Review article

Exposure to greenspaces could reduce the high global burden of pain

Jessica Stanhope[1,2], Martin F. Breed[3,4], Philip Weinstein[1,4,5¶]

[1]School of Biological Sciences, The University of Adelaide, North Tce, Adelaide, South Australia, Australia, 5005

[2]School of Allied Health Science and Practice, The University of Adelaide, North Tce, Adelaide, South Australia, Australia, 5005

[3]College of Science and Engineering, Flinders University of South Australia, Sturt Rd, Bedford Park, South Australia, Australia, 5042

[4]Healthy Urban Microbiome Initiative, Adelaide, South Australia, Australia (HUMI; www.humi.site)

[5]School of Public Health, The University of Adelaide, North Tce, Adelaide, South Australia, Australia, 5005

jessica.stanhope@adelaide.edu.au

martin.breed@flinders.edu.au

philip.weinstein@adelaide.edu.au

[¶]**Author for correspondence**: Philip Weinstein, Address: School of Public Health, University of Adelaide, North Tce, Adelaide, South Australia, Australia, 5005. Tel: +61 8 8313 6313, Email: philip.weinstein@adelaide.edu.au

ABSTRACT

Painful conditions are among the leading causes of years lived with disability. To reduce this burden, novel, cost-effective and accessible interventions are required. We propose that greenspace exposure may be one such intervention. Drawing on evidence from neuroscience, physiology, microbiology, and psychology, we articulate how and why exposure to greenspaces could improve pain outcomes and reduce the high global burden of pain. Greenspace exposure potentially provides opportunities to benefit from known or proposed health-enhancing components of nature, such as environmental microbiomes, phytoncides, negative air ions, sunlight, and the sights and sounds of nature itself. We review the established and potential links between these specific exposures and pain outcomes. While further research is required to determine possible causal links between greenspace exposure and pain outcomes, we suggest that there is already sufficient evidence to help reduce the global burden of pain by improving access and exposure to quality greenspaces.

KEYWORDS: greenspace; microbiome; pain; public health

INTRODUCTION

Greenspace exposure typically brings with it exposure to components of nature including biodiverse environmental microbiomes, phytoncides, negative air ions, sunlight, and the sights and sounds of nature itself. There is growing evidence of the benefits of exposure to greenspaces via these components for human health outcomes, including lower blood pressure, less cortisol, improved diabetes, reduced all-cause mortality, and fewer adverse birth outcomes (Twohig-Bennett and Jones, 2018). These benefits are particularly evident in more biodiverse greenspaces (Aerts et al., 2018), with several proposed mechanisms (Kuo, 2015). The impact of any type of greenspace exposure on pain, however, is under-investigated (Twohig-Bennett and Jones, 2018).

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (International Association for the Study of Pain (IASP), 2017). Painful conditions are among the leading causes of the global disease burden, with lower back pain, neck pain, ‘other’ musculoskeletal disorders, and migraines among the top 10 leading causes of years lived with painful disabilities (Vos et al., 2017). Indeed, lower back pain is the leading cause of years lived with disability in 65% of the 195 countries and territories investigated in the 2017 Global Burden of Disease study (James et al., 2018). This burden is likely to increase during and following the current coronavirus pandemic, because lockdowns and physical distancing has necessitated changes to healthcare services, including the closure of pain clinics (Eccleston et al., 2020), and the postponement or cancelation of elective surgeries (Liang et al., 2020; Sarac et al., 2020).

Chronic pain is considered a condition in its own right, not simply a symptom, and is defined as “pain that persists or recurs for longer than 3 months” (World Health Organization, 2018). The prevalence of chronic pain is high. For example, the estimated prevalence of chronic pain, when defined as persisting for 3 months or longer, in the United Kingdom is 43.5% (Fayaz et al., 2016), and when defined as 6 months or longer the prevalence is estimated to be 15.4% in Australia (Miller et al., 2017), 20.4% in the United States of America (Dahlhamer et al., 2018), and 27.2% in France (Chenaf et al., 2018). The prevalence of chronic pain is similar in low-middle income countries (Jackson et al., 2016). For those with chronic pain in the United Kingdom, 10.4-14.3% report being moderately to severely disabled by their pain (Fayaz et al., 2016). To reduce this disease burden, safe, effective and timely management options for people with pain are required, both to reduce the risk of transitioning from acute to chronic pain, and also to reduce the prevalence and impact of chronic pain. While many existing interventions contribute to reducing the community burden of chronic pain, novel interventions that further help are sought-after, and this paper explores a possible new approach – exposure to greenspace.

In this narrative review we probe the question – can exposure to greenspace reduce the high global burden of pain? To answer this question, we first review the nature of pain, followed by an exploration of the possible mechanisms by which exposure to greenspace could lead to more positive outcomes. ‘Greenspace’ has been defined in various ways in the existing literature (Taylor and Hochuli, 2017). For the purposes of this review, we have followed a broad definition of ‘greenspace’ as any natural environment, including, but not limited to, parks, ovals, forests and gardens.

PAIN MECHANISMS

Pain is a psychoneuroimmunoendocrinological process with three main types (nociceptive, neuropathic, nocipathic/nociplastic/algopathic; see Table 1 for descriptions), which can occur simultaneously in some people (Hainline et al., 2017). Pain processing occurs independent of pathology (Peppin and Schatman, 2016); hence, in this review, we discuss pain as a general condition, rather than focusing on pain from specific diseases or injuries (e.g. musculoskeletal, cancer, migraine).

Table 1. Characteristics for the three main pain categories

Pain category	Characteristics
Nociceptive pain	Involves the stimulation of nociceptors (the peripheral nerve terminals that detect noxious stimuli, which may be mechanical, chemical or thermal) (Hainline et al., 2017; Loeser and Treede, 2008) Includes inflammatory pain (Loeser and Treede, 2008) Protective mechanism – the body's 'first detection' system (Hainline et al., 2017; Loeser and Treede, 2008) Activation of nociceptors does not necessarily result in pain (Hainline et al., 2017) The relationship between nociceptor activity and the pain experience is not linear (Hainline et al., 2017)
Neuropathic pain	Involves a lesion of the somatosensory nervous system (International Association for the Study of Pain (IASP), 2017; Kosek et al., 2016; Loeser and Treede, 2008) May result from trauma or disease (Vardeh et al., 2016), or repetitive mechanical loading or inflammatory irritation of the peripheral nerves (Hainline et al., 2017)
Nocipathic/ nociplastic/ algopathic pain	Also described as 'dysfunctional pain' (Nagakura, 2015) Occurs in the absence of tissue threat or damage, and without somatosensory nervous system lesions (Kosek et al., 2016) Pain may occur through altered nociceptive pathway function, pathological changes of nociception, or central sensitisation (Hainline et al., 2017; Kosek et al., 2016) which occurs when the central nervous system nociceptors become hypersensitive (Loeser and Treede, 2008) Thought to be the pain type associated with visceral pain disorders, fibromyalgia and Complex Region Pain Syndrome Type 1 (Kosek et al., 2016)

Pain is not simply the result of damage, or even a sensory signal, but rather pain is a conscious event (Hainline et al., 2017). Pain is complex and varies widely between and within individuals, with a broad range of factors potentially playing a role, including neurophysiological, immunological, psychological, contextual, environmental, and social factors (Bushnell et al., 2013; Gatchel et al., 2007; Turk and Okifuji, 2002; Villemure and Bushnell, 2002). There are also many psychosocial factors associated with pain and poorer pain outcomes (e.g. transitioning from acute to chronic pain), such as stress, poorer mental health and lack of social coherence/support (see Box 1).

The brain integrates information from various sources (e.g. sensory information, pain perceptions), and pain may or may not result. The modulation of pain is influenced by non-nociceptive sensory input (Moseley and Arntz, 2007), affective and cognitive factors (Bushnell et al., 2013), and contextual cues (Moseley and Arntz, 2007). Pain modulation occurs through anatomical or functional neurological changes (Hainline et al., 2017), and/or through various processes of the peripheral and central nervous systems (Bushnell et al., 2013).

There are several neural factors potentially involved in the experience of pain. These neural factors include the activation of nociceptors (that detect noxious stimuli; (Hainline et al., 2017; Loeser and Treede, 2008), and the descending pathways (that influence pain at the dorsal horn of the spinal cord; (Guo et al., 2019; Zhuo, 2017). Pain modulation may also be influenced by pro-inflammatory mediators, nerve growth factor, hormones (e.g. endorphins), and epigenetic modifications, and involves immune cells, mast cells, macrophages, and leukocytes (Guo et al., 2019).

The activity of these cells is driven by several compounds, including short chain fatty acids and gamma-aminobutyric acid (GABA) (Guo et al., 2019). An awareness of the nature of pain is important for contextualising and interpreting the potential role of pain-reducing interventions. However, a further discussion regarding pain mechanisms is beyond the scope of this paper; interested readers are instead referred to other reviews for further information (e.g. Bushnell et al. (2013), Hainline et al. (2017), Fregoso et al. (2019), and Guo et al. (2019).

Box 1. Examples of psychosocial factors associated with pain outcomes

Stress (Drake et al., 2018; Jayakumar et al., 2018)
Poorer mental health (e.g. anxiety, depression) (Drake et al., 2018; Hruschak and Cochran, 2018; Jayakumar et al., 2018; Liu et al., 2018)
Lack of social coherence (Jayakumar et al., 2018) and support (Fregoso et al., 2019; Jayakumar et al., 2018)
Sleep problems (Andreucci et al., 2017; Haack et al., 2020)
Beliefs about pain (Morton et al., 2019) and pain control (de Raaij et al., 2018)
Poorer expectations regarding pain (Hruschak and Cochran, 2018)
Catastrophisation (Fregoso et al., 2019; Hruschak and Cochran, 2018)
Kinesiophobia/ fear-avoidance beliefs (Drake et al., 2018; Hruschak and Cochran, 2018; Jayakumar et al., 2018; Morton et al., 2019)
Fear of surgery (Fregoso et al., 2019)
Perceived self-helplessness (Fregoso et al., 2019)
Poor self-resilience (Fregoso et al., 2019)
Poor self-efficacy (Fregoso et al., 2019)
Having non-adaptive pain thoughts (Jayakumar et al., 2018)

HOW IS PAIN CURRENTLY TREATED?

Given the complex nature of pain, interventions can target various factors. Particularly in the acute phase, pain management may target nociception, including any underlying inflammation. In the acute phase, strategies to prevent the transition from acute to chronic pain may also be implemented, targeting any of the risk factors (Table 2). These factors may continue to be targeted in chronic pain management, although treatments aimed at reducing hypersensitivity may be added. Finally,

surgical options may be considered to address underlying problems (e.g. joint replacement, spinal fusion, nerve decompression), as well as strategies to reduce hypersensitivity. Chronic pain treatment is typically multidisciplinary and may be provided by a range of health professionals including physiotherapists, psychologists, occupational therapists, dentists, podiatrists, general practitioners, pain physicians, neurologists, anaesthetists, and appropriate surgeons (e.g. neurosurgeons, orthopaedic surgeons).

The treatment of chronic pain can be complex, resource intensive, and have varying levels of success. Novel treatments to reduce the risk of transition from acute to chronic pain and to treat chronic pain itself are both required. These treatments need to be accessible in a timely manner, acceptable to the patient, safe, and cost-effective. While existing strategies contribute to managing pain, new strategies to manage pain should be explored to reduce the global burden further. Recent work on greenspace may provide an appropriate option to help reduce the high global burden of pain, particularly chronic pain.

Table 2. Potential treatments for pain

Target	Examples of treatments
Reduce nociception & inflammation	• Analgesics (Fregoso et al., 2019; Nisbet and Sehgal, 2019) • Anti-inflammatory medications (Fregoso et al., 2019; Nisbet and Sehgal, 2019) • Joint and/or neural mobilisation (Alatawi, 2019; Coulter et al., 2019; Lucado et al., 2019) • Electrophysical agents (Binny et al., 2019; Hofmeister et al., 2019; Wu et al., 2019) • Surgery to address underlying problem (e.g. joint replacement) • Rhizotomy (Bakker et al., 2019; Xie et al., 2019) • Nerve blocks (Chang et al., 2016)
Improving the emotional & cognitive factors	• Pain education (Tegner et al., 2018) • Meditation/ mindfulness (Ball et al., 2017; Ngamkham et al., 2019) • Cognitive behavioural therapy (Baez et al., 2018; Hajihasani et al., 2019) • Graded exposure (López-de-Uralde-Villanueva et al., 2016)
Reduce hypersensitivity	• Antidepressants (to modulate the opioid system) (Nisbet and Sehgal, 2019) • Anticonvulsants (to increases gamma-aminobutyric acid levels in the brain) (Fregoso et al., 2019; Nisbet and Sehgal, 2019) • Electrophysical agents (Binny et al., 2019; Hofmeister et al., 2019)

COULD EXPOSURE TO GREENSPACE HELP REDUCE THE PAIN BURDEN?

Greenspace exposure has been associated with a range of positive health outcomes, including conditions associated with pain (e.g. lower stress levels, and better mental health; (Twohig-Bennett and Jones, 2018), providing some indication that greenspace exposure may have a beneficial impact on pain. Despite this, the relationship between greenspace and pain outcomes or painful conditions (e.g. musculoskeletal disorders) have not been adequately investigated (Twohig-Bennett and Jones, 2018).

To our knowledge, only two studies (Ihlebæk et al., 2018; Maas et al., 2009) have investigated the possible association between greenspace exposure and pain outcomes, with mixed findings. Maas et al. (2009) investigated the relationship between the percentage of greenspace in circles with 1 or 3 kilometre radii around the participants' places of residence, and health conditions reported in general practice notes in the 12 months prior. The health conditions targeted included musculoskeletal conditions such as neck/back complaints, severe back complaints, severe neck/back complaints, severe elbow/wrist/hand complaints, osteoarthritis, and arthritis (Maas et al., 2009). Of these musculoskeletal conditions, there was a significant negative association between the percentage of greenspace in the 1 km radius circle and the number of neck/back complaints, severe back complaints, severe neck/back complaints, severe elbow/wrist/hand complaints (Maas et al., 2009). No such significant association was found for the 3 km radius (Maas et al., 2009). The study is directly relevant to the question we are asking, because ache, pain, or discomfort are generally used as proxy-measures of musculoskeletal disorders (Kuorinka et al., 1987), indicating that these symptoms can be pathognomonic of musculoskeletal disorders and that people diagnosed with musculoskeletal conditions are therefore likely to have been experienced pain. However, one of the limitations of this study was that the patients with musculoskeletal complaints studied might not necessarily present with pain.

In the second relevant study, Ihlebæk et al. (2018) investigated the association between the degree of "vegetation cover greenness" and land use greenness within the participants' residential 'circuit', and whether the participant reported pain and/or

stiffness in their muscles/joints in the last four weeks in three or more (of six) body regions (although the body regions were not listed). No association between greenspace and pain for males was observed, but for females the prevalence of pain/stiffness was higher in those living in areas with more vegetation cover greenness and land use greenness (Ihlebæk et al., 2018). This unexpected finding should be interpreted with caution given a number of limitations. Firstly, the outcome measures employed were not tested for validity and reliability, and secondly there was no differentiation between pain and stiffness.

In both studies (Ihlebæk et al., 2018; Maas et al., 2009), the use of residential proximity to greenspace does not necessarily provide an accurate measure of a resident's greenspace exposure, owing to individual differences in exposure to greenspace.

We do however have additional corroborative evidence suggesting that a relationship is likely, and that further research in the area is worthwhile. There is evidence for example that forest therapy (Han et al., 2016; Kang et al., 2015), exercise in green areas (Huber et al., 2019) (not to be confused with 'green prescriptions' that refer to written advice to a patient regarding physical activity made by a health professional; (New Zealand Ministry of Health, 2016), and involvement in horticultural therapy (Kim et al., 2006; Verra et al., 2012) and conservation (Moore et al., 2007) are associated with better pain outcomes. However, these studies have not been designed with appropriate controls to ascertain whether greenspace exposure itself led to the benefits or whether these benefits could be due to other aspects, such as physical activity and/or social interaction. Furthermore, all used

lower level study designs (National Health and Medical Research Council, 2009; Oxford Centre for Evidence-Based Medicine, 2011) (e.g. observational studies), and some studies of forest therapy and green exercise actually also included interventions (e.g. walking/hiking (Han et al., 2016; Huber et al., 2019; Kang et al., 2015), being residential (Han et al., 2016; Huber et al., 2019), music therapy (Han et al., 2016) which were not provided to the comparison groups. As it stands, there is therefore some suggestion that greenspace exposure may assist in pain management, however the evidence to date is insufficient to determine whether the benefits are due to greenspace exposure per se.

In the following sections, we explore the biological plausibility of greenspace exposure per se leading to an improvement in pain outcomes (see conceptual model in Figure 1). These sections refer to the particular components of nature that greenspace exposure may provide, and we separately discuss those that are specific to greenspace (e.g. environmental microbiota, phytoncides, sights and sounds of greenspace) from those that are not greenspace-specific but are facilitated by greenspace exposure (e.g. sunlight, social integration and cohesion (Jennings and Bamkole, 2019), and physical activity (Keskinen et al., 2018). We detail how these greenspace components could be linked to pain outcomes via various ecophysiological linkage mechanisms, some mechanisms of which are known, but including others that are not. Not represented in the conceptual model are additional intrinsic linkages within the ecophysiological linkage mechanisms, such as the influence of gut microbiome on mental health (Liu et al., 2019; Vaghef-Mehrabany et al., 2019; Yang et al., 2019). These added layers of complexity and unknowns must remain as open questions and are not discussed further in our study.

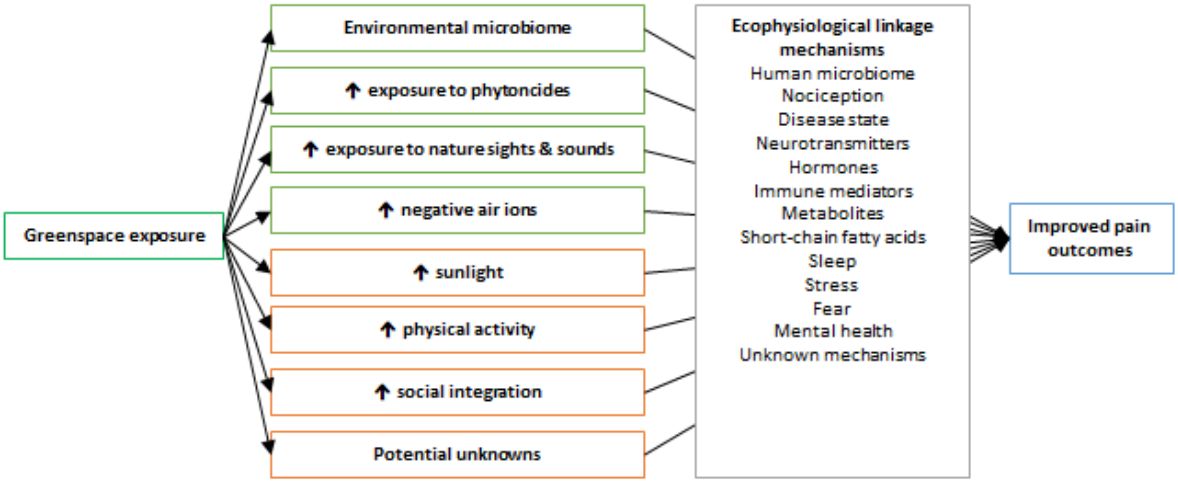

Figure 1. Conceptual model linking greenspace exposure to pain outcomes. Not shown are additional potential pathways joining different ecophysiological linkage mechanisms.

Environmental microbiomes

The 'old friends' hypothesis proposes that humans evolved alongside a diverse suite of environmental microbiota (collectively known as 'microbiomes'), and that co-evolved symbiotic relationships developed (Rook et al., 2004). This co-evolution underpins our argument that exposure to greenspace (with its microbiome) may positively influence pain outcomes. It has recently been demonstrated that direct soil contact changes the human skin microbiome (Grönroos et al., 2019), and that exposure to different environments (and their respective microbiomes) changes the human nasal and skin microbiome (Lai et al., 2017). Importantly, the latter study was conducted indoors and is therefore not susceptible to some of the potential confounding exposures present outdoors (e.g. direct plant/soil/animal interactions, exposure to sunlight and phytoncides) that may also influence the human microbiome (as discussed below). The influence of the environmental microbiome on the human gut microbiome is not currently well understood (Blum et al., 2019;

Tasnim et al., 2017), however animal studies indicate such an influence (Blum et al., 2019), even via indirect exposure to soil via the aerobiome only (Liddicoat et al., 2020).

The microbiome-gut-brain axis refers to the bidirectional communication between the gut microbiome, the gut and the brain, mediated by neurotransmitters, bacterial metabolites, cytokines, hormones and neural communication (Kelly et al., 2015; Mayer et al., 2014). Interest in the microbiome-gut-brain axis has increased dramatically since 2009, with over 500 papers published on the topic in 2018 alone (Zyoud et al., 2019). However, pain as an outcome has been relatively under-investigated, with studies predominantly focusing on visceral pain (Guo et al., 2019; Rea et al., 2019). The relationship between the human microbiome and pain outcomes has recently been comprehensively reviewed (Guo et al., 2019; Rea et al., 2019), hence we provide only a summary of the current evidence base, with interested readers referred to Guo et al. (2019) and Rea et al. (2019) for further detail.

Associations between the human microbiome and a range of painful conditions have been reported. These conditions include endometriosis (Leonardi et al., 2019), fibromyalgia (Malatji et al., 2017), myalgic encephalomyelitis/chronic fatigue syndrome (Nagy-Szakal et al., 2017), interstitial cystitis/bladder pain syndrome (Nickel et al., 2019), chronic prostatitis/chronic pelvic pain syndrome (Shoskes et al., 2016), dermatitis (Gulliver et al., 2018), and inflammatory bowel disease (Knights et al., 2013). Furthermore, there is emerging experimental evidence that changing the gut microbiome through probiotics (*Lactobacillus casei* Shirota (Lei et al., 2017), *L.*

293 *gasseri* OLL2809 (Itoh et al., 2011), and combined *L. acidophilus, L. plantarum, L.*
294 *fermentum* and *L. gasseri* (Khodaverdi et al., 2019) reduces pain in people with knee
295 osteoarthritis (Lei et al., 2017), and endometriosis (Itoh et al., 2011; Khodaverdi et
296 al., 2019). Recently, faecal microbiota transplants have also been shown to reduce
297 pain in those with fibromyalgia (Thurm et al., 2017) and Clostridium difficile infection
298 (Alukal et al., 2019). Although these positive results could be due either to changes
299 in the disease state or to changes in pain processing, they nonetheless suggest that
300 exposure to greenspace – and their associated environmental microbiomes – may
301 lead to reductions in pain, via changes in the human microbiome.
302
303 A recent study by Shiro et al. (2017) reported an association between stool
304 consistency (a proxy measure of the gut microbiome) and pain intensity (initiated by
305 mechanical stimulation of the inter-digital space between the second and third, and
306 the fourth-fifth digits of the right hand). This study provides some evidence of the
307 potential role of gut microbiome on pain perception, although the causal mechanisms
308 are still hypothetical.
309
310 As outlined above, the gut microbiome can influence the brain via various
311 microbially-mediated mechanisms, and those related to chronic pain have recently
312 been reviewed elsewhere (Guo et al., 2019). Microbiota-derived mediators may
313 decrease pain perception via peripheral and central mechanisms. For peripheral
314 mechanisms, the mediators that reduce hypersensitivity include proteases, kynurenic
315 acid, and GABA (Guo et al., 2019). Short-chain fatty acids regulate leucocyte
316 functions, and one of these short-chain fatty acids, butyrate, reduces pain associated
317 with nerve injury by inhibiting histone deacetylase (Guo et al., 2019). Bile acids are

another type of mediator, that may reduce pain by activating release of endogenous opioids from macrophages (Guo et al., 2019). The bacteria that could be implicated in the production of the abovementioned mediators include *L. rhamnosus* (Pokusaeva et al., 2017; Siragusa et al., 2007), *L. brevis* (Barrett et al., 2012), *L. buchneri* (Cho et al., 2007), *L. paracasei* (Komatsuzaki et al., 2005), *L. plantarum* (Siragusa et al., 2007), *L. delbruekii* subsp. *bulgaricus* (Siragusa et al., 2007), *Monascus purpureus* (Su et al., 2003), *Streptococcus salivarius* subsp. *thermophilus* (Yang et al., 2008), *Clostridium butyricum* (Liu et al., 2015; Rivière et al., 2016), *Coprococcus eutactus* (Rivière et al., 2016), *C. comes* (Rivière et al., 2016), *Bifidobacterium* spp. (Rivière et al., 2016), *B. dentium* (Barrett et al., 2012; Pokusaeva et al., 2017), B. infantis (Barrett et al., 2012), *B. adolescentis* (Barrett et al., 2012), *Bacteroides fragilis* (Strandwitz et al., 2019), *Parabacteroides* spp. (Strandwitz et al., 2019), *Faecalibacterium prausnitzii* (Rivière et al., 2016), *Eubacterium hallii* (Rivière et al., 2016), *E. rectale* (Rivière et al., 2016), *Anaerostripes butyraticus* (Rivière et al., 2016), *A. caccae* (Rivière et al., 2016), *A. hadrus* (Rivière et al., 2016), *Butyricicoccus pullicaecorum* (Rivière et al., 2016), *Roseburia faecis* (Rivière et al., 2016), *R. inulinivorans* (Rivière et al., 2016), *R. intestinalis* (Rivière et al., 2016), *R. hominis* (Rivière et al., 2016), and *Escherichia* spp. (Strandwitz et al., 2019) again supporting a potential association between gut microbiome and pain outcomes.

For central mechanisms, central sensitisation may be the result of glial activation which ultimately leads to decreased GABAergic synaptic neurotransmission and/or elevated glutamatergic synaptic neurotransmission, and the gut microbiome plays a role in microglial function, maturation and morphology (Guo et al., 2019). There is

however no direct evidence, to our knowledge, linking the gut microbiome to central sensitisation, although GABA-producing bacteria could theoretically be implicated.

In addition to the abovementioned mechanisms linking the human microbiome and pain outcomes, the human microbiome influences mental health outcomes. Probiotics (e.g. *Lactobaccilis* spp., *Bacillus* spp., *Clostridium* spp., *Bifidobacterium* spp.) can reduce anxiety (Liu et al., 2019) and depression (Liu et al., 2019; Vaghef-Mehrabany et al., 2019), and gut microbiome regulation (e.g. probiotics, dietary changes) can reduce anxiety (Yang et al., 2019). There is also an association between gut microbiome and sleep (Smith et al., 2019). Experimental sleep deprivation has been shown to influence the gut microbiome (Benedict et al., 2016; Poroyko et al., 2016), however to our knowledge no study has investigated whether changes to the microbiome influence sleep outcomes. By improving mental health and potentially sleep, due to the changes in gut microbiome, greenspace exposure may improve pain outcomes.

It has recently been demonstrated in a mouse study that a diverse gut microbiome is required for fear extinction learning to occur (Chu et al., 2019), which may have implications for chronic pain. There is some evidence to suggest that people with chronic pain have reduced differential learning (Harvie et al., 2017), and that fear-avoidance beliefs (Drake et al., 2018; Hruschak and Cochran, 2018; Jayakumar et al., 2018; Morton et al., 2019) are associated with chronic pain. Chu et al.'s (2019) suggested that interventions to reduce fear-avoidance (e.g. graded exposure) may have had limited success in those with lower gut microbiome diversity. These

findings may also have implications for changing other cognitive elements of the pain experience such as pain beliefs, expectations regarding pain and recovery.

Although the association between environmental microbiome and pain outcomes has not been investigated, we suggest that such an association is likely to exist owing to the influence of environmental microbiomes on human microbiomes, and the existence of multiple potential pathways linking the human microbiome and pain outcomes.

Sights and sounds of nature

The biophilia hypothesis – where humans have an innate and natural affiliation with nature (Wilson, 1986) – has traditionally been central to the proposed link between greenspace exposure and health outcomes, and relates to exposure to the sights and sounds of nature. Listening to pleasant nature sounds during elective Caesarean section has been shown to reduce post-operative pain severity (Farzaneh et al., 2019), and also resulted in lower pain for those undergoing mechanical ventilation (Saadatmand et al., 2015). Combined natural sounds and sights have resulted in lower pain severity compared with both city sounds and sights and with a control during bone marrow aspirate and biopsy (Lechtzin et al., 2010). Vincent et al. (2010) demonstrated differences in the effect of viewing an array of natural scenery on experimental pain sensation. They found that the combined prospect/refuge scenery resulted in lower pain sensation than prospect, refuge and hazard scenery and the control (a black screen). Listening to pleasant nature sounds has also been reported to improve sleep (Nasari et al., 2018), while a virtual nature experience reduced stress (Liszio et al., 2018), which may also lead to

a reduction in pain. Greenspace exposure could therefore result in a reduction in pain due to exposure to natural sights and sounds.

Phytoncides

The antimicrobial volatile organic compounds emitted as a defence mechanism by plants are called phytoncides, and they permeate the air particularly in or near greenspace (Franco et al., 2017). To our knowledge no study has investigated the relationship between phytoncides and pain in humans, however an analgesic effect has been reported for mice (Cheng et al., 2009).

Given their antimicrobial properties (Franco et al., 2017), phytoncides may also influence the microbiome. To our knowledge, the impact of phytoncides exposure on the microbiome has not been examined, however the effect of dietary phytoncide supplements on gut *Lactobacillus* spp. and *Escherichia coli* counts has (Kim et al., 2018a; Li et al., 2015; Zhang et al., 2012). These studies of livestock found that dietary phytoncides supplements reported mixed results, with one study reporting no change (Zhang et al., 2018), and others reporting a significantly higher *Lactobacillus* spp. counts (Kim et al., 2018a; Li et al., 2015; Zhang et al., 2012) and lower *Escherichia coli* counts (Kim et al., 2018a; Li et al., 2015) with the supplements. These alternations to the gut microbiome may influence pain perception, due to the mechanisms outlined above.

Phytoncides may also influence the human immune system, particularly natural killer cell function. In vitro studies have shown that phytoncides can enhance human natural killer cell function (Li et al., 2006). Natural killer cell function was enhanced

for people walking in forests, but not in cities, and importantly phytoncides were only detected in the forest and not in the city (Li et al., 2008). This study did not, however, account for the potential impact of other forest exposures (e.g. environmental microbiome) that may have influenced the relationship. Nonetheless, greenspace exposure appears to improve natural killer cell activity, and natural killer cells have recently been proposed as a treatment for some types of pain (Davies et al., 2019).

Phytoncides have also been shown to improve sleep and reduce anxiety in animal studies (Cheng et al., 2009), providing further evidence of a potential link between greenspace exposure, phytoncides, and pain outcomes. Different anxiety responses have been observed with exposure to different tree species in forest bathing (Guan et al., 2017), which could be explained by differences in the phytoncides released. A recent random crossover study (Horiuchi et al., 2014) compared two forest bathing exposures; one where participants could see the forest and the other where they could not. There was a significant reduction in trait-anxiety, depression, confusion and fatigue when the forest could be viewed, but not when the view was occluded, however there were no significant differences in the outcomes between the two exposures post-exposure (Horiuchi et al., 2014). Horiuchi et al.(2014) indicated that phytoncides are unlikely to be the sole reason for changes in human health outcomes related to greenspace exposure, but supported the notion that greenspace exposure may improve pain outcomes.

Negative air ions

Negative air ions are generated by plants (see Jiang et al. (2018) for a list), shear forces of water, sunlight, atmospheric radiant or cosmic rays, and natural and

442 artificial corona discharge (Jiang et al., 2018). They are less prevalent in urban
443 settings compared with forests, places with moving water, and mountainous areas
444 (Mao et al., 2012). There is some, albeit limited, evidence of negative air ion
445 exposure altering pain outcomes (David et al., 1960; Minehart et al., 1961;
446 Olivereau, 1970), through a range of potential effects on humans and other animals.
447 These effects include decreased cyclic nucleotides, lower dopamine, activation of
448 natural killer cells, and improved mental health (Jiang et al., 2018), all of which may
449 reduce pain, including chronic pain (Davies et al., 2019; Drake et al., 2018; Hruschak
450 and Cochran, 2018; Jayakumar et al., 2018; Li et al., 2019; Liu et al., 2018; Taylor et
451 al., 2016).
452
453 Negative air ions have also been shown to kill or reduce a range of microbes,
454 including *Serratia marcescens, Staphylococcus albus, S. aureus, S. epidermidis,*
455 *Pseudomonas veronii, P. fluorescens, Salmonella Enteritidis, Candida albicans,*
456 *Escherichia coli,* and *Penicillum notatum*, and have been shown to prevent
457 Acinetobacter infections (Jiang et al., 2018). These antimicrobial effects indicate that
458 negative air ions have the potential to alter the human microbiome, which may
459 therefore influence pain outcomes.
460
461 *Sunlight exposure*
462 Sunlight exposure is the first of three generic factors that we propose may link
463 greenspace exposure to pain outcomes. Depending on the weather, geographic
464 location, canopy cover and time of day, spending time in greenspace is likely to lead
465 to sunlight exposure. Sunlight exposure is perhaps most commonly associated with
466 vitamin D production, but exposure to sunlight also leads to the production of beta-

endorphin (an endogenous opioid peptide), melatonin, and nitric oxide (a vasodilator), as well as the release of carbon monoxide from haemoglobin (a vasodilator), and expression of the proopiomelanocortin gene (which results in the production of beta-endorphin and cortisol) (Holick, 2016).

Observational studies have identified an association between vitamin D levels and arthritis, muscle pain, chronic widespread pain (Wu et al., 2018), and low back pain (Zadro et al., 2017); however, studies investigating the impact of vitamin D supplementation on pain outcomes have generally shown that vitamin D supplementation is no better than placebo for people with lower back pain (Zadro et al., 2018) and non-specific musculoskeletal disorders (Gaikwad et al., 2017). However, there is some evidence of vitamin D lowering pain intensity for those with chronic widespread pain (Yong et al., 2017). The discrepancy between the observational and experimental evidence regarding the relationship vitamin D and pain may be the result of vitamin D acting as a proxy-measure of sunlight exposure. Sunlight exposure could lead to a change in pain through non-vitamin D pathways, including the release of beta-endorphins (Holick, 2016) and melatonin (Zhu et al., 2017), or indeed changes in the microbiome (Waterhouse et al., 2019). Furthermore, sunlight exposure (Düzgün and Durmaz Akyol, 2017) and vitamin D supplementation (Jamilian et al., 2019) have led to improved sleep including for people with chronic pain specifically (Huang et al., 2013). Vitamin D supplementation has also resulted in reduced inflammation (Jamilian et al., 2019) and improvements in depression (Jamilian et al., 2019), which may in turn contribute to improved pain outcomes.

Physical activity

Exposure to greenspace reportedly facilitates physical activity (Keskinen et al., 2018); the second generic factor in our review. Physical activity is commonly prescribed by health professionals, particularly for patients in pain. Evidence in support of physical activity for reducing the prevalence and impact of pain include findings of physical activity being associated with a lower incidence of neck pain (Kim et al., 2018b), and lower prevalence of lower back pain (Alzahrani et al., 2019b), including frequent and chronic lower back pain (Shiri and Falah-Hassani, 2017). Furthermore, interventions to increase incidental physical activity lead to improved lower back pain-related disability (Alzahrani et al., 2019a). For those with musculoskeletal conditions in particular, physical activity may decrease nociception by improving the underlying musculoskeletal condition. Exercise reduces inflammation (Stigger et al., 2019; Zheng et al., 2019) and stress (Bischoff et al., 2019; Rodriguez-Ayllon et al., 2019), improves sleep (Banno et al., 2018; Kreutz et al., 2019; Lederman et al., 2019; Lowe et al., 2019; Stutz et al., 2019) and mental health (Béland et al., 2019; McDowell et al., 2019; Morres et al., 2019; Nakamura et al., 2019; Rodriguez-Ayllon et al., 2019), and changes the human microbiome (Mailing et al., 2019). The health improvements associated with exercise may also influence pain perception and the risk of transitioning from acute to chronic pain. Thus, physical activity, particularly when facilitated by greenspace exposure, is likely to also contribute to a reduction in the global burden of pain.

Social integration

Although social integration is not specific to greenspace, greenspace exposure is associated with a range of social benefits and has been identified as a facilitator of social integration and cohesion (Jennings and Bamkole, 2019), and would therefore

be expected to improve social support. Social support has been associated with pain perception (Che et al., 2018b), including experimental pain (Che et al., 2018a), while low levels of social support are associated with a higher risk of transitioning from acute to chronic pain (Fregoso et al., 2019). In addition, higher levels of social support and integration are associated with lower inflammation (Uchino et al., 2018), better sleep (Kent de Grey et al., 2018), and better mental health (Tengku Moud et al., 2019) which may all in turn influence pain perception. Of note, sleep may also influence the gut microbiome (Benedict et al., 2016; Poroyko et al., 2016) and thus potentially pain perception through that mechanism as well. We therefore suggest that greenspace exposure is likely to decrease both pain perception, and the transition from acute to chronic pain, via improvements in social integration and support.

RECOMMENDATIONS

Here we argue that exposure to greenspace may be an effective, safe and accessible strategy to help alleviate the global burden of pain. With the exception of those with compromised immune systems, exposure to greenspace should therefore be encouraged for those experiencing pain.

The association and potential therapeutic benefit of greenspace exposure for those with pain should be further explored, with a particular focus on the transition from acute to chronic pain, and the prevalence and burden of chronic pain. To do this we need valid and reliable measures of exposure to greenspace (e.g. time spent in greenspace, characteristics of the greenspace), which, to our knowledge, do not currently exist.

One of the advantages of greenspace exposure as an intervention for pain, particularly chronic pain, is that it is not reliant on medical intervention, and could be implemented while on waiting lists for specialist appointments – a particularly important consideration in the socially isolating conditions of a pandemic, with elective surgery and pain clinics closed down. It can take years for patients to gain access to these services (Anderson, 2016), during which time their nervous systems change and the burden of their pain increases. The caveat to this is, however, that appropriate greenspaces must be accessible to those who require them. Several general barriers to such greenspace access have been suggested, and include a lack of amenities (Cronin-de-Chavez et al., 2019; Sefcik et al., 2019), safety concerns (Boyd et al., 2018; Cronin-de-Chavez et al., 2019; Sefcik et al., 2019; Selby et al., 2019), proximity to greenspace (Selby et al., 2019), and issues with transport (Boyd et al., 2018; Cronin-de-Chavez et al., 2019; Fretwell and Greig, 2019; Sefcik et al., 2019). Perhaps more importantly, a lack of interest (Boyd et al., 2018; Fretwell and Greig, 2019) and time (Boyd et al., 2018; Fretwell and Greig, 2019; Holt et al., 2019; Selby et al., 2019), and debilitating health conditions (Boyd et al., 2018; Cronin-de-Chavez et al., 2019; Fretwell and Greig, 2019; Sefcik et al., 2019) have also been identified as barriers. Finally, in the current COVID-19 situation, strict lockdowns in countries like Italy are likely to reduce greenspace exposure for many people. These barriers support the need to optimise opportunistic encounters with greenspace, such as advice to optimise private greenspaces to maximize benefits, as well as utilising verges and high-use areas (e.g. commuter paths, work place environments) for optimal greenspace, so that passive exposure to

the aerobiome is achieved. Stakeholder engagement is also essential to improve usage of public greenspaces (Roberts et al., 2016).

To optimise greenspaces to improve pain outcomes we need to understand which elements of greenspace have the most influence on pain outcomes (e.g. phytoncides, microbiome), what the most advantageous greenspaces comprise of (e.g. the specific microbes that should be in relative abundance), and how to encourage people, particularly those in pain, into such greenspaces.

With specific reference to the environmental microbiome, further work is required to characterise the components of the environmental microbiome that directly influence pain. Such health outcome-environmental microbiome association studies have begun in non-pain related areas (e.g. anxiety-like behaviour; (Liddicoat et al., 2020), and are a required precursor to not only understanding the level of exposure to these potential pain-mitigating microbiota from greenspaces, but also how to derive these pain management benefits via targeted changes to greenspaces.

CONCLUSIONS

Here we articulate how and why exposure to greenspaces is likely to reduce pain, particularly chronic pain. Greenspaces provide exposure to environmental microbiomes, phytoncides, negative air ions, natural sights and sounds, and sunlight, and may facilitate physical activity and social integration. We describe established or potential links between these specific exposures and pain outcomes. Further research is required to determine the mechanistic pathways that link greenspace and pain outcomes, as well as the nature and duration of specific exposures relevant to

591 optimising pain outcomes. By making available public and private greenspaces
592 accordingly, and reducing barriers to access, we are likely to see a reduction in the
593 global burden of pain.
594
595

Competing or Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing or conflict of interest.

Author Contributions

J.S., M.F.B. and P.W. contributed to the conception of the article; J.S, M.F.B. and P.W. contributed to manuscript writing, revision, read and approved the submitted version.

Data Accessibility Statement

There are no data used in this manuscript.

FIGURE LEGEND

Figure 1. Conceptual model linking greenspace exposure to pain outcomes. Not shown are additional potential pathways joining different ecophysiological linkage mechanisms.

TABLE TITLES

Table 1. Characteristics for the three main pain categories

Table 2. Potential treatments for pain

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