Greenspace, mental health, and psychological well-being: Exploring mechanisms and effect modification

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Abstract

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In an age where humans are spending an unprecedented portion of their time indoors, disconnected from nature and unaware of the ecosystem that surrounds them, research is beginning to unveil the intricate role of nature in human health. Not only does humanity rely on the natural world for food, water, and other ecosystem services, but also for psychological well-being, happiness, and mental health maintenance. Many individuals anecdotally understand that time spent in natural settings can ease negative mental health issues such as stress, anxiety, and depressive symptoms, while encouraging positive psychological states, such as happiness and relaxation.

Epidemiologists, ecologists, neuroscientists, and researchers from many other disciplines are digging deeply into these ideas, transforming anecdotes into scientific research, and

uncovering the mechanisms underlying the connection between mental health and natural environments. They are also exploring whether and to what extent existing trends between greenspace exposure and benefits to mental health may differ among different populations and individuals. To build upon this body of work and help fill critical research gaps, I conducted two research projects– an environmental epidemiological analysis of data from a large-scale health cohort and a narrative literature review on the Japanese health practice of forest-bathing.

The first project utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA), an epidemiologic cohort study with 6,814 participants from six sites across the US. In this analysis, I tested for association between residential proximity to greenspace, measured by the normalized difference vegetation index (NDVI), and scores from the Center for Epidemiologic Studies (CES) Depression Scale, a measure of depressive symptoms. To determine the role of individual-level characteristics in modifying this relationship, I assessed the degree to which chronic burden, a proxy for chronic stress, modified the effects of greenspace on depressive symptoms. This allowed me to determine if highly burdened individuals have pronounced mental health benefits associated with exposure to greenspace.

The second project was a narrative literature review on the mental health and psychological well-being benefits of forest exposure. This review builds upon the forest-bathing literature by exploring potential biological and psychological mechanisms underlying the association between forest terpene exposure and benefits to human health. Together, these two projects contribute to the growing body of nature and health literature by diving deeper into mechanistic pathways and by determining the role of individual-level characteristics in the effect of nature on mental health and well-being.

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Abstract

Mounting evidence from a variety of disciplines has demonstrated that living in close proximity to greenspace is associated with improvements in mental health and psychological well-being outcomes. However, it is not fully understood how individual-level characteristics may alter the magnitude and direction of this relationship. Preliminary epidemiologic research has suggested that individuals of lower socioeconomic status (SES) have pronounced health benefits resulting from residential proximity to greenspace. This comparatively larger improvement in health outcomes in response to green exposure may be partially explained by the chronic stress associated with poverty. Chronic stress can result in physiologic responses that make individuals more vulnerable to negative health outcomes. It may be that greenspace can lower these psychological stress levels, impacting both mental and physical health, particularly in those with high chronic stress.

Here, we test for association between residential proximity to greenspace, which we approximate with the normalized difference vegetation index (NDVI), and scores from the Center for Epidemiologic Studies Depression Scale (CES-D), an index for depressive symptoms. Building on previous research, we investigate chronic burden, a proxy for chronic stress, to evaluate effect modification. We hypothesize that highly burdened individuals will have a pronounced decrease in depressive symptoms associated with higher exposure to greenspace. We utilized data from the Multi-Ethnic Study of Atherosclerosis (MESA), a longitudinal epidemiologic cohort study with 6,814 participants from six sites across the US. NDVI values at

buffers of 250 and 500 meters surrounding the participants' addresses were used to approximate residential exposure to greenspace. We used a random effects regression model to evaluate the interaction between chronic burden and NDVI on depressive symptom outcomes. To account for repeat measures, we specified a person-level random intercept to allow for within-subject variation.

We found a significant interaction between NDVI and chronic burden ($p<0.001$). Among participants with high chronic burden, there was a decrease in CES-D scores with increasing NDVI, while there was an increase in CES-D scores with increasing NDVI for the low and medium chronic burden groups. We conclude that green environments may improve depressive symptoms by alleviating the psychological stress that is potentially underlying depressive symptoms in those with high chronic stress. Our findings highlight the role of individual-level characteristics, specifically variation in chronic stress, in the effect of residential greenspace exposure on depressive symptoms.

Introduction

Researchers from a variety of disciplines have demonstrated the multi-faceted ways in which nature affects mental health and psychological well-being[1,2]. This body of research emphasizes the fact that, in an increasingly urbanized world, contact with nature, even within urban areas, may support human health and well-being[3]. In particular, several studies have found associations between residential proximity to greenspace and improved psychological well-being, physical health, and mental health[4–7]. According to the United Nation's projections, by 2050 two thirds of the global population will live in urban areas[8]. Thus, it is critical to understand how, and to what extent, natural areas, particularly within urban spaces, can benefit human health and serve as public health assets. Nature has been defined in the environmental health literature as "areas containing elements of living systems that include plants and nonhuman animals across a range of scales and degrees of human management, from a small urban park through to relatively pristine wilderness"[9]. We focus in this paper on a particular type of nature – greenspace, which refers to areas of predominantly green vegetation, such as grass, shrubs, and trees, both within urban and undeveloped contexts[10].

In several disciplines, including geography, ecology, and epidemiology, greenspace is approximated quantitatively using the normalized difference vegetation index (NDVI). NDVI utilizes satellite land imaging to quantify vegetative surfaces, based on the fact that vegetation absorbs more red light and reflects more infrared radiation than non-vegetative surfaces[11]. Studies that use NDVI to quantify residential proximity to greenspaces have found associations between higher NDVI and health outcomes as diverse as decreased mortality following stroke[12], higher cognitive performance[13], and improved subjective general health[14]. Mental health outcomes that have been evaluated in relation to residential proximity to greenspace, often

utilizing NDVI, include measures of psychological distress[15], emotion and behavioral problems[16], anxiety[17], stress[18], perceived mental health[19], and depression[20]. Improvements in depressive symptoms in association with higher greenspace exposure have been found in a diversity of populations, including pregnant women[21], adolescents[22], and adults from several different countries and across socioeconomic groups[20,23,24]. The prevalence of mental illnesses, such as depression, have increased globally in recent decades[25,26]. In light of this, the potential for greenspace to serve as a modifiable and low-cost mental health intervention is promising.

While the connection between exposure to greenspace and improved mental health is relatively well-established[2,27,28], the role of individual-level characteristics is poorly understood. Few studies have investigated whether this association is modified within vulnerable and under-resourced subsets of the population. Determining whether, and to what extent, greenspace supports positive mental health in different populations is a critical step in ensuring that greenspace is integrated into health considerations in an equitable and broad-reaching manner[29–31]. Epidemiologists have suggested that social and environmental exposures, which have historically been studied separately, may interact to exacerbate health outcomes more so than one exposure alone[32]. For instance, air pollution exposure is thought to interact with socioeconomic status, resulting in worse health effects from pollution in individuals of lower SES groups compared to those in higher SES groups[32]. Preliminary cross-sectional work has indicated that the opposite pattern may hold for greenspace exposure, resulting in pronounced health benefits for disadvantaged populations, thereby lessening racial and socioeconomic inequities in health[33]– a pattern that has been called "equigenic effect"[34]. One example of equigenic effect was found in Mitchell and Popham's 2008 article, which evaluated the association between income deprivation and all-cause mortality. They discovered that the association between income and

mortality differed by levels of greenspace exposure; for those living in the greenest areas, income-related health inequalities were lower than for participants in less green neighborhoods[34]. Building on this work, Dadvand et.al found that surrounding greenspace, approximated with NDVI, was positively associated with birth weight, and that the relationship was strongest among mothers who lived in economically deprived neighborhoods and were less educated[21]. A similar trend was found in the Netherlands, where those with lower educational levels experienced a stronger relationship between greenspace exposure and better self-reported general health[35].

The equigenic effect has also been found in relation to mental health and psychological well-being outcomes, such as depressive symptoms. In a European study of socioeconomic-related health inequalities, increased access to greenspace was associated with less pronounced socioeconomic inequalities in mental well-being[36]. Additionally, McEachan et.al (2015) found that residential proximity to greenspace, approximated with NDVI, was associated with a reduction in depressive symptoms in pregnant women, and that the association was stronger in women from lower SES groups[37]. In an economically deprived community in the U.K., residential proximity to greenspace was significantly associated with a decrease in stress, which was measured through self-report and salivary cortisol patterns[38]. The equigenic effect is crucial to consider as health inequities in the United States continue to grow[39].

There are, however, mixed results for the equigenic effect in the relationship between health and greenspace in the literature, with some studies finding that higher SES groups see a larger health benefit from greenspace[40–42]. For instance, in a study of the equigenic effect in Australian youth, researchers failed to find effect modification by SES in the association between parent-reported quality of greenspace and parent-reported general health of the child[43].

Additionally, Browning et.al found that in cities with a high percentage of white residents, high levels of tree coverage were associated with lower levels of obesity. However, in cities with a lower percentage of white residents, the opposite trend was found– increased tree coverage was associated with higher obesity rates[44]. Dadvand et.al found that residential proximity to greenspace, using NDVI as a proxy, was positively associated with birth weight in a British community; however, the association was not significant among Pakistani mothers, a racialized group included in the study[21]. Given the pressing need to lower the health inequality gap across the globe, these mixed findings on the equigenic effect within the nature and health literature merit further investigation.

One explanation for why nature exposure may benefit lower SES or marginalized groups more than higher SES or privileged groups is that greenspace may attenuate the chronic stress associated with poverty, which creates health vulnerabilities[45]. Chronic stress, which puts individuals at higher risk for many physical and mental health issues, is thought to partially explain SES-related health disparities[46]. Mitchell et.al suggest that the health benefits of access to greenspaces may be greater among those under high levels of stress, and they call for an exploration of other equigenic characteristics[36]. This idea is supported by the finding that individuals who have suffered from highly stressful events may experience greater rehabilitative benefits from nature than people who have not experienced stressful events[47]. Thus, the equigenic effect may be an important consideration among highly stressed individuals, who may experience greater health benefits from access to greenspace than those with lower chronic stress. Exploration of the equigenic effect within the nature and mental health literature simultaneously investigates factors that may modify the greenspace and health association—an important research gap in the related literature[19].

One theoretical underpinning within the nature and health literature, Stress Reduction Theory (SRT), is further reason to hypothesize that chronic stress may be an important moderator to consider. According to SRT, exposure to natural environments leads to a faster and more complete physiological recovery from acute stressors[48]. Exposure to nature can also reduce chronic stress, possibly by reducing exposure to environmental conditions that may elicit stress, such as noise pollution and overcrowding[49].

Attention Restoration Theory (ART) is closely tied to SRT and explains the cognitive processes that may be at play in the stress reducing effects of nature. ART states that effortful, directed attention required by everyday demands, such as work, lead to mental fatigue, inability to concentrate, and stress[50]. Nature, in contrast, is thought to involuntarily and effortlessly capture one's attention, an idea known as "soft fascination", which demands less mental effort and provides an opportunity to recover from attention fatigue[50]. Taken together, SRT and ART support the idea that greenspace exposure leads to stress-reduction and mental restoration. As stress is known to exacerbate and, in some cases, cause other physical and mental health issues[51], decreased stress may partially explain the association between greenspace and beneficial health outcomes.

Chronic stress may act as a mediator between environmental conditions and health outcomes, as stress can be involved in the etiology of both physical and mental illnesses[52]. Given the important role that the stress-reducing capacity of nature plays on health outcomes, chronic stress may also modify the association between greenspace exposure and health outcomes. Individuals with high chronic stress may have more potential to benefit from the health benefits of stress reduction due to nature exposure, while those with low chronic stress may be impacted by nature exposure differently or less so. These two roles of chronic stress, as mediator and

effect modifier, are not mutually exclusive and both merit exploration; however, we focus in this paper on chronic stress as an effect modifier in the relationship between greenspace and depressive symptoms.

Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective cohort study that began in 2000 with the goal of understanding risk factors for subclinical cardiovascular disease (CVD), we explore how the equigenic effect applies to the association between residential proximity to greenspace and depressive symptoms. As previous literature suggests[1,27,28], we expect a decrease in depressive symptoms as residential proximity to greenspace increases. Based on equigenic effect findings, we also expect that highly chronically burdened participants will experience pronounced decreases in depressive symptoms in response to increasing greenspace[34,37]. Overall, this exploration will further our understanding of individual-level characteristics that may be critical in understanding how greenspace affects mental health and psychological well-being differently for various individuals and subpopulations.

Methods

Study design and subjects

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal, prospective health cohort that is funded by the National Heart, Lung, and Blood Institute. The primary goal of MESA is to understand risk factors for and pathogenesis of subclinical atherosclerosis and other cardiovascular diseases (CVD). Study participants, ages 45-84 years old at baseline in the year 2000, were recruited at 6 sites across the US: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota[53]. At baseline, the cohort consisted of 6,814 individuals, with roughly equal numbers of male and female participants. MESA recruited participants who did not have clinical cardiovascular disease at baseline and who spoke either English, Mandarin, Cantonese, or Spanish. MESA aimed to recruit people of color who were previously under-studied and that were hypothesized to experience different prevalence or incidence of cardiovascular diseases and associated risk factors. They recruited 38% White, 28% African-American, 22% Hispanic, and 12% Chinese participants to allow for comparisons among specific racial/ethnic groups[53].

The six field sites recruited subjects using a variety of techniques, and each site recruited from at least two of the four racial/ethnic groups of interest. Recruitment methods included random sampling of eligible individuals from the Department of Motor Vehicle and Centers for Medicare & Medicaid Services lists, and random digit dialing[54]. Additionally, informational brochures were mailed to residences in targeted neighborhoods, and two weeks later recruiters called these households and administered an eligibility questionnaire in the language spoken at that home[53]. MESA conducted six examinations between 2000 and 2016,

spaced approximately two years apart, with the first exam being the most comprehensive. This analysis is based on data from Exams 1 (2000-2002) and 3 (2004-2005), because these were the only exams that included both the CES-Depression and Chronic Burden scales. In addition, NDVI data came from an ancillary study—the MESA Air Pollution Study, which intended to study associations between air pollution exposure and subclinical atherosclerosis[55].

Depressive symptoms outcome

Our primary outcome of interest, depressive symptoms, was measured using the Center for Epidemiologic Studies Depression (CES-D) Scale. This continuous scale ranges from 0 to 60 and is based on a twenty-item questionnaire, in which each item is scored from 0 to 3[56]. The CES-D assesses depressive mood ("past week, I felt sad"), feelings of worthlessness ("past week, I felt I was not as good as other people"), feelings of hopelessness ("past week I felt hopeful about future"), poor concentration ("past week, I had trouble keeping my mind on what I am doing"), loss of appetite ("past week, I had poor appetite"), and sleep disturbance ("past week, sleep was restless")[57]. Higher scores represent more depressive symptoms[58]. Considered highly reliable and valid, the CES-D has been used since the 1970's to screen for depression across many adult populations[59]. The CES-Depression Scale was collected at Exams 1 and 3 in the participant's language of choice[60]. Figure 1 shows the distribution of CES-D scores for all participants.

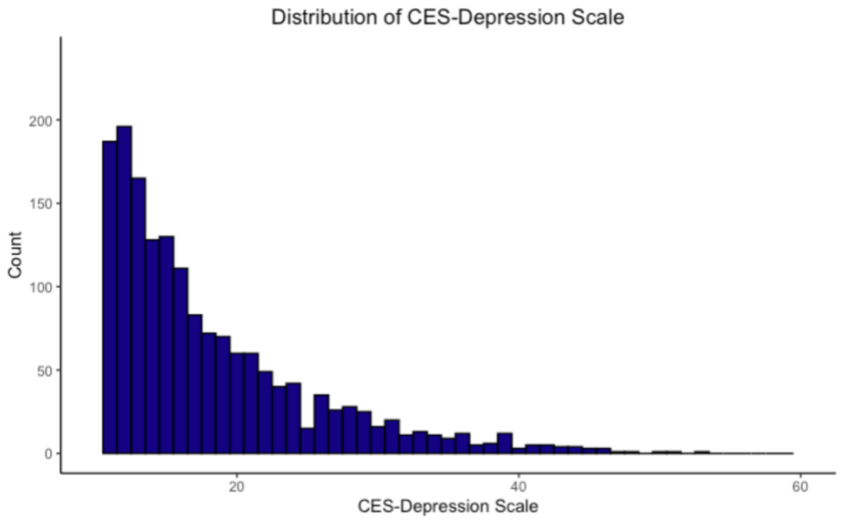

Figure 1. Distribution of baseline CES-D scores across all participants.

Proxy for greenspace exposure

We quantified greenspace exposure using the Normalized Difference Vegetation Index (NDVI), which utilizes high-resolution satellite imagery to calculate green vegetation on earth's surface. NDVI is computed by comparing wavelengths, or colors, of each pixel, based on the fact that green vegetation reflects more near-infrared radiation (NIR) and green light, and absorbs more red light than non-vegetative surfaces, or surfaces with dead vegetation[11]. NDVI has been utilized in many other environmental epidemiology studies as a proxy for exposure based on residential proximity to greenspace, and it has been evaluated in relation to health outcomes in several studies, as outlined in the introduction[5,14,22].

We obtained NDVI values geocoded to participants' addresses from the MESA Air ancillary study. These values were calculated by first averaging each pixel within certain Euclidean buffers around the participants address (radii of 250 m, 500 m, 1 km, and 5 km) for 16 days, and then taking the median value of those 16 days. The resulting number represents the average vegetation in the respective buffer around participants' addresses throughout the year of

2006. The 16 images were taken during all seasons, and thus are representative of annual vegetation variation[61]. As we include data from two separate rounds of data collection per participant, there are two NDVI values per person, corresponding to the address at which they lived at during Exams 1 and 3. If participants did not move, the value remains the same. We chose to use NDVI values from the 250 m and 500 m buffers around participant addresses for our analysis. These values are used in related studies, as the literature suggests these are reasonable proxies for exposure in order to most closely capture visual and physical access to nearby greenspace for participants[13,14,62].

NDVI was reported by MESA on a scale of 0-255, which had been converted from the -1 to 1 scale, with higher values indicating more greenspace[61]. We transformed this scale back to the original, and more widely used, -1 to 1 scale, as this is the standard in related literature. An NDVI value below zero indicates primarily water surfaces, known as blue space, and values above zero represent land, with higher values corresponding to more greenspace and vegetation[22]. We removed values below 0 because we wanted to focus on the effects of greenspace exposure compared to the built environment, without examining blue space. Blue space is a different form of nature exposure, which has been explored elsewhere in relation to mental health[27,63,64]. Figure 2 shows the distribution of NDVI values across participants at both buffer sizes used in our analysis. The bimodal distribution of NDVI values is due to differences in the six sites included in the study.

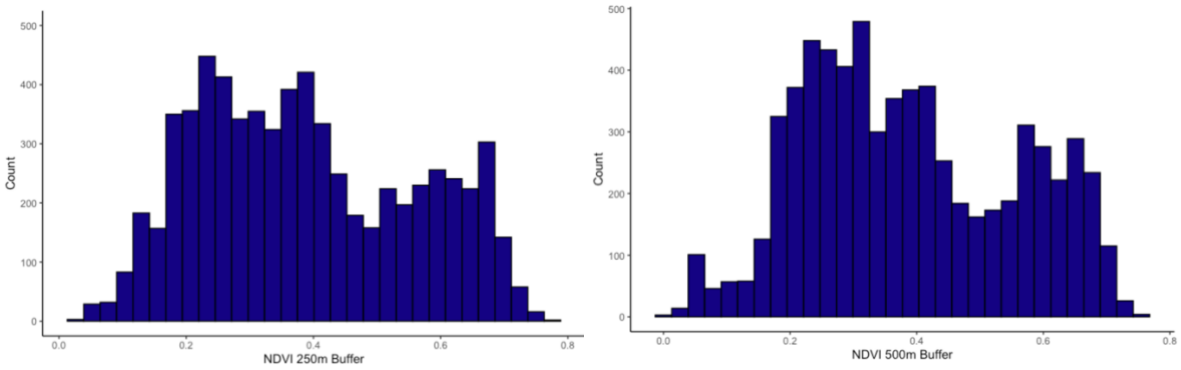

Figure 2. Distribution of NDVI values at the 250m buffer and 500m buffers around participant addresses at baseline.

Chronic Burden

To assess how chronic stress potentially moderates the relationship between greenspace exposure and depressive symptoms, we utilized the Chronic Burden Scale. This scale was initially created for the Study of Women's Health[65] and has been since utilized in various formats by other longitudinal cohort studies as a measure of chronic stress[51,66]. It is based on a five-item scale asking about ongoing job, relationship, health, and financial stress for the participant or someone close to them lasting six months or longer. Individuals were asked how stressful (ranging from not very to moderately to very stressful and coded as 1-3) each item was, and items with moderate to severe stress ratings were summed together to create the chronic burden score. Other studies utilizing MESA data have examined chronic burden as a proxy for chronic stress[65,67]. We analyzed chronic burden as a categorical variable with three bins: low (0), medium (1), and high (2-5)-- based on tertiles, an approach that has been used in another MESA

studies[68]. The distribution of chronic burden, by race and gender, is shown in Figure 4.

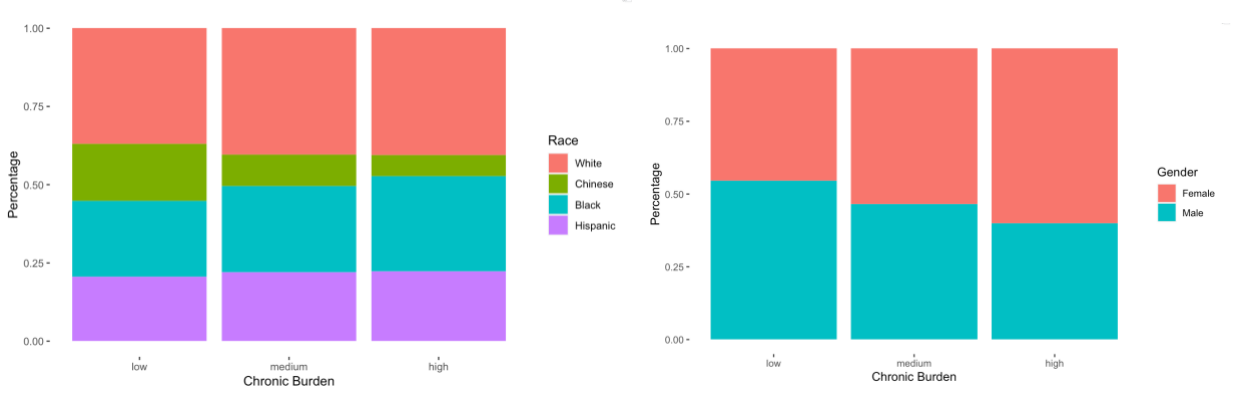

Figure 4. Categorical chronic burden distribution by gender and race.

Covariates

Site, age, race/ethnicity, gender, household income, use of antidepressants, marital status, emotional social support index, and education level were included as covariates. These covariates were selected based on the standard in related literature and known individual-level correlates of well-being and mental health outcomes, particularly depression[6,69,70]. We also controlled for the number of days that participants lived at their current address in order to more accurately reflect the NDVI greenspace exposure proxy.

Site, gender, education level, and race/ethnicity were assessed at MESA Exam 1. Site refers to which of the six MESA cities (Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota) in which the participant resides. Gender was categorized as male or female based on the participant's self-report. Highest level of education achieved was categorized by MESA's data analysts into nine categories, which we then combined to create

three levels: less than high school, high school completed, and education beyond high school. Education level usually does not change for a population of older adults; therefore, it was treated as time-fixed by utilizing the baseline education data for both time points. Race/ethnicity was classified as White, African American, Chinese American, or Hispanic, based on self-report using questions from the Year 2000 US census[70].

Age, household income, use of antidepressants, marital status, and emotional social support index were collected at each exam and correspond to the time of that exam. Age at baseline ranged from 45 to 84 and was treated as a continuous variable. MESA originally categorized gross annual household income over the past 12 months into 13 categories. We then combined these into three brackets: low (<$20,000), middle ($20,000-$49,999), and high (>49,999) based on other MESA studies[71]. The distribution of income, by race and gender, is displayed in Figure 3.

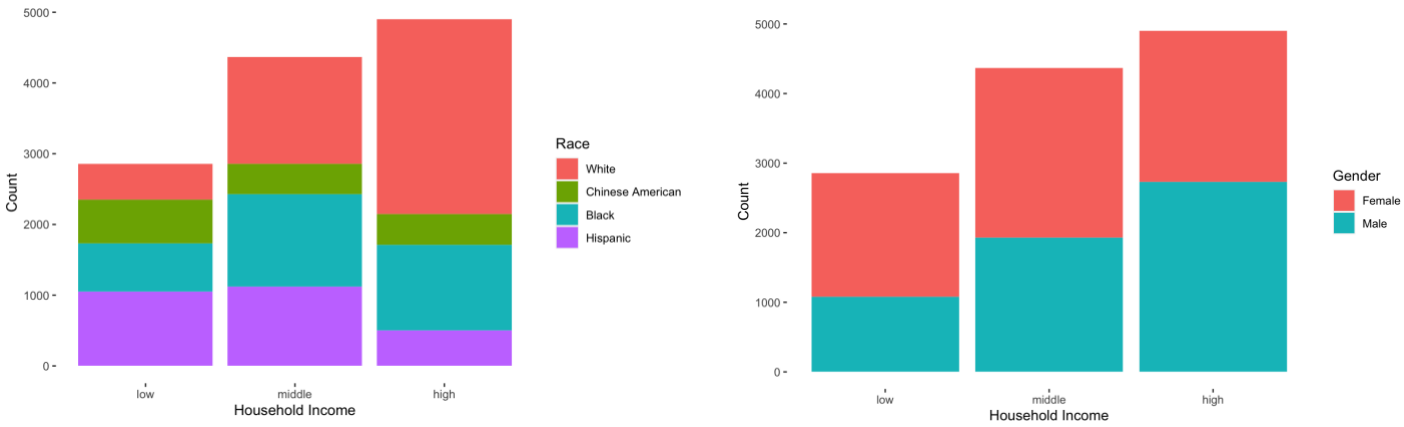

Figure 3. Categorical gross household income distribution by gender and race.

Antidepressant use was coded as yes/no, based on current usage of any one or more of the following medications: selective serotonin reuptake inhibitors, tricyclic antidepressants,

norepinephrine-dopamine reuptake inhibitors, serotonin antagonist with reuptake inhibitors, MAO inhibitors, serotonin-norepinephrine reuptake inhibitors, and non-tricyclic antidepressants. For the marital status variable, Exam 1 included six categories of marital status: married/living as married, widowed, divorced, separated, never married, and prefer not to answer. In contrast, the marital status variable for Exam 3 was less granular and was coded as yes/no based on the question: "are you currently married or living with a partner." To standardize the variable across both observations, we created a binary marriage/partnership variable for Exam 1 to match Exam 3, in which married/living as married is "yes", and widowed, divorced, separated, never married are "no." Lastly, emotional social support was measured at Exams 1 and 3, based on a six item validated scale that evaluated the degree to which the participant felt they had someone to talk to, get advice from, and confide in[72]. The index was coded as scores ranging from 6 to 30, in which higher scores indicate more social support.

Statistical analysis

We performed a staged modeling approach using mixed effect models in R, version 4.0, with the lme4 package, version 1.1-23. As there were two repeated observations for each person, we controlled for participant ID as a random effect to specify a person-level intercept and allow for clustering of the outcome by participant. For each phase in the analysis, we ran two models, one with the 250m buffer for NDVI, and another with the 500m buffer. As previously discussed, we excluded participants with NDVI values below 0 (N=17), since these values indicated the majority of residential land cover surrounding the home was water, rather than greenspace or unvegetated land. In addition, we excluded participants with missing values for either NDVI (N=86), CES-D (N=53), or Chronic Burden (N=99). Together, these exclusion criteria brought

our sample size to 6,701 participants at Exam 1, and 5,850 participants from Exam 3, a total of 12,551 observations. Not all participants had a repeated measure due to loss to follow up, which was primarily attributable to death, unwillingness to participate, or movement outside of the site range[73].

Our first phase of analysis tested for association between NDVI and depressive symptoms by regressing CES-D scores on NDVI values and controlling for gender, age, race/ethnicity, income, use of antidepressants, emotional social support, marital status, time lived at address, site, and education as covariates. Model 1 included NDVI at the 250m buffer and model 2 used the 500m buffer NDVI. We ran two sets of each of these models, one controlling for site as a covariate, and one without site. Since site drives much of the variability in NDVI, adjusting for site removes much of the variability in the exposure while not doing so allows for greater variability.

Our primary aim was to evaluate chronic burden as an effect modifier in the association between greenspace and depressive symptoms. To do this, we added an interaction term between NDVI and chronic burden to models 1 (250m buffer) and 2 (500m buffer), and kept all the same covariates, including site. Following up on the interaction findings, we used the package RegHelper, version 0.3.6, to calculate the "simple slopes," or the coefficient estimate for the effect of NDVI on CES-D scores for each of the three levels of chronic burden. As a secondary analysis, we ran the model with the NDVI and chronic burden interaction stratified by gender, as patterns in depressive symptoms are known to differ by gender[21,29,74]. We used a significance level of 0.05 for all analyses and all confidence intervals presented are at the 95% level.

Results

The distribution of participant characteristics, including gender, race, site, income, and education, along with each group's average CES-D score and NDVI at both buffer sizes are presented in Table 1. There were approximately 5% more females than males in our analysis, and female participants, on average, had a 2.2 higher CES-D score than male participants. Depressive symptoms were highest among Hispanic participants and lowest among Chinese American participants, with a difference of 3.2 on the CES-D scale (Table 1). There was high variation in depressive symptoms among the study sites. Participants in New York, on average, had the highest CES-D score, which was 3.4 points higher than Winston-Salem, the site with the lowest average CES-D score. Among the household income categories, the high-income group had an average CES-D score that was 3.5 points lower than the low-income group's average score. Lastly, the group with the highest education level had the lowest CES-D score, and the group with the lowest education level had the highest CES-D score, with a difference of 2.7.

The average NDVI values at the 250m buffer and 500m buffer were roughly equal for each group included in Table 1; thus, we highlight these summary statistics for the NDVI 250m buffer only. For male and female participants, there were no large differences in average NDVI values. However, among the racial/ethnic groups, black and white participants' had the same average NDVI value, which was 13% higher than the average NDVI of Hispanic participants and 12% higher than that of Chinese American participants. Among the sites, individuals in New York had the lowest average NDVI value, while those in Winston Salem had the highest value, which was 38% higher than that for New York. The average NDVI value in the highest income category was 9% higher than in the low-income group and 4% higher than the middle-income group (Table 1). Lastly, for participants who had not completed high school, the average NDVI

was 8% lower than other participants.

In the regression models without interaction terms, prior to controlling for site, higher NDVI values were significantly associated with a decrease in depressive symptoms (Table 2). At the 250m buffer radii, a change in NDVI from 0 to 1 was associated with a 1.05 decrease in CES-D scores ($p=0.025$). However, when site was added as a covariate, the relationship between NDVI and CES-D was no longer significant ($p=0.18$). As these findings were similar at the 500m buffer NDVI, we report here only the 250m buffer results (Table 2).

	Participant Group	*Sample Size (%)*	*Mean +/- S.D. CESD Score*	*Mean +/- S.D NDVI 250m*	*Mean +/- S.D NDVI 500m*
Overall		6,701	7.58 +/- 7.60	0.39 +/- 0.17	0.39 +/- 0.17
Gender	Male	3,155 (47.08)	6.39 +/- 6.58	0.39 +/- 0.17	0.39 +/- 0.17
	Female	3,546 (52.92)	8.63 +/- 8.26	0.38 +/- 0.17	0.38 +/- 0.17
Race	White	2,573 (38.40)	7.04 +/- 7.04	0.43 +/- 0.19	0.43 +/- 0.19
	Chinese American	801 (11.95)	6.26 +/- 6.53	0.31 +/- 0.11	0.31 +/- 0.10
	African American	1,848 (27.58)	7.36 +/- 7.30	**0.43** +/- 0.17	0.43 +/- 0.17
	Hispanic	1,479 (22.07)	9.50 +/- 8.97	**0.30** +/- 0.10	0.31 +/- 0.09
Site	New York	1,092 (16.30)	9.62 +/- 8.71	0.25 +/- 0.10	0.27 +/- 0.09
	Baltimore	1,030 (15.37)	7.22 +/- 6.88	0.51 +/- 0.14	0.51 +/- 0.14
	St. Paul	1,050 (15.67)	8.21 +/- 7.46	0.41 +/- 0.06	0.41 +/- 0.06
	Chicago	1,153 (17.21)	7.46 +/- 7.15	0.28 +/- 0.13	0.27 +/- 0.14
	Los Angeles	1,314 (19.61)	6.86 +/- 8.02	0.32 +/- 0.08	0.29 +/- 0.08
	Winston Salem	1,062 (15.85)	6.24 +/- 6.57	0.63 +/- 0.06	0.62 +/- 0.06
Income	Low (<20,000)	1,541 (23.00)	9.63 +/- 9.12	0.33 +/- 0.14	0.33 +/- 0.13
	Middle (20,000-49,999)	2,355 (35.14)	7.89 +/- 7.40	0.38 +/- 0.16	0.38 +/- 0.15
	High (>49,999)	2,559 (38.19)	6.14 +/- 6.41	0.42 +/- 0.18	0.42 +/- 0.18
	NA	246 (3.67)			
Education	Less than High School	1,207 (18.01)	9.54 +/- 8.90	0.32 +/- 0.13	0.32 +/- 0.12
	High School Completed	1,218 (18.18)	8.10 +/- 7.43	0.40 +/- 0.16	0.40 +/- 0.16
	Beyond High School	4,271 (63.74)	6.88 +/- 7.13	0.40 +/- 0.18	0.40 +/- 0.17
	NA	5 (0.07%)			

Table 1. Participant characteristics and descriptive statistics for Exam 1, including average NDVI and CES-D scores.

	Without Site			With Site		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
NDVI 250m	-1.05	-1.97, -0.13	**0.025**	0.93	-0.44, 2.31	0.184
Income: middle	-0.97	-1.32, -0.61	**<0.001**	-1.06	-1.42, -0.71	**<0.001**
Income:high	-1.64	-2.06, -1.22	**<0.001**	-1.83	-2.26, -1.40	**<0.001**
Age	-0.06	-0.08, -0.05	**<0.001**	-0.06	-0.08, -0.05	**<0.001**
Race: Chinese American	-1.68	-2.20, -1.17	**<0.001**	-1.53	-2.11, -0.96	**<0.001**
Race: African American	0.20	-0.18, 0.58	0.302	0.07	-0.32, 0.46	0.722
Race: Hispanic	1.40	0.95, 1.85	**<0.001**	1.39	0.91, 1.87	**<0.001**
Gender: Male	-1.28	-1.58, -0.98	**<0.001**	-1.26	-1.56, -0.96	**<0.001**
Antidepressants	2.75	2.29, 3.21	**<0.001**	2.76	2.30, 3.22	**<0.001**
Emotional Social Support Index	-0.53	-0.55, -0.50	**<0.001**	-0.52	-0.55, -0.50	**<0.001**
Married	0.15	-0.17, 0.47	0.367	0.19	-0.13, 0.51	0.246
Education: High School	-0.77	-1.28, -0.25	**0.003**	-0.80	-1.31, -0.29	**0.002**
Education: Beyond High School	-1.49	-1.95, -1.03	**<0.001**	-1.59	-2.05, -1.13	**<0.001**
Time at Address	0.00	0.00, 0.00	**0.043**	0.00	0.00, 0.00	0.275
Site: New York				1.82	1.07, 2.57	**<0.001**
Site: Baltimore				0.78	0.23, 1.34	**0.006**
Site: St. Paul				0.58	-0.05, 1.22	0.072
Site: Chicago				1.36	0.63, 2.09	**<0.001**
Site: Los Angeles				0.35	-0.39, 1.10	0.356

Table 2. Model summaries for association between NDVI and CES-D without interaction terms for chronic burden, with and without site included as a covariate.

When we added an interaction term for NDVI and chronic burden to the model with site, there was a significant difference in the effect of NDVI on depressive symptoms between the low and high chronically burdened group at both buffer radii of NDVI (Table 3). While the low and middle burden groups showed an increase in CES-D scores with increasing NDVI, the high burden group showed a decrease in CES-D scores with higher NDVI (Figure 4).

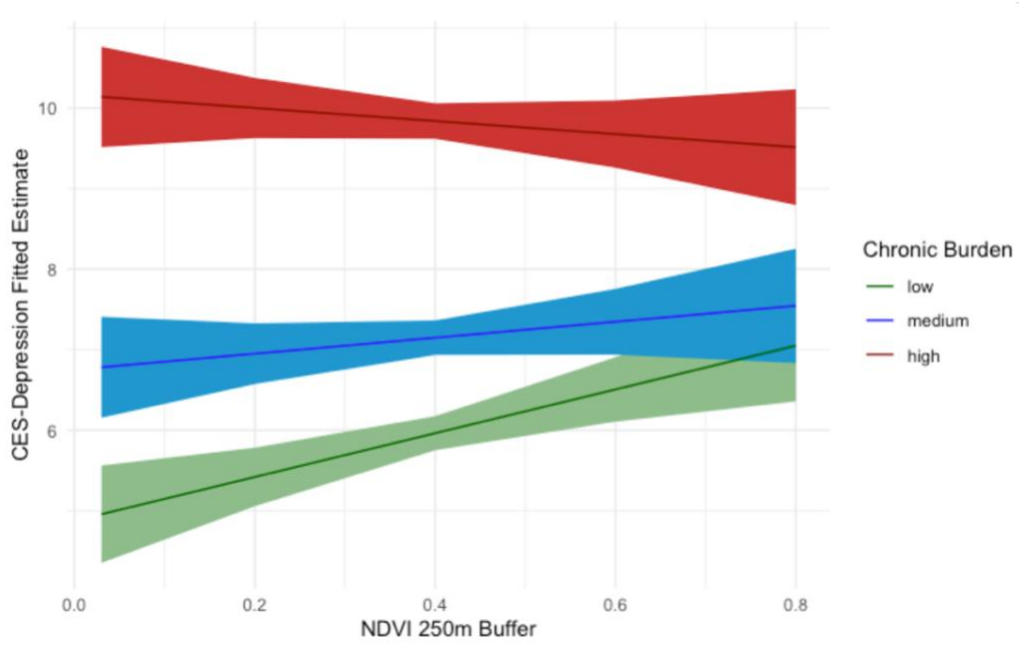

Figure 4. Relationship between NDVI at the 250m buffer and CES-D scores fitted from the interaction regression model, stratified by levels of chronic burden.

	250m NDVI model		
Predictors	*Estimates*	*CI*	*p*
NDVI 250m	2.72	1.13, 4.31	**0.001**
NDVI 250* Chronic Burden: medium	-1.73	-3.32, -0.13	**0.034**
NDVI 250* Chronic Burden: high	-3.53	-5.21, -1.85	**<0.001**
Chronic Burden: medium	1.88	1.20, 2.56	**<0.001**
Chronic Burden:high	5.29	4.58, 6.00	**<0.001**
Income: middle	-0.89	-1.23, -0.54	**<0.001**
Income:high	-1.50	-1.92, -1.08	**<0.001**
Site: COL	1.68	0.96, 2.40	**<0.001**
Site: JHU	0.68	0.15, 1.21	**0.012**
Site: UMN	0.49	-0.12, 1.09	0.116
Site: NWU	1.15	0.45, 1.86	**0.001**
Site: UCLA	0.36	-0.35, 1.08	0.321
Age	-0.04	-0.05, -0.02	**<0.001**
Race: Chinese American	-0.77	-1.33, -0.22	**0.006**
Race: African American	-0.05	-0.42, 0.33	0.807
Race: Hispanic	1.38	0.92, 1.84	**<0.001**
Gender: Male	-0.95	-1.24, -0.66	**<0.001**
Antidepressants	2.41	1.96, 2.86	**<0.001**
Emotional Social Support Index	-0.47	-0.49, -0.45	**<0.001**
Married	0.11	-0.20, 0.41	0.502
Education: High School	-0.92	-1.41, -0.43	**<0.001**
Education: Beyond High School	-1.87	-2.31, -1.42	**<0.001**
Time at Address	0.00	0.00, 0.00	0.222

Table 3. Model summaries for the association between NDVI and CES-D scores with chronic burden interaction (at the 250m buffer).

Following up on the significant interaction between NDVI and chronic burden, we calculated the average change in CES-D scores with increasing NDVI within each burden group, or what is referred to as the "simple slopes". These estimates were extracted from the same interaction model previously discussed, and thus take into account all the same covariates. For participants with low chronic burden, a change in NDVI from 0 to 1 was significantly associated with a 2.72 (1.13, 4.31) increase in CES-D scores ($p<0.001$). Among participants reporting medium chronic burden, a one-unit change (0 to 1) in NDVI was associated with a 0.99 (-0.65, 2.64) increase in CES-D scores, although this relationship was not significant ($p=0.24$). In contrast, among the high chronic burden group, a one-unit increase (0 to 1) in NDVI was associated with a 0.81 (-2.46, 0.84) decrease in CES-D scores ($p=0.33$), although this relationship was not significant. These estimates and 95% confidence intervals are illustrated in Figure 5.

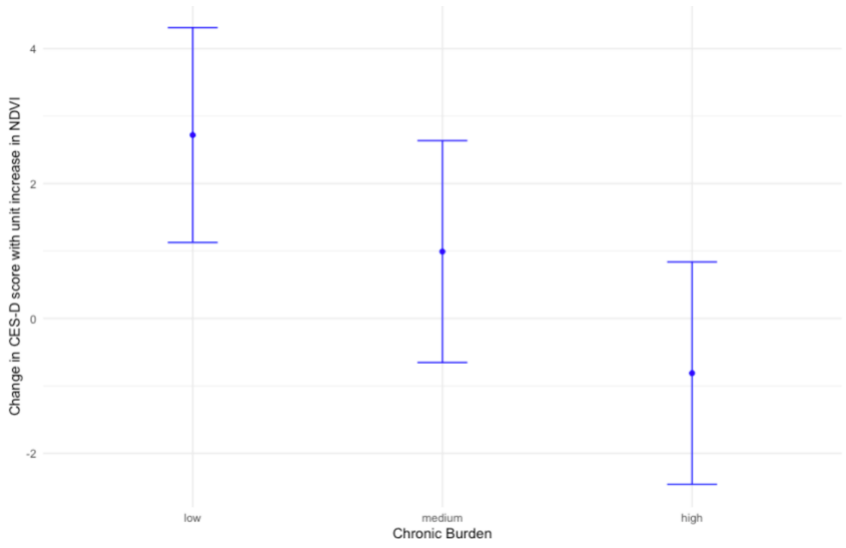

Figure 5. Coefficient estimates and 95% confidence intervals for the change in CES-D scores per 1 unit increase in NDVI (shift from 0-1) among the three burden groups.

When we stratified by gender, there was a significant interaction between NDVI and chronic burden (low vs. high) among men, but no significant interaction among women (Table 4). Men in the low and medium burden groups displayed an increase in depressive symptoms with increasing NDVI, while within the high burden group an increase in NDVI was associated with a decrease in CES-D (Figure 6). This pattern was consistent with the main findings, and model output is included in Table 4. Among women, there was no significant interaction between NDVI and chronic burden in their effect on depressive symptoms.

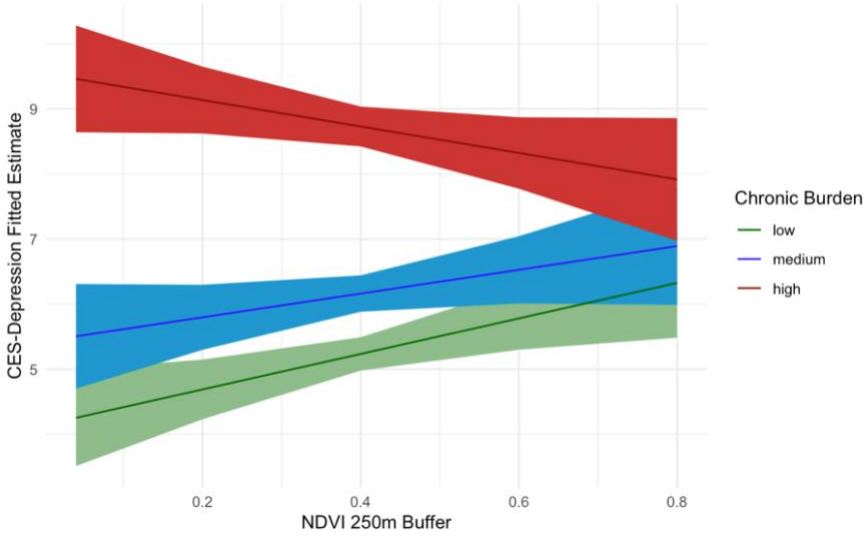

Figure 6. Relationship between NDVI and CES-D fitted estimates by levels of chronic burden in the stratified model with men only. There was no significant interaction among women.

	Men			Women		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
NDVI 250m	2.73	0.76, 4.70	**0.007**	2.39	-0.12, 4.91	0.062
Chronic Burden: medium	1.29	0.41, 2.16	**0.004**	2.36	1.33, 3.40	**<0.001**
Chronic Burden:high	5.40	4.46, 6.33	**<0.001**	5.08	4.02, 6.15	**<0.001**
Income: middle	-0.61	-1.08, -0.14	**0.011**	-1.12	-1.62, -0.63	**<0.001**
Income:high	-0.86	-1.41, -0.31	**0.002**	-2.17	-2.79, -1.55	**<0.001**
Site: COL	1.86	0.92, 2.80	**<0.001**	1.54	0.47, 2.62	**0.005**
Site: JHU	1.12	0.43, 1.82	**0.001**	0.27	-0.51, 1.06	0.496
Site: UMN	0.87	0.09, 1.66	**0.029**	0.12	-0.79, 1.03	0.796
Site: NWU	1.16	0.26, 2.06	**0.012**	1.27	0.20, 2.33	**0.020**
Site: UCLA	0.12	-0.80, 1.04	0.794	0.64	-0.44, 1.72	0.243
Age	-0.03	-0.05, -0.01	**0.001**	-0.04	-0.07, -0.02	**<0.001**
Race: Chinese American	-0.22	-0.94, 0.49	0.536	-1.34	-2.19, -0.50	**0.002**
Race: African American	-0.16	-0.66, 0.33	0.513	0.08	-0.48, 0.64	0.782
Race: Hispanic	1.12	0.53, 1.72	**<0.001**	1.58	0.89, 2.28	**<0.001**
Antidepressants	2.41	1.70, 3.11	**<0.001**	2.39	1.80, 2.98	**<0.001**
Emotional Social Support Index	-0.41	-0.45, -0.38	**<0.001**	-0.52	-0.55, -0.48	**<0.001**
Married	-0.01	-0.44, 0.41	0.955	0.22	-0.23, 0.66	0.341
Education: High School	-0.72	-1.40, -0.05	**0.036**	-1.04	-1.74, -0.35	**0.003**
Education: Beyond High School	-1.61	-2.20, -1.02	**<0.001**	-2.11	-2.77, -1.46	**<0.001**
Time at Address	-0.00	-0.00, 0.00	0.837	0.00	-0.00, 0.00	0.065
NDVI 250* Chronic Burden: medium	-0.90	-2.92, 1.12	0.381	-2.17	-4.64, 0.30	0.085
NDVI 250* Chronic Burden: high	-4.76	-6.93, -2.58	**<0.001**	-2.05	-4.63, 0.53	0.119

Table 4. Model summaries for the association between NDVI and CES-D scores with chronic burden interaction stratified by gender.

Discussion

Models without interaction

In our models without the chronic burden and NDVI interaction, we explored the main effect of NDVI on CES-D and found that there was only a significant association when site was not a covariate. Without site as a covariate, there was a significant decrease in depressive symptoms with an increase in greenspace exposure, which was in line with our hypothesis and previous literature[1,27,28]. This association likely went away when site was added as a covariate because the variation in the greenspace exposure was controlled out of the model. Due to the high variation in NDVI among the six study sites, but the low variation in NDVI within sites, there was likely not enough greenspace variability within each of the six sites to establish significance for this main effect[75]. For instance, in one MESA study investigating the effect of fine particular matter on cardiovascular health outcomes, researchers explored the role of study site[76]. They found that the significant association was driven mainly by the high variability in exposure between the six sites, rather than within each site. Despite the impact on exposure variability, it was still critical for us to control for site in all other models, including the chronic burden interaction models discussed below, as site is associated with both the outcome and exposure of interest, leading to the potential for site to confound our results.

Chronic burden interaction

Our results for the chronic burden interaction models showed that there was a significant interaction between chronic burden and NDVI in their effect on depressive symptoms. The direction of the interaction coefficient indicated that those with high and medium chronic burden experience a significantly stronger reduction in depressive symptoms with

increasing NDVI compared to those with low chronic burden. This significant interaction is in line with our hypothesis; however, our follow-up analysis on the interaction findings indicated unexpected directionality. While the interaction significance tells us that the relationship between NDVI and depressive symptoms depends upon level of chronic burden, it does not tell us the direction, magnitude, or significance of the NDVI and CES-D relationship within each level of chronic burden. To find this, we calculated the "simple slopes" at each level of chronic burden and found that the association between NDVI and depressive symptoms was only significant in individuals with low chronic burden. Furthermore, this association indicated that among the low chronic burden group, an increase in NDVI was associated with an increase in CES-D scores, which was unexpected. Within the high burden group, there was a decrease in CES-D scores with increasing NDVI, but this association was not significant. Overall, the significant interaction finding indicates that chronic burden is an effect modifier, and the direction of the interaction coefficient indicates that those with high chronic burden have a pronounced decrease in depressive symptoms with increasing greenspace exposure. Here, we explore possible explanations for the role of chronic burden as an effect modifier; second, we outline possible reasons for the unexpected findings within the low chronic burden group. Lastly, we discuss study limitations.

The significant interaction between NDVI and chronic burden may be explained by previous work investigating the role of chronic stress in the etiology of certain types of depressive symptoms[77]. It may be that those with higher chronic burden experience depressive symptoms partially as a result of the stressful stimuli in their lives, which greenspace access may help alleviate. Research has found that chronic stress is associated with depressive symptoms[78], and this finding has led to investigation on pathways linking stress and depression[77]. In certain

types of depression or depressive syndromes, the physiological changes associated with chronic stress may underlie, or may mimic, the biological changes that cause depression and depressive symptoms[79,80]. For instance, stressed-induced cortisol dysregulation may be associated with depressive symptom development in certain populations[81]. Additionally, stress-induced neuroinflammation may alter glutamate transmission and plasticity, which impacts depressive symptoms and depression[82]. In one study, burden, assessed through a series of questions about health, well-being, financial, and family burden, was a predictor of higher depressive symptoms a year later, as assessed by the Geriatric Depression Scale[83]. Given this strong connection between chronic stress and depressive symptoms, and the previously outlined association between greenspace and stress reduction, it may be that greenspace acts as a buffer between stress and the health manifestations of stress, including depressive symptoms, for those with high chronic burden[19,84].

The capacity of greenspace to act as an attenuating buffer between stressors and the physiological manifestations of stress has been studied in relation to acute stress by evaluating physiological stress recovery times with and without various nature exposures[48]. However, greenspace may also buffer chronic stress from impacting longer-term mental and physical health outcomes, potentially helping explain why those with high chronic stress have lower depressive symptoms in association with higher NDVI. Research has found that greenspace exposure buffers the association between stressful life events and perceived mental health, health complaints, and perceived general health in adults[19]. It may also buffer children from the negative psychological consequences of stressful life events, such as low self-worth[84]. Thus, the interaction between NDVI and chronic burden in this study may reflect the stress-associated etiology of the high burden groups' depressive symptoms, which may be attenuated by

greenspace exposure.

However, not all individuals necessarily experience depressive symptoms in association with chronic stress and life burden. There are many factors at play in the etiology of depressive symptoms aside from chronic burden, such as sociodemographic factors, access to health resources, and social support[85]. Depressive symptoms can also result from genetic variations in genes that impact dopamine neurotransmission and other pathways involved in the pathology of depressive symptoms and depression[86]. Childhood trauma is also thought to be a risk factor for depression[87]. Thus, the low and medium burden groups in this analysis might have depressive symptoms that are not stress related or are related to stress and trauma that has occurred in the past. In these instances, depressive symptoms may be rooted in causes and pathways that are not responsive to greenspace exposure. Stress has been investigated as a mechanism underlying the greenspace and mental health association[88]; however, more studies are needed to determine the role of stress as a mediator underlying the effect of environment on mental health outcomes. Future studies should also investigate whether pathways that are independent from stress may link nature exposure to attenuation of depressive symptoms in individuals suffering from high depressive symptoms but not chronic stress.

There may be other reasons for the significant interaction finding that explain why highly burdened individuals appear to gain more mental health benefit from greenspace than those with lower chronic burden. Individuals who are highly stressed are often suffering from poverty and racial discrimination, and have lower socioeconomic status[89,90]. The chronic burden survey scale in this analysis incorporates financial difficulties as one of the five burden categories. Thus, it is likely that the high chronic burden group is more financially strained than the rest of the study population and may have less access to mental health and stress-reducing

resources that are accessible for higher SES groups. The high chronic burden individuals, in turn, may be more reliant on neighborhood greenspace than the lower burden groups who are more likely to have the financial means to, for instance, travel further for greenspace access or who can utilize other costly mental health resources[35,40]. As chronic stress is often cited as one root cause of mental health disparities[91], differential access to coping resources that helps folks deal with this chronic stress may further exacerbate these inequities[92]. However, greenspace may serve as one coping resource that is more heavily used by lower SES groups when it is accessible in one's neighborhood[93]. Further analysis that disentangles SES from chronic burden would help elucidate the role of SES in explaining these interaction findings.

Unexpected findings

In our further exploration of the effect of NDVI on depressive symptoms within each of the three chronic burden groups (simple slopes), we found that the low chronic burden individuals had a significant increase in depressive symptoms with increasing NDVI. This was unexpected and contrary to the large body of literature supporting the mental health benefits of greenspace[28,29]. Here we outline possible reasons for this unexpected finding. Bos et. al also found an association between worse mental health and residential proximity to greenspace, although only among middle aged men[94]. They suggest that this population may have the financial means to live in green neighborhoods but not the leisure time to utilize local greenspaces[94]. As previously discussed, it may be that the low chronic burden group is composed of higher income individuals[89,90]; thus, this population may have more resources to self-select into neighborhoods with particular characteristics based on their needs and preferences[95]. Choices regarding residential location often are motivated by a desire to escape stressful stimuli

and access greenspace for restorative purposes[49]. It may be that individuals with higher depressive symptoms are seeking out restorative environments with more greenspace in order to alleviate these depressive symptoms. This may partially explain the unexpected association between higher NDVI and higher CES-D in low burdened participants. However, some studies suggest that individuals with better, rather than worse, overall health self-select into greener neighborhoods[96]. To unpack the role of self-selection in the relationship between residential greenspace and mental health, research is needed that investigates who intentionally seeks out greener neighborhoods and why they do so.

Safety concerns and crime associated with the presence of greenspace may also help explain the NDVI and CES-D pattern within the low burden group. Depending on neighborhood context, park amenities, and local social norms, greenspaces may attract violent crime[97]. This may deter folks from utilizing greenspace, and subsequently from gaining any mental health benefits from their local parks[98]. Additionally, fear of residential crime is associated with poor mental health[99]. Therefore, neighborhood greenspace that is consider unsafe or linked to crime may be detrimental to residents' mental health[93], whether or not individuals are utilizing that greenspace. Ambrey et.al found that the relationship between greenspace and well-being was dependent upon local crime rates[100], as high crime rates diminished the psychologically beneficial effects of greenspace. However, studies are needed that further explore these complexities, and investigate whether local parks associated with high crime are more detrimental to well-being than a lack of parks altogether.

Another unexpected finding was that there was no significant effect of NDVI on CES-D within the middle and high chronic burden groups. Although there was a decrease in depressive symptoms with increasing NDVI within the high burden group, this association was not

statistically significant. This finding is not consistent with the large body of literature supporting the mental health and psychological well-being benefits of nearby greenspaces[2,35,88]. While many studies have confirmed positive health associations with greenspace exposure, other investigations of greenspace and health have found null results[101]. For instance, van den Berg et.al found that greenspace buffered the effect of stress on health; however, they found no significant main effect of greenspace on perceived mental health or perceived physical health[19]. Additionally, Dzhambov et.al failed to find an association between residential NDVI and mental health, as assessed by the General Health Questionnaire[102]. Lastly, these null findings may be partially explained by the association between greenspace and crime previously discussed[97].

Role of gender

Our further analysis to investigate stratification by gender indicated that the interaction between chronic burden and NDVI was statistically significant among male participants, while only marginally significant among women. Previous literature indicates that the effect of greenspace on mental health outcomes differs by gender; however, the nature of that difference varies among studies. Some studies have found that greenspace is associated with better mental health and physical health only among men[15,49], while other analyses have demonstrated that the association between greenspace and mental health is stronger among women[94]. Both chronic burden and environmental exposures, such as greenspace, impact mental health differently among different genders[103,104]; thus, future studies that build upon our findings should continue to stratify results by gender to further understand the role of gender in the mental health, greenspace, and chronic burden relationship.

Limitations & Conclusion

There are several limitations in this study. We utilized residential proximity to greenspace, estimated with NDVI, as a proxy for nature "exposure"; however, there are several limitations to this approach. For instance, the presence of natural spaces near one's home does not necessarily reflect visitation or equitable access to these areas. Individuals of lower SES, of racial and ethnic minorities, and those in poor general health report visiting greenspaces less frequently than the general population, even when residential proximity to greenspace is taken into account[105]. This may be due to a lack of interest[106], safety concerns, lack of time, or poor pathways to and within the greenspaces[107]. To capture access and usage, rather than proximity alone, several studies investigating greenspace exposure and health used self-reported visitation to greenspaces or self-reported access to greenspaces as a measure of exposure[36]. However, exposure self-report alone may be subject to recall bias. To improve the accuracy of proximity to greenspace as a proxy for "exposure", future studies should utilize a combination of self-reported accessibility and objective measures, such as NDVI[102].

Furthermore, while NDVI captures the presence of vegetation surrounding one's residence, it does not take into consideration the quality or type of vegetation. The greenspace indicated by NDVI may, in some cases, lie within a public park, but vegetated surfaces may also be located on private property or along traffic medians on busy streets. These other types of residential vegetative surfaces may not be as accessible as public parks[108]. Even among public parks, there is high variation in quality and amenities that impact park visitation rates and may also affect associated mental health outcomes. Some parks have more litter, crime, noise, or crowds than others– deterring certain groups and creating perceptions of unsafe conditions [109]. Additionally, park amenities such as barbeques, playgrounds, maintained trails, water fountains,

picnic tables, and bathrooms are thought to increase park usage[109], particularly for marginalized populations[110]. Lastly, natural characteristics of greenspaces such as landscape type, biodiversity, species composition, and size of park may influence the effect of greenspace on mental health and well-being[2]. Among the six sites in this analysis, there was not enough diversity in ecosystem type to compare mental health benefits across a spectrum of ecosystems; however, future studies that explore this factor would illuminate how specific characteristics of natural spaces impact human health differently.

There are additionally limitations with utilization of the CES-D scale and the chronic burden scale. Due to differences between the CES-D self-reported depressive symptoms definition[56,67] and a clinical diagnosis of depressive symptoms, it is possible that there is misclassification of the outcome in some cases due to reporting bias[111]. Although study results were kept confidential, stigma surrounding mental health may still cause participants to under-report symptoms. Furthermore, CES-D scale items are prefaced with "please tell me how often you have felt this way in the past week"[112]. This phrasing may capture more short-term depressive symptoms, rather than the chronic trends we are investigating here. The chronic burden scale used to approximate chronic life stress is also self-reported and subject to reporting bias[113]. For instance, participants who answer the chronic burden questionnaire immediately following a stressful event will likely over-report on their chronic burden items.

Furthermore, due to the cross-sectional nature of our study, we cannot determine the temporal sequence of exposure and outcome necessary to assess for causality. Although we control for time lived at residence as a covariate, there is high variation in the amount of time participants have lived at the address used to approximate greenspace exposure. Thus, our analysis includes individuals who recently moved, and this shorter exposure time may not be

sufficient to have effects on depressive symptoms. We lacked the data to investigate whether and how participant's depressive symptoms differed prior to the greenspace exposure. However, as the MESA study continues, participants can be followed, and retrospective longitudinal studies can evaluate how changes in depressive symptoms correspond to residential moves. Additionally, the satellite data used to calculate NDVI was based on 2006 imagery, while participants' addresses and outcome data were taken from 2000-2002 for exam 1 and 2004-2005 for exam 3. There may have been new parks created or greenspaces removed between 2000 and 2006, which would cause the NDVI value to inaccurately represent the exposure approximation.

Lastly, there is selection bias possible due to differential recruitment of healthy individuals free from CVD[114], and the MESA population may be healthier than the general population, impacting the generalizability of this study. It should also be noted that the ecological validity of our findings is limited by the reported scale of exposure change relative to the effect sizes found. We reported changes in CES-D scores associated with a change in NDVI from 0 to 1, which is a dramatic shift from no greenspace to full greenspace coverage surrounding participant's addresses within each buffer. Overall, our study limitations reflect common shortcomings within the nature and health literature that are important to consider when planning future research agendas and implementing study findings into real world scenarios.

There are many strengths to this study as well; MESA is a large, multiethnic cohort with high standards for covariate and outcome measures[53]. This study augments greater efforts within the environmental epidemiology field to uncover how different populations and individual-level characteristics moderate the well-documented association between greenspace and improvements in mental health and psychological well-being. While previous research has investigated physical and cognitive health outcomes associated with greenspace within the

MESA population[13,115], this study is the first to evaluate how residential greenspace impacts mental health for the individuals in the MESA study. This dataset provides a rich array of neighborhood-level and individual-level characteristics, as well as sociodemographic data, with ample opportunity for future research to explore other potentially critical moderators. A deeper understanding of how diverse individuals differentially experience natural environments and greenspaces, through the lens of public health, will be essential as society begins to implement this growing body of literature into city planning and health practices with equity at the forefront.

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Chapter 2: Forest terpenes and psychological well-being: a review of potential biological mechanisms

Abstract

Mounting evidence from a variety of disciplines demonstrates an association between nature contact and human health, although underlying causal mechanisms are not well understood. One potential explanatory pathway involves olfactory stimuli. Researchers have posited that terpenes– a class of volatile organic compounds emitted from plants– may be partially responsible for the human health and psychological well-being outcomes associated with time spent in forests. Here we examine the evidence in support of the association between psychological well-being outcomes and olfactory exposure to forest terpenes. We categorize the pathways that may underlie these associations under two broad definitions of "physiological" or "psychological". Evidence from olfactory neuroscience and psychoneuroimmunology primarily supports the physiological pathway. Evidence from cognitive appraisal of smell– as well as the connection between the olfactory system and memory– primarily supports the psychological pathway. We conclude with a discussion of critical gaps in the research, and suggestions for future experimental work to further our understanding of the mechanisms at play connecting olfactory exposure to terpenes with human health and well-being.

Introduction

An emerging body of literature highlights the plethora of positive health benefits associated with spending time in forest environments [1]. This research, largely from Japan and Korea, has focused on "shinrin-yoku," or "forest bathing," a practice that has been implemented into the medical system in Japan through the work of groups such as the Japanese Society of Forest Medicine and the Therapeutic Effects of Forests Project [2]. Forest bathing involves sitting or walking in forested areas for a few hours, or for multiple days, sometimes accompanied by guides and instructors. Studies have found that these experiences can reduce stress and anxiety levels, as assessed through self-report measures, as well as psychophysiological correlates, such as reduced blood pressure, pulse rate, salivary cortisol concentration, and increased heart rate variability (HRV) [2–4]. Additionally, several studies have found significant decreases in self-reported assessments of negative affect, anxiety and depression, as well as increased self-reported positive affect from forest exposure ranging from a few hours to multi-day camping trips [4–7]. Forest-bathing is additionally thought to decrease inflammation, as evidenced by increases in Natural Killer (NK) Cell Activity, perforin, granulysin, and anti-inflammatory cytokine concentrations [8,9]. Additional health outcomes, such as chronic pain relief and insomnia mitigation, have also been explored in the literature [7,8,10]. Together these results highlight that exposure to forest environments is associated with improved psychological well-being, decreased inflammation, and other physical health benefits.

Inhalation of a class of volatile organic compounds (VOC) released from plants, known as terpenes, is commonly posited in the forest-bathing literature to be a component of the health-promoting effects of forest-bathing [11,12]. In some cases, olfactory stimuli may explain the health outcomes associated with forest exposure more so than visual or auditory stimuli. For

example, Hedblom et.al (2019) conducted a laboratory study evaluating the stress-reducing capacity of virtual reality nature, while isolating auditory, visual, and olfactory stimuli [13]. They found that olfactory stimuli, which they stated as odors from "two species of evergreen and mushrooms" most strongly predicted the magnitude of the stress reduction, as measured by skin conductance levels. While the role of the olfactory pathway is one likely pathway linking forest bathing and human health, the potential causal mechanisms underlying these associations are not well understood.

Although previous forest-bathing studies have speculated that the olfactory pathway generally, and terpenes in particular, play a critical role in the health benefits of forest bathing, no forest-bathing studies to date have isolated olfactory terpene exposure from other sensory stimuli present in forests. Previous experimental studies in laboratory settings have, however, found associations between terpenes and improved human health, both in-vitro and in-vivo. Thus, we review these studies with a focus on mental health and psychological well-being outcomes.

It is important to address that adverse health effects associated with terpene exposure have also been found. For example, alpha and beta-pinene and delta-3-carene may be skin irritants that cause dermatitis [14]. Terpenes may also have negative effects on respiration and pulmonary functioning. Exposure to reaction products of ozone and alpha-pinene, R-+-limonene, and isoprene may be associated with significant upper airway irritation [15]. Lastly, exposure to terpenes was shown to increase complaints of dyspnea and chest tightness in sawmill workers—although the specific terpene used in this study was not stated [16]. However, the terpene exposure concentrations associated with negative health outcomes are far higher than concentrations found in forests (Table 4).

Approach to the Review

Here, we outline the evidence in support of the association between exposure to terpenes present in the forest environment and psychological well-being outcomes. We do not review the literature on physiological outcomes of terpene exposure, except insofar as they are relevant to mental health or psychological outcomes. Inflammatory outcomes are included in the review because the anti-inflammatory properties of terpenes may play a role in the psychological well-being outcome pathways [17]. By psychological well-being we refer to "multiple affective and cognitive components, including happiness—both hedonic (enjoyment and pleasure) and eudemonic (purpose, meaning, and fulfillment)—self-actualization (accomplishments, optimism, and wisdom), resilience (capacity to cope, adaptive emotion regulation, and lack of maladaptive problem-solving), and healthy relationships" [18]. Acute stress, anxiety, and mood are specific psychological well-being outcomes in the literature we focus on in association with terpene exposure. We then consider two potential causal pathways that may explain the health outcomes associated with inhalation of forest terpenes. The first, which we refer to as the "physiological" pathway, relies on evidence from the fields of olfactory neuroscience and psychoneuroimmunology to link olfactory exposure to inflammation, and inflammation to psychological well-being. The second, which we refer to as the "psychological" pathway, focuses on the role of cognitive appraisal of smell and the connection between olfaction and memory to explain psychological well-being outcomes.

To review the literature on the psychological well-being outcomes of terpene exposure, we began by searching Google scholar and the University of Washington library database for the keyword combination "terpenes" or "terpene" and either "depression", "anxiety", "mood", or " mental health," filtering down to peer-reviewed studies that included

these keywords in the title. Using a "snowball" method, we read through these studies and mined the references by reading all titles in the references and selecting studies with titles containing either the word "terpenes," or the name of a specific terpene, and any word referencing mental health, inflammation, or psychological well-being (such as "anti-inflammatory", "mood", "anxiety", or "depression"). We then narrowed these findings down to studies that reported significant associations between terpene exposure and positive psychological well-being outcomes. Studies that evaluated negative health outcomes in association with terpenes were excluded, as those outcomes were outside the scope of our review. Additionally, several experiments looked at exposure to fragrances that contain terpenes, but the terpenes present in the fragrance were not stated—such as citrus scents, tea fragrances, or wood chip volatiles. These studies were excluded in order to focus on specific terpenes. This process is outlined in Figure 1.

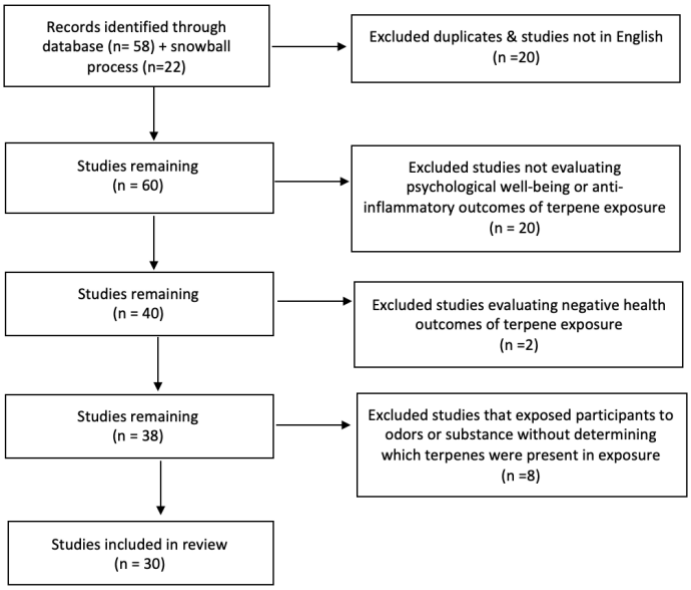

Figure 1. Article selection process for terpene exposure and psychological well-being or anti-inflammatory outcome studies.

We employed the same "snowball" method for our research on the two causal pathways. For the physiological pathway, we began by searching Google scholar and the University of Washington library database for keywords "inflammation" and either "olfactory/olfaction" or "psychological well-being," or "mental health." Mining through the references of these studies, we selected studies with titles that referred to connections between olfaction and mental health or psychological well-being, or connections between inflammation and mental health or psychological well-being. Lastly, our search for literature in support of the psychological pathway started with Google scholar and the University of Washington library database search results for peer-reviewed studies with titles including the words "smell" or "olfaction/olfactory" and "affect" or "mood" or "memory." In a similar process to that outlined above, we mined the resulting studies for references with titles that referenced the connections between the olfactory system and psychological well-being or memory.

Terpenes

Overview

Terpenes are a diverse class of biogenic VOCs, with structures that are derivatives of a 5-carbon isoprene subunit. Terpenes are further classified into different sub-groups based on the number of isoprene units, including monoterpenes, diterpenes, triterpenes, sesquiterpenes and tetraterpenes [19]. Terpenes, the compounds responsible for the aromas of various tree and plant species, constitute the largest class of organic compounds found in forest air [20]. While some species emit high levels of terpenes as volatiles into the surrounding air (without storing them), other species only synthesize and store terpenes, without volatile emission [20]. Terpenes that are emitted as volatiles function either to defend the plant against threats, such as microbes, or to attract pollinators [21]. Alpha-pinene, the most abundant terpene found in nature [22], inhibits seed germination and root growth when plants are under stress [23]. Linalool, which is present in many forests, is emitted by the petals of many flowering plants to produce a floral odor similar to lavender, attracting bees and butterflies [24]. Terpenes emitted as a defense mechanism are either antibacterial, antifungal, toxic to insects, or exhibit a combination of these properties [25]. Stored terpenes function to support the structure and physiology of a plant, acting as constituents of membranes, pigments, and electron transport systems [20]. Upon biosynthesis, plants store terpenes in secretory organs, such as glandular trichomes and resin ducts. These stored terpene pools contain what is commonly extracted as "essential oils" [26].

Over 40,000 terpenes have been identified and described in the literature [12]. We focus here on terpenes that are abundant in forests and that have been studied in connection to human health. Terpenes that are abundant in forest air and mentioned in the health literature include α-pinene, α-terpineol, bicyclogermacrene, β-pinene, β-caryophyllene, camphor,

camphene, carvacrol, cinnamaldehyde, cymene, eugenol, geranyl acetate, g-terpinene, limonene, linalool, menthol, menthone, myrcene, p-cymene, pulegone, sabinene, s-pinene, thymol, and 1,8-cineole. As terpenes are the main component of VOCs in forest air, human exposure to these terpenes when visiting a forest environment is likely [12]. Below, we review the evidence in support of an association between exposure to terpenes and human psychological well-being.

Terpenes and Psychological Well-Being Outcomes

The associations between terpene exposure and changes in anxiety, stress, and mood have been explored in several controlled laboratory studies involving healthy adult volunteers (Table 1) and also through randomized controlled animal studies (Table 2). These experiments study the role of the olfactory pathway, isolated from the auditory and visual pathways. In the studies with human participants, subjects in an enclosed room were exposed to terpenes that were volatilized into the room. However, a few studies utilize polyethylene terephthalate smell bags to expose participants to the volatilized terpene [27]. In some cases, participants are exposed to an individual terpene [28,29], while other studies utilize plant extracts that contain multiple terpenes [30]. Vaporized water or air were pumped into the air or smell bags to act as non-terpene controls [27,28]. Through self-reported indexes or physiological correlates of psychological outcomes, these studies have found participants exposed to terpenes display acute improvements in mood, anxiety, and stress outcomes (Table 1).

For example, Kim. et. al (2019) exposed participants to α-pinene, β-pinene, and d-limonene alone or in combination, for 2.5 minutes at low part-per-billion by volume concentrations (ppbv) similar to levels seen in forest environments. They found that participants showed a dose-dependent decrease in stress, assessed through alpha brain wave changes and a

self-reported stress index [29]. At the highest concentration of terpene exposure compared to no exposure, alpha brain wave values increased by a magnitude of 1.66 times and stress index values decreased by 1.33 times [29]. Changes in EEG activity, heart rate, and pulse rate that reflect a state of decreased stress have also been observed following α-pinene, β-pinene, and d-limonene exposure in controlled laboratory settings [27,31]. Additionally, linalool, a terpene found in lavender, and in many forests, improved self-reported mood, assessed through Profile of Mood States (POMS), when participants were exposed in an indoor setting [28]. In a similar experiment, p-cymene, linalool, menthone, pulegone, geranyl acetate, and bicyclogermacrene reduced self-reported anxiety, assessed by the State-Trait Anxiety Inventory (STAI) [30].

Psychological Outcome	**Terpene**	**Outcome Assessment Method**	**Terpene Concentration**
Anxiety	Linalool [28], combination of linalool, menthone, geranyl acetate, pulegone, isomenthone, bicyclogermacrene , bcaryophyllene and p-cimene [30]; cedrol [32]	Autonomic nerve activity [28]; STAI [30]; miosis rate of pupil dilation [32]	0.03 ppm [28]; 0.1 mL oil diffused in room [30]; 0.36 μm/l [32]
Stress	alpha-pinene [27], d-limonene [31]; cedrol [33]; d-cadinene,a-muurolene,a-cubebene,b-cubebene [34]	Brain Alpha waves [29]; HRV [27,31,33]; HR [31,33]; salivary alpha-amylase activity [34]	0.83 μL/L in smell bag with flow rate of 3 L/min [27]; 2.5 μL/L in smell bag flow rate of 3 L/min [31]; 20 ppb [29]; 14.2±1.7 μg/l [33]
Mood	Linalool [28]; limonene, linalyl acetate, γ-terpinen, β-pinene [35]	POMS [28,35]	530.6 +/- 73.2 ppb [28]; 400 μl in room [35]

Table 1. Psychological well-being outcomes from olfactory exposure to terpenes and methods employed in the literature for human studies.

Findings from animal studies also show associations between terpene exposure and correlates of psychological well-being (Table 2). Studies performed on mice have found that olfactory exposure to linalool and α-pinene can lead to a reduction in behaviors indicative of stress and anxiety *[36–38]*. Akutsu et.al (2002) exposed mice to the odor of alpha-pinene by dropping 200 ml of extract in their cages, while the controls received drops of an odorless solvent (triethyl citrate). The alpha-pinene attenuated stress-induced hypothermia, suggesting a calming effect of the odor [36]. Other studies have evaluated non-olfactory exposure to terpenes. Cheng et.al (2015) administered linalool orally to mice at 250 mg/kg and 500 mg/kg for 14 consecutive days, and measured a decrease in anxiety evaluated with an open field test (OFT), a light/dark test (LDT) and an elevated plus maze test (EPT) [37]. β-pinene and linalool injected intraperitoneally, at doses of 100 and 300 mg/kg, demonstrated "antidepressant-like effects" on mice, evaluated through the forced swimming test (FST), which is a standard test for studying anti-depressant drug efficacy in mice [38]. Taken together, these results suggest that terpenes may improve acute psychological well-being in both animals and humans.

Psychological Outcome	Terpene	Outcome Assessment Method	Terpene Concentration
Anxiety	linalool [37,39]; alpha-pinene [40,41]; *combination of longipinene, a-eudesmol, b-eudesmol, b-caryophyllene, and guaiol [42];* limonene [43,44]	open field test, elevated plus maze test [37,40–43], light/dark test [37,39]; *marble-burying test [44]*	500 mg/kg [37]; 3% dilution [39]; 10 µL/L [40,41]; *50-200 mg/kg [42]*; 0.1 mL/10 g body weight of 0.5 and 1.0% solution [43]; *25, 50 and 75 mg/kg [44]*
Stress	alpha-pinene [29,36]; *β*--pinene, d-limonene [29]	Behavioral analysis, body temperature, HR [36]	200 µl of 0.03% solution placed in rat cage [36]
Depression	*β-pinene and linalool [38]; terpineol [45]*	*forced swimming test (FST) [38]; tail suspension test [45]*	*100 and 300 mg/kg intraperitoneally [38]; injected 100 mg/kg intraperitoneally [45]*

Table 2. Psychological well-being outcomes from olfactory exposure to terpenes, and methods employed in the literature for animal studies. Studies that expose animals via non-olfactory methods (orally, intraperitoneally, etc.), including in-vitro studies, are italicized.

The Physiological Pathway

Overview

Although less well understood, the reasons for these associations could be explained by two underlying biological mechanisms, the "physiological" pathway and the "psychological" pathway—which are not necessarily mutually exclusive. One pathway through which terpene exposure may impact psychological well-being is through by decreasing inflammation. Terpenes in the forest air may decrease inflammation [17] following their entry into the olfactory pathway, and it may be these anti-inflammatory effects that subsequently result in beneficial psychological well-being outcomes. Several studies have linked terpene exposure to a decrease in serum levels of pro-inflammatory cytokines IL-6, IL-8, and TNF-α, suggesting that various terpenes may have

anti-inflammatory properties (Table 3) . These inflammatory cytokines can alter the neurological processes underlying stress, mood, and anxiety outcomes (Figure 2). This relationship between inflammatory cytokine levels and psychological well-being is bidirectional—a decrease in inflammatory cytokines can change psychological outcomes and vice versa *[46–48]*.

Study	Terpene	Outcome Assessment Method	Terpene Concentration
Animal	Linalool [49–51]; alpha-pinene [50,52,53] 1-octanol [50]; limonene [54,55]; *p-cymene [56]*	NF-κB expression and cytokine production [49,53,55]; cyclooxygenase-2 (COX-2) expression [50]; suppression of mitogen-activated protein kinases (MAPKs) and nuclear factor-kappa B (NF- kB)[57] ; *analysis of hemeoxygenase-1 and cytokines in lung tissue [54]; reduction in pro-inflammatory cytokines [56]; inflammatory mediators in macrophages by enzyme-linked immunosorbent assay and Western blot [51]*	10, 20 and 40 mg/kg [49]; 0.0593 - 0.359 mg/mL[50]; 0.2–20 μM [57]; 2342ng/mL [54]; *10% in diet [55]; 100 mg/kg [56]; 40- 120 ug/mL [51]*; 180 ng/L [53]
Human	*Alpha-pinene [58,59]; myrcene and limonene [60]*	*In-vitro chondrocyte cell inhibition of pro-inflammatory pathways [58]; in-vitro inhibition of IL-1β-induced nitric oxide production [60];in vitro inhibition of Nuclear Factor-κB (NF-κB)[59]*	*200 μg/mL [58]; 37.3-85.3 mg/ml [60]; 100 mg/L [59]*

Table 3. Inflammation outcomes from olfactory exposure to terpenes and methods employed in the literature for human and animal lab studies. Studies that expose participants via non-olfactory methods, including in-vitro studies, are italicized.

Terpenes and Inflammation

Forest-bathing studies have found decreases in inflammatory cytokines following time spent in forests [60,61]. Li et.al (2008) found that exposure to a forest environment was associated with an increase in NK cell activity, which signifies anti-inflammatory activity, in

adult volunteers [11]. They measured detectable levels of alpha-pinene, 1,8-cineole, and d-limonene in the forest air, and hypothesized that these terpenes were partially responsible for the anti-inflammatory outcomes of forest exposure. However, these studies do not separate olfactory terpene exposure from other stimuli in the forest. In contrast, experimental human, animal and *in vitro* studies in laboratories have shown that exposure to terpenes (isolated from other forest stimuli) is associated with anti-inflammatory responses (Table 3). Under controlled conditions, mice exposed to α-pinene via inhalation for 5 hours a day for 4 weeks showed an increase in anti-inflammatory B cells, CD4 T cells, and NK cell activity, compared to mice exposed to pure air [53]. Zhou et. al (2004) conducted an in vitro experiment to understand the mechanism underlying the association between terpene exposure and decreased inflammation. They found that α-pinene, a terpene abundant in forests, inhibited translocation of Nuclear Factor-κB (NF-κB) in human monocyte THP-1 cell line [59]. NF-κB regulates expression of inflammatory genes, such as those that encode inflammatory cytokines, which may explain the anti-inflammatory effects of α-pinene. Building on this work, Rufino et.al (2014) confirmed that α-pinene inhibited NF-κB activation in human chondrocyte cells, leading to a decrease in inflammatory cytokines in vitro; however, more studies are needed with larger sample sizes to investigate this mechanism [58]. In a later study, Rufino et.al found similar results from myrecene and limonene exposure [60]. Together, this research highlights the potential anti-inflammatory outcomes associated with terpene exposure.

In a forest environment, terpenes are present in the air [11], and human exposure occurs through inhalation of terpenes where they can directly influence the olfactory pathway. Inflammatory responses to substances entering the body through the olfactory pathway have been studied in relation to air pollution. This research on inflammatory response to air pollution

via the olfactory pathway provides a model that may elucidate the pathway of terpenes from inhalation to anti-inflammatory response. These studies have shown that inhaled ultrafine particles are first processed by the olfactory neuroepithelium (OE), then move to the olfactory bulb glomerulus, and then to the rest of the brain [37]. In the case of air pollution, movement of ultrafine particles through the olfactory bulb can induce an increase in proinflammatory cytokines TNF-α and IL-I-β in olfactory bulb tissue [62]. Inhaled particles can also translocate to the central nervous system (CNS), possibly via the olfactory nerve, but this movement depends on particle solubility, shape, and size [63–65].

Additionally, odorants can bind to the cilia of olfactory sensory neurons (OSNs) and directly signal the olfactory bulb, which is a part of the CNS [66]. As the CNS plays a key role in the physiology of stress, anxiety, and affect, the ability of inhaled particles to directly signal the CNS highlights the connection between olfaction and psychological well-being. Forest terpenes may follow the same physiological path through the olfactory system as ultrafine particles in the air pollution and inflammation literature; however, rather than leading to an increase in proinflammatory cytokines, terpenes are thought to decrease proinflammatory cytokines levels. The path terpenes take through the olfactory system depends upon their size. Volatile terpenes in the forest air can bind to ambient molecules, such as nitrogen dioxide, hydroxide or ozone, leading to variation in particle size [67]. For instance, alpha-pinene was found to form fine particles (10^{-7}-10^{-5}cm diameter) in the presence of nitrogen dioxide [68]. Gas-phase limonene reacts with ozone to produce ultrafine particles (<100nm diameter) [69]. Through experimentally changing ozone concentration, Rohr et.al outlined how pinene, isoprene, and limonene particles change diameter size with shifts in ozone [70]. Research that clarifies the average size of terpene

particles in the forest air would help elucidate how forest terpene particles move through the human olfactory system.

Inflammation and Psychological Well-being Connection

The field of psychoneuroimmunology has established that there is bidirectional communication between inflammatory response and processes in the CNS involved in psychological well-being outcomes [46–48]. Increased levels of inflammatory cytokines, such as TNF-α, IL-6, IL-1β and IL- 8, have been linked to mood state, generalized anxiety disorder, and chronic and acute stress in meta-analyses [46,47,71]— at times displaying a dose-dependent relationship [72–75]. The term "cytokine-induced sickness behavior" refers to depressive symptoms associated with increased inflammatory activity [76]. Additionally, low levels of anti-inflammatory cytokines IL-4 and IL-10 are associated with psychological stress symptoms [75]. These studies highlight the association between inflammation and affect, stress, anxiety, and depression; however, the possibility of reverse causality makes causation difficult to ascertain.

Inflammatory and anti-inflammatory ILs influence the production of corticotropin-releasing hormone (CRH) by the hypothalamus. In turn, CRH can affect the hypothalamic-pituitary-adrenal (HPA) axis and trigger increases in stress hormone levels [77] (Figure 2). Additionally, inflammatory changes may increase permeability of the blood-brain barrier (BBB), allowing inflammatory and anti-inflammatory molecules to enter the CNS environment and change hypothalamic functions, leading to shifts in psychological well-being [76]. In particular, IL-1 and TNF-α, when crossed over the BBB, function much like classical neurotransmitters by modulating calcium ion channels, which are thought to play a role in stress and depression pathophysiology [78]. Decreased levels of anti-inflammatory cytokines may stimulate the vagus nerve, alerting the CNS and altering levels of serotonin, norepinephrine, and dopamine— which

are all related to psychological well-being outcomes [75]. Overall, the physiological pathway may partially explain how terpenes, through the olfactory pathway, potentially create an anti-inflammatory effect that may alter psychological well-being through the nervous system and HPA axis (Figure 2).

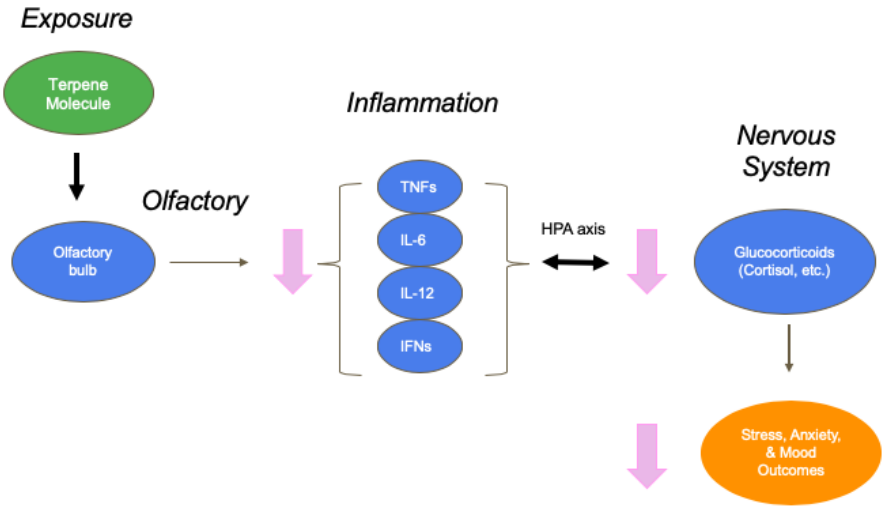

Figure 2. Physiological pathway: potential relationship among terpene exposure, olfactory, inflammation, and nervous system. Boldness of black arrows indicates richer support in the literature.

The Psychological Pathway

Overview

Another pathway through which terpene exposure may impact psychological well-being is through the cognitive appraisal of and memories associated with the smell of terpenes. This pathway is not mutually exclusive with the hypothesized physiological pathway (Figure 3),

but here we review the evidence separately. Through the hypothesized psychological pathway, upon entry of terpenes into the olfactory system, the smell of forest terpenes—which are usually floral, piney, earthy scents– may directly lead to affect changes [60]. Sense of smell is closely related to emotion and affect processing in the brain, and thus, the smell itself could directly shift psychological well-being. Cognitive appraisal is defined by Lazarus & Folkman (1984) as "the process of categorizing an encounter and its various facets with respect to its significance for well-being" [79]. Odors lead to emotional responses that are dependent on individual's cognitive appraisal of the smell, as well as their personal perceptions of and associations with the odor. Villemure et.al (2003) exposed participants to various odors and asked them to evaluate hedonic quality of the odor (pleasantness/unpleasantness) using a visual analog scale (VAS) [80]. They then evaluated anxiety and affect, and found that only odors that participants perceived as "pleasant" were associated with mitigation in anxiety outcomes and an increase in postive affect. Individuals may have established associations with particular terpene smells that are connected to pleasant or unpleasant memories; the smell of terpenes may evoke these memories, leading the affect change. In support of this, Yada et.al found that when participants rated the odor of the terpene cedrol as "pleasant," a greater improvement in psychological outcomes occured [32]. More studies evaluating the association between preference of terpene odors and the resulting psychological outcomes would help distinguish the psychological from the physiological pathway.

Odors are processed by the olfactory bulb, which is closely linked to limbic structures, such as the amygdala and hypothalamus, that regulate emotion and anxiety [81,82]. Studies have shown that exposure to odors increases blood flow to the amygdala, suggesting "hedonic or emotional processing of olfactory stimuli" [83]. The orbitofrontal cortex, where olfactory

information is processed, is also known to be instrumental in stimulus reinforcement association learning [84]. Thus, the brain readily attaches odors to new situations to facilitate emotional learning and stimulus conditioning, leading to strong neural associations between smells, experiences, and psychological well-being.

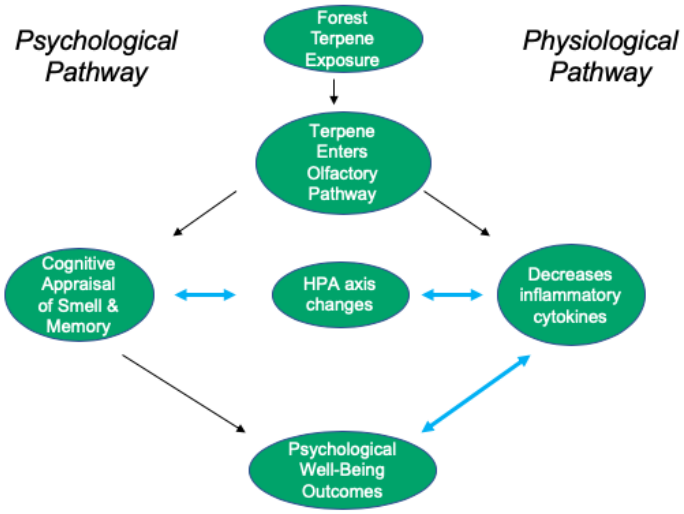

Figure 3. Two potential causal pathways, "psychological" and "physiological", and their connections. The blue arrows illustrate bidirectional connections.

Olfaction and Memory

Olfaction is linked more closed in the brain to memory than any other sense, and research has shown that memories evoked by scent are more vivid and emotionally-charged when compared to memories elicited by visual stimuli *[85–87]*. Information is readily transferred between the olfactory system and memory complexes, as only three neural synapses separate the olfactory nerve and the hippocampus– where both short and long-term memory is processed [88]. Exposure to odors associated with particular memories is thought to improve

recall of those memories. Glachet et.al (2019) asked participants with Alzheimer's disease to recall memories from childhood, adulthood, and recent life while either exposed to the odor of coffee or no odor. Those exposed to the odor recalled a higher number of and more specific memories, elucidating the connection between memory and olfaction [89]. It may be that personal positive associations with the smell of terpenes, which could evoke pleasant memories of nature, are partially responsible for the psychological well-being outcomes of terpene exposure during forest-bathing. An experimental study that exposed participants to specific terpenes and evaluated recall of specific memories and associated affect changes could help build support for the hypothesized psychological pathway.

In the psychological pathway, the anti-inflammatory outcomes found in association with terpenes could be a result of affect changes, as the inflammation and well-being connection is bidirectional (see blue arrows, Figure 3). Psychological stress leads to CRH production by the hypothalamus, followed by increased levels of glucocorticoids (GCs), such as cortisol, which can increase inflammatory cytokines [71]. In the same way, the psychological impacts of forest exposure, such as stress-reduction and positive affect changes resulting from cognitive appraisal of terpene smell, may lead to the anti-inflammatory outcomes associated with terpene exposure.

Forest Terpene Exposure and Dose

Terpene concentrations in the air

To further understand the biological mechanisms tying terpene exposure to psychological well-being and psychological well-being, it would be informative to measure terpene dose absorbed by the human body following forest exposure. To do this, we first must know about the presence of terpenes in the forest, the behavior of humans in the forest, and the measured amount of terpenes absorbed by the body. Relative and absolute ambient terpene

concentrations are most commonly measured with gas chromatography methods [90]. Several studies have measured ambient concentrations of the most abundant terpenes in forest air (Table 4). Pinene (α and β) are the most abundantly emitted terpenes in pine forests, and they have also been a major focus of terpene and health research [91,92]. The most concentrated terpenes in conifer forests are α-pinene, β-pinene, camphor, camphene, sabinene, limonene, menthol, cymene, and myrcene [12]. Li et. al (2007) measured terpene concentrations in a Japanese forest and in urban Tokyo, and found α-pinene, β-pinene, and isoprene in the forest; however, none of these terpenes were detectable in the urban setting [9].

Study	**α-pinene**	**camphene**	**β-pinene**	**terpinene**	**p-cymene**	**limonene**	**isoprene**
Amin et.al [93]	0.3-11 ng/L	0.02-2.5 ng/L	0.03-6.8 ng/L	0.02-0.47 ng/L	NM	NM	NM
Helmig et.al [94]	0-0.6 ppb	0-4 ppb	0-0.3 ppb	NM	0-0.3 ppb	0-0.2 ppb	0-8 ppb
Li et.al [9]	17.4-812.6 ng/m^3		2.3-41.6 ng/ m^3	NM	NM	NM	10.7-10850.8 ng/m^3
Hov et.al [95]	4.6-8.5 ppb	0.5-10.4 ppb	1.4-4.1 ppb	2.8-10.1 ppb	1.8-11.2 ppb	0.5-3.4 ppb	
Hakola et.al [96]	50-200 ppt	5-40 ppt	0-20 ppt	NM	NM	0-20 ppt	0-300 ppt
Schmidt et.al [97]	*2.6 ng/L*	*NM*	*NM*	*NM*	*NM*	*9.1 ng/L*	*NM*
Jia et.al [98]	*3.9 μg/m^3*	*NM*	*NM*	*NM*	*NM*	*5.5 3.9 μg/m^3*	*NM*

Table 4. Relative and absolute concentrations of the most abundant terpenes found in forests. Two indoor studies are included in italics for comparison. NM=not measured

Terpene concentrations and emissions in forests exhibit diurnal, seasonal, and species-dependent variation [20,91,99]. In general, terpene emissions are higher at night than during the day, and higher during the summer and fall months —although some terpenes do not follow this pattern [96]. Terpene emissions and volatilization of stored terpenes are additionally sensitive to climate change, and warming temperatures generally increase terpene emissions [100]. Terpenes are also present in indoor environments, although the composition and concentration of terpenes indoors differs from forest air, due to different sources [97]. Indoor terpene emission sources include consumer products (candles, cleaners, perfumes, etc.), infiltration from the outdoors, smoking, and cooking emissions [101]. Exposure to terpenes in the form of synthetic products such as scented cleaning agents may not engender the same health benefits as exposure to terpenes in the form of a complex natural mixture, or via a multisensory exposure such as forest bathing.

Dose as a measure of exposure

Dose is a measure of the mass of terpenes absorbed by the body, typically reported per kg of body weight, and over a defined time period (e.g. mg/kg/day). Dose represents the internal concentrations of the terpenes, integrated over multiple routes of exposure. Measurements of dose also account for a variety of person specific factors that may affect uptake of terpenes from the environment, including use of respiratory protection (e.g. face masks), individual differences in absorption, metabolism and elimination and differences in ventilation rate. Ventilation rate can increase by as much as 10-fold during strenuous exercise compared at rest, resulting in a substantial increase in absorbed dose for an inhaled chemical. Consequently, dose is frequently considered a more physiologically relevant measure of exposure than a direct measurement of atmospheric concentrations of the terpenes.

Absorbed dose of terpenes may not necessarily reflect the activity of the terpene on the olfactory system. The terpene molecules may just need to bind to olfactory neuron receptors to initiate neurochemical activity, acting like a neurotransmitter. Volatile molecules can bind to olfactory neurons and directly signal an electrical potential to olfactory bulb and then to the olfactory cortex [102]. Kessler et.al (2013) evaluated the ability of 13 terpenes to bind to receptor sites for the neurotransmitter GABA. They found that certain terpenes, such as α-pinene, b-pinene, and b-caryophyllene, enhanced GABA-gated responses to GABA, potentially explaining part of the underlying mechanisms for the calming effect of exposure to terpenes [103]. It could be that these terpenes bind to receptor sites and signal neurotransmitters, and then are exhaled out of the nose. Overall, terpenes creating neural signals and activity in the CNS may not fully be accounted for in blood or urine dose measurements.

In the context of the current review, interpretation of dose is complicated by the fact that for many people the major source of exposure to terpenes is through the diet. For example, the WHO reported that the intake of d-limonene from food for the general US population was estimated to be 0.27 mg/kg body weight per day, whereas intake of limonene from indoor air was estimated to be 0.01 mg/kg body weight per day, and from outdoor air <1 mg/kg body weight per day [104]. Additionally, the WHO estimated that the US population consumed on average 21 μg/kg body weight per day of linalool through food sources [105]. Furthermore, terpenes can be absorbed through dermal exposure from cosmetic skin products. One study estimated that dermal exposure on average for linalool is 0.32 mg/kg/day [106]. Distinguishing between terpene dose from inhalation and terpenes already in the body from other exposures will be important for future studies.

Measuring dose

Two approaches are commonly used to measure absorbed dose. One is to measure the parent terpene; the second is to measure metabolites of terpenes. The parent chemical can be measured in blood, exhaled breath or urine [107,108]. Terpene metabolites are most commonly measured in urine [109]. Terpene absorption in humans has been demonstrated following inhalation exposures in high concentration workplace air (i.e., 10-450 $\mu g/m^3$ α-pinene in a sawmill) [109,110], lower concentration ambient and indoor air (i.e., median 2.6 $\mu g/m^3$ α-pinene in daycare centers)[97], after a 60 min walk [111], and following oral administration [108]. Alpha-pinene builds up in the blood rapidly during inhalation exposure, and is cleared rapidly when the exposure ceases, with an elimination half-life of about 40 min [110]. Preliminary work by Alwis et.al (2016) measured indoor isoprene exposure through urinary levels of various isoprene metabolites, such as minor isoprene metabolite IPMA1. Urinary metabolites from α-pinene, carene, and R-limonene have also been measured, with strong correlation to exposure to respective terpenes [97]. A larger scale study measured 28 VOC metabolites in the urine of 488 subjects using liquid chromatography and mass spectrometry, finding a correlation between VOC exposure and metabolite concentration [112]. While the VOCs they investigated, including cyanide, benzene, and acrolein, were not all terpenes, their similar chemical structure may provide insights into utilizing similar methods for terpene dose measurements.

In contrast to the high levels of terpene exposure associated with adverse outcomes, such as 10-214 mg/m^3 of α-pinene, b-pinene, and carene found in worker personal air samplers [109], humans have a very low odor threshold for terpenes, around 5 ppb [29,113]. Thus, if odor detection is the threshold needed to deliver the psychological outcomes of stress and anxiety

reduction and positive affect changes, the necessary dose for benefits would be far below the estimate concentrations that lead to airway irritation and adverse health effects [15].

Conclusions

It is critical to isolate olfactory exposure to terpenes in future forest-bathing studies in order to determine the causal role of the olfactory pathway in psychological well-being outcomes. Isolating terpenes from other sensory stimuli, specifically in the forest environment, would help elucidate the degree to which terpenes explain the psychological well-being impacts of forest exposure. Additionally, there is a gap in the literature with respect to the role of the olfactory system in the terpene exposure and anti-inflammatory outcomes. Studies like Oberdörster et.al.'s (2004), which exposed mice to ultrafine particulate matter (UFP's) and found a resulting increase in inflammatory cytokine expression in the olfactory bulb tissue, could fill this research gap [64]. Future laboratory studies could apply this approach to terpene exposure rather than UFP's, and potentially evaluate expression of anti-inflammatory, rather than pro-inflammatory, cytokines in the olfactory bulb.

As the majority of observational studies investigating associations between inflammatory biomarkers and psychological well-being have largely been cross-sectional, there is a need for experimental studies to determine cause and effect, and to distinguish between acute and long-term impacts on inflammation resulting from changes in psychological well-being, and vice versa. Randomized controlled trials that expose subjects to terpenes and assess immediate physiological and psychological responses would elucidate acute outcomes, while longitudinal studies that regularly expose participants to terpenes would be instrumental in assessing long-term outcomes.

Future studies that, for example, inhibit smell to eliminate the role of cognitive appraisal of smell would help distinguish between the physiological and psychological mechanisms. To explore this idea with cedrol, a terpene with sedative effects, Kagawa et. al (2003) surgically inhibited olfactory function in mice and found that the sedative effects still occurred without smell– suggesting a physiological mechanism at play [114]. While no study has induced reversible anosmia in humans, lidocaine may cause a small decrease in olfactory perception [115]. Herz (2009) suggests the need for studies that compare the effects of inhaling compounds that smell the same, but are chemically different, to distinguish between mechanisms [116]. Future work could build on these results by, for example, exposing individuals with and without impaired smell to terpenes and evaluating changes in physiologic correlates of stress and self-reported affect.

The mechanisms we discuss here are not mutually exclusive. It is likely that several components of nature exposure, and various mechanisms, act together to explain why time spent in forests improves psychological well-being. However, understanding the specific components of forest exposure that may be most beneficial, and the underlying mechanisms at play, will allow for the most effective implementation of the nature and health research in planning, policy, and public health arenas.

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