The associations between greenspace exposure and health

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Abstract

The health benefits of greenspace have commanded the attention of researchers, policymakers and health practitioners since the 1800s, although the overall impact of greenspace on population disease burden is unknown. Indeed, there is a paucity of research investigating the potential mechanisms underlying the relationship between greenspace and health. There are the gaps in the literature than this thesis sets out to address. It presents a systematic review and meta-analysis of greenspace exposure and physical health outcomes. Following the inclusion of 143 papers investigating the relationship between greenspace and health outcomes, 24 novel meta-analyses were conducted, finding associations between greenspace exposure and health outcomes including significantly reduced incidence of type 2 diabetes and cardiovascular disease, as well as reductions in salivary cortisol and diastolic blood pressure. The subsequent chapters investigate the mechanisms underlying the relationship between greenspace and health. Based on existing evidence it is hypothesised that increased greenspace exposure may increase exposure to a diverse range of microbiota, thereby improving immunoregulatory and inflammatory processes, the first study investigates the relationship between neighbourhood greenspace exposure and gut microbial diversity using data from the TwinsUK dataset. No associations were found, but as greenspace exposure may be associated with inflammatory markers through a pathway other than microbial exposure, two subsequent studies set out to investigate the association between neighbourhood greenspace exposure and markers of inflammation using data from the EPIC Norfolk cohort and pooled data from the Leicester Diabetes Centre. No significant relationships between greenspace and inflammatory biomarkers were found in either, suggesting greenspace exposure is associated with wide ranging health benefits, but further research is required to understand the mechanisms underlying this association. Future focus on the development of datasets measuring greenspace use would further enhance the field.

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Abbreviations

CRP	C-reactive protein
DBP	Diastolic blood pressure
GEE	Generalised Estimating Equation
GP	General practitioner (family doctor)
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
HR	Heart rate
HRV	Heart rate variability
hs-CRP	High sensitivity C-reactive protein
IL-6	Interleukin-6
LDL	Low density lipoprotein
NHS	National Health Service
OTUs	Operational Taxonomic Units
SBP	Systolic blood pressure
SES	Socioeconomic status
T2DM	Type 2 diabetes
TNF-alpha	Tumour necrosis factor alpha
UK	United Kingdom
WHO	World Health Organisation

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Publication and statement of authorship

Publication arising from the thesis

Twohig-Bennett, C., Jones, A. (2018) The health benefits of the great outdoors: A systematic review and meta-analysis of greenspace exposure and health outcomes, Environmental Research, 166, pages 628-637

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Statement of authorship

The research reported is my own original work which was carried out in collaboration with others as follows:

Chapter 1: Written by Caoimhe Twohig-Bennett

Chapter 2: Caoimhe Twohig-Bennett was the lead author of a paper published as:

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Caoimhe Twohig-Bennett and Andy Jones designed the protocol and the search strategy which was executed by Caoimhe Twohig-Bennett. Caoimhe screened the initial results and extracted the data from primary studies. Caoimhe drafted the original manuscript which was critically reviewed by Andy Jones.

Chapter 3: Caoimhe Twohig-Bennett and Andy Jones designed the study. Caoimhe analysed the data and drafted the original manuscript which was critically reviewed by Andy Jones, Lee Shepstone and EPIC co-author Robert Luben.

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Chapter 6: Written by Caoimhe Twohig-Bennett

Chapter 1. Introduction

1.1. Background to the thesis

In March this year a panel of experts urged the NHS to move away from the Medical Model of Health, a framework that takes a curative approach to illness. In the panels' professional experiences, the majority of health issues that patients present to their GP surgeries with are largely driven by social factors, not medical factors[1]. This is reflected in the social ecological model of health, which is comprised of 'social' or societal factors, and 'ecological' factors, referring to the interrelationships between organisms and their environments[2], taking into account behavioural, social, and economic factors and inequalities that contribute to health.

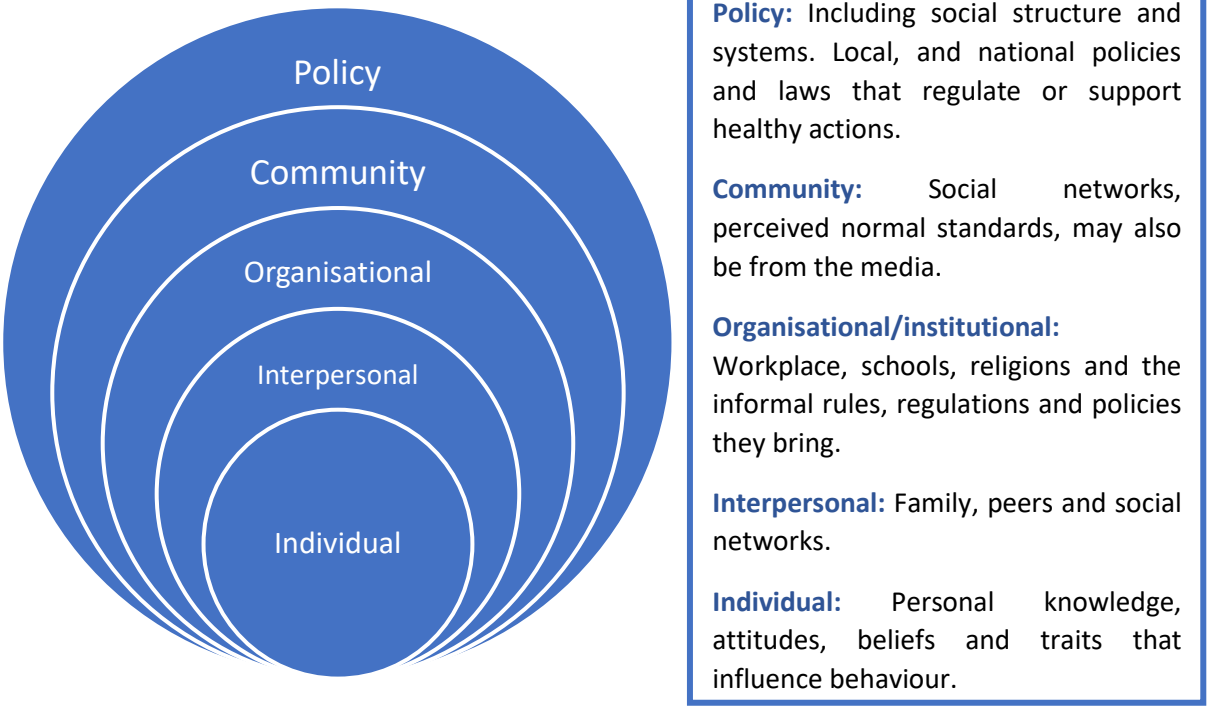


Figure 1. The social ecological model of health[3]

This framework takes a different approach to the curative medical model of health, focusing on the social and environmental causes of ill health, and in the prevention of illness happening in the first place. This model of health (seen in Figure 1) is comprised of five levels of factors that may influence an individual's health: 1) Individual level, 2) Interpersonal level including family and community health workers, 3) the organisational level, encompassing healthcare systems and academic medical institutions, 4) Community level, including regional, state and community organisations, and finally 5) Public policy: local,

national, and international laws and policies and how they impact upon an individual's health[3]. The social ecological model demonstrates that ill-health is largely a product of the social and economic organization of society[4].

Social determinants of health include factors such as the social gradient, early child development, gender equity, globalization, work, unemployment, health systems, and environmental factors[5]. Social determinants of health are of increasing importance globally, with the World Health Organisation setting up a Commission on Social Determinants of Health to review existing knowledge, raise societal debate, and promote the implementation of policies with the aim of reducing inequalities in health both within and between countries[5] [6].

Ecological or environmental determinants of health include a variety of factors to which we are exposed to through our home and work environments, that may influence health or health behaviours. The built environment has been broadly defined to include land use patterns, transportation infrastructure, as well as design features that provide physical activity opportunities, and has come under scrutiny as an influence on physical activity patterns[7]. This scrutiny is due to the impact of the built environment on which mode of transportation the inhabitants of an area use. For example, the density of development, connectivity of the street network, mix of land uses, and aesthetic qualities of an area may influence whether a person chooses to use an active mode of transport such as walking or cycling, to use public transport, or to drive[8]. The 'walkability' of a built environment can also have an impact on health, as higher neighbourhood walkability has been associated with significantly more physical activity through walking[9].

One element of the built environment – or perhaps, unbuilt environment - that has been shown to positively influence health, is greenspace. One definition of greenspace is "natural and undeveloped land"[10], although this definition is perhaps overly conservative, as it implies that the term greenspace only applies to untouched land, meaning that only those living on the outskirts of towns or in rural areas would have any greenspace in their neighbourhood. Therefore, for the purpose of the thesis this definition was extended to include developed greenspaces such as parks in urban and suburban areas, agricultural land, and street trees and greenery.

Greenspaces first became a priority for politicians as early as the 1830s. In 1833 Liberal MP Robert Slaney advocated to establish a Select Committee for public walks, to consider the best means for securing open places in towns for "healthful exercise of the population"[11]. However the aim of this committee was not solely to improve the health of the nation, but to engage workmen in health-promoting recreational activities so as they would not spend

time in public houses, “enter into conspiracies”, or encourage discontent which could lead to attacks upon the government[11]. The suggestion that spending time in parks and natural spaces could prevent public revolt and political disorder through healthy behaviours is certainly ambitious, but this is perhaps one of the earliest acknowledgements that good population health through outdoor exercise may have positive implications for society as a whole. The subsequent establishment of a National Health Society and the Metropolitan Public Gardens and Playgrounds Association in the late 19th century led to a number of prominent sanitarians, health professionals and philanthropic upper classes starting an urban parks movement[12]. This movement was in part, motivated by the rises in urbanisation, industrialisation, and commercialisation during the industrial revolution, seeking to limit the impacts on the natural environments of Britain[13]. It was in these societies that greenspaces were considered as the “lungs of a city” and recognised for their potential to benefit health, primarily through the reduction of air pollution[12].

In the early 20th Century, the 1906 Open Spaces Act and 1909 Town Planning Act, resulted in a surge of the creation of parks across England[14]. However, a class divide existed, meaning that it was predominantly the middle classes who used parks, and in some cases, separate parks of lesser quality existing for working class patrons[15]. With the subsequent World Wars, parks and greenspaces understandably were of a lesser priority for policy makers and the government. The increasing price of urban land and the reduced government funding available in the aftermath of both wars, meant that more green land was built on, and fewer parks were created[11].

The Blair government of 1997 brought with it a renewed interest and subsequent investment in the greenspaces of the UK. This was in part, motivated by a report from the Urban Green Spaces Task Force which found that park use was dominated by car owners who were able to access greenspaces much easier than those without cars[16], perhaps even facilitating widening health inequalities. The Parks for People programme was launched in 2006, funded by lottery money with grants available for existing greenspaces so that they may be freely accessible and involve local people in their day-to-day running[11].

Over the last two decades, research has championed ‘green exercise’, engaging in physical activity whilst being directly exposed to nature, for its’ significant psychological and physiological health benefits[17 18]. Walking has been a predominant focus in this respect, whether in a group situation[19] or with a canine friend[20], with other green exercise types including cycling and running, also showing significant benefits for health[21], with large health benefits even from as little as a 5 minute burst of green exercise[22]. Green exercise has even

been shown to have benefits above and beyond exercising in an urban or indoor gym environment[23-25].

1.2. Justification for the research

There is a growing body of research to illustrate the influence of greenspace and green environments on a broad range of health outcomes. A number of systematic reviews and review articles also exist that have investigated the relationship between one specific health outcome or behaviour including birth weight[26], physical activity[19], and obesity[27]. However, the wider health benefits of greenspace exposure have not yet been collated and quantified. This would inform researchers of the potential impact of greenspace on global disease burden, and of the potential of greenspace as a resource for health. This forms **research question one: What is the impact, if any, of greenspace on a wide range of physiological health outcomes?** which is addressed and presented in **Chapter 2: The health benefits of the great outdoors: A systematic review and meta-analysis of greenspace exposure and health outcomes.**

The systematic review presented in Chapter 2 provided evidence that greenspace was associated with a broad range of health benefits. However, the study also found a lack of studies investigating the mechanisms that underlie the relationship between greenspace and health. Studies included in the systematic review gave some suggestions as to what mechanisms may be pertinent. Amongst the studies that investigate underlying mechanisms for greenspace and health, the majority has focused mostly on physical activity, air quality, and psychological mechanisms. However new theoretical frameworks have also been proposed. These are considered below and identified in Figure 2.

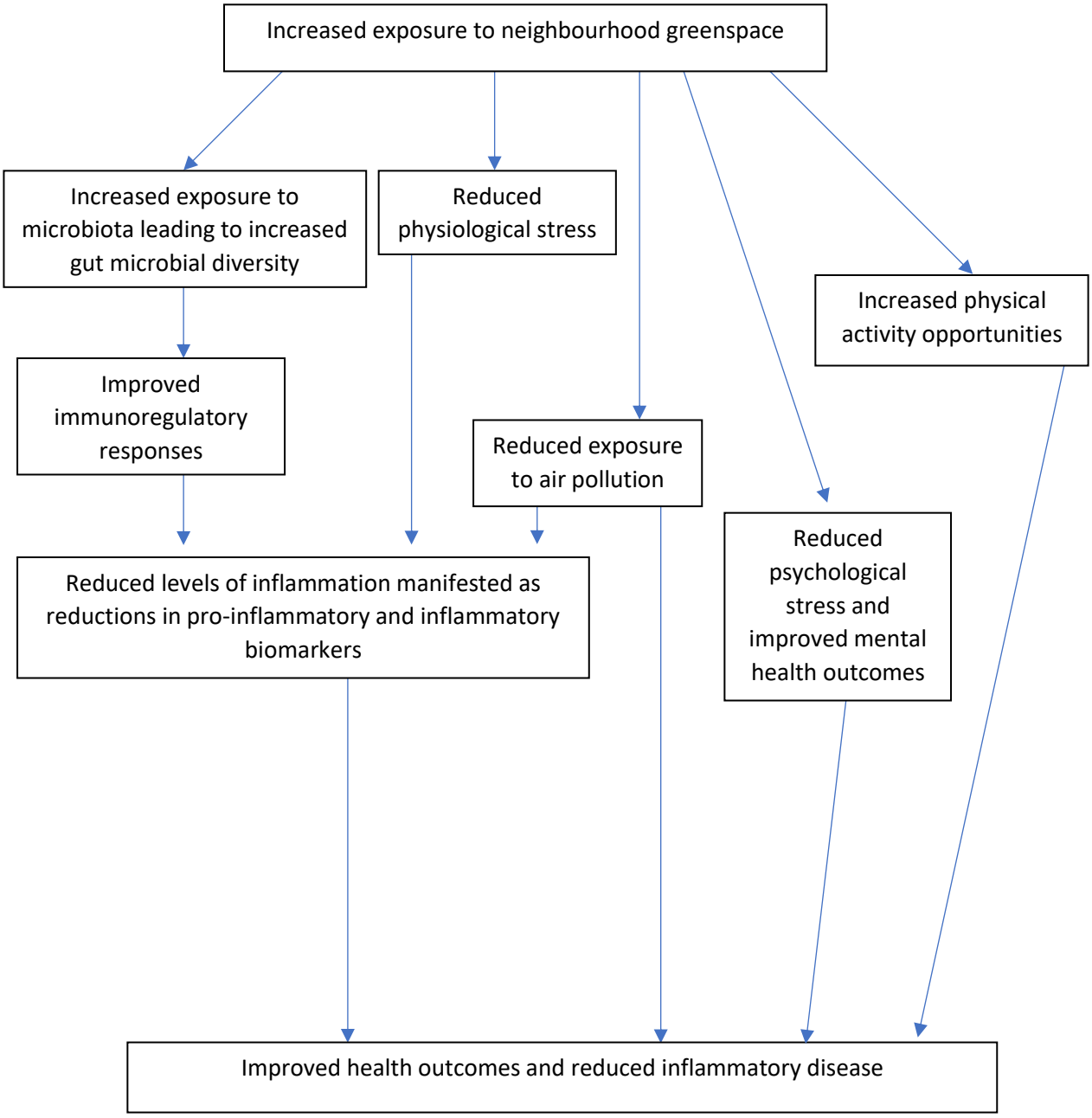
1.2.1. Physical activity

Physical activity has been demonstrated to influence both physiological and psychological health across a persons' lifespan[28 29]. There is evidence to suggest that physical activity in a green environment may be more beneficial for both mental and physical health than that in a gym or indoor environment[24 25]. Evidence also exists to suggest that provision of good access to urban greenspaces may promote physical activity[30], and a study by Flowers et al (2016) found that individuals are 4 times more likely to meet physical activity guidelines if they visit greenspace at least once per week[31]. Therefore, it is plausible that greenspace exposure may be beneficial for health due to the physical activity opportunities presented by accessible greenspaces.

Given the theoretical importance of the association between greenspace and physical activity, it is of surprise that much of the findings from the research investigating this mechanism are equivocal. A number of studies report no relationship between greenspace exposure and physical activity, with little evidence that physical activity mediates the relationship between greenspace and health[32-34]. Despite neighbourhood greenspace being associated with better cardiovascular and mental health, physical activity does not appear to explain this relationship[32]. A number of reasons have been proposed as to why the presence of greenspace does not necessarily imply its use for physical activity. Firstly some of the most green areas may require inhabitants to rely more on car transportation than active transport means (walking,cycling etc) to access local amenities[35 36]. It has been suggested that a mixture of green and non-green neighbourhood land uses could have optimal potential for health[37]. Secondly, not all greenspaces are optimal for physical activity, due to their size and available facilities. Larger parks with well maintained paths have been cited as more attractive for physical activity than smaller parks with a more recreational purpose[38].

Furthermore, certain green landcover types, which may be included in analyses investigating greenspace and health, may not be suitable for physical activity, e.g. agricultural land. Indeed, limited formal entry points and quality of available greenspaces may also influence their attractiveness and use for physical activity[39]. The Flowers study[31] showed that the subjective measure of greenspace quality was a bigger predictor of greenspace use than the objective measure of greenspace quantity. Indeed, there is further evidence to suggest that quality, as well as quantity, may be significant when determining health benefits[40]. This may in part explain why a number of studies[33 41 42] that investigate the relationship between greenspace exposure and physical activity without taking neighbourhood greenspace quality into consideration, suggest that neighbourhood greenspace exposure is not necessarily related to use of greenspace.

Figure 2. Hypothesized mechanisms for the relationship between greenspace exposure and health



1.2.2. Air pollution

Air pollution has been associated with a number of both respiratory and cardiovascular outcomes[43-45]. Whilst it is clear that trees and other greenery may successfully reduce air pollutants[43 46 47], certain species may also contribute to air pollution by releasing pollen, which has been associated with the aggravation of asthma, allergies and allergic rhinitis[48]. The role of trees and greenery as both reducing and contributing to air pollutants is complex and multidirectional, and indeed it may be the case that the detrimental influences of trees and greenery on asthma and allergies may outweigh their benefits to health through air

purification for those susceptible to asthma and allergies. In a number of studies investigating greenspace and health, air pollution has been treated as a possible confounder[48-50], although only one study has found evidence of this effect[51]. Air pollution may have been considered as a confounder instead of a mediator perhaps because it is unknown whether greenspace has an independent effect on health, as opposed to being simply an area with reduced air pollution levels[39]. The multidirectional relationship between greenspace and air pollution limit its' plausibility as the underlying mechanism for greenspace and health.

1.2.3. Psychological mechanisms

Greenspace exposure has been associated with a number of psychological health benefits. Research has linked increased neighbourhood greenspace with significantly lower levels of symptomology for depression, anxiety, and psychological stress[52]. Contact with nature has been associated with improved attention in children with attention deficit disorder[53]. Natural areas and greenery in a neighbourhood may be stress-reducing as they can reduce exposure to potential neighbourhood stressors, such as busy roads which omit both air and noise pollution[54], and unaestheically pleasing neighbourhood structures[55]. However natural areas can also provide people with a recreational setting away from stressors, and an opportunity for self-restoration. Indeed, there is a growing body of evidence illustrating the short-term restorative benefits of time spent in natural areas[56 57]. Greenspace has also been found to act as a 'buffer' from stressful life events, with participants with higher levels of neighbourhood greenspace less affected by experiencing a stressful life event than those with less neighbourhood greenspace[58]. Stress has been associated with substantial damaging impacts on physical and mental health across the lifespan[59 60].

Despite the presence of much positive evidence, methodological heterogeneity, as well as the use of varied subjective outcome measures limits the comparative ability of many of the studies investigating greenspace and mental health[61]. Therefore, it is difficult to determine the degree to which the relationship between greenspace and health is explained by psychological mechanisms.

1.2.4. Microbial exposures

There is evidence to suggest that greenspace exposure is associated with decreased incidence of inflammatory diseases such as type 2 diabetes (T2DM) and cardiovascular disease[62 63]. Increasing urbanisation has also been associated with a rise in failing immunoregulation and poorly regulated inflammatory response[64]. This may, in part, be due to the lack of exposure to organisms which are beneficial to immunoregulation such as

bacteria and other microbiota. These microbiota have a key role to play in the education and regulation of the immune system, and their decreased prevalence in the urban environment may be associated with increased inflammation, manifesting as chronically raised inflammatory cytokines[64 65]. As demonstrated in Figure 2, greenspace exposure may offer increased exposure to a diverse range of microbiota, benefiting immunoregulation and thereby reducing the incidence of chronic inflammation and the diseases associated with it. This is a relatively novel hypothesis for the mechanisms underlying the relationship between greenspace and health and forms the basis for **research question 2: Does neighbourhood greenspace have an association with the microbial diversity of the human gut, therefore mediating the relationship between greenspace and health?** This question was addressed by exploring whether neighbourhood greenspace exposure is associated with microbial diversity in the form of gut microbial diversity, using four diversity indexes and data from the TwinsUK database. The results of this study are presented in **Chapter 3: Does gut microbial diversity explain the relationship between greenspace and health? Results from the TwinsUK database**. This is the first study to investigate the relationship between greenspace exposure and gut microbial diversity.

In order to further explore the proposed hypothesis, it is necessary to also investigate whether a relationship exists between greenspace exposure and inflammation. This prompted research **question 3, Is there an association between neighbourhood greenspace and C-reactive protein, a common marker of inflammation?** This study, using data from the EPIC Norfolk study, is presented in **Chapter 4: Can hs-CRP explain the associations between neighbourhood greenspace exposure and health? The EPIC Norfolk study**. This research is necessary to determine if there is a relationship between neighbourhood greenspace and CRP, whether brought about by diverse microbial exposure from greenspace or through an alternative pathway. This would indicate whether a relationship exists between greenspace and immunoregulation and the regulation of inflammatory responses.

However the inflammatory process is complex, comprised of pro-inflammatory, inflammatory, and anti-inflammatory stages, each of which involve a range of cytokines or biomarkers[66-72]. If there is an association between greenspace and inflammation, exploring CRP alone may be overly restrictive. The hypothesis suggests that greenspace exposure will reduce overall inflammation, but hypothetically this could be achieved through any of three pathways: 1) a reduction in pro inflammatory cytokines, 2) a reduction in inflammatory cytokines, or 3) an increase in anti-inflammatory cytokines. This prompted **research question 4: Does neighbourhood greenspace have any association with the wider**

process of inflammation and its' associated markers? This study investigated the relationship between neighbourhood greenspace and six distinct inflammatory cytokines from different stages of the inflammatory process, and was conducted using data from the Leicester diabetes centre. This study is presented in **Chapter 5: Can markers of inflammation explain the relationship between residential neighbourhood greenspace and health in a pooled cross-sectional study?**

Chapter 6 then summarises the findings of each study, reflecting on the methods used, and suggests some areas for future research to further build on this thesis.

1.3. Outline of the thesis

This thesis is presented as four original research studies. The first has been published and the remaining three are undergoing preparation for submission to journals at the time of submission. This is outlined in the publications and statement of authorship section. Each study builds on the other and together they add to our understanding of the health benefits of exposure to greenspace. Each is presented as a separate chapter with a pre-amble at the beginning of chapters 3, 4, and 5 to contextualise the findings of each study to its preceding chapter and within the thesis as a whole.

Chapter 2: This study assesses the health benefits of greenspace exposure. This review used systematic review methods and multiple meta-analyses were conducted to examine the influence of greenspace exposure on a wide range of physiological health and well-being outcomes. A broad definition of greenspace was used for this chapter, to include natural, undeveloped land, as well as urban greenspaces and street greenery. For subsequent chapters, estimates of greenspace per 25m by 25m cell were computed from the Centre for Ecology and Hydrology Land Cover Map of the UK (2007)[73]. This is derived from satellite images and digital cartography, which record dominant land use types based on a 23-class typology, and then matched to the participants' postcodes. Classes considered to be greenspace for Chapters 3, 4, and 5 included broadleaf and coniferous woodland, arable, improved, and semi natural grassland as well as mountain, heath, and bog.

Chapter 3: Although chapter 2 demonstrates the abundance of research on the health benefits of greenspace exposure, it also highlighted the paucity of evidence concerning the underlying mechanisms for this association. Therefore in the following chapters the aim was to investigate one potential hypothesis. This study investigated whether greenspace around the home postcode was associated with diversity of the human gut using cross-sectional

data from the Twins UK study. Four validated diversity indexes were used to assess the diversity of microbiota in the gut.

Chapter 4: This study used cross-sectional data from the European Prospective Investigation into Cancer in Norfolk (EPIC Norfolk) study to investigate the relationship between neighbourhood greenspace exposure and C-reactive protein, a common marker of inflammation.

Chapter 5: Inflammation is a complex process involving numerous stages and a number of distinct cytokines and inflammatory factors. A gap in the literature was identified for a study to investigate the influence of neighbourhood greenspace on a number of markers involved in greenspace. This study uses data from the baseline of the ADDITION-Leicester and Walking Away From Diabetes datasets to investigate the influence of neighbourhood greenspace exposure on 6 distinct markers of inflammation: C-reactive protein, adiponectin, prostaglandins, interleukin-6, tumour necrosis factor-alpha, and resistin.

Chapter 6: This chapter summarises the principal findings of the thesis and reflects on the methodologies used. It will also describe the relevance of the findings to the existing literature, as well as implications and recommendations for future research.

Chapter 2: The health benefits of the great outdoors: A systematic review and meta-analysis of greenspace exposure and health outcomes

Abstract

Background: The health benefits of greenspaces have demanded the attention of policymakers since the 1800s. Although much evidence suggests greenspace exposure is beneficial for health, a gap exists for a systematic review and meta-analysis to synthesise and quantify the impact of greenspace on many health outcomes.

Objective: To quantify evidence of the impact of greenspace on a wide range of health outcomes.

Methods: We searched five online databases and reference lists up to January 2017. Studies satisfying *a priori* eligibility criteria were evaluated independently by two authors.

Results: We included 103 observational and 40 interventional studies investigating ~100 health outcomes. Meta-analysis results showed increased greenspace exposure was associated with decreased salivary cortisol -0.05 (95% CI -0.07, -0.04), heart rate -2.57 (95% CI -4.30, -0.83), diastolic blood pressure -1.97 (95% CI -3.45, -0.19), HDL cholesterol -0.03 (95% CI -0.05, <-0.01), low frequency heart rate variability (HRV) -0.06 (95% CI -0.08, -0.03) and increased high frequency HRV 91.87 (95% CI 50.92, 132.82), as well as decreased risk of preterm birth 0.87 (95% CI 0.80, 0.94), type II diabetes 0.72 (95% CI 0.61, 0.85), all-cause mortality 0.69 (95% CI 0.55, 0.87), small size for gestational age 0.81 (95% CI 0.76, 0.86), cardiovascular mortality 0.84 (95% CI 0.76, 0.93), and an increased incidence of good self-reported health 1.12 (95% CI 1.05, 1.19). Incidence of stroke, hypertension, dyslipidaemia, asthma, and coronary heart disease were reduced, as well as reductions in systolic blood pressure and fasting blood glucose, HbA1c, and increased gestational age were also found, however these results were not statistically significant. For several non-pooled health outcomes, between 66.7% and 100% of studies showed health-denoting associations with increased greenspace exposure including neurological and cancer-related outcomes, and respiratory mortality.

Conclusions: Greenspace exposure is associated with numerous health benefits in intervention and observational studies. These results are indicative of a beneficial influence of greenspace on a wide range of health outcomes, however a number of meta-analyses results are limited by poor study quality and high levels of heterogeneity. Green

prescriptions involving greenspace use may have substantial benefits. Our findings should encourage practitioners and policymakers to give due regard to how they can create, maintain, and improve existing accessible greenspaces in deprived areas. Furthermore the development of strategies and interventions for the utilisation of such greenspaces by those who stand to benefit the most.

2.1. Introduction

The idea that greenspaces are beneficial for the health of the population became a generally accepted principle as early as the 1800s, when various London-based organisations including the Commons Preservation Society and the National Health Society called for the preservation, creation, and accessibility of open spaces and parks within crowded residential areas, referring to them as the "lungs" of the town or city [12]. More recent Healthy City guidelines from the WHO support this view, defining a healthy city as "one that continually creates and improves its physical and social environments and expands the community resources that enable people to mutually support each other in performing all the functions of life and developing to their maximum potential" [74]. However, increasing urbanicity and modern lifestyles can mean that opportunities for human contact with nature become less frequent.

The term greenspace is typically defined as open, undeveloped land with natural vegetation[75], although it also exists in many other forms such as urban parks and public open spaces as well as street trees and greenery. Recognition of the health benefits of greenspace exposure was one of the motivations of Oxford General Practitioner William Bird MBE in establishing the UK's first health walk scheme at his practice in 1995, leading to the foundation of the English Walking for Health programme (WfH) [76]. Collaborations between health care providers and local nature partnerships are becoming increasingly common across the UK [77-80] and further afield [81], and aim to better capitalise on ways the health of the natural environment is intrinsically linked to human health, striving for "healthy communities in healthy environments" [77]. Yet a challenge is to ensure those who might benefit the most have sufficient opportunities for exposure to greenspace.

Socioeconomic health inequalities have consistently commanded the attention of researchers and policymakers, with evidence that inequalities are currently increasing [82]. Environmental factors form one of the many potential explanations as to their cause [83]. Research has shown that low income neighbourhoods have reduced greenspace availability [84], and residents of more deprived neighbourhoods are less likely to use those greenspaces that exist [41]. Park quality and frequency of park use have both been found to be higher amongst high-socioeconomic status (SES) residents [85]. It should also be noted that living in a greener neighbourhood has been linked with stronger greenspace-health associations [40 86 87] and that income-related health inequalities have been shown to be lower in greener neighbourhoods [88]. Greenspace may currently be overlooked as a resource for health and as part of a multi-component approach to decrease health inequalities.

Several hypotheses have been suggested to explain the relationship between nature and health and well-being. The first, is that natural and green areas promote health due to the opportunities for physical activity that they present. The health benefits of physical activity are well understood, with literature suggesting that exercising in a green environment may be more salutogenic than exercising in an indoor gym environment [89]. Secondly, public greenspaces have been associated with social interaction, which can contribute towards improved well-being [90]. Thirdly, exposure to sunlight, which is thought to counteract seasonal affective disorder [91] and a source of vitamin D [92] has been suggested as a causative pathway for this relationship. A fourth is the "Old friends" hypothesis, which proposes that use of greenspace increases exposure to a range of micro-organisms, including bacteria, protozoa and helminths, which are abundant in nature and may be important for the development of the immune system and for regulation of inflammatory responses [64]. Further potential mechanisms include the cooling influence of bodies of greenspace on surface radiating temperature (SRT), which has been documented as beneficial for health [93], as well as the mitigation of greenspace against environmental hazards such as air [94 95] and noise pollution [96 97].

Whilst there is a growing body of literature attempting to quantify the links between nature and improved health and well-being, systematic reviews in this area have largely focused on the association between greenspace and a specific health outcome or behaviour such as mortality [98 99], obesity [27], birth weight [26], physical wellbeing [89] as well as the acute health benefits of short term exposure to greenspace [61]. Associations have been reported with improved perceived general health, perceived mental health, as well as linking quality of neighbourhood greenness with improved general health [99]. Physical activity in a natural outdoor environment has been associated with reduced negative emotions and fatigue, increased energy [61 89], improved attention, as well as greater satisfaction, enjoyment and a greater intent to repeat the activity [61]. Additionally, meta-analyses have shown increased residential greenspace to be significantly associated with reduced cardiovascular and all-cause mortality [98], and increased birth weight [26]. Yet no systematic review has attempted to determine the impact of greenspace on a wide range of health outcomes.

With this systematic review, we aim to address a major gap in the evidence by identifying a set of health outcomes that have been investigated as being potentially associated with exposure to greenspace. Health outcome terms were taken from the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), a medical classification list produced by the World Health Organisation [100], with greenspace terms taken from a previous systematic review [27]. The clarification of the magnitude of

associations facilitates the investigation of potential underlying mechanisms in the relationship between nature and health. Furthermore, clinicians may use these findings to make recommendations to patients, which may convey health benefits or assist in tackling socio-economic health inequalities.

2.2. Methods

This systematic review followed Cochrane systematic review guidelines [101], requirements of the NHS National Institute of Health Research Centre for Reviews and Dissemination [102] and the PRISMA statement for reporting studies that evaluate healthcare interventions [103] [104]. Methods of the analysis and inclusion criteria were specified in advance and documented in a protocol registered as CRD42015025193 [102] available on the PROSPERO database http://www.crd.york.ac.uk/prospero/, and found in Appendix 1.

2.2.1. Data sources

Electronic databases including MEDLINE (US National Library of Medicine, Bethesda, Maryland, U.S.), EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands), AMED (Wolters Kluwer, Leicestershire, UK), CINAHL (EBSCO Publishing, Massachusetts, U.S.) and PsycINFO (American Psychological Association, Washington D.C., U.S.) were searched from inception to the end of September 2015, using specific search terms. The search was then updated to include studies published until mid-January 2017. Databases were selected to best represent source material in health, allied health and human science. Additionally, reference lists from included studies and previous systematic reviews on greenspace and health were hand searched.

2.2.2. Search strategy

Search terms associated with greenspace were developed with reference to a previous systematic review on greenspace and obesity [27]. For this review, 'greenspace' was defined as open, undeveloped land with natural vegetation as well as urban greenspaces, which included urban parks and street greenery. Health outcomes were taken from ICD-10 and then expanded to include the relevant metrics, for example "diabetes" was expanded to include "blood glucose" and glycated haemoglobin, commonly referred to as "HbA1c." To limit the scope of work, mental health and communicable diseases were excluded from this review after including them in initial scoping searches. Outcomes associated with weight status and birth weight were also excluded, as systematic reviews investigating them have recently been published[26 27 89].

The search strategy identified studies that contained at least one keyword or Medical Subject Heading (MeSH) from each list of search terms. The search was piloted to ensure known studies were identified and search syntax terms were adapted to suit each database. The electronic database search terms are detailed in table 8. The search strategy also incorporated limits to studies conducted on humans and studies written in English.

2.2.3. Study selection

All empirical studies where the outcome could be directly attributable to greenspace were included, including both intervention and observational studies. Titles and abstracts were examined by the primary reviewer (CB) to assess eligibility for the review using PICO criteria:

- **Participants:** Male and female, no age restrictions
- **Intervention:** Exposure to greenspace
- **Comparators:** There is no comparator restriction
- **Outcomes:** Any health outcome

Further details of the inclusion and exclusion criteria can be found in Table 1, below.

Table 1: Inclusion and exclusion criteria

Inclusion criteria for this review are:	*Exclusion criteria*
Empirical studies testing the relationships between greenspace and physical health outcomes	Studies that do not look at empirical evidence.
Studies that use human participants.	Studies that do not use human participants.
The study reports a physical health outcome other than BMI/physical activity/mental health/communicable disease/birth weight.	Studies where BMI/mental health/communicable disease/birth weight are the only outcome(s) or the study does not report a health outcome.
Papers and documents written in English.	Papers and documents not written in English.

Reviewer (CB) initially screened titles and abstracts to remove obviously irrelevant articles, and then two reviewers screened all full text articles independently (CB & AJ) to identify studies for inclusion in the systematic review. Discrepancies were resolved by discussion. Frequently abstracts used terms such as “neighbourhood environment”, “built environment” or “neighbourhood facilities” and did not specify the definition of these terms or if greenspace was investigated. These studies were retrieved as full texts and screened for greenspace as an outcome to ensure that none were excluded erroneously.

2.2.4. Data extraction

A data extraction sheet was developed by both authors to record the study type, population, type of greenspace under investigation, greenspace measurement tool used, health outcome under investigation and the outcomes. This was piloted on four manuscripts and refined accordingly. Data was extracted into a coding frame using Microsoft Excel, synthesised and tabulated. All studies underwent methodological critical appraisal using one of two checklists. For observational studies the Lachowycz and Jones [27] quality checklist (Table 2) was adapted and used. For intervention studies, a risk of bias tool employed by Hanson and Jones [19] and Ogilvie et al. [105], (Table 3) was adapted and used. Publication bias across studies within the meta-analysis was tested with funnel plots using SE as the measure of study size on the vertical axis and mean difference on the horizontal.

2.2.5. Narrative synthesis and meta-synthesis

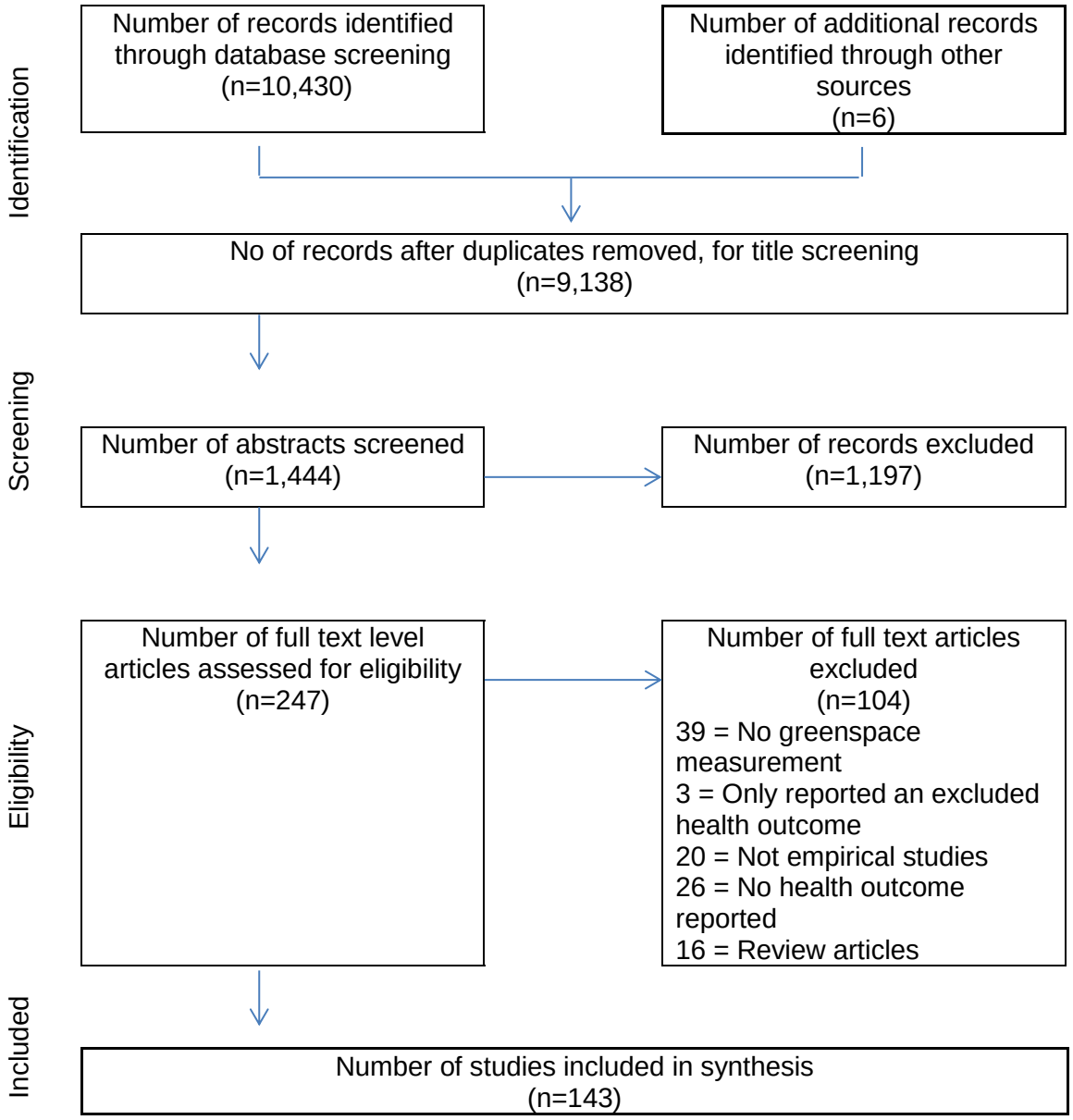
Following critical review of each study, a narrative synthesis was compiled. In order to be considered for meta-analysis, study authors needed to present either 1) mean difference, standard deviation (SD) and sample size for both the highest and lowest greenspace categories, or 2) number of cases of the reported condition/disease as well as sample size for both highest and lowest greenspace categories. If the required data was not reported in the paper, authors were contacted for this information. In total, 92 authors were contacted of which 32 responded with the data required for meta-analysis. In order for a specific health outcome to be considered for meta-analysis data from a minimum of two studies was required. Where data was given for different subgroups, each was input separately and combined in meta-analyses using the RevMan software package. All results are presented as forest plots with 95% confidence intervals. The I^2 statistic was calculated to quantify the degree of heterogeneity between studies[106]. A rough guide to interpreting heterogeneity is provided in the Cochrane handbook and gives I^2 values of 30-60% to represent moderate heterogeneity and values of 50-90% to represent substantial heterogeneity[101]. In cases of high heterogeneity, the known heterogeneity was assessed (i.e. populations, study design, exposure etc) to ensure that a meta-analysis was appropriate. A random effects model was employed for all meta-analyses as it is considered to represent a more conservative approach, suitable for cases of high heterogeneity [107].

Sensitivity analysis was then undertaken, which included studies which only scored 9 or above (out of a total of 11) in either the risk of bias tool or quality appraisal checklist, meaning that all but 2 risk of bias/quality checklist criteria had been met.

2.3. Results

The initial database search yielded 10,430 studies, of which 8,986 were removed as duplicates or as clearly irrelevant after reviewing titles. A further 6 studies were retrieved from reference lists of review articles. The abstracts of 1,444 studies were screened and any that did not provide enough information were retrieved for full text examination. A total of 247 papers were read as full texts to be assessed for eligibility. After independent assessment by the second reviewer (AJ), 143 studies met the inclusion criteria and were eligible to be included in the synthesis. The review flow chart is detailed in Figure 3. The characteristics and synthesised results for all 143 papers are detailed in Table 7 in Section 2.5.

Figure 3. Flow chart of studies



2.3.1. Study Characteristics

Although there was no date restriction on the search, 96% of the articles were studies from the past 10 years, illustrating recent growth in interest in greenspace and health, with no papers prior to 1984 meeting the inclusion criteria. Studies were in 20 different countries. Although 50% of studies were in Europe, the country with the highest frequency of included studies was Japan with 24. The populations under investigation varied greatly in size, with the smallest an intervention study of 9 participants [108], the largest study using primary data collection presented results for 2,593 primary schoolchildren [109], and the largest study using routinely collected data used 2011 UK census data with a population of >63 million [110]. In some papers, the number of participants was not reported.

Eleven different types of greenspace exposure were measured, the most common of which was neighbourhood greenspace (including residential greenspace, street greenery and tree canopy) measured by 56 studies, followed by greenspace-based interventions and proximity to a large greenspace. Several randomised studies compared a known green environment (i.e. a park or forest) with an urban or indoor environment. One study examined whether viewing trees through a hospital window had any association with post-operative recovery time when compared with a window view of a wall with no trees [111]. One included study investigated both green and blue (water) space. Studies investigating blue space alone with no investigation of greenspace exposure were excluded at the full text stage. A variety of greenspace measurement tools were used, including Normalised Difference Vegetation Index (NDVI), the Centre for Ecology and Hydrology (CeH) land cover map, and tree canopy and street tree data, as well as subjective measures of greenness such as self-reported quality of neighbourhood greenspace and self-reported frequency of walking in a green area.

Within the 143 studies, 40 were interventional and the remainder observational. Out of the 40 interventional studies, 27 were investigating the association between shinrin-yoku and various health outcomes. Shinrin yoku, or “forest bathing” is a popular practice in Japan and neighbouring countries, and is defined as “taking in the atmosphere of the forest” [112]. It is said to have health-promoting properties and to reduce stress [112]. Participants of shinrin-yoku spend time in the forest either sitting or lying down, or walking through the forest. In studies investigating forest bathing, a control group carried out the same activity in an urban environment. These studies typically had small numbers of participants (between 9 and 280 participants).

Of the 103 observational studies, 34 were cohort studies and 69 cross-sectional, including 18 large scale ecological studies investigating environmental influences on health amongst

the population using census data. Almost 100 health outcomes were investigated, with most manuscripts investigating more than one outcome. The most frequently investigated health outcomes were cardiovascular, including cardiovascular mortality, blood pressure, heart rate and incidence of angina and myocardial infarction. Other commonly reported health outcomes included pregnancy outcomes, self-reported health, mortality (all-cause, respiratory and intentional self-harm), and diabetes, as well as various blood biomarkers. The individual health outcomes investigated by each study are detailed in the table of study characteristics, Table 7 in Section 2.5.

2.3.2. Study quality

All 143 articles were assessed for quality using adapted versions of the Lachowycz and Jones checklist [27] for observational studies (Table 2) and the Hanson and Jones and Ogilvie et al. risk of bias tool [19 105] for interventional studies (Table 3). No study was excluded due to a low quality score. Assessments of quality were initially made by the first reviewer (CB) and then all studies were cross-checked by one other (AJ, SH or EC) for discrepancies.

An inter-rater reliability analysis using the κ statistic was performed and found κ 0.937, $p<0.001$ representing substantial agreement. Full consensus was reached after discussion. In the case that a checklist item consistently brought up discrepancies, clarification of the definition of the item was discussed. Individual quality analysis scores can be found in the Supplementary Tables 8 and 9, Section 2.6.

Table 2. Adapted Lachowycz and Jones quality appraisal checklist for observational studies

Item	Description	Scale
Methodological quality		
1. Population - Selection bias	Are the individuals selected to participate in the study likely to be representative of the target population?	1: Likely to be representative 0: Unlikely to be representative N: Insufficiently described
2. Population – Inclusion bias	Is there evidence of bias in the percentage of selected individuals who provided data for inclusion in the analysis?	1: No evidence of bias 0: Evidence of bias N: Insufficiently described
3. Outcome measure	Was the outcome objectively measured or self-reported?	1: Objectively measured outcome 0: Self reported N: Insufficiently described
4. Green space measure - derivation	Was derivation of the green space variable well described?	1: Derivation of green space measure well described 0: Derivation of green space measure not well described
5. Green space measure - type	Did the green space measure include information on type of green space?	1: Green space measure included information on type of green space 0: Green space measure did not include information on type of green space N: Insufficiently described
6. Use of green space	Use of green space was measured and included in analysis	1: Measured use of green space 0: Did not measure use of green space N: Insufficiently described
7. Statistical methodology	Was an appropriate statistical methodology used?	1: Evidence of appropriate methodology 0: No evidence of appropriate methodology N: Insufficiently described
8. Effect size	Was an effect size reported for green space variable?	1: Effect size reported for green space 0: Effect size not reported for green space N: Insufficiently described
9. Multiplicity	Was green space the main exposure being measured or one of many variables being tested?	1: Green space variable main exposure 0: Green space variable one of many variables being tested N: Insufficiently described
10. Level of analysis	Was analysis of green space in relation to outcome carried out at individual level or at ecological (area) level	1: Individual level 0: Ecological level N: Insufficiently described
11. Green space measure	Was greenspace exposure objectively measured or self-reported?	1: Objectively measured 0: Self-reported N: Insufficiently described

For the 103 observational studies assessed using the Lachowycz and Jones checklist [27] detailed in Table 2, scores ranged from 4 (one study) to 11 (one study), out of a total of 11 criteria. Only 12.6% of studies scored ≤7, with 39.8% of studies scoring 9 out of 11. The two

checklist criteria which were the most recurrently missing from were "*5. Did the green space measure include information on type of greenspace?"* and "*6. Use of greenspace was measured and included in the analysis".*

Table 3. Adapted Hanson and Jones and Ogilvie et al. risk of bias tool for intervention studies

Item	Description	Scale
Methodological quality		
1. Reporting: hypothesis	Is the hypothesis/aim/objective of the study clearly described?	1: Yes – clearly described 0: No
2. Reporting: outcome(s)	Are the main outcomes to be measured clearly described in the introduction or methods section? (if the main outcomes are first mentioned in the results section, this question should be answered no)	1: Yes – clearly described in introduction/methods 0: No – not clearly described/first mentioned in results
3. Reporting: intervention	Are the interventions of interest (greenspace and control or otherwise) clearly described?	1: Yes – clearly described 0: No
4. Randomisation	Was there sufficient description of a randomisation process or statistical test to show that comparability between the two groups has been adjusted for (no explanation scores zero)?	1: Yes – description of a randomisation process 0: No – no explanation
5. Exposure	Did the authors show that there was no evidence of a concurrent intervention which could have influenced the results (no explanation scores zero)?	1: Yes 0: No – no explanation N: Insufficiently described
6. Representativeness	Were the study samples shown to be representative of the study population?	1: Yes – shown to be representative 0: No – shown not to be representative N: Insufficiently described
7. Comparability	Were baseline characteristics of the intervention comparable with the control or were potential confounders at baseline approximately adjusted for in analysis?	1: Yes 0: No N: Insufficiently described
8. Attrition	Were numbers of participants at follow-up identifiable as at least 80% of the baseline?	1: Yes 0: No N: Insufficiently described
9. Outcome assessment: tools	Were valid and reliable tools used to assess participant outcomes?	1: Yes 0: No N: Insufficiently described
10. Follow-up time scale	Was the length of time to follow up assessment appropriate for the intervention?	1: Yes 0: No
11. Precision of the results	Were confidence intervals or p-values given?	1: Yes 0: No

For the 40 interventional studies assessed using the Hanson and Jones and Ogilvie et al. risk of bias tool [19 105] detailed in Table 3, scores ranged from 5 (one study) to 11 (one study) out of a total of 11 criteria. Only 7.7% of studies scored ≤7, with 66.7% of studies scoring 9

out of 11. The two checklist criteria which were the most recurrently missing from studies were "*5. Did the authors show that there was no evidence of a concurrent intervention which could have influenced the results?"* and "*6. Were the study samples shown to be representative of the study population?"*

2.3.3. Meta-analysis

The individual papers' results for their 'highest' and 'lowest' greenspace exposure/area categories were extracted for comparison by meta-analysis, for example highest quartile or quintile of greenspace exposure versus lowest quartile or quintile. Commonly reported outcome measures enabled meta-analysis of 24 health outcomes, summarised in Table 4 and 5 and presented in full in Figures 7-30 (Supplementary information). Statistically significant health denoting associations between high versus low greenspace exposure groups were identified for self-reported health, diastolic blood pressure (Figure 4), type II diabetes (Figure 5), all-cause and cardiovascular mortality, salivary cortisol, heart rate, heart rate variability (HRV), and HDL cholesterol as well as preterm birth and small size for gestational age births. Reductions were also found for incidence of stroke, hypertension, dyslipidaemia, asthma, and coronary heart disease, as well as improvements in systolic blood pressure, fasting blood glucose, and gestational age. However these results were not statistically significant.

Figure 4. Meta-analysis of the effects of greenspace exposure on diastolic blood pressure

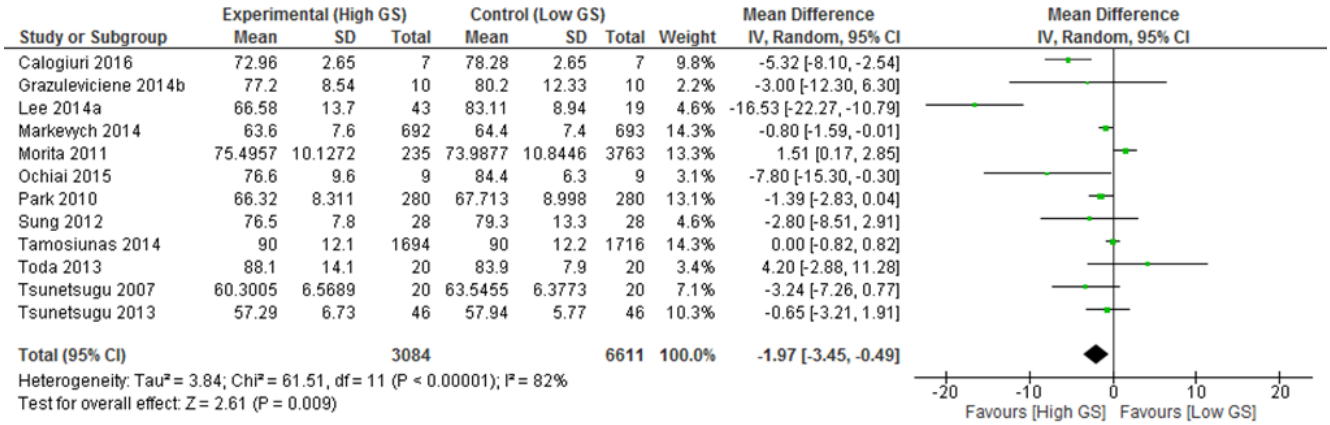
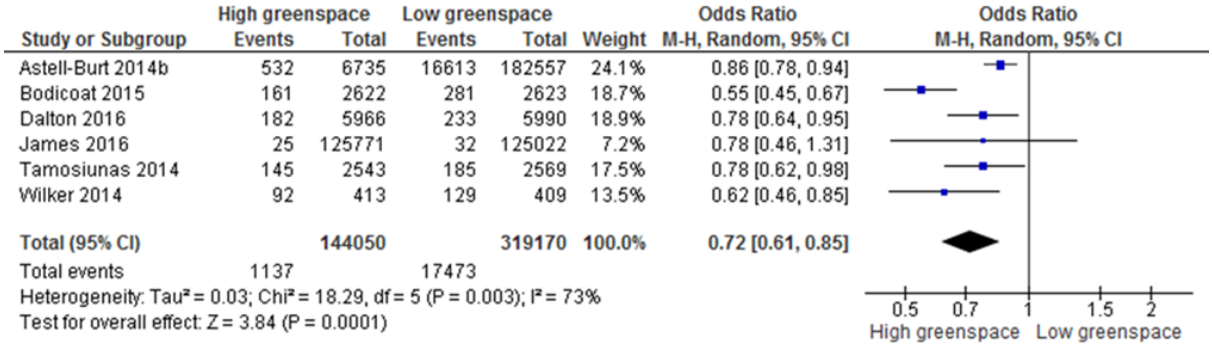


Figure 5. Meta-analysis of the effects of greenspace exposure on incidence of type II diabetes



Zero heterogeneity was reported for 8 of the analyses, 6 reported moderate heterogeneity (30-60%) with 10 having substantial heterogeneity (>60%). This suggests substantial heterogeneity between studies for heart rate, diastolic and systolic blood pressure, self-reported health, preterm birth, diabetes, all-cause mortality, small size for gestational age, hypertension and asthma. The I^2 score for the good self-reported health meta-analysis was 100%, indicating very high levels of inconsistency between studies. Using funnel plots, all studies were identified as visually symmetrical with a narrow spread at the top of the funnel indicating precision with results close to the pooled estimate and without bias towards smaller studies. Figure 6 (Supplementary information) shows an example funnel plot.

Table 4. Summary meta-analysis results table: mean difference (MD) between highest and lowest greenspace exposure groups

Outcome	**N (participants)**	**Effect MD (95% CI)**	**Heterogeneity I^2**	**P-value**
Salivary cortisol	*7 (954)*	*-0.05 (-0.07, -0.04)*	*0%*	*P<0.001*
Heart rate	*10 (1058)*	*-2.57 (-4.30, -0.83)*	*78%*	*P0.004*
HDL cholesterol	*2 (3474)*	*-0.03 (-0.05, <-0.01)*	*0%*	*p=0.02*
Diastolic blood pressure	*12 (9695)*	*-1.97 (-3.45, -0.49)*	*82%*	*p=0.009*
Systolic blood pressure	13 (9791)	-1.50 (-3.43, 0.44)	78%	p=0.13
Change in HF power of HRV	*7 (826)*	*91.87 (50.92, 132.82))*	*49%*	*p<0.001*
LF/(LF+HF)	*6 (266)*	*-0.06 (-0.08, -0.03)*	*0%*	*p<0.001*
HbA1c	2 (174)	-0.77 (-1.86, 0.32)	54%	P=0.16
Fasting blood glucose	2 (3474)	-0.01 (-0.08, 0.07)	0%	p=0.84
Total cholesterol	2 (3474)	0.03 (-0,05, 0.10)	0%	p=0.48
LDL cholesterol	2 (3474)	0.04 (-0.03, 0.11)	0%	p=0.23
Triglycerides	2 (3474)	0.06 (-0.01, 0.12)	0%	p=0.07
Gestational age	3 (22911)	<-0.01 (-0.05, 0.05)	0%	P=0.94

Table 5. Summary meta-analysis results table: odds ratios of disease incidence difference between high and low greenspace areas

Outcome	N (participants)	Odds ratio (95% CI)	Heterogeneity I^2	P-value
Good self-reported health	*10 (41873103)*	*1.12 (1.05, 1.19)*	*100%*	*p<0.001*
Preterm birth	*6 (1593471)*	*0.87 (0.80, 0.94)*	*68%*	*p<0.001*
Type II diabetes	*6 (463220)*	*0.72 (0.61, 0.85)*	*73%*	*p<0.001*
All-cause mortality	*4 (4001035)*	*0.69 (0.55, 0.87)*	*96%*	*P=0.002*
Hypertension	4 (11228)	0.99 (0.81, 1.20)	62%	P=0.91
Small for gestational age	*4 (1576253)*	*0.81 (0.76, 0.86)*	*65%*	*p<0.001*
Cardiovascular mortality	*2 (3999943)*	*0.84 (0.76, 0.93)*	*54%*	*p<0.001*
Stroke	3 (256727)	0.82 (0.61, 1.11)	59%	P=0.20
Dyslipidaemia	2 (5934)	0.94 (0.75, 1.17)	57%	P=0.56
Asthma	2 (2878)	0.93 (0.57, 1.52)	68%	P=0.78
Coronary heart disease	2 (255905)	0.92 (0.78, 1.07)	48%	P=0.26

To test whether significant meta-analysis results were due to inclusion of poor quality studies, sensitivity analysis was conducted where possible. Meta-analysis was repeated with only studies that scored ≥9 in either the quality appraisal checklist or risk of bias tool. This was only possible for heart rate, which showed a stronger effect size -3.46 (95% CI -4.05, -2.88) (2 studies removed), systolic blood pressure, which decreased in effect size and remained statistically non-significant -0.49 (95% CI -1.20, 0.22) (2 studies removed), and self-reported good health, which decreased in effect size and lost significance 1.06 (95% CI 0.96, 1.18) (6 studies removed). Table 6 shows the results from this sensitivity analysis. Fasting blood glucose, cholesterol, HbA1c, asthma, and triglycerides meta-analyses were not possible to include as there was only one remaining high quality study. The remaining meta-analyses consisted only of studies scoring ≥9, and so sensitivity analysis was not possible.

Table 6. Summary results table of sensitivity analysis meta-analysis consisting of only studies which scored ≥ 9 in quality checklist or risk of bias tool

Outcome	N (participants)	Effect MD or odds ratio (95% CI)	Heterogeneity I^2	P-value
Heart rate	*8 (842)*	*-3.46 (-4.05, -2.88)*	*83%*	*P<0.00001*
Systolic blood pressure	11 (9681)	-0.49 (-1.20, 0.22)	79%	p=0.17
Good self-reported health	4 (6577)	1.06 (0.96, 1.18)	88%	P=0.26

2.3.4. Non-pooled health outcomes

Meta-analysis was not possible for a number of health outcomes including cancer, respiratory mortality, neurological outcomes, and various biomarkers, as no two studies presented results on comparable outcomes. Three studies reported on cancer outcomes and found that living in the highest quartile of greenspace was associated with a significantly reduced risk of prostate cancer [113], OR 0.82 (95% CI 0.72, 0.92), as well as reduced incidence of overall cancer mortality (HR 0.87 (95% CI 0.78, 0.97) [114], whilst an Australian study found a significant increased risk of skin cancer for participants living in the highest greenspace quartile OR 1.07 (95% CI 1.01, 1.14) [115]. One study found living in the highest quartile of greenspace to be associated with reduced incidence of respiratory mortality [114] HR 0.66 (95% CI 0.52, 0.84). In terms of neurological outcomes, one study found that living in a neighbourhood with a low % of greenspace was associated with deficits in motor development in children [116], whilst another found no association between greenspace and cognitive development (Ward et al. 2016). A number of studies investigated a variety of biomarkers including natural killer cells [117], C-reactive protein [118], and perforin [119]. Individual study results can be found in the table of study characteristics, Table 7 in the Supplementary Information.

2.3. Discussion

This systematic review and meta-analysis of 143 studies provides evidence that exposure to greenspace is associated with wide-ranging health benefits. Meta-analyses results have shown statistically significant health-denoting associations for salivary cortisol -0.05 (95% CI -0.07, -0.04), heart rate -3.47 (95% CI -4.04, -2.90), diastolic blood pressure -1.97 (95% CI -3.45, -0.49), HDL cholesterol -0.03 (95% CI -0.05, <-0.01), and significant improvements in the HF power 91.87 (95% CI 50.92, 132.82) and LF/(LF+HF) -0.06 (95% CI -0.08, -0.03) of heart rate variability. As well as statistically significant reductions in the incidences of type II diabetes 0.72 (95% CI 0.61, 0.85), all-cause mortality 0.69 (95% CI 0.55, 0.87), cardiovascular mortality 0.84 (95% CI 0.76, 0.93), as well as pregnancy outcomes preterm birth 0.87 (95% CI 0.80, 0.94), and small size for gestational age 0.81 (95% CI 0.76, 0.86). A significant increase in incidence of reporting good health was also found 1.12 (95% CI 1.05, 1.19). Several meta-analyses results had high levels of heterogeneity (Tables 4 & 5), and should therefore be interpretted with caution. Included studies investigating non-pooled health outcomes also reported salutogenic associations for health outcomes such as cancer outcomes, respiratory mortality, sleep duration, various biomarkers, and neurological outcomes.

This review has comprehensively sought out empirically-reported studies investigating the association between greenspace and a wide range of health outcomes across five databases, covering a large number of relevant international journals. It has extensively analysed 143 different studies with the combined population size of >290 million. It has also extracted information for 24 novel meta-analyses to provide evidence of health benefits. A further major strength of this review is its inclusivity; studies were not excluded based on study design or type of greenspace, and as a result a broad range of greenspace exposures and health outcomes were identified by the 143 included studies. However, the inclusivity of this study can also be viewed as a limitation due to high heterogeneity across studies, and difficulties in comparing results from small-scale intervention studies and much larger ecological cross-sectional studies or in comparing studies that used objective measurements of greenspace with those that did not.

A number of studies reported stronger associations between greenspace exposure and self-reported health, birth outcomes and morbidity for those from low socioeconomic status (SES) groups and the most deprived areas [88 120-122]. Similar stronger associations were reported for birth outcomes and self-reported health for those with <10 years in education. Increased neighbourhood greenness was also reported to decrease the effect of income

deprivation on both all cause and cardiovascular mortality by one study [88]. Greenspaces may therefore form part of the arsenal in combatting health inequalities. Our findings should encourage practitioners and policymakers to give due regard to how they can create, maintain and improve existing accessible greenspaces in deprived areas. However this was only examined by a small number of studies so it was not possible to determine if this was the case for other health outcomes. As only a small number of studies presented results by proxy for SES group such as education level, occupation, or household income, it was not possible to conduct a formal subgroup analysis. Furthermore, the development of strategies and interventions for the utilisation of such greenspaces by those of low SES status who stand to benefit the most is needed.

Whilst previous systematic reviews have examined the relationship between greenspace and specific health outcomes or behaviours, this review investigated the potential impact of greenspace on a broad range of health outcomes. The findings of this review are consistent with previous systematic review results that suggest that greenspace is beneficial for health. Lachowycz and Jones [27] found that 68% of papers included in their systematic review found a positive or weak association between greenspace and obesity-related health indicators, although findings were inconsistent and mixed. Thomspon Coon et al. investigated the association between exercising in outdoor natural areas and health, and found physical activity in natural environments to be associated with increased energy, improved mental wellbeing and higher levels of intent in repeating the activity at a later date [89]. However, consistent with this systematic review, poor methodological quality of the available evidence and the heterogeneity of outcome measures hamper the interpretation and extrapolation of these findings [89]. Bowler et al. looked at studies comparing measurements of health in outdoor natural and synthetic environments such as indoor or outdoor built environments [61]. Findings suggest that a walk or run in a natural environment may convey greater health benefits than the same activity in a synthetic environment. This is consistent with the findings of Hanson and Jones, who conducted a systematic review and meta-analysis on outdoor walking groups [19]. Outdoor walking groups were found to significantly improve systolic and diastolic blood pressure, heart rate, body fat percentage, BMI, cholesterol, V02 max, depression and physical functioning, with no adverse side effects reported [19]. As with Bowler's systematic review and our findings, the evidence suggests that walking in a greenspace or natural area may offer health benefits above walking in an urban environment or on a treadmill [61]. In combination with the findings of this systematic review, it can be seen that there is a convincing body of evidence to suggest that greenspace is beneficial for health. Studies consistently reported that there are several substantial gaps

in knowledge remaining in this field, most commonly the mechanisms underlying the relationship between greenspace and health.

A high proportion of studies included in meta-analyses investigated Shinrin-yoku or forest-based interventions. Although 27 studies investigated the association between forest-based environments and health, only 5 looked at levels of street trees and tree canopy, with mixed results. It remains to be seen if the health benefits associated with forest bathing can be replicated in an urban environment by increasing street greenery and urban greenspace. Research in this field may inform national guidelines on the recommended number of trees necessary in urban and deprived areas to convey health benefits to the local populations. The findings of this review suggest that greenspace may be currently undervalued as a resource for health. Putting aside the health benefits of physical activity, which have been widely documented [28 29 123-125], the associations between greesnapce and health found in this study suggests that "green exercise" may have additional health benefits.

A strength of this review is that all papers underwent rigorous critical appraisal using one of two carefully chosen tools; the Lachowycz and Jones checklist [27] for observational studies and the Hanson and Jones and Ogilvie et al. risk of bias tool [19 105] for intervention studies. Both tools were tailored for the purposes of this systematic review and every study underwent quality appraisal by two reviewers, with a high level of inter-rater agreement. However, 58.3% of the observational studies and 77% of the interventional studies scored ≥9 out of 11 in their respective quality appraisal tools. This limited heterogeneity in study quality may suggest that the tools were not sensitive enough to capture certain aspects of quality of the studies reviewed and differentiate between studies. Sensitivity analysis was conducted using only high quality studies (studies scoring ≥9). This cut-off point was chosen priori to balance the need to retain some studies with a need to understand how sensitive the results were to the inclusion of weaker studies. A limitation of this cut off point is that it implied that all quality appraisal criteria were of equal value, which may not be the case. Results remained consistent for heart rate and systolic blood pressure, however self-reported good health had a reduced effect size and lost statistical significance, with the drop in statistical significance being possibly explained by the lower power of this sub-analysis. Furthermore, the self-reported good health meta-analysis had an I^2 of 100%, indicating a high risk of statistical heterogeneity. This result should therefore be interpreted cautiously.

A limitation of this review is that the search was restricted to manuscripts published in the English language. Furthermore, several health outcomes were only investigated in one or two studies, limiting comparability of results, for example, for respiratory mortality and various cancers. There were many differences between study populations; for example the

largest and smallest study populations were >63 million [110] and 9 participants [108] respectively. The exclusion of mental health and communicable disease outcomes, whilst done pragmatically, is also a limitation of this review.

One key area for further research is how health professionals and policymakers might encourage patients to increase their exposure or even time spent in green spaces, and in particular to target those from lower SES areas. A number of included studies in this review reported a stronger relationship between greenspace and health outcomes for participants who were from low SES neighbourhoods, had lowest education levels, or those who were from areas with the lowest surrounding neighbourhood greenness. However, results were often not presented according to SES, meaning that formal subgroup analysis by SES level was not possible. Therefore it is not known if this may be the case for other health outcomes. Evidence has shown increased odds of higher psychosocial distress in residents of low SES areas [126]. Our meta-analysis results suggest that greenspace exposure may reduce salivary cortisol, a physiological marker of stress. Further studies investigating greenspace and heath but with a focus on SES groups and subsequent health inequalities are required to fill this gap in the literature.

From the quality appraisal, it was evident that there were two criteria recurrently missing from both observational and intervention studies. For the 103 studies assessed using the observational study quality checklist [27] (Table 2), these were "*5. Did the green space measure include information on type of greenspace?"* and "*6. Use of greenspace was measured and included in the analysis"*. For the 40 intervention studies assessed using the risk of bias tool [19 105] (Table 3), these were "*5. Did the authors show that there was no evidence of a concurrent intervention which could have influenced the results?"* and "*6. Were the study samples shown to be representative of the study population?*" Future research should take this into consideration, with observational studies aiming to include data on type of greenspace under investigation and the participants' use of greenspace. Intervention studies should also aim to report on whether a concurrent intervention is in place, as well as commenting on the representativeness of the population.

Although this systematic review has uncovered a large body of research on the relationship between greenspace and health, there is a paucity of literature on the mechanisms underlying this relationship. Currently there are several suggested hypotheses. Greenspaces offer opportunities for physical activity, social cohesion, and stress reduction [36], which each carry their own numerous health benefits. Exposure to the diverse variety of bacteria present in natural areas may convey immunoregulatory benefits and reduce inflammation [64]. Much of the literature on forest bathing suggests that phytoncides (volatile

organic compounds with antibacterial properties) released by trees may explain the salutogenic properties of shinrin yoku [127] [128]. Further research should build on the findings of this systematic review by hypothesising and testing the potential mechanisms underlying the relationship between greenspace and health. The associations between greenspace and mental health outcomes and communicable diseases should also be explored further.

2.4. Conclusions

This review suggests that greenspace exposure is associated with wide ranging health benefits, with meta-analyses results showing statistically significant associations with reduced diastolic blood pressure, heart rate, salivary cortisol, incidence of type II diabetes and stroke, all-cause and cardiovascular mortality, as well as health-denoting associations with pregnancy outcomes, HRV, and HDL cholesterol, and self reported health. However some meta-analyses results are limited by poor study quality and high levels of heterogeneity and should therefore be interpreted with caution. Increased greenspace exposure was also associated with non-pooled outcomes including neurological outcomes, respiratory mortality, and increased sleep duration. The findings of this systematic review suggest that the creation, regeneration and maintenance of accessible greenspaces and street greenery may form part of a multi-faceted approach to improve a wide range of health outcomes.

2.5. Supplementary information

Table 7. Summary results for all 143 included studies

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Agay-Shay 2014, Israel [120]	To evaluate the associations between proximity to green spaces and surrounding greenness and pregnancy outcomes	Cohort study	39,132 singleton live births from a registry birth cohort in Tel Aviv during 2000-2006 (n = 39,132)	Birth weight (Including low and very low), gestational age and preterm deliveries/very preterm deliveries	National birth registry, Department of Mother and Child Health, Public Health Service of Israel	Residential surrounding greenness, Normalised Difference Vegetation Index, (NDVI), Landsat Enhanced Thematic Mapper +	Adjusted logistic regression models for infant's gender, infant's religion (Jewish/non-Jewish), maternal age, maternal marital status, maternal origin, year of birth and season of conception. Gestational age also adjusted for in birth weight analyses	Birth weight ↑ 250m buffer NDVI: 19.2g (95% CI 13.3, 25.1) Proximity to major green spaces (5000m^2): 18.1g (95% CI 8.7, 27.6) Low birth weight ↓ 250m buffer NDVI: OR 0.84 (95% CI 0.78,0.90) Proximity to major green spaces (5000m^2): OR 0.89 (95% CI 0.8, 0.99) Very low birth weight ↘ Preterm delivery ↗ Very preterm delivery ↘ *Stronger association for low SES participants*
Agyemang 2007, The Netherlands [129]	To investigate associations between neighbourhood-level environmental stressors (crime, housing density, nuisance from	Cross-sectional study	Individual data from the Amsterdam Health Survey 2004, sample consisted of 517 Dutch, 404 Turkish, 365	Blood pressure, hypertension	Primary measurement	Self-reported neighbourhood stressors from the Living in Amsterdam Survey 2003, Amsterdam Living and Security Survey 2004, The Social State of	Adjusted for potential confounding factors; age, sex, education level and BMI	Systolic blood pressure ↓ -4.92 (95% CI -9.21,-0.64) *Moroccan ethnic group only, Dutch and Turkish* ↘ Diastolic blood pressure ↘

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	alcohol and drug misuse, quality of green space and social participation), and blood pressure (BP) and hypertension among different ethnic groups.		Moroccans living in 15 neighbourhoods in Amsterdam. Sample taken from representative population (n = 1,286)			Amsterdam City Survey 2004		Hypertension ↓ 0.61 (95% CI 0.36, 0.99) *Moroccan ethnic group only, Dutch and Turkish* ↘
Andrusaityte 2016, Lithuania [130]	To investigate the associations between surrounding greenness levels and asthma among children, and to explore a possible change of this association by the distance of the residence to a city park	Nested case-control study	4-6 year old children of the KANC newborns cohort study (n = 1,489)	Doctor-diagnosed asthma	International Study of Asthma and Allergies in Childhood 9ISAAC) questionnaire	Residential surrounding greenness, Normalised Difference Vegetation Index, (NDVI) as well as distance to the nearest city park	ORs adjusted for individual-level mother's age at childbirth, maternal education, parental asthma, maternal smoking during pregnancy, breastfeeding, antibiotic use during the first year of life, keeping a cat during the past 12 months, living in a flat and yearly mean of ambient PM2.5 and NO_2	Asthma ↑ IQR increase in NDVI-100: 1.43 (1.10, 1.85)
Arbillaga-Etxarri 2016, Spain [131]	To validate the trail's design by assessing the physiological response to unsupervised walking trails of 1) different intensities in COPD patients,	Case control study	10 stable COPD patients (9 men, average age 67 ±9 years) and 10 healthy patients (5 men, average age 31 ±4 years) (n = 20)	VO_2, VCO_2, respiratory exchange ratio (RER), min ventilation (VE), heart rate (HR), energy expenditure volume (MET-	Primary measurement and bespoke questionnaire	Park walk vs boulevard walk vs beach	Matching of participants	VO2, VCO2, respiratory exchange ratio (RER), min ventilation (VE), heart rate (HR), energy expenditure volume (MET-min), walking time, walking speed, steps, time for breaks, final dyspnea, final leg fatigue ↔

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	and 2) same intensity from different public spaces in healthy adults			min), walking time, walking speed, steps, time for breaks, final dyspnea, final leg fatigue				
Astell-Burt 2014a, Australia [115]	Associations between incidence of melanoma or non-melanoma skin cancer and neighbourhood greenspace in the 45 and Up Study	Cross-sectional study	45 And Up Study, residents of New South Wales of 45 years and older. Randomly sampled from Australian universal health insurance database (n = 267,072)	Self-reported medically diagnosed skin cancer (melanoma and non-melanoma)	45 and Up Study bespoke questionnaire	Percentage greenspace within 1km buffer of home, Australian Bureau of Statistics (ABS) Meshblock 2006 classification	Models adjusted for measures of susceptibility (skin colour and tanning), socioeconomic variables, demographic and cultural characteristics (e.g. ancestry and country of birth)	Skin cancer ↑ When compared with <20% neighbourhood greenspace, odds of having non-melanoma skin cancer were significantly higher: 21-40% OR 1.05 (95% CI 1.03, 1.08), 41-60% OR 1.13 (95% CI 1.04,1.14), 61-80% OR 1.13 (95% CI1.06, 1.20), >80% OR 1.07 (95% CI 1.01, 1.14)
Astell-Burt 2013b, Australia [132]	To investigate whether neighbourhood greenspace was associated with a healthier duration of sleep (to the nearest hour) in the 45 and Up Study	Cross-sectional study	45 And Up Study, residents of New South Wales of 45 years and older. Randomly sampled from Australian universal health insurance database. Particpants completed baseline questionnaire between 2006 and 2009	Sleep duration	45 and Up Study bespoke questionnaire	Percentage greenspace within a 1km buffer around the census collection district (CCD), Australian Bureau of Statistics (ABS) Meshblock 2006 classification	Models adjusted for psychological distress, physical activity, and a range of demographic and socioeconomic characteristics	Sleep duration ↑ Risk of short sleep: >80% greenspace RR 0.86 (95%CI 0.81, 0.92) for 6-7 hours sleep and RR 0.68 (95% CI 0.57, 0.80)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
			(n = 259,319)					
Astell-Burt 2014b, Australia [133]	Investigate association between neighbourhood greenspace and the risk of T2DM in a large group of adult Australians	Cross-sectional study	45 And Up Study, residents of New South Wales of 45 years and older. Randomly sampled from Australian universal health insurance database (n = 267,072)	Medically diagnosed T2DM	45 and Up Study bespoke questionnaire	Percentage greenspace within 1km buffer of home, Australian Bureau of Statistics (ABS) Meshblock 2006 classification	Odds ratios controlled for measures of demographic, cultural health diet, active lifestyles, socioeconomic status, and neighbourhood circumstances	Risk of type II diabetes ↓ 41-60% GS: OR: 0.87, (95% CI 0.83, 0.92) 61-80% GS: OR 0.90, (95% CI 0.83, 0.97) >80% GS: OR 0.90 (95% CI 0.82, 0.99)
Beil 2013, Finland [134]	Investigate the effect of 4 urban environments on physiological and psychological stress measures	Pre-post study	Recruited from local community, average age 42.3 years (range 20-61 years), homogenous 'non-hispanic white' racial/ethnic background. 8 male, 7 female (n = 15)	Salivary cortisol and alpha-amylase, self-reported measures of stress	Primary measurement	'Very natural', 'mostly natural', 'mostly built' and 'very built'	Not specified	Salivary amylase ↓ Salivary cortisol ↘

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Besenyi 2014, USA [135]	To examine the spatial relationship between park availability and prevalence of chronic health conditions (CHCs) across adult age groups	Cross-sectional study	Participants who responded to a questionnaire as part of an initial cluster random sample of residential addresses. Mean age 51.7, 38.8% male, 61.2% female (n = 583)	Chronic health conditions (CHCs): Presence of heart problems (heart disease/BP/MI), cancer, diabetes, osteoporosis, depression/MH, asthma/allergies, disability, other	Bespoke questionnaire	Park availability within half mile of home, Kansas City Missouri (KCMO) Planning Department	All analyses controlled for gender, race/ethnicity, BMI, and household income	Chronic health conditions ↓ 40-59 age group without a park within one half mile from home, likelihood to have 2 or more CHCs: OR 2.28 (1.05, 4.94)
Bijnens 2015, Belgium [136]	To investigate the association between placental telomere length in twins and residential traffic exposure as well as semi-natural, forested, agricultural, residential and industrial areas within a 5000m radius from the residential address	Prospective study	Twins of Caucasian origin born between 1975 and 1982 who participated in a prenatal programming study selected from the East Flanders Prospective Twin Survey (EFPTS). Mean maternal age 27.5 years (range 19-40) (n = 211)	Placental telomere length	Primary measure	Semi-natural, forested, agricultural areas in a 5000m buffer, Corine landcover 2000	Covariates were selected a priori including newborn's sex, gestational age, birth weight, birth year (linear and quadratic), zygosity and chorionicity, maternal age, SES indicators, (maternal education and neighbourhood household income) and smoking during pregnancy	Placental telomere length ↑ An IQR increase (22%) in maternal residential surrounding greenness (5km buffer) associated with an increase of 3.62% (95% CI 0.20, 7.15%)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Bixby 2015, England [137]	To assess whether local associations between greenspace and physiological and psychological health are transferable to a larger scale	Ecological cross-sectional study	Populations of the 50 largest cities in England (n = not specified)	Risk of death from all causes, cardiovascular disease, lung cancer and suicide between 2002 and 2009	Individual-level mortality records, UK Small Area Health Statistics Unit	Proportion of city area covered by green land, Land Cover Map 2007	Adjusted for age, income deprivation and air pollution	All cause mortality ↘ Cardiovascular disease mortality ↘ Lung cancer ↗ Suicide mortality ↗
Bodicoat 2014, UK [138]	To investigate the relationship between neighbourhood greenspace and type 2 diabetes	Cross-sectional study	6,200 from general population, 4,276 from high-risk population. Mean age 59 years (range: 20-75 years). 47% female, 21% non-white ethnicity (n = 10,476)	Screen-detected type 2 diabetes	Primary measurement	Percentage neighbourhood greenspace, Land Cover Map 2007	Adjusted for ethnicity, age, sex, area social deprivation score and urban/rural status for increasing quartiles of neighbourhood greenspace, as well as BMI, physical activity, fasting glucose, 2h glucose and cholesterol for highest vs lowest quartile	Type II diabetes ↓ ORs for screen detected type 2 diabetes were 0.97 (0.80, 1.17), 0.78 (0.62, 0.98) and 0.67 (0.49, 0.93) for increasing quartiles of greenspace compared to the least green quartile after adjusting for confounders.
Botticello 2015, USA [139]	To assess the association between characteristics of the built environment and differences in perceived health among persons with spinal cord injury (SCI) using objective measures of the local	Secondary analysis of cross-sectional survey data	Spinal Cord Injury Model Systems (SCIMS) database participants, mean age 44.5 (±16.5) years, 80.5% male (n = 503)	Perceived health	Bespoke questionnaire	Percentage neighbourhood open space, dataset not specified	ORs adjusted for demographic, impairment and community socioeconomic differences	Perceived health ↑

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	community derived from GIS data							
Brown 2016, USA [140]	To examine the association between objective measures of block-level greenness (vegetative presence) and chronic medical conditions, including cardiometabolic conditions	Retrospective cohort study	Medicare beneficiaries, 76.33 (±7.5) years, 58.33% female (n = 249,405)	Number of chronic conditions (out of 27)	U.S. Centres for Medicare and Medicaid Services (CMS)' Master Beneficiary Summary File	Mean Normalised Difference Vegetation Index (NDVI) for all Miami-Dade County Census blocks	Not specified	Increase in mean NDVI: Total no. of chronic conditions ↓ Diabetes ↓ Hypertension ↓ Hyperlipidaemia ↓
Burkart 2016, Portugal [46]	To investigate the influence of urban vegetation and water bodies on heat-related excess mortality in the elderly >65 years old in Lisbon	Ecological study	Inhabitants of civil parishes in the Lisbon Metropolitan Area from 1998 to 2008 (n = not specified)	Heat-related excess mortality in the elderly	National mortality records	Amount and spatial distribution of urban green quantified using Normalised Difference Vegetation Index (NDVI)	Models adjusted for time trend, average daily mean PM_{10} and O_3 concentrations, percentage of the parish >65 years, building density, % college graduates and proportion of inhabitants receiving social benefits	With increasing NDVI quartiles: Heat-related excess mortality in the elderly ↓
Calogiuri 2016, Norway [141]	To investigate the impact of a green exercise intervention on psychological and physiological indicators of stress	RCT	Municipality employees, 49 (±8) years, 50% female (n = 14)	Potential for restoration, affective state, blood pressure, cortisol awakening response and cortisol serum levels	Primary measurement	Green/nature area vs indoor exercise setting	Not specified	Cortisol awakening response (improved) Diastolic BP ↓ BP ↔ Serum cortisol ↔

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	in municipality employees							
Casey 2016, USA [142]	To evaluate associations between prenatal residential greenness and birth outcomes across a range of community types	Cross-sectional study	Mothers from two hospitals who delivered between 2006 and 2013 (n = 20,569 delivery events and 20,598 neonates)	Term birth weight, small for gestational age birth, preterm birth and low 5 min Apgar score	Hospital records	Residential surrounding greenness, Normalised Difference Vegetation Index (NDVI)	Adjusted models controlled for neonate sex, year and season of birth, maternal age at delivery, maternal race/ethnicity, primary care status, smoking status during pregnancy, pre-pregnancy BMI, parity, receipt of Medical Assistance, number of antibiotic orders during pregnancy, distance to nearest major road, drinking water source within 20km of the home, exposure to swine operations, block group walkability and CSD quartiles	Higher greenness in cities: Preterm birth ↓ OR 0.78 (95% CI 0.61, 0.99) Small for gestational age birth ↓ OR 0.73 (95% CI 0.58, 0.97) Birth weight ↔ Apgar score ↔
Chum 2015, Canada [143]	To combine multiple neighbourhood influences in an integrated approach to understand the association between the built	Cross-sectional study	Cross-sectional survey across 87 census tracts in Toronto. Mean age 44 years, 53% female	Cardiovascular disease risk	Bespoke questionnaire	Percentage of local area used for parks, CanMap geo-database	Model 3 adjusted for individual level socio-demographic risk factors and health behaviours, model 4 is further adjusted for BMI and physical activity	Cardiovascular disease ↗

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	and social environment and and cardiovascular diseases (CVDs)		(n = 2,411)					
Coutts 2010, USA [144]	To examine the relationships neyween the presence and accessibility of greenspace and county-level mortality in the state of Florida	Cross-sectional ecologic al study	Data on all-cause mortality and mortality from major cardiovascular diseases in 2007 were obtained from the Florida Department of Health's Community Health Assessment Resource Tool Set (CHARTS). (n = 167,708 deaths from all-causes, 54,542 deaths from cardiovascular diseases)	All-cause and cardiovascular mortality	State mortality database	Greenness in census tracts, 2009 Public land file	Controlled for the proportion of the population in each county that are overweight or obese, the proportion who smoke, the proportion of people who report being moderately physically active, the % of the population 65 and older, and % of the population with a bachelor's degree or higher. Also controlled for ethnicity	All-cause mortality ↓ Cardiovascular mortality ↓
Coutts 2015, USA [145]	To determine if green space proximity to one's residential location at time of death was predictive of all-cause premature mortality	Cross-sectional study	Death certificate records obtained from the Florida State Department of Health, Bureau of Epidemiology for the years 2000-2012 (n = 2,216,641)	Premature mortality from all causes	State mortality databases	Distance from residential address to nearest greenspace, amount of greenspace within a set of defined distances from each residence; 2009 public land file	Four separate models for males and four separate models for females, controlling for education, race, Hispanic ethnicity, and marital status	Years of potential life lost ↓ with decreasing distance to nearest greenspace for both males and females

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Cusack 2017, USA [146]	To examine residential greenness and birth outcomes in Texas with large regional variation in greenness levels and a diverse population	Population-based cohort study	All births in Texas from 2000 to 2009 (n = 3,413,787)	Birth weight, odds of preterm birth, odds of being small for gestational age	Texas Vital Statistics program	Estimates of residential greenspace derived from MODIS satellite NDVI imagery	Adjusted for maternal and parental (if available) covariates age, smoking, education, race/ethnicity; pregnancy-related variables included method of delivery, parity, prenatal care, gestational age, baby's sex, month and year of birth, as well as neighbourhood variables, NO_A air pollution concentrations and population density	Birth weight, odds of preterm birth, odds of being small for gestational age ↔ *Associations became non-significant in fully adjusted models*
Dadvand 2012a, Spain [147]	To investigate the association between surrounding greenness and birth weight, head circumference and gestational age at delivery	Cohort study	Singleton live births from INfancia y Medio Ambiente (INMA Project); four Spanish cohorts between 2003-8. Pregnant women ≥16 years old, recruited in first trimester (n = 2,393)	Birth weight, gestational age and head circumference	Primary measurement	Residential surrounding greenness, Normalised Difference Vegetation Index (NDVI)	All analyses were adjusted for maternal age (continuous), ethnicity (white/other), socioeconomic status, education level, smoking, alcohol consumption, parity, infant sex (male/female), and season of conception. Birth weight analyses also adjusted for gestational age at	Birth weight ↑ 44.2g (95% CI 20.2, 68.2) Head circumference ↑ 1.7mm (95% CI 0.5, 2.9) Gestational age ↘

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
							delivery, maternal pre-gestational BMI, weight gain during pregnancy and paternal BMI. Analyses of head circumference further adjusted for gestational age at delivery, maternal height and paternal BMI	
Dadvand 2012b, Spain [148]	To investigate the effects of surrounding greenness and proximity to major green spaces on birth weight and gestational age at delivery and to describe the effect of socioeconomic position (SEP) on these relationships	Cohort study	Cohort of births in a Barcelona hospital between 2001-5 (n = 8,246)	Birth weight, gestational age at delivery and the effect of socioeconomic position on these relationships	Primary measurement	Residential surrounding greenness, Normalised Difference Vegetation Index, (NDVI)	Birth weight analysis: Adjusted for gestational age at delivery, neighbourhood SEP, degree of urbanisation, distance of residential place to major roads, maternal weight, age, ethnicity, academic level, occupation, smoking, alcohol consumption, parity, history of obs/gynae pathologies, use of assisted reproductive technologies Gestational age analysis: Adjusted for neighbourhood SEP, degree of	Birth weight ↑ *Beneficial association only amongst the lowest education level group who had higher surrounding NDVI (Regression coefficient: 436.3 (95% CI 43.1, 829.5)) or lived close to a major green space (Regression coefficient: 189.8 (95% CI 23.9, 355.7))* Gestational age ↔

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
							urbanisation, distance of residential place to major roads, maternal age, ethnicity, academic level, occupation, smoking, alcohol consumption, parity, history of preterm birth, history of obs/gynae pathologies, use of assisted reproductive technologies and sex of infant	
Dadvand 2014, Spain [149]	To evaluate health benefits and risks associated with different types of greenness in children, in terms of sedentary behaviour (excessive screen time), obesity, current asthma and allergic rhinoconjunctivitis	Cross-sectional study	Population-based sample of schoolchildren (9-12 years old) in Spain in 2006 (n = 3,178)	Sedentary behaviour, obesity, current asthma and allergic rhinoconjuncitivitis	Bespoke questionnaire	Residential surrounding greenness, Normalised Difference Vegetation Index, (NDVI) Residential proximity to greenspaces, Urban Atlas map (2007)	All analyses adjusted for indicators of individual SES, parental education, parental school (public/private), area-level SES at census tract level. Respiratory and allergic outcomes further adjusted for child's sex and age, exposure to tobacco smoke at home, having older siblings, parental history of asthma. Analyses of	Asthma ↗ Allergic rhinoconjunctivitis ↗

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
							overweight/obesity adjusted for sport activity at school or sport facilities and having siblings. Sedentary behaviour analyses controlled for child's sex and age and having siblings	
Dadvand 2015, Spain [109]	To assess the association between exposure to greenspace and measures of cognitive development in primary schoolchildren	Cohort study	Conducted as part of the brain development and air pollution ultrafine particles in schoolchildren (BREATHE) project. Mean age 8.5 years at baseline, 50% female (n = 2,593)	Developmental trajectory of working memory, superior working memory, and inattentiveness	Primary measurement	Residential and school surrounding greenness, Normalised Difference Vegetation Index (NDVI)	Model adjusted for age, sex and SES indicators at individual and area levels	Cognitive development ↑ Pre-post results for greenspace within and surrounding school grounds show significant improvements in working memory, superior working memory and a significant reduction in inattentiveness
Dadvand 2016, Spain [150]	To assess the association between greenness exposure and subjective general health (SGH), and to evaluate mental health status, social support and physical activity as mediators of this association	Cross-sectional study	Population-based randomised sample of adults residing in Barcelona (n = 3,461)	SGH, mental health	SGH: bespoke questionnaire Mental health: GHQ-12	Residential surrounding greenness as well as objective and subjective (perceived) proximity to greenspace; Normalised Difference Vegetation Index (NDVI), Parks and Garden Map of	Randomised sample Models further adjusted a priori for age, sex and indicators of SES at both individual and area levels	SGH ↑ 100m buffer OR 1.17 (95% CI 1.05, 1.31) 250m buffer OR 1.18 (95% CI 1.06, 1.32) 500m buffer OR 1.16 (95% CI 1.05, 1.29) Subjective proximity to greenspace OR 1.36 (95% CI 1.11, 1.67)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
						Barcelona, bespoke questionnaire		
Dalton 2016, UK [151]	To investigate the association between neighbourhood greenspace and the occurrence of incident diabetes over time	Prospective cohort study	EPIC Norfolk cohort study (n = 23,865)	Incident type 2 diabetes	Self-report of doctor diagnosed diabetes/questionnaire / self-report of diabetes-specific medication	Percentage neighbourhood greenspace, Land Cover Map 2007	Analysis adjusted for socio-economic status at both the individual and neighbourhood level	Diabetes ↓ HR 0.81 (95% CI 0.65, 0.99) for individuals living in the greenest quartiles
de Jong 2012, Sweden [152]	To assess how perceived green neighbourhood qualities were associated with three self-reported indicators of well-being (neighbourhood satisfaction, physical activity and general health)	Cross-sectional study	Questionnaire sent to 52,142 participants randomly selected from the population registry. 55% female (n = 24,847)	Three self-reported indicators of well-being: neighbourhood satisfaction, physical activity and general health	Public health survey data	Bespoke objective measurement of greenspace quality Availability of green qualities within 300m of residential address, CORINE land use data	Analyses were adjusted for possible confounding by sex, age, highest level of education, economic difficulties, country of origin and type of residence. Stratified analysis on neighbourhood satisfaction for type of residence	Self-reported health ↑

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Demoury 2016, Canada [113]	To assess whether living in the proximity of greener areas was related to prostate cancer risk	Population-based case-control study	Men younger than 76 years in the Montreal area (n = 1933 cases, 1994 controls)	Newly diagnosed with primary PCa	The Prostate Cancer & Environment Study (PROtEuS)	Residential greenspace at 2 time points, Landsat TM5 Normalised Difference Vegetation Index (NDVI)	Model 1: adjusted for age Model 2: adjusted for age, ancestry, first-degree family history of PCa, education, reported family income, marital status, smoking, alcohol consumption, dietary habits and a history of diabetes Model 3: Further adjusted for neighbourhood material and social deprivation	Prostate cancer ↓ 300m buffer, an IQR increase of 0.11 in recruitment OR 0.82 (95% CI 0.74, 0.92) 10 years previous: OR 0.86 (95% CI 0.74, 1.00) Remained significant for all buffer sizes at recruitment time point
de Vries 2003, The Netherlands [153]	To investigate the association between neighbourhood greenspace and self-reported health	Multilevel analysis (cross-sectional)	Health interview survey among random samples of practice populations of 103 general practices in the Netherlands (n = 10,179)	Number of symptoms experienced in the last 14 days, perceived general health, Dutch general health questionnaire (GHQ)	The Dutch National Survey of Morbidity and Interventions in General Practice	Percentage green and blue space in living environment; National Land Cover Classification, presence of a garden (yes/no)	The scores on all variables at the (semi-)interval level had been centred (but not standardised)	Self-reported health ↑
Donovan 2011, USA [154]	To investigate whether tree canopy cover is associated with reduced risk of poor birth	Cohort study	All singleton live births in Portland, Oregon during 2006-7, where the mothers' address was a single family	Preterm birth, gestational age of less than 37 weeks, small for gestational age, birth weight below the 10th percentile	Birth certificate data, Portland, Oregon	Percentage tree canopy in 50, 100, and 200m buffers surrounding residential address; Metro land cover classification 2007	To ensure that all confounders were included, any covariate with significant variation in canopy cover within 50m of a house that was not	Small for gestational age births ↓ 10% increase in tree canopy cover within 50m of a house reduced the number of small for gestational age births by 1.42 per 1000 births (95% CI -0.11, -2.72)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	outcomes in Portland, Oregon		home. Mean age 30.3 years (n = 5,696)	for gestational age and gender			selected for retention during thr backward selection process was re-introduced to the final model. If any re-introduced variable caused a 10% or greater change in any coefficients of interest, it was retained in the final model. None of the covariates evaluated met this threshold	
Droomers 2016, The Netherlands [155]	To investigate the impact of real-life changes in the quality and quantity of green space in severely deprived neighbourhood on physical activity and perceived general health	Quasi-experimental study	Dutch National Health Interview Survey from 2004 to 2011 (n = 48,132)	Perceived general health	Dutch National Health Interview Survey from 2004 to 2011	Local greenspaces that underwent improvement interventions	All analyses adjusted for age, sex, household composition, ethnicity, education and standardised disposable household income; additionally adjusted for overall intensity of District Approach	Perceived general health ↔
Dunstan 2013, Wales [156]	To determine the association between self-reported general health and an objectively assessed measure of the residential environment. (Using the	Cohort study	Caerphilly Prospective Study, taken from individual census records, 47.78% male (n = 31,442)	Self-reported general health	UK census data	Residential environment assessment tool (REAT)	Models fitted adding individual-level covariates: age, gender, marital status, housing tenure and employment status	Self-reported health ↘

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	Residential Environment Assessment Tool, REAT)							
Fjortoft 2004, Norway [157]	To investigate the relationship between children's motor development and playing in a natural environment	Quasi-experimental study (randomised)	Experimental and control groups selected from voluntary kindergartens with the same original playground opportunities in the same geographic area. Age range 5-7 years old (n = not specified)	Motor fitness, balance, co-ordination	Primary measurement	Forest playground vs traditional outdoor playground	Not stated	Motor development ↑ *in children*
Fuertes 2014, Germany [86]	To examine whether residential greenness is associated with childhood doctor diagnosed allergic rhinitis, eyes and nose symptoms	Cohort study	GINIplus and LISAplus birth cohorts (n = 5,803)	Childhood doctor-diagnosed allergic rhinitis, eyes and nose symptoms and aeroallergen sensitisation. Also air pollution data (stratified analysis)	Bespoke questionnaire	Mean residential greenness in a 500m buffer around the 10 year home address; Normalised Difference Vegetation Index, (NDVI)	Models were adjusted for age, sex, parental history of atopy, older siblings, maternal smoking during pregnancy, tobacco smoke exposure in the home (birth-4 years), cohort and parental education	Eye and nose symptoms ↓ GINI/LISA South (urban) OR 1.15 (95% CI 1.01, 1.31) GINI/LISA North (rural) OR 0.71 (95% CI 0.56, 0.89) Allergic rhinitis ↓ GINI/LISA North (rural) OR 0.75 (95% CI 0.60, 0.93)

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Gong 2014, UK [158]	To explore the role of neighbourhood greenspace in determining levels of participation in physical activity among elderly men with different levels of lower extremity function	Prospective study	Caerphilly Prospective Study (n = 1,010)	Lower extremity "physical function"; i.e. physical activity, Psychological health general stress	Bespoke questionnaire and General Health Questionnaire (GHQ-30)	Quantity and variation of neighbourhood greenspace; Normalised Difference Vegetation Index (NDVI)	Model 2 adjusted for lower extremity physical function, psychological distress, general health, car ownership, age group, marital status, social class and education level	Lower extremity physical function ↑ OR 1.92 (95% CI 1.12, 3.28)
Grazulevicience 2014a, Lithuania [159]	To investigate the effect of proximity to city parks on blood pressure categories during the first trimester of pregnancy	Cross sectional study	Pregnant women recruited to the European Commission's FP6 HiWATE project between 2007-9. 20-45 years old (n = 3,416)	Blood pressure in first trimester of pregnancy	Primary measurement	Distance to nearest park; unspecified land cover dataset	Models adjusted for age, education, socioeconomic position, passive smoking, BMI, chronic disease, parity and stress	Blood pressure ↓ >1000m green space distance odds ratio for increased blood pressure: OR 1.74 (95%CI 1.14,2.66)
Grazulevicience 2015b, Lithuania [160]	To investigate the effect of walking in a city park vs. an urban environment on coronary artery disease (CAD) patients haemodynamic parameters	Intervention study	Male and female Kaunas city residents, 62.3 ± 12.6 years of age with CAD (n = 20)	Haemodynamic parameters of CAD patients, including SBP/DBP, HR, exercise duration and HR recovery	Questionnaire, Primary measurement	Pine park vs urban busy street	Randomisation of participants	Heart rate ↓ Diastolic blood pressure ↓ Heart rate recovery ↓ Exercise duration ↑
Grazulevicience 2015a, Lithuania [161]	To investigate whether surrounding greenness levels and/or distance to city parks affect birth outcomes	Cohort study	Kaunas birth cohort, participants recruited between 2007-9 in the early stages of	Gestational age, preterm birth, birth weight, low birth weight, term low birth weight, and small for gestational age	Birth certificate data, Kaunas, Lithuania	Residential surrounding greenness, distance to nearest park; Normalised Difference Vegetation Index, (NDVI)	Low birth weight models adjusted for maternal marital status, education, smoking, blood pressure, BMI, parity, chronic	For subjects with low surrounding greenness and >1000m to the nearest park: Low birth weight↑ OR 2.23(95%CI 1.20,4.15)

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			pregnancy. Age range 20 to 45 years old (n = 3,292)				diseases, previous preterm birth, paternal smoking and infant sex Term low birth weight adjusted for maternal marital status, education, smoking, alcohol consumption, BMI, blood pressure, parity, paternal smoking and infant sex Preterm birth adjusted for maternal marital status, education, smoking, renal diseases, stress, previous preterm birth, parity and paternal smoking Small for gestational age adjusted for maternal age, marital status, education, social status, smoking, BMI, parity and previous preterm birth Birth weight adjusted for maternal height, smoking, marital	Term low birth weight ↑ OR 2.97 (95% CI 1.04, 8.45) Preterm birth ↑ OR 1.77 (95% CI 1.10, 2.81) Lower gestational age↑ Beneficial park effect on foetal growth in environment with least surrounding greenness ↗

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							status, BMI, diabetes and chronic health diseases, parity Gestational age adjusted for maternal marital status, education, smoking, renal diseases, stress, parity, previous preterm birth and paternal smoking	
Grazulevicience 2016, Lithuania [56]	To examine the effects of restorative walking in a park vs in an urban environment on coronary artery disease (CAD) patients stress parameters and cardiac function	RCT	Male and female Kaunas city residents with CAD, mean age 62.3 ±12.6 years (n = 20)	Heart rate, blood pressure, stress levels, mood	Primary measurement, Positive and Negative Effect Schedule (PANAS) mood score evaluation	Park vs urban environment	Participants randomly assigned to study arm	Salivary cortisol ↓ Blood pressure ↓
Grigsby-Toussaint 2015, USA [162]	To determine whether exposure to attributes of the natural environment (e.g. greenspace) attenuates the likelihood of reporting insufficient sleep among US adults.	Cross-sectional study	2020 Behavioural Risk Factor Surveillance System (BRFSS), a yearly, randomised telephone survey of behavioural risk factors among US adults ≥18	Self-reported sleep insufficiency	2010 Behavioural Risk Surveillance System (BRFSS) survey	County-level greenspace; Normalised Difference Vegetation Index, (NDVI)	Adjusted for age, gender, marital status, race, education, employment status, number of children, physical activity, smoking, income level, asthma, general health status, emotional support, disability,	Sleep quality ↑ Individuals reporting 7-13 days or 21-29 days of insufficient sleep. 7-13 days OR 0.995 (95% 0.988, 1.002) 21-29 days OR 0.991 (95% CI 0.986, 0.9996) Lower odds of exposure to natural amenities were observed for

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			years of age. 64.13% female. Average age 56.6 years. (n = 255,171)				BMI category and heavy alcohol use	individuals reporting 21-29 days of insufficient sleep OR 0.843 (95% CI 0.747, 0.951)
Gutierrez-Zornoza 2014, Spain [163]	To examine (a) whether distance from home to school is a determinant of active commuting to school (ACS), (b) the relationship between distance from home to heavily used facilities (school, green spaces and sports facilities) and the weight status and cardiometabolic risk categories and (c) whether ACS has a positive impact on schoolchildren's health.	Cross-sectional study	Cross-sectional study of the final measurements taken in a cluster randomized trial to evaluate the effectiveness of leisure-time physical activity on preventing childhood obesity (the MOVI programme). Schoolchildren aged 10-12 years old. 49.37% male, average age 11 years. (n = 956)	BMI and fat mass, blood pressure, fasting plasma lipid profile, insulin, fitness, physical activity and active commuting to school (ACS)	Primary measurement	Distance from home to greenspace; National Plan for Aerial Orthophotography 2007	Model 1 controlled for age, fat mass percentage, and fitness according to age Model 2 controlled for controlled for age, commuting, fitness according to gender Model 3 adjusted for age and cardiovascular fitness; for the MetS index, adjusted for age, cardiovascular fitness and fat mass; for cardiovascular fitness adjusted for age and fat mass	Cardiometabolic risk ↔

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Hartig 2003, USA [164]	To compare "restoration" in natural and urban field settings.	RCT	A group of normotensive students mean age 20.8 years (SD 3.7), 50% female and 97% non-smokers. (n = 112)	Systolic and diastolic blood pressure, emotional states	Primary measurement, Zuckerman's Inventory of Personal Reactions (ZIPERS)	Green vs urban environment	Participants randomly assigned to study arm	Systolic blood pressure ↘ Diastolic blood pressure ↓
Hoehner 2013, USA [165]	To examine the associations of built environment features around the home and workplace with cardiorespiratory fitness (CRF) based on a treadmill test and BMI.	Cross-sectional study	The Cooper Centre Longitudinal Study. 70.9% male. (n = 8,857)	Cardiorespiratory fitness	Primary measurement	Neighbourhood greenspace in buffers surrounding residential address. Dataset unspecified.	Adjusted for age, sex, education, race, marital status, presence of children in the home, cigarette smoking, BMI, and all other built environment variables for the respective location of interest as well as weekly MET-minutes of physical activity	Cardiorespiratory fitness ↗
Hu 2008, USA [166]	To examine if there is association of stroke with air pollution, income and greenness in northwest Florida	Ecological geographical study	Stroke death count data at the census tract level was obtained (n = not specified)	Stroke mortality rates	State mortality records (Florida CHARTS)	Self-reported frequency of visits to greenspace, residential neighbourhood and work buffer; Landsat 7 Enhanced Thematic Mapper Plus (ETM+)	Calculated standardized mortality rates	Stroke mortality ↓ 95% Credible set (-0.289, -0.031)
Hystad 2014, USA [49]	To investigate associations between residential greenness and birth outcomes and	Cohort study	All births between 1999-2002 in the metropolitan	Birth weight, preterm deliveries, gestational age	National birth registry	Residential surrounding greenness; Normalised Difference	Analyses adjusted for month and year of birth, infant sex, first nations status, parity, maternal age,	Birth weight ↑ An interquartile increase in greenness (0.1 in residential NDVI)

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	evaluate the influence of spatially correlated built environment factors on these associations		area of Vancouver (n = 64,705)			Vegetation Index (NDVI)	maternal smoking during pregnancy as well as maternal education and income quintiles	associated with higher term birth weight: 20.6g (95% CI 16.5, 24.7) Small for gestational age ↓OR 0.97 (0.94, 1.00) Very preterm birth ↓ OR 0.91 (0.77, 1.07) Moderately preterm birth ↓ OR 0.95 90.91, 0.99)
James 2016, USA [114]	To examine the prospective association between residential greenness and mortality	Cohort study	U.S.-based Nurses Health Study (NHS), female registered nurses from 11 states in 1976 (n = 121,701)	Mortality rate and cause-specific mortality	National Death Index	Residential surrounding greenness; Normalised Difference Vegetation Index (NDVI)	Examined the following covariated as potential confounders, effect modifiers or mediators: fixed ethnicity/race, smoking status, fixed individual-level SES, area-level SES, weight status, region, urbanicity, whether a participant had changed addresses during follow-up, physical activity, air pollution, social engagement and mental health	Mortality ↓ Highest greenness quintile (Q5) in 250m buffer: HR 0.88 (95% CI 0.82, 0.94) Cancer ↓ Q5 HR 0.87 (95% CI 0.78, 0.97) Respiratory ↓ Q5 HR 0.66 (95% CI 0.52, 0.84) Stroke ↓ Q2 HR 0.76 (0.59, 0.97)

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Jia 2016, China [119]	To determine the health benefits of forest bathing trips on elderly patiends with chronic obstructive pulmonary disease (COPD)	RCT	COPD patients from Hangzhou (n = 20)	Flow cytometry, ELISA and profile of mood states (POMS)	Primary measurement	Forest vs city settings	Not specified	Perforin ↓ Granzyme B expression ↓ Pro-inflammatory cytokines ↓ Stress hormones ↓
Jonker 2014, The Netherlands [167]	To investigate the impact of three different measures of urban green on small-area life expectancy (LE) and healthy life expectancy (HLE) in The Netherlands	Cohort study	Standard 5 year abridged table data for the estimation of male and female LE and HLE for neighbourhoods in all 22 metropolitan agglomerations in neighbourhoods in The Netherlands in the 2006-2009 period were obtained (n = minimum required population size of 1,750 person years, exact population not specified)	Small-area life expectancy (LE) and healthy life-expectancy (HLE)	Life and healthy life expectancy estimates, Statistics Netherlands	% greenspace in neighbourhood; Dutch Land Use Database 2008 (BBG), average distance (km) to nearest public green; Statistics Netherlands, self-reported measure of greenspace quality; bespoke questionnaire	Standardized coefficients used	Life expectancy ↑ An increase in 1 SD in % urban greenspace is associated with a 0.1 year higher LE. An increase in 1 SD of quality of greenspace is associated with approximately 0.3-year higher LE and HLE. Average distance to public green is unrelated to population health

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Kabisch 2016, Germany [116]	To analyse the potential intra-urban relationships between childrens' health determinants, in particular deficits in viso-motoric development, and outcomes and natural areas in Berlin	Ecological study	Population of Berlin (n = 3,562,166)	Deficits in viso-motoric development in children	Berlin's Senate Department for Health and Social Issues	% natural area, per capita natural area, availability of natural area; Local land use data from Berlin's Senate Department of Urban Development and the Environment	Not specified	Low % natural areas ↑ deficits in viso-motoric development in children
Kardan 2015, Canada [168]	To examine the association between tree canopy density beside the streets and in other areas such as parks and domestic gardens with an individual's health. The health variables focused on are 1) overall health perception, 2) presence of cardio-metabolic conditions, 3) mental health problems	Cohort study	Subset of the Ontario Health Study. 59% female, mean age 43.8 years (range 18-99) (n = 31,109)	Self-reports of general health perception, cardio-metabolic conditions and mental illnesses	Ontario Health Study questionnaire	Toronto Street Tree General Data and GIS Forest and Land Cover	None specified	Self-reported health ↑ Cardiometabolic conditions ↓
Kihal-Talantikite 2013, France [169]	To investigate the relationship between green spaces and the spatial distribution of infant mortality taking account	Ecological study	Prevalence of infant death in the Lyon metropolitan area over the	Neonatal mortality	Equit'Area project municipality mortality records, National Institute for Statistics and Economic Studies	Spatial land cover datasets for Lyon Metropolitan area	Stage 1: Unadjusted Stage 2: Adjusted for greenness level or socioeconomic	Neonatal mortality ↓

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	neighbourhood deprivation levels		study period 2000-2009 (n = 1,340,155 population of Lyon metropolitan area)				neighbourhood (deprivation index) Stage 3: Adjusted for greenness level and deprivation index at the neighbourhood level including the interaction between the two variables	
Kim 2015, South Korea [117]	To assess the feasibility of forest therapy as an adjuvant to enhance natural cytotoxicity.	Feasibility study	Volunteer women aged 25-60 years with stage III breast cancer. All subjects exposed to daily forest therapy for 14 days. Mean age 56 years. (n = 11)	Natural killer cell population, perforin and granzyme B levels	Primary measurement	Forest	Matching of participants	Natural killer cell population ↑ MD 125.3 (95% CI 43.1, 207.4) Level of perforin ↗ MD 128.1 (-28.4, 284.5) Level of granzyme B ↗ MD 6.7 (-2.8, 16.3)
Kim 2016, South Korea [170]	To investigate the association between parks and green areas and hyperlipidaemia in adults	Cross-sectional study	Adults participating in the 2009 Korean Community Health Survey (KCHS) (n = 212,584)	Hyperlipidaemia	Bespoke questionnaire	Parks and green areas per capita in 2009 using data from the Korean Statistical Information Service	Models adjusted for age, sex, marital status, education, monthly income, jobs, smoking status, alcohol drinking, a history of diabetes mellitus, BMI, self-reporting stress and moderate physical activity	Hyperlipidaemia ↓ Lowest greenspace quartile - diagnosed hyperlipidaemia: OR 1.23 (95% CI 1.17, 1.29) Lowest greenspace quartile - treatment of hyperlipidaemia: OR 1.45 (95% CI 1.35, 1.56)

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Lachowycz 2014, England [171]	To examine the relationship between greenspace access, walking and mortality	Cross-sectional study	Individual level data sourced from the Active People Survey (APS). 60% female, mean age 55.0 years (n = 165,424)	Premature mortality from circulatory disease	Standardised mortality ratios	Access to greenspace; Generalized Land Use Data 2005 dataset (GLUD)	Model 1: Unadjusted Model 2: Adjusted for individual level covariates: age, gender, ethnicity, social class, car ownership, month of data collection Model 3: Further adjusted for MSOA-level environmental variables: index of multiple deprivation, urban-rural classification, population density	Cardiovascular mortality ↓ *Tests for mediation found no evidence to suggest that recreational walking explained the relationship greenspace and mortality*
Larson 2016, USA [172]	To evaluate the relationship between urban park quantity, quality and accessibility and aggregate self-reported wellbeing scores	Ecological study	2014 data from 44 U.S. cities (n = 44 cities ranging in size from New York, NY 8.175,136 to Wichita KS 382,373, exact population not specified)	Physical wellbeing	Gallup-Healthways Well-being Index (WBI)	Trust of Public Land's (TPL) Park Score Index	Controlled for a range of potential geographical and socioeconomic correlates	Physical wellbeing ↑ with park quantity ↗ with park quality and park accessibility
Laurent 2013, USA [173]	To study the relationship between greenspace exposure and 3 pregnancy outcomes; birth weight in term born infants, preterm	Cohort study	Neonatal records from 1997-2006 were extracted from a perinatal research database of four	Birth weight, preterm deliveries and preeclampsia	Hospital database	Residential surrounding greenness; Normalised Difference Vegetation Index (NDVI)	Models adjusted for maternal age, poverty, length of gestation, maternal race/ethnicity, insurance status, parity, infant's gender (birth weight analysis only),	Birth weight ↑ Increase in birth weight with a 1 IQR increase in greenspace in 50m buffer: 6.22g (95% CI 3.22, 9.22)

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	deliveries and preeclampsia		hospitals in California (n = 81,186)				pyelonephritis (preterm birth analysis only) and diabetes (preeclampsia and birth weight analyses only)	Preterm birth ↓OR 0.984 (95% CI 0.961, 1.007) Preeclampsia ↔
Lee 2011, Japan [174]	To provide scientific evidence supporting the efficacy of forest bathing as a natural therapy by investigating its physiological benefits using biological indicators in outdoor settings	RCT	Young male Japanese adults recruited from local universities. Mean age 21.2 years (n = 12)	Heart rate variability, LF/HF ratio in R-R interval variability (parasympathetic and sympathetic nervous system activity), cortisol levels, pulse rate, systolic blood pressure, diastolic blood pressure	Primary measurement Self-reported psychological measures	Forest	Matching of participants	Parasympathetic activity ↑ Sympathetic activity ↓ Heart rate↓ Salivary cortisol ↓
Lee 2014a, South Korea [175]	Investigating the health benefits of forest walking on cardiovascular reactivity	RCT	Young Japanese adult males. Mean age 21.2 years (n = 48)	Blood pressure, heart rate, heart rate variability	Primary measurement	Forest vs urban	Matching of participants	Parasympathetic activity ↑ Sympathetic activity ↓ Heart rate ↓
Lee 2014b, South Korea [176]	To investigate the acute effects of forest walking on arterial stiffness and pulmonary function in Korean elderly women	RCT	Recruited by advertisement at a senior welfare centre. Participants were all female. Average age of city walking group (n=19) 71.1 years, average age for	Blood pressure, arterial stiffness (CAV1), pulmonary function (FEV1, FEV)	Primary measurement	Forest/city walking intervention	Matching of participants	Blood pressure ↓ CAVI ↓ FEV1 ↑ FEV6 ↑

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			forest walking group (n=43) 70.2 years (n = 62)					
Li 2008a, Japan [177]	To investigate the effect of a forest bathing trip on human NK activity in female subjects	Interventi on study	Healthy nurses aged 25-43 years, selected with informed consent (n = 13)	Blood and urine sampled for: Nk activity, numbers of NK and T cells, granulysin, perforin, granzymes A/B-expressing lymphotcytes, estradiol and progesterone concentration in serum, Adrenaline and noradrenaline concentration in urine. Phytoncides were also measured in the forest	Primary measurement	Forest	Matching of participants	Natural killer cell population and activity ↑ Perforin ↑ Granulysin ↑ Granzymes A/B expressing lymphotcytes ↑

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Li 2008b, Japan [178]	To investigate the effect of forest bathing on NK activity compared with a trip to a city, and to measure how long the effect on NK activity lasts	Intervention study	Twelve healthy male subjects aged 35-56 years (n = 12)	Blood and urine sampled for: Natural killer cell (NK) activity, numbers of NK and T cells, granulysin, perforin, granzymes A/B-expressing lymphotcytes, adrenaline concentration in urine. Phytoncides were also measured in the forest	Primary measurement	Forest	Matching of participants	Natural killer cell population and activity ↑ Level of perforin ↑ Granulysin ↑ Granzymes A/B expressing lymphotcytes ↑ Adrenaline concentration in urine ↓
Li 2009, Japan [179]	To investigate the effects of a day trip to a forest park on human NK activity in forest parks	Intervention study	Healthy male subjects aged between 35-53 years (n = 12)	Blood and urine sampled for: Natural killer cell (Nk) activity, numbers of NK and T cells, granulysin, cortisol (blood), perforin, granzymes A/B-expressing lymphotcytes, adrenaline concentration in urine. Phytoncides were also measured in the forest	Primary measurement	Forest	Matching of participants	Natural killer cell activity ↑ CD16+ and CD56+ natural killer cell population ↑ Perforin ↑ Granulysin ↑ Granzyme A/B expressing NK cells ↑ Blood cortisol ↑ Urinary adrenaline ↑ CD4+ cells ↓

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Li 2011, Japan [180]	To investigate the effects of walking under forest environments on cardiovascular and metabolic parameters	Intervention study	Healthy male subjects, mean age 57.4 years (range 36-77 years) (n = 16)	Blood pressure, urinary noradrenaline, dopamine, serum adiponectin, dehydroepiandosterone sulfate (DHEA-S) levels, serum N-terminal pro B-type natriuretic peptide (NT-proBNP) and urinary dopamine	Primary measurement	Forest	Matching of participants	Serum adiponectin ↑ DHEA-S level ↑ Blood pressure ↓ Noradrenaline ↓ Dopamine NT-pro-BNP↓ Urinary dopamine ↓
Li 2016, Japan [181]	To investigate the effects of forest bathing on cardiovascular and metabolic parameters	Intervention study	Middle-aged male subjects with high-normal blood pressure or hypertension who were not taking antihypertensive drugs, 51.2 ±8.8 years (range 40-69 years) (n = 19)	Blood pressure, heart rate, blood analysis (serum triglycerides, total cholesterol, LDL, HDL, remnant-like particles, adiponectin, blood glucose, insulin level, DHEA-S, hs-CRP) urinary adrenaline, noradrenaline and dopamine, POMS score	Primary measurement	Forest vs urban environment	Matching of participants	Heart rate ↓ Urinary noradrenaline ↓ Adiponectin ↑ Blood pressure, urinary adrenaline, urinary dopamine, other metabolic parameters ↔
Lovasi 2008, USA [182]	To describe the direction and magnitude of any association between street trees and childhood asthma	Ecological cross-sectional study	Asthma prevalence for 4-5 year old children in 1999 and asthma hospitalisations among children <15 years in 1997 as	Asthma prevalence among children aged 4-5 years old and asthma hospitalisations among children	School asthma screening, hospitalisation for asthma	1995 New York street tree census	Models controlled for population density, demographic and socioeconomic characteristics (percent poverty, percent African American, and	Asthma prevalence ↓ A 1 SD (343 trees/km2) increase in street tree density associated with a 24% lower asthma prevalence: RR 0.74 (95% CI 0.62, 0.87) Asthma hospitalisation ↘

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			assessed by NYC Dept of Health (n = not specified)	less than 15 years old			percent Latino), and proximity to pollution sources	
Lovasi 2013, USA 183	To investigate the association of tree canopy cover with subsequent development of childhood asthma, wheeze, rhinitis, and allergic sensitization	Cohort study	The CCCEH birth cohort in NYC. Pregnant women recruited through prenatal clinics. Dominican or African-American children born in 1998-2006 and living in economically disadvantaged areas of NYC (n = 549)	Childhood asthma, wheeze, rhinitis, and allegic sensitisation	Brief Respiratory Questionnaire (BRQ), International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire	2010 New York Tree Canopy Data (Mac Faden et al. 2012); surrounding prenatal address	Covariates included sex, age at time of outcome measurement, ethnicity, maternal asthma, previous birth, other previous pregnancy, Medicaid enrolment, tobacco smoke in the home, active maternal smoking, and the following characteristics of 0.25km buffers: population density, percent poverty, percent park land, and estimated traffic volume	Asthma ↑ Significant positive association of tree canopy coverage with diagnosed asthma at 7 years of age consistent with a 17% increase in the prevalence of asthma with each SD increase in tree canopy coverage. RR: 1.17 (95%CI 1.02, 1.33) Allergic sensitisation ↑ IgE antibody response to the tree pollen mix ↑ RR 1.43 (95% CI 1.19, 1.72) IgE antibody response to any of the 9 allergens ↑ RR 1.20 (95% CI 1.05, 1.37)
Maas 2006, The Netherlands 184	To investigate the strength of the relationship between the amount of green space in people's living environment and their perceived general health	Cross-sectional study	Representative of the Dutch population in terms of age, gender and health insurance type (n = 250,782)	Perceived general health	The second Dutch national survey of general practice (DNSGP-2)	% neighbourhood greenspace; National Land Cover Database (LGN4)	Controlled for urbanity, sociodemographic and socioeconomic characteristics	Self-reported health ↑

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Maas 2008, The Netherlands [33]	To investigate whether physical activity mediates the relationship between neighbourhood greenspace and self-perceived health	Multilevel analysis, cross-sectional study	A subset of the second Dutch national survey of general practice (DNSGP-2). Representative of the Dutch population in terms of age, gender and health insurance type, 54.4% female (n = 4,899)	Perceived general health	The second Dutch national survey of general practice (DNSGP-2)	% neighbourhood greenspace; National Land Cover Database (LGN4)	Controlled for urbanity, sociodemographic and socioeconomic characteristics	Self-reported health ↑
Maas 2009a, The Netherlands [185]	To explore whether social contacts are an underlying mechanism behind the relationship between green space and health	Multi-level analysis, cross sectional study	The second Dutch national survey of general practice (DNSGP-2). Representative of the Dutch population in terms of age, gender and health insurance type, 54.9% female (n = 10,089)	Self-reported health indicators: perceived general health, number of health complaints, self-rated propensity to psychiatric morbidity	The second Dutch national survey of general practice (DNSGP-2)	% neighbourhood greenspace; National Land Cover Database (LGN4)	Controlled for age, gender, household size, level of education, income and urbanicity	Self-reported health ↑

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Maas 2009b, The Netherlands [186]	To investigate whether physician-assessed morbidity is also related to green space in people's living environment	Cross-sectional study	The second Dutch national survey of general practice (DNSGP-2). Representative of the Dutch population in terms of age, gender and health insurance type (n = 345,143)	Morbidity data on physical and mental health	National mortality records	% neighbourhood greenspace; National Land Cover Database (LGN4)	Controlled for urbanity, demographic and socioeconomic characteristics	Morbidity ↓ Annual prevalence rates of 24 disease clusters for people who have 10% more green space than average, for 1km radius: High BP ↓ OR 0.99 (95% CI 0.98, 1.00) Cardiac disease ↓ OR 0.98 (95% CI 0.97, 0.99) CHD ↓ OR 0.97 (95% CI 0.95, 0.99) p<0.01 Stroke, brain haemorrhage ↓ OR 0.98 (95% CI 0.95, 1.00) Neck and back complaints ↓ OR 0.98 (95% CI 0.97, 0.99) p<0.01 Severe back complaints ↓ OR 0.98 (95% CI 0.97, 0.99) p<0.01 Severe neck and shoulder complaints ↓ OR 0.98 (95% CI 0.97, 0.99) p<0.01 Severe elbow, wrist and hand complaints ↓ OR 0.97 (95% CI 0.96, 0.98) p<0.01 Upper respiratory tract infection ↓ OR 0.97 (95% CI 0.96, 0.98) p<0.01 Bronchitis/pneumonia ↓ OR 0.97 (95% CI 0.97, 1.00)

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								Asthma, COPD ↓ OR 0.97 (95% CI 0.96, 0.98) p<0.01 Migraine/severe headache ↓ OR 0.98 (95% CI 0.97, 0.99) p<0.01 Vertigo ↓ OR 0.97 (95% CI 0.95, 0.99) p<0.01 Severe intestinal complaints ↓ OR 0.98 (95% CI 0.96, 1.00) Infectious disease of the intestinal canal ↓ OR 0.97 (95% CI 0.95, 0.99) p<0.01 MUPS ↓ OR 0.97 (95% CI 0.96, 0.98) p<0.01 Chronic eczema ↓ OR 0.99 (95% CI 0.97, 1.00) Acute urinary tract infection ↓ OR 0.97 (95% CI 0.96, 0.98) p<0.01 Diabetes mellitus ↓ OR 0.98 (95% CI 0.97, 0.99) p<0.01

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Mao 2012a, China [187]	To provide scientific evidence supporting the efficacy of forest bathing as a natural therapy for human hypertension.	Intervention study	Hypertension patients, randomly divided into 2 groups of 12. (n = 24)	BP, cardiovascular disease-related pathological factors including endothelin-1, homocysteine, renin, angiotensin, angiotensin II, angiotensin II type 1 recentor, angiotensin II type 2 receptor, inflammatory cytokines interleukin-6 and TNF alpha. Mood states (POMS), airquality.	Primary measurement POMS, air quality	Forest	Randomisation	Blood pressure ↓ Bioindicators ↓
Mao 2012b, China [118]	To investigate the effects of short-term forest bathing on human health.	Intervention study	Twenty healthy male university students, randomly divided into 2 groups of 10. (n = 20)	BMI, SBP, DBP HR, IL-6, TNF-alpha, T-SOD, MDA, ET-1, Cortisol, testosterone, T-cell, B-cell, Thylymphocyte, tslymphocyte, NK cell, CD4/CD8, Platelet activation (CD42a, CD14)	Primary measurement	Forest	Randomisation	TNF-alpha ↓ IL6 ↓ C-reactive protein ↓ High-sensitivity C-reactive protein ↓ MDA ↓ ET-1 Serum cortisol ↓ Leukocytes ↑ T-, T-helper cells, NK lymphocytes, T suppressor cells, testosterone levels ↗

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Markevych 2014, Germany [50]	To assess whether surrounding residential greenness is associated with blood pressure in 10 year old German children	Cross-sectional analysis	Based on two birth cohorts, GINIplus and LISAplus, recruited healthy full term neonates (n = 2,078)	Blood pressure	Primary measurement	Residential surrounding greenness; Normalised Difference Vegetation Index (NDVI)	Models adjusted for study (GINIplus/LISAplus), sex, parental education, parental hypertension, child's age (years), season of blood pressure measurements, BMI of each child at at 10 years old	Blood pressure ↓
Markevych 2016, Germany [188]	To investigate the association between residential greenness and blood lipids in children	Longitudinal analysis	Based on two birth cohorts, GINIplus and LISAplus, recruited healthy full term neonates, 10 and 15 year follow ups (n = 1,552)	Blood lipids	Primary measurement	Residential surrounding greenness; Normalised Difference Vegetation Index (NDVI)	All models adjusted for exact age at time of blood lipid measurement, sex, study (GINIplus/LISAplus), study areaparental education, fasting status and BMI; models additionally adjusted for weekly physical activity, puberty category, and area-level SES	Blood lipids ↔
Matsunaga 2011, Japan [189]	To investigate the association between a hospital rooftop garden and physiological relaxation (HRV) on elderly people requiring care	Cross-sectional, within subject study	Elderly women requiring help walking, without dementia or pacemakers, mean age 81.7 years (n = 30)	Heart rate variability (HRV)	Primary measurement	Hospital garden	Matching of participants	Heart rate variability ↓

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McCracken 2016, UK [190]	To examine the health-related quality of life of children in relation to quality and use of greenspace	Cross-sectional study	Children at participating schools aged 8-11, mean age 9.7 ±9 years, 55.6% female (n = 276)	Health-related quality of life, self-reported	Kid-KINDL questionnaire	Residential greenspace: Central Scotland Green Network Use of urban greenspace: bespoke questionnaire	Additional demographic information collected included: page, gender, number of siblings, type of home, and presence of a garden	Health related quality of life ↑
Mitchell 2007, England [40]	To determine the association between the percentage of greenspace in an area and the standardised rate of self-reported "not good" health, and to explore whether this association holds for areas exhibiting different combinations of urbanity and income deprivation.	Cross-sectional, ecological study	Respondents to the 2001 census who were asked whether their health was "good", "fairly good" or "not good". (All residents in England as at the 2001 census, number not stated)	"Not good" health status	England 2001 census	Generalized Land Use Data 2005 dataset (GLUD)	Each model controlled for urban higher income, urban lower income, suburban higher income, suburban lower income, rural higher income and rural lower income (unless model was stratifying by characteristic)	Self-reported health ↗
Mitchell 2008, England [88]	To investigate whether the magnitude of income-related health inequality varies by exposure to green space	Cross-sectional, ecological study	Anonymised individual mortality records. Populations older than retirement age were excluded as inequalities in mortality tend to be at a maximum in the	All-cause mortality, cause specific mortality (circulatory disease, lung cancer, and intentional self-harm)	Individual-level mortality records	Generalized Land Use Data 2005 dataset (GLUD)	All models adjusted for age group, sex, deprivation in education, skills and training, deprivation in living environment, population density and urban or rural classification	All-cause mortality ↓ Incidence rate ratio for all-cause mortality for the most income deprived quartile compared with the least deprived was 1.93 (95% CI 1.86, 2.01) in the least green areas, whereas it was 1.43 (95% CI 1.34, 1.53) in the most green areas Cardiovascular mortality ↓

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			working age population (n = 40,813,236, with 366,348 deaths)					IRR 2.19 (95% CI 2.04, 2.34) least green IRR 1.54 (95% CI 1.38, 1.73) most green Intentional self harm ↔
Mitchell 2010, UK [191]	To investigate whether associations between greenspace exposure and health vary according to the origins of the green space indicator and, by proxy, the type of green spaces captured by the indicator	Ecological study	286 small areas in four British cities (York, Exeter, Edinburgh and Glasgow). Each "small area" was a Census Area Statistic (CAS) ward (n = 1,625,495)	Mortality and self-reported morbidity	Mortality records and census data	Coordination of information on the Environment (CORINE), British Ordnance Survey's master map (OSMM), Generalized Land Use Data 2005 dataset (GLUD)	All models controlled for age and sex of the exposed populations	Self-reported health ↑ Mortality ↓
Morita 2011, Japan [192]	To study the non-temporary effects of successive walks in forested areas (shinrin-yoku) on hypertension prevalence and blood pressure levels	Cohort study	Results from the baseline survey of the Japan Multi-Institutional Collaborative Cohort (J-MICC) study, mean age 52.1 years, 68% male (n = 4,666)	Blood pressure, hypertension	Primary measurement, bespoke questionnaire	Self-reported frequency of forest walking	Adjusted for age, BMI, smoking status, alcohol consumption and habitual exercise	Blood pressure ↔

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Nakau 2013, Japan [193]	To examine the effect of spiritual care of cancer patients by integrated medicine in a green environment	Pilot study – pre-post	Cancer patients, mean age 58.1 years, 18 females (mean age 56.6 years) and 4 males (mean age 65.3 years) with breast or lung cancer (n = 22)	QOL questionnaire, spirituality, fatigue (cancer fatigue scale), psychological state and Natural Killer (NK) cell activity	Primary measurement, bespoke questionnaire	Forest	Matching of participants	Natural killer cell activity ↑ Cancer-associated fatigue ↓ Self-reported health ↑
Ngom 2016, Canada [194]	To determine the role of proximity to specific types of greenspaces as well as their spatial location in the relationship with the most morbid cardiovascular diseases (CVD) and diabetes	Cross-sectional study	Sample of data from the Quebec Integrated Chronic Disease Surveillance System (QICDSS) (n = 3,920,000)	Diabetes, ischaemic heart disease, cerebrovascular diseases, heart failure	Quebec Integrated Chronic Disease Surveillance System (QICDSS)	Nearest distance to several types of greenspace and the presence of vegetation in open areas using CanMap	Controlled for several social and environmental factors	Cerebrovascular prevalence ↓ Highest distance to greenspace with sports facilities: PRR 1.11 (95% CI 1.01, 1.22) Diabetes ↓ Highest distance to greenspace with sports facilities: PRR 1.09 (95% CI 1.03, 1.13) Heart failure ↔ Ischaemic heart disease ↔
Ochiai 2015, Japan [108]	To assess the physiological and psychological effects of forest therapy on middle aged males with high-normal blood pressure.	Pre-post study	Japanese males (mean age 56 years, range 40-72 years) with high-normal blood pressure (n = 9)	Blood pressure, urinary adrenaline and serum cortisol (not salivary)	Primary measurement	Forest	Matching of participants	Blood pressure ↓ Urinary adrenaline ↓ Serum cortisol ↓

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Ohtsuka 1998, Japan [195]	To investigate the effect of shinrin-yoku on blood glucose in diabetic patients	Pre-post study	58 female and 29 male non-insulin dependent diabetic patients volunteered for the study, mean age 61 years (n = 87)	Blood glucose (non-fasting) and HbA1c	Primary measurement	Forest	Not specified	Non-fasting blood glucose ↔ HbA1c ↔
Padilla 2016, France [196]	To identify and describe how socioeconomic, health accessibility and exposure factors accumulate and interact in small areas in a French urban context, to assess environmental health inequalities related to infant and neonatal mortality	Ecological study	Population of Nice metropolitan area, France (n = approximately 537,769)	Infant and neonatal mortality rate	Death certificate records	Proportion of geographic area occupied by greenspaces, Coordination of Information on the Environment (CORINE)	Not specified	Infant and neonatal mortality ↔
Paquet 2014, Australia [197]	To investigate whether residential environment characteristics related to food, walkability and public open spaces were associated with incidence of four cardio-metabolic risk	Cohort study	North West Adelaide Health Study (NWAHS), a longitudinal biomedical cohort. 52.4% female, mean age 51.5 years (n = 3,145)	Pre-diabetes/diabetes, hypertension, dislipidaemia, abdominal obesity	Primary measurement	Road network distance to public open space (POS); defined by Normalised Difference Vegetation Index (NDVI)	Analyses accounted for spatial clustering, gender, age, household income, education, duration of follow up and area-level socio-economic deprivation	Diabetes ↔ Prediabetes ↔ Hypertension ↔ Dyslipidaemia ↔

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	factors in a biomedical cohort							
Park 2007, Japan [198]	To examine the physiological effects of shinrin yoku	RCT	Healthy male students, mean age 22.8 years (n = 12)	Salivary cortisol and cerebral activity, sensory evaluation	Primary measurement, bespoke self-reported sensory evaluation	Forest	Matching of participants	Cerebral activity ↓ Salivary cortisol ↓
Park 2009, Japan [199]	To examine the physiological effects of forest recreation on autonomic nervous activity.	RCT	Male university students, mean age 21.8 years. (n = 12)	BP, HR, HRV	Primary measurement	Forest	Matching of participants	Blood pressure ↓ Heart rate ↓ Heart rate variability ↓
Park 2010, Japan [112]	To review previous research on Shinrin yoku and present new results to clarify physiological effects.	Intervention study	12 healthy male university students in 24 areas between 2005-6, 280 students in total. Mean age 21.7 years. (n = 280)	Salivary cortisol, BP, HR, HRV	Primary measurement	Forest	Matching of participants	Blood pressure ↓ Heart rate ↓ Heart rate variability ↓ Salivary cortisol↓ Sympathetic nervous activity ↓ Parasympathetic nervous activity ↑
Pasanen 2014, Finland [24]	To investigate the relationship between perceived health and physical activity indoors, outdoors in built	Longitudinal survey	National survey data from Finland. 55.6% female, mean age 45.2 years	Perceived general health, emotional well-being and sleep quality	Bespoke questionnaire	Outdoor Recreation Demand Inventory (LVVI2), Finnish Forest Research Institute	Adjusted for covariates	Self-reported health ↑ Sleep quality ↗

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	environments and outdoors in nature		(range 15-74 years) (n = 2,070)					
Pereira 2012, Australia [37]	To investigate the effect of neighbourhood greenness in relation to coronary heart disease risk	Cross-sectional study	Residents of the Perth metropolitan area. 59% female (n = 11,404)	Coronary heart disease, stroke	Health and Wellbeing Survey, hospital records; Western Australian Department of Health	Residential surrounding greenness; Normalised Difference Vegetation Index (NDVI)	Adjusted for age, sex, possession of healthcare card, education, household income, non-gestational diabetes, BMI, hypertension, high cholesterol, daily fruit and vegetable intake, risky drinking behaviour, smoking and a proxy for air quality	Hospitalisation for heart disease or stroke ↓ OR 0.63 (95%CI 0.43, 0.92) among neighbourhoods with highly variable greenness (highest tertile) compared to those in predominantly green or predominantly non-green neighbourhoods
Picavet 2016, The Netherlands [200]	To explore the cross-sectional and longitudinal associations between greenspace and physical activity and several health indicators	Cross-sectional and longitudinal study	Doetinchem Cohort Study, adults aged 20-59 (n = 4,005)	Health-related quality of life, chronic diseases, blood pressure	Health-related quality of life measured by the RAND36 (similar to SF-36), chronic diseases self-reported	Percentage greenspace in the living environment and change in percentage green, National Land Cover Classification Database	All analyses adjusted for differences by age, sex and socioeconomic status	Systolic blood pressure ↓ 1km radius green 0.40 (95% CI 0.15, 0.66) Agricultural green 0.25 (95% CI 0.08, 0.43) Urban green -0.40 (95% CI -0.74, -0.06) Hypertension, diabetes, CVD, asthma complaints, COPD complaints ↔

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Piccolo 2015, USA [201]	To identify and estimate the contribution of specific aspects of neighbourhoods that may be associated with racial/ethnic disparities in T2DM	Cohort study	A community-based random-sample survey, the Boston Area Community Health (BACH) survey III, from 3 racial/ethnic groups (black, Hispanic, and white). Mean age 55.89 years, 55.43% female (n = 2,764)	Prevalent T2DM; fasting glucose <125mg/dL, HbA1c ≥ 6.5%, or self-report of a T2DM diagnosis	Primary measurement, Boston Area Community Health III Survey	Percentage recreational open space per census tract; Massachusetts Office of Geographic Information 2013	Adjusted for demographic and socioeconomic variables	Type II diabetes ↔
Pietila 2015, Finland [202]	To examine how the presence of and access to green spaces is related to the level of physical activity and self-rated health	Cross-sectional study	Finnish Outdoor Recreation Demand Inventory (LVVI) survey data. Age range 15-74, 55.4% female (n = 3,108)	Self-reported health	Bespoke questionnaire	Self-reported quality and availability of greenspace; Finnish National Outdoor Recreation Demand Inventory (LVVI)	Adjusted for age, gender, education and experience of an exceptional or difficult situation in life prior to the survey	Self-reported health ↔
Putrik 2015, The Netherlands [203]	To explore associations between certain features of neighbourhood environment and self-rated health and depressive symptoms in Maastrict	Cross-sectional study	Survey data. Mean age 55 years, 52% female (n = 9,879)	Self-rated health and presence of depressive symptoms	Bespoke survey	Neighbourhood environment characteristics; bespoke survey	Models adjusted for individual age, gender, education and income group	Self-reported health ↗

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Qin 2013, China [204]	To investigate the influence of urban greenspaces on physiological status	Cross-sectional observational study	Visitors to the Shanghai Botanical Garden (n = 64)	Heart rate variability; electroencephalogram (EEG), electrocardiogram (ECG)	Primary measurement of park visitors	Shanghai botanical gardens	None specified	Heart rate variability ↓
Reklaitiene 2014, Lithuania [205]	To assess the relationship between greenspace proximity, use of green space and depressive symptoms and perceived general health amongst a random sample	Cross-sectional study	Population-based sample in Kaunas, Lithuania. Age range 45-72, 54.7% female (n = 6,944)	Health behaviours, depressive symptoms and poor and very poor perceived general health	Bespoke questionnaire, depressive systems assessed using CES-D10 scale	Distance to city park and park use; unspecified dataset	Analyses adjusted for age, marital status, education, smoking, use of alcohol and BMI	Self-reported health ↑ *Women only, non-significant for men*
Requia 2016, Brazil [206]	To quantify the distance-decay cardiorespiratory diseases risk related to 28 neighbourhood aspects in the Federal District, Brazil	Cross-sectional study	Hospital admissions for cardiorespiratory disease in Brazil (n = not specified)	Cardiorespiratory diseases risk	Brazilian National Health Database	Natural environment land use, Sedhab (2012) database	Not specified	Cardiorespiratory diseases risk ↓ 1km^2 increase in green areas intra urban was associated with reduced risk of hospital admission
Richardson 2010a, New Zealand [207]	To investigate whether there is a socioeconomic gradient in green space exposure and whether green space exposure is associated with cause-specific	Ecological study	Anonymised individual-level mortality data for every registered death between 1996 and 2005 from the New Zealand Ministry of Health.	Risk of mortality from cardiovascular disease and from lung cancer	Individual-level mortality records, New Zealand Ministry of Health 2001	Census area unit greenspace coverage; Department of Conservation (DOC) Conservation Boundaries data set (2003), Land Information New Zealand's (LINZ) Core Records System	Controlled for census level data on income, employment, communication, support, transport, qualifications, living space, home ownership, smoking, air pollution, and	Cardiovascular mortality and respiratory mortality ↗

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	mortality (CVD and lung cancer)		Limited to adults under 65 (n = 1,546,405)			(2004), Ministry for the Environment Land Cover Database 2 (LCDB2 2001)	population density as a measure of urbanity	
Richardson 2010b, UK [208]	To examine the relationship between urban greenspace and health and to investigate gender differences in this relationship	Ecological cross-sectional study	Individual-level mortality records were obtained and matched to CAS wards with an estimate of green space coverage (n = 28,600,000)	Cardiovascular disease mortality, respiratory disease mortality, self-reported limiting long-term illness	Individual-level mortality records, Office of National Statistics (England and Wales), General Register Office for Scotland, Northern Ireland Statistics and Research Agency (NISRA)	Generalised Land Use Database (GLUD) and Coordination of Information on the Environment (CORINE)	All models adjusted for age-group, income deprivation quartile, air pollution and country	Cardiovascular mortality ↓ *men only* IRR 0.95 (95% CI 0.91, 0.98) greenest wards Respiratory mortality ↓ *men only* IRR 0.89 (95% CI 0.83, 0.96) greenest wards
Richardson 2011, USA [35]	To investigate whether a relationship between green space coverage and selected mortality rates exists at the city level in the USA	Ecological cross-sectional study	Populations of the 49 largest US cities (n = 43,000,000)	City-level standardised rates of mortality from heart disease, diabetes, lung cancer, motor vehicle fatalities and all-causes	City-level standardised rates of mortality from various causes, 2004	City-level greenspace coverage; National Land Cover Database (NCD, 2001)	Adjusted for socioeconomic characteristics, household income, ethnicity, air pollution, percentage of households without a car and sprawl index	Mortality from cardiovascular disease ↘, diabetes↘, lung cancer↘, automobile accidents ↘ All-cause mortality ↑ highest greenness level Men 132.90 (95% CI 18.33, 247.46) Women 94.21 (95% CI 21.76, 166.66)
Richardson 2013, New Zealand [209]	To investigate whether urban greenspace is related to individual-level health outcomes, and if physical activity is a mediating factor	Cross-sectional study	Respondents to the New Zealand Health Survey 2006/7, 56.5% female (n = 8,157)	Cardiovascular disease, poor general health, poor mental health, overweight status	2006/7 New Zealand Health Survey (NZHS)	Neighbourhood level greenspace availability; Department of Conservation's Conservation Area Boundaries (2003), Land Information New Zealand's Core	Adjusted for individual level covariates including sex, age group, smoking behaviour, and an index of individual socioeconomic deprivation	Cardiovascular disease risk ↘ Self-reported health ↘

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						Record System (2004) and the Ministry for Environment's Land Cover Database (2001)		
Roe 2013, UK [210]	To investigate the relationship between greenspace and stress (perceived stress and salivary cortisol) in deprived urban communities	Cross-sectional study	Men and women aged 33-55 years of age from socio-economically deprived areas of Dundee. Mean age 44.75 years, 50% male (n = 106)	Salivary cortisol levels and perceived stress	Primary measurement, perceived stress scale (PSS) psychological stress measures	Percentage neighbourhood greenspace; Census Area Statistics Ward (CAS), Centre for Research on Environment Society and Health (CRESH)	Adjusted for access to a garden	Salivary cortisol ↓*women only*
Roe 2016, UK [122]	To explore the relationship between general health and a range of individual, social and physical environmental predictors in deprived neighbourhoods	Multi-case study	Participants from 6 ethnic groups in 6 case-study locations (London: Hackney and Islington, West Midlands: Coventry and Wolverhampton, and Greater Manchester: Rochdale and Oldham) (n = 523)	Self-reported general health	Ethnic Focus survey	Perceptions of local greenspace and self-reported use of local greenspace	Not specified	Self-reported general health ↑ *for poorest health group only*

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Ruokolainen 2015, Estonia and Finland [211]	To test the diversity hypothesis by analysing the relationship between land use around the home and atopic sensitisation in children	Cohort study	Four cohorts of children and adolescents 0.5-20 years (n = 1,044)	Serum IgE specific to inhallant allergens, proteobacteria on the skin of healthy individuals. Prevalence of atopic sensitisation in children and adolescents aged 0.5-20 years	Primary measurement, DIABIMMUNE, LUKAS, KARA datasets	Percentage neighbourhood greenspace; Coordination of Information on the Environment (CORINE)	Adjusted for potential confounding factors	Atopic sensitisation ↓ *children*
Sbihi 2015, Canada [48]	To investigate the effect of early-life exposure to surrounding residential greenness on asthma incidence	Cohort study	All 1999-2002 single births in the metropolitan area of Vancouver, British Columbia (n = <65,000 children)	Asthma diagnosis	Physician billing and hospital discharge records	Residential surrounding greenness; Normalised Difference Vegetation Index (NDVI)	Sex and age matched to 5 randomly chosen controls; models adjusted for covariates including month/year of birth, sex, first nation status, as well as maternal parity, age, smoking during pregnancy and initiation of breastfeeding and assigned socioeconomic indicators	Asthma ↓
Skarkova 2015, Czech Republic [212]	To assess the impact of the environment on asthma prevalence	Cross-sectional study	Representative sample of children aged 5, 9, 13 and 17 from the Czech Republic	Asthma prevalence	National Institute of Public Health (NIPH) questionnaire survey	Land cover data; Fundamental Base of Geographic Data (ZABAGED) administered by the Czech Office for	Adjusted regression coefficients calculated	Asthma prevalence: ↓ with presence of natural forests ↑ with agricultural land use

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			(n = 13,456)			Surveying, Mapping and Cadastre		
Song 2013, Japan [213]	To investigate the physiological and psychological effects of walking in urban parks in winter on young males	Controlled trial	Japanese male university students, mean age 22.5 years (n = 13)	Heart rate, Heart rate variability (HRV), mood states	Primary measurement, Profile of Mood State (POMS) questionnaire, State-Trait Anxiety Inventory (STAI)	Walking intervention; urban park/city area	Matching of participants	Heart rate ↓ Heart rate variability ↓
Song 2015a, Japan [214]	To investigate the effect of forest walking on autonomic nervous system activity in middle aged hypertensive individuals	Intervention study	Japanese men, mean age 58.0 years (n = 20)	Heart rate, Heart rate variability (HRV), relaxation questionnaire	Primary measurement, Profile of Mood State (POMS) questionnaire, modified semantic differential method (SD)	Walking intervention; forest/urban setting	Matching of participants	Heart rate ↓ Heart rate variability ↓
Song 2015b, Japan [215]	To clarify the physiological and psychological effects of walking in urban green areas	Intervention study	Japanese males, mean age 22.3 ±1.2 years (n = 23)	Heart rate, heart rate variability, Profile of Mood States (POMS), State-Trait Anxiety Inventory	Primary measurement, POMS questionnaire, State-Trait Anxiety Inventory	Urban park vs city area	Matching of participants	Heart rate ↓ Sympathetic nervous activity ↓ Parasympathetic nervous activity ↑
Stigsdotter 2010, Denmark [216]	To investigate the associations between greenspace and health, health-related quality of life and stress	Cross-sectional study	2005 Danish Health Interview Survey, age range 16-64 years (n = 21,832)	Health-related quality of life and stress	Danish Institute of Public Health 2005 health interview survey, Short form health survey (SF-36)	Self-reported proximity to a greenspace; Danish Institute of Public Health 2005 health interview survey	Analyses adjusted for gender, age, cohabitation status, combined school and vocational education, accommodation type, size of	Self-reported health ↑ >1km from a greenspace/natural area OR 1.42 (95% CI 1.17, 1.73)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
							municipality and ethnic background	
Sugaya 2011, Japan [217]	To compare oxidative damage levels after urban walking and forest walking	Intervention study	Female patients with rheumatoid arthritis aged 48-62 years old (n = 12)	serum hydroperoxide, MMP-3, uringary 8-OHdG, and salivary IgA	Primary measurement	Forest vs urban environment	Matching of participants	Urine 8-0 HdG levels, MMP-3, salivary IgA ↑ Serum hydroperoxide ↓
Sugiyama 2008, Australia [218]	To examine associations of perceived neighbourhood greenness with perceived physical and mental health, and to investigate whether walking and social factors account for these relationships	Cross-sectional study	Observational epidemiological study, 63% female, mean age 45 years (n = 1,895)	Physical and mental health scores	Short-form health survey (SF-12), physical component scores (PCS), mental component scores (MCS)	Perceived neighbourhood greenness; Neighbourhood Environment Walkability Scale	Model adjusted for age, education, work status, household income, marital status, and a further model also adjusted for walking for recreation, social coherence score and local social interaction	Self-reported health ↗
Sugiyama 2009, UK [219]	To examine what aspects of neighbourhood open space are associated with walking for recreation and for transport by older people	Cross-sectional study	60.8% female, mean age 75.0 years, 10% non-white (n = 284)	Self-reported quality of life (QOL) and "health status"	Behavioural Risk Factor Surveillance Scheme (BRFSS), Satisfaction With Life Scale (SWLS)	Bespoke scale measuring quality of neighbourhood open space (NOS)	All models adjusted for participants' age, functional capability and their level of educational attainment	Self-reported health ↗

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Sulander 2016, Finland [220]	To investigate the relationship between urban greenspace visits and mortality among adults	Cross-sectional study	939 women; mean age 82 years, 456 men; mean age 81 years (n = 1,395)	Mortality	National Population Information System survey	Frequency of visiting urban green areas, bespoke questionnaire	Model 1: Adjusted for sociodemographics and education Model 2: Adjusted for sociodemographics and self-reported diseases Model 3: Adjusted for sociodemographics, self-reported diseases and functional capacity	Mortality ↓ Visit a green area few times a year or less: HR 2.2 (95% CI 1.2, 4.1) *Model 3, but significant for all models*
Sung 2012, Japan [221]	To investigate the effects of forest therapy on blood pressure, salivary cortisol and quality of life in patients with hypertension	Controlled trial	Enrolled for the study after referral from local health centres (n = 56)	Blood pressure, salivary cortisol and quality of life	Primary measurement, bespoke questionnaire	Forest and control setting	Not specified	Quality of life ↑ Salivary cortisol ↓
Takano 2002, Japan [222]	To investigate the association between greenery filled public areas in close proximity to residences and the longevity of senior citizens in a densely populated, developed megacity	Cohort study	Representative sample of residents born in 1903, 1908, 1913 and 1918 (n = 3,144)	Longevity	Official 5 year survival rates	Self-reported neighbourhood greenspace and frequency of use; bespoke questionnaire	Controlled for age, sex, marital status and socioeconomic status	Longevity ↑ OR 1.13 (95% CI 1.03, 1.24)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Tamosiunas 2014, Lithuania [223]	To explore the associations of the distance and use of urban greenspaces with the prevalence of cardiovascular diseases and its risk factors. To evaluate the impact of accessibility and use of greenspaces on the incidence of CVD	Cohort study	Kaunas cohort study. Mean age 60.4 years, 57% female (n = 5,112)	Blood pressure, cognitive function, serum lipids, fasting glucose, self-reported health, symptoms of depression, coronary heart disease measured by a history of myocardial infarction or ischaemic changes in ECG. Angina, diabetes and stroke diagnosis recall	Primary measurement, 10-item Centre for Epidemiologic Studies Depression Scale (CES-D 10), medical records, bespoke questionnaire	Distance to nearest greenspace; unspecified special land cover dataset for Kaunas city	Adjusted for age	Total CVD ↓ *men only* 3rd tertile compares to 1st: HR 1.36 (95% CI 1.03, 1.80) Non-fatal CVD ↓ *women only* 2nd and 3rd tertile compared to 1st: HR 2.78 (95% CI 1.16, 6.70)
Toda 2013, Japan [224]	To investigate the effect of walking through woodland on salivary endocrinological stress makers, cortisol and chromogranin A	Pre post study	Healthy males, mean age 67.6 years (n = 20)	Salivary cortisol and chromogranin A, visual analogue scales of perceived stress	Primary measurement, self-reported stress visual analogue scale	Forest vs office	Matching of participants	Systolic blood pressure ↓ Salivary cortisol ↓ Heart rate ↑
Triguero-Mas 2015, Spain [225]	To investigate the association between natural outdoor environments (separately blue and green spaces) and health (general and mental) and its	Cross-sectional study	Catalonia Health Survey. 50.06% female, mean age 48 years (n = 8,793)	Self-perceived general health	Short form health survey (SF-36), General health questionnaire (GHQ-12), questions from ESCA questionnaire	Access to natural outdoor environments and surrounding greenness; Normalised Difference Vegetation Index (NDVI)	Adjusted for gender, age, education completed, birth place, type of health insurance, marital status and indicators of household and neighbourhood	Self-reported health ↑ Surrounding greenness within 300m, OR for less than good self-perceived general health: OR 0.90 (95% CI 0.83, 0.98)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	possible mediators and modifiers						socioeconomic status	
Tsunetsugu 2007, Japan [226]	To investigate the physiological effects of shinrin-yoku on blood pressure, pulse rate, HRV, salivary cortisol and immunoglobin A	RCT	Male university students, mean age 22 years (range 21-23) (n = 12)	Blood pressure, heart rate, heart rate variability (LF&HF), salivary cortisol and mental health	Primary measurement, bespoke 13-point scale	Forest vs city	Matching of participants	Blood pressure ↓ Heart rate ↓ Heart rate variability ↓ Salivary cortisol ↓
Tsunetsugu 2013, Japan [227]	To investigate the physiological and psychological effects of viewing urban forest landscapes on 48 young male urban residents	Controlled trial	12 university students who participated in each of the four experimental areas. Mean age 21.1 years (n = 12)	Blood pressure, heart rate, heart rate variability	Primary measurement	Forest vs urban site	Matching of participants	Diastolic blood pressure ↓ Heart rate ↓ Heart rate variability ↓
Tyrvainen 2014, Finland [57]	To investigate the psychological and physiological effects of short-term visits to urban nature environments	RCT	Healthy non-smoking adults, mean age 47.64 years (range 30-61 years), 87.17% female (n = 77)	Salivary cortisol concentration as well as psychological symptoms	Primary measurement, Focus of Attention Scale (TFOAS), Restoration Outcome Scale (ROS), Perceived Restorativeness Scale (PRS), Positive and Negative Affect Scale (PANAS), Creativity Scale, Subjective Vitality Scale	Forest vs urban park vs city centre	Matching of participants	Salivary cortisol ↔

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Ulmer 2016, USA [228]	To enhance the understanding of the health-promoting potential of trees in an urbanised region of the US	Cross-sectional study	California Health Interview Survey (CHIS); 58% female, mean age 46 years (n = 7,910)	Diabetes, blood pressure, asthma, general health status	California Health Interview Survey (CHIS)	LiDAR tree canopy cover data	All demographic, socio-economic and built environment variables were included in every model as covariates, and all models included adjustment for the DAC-provided raked sample weights	Poor general health ↓ OR 0.871 (0.799, 0.949) Blood pressure, asthma, diabetes ↘

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Ulrich 1984, USA [111]	To investigate the influence of a hospital window view on patients' emotional state and recovery	Retrospective cohort study	Cholecystectomy patients assigned to rooms on the second and third floors of a hospital between 1972 and 1981, during months when the trees had foliage. Age range 20-69. 65% female (n = 46)	Number of days hospitalisation, number and strength of analgesics each day, number and strength of doses for anxiety, including tranquilisers and barbiturates, each day, minor complications such as persistent headache and nausea requiring medication-symptoms which are considered to result frequently from conversion reactions, and all nurses' notes relating to a patients condition or course of recovery	Hospital records on stay duration and medication type/frequency, nurses' notes	View from hospital window	Participants matched for age, sex, smoking status, obesity, history of hospitalisation, year of surgery and floor level	Post-operative recovery time ↓
van Dillen 2012, The Netherlands [229]	To investigate the link between the objectively assessed quantity and quality of (1) green areas and (2) streetscape greenery on the one hand and three self-reported health	Cross-sectional study	Questionnaires sent to a random sample of 100 households in each neighbourhood, non-western ethnic minorities heavily under-represented	Health questionnaire: general health, acute health complaints, general mental health status	Bespoke questionnaire	Objectively measured quantity of green area; Pikora et al and Hillsdon et al tools	Adjusted for gender, age, education level and income	Self-reported health ↑

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	indicators on the other		(n = 1,641)					
Van Herzele 2012, Belgium [230]	To investigate the relationship between local greenness and health and wellbeing of inhabitants by looking at possible mediators :PA, stress, ability to concentrate, social cohesion and neighbourhood satisfaction	Cross-sectional study	Two neighbourhoods, Dierentuin (More green, n=97, 53.6% female, mean age 43.2 years) and Sint-Jacobs (Less green, n=93, 54.8% female, mean age 43.6 years) (n = 190)	Self-reported general health, bodily functioning and general wellbeing	Bespoke questionnaire	Van Herzele and Wiedemann green space monitoring tool	Adjusted for gender, age, education, income, smoking, alcohol consumption and having a pessimistic personality	Self-reported health ↗
Villeneuve 2012, Canada [231]	To investigate the relationship between urban greenspace and mortality in Ontario, Canada	Cohort study	Randomly selected from 10 urban areas in Ontario, >35 years, 50.8% male (n = 574,840)	Canadian mortality database	Canadian mortality database, 2001 Canadian Community Health Survey	% neighbourhood greenspace; Normalised Difference Vegetation Index (NDVI)	Adjusted for smoking, physical activity and BMI category	Non-accidental mortality ↓ A 1IQR increase in greenspace in a 500m buffer associated with reduced non-accidental mortality: RR 0.95 (95% CI 0.94, 0.96) Respiratory disease mortality ↓ RR 0.91 (95% CI 0.89, 0.93)
Vogt 2015, Germany [232]	To examine the associations between proximity to two features of the residential environment and	Cross-sectional study	KORA (Cooperative Health Research in the Region of Augsburg)-Age study	Health-related quality of life	KORA-Age study survey	Distance to public green space, Augsburg city records	Model 2 controlled for age, sex and per capita income	Health-related quality of life ↔

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	three aspects of health aging		participants aged 65 or over (n = 1,711)				Model 3 also controlled for regional deprivation	
Wang 2016, China [233]	To examine the impact of both indoor and outdoor spatial factors on lung cancer	Hospital-based case-control study	62% female (n = 472)	Lung cancer morbidity	Bespoke questionnaire	Distance to parks, internal greenspace, dataset not specified	Participants matched for age and gender Adjusted for other demographic and lifestyle factors	Lung cancer morbidity ↓ with internal greenspace ↑ with distance to parks
Ward 2016, New Zealand [234]	To investigate the relationship between children's time spent in greenspace with various physiological and psychological variables	Cross-sectional study	59% female, mean age 12.66 years (n = 108)	Cognitive development: visual memory, verbal memory, processing speed, psychomotor speed, reaction time, cognitive flexibility and executive function	Computerised neurocognitive testing conducted using CNS Vital Signs	Locational data from GPS, greenspace exposure calculated using Personal Activity Location Measurement System (PALMS)	All models included sex, age and school as covariates	Cognitive development ↔
Ward Thompson 2012, Scotland [235]	To investigate the relationship between greenspace in urban deprived areas and stress (salivary cortisol and self-report) and general wellbeing	Exploratory study	People not-in-work were recruited through community centres and training opportunity centres in Dundee. Mean age 43.4 years (age range 33-57 years), 52% female	Salivary cortisol, self-reported measures of stress and well-being	Primary measurement	Percentage neighbourhood greenspace in Census Area Statistics Ward; data from Centre for Research on Environment Society and Health (CRESH)	Not specified	Salivary cortisol ↓

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
			(n = 25)					
Ward Thompson 2016, Scotland [236]	To investigate the nature of access to greenspace necessary before any health benefit is found	Cross-sectional survey	54.7% female, mean age 44 ±17.1 years (n = 406)	General health	Bespoke single-item assessment	Self-reported access to greenspace and objective measure using Ordnance Survey MasterMap	Not specified	General health ↑
Weimann 2015, Sweden [237]	To investigate the effects of changing exposure to neighbourhood greenness on general and mental health	Longitudinal survey	Prognostic group for good general health at baseline: 48% male. Age range 18-80 (n = 8,891)	Self-reported general health	Bespoke questionnaire	Perceived neighbourhood greenness, public health survey	Adjusted for covariates associated with general or mental health	Self-reported health ↑ Evidence of beneficial effect of increased greenness indicated among subjects with lowest prognostic of good general health: OR 1.24 (95% CI 1.01, 1.52)
Weltin 2012, USA [238]	To investigate whether a community garden could provide improved diabetes control	A mixed-convergent parallel designed intervention study	Members of a Midwest community of immigrants from the Marshall Islands. Mean age 51 years (range 33-81 years), 52.9% male (n = 17)	HgA1c levels	Primary measurement	Community garden	Matching of participants	HbA1c ↓
Wheeler 2012, UK [239]	To investigate whether rates of good health improve with proximity to the	Cross-sectional ecological study	2001 census data for England (n = 48,200,000)	Self-reported "good" health	2001 census data for England	% land area classified as greenspace in Lower-layer Super Output Areas (LSOA),	Not specified	Self-reported health ↑ Quintile 3: Rural: 0.31 (95% CI 0.04, 0.57)

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
	coast and percentage green space					Generalised Land Use Database		Quintile 4: Urban: 0.23 (95% CI 0.13, 0.33) Town/fringe: 0.49 (95% CI 0.19, 0.79) Quintile 5: Rural 0.36 (95% CI 0.26, 0.47) Town/fringe: 0.69 (95% CI 0.39, 0.99) Rural: 0.59 (95% CI 0.30, 0.88)
Wheeler 2015, UK [110]	To investigate the relationship between different types and qualities of natural environments on health and well-being	Ecological study	2011 UK census data (n = 63,260,000)	Age/sex standardised prevalence of both good and bad health	2011 census data for Great Britain	Greenspace per Lower-layer Super Output Areas (LSOA) for England and Wales, and Data Zones (DZs) for Scotland; UK Land Cover Map 2007	Regression analyses adjusted for income, education and employment scores and models also adjusted for urban/rural classification	Self-reported health ↑ Significant positive associations observed between good health prevalence and the density of several greenspace types: 'broadleaf woodland', 'arable and horticulture' and 'improved grassland' as well as 'saltwater' and 'coastal' after adjusting for confounders. Broadleaf woodland: 0.32 (95% CI 0.029, 0.035) Arable and horticulture: 0.004 (95% CI 0.002, 0.005) Improved grassland: 0.016 (95% CI 0.014, 0.018)
Wilker 2014, USA [240]	To investigate the association between greenspace and post-stroke mortality	Hospital-based cohort study	Patients ≥21 years admitted to Beth Israel Deaconess Medical Centre (BIDMC) between 1999-	History of acute ischaemic stroke	Hospital admission records; Beth Israel Deaconess Medical Centre (BIDMC)	Residential greenspace; Normalised Difference Vegetation Index (NDVI)	Model 1: adjusted for age, sex Model 2: adjusted for age, sex, race. Hispanic, smoking status, history of	Mortality after ischaemic stroke ↓ Quartile 3: HR 0.79 (95% CI 0.65, 0.96)

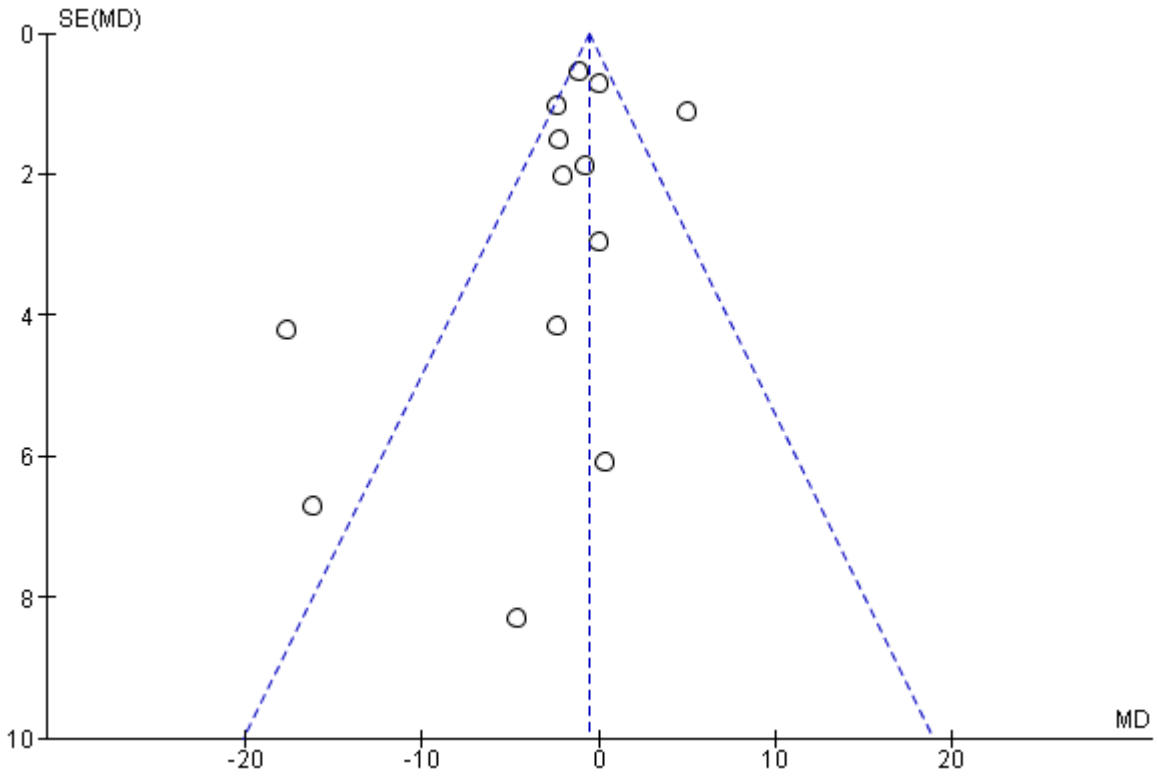
Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
			2008 with acute ischaemic stroke. Mean age and gender by GS quartile: Q1: 73 years, 46% male; Q2: 75 years, 41% male; Q3: 76 years, 47% male; Q4: 77 years, 46% male (n = 1,645)				coronary artery disease, history of stroke, atrial fibrillation, heart failure, diabetes, dyslipidaemia, hypertension, education and household income Model 3: adjusted for model 2 covariates and the log of distance to a road with >10,000 cars/day	Quartile 4: HR 0.80 (95% CI 0.65, 0.99) (fully adjusted models)
Wolfe 2014, The Netherlands [241]	To investigate changes in self-rated health of chronically ill people in relation to greenspace in their living environment at baseline	Prospective study	Health data from the national panel of people with chronic illness or disability (NPCD). ≥15 years and with a medically diagnosed somatic chronic disease on average 9.7 years prior to inclusion (n = 1,112)	Self-rated health	Bespoke questionnaire including 5-item General Health Perception Scale of the RAND-36	Perceived neighbourhood greenness and urbanity; National Land Cover Classification Database 2003/2004 and Statistics Netherlands 2004	Controlled for 'other correlates of health'	Self-reported health ↗

Lead author, year, location	Study aim	Study design	Participant characteristics (n)	Health outcomes measured	Health outcome assessment tool or dataset	Greenspace measurement dataset or study setting	Treatment for confounding	Arrows showing direction of association, 95% CI of significant results where stated
Wu 2015, England [242]	To investigate the impact of the community environment on cognition in later life	Cross-sectional study	The MRC Cognitive Function and Ageing Study (CFAS). 60.7% female, mean age 81.7 years (n = 2,424)	Cognitive impairment and dementia	Bespoke questionnaire including self-reported past medical history	Land use per Lower-layer Super Output Areas (LSOA); Generalised Land Use Dataset (GLUD) 2001	Adjusted for age, gender, education, social class and number of chronic illnesses with a further adjustment for area deprivation	Dementia ↑ Quartile 4 (Highest % natural environment) OR 2.23 (95% CI 1.17, 4.24) Cognitive impairment ↑ Quartile 4 OR (95% CI 1.00, 1.98)
Yamaguchi 2006, Japan [243]	To investigate the effects of exercise in forest and urban environments on sympathetic nervous activity of normal young adults	Intervention study	Healthy male university students, mean age 22.2 years (n = 15)	Salivary amylase activity, sympathetic nervous activity (heart rate variability)	Primary measurement	Forest vs urban environment	Matching of participants	Heart rate variability ↓
Young 2016, USA [244]	To determine the risk of gestational diabetes (GDM) and preeclampsia associated with various community response	Ecological study	Los Angeles and Orange Counties birth records (n = 6,567,580 women, 362,525 pregnancies)	Gestational diabetes and preeclampsia	California Birth Certificate database	Ratio and km of park area in each zipcode; land use data from Southern California Association of Government	Adjusted model accounted for maternal age, prepregnancy BMI, race, ethnicity and median household income	Gestational diabetes and preeclampsia ↔

Table 8. Search strategy terms for electronic databases

Health outcome search terms	disease* OR lower respiratory infection* OR upper respiratory infection* OR otitis media OR food-borne trematodiases OR maternal complication* OR pregnancy complica* OR hypertensive disorder* of pregnan* OR obstructed labour OR abortion OR maternal problem* OR birth complication* OR neonatal encephalopathy OR birth asphyxia OR birth trauma OR birth sepsis OR disorder* of the newborn baby OR neonatal disorder* OR hepatitis OR cancer* OR melanoma OR non-Hodgkin lymphoma OR leuk*mia OR neoplasm* OR cardiomyopathy OR myocarditis OR atrial fibrillation OR atrial flutter* OR aortic aneurysm OR endocarditis OR COPD OR pneumoconiosis OR asthma OR pulmonary sarcoidosis OR cirrhosis OR peptic ulcer* OR gastritis OR duodenitis OR appendicitis OR paralytic ileus OR intestinal obstruction* OR hernia* OR vascular disorder* OR pancreatitis OR Alzheimer's OR dementia OR Parkinson's OR epilepsy OR multiple sclerosis OR migraine* OR tension?type headache* OR neurological disorder* OR schizophrenia OR development disorders* OR behavioural disorder* OR intellectual disability* OR behavioural disorder* OR diabet* OR glomerulonephritis OR urinary OR infertility OR h*moglobinopath* OR haemolytic an*mia* OR endocrine disorder* OR blood disorder* OR immune disorder* OR rheumatoid arthritis OR osteoarthritis OR low* back pain OR neck pain OR gout OR musculoskeletal disorder* OR congenital anomal* OR neural tube defect* OR congenital heart OR oral disorder* OR sudden infant death OR road injury OR transport injury OR drowning OR poisoning* OR exposure to mechanical forces OR adverse effect* of medical treatment OR animal contact OR unintentional injur* OR Self?harm OR interpersonal violence OR health outcome* OR health stat* OR mortalit* OR morbidit* OR chronic disease* OR life expectanc* OR work* stress OR work related stress OR hypertension OR stroke* OR disability?adjusted life year* OR quality?adjusted life year* OR daly* OR qaly* OR industrial *cident* OR industrial injur* OR birth weight OR physiological effects OR motor development OR heart rate variability OR blood pressure OR physical function OR cognitive function OR thyroid OR nutritional deficiency OR metabolic disorder OR inflammat* OR degenerative disease OR ischaemic heart disease OR pulmonary disease OR digestive system disorder OR bone density OR blood glucose OR HbA1c OR red blood cell count OR white blood cell count OR serum enzyme level OR serum antibody level OR plasma protein level OR hormone level OR autoimmune
Greenspace terms	Green space OR greenspace* OR greenness OR greenery OR wilderness OR wild land OR natural land OR municipal land OR community land OR public land OR open land OR wild space OR municipal space OR natural space OR open space OR municipal park OR botanic park OR park access OR urban park OR city park OR park availability OR public garden OR natural (within 3 words of) neighbourhood OR natural (within 3 words of) facilities OR vegetation (within 3 words of) natural OR belt (within 3 words of) green OR trial (within 3 words of) recreation OR wild area OR trail (within 3 words of) green OR trail (within 3 words of) cycl* OR trail (within 3 words of) walk OR recreation destination OR recreation opportunities OR physical activity destination OR physical activity resource OR natural area* OR green area* OR walkability* OR built environment OR urban design OR physical activity amenities OR recreation resource OR woodland OR cycle path OR shinrin-yoku OR forest bathing

Figure 6. Example funnel plot: systolic blood pressure



Supplementary results from meta-analysis

Figure 7. Systolic blood pressure

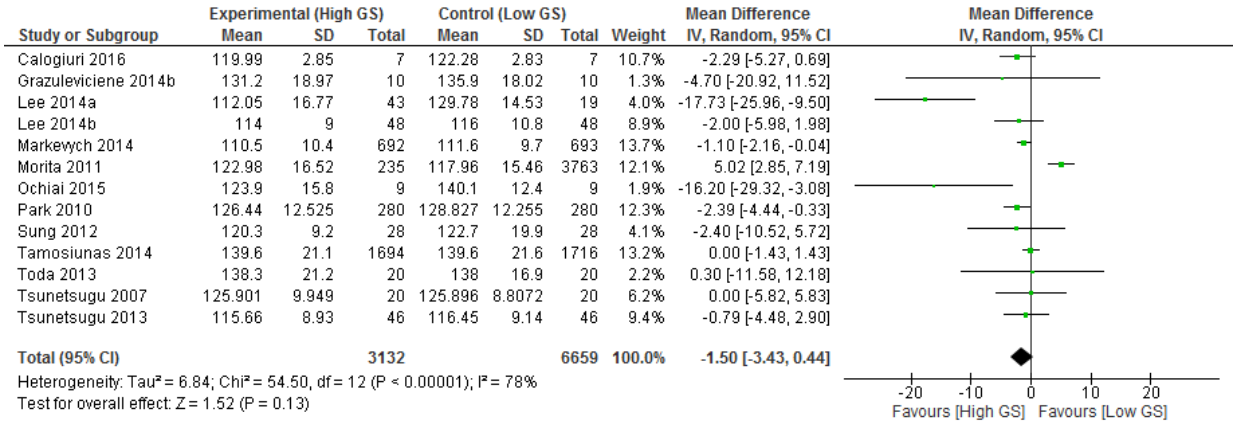


Figure 8. Diastolic blood pressure

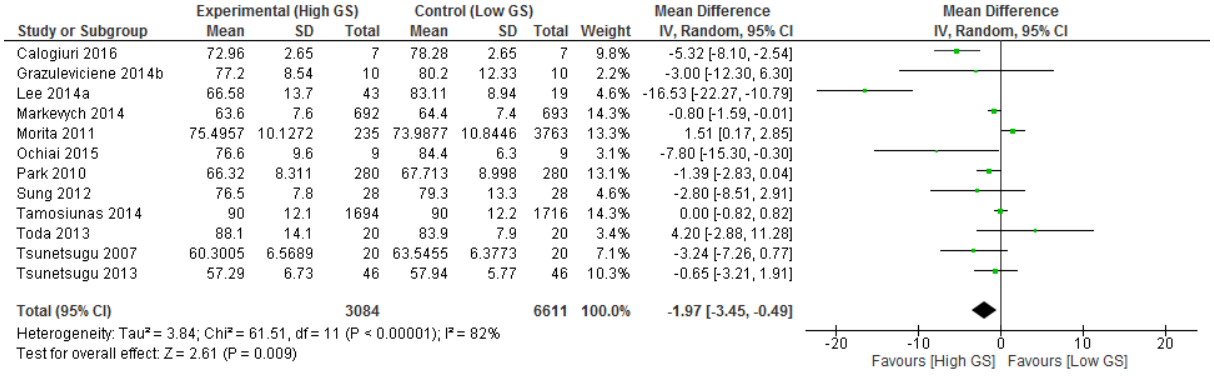


Figure 9. Heart rate

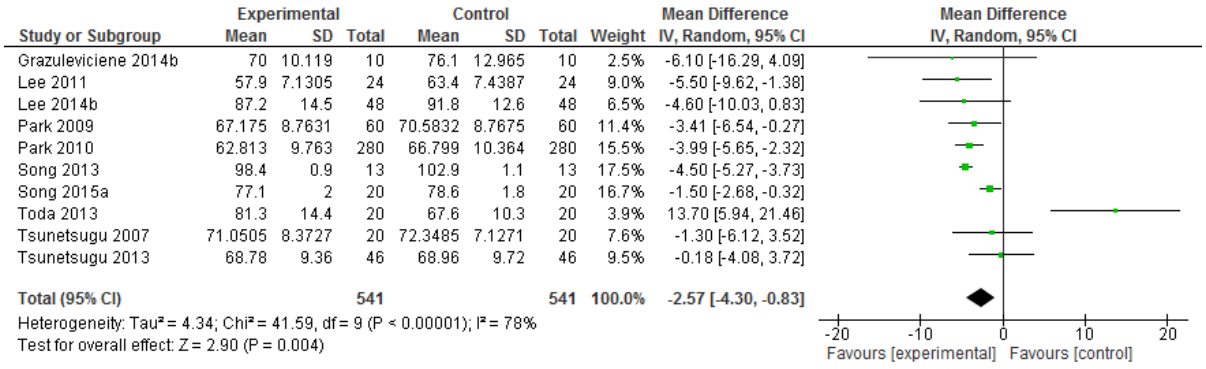


Figure 10. Incidence of good self-reported health

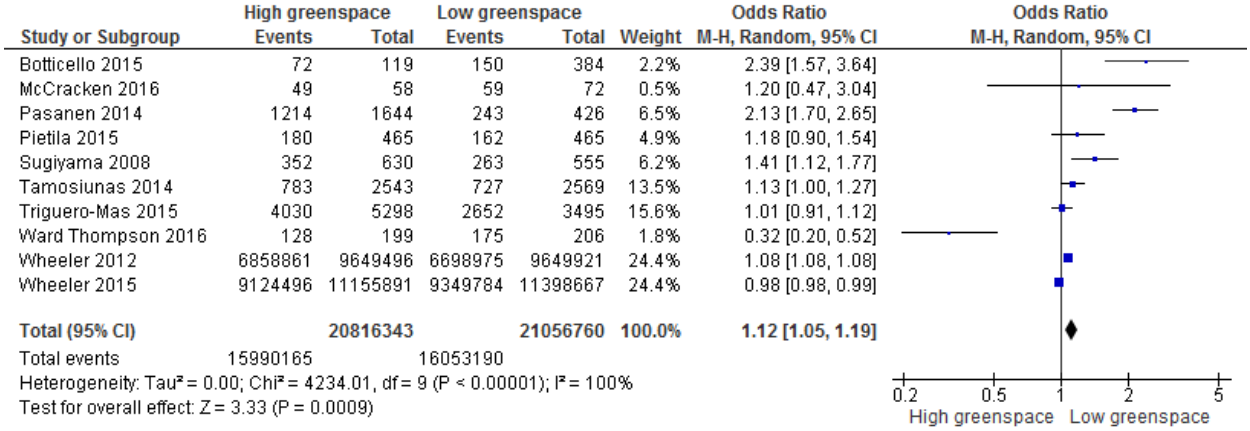


Figure 11. Salivary cortisol

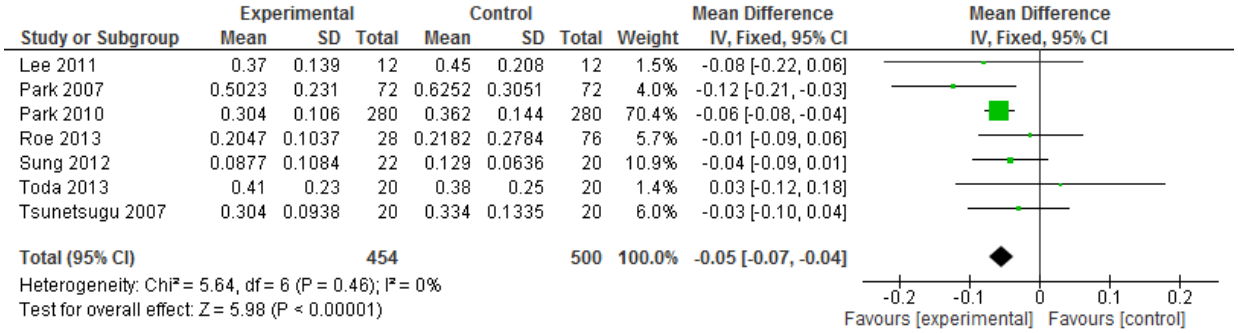


Figure 12. Incidence of type II diabetes

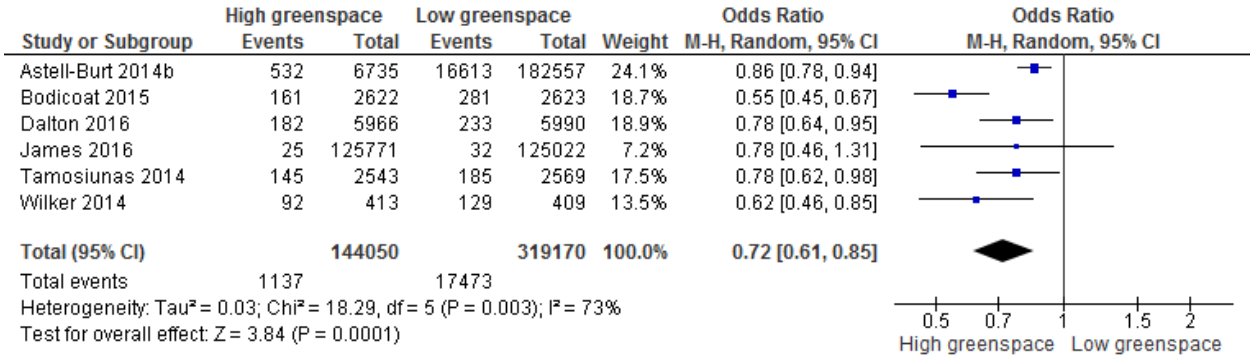


Figure 13. Incidence of hypertension

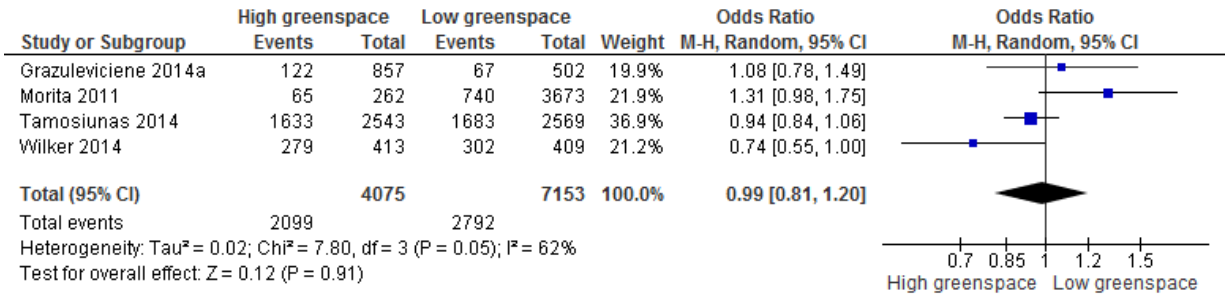


Figure 14. Incidence of dyslipidaemia

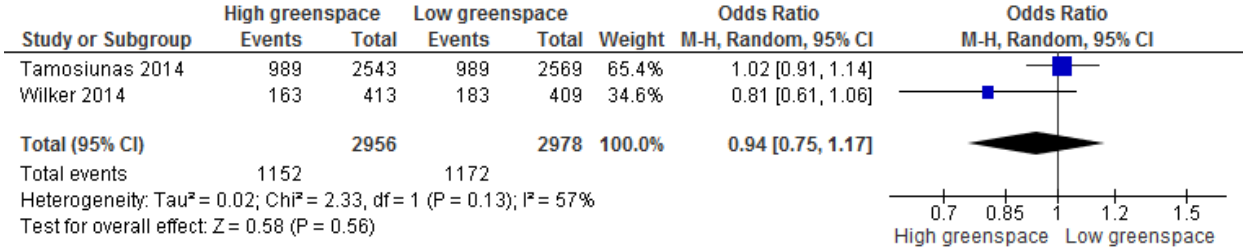


Figure 15. Incidence of stroke

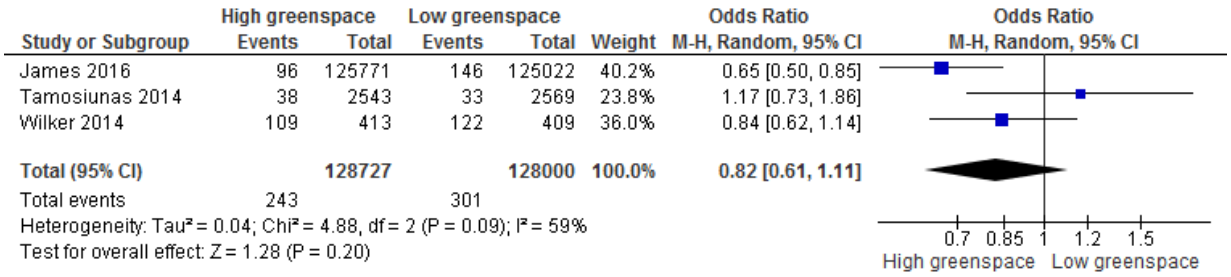


Figure 16. Incidence of asthma

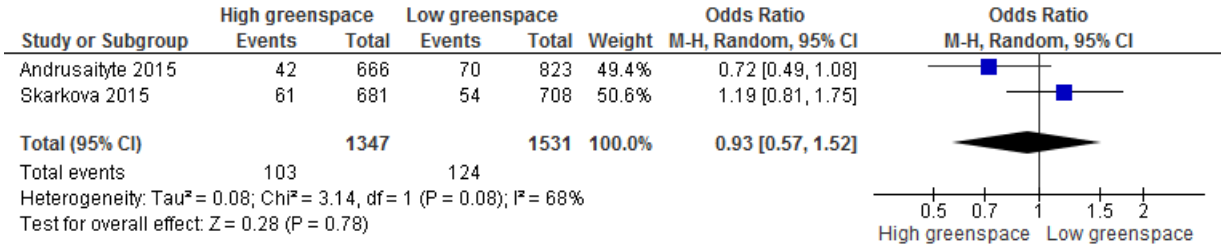


Figure 17. All-cause mortality

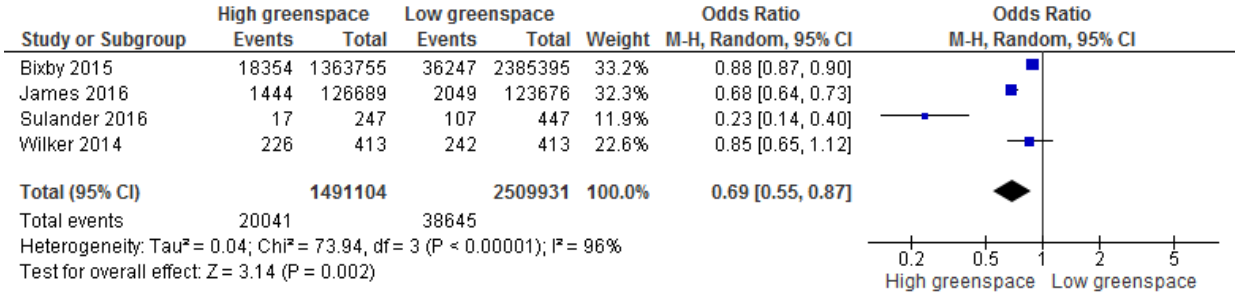
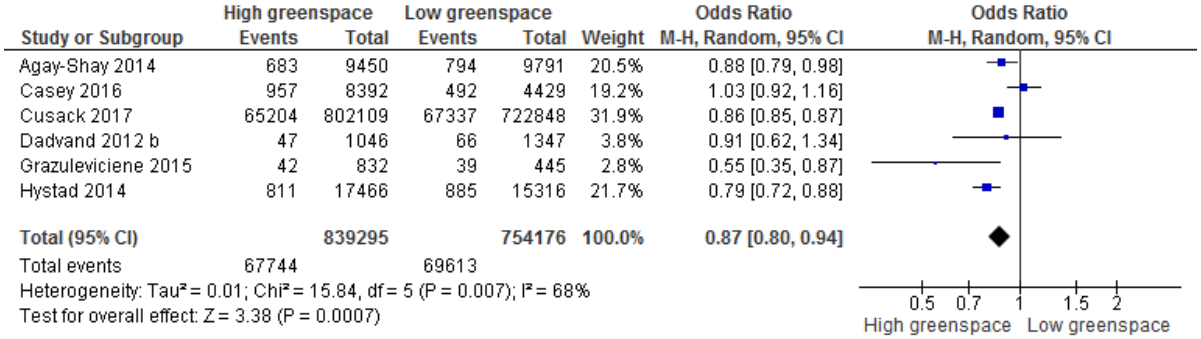


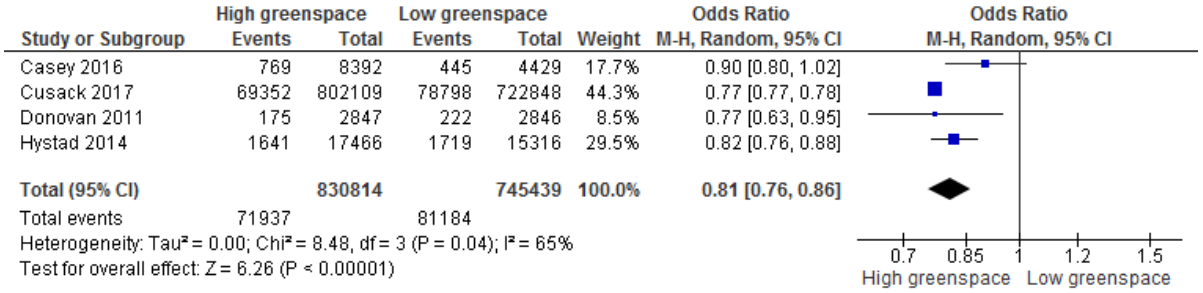
Figure 18. Preterm birth



Study or Subgroup	High greenspace Events	Total	Low greenspace Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Agay-Shay 2014	683	9450	794	9791	20.5%	0.88 [0.79, 0.98]
Casey 2016	957	8392	492	4429	19.2%	1.03 [0.92, 1.16]
Cusack 2017	65204	802109	67337	722848	31.9%	0.86 [0.85, 0.87]
Dadvand 2012 b	47	1046	66	1347	3.8%	0.91 [0.62, 1.34]
Grazuleviciene 2015	42	832	39	445	2.8%	0.55 [0.35, 0.87]
Hystad 2014	811	17466	885	15316	21.7%	0.79 [0.72, 0.88]
Total (95% CI)		**839295**		**754176**	**100.0%**	**0.87 [0.80, 0.94]**
Total events	67744		69613			

Heterogeneity: Tau² = 0.01; Chi² = 15.84, df = 5 (P = 0.007); I² = 68%
Test for overall effect: Z = 3.38 (P = 0.0007)

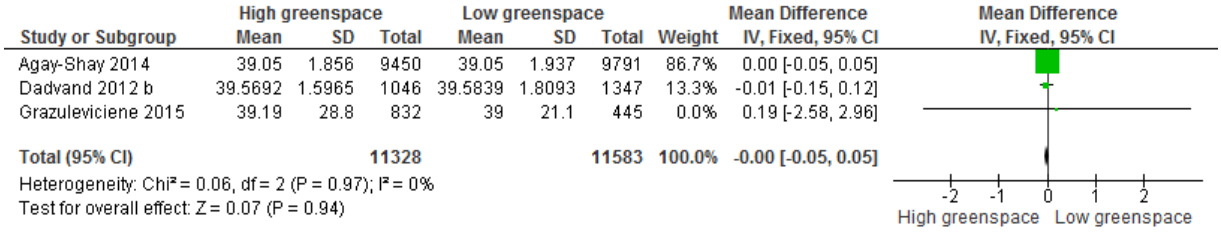
Figure 19. Small for gestational age



Study or Subgroup	High greenspace Events	Total	Low greenspace Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Casey 2016	769	8392	445	4429	17.7%	0.90 [0.80, 1.02]
Cusack 2017	69352	802109	78798	722848	44.3%	0.77 [0.77, 0.78]
Donovan 2011	175	2847	222	2846	8.5%	0.77 [0.63, 0.95]
Hystad 2014	1641	17466	1719	15316	29.5%	0.82 [0.76, 0.88]
Total (95% CI)		**830814**		**745439**	**100.0%**	**0.81 [0.76, 0.86]**
Total events	71937		81184			

Heterogeneity: Tau² = 0.00; Chi² = 8.48, df = 3 (P = 0.04); I² = 65%
Test for overall effect: Z = 6.26 (P < 0.00001)

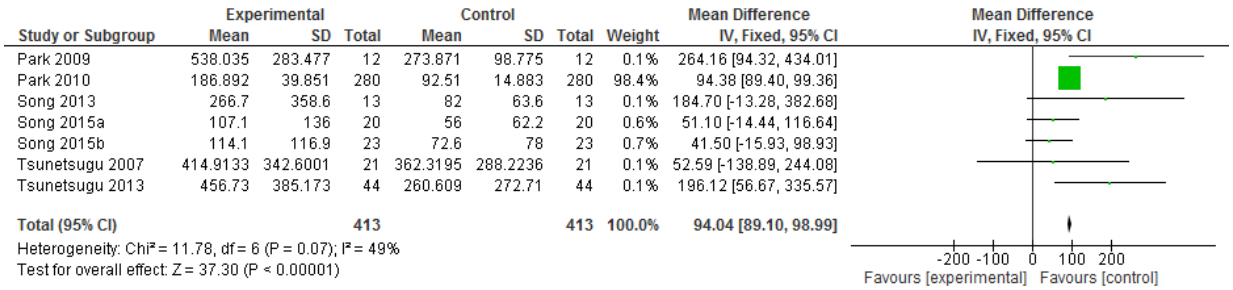
Figure 20. Gestational age



Study or Subgroup	High greenspace Mean	SD	Total	Low greenspace Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Agay-Shay 2014	39.05	1.856	9450	39.05	1.937	9791	86.7%	0.00 [-0.05, 0.05]
Dadvand 2012 b	39.5692	1.5965	1046	39.5839	1.8093	1347	13.3%	-0.01 [-0.15, 0.12]
Grazuleviciene 2015	39.19	28.8	832	39	21.1	445	0.0%	0.19 [-2.58, 2.96]
Total (95% CI)		**11328**				**11583**	**100.0%**	**-0.00 [-0.05, 0.05]**

Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)

Figure 21. Change in HF power of heart rate variability (HRV)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Park 2009	538.035	283.477	12	273.871	98.775	12	0.1%	264.16 [94.32, 434.01]
Park 2010	186.892	39.851	280	92.51	14.883	280	98.4%	94.38 [89.40, 99.36]
Song 2013	266.7	358.6	13	82	63.6	13	0.1%	184.70 [-13.28, 382.68]
Song 2015a	107.1	136	20	56	62.2	20	0.6%	51.10 [-14.44, 116.64]
Song 2015b	114.1	116.9	23	72.6	78	23	0.7%	41.50 [-15.93, 98.93]
Tsunetsugu 2007	414.9133	342.6001	21	362.3195	288.2236	21	0.1%	52.59 [-138.89, 244.08]
Tsunetsugu 2013	456.73	385.173	44	260.609	272.71	44	0.1%	196.12 [56.67, 335.57]
Total (95% CI)			**413**			**413**	**100.0%**	**94.04 [89.10, 98.99]**

Heterogeneity: Chi² = 11.78, df = 6 (P = 0.07); I² = 49%
Test for overall effect: Z = 37.30 (P < 0.00001)

Figure 22. LF/(LF+HF) in HRV

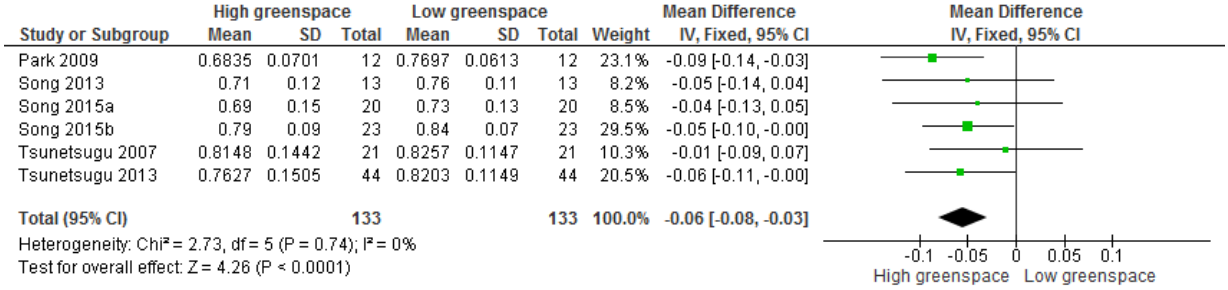


Figure 23. Fasting glucose

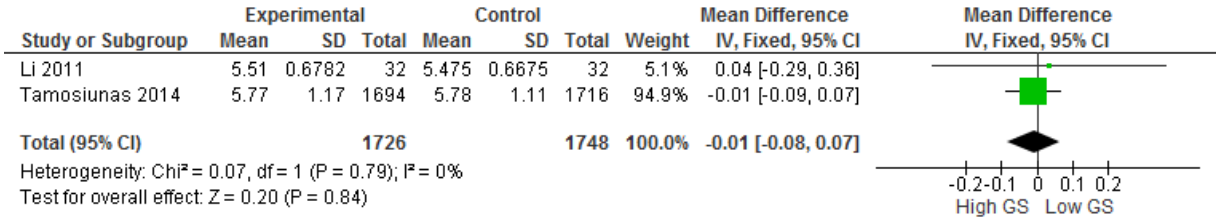


Figure 24. Total cholesterol

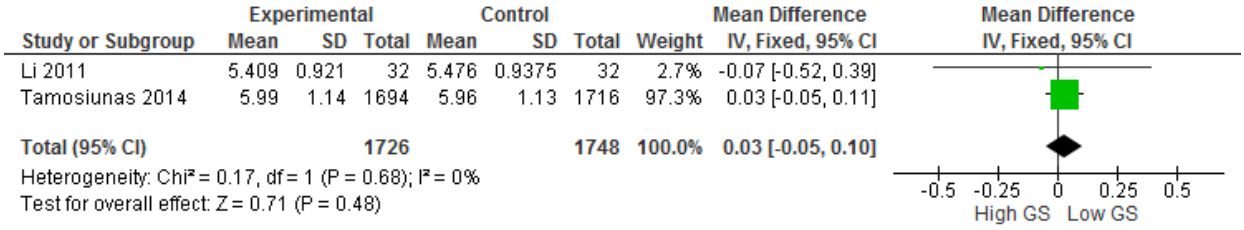


Figure 25. HDL cholesterol

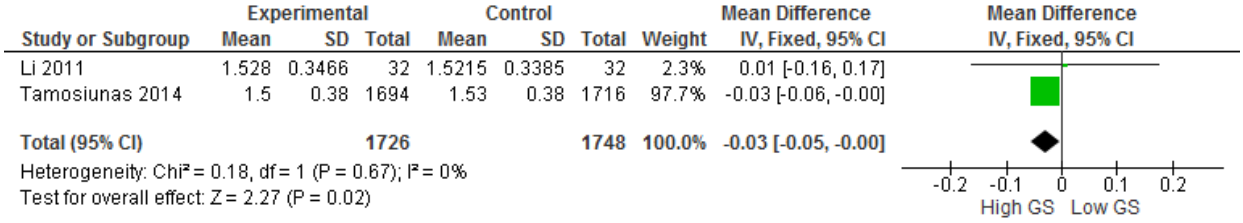


Figure 26. LDL cholesterol

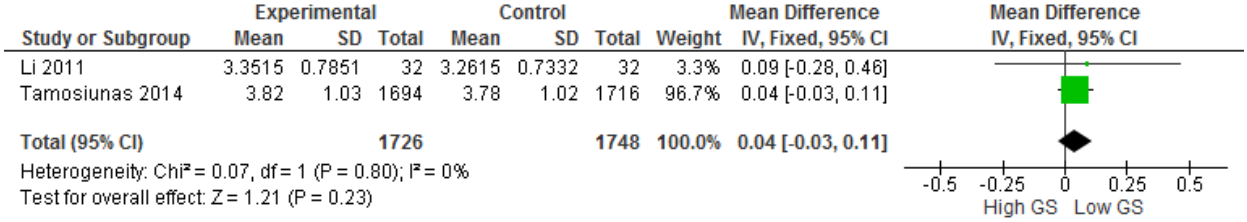


Figure 27. Triglycerides

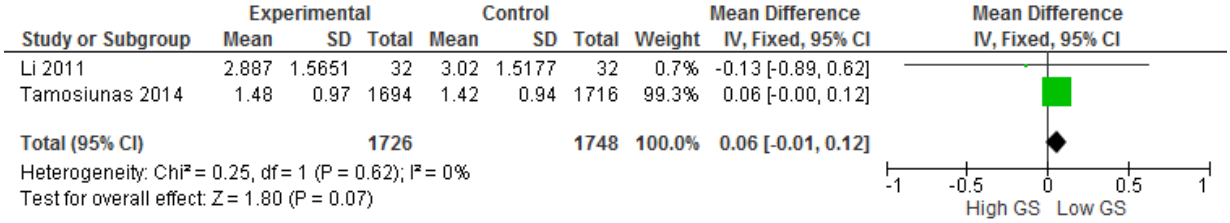


Figure 28. HbA1c

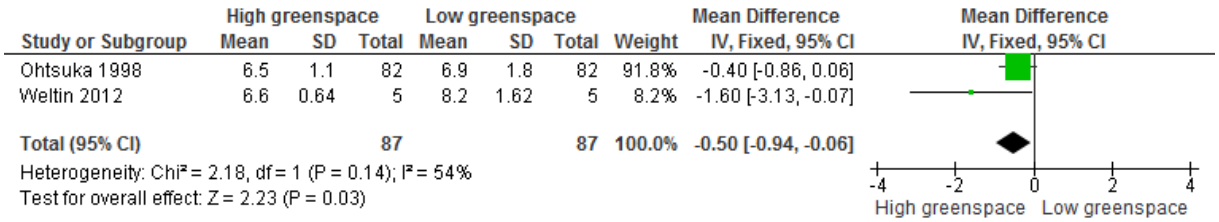


Figure 29. Cardiovascular mortality

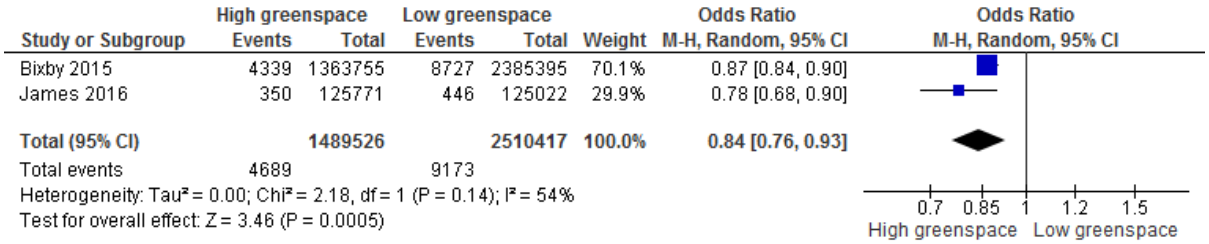


Figure 30. Coronary heart disease

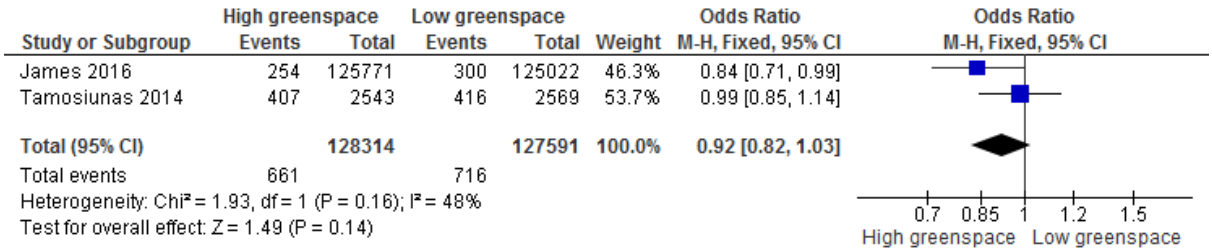


Table 9. Quality appraisal results for observational studies using an adapted version of the Lachowycz and Jones (2011) quality appraisal checklist

	Adapted Lachowycz and Jones (2011) quality appraisal checklist											
Lead author, year, *location*	**1. Selection bias**	**2. Inclusion bias**	**3. Outcome measure**	**4. Greenspace measure -**	**5. Greenspace measure - type**	**6. Use of greenspace**	**7. Statistical methodology**	**8. Effect size**	**9. Multiplicity**	**10. Level of analysis**	**11. Greenspace measure**	**Total score**
[120]	1	1	1	1	0	0	1	1	1	1	1	9
[129]	1	1	1	0	0	0	1	1	0	0	0	5
[130]	1	1	1	1	1	0	1	1	1	1	1	10
[115]	1	1	0	1	1	0	1	1	1	1	1	9
[245]	1	1	0	1	1	0	1	1	1	0	1	8
[133]	1	1	1	1	0	N	1	1	1	1	1	9
[135]	1	1	0	1	1	0	1	1	1	1	1	9
[136]	1	1	1	1	0	0	1	1	0	1	1	8
[137]	1	1	1	1	1	0	1	1	1	0	1	9
[138]	1	1	1	1	1	0	1	1	1	1	1	10
[139]	1	1	0	1	1	0	1	1	0	1	1	8
[140]	1	1	1	1	0	0	1	1	1	0	1	8
[46]	1	1	1	1	0	0	1	1	0	0	1	7
[142]	1	1	1	1	0	0	1	1	1	1	1	9
[143]	1	1	0	1	0	0	1	1	0	1	1	7
[144]	1	1	1	1	1	0	1	1	1	0	1	9
[145]	1	1	1	1	1	0	1	1	1	1	1	10
[146]	1	1	1	1	0	0	1	1	1	1	1	9
[246]	1	1	1	1	0	0	1	1	1	1	1	9
[121]	1	1	1	1	0	0	1	1	1	1	1	9
[149]	1	1	0	1	0	0	1	1	1	1	1	8
[109]	1	1	1	1	1	0	1	1	1	1	1	10
[150]	1	1	0	1	1	0	1	1	1	1	1+0	9
[151]	1	1	1	1	1	0	1	1	1	1	1	10
[152]	1	1	0	1	0	0	1	1	1	1	1	8

	Adapted Lachowycz and Jones (2011) quality appraisal checklist											
Lead author, year, *location*	**1. Selection bias**	**2. Inclusion bias**	**3. Outcome measure**	**4. Greenspace measure**	**5. Greenspace measure - type**	**6. Use of greenspace**	**7. Statistical methodology**	**8. Effect size**	**9. Multiplicity**	**10. Level of analysis**	**11. Greenspace measure**	**Total score**
113	1	1	1	1	0	0	1	1	1	1	1	9
153	1	1	0	1	1	0	1	1	1	1	1	9
154	1	1	1	1	1	0	1	1	1	1	1	10
155	1	1	0	1	1	0	1	1	1	1	1	9
156	1	1	0	0	N	0	1	1	0	1	1	6
86	1	1	1	1	0	0	1	N	1	1	1	8
158	1	1	0	1	N	0	1	1	1	1	1	8
247	1	1	1	1	0	0	1	1	1	1	1	9
161	1	1	1	1	0	0	1	1	1	1	1	9
162	1	1	0	1	0	0	1	1	1	1	1	8
163	1	1	1	0	0	0	1	1	0	1	1	7
165	1	1	1	1	N	0	1	1	0	1	1	8
166	1	1	1	1	0	0	1	1	1	0	1	8
49	1	1	1	1	0	0	1	1	1	1	1	9
114	1	1	1	1	0	0	1	1	1	1	1	9
167	1	1	1	1	1	0	1	1	1	1	1	10
116	1	1	1	1	0	0	1	1	1	0	1	8
168	1	1	0	1	1	0	1	1	1	0	1	8
169	1	1	1	1	0	0	1	N	1	0	1	7
170	1	1	1	1	1	0	1	1	1	1	1	10
171	1	1	1	1	1	0	1	1	1	1	1	10
172	1	1	0	1	1	0	1	1	1	0	1	8
173	1	1	1	1	0	0	1	1	1	1	1	9
182	N	1	1	1	1	0	1	1	1	0	1	8
183	1	1	1	1	1	0	1	1	1	N	1	9
184	1	1	0	1	1	0	1	1	1	1	1	9
33	1	1	0	1	1	0	1	1	1	1	1	9

	Adapted Lachowycz and Jones (2011) quality appraisal checklist											
Lead author, year, *location*	**1. Selection bias**	**2. Inclusion bias**	**3. Outcome measure**	**4. Greenspace measure**	**5. Greenspace measure - type**	**6. Use of greensnace**	**7. Statistical methodology**	**8. Effect size**	**9. Multiplicity**	**10. Level of analysis**	**11. Greenspace measure**	**Total score**
185	1	1	0	1	0	0	1	1	1	1	1	9
186	1	1	1	1	0	0	1	1	1	1	1	9
50	1	1	1	1	0	0	1	1	1	1	1	9
188	1	1	1	1	1	0	1	1	1	1	1	10
190	1	1	0	1	1	1	1	1	1	1	1+0	10
40	1	1	0	1	n	0	1	1	1	0	1	7
88	1	1	1	1	1	0	1	1	1	0	1	9
191	1	1	1	1	0	0	1	1	1	0	1	8
192	1	1	1	1	1	1	1	1	1	1	0	10
194	1	1	1	1	1	0	1	1	1	1	1	10
196	1	1	1	1	0	0	1	1	1	0	1	8
197	1	1	1	1	1	0	1	1	0	1	1	9
24	1	1	0	1	0	0	1	1	1	1	1	8
37	1	1	1	1	1	0	1	1	1	1	1	10
200	1	1	1	1	1	0	1	1	1	1	1	10
201	1	1	1	1	1	0	1	N	0	1	1	8
202	1	1	0	1	1	0	1	1	1	1	1	9
203	1	1	0	0	N	N	1	0	0	1	0	4
205	1	1	0	1	1	1	1	1	1	1	1	10
206	1	1	1	1	1	0	1	1	0	0	1	8
207	1	1	1	1	1	0	1	1	1	0	1	9
208	1	1	1	1	0	0	1	1	1	0	1	8
35	1	1	1	1	0	0	1	1	1	0	1	8
32	1	N	1	1	0	1	1	1	1	1	1	9
210	N	1	1	1	1	0	1	1	1	1	1	9
122	1	1	0	1	0	1	1	1	0	1	0	7
211	1	1	1	1	1	0	1	N	1	1	1	9

	Adapted Lachowycz and Jones (2011) quality appraisal checklist											
Lead author, year, *location*	**1. Selection bias**	**2. Inclusion bias**	**3. Outcome measure**	**4. Greenspace measure - **	**5. Greenspace measure - type**	**6. Use of greenspace**	**7. Statistical methodology**	**8. Effect size**	**9. Multiplicity**	**10. Level of analysis**	**11. Greenspace measure**	**Total score**
[48]	1	1	1	1	0	0	1	1	1	1	1	9
[212]	1	1	1	1	1	0	1	1	0	0	1	8
[216]	1	1	0	1	1	1	1	1	1	1	0	9
[218]	1	1	0	1	1	0	1	1	1	1	0	8
[219]	1	1	0	1	1	0	1	0	0	1	0	6
[220]	1	1	1	0	1	1	1	1	1	1	N	9
[222]	1	1	1	1	1	0	1	1	0	1	0	8
[223]	1	1	1	1	0	1	1	1	1	1	1	10
[225]	1	1	0	1	0	0	1	1	1	1	1	8
[228]	1	1	1	1	1	0	1	1	1	1	1	10
[248]	1	1	0	1	1	0	1	1	1	0	1	8
[230]	1	1	0	1	1	0	1	1	0	0	0	6
[231]	1	1	1	1	0	0	1	1	1	1	1	9
[232]	1	1	0	1	1	0	1	1	1	1	1	9
[233]	1	1	1	1	1	0	1	1	0	1	1	9
[234]	1	1	1	1	1	1	1	1	1	1	1	11
[235]	1	1	1	1	1	0	1	1	1	1	1	10
[236]	1	1	0	1	0	1	1	1	1	1	1	9
[237]	1	1	0	1	1	0	1	1	1	1	1	8
[239]	1	1	0	0	N	0	1	1	0	0	1	5
[110]	1	1	0	1	1	0	1	1	1	0	1	8
[240]	1	1	1	1	0	0	1	1	1	1	1	9
[241]	1	1	0	0	0	1	1	1	1	1	1	8
[242]	1	1	0	1	0	0	1	1	0	1	1	7
[244]	1	1	1	1	1	0	1	1	0	1	1	9

Table 10. Quality appraisal results for intervention studies using an adapted version of the Hanson and Jones and Ogilvie et al. risk of bias tool

	***Adapted Hanson and Jones risk of bias checklist* results**											
Lead author, year, location	**1. Reporting: hypothesis**	**2. Reporting: outcome(s)**	**3. Reporting: intervention**	**4. Randomisation**	**5. Exposure**	**6. Representativeness**	**7. Comparability**	**8. Attrition**	**9. Outcome assessment tools**	**10. Follow-up time scale**	**11. Precision of the results**	**Total score (out of 11)**
[131]	1	1	1	1	N	1	N	1	1	1	1	9
[249]	1	1	1	1	1	1	1	1	1	1	1	11
[141]	1	1	1	1	N	1	1	1	1	1	1	10
[157]	1	1	1	0	N	N	N	1	1	1	1	7
[160]	1	1	1	1	N	N	1	1	1	1	1	9
[56]	1	1	1	1	N	N	1	1	1	1	1	9
[119]	1	1	1	1	N	N	1	1	1	1	1	9
[117]	1	1	1	1	N	1	1	1	1	1	1	10
[174]	1	1	1	1	N	N	1	1	1	1	1	9
[175]	1	1	1	0	N	1	1	1	0	1	1	8
[176]	1	1	1	0	N	1	1	1	1	1	1	9
[177]	1	1	1	1	N	N	1	1	1	1	1	9
[178]	1	1	1	1	N	N	1	1	1	1	0	9
[179]	1	1	1	1	N	N	1	1	1	1	0	8
[180]	1	1	1	0	N	N	1	1	1	1	1	8
[181]	1	1	1	1	N	N	1	1	1	1	1	9
[187]	1	1	1	1	N	N	1	1	1	1	1	9
[118]	1	1	1	1	N	N	1	1	1	1	1	8
[189]	1	1	1	1	N	N	1	1	1	1	1	9
[193]	1	1	1	1	N	1	1	0	1	1	1	9
[108]	1	1	1	1	N	N	1	1	1	1	1	9
[195]	1	1	1	1	N	N	1	1	1	1	1	9
[198]	1	1	1	1	N	N	1	1	1	1	1	9
[199]	1	1	1	1	N	N	0	0	1	1	1	7
[112]	1	1	1	1	N	N	1	1	1	1	1	9
[204]	1	1	1	1	N	1	0	1	1	1	1	9
[213]	1	1	1	1	N	N	1	1	1	1	1	9
[214]	1	1	1	1	N	N	1	1	1	1	1	9

215	1	1	1	1	N	N	1	1	1	1	1	9
217	1	1	1	1	N	N	1	1	1	1	1	9
221	1	1	1	1	N	N	1	1	1	1	1	9
224	1	1	1	1	N	1	1	1	1	1	1	10
226	1	1	1	1	N	N	1	1	1	1	1	9
227	1	1	1	1	N	N	1	1	1	1	1	9
57	1	1	1	1	N	N	1	1	1	1	1	9
111	1	1	1	1	N	1	1	1	1	1	1	10
238	1	1	1	0	N	N	1	1	1	1	1	8
243	1	1	1	1	N	N	1	0	1	1	1	8

Chapter 3: Does gut microbial diversity explain the relationship between greenspace and health? Results from the TwinsUK database

Preamble

Chapter 2 demonstrated the wide range of physiological health benefits associated with exposure to greenspace, notably the association between increasing greenspace and decreased incidence of inflammatory diseases such as type 2 diabetes, cardiovasuclar mortality, and reduced diastolic blood pressure. The chapter also highlighted a paucity of literature investigating the mechanisms underlying this relationship.

One hypothesised mechanism for greenspace and health is that greenspace exposure offers exposure to a diverse range of microbiota, which are beneficial in the education and regulation of the immune system. This in turn, may lead to regulation of the inflammatory response, and a subsequent reduction in low-lying levels of chronic inflammation. Chapter 3 investigates this hypothesis by investigating whether an association between neighbourhood greenspace and gut microbial diversity exists.

Abstract

This study investigated the possible association between neighbourhood greenspace and gut microbial diversity as a mechanism underlying the relationship between greenspace and health, using data from the TwinsUK database. Neighbourhood greenspace for each participant was obtained from a land cover map (2007), with biomedical, health, and lifestyle variables extracted from the dataset. Five different indices of microbial diversity were employed. Data were used from 1908 participants with a mean age of 61.6 years (SD: 11). Associations between neighbourhood greenspace and each of the individual microbial diversity indices were estimated using Generalised Estimating Equation (GEE) estimates both with and without adjustment for potential confounders. No statistically significant association was found between neighbourhood greenspace and gut microbial diversity for any diversity index, before or after adjustment for potential confounders. The findings suggest that gut microbial diversity does not mediate previously observed associations between the greenness of residential neighbourhoods and the health of residents.

3.1. Introduction

According to the 2011 United Nations World Urbanisation Prospects, 67% of the world's population will live in urban areas by 2050, an increase from 52% in 2011[250]. Urbanization has been associated with increasing incidence of non-communicable and inflammatory diseases including type II diabetes, hypertension and cardiovascular diseases[251-253]. Increasing population density in urban areas has also been associated with increased risk of transmission of infectious diseases[252]. Understanding the interplay between neighbourhood environments and health should therefore be a high priority for researchers. One environmental factor for which there is a growing body of evidence is greenspace and its' beneficial relationship with health[254].

Greenspace has been defined by the European Environment Agency as "a plot of vegetated land separating or surrounding areas of intensive residential or industrial use and devoted to recreation or park uses"[255]. Increased exposure to greenspace has been associated with health benefits such as reduced incidence of diabetes[133 151], heart disease[37 56 143 194 256], and blood pressure[50 108 129 247], as well as a variety of mental health benefits[32 150 225 249]. It may be that the integration of urban greenspaces or street greenery in urban areas could mitigate the health problems associated with urbanisation. Little is known however on the mechanisms underlying these relationships. One potential hypothesised mechanism is that living in a neighbourhood with a high level of greenspace would lead to increased gut microbial diversity through increased exposure to natural areas[64]. It is hypothesised that this would then carry health benefits such as improved regulation of the immune system and reduced inflammation[64]. One previous study has found an association between bacteria in the neighbourhood environment and skin microbiota[257]. There is some evidence to suggest that healthy adults from remote rural communities have higher gut bacterial species richness compared to urban populations[258-261]. However, to the authors' knowledge, no previous study has investigated the relationship between the land use of participants' neighbourhood environment, including neighbourhood greenspace, and the microbiota of the gut.

In recent years the human microbiome has increasingly commanded attention from researchers[64 262-265]. In humans, almost immediately after birth, the skin, mouth, gut, and vagina, undergo colonisation by microorganisms[266], and it has been suggested that the adult human body contains more bacterial cells than human cells[267]. The bacteria colonising human bodies play a variety of important roles for health, for example developing and regulating the immune system[268]. The microbiome of the gut has been linked with obesity[269], type II diabetes[270], depression[271], and anxiety[272]. Genetic and lifestyle factors including diet,

antibiotic use, and disease, can impact upon microbial composition[260]. Repeat antibiotic use has been associated with profound alterations of the gut microbiota[273 274] and differences in the composition of the gut microbiota have been found between healthy and diseased patients[270 275-278], with the gut microbiota playing a key role in shaping the intestinal immune response to disease[279].

Research into environmental influences on the gut microbiome has focused on diet, antibiotic use, sanitation, and level of cleanliness, as well as cultural factors[280]. There is a paucity of literature concerning the relationship between neighbourhood or built environment factors and the human microbiome. The author found one study that reported a relationship between forest and agricultural land cover in participants' neighbourhood environments and increased diversity of proteobacteria on the skin[257]. There is however much evidence to suggest a relationship between microbial composition of habitat and gut microbial diversity in animals[281-284]. Animals are perhaps more integrated into their habitats than humans[284]. No previous study has attempted to link neighbourhood greenspace exposure with microbial diversity of the human gut.

Using data from the TwinsUK Cohort, this study aims to investigate whether a relationship exists between greenspace exposure and gut microbial diversity, thus potentially explaining the relationship between greenspace and health. Gut microbial diversity is quantified using 4 commonly used ecological indices, the Shannon index, the Simpson index, [285]; Chao1, and Observed Operational Taxonomic Units (OTUs). We hypothesised that increased percentage neighbourhood greenspace would be associated with an increase in gut microbial diversity.

3.2. Methods

3.2.1 Study population

TwinsUK is an adult twin registry originally instigated in 1993 to study osteoporosis. The registry consists of approximately 10,000 monozygotic and dizygotic adult Caucasian twins aged 16 to 100 years from across the UK[263]. It is a volunteer sample recruited by successive media campaigns unselected for particular diseases or traits. Twins were invited to take part but recruited as individuals, i.e. both twins were not required for an individuals data to be accepted. A high proportion of the registry are female as the registry was originally set up to study osteoporosis, which introduced a bias towards women[263]. Information is derived from a series of detailed disease and environmental questionnaires plus clinical assessments[263]. This study used data obtained from 1908 participants who provided both baseline information and faecal samples to enable measurement of gut microbial diversity. Participants completed health checks at several time points, and so data from the closest time point to the faecal samples was used.

3.2.2. Gut microbial diversity measurement

We employed four commonly used ecological indices to quantify gut microbial diversity: the Shannon index, believed to emphasise the richness component of diversity[286 287]; the Simpson index believed to emphasise the evenness component[285]; Chao1 a measure of diversity[286], and Observed Operational Taxonomic Units (OTUs) which distinguishes between microbiota at the species level[286].

3.2.3. Greenspace measurement

The exposure of interest was the percentage of greenspace in the participants' home neighbourhood based on their residential location. A geographic information system (GIS), ArcGIS 10.3[288] was used to delineate neighbourhood boundaries around the postcodes (zip codes) of each participant based on postcode locations extracted from the UK Ordnance Survey Code-Point database[289]. In previous studies[138 151], neighbourhoods were delineated using road network buffers of 800m (an approximate 10 minute walk) from each home postcode location[290]. Recent research however suggests that this may be overly conservative as many people will travel much further distances on foot from home to access resources[291] and 3 neighbourhood buffers were therefore derived: 800m, 3km, and 5km. The 3km measurement was chosen for the primary analysis, with the 800m and 5km buffers used for sensitivity analysis.

Estimates of greenspace per 25m by 25m cell across England, Scotland, and Wales were computed from the Centre for Ecology and Hydrology Land Cover Map of the UK (2007)[73], derived from satellite images, and digital cartography. It records dominant land use types based on a 23-class typology, and then matched to the participants' postcodes. Cells containing the categories of broadleaved and coniferous woodland, arable, improved grassland, semi-natural grassland, mountain, heath, bog and freshwater were classed as greenspace for this analysis. Each participant's exposure was computed by overlaying the mapped greenspace with the neighbourhood boundaries in the GIS to calculate the percentage of each neighbourhood area that contained these land cover types.

3.2.4. Potential confounders and moderators

Characteristics collected at the health check closest to the timepoint of the faecal sample were chosen for this analysis based on empirical evidence or theoretical relevance of associations with the gut microbiome and greenspace. They included information on age, sex, socioeconomic status, body mass index (BMI), antibiotic use, and diet. BMI has been associated with reduced bacterial diversity and alterations in the gut microbiome[292], and neighbourhood greenspace has also been found to be associated with obesity[27]. Antiobiotic use can profoundly affect gut microbial composition[273 274]. Diet has been shown to be one of the most influential factors on the gut microbiome, with changes in dietary pattern able to alter the structure of gut microbiota in as little as one day[293 294]. The relationships between diet[295 296], antiobiotic use[297], and obesity[296 298 299] with socioeconomic status have previously been established, and decreased neighbourhood greenspace has also previously been associated with lower socioeconomic status (SES)[88]. Therefore, obesity and SES were adjusted for as potential confounders, and diet and antibiotic use were adjusted for as covariates. The dietary variable used was a Healthy Eating Index (HEI), which was created using food frequency questionnaire (FFQ) results and has been shown to be the most suitable index for controlling for diet in human microbiota studies[300]. The antibiotic use variable was derived from questionnaire data, and BMI was measured at each health check. The variable used to assess social and economic deprivation was the ward-level area-based English Index of Multiple Deprivation (IMD), which is a score of the social and economic deprivation at ward level[301]. Ethnicity was not included in this analysis as over 99% of the sample were white British.

3.2.5. Statistical analysis

Participants were classified into quartiles of percentage of greenspace area within their neighbourhood. This was done by ranking participants in order of percentage neighbourhood greenspace and then splitting into quartiles with approximately equal

numbers of participants. As sample participants were either individual twins or twin pairs, data within twin pairs were likely to be correlated and, therefore, Generalised Estimating Equations (GEE) were used to estimate the association between neighbourhood greenspace and each of the indices of gut microbial diversity.

Three models were fitted. Model 1 estimated the 'unadjusted' relationship between neighbourhood greenspace exposure and each of the four indices of gut microbial diversity, i.e. with no other explanatory variables in the model other than greenspace. Model 2 was adjusted for age, sex, and IMD, and Model 3 was adjusted for the same variables as Model 2, with additional adjustments for diet (HEI), antibiotic use, and BMI. Models were then repeated for each outcome: Shannon index, Simpson index, Chao1, and Observed OTUs.

Sensitivity analyses consisted of re-fitting each model using the two remaining neighbourhood buffer sizes (800mand 5km). Tests for linear trend were performed by fitting greenspace quartiles as a continuous variable. All analyses were performed in SPSS 22 and statistical significance was set at the two-tailed 5% level.

3.3. Results

3.3.1. Sample characteristics

Participant characteristics can be found in Table 11. A total of 1908 participants were included in this analysis, consisting of 663 twin pairs and 582 twins who were not in a pair, due to their twin either not being recruited into the study, or missing data from their twin. Participants had a mean age of 61.6 years (SD 11), and 91.2% of the total sample were female. Average greenspace percentages ranged between 44% in the 800m buffer, 59.2% in the 3km buffer, and 63.3% in the 5km buffer.

Table 11. Participant study characteristics

Variable	Men	Women	All
n	167	1,741	1908
Age (years)	61.40 (11.8)	61.61 (10.9)	61.60 (11.0)
IMD	14.44 (10.8)	13.75 (10.9)	13.81 (10.9)
BMI (kg/m^2)	26.50 (4.3)	25.88 (4.8)	25.94 (4.8)
% taking antibiotics	4.8%	6.3%	6.1%
% greenspace			
800m buffer	42.4%	44.1%	44.0%
3km buffer	59.4%	59.2%	59.2%
5km buffer	64.2%	63.2%	63.3%
Healthy Eating Index (HEI)	57.51 (9.9)	60.74 (10.1)	60.44 (10.1)
Diversity indices			
Shannon (Range: 1.255 - 6.925)	5.239 (0.75)	5.160 (0.73)	5.166 (0.74)
Simpson (Range: 0.248 - 0.985)	0.925 (0.07)	0.922 (0.06)	0.922 (0.06)
Chao1 (Range: 151.88 - 3972.7)	1001.54 (490.2)	875.90 (442.7)	886.72 (448.7)
OTUs (Range: 69.92 - 808.46)	372.09 (105.6)	347.40 (100.8)	349.42 (101.6)

Characteristics of participants in the highest and lowest quartiles of greenspace can be found in Table 12. The 477 participants in the highest greenspace quartile had a mean age of 63 and on average 92.8% greenspace within 3km of their home postcode, whereas participants in the lowest quartile of greenspace had a mean age of 59 and on average 21.7% greenspace in their neighbourhood area. Participants in the highest quartile of greenspace had on average higher scores for all 4 diversity indices compared with participants in the lowest greenspace quartile. No statistically significant differences were seen between the two quartiles other than for % greenspace.

Table 12. Participant study characteristics for participants in the highest and lowest greenspace quartiles for the 3km buffer

Variable	Highest quartile	Lowest quartile
n	477	463
Age (years)	63	59
IMD	11	19
BMI	26	26
% taking antibiotics	5.2%	4.1%
% greenspace	92.8%	21.7%
Hs-CRP (mg/L)	2.61	2.78
Healthy Eating Index (HEI)	57.51 (9.9)	60.74 (10.1)
Diversity indices		
Shannon	5.19	5.14
Simpson	0.923	0.919
Chao1	902.53	851.27
OTUs	354.51	342.11

Data are mean values or percentage prevalence.

3.3.2. Neighbourhood greenspace and gut microbial diversity

GEE estimates for the relationship between neighbourhood greenspace quartiles and 4 indices of gut microbial diversity can be found in Table 13. Although the results in Model 1 suggested a dose-response relationship between quartiles of increasing greenspace and the Chao1 and Observed OTUs indices, these trends were not statistically significant and did not remain after adjustment in Models 2 and 3. No relationship was observed between neighbourhood greenspace and the Simpson, and Shannon indices, either before or after adjustment. A linear trend was apparent between was found for greenspace and OTUs in Model 1. However, this was again no longer seen after adjustment for potential confounders.

Sensitivity analysis results using different buffer sizes (800m and 5km) were consistent with the results for the 3km buffer. The sensitivity analysis results can be found in the Supplementary Tables 14 and 15 (Section 3.5.).

Table 13. Model summary of generalised estimating equation estimates (GEEs) with diversity indices as outcomes with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for a 3km buffer. Model 1: 1920 participants, unadjusted; model 2: 1401 participants, adjusted for age, sex, and index of multiple deprivation (IMD); model 3: 1201 participants, adjusted for the same potential confounders as model 2, as well as BMI, antibiotic use (yes/no), and Healthy Eating Index (HEI).

Shannon index	**Model 1 (n=1920)**	**p trend**	**Model 2 (n=1401)**	**p trend**	**Model 3 (n=1201)**	**p trend**
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	-0.007 (-0.105, 0.091)	0.223	-0.064 (-0.180, 0.052)	0.364	-0.031 (-0.152, 0.091)	0.177
Quartile 3	0.045 (-0.053, 0.143)		-0.049 (-0.166, 0.067)		0.005 (-0.115, 0.124)	
Quartile 4 (most green)	0.045 (-0.052, 0.141)		0.046 (-0.068, 0.161)		0.072 (-0.047, 0.190)	
Simpson index	**Model 1**		Model 2		Model 3	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	0.002 (-0.006, 0.011)	0.296	-0.002 (-0.012, 0.008)	0.360	-0.002 (-0.012, 0.008)	0.215
Quartile 3	0.004 (-0.005, 0.013)		-0.001 (-0.010, 0.009)		0.001 (-0.008, 0.011)	
Quartile 4 (most green)	0.004 (-0.004, 0.013)		0.004 (-0.005, 0.014)		0.005 (-0.004, 0.014)	
Chao1 index	**Model 1**		Model 2		Model 3	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	43.183 (-10.055, 96.421)	0.105	39.730 (-24.782, 104.242)	0.253	70.810 (-0.754, 142.374)	0.226
Quartile 3	45.790 (-8.164, 99.743)		10.279 (-52.189, 72.748)		26.776 (-42.249, 95.800)	
Quartile 4 (most green)	51.259 (-7.385, 109.902)		51.427 (-16.186, 119.040)		64.939 (-10.516, 140.394)	
Observed OTUs	**Model 1**		Model 2		Model 3	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	5.178 (-7.783, 18.139)	**0.043***	0.920 (-14.760, 16.600)	0.268	9.211 (-7.405, 25.827)	0.210
Quartile 3	11.353 (-1.252, 23.958)		-3.342 (-17.993, 11.309)		3.412 (-11.885, 18.709)	
Quartile 4 (most green)	12.400 (-0.699, 25.500)		10.349 (-5.176, 25.875)		13.283 (-3.445, 30.010)	

3.4. Discussion

It was hypothesised that a greater amount of neighbourhood greenspace would be associated with increased bacterial exposure, manifesting as increased gut microbial diversity. However, this large, cross-sectional study using the TwinsUK data found no evidence of a relationship between neighbourhood greenspace and any of the four indices of gut microbial diversity. This study therefore presents no evidence that gut microbial diversity plays a role in the relationship between greenspace and health.

There are several possible explanations for these findings. It could simply be that gut microbial diversity plays no role in the mechanisms underlying the relationship between neighbourhood greenspace and health. The gut microbial diversity of animals has been linked with their habitat[281-284], but perhaps sanitation and cleanliness may be preventing neighbourhood greenspace from influencing human gut microbiota in the same manner. Although several potential confounding variables were adjusted for, there is a possibility that others may not have been accounted for. For example, it was not possible to adjust for smoking due to the high level of missing values. There may also have been measurement error in some of the variables used; we used the area-based Index of Multiple Deprivation (IMD) as an indicator of social and economic deprivation because an individual-level index was not available in the TwinsUK dataset. An individual-level index may have been a more accurate indicator of participants' socioeconomic status. However, it is unlikely that the magnitude of these problems would lead to the null findings of this study.

To my knowledge, this is the first study to investigate the relationship between greenspace exposure and gut microbial diversity. The author found one previous study that reported higher percentages of forest and agricultural land in participants' surrounding neighbourhoods to be associated with increased microbial diversity of participants' skin[257]. The difference with our findings may be because skin is more directly exposed to the outdoor elements than the human gut. The microbiota of the skin may also be less likely to be influenced by factors such as diet, antibiotic use, and BMI. The participant data used in that study was also very different as it was from a smaller group (n = 116) of adolescents[257]. It has previously been reported that time spent outdoors decreases with age[302], and so the adolescent participants in this study may have spent more time in direct contact with greenspace than our participants who had a mean age of 61.6 years.

There are several strengths to this study. The author believes it is the first to examine the relationship between neighbourhood greenspace exposure and gut microbial diversity in a large well characterised population cohort. An objective measure of neighbourhood

greenspace across 3 buffer sizes was used. Gut microbial diversity was assessed across four commonly used diversity indices as well as a novel health-mediated index of gut microbial diversity. The data came from twins from across England, Scotland, and Wales, and from age 16-85, suggesting that results may be generalisable across the UK and to other populations.

There are also a number of limitations to the study. Although an objective measurement of neighbourhood greenspace was employed, it may not have been an accurate indicator of actual greenspace usage: no direct data on participants' greenspace use were available. Increased neighbourhood greenspace has previously been associated with increased time spent outdoors[41]. However, it is not possible to derive objective measures of greenspace use from data on percentage neighbourhood greenspace. One potential confounder was smoking status, which has been associated with changes to the gut microbiome[303] as well as being linked with socioeconomic status[304 305]. It was not possible to adjust for this due to a high level of missing data for this variable. Another limitation is that the sample of TwinsUK participants was over 91.2% female. The female majority is largely because the dataset was initially set up to investigate osteoporosis, which introduced a bias towards women[263]. This high proportion of female participants may limit the generalizability of the findings to males, particularly as gender has been previously associated with gut microbial composition[306 307]. Additionally, the dataset contains only Caucasian participants, which may further limit generalizability. The UK is approximately 87% White British, with the remaining 13% made up of other ethnic groups[308].

Although data was not available to enable it here, alternative approaches to investigate the relationship between neighbourhood greenspace and microbial diversity could be useful. There may be benefit to comparing gut microbial diversity before and at regular intervals after greenspace exposure. This provide insight into whether acute greenspace exposure evokes short term changes in gut microbial diversity, and if so, for how long these changes may last. Although increased microbial diversity of the gut has been associated with improved health[309], a future direction may be to investigate the prevalence of healthy and unhealthy gut bacteria in relation to environmental exposures to help better establish how gut health is influenced by the environment. It may also be the case that greenspace exposure is associated with immunoregulation and the regulation of inflammatory processes, but through a pathway other than gut microbial diversity.

In conclusion, this study has found no evidence linking percentage neighbourhood greenspace and gut microbial diversity in the TwinsUK study. Neighbourhood greenspace has been reported to be beneficial for health, but the underlying mechanisms of this

relationship are still unclear. Objective measurements of greenspace use may enable researchers to understand the spatial and temporal factors that influence the relationship between greenspace and health, as well as providing further insight into putative underlying mechanisms.

3.5. Supplementary tables

*Supplementary Table 14. Model summary of generalised estimating equation estimates (GEEs) with diversity indices as outcomes with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for an **800m buffer**. Model 1: 1920 participants, unadjusted; model 2: 1401 participants, adjusted for age, sex, and index of multiple deprivation (IMD); model 3: 1201 participants, adjusted for the same potential confounders as model 2, as well as BMI, antibiotic use (yes/no), and Healthy Eating Index (HEI).*

Shannon index	**Model 1 (n=1920)**	**p trend**	**Model 2 (n=1401)**	**p trend**	**Model 3 (n=1201)**	**p trend**
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	-0.018 (-0.115, 0.079)	0.337	-0.020 (-0.137, 0.097)	0.263	0.046 (-0.076, 0.168)	0.103
Quartile 3	-0.038 (-0.137, 0.061)		-0.049 (-0.171, 0.074)		0.020 (-0.107, 0.147)	
Quartile 4 (most green)	0.056 (-0.040, 0.152)		0.076 (-0.044, 0.195)		0.116 (-0.009, 0.242)	
Simpson index	**Model 1**		**Model 2**		**Model 3**	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	0.001 (-0.008, 0.009)	0.596	-0.001 (-0.011, 0.009)	0.495	0.004 (-0.006, 0.014)	0.182
Quartile 3	-0.004 (-0.012, 0.005)		-0.004 (-0.014, 0.006)		0.001 (-0.009, 0.011)	
Quartile 4 (most green)	0.004 (-0.004, 0.012)		0.004 (-0.006, 0.014)		0.008 (-0.002, 0.018)	
Chao1 index	**Model 1**		**Model 2**		**Model 3**	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	-10.783 (-63.234, 41.669)	**0.033**	-20.081 (-81.959, 41.797)	**0.137**	-6.914 (-75.974, 62.147)	0.137
Quartile 3	45.547 (-14.641, 105.735)		28.790 (-43.043, 100.622)		45.632 (-34.179, 125.443)	
Quartile 4 (most green)	51.871 (-10.076, 113.818)		41.439 (-32.557, 115.436)		47.796 (-34.672, 130.265)	
Observed OTUs	**Model 1**		**Model 2**		**Model 3**	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	-3.962 (-16.576, 8.651)	**0.011****	-3.022 (-18.036, 11.992)	0.083	4.676 (-11.238, 20.589)	0.064
Quartile 3	9.344 (-4.441, 23.129)		5.452 (-11.118, 22.022)		13.054 (-4.688, 30.797)	
Quartile 4 (most green)	14.414 (0.611, 28.217)*		12.450 (-4.326, 29.226)		15.303 (-2.805, 33.411)	

Supplementary Table 15. Model summary of generalised estimating equation estimates (GEEs) with diversity indices as outcomes with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for a 5km buffer.Model 1: 1920 participants, unadjusted; model 2: 1401 participants, adjusted for age, sex, and index of multiple deprivation (IMD); model 3: 1201 participants, adjusted for the same potential confounders as model 2, as well as BMI, antibiotic use (yes/no), and Healthy Eating Index (HEI).

Shannon index	**Model 1 (n=1920)**	**p trend**	**Model 2 (n=1401)**	**p trend**	**Model 3 (n=1201)**	**p trend**
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	0.047 (-0.052, 0.145)	0.223	-0.004 (-0.122, 0.114)	0.319	0.019 (-0.107, 0.145)	0.107
Quartile 3	0.102 (0.005, 0.198)		0.005 (-0.113, 0.124)		0.059 (-0.064, 0.182)	
Quartile 4 (most green)	0.046 (-0.054, 0.146)		0.060 (-0.060, 0.180)		0.094 (-0.031, 0.219)	

Simpson index	**Model 1**		**Model 2**		**Model 3**	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	0.006 (-0.003, 0.015)	0.286	0.003 (-0.007, 0.013)	0.329	0.003 (-0.008, 0.013)	0.162
Quartile 3	0.010 (0.002, 0.019)*		0.005 (-0.004, 0.014)		0.007 (-0.003, 0.016)	
Quartile 4 (most green)	0.004 (-0.005, 0.013)		0.005 (-0.006, 0.015)		0.006 (-0.004, 0.016)	

Chao1 index	**Model 1**		**Model 2**		**Model 3**	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	59.526 (6.960, 112.092)*	0.123	52.618 (-8.930, 114.167)	0.115	81.537 (12.571, 150.503)*	0.141
Quartile 3	41.280 (-13.835, 96.394)		23.343 (-41.682, 88.368)		39.713 (-31.925, 111.352)	
Quartile 4 (most green)	54.005 (-1.450, 109.459)		67.596 (0.745, 134.447)*		74.523 (0.611, 148.434)*	

Observed OTUs	**Model 1**		**Model 2**		**Model 3**	
Greenspace quartiles						
Quartile 1 (least green)	Reference					
Quartile 2	9.383 (-3.396, 22.162)	0.085	4.343 (-10.498, 19.183)	0.202	10.526 (-5.399, 26.451)	0.134
Quartile 3	10.871 (-2.012, 23.755)		-0.600 (-15.892, 14.693)		6.496 (-9.534, 22.526)	
Quartile 4 (most green)	11.741 (-1.182, 24.664)		12.416 (-3.176, 28.008)		14.787 (-1.915, 31.488)	

Chapter 4: Can hs-CRP explain the associations between neighbourhood greenspace exposure and health? The EPIC Norfolk study

Preamble

The results presented in Chapter 3 did not suggest an association between quartiles of neighbourhood greenspace and gut microbial diversity, raising the possibility that gut microbial diversity does not play a role in the underlying mechanism between greenspace exposure and health. However, Chapter 2, found that increased greenspace exposure was associated with decreased incidence of inflammatory diseases including type 2 diabetes and cardiovascular disease. It may therefore be that inflammation plays a role in the mechanisms underlying this relationship, but through a pathway other than microbial diversity.

There are a number of alternatie pathways through which greenspace may influence inflammation. Firstly, greenspace has been found to be beneficial in the reduction of both physiological and psychological symptoms of stress[141 210 235 249]. States of physiological and psychological stress have also been associated with poorly regulated inflammatory responses[310 311], and so stress is one possible pathway. A second potential pathway may be volatile essential oild released by plants and trees, called phytoncides, which have been found to have anti-inflammatory properties in both animal[312] and human studies[127 313]. However it is not clear what level of exposure would be required for phytoncides to have an anti-inflammatory relationship, i.e. is airborne exposure enough, or would physical contact with phytoncide-emitting plants be necessary. Thirdly, as presented at the beginning of the thesis, greenspace has been shown to reduce air pollution, consisting of ozone and particulate matter (PM)[43]. PM has previously been associated with increased blood markers of inflammation[314], suggesting another potential pathway.

Chapter 4 aims to further examine if inflammation plays a role in the mechanisms underlying the relationship between greenspace and health. This chapter does so by investigating whether neighbourhood greenspace is associated with a common marker of inflammation, C-reactive protein, in the EPIC Norfolk dataset.

Abstract

This study investigates a potential mechanism underlying the relationship between exposure to natural environments and health by examining whether there is an association between neighbourhood greenspace and inflammation in a large population cohort. Data from the third health check (2004-2011) of the European Prospective Investigation into Cancer Norfolk Cohort (EPIC) was used. The percentage of greenspace in each participants home neighbourhood was obtained from a land cover map (2007), biomedical variables were measured, and anthropometric measures were extracted from a health and lifestyle questionnaire. Data was used from 5,098 participants with a mean age of 69.5 years (SD: 7.9) of which 56.6% were female. Associations between neighbourhood greenspace and level of hs-CRP were estimated using univariate regression both with and without adjustment for potential confounders. No statistically significant association between greenspace and hs-CRP was found both before and after adjustment. The findings suggest that inflammatory processes do not mediate previously observed associations between the greenness of residential neighbourhoods and the health of their residents.

4.1. Introduction

There is a growing body of evidence documenting the health benefits of greenspace. These include reduced mortality rates[1-3], improved cardiovascular outcomes[1 4 5], birth outcomes[6-8], and reduced incidence of diabetes[9-11] as well as improvements in self-reported health[12-14]. Additionally, there is evidence to suggest that physical activity in a greenspace is more salutogenic than indoor environments[13 15]. Yet despite the large number of studies examining the relationships between health and greenspace, there is a paucity of evidence investigating the underlying mechanisms.

Conceptual frameworks have suggested that accessible greenspaces may promote health via the physical activity opportunities they present. However, Lachowycz and Jones found that a previously observed association between greenspace exposure and reduced mortality in England did not appear explained by physical activity[16]. Further, the reduced risk of screen-detected type II diabetes observed by Dalton et al. [10] appeared not to be mediated by physical activity. If physical activity does not explain associations between greenspace and health, alternative mechanisms need considering.

According to the 2011 United Nations World Urbanisation Prospects, by 2050, 67% of the world's population will live in urban areas[17]. Urbanisation may be detrimental to health for several reasons, including overcrowding, increased pollution, social deprivation, and psychological stress[18]. Further, urbanisation has been associated with increased prevalence of inflammatory disease including diabetes, hypertension, cardiovascular disease, and asthma[18]. One implication of increasing urbanisation may be reduced exposure to greenspace and associated soil microbiota[19]. This is potentially important because evidence exists that exposure to microbiota may be important for regulation of inflammatory responses[20 21]. For example, those living close to agricultural land have been found to have higher diversity of proteobacteria in their skin microbiota and a lower prevalence of atopic sensitization[20]. Greenspaces may therefore be an important source of environmental microbiota exposure, and in turn immune regulation associated with exposure to microbial diversity may form part of the underlying salutogenic mechanism for the relationship between greenspace and health. Given that chronic inflammation is a characteristic of impaired immune response[64], it could be that those exposed to less greenspace are more prone to chronic inflammation, manifesting as higher levels of inflammatory biomarkers[65].

C-reactive protein (CRP) is a central component of innate immune defences, and the measurement high sensitivity CRP (hs-CRP) has emerged as an important biomarker of

chronic inflammation and cardiovascular disease risk[22]. Inflammation is a key part of the immune response, the markers of which are associated with atherosclerotic disease processes[23 24]. Products of the inflammatory response to injury further make up the constituents of the atherosclerotic plaque[23 25]. Failing immunoregulation and poorly regulated inflammatory responses can often manifest as chronically-raised CRP and proinflammatory cytokines[22]. Two previous studies have investigated the association between CRP and exposure to a forest environment[181 118]. One of these[118] found a slight significant decrease in CRP with forest exposure. However, both studies had very small sample sizes of 19[181] and 20[118] participants.

This study investigates the relationship between greenspace and inflammation using data from the European Prospective Investigation Into Cancer (EPIC) Norfolk cohort, a well-characterised population, using objective measurements of neighbourhood greenspace and hs-CRP measured in blood samples. It is hypothesised that a greater amount of greenspace in the residential neighbourhood of participants is associated with lower levels of inflammation, manifesting as reduced hs-CRP.

4.2. Methods

4.2.1. Study population

This study uses data from the European Prospective Investigation of cancer (EPIC) Norfolk. Participants were recruited for the EPIC-Norfolk study[28] between 1993 and 1997 when men and women aged between 40-79 years were identified from 35 primary care centres in Norfolk. Norfolk is a county in East Anglia, England. The largely rural county covers an area of 5,370km and has a population of approximately 860,000 individuals[29]. Data on a broad range of health and lifestyle factors were obtained through baseline and follow-up questionnaires, together with blood tests and primary measurements. Follow-up is ongoing. This study uses data obtained from the 8,623 participants who took part in the 3rd EPIC data collection ("health check") which ran from 2004 until the end of 2011. Data from the 3rd health check was used due to the measurement of high-sensitivity C-reactive protein.

4.2.2. High sensitivity C-reactive protein measurement

The CDC/AHA scientific statement for markers of inflammation and inflammatory disease has stated that high-sensitivity CRP (hs-CRP) assay is at present the best measurement of inflammation[30]. Unlike a standard CRP assay, hs-CRP assay has detection limits of lower than 10µg/dl. This is beneficial when measuring levels of chronic or low inflammation as opposed to acute inflammation where CRP levels are generally higher[31]. In this study, neighbourhood greenspace constitutes a chronic exposure, and therefore the outcome was chosen to reflect this. hs-CRP measurement was obtained from a blood sample taken during the third health check, with a reference range of 0-6mg/L. There is evidence from the EPIC Norfolk study associating serum CRP levels with cardiovascular mortality and all-cause mortality[32], as well as potential associations with type 2 diabetes[33] and fracture risk[34], with one analysis finding high levels of CRP to be a strong predictor of coronary artery disease incidence and mortality[35].

4.2.3. Greenspace measurement

The main exposure was the percentage of greenspace in the participants' home neighbourhood based on their residential location at the time of the 3rd Health Check. A geographic information system (GIS), ArcGIS 10.3[36] was used to delineate neighbourhood boundaries around the postcodes (zip codes) of each participant based on postcode locations extracted from the UK Ordnance Survey Code-Point database[37]. In previous studies[9 10], neighbourhoods were delineated using road network buffers of 800m (an approximate 10 minute walk) from each home postcode location[38]. Recent research

however suggests that this may be overly conservative as people will typically travel much further distances on foot from home to access resources[39] and 3 neighbourhood boundaries were therefore derived: 800m, 3km, and 5km. Greenspace within the 3km measurement was chosen at the primary exposure measure, with the 800m and 5km buffers considered in sensitivity analyses.

Estimates of greenspace per 25m by 25m cell across the study area were computed from the Centre for Ecology and Hydrology Land Cover Map of the UK (2007)[40], derived from satellite images, digital cartography, and recording dominant land use types based on a 23 class typology. Cells containing the categories of broadleaved and coniferous woodland, arable, improved grassland, semi-natural grassland, mountain, heath, bog and freshwater were classed as greenspace for the purpose of this analysis. Each participant's exposure was computed by overlaying the mapped greenspace with the neighbourhood boundaries in the GIS to calculate the percentage of each neighbourhood area that contained these land cover types.

4.2.4. Potential confounders and moderators

Characteristics collected using the baseline Health and Lifestyle Questionnaire were chosen for this analysis based on empirical evidence and theoretical relevance of associations with CRP level and greenspace. They included self-reported information on age, sex, smoking status, employment, physical activity level, dog ownership and walking, and weekly alcohol consumption, as well as data on number of comorbidities and measurement of waist-hip ratio. The comorbidities variable was derived from the number of comorbidities a participant disclosed on the Health and Lifestyle Questionnaire and ranged from 0 to 23, including myocardial infarction, hypertension, cancer, diabetes and Parkinson's Disease.

The relationship between greenspace and CRP may be confounded by socio-economic status (SES), due its associations with neighbourhood greenspace[41]. Analyses were therefore adjusted for SES at the individual level using employment-derived social class. Employment at the time of the questionnaire was classed as professional/managerial, skilled manual/non-manual, and semi/unskilled unless participants were retired, in which case their last employment was used. Social class for women was determined from their partner's occupation. Ethnicity was not included in these analyses as 99.3% of the sample were white British.

4.2.5. Statistical analysis

Participants were classified into quartiles based on percentage of greenspace within their neighbourhood. This was done by ranking participants in order of percentage neighbourhood greenspace and then splitting into quartiles with approximately equal numbers of participants. The association between neighbourhood greenspace and hs-CRP level was estimated using two statistical methods. First, linear models were constructed to investigate the relationship between quartiles of neighbourhood greenspace and hs-CRP as a continuous measure. The continuous hs-CRP measure was not normally distributed and so was log transformed prior to fitting the models. Discussions with the EPIC Norfolk data collection team revealed that very low levels of hs-CRP had been coded as 0. As a result, a second, binary outcome variable, which was not affected by rounding down of low hs-CRP levels, was created for sensitivity analysis which identified individuals as having a hs-CRP level within or above 0-6mg/L, the reference range. Binary logistic regression models were constructed to test for associations with this measure.

Both types of model were fitted with and without adjusting for potential confounders. Three models were fitted for both the linear binary regression investigating the binary within/above hs-CRP reference range. Model 1 contained only the exposure, quartiles of neighbourhood greenspace. Model 2 was additionally adjusted for age, sex, smoking status and social class by occupation, and model 3 was further adjusted for weekly alcohol consumption, number of comorbidities, amount of physical activity, and waist-hip ratio. Sensitivity analysis involved repeating analyses for the 800m and 5km neighbourhood buffer sizes. Tests for linear trend were performed by fitting greenspace quartiles as a continuous variable. Tests for linear trend were also conducted for quartiles of waist-hip ratio and physical activity. p Values <0.05 were treated as statistically significant. All analyses were performed in SPSS 22.

4.3. Results

4.3.1. Sample characteristics

Of the 8,623 participants who took part in the third health check, we excluded 2,327 (27.0%) who did not have a valid postcode that allowed their residential location to be determined, leaving 6,296 participants. A further 991 participants (11.5%) did not have data on hs-CRP recorded, and 207 participants did not have data on alcohol consumption, so were excluded from this study. Participant characteristics can be found in Table 16. A total of 5,098 participants were included in the analysis, with a mean age of 69.5 years (SD 7.9). 88.9% of the total sample had a hs-CRP level that was within the reference range of 0-6mg/L and the mean hs-CRP level was 3.41mg/L (SD 5.5). The mean percentage of neighbourhood greenspace ranged from 50.2% in the 800m buffer, 68.5% in the 3km buffer, and 75% in the largest buffer of 5km. There were no statistically significant differences between characteristics of excluded and included participants (differences not presented). Participant characteristics for participants in the highest and lowest greenspace quartiles can also be found in Table 17.

Table 16. Participant study characteristics by sex and for the entire sample combined for the third health check (3HC)

Variable	Men	Women	All
n	2217	2881	5098
Age (years)	70.5 (7.9)	68.7 (7.8)	69.5 (7.9)
hs-CRP (mg/L)	3.52 (6.6)	3.34 (4.5)	3.41 (5.5)
% within hs-CRP reference range: 0-6mg/L	89.6%	88.4%	88.9%
Social class by occupation*			
Professional/manager	53.2%	48.0%	50.3%
Skilled manual/non-manual	34.4%	38.5%	26.7%
Semi-skilled/unskilled	12.4%	13.5%	13.0%
Waist-hip ratio	0.954 (0.06)	0.849 (0.07)	0.894 (0.08)
% Current smokers	3.0%	4.0%	3.6%
% Former smokers	58.9%	35.8%	45.8%
% white British	99.2%	99.4%	99.3%
Self-reported comorbidities			
Heart attack	5.4%	2.1%	3.5%
Stroke	3.4%	1.5%	2.3%
Type II Diabetes	3.8%	2.2%	2.9%
Cancer	8.1%	11.2%	9.8%
Self-report of at least 1 of heart attack/stroke/diabetes/cancer	17.5%	15.6%	16.4%
% greenspace			
800m buffer	50.28%	50.23%	50.25%
3km buffer	68.42%	68.58%	68.51%
5km buffer	74.95%	75.06%	75.01%
Physical activity (Total PAEE met-hrs/week)	104.37 (63.5)	110.61 (52.9)	107.90 (57.8)
Mean weekly alcohol consumption (units)	8.23 (9.6)	4.18 (5.8)	5.94 (8.0)

Data are mean (SD) or percentage. Missing data: 991 hs-CRP, 207 alcohol, 76 smoking, 49 social class, 13 physical activity, 13 waist-hip ratio, 9 dog walking
*Last occupation used if participant was retired at time of survey

4.3.2. Neighbourhood greenspace and C-reactive protein

Table 18 presents the linear regression model parameter estimates with hs-CRP as outcome in relation to quartiles of neighbourhood greenspace. Estimates were for the 5,098 included participants using a 3km buffer around their home postcode. Hs-CRP was associated with age, sex, social class by occupation, number of self-reported diseases, waist-hip ratio quartile and physical activity quartile, as can be seen in Models 2 and 3 (Table 18). No association was found between neighbourhood greenspace and hs-CRP either before or after adjustment for potential confounders. Sensitivity analyses for different buffer sizes (800m and 5km) did not produce results differing substantially from the 3km buffer results. These can be found in the Supplementary Tables 20 and 21 in section 4.5.

Table 19 provides the model summaries of the odds of being within (less than 1) or above (more than 1) the reference range for hs-CRP (6mg/L) as outcome resulting from the

logistics regression model. The odds of being within the reference range for hs-CRP did not differ according to quartile of greenspace exposure. Sensitivity analysis results for different buffer sizes (800m and 5km) did not differ substantially from the results for the 3km buffer. Results for the 800m and 5km buffers can be found in the Supplementary Tables 22 and 23 in section 4.5.

Table 17. Participant study characteristics for participants in the highest and lowest greenspace quartiles for the 3km buffer

Variable	Highest quartile	Lowest quartile
n	1574	1573
Age (years)	68.4	68.9
Female	58.6%	45.8%
hs-CRP (mg/L)	3.326	3.554
% greenspace	96.8%	32.4%
Waist-hip ratio	0.896	0.890
Social class by occupation		
Professional/manager	48.6%	48.6%
Skilled manual/non-manual	37.0%	36.8%
Semi-skilled/unskilled	14.4%	14.6%

Data are mean values or percentage prevalence.

Table 18. Model summary table of linear regression parameter estimates with loge high sensitivity C-reactive protein (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in 5,098 participants for a 3km buffer. Model 1: unadjusted; model 2: adjusted for age, sex, smoking and socioeconomic class; model 3: adjusted for age, sex, smoking, alcohol consumption (units/week), number of self-reported diseases, socioeconomic class, waist-hip ratio and physical activity (Total PAEE Met-hrs/week).*

	Model 1	p trend	**Model 2**	p trend	**Model 3**	p trend
Greenspace quartiles						
Quartile 4 (most green)			Reference			
Quartile 3	0.002 (-0.054, 0.059)	0.205	-0.018 (-0.074, 0.039)	0.488	-0.018 (-0.074, 0.039)	0.321
Quartile 2	0.030 (-0.027, 0.087)		0.003 (-0.060, 0.054)		-0.001 (-0.059, 0.056)	
Quartile 1 (least green)	0.030 (-0.027, 0.087)		0.015 (-0.041, 0.07)		0.024 (-0.033, 0.080)	
Age (years)	-		**0.012 (0.009, 0.014)*** **		**0.006 (0.003, 0.009)*** **	
Male sex	-		**-0.067 (-0.109, -0.025)** **		**-0.228 (-0.285, -0.171)*** **	
Smoking status						
Never smoked			Reference			
Former smoker	-		**0.071 (0.029, 0.113)** **		**0.049 (0.006, 0.092)* **	
Current smoker	-		**0.248 (0.138, 0.358)*** **		**0.198 (0.087, 0.309)*** **	
Social class by occupation						
SC=3 Semi/unskilled			Reference			
SC=2 Skilled M/NM	-		-0.031 (-0.096, 0.034)		-0.029 (-0.094, 0.037)	
SC= 1 Prof/manager	-		**-0.106 (-0.168, -0.043)** **		**-0.104 (-0.168, -0.040)** **	
Waist-hip ratio						
Quartile 4 (largest)			Reference			
Quartile 3	-		-		**-0.159 (-0.218, -0.101)*** **	**<0.001**
Quartile 2	-		-		**-0.258 (-0.326, -0.190)*** **	
Quartile 1 (smallest)	-		-		**-0.389 (-0.464, -0.314)*** **	
Physical activity (PAEE)						
Quartile 4 (least)			Reference			
Quartile 3	-		-		**-0.072 (-0.130, -0.014)* **	**0.001**
Quartile 2	-		-		-0.056 (-0.116, 0.005)	
Quartile 1 (most)	-		-		**-0.121 (-0.183, -0.058)*** **	
Alcohol (units/week)	-		-		-0.002 (-0.005, 0.000)	
Number of self-reported diseases	-		-		**0.014 (0.006, 0.021)*** **	

*p<0.05; **p<0.01; ***p<0.001.

Table 19. Model summary table of binary regression odds ratios for within (less than 1) or above (more than 1) the reference range (6mg/L) high sensitivity C-reactive protein as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in 5,098 participants for a 3km buffer. Model 1: unadjusted; model 2: adjusted for age, sex, smoking and socioeconomic class; model 3: adjusted for age, sex, smoking, alcohol consumption (units/week), number of self-reported diseases, socioeconomic class, waist-hip ratio and physical activity (Total PAEE Met-hrs/week).*

	Model 1	p trend	**Model 2**	p trend	**Model 3**	p trend
Greenspace quartiles						
Quartile 4 (most green)			Reference			
Quartile 3	0.863 (0.674,1.104)	0.648	0.816 (0.635, 1.050)	0.858	0.812 (0.627, 1.053)	0.619
Quartile 2	1.025 (0.808, 1.300)		0.947 (0.740, 1.211)		0.970 (0.753, 1.249)	
Quartile 1 (least green)	1.004 (0.790, 1.104)		0.973 (0.762, 1.243)		1.007 (0.784, 1.295)	
Age (years)	-		**1.036 (1.025, 1.048)*** **		**1.020 (1.007, 1.033)** **	
Male sex	-		**0.825 (0.686, 0.992)***		**0.559 (0.437, 0.716)*** **	
Smoking status						
Never smoked			Reference			
Former smoker	-		**1.210 (1.004, 1.457)***		1.137 (0.937, 1.380)	
Current smoker	-		**2.017 (1.336, 3.045)** **		**1.716 (1.109, 2.655)***	
Social class by occupation						
SC=3 Semi/unskilled			Reference			
SC=2 Skilled M/NM	-		0.825 (0.634,1.074)		0.908 (0.688, 1.199)	
SC= 1 Prof/manager	-		0.909 (0.693, 1.191)		0.809 (0.615, 1.064)	
Waist-hip ratio						
Quartile 4 (largest)			Reference			
Quartile 3	-		-		**0.722 (0.562, 0.926)** **	**<0.001**
Quartile 2	-		-		**0.522 (0.390, 0.699*** **	
Quartile 1 (smallest)	-		-		**0.351 (0.252, 0.489)*** **	
Physical activity (PAEE)						
Quartile 4 (least)			Reference			
Quartile 3	-		-		0.845 (0.659, 1.082)	0.119
Quartile 2	-		-		0.943 (0.730, 1.219)	
Quartile 1 (most)	-		-		**0.748 (0.563, 0.992)***	
Alcohol (units/week)	-		-		0.992 (0.980, 1.004)	
Number of self-reported diseases	-		-		**1.059 (1.029, 1.090)*** **	

*p<0.05; **p<0.01; ***p<0.001. Dependent variable is below/above 6 mg/L hs-CRP.

4.4. Discussion

It was hypothesised that a greater amount of greenspace in the neighbourhood of members of the EPIC Norfolk cohort would be associated with lower levels of inflammation, manifesting as reduced hs-CRP levels. However, this large, cross-sectional study found no evidence of a relationship between neighbourhood greenspace exposure and hs-CRP. This was the case both before and after adjustment for a wide range of potentially confounding factors. This study therefore finds no evidence to suggest that chronic inflammation, as measured by hs-CRP, plays a role in the relationship between greenspace and health.

These findings differ to those of the only two previous studies found that measured CRP (as a secondary outcome) after short term exposure to either a forest or a city environment[43]. These studies, with just 19 and 20 male participants, investigated the predominantly Asian practice of "forest bathing" or shinrin-yoku, which means 'taking in the atmosphere of the forest'[43]. They found forest exposure to be associated with a non-significant decrease in both CRP and hs-CRP, in contrast to this study which found no association. The difference in findings between this study and those using forest bathing may in part be due to the substantially different methods employed in the forest bathing studies, in terms of the acute exposures captured, and the small sample sizes. Furthermore, neither forest bathing study adjusted for potential confounders, such as age, sex, smoking, and socioeconomic status, which may suggest that their results were due to the effect of confounding. It is also possible that the findings from the forest bathing studies may be explained by the short-term relaxation associated with their intervention of spending time in the forest, compared with the influence of living in a 'greener' neighbourhood over a longer period of time.

This study has several strengths. The author believes it to be the first study to examine the relationship between neighbourhood greenspace exposure and hs-CRP as a marker of inflammation in a large population. We used objective measures of greenspace and potential confounders, as well as a large sample size. An objective measurement of CRP was also used, with hs-CRP perceived to be the best available measurement of inflammation at present[30]. However sleep-loss[44 45], psychological stress[46], and physical activity[47] can all evoke a short-term change in CRP level, which may mask potential associations between CRP and greenspace. An objective measurement of neighbourhood greenspace exposure using detailed land cover data across three neighbourhood buffer sizes was used. However there was no available data on the actual greenspace use by participants. Indicators of greenspace quality such as well-maintained, absence of litter, and

good level of safety, have previously been associated with improved general and mental health, as well as fewer acute health-related complaints[48], but it was not possible to assess this.

There are a number of possible explanations for the findings of this study. Firstly, it could simply be the case that hs-CRP does not play a role in the mechanisms underlying the relationship between neighbourhood greenspace and health. Although several potential confounding variables were adjusted for, there is a possibility that some may have been overlooked although this is unlikely to be an explanation for the null findings here. This is also likely some measurement error in some of the variables used. For example, physical activity was adjusted for using a self-reported measure of MET hours per week. This self-reported measure of physical activity would not have been as accurate as an objective measurement, for example, accelerometer data. However, measurement error in confounding variables would likely increase the likelihood of a positive finding, and so is unlikely to be a significant problem here.

In the future, researchers should investigate greenspace exposure using more accurate measurements of greenspace use which would quantify how much time participants actually spend in greenspaces rather than simply the amount of greenspace within their neighbourhood. Such indicators could be generated using data from wearable devices, such as smartwatches, with geo-positioning functionality that could be worn by participants for a period of time. As well as informing the investigation of the relationship between greenspace use and level of inflammatory markers in the body, this data would also enable other hypothesized underlying mechanisms for the relationship between greenspace and health to be examined.

In conclusion, this study has found no association between neighbourhood greenspace exposure and hs-CRP in the EPIC Norfolk study. Neighbourhood greenspace has been reported to be beneficial for health, but the underlying mechanisms of this relationship are still unclear.

4.5. Supplementary Tables

The models in the supplementary tables were as follows:

Model 1: unadjusted
Model 2: adjusted for age, sex, smoking, and socioeconomic class
Model 3: adjusted for age, sex, smoking, alcohol consumption (units/week), number of self-reported diseases, socioeconomic class, waist-hip ratio and physical activity (Total PAEE Met-hrs/week).

Supplementary Table 20. Model summary table of linear regression parameter estimates with loge high sensitivity C-reactive protein (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in 5,098 participants for an **800m buffer**.*

	Model 1	p trend	**Model 2**	p trend	**Model 3**	p trend
Greenspace quartiles						
Quartile 4 (most green)			Reference			
Quartile 3	0.003 (-0.054, 0.059)	0.177	-0.017 (-0.073, 0.039)	0.488	-0.027 (-0.084, 0.029)	0.763
Quartile 2	0.076 (0.019, 0.133)		0.046 (-0.012, 0.103)		0.037 (-0.021, 0.095)	
Quartile 1 (least green)	0.017 (-0.040, 0.074)		-0.013 (-0.070, 0.044)		-0.012 (-0.070, 0.045)	
Age (years)	-		**0.12 (0.009, 0.014)*** **		**0.006 (0.003, 0.009)*** **	
Male sex	-		**-0.067 (-0.108, -0.025)** **		**-0.227 (-0.284, -0.171)*** **	
Smoking status						
Never smoked			Reference			
Former smoker	-		**0.071 (0.029, 0.113)** **		**0.049 (0.006, 0.092)***	
Current smoker	-		**0.247 (0.137, 0.357)*** **		**0.197 (0.087, 0.308)*** **	
Social class by occupation						
SC=3 Semi/unskilled			Reference			
SC=2 Skilled M/NM	-		-0.031 (-0.096, 0.034)		-0.029 (-0.094, 0.037)	
SC= 1 Prof/manager	-		**-0.105 (-0.168, -0.043)** **		**-0.104 (-0.168, -0.040)** **	
Waist-hip ratio						
Quartile 4 (largest)			Reference			
Quartile 3	-		-		**-0.160 (-0.219, -0.102)*** **	
Quartile 2	-		-		**-0.258 (-0.326, -0.190)*** **	
Quartile 1 (smallest)	-		-		**-0.390 (-0.464, -0.315)*** **	
Physical activity (PAEE)						
Quartile 4 (least)			Reference			
Quartile 3	-		-		**-0.072 (-0.130, -0.013)***	
Quartile 2	-		-		-0.056 (-0.116, 0.005)	
Quartile 1 (most)	-		-		**-0.117 (-0.180, -0.055)*** **	
Alcohol (units/week)	-		-		-0.002 (-0.005, 0.000)	
Number of self-reported diseases	-		-		**0.014 (0.006, 0.021)*** **	

*p<0.05; **p<0.01; ***p<0.001. Dependent variable is $\log_e$ hs-CRP.

Supplementary Table 21. Model summary table of linear regression parameter estimates with loge high sensitivity C-reactive protein (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in 5,098 participants for a 5km buffer.*

	Model 1	p trend	**Model 2**	p trend	**Model 3**	p trend
Greenspace quartiles						
Quartile 4 (most green)			Reference			
Quartile 3	0.043 (-0.014, 0.100)	0.076	0.024 (-0.033, 0.081)	0.278	0.025 (-0.032, 0.082)	0.143
Quartile 2	0.027 (-0.030, 0.083)		0.002 (-0.055, 0.058)		0.011 (-0.045, 0.067)	
Quartile 1 (least green)	**0.060 (0.003, 0.117)***		0.039 (-0.018, 0.096)		0.048 (-0.009, 0.105)	
Age (years)	-		**0.012 (0.009, 0.014)*****		**0.006 (0.004, 0.009)*****	
Male sex	-		**-0.067 (-0.109, -0.025)****		**-0.228 (-0.285, -0.171)*****	
Smoking status						
Never smoked			Reference			
Former smoker	-		**0.071 (0.029, 0.114)****		**0.049 (0.006, 0.092)****	
Current smoker	-		**0.246 (0.136, 0.356)*****		**0.196 (0.086, 0.307)*****	
Social class by occupation						
SC=3 Semi/unskilled			Reference			
SC=2 Skilled M/NM	-		-0.031 (-0.096, 0.034)		-0.029 (-0.095, 0.036)	
SC= 1 Prof/manager	-		**-0.104 (-0.167, -0.042)****		**-0.103 (-0.166, -0.039)****	
Waist-hip ratio						
Quartile 4 (largest)			Reference			
Quartile 3	-		-		**-0.160 (-0.218, -0.101)*****	**0.000**
Quartile 2	-		-		**-0.258 (-0.326, -0.190)*****	
Quartile 1 (smallest)	-		-		**-0.391 (-0.466, -0.316)*****	
Physical activity (PAEE)						
Quartile 4 (least)			Reference			
Quartile 3	-		-		**-0.070 (-0.129, -0.012)***	**0.001**
Quartile 2	-		-		-0.053 (-0.114, 0.007)	
Quartile 1 (most)	-		-		**-0.122 (-0.185, -0.060)*****	
Alcohol (units/week)	-		-		-0.002 (-0.005, 0.000)	
Number of self-reported diseases	-		-		**0.014 (0.006, 0.021)*****	

*p<0.05; **p<0.01; ***p<0.001. Dependent variable is $\log_e$ hs-CRP.

Supplementary Table 22. Model summary table of binary regression odds ratios for within (less than 1) or above (more than 1) the reference range (6mg/L) high sensitivity C-reactive protein as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in 5,098 participants for an **800m buffer**.*

	Model 1	p trend	**Model 2**	p trend	**Model 3**	p trend
Greenspace quartiles						
Quartile 4 (most green)			Reference			
Quartile 3	1.086 (0.850, 1.386)	0.421	1.051 (0.820, 1.348)	0.874	1.029 (0.797, 1.328)	0.983
Quartile 2	1.202 (0.942, 1.535)		1.099 (0.854, 1.415)		1.072 (0.827, 1.389)	
Quartile 1 (least green)	1.076 (0.839, 1.379)		1.008 (0.782, 1.299)		0.986 (0.759, 1.281)	
Age (years)	-		1.036 (1.024, 1.047)		**1.018 (1.005, 1.032)****	
Male sex	-		**0.827 (0.687, 0.994)***		**0.529 (0.415, 0.674)*****	
Smoking status						
Never smoked			Reference			
Former smoker	-		**1.216 (1.010, 1.465)***		1.131 (0.932, 1.373)	
Current smoker	-		**2.019 (1.338, 3.047)****		**1.639 (1.058, 2.540)***	
Social class by occupation						
SC=3 Semi/unskilled			Reference			
SC=2 Skilled M/NM	-		0.907 (0.692, 1.189)		0.915 (0.693, 1.210)	
SC= 1 Prof/manager	-		0.825 (0.633, 1.074)		0.816 (0.620, 1.075)	
Waist-hip ratio						
Quartile 4 (largest)			Reference			
Quartile 3	-		-		**0.722 (0.562, 0.926)****	**0.000**
Quartile 2	-		-		**0.523 (0.390, 0.700)*****	
Quartile 1 (smallest)	-		-		**0.351 (0.252, 0.489)*****	
Physical activity (PAEE)						
Quartile 4 (least)			Reference			
Quartile 3	-		-		1.323 (0.996, 1.756)	0.115
Quartile 2	-		-		1.120 (0.846, 1.482)	
Quartile 1 (most)	-		-		1.254 (0.953, 1.650)	
Alcohol (units/week)	-		-		0.992 (0.980, 1.005)	
Number of self-reported diseases	-		-		**1.059 (1.029, 1.090)*****	

*p<0.05; **p<0.01; ***p<0.001. Dependent variable is below/above 6 mg/L hs-CRP.

Supplementary Table 23. Model summary table of binary regression odds ratios for within (less than 1) or above (more than 1) the reference range (6mg/L) high sensitivity C-reactive protein as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in 5,098 participants for a **5km buffer.***

	Model 1	p trend	**Model 2**	p trend	**Model 3**	p trend
Greenspace quartiles						
Quartile 4 (most green)			Reference			
Quartile 3	0.918 (0.717, 1.176)	0.369	0.868 (0.673, 1.119)	0.592	0.855 (0.658, 1.112)	0.363
Quartile 2	0.969 (0.762, 1.232)		0.907 (0.708, 1.161)		0.955 (0.742, 1.229)	
Quartile 1 (least green)	1.105 (0.871, 1.403)		1.054 (0.826, 1.344)		1.087 (0.846, 1.397)	
Age (years)	-		**1.036 (1.025, 1.048)*** **		**1.020 (1.006, 1.033)** **	
Male sex	-		**0.826 (0.687, 0.993)***		**0.559 (0.437, 0.716)*** **	
Smoking status						
Never smoked			Reference			
Former smoker	-		**1.208 (1.003, 1.456)***		1.136 (0.936, 1.379)	
Current smoker	-		**2.004 (1.327, 3.026)** **		**1.710 (1.105, 2.646)***	
Social class by occupation						
SC=3 Semi/unskilled			Reference			
SC=2 Skilled M/NM	-		0.911 (0.695, 1.194)		0.910 (0.689, 1.202)	
SC= 1 Prof/manager	-		0.829 (0.637, 1.079)		0.812 (0.617, 1.068)	
Waist-hip ratio						
Quartile 4 (largest)			Reference			
Quartile 3	-		-		**0.732 (0.564, 0.928)***	**0.000**
Quartile 2	-		-		**0.519 (0.387, 0.695)*** **	
Quartile 1 (smallest)	-		-		**0.351 (0.252, 0.489)*** **	
Physical activity (PAEE)						
Quartile 4 (least)			Reference			
Quartile 3	-		-		**1.336 (1.007, 1.773)***	0.122
Quartile 2	-		-		1.134 (0.857, 1.500)	
Quartile 1 (most)	-		-		1.261 (0.958, 1.659)	
Alcohol (units/week)	-		-		0.992 (0.979, 1.004)	
Number of self-reported diseases	-		-		**1.060 (1.029, 1.091)*** **	

*p<0.05; **p<0.01; ***p<0.001. Dependent variable is below/above 6 mg/L hs-CRP.

Chapter 5: Can markers of inflammation explain the relationship between residential neighbourhood greenspace and health in a pooled cross-sectional study?

Preamble

Chapter 4 failed to detect an association between neighbourhood greenspace and CRP, a key marker of inflammation, raising the possibility that inflammation does not play a role in the relationship between greenspace and health. However, inflammation is a complex process, made up of different stages including proinflammatory, inflammatory, and anti-inflammatory. Chapter 4, investigated levels of CRP, a common biomarker from the general inflammatory stage, however this may have been too narrow an approach to take. Each of the stages of inflammation involves a range of diverse biomarkers, including proinflammatory cytokines such as TNF-α and resistin, inflammatory markers such as CRP, anti-inflammatory cytokines such as adiponectin, and IL-6 and prostaglandins, which play roles in both the propagation and reduction of inflammation. It may be the case that neighbourhood greenspace is associated with inflammation, but with an aspect of inflammation other than CRP alone. Chapter 5 aims to investigate this by investigating the relationship between neighbourhood greenspace and six markers of inflammation from the proinflammatory, inflammatory, and anti-inflammatory stages of the inflammatory process.

Abstract

Although there is much evidence to suggest that exposure to greenspace is beneficial for health, the underlying mechanisms for this relationship are not understood. This study investigates whether markers of inflammation (including hs-CRP, IL-6, adiponectin, TNF-alpha, prostaglandins, and resistin) might act as a mediating mechanism in the relationship between greenspace and health. Data was pooled from two diabetes screening studies conducted in Leicestershire, UK in 2004-2011. The percentage of greenspace in each participant's home neighbourhood was obtained from a Land Cover Map (2007). Health and lifestyle variables were collected at baseline using objective and subjective measures. Data from 1661 participants (Mean age: 61 years (SD: 9.2); 58.3% male) was included. Associations between neighbourhood greenspace and level of inflammatory markers were estimated using multivariate and univariate regression both with and without adjustment for

potential confounders. No significant associations were observed between greenspace and markers of inflammation. This evidence suggests that inflammatory markers appear not to play a role in the beneficial health impacts of exposure to greenspace.

5.1. Introduction

Greenspace exposure has consistently been linked to benefits across a diverse range of health outcomes. Numerous studies have found an association between increased neighbourhood greenspace and reduced risk of type 2 diabetes (T2DM) [114 133 138 151 194 223], cardiovascular disease[56 181 194 223], cardiovascular[88 144 171] and all-cause mortality[88 114 191 207 231], as well as significantly reduced blood pressure[129 140 141 159] and cholesterol[140 170]. Despite this growing body of evidence, the mechanisms underlying observed associations between greenspace and health are not well understood.

Conceptual frameworks have suggested that greenspaces are likely to promote health due to the physical activity opportunities they present[36]. However, analysis by Lachowycz and Jones found that a previously described association between greenspace and reduced mortality risk across English districts was not explained by population levels of physical activity[171]. Another study found an association between increasing amounts of neighbourhood greenspace and reduced risk of screen-detected T2DM[151], but the association appeared not to be mediated by physical activity levels. If physical activity does not explain the association between greenspace and health, alternative potential underlying mechanisms need to be considered.

One hypothesis proposed suggests use of green environments may increase exposure to a variety of micro-organisms, including microbiota, helminths and ecoparasites, which may be important for the regulation of immune and inflammatory responses[64]. Therefore exposure to greenspaces could potentially contribute to downregulation of inflammatory processes, thereby effecting a range of health outcomes. High levels of inflammation have been associated with increased risk of diseases including cardiovascular disease[315-317] and T2DM [69 318], indicating that lower levels of inflammation are more beneficial for health. Exposure to these micro-organisms has decreased with urbanisation[319], and in recent decades the prevalence of diseases associated with chronic inflammation such as hypertension, T2DM and obesity[316] have been rapidly increasing amongst urban populations[320 321]. Inflammation is a key part of the immune response, the markers of which are associated with atherosclerotic disease processes[322 323]. Products of the inflammatory response to injury further make up the constituents of the atherosclerotic plaque[317 322]. It

may therefore be that reduced disease risk amongst those with higher greenspace exposure is mediated by inflammation.

In order to examine how greenspace exposure is associated with inflammation, it is necessary to identify suitable measurable markers of inflammation that can be derived from blood samples. Proinflammatory cytokines are chemical messengers that are released during endothelial activation by immune cells to illicit an inflammatory response[316]. They include tumour necrosis factor alpha (TNF-alpha)[70] and resistin[68]. These cytokines can be an early indicator of an inflammatory response. TNF-α is secreted by macrophages, adipocytes and neurons in response to various pathological processes, and precedes the infiltration of inflammatory cells to the location of an injury[324]. Resistin is a marker of inflammation that is predictive of coronary atherosclerosis[325] due to its role in endothelial activation. Perhaps the most well-known and widely used marker of inflammation is C-reactive protein (CRP). CRP is a central component of innate immune defences and failing immunoregulation and poorly regulated inflammatory responses can often manifest as chronically-raised CRP and proinflammatory cytokines[316 71]. In subsequent stages of an inflammatory response, anti-inflammatory factors are released to attenuate and regulate inflammation thus preventing potential damage. This includes adiponectin, for which several clinical studies have demonstrated an inverse relationship with CRP levels[66 68]. Adiponectin has potent immune-suppressive properties, as it induces the production of anti-inflammatory mediators, as well as impairing production of pro-inflammatory cytokines[326]. Interleukin-6 (IL-6) is a cytokine and prostaglandins are a group of lipids, and both markers have been demonstrated to play roles in both the propagation and regulation of inflammation[327-329]. Inflammation is a complex process involving a number of acute phase proteins, complement factors, and cytokines[316], and so it may be useful to investigate the levels of a variety of proinflammatory and anti-inflammatory markers from different stages of inflammation when considering a potential relationship with neighbourhood greenspace.

The author found only two previous studies have investigated greenspace exposure and inflammation. These were intervention studies of 19 and 20 participants that compared short-term exposures to forest and urban environments and measured CRP as a secondary outcome after each exposure[118 181]. Both studies found exposure to a forest environment to be associated with a non-significant reduction in CRP.

This cross-sectional study will investigate if any association exists between neighbourhood greenspace exposure and levels of biological markers of inflammation using data from the "ADDITION" and "Walking Away from Diabetes" cohorts. The inflammatory markers of interest were high sensitivity C-reactive protein (hs-CRP), tumour necrosis factor alpha

(TNF-alpha), adiponectin, resistin, interleukin-6 (IL-6), and prostaglandin. It is hypothesised that an increase in participants' residential neighbourhood greenspace is associated with decreases in levels of inflammatory markers such as CRP, pro-inflammatory cytokines TNF-alpha and resistin, and an increase in anti-inflammatory adiponectin. It is further hypothesised that there will be an overall decrease in IL-6 and prostaglandins, which have both pro- and anti-inflammatory properties.

5.2. Methods

5.2.1. Study population

Data was derived from two T2DM screening trials conducted by the Leicester Diabetes Centre, UK, using identical standard operating procedures: ADDITION-Leicester (ClinicalTrials.gov registration number: NCT00318032) and Walking Away from Diabetes ('Walking Away': NCT00941954). Cross-sectional data from the screening stage of both trials was used. Full study descriptions are available elsewhere[330 331]. In short, ADDITION-Leicester was a population-based study to screen for T2DM. Individuals were selected at random from participating general practices in urban, suburban and rural Leicestershire, England who met the eligibility criteria (age 40-75 years (white Europeans) or 25-75 years (other ethnicities), and no T2DM diagnosis). Individuals in Walking Away were selected from participating general practices in Leicestershire and were between 18-74 years and at high risk (individuals at each practice scoring within the 90th percentile) of T2DM based on the Leicester Practice Risk Score. All participants gave written informed consent. Participants were excluded from the current analyses if their postcode (zip-code) was missing or invalid. If they took part in more than one of the trials, then their most recent record was kept. In both studies, participants attended a clinic at baseline where they completed questionnaires and underwent primary measurements.

5.2.2. Outcomes

Biomarker levels were derived from blood samples taken at the baseline data collection. Venous blood samples were obtained following an overnight fast, with individuals abstaining from caffeine and moderate/vigorous physical activity (MVPA) for 48 hours prior to the appointment. This included proinflammatory cytokines TNF-α and resistin, inflammatory marker CRP, and anti-inflammatory adiponectin. IL-6 and prostaglandins, which play roles in both the propagation and reduction of inflammation, were also included. High sensitivity C-reactive protein (hs-CRP) was measured as a more reliable indicator of chronic, low

grade inflammation than CRP, which is more susceptible to short term variations[332-336]. CRP was analysed using a high sensitivity (Minimum Interpretation Limit = 0.1mg/L) HORIBA ABX clinical chemistry analyser. IL-6 was analysed using quanitikine high-sentivity enzyme-linked immunosorbent assays (R&D systems). Adiponectin was quantified using a time-resolved fluorescence immunoassay (R&D systems antibodies) on the AutoDELFIA (Perkin Elmer Life Sciences). All ELISA and fluorescence immunoassays were conducted in replicate on the same sample and the average value obtained. The IL-6 assay was repeated if the concentration was >2pg/ml and the coefficient of variation >20% or the concentration was <2pg/ml and the coefficient of the variation >25%. Similarly, if the intra-assay coefficient exceeded 15% for adiponectin, the assay was repeated using the same technique.

5.2.3. Greenspace measurement

The main exposure was the percentage of greenspace in the participants' home neighbourhood based on their residential postcode (zip code) at the time of their baseline appointment. ArcGIS 10.3[288], a geographic information system (GIS), was used to delineate neighbourhood boundaries around the residence of each participant based on postcode locations extracted from the UK Ordnance Survey Code-Point database[289]. In previous studies[138 151], neighbourhoods were delineated using road network buffers of 800m (an approximate 10 minute walk) from each home postcode location[290]. Buffers of 800m (an approximate 10 minute walk) have previously been used[138 151 290], however recent research suggests that this may be overly conservative as to access resources people typically travel much further distances on foot from home[291]. Three neighbourhood boundaries were therefore derived: 800m, 3km, and 5km, with greenspace within the 3km measurement chosen as the primary exposure measure, with the 800m and 5km buffers considered in sensitivity analyses.

Estimates of greenspace were computed from the Centre for Ecology and Hydrology Land Cover Map of the UK[73] (2007), derived from satellite images and digital cartography, and records the dominant land use type, based on a 23 class typology, per 25m by 25m cell across the study area. Areas of broadleaved and coniferous woodland, arable, improved grassland, semi-natural grassland, mountain, heath, bog and freshwater were classed as greenspace. This is a commonly used dataset for investigating neighbourhood land use exposure [138 151]. Each participant's exposure was computed by overlaying the mapped greenspace with the neighbourhood boundaries in the GIS software to calculate the percentage of each neighbourhood area that contained these land cover types.

5.2.4. Covariates, potential confounders and moderators

Characteristics collected using the baseline questionnaire were chosen for this analysis based on empirical evidence and theoretical relevance of associations with level of inflammatory markers and neighbourhood greenspace. These included information on age, sex, smoking status, socioeconomic status (SES), ethnicity, glycated haemoglobin (HbA1c), body mass index (BMI), physical activity level, and medication use. Increasing age and female gender has been associated with chronic, low grade inflammation characterised by increasing levels of inflammatory markers and pro-inflammatory cytokines[315 337]. Cigarette smoking has also been found to induce chronic inflammation[338]. Ethnicity has been linked with various inflammatory markers including prostaglandins[339]. T2DM and obesity have both been associated with increasing inflammation[318], and physical activity can cause an acute increase in C-reactive protein, IL-6 and other inflammatory markers[336]. Therefore sex, smoking, ethnicity, BMI, HbA1c, and physical activity were treated as covariates and adjusted for. HbA1c was analysed using the Bio-Rad Variant II HPLC system (Bio-Rad Clinical Diagnostics, Hemel Hempstead, UK). Physical activity data was collected using the short form of the International Physical Activity Questionnaire (IPAQ). Information on medication, ethnicity, and smoking was obtained following an interview administered protocol conducted by a healthcare professional. The relationship between greenspace and inflammatory markers may be confounded by socio-economic status[340 341] due to the association between lower SES and higher levels of inflammation[69 316], and higher levels of neighbourhood greenspace being linked with higher levels of SES[88]. Therefore, SES was treated as a potential confounder and analyses were adjusted for SES at area level using the index of multiple deprivation (IMD)[301]. Various medications can influence inflammatory markers in opposing directions[342-346]. An a priori decision was also taken to test for moderation by fitting interaction terms for greenspace and HbA1c, physical activity and BMI.

5.2.5. Statistical analysis

Participants were divided into quartiles based on percentage of greenspace within their neighbourhood to ascertain any dose-response. This was done by ranking participants in order of percentage neighbourhood greenspace and then splitting into quartiles with approximately equal numbers of participants. The association between greenspace and level of each inflammatory marker was estimated using two statistical analysis methods. Firstly, multivariate regression (MR) was conducted to explore the patterning of response on three of the biomarkers: hs-CRP, adiponectin, and IL-6, as they were measured in both ADDITION and Walking Away trials. The author decided that Hotelling's Trace was the most

appropriate MR statistic to extract for the purpose of this analysis. Two biomarkers (resistin and prostaglandins) were only measured in ADDITION, and TNF-alpha was only measured in Walking Away. These biomarkers could not therefore be included in the pooled MR analysis due to the high proportion of missing data. Associations for these three biomarkers were therefore estimated separately using univariate linear regression models.

For both statistical analysis methods, three models were fitted both with and without adjusting for potential confounders. Model 1 was adjusted only for study i.e. ADDITION or Walking Away in MR analysis of hs-CRP, adiponectin and IL-6, and unadjusted in the separate linear regression estimates for resistin, prostaglandins, and TNF-alpha. Model 2 was additionally adjusted for the influence of covariates associated with inflammation level (age, sex, smoking status, ethnicity, and IMD) [315 341 347 348]. Model 3 was then adjusted for all variables in Model 2 plus biochemical and lifestyle factors (HbA1c, BMI, physical activity, and medication use) [317 344 345 349-352].. Adjustments in Models 2 and 3 were the same for both the MR analysis and separate linear regression estimates.

No inflammatory marker was normally distributed (all appearing positively skewed) and so all were log transformed prior to fitting the models. Sensitivity analysis involved repeating the analysis for each neighbourhood buffer size (800m, 3km, 5km). Tests for linear trend were performed by fitting the greenspace quartiles as a continuous variable. All analyses were two sided; with p-values <0.05 treated as statistically significant. P<0.1 was considered significant for interactions. Analysis was performed in SPSS V.22.

5.3. Results

5.3.1. Sample characteristics

Sample characteristics are presented in Table 24. A total of 1661 participants were included in this analysis, with a mean age of 61 years (SD 9.5), and 58.3% of the total sample were male. The 6 markers of inflammation were found to be highly correlated as anticipated. No statistically significant differences were observed between excluded and included participants. Characteristics for participants in the highest and lowest greenspace quartiles can be found in Table 25.

Table 24. Participant study characteristics by study and for the entire sample combined

Variable	ADDITION	Walking Away From Diabetes	All
n	987	674	1661
Age	59.64 (10.0)	63.06 (8.2)	61.03 (9.5)
Male	54.2	64.4	58.3
Area social deprivation score	21.12 (13.4)	19.78 (16.3)	20.57 (14.7)
BMI	29.4 (4.8)	32.49 (5.6)	30.73 (5.4)
Current smokers	31.8	9.05	22.1
Ethnicity:			
White British	68.5	89.3	77.4
South Asian	30.7	8.0	21.0
Other	0.9	2.7	1.6
Impaired glucose regulation	54.8	25.8	43.0
% greenspace			
800m buffer	25.1	37.8	30.3
3km buffer	41.4	51.3	45.5
5km buffer	49.5	56.6	52.4
Physical activity (total METs)	3195.1 (3574.8)	3470.6 (4002.0)	3317.0 (3770.8)
Markers of inflammation			
hs-CRP (mg/L)	4.13 (6.2)	3.32 (5.0)	3.8 (5.8)
Prostaglandins (ng/ml)	3.58 (32.0)	-	3.58 (32.0)
TNF-alpha (pg/ml)	1.81 (1.6)	-	1.81 (1.6)
Adiponectin (µg/dl)	16.63 (11.7)	12.94 (6.7)	15.15 (10.2)
Resistin (ng/ml)	5.41 (2.4)	-	5.41 (2.4)
IL-6 (pg/ml)	2.66 (2.1)	2.41 (1.5)	2.56 (1.9)

Data are mean (SD) or percentage
Impaired glucose regulation: T2DM or prediabetes at baseline
Missing data: 78 BMI, 81 smoking, 80 ethnicity, 20 area social deprivation score, 4 impaired glucose regulation

5.3.2. Neighbourhood greenspace and markers of inflammation

Table 26 presents the MR analysis results as standardised regression coefficients with hs-CRP, IL-6 and adiponectin as outcomes in relation to quartiles of neighbourhood greenspace. Estimates were for the 1,596 participants in Model 1, 1,513 participants in Model 2, and 1,246 participants in Model 3 using a 3km neighbourhood buffer around home postcodes. The Hotelling's Trace results for Models 1, 2, and 3 for the 3km buffer were p=0.198, p=0.375, and p=2.84, respectively, showing no evidence of an association

between neighbourhood greenspace exposure and hs-CRP, IL-6, and adiponectin. In Model 1, adiponectin level was elevated for the two highest greenspace quartiles, with evidence of a dose response and statistically significant linear trend (p=0.015). However, statistical significance was lost after adjustment for covariates and potential confounders in Models 2 and 3. No associations, either before or after adjustment, were found for levels of hs-CRP and IL-6 in relation to quartiles of neighbourhood greenspace.

Table 27 presents the univariate linear regression estimates with prostaglandins, TNF-alpha, and resistin as outcomes in relation to quartiles of neighbourhood greenspace. Estimates were for the 957 participants in Model 1, 875 participants in Model 2, and 707 participants in Model 3 using a 3km neighbourhood buffer around their home postcode. In Model 1, level of prostaglandins were elevated for the highest two quartiles of greenspace with a statistically significant linear trend (p<0.001). However, there was no dose-response trend after adjustment in Models 2 and 3. Levels of TNF-alpha and resistin were statistically significantly reduced in the highest quartile of greenspace, with statistically significant linear trends, but again these were attenuated after adjustment.

Tests for moderation (not presented) by HbA1c, physical activity and BMI gave no statistically significant results. Findings for sensitivity analysis results using different buffer sizes (800m and 5km) were consistent with the results for the 3km buffer and can be found in Supplementary Tables 28-31, in section 5.5.

Table 25. Participant study characteristics for participants in the highest and lowest greenspace quartiles for the 3km buffer

Variable	Highest quartile	Lowest quartile
n	408	396
Age (years)	63.5	58.2
Female	39.5%	46.5%
% greenspace	79.1%	17.4%
BMI (kg/m2)	31.3	30.7
Index of Multiple Deprivation	10.28	31.16
Markers of inflammation (mg/L)		
Hs-CRP	3.66	4.01
IL-6	2.48	2.59
TNF-alpha	1.69	1.84
Resistin	4.98	5.37
Adiponectin	14.73	15.14
Prostaglandin	8.57	2.24

Data are mean values or percentage prevalence.

Supplementary Table 26. Model summary table of multivariate regression parameter estimates with loge hs-CRP (mg/L), loge IL-6 (mg/L), loge adiponectin (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for a 3km buffer. Results presented as standardised regression coefficients.*

Hs-CRP	**Model 1 (n=1,596)**	**p trend**	**Model 2 (n=1,513)**	**p trend**	**Model 3 (n=1,246)**	**P trend**
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.112 (-0.088, 0.312)	0.575	**0.215 (0.007, 0.422)***	0.102	0.213 (-0.003, 0.430)	0.489
Quartile 3	-0.021 (-0.222, 0.179)		0.138 (-0.087, 0.363)		0.077 (-0.151, 0.305)	
Quartile 4 (most green)	-0.016 (-0.222, 0.189)		**0.252 (0.003, 0.500)***		0.138 (-0.112, 0.388)	
Study = Addition	**0.251 (0.103, 0.398)****		**0.248 (0.087, 0.410)****		**0.548 (0.372, 0.724)*****	
	-					
Interleukin 6	**Model 1 (n=1,596)**		**Model 2 (n=1,513)**		**Model 3 (n=1,246)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.064 (-0.034, 0.097)	0.386	0.086 (-0.007, 0.179)	0.482	0.085 (-0.015, 0.184)	0.806
Quartile 3	-0.035 (-0.124, 0.054)		0.024 (-0.077, 0.126)		-0.017 (-0.122, 0.088)	
Quartile 4 (most green)	-0.008 (-0.099, 0.083)		0.061 (-0.051, 0.173)		0.021 (-0.094, 0.136)	
Study = Addition	0.031 (-0.034, 0.097)		0.022 (-0.051, 0.094)		**0.133 (0.052, 0.214)****	
Adiponectin	**Model 1 (n=1,596)**		**Model 2 (n=1,513)**		**Model 3 (n=1,246)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.056 (-0.027, 0.140)	**0.015***	-0.007 (-0.083, 0.070)	0.115	-0.013 (-0.094, 0.068)	0.092
Quartile 3	**0.099 (0.015, 0.183)***		-0.019 (-0.102, 0.064)		-0.011 (-0.096, 0.075)	
Quartile 4 (most green)	**0.095 (0.009, 0.181)***		-0.070 (-0.162, 0.021)		-0.080 (-0.174, 0.014)	
Study = Addition	**0.189 (0.128, 0.251)*****		**0.244 (0.184, 0.304)*****		**0.193 (0.127, 0.259)*****	

Model 1: adjusted only for study; Model 2: adjusted for study, age, sex, smoking, socioeconomic class and ethnicity; Model 3: adjusted for the same confounders as Model 2 as well as HbA1c, BMI, physical activity (Total PAEE Met-hrs/week), and medication use. Number of participants as stated.

Table 27. Model summary table of univariate linear regression parameter estimates with loge prostaglandins (mg/L), loge TNF alpha (mg/L), loge resistin (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for a 3km buffer.*

Prostaglandins	**Model 1 (n=957)**	**p trend**	**Model 2 (n=875)**	**p trend**	**Model 3 (n=707)**	**p trend**
Constant	**0.559 (0.478, 0.641)*** **		**0.851 (0.471, 1.231)*** **		**1.443 (0.775, 2.111)*** **	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.039 (-0.087, 0.164)	**0.001****	0.010 (-0.123, 0.143)	0.670	-0.029 (-0.177, 0.120)	0.508
Quartile 3	**0.196 (0.077, 0.316)****		0.071 (-0.068, 0.211)		0.059 (-0.092, 0.209)	
Quartile 4 (most green)	**0.170 (0.035,0.305)***		0.007 (-0.159, 0.173)		0.035 (-0.141, 0.212)	
	-					
TNF Alpha	**Model 1 (n=957)**		**Model 2 (n=876)**		**Model 3 (n=709)**	
Constant	**0.234 (0.132, 0.335)*** **		**-0.367 (-0.725, -0.010)***		-0.434 (-1.068, 0.199)	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.038 (-0.079, 0.155)	**0.031***	0.080 (-0.044, 0.204)	0.544	0.009 (-0.131, 0.148)	0.254
Quartile 3	-0.007 (-0.119, 0.104)		0.064 (-0.067, 0.194)		0.027 (-0.115, 0.169)	
Quartile 4 (most green)	**-0.158 (-0.285, -0.031)***		-0.081 (-0.236, 0.075)		-0.132 (-0.299, 0.034)	
Resistin	**Model 1 (n=591)**		**Model 2 (n=523)**		**Model 3 (n=446)**	
Constant	**1.611 (1.553, 1.670)*** **		**1.654 (1.357, 1.950)*** **		**1.926 (1.340, 2.512)*** **	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.054 (-0.033, 0.142)	**0.036***	0.039 (-0.055, 0.132)	0.198	0.014 (0.093, 0.119)	0.126
Quartile 3	-0.011 (-0.098, 0.075)		-0.004 (-0.104, 0.096)		-0.015 (-0.123, 0.093)	
Quartile 4 (most green)	**-0.121 (-0.224, -0.018)***		-0.093 (-0.216, 0.030)		-0.119 (-0.251, 0.013)	

Model 1: adjusted only for study; Model 2: adjusted for study, age, sex, smoking, socioeconomic class and ethnicity; Model 3: adjusted for the same confounders as Model 2 as well as HbA1c, BMI, physical activity (Total PAEE Met-hrs/week), and medication use. Number of participants as stated.

5.4. Discussion

This large cross-sectional study aimed to investigate the relationship between quartiles of neighbourhood greenspace and six markers of inflammation. Markers of inflammation were found to have statistically significant associations with age, sex, IMD, ethnicity, HbA1c, BMI, physical activity and use of some medications (data not shown). Before adjustment, quartiles with a higher percentage of neighbourhood greenspace were significantly associated with increases in adiponectin and prostaglandins, and decreases in TNF-alpha and resistin. The increased adiponectin and decreased TNF-alpha and resistin were in keeping with our hypotheses, although the increase in prostaglandins was not. However, no statistically significant trends remained after adjustment for covariates and potential confounders.

The findings of this study are in contrast to the findings of two previous studies that investigated the relationship between exposure to a forest environment and a number of health outcomes including CRP[118 181]. They found non-significant reductions in the level of CRP in forest intervention groups, however the methods employed were very different to this study. The forest-based studies used a randomised controlled trial study design, with short-term greenspace and urban exposures, in comparison to our cross-sectional study investigating the chronic exposure of neighbourhood greenspace exposure. The forest studies also used sample sizes of 19 and 20 participants and did not adjust for potential confounders. This study found statistically significant raised adiponectin and prostaglandins, and reduced TNF-alpha and resistin amongst those exposed to the most greenspace, but these associations became did not persist after adjustment.

There are several possible explanations for the results of this study. Firstly, it may simply be the case that there is no relationship between neighbourhood greenspace and markers of inflammation, and that inflammation does not mediate the relationship between greenspace and health. Secondly, the null findings may be due to measurement error, which meant that we were unable to detect any association; inflammatory markers are highly susceptible to short term changes from environmental exposures[332] and individual behaviours[333-336] including physical activity, smoking, and certain medications. Furthermore, an objective measure of neighbourhood greenspace was used across 3 buffer sizes. A high percentage of accessible neighbourhood greenspace has been associated with increased greenspace use[41 353] but no information was available on actual use of greenspace and so could not therefore investigate the relationship between greenspace use and inflammatory markers. As the findings were not statistically significant, residual confounding is unlikely to be responsible for differences in findings.

This study has a number of strengths. To the authors' knowledge this the first study to examine the relationship between neighbourhood greenspace and established biomarkers of inflammation in a population at high risk of T2DM. The study used objective measures of both greenspace and the inflammatory markers, and a large, geographically, and multi-ethnic population sample. The diverse ethnic, socioeconomic, and geographical distribution of this population means that the findings of this study may be generalizable to other populations.

This study also has limitations. The cross-sectional design of this study means that causality could not have been determined from findings. The best available objective measurements of both exposures and outcomes were used, although they too had limitations. The study participants were from two T2DM screening trials, ADDITION-Leicester and Walking Away from Diabetes. Although measurements were taken prior to the implementation of any intervention, a high percentage of participants had impaired glucose regulation (either T2DM or prediabetes), with 54.8% in ADDITION and 25.8% in Walking Away (an average of 43% across the two trials). Currently 6% of the UK population have a diagnosis of T2DM[354]. T2DM has previously been linked with increased levels of inflammation, as well as endothelial dysfunction and atherosclerosis[318], and although HbA1c level was adjusted for, this may have limited our ability to detect associations with greenspace exposure. Certain limitations of this study highlight the broader challenges facing researchers in disentangling relationships that vary geographically and temporally. For example, although neighbourhood greenspace exposure was examined, it was not possible to consider actual use of greenspace. Furthermore, there are a range of factors in people's lives that can influence levels of inflammatory markers. Adjustments were possible for a range of demographic, biochemical and lifestyle factors, however they were not possible for other factors that have been shown to evoke short term changes in inflammation including acute illness[355], air pollution[332], sleep loss[333 334], and psychological stress[335].

If inflammatory markers do not form part of the underlying mechanism for the relationship between greenspace and health, further causative mechanisms should be hypothesised and investigated. The creation of datasets objectively measuring actual greenspace use across a large population should be a priority for researchers, enabling spatial and temporal variations in greenspace exposure to be considered. Studies using wearable tracking devices, including global positioning systems, or data from mobile telephones would enable researchers to more closely examine how people use their neighbourhood greenspace and may assist in determining the mechanisms underlying the relationship between greenspace and health.

In conclusion, this study has found no evidence of an association between neighbourhood greenspace exposure and markers of inflammation. These findings suggest that inflammation may not play a mediating role in the relationship between increasing greenspace exposure and improved health outcomes.

5.5. Supplementary tables

Supplementary Table 28. Model summary table of multivariate regression parameter estimates with loge hs-CRP (mg/L), loge IL-6 (mg/L), loge adiponectin (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for an **800m buffer**. Results presented as standardised regression coefficients.*

Hs-CRP	**Model 1 (n=1,596)**	**p trend**	**Model 2 (n=1,513)**	**p trend**	**Model 3 (n=1,246)**	**P trend**
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.043 (-0.320,0.406)	0.429	**0.265 (-0.381, 0.911)**	0.269	0.046 (-0.338, 0.430)	0.546
Quartile 3	-0.183 (-0.540, 0.174)		0.382 (-0.255, 1.019)		0.029 (-0.350, 0.408)	
Quartile 4 (most green)	-0.324 (-0.669, 0.021)		**0.542 (-0.103, 1.1187)**		-0.090 (-0.479, 0.300)	
Interleukin 6	**Model 1 (n=1,596)**		**Model 2 (n=1,513)**		**Model 3 (n=1,246)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	-0.001 (-0.163, 0.160)	0.587	0.123 (-0.169, 0.415)	0.569	0.037 (-0.118, 0.191)	0.486
Quartile 3	-0.090 (-0.249, 0.069)		0.096 (-0.192, 0.385)		0.024 (-0.129, 0.176)	
Quartile 4 (most green)	-0.114 (-0.267, 0.040)		0.182 (-0.110, 0.473)		-0.036 (-0.193, 0.121)	
Adiponectin	**Model 1 (n=1,596)**		**Model 2 (n=1,513)**		**Model 3 (n=1,246)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.009 (-0.142, 0.161)	0.103	0.233 (-0.003, 0.469)	0.406	0.065 (-0.061, 0.190)	0.843
Quartile 3	-0.005 (-0.155, 0.144)		0.127 (-0.106, 0.360)		0.043 (-0.081, 0.167)	
Quartile 4 (most green)	0.031 (-0.113, 0.175)		**0.262 (0.026, 0.498)***		0.035 (-0.093, 0.162)	

Model 1: adjusted only for study; Model 2: adjusted for study, age, sex, smoking, socioeconomic class and ethnicity; Model 3: adjusted for the same confounders as Model 2 as well as HbA1c, BMI, physical activity (Total PAEE Met-hrs/week), and medication use. Number of participants as stated.

Table 29. Model summary table of univariate linear regression parameter estimates with loge prostaglandins (mg/L), loge TNF alpha (mg/L), loge resistin (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for a **800m buffer**.*

Prostaglandins	**Model 1 (n=957)**	**p trend**	**Model 2 (n=875)**	**p trend**	**Model 3 (n=707)**	**p trend**
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	**0.367 (0.004, 0.730)***	**0.000**	-0.120 (-0.536, 0.296)	0.076	-0.036 (-0.332, 0.260)	**0.033**
Quartile 3	**0.407 (0.031, 0.783)***		0.117 (-0.323, 0.557)		0.266 (-0.031, 0.562)	
Quartile 4 (most green)	**0.863 (0.473, 1.253)*****		0.396 (-0.080, 0.872)		0.247 (-0.050, 0.544)	
	-					
TNF Alpha	**Model 1 (n=957)**		**Model 2 (n=876)**		**Model 3 (n=709)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.010 (-0.104, 0.123)	0.673	-0.044 (-0.440, 0.351)	0.393	0.057 (-0.227, 0.340)	0.070
Quartile 3	-0.050 (-0.166, 0.066)		-0.126 (-0.544, 0.293)		-0.046 (-0.327, 0.236)	
Quartile 4 (most green)	-0.004 (-0.127, 0.119)		-0.258 (-0.718, 0.201)		-0.020 (-0.305, 0.266)	
Resistin	**Model 1 (n=591)**		**Model 2 (n=523)**		**Model 3 (n=446)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.058 (-0.029, 0.145)	0.734	0.141 (-0.137, 0.419)	0.471	0.140 (-0.080, 0.360)	0.471
Quartile 3	-0.077 (-0.167, 0.013)		0.030 (-0.267, 0.326)		0.065 (-0.159, 0.289)	
Quartile 4 (most green)	0.033 (-0.064, 0.130)		-0.123 (-0.487, 0.241)		0.043 (-0.190, 0.276)	

Model 1: adjusted only for study; Model 2: adjusted for study, age, sex, smoking, socioeconomic class and ethnicity; Model 3: adjusted for the same confounders as Model 2 as well as HbA1c, BMI, physical activity (Total PAEE Met-hrs/week), and medication use. Number of participants as stated.

Supplementary Table 30. Model summary table of multivariate regression parameter estimates with loge hs-CRP (mg/L), loge IL-6 (mg/L), loge adiponectin (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for a **5km buffer.** Results presented as standardised regression coefficients.*

Hs-CRP	**Model 1 (n=957)**	**p trend**	**Model 2 (n=875)**	**p trend**	**Model 3 (n=707)**	**p trend**
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	-0.255 (-0.590, 0.080)	0.706	0.442 (-0.233, 1.116)	0.074	0.116 (-0.260, 0.492)	0.942
Quartile 3	-0.303 (-0.653, 0.047)		0.197 (-0.472, 0.867)		0.090 (-0.330, 0.510)	
Quartile 4 (most green)	**-0.379 (-0.716, -0.042)***		-0.088 (-0.729, 0.554)		0.040 (-0.397, 0.477)	
Il-6	**Model 1 (n=957)**		**Model 2 (n=876)**		**Model 3 (n=709)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.012 (-0.137, 0.160)	0.556	0.056 (-0.248, 0.361)	0.205	0.097 (-0.055, 0.248)	0.749
Quartile 3	-0.057 (-0.212,0.098)		-0.002 (-0.305, 0.300)		0.076 (-0.093, 0.245)	
Quartile 4 (most green)	**-0.057 (-0.207, 0.093)**		-0.058 (-0.348, 0.231)		0.068 (-0.108, 0.244)	
Adiponectin	**Model 1 (n=591)**		**Model 2 (n=523)**		**Model 3 (n=446)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.010 (-0.129, 0.150)	**0.015**	-0.065 (-0.298, 0.169)	**0.021**	-0.007 (-0.130, 0.116)	0.946
Quartile 3	0.094 (-0.052, 0.239)		0.062 (-0.182, 0.305)		0.031 (-0.107, 0.168)	
Quartile 4 (most green)	0.079 (-0.062, 0.219)		0.032 (-0.213, 0.278)		-0.004 (-0.147, 0.139)	

Model 1: adjusted only for study; Model 2: adjusted for study, age, sex, smoking, socioeconomic class and ethnicity; Model 3: adjusted for the same confounders as Model 2 as well as HbA1c, BMI, physical activity (Total PAEE Met-hrs/week), and medication use. Number of participants as stated.

Supplementary Table 31. Model summary table of univariate linear regression parameter estimates with loge prostaglandins (mg/L), loge TNF alpha (mg/L), loge resistin (mg/L) as outcome with 95% confidence intervals in relation to quartiles of neighbourhood greenspace in participants for a **5km buffer**.*

Prostaglandins	**Model 1 (n=957)**	**p trend**	**Model 2 (n=875)**	**p trend**	**Model 3 (n=707)**	**p trend**
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.084 (-0.047, 0.216)	**0.000**	-0.076 (-0.538, 0.387)	0.751	0.009 (-0.336, 0.353)	0.641
Quartile 3	**0.259 (0.131, 0.387)*** **		0.349 (-0.090, 0.788)		0.160 (-0.168, 0.487)	
Quartile 4 (most green)	**0.196 (0.066, 0.326)** **		-0.027 (-0.461, 0.407)		0.040 (-0.284, 0.363)	
TNF Alpha	**Model 1 (n=957)**		**Model 2 (n=876)**		**Model 3 (n=709)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	0.106 (-0.011, 0.223)	**0.010**	-0.126 (-0.557, 0.305)	0.368	-0.002 (-0.320, 0.316)	0.181
Quartile 3	0.068 (-0.047, 0.183)		-0.083 (-0.496, 0.329)		0.031 (-0.274, 0.336)	
Quartile 4 (most green)	**-0.183 (-0.299, -0.064)** **		-0.237 (-0.641, 0.167)		-0.189 (-0.491, 0.114)	
Resistin	**Model 1 (n=591)**		**Model 2 (n=523)**		**Model 3 (n=446)**	
Greenspace quartiles						
Quartile 1 (least green)			Reference			
Quartile 2	**0.111 (0.024, 0.197)***	**0.024**	0.119 (-0.161, 0.400)	0.195	0.050 (-0.178, 0.278)	0.087
Quartile 3	0.036 (-0.051, 0.123)		-0.035 (-0.317, 0.247)		-0.004 (-0.233, 0.225)	
Quartile 4 (most green)	**-0.141 (-0.241, -0.042)** **		-0.277 (-0.599, 0.045)		-0.134 (-0.372, 0.104)	

Model 1: adjusted only for study; Model 2: adjusted for age, sex, smoking, socioeconomic class and ethnicity; Model 3: adjusted for the same confounders as Model 2 as well as HbA1c, BMI, physical activity (Total PAEE Met-hrs/week), and medication use. Number of participants as stated.

Chapter 6: Discussion

6.1. Chapter overview

This thesis set out firstly to investigate the associations between greenspace exposure and a broad range of health outcomes, and secondly to hypothesise and investigate potential underlying mechanisms in the relationship between greenspace and health. To meet these aims, four studies were conducted around a series of questions. The first study was a systematic review with a deliberately broad scope that set out to answer *Question 1. What is the impact, if any, of greenspace on a wide range of physiological health outcomes?* Based on theoretical frameworks and available evidence, a hypothesis was proposed for the underlying mechanisms for the relationship between greenspace and health. It was hypothesized that increased greenspace exposure leads to increased contact with a diverse range of microbiota. This has subsequent benefits for the regulation of immune and inflammatory processes, manifesting itself as reduced levels of inflammatory markers in the blood.

The three following studies of the thesis, (Chapters 3, 4, and 5) set out to investigate this proposed mechanism, by investigating whether neighbourhood greenspace exposure is associated with 1) microbial diversity and 2) biomarkers of inflammation. Chapters 3, 4, and 5, aimed to answer the following questions:

Question 2. Does neighbourhood greenspace have an association with the microbial diversity of the human gut, therefore mediating the relationship between greenspace and health?

Question 3. Is there an association between neighbourhood greenspace and C-reactive protein, a common marker of inflammation?

Question 4. Does neighbourhood greenspace have any association with the wider process of inflammation and its' associated markers?

This concluding chapter has four parts. Firstly, it summarises the principal findings from the research presented. Secondly, it reflects on the methodologies used, including their strengths and limitations. Thirdly, it outlines suggestions for future research, before, fourthly, concluding with some final comments.

6.2. Summary of principal findings

6.2.1. Chapter 2: The health benefits of the great outdoors: A systematic review and meta-analysis of greenspace exposure and health outcomes

Chapter 2 aimed to quantify the health benefits of exposure to greenspace in a systematic review and meta-analysis. One hundred and forty-three studies were identified that investigated the impact of greenspace on a broad range of over 100 physiological health outcomes. Included papers were either observational studies (103 papers) investigating the influence of neighbourhood greenspace on health or intervention studies (40 papers) comparing green and urban interventions on health. Two separate tools were used to appraise quality of included papers across a number of areas such as randomization, the use of objective measures, and representativeness of samples.

The use of common outcome measures enabled novel meta-analyses of 24 health outcomes and conditions. Statistically significant health denoting associations between high versus low greenspace exposure groups were identified for self-reported health, diabetes, all-cause and cardiovascular mortality, diastolic blood pressure, salivary cortisol, heart rate, heart rate variability (HRV), and high density lipoprotein (HDL) cholesterol, as well as preterm birth and small size for gestational age births. These vastly different outcomes such as increased birth weight and decreased all-cause and cardiovascular mortality demonstrate that greenspace is beneficial for health across the lifespan. Included studies presented results from 20 different countries, with 50% of studies from European countries and 24 studies from Japan demonstrating geographically-diverse study populations. No adverse effects of greenspace on health were apparent through the meta-analyses. The findings of wide ranging physiological health benefits suggest that greenspaces may be a useful health resource.

In terms of the meta-analysis results obtained, it is useful to give consideration to effect sizes and minimal clinically important differences. For example, Chapter 2 demonstrated a statistically significant reduction of almost 2mmHg diastolic blood pressure across the range of greenspace exposure variables. However for many individuals, 2mmHg reduction in diastolic blood pressure is not enough to make a clinical difference[356]. Chapter 2 also presented a statistically significant reduction in heart rate by 2.57 beats per minute (bpm). Evidence has shown that for every 5 bpm reduction in heart rate with beta blocker treatment the relative risk of death was reduced by 18%[357]. Although greenspace exposure may not

have as large an effect size on blood pressure and heart rate as commonly used therapeutics, the magnitude of effect sizes suggests that greenspace exposure may have potential as an adjunctive therapy alongside medication and or lifestyle changes, such as exercise and diet.

There were several questions that could not be answered in the systematic review. A small number of included papers reported stronger health benefits for participants who were living in more deprived neighbourhoods compared with those living in less deprived neighbourhoods. However, as results were not widely reported by proxy for socioeconomic status (SES) level such as education level, occupation, or household income, it was not possible to conduct sensitivity analysis to test this. If stronger benefits were observed for those from lower SES groups across a range of health outcomes, it may suggest that greenspaces and greenspace exposure may have the potential to mitigate health inequalities. Practitioners and policymakers may wish to promote greenspace use, with particular focus on those who stand to benefit the most, which could be actioned through the considered creation or regeneration of greenspaces in deprived areas, or by encouraging use of existing greenspaces.

The main gap in the literature that this systematic review highlighted was the paucity of empirical studies investigating the mechanisms underlying the relationship between greenspace and health. Previously suggested mechanisms included the opportunities that greenspaces presents for physical activity, improved air quality, and psychological benefits[36]. Theoretical frameworks for the underlying mechanisms have also been proposed, suggesting that greenspace exposure is associated with immunoregulation and the regulation of inflammatory processes in the body, driven by exposure to microbial organisms in greenspace[64 65].

6.2.2. Chapter 3: Does gut microbial diversity explain the relationship between greenspace and health? Results from the TwinsUK database

The existing evidence suggests that compared with urban environments, greenspace and natural areas carry increased exposure to a range of microbiota such as bacteria, helminths, and ecoparasites[358]. Contact with microbiota plays an important role in the education and regulation of the immune system, thereby helping with immunoregulation and, by association, the inflammatory response. If increased greenspace exposure is associated with increased microbial exposure, this would have subsequent benefits on the immune system and associated inflammatory processes. Indeed, Chapter 2 demonstrated that

increased greenspace exposure is associated with reduced incidence of inflammatory diseases, including type 2 diabetes and cardiovascular disease. It was therefore hypothesized that increased greenspace exposure is associated with increased microbial exposure. Chapter 3 set out to investigate this hypothesis by investigating whether neighbourhood greenspace is associated with gut microbial diversity.

It was hypothesised that higher levels of neighbourhood greenspace would be associated with greater gut microbial diversity. This was tested using data from 1,908 participants from the TwinsUK study, using quartiles of neighbourhood greenspace and across four validated indices for gut microbial diversity. No association was detected between quartiles of neighbourhood greenspace and gut microbial diversity for any of the diversity indices.

This study was the first to investigate the relationship between greenspace exposure and gut microbial diversity. Clear associations have been demonstrated between increased neighbourhood greenspace exposure and decreased inflammatory disease[37 56 114 133 138 151 194 223 359], and yet, based on the findings of Chapter 3, this association appears not to be driven by microbial diversity. It may be that greenspace exposure has an impact on inflammation and inflammatory disease, but through pathways other than microbial exposure. For example, Chapter 2 found that greenspace exposure is associated with a statistically significant reduction in salivary cortisol, a physiological marker of stress[254]. Research investigating the relationship between psychological health outcomes and greenspace exposure has demonstrated lower levels of self-reported stress with increased greenspace exposure[56 57 141 235 236 249]. Stress and salivary cortisol have been associated with markers of inflammation[310 360], and chronic psychological stress has been associated with poor regulation of inflammatory processes[311]. Therefore, investigating the relationship between greenspace exposure and inflammation may offer insight as to what underlying mechanisms are at play.

6.2.3. Chapter 4: Can hs-CRP explain the associations between neighbourhood greenspace exposure and health? The EPIC Norfolk study

Chapter 4 therefore set out to investigate the hypothesis that increased greenspace exposure is associated with decreased levels of inflammation by investigating the relationship between neighbourhood greenspace and level of high sensitivity C-reactive protein, a common marker of inflammation in the blood. The study employed a cross-sectional approach using data from 5,098 participants of the EPIC Norfolk study. Two hs-CRP variables were used; the first, a continuous measure of hs-CRP, and the second, a

binary measure of whether hs-CRP was within the reference range (0-6mg/dL) or not. The association between each of these measures and quartiles of neighbourhood greenspace in a 3km buffer around the home was assessed in separate statistical analyses. No association was detected between quartiles of neighbourhood greenspace and hs-CRP level in the EPIC Norfolk study either before or after adjustment for potential confounders.

Given that neighbourhood greenspace has been associated with decreased incidence of inflammatory disease[56 114 133 138 151 194], it is somewhat surprising that no association was observed between neighbourhood greenspace and hs-CRP, a common marker of inflammation. However, as the inflammatory process is complex, consisting of distinct pro-inflammatory, inflammatory, and anti-inflammatory stages each with unique biomarkers and cytokines, and given the availability of secondary data, it may be beneficial to investigate whether an association between neighbourhood greenspace and the wider inflammatory process exists. Chapter 5 set out to do this.

6.2.4. Chapter 5: Can markers of inflammation explain the relationship between residential neighbourhood greenspace and health in a pooled cross-sectional study?

Chapter 5 set out to investigate whether inflammatory markers from the various stages of the inflammatory process mediate the relationship between greenspace and health. This cross-sectional study, using data from the ADDITION and Walking Away From Diabetes datasets from the Leicester Diabetes Centre, investigated the association between quartiles of neighbourhood greenspace and six distinct biomarkers from the various stages of the inflammatory process including pro-inflammatory and anti-inflammatory cytokines. The biomarkers were hs-CRP, tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), adiponectin, resistin, and prostaglandins. Residence in quartiles with the most greenspace was found to be associated with significantly increased adiponectin and prostaglandins, and decreased TNF-alpha and resistin. However, these associations disappeared after adjustment for a number of potential confounders including age, gender, and SES. No associations were found for hs-CRP or IL-6 both before and after adjustment for potential confounders.

The studies in Chapters 4 and 5 therefore both seem to suggest that there may not be an association between neighbourhood greenspace and markers of inflammation. It must be critically considered whether the methodologies or study design used in these chapters are responsible for the results.

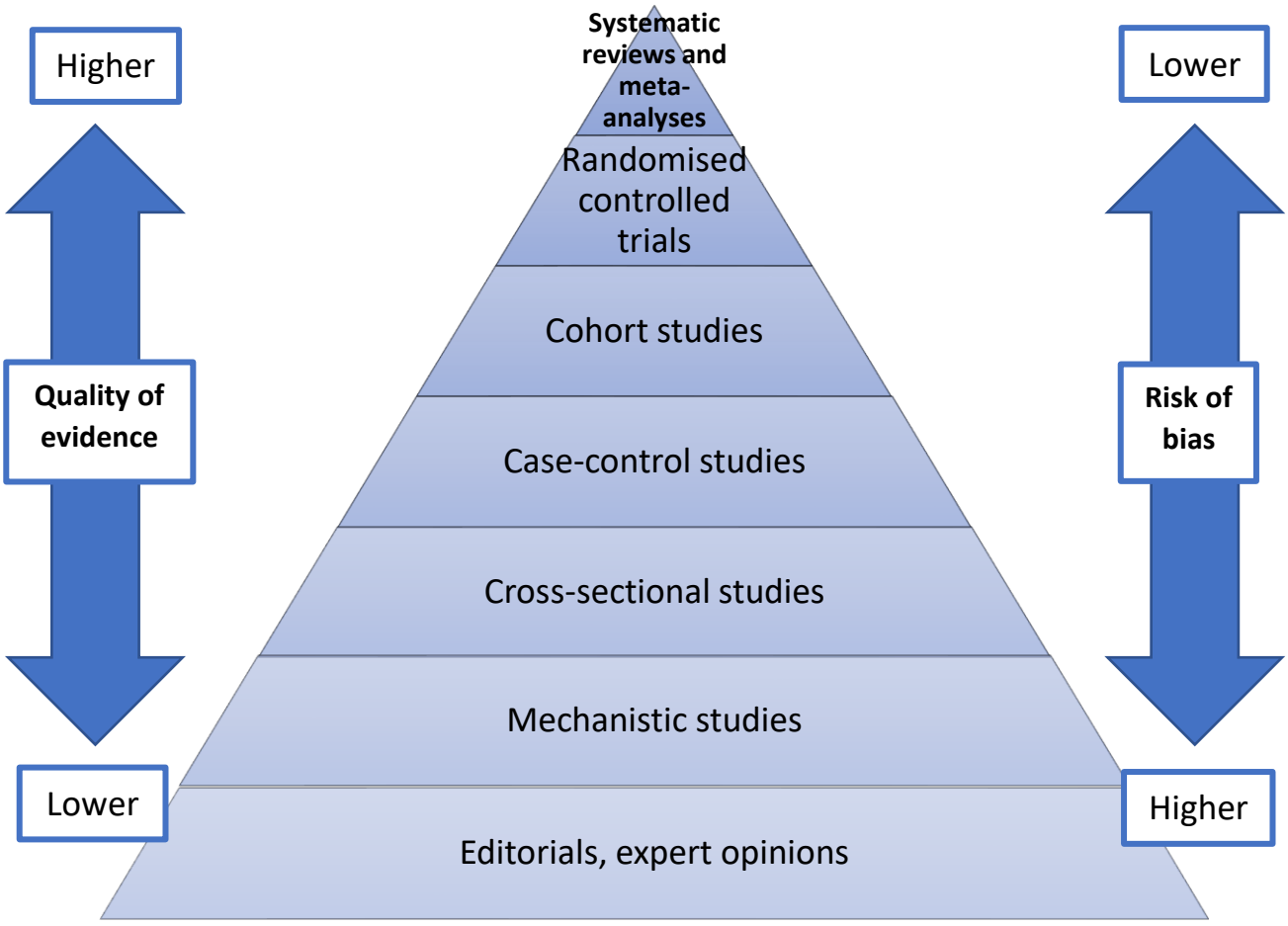
In terms of the measurements of inflammatory markers, evidence has shown that CRP and other inflammatory markers are highly susceptible to short term changes due to medication use, or behaviours such as physical activity and sleep[361]. Whilst the analysis in Chapter 4 using the EPIC Norfolk dataset was conducted both with and without adjustments for potential confounding biomedical, behavioural, and lifestyle factors including physical activity, data was not available on sleep duration or medication use, meaning that these could not be adjusted for. In Chapter 5 however, Leicester Diabetes Centre ADDITION and Walking Away study participants avoided moderate-vigorous physical activity and caffeine for 48 hours before baseline blood tests, therefore reducing the risk of short-term variations in inflammatory markers due to physical activity or sleep pattern.

Both Chapters also investigated the chronic exposure of neighbourhood greenspace. Although this exposure measurement indicated the level of greenspace within participants' neighbourhoods, it gives no information on participants' use of neighbourhood greenspace. To the authors' knowledge, only two previous studies have investigated the relationship between greenspace exposure and CRP. These studies measured CRP levels after a short-term visit to a forest environment in comparison to an urban environment, and found forest exposure was associated with a small but significant decrease in CRP level[26 27]. Although these studies involved small numbers of participants (19 and 20 participants), if CRP is susceptible to short-term changes, it may be the case that an RCT study design investigating the impact of a short term greenspace exposure is more appropriate to measure than the methods used in this thesis which capture more chronic exposures and outcomes. This concept will be discussed in section, 6.4.

6.3. Reflections on the methods used in the thesis

The quantitative methodology employed in this thesis enabled the four separate research questions to be addressed using a range of tools appropriate to the research aim. This has facilitated an expansive analysis into both the health benefits of greenspace, and the potential mechanisms underlying this relationship.

Figure 31. The Hierarchy of Evidence



In order to reflect on the methods used in the thesis, it is useful to consider the positioning of the study designs employed on the Hierarchy of Evidence, depicted in Figure 31.[362]. This illustrates the hierarchy of research study designs, and how research designs are considered in terms of quality of evidence and risk of bias. Chapter 2 followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, and where possible, followed the methodology of a Cochrane Review[363]. According to the Hierarchy of Evidence, systematic reviews and meta-analyses of RCTs are considered to provide the highest quality of evidence and the lowest risk of bias[362]. However, the systematic review in Chapter 2 included all empirical studies that met the inclusion criteria, meaning that both interventional (RCTs and case control) studies and observational (cross-sectional and cohort) were included. If only RCTs had been included, the review may have been of higher quality in terms of the Hierarchy of Evidence. The inclusivity of the review also led to high heterogeneity across studies and difficulties in comparing results from varying study designs, for example small-scale intervention studies with as few as 9

participants[108] and larger ecological cross-sectional studies with populations as big as >63 million[110], or in comparing studies that used objective and subjective measurements of greenspace.

The subsequent three studies (Chapters 3, 4, and 5) were cross-sectional in design, with statistical analyses adapted to suit the individual datasets. As detailed on the hierarchy of evidence, cross-sectional studies are regarded as poorer methodological quality and with a higher risk of bias than more robust study designs such as systematic reviews, meta-analyses, and randomised controlled trials (RCTs). For these mechanistic studies quartiles of greenspace were devised by ranking all included participants in order from highest to lowest % neighbourhood greenspace exposure, and then divided into groups with roughly equal numbers of participants. This method meant that there are some discrepancies between quartiles when comparing the highest and lowest quartiles across the three studies due to differences in the samples used. For example, the percentage greenspace in the highest and lowest quartiles varied, with EPIC Norfolk participants in the highest quartile (n = 1574) having the highest mean percentage greenspace of 96.8%. TwinsUK participants in the highest greenspace quartile (n = 447) had 92.8% greenspace, whilst Leicester (ADDITION and Walking Away) participants in the highest quartile (n = 408) had the lowest value at 79.1%. In terms of the lowest greenspace quartiles, EPIC Norfolk participants in the lowest quartile (n = 1573) had the highest value at 32.4%. This is in comparison with TwinsUK lowest quartile participants with a mean neighbourhood greenspace of 21.7%, and Leicester lowest quartile participants with just 17.4%.

Participant characteristics also varied between the chapters' according to greenspace quartiles. For example, hs-CRP was measured across the 3 datasets; TwinsUK participants had the lowest mean hs-CRP level with 2.61mg/L, which was reported for participants in the highest greenspace quartile (TwinsUK lowest greenspace quartile reported 2.78mg/L). Participants from ADDITION and Walking Away had, on average, the highest mean hs-CRP level for both participants in the highest (3.66mg/L) and lowest (4.01mg/L) greenspace quartiles. This is perhaps unsurprising due to the high number of participants with type II diabetes in the Leicester datasets; type II diabetes is an inflammatory condition and therefore may explain the higher levels of CRP.

No statistically significant associations were found between neighbourhood greenspace and gut microbial diversity (Chapter 3) or markers of inflammation (Chapters 4 & 5). It is unclear whether the results were because there were no associations to be found, or whether the methods and analytical design used failed to detect an association which may actually be present. The studies in Chapters 3, 4, and 5 all employed neighbourhood

greenspace as the exposure of interest, a long-term or "chronic" exposure from which it is not possible to estimate participants' actual greenspace use. Firstly, greenspace exposure was measured around the home environment, but this does not take into account participants' time spent away from the home, for example at work or school, and the potentially differing levels of exposure these environments may present. Evidence suggests that participants of higher SES groups are more likely to live in neighbourhoods with a higher greenspace proportion of greenspace[88] yet, participants from higher SES groups are more likely to be car owners, and so are able to travel easily to areas with different proportions of greenspace to their home neighbourhoods[364 365]. Participants from lower SES groups are also likely to be less mobile, and therefore more dependent on the greenspace levels in their home neighbourhood[33 366]. Several studies have found stronger health benefits for participants from more deprived backgrounds, which may in part be due to reduced mobility and therefore more time spent within their neighbourhood greenspace.

A longitudinal measure of neighbourhood greenspace may have offered an improved measure of chronic exposure compared to the use of a cross-sectional measure. Cohort study designs are considered to be of higher quality and with less risk of bias than cross-sectional studies. Conducting a longitudinal study using the datasets of interest would have involved tracking participants who had moved location during the follow-up period of the study, either from an area of lower greenspace coverage to an area of higher greenspace, or vice versa, and assessing for differences in the markers of interest. Tracking participant moves can be difficult, and the ability to do so is largely limited by the data collection methods used. For example, in the EPIC Norfolk dataset, no information on the exact date of moves was recorded, despite 6.2% (1486 participants) of the total sample moving during the 13 year follow up period[151]. Even if participant moves had been fully documented and recorded, exposure to greenspace varies over time and years, due to a number of locational, behavioural, and lifestyle factors[353], and so it would be difficult to capture such heterogeneity within moves. A further issue is that participants with more greenspace in their home neighbourhood will undoubtedly be subject to more greenspace exposure than those without, and proximity to greenspace has also been associated with spending time in greenspace[41 353], but this is still not an accurate indicator of greenspace use, which is additionally influenced by behavioural factors, seasonality, gender, age, education marital status and ethnic background[41 353 367-369]. Whilst potentially attractive, an RCT study design would be difficult to conduct using the chronic exposure of neighbourhood greenspace, as it would be untenable to randomise participants so that one study arm did not come into any contact with greenspace over an extended period of time.

Inflammatory biomarkers are highly susceptible to short-term changes evoked by behaviours such as sleep and physical activity. An RCT with acute exposures may enable researchers to explore potential acute dose-response relationships. Indeed two forest bathing studies that were included in the systematic review investigated CRP as a secondary measure, with one finding a small but significant decrease in CRP with forest bathing[26 27]. Both studies had small participant groups of 19 and 20 participants, who were from the same demographic and ethnic groups (Young, Asian male students).

Of the 143 studies included in the systematic review, only 12 studies were RCTs, compared with 103 cross-sectional and cohort studies and 28 non-randomised interventional studies. This may be illustrative of the level of complexity and difficulty involved in conducting an RCT, including issues such as collection of data, financial costs, and time available. These factors along with the availability of secondary datasets with the variables of interest, were in part factors that influenced the study design of Chapters 3, 4, and 5.

6.3.1. Strengths and limitations

The strengths and limitations of each study and the methodologies used have been evaluated within each chapter. This section of the thesis considers the strengths and weaknesses of the body of work taken as a whole.

There are several strengths to this thesis. Firstly, the contribution that the systematic review makes to the evidence base of the impact of greenspace exposure on health, outlining the broad range of physiological health benefits. Secondly, the results of the systematic review and meta-analysis form an evidence base in support of the use of and advocacy for greenspace as a resource for health, particularly with regards to SES groups that may stand to benefit the most. The thesis has also addressed the paucity of evidence investigating the mechanisms underlying the relationship between greenspace and health, by investigating one potential hypothesis across three large, varied datasets within the limited funding and time constraints associated with a PhD studentship. However, these three studies did not detect an association between greenspace and gut microbial diversity or markers of inflammation.

There are also limitations to this thesis. Firstly, a number of meta-analyses conducted as part of the systematic review had high levels of heterogeneity, and so their results should be interpreted with caution. Secondly, although a small number of included studies reported stronger health-denoting associations for participants from more deprived areas, most studies did not present results by proxy for social class such as education level, occupation, or household income, and so it was not possible to conduct subgroup analysis test whether

this was the case for other included studies also. Subgroup analysis by social class may would improve understanding of the extent to which greenspace exposure may or may not mitigate health inequalities. The systematic review demonstrated that greenspace has potential as a health resource, but subgroup analysis by social class may empirically demonstrate the potential of greenspace exposure to mitigate health inequalities.

The subsequent three chapters of the thesis used secondary cross-sectional data, which as seen in Figure 6.3.1, is widely regarded as one of the poorer methodological quality study designs. The use of the chronic measure of neighbourhood greenspace meant that it was not possible to objectively derive participants' greenspace use. Furthermore, Chapter 5 used data from participants who either were at high risk of type 2 diabetes or were considered to be prediabetic, and therefore may have had a higher than normal chronic level of inflammation.

6.4. Suggestions for future research

From the findings of the four studies in this thesis, it is possible to make a series of recommendations for future research. In the systematic review, it was not possible to investigate associations between greenspace exposure and psychological health outcomes and communicable diseases, as to include them would have greatly increased the scope of the review. However, during the initial scoping exercise and in refining the search strategy, a substantial body of literature was uncovered documenting the mental health benefits of greenspace exposure[108 213 227 234 249 370]. A systematic review and meta-analysis would provide further evidence of the health benefits of greenspace. As mentioned in Chapter 2, 11 million working days are lost to stress, depression, and anxiety in the UK each year[371]. Chapter 2 found a significant decrease in salivary cortisol with exposure to greenspace, and it was also hypothesised that stress and psychological mechanisms may have a role in the relationship between greenspace and health. A review of the psychological effects of greenspace may provide evidence in support or in contrast to this hypothesis.

A review on the relationship between communicable disease and exposure to greenspace would also be welcome. It was not possible to investigate communicable diseases in the systematic review in Chapter 2 as they were beyond the scope of the review. This may be integral to illustrating the potential detrimental effects of spending time in greenspaces. Marshland, lakes, and ponds are known to be home to mosquitoes, which are known to spread diseases such as malaria, yellow fever, encephalitis and dengue fever[372 373]. Whereas ticks are known to live in ground-level vegetation such as garden lawns and shrubs, and are mostly notably known to carry Lyme disease[374]. It may therefore be particularly worthwhile to investigate the relationship between infectious, vector-borne diseases and neighbourhood greenspace. Vector-borne diseases account for more than 17% of all infectious diseases, causing more than 700,000 deaths annually. Malaria accounts for over half of these deaths, and there are an estimated 96 million cases of dengue fever each year. Research into this area may be particularly relevant for low and middle income countries (LMICs), as the burden of these diseases is highest in tropical and subtropical areas and they disproportionately affect poorer populations[373]. Out of the 143 studies included in the systematic review, only 11 were located in LMICs (5 located in China and 4 in Korea).

A number of studies that were included in the systematic review reported stronger associations between greenspace exposure and self-reported health, birth outcomes and morbidity for those from low SES groups and the most deprived areas [88 120-122]. Increased

neighbourhood greenness has also been reported to decrease the effect of income deprivation on both all cause and cardiovascular mortality by one study[88]. As only a small number of studies presented results by SES group, it was not possible to conduct a formal subgroup analysis. Future research would investigate whether increased neighbourhood greenspace, through parks, recreational areas, or street greenery, can be used to successfully mitigate health inequalities. Physical activity in a green environment may have additional health benefits than when conducted in an indoor or gym environment[11 23 141]. It could be that investigations into green exercise schemes and programmes, using participants from low SES areas may be an appropriate way to test this.

A previous meta-analysis investigating exercise referral schemes (ERS) found very limited evidence of their clinical effectiveness and cost-effectiveness, and no association between taking part in an ERS and reduction in diastolic blood pressure 0.11 (-0.92 to 1.13)[375]. These ERS were in a leisure-centre setting. This is in contrast with Chapter 2's finding of a small, but statistically significant, decrease in diastolic blood pressure with increasing greenspace exposure -1.97 (-4.30 to -0.83) (mmHg). Indeed, the findings presented in Chapter 2 reinforce previous research that has demonstrated additional health benefits of conducting physical activity in a green environment than in an indoor or gym environment[24 25]. This suggests that there may be potential to revise guidelines on ERS' to promote the use of local and accessible green environments for activities where possible. Offering patients green prescriptions and encouragement to spend more time in local greenspaces may also result in health benefits[22 376 377]. Further, investing in the creation, maintenance and regeneration of these areas may also go some way to improving the health and well-being of the populations as well as reducing the burden of treating disease on health services.

Chapter 3, investigated the relationship between neighbourhood greenspace and gut microbial diversity, finding no association between the two. The best available diversity indexes were used to measure gut microbial diversity, however as mentioned in Chapter 5, there may be better variables to test the impact of neighbourhood greenspace exposure on gut health. This may include comparisons between the species of bacteria present in greenspace and that present in the gut.

Chapters 4 and 5 investigated the relationship between markers of inflammation and neighbourhood greenspace within a 3km buffer, with sensitivity analysis of 800m and 5km buffers. A limitation of the work presented in this thesis is that it was not possible to derive participants' actual greenspace use from percentage neighbourhood greenspace. Future focus on the development of datasets measuring greenspace use would enhance the field. With the increasing use of smartphones and smart watch devices with built-in accelerometer

and GPS technology, these could perhaps be used to accurately quantify how much time participants actually spend in greenspace. This would also enable accurate adjustment for physical activity as a confounder. Data on actual greenspace use may then be used to investigate whether greenspace use has any acute impact on inflammatory processes and markers of inflammation.

Following on from this thesis, an RCT investigating the relationship between an acute greenspace exposure, where participants spend a short amount of time in a greenspace such as a forest or park environment, in comparison to exposure to an urban environment may help establish the underlying mechanisms. This could utilise a design similar to a number of the forest bathing studies included in the systematic review[112 119 181 195 378], and use markers of inflammation as the outcomes of interest. These forest bathing studies used various types of forest immersion techniques, with participants in the forest exposure group simply spending time in or walking through a forest, comparing results with participants doing the same activity but in an urban or indoor environment. It is noteworthy that these studies found more promising associations than detected in the research presented in the mechanistic studies of this thesis.

In this study, a power calculation would be conducted prior to recruitment to calculate the minimum sample size required. Recruited participants would then be randomised into either the green environment exposure group, or the urban environment exposure group. Each group would spend the same period of time e.g. 1 hour, walking through their allocated environment. Participants' inflammatory biomarkers would be measured before, at baseline, during and after the intervention, as well as at regular intervals afterwards. This may indicate whether there is any lasting effect of exposure to greenspace, and if so, how long for. Participant demographic, social, and health data would also be collected, which may include self-reported health/quality of life data from questionnaires (e.g. SF-36), mental health indicators, as well as variables such as salivary cortisol as a marker of stress, heart rate, and blood pressure. This data would enable testing for potential mediators and moderators. For example, if the greenspace intervention is associated with reduced levels of inflammatory biomarkers, this may be mediated by reduced stress levels (whether reported or measured physiologically by salivary cortisol levels). This RCT design would enable the investigation of a potential cause-effect relationship, in comparison to the cross-sectional mechanistic studies of chapters 3, 4, and 5.

One disadvantage of such a study however, would be that it would only pick up on acute changes from the acute exposures. Furthermore, it would not be possible to investigate changes in gut microbial diversity due to the short-term nature of the intervention exposures

and the reported relative stability of the gut microbiome[280]. However, a more suitable study type to investigate the association between changing environmental exposures and gut microbial diversity, could be a migration study. Such a study would measure the gut microbial diversity of participants who have migrated from a predominantly green environment, to a predominantly urban environment, and vice versa. Migration studies have previously been used to investigate changes in the gut microbiome in first and second generation Thai immigrants who have moved to the United States[379]. This design would enable investigation of change in chronic environmental exposures on gut microbial diversity by comparing measurements before and after migration. Markers of inflammation could also be measured to assess potential changes before and after migration. Participant demographic, health, and social data would also be collected in order to adjust for any potential confounders, mediators, or moderators. This would include lifestyle factors such as diet, antibiotic use, physical activity levels, and BMI, all of which may have been altered as a result of migration[380 381], and which have the potential to influence gut microbial diversity[382].

If the underlying mechanisms of the relationship between greenspace and health are established, this evidence, along with the results of the systematic review, may provide grounds for health professionals and policymakers to promote greenspace use and exposure as a potential resource for health. These pieces of research will provide important insight into the impacts of greenspace on health, and to further investigate the potential underlying mechanisms for the relationship.

6.5. Concluding comments

Urbanisation across the world presents a major health challenge. The systematic review presented at the beginning of this thesis has illustrated the many physiological health benefits that living close to or spending time in greenspace can have. In some cases, the benefits appear to even be comparable to current clinical treatments. Secondly, the thesis has investigated a novel hypothesis for a potential mechanism underlying the relationship between greenspace and health. Recommendations for future research to further examine the underlying mechanisms for the relationship between greenspace and health have also been made.

In conclusion, it is hoped that this thesis, and any publications arising from it, make a contribution to our knowledge on greenspace and health. In order for researchers to determine the mechanisms underlying greenspace and health, the focus must be on the creation of datasets that include objective and empirical measurements of participants' use of greenspace.

Appendix: PROSPERO systematic review protocol

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The health benefits of the great outdoors: a systematic review and meta-analysis of greenspace exposure and health outcomes

32 words remaining

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

50 words remaining

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

05/01/2015

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

15/10/2015

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Caoimhe Bennett

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

Give the electronic mail address of the named contact.
c.m.bennett@uea.ac.uk

8. Named contact address

Give the full postal address for the named contact.
Room 1.23 Queen's Building
University of East Anglia
Norwich Research Park
NR4 7TJ

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.
+44 (0)7845 282472

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
University of East Anglia

Organisation web address:

www.uea.ac.uk

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Miss Caoimhe Bennett. PhD Candidate, UEA
Professor Andy Jones. Professor of Public Health, UEA

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

CEDAR - Centre for Diet and Activity Research

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Objective: To determine the impact of greenspace on the population disease burden.

238 words remaining

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

CINAHL, PsycINFO, AMED, EMBASE and MEDLINE were all searched from inception to 17/2/15. Restricted to English language studies only due to lack of translation capability. Searches will be rerun in September.

270 words remaining

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

The effects of exposure to greenspace on any health outcome excluding mental health, communicable disease, birth weight, BMI/obesity and physical activity. Studies should report health outcomes.

174 words remaining

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Human participants, male and female with no age restrictions.

191 words remaining

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Exposure to greenspace.
197 words remaining

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

There is no comparator restriction.
195 words remaining

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria:-Empirical studies testing the relationships between greenspace and health excluding studies looking at mental health, physical activity or BMI. -The study reports a health outcome other than mental health/physical activity/BMI.-Studies that use human participants.-Papers and documents written in English due to lack of translational capability.Exclusion criteria:-Studies where mental health/physical activity/BMI are the only outcomes. -Studies that do not look at empirical evidence.-Studies that do not look at human participants or use animals.-Studies not in English due to lack of translational capability.
61 words remaining

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

250 words remaining

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Studies should report a health outcome.
194 words remaining

Timing and effect measures

200 words remaining

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None
299 words remaining

Timing and effect measures

300 words remaining

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Data extraction will be performed by the two reviewers. Discrepancies will be resolved by discussion, and failing this, a third party will resolve disputes.
276 words remaining

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

All included papers have been critically appraised using adapted versions of the Lachowycz and Jones quality assessment checklist for observational studies and the Hanson and Jones risk of bias tool for interventional studies. Heterogeneity has been assessed using the I-squared statistic.
159 words remaining

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

Where appropriate, data was synthesised and a meta-analysis undertaken.
291 words remaining

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Subgroup analysis was conducted for forest-based intervention studies. Meta-analysis results were also stratified by study quality.
234 words remaining

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
Yes

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.
England

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

50 words remaining

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Greenspace
Health
Greenness
Green space

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

50 words remaining

38. * Current review status.

Review status should be updated when the review is completed and when it is published.
Please provide anticipated publication date

Review_Completed_published

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.
https://www.ScienceDirect.com/science/article/pii/S0013935118303323

Give the link to the published review.

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