 (7.15, 8.37)	55.12 (48.10, 61.98)	50.70 (36.16, 61.52)
Moderately urban (1000-1500)	19.42	62.14 (57.30, 66.97)	29.10 (24.28, 35.06)	7.59 (7.09, 8.16)	46.48 (40.54, 52.30)	31.87 (18.71, 43.45)
Strong urban (1500-2500)	25.95	55.49 (50.82, 60.48)	28.16 (24.32, 32.72)	7.46 (7.00, 8.07)	38.58 (34.04, 44.44)	14.54 (6.70, 25.09)
Very strong urban (≥2500)	21.23	48.43 (43.09, 53.98)	27.31 (24.25, 30.91)	7.19 (6.69, 7.79)	29.88 (25.90, 34.70)	1.31 (0.09, 5.51)

[1] A total of 7.84% of the population belongs to other ethnicity groups and is not shown here.

[2] Household socio-economic status (SES) score is developed by Statistics Netherlands based on standardized disposable income, taxable assets, highest level of education, and recent labour participation. A total of 1.80% of the population was missing in SES score.

CHAPTER 4

Longitudinal associations of air pollution and green space with cardiometabolic risk factor clustering among children in the Netherlands

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Environment International, 2024: 108852

Abstract

Background: This study examines longitudinal associations of air pollution and green space with cardiometabolic risk among children in the Netherlands.

Methods: Three Dutch prospective cohorts with a total of 13,822 participants aged 5 to 17 years were included: (1) the Amsterdam Born Children and their Development (ABCD) study from Amsterdam (n=2,547), (2) the Generation R study from Rotterdam (n=5,431), and (3) the Lifelines study from northern Netherlands (n=5,844). Air pollution ($PM_{2.5}$, PM_{10}, NO_2, and elemental carbon (EC)) and green space exposures (density in multiple Euclidean buffer sizes) from 2006 to 2017 at home address level were used. Cardiometabolic risk factor clustering was assessed by a MetScore, which was derived from a confirmatory factor analysis of six cardiometabolic risk factors to assess the overall risk. Linear regression models with change in Metscore as the dependent variable, adjusted for multiple confounders, were conducted for each cohort separately. Meta-analyses were used to pool cohort-specific estimates.

Results: Exposure to higher levels of NO_2 and EC was significantly associated with increases in MetScore in Lifelines (per SD higher exposure: β_{NO2}=0.006, 95% CI=0.001 to 0.010; β_{EC}=0.008, 95% CI=0.002 to 0.014). In the other two cohort studies, these associations were in the same direction but these were not significant. Higher green space density in 500-meter buffer zones around participants' residential addresses was not significantly associated with decreases of MetScore in all three cohorts. Higher green space density in 2000-meter buffer zones was significantly associated with decreases of MetScore in ABCD and Lifelines (per SD higher green space density: β_{ABCD}=-0.008, 95% CI=-0.013 to -0.003; $\beta_{Lifelines}$=-0.002, 95% CI=-0.003 to -0.00003). The pooled estimates were β_{NO2}=0.003 (95% CI=-0.001 to 0.006) for NO_2, β_{EC}=0.003 (95% CI=-0.001, 0.007) for EC, and $\beta_{500m\ buffer}$=-0.0014 (95% CI=-0.0026 to -0.0001) for green space.

Conclusions: More green space exposure at residence was associated with decreased cardiometabolic risk in children. Exposure to more NO_2 and EC was also associated with

increased cardiometabolic risk.

Introduction

Cardiometabolic risk factors are the largest contributors to the global disease burden [1]. In terms of disability-adjusted life-years, high systolic blood pressure (SBP), high fasting plasma glucose, high Body Mass Index (BMI), and high low-density lipoprotein cholesterol (LDL-C) were among the top 10 risk factors in 2017 [1]. Although cardiometabolic diseases (CMDs) occur most frequently among middle-aged and older adults, cardiometabolic risk factor clustering has been shown to be stable from childhood into adulthood [2], which emphasizes that risk factors in early life have later life consequences [3].

Exposure to environmental characteristics, such as air pollution and green space, may be important factors of cardiometabolic alterations among children [4–7]. Exposure to higher levels of air pollution may negatively impact cardiometabolic health through autonomic nervous system imbalance, pulmonary and systemic inflammation, and oxidative stress [4,5]. Children are suggested to be more vulnerable to the harmful effects of air pollutants than adults, because their immune system is still evolving and because they inhale a higher volume of air pollutants per body weight than adults [8]. On the contrary, green space may improve cardiometabolic health by its restoration and building capacities [6,7]. For restoration, green space relieves psychological stress [7], which is associated with cardiometabolic diseases [9]. For building, green space releases certain chemical agents with cardiometabolic health implications (e.g., phytoncides) [7]. It also has an indirect effect on cardiometabolic health. Specifically, green space can reduce harm from exposure to air pollution, heat, and noise, and can encourage healthy lifestyle like outdoor physical activity [6].

Previous evidence on the associations of air pollution and green space with cardiometabolic risk among children is limited and inconsistent. A nationwide school-based study in Iran investigated the association between air quality and individual

cardiometabolic risk factors, and found significant positive associations for SBP, total cholesterol, and triglycerides (TG) [10]. A study in Spain showed that the distance from home to green spaces was not significantly associated with cardiometabolic risk in primary students [11]. Another study did not provide evidence for beneficial effects of green space or adverse effects of air pollution on cardiometabolic health in Dutch adolescents [12]. These three studies are all based on cross-sectional designs, thus a longitudinal study to provide evidence of a temporal relationship is merited.

Previous studies focused on individual cardiometabolic risk factors or sum of standardized scores (z-scores) [10–12], which are not ideal indicators of overall cardiometabolic risk [13]. An alternative indicator is metabolic syndrome (MetS), which is a standard measure in adults referring to the presence of at least three of the following five conditions: abdominal obesity, high blood pressure (BP), high blood glucose, high serum TG, and low serum high-density lipoprotein (HDL-C) [14]. More than 40 unique definitions of MetS have been identified in literature [15]. However, to date, there is no consensus on whether MetS should be defined in pediatric populations and, if defined, which definition to use [13]. Furthermore, studies found that the diagnosis of MetS is highly unstable and fluctuates throughout childhood [16,17]. Thus its predictive value of future risk is unclear [13].

To address these issues, it has been recommended to focus on cardiometabolic risk clustering, and to use a continuous latent variable of cardiometabolic risk score, such as MetScore [13]. The MetScore as a continuum has been demonstrated to better predict adult risk from early adolescence as compared to MetS or summed z-scores [2,13,18]. To our knowledge, this new approach has not been previously used to analyse the association of air pollution and green space with cardiometabolic risk. The current study aimed to examine the prospective associations of air pollution and green space density with cardiometabolic risk factor clustering among children in the Netherlands. It was hypothesized that higher exposure levels of air pollution and green space are associated with a higher and lower MetScore among children in the Netherlands, respectively.

Methods

Study populations

Data were derived from three Dutch population-based prospective cohort studies: Amsterdam Born Children and their Development (ABCD) study, Generation R study, and Lifelines. All three cohort studies have been described in detail previously [19–21]. The three cohort studies were approved by the Ethical Review Boards of the respective institutions, and written informed consent from participants were obtained by each cohort study.

The ABCD study is a prospective cohort study with the aim to examine the associations of maternal and early-life conditions with children's health [19]. In brief, between January 2003 and March 2004, all pregnant women (n=12,373) in Amsterdam attending their first prenatal visit were invited to participate in the study. Mothers of singleton infants were contacted for follow-up measurements. The current study included data from two follow-up waves when children from this pregnancy were about five (2009) and eleven (2015-2016) years old, respectively.

The Generation R study is a population-based prospective cohort study from early pregnancy onwards in Rotterdam, aiming to identify early environmental and genetic determinants of growth, development and health from foetal life until young adulthood. [20]. All pregnant women living in the study area with a delivery date between April 2002 and January 2006 were invited to participate, resulting in 9,778 mothers and their children enrolled in the study. The current study included data from two follow-up waves when children were about five (2007-2011) and nine (2011-2015) years old, respectively.

The Lifelines study is a multi-disciplinary prospective cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in three northern provinces of the Netherlands (Groningen, Friesland and Drenthe) [21]. It employs a broad range of investigative procedures in assessing the biomedical,

socio-demographic, behavioural, physical, and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The current study included data from baseline (2007-2013) – with children aged 8 to 17 years – and the first follow-up wave (2014-2017).

Combining the three cohorts resulted in a study sample size of 14,097 (ABCD: 2,811; Generation R: 5,431; and Lifelines: 5,855) children aged 5 to 17 years who attended both surveys. Of those participants, 18 (ABCD: 7; and Lifelines: 11) participants were excluded because they had a history of diabetes, hypertension, stroke, heart disease, or disease precocious puberty, and 257 (ABCD: 257) participants were excluded because they used certain medication that may influence the cardiometabolic risk factor levels (medication with ATC codes [22]: B01, C01, H01, H02, J01, D06, H03, and M01). The analytical sample included 13,822 participants (ABCD: 2,547; Generation R: 5,431; and Lifelines: 5,844).

Exposure assessment

Data on air pollution and green space were obtained from the Geoscience and Health Cohort Consortium (GECCO) [23,24]. The environmental exposure data at the home address-level were linked to participants.

Data on annual average outdoor concentrations of particulate matter with diameters <2.5 μm ($PM_{2.5}$) and <10.0 μm (PM_{10}), nitrogen dioxide (NO_2), and elemental carbon (EC) were modeled by the Institute for Public Health and the Environment [25,26]. These data were based on a combination of dispersion and chemical transport model calculations and measurements from National Air Quality monitoring locations. Data were available on 1×1 km resolution from 2006 to 2017 annually, and on 25×25 m resolution from 2013 to 2017 annually. The data in 1×1 km resolution were used to back-extrapolate data in 25×25 m resolution for years before 2013 [27]. We scaled 25×25 m map in 2013 by ratio of the 1×1 km map of the years prior to 2013 to the 1×1 km map in 2013, and assumed this to be applicable to all 25*25 m grids in a 1*1 km grid.

Residential green space exposure was assessed by green space density. This refers to the percentage of area devoted to green space (i.e., parks, public gardens, forests, graveyards, and agriculture) within a Euclidean buffer (radii of 150, 250, 350, 500, 750, 1000, 1650, and 2000 m) around residential addresses. These data were based on the land area coverage statistics from Statistics Netherlands [28], and were available for 2006, 2008, 2010, 2012, and 2015. Applying situational interpretation on all available sources, a minimum lower limit of 1 hectare was used for green space [28]. Both air pollution and green space data were used by averaging over the study period corresponding to each cohort.

Assessment of cardiometabolic risk factors

Assessed cardiometabolic risk factors for deriving the MetScore consisted of total cholesterol, HDL-C, TG, BMI, SBP, and diastolic blood pressure (DBP) (**Figure 1**). The measurement methods for each cohort are described in **Appendix 1**.

Calculation of MetScore

A consistent confirmatory factor analysis (CFA) was conducted in a pooled dataset to derive the MetScore across all cohorts. CFA allows for the testing of hypotheses or theories about the relationships between observed variables and their underlying latent constructs [29]. In the current study, it was used to validate the MetScore, ensuring that MetScore adequately represents the six component cardiometabolic risk factors [29]. BMI was standardized by age and sex using LMS tables (Lambda for the skew, Mu for the median, and Sigma for the generalized coefficient of variation [30]) from a Dutch nationwide growth study [31] and a German cohort study [32], respectively. The SBP and DBP were standardized by age and sex using LMS tables from a reference for Caucasian children [33]. TG was log-transformed because its distribution was skewed. The reciprocal of HDL-C was used when standardizing so that the interpretation of higher factor loading scores is the same with other measures. Subsequently, the z-scores for all CFA components were created.

The goodness of fit indices included the Comparative Fit Index (good fit: CFI, ≥0.90), the

Tucker-Lewis Index (good fit: TLI, ≥0.90), the Root Mean Square Error of Approximation (good fit: RMSEA, ≤0.06), and the Standardized Root Mean Square Residual (good fit: SRMR, <0.08) [34]. The standardized factor loadings were used to calculate the factor score of MetScore for each participant, separately. This score can be interpreted as a z-score, the value is positively correlated with cardiometabolic risk and where zero indicates the population mean.

Covariates

Based on confounders used in previous studies [10,12,35], a directed acyclic graph was created to choose confounders (**Appendix Figure S1**). At two surveys of each cohort, participants' parents provided information about age, sex (male, female), ethnicity (Dutch, Non-western other, Western other), parental education level (low to low-intermediate, high-intermediate, high), maternal smoking during pregnancy (no, <1 a day, ≥1 a day), child screen time (<1 hour a day, 1 to 2 hours a day, >2 hours a day), child leisure time physical activity (<1 hour a week, 1 to 2 hours a week, 2 to 4 hours a week, >4 hours a week), parental marital status (married / live together, divorced / don't live together), and year of birth. The duration between these two surveys was also obtained. Urbanization degree within a Euclidean buffer of 1 km around each address was obtained from GECCO [23,24]. Objectively measured neighborhood socioeconomic status (SES) scores were obtained from the Netherlands Institute for Social Research [36]. These scores are based on the average income, the percentage of residents with a low income, the percentage of residents with a low level of education, and the percentage of unemployed residents in the neighborhood [36]. Higher scores indicate higher area-level SES.

Statistical analysis

Characteristics of the study sample and the area-level exposure measures were presented using descriptive statistics for each cohort, separately. The relative variability between exposures was compared by coefficient of variation, which is calculated by dividing the standard deviation by the mean and then multiplying by 100. The average of environmental exposures across years (air pollution with 25×25 m resolution and

green space density in 500 m, 1000 m, and 2000 m buffers) were calculated and used in longitudinal analyses. Since all three cohorts have two waves of measurements, the change of MetScore between the two waves was used as dependent variable. Linear regression models were conducted for the association between average environmental exposure over time and change of MetScore over time. Models were adjusted for age, sex, ethnicity, baseline MetScore, highest parental education level, maternal smoking during pregnancy, screen time, leisure time physical activity, parental marital status, year of birth, duration between two surveys, neighborhood SES score, and urbanization degree. For sensitivity analyses, mutual confounding between air pollution and green space exposure was further considered in models by adjusting for each other. Air pollution with 1×1 km resolution across all years and green space density in other Euclidean buffer sizes (radii of 150, 250, 350, 750, and 1650m) were also modelled in sensitivity analyses. In all analyses, unit of air pollution and green space were per standard deviation (SD).

Within each cohort, multiple imputation was conducted to deal with missing data. For each variable with missing values, the specified imputation model replaced missing values with values randomly drawn from the predictive distribution of the variable conditional on other observed data. This process created multiple imputed datasets with no missing values that reflected the uncertainty of missing data. All variables in the analytical model were included in the imputation model. We generated twenty imputed datasets that were analysed separately and pooled the estimates based on Rubin's rules [37]. Lastly, random-effect meta-analyses were conducted to synthesize the results from the three cohorts. The I^2 statistic was obtained as a measure of heterogeneity across cohorts. All analyses were performed using R software [38]. Statistical significance was defined as $P < 0.05$ (2-sided).

Results

The characteristics at baseline of the study sample and the area-level exposure measures for each cohort are presented in **Table 1**. The mean ages at baseline were 5.5 ± 0.5 years for ABCD, 6.1 ± 0.5 years for Generation R, and 9.5 ± 2.7 years for Lifelines, respectively. The percentages of male participants were 50.4% for ABCD, 49.9% for Generation R, and 48.6% for Lifelines. Participants in Lifelines were mostly ethnically Dutch (96.6%), while Generation R had more ethnical diversity (Dutch: 58.0%). Participants in ABCD had more children with high parental education level (75.9%) and more parents divorced or not living together (17.4%). Participants in Generation R had more events of maternal smoking during pregnancy. Children in Lifelines had more screen time and underwent more physical activities during leisure time. Participants in ABCD had higher neighborhood SES score. Participants in ABCD and Generation R mostly lived in urban areas while participants in Lifelines mostly lived in rural areas. Participants in Lifelines were generally exposed to less air pollution and more green space at residence. The coefficient of variations ranged from 5.5% to 8.2% for particulate matter, and ranged from 13.9% to 20% for NO_2 and EC. **Appendix Figure S1** shows the Spearman correlations between green space and air pollutants in the three cohorts, respectively. Green space density was moderately, negatively correlated with air pollutants (r=-0.39 to -0.62), expect for particulate matter in Lifelines (r=-0.10 to -0.12).

Table 1. Characteristics of participants by cohorts.

Variables[1]	Cohorts		
	ABCD 2009-2016	Generation R 2007-2015	Lifelines 2007-2017
n	2,547	5,431	5,844
Age at baseline (year)	5.5 ± 0.5	6.1 ± 0.5	9.5 ± 2.7
Male (%)	50.4	49.9	48.6
Ethnicity (%)			
Dutch	73.7	58.0	96.6

Non-western other	13.0	15.2	2.0
Western other	13.4	26.8	1.4
Highest parental education level (%)			
Low to Low-intermediate	7.7	15.2	8.4
High-intermediate	16.5	26.8	41.7
High	75.9	58.1	49.9
Maternal smoking during pregnancy (%)			
No	93.0	73.2	90.4
<1 a day	2.3	4.5	0.9
≥1 a day	4.7	22.4	8.7
Child Screen time (%)			
<1 hour a day	38.1	42.7	15.8
1 to 2 hours a day	46.2	40.1	36.8
>2 hours a day	15.7	17.3	47.5
Child Leisure time physical activity (%)			
<1 hour a week	10.5	5.3	2.5
1 to 2 hours a week	19.4	27.7	3.5
2 to 4 hours a week	33.1	44.1	60.2
>4 hours a week	37.0	22.8	33.9
Parental marital status (%)			
Married / live together	82.6	88.9	93.7
Divorced / don't live together	17.4	11.1	6.3
Neighborhood socio-economic status score[2]	0.6 (-0.5, 1.3)	-0.4 (-1.3, 1.2)	-0.5 (-1.4, 0.2)
Residence density (addresses per km^2)	2,529 (1,566, 5,698)	2,629 (1,604, 4,605)	449 (171, 913)
Urbanicity degree (%)			
Non-urban (<500 addresses per km^2)	4.5	2.8	53.6
Limited urban (500-1000 addresses per km^2)	7.7	7.9	25.4
Moderately urban (1000-1500 addresses per km^2)	10.4	11.5	12.4
Strong urban (1500-2500 addresses per km^2)	26.8	25.0	6.2
Very strong urban (≥2500 addresses per km^2)	50.7	52.8	2.5
Duration between two surveys (years)	6.1 ± 0.5	3.7 ± 0.5	2.9 ± 0.8
Average $PM_{2.5}$ concentration ($\mu g/m^3$)	15.1 ±1.2	15.8 ± 1.3	9.5 ± 0.7
Average PM_{10} concentration ($\mu g/m^3$)	23.4 ± 1.7	24.3 ± 1.7	16.3 ± 0.9
Average NO_2 concentration ($\mu g/m^3$)	25.5 ± 4.5	31.2 ± 4.5	12.2 ± 1.7

Average elemental carbon concentration (μg/m^3)	1.1 ± 0.2	1.3 ± 0.2	0.5 ± 0.1
Average Green space density in 1 km buffer (percentage)[3]	18.8 ± 15.9	16.5 ± 13.7	54.1 ± 26.8
Average Agriculture density in 1 km buffer (percentage)	8.7 ± 16.0	7.4 ± 12.9	46.9 ± 29.2
Baseline MetScore[4]	-0.03 ± 0.06	0.01 ± 0.06	-0.01 ± 0.07
Total cholesterol (mmol/L)	4.0 ± 0.7	4.2 ± 0.6	4.1 ± 0.7
High-density lipoprotein (mmol/L)	1.3 ± 0.3	1.4 ± 0.3	1.6 ± 0.3
Triglyceride (mmol/L)	0.7 ± 0.3	1.0 ± 0.5	0.7 ± 0.4
Body mass index (kg/m^2)	15.5 ± 1.4	16.2 ± 1.9	18.7 ± 3.2
Systolic blood pressure (mmHg)	98.4 ± 8.5	103.3 ± 8.0	106.4 ± 10.8
Diastolic blood pressure (mmHg)	59.1 ± 8.2	61.4 ± 6.7	59.5 ± 6.3
Change of MetScore	0.01 ± 0.06	-0.01 ± 0.05	0.01 ± 0.05

[1] Values are mean ± SD or median (first quartile, third quartile) for continuous variables and % for categorical variables. The values for environmental exposures have been averaged over the study period corresponding to each cohort.

[2] This score is based on the average income, the percentage of residents with a low income, the percentage of residents with a low level of education, and the percentage of unemployed residents in the neighborhood.

[3] Green space are aggregates of parks, public gardens, forests, graveyards, and agriculture.

[4] Cardiometabolic risk factor clustering, derived from a factor analysis of six components: total cholesterol, HDL-C, TG, BMI, SBP, and DBP. All in z-scores.

Figure 1 presents the model fit indices and factor loadings of the CFA model of MetScore. The model fit indices overally showed good fit. All components were significantly contributing to the MetScore. The variance in MetScore was mostly explained by BMI z score (46.9%, the square of the standardized factor loadings).

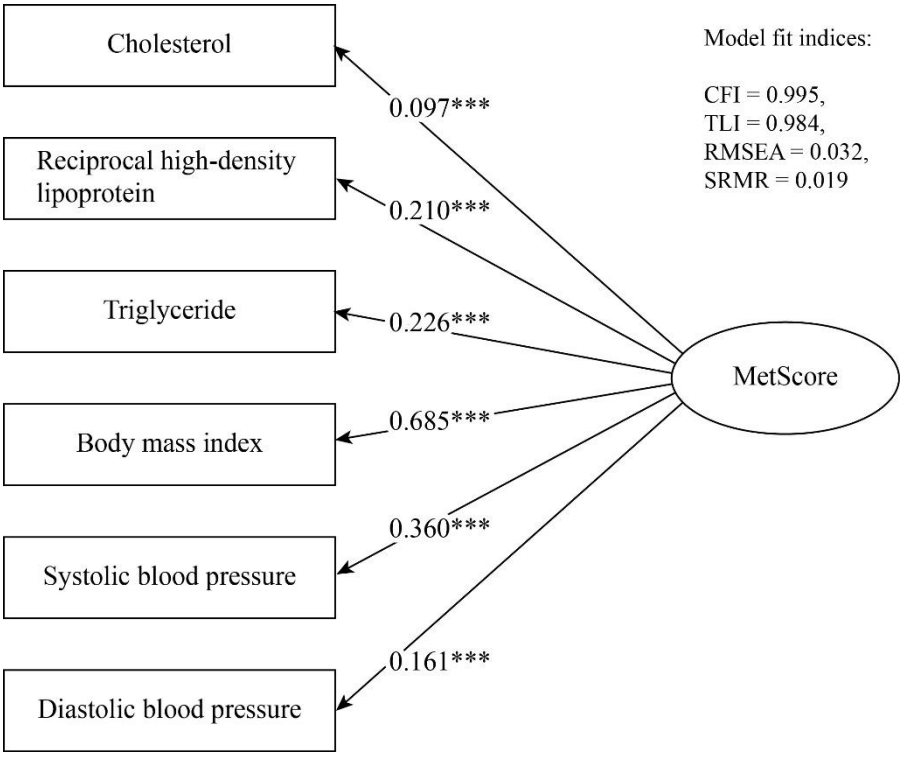

Figure 1. Factor loadings for cardiometabolic risk factor clustering (MetScore), combing data from the first waves of three cohorts: ABCD, Generation R and Lifelines. All components are standardized into z-scores. Abbreviations: CFI= Comparative Fit Index, TLI=Tucker-Lewis Index, RMSEA=Root Mean Square Error of Approximation, SRMR=Standardized Root Mean Square Residual.

The associations of air pollution and green space exposure with change of MetScore for each separate cohort are shown in **Table 2**. There is no multicollinearity problem in the models. After adjusting for multiple confounders, exposures to higher levels of NO_2 and EC were significantly associated with increases of MetScore in Lifelines (per SD higher exposure: β_{NO2}=0.006, 95% CI=0.001 to 0.010; β_{EC} =0.008, 95% CI=0.002 to 0.014). In

ABCD and Generation R, these associations were in the same direction, but these were not statistically significant. The associations of $PM_{2.5}$ and PM_{10} with change of MetScore were not significant in all three cohorts. Higher green space density in 500-meter buffer zones around participants' residential address was significantly associated with decreases of MetScore in ABCD and Lifelines (per SD higher green space: β_{ABCD}=-0.003, 95% CI=-0.011 to 0.005; $\beta_{Lifelines}$=-0.001, 95% CI=-0.003 to 0.00004). All observed associations were not significant in Generation R. In sensitivity analyses, after considering mutual confounding between air pollution and green space, or modeling in another resolution (i.e., 1×1 km) and other buffer sizes (i.e., 150, 250, 350, 750, and 1650 m), models showed similar results (**Appendix Table S1-S3**).

Figure 2 presents the meta-analyses of results from three cohorts. The pooled estimates were 0.003 (95% CI=-0.001 to 0.006; *P*=0.13) for NO_2, 0.003 (95% CI=-0.001, 0.007; *P*=0.13) for EC, and -0.0014 (95% CI=-0.0026 to -0.0001; *P*=0.03) for green space in 500-meter buffer zones. The pooled estimates were marginally significant for green space in other buffer zones, but were not significant for particulate matter.

Table 2. Linear relation between air pollution, green space exposure, and change of cardiometabolic risk factor clustering (MetScore)[1,2]

Exposure	Change of MetScore in ABCD, n=2,547		Change of MetScore in Generation R, n=5,431		Change of MetScore in Lifelines, n=5,844	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
$PM_{2.5}$ concentration	0.0001 (-0.006, 0.006)	0.98	0.001 (-0.001, 0.004)	0.25	-0.0003 (-0.004, 0.003)	0.86
PM_{10} concentration	0.0005 (-0.005, 0.006)	0.86	0.001 (-0.001, 0.003)	0.31	-0.001 (-0.005, 0.002)	0.50
NO_2 concentration	0.003 (-0.003, 0.009)	0.39	0.001 (-0.001, 0.003)	0.43	**0.006 (0.001, 0.010)***	**0.02**
Elemental carbon concentration	0.003 (-0.004, 0.009)	0.42	0.001 (-0.002, 0.004)	0.48	**0.008 (0.002, 0.014)***	**0.01**
Green space density in 500 m buffer	-0.003 (-0.011, 0.005)	0.46	-0.001 (-0.004, 0.002)	0.46	-0.001 (-0.003, 0.00004)	0.06
Green space density in 1000 m buffer	**-0.007 (-0.013, -0.0005)***	**0.04**	-0.001 (-0.004, 0.003)	0.64	-0.001 (-0.003, 0.0002)	0.08
Green space density in 2000 m buffer	**-0.008 (-0.013, -0.003)****	**0.003**	-0.001 (-0.004, 0.002)	0.45	**-0.002 (-0.003, -0.00003)***	**0.048**

[1] Unit of air pollution is per standard deviation (SD) based on data of a resolution of 25×25 m raster. Unit of green space is per SD. The SDs were 1.1, 1.4, 3.6, 0.2, 21.1, 20.6, and 19.0 for $PM_{2.5}$, PM_{10}, NO_2, elemental carbon, and green space in 500 m buffer, 1000 m buffer, and 2000 m buffer, respectively.

[2] Models adjusted for age, sex, ethnicity, baseline MetScore, highest parental education level, maternal smoking during pregnancy, screen time, leisure time physical activity, parental marital status, year of birth, duration between two surveys, neighborhood socioeconomic status score, and residence density.

$^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001

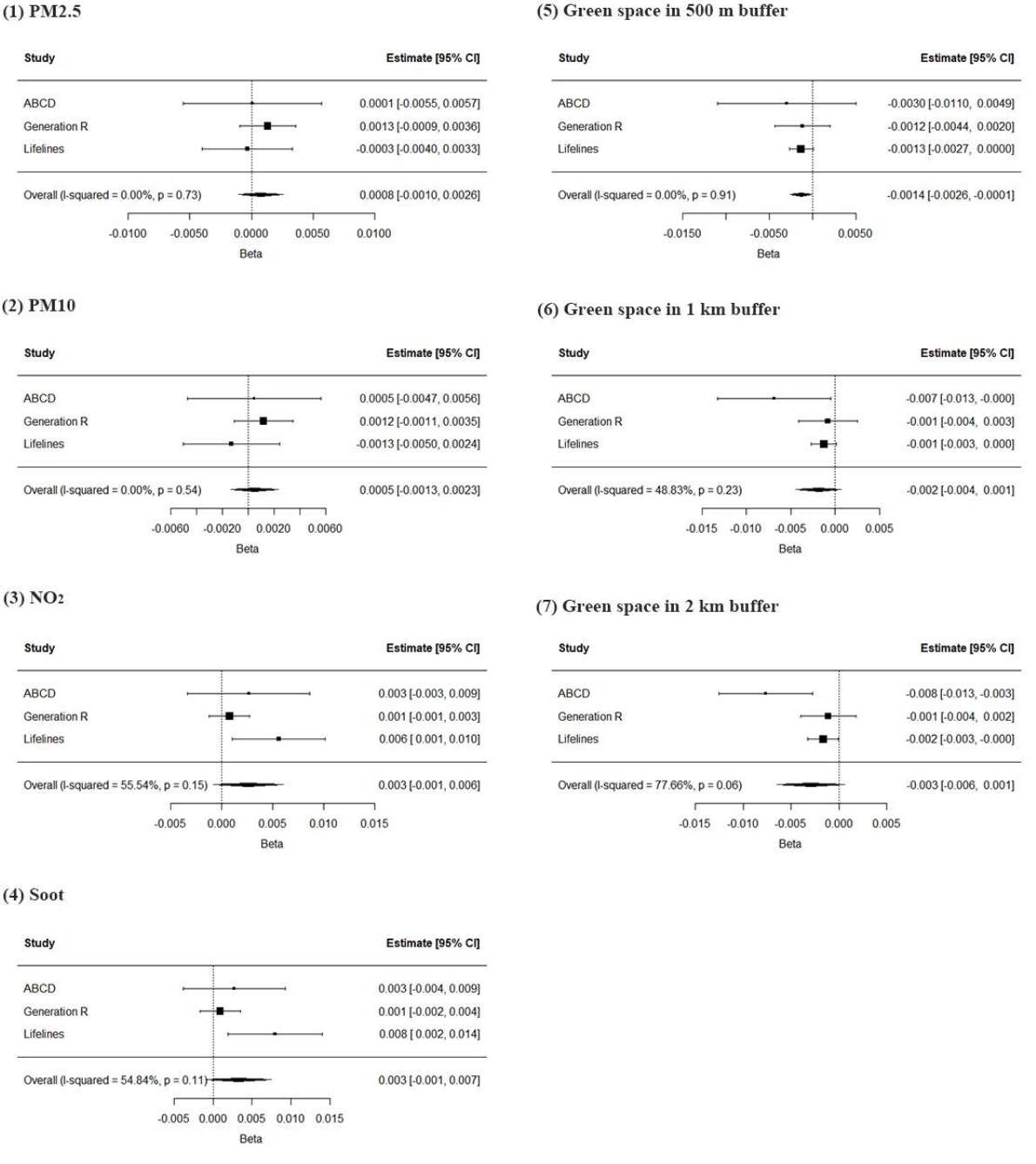

Figure 2. Meta-analyses of linear associations of air pollution and green space exposure with change of cardiometabolic risk factor clustering in children participating in three Dutch cohort studies. Unit of air pollution is per standard deviation (SD) based on data

of a resolution of 25×25 m raster. Unit of green space is per SD. The SDs were 1.1, 1.4, 3.6, 0.2, 21.1, 20.6, and 19.0 for $PM_{2.5}$, PM_{10}, NO_2, elemental carbon, and green space in 500 m buffer, 1000 m buffer, and 2000 m buffer, respectively

Discussion

More green space exposure at residence was associated with decreased cardiometabolic risk as measured by MetScore over time among children. Results for air pollution were inconsistent among pollution indicators. Higher concentrations of NO_2 and EC were associated with increased cardiometabolic risk in Lifelines. The pooled estimates were marginally significant for NO_2 and EC. There was no statistical evidence found for the association of $PM_{2.5}$ and PM_{10} with cardiometabolic risk. Results are robust after considering mutual confounding between air pollution and green space, or modeling in other resolution and buffer sizes.

The current results strengthen the evidence of a protective effect of green space exposure against cardiometabolic risk among children. Several previous studies reported associations between green space exposure and individual cardiometabolic risk factors among children, like lower BMI [39,40] and lower BP [41]. However, to the best of our knowledge, this is the first study that found a significant association for overall cardiometabolic risk. A previous study in The Netherlands did not find an association between green space and overall cardiometabolic risk at ages 12 and 16 years, respectively [12]. Neither a Spanish study in rural areas found an association between distance from children's home to green space and overall risk [11]. Both studies applied a cross-sectional design, and both studies measured the overall risk by summing the z-scores of individual risk factors, which gives equal weight to components. Instead, the current study used a prospective design and derived a MetScore by a CFA of component risk factors, which takes the weight of separate components into account, as recommended [13]. Therefore, the present study expands the current literature and strengthens the evidence base on the association between green space and cardiometabolic risk among children.

For air pollution, there was large heterogeneity among the current study and previous ones. A study in the Netherlands investigated the associations of $PM_{2.5}$, PM_{10}, and NO_2 at residence with overall cardiometabolic risk (summed z-scores), and found no significant results [12]. A national study in the US used residential concentrations of volatile organic compounds as indicator of air pollution and found an elevated overall

risk (summed z-scores) [35]. A study in China investigated the $PM_{2.5}$ constituents at school in relation to MetS and indicated a robust association for EC [42]. All of them were cross-sectional studies among children. The current prospective study found evidence for NO_2 and EC, but not for particulate matter.

Even when using the same exposure and overall risk measures in the current study, there was large heterogeneity among the three cohorts (**Table 1**). For example, Generation R was more ethnically diverse while Lifelines is predominantly Dutch. Children in Generation R were more predisposed to cardiometabolic risk because more mothers smoked during pregnancy. Children in ABCD lived in neighborhoods characterized by a substantially higher SES. Children in Lifelines mostly lived in rural areas, while children in ABCD and Generation R mostly lived in strong urban areas. However, this heterogeneity cannot be addressed by meta-regression since there is a small number of studies. The credibility of the current results from meta-analysis is low. We therefore emphasize to interpret the results of the meta-analyses with caution.

Literature has proposed several mechanisms that green space exposure may decrease cardiometabolic risk. As discussed earlier, green space can release certain chemical agents like phytoncides that directly inhibit inflammation [43], which is associated with cardiometabolic health in the long term. Apart from direct effect, green space may indirectly benefit cardiometabolic health by releasing stress, encouraging physical activity and depositing air pollution [44]. Therefore, air pollution may play a role as a mediator in the association between green space and cardiometabolic risk. It has been recommended in a recent review that primary study should consider interrelationships between these built environment aspects in relation to cardiometabolic risk [45]. The current study included mutual confounding of air pollution and green space in models and found their independent associations with cardiometabolic risk. However, simply adjusting for each other does not address the interrelationship since there could partially be a mediation effect, a moderation effect, or both. Future studies should investigate the mediation and moderation effects, while taking into account the types of green space, because vegetation of different heights may interact with air pollution differently [46].

The current study found an increasing risk for NO_2 and EC, but not for $PM_{2.5}$ and PM_{10}. Statistic description showed that particulate matter exposures had small variation within cohorts while NO_2 and EC exposures had larger variation. This small variation

within cohorts could impede the finding of significant associations. Another potential explanation is that particulate matter comprises a wide range of particles. Some particles may be less associated with cardiometabolic health, but may be more related to allergy and respiratory issues, like pollen and spores [47,48]. Other particles, such as EC, are more strongly associated with cardiometabolic risk [49]. Both NO_2 and EC are primarily produced by combustion processes, particularly in vehicles, power plants, and industrial facilities. EC is generated by the incomplete combustion of carbon-based fuels [50]. In the context of the Netherlands, NO_2 and EC are mostly traffic-related diesel exhaust. Randomized trials showed that their exposures are associated with acute endothelial dysfunction and vasoconstriction in vivo [51,52], which in turn can increase cardiometabolic risk.

Strengths and limitations

The current study has several strengths, including a relatively large sample size as compared to previous studies, use of a longitudinal design and applying a recommended MetScore to assess overall cardiometabolic risk among children. There are also several limitations to consider when interpreting the results. First, there was little variability in the environmental exposures which impede the finding of significance. Second, the exposures were only measured at residence in the current study. The mobility of individuals should be considered in future study including exposures at school and commute [53]. Third, due to data availability across three cohorts, the MetScore was constructed based on an incomplete list of components. Future study should add other components like fasting glucose and HbA1c. Lastly, due to the small number of studies included, heterogeneity cannot be addressed via a meta-regression.

Conclusion

Among children, more green space exposure at residence was associated with decreased cardiometabolic risk over time. Some evidence was found for the association between air pollution and increased cardiometabolic risk. Exposure to higher concentrations of NO_2 and EC was associated with increased cardiometabolic risk in the Lifelines cohort. No evidence was found for $PM_{2.5}$ and PM_{10}, probably due to the small variations in exposures. More research is needed to investigate the longitudinal effect of air pollution and green space on cardiometabolic risk among children; this should involve application of the MetScore and consideration of the interrelationship between exposure measures.

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CHAPTER 4 Appendices

Appendix 1. **Assessment of cardiometabolic risk factors in each cohort**

The ABCD study used a Leicester portable height measure (Seca, Hamburg, Germany) and a Marsden weighing scale (Model MS-4102, Rotherham, United Kingdom) to measure height and weight, respectively. WC was measured with a non-elastic measuring tape (Seca, Hamburg, Germany). BP was measured twice using an Omron 705 IT device (Omron Healthcare Inc, Bannockburn, IL, USA) in the supine position. If the two measurements differed >10 mm Hg, a third assessment was performed [1]. At ages 5 to 6 years, the overnight fasting blood samples were collected by the Lab Anywhere kit (Haarlem, The Netherlands) and analysed in the Regional Laboratory of Amsterdam. At ages 11 to 12 years, capillary blood was collected by finger puncture after 3 h fasting and analysed by the point-of-care analyser Alere Cholestech LDX machine using Lipid Profile and GLU cassettes (Cholestech Alere Health Hayward, CA, USA) [2].

The Generation R study used standardized procedures to measure height and weight: underwear only and barefooted standing position. BP was measured at the right brachial artery, four times with one-minute intervals, using the validated automatic sphygmanometer Datascope Accutor Plus TM (Paramus, NJ). The mean values for systolic and diastolic BP were calculated using the last three blood pressure measurements of each participant. Thirty-minutes fasting blood sample was analysed using the Cobas 8000 analyzer (Roche, Almere, The Netherlands) [3].

The Lifelines used a SECA 222 stadiometer and a SECA 761 scale to measure height and weight, respectively, without shoes and heavy clothing. BP was measured ten times during 10min with Dynamap, PRO 100V2. The fasting blood sample was collected and transported to the central LifeLines laboratory in Groningen for analyses [4]. For all cohorts, BMI was calculated, and the mean value of BP measurements was used.

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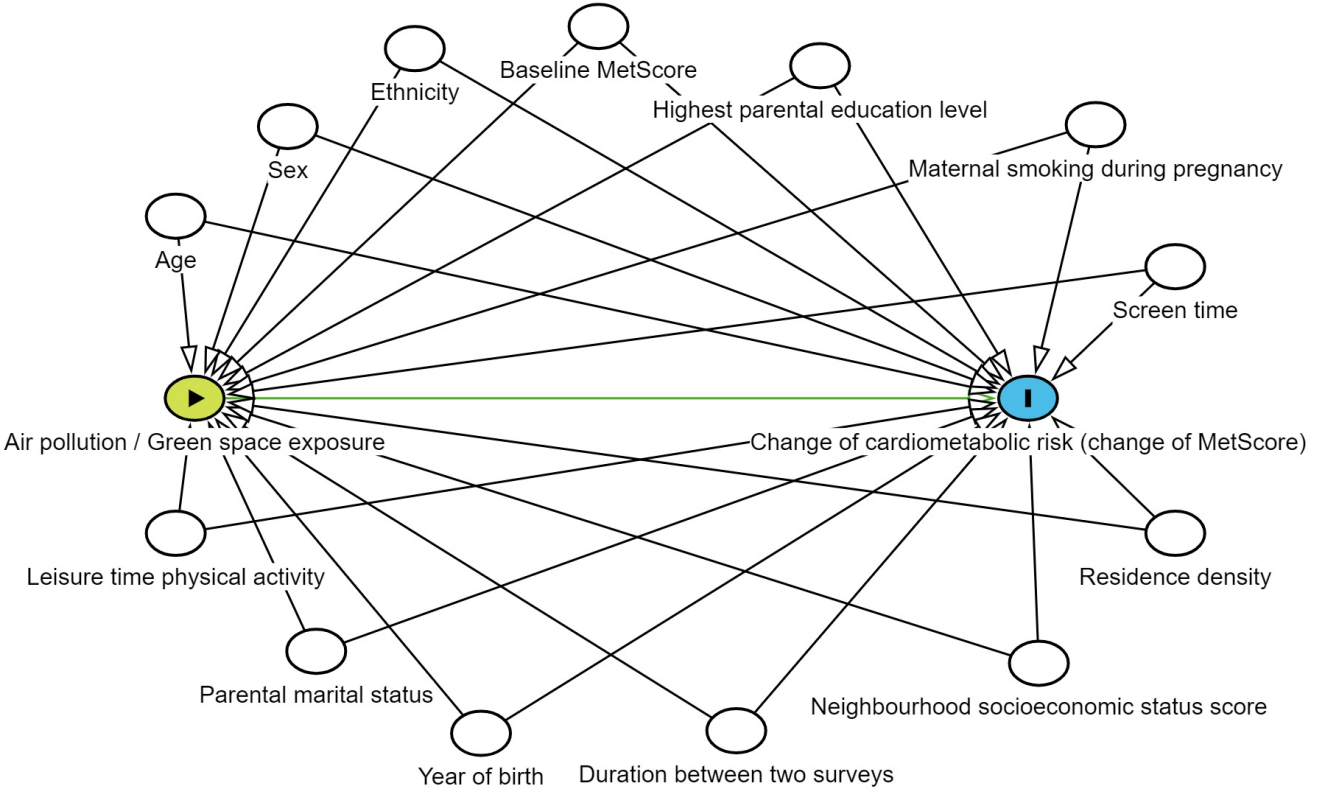

Figure S1. Directed acyclic graph of the association between air pollution / green space exposure and change of cardiometabolic risk.

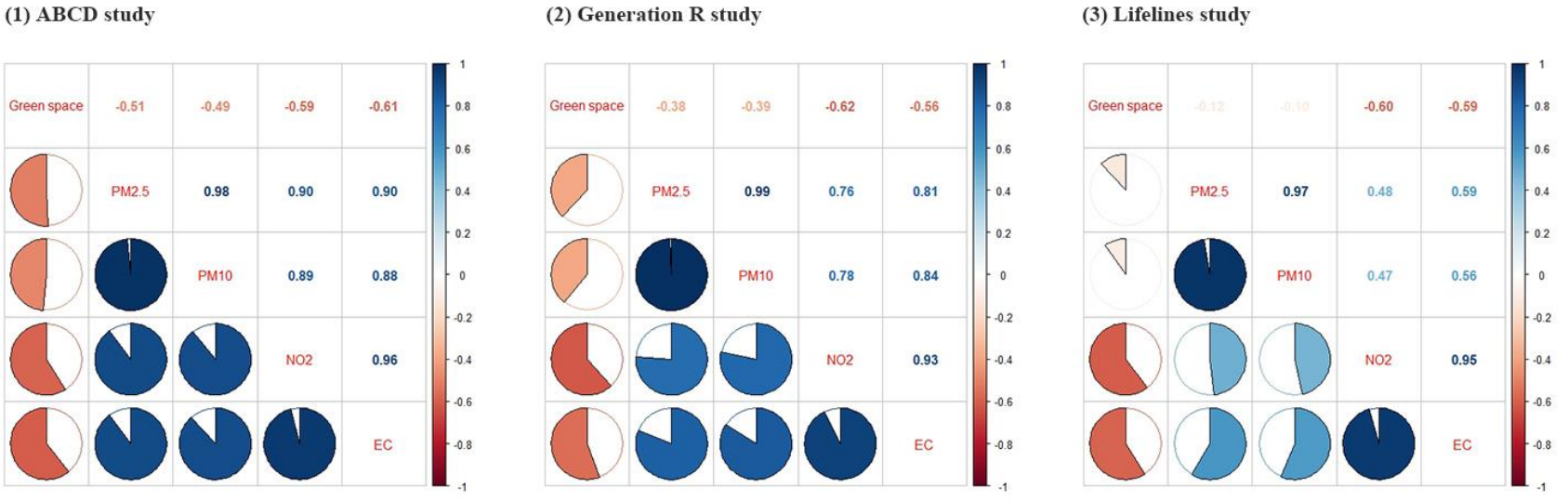

Figure S2. Correlation matrix of environmental exposures of children participating in three Dutch cohort studies. Green space was measured by the percentage of area devoted to green space within a Euclidean buffer of 1000 m around residential addresses. $PM_{2.5}$, PM_{10}, NO_2, and elemental carbon (EC) were based on data of a resolution of 25*25 m raster.

Table S1. Linear relation between air pollution, green space exposure (mutual confounded), and change of cardiometabolic risk factor clustering (MetScore)[1,2]

Exposure	Change of MetScore in ABCD, n=2,547		Change of MetScore in Generation R, n=5,431		Change of MetScore in Lifelines, n=5,844	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
$PM_{2.5}$ concentration	-0.001 (-0.007, 0.005)	0.76	0.0002 (-0.003, 0.003)	0.91	-0.001 (-0.004, 0.003)	0.71
PM_{10} concentration	-0.0003 (-0.006, 0.005)	0.90	0.0001 (-0.003, 0.003)	0.92	-0.002 (-0.005, 0.002)	0.41
NO_2 concentration	0.001 (-0.005, 0.007)	0.72	0.001 (-0.001, 0.004)	0.37	0.006 (0.00001, 0.011)	0.05
Soot concentration	0.001 (-0.006, 0.008)	0.82	0.001 (-0.003, 0.004)	0.74	**0.008 (0.001, 0.015)***	**0.03**
Green space density in 500 m buffer	-0.003 (-0.011, 0.005)	0.46	-0.0004 (-0.004, 0.003)	0.85	-0.001 (-0.003, 0.00001)	0.05
Green space density in 1000 m buffer	**-0.007 (-0.014, -0.0005)***	**0.04**	0.001 (-0.003, 0.005)	0.59	-0.001 (-0.003, 0.0001)	0.07
Green space density in 2000 m buffer	**-0.008 (-0.013, -0.003)****	**0.002**	-0.0005 (-0.004, 0.003)	0.77	**-0.002 (-0.003, -0.0001)***	**0.04**

[1] Unit of air pollution is per SD based on data of a resolution of 25×25 m raster. Unit of green space is per SD. The SDs were 1.1, 1.4, 3.6, 0.2, 21.1, 20.6, and 19.0 for $PM_{2.5}$, PM_{10}, NO_2, elemental carbon, and green space in 500 m buffer, 1000 m buffer, and 2000 m buffer, respectively.

[2] Models adjusted for age, sex, ethnicity, baseline MetScore, highest parental education level, maternal smoking during pregnancy, screen time, leisure time physical activity, parental marital status, year of birth, duration between two surveys, neighborhood socioeconomic status score, and urbanicity degree. Models of air pollution additionally adjusted for green space density in 1000 m buffer. Models for green space additionally adjusted for $PM_{2.5}$ concentration.

$^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001

Table S2. Linear relation between air pollution, green space exposure, and change of cardiometabolic risk factor clustering (MetScore)[1,2]

Exposure	Change of MetScore in ABCD, n=2,547		Change of MetScore in Generation R, n=5,431		Change of MetScore in Lifelines, n=5,844	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
$PM_{2.5}$ concentration	0.001 (-0.006, 0.007)	0.80	0.001 (-0.001, 0.003)	0.22	-0.0003 (-0.004, 0.003)	0.88
PM_{10} concentration	0.002 (-0.005, 0.008)	0.66	0.001 (-0.001, 0.003)	0.22	-0.001 (-0.005, 0.002)	0.52
NO_2 concentration	0.002 (-0.004, 0.009)	0.43	0.001 (-0.001, 0.003)	0.29	**0.006 (0.001, 0.010)***	**0.01**
Soot concentration	0.002 (-0.004, 0.007)	0.51	0.001 (-0.001, 0.002)	0.31	**0.008 (0.002, 0.014)***	**0.01**
Green space density in 150 m buffer	-0.002 (-0.009, 0.005)	0.55	-0.002 (-0.005, 0.001)	0.17	-0.001 (-0.002, 0.0004)	0.16
Green space density in 250 m buffer	-0.001 (-0.008, 0.006)	0.70	-0.002 (-0.005, 0.001)	0.21	-0.001 (-0.003, 0.00003)	0.06
Green space density in 350 m buffer	-0.002 (-0.009, 0.006)	0.70	-0.002 (-0.005, 0.001)	0.25	**-0.001 (-0.003, -0.00004)***	**0.04**
Green space density in 750 m buffer	-0.005 (-0.013, 0.002)	0.19	-0.001 (-0.004, 0.002)	0.54	-0.001 (-0.003, 0.0002)	0.08
Green space density in 1650 m buffer	**-0.008 (-0.013, -0.003)****	**0.004**	-0.001 (-0.004, 0.002)	0.58	-0.001 (-0.003, 0.0001)	0.07

[1] Unit of air pollution is per SD based on data of a resolution of 1000 m raster. Unit of green space is per SD. The SDs were 1.0, 1.4, 3.7, 0.2, 21.9, 21.9, 21.3, 20.8, and 19.7 for $PM_{2.5}$, PM_{10}, NO_2, elemental carbon, and green space in 150 m buffer, 250 m buffer, 350 m buffer, 750 m buffer, and 1650 m buffer respectively.

[2] Models adjusted for age, sex, ethnicity, baseline MetScore, highest parental education level, maternal smoking during pregnancy, screen time, leisure time physical activity, parental marital status, year of birth, duration between two surveys, neighborhood socioeconomic status score, and residence density.

$^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001

Table S3. Linear relation between air pollution, green space exposure (mutual confounded), and change of cardiometabolic risk factor clustering (MetScore)[1,2]

Exposure	Change of MetScore in ABCD, n=2,547		Change of MetScore in Generation R, n=5,431		Change of MetScore in Lifelines, n=5,844	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
$PM_{2.5}$ concentration	-0.0005 (-0.007, 0.006)	0.89	0.0003 (-0.002, 0.003)	0.77	-0.001 (-0.004, 0.003)	0.73
PM_{10} concentration	0.0001 (-0.007, 0.007)	0.97	0.0005 (-0.002, 0.003)	0.73	-0.002 (-0.005, 0.002)	0.42
NO_2 concentration	0.001 (-0.006, 0.007)	0.85	0.002 (-0.001, 0.004)	0.14	**0.006 (0.0004, 0.011)***	**0.04**
Soot concentration	0.0001 (-0.006, 0.006)	0.98	0.001 (-0.001, 0.003)	0.33	**0.008 (0.002, 0.015)***	**0.02**
Green space density in 150 m buffer	-0.002 (-0.009, 0.005)	0.56	-0.001 (-0.004, 0.003)	0.61	-0.001 (-0.002, 0.0004)	0.16
Green space density in 250 m buffer	-0.001 (-0.008, 0.006)	0.72	-0.001 (-0.004, 0.003)	0.78	-0.001 (-0.003, 0.00002)	0.06
Green space density in 350 m buffer	-0.001 (-0.009, 0.006)	0.72	-0.001 (-0.004, 0.003)	0.66	**-0.001 (-0.003, -0.0001)***	**0.04**
Green space density in 750 m buffer	-0.005 (-0.013, 0.003)	0.20	0.001 (-0.003, 0.005)	0.60	-0.001 (-0.003, 0.0001)	0.07
Green space density in 1650 m buffer	**-0.008 (-0.014, -0.003)****	**0.003**	-0.00001 (-0.004, 0.004)	1.00	-0.001 (-0.003, 0.00004)	0.06

[1] Unit of air pollution is per SD based on data of a resolution of 1000 m raster. Unit of green space is per SD. The SDs were 1.0, 1.4, 3.7, 0.2, 21.9, 21.9, 21.3, 20.8, and 19.7 for $PM_{2.5}$, PM_{10}, NO_2, elemental carbon, and green space in 150 m buffer, 250 m buffer, 350 m buffer, 750 m buffer, and 1650 m buffer respectively.

[2] Models adjusted for age, sex, ethnicity, baseline MetScore, highest parental education level, maternal smoking during pregnancy, screen time, leisure time physical activity, parental marital status, year of birth, duration between two surveys, neighbourhood socioeconomic status score, and urbanicity degree. Models of air pollution additionally adjusted for green space density in 1000 m buffer. Models for green space additionally adjusted for $PM_{2.5}$ concentration.

$^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001

CHAPTER 5

Changes in neighbourhood walkability and incident CVD: a population-based cohort study of three million adults covering 24 years

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Abstract

Objectives: To investigate the relationship between changes in residential neighbourhood walkability and cardiovascular disease (CVD) incidence in adults.

Background: To investigate the relationship between changes in residential neighbourhood walkability and cardiovascular disease (CVD) incidence in adults.

Methods: Using data from Statistics Netherlands we included all Dutch residents aged 40 or older at baseline (2009), without a history of CVD, and who did not move house after baseline (n = 3,019,069). A nationwide, objectively measured walkability index was calculated for Euclidean buffers of 500m around residential addresses for the years 1996, 2000, 2003, 2006 and 2008. To identify changes in neighbourhood walkability, latent class trajectory modelling was applied. Incident CVD between 2009 and 2019 was assessed using the Dutch Hospital Discharge Register and the National Cause of Death Register. Cox proportional hazards modelling was used to analyse associations between walkability trajectories and subsequent CVD incidence, adjusted for individual- and area-level sociodemographic characteristics.

Findings: We observed a stable but relatively low walkability trajectory (Stable low, 91.1 %), a stable but relatively higher walkability trajectory (Stable high, 0.6%), a relatively higher initial neighbourhood walkability which decreased over time (Decreasing, 1.7%), and relatively lower neighbourhood walkability which increased over time (Increasing, 6.5%). Compared to stable high walkability, individuals exposed to stable low, and increasing walkability, had a 5.1% (HR: 1.051; CI: 1.011 to 1.093) and 4.9% (HR: 1.049; CI: 1.008 to 1.092) higher risk of any CVD. Similar associations were observed for coronary heart disease and stroke, though not statistically significant. No significant associations were found for heart failure, and CVD mortality.

Conclusion: Adults exposed to low walkability over time had a higher risk of CVD compared to those in stable high walkability neighborhoods. Additionally, an increasing walkability trend was associated with higher CVD risk, likely due to the

overall lower cumulative walkability during the exposure period. These findings highlight the importance of longitudinal research in this field, and of long-term urban planning for cardiovascular health.

What is already known on this topic

- In recent years, the concept of neighbourhood walkability has shown to be a potential upstream determinant of cardiovascular disease.
- However, the evidence of the relation between walkability and CVD is still thin, and largely relies on cross-sectional studies.
- Studies also largely evaluated static walkability levels and did not account for changes in neighbourhood walkability over time.

What this study adds

- In our nationwide study among three million Dutch adults aged 40+, four distinct trajectories of changes in neighbourhood walkability over 13 years were observed.
- Cox regression models suggests that exposure to stable low walkability, as well as increasing walkability, was associated with an approximate five percent higher risk of any CVD compared to stable high walkability.
- Associations were more evident in middle aged compared to older adults, and urban compared to rural residents.

Introduction

Cardiovascular diseases (CVD) are a major public health concern, contributing substantially to the overall disease burden and rising healthcare expenses.[1,2] The worldwide prevalence of CVD has almost doubled from 271 million in 1990 to 523 million in 2019, and the economic impact is expected to rise from $863 billion in 2010 to around $1,044 billion by 2030.[1] It is therefore important to deepen our understanding of the determinants of CVD and develop sustainable strategies for wide-reaching prevention.

Low levels of physical activity (PA) and prolonged sedentary behaviour are established risk factors for CVD.[1,3] More than 25% of adults worldwide do not meet the recommended guideline of 150 minutes of moderate-intensity PA per week.[4] In the Netherlands, this comprises even more than half of all adults.[5] Efforts to increase activity levels are required. Active transportation such as commute walking or cycling may offer a practical means to incorporate PA into daily life and promote cardiovascular health. This is recently substantiated by a large meta-analysis which demonstrates that a higher daily step count is associated with a lower risk of CVD mortality.[6]

To encourage active transportation, it is important to recognise that the built environment plays a crucial role in shaping individuals' activity patterns. Currently, one third of all car trips are under five kilometres, [7] and neighbourhoods designed to be walkable may facilitate residents to choose active transportation rather than sedentary modes of travel (i.e. driving).[8-11] In recent years, the concept of neighbourhood walkability gained interest as a potential upstream determinant of cardiovascular health.[12] Neighbourhood walkability may be defined as a composite measure of built environment characteristics that facilitate walking. Walkability indices often include components such as land use mix, population density, and street connectivity.[13] Higher neighbourhood walkability levels have been linked to higher levels of walking and other forms of PA.[14,15] Higher neighbourhood walkability has also been linked to lower body mass index and lower blood pressure levels,[16,17] and an overall improved cardiovascular

risk profile.[18,19] A systematic review found strong evidence for longitudinal relationships between neighbourhood walkability and obesity, hypertension, and type 2 diabetes.[20] One large longitudinal study in Canada observed that living in the most walkable neighbourhoods compared to living in the least walkable neighbourhoods was associated with a reduction in CVD mortality.[21]

However, the evidence of the relation between walkability and CVD is still thin, and largely relies on cross-sectional studies. An umbrella review indicated that prospective designs in this field of research are still lacking.[22] Furthermore, longitudinal studies should not only focus on changes in the outcome (i.e. CVD incidence over the years), but should also regard changes in exposures. Built environmental factors can change over time,[23,24] and exposures also change due to residential relocation.[25] For example, a study conducted in Australia points to a potential link between increases in walkability aspects (street connectivity, residential density, and land-use mix) and a higher likelihood of walking for transport.[26] Studies that try to capture changes in walkability and their association with health outcomes are scarce. This dynamic aspect is relevant for urban planners and policymakers to assess the potential of policies regarding neighbourhood walkability. CVD typically exhibits a long latency period, during which the effects of environmental exposures may gradually manifest as clinical outcomes.[27] It has been recommended to apply longitudinal approaches to evaluate environmental changes that precede individual behaviour and/or health changes. Moreover, to examine the potentially long latency period between initial exposure to a walkable environment and CVD.[27]

Therefore, this study examines whether changes in residential neighbourhood walkability from 1996 to 2008 are associated with subsequent incidence of CVDs from 2009 to 2019 in adults. First, we use latent class trajectory modelling to identify trajectories of neighbourhood walkability over time. Second, we assess whether different trajectories are associated with CVD incidence.

Methods

Study population

We used national register data from Statistics Netherlands (Centraal Bureau voor de Statistiek, CBS in Dutch) covering yearly data for a time period of 24 years from 1996 through 2019. The study cohort was built by combining four national registers from CBS, including the Population Register,[28] the Hospital Discharge Register,[29] the National Cause of Death Register,[30] and the system of social statistical datasets.[31] The Population Register is based on municipal records which provide demographic information (e.g. date of birth, sex, and residential address) for every registered resident in the Netherlands.[28] The Dutch Hospital Discharge Register contains data on the cause of admission from all hospitals in the Netherlands. The administrative Landelijke Medische Registratie "national medical registration" (LMR) data are recorded by the hospital administration at each admission. Upon discharge, the medical data are completed by or on behalf of the medical specialist on the discharge form. These data are then coded and registered in the LMR by the hospital's medical administration. The hospitals provide the LMR data to the registrar, who performs checks. Subsequently, Statistics Netherlands receives the final annual LMR files from Dutch Hospital Data. Hospital admission data included inpatient hospital care, day care and observations (≥ 4 h). Admission causes are classified according to the 9th and 10th revision of the International Classification of Diseases (ICD-9 and ICD-10). For all admissions up to and including 2013 ICD-9 was used for disease classification, and for all admissions after 2013, ICD-10 was used. The National Cause of Death Register receives information on cause and date of all deceased persons in the Netherlands from the legal reporting system. Til 2012, each death, inside or outside a hospital, a physician issues the death certificate including a cause of death according to ICD-10.[30] From 2012 onwards, an automatic coding of mortality statistics was used.

For this study, the exposure period in which walkability trajectories were defined is from 1996 to 2008 and the outcome follow-up is from 2009 to 2019. Residents were included if they (1) lived at a residential address from 1996 to 2019 or until the first CVD event;

(2) were alive at baseline (2009); (3) were 40 years or older at baseline; and (4) had no recorded history of CVD before baseline, defined as no hospital admission for CVD between 1st January 1996 to 31st December 2008. We excluded residents if they (1) had individual records affiliating to institutional addresses; and (2) moved house after baseline. Individuals were considered to have moved if they changed an address and did not change back to the same address for more than 92 days. All data linkages and analyses were conducted in line with the policy from CBS and privacy legislation in the Netherlands. Ethical approval was not required for the present study.

Exposure measure: walkability index

To assess neighbourhood walkability, we used an objectively measured nationwide walkability index. The development of this index has been described in detail elsewhere.[32,33] Briefly, the Dutch walkability index consists of seven components: population density, retail and service density, land use mix, intersection density, green space density, sidewalk density, and public transport density. Since public transport density was only available from 2015 onwards, it was not included in the longitudinal index used in this study. **Appendix Table S1** presents details on individual components and original data sources. All geographical data for the components of the walkability index were centralised, operationalised, and provided by the Geoscience and Health Cohort Consortium (GECCO).[34,35] For each of the six components, we calculated z-scores based on the mean and standard deviation (SD) over all addresses in the Netherlands. The walkability index was then calculated as the average of the six individual components. We rescaled the index score to range from 0 to 100, such that higher scores indicate higher walkability. The index and its six components were calculated for Euclidean buffers of 500m around each participants' residential address for the years that exposure data were available (1996, 2000, 2003, 2006, and 2008).

Outcome: Incident CVD

Incident CVD was obtained from the Dutch Hospital Discharge Register and the National Cause of Death Register.[29,30] We collected the primary and secondary causes of hospital admission, the date of hospital admission, as well as the cause and date of death. The

ICD codes used for CVD are provided in **Appendix Table S2**. Incidence of CVD was defined as the first hospital admission due to any CVD, or out of hospital death due to any CVD, whichever came first. We also assessed the incidence of specific CVD events including hospital admission or death due to coronary heart disease (CHD), stroke, or heart failure (HF). Other specific CVD events like rheumatic heart disease and pulmonary heart disease were not considered independently in the current study.

Covariates

Individual- and area-level sociodemographic characteristics were obtained from CBS using the population register (i.e., biological sex, date of birth, ethnicity, partner status), the system of social statistical datasets (household income); and CBS geospatial data (neighbourhood urbanisation levels). We determined age in years at baseline using the date of birth. We included age as a continuous variable in the main analysis and as a dichotomous variable (40-60 years and ≥60 years) for stratified analyses. Ethnicity was categorised into 1) Native Dutch, 2) Non-Dutch Western and 3) Non-Dutch non-western. Change in partner status in exposure period was categorized into remained with partner (married or registered partnership), remained without partner (single, separated or widowed), partner to no partner, and no partner to partner. Urbanicity at baseline was categorised as rural (≤ 1000 addresses/km^2), urban (1000–2500 addresses/km^2) and very urban (≥2500 addresses/km^2). Standardised household income was derived as an indicator of individual-level socio-economic status (SES). The tertiles of the mean value of household income over the exposure years were used. Area-level SES scores and air pollution data on annual average outdoor concentrations of particulate matter with diameters <2.5μm ($PM_{2.5}$) and <10.0μm (PM_{10}), and nitrogen dioxide (NO_2) in $\mu g/m^3$ at the residential address-level were obtained from GECCO.[34,35] Objectively measured area-level SES score is a composite indicator consisting of neighbourhood-average education, income and position in the labour market.[36,37] Higher scores indicate a higher area-level SES. Air pollution was derived based on a combination of model calculations and measurements from official measurement locations.[38] Air pollution data with a resolution of 25 × 25 meter were linked to all residential addresses in the

Netherlands.[34,35]

Statistical analysis

To assess changes in individual exposure to walkability from 1996 to 2008, we applied latent class trajectory modelling. The output trajectory classes are subpopulations that share similar patterns of walkability exposure over time. We used the Guidelines for Reporting on Latent Trajectory Studies as a guidance to construct and interpret the latent class trajectory modelling.[39] In order to find the model that best described the data, we fitted latent class growth models with fixed class-specific intercepts and slopes, as well as more flexible growth mixture models (GMM) with (1) a random class-specific intercept and fixed slope per class and (2) random class-specific intercepts and slopes.

First, one-class latent growth models with linear and quadratic growth parameters were compared to examine which approach best captured the trajectories' growth. Subsequently, we estimated GMM models with increasing number of classes. The optimal model was selected based on a combination of statistical criteria, parsimony and interpretability.[40,41] Several model fit indices were used, including (1) the model with the lowest Akaike information criterion (AIC) and lowest Bayesian Information Criterion (BIC) value was favoured; (2) the entropy of the model, with high entropy (>0.80) indicating strong distinctive capabilities between trajectory classes; and (3) the average posterior probability for each class. The interpretability of the trajectory shape and the number of participants in each class were also taken into consideration.

The large sample size of our cohort resulted in computational limitations. Therefore, we performed the latent class trajectory modelling on a random five percent subset (n=178,517) of the full data. After selecting the final model, we extrapolated the results to the complete cohort by using a function that calculates the posterior classification and posterior individual class-membership probabilities, based on the observed data and the estimated model parameters.

We summarised the baseline characteristics as mean ± standard deviation (SD) or

median and interquartile range (IQR) as appropriate for continuous variables, and N with percentage for categorical variables; for the total sample and also by walkability trajectories. For our main analyses, Cox proportional hazards modelling was used to estimate the association between the neighbourhood walkability trajectories and incidence of CVD, as well as CVD mortality, and separate for CHD, stroke, and HF, respectively. Person-time for each individual was calculated from baseline until the first hospital admission due to any CVD, or death due to any CVD, death due to other causes, or end-of-study date, whichever came first. We reported hazard ratios (HR) and 95% confidence intervals (CI) for each neighbourhood walkability trajectory after adjusting for age at baseline, sex, ethnicity, change of partner status, average household income, baseline area-level socio-economic status, mean air pollution concentration during follow-up, urbanicity, and residential relocation. We also stratified primary analyses by sex (males and females), age group (middle aged (40 to 60 years) and older adults (≥60 years)), rural (< 1000 addresses/km^2) and urban areas (≥ 1000 addresses/km^2)), residential relocation at exposure period (movers and non-movers), household income (above and below yearly average income (€ 24421.53), and area-level SES (above and below average area-level SES score). Statistical significance is defined as *p*-value < 0.05 (two-sided) and a false discovery rate correction of multiple testing was applied. Statistical analysis were carried out using R 4.2.3.[42] The trajectory modelling was performed with the *lcmm* package.[43]

Results

Of 3,064,179 individuals who met the inclusion criteria and had walkability data, we additionally excluded 45,110 (1.5%) individuals who had one or more missing covariates, resulting in an analytical sample of 3,019,069 individuals (**Figure 1**). The statistics of missing data are presented in **Appendix Table S6**.

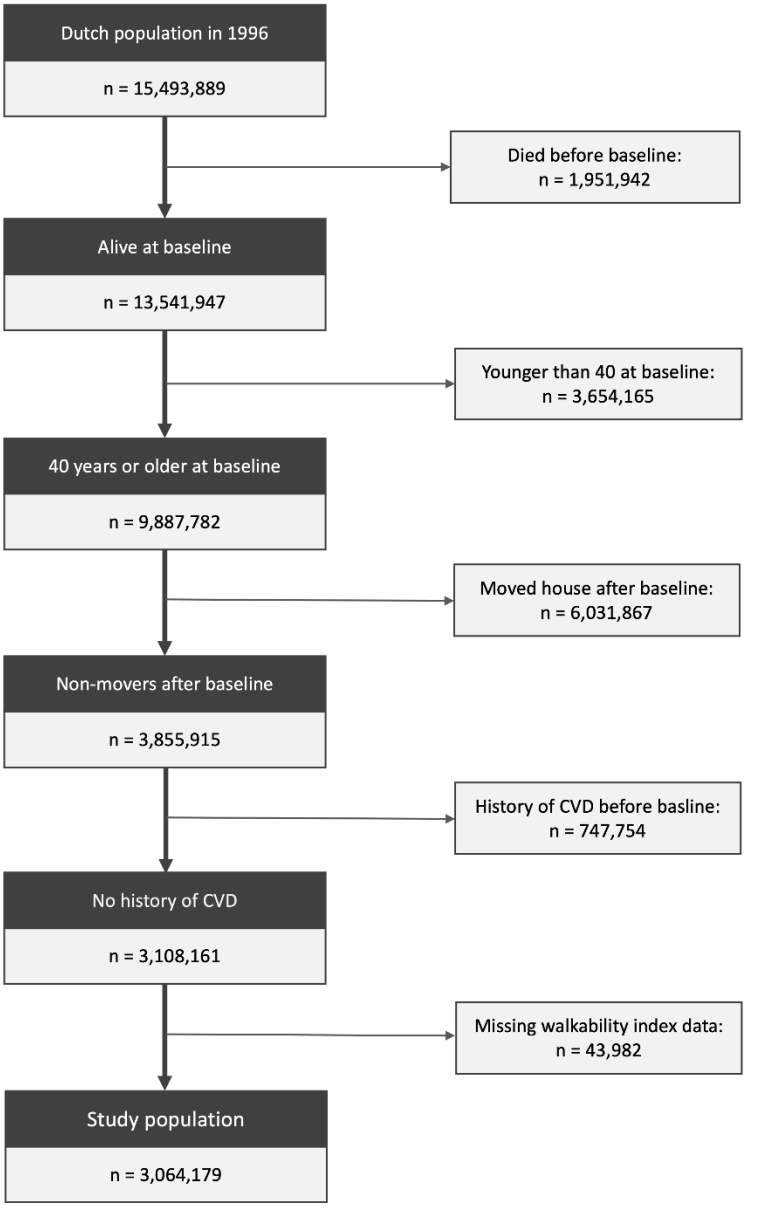

Figure 1. Flowchart of study population.

Walkability trajectories

We observed that the model with linear growth parameters, random intercept, and random slope, performed best (**Table 1**, **Appendix Table S3-S5**). The four-class model provided the most optimal fit for the data, as indicated by the low BIC, high entropy, and acceptable class sizes. Class 1 (referred to as "Stable low", n = 2,751,642, 91.1%) was characterised by a stable but relatively lower walkability score of 30 over time (**Figure 2**). Class 2 (referred to as "Decreasing", n = 52,678, 1.7%) began with a relatively higher walkability and it decreased from 47 to 30. Class 3 (referred to as "Stable High", n = 17,845, 0.6%) was characterised by a stable but relatively higher walkability score of 40 over time. Class 4 (referred to as "Increasing", n=196,904, 6.5%) was characterized by an increase from 30 to 46.

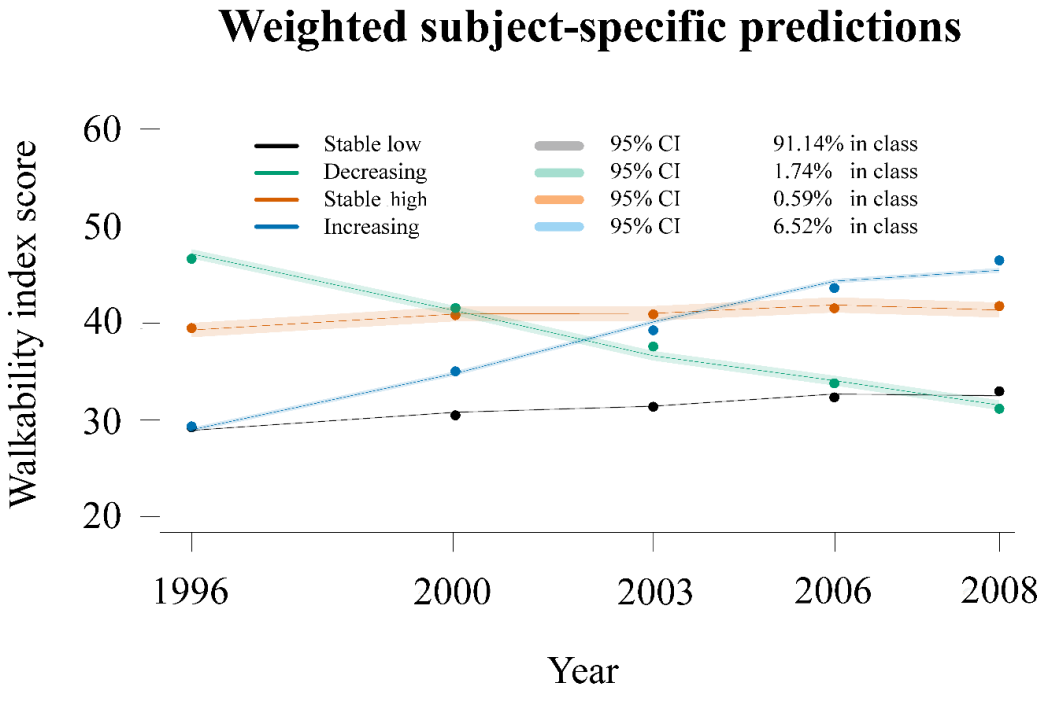

Figure 2. Class-specific mean predicted walkability trajectories.

Table 1. Model fit of Growth Mixture Models with 1-6 classes (n = 153,127) using a linear trajectory function

						Percentage of people per class (%)					
Classes	**NPM[1]**	**Log-likelihood**	**AIC[2]**	**BIC[3]**	**Entropy**	**1**	**2**	**3**	**4**	**5**	**6**
1	6	-2331916	4663844	4663904	1	100.00					
2	10	-2313987	4627995	4628094	0.91	2.47	97.53				
3	14	-2308343	4616713	4616852	0.91	1.98	92.72	5.30			
4*	18	-2305259	4610554	4610733	0.93	0.64	91.12	1.85	6.40		
5	22	-2302607	4605257	4605476	0.81	1.82	15.01	5.62	77.03	0.52	
6	26	-2295030	4590112	4590370	0.83	1.95	18.06	4.40	70.54	4.60	0.44

[1] Number of parameters

[2] Akaike information criterion

[3] Bayesian information criterion

* Selected model

Table 2. Population characteristics of the total study sample as well as stratified by neighbourhood walkability trajectory

	Category	All	Stable high	Stable low	Decreasing	Increasing
n		3019069	17845 (0.59%)	2751642 (91.14%)	52678 (1.74%)	196904 (6.52%)
Follow-up time in years (median [IQR])		11.00 [11.00, 11.00]	11.00 [11.00, 11.00]	11.00 [11.00, 11.00]	11.00 [11.00, 11.00]	11.00 [11.00, 11.00]
Sex (%)	*Men*	47.9	52.4	47.8	52.7	47.7
	Women	52.1	47.6	52.2	47.3	52.3
Age in years at baseline (median [IQR])		57.0 [49.0, 65.0]	48.0 [43.0, 57.0]	57.0 [50.0, 65.0]	48.0 [43.0, 58.0]	55.0 [48.0, 64.0]
Ethnicity (%)	*Native Dutch*	91.8	82.7	92.3	87.3	87.5
	Non-Dutch western	4.1	5.2	4.0	5.0	4.9
	Non-Dutch non-western	4.1	12.1	3.7	7.7	7.6
Moved[1] (%)	*No*	93.6	18.3	96.1	30.5	82.2
	Yes	6.4	81.7	3.9	69.5	17.8
Change in partner[2] status (%)	*Remained without partner*	18.2	35.0	17.5	28.1	23.3
	Remained with partner	71.0	35.0	72.3	43.9	62.8
	Partner to no partner	6.6	9.7	6.5	6.9	7.7
	No partner to partner	4.2	20.3	3.6	21.1	6.2

Mean household income in € (%)	*Lowest tertile (< 18786)*	33.1	35.0	32.9	32.4	35.3
	Middle tertile (18786 – 25807)	33.5	29.5	33.6	31.3	33.1
	Highest tertile (> 25807)	33.5	35.5	33.5	36.3	31.6
Baseline area-level SES[3] (mean ± SD)		-0.03 (0.93)	0.05 (1.15)	-0.03 (0.92)	0.16 (1.04)	-0.02 (1.03)
Urbanicity (addresses/km^2, %)	*Less than 1000*	43.0	29.4	45.1	22.7	21.2
	1000 to 2500	43.1	32.1	42.2	40.6	58.0
	More than 2500	13.8	38.5	12.7	36.7	20.8
NO_2 in µg/m3 (mean ± SD)		19.50 (4.83)	21.41 (5.57)	19.37 (4.79)	21.77 (5.46)	20.49 (4.80)
PM_{10} in µg/m3 (mean ± SD)		20.26 (1.61)	20.67 (1.75)	20.24 (1.60)	20.74 (1.67)	20.47 (1.60)
$PM_{2.5}$ in µg/m3 (mean ± SD)		12.58 (1.32)	12.89 (1.42)	12.56 (1.32)	12.95 (1.35)	12.71 (1.29)

[1] Moved during exposure period (1996-2008)

[2] Partner included both marriage and registered partnership

[3] Socio-economic status

Study sample characteristics by trajectory classes

Men and women were fairly evenly distributed in the study population and in the trajectories (**Table 2**). The median age at baseline was 57 (IQR: 49 to 65) years and the stable high and decreasing trajectory was the youngest with a median age of 48 years. The stable high trajectory had the largest proportion of people with a non-western origin (12.1%). The stable low trajectory rarely moved house (3.9%) during the exposure period. A notably higher percentage of individuals moved house in the stable high (81.7%) and decreasing (69.5%) trajectories. In the stable low trajectory, 45.1% lived in rural areas, while the stable high and decreasing groups had the highest percentage residing in urban areas.

Walkability trajectories and cardiovascular outcomes

During a median follow-up of 11.0 years, a total of 644,785 individuals developed CVD (21.4%), of which 148,191 developed CHD (4.9%), 71,289 stroke (2.4%), and 31,007 HF (1.0%). Among these CVD outcomes, there were 81,600 deaths due to any CVD (2.7%), of which 21,344 due to CHD (0.7%), 17,790 due to stroke (0.6%), and 12,572 due to HF (0.4%).

Compared to stable high walkability, individuals exposed to stable low, and increasing walkability, had a 5.1% (HR: 1.051; CI: 1.011 to 1.093) and a 4.9% (HR: 1.049; CI: 1.008 to 1.092) higher risk of any CVD during follow-up (**Figure 3**). Similar associations were observed for CHD and stroke, though not statistically significant. We did not observe statistically significant associations of walkability trajectories with CVD mortality and HF. Furthermore, **Appendix Table S7** shows that no associations were found between walkability trajectories and mortality due to CHD, stroke, and HF.

Based on observed differences in **Table 2**, we present stratified associations by age, urbanicity, and residential relocation in **Figure 4**. For all details of the stratified analyses, please refer to the **Appendix Table S8-S14**. For any CVD and CHD, associations were more apparent in middle aged adults relative to older adults. On the contrary, for stroke, all walkability trajectories as compared to the stable high were associated with a higher

risk in older adults, but not in middle aged adults. We also observed a clear difference between rural and urban areas (**Figure 4**). In urban areas, stable low and increasing walkability were associated with a higher risk of any CVD. In rural areas, on the other hand, we did not find statistically significant associations. There was no apparent difference between the associations observed in the models stratified by movers and non-movers for any CVD. However, stable low and increasing walkability were associated with a higher risk of CHD only in non-movers.

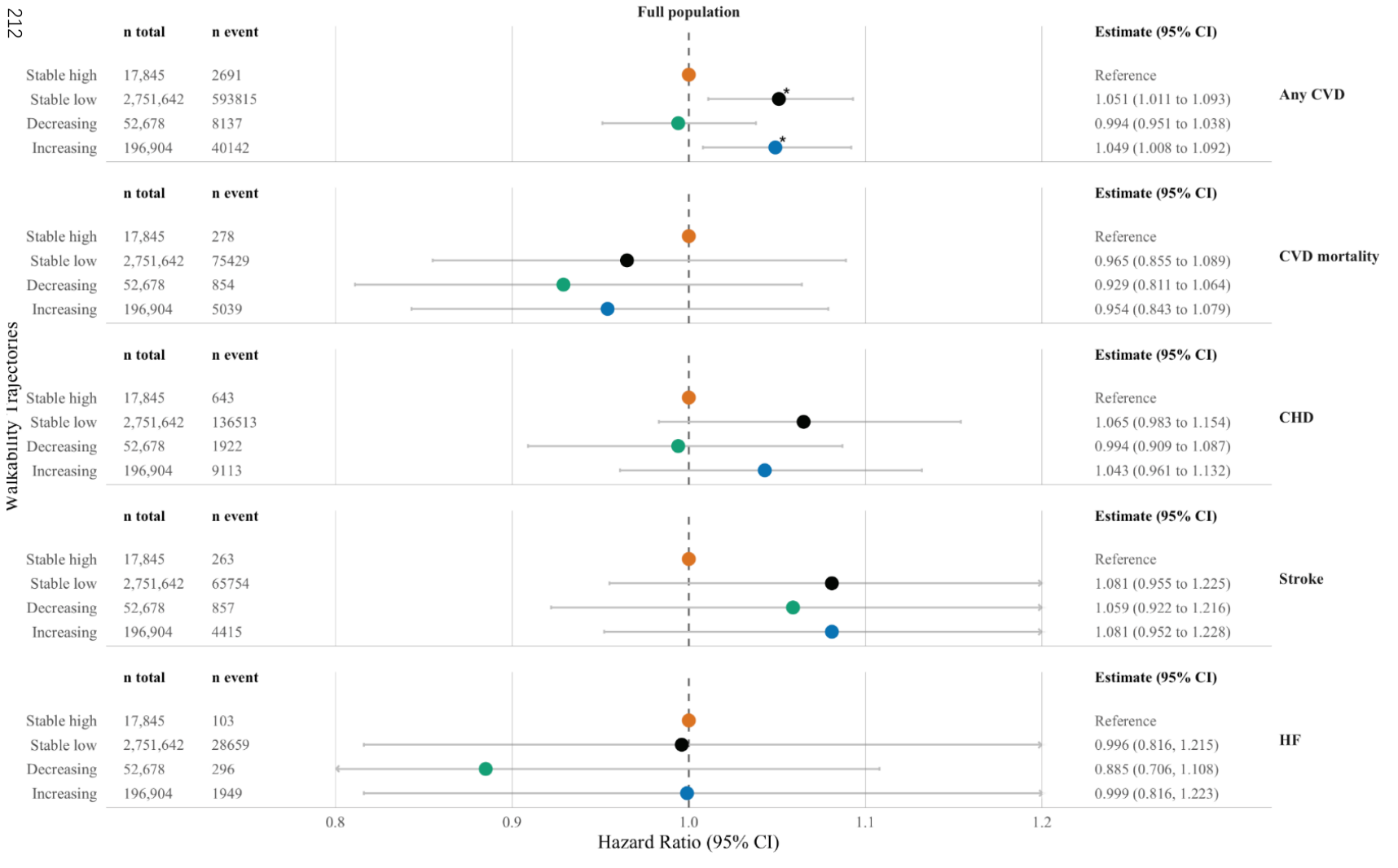
Full population
Walkability Trajectories
n total
n event
Estimate (95% CI)
Stable high 17,845 2691 Reference
Stable low 2,751,642 593815 1.051 (1.011 to 1.093)
Decreasing 52,678 8137 0.994 (0.951 to 1.038)
Increasing 196,904 40142 1.049 (1.008 to 1.092)
Any CVD
Stable high 17,845 278 Reference
Stable low 2,751,642 75429 0.965 (0.855 to 1.089)
Decreasing 52,678 854 0.929 (0.811 to 1.064)
Increasing 196,904 5039 0.954 (0.843 to 1.079)
CVD mortality
Stable high 17,845 643 Reference
Stable low 2,751,642 136513 1.065 (0.983 to 1.154)
Decreasing 52,678 1922 0.994 (0.909 to 1.087)
Increasing 196,904 9113 1.043 (0.961 to 1.132)
CHD
Stable high 17,845 263 Reference
Stable low 2,751,642 65754 1.081 (0.955 to 1.225)
Decreasing 52,678 857 1.059 (0.922 to 1.216)
Increasing 196,904 4415 1.081 (0.952 to 1.228)
Stroke
Stable high 17,845 103 Reference
Stable low 2,751,642 28659 0.996 (0.816, 1.215)
Decreasing 52,678 296 0.885 (0.706, 1.108)
Increasing 196,904 1949 0.999 (0.816, 1.223)
HF
0.8
0.9
1.0
1.1
1.2
Hazard Ratio (95% CI)

Figure 3. Associations between trajectories of neighbourhood walkability and subsequent cardiovascular outcomes.
Models are adjusted for age at baseline, sex, ethnicity, change in partner status, mean household income, area level SES, mean $PM_{2.5}$ exposure, urbanicity and residential relocation.
* Remained statistically significant after false discovery rate correction for multiple testing.
CVD, cardiovascular disease; CHD, coronary heart disease; HF, heart failure

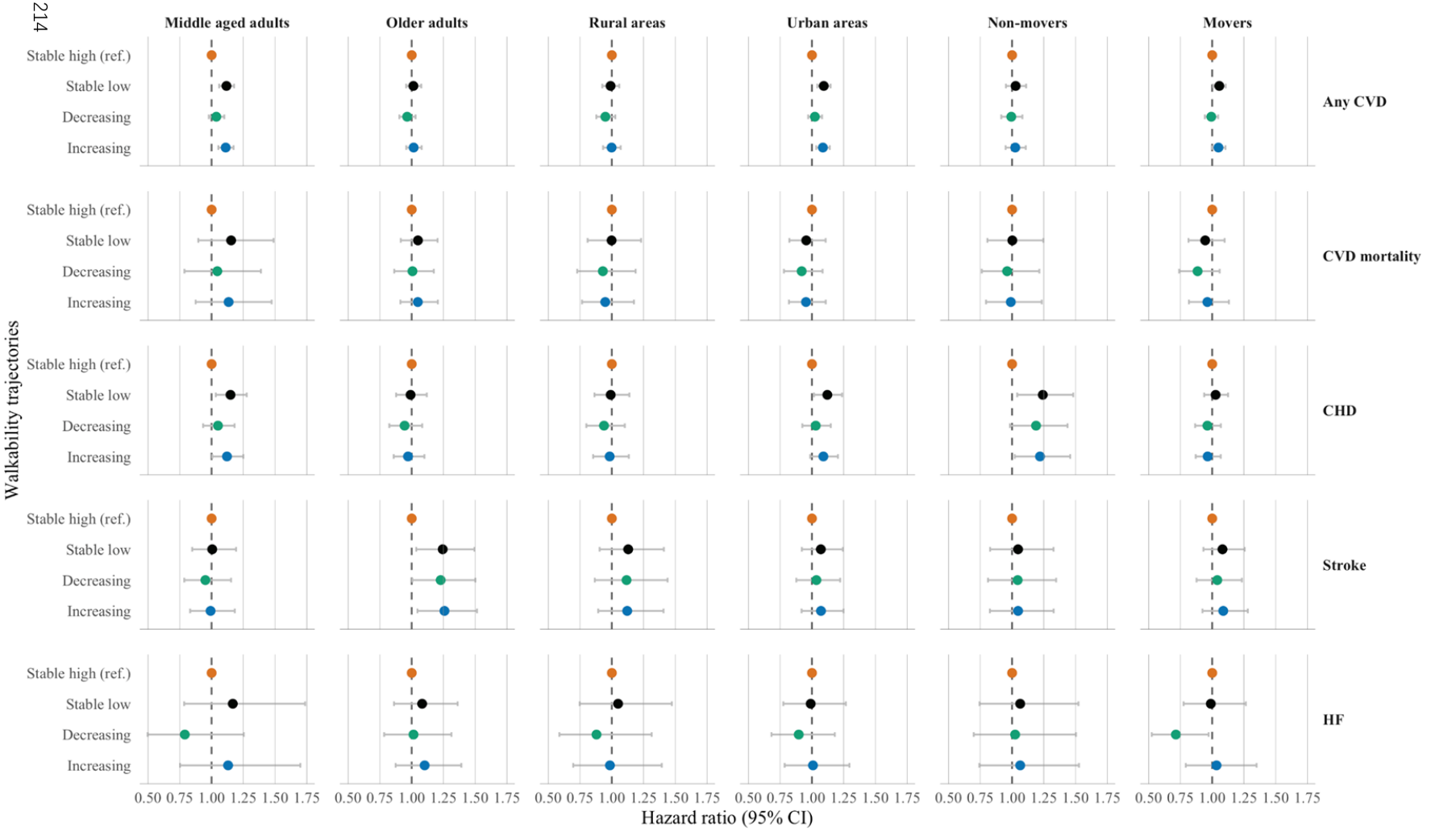
Middle aged adults
Older adults
Rural areas
Urban areas
Non-movers
Movers
Any CVD
CVD mortality
CHD
Stroke
HF
Stable high (ref.)
Stable low
Decreasing
Increasing
Walkability trajectories
0.50 0.75 1.00 1.25 1.50 1.75
Hazard ratio (95% CI)

Figure 4. Associations between trajectories of neighbourhood walkability and subsequent cardiovascular outcomes, stratified by age group, urbanicity, and residential relocation.
CVD, cardiovascular disease; CHD, coronary heart disease; HF, heart failure

Discussion

In this large-scale population-based cohort study, we assessed the association between longitudinal changes in neighbourhood walkability and the subsequent incidence of CVD. We observed four distinct trajectories of neighbourhood walkability over 13 years. Exposure to stable low walkability, as well as increasing walkability, was associated with an approximate five percent higher risk of any CVD compared to the stable high walkability trajectory. Associations were more evident in middle aged compared to older adults, and urban compared to rural residents.

The observed associations revealed some unexpected patterns, particularly the higher risk observed for increasing walkability and the lack of an association in the decreasing walkability trajectory. These findings suggest that changes in walkability over time may not influence CVD risk in a straightforward manner. Although walkability in the 'increasing' trajectory ends higher than the 'stable high' reference category, it starts from a much lower score, resulting in a lower overall walkability over the exposure period. Hence, the cumulative exposure of residents may have influenced their risk. This is corroborated by Le et al., who investigated associations of cumulative and point-in-time neighbourhood walkability with BMI.[44] They found that cumulative walkability was associated with lower BMI, but found no associations for point-in-time walkability. Moreover, while walkability exposure in our study may have improved in the increasing trajectory, it started at a lower level. Despite later improvements, individuals in that group likely have lived in this low walkable area for a significant period, potentially resulting in latent effects on their activity patterns and cardiometabolic health. Conversely, in the decreasing walkability trajectory, initial high walkability may have had lasting benefits despite later declines. These observations underscore the importance of adopting a longitudinal perspective when studying neighbourhood walkability.

Unlike previous studies that largely evaluated static walkability levels,[45,46] our research delves into the dynamic nature of neighbourhood environments over time. A Dutch regional study by Timmermans et al.'s found minimal changes in a similar walkability

index and its components between 2005 and 2011.[33] Our findings also show that neighbourhood walkability is relatively stable for the majority of our study population, who are mostly non-movers. This suggests that walkability levels of most Dutch residential neighbourhoods, as measured by six built environment components, do not change much over time. However, we were able to capture some significant changes, mostly in movers, which Timmermans et al. did not include.

Previous longitudinal studies have mostly provided evidence for associations between higher levels of neighbourhood walkability and lower levels of cardiometabolic risk factors, such as obesity, hypertension, and type 2 diabetes.[12,20] A national ecological study in Japan found that CVD mortality was significantly higher in municipalities of lower walkability (lowest tertile), this association was independent of area-level SES.[47] This finding was based on a 3 component walkability index (population density, street density, and access to commercial areas). More similar to our work is a longitudinal study that used a nationally representative cohort of Canadian adults with 15 years of follow-up.[21] The authors observed that living in a highly walkable neighbourhood at baseline compared to the least walkable neighbourhoods was associated with a 9% reduced risk of CVD mortality. However, no changes in walkability were assessed. We found a higher CVD risk for both stable low and increasing walkability groups. While the results are not directly comparable, we did observe that all trajectories had lower walkability levels at some point in time compared to the stable high trajectory, resulting in an overall lower cumulative exposure.

Our stratified analyses showed that the associations for any CVD were mostly present in middle aged adults and in urban residents. One possible explanation is that the spatial components in the current walkability index might be more relevant for middle aged adults than for older adults. Aspects like cross-overs, street furniture, street lights, pavement types and slopes might be more relevant for older adults' walking behaviour.[48] But, these are not included in the current walkability index. Another possibility is that neighbourhood walkability facilitates activity especially in those who are already more physically active. This is also supported by an Australian study, where

the association between walkable neighbourhoods and cardiometabolic risk factors was partly attributed to baseline PA levels, but not to changes in PA.[18] In the Netherlands, younger adults are more active than the older (senior) adults.[5] We did not have data on individual PA levels in our study, and therefore, we could not explore this further.

Encouraging (travel-related) PA is the most intuitive mechanism through which neighbourhood walkability could affect the risk of CVD. This is supported by previous studies. A Dutch study found a positive association between neighbourhood walkability and walking time.[32] A study of Chinese citizens found that PA partly explained the association between neighbourhood walkability and CVD.[49] In addition, a study in Portugal found that a built environment intervention aimed at increasing walkability levels was associated with an increase in pedestrian volumes.[50] There are also potential pathways linking walkability to CVD beyond PA, including air pollution and social context.[27] More walkable neighbourhoods were previously linked to less vehicle mileage and thus lower levels of sedentary behaviour and less air pollution.[51] Neighbourhood walkability may also be related to differences in the social characteristics of neighbourhoods, such as social disadvantages or social cohesion.[52] Which could in turn be determinants of CVD risk.[53]

Our study population includes both individuals who relocated during the exposure period (movers) and those who remained at the same address (non-movers). This approach comes with specific challenges, especially since changes in an individual's walkability score can either result from residential relocation or actual environmental changes in the same neighbourhood. We observed that the allocation of walkability trajectories was associated with residential relocation. For instance, the stable high and decreasing trajectories primarily consisted of movers (81.7% and 69.5%), while the stable low trajectory mostly comprised non-movers (96.1%). To address potential confounding by residential relocation, we conducted stratified analyses specifically for movers/non-movers. The resulting pattern of associations was generally consistent between the full population and non-movers. This indicates that differences in the percentage of movers in trajectory groups do not fully explain our findings. We also

addressed potential confounding by adjusting our models for factors known to be associated with residential relocation, including sex, changes in marital status, and individual- and area-level SES. Additionally, Saucy et al. found no significant associations between various health conditions (such as asthma, chronic obstructive pulmonary disease, body mass index, hypertension, and CVD) and the likelihood of residential relocation.[25] Although we acknowledge that the current analyses may not eliminate the confounding effect of relocation on identified associations between walkability trajectories and CVD outcomes, this finding suggests that health status is unlikely to be associated with relocation, further strengthening the validity of our approach.

The strengths of this study include the large nationwide cohort, longitudinal design, use of a comprehensive and validated walkability index, and trajectory modelling. However, our study also has several limitations. First, the trajectory modelling was restricted to a random five percent subset of the cohort due to computational limitations posed by the large size of the data. When extrapolating the trajectories to the full population, the percentage of individuals in each trajectory remained the same. This indicates that the subset is representative of the full population. Second, despite adjusting for multiple covariates in the analyses, there remains a possibility of residual confounding due to unmeasured or unknown confounders, or imprecise measurement. Third, this study focused on walkability within residential settings, overlooking various places where individuals allocate a noteworthy amount of their time, including workplaces, shopping districts, and recreational areas. Fourth, because climate, landform, and culture are contextual variables with the potential to affect the relationship between walkability and CVD,[53] the generalizability of the current findings to other countries may be limited. Therefore, it warrants additional research in other regions, considering these factors. Fifth, not all hospitals participated in the Hospital Discharge Register before 2014, varying around 10% non-participation. However, the hospitals that did not participate were both academic and non-academic hospitals, spread across the country.[54] We have no reason to believe that the non-participation of hospitals is in any way related to walkability levels in the Netherlands, but this nondifferential misclassification of the

outcome may have led to lower event rates and an underestimation of the observed associations. Last, the switch from manual to automatic coding of mortality statistics by Statistics Netherlands in 2012, resulted in a shift in primary diagnoses. However, given the high agreement between the two methods, particularly for major disease categories like cancer and cardiovascular diseases, we believe our study's overall trends and outcomes remain unaffected.[54]

At first sight, the observed effect estimates may seem minor, but the exposure of the entire population to neighbourhood walkability emphasizes the substantial reach of this effect and its significant impact on public health. Given that neighbourhoods with diverse walkability levels are widespread and influence a broad cross-section of society, the collective effect becomes considerable. This underscores the importance of considering the cumulative influence of neighbourhood walkability on cardiovascular health. Policy adjustments, even if incremental, may contribute to meaningful improvements in cardiovascular health at the population level. Therefore, further research is needed to explore how individual choices and behaviours interact with walkability trajectories. Assessing age-specific effects, and considering multiple settings of exposure would contribute to a more comprehensive understanding of how changes in neighbourhood walkability influence cardiovascular health.

Walkability is inherently a multifaceted concept encompassing various interconnected elements.[32] Employing a comprehensive and validated walkability index allowed us to capture the co-occurrence of these elements, providing a holistic assessment of the neighbourhood environment. This approach mitigates issues such as multicollinearity and measurement error while aligning with our objective of understanding the broader relationship between neighbourhood walkability and cardiovascular disease incidence. Future research could further enhance our understanding by systematically investigating the individual components of walkability, to identify the specific contributions of each component to overall walkability and health outcomes.

Conclusions

We identified four trajectories of residential neighbourhood walkability in Dutch residents from 1996 to 2008. As compared to the stable but relatively higher walkability group, residing in stable low and increasing walkability areas was associated with a higher CVD risk. These findings were especially pronounced in middle aged adults, and urban dwellers. The results suggest that adults exposed to low walkability over time had a higher risk of CVD compared to residents in the stable high walkability neighbourhoods. An increasing walkability trend over time was linked to higher CVD risk, likely because the cumulative walkability in the exposure period was lower than the stable high category. The findings emphasise the relevance of longitudinal research in this field, and of long-term urban planning considerations for cardiovascular health.

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Data availability statement

Results are based on calculations using geodata and non-public microdata from Statistics Netherlands. Under certain conditions, the underlying encrypted microdata are accessible for statistical and scientific research. For further information contact microdata@cbs.nl. If verification of the analyses is desired and Statistics Netherlands provides access to the microdata, we will provide the R-scripts for cohort-building and analyses upon request to the corresponding author. The geodata can be requested from the Geoscience and Health Cohort Consortium (www.gecco.nl).

Transparency statement

The lead authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contributors

PM, ML, TML, IV, EJT, and JL participated in project conception and development of research methods. YK, MGP, DEG, and JWJB contributed to drafting and revising the protocol. PM, ML and YK contributed to data curation, including activities to clean and maintain research data. Formal analysis was performed by PM, supported by ML. PM and ML drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final manuscript. PM and ML have contributed equally and are joint first authors. JL and EJT are guarantor. The

corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests

All authors have completed the ICMJE uniform disclosure form http://www.icmje.org/disclosure-of-interest/ and declare: support for the submitted work from NWO Gravitation grant Exposome-NL under grant No. 024.004.017; support from the EC-Horizon 2020 EXPANSE project under grant number No. 874627; JL received a grant from the European Union's Horizon Europe research and innovation programme under grant agreement OBCT No. 101080250; MGP received a seed fund from the Seed Fund Alliance TU/e, WUR, UU and UMC Utrecht; no other relationships or activities that could appear to have influenced the submitted work.

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CHAPTER 5 Appendices

Table S1. Exposure measurements and data sources

Walkability Components	Definition	Source	Years
Population density	Number of inhabitants per hectare	CBS	1996, 2000, 2003, 2006, 2008
Retail and service density	Area proportion devoted to two land use classes "commercial" and "socio-cultural services" in each analysis unit	Data service of ESRI the Netherlands	1996, 2000, 2003, 2006, 2008
Land use mix	Level of integration among different land use types in each analysis unit	Dutch land use dataset from the National Georegister	1996, 2000, 2003, 2006, 2008
Street connectivity	Point density of true intersections (i.e., three or more legs) on road segments that are accessible for pedestrians (e.g., excluding highways)	Topographical maps of the Netherlands	2000, 2003
Green space density	Proportions of land devoted to parks, public gardens, forests and graveyards	The Dutch land use dataset	1996, 2000, 2003, 2006, 2008
Sidewalk density	Area proportion of sidewalk	The topographic map via ESRI the Netherlands	1996, 2000, 2003, 2008

Table S2. ICD codes used for cardiovascular diseases

	Codes
ICD-9	390, 391, 3910, 3911, 3912, 3918, 3919, 392, 3920, 3929, 393, 394, 3940, 3941, 3942, 3949, 395, 3950, 3951, 3952, 3959, 396, 3960, 3961, 3962, 3963, 3968, 3969, 397, 3970, 3971, 3979, 398, 3980, 3989, 39890, 39891, 39899, 401, 4010, 4011, 4019, 402, 4020, 40200, 40201, 4021, 40210, 40211, 4029, 40290, 40291, 403, 4030, 40300, 40301, 4031, 40310, 40311, 4039, 40390, 40391, 404, 4040, 40400, 40401, 40402, 40403, 4041, 40410, 40411, 40412, 40413, 4049, 40490, 40491, 40492, 40493, 405, 4050, 40501, 40509, 4051, 40511, 40519, 4059, 40591, 40599, 410, 4100, 41000, 41001, 41002, 4101, 41010, 41011, 41012, 4102, 41020, 41021, 41022, 4103, 41030, 41031, 41032, 4104, 41040, 41041, 41042, 4105, 41050, 41051, 41052, 4106, 41060, 41061, 41062, 4107, 41070, 41071, 41072, 4108, 41080, 41081, 41082, 4109, 41090, 41091, 41092, 411, 4110, 4111, 4118, 41181, 41189, 412, 413, 4130, 4131, 4139, 414, 4140, 41400, 41401, 41402, 41403, 41404, 41405, 41406, 41407, 4141, 41410, 41411, 41412, 41419, 4142, 4143, 4144, 4148, 4149, 415, 4150, 4151, 41511, 41512, 41513, 41519, 416, 4160, 4161, 4162, 4168, 4169, 417, 4170, 4171, 4178, 4179, 420, 4200, 4209, 42090, 42091, 42099, 421, 4210, 4211, 4219, 422, 4220, 4229, 42290, 42291, 42292, 42293, 42299, 423, 4230, 4231, 4232, 4233, 4238, 4239, 424, 4240, 4241, 4242, 4243, 4249, 42490, 42491, 42499, 425, 4250, 4251, 42511, 42518, 4252, 4253, 4254, 4255, 4257, 4258, 4259, 426, 4260, 4261, 42610, 42611, 42612, 42613, 4262, 4263, 4264, 4265, 42650, 42651, 42652, 42653, 42654, 4266, 4267, 4268, 42681, 42682, 42689, 4269, 427, 4270, 4271, 4272, 4273, 42731, 42732, 4274, 42741, 42742, 4275, 4276, 42760, 42761, 42769, 4278, 42781, 42789, 4279, 428, 4280, 4281, 4282, 42820, 42821, 42822, 42823, 4283, 42830, 42831, 42832, 42833, 4284, 42840, 42841, 42842, 42843, 4289, 429, 4290, 4291, 4292, 4293, 4294, 4295, 4296, 4297, 42971, 42979, 4298, 42981, 42982, 42983, 42989, 4299, 430, 431, 432, 4320, 4321, 4329, 433, 4330, 43300, 43301, 4331, 43310, 43311, 4332, 43320, 43321, 4333, 43330, 43331, 4338, 43380, 43381, 4339, 43390, 43391, 434, 4340, 43400, 43401, 4341, 43410, 43411, 4349, 43490, 43491, 435,

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ICD-10	I00, I01, I010, I012, I018, I019, I02, I020, I029, I05, I050, I051, I052, I058, I059, I06, I060, I061, I062, I068, I069, I07, I070, I071, I072, I078, I079, I08, I080, I081, I082, I083, I088, I089, I09, I090, I091, I092, I098, I099, I10, I11, I110, I119, I12, I120, I129, I13, I130, I131, I132, I139, I15, I150, I151, I152, I158, I159, I20, I200, I201, I208, I209, I21, I210, I211, I212, I213, I214, I219, I22, I220, I221, I228, I229, I23, I230, I231, I232, I233, I234, I235, I236, I238, I24, I240, I241, I248, I249, I25, I250, I251, I252, I253, I254, I255, I256, I258, I259, I26, I260, I269, I27, I270,

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Table S3. Comparison of model fit between two functional forms of latent class growth curves

Form	G	npm	Log-likelihood	AIC[1]	BIC[2]
Linear	1	3	-3166239	6332484	6332514
Quadratic	1	3	-3166239	6332484	6332514
Cubic	1	3	-3166229	6332468	6332518

[1] Akaike information criterion

[2] Bayesian information criterion

Table S4. Model fit of LGCA with 1-6 classes (n = 153,127) using a linear trajectory function

		Log-				Percentage of people per class (%)					
G	NPM	likelihood	AIC[1]	BIC[2]	Entropy	1	2	3	4	5	6
1	3	-3166239	6332484	6332514	1	100					
2	7	-2897627	5795268	5795338	0.91	46.61	53.39				
3	11	-2738731	5477485	5477594	0.93	26.77	46.28	26.95			
4	15	-2635283	5270595	5270744	0.93	17.39	33.47	35.31	13.84		
5	19	-2560289	5120616	5120805	0.94	11.57	23.90	30.78	25.06	8.69	
6	23	-2510420	5020886	5021115	0.93	8.70	18.34	25.39	24.58	17.47	5.52

[1] Akaike information criterion

[2] Bayesian information criterion

Table S5. Model fit of GMM with 1-6 classes (n = 153,127) using a linear trajectory function

		Log-				Percentage of people per class (%)					
G	NPM	likelihood	AIC[1]	BIC[2]	Entropy	1	2	3	4	5	6
1	4	-2408534	4817075	4817115	1	100					
2	8	-2371531	4743078	4743157	0.82	86.85	13.15				
3	12	-2328326	4656676	4656795	0.91	1.50	86.33	12.17			
4	16	-2316043	4632118	4632277	0.84	1.45	76.19	20.56	1.79		
5	20	-2311681	4623403	4623602	0.78	1.41	4.31	65.51	28.36	0.42	
6	24	-2304205	4608458	4608697	0.83	0.50	69.38	1.74	24.24	3.76	0.39

[1] Akaike information criterion

[2] Bayesian information criterion

Table S6. Percentage of missing data in each variable of the total study sample as well as stratified by neighbourhood walkability trajectory

	All	**Stable high**	**Stable low**	**Decreasing**	**Increasing**
n	3019069	17845 (0.59%)	2751642 (91.14%)	52678 (1.74%)	196904 (6.52%)
Follow-up time in years	0	0	0	0	0
Sex	0	0	0	0	0
Age in years at baseline	0	0	0	0	0
Ethnicity	0	0	0	0	0
Moved[1]	0	0	0	0	0
Change in partner[2]	0	0	0	0	0
Baseline area-level SES[3]	0.47	2.27	0.47	0.59	0.28
Mean household income in €	0.02	0.03	0.02	0.04	0.02
Urbanicity (addresses/km$^{2)}$	0.01	0.19	0.01	0.06	0.01
NO_2 in µg/m3	1.08	9.60	0.95	4.08	1.14
PM_{10} in µg/m3	1.08	9.60	0.95	4.08	1.14
$PM_{2.5}$ in µg/m3	1.08	9.60	0.95	4.08	1.14

[1] Moved during exposure period (1996-2008)

[2] Partner included both marriage and registered partnership

[3] Socio-economic status

Table S7. Associations between trajectories of neighbourhood walkability and mortality due to CHD, Stroke and, HF

			Full model	
	N	Event N	HR (95% CI)1	*p*-value[2]
Coronary heart disease mortality				
Walkability				
Stable high	17,845	78	—	
Stable low	2,751,642	19,721	1.021 (0.812 to 1.285)	0.95
Decreasing	52,678	245	1.009 (0.781 to 1.303)	0.95
Increasing	196,904	1,300	0.985 (0.780 to 1.244)	0.95
Stroke mortality				
Walkability				
Stable high	17,845	51	—	
Stable low	2,751,642	16,436	1.132 (0.854 to 1.501)	0.57
Decreasing	52,678	185	1.095 (0.802 to 1.495)	0.57
Increasing	196,904	1,118	1.142 (0.858 to 1.520)	0.57
Heart failure mortality				
Walkability				
Stable high	17,845	37	—	
Stable low	2,751,642	11,638	0.921 (0.661 to 1.283)	0.67
Decreasing	52,678	113	0.806 (0.555 to 1.172)	0.67
Increasing	196,904	784	0.929 (0.663 to 1.301)	0.67

[1] HR = Hazard Ratio, CI = Confidence interval

[2] *P* values after false discovery rate correction for multiple testing

Models adjusted for age, ethnicity, change in partner status, mean household income, area level SES, mean $PM_{2.5}$ exposure, urbanicity and residential relocation.

Table S8. Associations between trajectories of neighbourhood walkability and incident CVD stratified by sex

	Male				Female			
	N	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**	**N**	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	9,343	1,472	—		8,502	1,219	—	
Stable low	1,315,093	318,223	1.104 (1.047 to 1.164)	**<0.001**	1,436,549	275,592	0.989 (0.933 to 1.048)	0.71
Decreasing	27,745	4,668	1.039 (0.980 to 1.102)	0.20	24,933	3,469	0.937 (0.878 to 1.001)	0.16
Increasing	94,011	21,294	1.106 (1.048 to 1.167)	**<0.001**	102,893	18,848	0.983 (0.926 to 1.043)	0.71
CVD mortality								
Walkability								
Stable high	9,343	141	—		8,502	137	—	
Stable low	1,315,093	38,693	1.051 (0.887 to 1.247)	0.77	1,436,549	36,736	0.878 (0.739 to 1.044)	0.15
Decreasing	27,745	457	1.029 (0.851 to 1.244)	0.77	24,933	397	0.816 (0.671 to 0.993)	0.13
Increasing	94,011	2,471	1.028 (0.864 to 1.222)	0.77	102,893	2,568	0.879 (0.737 to 1.048)	0.15
Coronary heart disease								
Walkability								
Stable high	9,343	419	—		8,502	224	—	
Stable low	1,315,093	90,556	1.154 (1.045 to 1.274)	**0.014**	1,436,549	45,957	0.892 (0.779 to 1.022)	0.10
Decreasing	27,745	1,380	1.089 (0.976 to 1.215)	0.13	24,933	542	0.804 (0.688 to 0.940)	**0.019**
Increasing	94,011	5,976	1.125 (1.017 to 1.245)	**0.033**	102,893	3,137	0.879 (0.765 to 1.011)	0.10
Stroke								
Walkability								
Stable high	9,343	145	—		8,502	118	—	
Stable low	1,315,093	34,578	1.092 (0.923 to 1.293)	0.45	1,436,549	31,176	1.069 (0.888 to 1.288)	0.56
Decreasing	27,745	464	1.039 (0.862 to 1.253)	0.69	24,933	393	1.081 (0.880 to 1.329)	0.56
Increasing	94,011	2,303	1.103 (0.929 to 1.309)	0.45	102,893	2,112	1.057 (0.875 to 1.278)	0.56
Heart failure								
Walkability								
Stable high	9,343	55	—		8,502	48	—	
Stable low	1,315,093	13,400	0.916 (0.696 to 1.204)	0.79	1,436,549	15,259	1.092 (0.817 to 1.460)	0.89
Decreasing	27,745	139	0.800 (0.584 to 1.094)	0.49	24,933	157	0.977 (0.706 to 1.352)	0.89
Increasing	94,011	923	0.963 (0.729 to 1.273)	0.79	102,893	1,026	1.052 (0.783 to 1.413)	0.89

[1] HR = Hazard Ratio, CI = Confidence interval

[2] *P* values after false discovery rate correction for multiple testing

Models adjusted for age, ethnicity, change in partner status, mean household income, area level SES, mean $PM_{2.5}$ exposure, urbanicity and residential relocation.

Table S9. Associations between trajectories of neighbourhood walkability and incident CVD stratified by two age groups

	Middle aged adults (40 to 60)				Older adults (60 or older)			
	N	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**	**N**	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	14,090	1,498	—		3,755	1,193	—	
Stable low	1,571,725	221,542	1.117 (1.060 to 1.177)	**<0.001**	1,179,917	372,273	1.013 (0.956 to 1.075)	0.66
Decreasing	40,949	4,554	1.037 (0.979 to 1.100)	0.22	11,729	3,583	0.964 (0.903 to 1.030)	0.66
Increasing	123,178	16,786	1.111 (1.053 to 1.173)	**<0.001**	73,726	23,356	1.015 (0.957 to 1.078)	0.66
CVD mortality								
Walkability								
Stable high	14,090	64	—		3,755	214	—	
Stable low	1,571,725	8,874	1.154 (0.895 to 1.488)	0.52	1,179,917	66,555	1.049 (0.914 to 1.204)	0.77
Decreasing	40,949	184	1.045 (0.786 to 1.389)	0.76	11,729	670	1.006 (0.862 to 1.174)	0.94
Increasing	123,178	690	1.134 (0.874 to 1.473)	0.52	73,726	4,349	1.048 (0.911 to 1.206)	0.77
Coronary heart disease								
Walkability								
Stable high	14,090	366	—		3,755	277	—	
Stable low	1,571,725	54,672	1.149 (1.033 to 1.277)	**0.031**	1,179,917	81,841	0.991 (0.877 to 1.119)	0.88
Decreasing	40,949	1,129	1.050 (0.933 to 1.181)	0.42	11,729	793	0.944 (0.823 to 1.083)	0.88
Increasing	123,178	4,097	1.121 (1.005 to 1.250)	**0.060**	73,726	5,016	0.971 (0.858 to 1.100)	0.88
Stroke								
Walkability								
Stable high	14,090	142	—		3,755	121	—	
Stable low	1,571,725	18,882	1.005 (0.847 to 1.193)	0.95	1,179,917	46,872	1.244 (1.036 to 1.494)	**0.029**
Decreasing	40,949	392	0.951 (0.785 to 1.153)	0.95	11,729	465	1.228 (1.004 to 1.501)	**0.045**
Increasing	123,178	1,422	0.992 (0.831 to 1.183)	0.95	73,726	2,993	1.258 (1.045 to 1.514)	**0.029**
Heart failure								
Walkability								
Stable high	14,090	26	—		3,755	77	—	
Stable low	1,571,725	3,976	1.167 (0.784 to 1.737)	0.56	1,179,917	24,683	1.082 (0.860 to 1.362)	0.75
Decreasing	40,949	57	0.789 (0.496 to 1.254)	0.56	11,729	239	1.014 (0.783 to 1.313)	0.91

Increasing	123,178	304	1.130 (0.751 to 1.699)	0.56	73,726	1,645	1.102 (0.873 to 1.391)	0.75

[1] HR = Hazard Ratio, CI = Confidence interval

[2] *P* values after false discovery rate correction for multiple testing

Models adjusted for sex, ethnicity, change in partner status, mean household income, area level SES, mean $PM_{2.5}$ exposure, urbanicity and residential relocation.

Table S10. Associations between trajectories of neighbourhood walkability and incident

			40 to 50				50 to 60	
	n	**event n**	**HR (95% CI)[1]**	***p*-value[2]**	**n**	**event n**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	10,111	835	—		3,979	663	—	
Stable low	668,135	66,888	1.104 (1.029 to 1.185)	**0.009**	903,59	154,654	1.093 (1.011 to 1.183)	0.075
Decreasing	29,037	2,447	1.023 (0.946 to 1.107)	0.57	11,912	2,107	1.083 (0.992 to 1.181)	0.075
Increasing	60,464	6,054	1.121 (1.041 to 1.207)	**0.007**	62,714	10,732	1.082 (0.999 to 1.172)	0.075
CVD mortality								
Walkability								
Stable high	10,111	32	—		3,979	32	—	
Stable low	668,135	2,036	0.938 (0.651 to 1.350)	0.88	903,59	6,838	1.331 (0.932 to 1.900)	0.18
Decreasing	29,037	71	0.830 (0.547 to 1.260)	0.88	11,912	113	1.321 (0.891 to 1.956)	0.18
Increasing	60,464	191	0.971 (0.663 to 1.422)	0.88	62,714	499	1.285 (0.894 to 1.848)	0.18
Coronary heart disease								
Walkability								
Stable high	10,111	212	—		3,979	154	—	
Stable low	668,135	15,686	1.048 (0.910 to 1.206)	0.77	903,59	38,986	1.231 (1.047 to 1.448)	**0.036**
Decreasing	29,037	631	1.034 (0.885 to 1.208)	0.77	11,912	498	1.098 (0.917 to 1.316)	0.31
Increasing	60,464	1,391	1.022 (0.882 to 1.184)	0.77	62,714	2,706	1.209 (1.025 to 1.426)	**0.036**
Stroke								
Walkability								
Stable high	10,111	74	—		3,979	68	—	
Stable low	668,135	5,584	1.044 (0.822 to 1.325)	0.72	903,59	13,298	0.944 (0.738 to 1.208)	0.97
Decreasing	29,037	194	0.922 (0.705 to 1.205)	0.72	11,912	198	1.005 (0.763 to 1.325)	0.97
Increasing	60,464	515	1.069 (0.834 to 1.370)	0.72	62,714	907	0.917 (0.712 to 1.179)	0.97
Heart failure								
Walkability								
Stable high	10,111	13	—		3,979	13	—	
Stable low	668,135	942	0.857 (0.484 to 1.519)	0.81	903,59	3,034	1.443 (0.826 to 2.520)	0.47
Decreasing	29,037	20	0.558 (0.277 to 1.122)	0.30	11,912	37	1.077 (0.572 to 2.027)	0.82
Increasing	60,464	90	0.928 (0.512 to 1.682)	0.81	62,714	214	1.341 (0.759 to 2.366)	0.47

(to continue)

			60 to 70				70 or older	
	n	**event n**	**HR (95% CI)[1]**	***p*-value[2]**	**n**	**event n**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	2,489	732	—		1,266	461	—	
Stable low	730,707	198,526	0.971 (0.901 to 1.047)	0.44	449,21	173,747	1.044 (0.951 to 1.147)	0.55
Decreasing	7,332	1,929	0.905 (0.831 to 0.985)	0.065	4,397	1,654	1.025 (0.923 to 1.137)	0.65
Increasing	44,387	12,083	0.967 (0.896 to 1.044)	0.44	29,339	11,273	1.051 (0.956 to 1.156)	0.55
CVD mortality								
Walkability								
Stable high	2,489	61	—		1,266	153	—	
Stable low	730,707	15,066	1.070 (0.825 to 1.386)	0.99	449,21	51,489	0.954 (0.811 to 1.123)	0.70
Decreasing	7,332	168	1.034 (0.771 to 1.387)	0.99	4,397	502	0.926 (0.772 to 1.112)	0.70
Increasing	44,387	904	0.998 (0.766 to 1.301)	0.99	29,339	3,445	0.967 (0.820 to 1.142)	0.70
Coronary heart disease								
Walkability								
Stable high	2,489	172	—		1,266	105	—	
Stable low	730,707	45,638	0.970 (0.831 to 1.133)	0.70	449,21	36,203	0.999 (0.820 to 1.217)	>0.99
Decreasing	7,332	440	0.894 (0.749 to 1.067)	0.64	4,397	353	1.00 (0.802 to 1.245)	>0.99
Increasing	44,387	2,722	0.946 (0.808 to 1.108)	0.70	29,339	2,294	0.982 (0.804 to 1.199)	>0.99
Stroke								
Walkability								
Stable high	2,489	55	—		1,266	66	—	
Stable low	730,707	20,177	1.330 (1.014 to 1.745)	0.059	449,21	26,695	1.109 (0.866 to 1.421)	0.41
Decreasing	7,332	199	1.261 (0.934 to 1.701)	0.13	4,397	266	1.142 (0.870 to 1.498)	0.41

Increasing	44,387	1,242	1.337 (1.015 to 1.760)	0.059	29,339	1,751	1.123 (0.874 to 1.443)	0.41
Heart failure								
Walkability								
Stable high	2,489	27	—		1,266	50	—	
Stable low	730,707	5,975	0.964 (0.652 to 1.425)	0.85	449,21	18,708	1.046 (0.787 to 1.390)	0.96
Decreasing	7,332	64	0.906 (0.577 to 1.423)	0.85	4,397	175	0.993 (0.723 to 1.362)	0.96
Increasing	44,387	379	0.934 (0.626 to 1.393)	0.85	29,339	1,266	1.075 (0.806 to 1.435)	0.96

[1] HR = Hazard Ratio, CI = Confidence Interval

[2] False discovery rate correction for multiple testing

Models adjusted for sex, ethnicity, change in partner status, mean household income, area level socio-economic status, mean $PM_{2.5}$ exposure, urbanicity and residential relocation.

Table S11. Associations between trajectories of neighbourhood walkability and incident CVD stratified by stratified by urbanicity

	Rural areas				Urban areas			
	N	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**	**N**	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	5,248	926	—		12,597	1,765	—	
Stable low	1,240,416	261,523	0.990 (0.925 to 1.059)	0.95	1,511,226	332,292	1.093 (1.042 to 1.147)	**<0.001**
Decreasing	11,978	2,050	0.949 (0.878 to 1.027)	0.58	40,700	6,087	1.023 (0.970 to 1.079)	0.40
Increasing	41,688	8,474	0.998 (0.931 to 1.070)	0.95	155,216	31,668	1.086 (1.034 to 1.140)	**0.001**
CVD mortality								
Walkability								
Stable high	5,248	97	—		12,597	181	—	
Stable low	1,240,416	31,589	0.998 (0.809 to 1.231)	0.99	1,511,226	43,840	0.955 (0.822 to 1.108)	0.54
Decreasing	11,978	210	0.929 (0.727 to 1.187)	0.93	40,700	644	0.919 (0.779 to 1.084)	0.54
Increasing	41,688	1,014	0.948 (0.765 to 1.174)	0.93	155,216	4,025	0.953 (0.819 to 1.109)	0.54
Coronary heart disease								
Walkability								
Stable high	5,248	222	—		12,597	421	—	
Stable low	1,240,416	60,574	0.991 (0.863 to 1.138)	0.90	1,511,226	75,939	1.121 (1.016 to 1.237)	0.069
Decreasing	11,978	479	0.938 (0.799 to 1.102)	0.90	40,700	1,443	1.030 (0.924 to 1.148)	0.60
Increasing	41,688	1,946	0.983 (0.853 to 1.134)	0.90	155,216	7,167	1.090 (0.986 to 1.205)	0.14
Stroke								
Walkability								
Stable high	5,248	85	—		12,597	178	—	
Stable low	1,240,416	28,576	1.129 (0.904 to 1.410)	0.40	1,511,226	37,178	1.070 (0.920 to 1.244)	0.58
Decreasing	11,978	218	1.116 (0.866 to 1.439)	0.40	40,700	639	1.035 (0.877 to 1.222)	0.68
Increasing	41,688	915	1.121 (0.893 to 1.407)	0.40	155,216	3,500	1.071 (0.918 to 1.248)	0.58
Heart failure								
Walkability								
Stable high	5,248	37	—		12,597	66	—	
Stable low	1,240,416	12,067	1.049 (0.747 to 1.473)	0.93	1,511,226	16,592	0.990 (0.774 to 1.267)	0.95
Decreasing	11,978	73	0.879 (0.587 to 1.314)	0.93	40,700	223	0.896 (0.681 to 1.180)	0.95

Increasing	41,688	390	0.985 (0.696 to 1.393)	0.93	155,216	1,559	1.008 (0.785 to 1.295)	0.95

[1] HR = Hazard Ratio, CI = Confidence interval

[2] *P* values after false discovery rate correction for multiple testing

Models adjusted for age, sex, ethnicity, change in partner status, mean household income, area-level SES, and mean $PM_{2.5}$ exposure, and residential relocation.

Table S12. Associations between trajectories of neighbourhood walkability and incident CVD stratified by residential relocation

	Non-movers				Movers			
	N	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**	**N**	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	3,267	652	—		14,578	2,039	—	
Stable low	2,645,076	578,075	1.028 (0.952 to 1.111)	0.79	106,566	15,740	1.056 (1.008 to 1.106)	0.062
Decreasing	16,047	3,591	0.994 (0.915 to 1.081)	0.90	36,631	4,546	0.993 (0.942 to 1.047)	0.80
Increasing	161,814	34,600	1.025 (0.949 to 1.108)	0.79	35,090	5,542	1.049 (0.997 to 1.104)	0.10
CVD mortality								
Walkability								
Stable high	3,267	81	—		14,578	197	—	
Stable low	2,645,076	74,059	1.002 (0.806 to 1.246)	0.99	106,566	1,370	0.945 (0.813 to 1.098)	0.64
Decreasing	16,047	536	0.961 (0.761 to 1.215)	0.99	36,631	318	0.885 (0.739 to 1.059)	0.55
Increasing	161,814	4,487	0.990 (0.795 to 1.234)	0.99	35,090	552	0.962 (0.817 to 1.132)	0.64
Coronary heart disease								
Walkability								
Stable high	3,267	123	—		14,578	520	—	
Stable low	2,645,076	132,566	1.242 (1.040 to 1.482)	**0.043**	106,566	3,947	1.027 (0.937 to 1.125)	0.57
Decreasing	16,047	793	1.189 (0.983 to 1.437)	0.075	36,631	1,129	0.962 (0.866 to 1.068)	0.57
Increasing	161,814	7,798	1.220 (1.021 to 1.458)	**0.043**	35,090	1,315	0.964 (0.870 to 1.067)	0.57
Stroke								
Walkability								
Stable high	3,267	69	—		14,578	194	—	
Stable low	2,645,076	64,217	1.047 (0.827 to 1.327)	0.74	106,566	1,537	1.081 (0.931 to 1.256)	0.48
Decreasing	16,047	426	1.044 (0.810 to 1.347)	0.74	36,631	431	1.040 (0.877 to 1.234)	0.65
Increasing	161,814	3,852	1.047 (0.825 to 1.328)	0.74	35,090	563	1.087 (0.923 to 1.281)	0.48
Heart failure								
Walkability								
Stable high	3,267	30	—		14,578	73	—	
Stable low	2,645,076	28,137	1.064 (0.744 to 1.523)	0.90	106,566	522	0.989 (0.774 to 1.265)	0.93
Decreasing	16,047	201	1.024 (0.698 to 1.503)	0.90	36,631	95	0.714 (0.524 to 0.972)	0.10

Increasing	161,814	1,735	1.064 (0.742 to 1.527)	0.90	35,090	214	1.034 (0.792 to 1.350)	0.93

[1] HR = Hazard Ratio, CI = Confidence interval

[2] *P* values after false discovery rate correction for multiple testing

Models adjusted for age, sex, ethnicity, change in partner status, mean household income, area-level SES, mean $PM_{2.5}$ exposure, and urbanicity

Table S13. Associations between trajectories of neighbourhood walkability and incident CVD stratified by household income

	Below average household income				Above average household income			
	N	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**	**N**	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	10,606	1,761	—		7,239	930	—	
Stable low	1,673,477	379,785	1.054 (1.004 to 1.106)	0.069	1,078,165	214,030	1.038 (0.971 to 1.110)	0.28
Decreasing	30,828	5,248	1.014 (0.961 to 1.070)	0.61	21,850	2,889	0.956 (0.888 to 1.029)	0.28
Increasing	124,012	26,791	1.051 (1.001 to 1.104)	0.069	72,892	13,351	1.040 (0.971 to 1.113)	0.28
CVD mortality								
Walkability								
Stable high	10,606	213	—		7,239	65	—	
Stable low	1,673,477	55,830	0.994 (0.866 to 1.142)	0.94	1,078,165	19,599	0.876 (0.680 to 1.128)	0.30
Decreasing	30,828	654	0.986 (0.844 to 1.152)	0.94	21,850	200	0.772 (0.583 to 1.024)	0.22
Increasing	124,012	3,939	0.991 (0.861 to 1.141)	0.94	72,892	1,100	0.862 (0.666 to 1.115)	0.30
Coronary heart disease								
Walkability								
Stable high	10,606	416	—		7,239	227	—	
Stable low	1,673,477	86,871	1.074 (0.972 to 1.186)	0.48	1,078,165	49,642	1.041 (0.909 to 1.193)	0.68
Decreasing	30,828	1,255	1.036 (0.927 to 1.158)	0.53	21,850	667	0.922 (0.793 to 1.072)	0.68
Increasing	124,012	6,020	1.047 (0.946 to 1.159)	0.53	72,892	3,093	1.029 (0.896 to 1.182)	0.68
Stroke								
Walkability								
Stable high	10,606	173	—		7,239	90	—	
Stable low	1,673,477	43,893	1.153 (0.989 to 1.343)	0.11	1,078,165	21,861	0.929 (0.748 to 1.152)	0.53
Decreasing	30,828	577	1.132 (0.955 to 1.343)	0.15	21,850	280	0.914 (0.720 to 1.160)	0.53
Increasing	124,012	3,094	1.154 (0.987 to 1.349)	0.11	72,892	1,321	0.933 (0.748 to 1.162)	0.53
Heart failure								
Walkability								
Stable high	10,606	73	—		7,239	30	—	
Stable low	1,673,477	21,171	1.102 (0.870 to 1.395)	0.63	1,078,165	7,488	0.754 (0.518 to 1.097)	0.17

Decreasing	30,828	232	1.042 (0.800 to 1.356)	0.76	21,850	64	0.547 (0.353 to 0.846)	0.020
Increasing	124,012	1,508	1.108 (0.872 to 1.407)	0.63	72,892	441	0.767 (0.523 to 1.125)	0.17

[1] HR = Hazard Ratio, CI = Confidence interval

[2] *P* values after false discovery rate correction for multiple testing

Models adjusted for age, sex, ethnicity, change in partner status, area level SES, mean $PM_{2.5}$ exposure, urbanicity and residential relocation.

Table S14. Associations between trajectories of neighbourhood walkability and incident CVD stratified by area-level SES

	Below average area-level SES				Above average area-level SES			
	N	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**	**N**	**Event N**	**HR (95% CI)[1]**	***p*-value[2]**
Any CVD								
Walkability								
Stable high	12,809	2,071	—		5,036	620	—	
Stable low	2,073,106	460,796	1.059 (1.013 to 1.107)	**0.034**	678,536	133,019	1.014 (0.934 to 1.101)	0.74
Decreasing	37,075	6,162	1.003 (0.954 to 1.054)	0.91	15,603	1,975	0.944 (0.862 to 1.033)	0.63
Increasing	151,653	32,245	1.054 (1.007 to 1.103)	**0.035**	45,251	7,897	1.016 (0.934 to 1.106)	0.74
CVD mortality								
Walkability								
Stable high	12,809	235	—		5,036	43	—	
Stable low	2,073,106	63,418	0.992 (0.869 to 1.131)	0.90	678,536	12,011	0.786 (0.575 to 1.073)	0.13
Decreasing	37,075	734	0.973 (0.840 to 1.128)	0.90	15,603	120	0.676 (0.476 to 0.960)	0.086
Increasing	151,653	4,451	0.982 (0.859 to 1.123)	0.90	45,251	588	0.771 (0.560 to 1.061)	0.13
Coronary heart disease								
Walkability								
Stable high	12,809	489	—		5,036	154	—	
Stable low	2,073,106	105,896	1.084 (0.989 to 1.188)	0.25	678,536	30,617	1.001 (0.848 to 1.180)	>0.99
Decreasing	37,075	1,469	1.024 (0.924 to 1.134)	0.66	15,603	453	0.885 (0.737 to 1.063)	0.57
Increasing	151,653	7,282	1.054 (0.960 to 1.158)	0.40	45,251	1,831	0.990 (0.835 to 1.172)	>0.99
Stroke								
Walkability								
Stable high	12,809	203	—		5,036	60	—	
Stable low	2,073,106	52,142	1.134 (0.984 to 1.307)	0.11	678,536	13,612	0.880 (0.675 to 1.146)	0.36
Decreasing	37,075	688	1.138 (0.972 to 1.331)	0.11	15,603	169	0.795 (0.592 to 1.068)	0.36
Increasing	151,653	3,652	1.133 (0.981 to 1.309)	0.11	45,251	763	0.882 (0.673 to 1.157)	0.36
Heart failure								
Walkability								
Stable high	12,809	83	—		5,036	20	—	
Stable low	2,073,106	24,160	1.071 (0.858 to 1.336)	0.79	678,536	4499	0.663 (0.418 to 1.052)	0.10
Decreasing	37,075	253	0.966 (0.753 to 1.239)	0.79	15,603	43	0.535 (0.314 to 0.912)	0.065

Increasing	151,653	1,719	1.073 (0.857 to 1.343)	0.79	45,251	230	0.673 (0.419 to 1.080)	0.10

[1] HR = Hazard Ratio, CI = Confidence interval

[2] *P* values after false discovery rate correction for multiple testing

Models adjusted for age, sex, ethnicity, change in partner status, mean household income, mean $PM_{2.5}$ exposure, urbanicity and residential relocation.

CHAPTER 6

Impact of green space exposure on blood pressure in Guangzhou, China: mediation by air pollution, mental health, physical activity, and weight status

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Abstract

Background: Green space exposure has been inversely associated with blood pressure (BP) levels and hypertension risk. However, empirical evidence on the underlying mechanisms are lacking. This study examined the association of green space exposure with BP and hypertension, and assessed the mediating effects by air pollution, mental health, physical activity, and weight status.

Methods: Survey data from 719 adults, who lived in Guangzhou (China) in 2016, were used. Three area-level green space indicators, including network distance to the nearest park, percentage of green space and Normalized Difference Vegetation Index within a 1km Euclidean buffer around residence and workplace, were calculated and linked to individual-level BP measurements. Structural equation models were applied to estimate the direct and indirect associations of the various green space indicators on systolic BP (SBP), diastolic BP (DBP), and hypertension, respectively.

Results: After adjusting for multiple covariates, longer network distance to green space was directly associated with higher SBP. Compared to the reference group (0-500m), the differences were 0.11 mmHg (95% CI=0.03 to 0.19, *P*=0.006) for 500-1000m, 0.03 mmHg (95% CI=-0.05 to 0.12, *P*=0.45) for 1000-1500m, and 0.16 mmHg (95% CI=0.09 to 0.23, *P*<0.001) for >1500m, respectively. The overall and direct associations were significant for all three indicators (distance or density) with or without considering workplace exposure. The association between network distance to green and SBP was partially (18.4%, 95% CI=0 to 42.1%) mediated by mental health. There was no statistical evidence that air pollution, physical activity, or weight status mediate the association. Secondary analyses for other indicators and other outcomes showed similar results.

Conclusion: Both distance to green space and more green space around residence and workplace were associated with lower BP and lower risk of hypertension in adults living in a Chinese metropolitan. Mental health partly mediated the association.

Introduction

Hypertension remains the top risk factor for global burden of cardiovascular disease, which is the leading cause of global disability and mortality [1]. The number of hypertensive adults aged 30 to 79 years has doubled from 650 million in 1990 to 1.28 billion in 2019 [2]. Most significant increase has been reported in low- and middle-income countries [2]. In China, the number of hypertensive adults increased from about 90 million in 1990 to 244.5 million in 2012-2015 [3,4]. Identifying modifiable risk factors of hypertension is urgently needed to inform policies and strategies to prevent adults from hypertension.

Among modifiable risk factors against hypertension, green space exposure (areas with vegetation) is an upstream determinant that drives other relevant factors, such as mental disorders, BMI, and physical activity [5]. A recent systematic review and meta-analysis on the association between green space and blood pressure (BP) identified 38 studies globally till 2021, and found a significant protective association of green space exposure on BP [6]. This review indicated that the underlying mechanisms linking green space to BP have not been clearly established in previous research, and that additional research is needed to examine potential underlying mechanisms [6]. In the literature, three main biopsychosocial pathways have been suggested on how green space exposure can favorably affect BP [7]. First, green space could reduce harmful exposures. For instance, green space can reduce air pollution via deposition, and in turn reduced air pollution is associated with lower BP [7,8]. Second, green space may can reduce physiological stress and improve mental health, which is an important determinant of BP [7]. Third, green space may can encourage physical activity, which is protective against high BP [7]. Besides, green space exposure is associated with overweight and obesity [9], which are widely recognized as major causes of hypertension [10]. Although several pathways have been proposed, empirical evidence on these mechanisms are currently lacking [7].

In addition, the same review found inconsistent results for different measures of green

space [6]. Significant pooled evidence was found for inverse associations of Normalized Difference Vegetation Index (NDVI) and the proportion of green space in the residential environment with BP, but not for the distance to residential green space [6]. The credibility of the pooled evidence was rated as low-to-moderate for NDVI, and very low for proportion of green space and distance to green space [6]. In addition, previous studies mainly focused on residential green space exposure and ignored the green space exposure from workplaces. Therefore, high-quality research is required to provide evidence for various measures of green space exposure, including green space exposure measures from workplace.

The present study aims to examine the impact of objectively measured green space exposure in the residence and combined residence-work environment on blood pressure (BP) and hypertension in adults living in Guangzhou, China, and to assess whether these associations are mediated by air pollution, mental health, physical activity, and weight status. It is hypothesized that higher levels of green space exposure are associated with lower BP and lower risk of hypertension, and that this can be partly attributed to lower levels of air pollution exposure and Body Mass Index (BMI), and higher levels of mental health and physical activity.

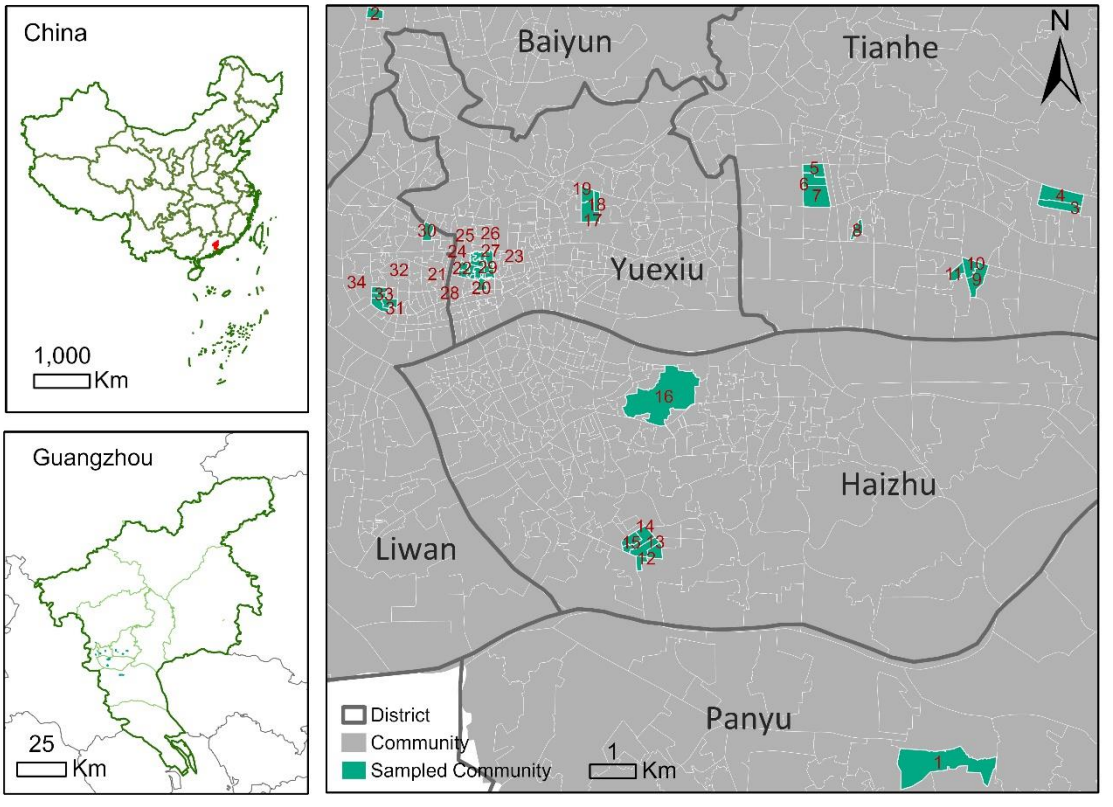
Materials and Methods

Data collection and study population

A cross-sectional study was conducted in January 2016 in Guangzhou city, China. A stratified random sampling method was used to select a sample of participants who was representative for the 34 communities in Guangzhou. Specifically, the sampled communicates are located in central, transitional, and marginal areas of Guangzhou and make a good representation for Guangzhou with regard to population and housing condition [11]. The study areas and sampled communities are shown in **Figure 1**. Based on the population size of adults in each community, a total of 1050 questionnaires were proportionally distributed to the 34 communities. Then, within each community, adult participants were randomly selected. All participants underwent a face-to-face

interview at home to complete a questionnaire and underwent a physical examination. Trained interviewers and technicians administered the process. Each interview took about 20 to 25 minutes. The questionnaire concerns sociodemographic information, migration history, living and working conditions, health behaviours, and health conditions. In addition, information on each participant's home address and workplace address were collected. The recruitment and data collection took two months. More information on study design is available elsewhere [11]. Ethical approval for this study was obtained from the Review Board of Sun Yat-sen University. All participants provided informed consent.

Adults aged ≥19 years, who lived in the corresponding community, and who were not students were eligible for inclusion. Of all 1050 participants who received a questionnaire, twenty-one participants with incomplete and inconsistent responses were excluded, resulting a valid response rate of 98%. We further excluded seven participants who had unrealistic values on height (<100 cm), weight (<10 kg), systolic BP (SBP >300 mmHg), or diastolic BP (DBP <10 mmHg). These unrealistic values were assumed to be measurement error or typos. Finally, we excluded 303 participants who missed values on physical activity. The analytical sample included 719 participants.



1. Huananxincheng; 2. Jide; 3. Tangdenan; 4. Tangdebei; 5. Qiaoting; 6. Yakang; 7. Huaxin; 8. Lvhe; 9. Xinjie; 10. Changleyuan; 11. Xincun; 12. Mingyuan; 13. Ruibao; 14. Xiaogangwan; 15. Qiaocheng; 16. Zhongda; 17. Ermalu; 18. Liumalu; 19. Zhongmalu; 20. Qingfuli; 21. Sanyuanxiang; 22. Zaozixiang; 23. Yuhuafang; 24. Heyixiang; 25. Yileli; 26. Xiaoyoudong; 27. Huilongli; 28. Xinghuaxiang; 29. Yuntaili; 30. Jixiang; 31. Taihua; 32. Baoyuan; 33. Xinfeng; 34. Zhibao

Figure 1. Study areas and sampled communities.

Dependent variables: blood pressure and hypertension

The questionnaire collected participants' history of use of anti-hypertensive medicine. After the 20-25 min interview, trained technicians followed a research protocol and measured BP in mmHg of participants in seated position on the right arm. Using a standard mercury sphygmomanometer, the SBP and DBP were measured once for each

participant. Hypertension was ascertained by meeting at least 1 of 3 criteria: (1) SBP ≥140 mmHg; (2) DBP ≥90 mmHg; (3) use of anti-hypertensive medicine.

Independent variables: green space exposure measures

Three objectively measured indicators of green space were calculated in the residential environment and workplace environment of each participant: (1) network distance to nearest entrance of a park, (2) percentage of area devoted to green space in a 1km Euclidean buffer zone, and (3) the NDVI. These three indicators were calculated by applying Geographical Information System techniques in ArcGIS [12].

The first indicator was the network distance (distance along roads) to the nearest entrance of a park (public garden). A land classification database defining green space and an open street map of Guangzhou in 2014 were used to identify all locations where roads and paths crossed the entrance location of a park [13]. Subsequently, various street-network based service areas were calculated. A network service area is an area that encloses all accessible streets within a specified street network distance. Service areas of 500m, 1000m, 1500m, and 2000m around park entrances were created. Each address was labeled to be located within a certain service area (0-500m, 500-1000m, 1000-1500m, or >1500m). As an example, the network service area of 500 m is given in **Figure 2**.

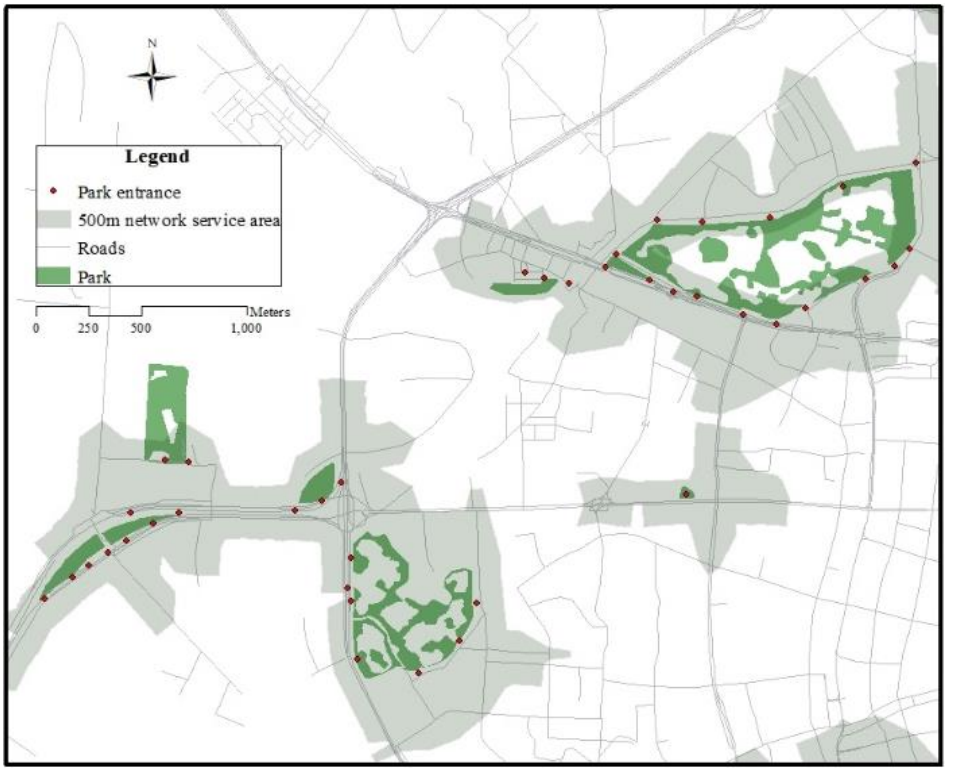


Figure 2. Network service area of 500m in a neighborhood of Guangzhou, China.

The second green space indicator was the percentage of total green space (parks and other not specified green space categories) in an Euclidean buffer of 1km around each address was calculated based on the land classification database in 2014 [13].

The third green space indicator was NDVI in a Euclidean buffer of 1km around each residential address. The NDVI was assessed by using Landsat 7-8 satellite images at 30m × 30m spatial resolution [14]. The cloud-free images in 2014 were derived. Guangzhou has a maritime subtropical monsoon climate, which means there is little seasonal change in vegetation. Therefore, seasonal differences were ignored when selecting a satellite image. The NDVI values range from -1 to 1, with higher values indicating a higher density of green vegetation. Negative values correspond to cloud or water, and were set to zero.

Potential mediators

Annual average outdoor concentrations of particulate matter with a diameter of

<2.5μm ($PM_{2.5}$) in μg/m^3 were obtained at the 1 km ground-level for 2014 from the ChinaHighAirPollutants dataset [15,16]. It is a product generated from big data (ground-based measurements, satellite remote sensing products, atmospheric reanalysis, and chemical transport model simulations) using the artificial intelligence approach by considering the spatiotemporal heterogeneity of air pollution [15,16]. Mental health was measured using the World Health Organization's Five Well-Being Index (WHO-5) [17]. The WHO-5 consists of five questions each in a 6-point Likert scale. The questions are about feelings of "cheerful and in good spirits", "calm and relaxed", "active and vigorous", "fresh and rested", and "daily life has been filled with things that interest me" during the past two weeks. The WHO-5 score ranges from 0 to 25, with 0 representing worst possible and 25 representing best possible mental wellbeing. The time spent on outdoor physical activity in hours during the previous week was self-reported. Weight (in kg) and height (in m) were measured by trained technicians using standardized methods. BMI was computed as weight divided by square of height.

Covariates

A directed acyclic graph was adopted to choose confounders (**Appendix Figure S1**). Covariates that were included in this study were age, sex (male, female), educational level (primary or middle school, high school, college, university bachelor or higher), marital status (not married, divorced, or widowed; married), occupational status (employed, unemployed), smoking history (yes, no), alcohol use (yes, no), household income (<10000 Yuan/month, 10000-15000 Yuan/month, 15000-20000 Yuan/month, ≥20000 Yuan/month), number of family members, district (Tianhe, Baiyun, Fanyu, Haizhu, Liwan, Yuexin), and use of anti-hypertensive medicine (yes, no. only in blood pressure models). They were also frequently included in previous studies of green space and BP [6]. Information on these covariates were collected in the questionnaire.

Statistical analysis

Structural Equation Models were used to estimate the direct and indirect associations of the various green space indicators on SBP, DBP and hypertension. The theoretical framework for these models is based on previous literature, and is presented in **Figure**

3 [7]. In primary analyses, the model was constructed for network distance to green space from residence and for SBP. In order to evaluate the model fit, the Comparative Fit Index (CFI, >0.90 good fit), the Tucker Lewis Index (TLI, >0.90 good fit), Root Mean Square Error of Approximation (RMSEA, ≤0.05 good fit, ≤0.08 reasonable fit), and Standardized Root Mean-square Residual (SRMR, <0.08 good fit) were used. In secondary analyses, the models were constructed for the other two exposure indicators (percentage of total green space and NDVI around residence) and for the other two outcomes (DBP and hypertension). In addition, a combined residence and workplace exposure was calculated giving weights of 2/3 for values of residence and 1/3 for values of workplace. All statistical analyses were conducted using the lavaan package in R software [18]. Statistical significance was defined as *P*<0.05 (two-sided).

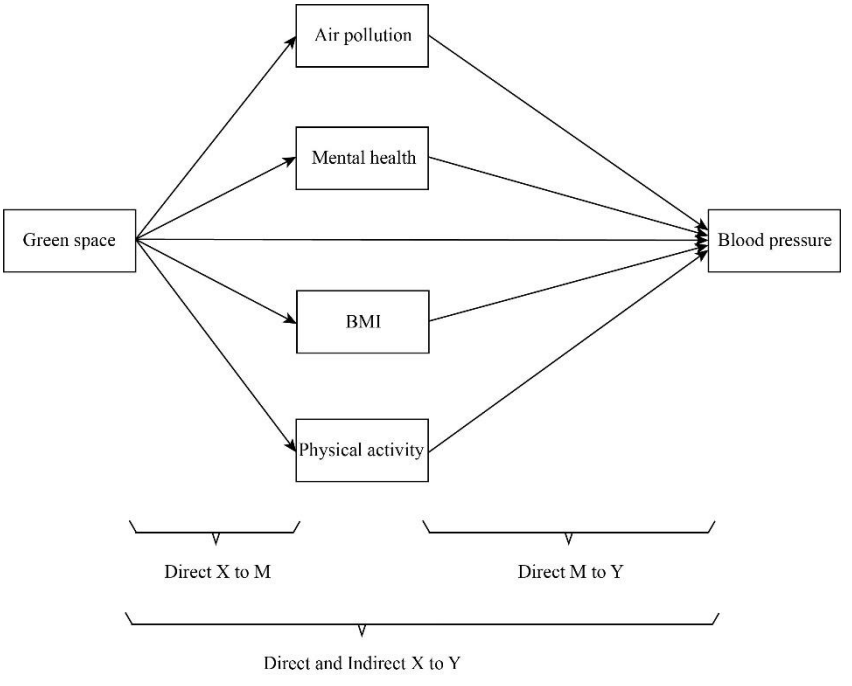


Figure 3. Theoretical framework on which the Structural Equation Models were based. Air pollution, mental health, physical activity, and weight status are mediators (M) in the relation of green space (X) and systolic blood pressure (Y).

Results

Characteristics of the study sample are shown in **Table 1**. The mean age of participants was 42.3 years (SD=13.7). The percentage of male participants was 49.4%. The mean SBP and DBP of participants were 119.2 mmHg (SD=16.3) and 78.5 mmHg (SD=10.2), respectively. The hypertensive adults consisted 17.0% of all participants. The percentages of participants in each category of network distance to green space were 17.1% for 0-500m, 45.5% for 500-1000m, 25.9% for 1000-1500m, and 11.5% for >1500m, respectively. The mean annual average concentration of $PM_{2.5}$ at participants' residence was 43.7 μg/m^3 (SD=1.8). The mean WHO-5 score for mental health was 12.1 (SD=3.8). The mean time spent on outdoor physical activity was 4.6 hours per week (SD=3.3).

Table 1. Characteristics of the analytic sample (n=719)

Variables	Participants
Age (years), mean ± SD	42.3 ± 13.7
Male (%)	49.4
Education (%)	
Primary or middle school	15.7
High school	37.4
College	28.1
University bachelor or higher	18.8
Marital status (%)	
Not married, divorced, or widowed	17.5
Married	82.5
Occupation status (%)	
Employed	83.0
Unemployed	17.0
Smoking history (%)	40.3
Alcohol use (%)	24.2
Household income (%)	
<10000 Yuan/month	28.4
10000-15000 Yuan/month	33.7

15000-20000 Yuan/month	24.0
≥20000 Yuan/month	13.9
Number of family members, mean ± SD	3.3 ± 0.9
District (%)	
Tianhe	42.7
Baiyun	9.0
Fanyu	12.1
Haizhu	20.6
Liwan	8.8
Yuexiu	6.8
Use of anti-hypertensive medicine (%)	3.6
$PM_{2.5}$ (μg/m^3), mean ± SD	43.7 ± 1.8
Mental health, mean ± SD[1]	12.1 ± 3.8
Outdoor physical activity (hours in a week), mean ± SD	4.6 ± 3.3
Network distance to green space from residence (%)	
0-500m	17.1
500-1000m	45.5
1000-1500m	25.9
>1500m	11.5
Percentage of green space within 1 km buffer of residence, mean ± SD	4.4 ± 4.1
NDVI within 1km buffer of residence, mean ± SD[2]	0.12 ± 0.04
Systolic blood pressure (mmHg), mean ± SD	119.2 ± 16.3
Diastolic blood pressure (mmHg), mean ± SD	78.5 ± 10.2
Hypertension (%)	17.0

[1] The mental health was assessed by the World Health Organization's Five Well-Being Index. The score ranges from 0 to 25, 0 representing worst possible and 25 representing best possible quality of life.

[2] Normalized Difference Vegetation Index (NDVI)

Standardized total associations of all models between green space exposure and blood pressure are summarized in **Table 2**. Almost all models showed significant associations, no matter using the SBP, DBP, or hypertension as the outcome; no matter using the network distance, percentage of green space, or NDVI as indicator for green space exposure; and no matter using the residence exposure or residence and workplace

combined exposure. Higher distance to green space was associated with higher BP and a higher risk of hypertension. Higher percentage of green space or higher NDVI was associated with lower BP and a lower risk of hypertension.

Table 2. Standardized total associations between green space exposure[1] and blood pressure using Structural Equation Model, n=719[1,2]

Models	Standardized estimate (95% CI)[3]	*P* value
Outcome: SBP		
Model 1a: network distance from residence	0.07 (0.01, 0.13)	0.02*
Model 2a: percentage from residence	-0.09 (-0.16, -0.03)	0.007**
Model 2b: weighted percentage from residence and workplace	-0.07 (-0.13, -0.01)	0.03*
Model 3a: NDVI from residence	-0.15 (-0.22, -0.08)	<0.001***
Model 3b: weighted NDVI from residence and workplace	-0.12 (-0.19, -0.06)	<0.001***
Outcome: DBP		
Model 1b: network distance from residence	0.11 (0.05, 0.18)	0.001**
Model 2c: percentage from residence	0.01 (-0.07, 0.08)	0.84
Model 3c: NDVI from residence	-0.29 (-0.37, -0.21)	<0.001***
Outcome: hypertension		
Model 1c: network distance from residence	1.00 (0.94, 1.07)	0.98
Model 2d: percentage from residence	0.93 (0.87, 0.99)	0.03*
Model 3d: NDVI from residence	0.87 (0.81, 0.94)	<0.001***

[1] Total associations estimated in models 1a, 1b and 1c were calculated treating the network distance as a continuous variable.

[2] For model 2b and 3b, the weights were 2/3 for value of residence and 1/3 for value of workplace.

[3] The standardized estimates were beta for models using SBP and DBP as outcome. The standardized estimates were OR for models using hypertension as outcome.

*P <0.05, **P <0.01, ***P <0.001.

Standardized direct association estimates of network distance to green space from residence on SBP are presented in **Figure 4**. The model goodness-of-fit was acceptable. After adjusting for age, sex, educational level, marital status, occupational status, smoking history, alcohol use, household income, number of family members, district, and use of anti-hypertensive medicine, longer network distance to green space was associated with higher SBP. Compared to the reference group (0-500m), the differences were 0.11 mmHg (95% CI=0.03 to 0.19, *P*=0.006) for 500-1000m, 0.03 mmHg (95% CI=-0.05 to 0.12, *P*=0.45) for 1000-1500m, and 0.16 mmHg (95% CI=0.09 to 0.23, *P*<0.001) for >1500m, respectively. The direct pathways from green space exposure to air pollution, mental health, and physical activity were all statistically significant. The direct pathway from BMI to SBP was also statistically significant.

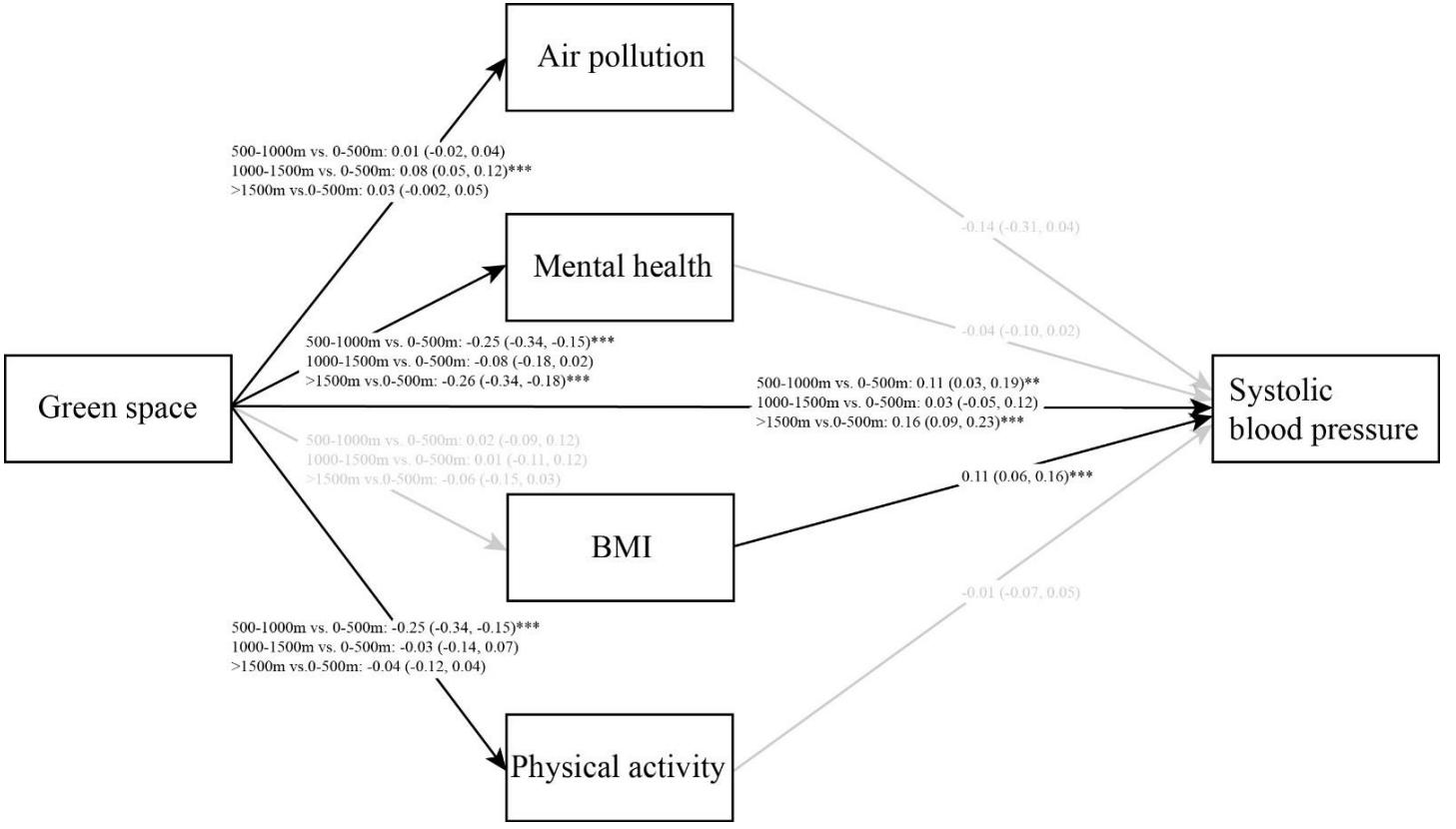


Figure 4. Structural Equation Model of network distance from residence to green space and systolic blood pressure. CFI=0.981, TLI=0.908, RMSEA=0.061, SRMR=0.010. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001

Table 3 presents the standardized indirect associations and total associations of network distance to nearest green space on BP. The indirect association of green space exposure on SBP via mental health was significant (β=0.013, 95% CI=0.0003 to 0.026, *P*=0.045). The indirect association via air pollution (β=-0.006, 95% CI=-0.013, 0.002, *P*=0.12), via physical activity (β=0.002, 95% CI=-0.005 to 0.009, *P*=0.64), and via BMI (β=0.001, 95% CI=-0.008 to 0.009, *P*=0.90) were not significant. The total association combining direct and indirect associations was significant (β=0.070, 95% CI=0.010 to 0.131, *P*=0.02). Therefore, 18.4% (95% CI=0 to 42.1%) of the total association between network distance to green space and SBP was explained by the mediating effect of mental health.

Table 3. Standardized indirect associations and total associations of green space exposure[1] on blood pressure using Structural Equation Model, n=719

	Standardized estimate (95% CI)	*P* value	Percentage of total associations explained by the mediation (95% CI)
Specific indirect associations			
Via air pollution	-0.006 (-0.013, 0.002)	0.12	8.2 (0, 21.1)
Via mental health	**0.013 (0.0003, 0.026)**	**0.045***	18.4 (0, 42.1)
Via physical activity	0.002 (-0.005, 0.009)	0.64	2.4 (0, 12.4)
Via BMI	0.001 (-0.008, 0.009)	0.90	0.8 (0, 12.6)
Total indirect associations	0.009 (-0.009, 0.027)	0.31	13.3 (0, 40.1)
Total associations	**0.070 (0.010, 0.131)**	**0.02***	

[1] Network distance from residence. Associations were calculated treating the network distance as a continuous variable.

**P* <0.05, ***P* <0.01, ****P* <0.001

The secondary analyses, focusing on the associations of percentage of green space and NDVI in relation to DBP and hypertension, showed similar results as the primary analyses on network distance to green space. Compared to the primary analyses of network distance, the models including NDVI revealed one contrasting finding: the

significant indirect association via mental health was in the unexpected direction. The same contrasting findings were found in models of SBP and hypertension, while models of DBP did not find significant indirect association via mental health (**Appendix Table S1 to S3**). **Appendix Figure S2 to S5** and **Appendix Table S1** showed results for percentage of total green space and NDVI from residence or from combined residence and workplace exposure in relation to SBP. **Appendix Figure S6 to S8** and **Appendix Table S2** showed results for three indicators from residence in relation to DBP. **Appendix Figure S9 to S11** and **Appendix Table S3** showed results for three indicators from residence in relation to hypertension.

Discussion

This study examined the association of three area-level green space measures with BP and hypertension in adults in Guangzhou, China, and assessed whether these associations were mediated by air pollution, mental health, physical activity, and weight status. The findings suggest that green space exposure may be associated with lower BP and lower risk of hypertension through two pathways: (1) a direct beneficial association of green space exposure on BP; and (2) an indirect association through the mediation of mental health. Though, the current study did not provide statistical evidence for mediating effects of air pollution, physical activity, and BMI in the relationship of green space with BP and hypertension.

The current results further strengthen the evidence of a beneficial association of green space exposure on BP. A recent systematic review and meta-analysis indicated mixed results regarding the association of green space with BP, and attributed this to the heterogeneity in green space exposure measures [6]. Of all included studies, 65% reported beneficial associations, of which the meta-analysis found significant associations for proportion of green space and NDVI but not for distance to green space [6]. Six studies have been identified in China and all reported significant negative relationships [19–24]. Among those, five used NDVI [20–24] and one used proportion of green space [19]. The current study provides robust evidence on green space exposure lowering BP for all

three green space indicators.

With regard to mechanisms, a direct association of green space exposure with BP and hypertension was found for all three green space indicators. The direct association was shown to be independent of air pollution, mental health, physical activity, weight status, age, sex, socio-economic status, and various lifestyle behaviours. There could be several plausible biological mechanisms that explain the direct association of green space on BP, which need to be confirmed in future research. First, exposure to green space may increase heart rate variability and vagal tone [25], which is associated with lower BP. Even just viewing the green space can elicit the response [25]. Second, trees can release certain chemicals like phytoncides that may inhibit inflammation in the body [26], which is associated with lower BP [27]. Third, interacting with diverse plant life exposes us to various microbes that may change the composition of gut microbiota [28], which influences metabolism, inflammation and decrease BP [29]. Besides, the identified direct association may also suggest residual mediation in the model. For instance, the current measurement of mental health may not perfectly capture the stress level of participants. However, green spaces exposure has been associated with decreased levels of cortisol [30], the stress hormone related to BP.

With regard to indirect associations, the findings in the current study support the view that mental health mediates the association of green space exposure with SBP and hypertension. This mediating effect was seldom tested by previous studies [6] and was not tested by previous studies in China [22–24]. A study in urban forest California and a study in an alpine valley Austria tested the mediation association by mental health but found no significant result [31,32]. Some field and laboratory experiments and observational studies have found evidence to support the potential role of green space reducing stress or increasing calmness [33–35]. But there is a lack of empirical evidence [7]. In our secondary analysis, the mediating effect via mental health was in the unexpected direction for NDVI. This was due to an inverse association between NDVI and mental health. A previous study in the same region also found an inverse association between NDVI and mental health [36]. The authors suggested that this relationship was moderated

by income level, i.e., there was a positive association in the low income group and an inverse association in the middle and high income groups [36]. It merits further research with larger sample sizes to explore this moderating effect by income.

The current study did not provide evidence of the mediating effect of air pollution, physical activity, and BMI. Previous studies in China found different results [22–24,37,38]. One study in central China found that the association of green space with BP was partly mediated by physical activity [22]. One study in Northeastern China found that the association was partly mediated by air pollution and weight status [23]. One study, covering a wide geographic area in China, found that the association was partly mediated by air pollution [24]. A nationwide study of Chinese middle-aged and elderly population found that the association was partially mediated by BMI [37]. Another nationwide study of Chinese children did not find evidence of mediation for air pollution and BMI [38]. They all used NDVI as green space indicator [22–24,37,38]. One explanation of this inconsistency is that mediating effect could be context-specific. The current study took samples in South China where the climate, land form and culture are different from other regions in China and from other parts of the world. For example, Guangzhou has little seasonal change in vegetation, which makes the vision of green space different from cities with four seasons. Guangzhou is mostly plain, which makes the distance to green space different from mountain cities. The culture of long-distance commute and work pressure makes the utilization of green space different from cities with different culture. On the other side, emerging green space indicators like neighborhood street-view greenery may be more directly associated with these mediators and should be employed in future research [39].

Strengths and limitations

The current study has several strengths, including the solid theoretical design, the inclusion of different types of green space indicators (accessibility and coverage), and taking into account exposures from both residence and workplace. However, there are several limitations to consider as well. First, the cross-sectional design impedes the inferring of causal relationship. Second, the relatively small sample size could limit the

generalization of the current results. Third, we acknowledge that measuring BP only once could lead to misclassification bias. However, it is unlike that the misclassification would be different depending on residence. Therefore, the misclassification bias did not impact the association between green space exposure and BP. Fourth, the green space indicators did not include types of vegetation such as trees, shrubs, or grass. The mechanism of how green space may decrease air pollution and further decrease BP may vary by types of vegetation. Fifth, the studied mediators may include measurement errors. Because the $PM_{2.5}$ concentration was based on 1km raster not on specific address, the WHO-5 only reflects state of mind in the recent period, and the physical activity was assessed by recall. Lastly, despite comprehensive adjustment for multiple covariates, there could be residual confounding due to unmeasured or imprecisely measured determinants of BP related to the exposure. Therefore, future longitudinal studies with a larger study sample, new indicators with specific types of vegetation and better mediator and outcome measurements are needed to appropriately assess mediating effects of air pollution, mental health, physical activity, and weight status in this region.

Conclusions

Both distance to green space and more green space coverage around residence and workplace were associated with lower SBP, lower DBP and lower risk of hypertension. Our findings support policies aiming to increase green space in public areas and especially for increasing the accessibility of parks in urban settings. The observed inverse associations of green space exposures with BP and hypertension were partly explained by better mental health. However, a mediating role for air pollution, physical activity, and weight status is not supported by our findings. Generalizing the current findings should take contextual factors, such as climate, land form and culture into account.

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Contributors:

M. Liu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Writing - original draft. **E.J. Timmermans:** Conceptualization; Project administration; Supervision; Writing - review & editing. **D. Zou:** Data curation; Methodology; Resources; Validation; Writing - review & editing. **D.E. Grobbee:** Supervision; Validation; Writing - review & editing. **S. Zhou:** Conceptualization; Supervision; Resources; Validation; Writing - review & editing. **I. Vaartjes:** Conceptualization; Project administration; Supervision; Validation; Writing - review & editing.

Conflicts of Interest: None.

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CHAPTER 6 Appendices

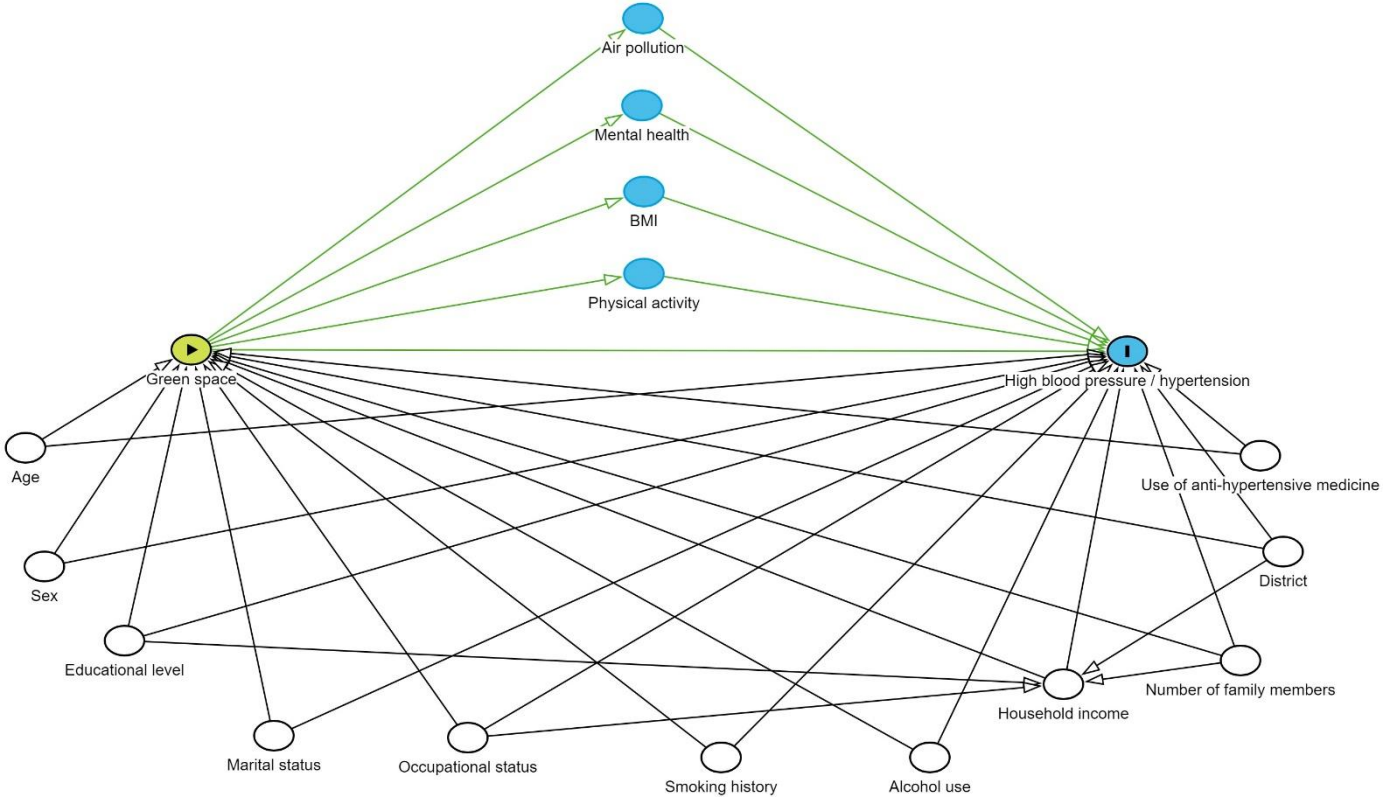


Figure S1. Directed acyclic graph of the association between green space and blood pressure.

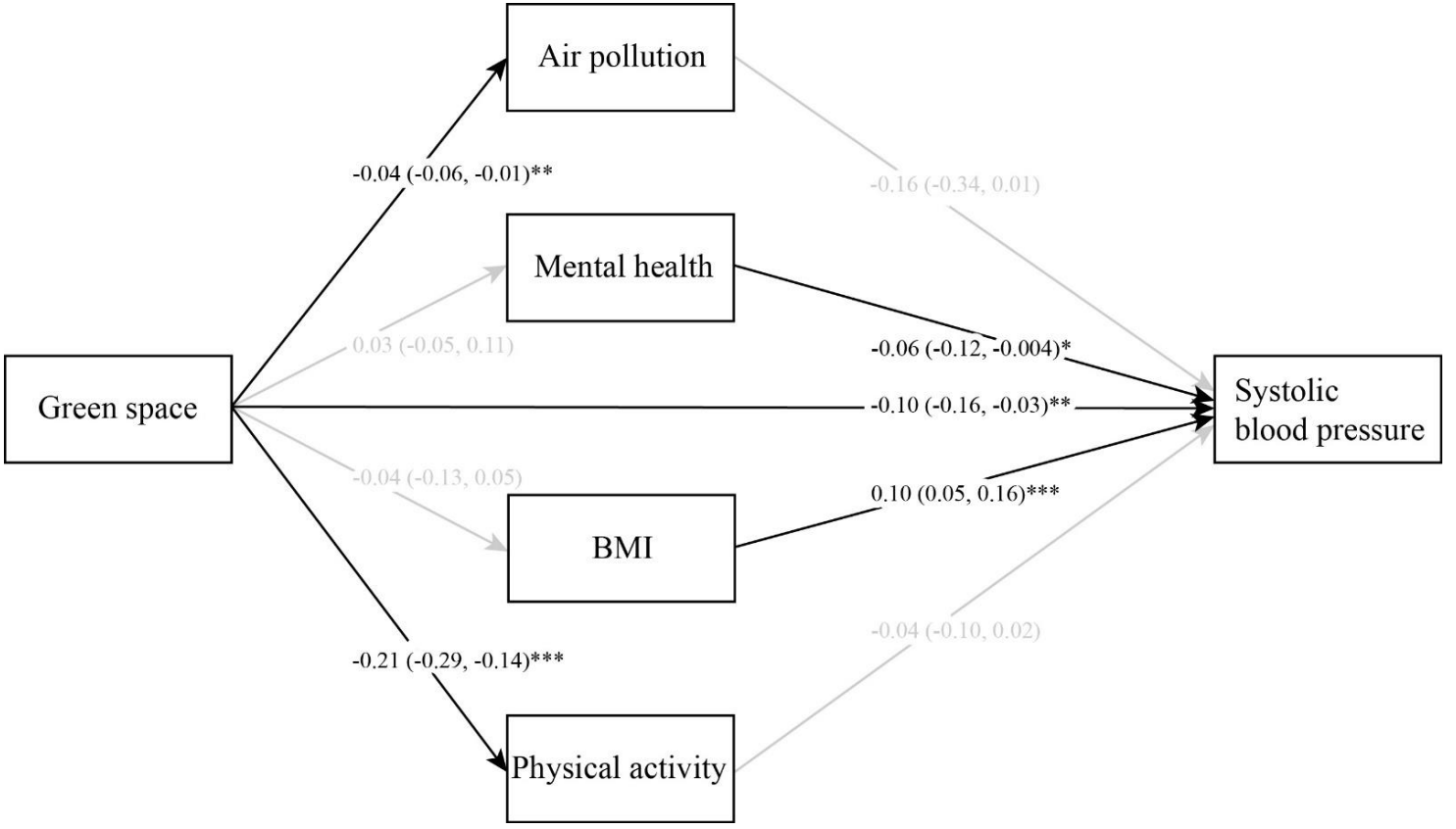


Figure S2. Model 2a. Structural Equation Model of percentage of green space within 1 km buffer of residence and systolic blood pressure. CFI=0.972, TLI=0.879, RMSEA=0.072, SRMR=0.014. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

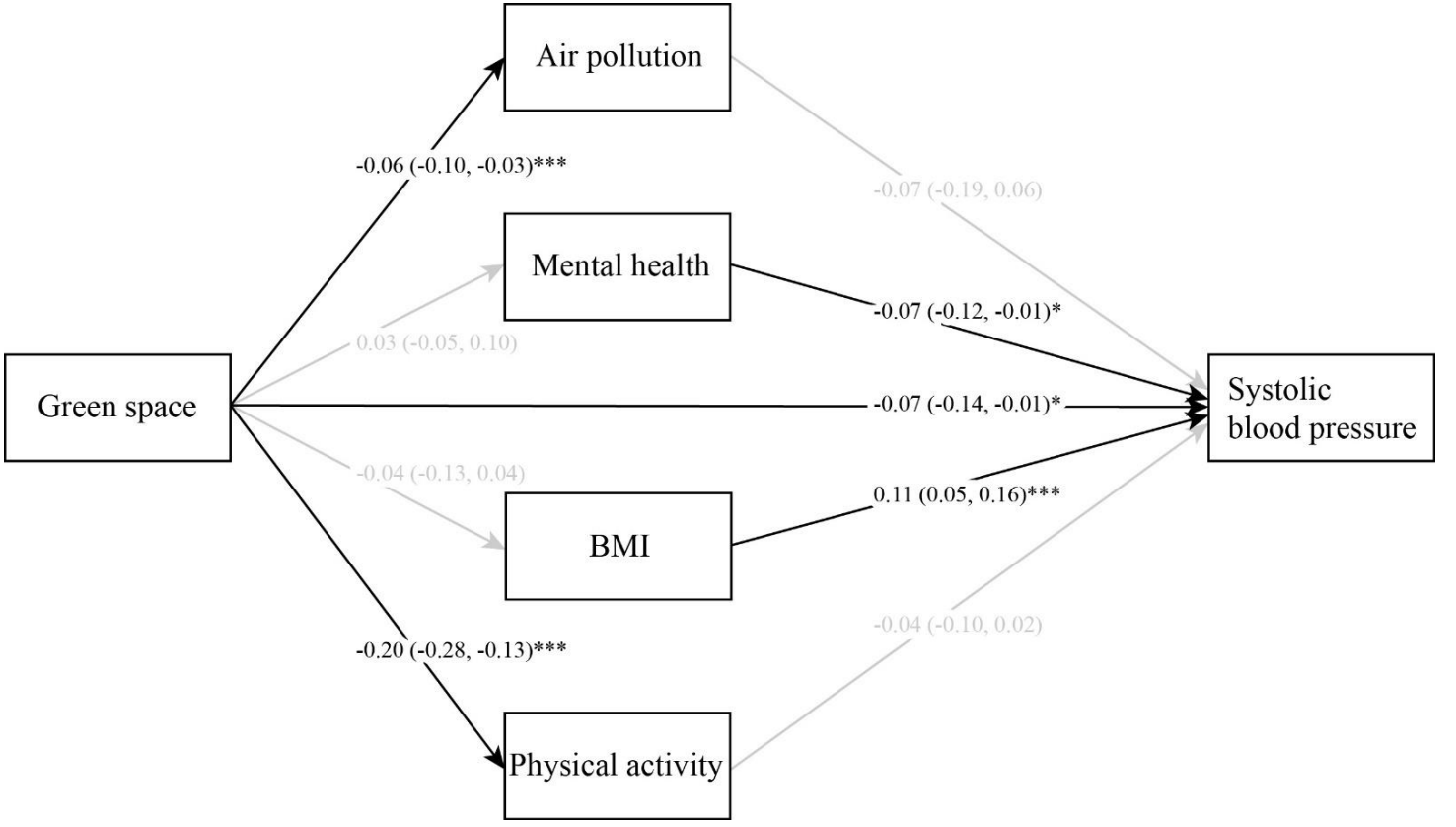


Figure S3. Model 2b. Structural Equation Model of weighted percentage of green space within 1 km buffer of residence and workplace and systolic blood pressure. CFI=0.962, TLI=0.840, RMSEA=0.076, SRMR=0.017. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

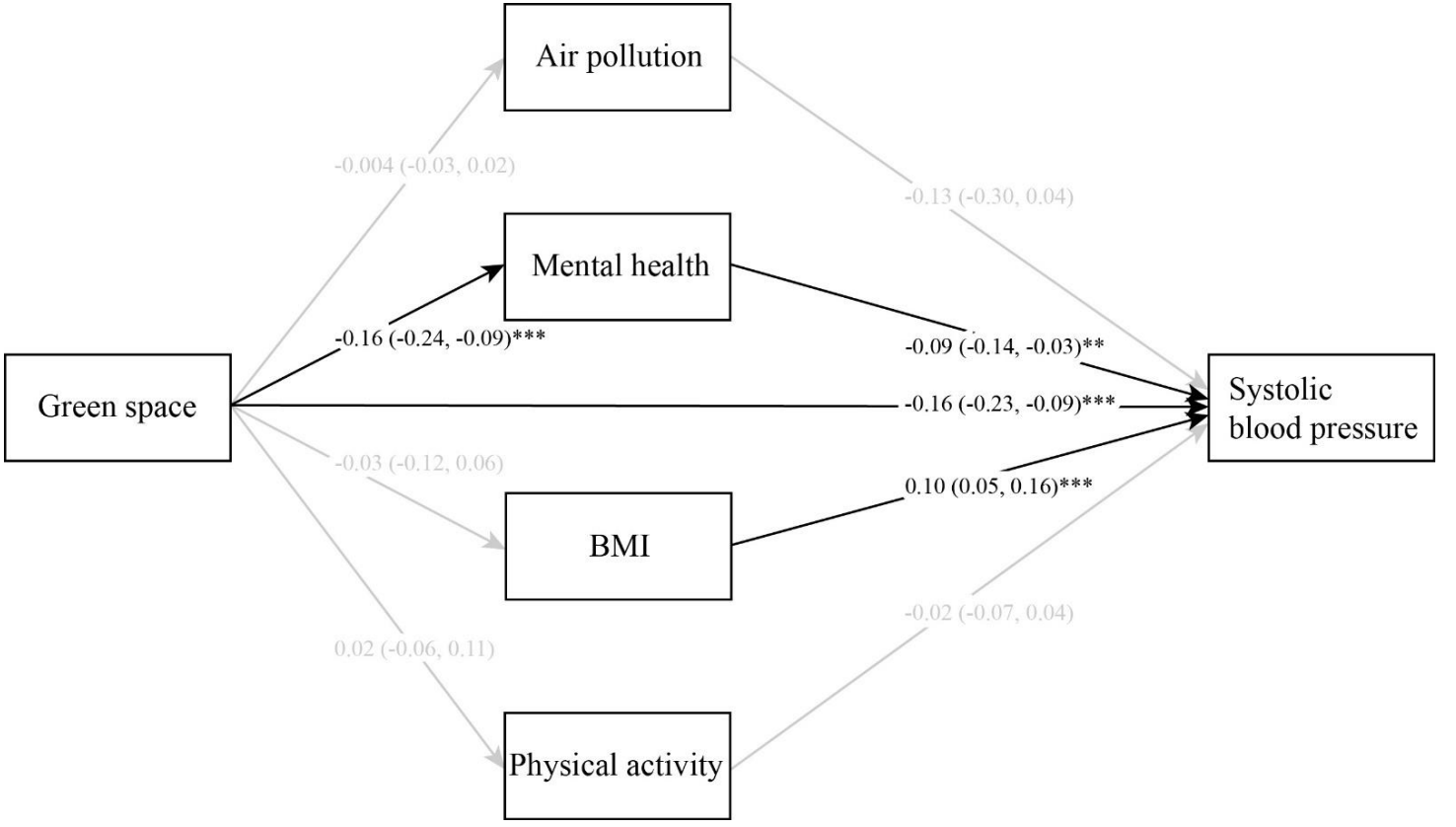


Figure S4. Model 3a. Structural Equation Model of NDVI within 1km buffer of residence and systolic blood pressure. CFI=0.975, TLI=0.900, RMSEA=0.066, SRMR=0.013. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

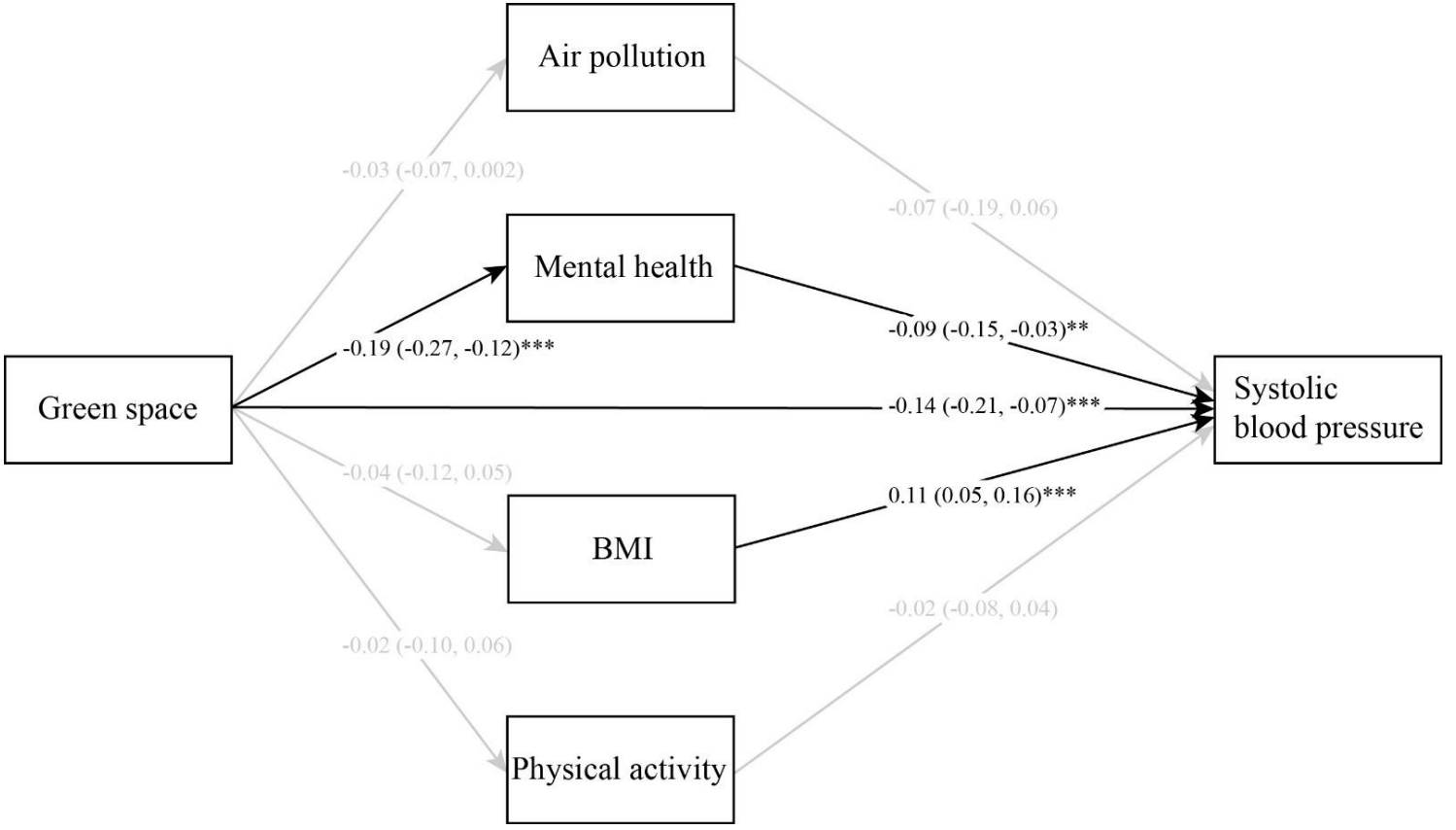


Figure S5. Model 3b. Structural Equation Model of weighted NDVI within 1km buffer of residence and workplace and systolic blood pressure. CFI=0.968, TLI=0.864, RMSEA=0.070, SRMR=0.015. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

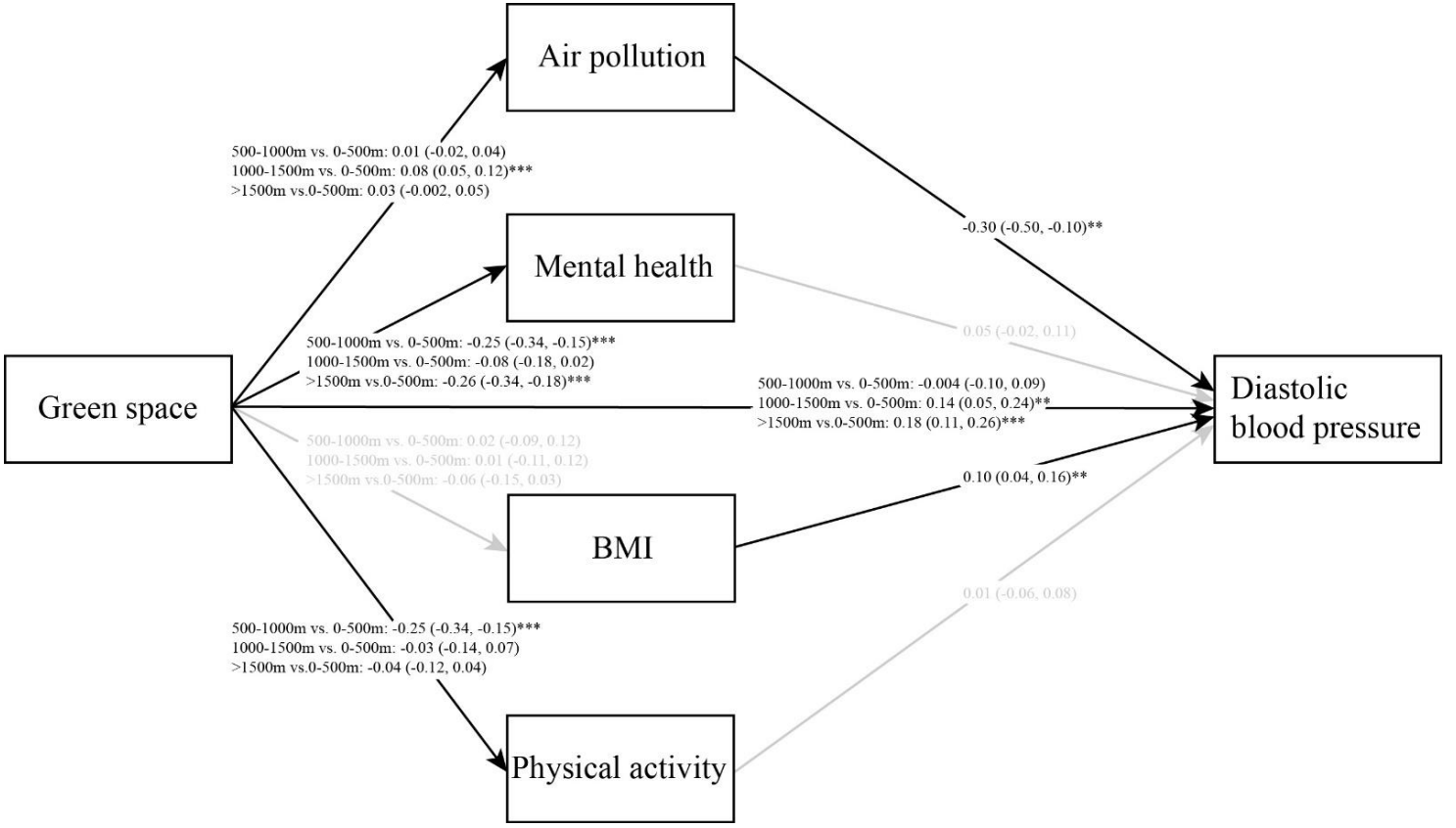


Figure S6. Model 1b. Structural Equation Model of network distance from residence to green space and diastolic blood pressure. CFI=0.975, TLI=0.880, RMSEA=0.068, SRMR=0.011. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

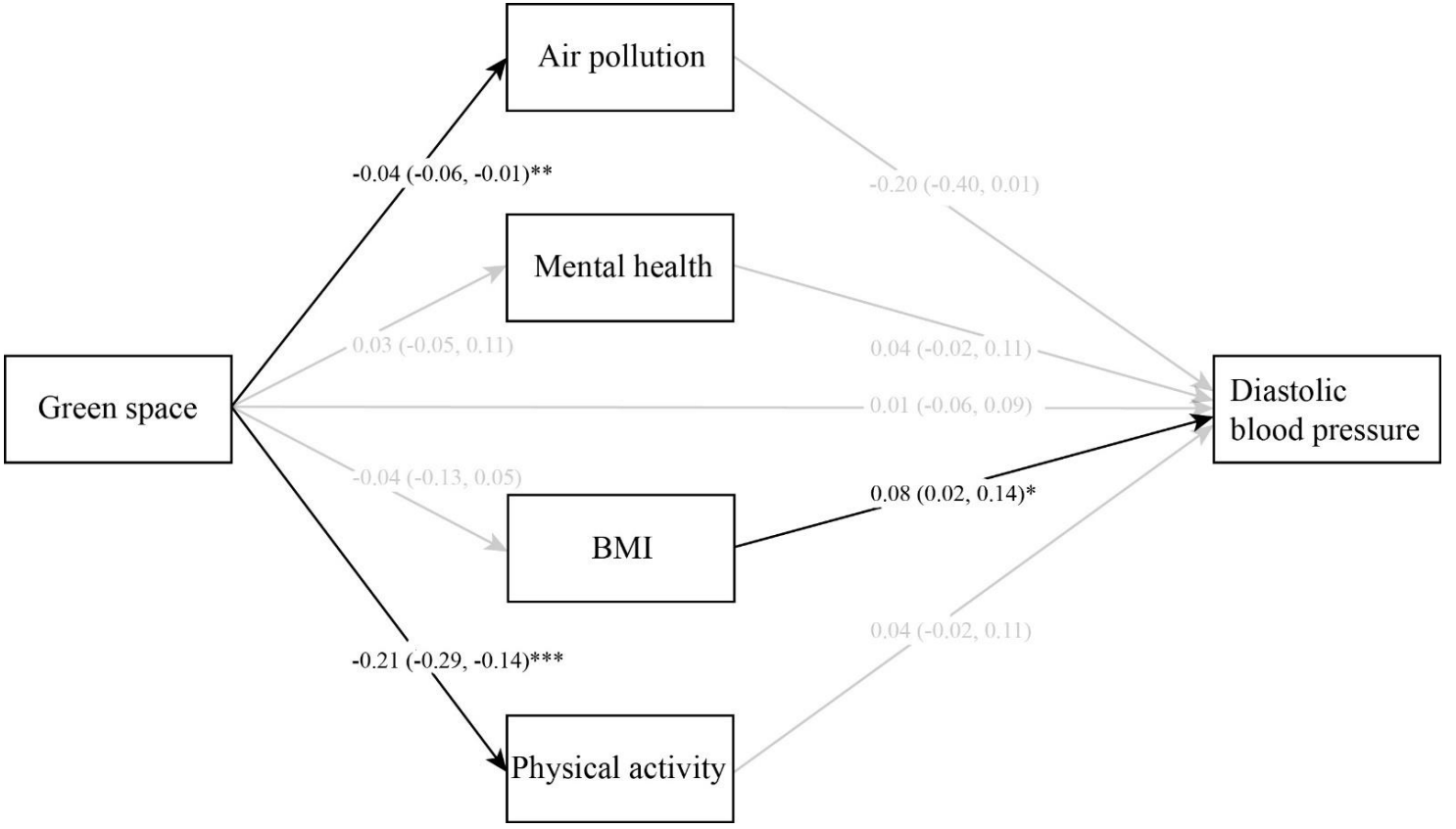


Figure S7. Model 2c. Structural Equation Model of percentage of green space within 1km buffer of residence and diastolic blood pressure. CFI=0.963, TLI=0.839, RMSEA=0.081, SRMR=0.015. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

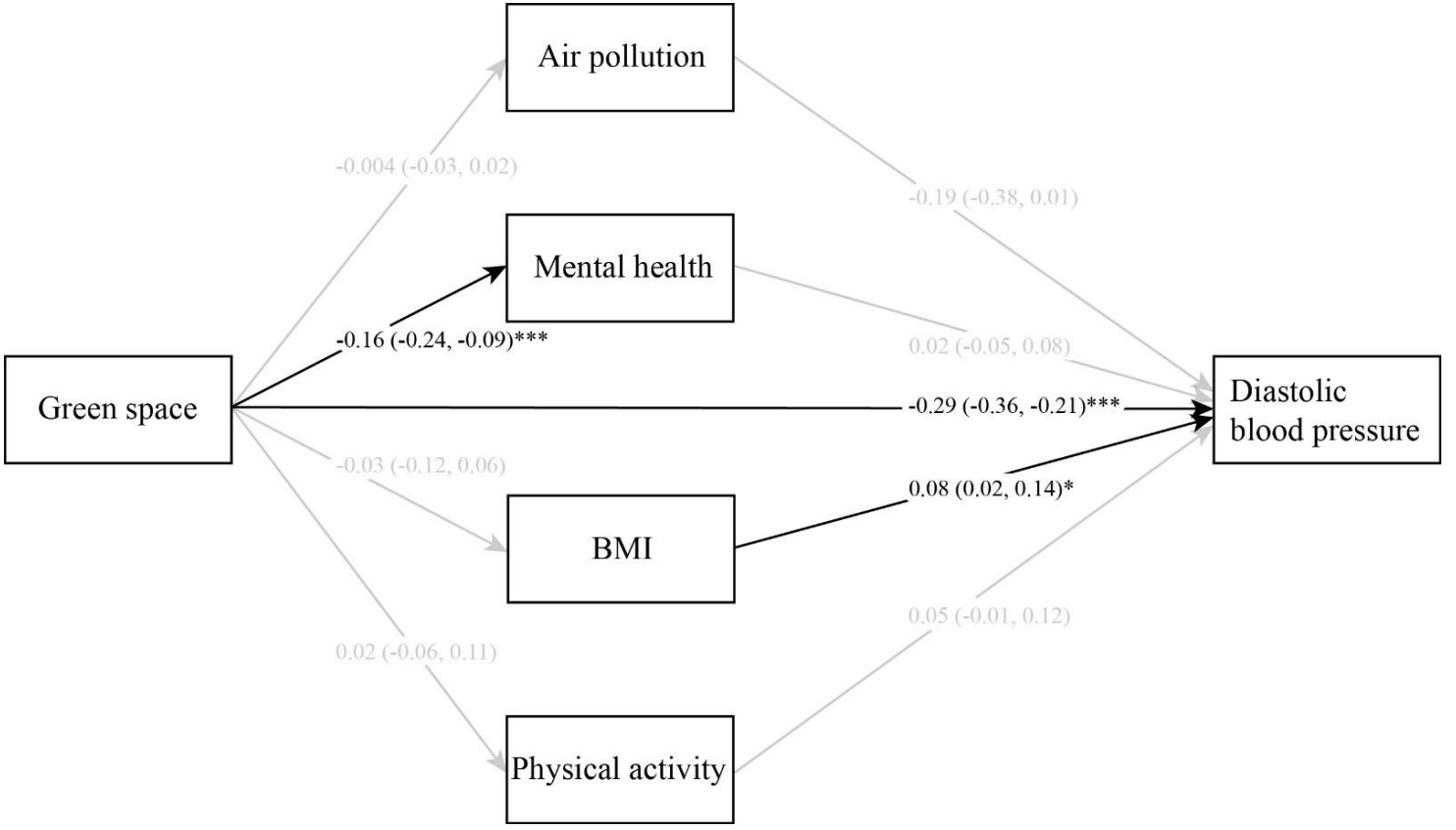


Figure S8. Model 3c. Structural Equation Model of NDVI within 1km buffer of residence and diastolic blood pressure. CFI=0.966, TLI=0.864, RMSEA=0.075, SRMR=0.014. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

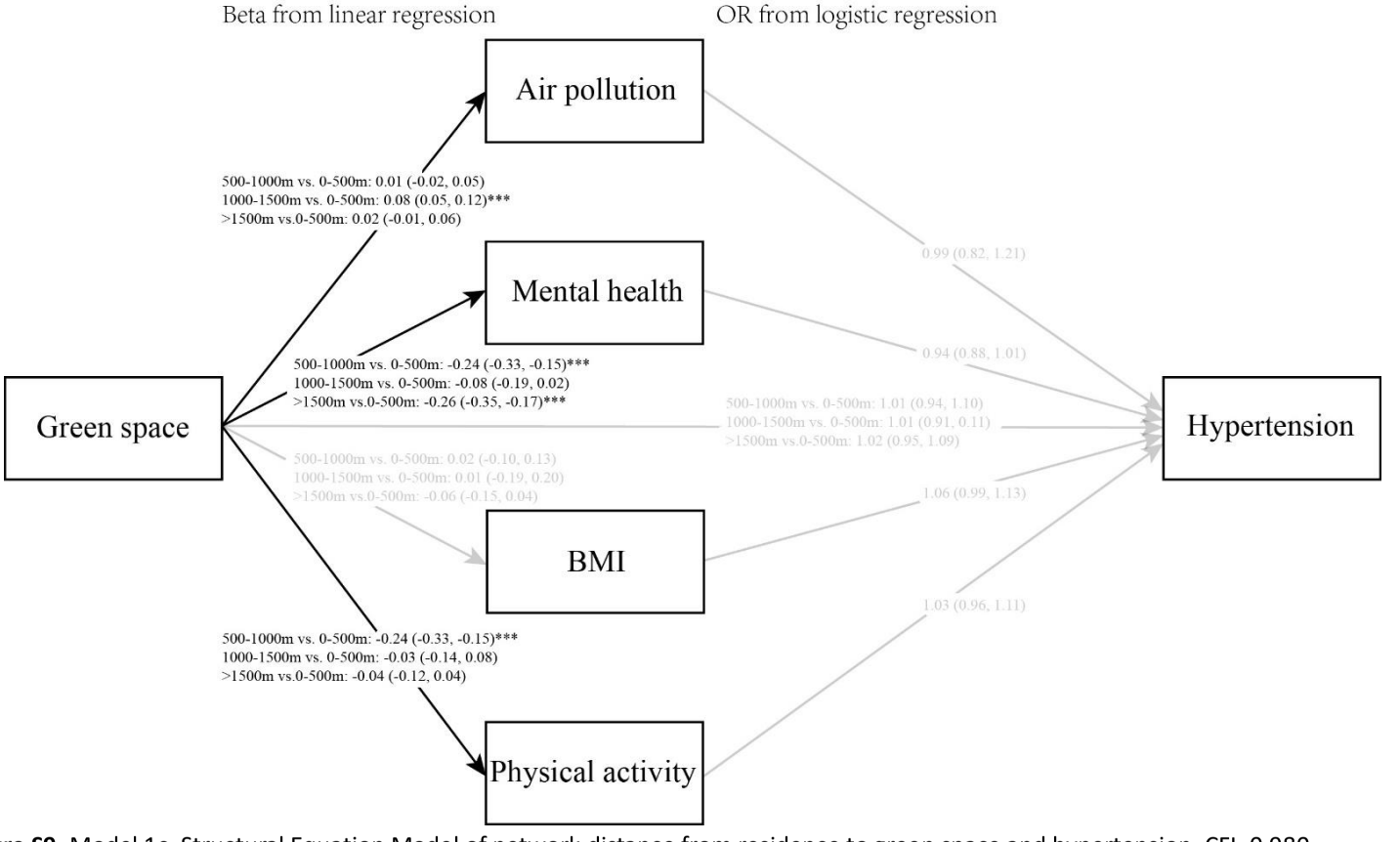


Figure S9. Model 1c. Structural Equation Model of network distance from residence to green space and hypertension. CFI=0.980, TLI=0.903, RMSEA=0.061, SRMR=0.010. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

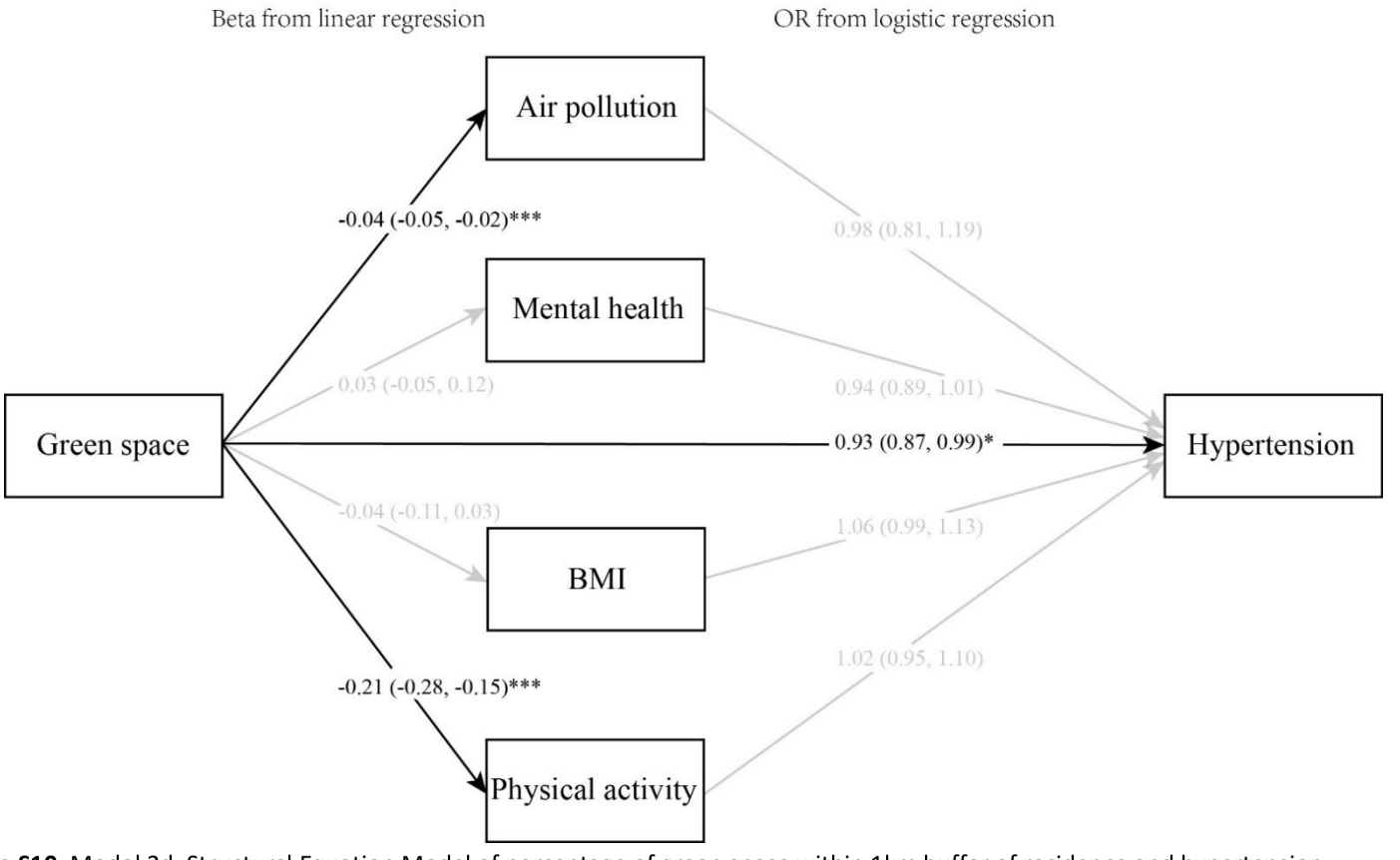


Figure S10. Model 2d. Structural Equation Model of percentage of green space within 1km buffer of residence and hypertension. CFI=0.971, TLI=0.874, RMSEA=0.073, SRMR=0.014. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

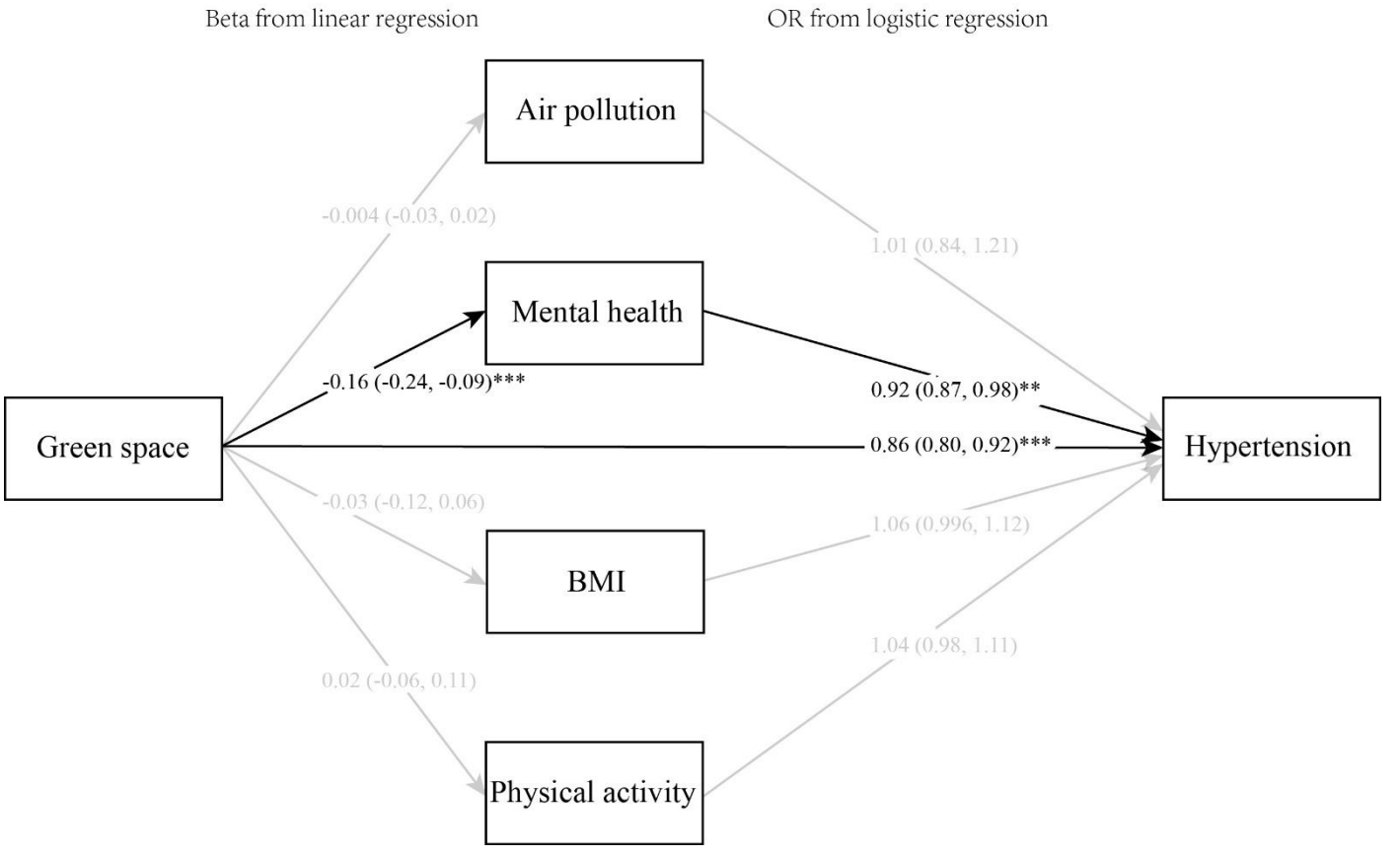


Figure S11. Model 3d. Structural Equation Model of NDVI within 1km buffer of residence and hypertension. CFI=0.974, TLI=0.896, RMSEA=0.066, SRMR=0.013. $^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

Table S1. Standardized indirect associations and total associations of green space exposure on systolic blood pressure using Structural Equation Model, n=719. [1,2]

	Model 1a: network distance from residence		Model 2a: percentage from residence		Model 2b: weighted percentage from residence and workplace	
	Standardized estimate (95% CI)	*P* value	Standardized estimate (95% CI)	*P* value	Standardized estimate (95% CI)	*P* value
Specific indirect associations						
Via air pollution	-0.006 (-0.013, 0.002)	0.12	0.006 (-0.002, 0.014)	0.12	0.004 (-0.004, 0.012)	0.33
Via mental health	**0.013 (0.0003, 0.026)**	**0.045***	-0.002 (-0.007, 0.003)	0.44	-0.002 (-0.007, 0.003)	0.47
Via physical activity	0.002 (-0.005, 0.009)	0.64	0.008 (-0.005, 0.021)	0.24	0.008 (-0.005, 0.020)	0.22
Via BMI	0.001 (-0.008, 0.009)	0.90	-0.004 (-0.013, 0.005)	0.40	-0.005 (-0.014, 0.004)	0.32
Total indirect associations	0.009 (-0.009, 0.027)	0.31	0.008 (-0.011, 0.027)	0.40	0.005 (-0.013, 0.024)	0.56
Total associations	**0.070 (0.010, 0.131)**	**0.02***	**-0.090 (-0.155, -0.025)**	**0.007****	**-0.069 (-0.131, -0.007)**	**0.03***
Percentage of total associations explained by the mediation (95% CI)						
Via air pollution	8.2 (0, 21.1)		6.8 (0, 16.7)		6.0 (0, 19.3)	
Via mental health	18.4 (0, 42.1)		2.3 (0, 8.1)		2.8 (0, 10.5)	
Via physical activity	2.4 (0, 12.4)		8.8 (0, 25.0)		11.4 (0, 32.6)	
Via BMI	0.8 (0, 12.6)		4.5 (0, 14.8)		6.7 (0, 20.3)	
Total indirect associations	13.3 (0, 40.1)		8.9 (0, 31.2)		8.0 (0, 36.3)	

(to be continued)

(continued)

	Model 3a: NDVI from residence		Model 3b: weighted NDVI from residence and workplace	
	Standardized estimate (95% CI)	*P* value	Standardized estimate (95% CI)	*P* value
Via air pollution	0.001 (-0.003, 0.004)	0.75	0.002 (-0.003, 0.007)	0.37
Via mental health	**0.014 (0.003, 0.025)**	**0.02***	**0.017 (0.004, 0.030)**	**0.009****
Via physical activity	-0.0004 (-0.002, 0.002)	0.71	0.0005 (-0.002, 0.003)	0.68
Via BMI	-0.003 (-0.013, 0.006)	0.51	-0.004 (-0.013, 0.005)	0.42
Total indirect associations	0.011 (-0.004, 0.026)	0.16	0.016 (-0.001, 0.033)	0.06
Total associations	**-0.146 (-0.216, -0.076)**	**<0.001*****	**-0.123 (-0.189, -0.056)**	**<0.001*****
Percentage of total associations explained by the mediation (95% CI)				
Via air pollution	0.4 (0, 2.8)		1.8 (0, 5.8)	
Via mental health	9.6 (0.4, 18.8)		14.0 (0.7, 27.3)	
Via physical activity	0.2 (0, 1.5)		0.4 (0, 2.1)	
Via BMI	2.2 (0, 8.6)		3.1 (0, 10.6)	
Total indirect associations	7.6 (0, 19.1)		13.1 (0, 29.2)	

[1] Indirect associations of model 1a was calculated treating the network distance as a continuous variable.

[2] For model 2b and 3b, the weights were 2/3 for value of residence and 1/3 for value of workplace.

**P* <0.05, ***P* <0.01, ****P* <0.001.

Table S2. Standardized indirect associations and total associations of green space exposure on diastolic blood pressure using Structural Equation Model, n=719. [1]

	Model 1b: network distance from residence			Model 2c: percentage from residence		
	Standardized estimate (95% CI)	*P* value	Percentage of total associations explained by the mediation (95% CI)	Standardized estimate (95% CI)	*P* value	Percentage of total associations explained by the mediation (95% CI)
Specific indirect associations						
Via air pollution	-0.009 (-0.018, 0.0001)	0.05	8.1 (0, 17.9)	0.007 (-0.002, 0.016)	0.11	95.2 (0, 100)
Via mental health	-0.013 (-0.027, 0.001)	0.07	11.7 (0, 26.1)	0.001 (-0.003, 0.005)	0.48	19.0 (0, 100)
Via physical activity	-0.006 (-0.015, 0.002)	0.15	5.6 (0, 14.1)	-0.009 (-0.025, 0.006)	0.22	100 (0, 100)
Via BMI	0.0004 (-0.006, 0.007)	0.90	0.4 (0, 5.9)	-0.003 (-0.010, 0.004)	0.41	40.6 (0, 100)
Total indirect associations	**-0.028 (-0.048, -0.009)**	**0.005****	25.0 (0, 5.9)	-0.004 (-0.023, 0.016)	0.70	50.0 (0, 100)
Total associations	**0.113 (0.045, 0.182)**	**0.001****		0.008 (-0.067, 0.082)	0.84	

(to be continued)

(continued)

	Model 3c: NDVI from residence		
	Standardized estimate (95% CI)	*P* value	Percentage of total associations explained by the mediation (95% CI)
Specific indirect associations			
Via air pollution	0.001 (-0.004, 0.006)	0.74	0.3 (0, 2.0)
Via mental health	-0.003 (-0.013, 0.008)	0.61	0.9 (0, 4.5)
Via physical activity	0.001 (-0.003, 0.006)	0.60	0.4 (0, 2.0)
Via BMI	-0.002 (-0.009, 0.005)	0.52	0.8 (0, 3.3)
Total indirect associations	-0.003 (-0.017, 0.011)	0.68	1.0 (0, 6.0)
Total associations	**-0.289 (-0.365, -0.213)**	**<0.001*****	

[1] Indirect associations of model 1b was calculated treating the network distance as a continuous variable.

$^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

Table S3. Standardized indirect associations and total associations of green space exposure on hypertension using Structural Equation Model, n=719. [1]

	Model 1c: network distance from residence			Model 2d: percentage from residence		
	Standardized estimate (95% CI)	*P* value	Percentage of total associations explained by the mediation (95% CI)	Standardized estimate (95% CI)	*P* value	Percentage of total associations explained by the mediation (95% CI)
Specific indirect associations						
Via air pollution	1.000 (0.993, 1.007)	0.99	4.1 (0, 100)	1.001 (0.994, 1.008)	0.83	1.0 (0, 10.7)
Via mental health	**1.014 (1.000, 1.028)**	**0.046***	100 (0, 100)	0.998 (0.993, 1.003)	0.46	2.6 (0, 9.4)
Via physical activity	0.996 (0.989, 1.004)	0.35	100 (0, 100)	0.995 (0.980, 1.012)	0.58	6.0 (0, 27.4)
Via BMI	1.000 (0.996, 1.005)	0.90	43.9 (0, 100)	0.998 (0.994, 1.002)	0.32	2.8 (0, 8.6)
Total indirect associations	1.010 (0.993, 1.028)	0.24	100 (0, 100)	0.992 (0.973, 1.012)	0.44	10.3 (0, 36.6)
Total associations	1.001 (0.938, 1.068)	0.98		**0.927 (0.866, 0.992)**	**0.03***	

(to be continued)

(continued)

	Model 3d: NDVI from residence		
	Standardized estimate (95% CI)	*P* value	Percentage of total associations explained by the mediation (95% CI)
Specific indirect associations			
Via air pollution	1.000 (0.999, 1.001)	0.96	0.01 (0, 0.6)
Via mental health	**1.013 (1.001, 1.025)**	**0.03***	9.2 (0, 18.9)
Via physical activity	1.001 (0.997, 1.004)	0.62	0.6 (0, 3.1)
Via BMI	0.998 (0.993, 1.004)	0.53	1.2 (0, 4.9)
Total indirect associations	1.012 (0.999, 1.026)	0.07	8.7 (0, 19.3)
Total associations	**0.868 (0.806, 0.935)**	**<0.001*****	

[1] Indirect associations of model 1c was calculated treating the network distance as a continuous variable.

$^{*}P$ <0.05, $^{**}P$ <0.01, $^{***}P$ <0.001.

CHAPTER 7

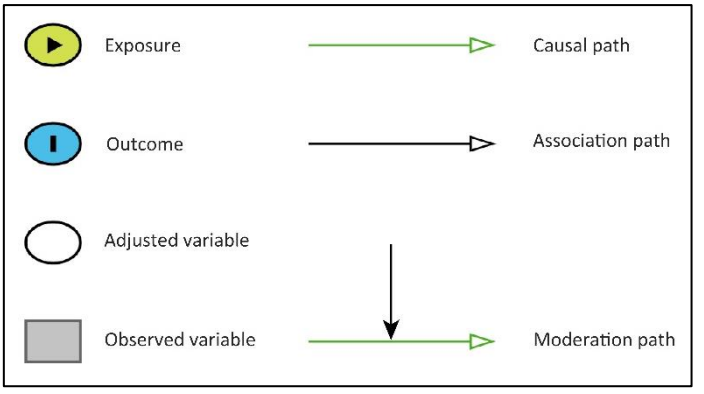
General discussion

The environment and cardiovascular disease: causality, confounding, mediation and moderation

Cardiovascular diseases (CVD) are a major global health issue [1]. Determinants of CVD have been widely investigated in terms of behavioural and clinical risk factors [2,3]. In recent years, the "upstream" external determinants like the built environment and its by-products have drawn more attention [4].

The built environment has many attributes including air pollution, food environment, physical activity environment (green space, walkability, and bikeability), urbanization, light pollution, residential noise, and ambient temperature. A recent umbrella review in the current thesis (Chapter 2) gathered current evidence of the associations between built environment attributes and CVD in adults [5]. This review found a limitation in the literature indicating that most existing systematic reviews and meta-analyses focus on a single attribute of the built environment [5]. However, people are exposed to multiple built environmental attributes at the same time, and many attributes may be interconnected, leading to mutual confounding and interaction effects in relation to CVD [5,6]. These interrelationships among built environment attributes in relation to CVD are not well understood. The empirical evidence is not sufficient [5].

Several approaches to investigate the interrelationships among built environment attributes in relation to CVD can be applied and are discussed below. Throughout the discussion, the association between green space exposure and CVD was taken as an example (**Figure 1**).



Box. Legend of symbols used in the current discussion.

Figure 1. Example study design of the association between green space exposure and cardiovascular disease

Mutual confounding

The most common approach is to treat correlated attributes as confounders and adjust for them in statistical models. This approach examines the independent effect of the studied built environment attribute on CVD and thus facilitates causal inference. In the example study, air pollution exposure might confound the association between green space exposure and CVD, if we assume that air pollution is associated with green space, air pollution is an independent risk factor of CVD, and air pollution is not an intermediate step in the causal path between green space and CVD. In the statistical model, we can adjust for air pollution to examine the "independent" effect of green space on CVD as depicted in **Figure 2**.

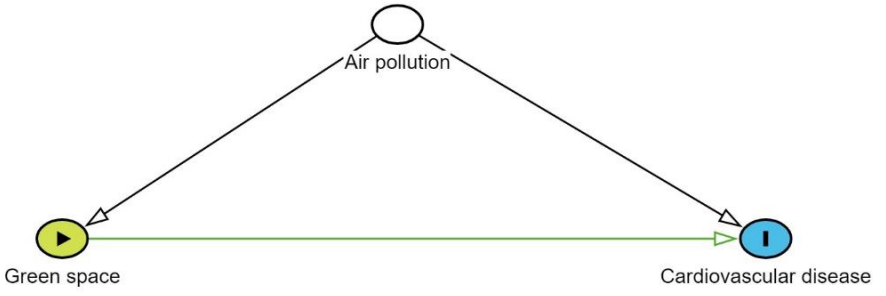


Figure 2. Example study design of the association between green space exposure and cardiovascular disease, confounded by air pollution

Likewise, green space could also confound the association between air pollution and CVD, if we assume that green space is associated with air pollution, green space is an independent risk factor of CVD, and green space is not an intermediate step in the causal path between air pollution and CVD. In practice, many studies examined both as principle exposures and adjusted for each other as depicted in **Figure 3**.

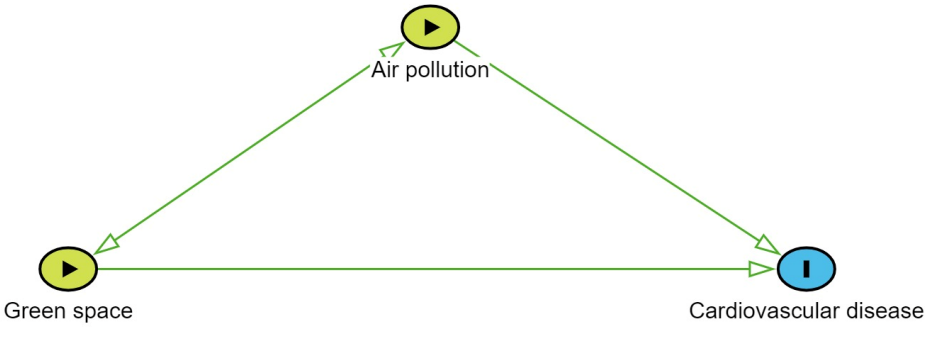


Figure 3. Example study design of the association of green space and air pollution exposures in relation to cardiovascular disease, confounded by each other

There is some literature that considered mutual confounding of built environment attributes in relation to CVD. One systematic review by Rugel et al. found an association between higher noise exposure and increased CVD morbidity, after adjusting for traffic-related air pollution in four studies [7]. Furthermore, they found no indication of an association between air pollution and CVD after adjusting for noise in eleven studies [7].

A meta-analysis by Vienneau et al. observed an association between higher noise levels and increased ischemic heart disease which remained robust after only including studies that adjusted for air pollution exposure [8]. An American cohort study found that long-term air pollution exposure and colder temperatures are independently associated with an increased risk of CVD [9]. A Dutch cohort study in the current thesis (Chapter 4) found that the associations of air pollution and green space in relation to cardiometabolic risk clustering among children were robust after adjusting for each other [10]. Another Dutch cohort study in the current thesis (Chapter 5) found significant associations between changes in neighbourhood walkability and CVD after adjusting for air pollution [11]. However, this approach was not applied in most of previous studies [5,6]. Even when focusing on a single built environment attribute, it is recommended to adjust for relevant built environment attributes that might act as confounders.

Specific interrelationships: moderation or mediation

When looking into specific interrelationships, interaction or moderation effects may exist for some built environment attributes in relation to CVD. In the example study, air pollution could moderate the association between green space and CVD: this implies interrelationships between the variables beyond simple confounding. The mechanisms of green space decreasing the risk of CVD include reducing stress, encouraging physical activity, and promoting social interaction [12]. However, if the green space is located in an area with high levels of air pollution, the harmful effects of the pollution could offset some of the benefits of the green space. In other words, in the presence of air pollution, the beneficial association between green space and cardiovascular disease becomes weaker. An example moderation model is shown in **Figure 4**.

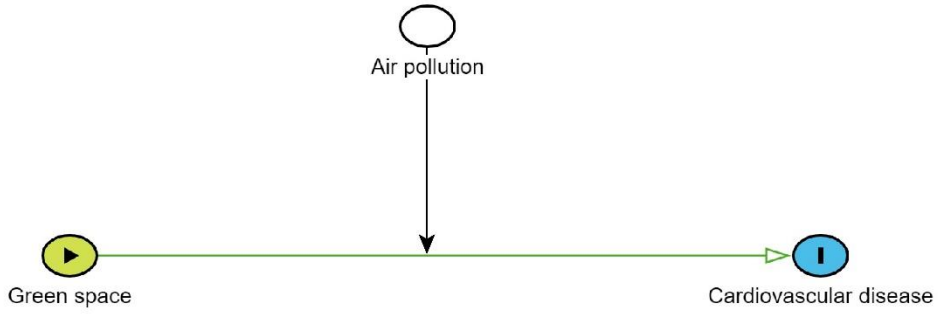


Figure 4. Example study design of the association between green space exposure and cardiovascular disease, moderated by air pollution

Some previous studies investigated the moderation effects of built environment attributes to the association between other attribute and CVD. An American cohort study found that the association between higher $PM_{2.5}$ and CVD was stronger in areas with higher green space, lower ozone levels, and lower temperatures [13]. Possible explanation for the identified moderation effects are that green space and temperature could influence the susceptibility to air pollution, and that temperature is associated with the composition of air pollution mixture [13]. An Australian cohort study found that the associations of neighbourhood walkability with cardiovascular risk factors (blood pressure and low-density lipoprotein cholesterol) were moderated by air pollution [14]. The associations were stronger in low air pollution neighbourhoods [14].

Another form of interrelationship is a mediation effect. In the example study, when the context is about intervention that changes green space, air pollution can mediate the association between green space and CVD. A theoretical pathway has been proposed suggesting that green space may can decrease CVD risk via reducing the harmful exposure to air pollution [12]. The model should be built as in **Figure 5**.

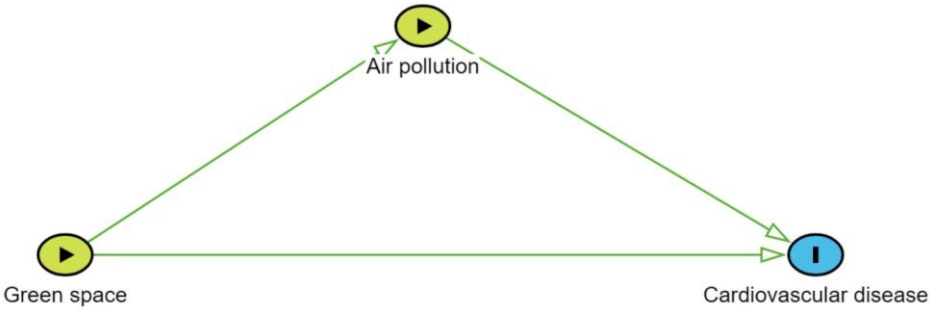


Figure 5. Example study design of the association between green space exposure and cardiovascular disease, mediated by air pollution

However, empirical research to support this assumption is limited [12]. A Chinese study in the current thesis (Chapter 6) tested the mediating role of air pollution in the association between green space and blood pressure, and found no supporting evidence for a mediating effect [15]. A study in Northeastern China found that air pollutants mediated up to 16% of the association between community greenness levels and blood pressure levels [16]. Another study, covering a wide geographic area in China, found that the association was completely mediated by air pollution in urban areas and was partly mediated by air pollution in rural areas [17].

Dual interrelationships

For some built environment attributes, the interrelationship could reflect both mediation and confounding. The interrelationship between green space and air pollution is a good example. In terms of mediation, green space can deposit air pollutants. It has been suggested to be a unidirectional causal relationship [12]. In terms of confounding, areas with more green space may have less traffic thus less traffic-related air pollution, and vice versa. It is a bidirectional association. The choice of modelling mediation or confounding effect should be theory driven. A study by Klompmaker et al. tested the independent effects of green space, air pollution, and noise on mental health by using a mutual confounding approach [18]. All associations attenuated, but remained statistically significant [18]. It has also been discussed that when the context is causal like when studying intervention or seasonal changes in green space, air pollution should better be treated as a mediator, instead of a confounder, in the

green space-CVD association [18].

The same goes with moderation and mediation. For example, both moderation and mediation relationships for air pollution and green space with regard to CVD risk have been found in previous studies [12,13]. The choice of modelling should be context specific and theory driven. Depending on the research question, it is also possible to apply the moderated-mediation model to investigate how the mediation effect varies across different levels of a moderating variable [19,20]. For example, the mediation effect of air pollution on the green-CVD association may differ across different levels of air pollution as shown in **Figure 6**.

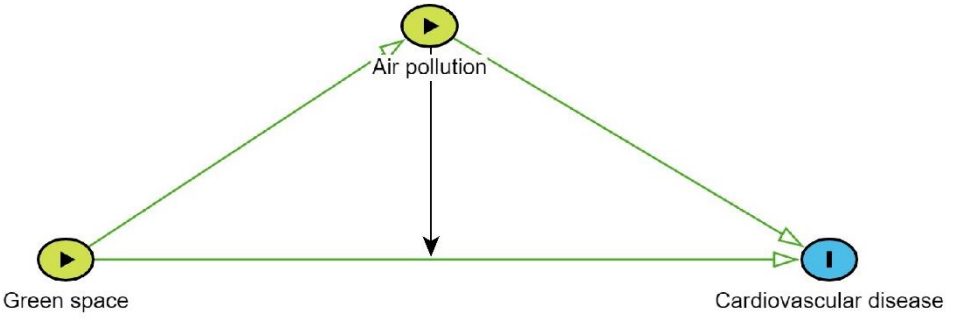


Figure 6. Example study design of the association between green space exposure and cardiovascular disease, a moderated-mediation model via air pollution

Composite exposure: index approach

The mutual confounding approach holds when there is no multi-collinearity between several built environment attributes. Previous studies reported moderate correlations between green space, air pollution, and traffic noise [18,21,22]. So, the mutual confounding model can be applied to these attributes. However, there are some built environment attributes that are intrinsically highly correlated and thus mutual confounding adjustments are not possible. For example, when we consider green space as a neighbourhood walkability component, other components like land use mix, density of retail and service destinations, street connectivity are highly correlated in some settings

like city centers.

Alternatively, researchers can develop a composite index to measure the relevant built environment attributes together as a domain and relate it to CVD. Such an approach ignores the complex interrelationships among attributes. For example, Lam et al. developed and verified a Dutch walkability index, which consists of seven components: population density, retail and service density, land use mix, intersection density, green space density, sidewalk density, and public transport density (**Figure 7**) [23]. Each component was standardized into a z-score [23]. The walkability index was then calculated as averaging the component z-scores, and normalizing the result into a score between 0 and 100, with higher scores indicating higher neighbourhood walkability [23]. A Dutch cohort study in the current thesis (Chapter 5) investigated the changes of this walkability index over time and its association with subsequent risk CVD [11]. The study found that exposure to stable low walkability, as well as increasing walkability, was associated with an approximate five percent higher risk of CVD compared to stable high walkability [11]. Based on theory [24,25] and empirical evidence [26], Lam et al. also developed the Obesogenic Built Environment CharacterisTics (OBCT) index based on five subdomains and a total of 17 components [27]. The subdomains include driveability, walkability, bikeability, sport facilities density, and obesogenic food [27]. The index approach is context-specific and thus should also be developed in other countries. Because the quantification of built environment quality is helpful for interpretation with regard to CVD and can facilitate policy applications [27].

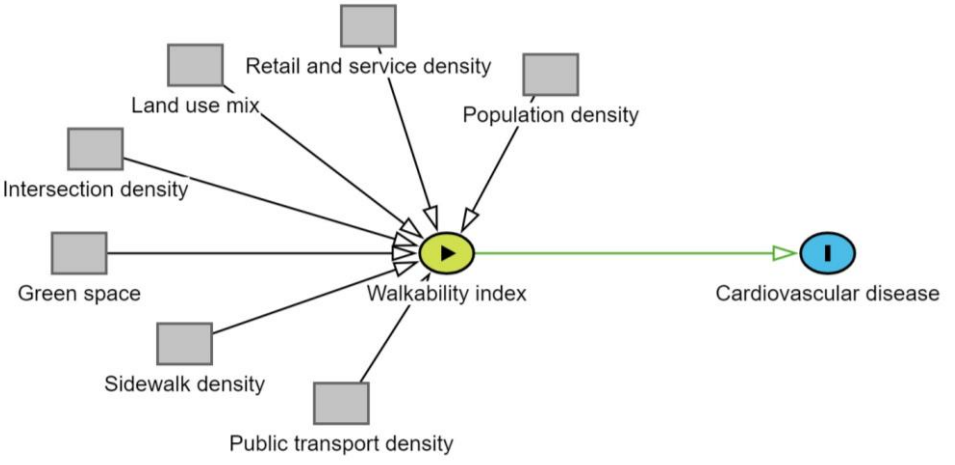


Figure 7. Example study design of the association between walkability exposure and cardiovascular disease, where walkability is a composite index of seven components

Pathways

Lastly, for causality inference, pathways from environmental attributes to CVD, as presented by directed acyclic graphs (DAG) [28], are an "ultimate tool" to comprehensively understand the interrelationships among multiple built environment attributes (see **Figure 8** for an example). For practical public health, pathways with specific estimates for the strength of each path can help identify critical paths, which may act as an entry point for population-level action to prevent CVD.

There are several approaches to provide empirical evidence for these pathways. When there is a theoretical framework of the interrelationships between built environment attributes in relation to CVD, structural equation modelling is a proper method to validate the framework. The moderation, mediation, and confounding effect can be explicitly modelled together in such models. Furthermore, longitudinal structural equation models provide stronger causality evidence because of the prospective design [29]. In the example study, we can consider multiple built environment attributes in relation to CVD at the same time (**Figure 8**). Temperature, air pollution, and traffic noise are all mediators in the association between green space and CVD [12]. Meanwhile, temperature moderates the association between green space and air pollution, because

temperature may affect the capacity of green space to absorb or filter pollutants [30].

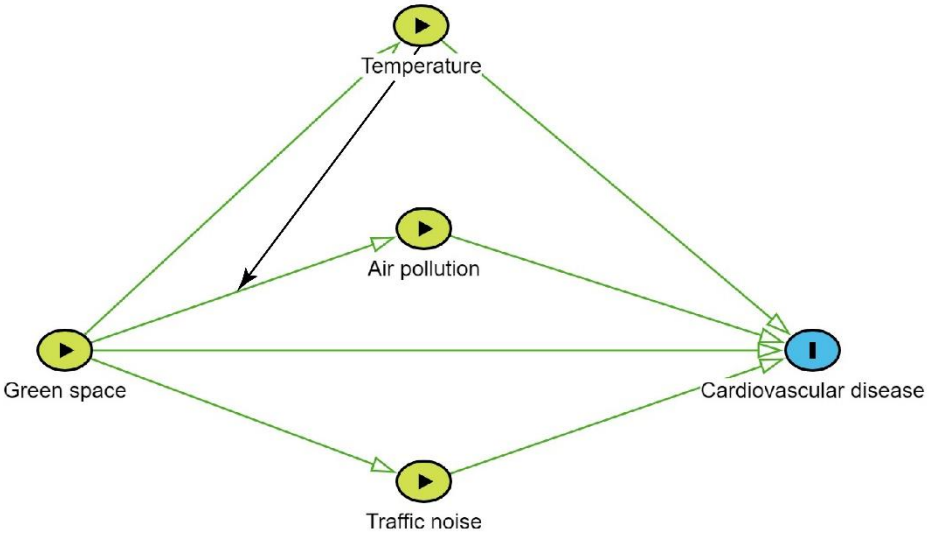


Figure 8. Example study design of the association between multiple built environment attributes and cardiovascular disease

However, in the field of built environment and CVD, there are a limited number of well-developed theoretical frameworks. Exploratory approaches are available like some extension methods of the Least Absolute Shrinkage and Selection Operator (LASSO) regression [31] and Bayesian Network [32]. They can start from scratch to develop pathways. LASSO is a regression analysis method that performs both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the statistical model it produces. Graphical LASSO [33] and Network LASSO [34] are extensions of LASSO that are designed to infer the undirected structure of a network without requiring the prior knowledge about the network structure. Further, Meinshausen and Bühlmann developed the neighbor selection approach that use the LASSO to develop DAG [35]. Bayesian Network is a probabilistic graphical model that generate DAG out of a set of variables [36]. However, it should be noted that the above mentioned exploratory methods suggest potential causal relationships solely based on the data. These relationships need to be validated through further analysis or experimental studies [35,36].

Conclusion

In conclusion, the present thesis provides insights into the association between the built environment and CVD. To deepen our understanding of the association between built environmental attributes and CVD, future studies should take into account the interrelationships between built environmental attributes. The decision of a proper approach to deal with interrelationships should be based on study question, theoretical framework, and the specific context. A comprehensive pathway from built environment to CVD is at the exploration stage.

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CHAPTER 8

Summary

Samenvatting

总结

Acknowledgements

About the author

List of publications

Summary

This thesis has described the current evidence of the association between the built environment and cardiovascular risk, and has originally investigated this long-term association and its underlying mechanisms.

Chapter 1 introduces the epidemiology of cardiovascular disease (CVD), determinants of CVD, and gaps in current evidence. To sum up, it introduces the outline of the current thesis.

Chapter 2 provides a comprehensive overview of the current evidence on objectively measured neighbourhood built environment exposures in relation to CVD events in adults. We searched seven databases for systematic reviews covering at least one domain of built environment and CVD events in adults between January 2000 and April 2021. From the 3,304 initial hits, 51 systematic reviews were included. There was strong evidence of the associations between increased air pollutants (especially $PM_{2.5}$ exposure) and increased residential noise with greater risk of CVD. Highly suggestive evidence was found for an association between increased ambient temperature and greater risk of CVD. Systematic reviews on physical activity environment, food environment, light pollution and urbanisation in relation to CVD were scarce or lacking.

Chapter 3 maps the spatial distribution of green space by all vegetation, trees, shrubs, low vegetation, grass field, and agriculture in the Netherlands in 2017. Furthermore, it assesses socio-demographic and socio-economic differences in the availability of green space in the Netherlands. Data from 16,440,620 individuals aged one and above of the Netherlands on January 1, 2017, were analyzed. Little differences in the availability of green space were found across age and sex groups. Ethnic Dutch and Indonesian had more green space coverage around residence than Turkish and Moroccan. People with higher household SES had gradually more green space coverage, while in the highest SES level, the coverage decreased a little. Higher urbanicity levels were monotonously associated with lower green space exposure. The differences between ethnic groups

and household SES groups were originated from the differences in the availability of low vegetation, and mostly present in rural areas.

Chapter 4 originally investigates the longitudinal associations of air pollution and green space with cardiometabolic risk among children in the Netherlands. Three Dutch prospective cohorts with a total of 13,822 participants aged 5 to 17 years were included: the Amsterdam Born Children and their Development (ABCD) study from Amsterdam, the Generation R study from Rotterdam, and the Lifelines study from northern Netherlands. Cardiometabolic risk factor clustering was assessed by a recommended MetScore. More green space exposure at residence was associated with decreased cardiometabolic risk over time. Some evidence was found for the association between air pollution and increased cardiometabolic risk. Exposure to higher concentrations of NO_2 and elemental carbon was associated with increased cardiometabolic risk in the Lifelines cohort. No evidence was found for $PM_{2.5}$ and PM_{10}, probably due to the small variations in exposures.

Chapter 5 presents findings from a nationwide cohort study that investigate the relationship between changes in residential neighbourhood walkability and CVD incidence in adults. Three million Dutch adults aged 40 and above were followed for 24 years. The growth mixture model identified four distinct trajectories of changes in neighbourhood walkability from 1996 to 2008, which were described as a stable but relatively low walkability trajectory (Stable low, 91.1 %), a stable but relatively higher walkability trajectory (Stable high, 0.6%), a relatively higher initial neighbourhood walkability which decreased over time (Decreasing, 1.7%), and relatively lower neighbourhood walkability which increased over time (Increasing, 6.5%). In the subsequent years till 2019, a total of 644,785 individuals (21.0%) developed CVD. As compared to the stable but relatively higher walkability group, residing in stable low and increasing walkability areas was associated with a higher CVD risk. These findings were especially pronounced in middle aged adults, and urban dwellers.

Chapter 6 explores the underlying mechanism of the association between exposure to

green space and blood pressure (BP) levels based on a theoretical framework. Three area-level green space indicators were calculated, including network distance to the nearest park, percentage of green space and Normalized Difference Vegetation Index within a 1km Euclidean buffer around residence and workplace. Structural equation models were applied to estimate the direct and indirect associations of the various green space indicators on systolic BP (SBP), diastolic BP (DBP), and hypertension, respectively. Both shorter distance to green space and more green space coverage around residence and workplace were associated with lower SBP, lower DBP and lower risk of hypertension. The observed inverse associations of green space exposures with BP and hypertension were partly explained by better mental health. However, a mediating role for air pollution, physical activity, and weight status is not supported by the findings of this study.

Chapter 7 discusses several approaches to investigate the interrelationships among built environment attributes in relation to CVD. To deepen our understanding of the association between built environmental attributes and CVD, future studies should take into account the interrelationships between built environmental attributes. Multiple scenarios are discussed, including mutual confounding, moderation, mediation, dual interrelationships, index approach, and pathways. The decision of a proper approach to deal with interrelationships should be based on study question, theoretical framework, and the specific context. A comprehensive pathway from built environment to CVD is at the exploration stage.

Samenvatting

Dit proefschrift beschrijft de huidige kennis over het verband tussen de bebouwde omgeving en het risico op hart- en vaatziekten (HVZ) en heeft dit verband en de onderliggende mechanismen verder onderzocht.

Hoofdstuk 1 introduceert de epidemiologie van HVZ, determinanten van HVZ en hiaten in het huidige bewijs. Samengevat introduceert het de opzet van dit proefschrift.

Hoofdstuk 2 biedt een uitgebreid overzicht van de huidige kennis over objectief gemeten blootstellingen aan de bebouwde omgeving in relatie tot HVZ bij volwassenen. In zeven databases werd gezocht naar systematische reviews die minstens één domein van de bebouwde omgeving in relatie tot HVZ bij volwassenen onderzochten tussen januari 2000 en april 2021. Van de 3.304 hits werden uiteindelijk 51 systematische reviews geïncludeerd. Er was sterk bewijs voor een verband tussen verhoogde blootstelling aan luchtverontreinigende stoffen (vooral PM2.5-blootstelling) en een hoger risico op HVZ. Hetzelfde gold voor verhoogd blootstelling aan omgevingsgeluid. Ook werd er zeer suggestief bewijs gevonden voor een verband tussen verhoogde omgevingstemperatuur en een hoger risico op HVZ. Systematische reviews over de fysieke activiteit omgeving, voedselomgeving, lichtvervuiling en verstedelijking in relatie tot HVZ waren schaars of ontbraken.

Hoofdstuk 3 brengt de ruimtelijke verdeling van groene ruimte in kaart door te kijken naar alle vegetatie, bomen, struiken, lage vegetatie, grasveld en landbouw in Nederland in 2017. Daarnaast werden de sociaal-demografische en sociaaleconomische verschillen in de beschikbaarheid van groene ruimte in Nederland onderzocht. Gegevens van 16.440.620 inwoners van één jaar en ouder in Nederland op 1 januari 2017 werden geanalyseerd. Er werden weinig verschillen gevonden in de beschikbaarheid van groene ruimte tussen leeftijds- en geslachtsgroepen. Inwoners met een Nederlandse of Indonesische achtergrond hadden meer groene ruimte rond de woning dan inwoners met een Turkse of Marokkaans achtergrond. De beschikbaarheid van groende ruimte

nam geleidelijk toe met een hogere huishoudelijk sociaaleconomische status (SES), maar op het hoogste SES-niveau nam de dekking een beetje af. Hogere niveaus van verstedelijking waren eenduidig geassocieerd met lagere blootstelling aan groene ruimte. De verschillen tussen etnische groepen en huishoudelijke SES-groepen konden met name worden toegeschreven aan de verschillen in beschikbaarheid van lage vegetatie en waren voornamelijk aanwezig in landelijke gebieden.

Hoofdstuk 4 onderzoekt de longitudinale associaties van luchtvervuiling en groene ruimte met het cardiometabool risico bij kinderen in Nederland. Gegevens van drie Nederlandse prospectieve cohorten met in totaal 13.822 deelnemers van 5 tot 17 jaar werden gebruikt: de Amsterdam Born Children and their Development (ABCD) studie uit Amsterdam, de Generation R studie uit Rotterdam en de Lifelines studie uit Noord-Nederland. Het clusteren van cardiometabole risicofactoren werd beoordeeld door een aanbevolen MetScore. Meer blootstelling aan groene ruimte bij de woning was geassocieerd met een afname van het cardiometabool risico in de loop van de tijd. Er werd ook bewijs gevonden dat wijst op een verband tussen luchtvervuiling en een verhoogd cardiometabool risico. Blootstelling aan hogere concentraties NO2 en elementair koolstof was geassocieerd met een verhoogd cardiometabool risico in het Lifelines-cohort. Er werd echter geen bewijs gevonden voor PM2.5 en PM10, waarschijnlijk vanwege de kleine variaties in blootstellingen.

Hoofdstuk 5 onderzoekt de relatie tussen veranderingen in de beloopbaarheid van woonwijken en het voorkomen van HVZ bij volwassenen in een landelijke cohortstudie. Drie miljoen Nederlandse volwassenen van 40 jaar en ouder werden 24 jaar lang gevolgd. Het gebruikte statistische model (growth mixture model) identificeerde vier verschillende trajecten van verandering in de beloopbaarheid van wijken tussen 1996 en 2008. De trajecten werden beschreven als een stabiel maar relatief laag beloopbaarheidstraject (Stabiel laag, 91,1%), een stabiel maar relatief hoger beloopbaarheidstraject (Stabiel hoog, 0,6%), een relatief hogere initiële beloopbaarheid van de wijk die in de loop van de tijd afnam (Afnemend, 1,7%), en relatief lagere beloopbaarheid van de wijk die in de loop van de tijd toenam

(Toenemend, 6,5%). In de daaropvolgende jaren tot 2019 ontwikkelden in totaal 644.785 personen (21,0%) HVZ. In vergelijking met de stabiele maar relatief hogere beloopbaarheidsgroep, was wonen in gebieden met een stabiele lage en toenemende beloopbaarheid geassocieerd met een hoger risico op HVZ. Deze bevindingen waren meer uitgesproken bij volwassenen van middelbare leeftijd en stadsbewoners.

Hoofdstuk 6 onderzoekt het onderliggende mechanisme van het verband tussen blootstelling aan groene ruimte en bloedruk, op basis van een theoretisch kader. Er werden drie indicatoren voor groene ruimte op gebiedsniveau berekend: de netwerkafstand tot het dichtstbijzijnde park, het percentage groene ruimte en de Normalized Difference Vegetation Index binnen een Euclidische buffer van 1 km rond de woning en werkplek. Statistische modellen (structural equation models) werden toegepast om de directe en indirecte associaties van de verschillende indicatoren van groene ruimte met systolische bloeddruk (SBP), diastolische bloeddruk (DBP) en hypertensie te schatten. Zowel een kortere afstand tot groene ruimte als meer groene ruimte rond de woning en werkplek waren geassocieerd met een lagere SBP, lagere DBP en een lager risico op hypertensie. De waargenomen associaties van blootstelling aan groene ruimte met BP en hypertensie werden deels verklaard door een betere geestelijke gezondheid. Echter, een rol voor luchtvervuiling, lichamelijke activiteit en gewichtsstatus in het onderliggende mechanisme wordt niet ondersteund door de bevindingen van deze studie.

Hoofdstuk 7 bespreekt verschillende benaderingen om de onderlinge relatie tussen kenmerken van de bebouwde omgeving en hun invloed op HVZ te onderzoeken. Om ons begrip van het verband tussen kenmerken van de bebouwde omgeving en HVZ te verdiepen, moeten toekomstige studies rekening houden met de onderlinge relatie tussen kenmerken van de bebouwde omgeving. Er worden meerdere scenario's besproken, waaronder wederzijdse verstorende factoren, moderatie, mediatie, dubbele onderlinge relaties, indexbenadering en trajecten. De beslissing over een juiste benadering om met onderlinge relaties om te gaan, moet gebaseerd zijn op de onderzoeksvraag, het theoretisch kader en de specifieke context. Het begrijpen van alle

onderliggende stappen in het verband tussen de bebouwde omgeving en HVZ bevindt zich in de verkenningsfase.

总结

本论文分析阐述了建成环境与心血管疾病风险关联的现有研究证据，原创研究了建成环境长期暴露与心血管疾病风险的关联，并且研究了此关联的潜在机制。

第一章介绍了心血管疾病的流行病学特征、心血管疾病的决定因素、以及现有研究证据不足的方面。最后，本章介绍了本论文的提纲。

第二章对客观测量的社区建成环境暴露与成年人心血管事件关联的现有证据，做了系统全面的综述。在七大科学文献数据库中，本研究系统检索了 2000 年 1 月至 2021 年 4 月间发表的，有关建成环境至少一个领域的因素与成年人心血管事件的系统综述。从 3304 个检索结果中筛选，最终纳入了 51 篇系统综述。分析结果显示：在建成环境领域中，空气污染，特别是 $PM_{2.5}$ 暴露增加，居住噪音增加，与心血管疾病风险增加的关联，存在强有力的证据；环境温度增加与心血管疾病风险增加的关联，存在高度暗示性的证据；体育活动环境、食物环境、光污染、都市化程度等领域因素与心血管疾病关联的系统综述缺失。

第三章绘制了 2017 年全荷兰绿地空间分布地图，并按照所有绿地、树木、灌木、低矮植被、草地、和农业农地分类。本章进一步检测了全荷兰绿地空间分布在社会人口统计学和社会经济学指标上的差异。本研究提取分析了 2017 年 1 月 1 日 16,440,620 名 1 岁以上的荷兰居民的数据。绿地空间的可及性在年龄和性别组间存在很小差异。荷兰族和印度尼西亚族居民比土耳其族和摩洛哥族居民，在住宅周围有更多绿色空间。具有较高社会经济地位的人，住宅周围拥有更多的绿色空间覆盖率，但是在最高社会经济地位的人的住宅周围，绿色空间覆盖率降低了一点。住宅周围城市化程度与绿色空间的关系是单调递减。不同种族、不同社会经济地位人群在绿色空间可及性上的差别，主要来源于低矮植被可及性的差别，并且可及性的差别主要体现在农村地区。

第四章原创研究了长期空气污染、绿地空间暴露与荷兰儿童心血管代谢风险的关系。本研究共纳入了来自三个荷兰队列的 13,822 名 5 到 17 岁儿童，三个队列分别是阿姆斯特丹的 the Amsterdam Born Children and their Development (ABCD)，

鹿特丹的 the Generation R study，和荷兰北方三省的 the Lifelines study。本研究使用一个推荐的心血管代谢风险指数 MetScore 测量心血管代谢性危险因素聚集。结果显示，儿童家庭住宅周围更多绿地空间与心血管代谢风险降低相关。本研究结果为空气污染的长期暴露和心血管代谢风险增加的相关性提供了一些证据：在 Lifelines 队列中，长期暴露于高浓度的 NO_2 和大气元素碳和心血管代谢风险增加相关。可能是由于在研究人群中污染暴露水平的差异小，本研究没有发现 $PM_{2.5}$ 和 PM_{10} 长期暴露与心血管代谢风险相关性的证据。

第五章展示了一项荷兰全国范围队列研究的结果，本研究调查了居住区的步行友好度的长期变化与成年人心血管疾病发生率的关系。本研究跟踪了 300 万名 40 岁及以上的荷兰成年人 24 年。增长曲线模型发现了 1996 年至 2008 年步行友好度指数变化的四种发展轨迹，它们分别是：长期稳定并相对较低（91.1%），长期稳定并相对较高（0.6%），初始相对较高并随时间下降（1.7%），和初始相对较低并随时间上升（6.5%）。在 2008 年后直到 2019 年，参与者中 644,785（21.0%）人首发心血管疾病。与长期稳定并相对较高的组相比，居住在步行友好度长期稳定并相对较低和初始相对较低并随时间上升地区的组有更高的心血管疾病风险。这一相关性在中年人和城市居民中尤为显著。

第六章基于理论框架，探索了绿地空间暴露和血压水平相关的潜在机制。本研究计算了三个地区水平的绿地空间暴露指标：居住地、工作地点到最近公园的网络距离；居住地、工作地点 1 公里欧氏缓冲区内的绿地空间的百分比；和居住地、工作地点 1 公里欧氏缓冲区内的归一化植被指数。本研究使用结构方程模型分别拟合了三种绿地空间指标对收缩压、舒张压、和高血压的直接、间接关联。居住地、工作地点距离公园越近，居住地周围绿地空间的百分比越大，与收缩压、舒张压、和高血压患病风险降低有关。本研究所观察到的绿地空间暴露与血压值、高血压的关系，可以部分被心理健康这一因素所解释。但是，本研究没有为空气污染、体力活动和体重状态的中介效应提供证据支持。

第七章讨论了在心血管疾病风险的研究背景下，探索建成环境各领域多因素间相互关联的方法。为加深我们对建成环境各领域因素与心血管疾病之间关系的理解，未来的研究应该考虑到建成环境各领域因素的相互关联。本章讨论了多种

可能的情况，包括因素间相互的混杂作用、调节效应、中介效应、双重相互关系、指数整合、以及路径分析。选择合适的方法处理建成环境各领域因素的相互关联应该基于研究问题、理论框架、和具体的研究背景。从建成环境各领域因素到心血管疾病的完整全面的路径分析还处于探索阶段。

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知忘是非，心之适也。

About the author

Mingwei Liu was born on December 23, 1995, in Nanchang, Jiangxi Province, China. He obtained his Bachelor's degree in Public Health Management from the Tongji Medical College, Huazhong University of Science and Technology in 2017. Under the guidance of prof. dr. Yinhuan Hu, Mingwei developed an interest in Medical Statistics and scientific research. He decided to further his academic training in the School of Health Sciences at Wuhan University. Between 2017 and 2020, prof. dr. Qiqiang He supervised his research projects in the field of Nutritional Epidemiology. He had the opportunity to present at international conferences and do visiting research at Deakin University in Australia. These experiences and the great unknown motivated him to do a PhD overseas. In November 2020, Mingwei started his PhD trajectory at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMCU), under the supervision of prof. dr. Diederick E Grobbee, prof. dr. Ilonca Vaartjes, and dr. Erik Timmermans. He was funded by the China Scholarship Council. The research projects were part of the Exposome-NL and were funded by the Gravitation programme of the Dutch Ministry of Education, Culture, and Science and the Netherlands Organization for Scientific Research. During the PhD program, he completed a postgraduate Master of Clinical Epidemiology in 2024. The research and study expanded his perspective to consider the impact of broader external environmental factors on health.

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