Examining the effect of terpene exposure on stress-related outcomes in adults

Chaja M. Levy

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2024

Committee:

Gregory Bratman

Peter Kahn

Anne Riederer

Christopher Simpson

Program Authorized to Offer Degree:

Environmental and Forest Science

University of Washington

Abstract

Examining the effect of terpene exposure on stress-related outcomes in adults

Chaja M. Levy

Chair of the Supervisory Committee:
Gregory Bratman
School of Environmental and Forest Sciences

Nature contact has been shown to improve psychological and physiological stress-related outcomes, although the underlying mechanisms are less understood. The purpose of this study was to determine the effect of terpene exposure on stress-related outcomes in adults following a seated forest exposure. In a double-blind, randomized crossover trial, participants were exposed to a seated forest intervention with terpenes filtered out of the air and an identical session without the filtration of terpenes. The sessions were separated by an eight-day washout period. The primary outcome measured was the high frequency (HF) component of heart rate variability (HRV). Secondary outcomes included measures of blood pressure, skin conductance levels, heart rate, self-reported stress and affect, and levels of inflammatory cytokines in serum. Outcomes were measured via mobile physiology equipment, self-report questionnaires, and serum samples. This is the first study to investigate the effect of terpene exposure during a seated forest exposure in adults in a randomized crossover trial and furthers scientific understanding of the role that olfactory stimuli and terpene exposure play in the multisensory pathways that link well-being and forest exposure.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

Research reported in this thesis was supported by the National Center for Complementary and Integrative Health of the National Institutes of Health under award number 1R21AT011242-01A1. Partial support for this research came from a Eunice Kennedy Shriver National Institute of Child Health and Human Development research infrastructure grant, P2C HD042828, to the Center for Studies in Demography and Ecology at the University of Washington. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health.

The completion of this thesis would not have been possible without the intellectual challenge, continual support, and guidance offered by my committee chair, Dr. Gregory Bratman. I would like to thank my committee members, Drs. Peter Kahn, Chris Simpson, and Anne Riederer, for their invaluable feedback and guidance throughout the process of completing my thesis. I would also like to thank Amanda Gassett for crucial statistical analysis and data management guidance.

Thank you to every staff member who worked on Team Terpenes in 2023 and 2022: Olivia Hill, Connor Lashus, Amishi Singh, Zack Streit, Andrew Shireman, Dr. Philip Lindholm, Jack Sanfilippo, Nate Denke, Colleen Kimseylove, Kathryn Hopkins, Michele Grantham, and Susan Washington. Data collection was also made possible with generous support from the RAIN Incubator in Tacoma, including Drs. Jennifer McKee-Johnson, Paul Amoroso, and David Hirschberg, and the UW Pack Forest, including Dr. Greg Ettl, Chase Beyer, Terri McCauley, Wendy Vail, Paul Roe, Sara Allison, and John Hayes. Vital field assistance was provided by the Simpson Laboratory, including Mike Paulsen, Abigail Gilbert, and David Hardie.

I am forever grateful to my Seattle family: Bill and Linda Conlin, Marcel, Rachael, Sam, Max, and Ivan Levy, and partner, Matthias Gibb, for their steady support, encouragement, and invaluable advice.

DEDICATION

To my parents, Rachael and Marcel Levy, who taught me how to ask questions.

Chapter 1. INTRODUCTION

Nature contact has been linked to psychological and physiological well-being in humans (Bratman et al., 2019). As outlined by Frumkin et al. (2017), these benefits include stress reduction (observed via decreased heart rate, blood pressure, cortisol levels, and self-report measures), decreased anxiety, negative affect, and depressive symptoms, and increased positive affect, prosocial behavior, and attentional capacity (Beil & Hanes, 2013; Berman et al., 2008; Bratman et al., 2015; Duncan et al., 2014; Ewert & Chang, 2018; Hong et al., 2018; Hunter et al., 2019; Jiang et al., 2014; Kaźmierczak, 2013; McAllister et al., 2017; Piff et al., 2015; Putra et al., 2020; Ward Thompson et al., 2016; Zhao et al., 2022). Additionally, nature contact has been associated with improved sleep, reduced mortality, and reduced risk of Type II diabetes (Astell-Burt et al., 2014; Astell-Burt & Feng, 2020; Bodicoat et al., 2014; Gascon et al., 2016; James et al., 2016; Johnson et al., 2018; Shin et al., 2020). Despite these demonstrated associations, what is less known are what causal mechanisms may be responsible for these effects. One possible pathway is reduction of stress and the inflammation that can accompany it (Hartig et al., 2014; Kuo, 2015; Ulrich et al., 1991).

According to The Global Burden of Disease Study 2019, the prevalence of mental disorders increased worldwide from 2010 to 2019, including anxiety, depressive disorders, major depressive disorder, and other mental disorders (GBD 2019 Mental Disorders Collaborators, 2022). The causes of these trends are complex and not yet fully understood, although they can be broadly categorized as biological, genetic, individual, social, and cultural factors (Clark et al., 2017). Across many of these categories, stress can play a key role in the susceptibility, progress, and outcomes of mental disorders (Esch et al., 2002).

1.1 STRESS

A stress response is often defined as the mechanisms and systems that activate when homeostasis is threatened, or when individuals face demands that are greater than their resources (Agorastos & Chrousos, 2022; Charmandari et al., 2005; Chrousos, 2009; Cohen et al., 2007; Lucassen et al., 2014; Patchev & Patchev, 2006). The human body responds to stressors by activating many systems and pathways, including the central and peripheral nervous systems (Agorastos & Chrousos, 2022; Charmandari et al., 2005; Chrousos, 2009; Patchev & Patchev, 2006). The stress response system also integrates the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), sympathetic nervous system (SNS), parasympathetic nervous system (PNS) and the sympathetic–adrenal–medullary axis (SAM; (Agorastos & Chrousos, 2022; Charmandari et al., 2005; Chrousos, 2009; Cohen et al., 1983; Lucassen et al., 2014; Patchev & Patchev, 2006). Additionally, cascading effects during a stress response interact with the mesocortical and mesolimbic pathway (MC/ML), cardiovascular system, immune system, amygdala and hippocampal complex, endocannabinoid system, hypothalamic–pituitary–growth, thyroid, and gonadal axes, and the central circadian system (Agorastos & Chrousos, 2022; Charmandari et al., 2005).

1.1.1 *Autonomic Nervous System (ANS)*

The ANS stress response can prompt systemic changes in the immune system, including increased production of inflammatory cytokines and glucocorticoids (Charmandari et al., 2005). This ANS response is often referred to as the “fight-fright-flight” response, as it prepares bodily response to threat by increasing epinephrine and norepinephrine levels (Lucassen et al., 2014). Epinephrine and norepinephrine regulate blood pressure, and can increase basal metabolic rate, respiration, and blood flow. The SNS and PNS modulate the cardiovascular, respiratory,

gastrointestinal, renal, and endocrine systems (Murison, 2016). The PNS, known as the "rest and digest" system, regulates basic body function and energy use by withdrawing or engaging to modulate sympathetic function (Charmandari et al., 2005; Gibbons, 2019). Increased PNS activity can result in higher levels of acetylcholine, which can prevent increases in inflammatory cytokines like interleukin 1(IL-1), interleukin 2 (IL-2), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α; Sara et al., 2022). Following decreased PNS activity, catecholamine binding allows for C-reactive protein (CRP), IL-1, IL-6, and TNF-α expression.

1.1.2 *Hypothalamic-pituitary-adrenal (HPA) axis*

Activation of the HPA axis by corticotropin-releasing hormones (CRH) results in adrenocorticotrophic hormone release (ACTH; Lucassen et al., 2014; Patchev & Patchev, 2006). Regulated by brain signaling, stress can create a cascading effect beginning with hypothalamic secretion of corticotropin-releasing factor (CRF) and arginine vasopressin (AVP; Stephens & Wand, 2012). In turn, these two hormones stimulate production of ACTH by the anterior pituitary gland. In humans, ACTH stimulates cortisol production and release, resulting in glucocorticoid (GC) and receptor interaction in the nervous, cardiovascular, immune, respiratory, reproductive, musculoskeletal, visual, and integumentary systems (Kadmiel & Cidlowski, 2013).

1.1.3 *Cardiovascular System*

Heart rate and blood pressure changes follow ANS interaction with the cardiovascular system via increased levels of epinephrine and norepinephrine (Lucassen et al., 2014; Patchev & Patchev, 2006). Variability in interbeat intervals, also referred to as heart rate variability (HRV), can be used to assess the cardiovascular system response following stress exposure (Mackersie & Calderon-Moultrie, 2016; Shaffer & Ginsberg, 2017). High frequency heart rate variability (HF

HRV) refers to activity in the range from 0.15 to 0.4 Hz and is measured as an indicator of PNS activity (Shaffer et al., 2014). Spontaneous depolarization and the combined activity of SNS and PNS at the sinoatrial node regulate heart rate (HR; (He, 2020; Thayer et al., 2009).

1.1.4 *Affect*

Emotions are linked with diverse physiological arousal responses, the generation of which involves the ANS (Appelhans & Luecken, 2006; Levenson, 2003). The SNS and PNS work in balance in healthy systems, but the dominance of one branch is associated with ill-being and pathological conditions, typically occurring when a hyperactive SNS "dominates" a hypoactive PNS (Thayer et al., 2010). Engagement of the SNS for long periods can lead to high energy use and extended states of stress and negative affect.

1.1.5 *Stress Response*

Taken together, psychophysiological change following stress system activation can be assessed by measuring self-reported stress and well-being, cardiac and circulatory function (e.g., blood flow, HR, HRV, pulse pressure, systolic and diastolic blood pressure, systemic vascular resistance, flow-mediated dilation, changes in blood viscosity and thrombus formation), and levels of inflammatory cytokines, transcription factors, and stress-related hormones (e.g., IL-1, IL-2, IL-6, TNF-α, NF-κβ, CRP, catecholamines, and cortisol; Sara et al., 2022). Capturing both the psychological and physiological indicators of stress should be prioritized, as the individual perception of a stressor (i.e., self-report) can deviate from measured physiological responses.

Despite being associated with negative health effects, some levels of stress are not always an unfavorable experience. Agorastos & Chrousos (2022) differentiate between "eustress" (healthy or optimal levels of stress) and "distress" (unhealthy levels of stress) to emphasize how

stress can be moderated by magnitude, subjective appraisal, context, and chronicity. Stress system effects are often described using the inverse-U to allow for the visualization of beneficial (e.g., enrichment) versus detrimental (e.g., lacking sufficient stimulation or exceeding resource capacity) types of stress. Sapolsky (2015) represents this curve with neurobiological endpoints ranging from deleterious to salutary as a function of corticosterone (representing the range of stress from under-stimulation to stress with increasing corticosterone levels). Peak salutatory effects occur in the 10-20 μg/dl range of corticosterone levels, corresponding with moderate stress or stimulation. Chrousos (2009) represents this relationship with homeostatic effect as a function of homeostatic system activity with optimal levels of the homeostatic effect occurring in the middle of the curve (state of "eustasis") and deficient and excess homeostatic effect on either side (state of "cacostasis").

1.2 Nature Contact and Stress

Several theories and hypotheses have emerged to explain the measured health benefits from nature exposure. Attention Restoration Theory, developed by Rachel Kaplan and Stephen Kaplan (1989), posits that the main cognitive benefit of nature exposure is the replenishment of directed attention. According to the theory, directed attention is a limited resource under voluntary control that is exhausted by use and must be replenished. The natural environment is particularly suited to meet this need for attention restoration due to specific components in the natural environment labeled as "soft fascination", "being away", "extent", and "compatibility" (S. Kaplan, 1995). "Soft fascination" refers to environmental elements that are interesting but can capture attention without effort. "Being away" describes how natural environments can offer distance (both physical and metaphorical) from day-to-day life. "Extent" refers to an "other

world" quality that provides a cohesive engagement of the mind. Finally, "compatibility" is the agreement of one's goals or motivations and the environment.

Stress Reduction Theory is an alternative, psycho-evolutionary hypothesis put forward by Roger S. Ulrich (1991), which postulates that immediate and automatic affective responses play a key role in the human response to nature. These restorative responses to certain non-threatening natural stimuli provided an evolutionary advantage by allowing for physical and psychological recovery following a stressful event. Ulrich posits that modern human beings may be biologically predisposed to respond in a restorative way to many natural settings, but not to most urban or built environments.

The Biophilia Hypothesis, originally proposed by Edward O. Wilson and further developed by Stephen R. Kellert, theorizes that humans form deep relationships with living things in the natural world (i.e., "love of life") because it had an evolutionary advantage (Kellert & Wilson, 1993; Wilson, 1994). Kellert and Wilson argue that the human brain "evolved in a biocentric world, not a machine-regulated world," and that evidence of this human-living organism relationship appears in cultural symbols, beliefs, and individual responses (Kellert & Wilson, 1993). Similarly, the Savanna Hypothesis is also based on evolutionary psychology and biology and may have originated with 17th-century naturalists and biologists, including Charles Darwin and Jean-Baptiste Lamarck, and further expanded by Raymond A. Dart, who discuss the emergence of bipedalism coinciding with, and perhaps triggered by, an environmental shift from heavily wooded areas to more open savanna environments (Bender et al., 2012; Dart, 1925). However, more recent research indicates these hypothesized savanna environments may not have resembled the savanna ecosystems of today, and evidence of a savanna, mosaic, or wooded environment during this period exists (Domínguez-Rodrigo, 2014).

1.2.1 *Shinrin-yoku ("Forest Bathing")*

Psychological and physiological indicators of stress reduction, particularly HR, HRV, blood pressure, and self-report outcomes, have been linked with nature exposure (Hazer et al., 2018; Kondo et al., 2018; Ulrich et al., 1991). *Shinrin-yoku*, also known as "forest bathing", is a specific human-nature interaction that has been shown to have stress-reducing effects via changes in the immune, cardiovascular, and respiratory systems, and anxiety and depressive symptoms following exposure (Hansen et al., 2017; Li et al., 2008; B. J. Park et al., 2009). Forest bathing exposure has also been observed to have an association with mental restoration and sensations of "awe" in people (Hansen et al., 2017). Studies comparing the effects of forest exposure to control, urban, or baseline measurements have observed improvements in mood, reduction of anxiety and depressive symptoms, and therapeutic effects on HRV, blood pressure, HR, stress hormone levels, and inflammatory biomarkers (De Brito et al., 2020; Furuyashiki et al., 2019; Horiuchi et al., 2014; D.-S. Kim et al., 2015, 2015; Kobayashi et al., 2017, 2018; Lanki et al., 2017; J. Lee et al., 2015; Li et al., 2007, 2008; Mao, Cao, et al., 2012; Mao, Lan, et al., 2012; Ochiai et al., 2015; Oomen-Welke et al., 2022; B. J. Park et al., 2009; B.-J. Park et al., 2007; Song et al., 2015, 2017; Stigsdotter et al., 2017; Tsunetsugu et al., 2013; Yu et al., 2017). However, some studies have not observed significant changes or reported contrary observations between outcomes following forest exposure and outcomes from control groups or baseline measurements, including no significant difference or a difference against the hypothesized direction in mood, stress hormone levels, blood pressure, and HRV (De Brito et al., 2020; Furuyashiki et al., 2019; Gidlow et al., 2016, 2016; Horiuchi et al., 2014; Kavanaugh et al., 2022; Y. Kim et al., 2022; Lanki et al., 2017; Mao, Cao, et al., 2012; Oomen-Welke et al., 2022; Stigsdotter et al., 2017; Yu et al., 2017).

Forest type and biodiversity may also impact the effects of forest exposure on outcomes of interest. In an experimental study of college students randomly assigned to walk in natural versus urban environments, higher perceived animal diversity was associated with improvements in self-reported affect (Nghiem et al., 2021). In the United Kingdom, older mixed deciduous forest air samples measure higher and more diverse biogenic volatile organic compound (BVOC) concentrations when compared to a walled garden environment (Walker et al., 2023). Additionally, Simkin et al. (2020) found that in a within-subject study of 39 women and 27 men exposed to four different forest management types, old-growth and mature commercial forests were significantly more restorative compared to urban and young commercial forests when assessed using the Perceived Restorativeness Scale (PRS).

1.3 Terpene Exposure

One possible pathway for the psychophysiological benefits of forest bathing is through terpene compounds that contribute to the smell of the forest (Li et al., 2008). Terpenes are a type of biogenic volatile organic compound (BVOC). Over 55,000 different chemically structured terpenes have been identified, all generally with a $(C_5H_8)_n$ chemical formula, and classified by differences in linked isoprene units (Kanwal et al., 2022). Emitted by plants, terpenes aid in plant reproduction, defense, inter- and intraspecific interactions, and abiotic stress response (Dudareva et al., 2006). The fourteen most commonly occurring terpene compounds in tree species emissions in the United States are α-pinene, β-pinene, Δ-3-carene, d-limonene, camphene, myrcene, α-terpinene, β-phellandrene, sabinene, o-cymene, ocimene, α-thujene, terpinolene, and γ-terpinene (Geron et al., 2000).

1.3.1 *Anti-inflammatory Effect of Terpene Exposure*

In animal and *in vitro* experiments, terpenes have demonstrated anti-inflammatory, anti-tumorigenic, and neuroprotective action (Cho et al., 2017). As summarized by De Cássia Da Silveira E Sá et al. (2013) and Eddin et al. (2021), rats, mice, and guinea-pigs exposed to terpenes displayed anxiolytic and anti-inflammatory properties via reduced plasma corticosterone levels, inflamed colonic tissue, bronchial resistance, paw edema, and leukocyte, neutrophil, IL-1β, TNF-α, and IL-6 levels (Bastos et al., 2011; De Almeida et al., 2017; Nascimento et al., 2009; Saiyudthong & Marsden, 2011; Santos, 2004; N. Zhang et al., 2018). Additionally, terpene exposure was shown to increase white blood cell count, IL-2, IL-10, T cell, and lymphocyte levels, and antibody cell production (Badr et al., 2011; Raphael & Kuttan, 2003; Trinh et al., 2011). In human monocytes, terpenes can inhibit production of inflammatory cytokines, leukotrienes, and associated metabolites, including TNF-α, IL-1β, Il-4, Il-5, IL-6, IL-8, and leukotriene B4 (LTB4; De Cássia Da Silveira E Sá et al., 2013; Hart et al., 2000; Juergens et al., 1998, 2004). In humans, terpene or essential oil exposure has led to clinically relevant anti-inflammatory effects in bronchial asthma patients, reduced anxiety and depressive symptoms, reduced stress, increased positive affect, and improved cognitive function and sleep (Chen et al., 2022; Fung et al., 2021; Goes et al., 2012; Juergens et al., 2003; Kerr et al., 2021; Koyama & Heinbockel, 2020; M. Lee et al., 2017; Moss & Oliver, 2012; Woo et al., 2023).

It should be noted that essential oils often contain multiple types of terpenes. Essential oil exposure studies frequently hypothesize that the main active ingredients are terpene compounds (i.e., the active ingredients of lavender essential oil are linalyl acetate, linalool, (E)-β-stilbene, and limonene; Cui et al., 2022). Anti-inflammatory, anti-cancer, antioxidative, and neuroprotective properties of forest-derived terpenes may be mediated by transcription factors

and signal transduction (Cui et al., 2022; D.-S. Kim et al., 2015; Rufino et al., 2014). However, lavender and tea tree essential oil product use has been linked to cases of prepubertal gynecomastia (abnormal breast tissue growth in children) and premature thelarche (abnormal breast development before puberty; Diaz et al., 2016; Henley et al., 2007; Ramsey et al., 2019, 2020). Additionally, terpenes are also highly unstable and have low solubility, creating challenges for therapeutic applications (Del Prado-Audelo et al., 2021).

1.3.2 *Exposure Pathways*

Aoshima and Hamamoto (1999) proposed several pathways through which fragrant compounds might affect the brain: stimulation of the olfactory system and resulting psychological effects, absorption into the blood via the lungs by respiration, skin application, and gastrointestinal exposure via food. Similar pathways for essential oil inhalation were summarized by Fung et al. (2021). Essential oil molecules can bind to olfactory chemoreceptors in the nasal cavity and activate olfactory signaling, resulting in psychological changes (Cui et al., 2022; Faturi et al., 2010; Kagawa et al., 2003). Additionally, essential molecules may move through the olfactory system neuronal network via extracellular delivery or mucosa, arriving in the brain in a similar way to nasally delivered medications (Chioca et al., 2013; Cui et al., 2022; Fung et al., 2021; Hanson & Frey, 2008). From there, the essential oil molecules may interact with transient receptor potential channels (TRP), gamma-aminobutyric acid, serotonin, and dopamine receptors (Hanson & Frey, 2008). Finally, essential oil molecules may also be transported via lung alveoli and blood to interact directly with the CNS (Chioca et al., 2013; Faturi et al., 2010; Fung et al., 2021; Kagawa et al., 2003)

1.3.3 *The Olfactory Pathway*

Terpene exposure in this study occurs via inhalation of air during respiration. Most inhaled air enters through the nose, and although humans switch to oral breathing during exercise, approximately 30-35% of air is still inhaled via the nose (Koenig, 2000). Sense of smell, or olfaction, refers to the sensory process through which the olfactory system and brain interpret odors from the surrounding environment (Doty, 2001). The olfactory epithelium that lines the interior of the nose consists of olfactory receptor neurons (ORNs) that bind with odorants (Purves & Williams, 2001). ORN axons project sensory information to neurons in the olfactory bulb, which then project to the pyriform cortex in the temporal lobe, as well as the hypothalamus and the amygdala.

As a set of chemosensory processes that helps organisms identify chemical information, olfaction serves an important role in guiding humans towards beneficial environmental factors (i.e., food or mates), and away from environmental hazards (i.e., rotting food and toxins; (Hoover, 2010; Reed & Knaapila, 2010). Experimental studies show that individuals have demonstrated a preference for others with human leucocyte antigen (HLA)-associated odors that match their genetic make-up and women who detected androstadienone, a molecule found in male sweat, had significantly higher cortisol levels (Jacob et al., 2002; Wyart et al., 2007). De Araujo et al. (2005) found via an experimental study design that context can modulate olfactory odor preference. Participants exposed isovaleric acid with cheddar cheese flavor labeled as "cheddar cheese" rated odor pleasantness higher than those exposed to the same odor labeled as "body odor." Culture can also mediate preference for odors that other individuals may find averse, particularly "tastily rotten" smells and odors associated with fermentation and bitterness (Reed & Knaapila, 2010; Yamin-Pasternak et al., 2014).

1.3.4 *Olfaction and Affect*

Olfaction and affective responses are linked in experimental studies, because odors can elicit individual positive and negative affect responses following exposure (Kontaris et al., 2020; Retiveau et al., 2004; Seubert et al., 2008). Some odors may impair working memory, while others reduce anger and depressive symptoms, and improve mood (Komori et al., 1995; Martin & Chaudry, 2014; Retiveau et al., 2004; Schiffman et al., 1995). Herz (2009) posits that responses to odors are learned through associations with affective experiences. Odors become linked with associated emotions and follow-up exposure can result in psychophysiological effects. In an experimental study, participants exposed to an unfamiliar pleasant odor paired with a negative emotional experience rated the odor as less pleasant one day and one week after exposure (Herz et al., 2004). Participants only exposed to the unfamiliar pleasant odor did not show any significant change in odor pleasantness rating.

1.3.5 *The Olfactory Bulb and the Immune System*

The olfactory bulb is considered an immunosensory effector organ because it provides early virologic control (Durrant et al., 2016). Given the pathway from the nasal cavity to the CNS via ORNs and the olfactory bulb, multiple studies suggest that one route for viral invasion of the CNS is through the olfactory pathway (Durrant et al., 2016; Jang et al., 2009; Majde et al., 2007). As outlined by Durrant et al. (2016), the olfactory bulb might also be the site of an early innate immune response, because experimental studies of mice found olfactory bulb expression of proinflammatory cytokines, including TNF-α, TNFR1, IL-1β, IL-6, and IκB kinase (Aniszewska et al., 2015; Leyva-Grado et al., 2009; Mori et al., 2005). In-vitro experiments have also shown that olfactory ensheathing cells (OECs) may activate NF-κB transcription factors, express Toll-like receptors (TLR) 2 and 4, and express inducible nitric oxide synthase (iNOS) mRNA and

enzymes in response to bacteria and pathogen incubation (Harris et al., 2009; Vincent et al., 2007).

1.4 The Present Study

Here, we aim to fill a critical gap in knowledge by examining how terpenes play a role in the health effects of nature contact in a real-world forest environment by assessing whether the mechanism of terpene inhalation impacts stress reduction and affective outcomes using a randomized control trial design. The primary outcome measured was the high frequency (HF) component of heart rate variability (HRV). Secondary outcomes included measures of blood pressure, skin conductance levels (SCL), HR, self-reported stress and affect, and levels of inflammatory cytokines in serum. Outcomes were measured via mobile physiology equipment, self-report questionnaires, and serum samples. We predicted that exposure to terpenes would regulate greater increases in HF HRV and positive affect, and greater decreases in SCL, blood pressure, HR, self-reported stress, negative affect, and levels of inflammatory cytokines in serum as opposed to the condition with no terpenes exposure.

This study also addresses the need to explore nature properties and function, as proposed by Frumkin et al. (2017). In nature and health research, "nature contact" is often assessed via exposure proxies such as residential proximity to nature. When time in nature is directly assessed, this exposure is often defined through visual contact, or is undefined, leaving auditory, tactile, and olfactory contact with nature less explicitly explored (Bratman et al., 2019). Ambient terpene concentrations are one characteristic of the air in natural environments that could account for some of the observed health benefits in the literature, as terpenes have demonstrated anti-inflammatory, anti-tumorigenic, or neuroprotective action in animal and *in vitro* studies (Cho et al., 2017). However, to our knowledge, no study has been conducted that investigated real-world

ambient terpene exposure in a forest, absorption of these terpenes, and dose-response relationships with psychophysiological and immunological effects in human beings. Therefore, this study furthers scientific understanding of the role that olfactory stimuli and forest terpenes inhalation play in the multisensory pathways that link well-being and forest exposure.

Chapter 2. THE EFFECTS OF TERPENE EXPOSURE ON STRESS-RELATED OUTCOMES

2.1 METHOD

2.1.1 *Design*

A group of 43 adult participants were randomly assigned to a treatment sequence in a double-blind, randomized crossover trial of healthy adult participants engaged in seated forest exposure sessions in a stand of old- and second-growth conifer trees at the University of Washington Charles L. Pack Experimental Forest located near Eatonville, Washington ("Pack Forest"). To isolate the olfactory pathway, participants wore powered air-purifying respirators (PAPRs; 3M™ Versaflo™ Powered Air Purifying Respirator, product number TR-800-PSK/94248) for two 60-minute seated forest exposure sessions. A washout period of eight days was included to reduce the carryover effect of one treatment on the other (Sibbald & Roberts, 1998). In one session, the PAPR mask was fitted with a particle-only filter (3M™ TR-6710N Versaflo™ High-Efficiency Filter, product number TR-6710N-5) to allow for the inhalation of terpenes ("terpenes-on"). In the other session, the mask was fitted with a charcoal filter (3M TR-6510N Versaflo Organic Vapor/HEPA Cartridge, product number TR-6510N) that removed particles, terpenes, and other BVOCs ("terpenes-off") to prevent the inhalation of terpenes. To evaluate terpene inhalation contributions to the effects of forest bathing on anxiety, stress, and affect, outcomes between the two sessions were compared.

Given the lack of meta-analyses of seated forest bathing crossover trials and other empirical data on expected effect sizes, we used effect sizes from other nature contact crossover studies (e.g., nature vs. urban contact) for sample size estimation. Our approach was based on the

estimated difference in outcomes between sessions, controlling for order effects and the measurement variance expected in the outcomes independent of session due to intra-individual differences. We considered population effect sizes of our outcomes when possible, integrating this with sample effect sizes from the available forest bathing literature, and estimated sample size using the significance criterion of $\alpha = .05$ and power = .80. Integrating this with mean effect sizes and pooled standard deviations for relevant outcomes from existing forest bathing crossover studies (although contrasting conditions in these studies are typically forest vs. urban, instead of our planned contrast of terpenes-on vs. terpenes-off within forest) yielded an expected mean 5% reduction in HR (Hedges' g =0.4), 2% reduction in BP (Hedges' g = 0.17), 35% increase in HF HRV (Hedges' g = 0.12), and 32% decrease in self-reported tension and anxiety (Hedges' g = 0.76; Lee et al., 2011; B. J. Park et al., 2009; Tsunetsugu et al., 2007). Our target sample size of 40 participants was based on the estimated numbers needed to detect minimum differences in the study outcomes in the contrasting conditions for the same participant, based on the minimums in the ranges of Hedges' g values from prior studies and standard population-level intra-individual differences.

2.1.2 *Study Site*

Forest-sitting sessions were conducted between 10:00 AM and 4:00 PM in a stand of old- and second-growth Douglas Fir, Western Red Cedar, and other conifers in Pack Forest, accessible by a 10-minute drive on an unpaved single-lane road from the Pack Forest Conference Center.

2.1.3 *Participants*

We enrolled 43 adult participants between July 12, 2022, and September 21, 2023. Healthy adult participants were recruited from the Tacoma and Seattle area using a combination of physical

flyers in community centers, libraries, and local universities, and electronic listings on Craigslist and the University of Washington Institute of Translational Health Sciences study recruitment site. Potential participants were screened via a phone call and excluded if they were pregnant, smoking, not fluent in English, and/or had a current or prior diagnosis of neurologic, hypertensive, psychiatric, or respiratory disorder, or anosmia/hyposmia. Participants were also excluded if they were prescribed a short list of prescription medications known to influence terpene metabolic pathways and short-term inflammatory biomarkers including beta-blockers, antibiotics, statins, hypertension medications, steroid medications, and diabetes control medications. Eligible participants were asked to avoid certain consumer products, foods, beverages, cleaning products, alcohol, marijuana, e-cigarettes, and supplements that contain terpene compounds in the 24 hours leading up to their forest-sitting experience (see Appendix A for a complete list).

Additionally, the clinically validated University of Pennsylvania Smell Identification Test (UPSIT; Sensonics International, Haddon Heights, NJ) was administered to determine whether participants had anosmia/hyposmia (full or partial smell loss). The UPSIT is a 40-item, self-administered "scratch-and-sniff" test that uses microencapsulated odorants that are released by scratching designated spaces on a paper test booklet. Summed scores were used to evaluate olfactory function and exclude participants with undiagnosed full or partial smell loss (summed UPSIT score $\leq$18).

Study participants met research staff at a study site in Tacoma, Washington for informed consent, initial surveys, and measurements. Participants were then transported to Pack Forest (~one hour drive) in a vehicle fitted with a fan that blew filtered air into their seating area to reduce terpene exposure prior to their study session. Upon arrival at Pack Forest, participants

were outfitted with a charcoal filter (3M TR-6510N Versaflo Organic Vapor/HEPA Cartridge, product number TR-6510N) that removed particles, terpenes, and other BVOCs (zero filter) to prevent the inhalation of terpenes during initial study protocols. Participants were then outfitted with physiology equipment in a clinic room, rested for 10 minutes, and completed a baseline surveys, measures, and the initial blood draw, before being transported to the forest site where the assigned treatment filter was swapped for the zero filter. Blood pressure, HR, and self-reported affect and stress were assessed at the beginning of the intervention (T1; 0-5 minutes elapsed) and the end of the intervention (T4; 55-60 minutes elapsed). Self-reported affect and stress were also assessed at two additional points: T2 (17.5-22.5 minutes elapsed) and T3 (37.5-42.5 minutes elapsed). Blood samples were collected at T4 following intervention completion. HF HRV and SCL were assessed continuously. A full daily protocol is outlined in Figure 2.1.

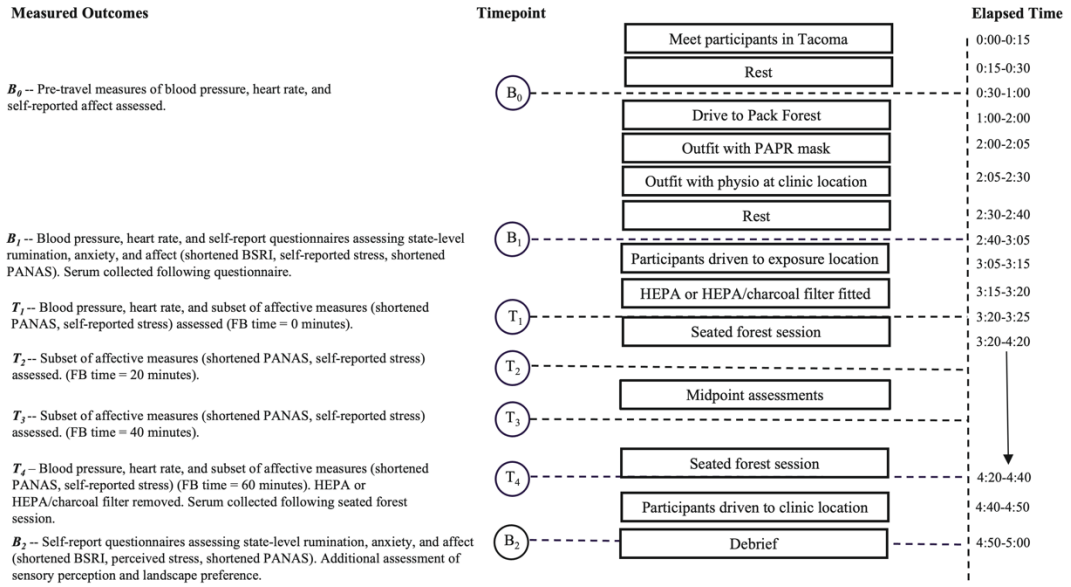

Figure 2.1. Overview of procedure sequence for a study session.

Study sessions were conducted from June to September of 2022 and 2023 to avoid rain, snow, and cold weather. Following enrollment, participants were randomly assigned to a treatment arm using a computer-randomized order created by an investigator who was not a member of the field team that determined whether a participant received “terpenes-off” versus “terpenes-on” exposure first. 21 participants were assigned to sequence AB (“terpenes-on” followed by “terpenes-off”) and 22 participants were assigned to BA (“terpenes-off” followed by “terpenes-on”; see Figure 2.2). Among AB participants, one participant was recommended for exit by staff, one participant was excluded before their second session, and one participant was lost to follow-up. Among BA participants, one participant was recommended for exit by staff, one participant was excluded before their second session, one participant withdrew during their first session, two participants were lost to follow-up, and four participants withdrew before their second session. The higher instances of withdrawal and loss to follow-up in the BA arm were likely due to a greater number of BA participants being enrolled during the first summer, when wildfire smoke and extreme events had a greater impact on data collection.

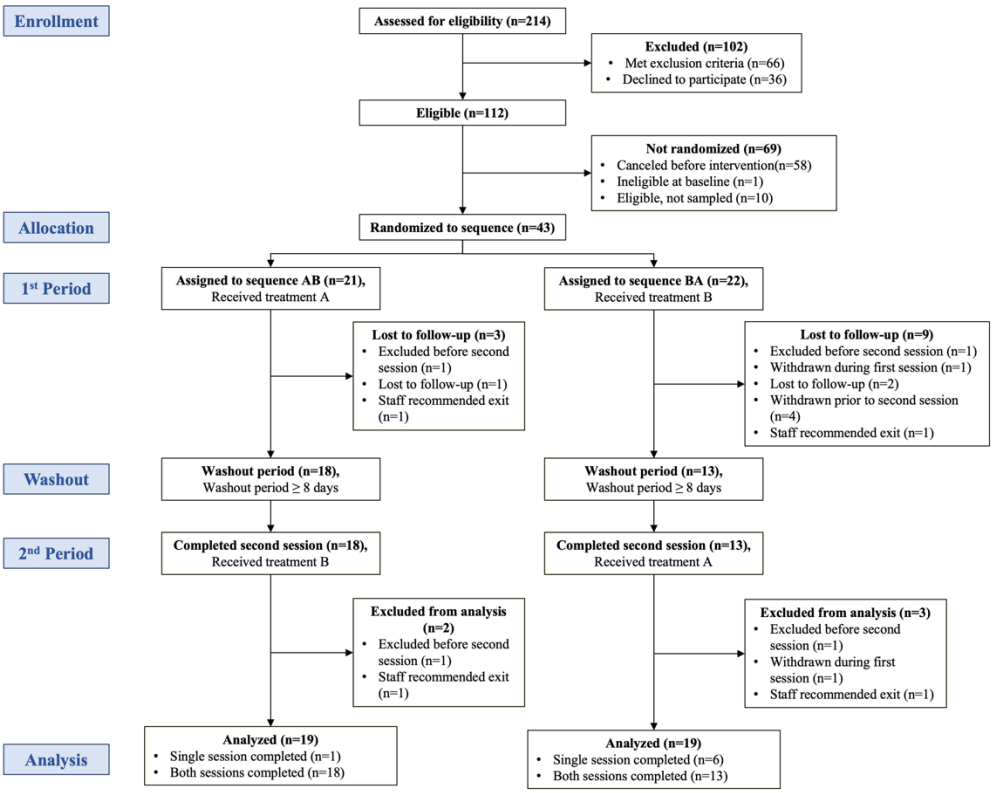

Figure 2.2. CONSORT enrollment, randomization, and retention of study participants among 43 adult participants in a randomized crossover "terpenes-on" vs. "terpenes-off" seated forest intervention trial.

Note: CONSORT, Consolidated Standards of Reporting Trials; A/B, "terpenes-on"/ "terpenes-off"; B/A, "terpenes-off"/ "terpenes-on."

The study protocol was approved by the University of Washington Institutional Review Board (approval number STUDY00013134). This trial was registered at www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT05316597) on March 30, 2022. All participants provided written informed consent. Participants received $180 in the form of a cash card or gift card upon

study completion ($90 per session). A $60 bonus for completing the second session was introduced with IRB approval in 2023 to reduce attrition.

2.2 Measures

2.2.1 *Nature Contact*

Average amount of nature contact frequency and duration measures was assessed using measures from Bratman et al. (2024) and Bratman et al. (2021), based on operationalizations from other nature exposure papers (Shanahan et al., 2016; M. P. White et al., 2019). Average frequency was assessed by presenting participants with the following question: “About how often do you usually visit or pass through outdoor natural areas for any reason? This includes, for example, walking, biking, or recreating outside in local, regional, or national parks, at the beach, beside or within lakes, creeks, or the ocean, gardening or tending to plants, camping, fishing, reading or walking outside next to trees, engaging in yard work with natural elements, etc...” Participants selected an answer from following options: “Never”, “Once a year”, “Once every three months”, “Once a month”, “2-3 times a month”, “Once a week”, “2-3 days a week”, “4-5 days a week”, or “6-7 days a week” (Bratman et al., 2024). Average duration was measured by presenting participants with the following question: “Over the last month, approximately how many HOURS PER WEEK do you consider yourself to have interacted with nature? This includes, for example, walking, biking, or recreating outside in local, regional, or national parks, at the beach, beside or within lakes, creeks, or the ocean, gardening or tending to plants, camping, fishing, reading or walking outside next to trees, engaging in yard work with natural elements, etc...” (Bratman et al., 2021). Participants entered their response in a provided text box.

2.2.2 *Nature Relatedness*

Nature relatedness was measured during baseline measurements using the short-form nature relatedness scale (NR-6; Nisbet & Zelenski, 2013). The NR-6 consists of six items designed to capture how people view their relationship with nature (e.g., "My relationship to nature is an important part of who I am"). Each item is rated on a five-point scale, ranging from 1 ("Disagree strongly") to 5 ("Agree strongly") from which a total score is calculated by averaging all six items. Cronbach's α was used to measure how closely correlated related scale items were as a group. In the current study, NR-6 showed good reliability (Cronbach's α = .76).

2.2.3 *High-Frequency Heart Rate Variability*

High-frequency heart rate variability (HF HRV) was assessed as a physiological metric of PNS activity in milliseconds squared (ms^2), using a portable, continuous electrocardiogram sensor (EcgMove4; Movisens®, Karlsruhe, Germany, part number 10402) worn directly on the chest with adhesive electrodes (ECG Electrodes; Movisens®, Karlsruhe, Germany, part number 40104). We applied a natural logarithmic transformation to 5-minute averages of HF HRV (" ln-HF HRV") following established precedent in prior literature (Shaffer & Ginsberg, 2017).

2.2.4 *Blood Pressure and Heart Rate*

Systolic and diastolic blood pressure was measured with an automated cuff monitor (GE Healthcare CARESCAPE V100 Vital Signs Monitor) in millimeters of mercury (mmHg). Heart rate was also measured with the automated cuff monitor in beats per minute (BPM).

2.2.5 *Skin Conductance Levels*

Skin conductance level (SCL) was assessed as a physiological metric of SNS activity in microsiemens (μS) using a portable, continuous electrodermal sensor (EdaMove4; Movisens®, Karlsruhe, Germany, part number 10403) worn on a wristband and attached to the palm with adhesive electrodes (EDA Adhesive Electrodes; Movisens®, Karlsruhe, Germany, part number 40400).

2.2.6 *Affect*

General levels of positive and negative affect were assessed using the 20-item Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) during baseline measurements and state levels were assessed using the 10-item, shortened PANAS (I-PANAS-SF; (Thompson, 2007). The PANAS consists of 20 items designed to assess affect over the past month; 10 items are used to assess positive affect (e.g., “Interested,” “Active”) and 10 items are used to assess negative affect (“Distressed,” “Irritable”). Each item was rated on a five-point scale, ranging from 1 (“very slightly or not at all”) to 5 (“extremely”) from which sum positive and negative affect scores were calculated. In the current study, the PANAS showed good reliability for positive affect ($\alpha = .88$) and negative affect ($\alpha = .85$). State-level affect was captured by the I-PANAS-SF, which consists of 10 items. Five items were used to assess positive affect (e.g., “Inspired”, “Alert”), and five items were used to assess negative affect (“Upset”, “Hostile”) at the present. Each item was rated on a five-point scale, ranging from 1 (“very slightly or not at all”) to 5 (“extremely”) from which sum positive and negative affect scores were calculated. In the current study, I-PANAS-SF showed good reliability for positive affect (Cronbach’s $\alpha = .86$) and lower reliability for negative affect (Cronbach’s $\alpha = .40$).

2.2.7 *Self-reported Stress*

Participants were asked to rate to what extent they felt stressed at the moment on a five-point scale, ranging from 1 (“very slightly or not at all”) to 5 (“extremely”) at baseline and times points 1-4. Perceived stress was assessed using the four-item version of the Perceived Stress Scale (PSS-4; Cohen et al., 1983). This scale consists of four items designed to assess perceptions of stress over the last month (e.g., “In the last month, how often have you felt that you were unable to control the important things in your life?”). Each item was rated on a 5-point scale, ranging from 0 (“never”) to 4 (“very often”) from which a sum score was calculated. In the current study, PSS-4 showed good reliability (Cronbach’s $\alpha = .78$).

2.2.8 *Perception of Forest Setting*

Perception of the forest setting was assessed following each forest session using a combination of questions about the sensory experience and the perceived restorativeness of the forest. Perceived restorativeness was assessed using the adapted 11-item Perceived Restorativeness Scale (PRS-11; Pasini et al., 2014), which asks participants to rate the degree to which they agreed with statements such as “Places like that are fascinating” using an 11-point scale, ranging from 0 (“not at all”) to 10 (“completely”). Additionally, participants were asked to rate the pleasantness of their sensory experience of the forest for sight, smell, and visual experience on a 10-point scale ranging from 1 (“not pleasant”) to 10 (“extremely pleasant”). Participants were also provided a text box to describe any further thoughts or feelings they had about the sensory experience of the forest.

2.2.9 *Serum Sample Collection and Handling*

A trained phlebotomist or registered nurse collected approximately 5 mL of blood via venipuncture before and after forest sessions using BD Vacutainer™ Push Button Blood Collection Sets (Fisher Scientific, catalog number 14-816-153) into 6 ml BD Vacutainer™ Venous Blood Collection Tubes: Vacutainer Plus™ Plastic Serum Tubes, Silicone-Coated, with Hemogard™ Closures (Fisher Scientific, catalog number 02-683-94). Samples were then stored at room temperature for 30 minutes to allow for blood clotting before being placed in a 4°C refrigerator. Blood samples were centrifuged at 3,000 rpm for 10 minutes and aliquots of serum were separated into 2 ml Fisherbrand™ Externally and Internally Threaded Cryogenic Storage Vials (Fisher Scientific, catalog number 10-500-26 Accessories) and stored at -80°C before being transported on dry ice to the Center for Disease Control (CDC) Tobacco and Volatiles Branch and the University of Washington Center for Studies in Demography and Ecology Biodemography Lab for analysis.

2.2.10 *Serum Biomarker Concentrations*

Acute cytokine response was assessed using a custom three-plex enzyme immunoassay microarray (Quansys Biosciences, part number 107749GR) to measure levels of CRP, TNF-α, IL-6, and serum cortisol. Chemiluminescence was quantified using a Quansys Q-view Imager LS. An eight-point, five-parameter standard curve was used to estimate cytokine concentrations and assay limits of detection (Q-view software, Quansys Biosciences).

A competitive microplate enzyme immunoassay, previously validated for use with plasma (Munro & Stabenfeldt, 1984), was adapted to measure cortisol in serum extracts using a purified polyclonal anti-cortisol antibody, R4866 (provided by C. Munro, UC Davis), and cortisol reference calibrators (Steraloids, catalog number Q3880). This assay has been used

successfully with saliva, urine, hair, and dried blood spot samples (Doyle et al., 2019; Heller et al., 2018; Konishi et al., 2012; Trumble et al., 2010). The anti-cortisol antibody cross-reacts 100% with cortisol, 10% with prednisolone, 6% with prednisone, 6% with 11-deoxycortisol, 5% with cortisone, and less than 1% with all other steroids (data provided by C. Munro). Color reactions were quantified at 405 nanometers (nm; test) and 570 nm (reference) using a Synergy HT microplate reader (Bio Tek Instruments, Inc.). A five-parameter standard curve was used to estimate cortisol concentrations (Gen5, Bio Tek Instruments Inc.). For both acute cytokine and cortisol response analyses, all samples, standards, and controls were assayed in duplicate wells.

2.2.11 *Serum Terpene Concentrations*

Serum terpene concentrations of α-pinene, β-caryophyllene, β-myrcene, β-pinene, Δ-3-carene, and limonene were assessed using the quantification method developed by the CDC's Tobacco and Volatiles Branch and detailed in Silva et al. (2020). Thawed serum samples were mixed using a hematology mixer (Fisher Scientific Inc., Pittsburgh, PA), and a 0.50 mL aliquot of the sample was dispensed into a 10 mL solid phase microextraction vial. Purge-and-trap grade methanol was used to dilute pure chemicals into the primary standard and internal standard (ISTD) stock solutions. A 40µL spike of the ISTD solution was added the sample, which was then crimp-sealed and mixed with a vortexer (S/P Multi-Tube Vortexer, Baxter Diagnostics Inc., Minster, OH) for 5 minutes. Blank and quality control samples were also prepared with a 40µL ISTD spike. Standards prepared following an identical method were included with each analytical run. Vials were placed on a Peltier-cooled sample tray (15°C) on an Agilent 7890 GC (Agilent, Santa Clara, CA) coupled to an Agilent 7010 triple-quadrupole MS (Agilent, Santa Clara, CA) with a mounted CombiPAL autosampler and extra PAL autosampler arm (CTC Analytics AG, Zwingen, Switzerland) to analyze all samples. The six target analytes were

analyzed in positive ion electron-impact ionization with multiple reaction monitoring (MRM) modes using triple quadrupole mass spectrometers (TQMS).

2.2.12 *Terpene Concentrations in Air*

Terpene concentrations in the air were measured throughout each day using an adaptation of NIOSH Manual of Analytical Methods (NMAM) 1552 (National Institute for Occupational Safety and Health, 1996). This method implemented a personal sampling pump connected to a multi-bed thermal desorption tube (CT 420, Millipore, USA) to collect BVOCs in ambient air. The thermal desorption tube was mounted on a metal stand, near the participant, at PAPR filter height (~ 1.5 ft above the ground). The tube was analyzed for terpenes using thermal desorption-gas chromatography–mass spectrometry (TD-GC/MS).

2.3 STATISTICAL ANALYSIS

2.3.1 *Aim 1: Assess whether BVOC inhalation regulates stress reduction and affective outcomes of the "terpenes-on" vs. "terpenes-off" sessions*

We calculated the main effect of the filter on the difference between baseline measurements and time point 2 (T2) for ln-HF HRV, skin conductance levels, self-reported stress, positive and negative affect levels (I-PANAS-SF), and timepoint 4 (T4) for systolic blood pressure, diastolic blood pressure, heart rate, inflammatory biomarkers, and cortisol using a mixed-effects regression model. HF HRV values were winsorized and log transformed. As the machine values for left-censored IL-6 observations are closest to the true values, machine values were used for censored observations for the primary analysis. Sensitivity analyses were performed for the IL-6 analysis by comparing model output using machine values to model output using $\frac{limit\ of\ detection\ (LOD)}{\sqrt{2}}$ and zero imputation. Participants who completed only one session were

included in the analyses. Analyses were conducted in R (version 4.3.1; R Core Team, 2023) using the lme4 and lmerTest R packages (Bates et al., 2015; Kuznetsova et al., 2017). The criterion for statistical significance was $p \leq .05$. Results and associated statistics, including effect sizes and confidence intervals, are presented in Section 2.3.

2.3.2 *Linear Mixed-effects Model at Time Points 2 and 4*

We fit a mixed-effects model to estimate the differences in effect between the "terpenes-on" and "terpenes-off" sessions at T2 for ln-HF HRV, SCL, PA, NA, and stress, and T4 for SBP, DBP, HR, inflammatory biomarkers, and cortisol, controlling for the baseline (pre-session measurement at the clinic location at Pack Forest) using the following model specification:

For ln-HF HRV, SCL, and self-reported stress, where:

$$Y_{is} = \beta_0 + \beta_1 baseline_{is} + \beta_2 filter_{is} + \alpha_i + \varepsilon_{is}$$

Where Y_{is} is the observed average outcome for individual *i* at T2, and session *s* where *s* is session 1 or session 2, β_0 is the average Y_{is} for the study population at T2 when they were assigned the "terpenes-off" filter, adjusting for baseline, β_1 is the estimated difference in Y_{is} at T2 between two groups differing in baseline by 1 unit, β_2 is our primary coefficient of interest and is the estimated difference in Y_{is} between the "terpenes-off" filter and the "terpenes-on" filter at T2, adjusting for baseline, α_i is the random intercept for subjects to account for repeated measures within individuals, and ε_{is} is the observation-specific error.

For positive and negative affect levels (I-PANAS-SF):

$$Y_{is} = \beta_0 + \beta_1 baseline_{is} + \beta_2 filter_{is} + \beta_2 missingscaleitem_{is} + \alpha_i + \varepsilon_{is}$$

Where Y_{is} is the observed average outcome for individual *i* at T2, and session *s* where *s* is session 1 or session 2, β_0 is the average Y_{is} for the study population at T2 when they were assigned the "terpenes-off" filter, adjusted for baseline and missing scale items (items left

unanswered on the I-PANAS-SF scale), β_1 is the estimated difference in Y_{is} at T2 between two groups differing in baseline by 1 unit, β_2 is our primary coefficient of interest and is the estimated difference in Y_{is} between the "terpenes-off" filter and the "terpenes-on" filter at T2, adjusted for baseline and missing scale items, β_3 is the estimated difference in Y_{is} between two groups differing in missing affect scale items by 1 item, adjusted for baseline, α_i is the random intercept for subjects to account for repeated measures within individuals, and ε_{is} is the observation-specific error.

For SBP, DBP, HR, inflammatory biomarkers, and cortisol, where Y_{is} is the observed outcome for individual *i*, at time point *t* where *t* is T4, and session *s* where *s* is session 1 or session 2, β_0 is the average Y_{is} for the study population at T4 when they were assigned the "terpenes-off" filter, adjusting for baseline, β_1 is the estimated difference in Y_{is} at T4 between two groups differing in baseline by 1 unit, β_2 is the average difference in Y_{is} between the "terpenes-off" filter and the "terpenes-on" filter, adjusting for baseline, α_i is the random intercept for subjects to account for repeated measures within individuals, and ε_{is} is the observation-specific error.

2.3.3 *Nested Mixed-effects Models Across Time Points*

We performed a two-way analysis of variance (ANOVA) to test the null hypothesis that there is no difference in the expected difference of ln-HF HRV, SCL, PA, NA, and stress at T1, T2, T3, and T4 between groups who differed in terpene exposure, controlling for baseline using the following model specification:

For ln-HF HRV, skin conductance levels, and self-reported stress:

Null model:

$$Y_{its} = \beta_0 + \beta_1 baseline_{is} + \beta_2 T2_{is} + \beta_3 T3_{is} + \beta_4 T4_{is} + \alpha_i + \varepsilon_{its}$$

Where Y_{its} is the observed average outcome for individual *i*, at time point *t* where *t* is T1, T2, T3, or T4, and session *s* where *s* is session 1 or session 2, β_0 is the value of Y_{its} at T1 and adjusted for baseline, β_1 is the estimated difference in Y_{its} at T1, T2, T3, or T4 between two groups differing in baseline by 1 unit, β_2 is the difference between Y_{its} comparing T1 and T2, β_3 is the difference between Y_{its} comparing T1 and T3, β_4 is the difference between Y_{its} comparing T1 and T4, α_i is the random intercept for subjects to account for repeated measures within individuals, and ε_{its} is the observation-specific error.

Full model:

$$Y_{its} = \beta_0 + \beta_1 baseline_{is} + \beta_2 T2_{is} + \beta_3 T3_{is} + \beta_4 T4_{is} + \beta_5 filter_{is} + \beta_6 T2_{is} * filter_{is} + \beta_7 T3_{is} * filter_{is} + \beta_8 T4_{is} filter_{is} + \alpha_{is} + \varepsilon_{its}$$

Where Y_{its} is the observed average outcome for individual *i*, at time point *t* where *t* is T1, T2, T3, or T4, and session *s* where *s* is session 1 or session 2, β_0 is the average Y_{its} at T1 and adjusted for baseline for the study population when they were assigned the "terpenes-off" filter, β_1 is the estimated difference in Y_{its} at T1, T2, T3, or T4 between two groups differing in baseline by 1 unit, β_2 is the average difference in Y_{its} comparing T1 and T2 for the study population when they were assigned the "terpenes-off" filter, adjusting for baseline, β_3 is the average difference in Y_{its} comparing T1 and T3 for the study population when they were assigned the "terpenes-off" filter, adjusting for baseline, β_4 is the average difference in Y_{its} comparing T1 and T4 for the study population when they were assigned the "terpenes-off" filter, adjusting for baseline, β_5 is the average difference between Y_{its} at T1 when the study population was assigned the "terpenes-off" filter and Y_{its} at T1 when they were assigned the "terpenes-on" filter, adjusted for baseline, β_6 is the average difference between Y_{its} at T1 and T2 when the study population was assigned the

"terpenes-on" filter, adjusted for baseline, β_7 is the average difference between Y_{its} at T1 and T3 when the study population was assigned the "terpenes-on" filter, adjusted for baseline, β_8 is the average difference between Y_{its} at T1 and T4 when the study population was assigned the "terpenes-on" filter, adjusted for baseline, α_i is the random intercept for subjects to account for repeated measures within individuals, and ε_{its} is the observation-specific error.

For positive and negative affect levels (SF-PANAS):

Null model:

$$Y_{its} = \beta_0 + \beta_1 baseline_{is} + \beta_2 T2_{is} + \beta_3 T3_{is} + \beta_4 T4_{is} + \beta_5 missingscaleitems_{is} + \alpha_i + \varepsilon_{its}$$

Where Y_{its} is the observed average outcome for individual *i*, at time point *t* where *t* is T1, T2, T3, or T4, and session *s* where *s* is session 1 or session 2, β_0 is the value of Y_{its} at T1 and adjusted for baseline and missing scale items, β_1 is the estimated difference in Y_{its} at T1, T2, T3, or T4 between two groups differing in baseline by 1 unit, adjusted for missing scale items (items left unanswered on the I-PANAS-SF scale), β_2 is the difference between Y_{its} comparing T1 and T2, adjusted for baseline and missing scale items, β_3 is the difference between Y_{its} comparing T1 and T3, adjusted for baseline and missing scale items, β_4 is the difference between Y_{its} comparing T1 and T4, adjusted for baseline and missing scale items, β_5 is the estimated difference in Y_{its} between two groups differing in missing affect scale items by 1 item, adjusted for baseline, α_i is the random intercept for subjects to account for repeated measures within individuals, and ε_{its} is the observation-specific error.

Full model:

$$Y_{its} = \beta_0 + \beta_1 baseline_{is} + \beta_2 T2_{is} + \beta_3 T3_{is} + \beta_4 T4_{is} + \beta_5 filter_{is} + \beta_6 T2_{is} * filter_{is} + \beta_7 T3_{is} * filter_{is} + \beta_8 T4_{is} filter_{is} + \beta_9 missingscaleitems_{is} + \alpha_{is} + \varepsilon_{its}$$

Where Y_{its} is the observed average outcome for individual *i*, at time point *t* where *t* is T1, T2, T3, or T4, and session *s* where *s* is session 1 or session 2, β_0 is the average Y_{its} at T1 and adjusted for baseline and missing scale items for the study population when they were assigned the "terpenes-off" filter, β_1 is the estimated difference in Y_{its} at T1, T2, T3, or T4 between two groups differing in baseline by 1 unit, adjusted for missing scale items, β_2 is the average difference in Y_{its} comparing T1 and T2 for the study population when they were assigned the "terpenes-off" filter, adjusted for baseline and missing scale items, β_3 is the average difference in Y_{its} comparing T1 and T3 for the study population when they were assigned the "terpenes-off" filter, adjusted for baseline and missing scale items, β_4 is the average difference in Y_{its} comparing T1 and T4 for the study population when they were assigned the "terpenes-off" filter, adjusted for baseline and missing scale items, β_5 is the average difference between Y_{its} at T1 when the study population was assigned the "terpenes-off" filter and Y_{its} at T1 when they were assigned the "terpenes-on" filter, adjusted for baseline and missing scale items, β_6 is the average difference between Y_{its} at T1 when the study population was assigned the "terpenes-off" filter and Y_{its} at T1 when they were assigned the "terpenes-on" filter, adjusted for baseline and missing scale items, β_7 is the average difference between Y_{its} at T1 and T3 when the study population was assigned the "terpenes-on" filter, adjusted for baseline and missing scale items, β_8 is the average difference between Y_{its} at T1 and T4 when the study population was assigned the "terpenes-on" filter, adjusted for baseline and missing scale items, β_9 is the estimated difference in Y_{its} at T1, T2, T3, or T4 between two groups differing in missing affect scale items by 1 item, adjusted for baseline, α_i is the random intercept for subjects to account for repeated measures within individuals, and ε_{its} is the observation-specific error.

2.3.4 *Aim 1a: Assess the degree of association of absorbed dose of six forest-derived VOCs in serum with these outcomes*

We calculated the association of absorbed dose (difference between baseline and T4 serum terpene levels) and T2 measurements for ln-HF HRV, skin conductance levels, self-reported stress, positive and negative affect levels (I-PANAS-SF) and T4 measurements for systolic blood pressure, diastolic blood pressure, heart rate, inflammatory biomarkers, and cortisol while controlling for baseline outcome and terpene measurements using a similar model from Section 2.3.2 (absorbed dose replaced terpene exposure variable). Additionally, we examined the association between absorbed dose and ln-HF HRV, skin conductance levels, self-reported stress, positive and negative affect levels across timepoints while controlling for baseline outcome and terpene measurements using a similar model from Section 2.3.3 (absorbed dose replaced terpene exposure variable). Participants who completed only one session were also included in the analyses.

2.3.5 *Data Exclusions*

Five participants were removed from the analysis: two participants who were recommended for exit by UW IRB staff following responses to study protocols, one participant who withdrew mid-session, and two participants who were found to meet exclusion criteria following their first session.

2.3.6 *Missing Data*

We imputed missing values for two types of data, (1) missing questionnaire items (relevant to secondary outcomes) and (2) missing baseline ln-HF HRV (relevant to primary outcome). The I-

PANAS-SF positive affect (PA) and negative affect (NA) outcomes are scored by summing five individual PA and NA items. 16 (3.9%) of the 414 questionnaires were missing one to two items at one of the time points, although the data were typically complete for other time points. Because answers for the same item were modestly correlated between timepoints from the same day (mean R^2 =.58), but still performed better than other imputation approaches (random PA and NA item from the day, mean PA or NA score, and regression imputation), we used the mean available item value for missing items. This methodology is similar to the mean imputation approach demonstrated in Shrive et al. (2006), but employs individual item row mean imputation, a single item imputation approach that can be used for longitudinal data (Engels & Diehr, 2003).

For ln-HF HRV, there were five participants whose ln-HF HRV was partially captured both before and during exposure but missing during the window of our standard baseline time timepoint (i.e., B1). Additional 5 minute periods of ln-HF HRV were calculated using continuous data from before treatment exposure, including 10-5 minutes before B1 (R1), 5-0 minutes before B1 (R2), 0-5 minutes into the venipuncture procedures (V1), 5-10 minutes into the venipuncture procedure (V2), 0-5 minutes into the drive up to the forest site (D1), and 5-10 minutes into the drive up to the forest site (D2). Correlations between B1 ln-HF HRV and each additional time point before exposure were assessed using a complete case data set. Time points with the highest correlations (R1, R2, V1, D1) were included in single linear regression models to predict B1 values using a complete case data set. One participant did not have any additional time points available, so we used a regression model with the B1 measurement from the other session as a predictor (s2_b1_hrv ~ s1_b1_hrv). Each single linear regression model (b1_hrv ~ r1_hrv, b1_hrv ~ r2_hrv, b1_hrv ~ v1_hrv, b1_hrv ~ d1_hrv, s2_b1_hrv ~ s1_b1_hrv) was cross-

validated using a complete-case dataset to assess R^2 values (0.92, 0.95, 0.98, 0.85, and 0.83, respectively). Models were preferentially ranked based on R^2 values and predicted values for B1 were imputed depending on R1, R2, V1, D1, and S1B1 (session 1 baseline 1) timepoint availability. Of the missing baseline observations, there is one person for whom we used V1 to predict B1, three people for whom we used D1 to predict B1, and one person for whom we used S1B1 to predict S2B1.

2.3.7 *Non-detect Observations*

Maximum likelihood estimation (MLE) was used to impute non-detect observations for serum α-pinene, β-myrcene, and Δ-3-carene for the absorbed dose calculations. Due to a low proportion of non-detect observations, $\frac{LOD}{\sqrt{2}}$ was used to impute non-detect observations for limonene. Sum composite absorbed dose was calculated as the sum of α-pinene, β-myrcene, Δ-3-carene, and limonene absorbed doses. Due to high (i.e., > 50%) proportions of non-detects, β-pinene and β-caryophyllene were excluded from the absorbed dose calculations.

2.4 RESULTS

The characteristics of the 43 adults enrolled in the study are shown in Table 2.1. The mean age was 35.1±14.3 years and 51.2% described their gender as female, 39.5% described their gender as male, and 9.4% described their gender as non-binary or preferred to self-describe. 2.3% of participants described their race as American Indian or Alaska Native, 11.6% as Asian, 7.0% as Black or African American, 72.1% as White, and 7.0% as Other. Over half of participants had at least a bachelor's degree (51.2%) and 58.3% reported an annual household income below $80,000, approximately equal to Tacoma's 2022 median annual household income of $80,784

(U.S. Census Bureau, 2022). Nearly half of participants were working (48.8%), 18.6% were students, and 32.2% were not working or preferred not to answer.

Table 2.1. Baseline characteristics and demographic information of study participants.

	AB (N=21)	BA (N=22	Overall (N=43)
Age (years)			
Mean (SD)	33.0 (14.2)	37.1 (14.5)	35.1 (14.3)
Median [Min, Max]	28.0 [20.0, 65.0]	35.5 [19.0, 68.0]	29.0 [19.0, 68.0]
Gender			
Male	7 (33.3%)	10 (45.5%)	17 (39.5%)
Female	12 (57.1%)	10 (45.5%)	22 (51.2%)
Prefer to self-describe	1 (4.8%)	1 (4.5%)	2 (4.7%)
Non-binary	1 (4.8%)	1 (4.5%)	2 (4.7%)
Race			
American Indian or Alaska Native	0 (0%)	1 (4.5%)	1 (2.3%)
Asian	2 (9.5%)	3 (13.6%)	5 (11.6%)
Black or African American	1 (4.8%)	2 (9.1%)	3 (7.0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)
White	16 (76.2%)	15 (68.2%)	31 (72.1%)
Other	2 (9.5%)	1 (4.5%)	3 (7.0%)
Ethnicity			
Hispanic, Latino or Spanish origin	2 (9.5%)	3 (13.6%)	5 (11.6%)
Non-Hispanic, Latino or Spanish origin	19 (90.5%)	19 (86.4%)	38 (88.4%)
Education			
High school graduate (high school diploma or equivalent including GED)	1 (4.8%)	3 (13.6%)	4 (9.3%)
Some college but no degree	5 (23.8%)	1 (4.5%)	6 (14.0%)
Associate degree in college (2-year)	1 (4.8%)	1 (4.5%)	2 (4.7%)
Bachelor's degree in college (4-year)	11 (52.4%)	11 (50.0%)	22 (51.2%)

	AB (N=21)	BA (N=22	Overall (N=43)
Master's degree	3 (14.3%)	5 (22.7%)	8 (18.6%)
Professional degree (JD, MD)	0 (0%)	1 (4.5%)	1 (2.3%)
Income			
Less than $19,999	2 (9.6%)	1 (4.5%)	3 (7.0%)
$20,000 to $39,999	9 (42.8%)	4 (18.2%)	13 (30.3%)
$40,000 to $59,999	3 (14.3%)	3 (13.6%)	6 (14.0%)
$60,000 to $79,999	0 (0%)	3 (13.6%)	3 (7.0%)
$80,000 to $99,999	1 (4.8%)	0 (0%)	1 (2.3%)
$100,000 to $149,999	1 (4.8%)	7 (31.8%)	8 (18.6%)
$150,000 to $299,999	2 (9.5%)	2 (9.0%)	4 (9.3%)
$300,000 or more	2 (9.5%)	0 (0%)	2 (4.7%)
Prefer not to answer	1 (4.8%)	2 (9.1%)	3 (7.0%)
Employment			
Student	6 (28.6%)	2 (9.1%)	8 (18.6%)
Working (paid employee)	5 (23.8%)	11 (50.0%)	16 (37.2%)
Working (self-employed)	3 (14.3%)	2 (9.1%)	5 (11.6%)
Not working (looking for work)	4 (19.0%)	2 (9.1%)	6 (14.0%)
Not working (retired)	2 (9.5%)	3 (13.6%)	5 (11.6%)
Not working (disabled)	0 (0%)	1 (4.5%)	1 (2.3%)
Not working (other)	1 (4.8%)	0 (0%)	1 (2.3%)
Prefer not to answer	0 (0%)	1 (4.5%)	1 (2.3%)
Relationship Status			
Married	3 (14.3%)	6 (27.3%)	9 (20.9%)
Widowed	0 (0%)	1 (4.5%)	1 (2.3%)
Divorced	1 (4.8%)	0 (0%)	1 (2.3%)
Separated	0 (0%)	1 (4.5%)	1 (2.3%)
Never married	17 (81.0%)	14 (63.6%)	31 (72.1%)
UPSIT Score			
Mean (SD)	33.6 (2.56)	32.1 (3.19)	32.8 (2.96)
Median [Min, Max]	35.0 [28.0, 37.0]	33.0 [25.0, 37.0]	33.0 [25.0, 37.0]

	AB (N=21)	BA (N=22	Overall (N=43)
Baseline Perceived Stress Score (PSS)			
Mean (SD)	7.76 (1.51)	8.09 (1.15)	7.93 (1.33)
Median [Min, Max]	8.00 [4.00, 11.0]	8.00 [6.00, 10.0]	8.00 [4.00, 11.0]
Nature Relatedness Scale			
Mean (SD)	4.17 (0.593)	4.30 (0.617)	4.24 (0.601)
Median [Min, Max]	4.33 [2.50, 5.00]	4.50 [2.83, 5.00]	4.50 [2.50, 5.00]
Nature Frequency			
Once a month	1 (4.8%)	1 (4.5%)	2 (4.7%)
2-3 times a month	1 (4.8%)	1 (4.5%)	2 (4.7%)
Once a week	3 (14.3%)	1 (4.5%)	4 (9.3%)
2-3 days a week	8 (38.1%)	7 (31.8%)	15 (34.9%)
4-5 days a week	3 (14.3%)	8 (36.4%)	11 (25.6%)
6-7 days a week	5 (23.8%)	4 (18.2%)	9 (20.9%)
Nature Duration (hours/week)			
Mean (SD)	13.4 (13.6)	16.4 (19.9)	14.9 (16.9)
Median [Min, Max]	10.0 [3.00, 50.0]	12.0 [5.00, 100]	10.0 [3.00, 100]
Missing	0 (0%)	1 (4.5%)	1 (2.3%)

Field experiments consisted of collecting air samples inside a PAPR mask fitted with the "terpenes-on" filter, and simultaneously collecting air samples from a collocated PAPR mask fitted with the "terpenes-off" filter, and ambient air. We observed an average 68% reduction in α-pinene concentrations and 80% reduction in β-pinene concentrations from the "terpenes-off" filter compared to the "terpenes-on" filter. Full results are displayed in Table 2.2. Variability that we observed in Table 2.2 likely represents "measurement error" (i.e. variability in our experimental procedures for measuring terpenes), rather than true variability in filter

effectiveness. For most cases, we believe that the “terpenes-off” (B filter) was filtering terpenes to a greater degree compared to the “terpenes-on" (A filter).

Table 2.2. α-pinene and β-pinene levels inside PAPR helmet fitted with “terpenes-on” vs. “terpenes-off” filter.

	α-Pinene (ng)				**β-Pinene (ng)**			
Date	*Ambient*	*Filter A*	*Filter B*	*A vs. B % reduction*	*Ambient*	*Filter A*	*Filter B*	*A vs. B % reduction*
6/22/23	5.65	28.9	14.7	49%	< 0.500	11.6	2.93	75%
6/23/23	11.6	15.7	4.18	73%	1.88	2.71	< 0.500	91%
8/2-8/3/23*	2.53	20.4	3.07	85%	< 0.250	10.3	0.64	94%
8/16/23	37.3	94.2	< 0.250	100%	9.53	25.6	< 0.500	99%
9/5/23	0.69	4.23	2.73	35%	0.68	2.66	1.63	39%

Note: Filter A, “terpenes-on;” Filter B, “terpenes-off.”

**Ambient and Filter B sample collected on 8/2/2023, Filter A sample collected on 8/3/2023.*

Air was also filtered in the study vehicle during participant transportation to Pack Forest from Tacoma. When comparing air samples from the vehicle air samples when the filter was on to when the filter was off, we observed an average 91% reduction in α-pinene concentrations and 90% reduction in β-pinene concentrations when the filter was on (see Table 2.3 for full results).

Table 2.3. α-pinene and β-pinene levels in study vehicle comparing filter on versus filter off condition.

	Date	**α-Pinene (ng)**	**β-Pinene (ng)**
Filter Off	6/28/22	9.91	7.99
	6/28/22	10	8.51
	8/15/23	185	53.8
	9/21/23	19.5	5.7
Average		**56.1**	**19**
Filter On	6/28/22	0.71	< 0.500
	6/28/22	0.88	0.51
	8/15/22	4.29	1.74
	9/22/22	16.8	4.8
	8/1/23	3.16	0.65
	9/13/23	3.52	2.19

	Date	α-Pinene (ng)	β-Pinene (ng)
Average		4.89	1.98
% Reduction		**91%**	**90%**

2.4.1 *H1: Terpenes Exposure is Associated with Reduction of Stress Outcomes*

2.4.1.1 Effect of Exposure on Outcomes at Time Points 2 and 4

We observed a statistically significant effect of terpene exposure on IL-6 of -0.19 pg/mL (95% CI: -0.35, -0.03, p-value = .05). Sensitivity analyses were performed for the IL-6 analysis by comparing model output using machine generated values to model output using $\frac{limit\ of\ detection\ (LOD)}{\sqrt{2}}$ and zero imputation. Full sensitivity results are presented in Appendix B, and yielded similar effect estimates to our primary analysis.

We observed a marginally significant effect of terpene exposure on SCL at time point 2 of -0.84 μS (95% CI: -1.73, 0.06; p-value =.08).

Counter to our hypothesis, we did not observe a significant effect of terpene exposure at time point 2 on ln-HF HRV, PA, NA, and self-reported stress, or timepoint 4 for cortisol, TNF-α, or CRP. See Table 2.4 for all results. Figures displaying outcome trends over time by exposure group are in presented in Appendix B.

Table 2.4. Estimated differences in study outcomes between participants exposed to terpenes and participants not exposed to terpenes at T2 and T4.

Parameter	Estimate	95% CI	*p*
Ln HF-HRV	0.01	(-0.18, 0.21)	.914
SCL	-0.84	(-1.73, 0.06)	.076
PA	0.70	(-0.37, 1.77)	.210
NA	-0.16	(-0.43, 0.12)	.265
Stress	0.01	(-0.19, 0.21)	.921

Parameter	Estimate	95% CI	*p*
DBP	1.13	(-2.58, 4.85)	.554
SBP	-0.53	(-6.06, 5.00)	.852
HR	0.13	(-1.93, 2.18)	.905
Cortisol	-2.85	(-17.95, 12.24)	.716
IL-6	-0.19	(-0.35, -0.03)	**.046**
TNF-α	-0.79	(-1.88, 0.31)	.166
CRP	-0.34	(-2.2, 1.52)	.724

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; PA, positive affect; NA, negative affect; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate.

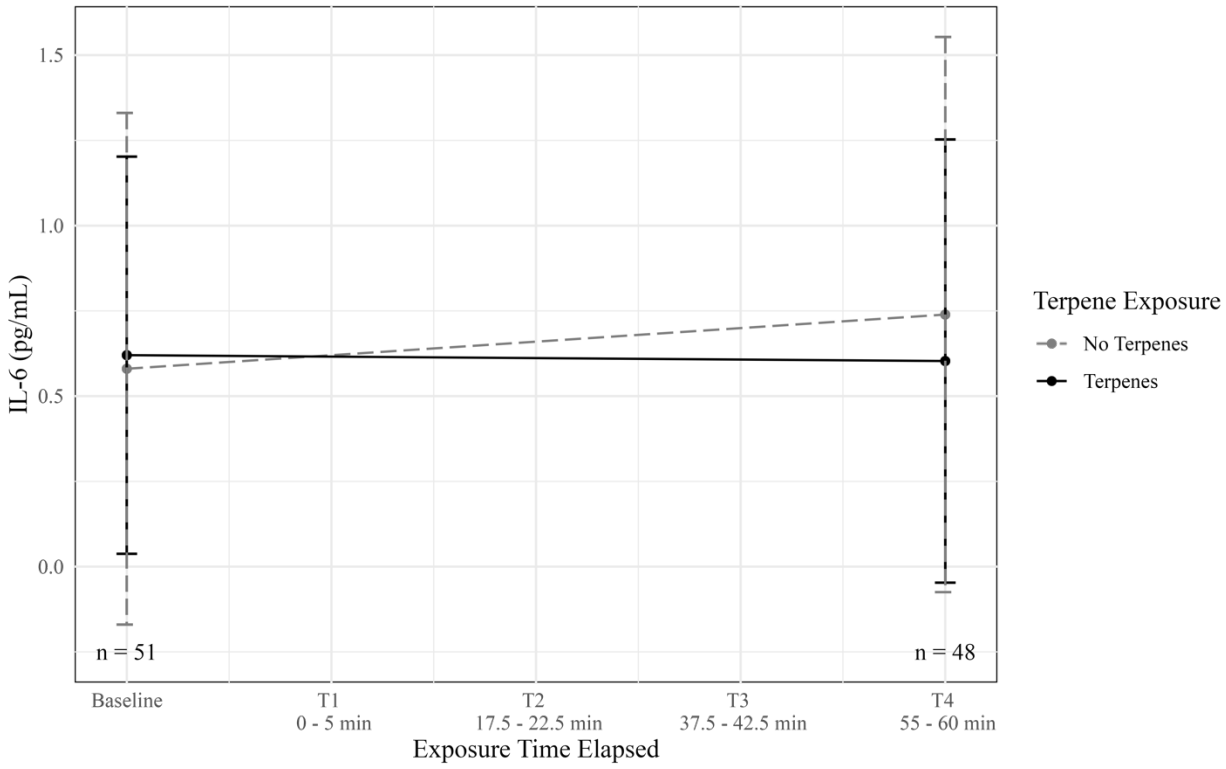

Figure 2.3. IL-6 across time points comparing “terpene-off” and “terpenes-on” conditions.

2.4.1.2 Effect of Exposure on Outcome Pattern Over Time

In support of our hypothesis, we observed a statistically significant effect of terpene exposure on the pattern of SCL over time (p-value = .02). Terpene exposure led to a difference in SCL of -0.9 μS at time point 2 (95% CI: -2.15, 0.35), -1.56 μS at time point 3 (95% CI: -2.81, -0.31), and -0.92 μS at time point 4 (95% CI -2.17, 0.33). All other ANOVA tests for ln-HF HRV, positive affect, negative affect, and stress were not statistically significant at the $\alpha = 0.05$ level. See Table 2.5 for full results.

Table 2.5. ANOVA results comparing full and reduced models to test the effect of terpene exposure on pattern of outcome over time.

Model	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
HRV							
Reduced	296.26	320.42	-141.13	282.26			
Full	300.11	338.07	-139.06	278.11	4.15	4	.39
SCL							
Reduced	1366.73	1391.86	-676.36	1352.73			
Full	1363.20	1402.70	-670.60	1341.20	11.53	4	**.02**
Positive Affect							
Reduced	1280.38	1305.49	-633.19	1266.38			
Full	1285.45	1324.91	-631.73	1263.45	2.93	4	.57
Negative Affect							
Reduced	575.95	601.06	-280.97	561.95			
Full	581.35	620.81	-279.68	559.35	2.59	4	.63
Stress							
Reduced	301.63	325.60	-143.81	287.63			
Full	308.11	345.78	-143.05	286.11	1.52	4	.82

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; AIC, Akaike information criterion; BIC, Bayesian information criterion.

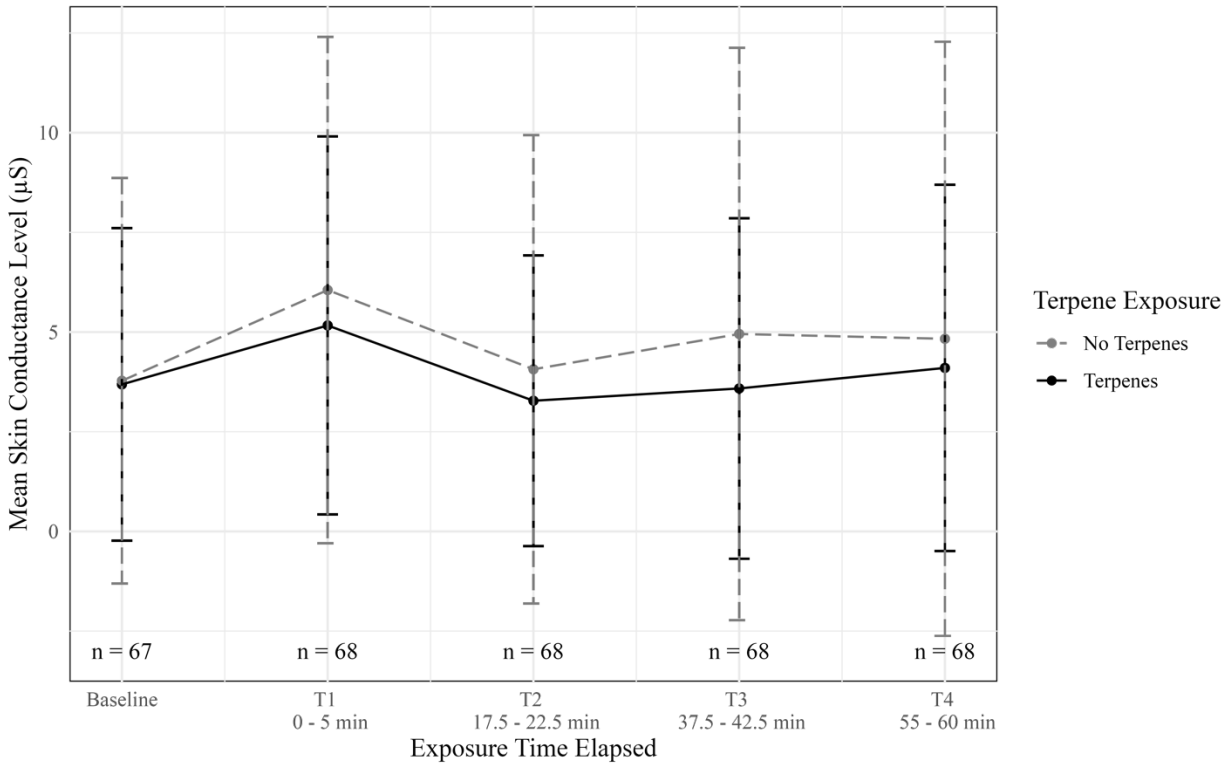

Figure 2.4. SCL across all time points comparing terpene-off and "terpenes-on"" conditions.

Sensitivity analyses were performed by comparing model results for ln-HF HRV to model results from data with no baseline imputation and model results from positive and negative affect outcomes to an imputed data set. Results were unchanged and are presented in Appendix B.

2.4.2 *H1a: Absorbed Dose is Associated with Reduction of Stress Outcomes*

Serum terpene concentrations were assessed before and after forest exposure (time points B1, and T4, respectively). Descriptive statistics are displayed in Table 2.6 and include detect, non-detect, low sample volume, and missing percentages. All non-detect observations were left-censored. In the "terpenes-on" condition, 9 (38%) B1 samples were missing and 15 (46.9%) T4 samples were missing. In the "terpenes-off" condition, 10 (27%) B1 samples were missing and 10 (27.0%) T4 samples were missing. High levels of missingness, particularly at T4, can be attributed to difficulties collecting samples in a remote forest environment.

Table 2.6. Non-imputed serum terpene concentrations at baseline and time point 4, stratified by filter.

	"Terpenes-on" (N=32 sessions)		**"Terpenes-off" (N=37 sessions)**	
	B1	*T4*	*B1*	*T4*
α-Pinene (µg/L)				
Mean (SD)	0.0632 (0.0117)	0.0635 (0.0126)	0.0765 (0.0177)	0.0783 (0.0204)
Median [Min, Max]	0.0596 [0.0506, 0.0880]	0.0599 [0.0509, 0.0951]	0.0719 [0.0570, 0.120]	0.0755 [0.0535, 0.122]
Detect	14 (43.8%)	9 (28.1%)	14 (37.8%)	18 (48.6%)
Non-detect	9 (28.1%)	8 (25.0%)	13 (35.1%)	7 (18.9%)
β-Pinene (µg/L)				
Mean (SD)	0.0965 (0.0505)	0.0966 (0.0355)	0.104 (0.0324)	0.0980 (0.0300)
Median [Min, Max]	0.0895 [0.0597, 0.240]	0.0850 [0.0685, 0.162]	0.0958 [0.0712, 0.161]	0.0875 [0.0575, 0.153]
Detect	11 (34.4%)	6 (18.8%)	10 (27.0%)	16 (43.2%)
Non-detect	12 (37.5%)	11 (34.4%)	17 (45.9%)	9 (24.3%)
β-Caryophyllene (µg/L)				
Mean (SD)	1.45 (0.361)	1.11 (NA)	1.00 (0.457)	1.29 (0.420)
Median [Min, Max]	1.45 [1.19, 1.70]	1.11 [1.11, 1.11]	0.796 [0.644, 1.79]	1.16 [0.943, 1.90]
Detect	2 (6.3%)	1 (3.1%)	6 (16.2%)	4 (10.8%)
Non-detect	21 (65.6%)	16 (50.0%)	21 (56.8%)	21 (56.8%)
β-Myrcene (µg/L)				
Mean (SD)	0.171 (0.0542)	0.173 (0.0400)	0.186 (0.0473)	0.181 (0.0442)
Median [Min, Max]	0.171 [0.0850, 0.293]	0.174 [0.106, 0.238]	0.179 [0.116, 0.306]	0.170 [0.111, 0.260]
Detect	22 (68.8%)	17 (53.1%)	23 (62.2%)	20 (54.1%)
Non-detect	1 (3.1%)	0 (0%)	4 (10.8%)	5 (13.5%)
Δ-3-Carene (µg/L)				
Mean (SD)	0.0514 (0.0118)	0.0523 (0.0154)	0.0600 (0.0334)	0.0591 (0.0300)
Median [Min, Max]	0.0533 [0.0333, 0.0699]	0.0514 [0.0328, 0.0837]	0.0518 [0.0351, 0.204]	0.0453 [0.0321, 0.128]
Detect	19 (59.4%)	15 (46.9%)	25 (67.6%)	21 (56.8%)
Non-detect	4 (12.5%)	2 (6.3%)	2 (5.4%)	4 (10.8%)
Limonene (µg/L)				
Mean (SD)	0.432 (0.367)	0.412 (0.348)	0.920 (1.10)	0.889 (0.978)
Median [Min, Max]	0.304 [0.115, 1.93]	0.341 [0.163, 1.67]	0.596 [0.183, 5.35]	0.628 [0.226, 4.64]
Detect	22 (68.8%)	17 (53.1%)	27 (73.0%)	25 (67.6%)

	"Terpenes-on" (N=32 sessions)		"Terpenes-off" (N=37 sessions)	
	B1	*T4*	*B1*	*T4*
Non-detect	1 (3.1%)	0 (0%)	0 (0%)	0 (0%)

Notes: Two samples in the "terpenes-off" condition had low volume and could not be analyzed. In the "terpenes-on" condition, 9 (38%) B1 samples were missing and 15 (46.9%) T4 samples were missing. In the "terpenes-off" condition, 10 (27%) B1 samples were missing and 10 (27.0%) T4 samples were missing.

Absorbed dose descriptive statistics at timepoint 4, stratified by filter, are reported in Table 2.7, and indicate a slight average decrease in serum terpene concentrations following "terpenes-on" sessions, excluding α-pinene, which increased. Following "terpenes-off" sessions, there was a slight average increase in α-pinene, β-pinene, and β-caryophyllene, and a slight average decrease in β-myrcene, Δ-3-carene, and sum composite absorbed dose. Table 2.7 and Figure 2.5 indicate small or no difference in terpenes absorption between exposure conditions.

Table 2.7. Serum terpenes absorbed dose time point 4, stratified by filter.

	"Terpenes-on" (N=32 sessions)	"Terpenes-off" (N=37 sessions)	Overall (N=69 sessions)
α-Pinene (µg/L)			
Mean (SD)	0.0635 (0.0126)	0.0783 (0.0204)	0.0733 (0.0193)
Median	0.0599	0.0755	0.0659
[Min, Max]	[0.0509, 0.0951]	[0.0535, 0.122]	[0.0509, 0.122]
Missing	23 (71.9%)	19 (51.4%)	42 (60.9%)
β-Pinene (µg/L)			
Mean (SD)	-0.0124 (0.0502)	0.000113 (0.0197)	-0.00406 (0.0312)
Median	-0.00715	0.000850	-0.00130
[Min, Max]	[-0.0780, 0.0427]	[-0.0254, 0.0291]	[-0.0780, 0.0427]
Missing	28 (87.5%)	29 (78.4%)	57 (82.6%)
β-Caryophyllene (µg/L)			
Mean (SD)	-0.0800 (NA)	0.0920 (0.625)	0.0490 (0.518)
Median	-0.0800	0.296	0.108
[Min, Max]	[-0.0800, -0.0800]	[-0.610, 0.590]	[-0.610, 0.590]
Missing	31 (96.9%)	34 (91.9%)	65 (94.2%)

	"Terpenes-on" (N=32 sessions)	"Terpenes-off" (N=37 sessions)	Overall (N=69 sessions)
β-Myrcene (µg/L)			
Mean (SD)	-0.00253 (0.0627)	-0.00559 (0.0716)	-0.00426 (0.0670)
Median	0.0110	-0.0185	-0.00900
[Min, Max]	[-0.115, 0.0920]	[-0.123, 0.149]	[-0.123, 0.149]
Missing	15 (46.9%)	15 (40.5%)	30 (43.5%)
Δ-3-Carene (µg/L)			
Mean (SD)	-0.000941 (0.0128)	-0.00709 (0.0265)	-0.00441 (0.0216)
Median	0	-0.00850	-0.00200
[Min, Max]	[-0.0290, 0.0210]	[-0.0980, 0.0440]	[-0.0980, 0.0440]
Missing	15 (46.9%)	15 (40.5%)	30 (43.5%)
Limonene (µg/L)			
Mean (SD)	-0.0320 (0.0929)	-0.00873 (0.110)	-0.0189 (0.102)
Median	-0.0260	0.0280	-0.0120
[Min, Max]	[-0.260, 0.144]	[-0.260, 0.163]	[-0.260, 0.163]
Missing	15 (46.9%)	15 (40.5%)	30 (43.5%)
Sum Composite (µg/L)			
Mean (SD)	-0.0380 (0.0924)	-0.0147 (0.130)	-0.0249 (0.114)
Median	-0.0350	-0.0480	-0.0400
[Min, Max]	[-0.208, 0.135]	[-0.191, 0.288]	[-0.208, 0.288]
Missing	15 (46.9%)	15 (40.5%)	30 (43.5%)

Note: Maximum likelihood estimation (MLE) regression was used to impute non-detect observations for α-pinene, β-myrcene, and Δ-3-carene to calculate absorbed dose (T4 serum concentrations – baseline serum concentrations). Due to a low proportion of non-detect observations, $\frac{LOD}{\sqrt{2}}$ *was used to impute non-detect observations for limonene. Due to a high left-censoring, no imputation was performed on β-pinene and β-caryophyllene data. Sum composite absorbed dose was calculated as the sum of α-pinene, β-myrcene, Δ-3-carene, and limonene absorbed doses (β-pinene and β-caryophyllene were not included due to low detection levels).*

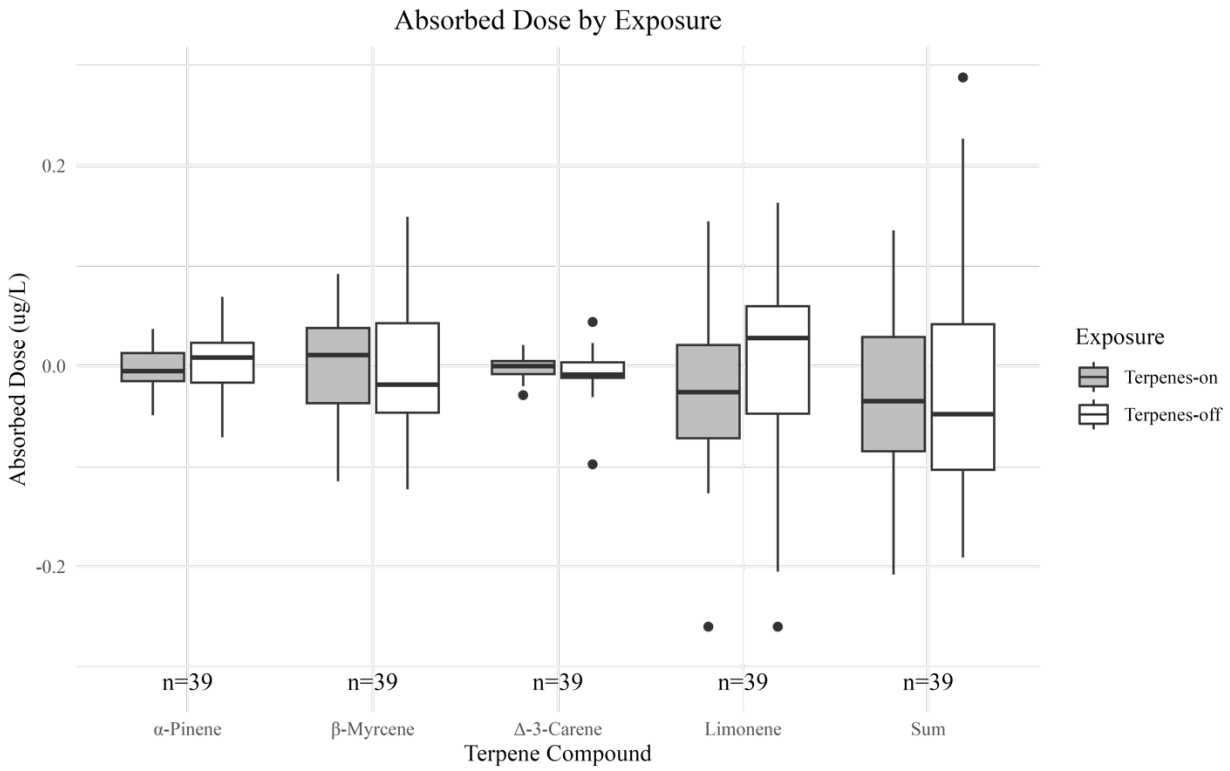

Figure 2.5. Imputed absorbed dose by treatment for terpenes included in analysis (α-pinene, β-myrcene, Δ-3-carene, limonene and sum composite absorbed dose)

Note: Sum composite absorbed dose was calculated as the sum of α-pinene, β-myrcene, Δ-3-carene, and limonene.

The association between absorbed dose and study outcomes was assessed by estimating the difference in study outcomes at T2 and T4 between participants differing in absorbed dose by 1 unit and performing an analysis of variance to test whether the association between absorbed dose and study outcome pattern over time was significant. β-pinene and β-caryophyllene absorbed doses were not included in analysis due to low detection frequencies. Estimated differences in study outcomes at T2 and T4 are presented in Table 2.8. For each terpene, results are reported below.

Table 2.8. Estimated associations of absorbed dose with study outcomes at T2 and T4.

	Sum Composite		**α-Pinene**		**β-Myrcene**		**Δ-3-Carene**		**Limonene**	
	Estimate (95% CI)	*p*	*Estimate* (95% CI)	*p*	*Estimate* (95% CI)	*p*	*Estimate* (95% CI)	*p*	*Estimate* (95% CI)	*p*
Ln-HF HRV	1.34 (-0.47, 3.15)	.158	2.83 (-9.13, 14.78)	.647	1.06 (-2.87, 4.98)	.602	5.97 (-5.43, 17.36)	.314	1.15 (-1.45, 3.75)	.393
SCL	-8.61 (-17.51, 0.28)	.066	-5.81 (-48.22, 36.6)	.790	-6.41 (-24.48, 11.66)	.493	-8.63 (-62.62, 45.35)	.756	-5.14 (-17.37, 7.08)	.415
DBP	14.00 (-5.66, 33.66)	.172	62.11 (-28.78, 153.00)	.190	13.99 (-26.36, 54.34)	.502	37.73 (-89.07, 164.53)	.564	20.42 (-5.26, 46.10)	.128
SBP	18.75 (-11.71, 49.2)	.236	102.37 (-49.46, 254.21)	.195	7.23 (-60.87, 75.34)	.836	89.69 (-108.47, 287.86)	.381	33.00 (-7.14, 73.14)	.116
HR	8.43 (-7.29, 24.15)	.300	42.94 (-30.32, 116.20)	.259	11.12 (-22.02, 44.25)	.516	82.04 (-9.86, 173.93)	.090	-6.68 (-27.57, 14.22)	.535
PA	6.36 (-2.46, 15.18)	.166	-0.43 (-42.46, 41.59)	.984	11.84 (-6.11, 29.78)	.207	28.87 (-25.55, 83.30)	.306	5.17 (-6.53, 16.87)	.393
NA	-0.39 (-1.86, 1.09)	.612	-2.26 (-9.01, 4.49)	.516	-2.99 (-5.68, -0.30)	**.041**	-3.79 (-12.84, 5.27)	.418	0.56 (-1.42, 2.54)	.582
Stress	-0.51 (-2.11, 1.09)	.535	-2.03 (-9.15, 5.09)	.581	1.48 (-1.53, 4.50)	.343	3.81 (-5.04, 12.67)	.406	-1.42 (-3.51, 0.68)	.195
Cortisol	-45.45 (-150.06, 59.17)	.401	-535.04 (-973.19, -96.89)	**.024**	116.86 (-85.47, 319.18)	.272	-205.71 (-842.84, 431.42)	.532	-67.13 (-197.17, 62.91)	.321
IL-6	-0.60 (-1.63,	.259	-0.76 (-5.9,	.772	-1.67 (-3.90,	.153	-0.45 (-7.07,	.896	-0.22 (-1.68,	.769

	Sum Composite		**α-Pinene**		**β-Myrcene**		**Δ-3-Carene**		**Limonene**	
	Estimate (95% CI)	*p*	*Estimate* (95% CI)	*p*	*Estimate* (95% CI)	*p*	*Estimate* (95% CI)	*p*	*Estimate* (95% CI)	*p*
	0.43)		4.37)		0.57)		6.18)		1.24)	
TNF-α	-5.73 (-10.95, -0.51)	**.038**	-10.65 (-36.5, 15.19)	.425	-10.63 (-22.07, 0.82)	.077	-21.42 (-55.40, 12.57)	.225	-3.01 (-10.16, 4.13)	.414
CRP	-0.70 (-1.64, 0.25)	.159	-1.02 (-5.82, 3.77)	.679	-1.00 (-3.17, 1.17)	.371	-2.03 (-8.11, 4.06)	.518	-0.48 (-1.76, 0.81)	.473

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; PA, positive affect; NA, negative affect.

2.4.2.1 Sum Composite Absorbed Dose

2.4.2.1.1 Association of Sum Composite Absorbed Dose and Outcomes at Time Points 2 or 4

In support of our hypothesis, we observed a statistically significant association between sum composite absorbed dose and TNF-α at time point 4. Specifically, a difference of 0.14 µg/L (IQR for sum composite absorbed dose) was associated with a difference in TNF-α of -0.78 pg/mL (95% CI: -1.49, -0.07; p-value = .04). Additionally, we observed a marginally significant association between sum composite absorbed dose and SCL levels at time point 2, where a difference of 0.14 µg/L was associated with a difference in SCL of -1.18 µS (95% CI: -2.39, 0.04; p-value = .07). Counter to our hypothesis, we did not observe a significant association of sum composite absorbed dose at time point 2 with ln-HF HRV, positive affect, and stress or time point 4 on SBP, DBP, HR, cortisol, IL-6, and CRP. The association of sum composite absorbed dose on ln-HF HRV and positive affect was positive and in the hypothesized direction, although

the association was non-significant. For stress, negative affect, cortisol, Il-6, TNF-α, and CRP, the non-significant association was negative and in the hypothesized direction. For DBP, SBP, and HR, the non-significant association was positive and against the hypothesized direction.

2.4.2.1.2 Association of Sum Composite Absorbed Dose and Outcome Pattern Over Time

In support of our hypothesis, we observed a statistically significant association between sum composite absorbed dose and ln-HF HRV (p-value < .001), SCL (p-value = .02), and positive affect (p-value = .03) response pattern over time. A difference of 0.14 μg/L of sum composite absorbed dose at time point 4 was associated with a difference in ln-HF HRV at time point 2 of 0.46 ms^2 (95% CI: 0.28, 0.65), 0.29 ms^2 at time point 3 (95% CI: 0.11, 0.48), and 0.15 ms^2 at time point 4 (95% CI: -0.03, 0.34). A difference of 0.14 μg/L of sum composite absorbed dose at time point 4 was associated with a difference in in SCL at time point 2 of -1.67 μS (95% CI: -2.99, -0.35), -1.93 μS at time point 3 (95% CI: -3.25, -0.61), and -1.69 μS at time point 4 (95% CI: -3.01, -0.38). A difference of 0.14 μg/L of sum composite absorbed dose at time point 4 was associated with a difference in positive affect of 0.50 scale points at time point 2 (95% CI: -0.6, 1.59), 0.51 scale points time point 3 (95% CI: -0.55, 1.57), and 0.38 scale points at time point 4 (95% CI: -0.68, 1.44). Counter to our hypothesis, we did not observe a significant association of sum composite absorbed dose and negative affect and stress pattern over time.

Table 2.9. ANOVA results comparing full and reduced models to test the association of sum composite absorbed dose and the pattern of study outcome response.

Model		AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
HRV								
	Reduced	146.50	166.29	-66.25	132.50			
	Full	132.19	166.13	-54.10	108.19	24.30	5	**.0002**

Model		AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
SCL								
	Reduced	807.66	829.01	-396.83	793.66			
	Full	804.51	841.11	-390.26	780.51	13.15	5	**.022**
Positive Affect								
	Reduced	724.89	746.20	-355.45	710.89			
	Full	722.36	758.88	-349.18	698.36	12.53	5	**.028**
Negative Affect								
	Reduced	280.26	301.56	-133.13	266.26			
	Full	286.06	322.58	-131.03	262.06	4.20	5	.522
Stress								
	Reduced	125.50	145.41	-55.75	111.50			
	Full	133.85	167.98	-54.92	109.85	1.65	5	.895

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; *AIC, Akaike information criterion; BIC, Bayesian information criterion.*

2.4.2.2 α-Pinene Absorbed Dose

2.4.2.2.1 Association of α-Pinene Absorbed Dose and Study Outcomes at Time Points 2 or 4

In support of our hypothesis, we observed a statistically significant association between α-pinene absorbed dose and cortisol at time point 4, where a difference of 0.03 μg/L (IQR for α-pinene absorbed dose) was associated with a difference in cortisol of -16.32 ng/mL (95% CI: -29.68, -2.95; p-value = .02). Counter to our hypothesis, we did not observe a significant association between α-pinene absorbed dose and ln-HF HRV, SCL, positive affect, and stress at time point 2 or SBP, DBP, HR, TNF-α, IL-6, and CRP at time point 4. The association of α-pinene absorbed dose with ln-HF HRV was positive and in the hypothesized direction, although the effect was

non-significant. For stress, cortisol, negative affect, Il-6, and CRP, the non-significant effect was negative and in the hypothesized direction. For DBP, SBP, HR, and positive affect, the non-significant effect was positive and against the hypothesized direction.

2.4.2.2.2 Association of α-Pinene Absorbed Dose and Outcome Pattern Over Time

Counter to our hypothesis, we did not observe a significant association of α-pinene absorbed dose and ln-HF HRV, SCL, positive affect, negative affect, and stress pattern over time. Additionally, while there was a significant association of of α-pinene absorbed dose positive affect pattern over time (p-value = .04), the association at each time point was negative and against the hypothesized direction. A difference in α-pinene absorbed dose of 0.03 μg/L was associated with a difference in positive affect of -0.18 scale points at time point 2 (95% CI: -1.11, 0.74), -0.13 scale points at time point 3 (95% CI: -1.05, 0.79), and -0.37 scale points at time point 4 (95% CI: -1.29, 0.55).

Table 2.10. ANOVA results comparing full and reduced models to test the association of α-pinene absorbed dose and the pattern of study outcome response.

	Model	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
HRV								
	Reduced	146.50	166.29	-66.25	132.50			
	Full	152.67	186.61	-64.34	128.67	3.82	5	.575
SCL								
	Reduced	807.66	829.01	-396.83	793.66			
	Full	812.24	848.84	-394.12	788.24	5.42	5	.367
Positive Affect								
	Reduced	724.89	746.20	-355.45	710.89			
	Full	723.44	759.97	-349.72	699.44	11.45	5	**.043**

Model	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
Negative Affect							
Reduced	280.26	301.56	-133.13	266.26			
Full	286.95	323.47	-131.47	262.95	3.31	5	.652
Stress							
Reduced	125.50	145.41	-55.75	111.50			
Full	132.71	166.84	-54.35	108.71	2.79	5	.733

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; AIC, Akaike information criterion; BIC, Bayesian information criterion.

2.4.2.3 β-Myrcene Absorbed Dose

2.4.2.3.1 Association of β-Myrcene Absorbed Dose and Outcomes at Time Points 2 and 4

In support of our hypothesis, we observed a statistically significant association between β-myrcene absorbed dose and negative affect score at time point 2, where a difference of 0.08 μg/L (IQR for β-myrcene absorbed dose) was associated with a difference in negative affect score of -0.26 points (95% CI: -0.5, -0.03; p-value = .04). Counter to our hypothesis, we did not observe a significant association of β-myrcene absorbed dose at time point 2 on ln-HF HRV, SCL, positive affect, and stress or time point 4 on SBP, DBP, HR, cortisol, TNF-α, IL-6, and CRP. The association of absorbed dose on ln-HF HRV and positive affect was positive and in the hypothesized direction, although the association was non-significant. For SCL, TNF-α, Il-6, and CRP, the non-significant association was negative and in the hypothesized direction. For DBP,

SBP, HR, stress, and cortisol, the non-significant association was positive and against the hypothesized direction.

2.4.2.3.2 Association of β-Myrcene Absorbed Dose and Outcome Pattern Over Time

Counter to our hypothesis, we did not observe a significant association of β-myrcene absorbed dose with ln-HF HRV, SCL, positive affect, negative affect, and stress response over time.

Table 2.11. ANOVA results comparing full and reduced models to test the association of β-myrcene absorbed dose and the pattern of study outcome response.

	Model	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
HRV								
	Reduced	146.50	166.29	-66.25	132.50			
	Full	148.01	181.95	-62.01	124.01	8.48	5	.132
SCL								
	Reduced	807.66	829.01	-396.83	793.66			
	Full	812.83	849.43	-394.42	788.83	4.83	5	.437
Positive Affect								
	Reduced	724.89	746.20	-355.45	710.89			
	Full	731.74	768.26	-353.87	707.74	3.16	5	.676
Negative Affect								
	Reduced	280.26	301.56	-133.13	266.26			
	Full	285.28	321.80	-130.64	261.28	4.98	5	.418
Stress								
	Reduced	125.50	145.41	-55.75	111.50			
	Full	128.07	162.20	-52.03	104.07	7.43	5	.191

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; AIC, Akaike information criterion; BIC, Bayesian information criterion.

2.4.2.4 Δ-3-Carene Absorbed Dose

2.4.2.4.1 Association of Δ-3-Carene Absorbed dose and Study Outcomes at Time Points 2 and 4

Counter to our hypothesis, we did not observe a significant association of Δ-3-carene absorbed dose at time point 2 with ln-HF HRV, SCL, positive affect, and stress or time point 4 with SBP, DBP, HR, cortisol, TNF-α, IL-6, and CRP. The association of absorbed dose with ln-HF HRV and positive affect was positive and in the hypothesized direction, although the association was non-significant. For SCL, TNF-α, Il-6, cortisol, and CRP, the non-significant association was negative and in the hypothesized direction. For DBP, SBP, HR, and stress, the non-significant association was positive and against the hypothesized direction.

2.4.2.4.2 Association of Δ-3-Carene Absorbed Dose and Outcome Pattern Over Time

In support of our hypothesis, we observed a statistically significant association between Δ-3-carene absorbed dose and SCL response over time (p-value = .04). A difference of 0.01 µg/L (IQR for Δ-3-carene absorbed dose) of Δ-3-carene absorbed dose at time point 4 was associated with a difference in SCL of 0.12 µS at time point 2 (95% CI: -0.69, 0.93), -0.10 µS at time point 3 (95% CI: -0.91, 0.71), and -0.09 µS at time point 4 (95% CI: -0.9, 0.72). Counter to our hypothesis, we did not observe a significant association of Δ-3-carene absorbed dose with ln-HF HRV, positive affect, negative affect, and stress response over time.

Table 2.12. ANOVA results comparing full and reduced models to test the association of Δ-3-carene absorbed dose and the pattern of study outcome response.

	Model	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
HRV								
	Reduced	146.50	166.29	-66.25	132.50			
	Full	149.97	183.91	-62.99	125.97	6.52	5	.259
SCL								
	Reduced	807.66	829.01	-396.83	793.66			
	Full	806.39	842.98	-391.19	782.39	11.27	5	**.046**
Positive Affect								
	Reduced	724.89	746.20	-355.45	710.89			
	Full	731.09	767.61	-353.55	707.09	3.80	5	.578
Negative Affect								
	Reduced	280.26	301.56	-133.13	266.26			
	Full	288.59	325.11	-132.29	264.59	1.67	5	.892
Stress								
	Reduced	125.50	145.41	-55.75	111.50			
	Full	128.53	162.66	-52.27	104.53	6.97	5	.223

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; AIC, Akaike information criterion; BIC, Bayesian information criterion.

2.4.2.5 Limonene Absorbed Dose

2.4.2.5.1 Association of Limonene Absorbed Dose and Outcomes at Time Points 2 and 4

Counter to our hypothesis, we did not observe a significant association of limonene absorbed dose at time point 2 with ln-HF HRV, SCL, positive affect, and stress or time point 4 with SBP, DBP, HR, cortisol, TNF-α, IL-6, and CRP. The association of absorbed dose with ln-HF HRV

and positive affect was positive and in the hypothesized direction, although the association was non-significant. For SCL, stress, HR, cortisol, TNF-α, Il-6, and CRP, the non-significant association was negative and in the hypothesized direction. For DBP and SBP, the non-significant association was positive and against the hypothesized direction.

2.4.2.5.2 Association of Limonene Absorbed Dose and Outcome Pattern Over Time

In support of our hypothesis, we observed a marginally significant association between limonene absorbed dose and positive affect response over time (p-value = .06). A difference of 0.11 μg/L (IQR for limonene absorbed dose) of limonene absorbed dose was associated with a difference in positive affect of 0.57 scale points at time point 2 (95% CI: -0.46, 1.60), 0.75 scale points at time point 3 (95% CI: -0.26, 1.75), and 0.79 scale points at time point 4 (95% CI: -0.22, 1.80). Counter to our hypothesis, we did not observe a significant association of limonene absorbed dose and ln-HF HRV, SCL, negative affect, and stress response over time.

Table 2.13. ANOVA results comparing full and reduced models to test the association of limonene absorbed dose and the pattern of study outcome response.

	Model	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
HRV								
	Reduced	146.50	166.29	-66.25	132.50			
	Full	148.12	182.06	-62.06	124.12	8.38	5	.137
SCL								
	Reduced	807.66	829.01	-396.83	793.66			
	Full	815.75	852.35	-395.88	791.75	1.91	5	.862
Positive Affect								
	Reduced	724.89	746.20	-355.45	710.89			
	Full	724.14	760.66	-350.07	700.14	10.75	5	.057

	Model	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
Negative Affect								
	Reduced	280.26	301.56	-133.13	266.26			
	Full	284.88	321.40	-130.44	260.88	5.38	5	.372
Stress								
	Reduced	125.50	125.50	145.41	-55.75			
	Full	127.67	161.80	-51.83	103.67	7.83	5	.166

Note: Ln-HF HRV, ln high frequency heart rate variability; SCL, skin conductance level; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; AIC, Akaike information criterion; BIC, Bayesian information criterion.

2.4.3 *Smell Perception and Experience*

Debrief interview responses and notes were coded to assess smell perception for each session. If a participant mentioned that they could not smell anything or that is was difficult with no mention of their olfactory experience (i.e., pleasant or unpleasant), the session smell perception experience was coded as “Could not smell anything” If a participant mentioned that they could smell the forest or other scents or that it was difficult to smell the forest but described their olfactory experience (i.e., pleasant or unpleasant), the session was coded as “Could smell the forest or other scents.” Finally, if the participant did not mention smells or the olfactory experience, the session was coded as “No mention of smell.” Additionally, participants were asked to rate the pleasantness of their sensory experience of the forest for sight, smell, and visual experience on a 10-point scale ranging from 1 (“not pleasant”) to 10 (“extremely pleasant”). Summary statistics are presented in Table 2.14.

Table 2.14. Sensory perception and pleasantness stratified by session exposure.

	"Terpenes-on" (N=32 sessions)	**"Terpenes-off"** (N=37 sessions)	**Overall** (N=69 sessions)
Smell Perception			
Could not smell anything	12 (37.5%)	14 (37.8%)	26 (37.7%)
Could smell the forest or other scents	6 (18.8%)	2 (5.4%)	8 (11.6%)
No mention of smell	14 (43.8%)	20 (54.1%)	34 (49.3%)
Missing	0 (0%)	1 (2.7%)	1 (1.4%)
Smell Pleasantness			
Mean (SD)	6.45 (2.23)	6.83 (2.18)	6.65 (2.19)
Median [Min, Max]	7.00 [2.00, 10.0]	6.00 [3.00, 10.0]	6.00 [2.00, 10.0]
Missing	1 (3.1%)	2 (5.4%)	3 (4.3%)
Visual Pleasantness			
Mean (SD)	9.09 (1.03)	9.03 (1.21)	9.06 (1.12)
Median [Min, Max]	9.00 [6.00, 10.0]	9.00 [5.00, 10.0]	9.00 [5.00, 10.0]
Missing	0 (0%)	1 (2.7%)	1 (1.4%)
Sound Pleasantness			
Mean (SD)	7.61 (2.01)	7.63 (2.18)	7.62 (2.09)
Median [Min, Max]	8.00 [2.00, 10.0]	7.00 [4.00, 10.0]	8.00 [2.00, 10.0]
Missing	1 (3.1%)	2 (5.4%)	3 (4.3%)

Only 18.8% of participants in the "terpenes-on" condition mentioned being able to smell the forest or other scents and 5.4% of participants in the "terpenes-off" condition mentioned being able to smell the forest or other scents (See Figure 2.6).

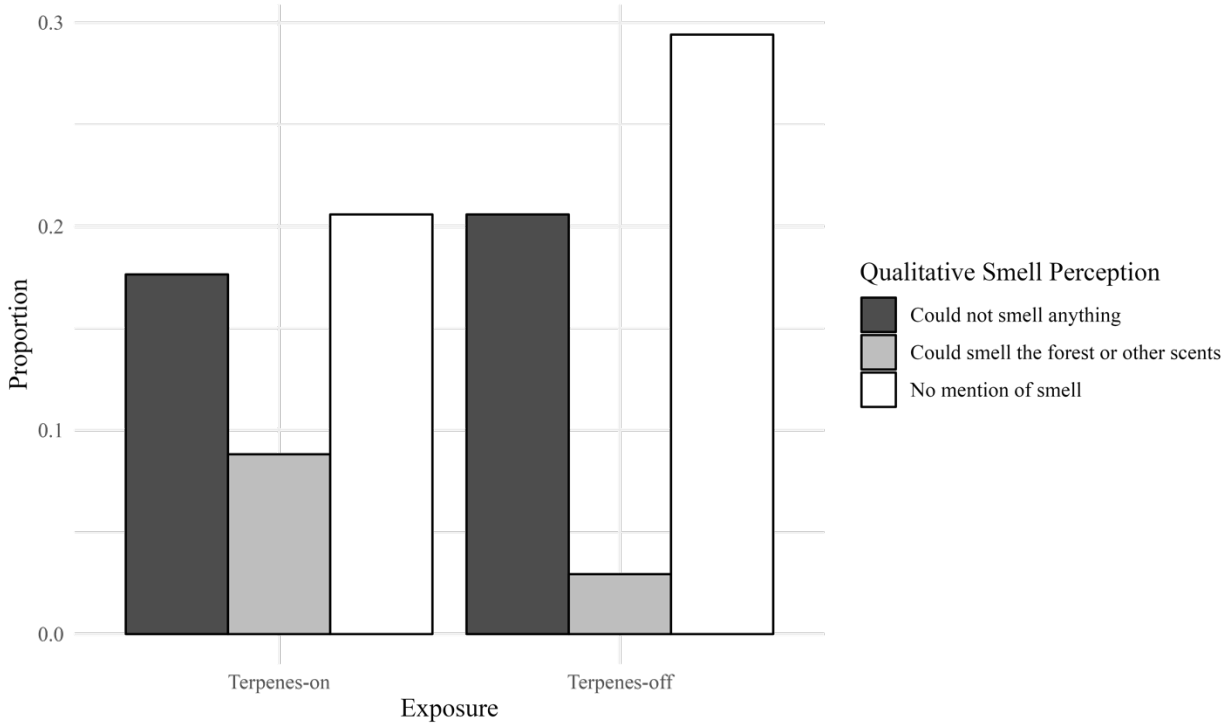

Figure 2.6. Participant smell perception by exposure.

Mean smell pleasantness ratings for each exposure were similar (6.45± 2.23 for "terpenes-on" condition and 6.83±2.18 for "terpenes-off" condition). Only 16.6% of participants were able to correctly identify when they had been exposed to the "terpenes-on" condition, while 76.6% could not identify a difference in smell between session and 6.6% indicated that they thought the "terpenes-off" condition had the greatest olfactory experience (See Figure 2.7).

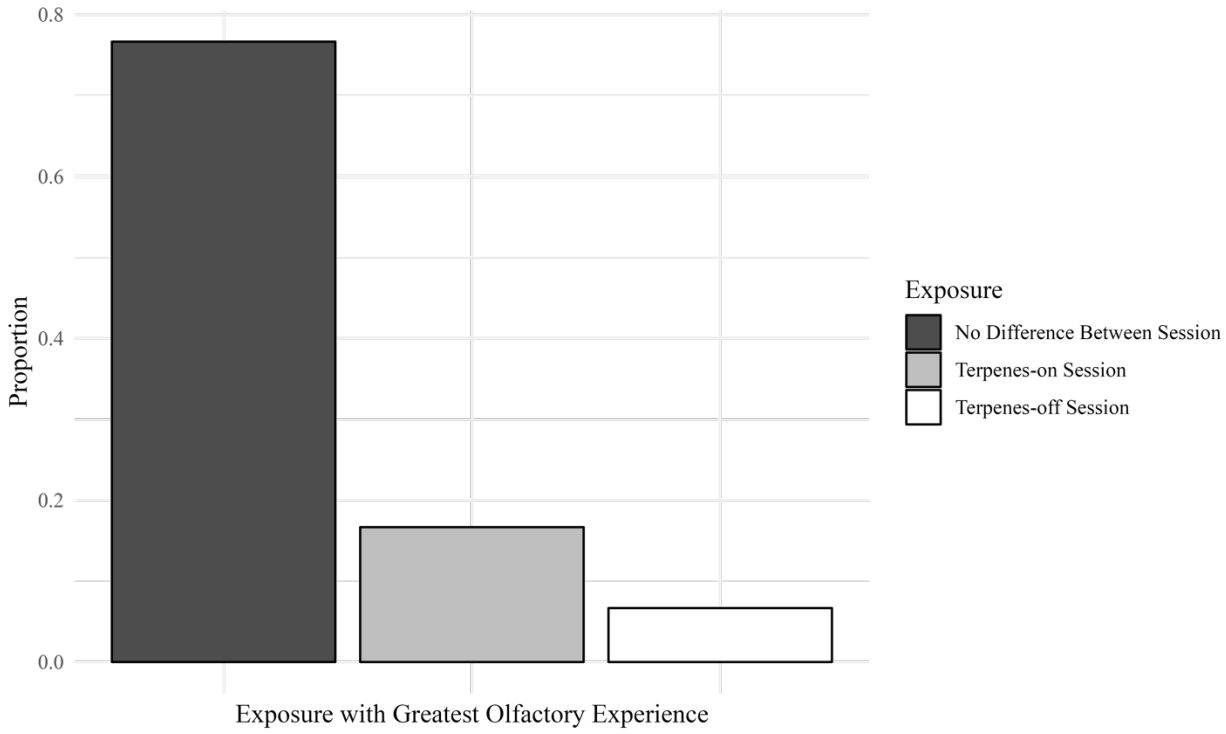

Figure 2.7. Participant indication of session with the greatest olfactory experience.

2.5 Discussion

To our knowledge, this investigation is the first randomized crossover trial examining the effects of terpene exposure on stress outcomes in a forest setting. The objectives of the study were (1) to examine whether terpenes played a role in stress reduction following exposure to ambient forest air, and (2) to assess whether there was an association between absorbed terpene dose and stress outcomes. We found a significant effect of terpene exposure on IL-6 serum levels after 60 minutes of exposure and a significant effect of terpene exposure on skin conductance level response over time. The significant effect of terpene exposure on IL-6 levels is supported by previous work, although this research did not take place in a forest setting for human volunteers. Following ischemic stroke induction in male Wistar rats, α-pinene administration significantly reduced IL-6 concentration in the hippocampus, cortex, and striatum (Khoshnazar et al., 2019). Additionally, α-pinene has been shown to significantly reduce IL-6 production in mouse

peritoneal macrophages following lipopolysaccharide-induced inflammation and to decrease IL-6 expression in male Wistar rats following isoproterenol (ISO)-induced inflammation (D.-S. Kim et al., 2015; B. Zhang et al., 2020). The effect of terpene exposure after 20 minutes on skin conductance levels was negative and in the hypothesized direction, but only marginally significant. However, the effect of terpene exposure on the pattern of skin conductance level response over time was statistically significant, and the effect at each time point was negative and in the hypothesized direction.

We found no significant effect of terpene exposure on ln-HF HRV, self-reported stress and affect, systolic blood pressure, diastolic blood pressure, heart rate, cortisol, TNF-α, and CRP. For ln-HF HRV and positive affect, the effect of terpene exposure was positive and in the hypothesized direction, but the effects were small, with confidence intervals that included the null. For negative affect, systolic blood pressure, cortisol, TNF-α, and CRP, the effect of terpene exposure was negative and in the hypothesized direction, but the effect sizes were small, with confidence intervals that included the null. Interestingly, the effect of terpene exposure on self-reported stress, diastolic blood pressure, and heart rate was positive and against the hypothesized direction, however, the effect sizes were small and not statistically significant.

Approximately 20% of blood samples were missing, including nearly 50% of post-exposure samples from the “terpenes-on” session, reflecting the challenge of venipuncture sampling in a forest environment. Additionally, frequency of non-detects was relatively high for several analytes, notably β-pinene and β-caryophyllene, indicated that a more sensitive serum terpenes assay is needed for this application. Given the high levels of missingness, very few participants had all four blood samples (pre- and post-exposure from both sessions), which prevented us from being fully powered for our absorbed dose association analyses.

There was a significant association of increased sum absorbed dose and lower TNF-α after 60 minutes of exposure, and marginally significant association with lower SCL after 20 minutes of exposure. We observed an association of sum absorbed dose with higher ln-HF HRV and positive affect, and lower SCL at each time point. Additionally, there was a significant association of increased α-pinene absorbed dose and decreased cortisol. Higher β-myrcene absorbed dose was negatively correlated with negative affect following 20 minutes of exposure. There was a significant association of Δ-3-carene absorbed dose with lower SCL response over time and limonene with higher positive affect response over time, both in the hypothesized direction.

Counter to our hypothesis, there was also a significant association of α-pinene at each time point with positive affect that was against the hypothesized direction (lower positive affect was associated with higher absorbed α-pinene dose). All other interactions between absorbed dose and outcome were not significant.

Some of our results differ from previous research – although these studies had different designs and did not take place in a forest setting – including studies of humans that have found significant decreases in heart rate, systolic blood pressure, and diastolic blood pressure following fir essential oil exposure and significant increases in ln-HF HRV following aromatherapy exposure (Chang & Shen, 2011; Huang & Capdevila, 2017). In a similar study design from Chuang et al. (2014), observed mean VOC concentrations in the essential oil exposure condition ranged from 50.6–120.5 ppb (average of 82.2 ppb). In male Wistar rats, intravenous terpene exposure had a hypotensive effect on mean arterial pressure and heart rate and reduced TNF-α levels (Menezes et al., 2010; Rahimi et al., 2023; B. Zhang et al., 2020) and in zebrafish, acute limonene and β-myrcene exposure decreased anxiety-like behavior, although repeated exposure

did not have an effect (Szaszkiewicz et al., 2021). A longitudinal study of inhaled essential oil exposure over 4 weeks in humans found a significant difference in the reduction of subjective stress, blood pressure, and serum cortisol levels in the essential oil treatment group (Hwang, 2006). In humans exposed to eucalyptus essential oil or a control via passive inhalation for 30 minutes per day over three days, systolic blood pressure and diastolic blood pressure were significantly lower in the group exposed to eucalyptus essential oil (Jun et al., 2013). However, these studies differ in treatment length, and results may not be easily compared to our study. Additionally, essential oils contain highly concentrated plant derivatives (Masyita et al., 2022). Importantly, terpene concentrations in the air following essential diffusion may differ substantially from ambient terpene concentrations in forest air. In a study measuring terpene concentration following tea tree essential oil diffusion in a 40 m^3 room, peak concentrations ranged from 100 ± 10 ppb for α-pinene to 790 ± 17 ppb for 4-terpineol (Angulo-Milhem et al., 2023). Su et al. (2007) observed an average total terpene concentration of 740 ± 450 ppb during essential oil evaporation.

Previous studies of essential oil or terpene exposure have found similar results, including no significant differences in ln-HF HRV, HR, and CRP levels when comparing groups of people exposed to essential oils versus a control (Jun et al., 2013; C. Kim & Song, 2022; Yoshizawa et al., 2015). In humans, inhalation of (+)- and (-)-limonene led to increased systolic blood pressure and no significant difference in skin conductance levels (Heuberger, 2001).

Humans differ in the ways in which they process sensory stimuli and perceive different aspects of their environments (Gentilucci & Cattaneo, 2005; Khaw et al., 2021; Kitayama et al., 2003; Partos et al., 2016; Simmons & Estes, 2008; Stevens, 1996; D. White & Burton, 2022). Nature contact is simultaneously a biophysical interaction between human and environmental

systems, and a contextual and negotiated encounter for an individual that includes a combination of diverse sensory, psychological, and physiological experiences. In this experiment, we focus on one feature of an experience with nature, specifically terpene inhalation exposure, and do not consider the diverse array of other nature interactions that can be experienced by an individual. Therefore, this research must be contextualized in the broader nature and health literature as a step forward in isolating a potential pathway, but not an attempt to explain all well-being effects following nature contact.

2.5.1 *Limitations and Future Directions*

Our study had several limitations. First, our target sample size was 40 participants, and while we enrolled 43 people, only 31 participants completed both sessions, preventing us from being fully powered for our within-subjects analytic design. With N = 40, we were powered to detect an expected mean 5% reduction in heart rate (Hedges' g =0.4), 2% reduction in blood pressure (Hedges' g = 0.17), 35% increase in high frequency heart rate variability (Hedges' g = 0.12), and 32% decrease in self-reported tension and anxiety. Our target sample size of 40 participants was based on the estimated numbers needed to detect minimum differences in the study outcomes in the contrasting conditions for the same participant, based on the minimums in the ranges of Hedges' g values from prior studies and standard population-level intra-individual differences.

Several factors impacted participant attrition, including lack of available study session days due to wildfire smoke, extreme heat conditions, and the limitation of sampling to June through September due to precipitation and temperature during the rest of the year. Attrition issues were addressed following the first summer of sampling by implementing air conditioning

in study rooms to increase available sampling days and a small increase in participant compensation.

Second, due to a lack of instructed attention to odors, participants may not have been able to detect or notice forest smells, potentially interfering with psychological responses. While smell perception and experience results suggest that treatment blinding was effective, they also indicate that participants may not have been able to notice terpenes when they were exposed to them, potentially preventing some psychological responses and conscious appraisals of odors. Because participants were blinded to exposure but always breathing some form of filtered air via PAPR masks during each session, participants may have been primed to not expect odors regardless of treatment. Selective attention is a mechanism of sensory information filtration that allows the brain to direct attention to specific stimuli over others (Carlson et al., 2018). While most studies of attentional deployment have focused on auditory and visual stimuli, some research indicates that attention may modulate olfaction, as attention towards odors significantly increases the speed and amplitude of an individual's electrophysiological response to specific stimuli, as indicated by olfactory event-related potentials (OERP) in the brain (Arpaia et al., 2022; Masago et al., 2001; Singh et al., 2019). As outlined by Singh et al. (2019), similar studies have found that directing attention toward an odorant increases the response time of neurological indicators of odor detection and increases the amplitude of OERP components, particularly the P3 component, an indication of neuronal resource recruitment and odorant evaluation (Andersson et al., 2011; Geisler & Murphy, 2000; Krauel et al., 1998). In summary, attention may modulate olfactory awareness and future studies might try to control for the effect of attention through participant instruction.

Third, although participants were asked to avoid certain foods, beverages, and products in the 24 hours before each session, this design aspect relied on participant compliance. Future studies might try to control diet and product exposure for a longer period by providing meals and lodging before each experience.

Fourth, there was not a clear relationship between absorbed dose and filter exposure, although previous work has also pointed to the lack of a clear correlation between exposure to terpene-rich environments and higher levels of terpenes in serum (Bach et al., 2021). Bach et al. observed no significant difference in terpene absorbed dose between humans 2-hour exposure in either a city or forest environment while restricting the use of alcohol and fragranced products prior to their exposure session. For their sum monoterpene outcome (sum concentration of α-pinene, β-pinene, α-phellandrene, and limonene), the city group had a mean pre-exposure concentration of 14.1 ± 19.8 nM and mean post-exposure concentration of 14.5 ± 20.3 nM, while the forest group had a mean pre-exposure concentration of 15.3 ± 22.7 nM and mean post-exposure concentration of 9.4 ± 11.1 nM. The difference in absorbed dose between the two groups was not statistically significant. In the current study, many absorbed dose observations were negative and some participants may have experienced a decay of terpene serum concentrations, potentially due to ready metabolism by the liver of terpenes that were present in their circulation prior to the forest bathing session (Falk et al., 1990).

Fifth, participants had limited interaction beyond visual and olfactory exposure. Participants were seated for one hour while wearing the PAPR helmet, so other sensory interactions (e.g., tactile or auditory interaction) were limited.

Finally, for the effects that we did observe on IL-6 and skin conductance, in addition to the trend-level results that were in line with our hypotheses, our study design did not allow for

the differentiation between the causal effects mediated by terpene binding with olfactory receptor neurons and effects mediated by terpene influence of biochemical pathways following via lung, skin, or gastrointestinal exposure.

This study focused on a particular aspect of nature contact – terpene exposure in a real-world setting and aimed to control for other variables via our experimental design. The work is a starting point for future exploration into the multi-sensory aspects of nature experience and one of the many potential pathways and mechanisms that could explain the positive health benefits of nature contact.

2.6 Conclusion

This study examined the effect of terpene exposure via a real-world seated forest intervention in a randomized crossover trials in adults. With respect to our first set of hypotheses (regarding the association of terpene exposure with outcomes), results indicate that IL-6 and skin conductance levels significantly decreased in the "terpenes-on" exposure condition compared to the "terpenes-off" exposure condition. There were no significant changes in high frequency heart rate variability, positive affect, negative affect, self-reported stress, blood pressure, heart rate, TNF-α, CRP, and cortisol when comparing the two conditions across time and at specific time points of interest. However, the effect of terpene exposure on high frequency heart rate variability, positive affect, negative affect, systolic blood pressure, cortisol, TNF-α, and CRP was in the hypothesized direction.

It should be noted that we had high levels of missingness and non-detect observations for serum terpene concentrations that prevented us from being fully powered for our absorbed dose association analyses. With respect to our second set of hypotheses (regarding the association of

absorbed dose of terpenes with outcomes) there was a significant association of increased sum composite absorbed dose and lower TNF-α following 60 minutes of exposure, and a marginally significant association with lower SCL following 20 minutes of exposure. With respect to specific terpenes, higher absorbed dose of β-myrcene was negatively associated with negative affect following 20 minutes of exposure. Additionally, there was a significant association of increased absorbed dose of α-pinene and decreased cortisol. At each time point, higher sum composite absorbed dose was associated with higher ln-HF HRV and positive affect, and lower SCL. Additionally, higher absorbed dose of Δ-3-carene was associated with the pattern of SCL response across time, and higher absorbed dose of limonene was associated with higher positive affect across time, both in the hypothesized directions. However, there was also a significant effect of absorbed dose of α-pinene on the pattern of positive affect response that went against the hypothesized direction (higher absorbed α-pinene dose was associated with lower positive affect at each time point). All other associations between absorbed dose and outcomes were not significant. The relationship between terpene exposure – particularly at naturally occurring ambient levels – and human psychological and physiological health should be further studied.

BIBLIOGRAPHY

Agorastos, A., & Chrousos, G. P. (2022). The neuroendocrinology of stress: The stress-related continuum of chronic disease development. *Molecular Psychiatry*, *27*(1), 502–513. https://doi.org/10.1038/s41380-021-01224-9

Andersson, L., Lundberg, C., Åström, J., & Nordin, S. (2011). Chemosensory attention, habituation and detection in women and men. *International Journal of Psychophysiology*, *79*(2), 316–322. https://doi.org/10.1016/j.ijpsycho.2010.11.008

Angulo-Milhem, S., Verriele, M., Nicolas, M., & Thevenet, F. (2023). Full-scale determination of essential oil diffusion: Impact on indoor air quality. *Atmospheric Environment*, *315*, 120141. https://doi.org/10.1016/j.atmosenv.2023.120141

Aniszewska, A., Chłodzińska, N., Bartkowska, K., Winnicka, M. M., Turlejski, K., & Djavadian, R. L. (2015). The expression of interleukin-6 and its receptor in various brain regions and their roles in exploratory behavior and stress responses. *Journal of Neuroimmunology*, *284*, 1–9. https://doi.org/10.1016/j.jneuroim.2015.05.001

Aoshima, H., & Hamamoto, K. (1999). Potentiation of GABA Receptors Expressed in Xenopus Oocytes by Perfume and Phytoncid. *Bioscience, Biotechnology, and Biochemistry*, *63*(4), 743–748. https://doi.org/10.1271/bbb.63.743

Appelhans, B. M., & Luecken, L. J. (2006). Heart Rate Variability as an Index of Regulated Emotional Responding. *Review of General Psychology*, *10*(3), 229–240. https://doi.org/10.1037/1089-2680.10.3.229

Arpaia, P., Cataldo, A., Criscuolo, S., De Benedetto, E., Masciullo, A., & Schiavoni, R. (2022). Assessment and Scientific Progresses in the Analysis of Olfactory Evoked Potentials. *Bioengineering*, *9*(6), 252. https://doi.org/10.3390/bioengineering9060252

Astell-Burt, T., & Feng, X. (2020). Does sleep grow on trees? A longitudinal study to investigate potential prevention of insufficient sleep with different types of urban green space. *SSM - Population Health*, *10*, 100497. https://doi.org/10.1016/j.ssmph.2019.100497

Astell-Burt, T., Feng, X., & Kolt, G. S. (2014). Is Neighborhood Green Space Associated With a Lower Risk of Type 2 Diabetes? Evidence From 267,072 Australians. *Diabetes Care*, *37*(1), 197–201. https://doi.org/10.2337/dc13-1325

Bach, A., Maneja, R., Zaldo-Aubanell, Q., Romanillos, T., Llusià, J., Eustaquio, A., Palacios, O., & Penuelas, J. (2021). Human absorption of monoterpenes after a 2-h forest exposure: A field experiment in a Mediterranean holm oak forest. *Journal of Pharmaceutical and Biomedical Analysis*, *200*, 114080. https://doi.org/10.1016/j.jpba.2021.114080

Badr, G., Alwasel, S., Ebaid, H., Mohany, M., & Alhazza, I. (2011). Perinatal supplementation with thymoquinone improves diabetic complications and T cell immune responses in rat offspring. *Cellular Immunology*, *267*(2), 133–140. https://doi.org/10.1016/j.cellimm.2011.01.002

Bastos, V. P. D., Gomes, A. S., Lima, F. J. B., Brito, T. S., Soares, P. M. G., Pinho, J. P. M., Silva, C. S., Santos, A. A., Souza, M. H. L. P., & Magalhães, P. J. C. (2011). Inhaled 1,8-Cineole Reduces Inflammatory Parameters in Airways of Ovalbumin-Challenged Guinea Pigs: ANTI-INFLAMMATORY EFFECTS OF 1,8-CINEOLE ON GUINEA PIG AIRWAYS. *Basic & Clinical Pharmacology & Toxicology*, *108*(1), 34–39. https://doi.org/10.1111/j.1742-7843.2010.00622.x

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Beil, K., & Hanes, D. (2013). The Influence of Urban Natural and Built Environments on Physiological and Psychological Measures of Stress—A Pilot Study. *International Journal of Environmental Research and Public Health*, *10*(4), 1250–1267. https://doi.org/10.3390/ijerph10041250

Bender, R., Tobias, P. V., & Bender, N. (2012). The Savannah Hypotheses: Origin, Reception and Impact on Paleoanthropology. *History and Philosophy of the Life Sciences*, *34*(1/2), 147–184. JSTOR.

Berman, M. G., Jonides, J., & Kaplan, S. (2008). The Cognitive Benefits of Interacting With Nature. *Psychological Science*, *19*(12), 1207–1212. https://doi.org/10.1111/j.1467-9280.2008.02225.x

Bodicoat, D. H., O'Donovan, G., Dalton, A. M., Gray, L. J., Yates, T., Edwardson, C., Hill, S., Webb, D. R., Khunti, K., Davies, M. J., & Jones, A. P. (2014). The association between neighbourhood greenspace and type 2 diabetes in a large cross-sectional study. *BMJ Open*, *4*(12), e006076. https://doi.org/10.1136/bmjopen-2014-006076

Bratman, G. N., Anderson, C. B., Berman, M. G., Cochran, B., de Vries, S., Flanders, J., Folke, C., Frumkin, H., Gross, J. J., Hartig, T., Kahn, P. H., Kuo, M., Lawler, J. J., Levin, P. S., Lindahl, T., Meyer-Lindenberg, A., Mitchell, R., Ouyang, Z., Roe, J., … Daily, G. C. (2019). Nature and mental health: An ecosystem service perspective. *Science Advances*, *5*(7), eaax0903. https://doi.org/10.1126/sciadv.aax0903

Bratman, G. N., Daily, G. C., Levy, B. J., & Gross, J. J. (2015). The benefits of nature experience: Improved affect and cognition. *Landscape and Urban Planning*, *138*, 41–50. https://doi.org/10.1016/j.landurbplan.2015.02.005

Bratman, G. N., Mehta, A., Olvera-Alvarez, H., Spink, K. M., Levy, C., White, M. P., Kubzansky, L. D., & Gross, J. J. (2024). Associations of nature contact with emotional ill-being and well-being: The role of emotion regulation. *Cognition and Emotion*, 1–20. https://doi.org/10.1080/02699931.2024.2316199

Bratman, G. N., Young, G., Mehta, A., Lee Babineaux, I., Daily, G. C., & Gross, J. J. (2021). Affective Benefits of Nature Contact: The Role of Rumination. *Frontiers in Psychology*, *12*, 643866. https://doi.org/10.3389/fpsyg.2021.643866

Carlson, K. S., Gadziola, M. A., Dauster, E. S., & Wesson, D. W. (2018). Selective Attention Controls Olfactory Decisions and the Neural Encoding of Odors. *Current Biology*, *28*(14), 2195-2205.e4. https://doi.org/10.1016/j.cub.2018.05.011

Chang, K.-M., & Shen, C.-W. (2011). Aromatherapy benefits autonomic nervous system regulation for elementary school faculty in taiwan. *Evidence-Based Complementary and Alternative Medicine: eCAM*, *2011*, 946537. https://doi.org/10.1155/2011/946537

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). ENDOCRINOLOGY OF THE STRESS RESPONSE. *Annual Review of Physiology*, *67*(1), 259–284. https://doi.org/10.1146/annurev.physiol.67.040403.120816

Chen, M.-L., Chen, Y.-E., & Lee, H.-F. (2022). The Effect of Bergamot Essential Oil Aromatherapy on Improving Depressive Mood and Sleep Quality in Postpartum Women: A Randomized Controlled Trial. *Journal of Nursing Research*, *30*(2), e201. https://doi.org/10.1097/jnr.0000000000000459

Chioca, L. R., Antunes, V. D. C., Ferro, M. M., Losso, E. M., & Andreatini, R. (2013). Anosmia does not impair the anxiolytic-like effect of lavender essential oil inhalation in mice. *Life Sciences*, *92*(20–21), 971–975. https://doi.org/10.1016/j.lfs.2013.03.012

Cho, K. S., Lim, Y., Lee, K., Lee, J., Lee, J. H., & Lee, I.-S. (2017). Terpenes from Forests and Human Health. *Toxicological Research*, *33*(2), 97–106. https://doi.org/10.5487/TR.2017.33.2.097

Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology*, *5*(7), 374–381. https://doi.org/10.1038/nrendo.2009.106

Chuang, K.-J., Chen, H.-W., Liu, I.-J., Chuang, H.-C., & Lin, L.-Y. (2014). The effect of essential oil on heart rate and blood pressure among solus por aqua workers. *European Journal of Preventive Cardiology*, *21*(7), 823–828. https://doi.org/10.1177/2047487312469474

Clark, L. A., Cuthbert, B., Lewis-Fernández, R., Narrow, W. E., & Reed, G. M. (2017). Three Approaches to Understanding and Classifying Mental Disorder: *ICD-11, DSM-5* , and the National Institute of Mental Health's Research Domain Criteria (RDoC). *Psychological Science in the Public Interest*, *18*(2), 72–145. https://doi.org/10.1177/1529100617727266

Cohen, S., Janicki-Deverts, D., & Miller, G. E. (2007). Psychological Stress and Disease. *JAMA*, *298*(14), 1685. https://doi.org/10.1001/jama.298.14.1685

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior*, *24*(4), 385–396.

Cui, J., Li, M., Wei, Y., Li, H., He, X., Yang, Q., Li, Z., Duan, J., Wu, Z., Chen, Q., Chen, B., Li, G., Ming, X., Xiong, L., & Qin, D. (2022). Inhalation Aromatherapy via Brain-Targeted Nasal Delivery: Natural Volatiles or Essential Oils on Mood Disorders. *Frontiers in Pharmacology*, *13*, 860043. https://doi.org/10.3389/fphar.2022.860043

Dart, R. A. (1925). Australopithecus africanus The Man-Ape of South Africa. *Nature*, *115*(2884), 195–199. https://doi.org/10.1038/115195a0

De Almeida, A. A. C., Silva, R. O., Nicolau, L. A. D., De Brito, T. V., De Sousa, D. P., Barbosa, A. L. D. R., De Freitas, R. M., Lopes, L. D. S., Medeiros, J.-V. R., & Ferreira, P. M. P. (2017). Physio-pharmacological Investigations About the Anti-inflammatory and Antinociceptive Efficacy of (+)-Limonene Epoxide. *Inflammation*, *40*(2), 511–522. https://doi.org/10.1007/s10753-016-0496-y

de Araujo, I. E., Rolls, E. T., Velazco, M. I., Margot, C., & Cayeux, I. (2005). Cognitive Modulation of Olfactory Processing. *Neuron*, *46*(4), 671–679. https://doi.org/10.1016/j.neuron.2005.04.021

De Brito, J. N., Pope, Z. C., Mitchell, N. R., Schneider, I. E., Larson, J. M., Horton, T. H., & Pereira, M. A. (2020). The effect of green walking on heart rate variability: A pilot crossover study. *Environmental Research*, *185*, 109408. https://doi.org/10.1016/j.envres.2020.109408

De Cássia Da Silveira E Sá, R., Andrade, L., & De Sousa, D. (2013). A Review on Anti-Inflammatory Activity of Monoterpenes. *Molecules*, *18*(1), 1227–1254. https://doi.org/10.3390/molecules18011227

Del Prado-Audelo, M. L., Cortés, H., Caballero-Florán, I. H., González-Torres, M., Escutia-Guadarrama, L., Bernal-Chávez, S. A., Giraldo-Gomez, D. M., Magaña, J. J., & Leyva-Gómez, G. (2021). Therapeutic Applications of Terpenes on Inflammatory Diseases. *Frontiers in Pharmacology*, *12*, 704197. https://doi.org/10.3389/fphar.2021.704197

Diaz, A., Luque, L., Badar, Z., Kornic, S., & Danon, M. (2016). Prepubertal gynecomastia and chronic lavender exposure: Report of three cases. *Journal of Pediatric Endocrinology and Metabolism*, *29*(1). https://doi.org/10.1515/jpem-2015-0248

Domínguez-Rodrigo, M. (2014). Is the “Savanna Hypothesis” a Dead Concept for Explaining the Emergence of the Earliest Hominins? *Current Anthropology*, *55*(1), 59–81. https://doi.org/10.1086/674530

Doty, R. L. (2001). Olfaction. *Annual Review of Psychology*, *52*(1), 423–452. https://doi.org/10.1146/annurev.psych.52.1.423

Doyle, J. A., Brindle, E., & Bolden, T. S. (2019). Development and validation of hair specimen collection methods among extremely short-length Afro-textured hair. *American Journal of Human Biology*, *31*(3), e23222. https://doi.org/10.1002/ajhb.23222

Dudareva, N., Negre, F., Nagegowda, D. A., & Orlova, I. (2006). Plant Volatiles: Recent Advances and Future Perspectives. *Critical Reviews in Plant Sciences*, *25*(5), 417–440. https://doi.org/10.1080/07352680600899973

Duncan, M. J., Clarke, N. D., Birch, S. L., Tallis, J., Hankey, J., Bryant, E., & Eyre, E. L. J. (2014). The effect of green exercise on blood pressure, heart rate and mood state in primary school children. *International Journal of Environmental Research and Public Health*, *11*(4), 3678–3688. https://doi.org/10.3390/ijerph110403678

Durrant, D. M., Ghosh, S., & Klein, R. S. (2016). The Olfactory Bulb: An Immunosensory Effector Organ during Neurotropic Viral Infections. *ACS Chemical Neuroscience*, *7*(4), 464–469. https://doi.org/10.1021/acschemneuro.6b00043

Eddin, L. B., Jha, N. K., Meeran, M. F. N., Kesari, K. K., Beiram, R., & Ojha, S. (2021). Neuroprotective Potential of Limonene and Limonene Containing Natural Products. *Molecules*, *26*(15), 4535. https://doi.org/10.3390/molecules26154535

Engels, J., & Diehr, P. (2003). Imputation of missing longitudinal data: A comparison of methods. *Journal of Clinical Epidemiology*, *56*(10), 968–976. https://doi.org/10.1016/S0895-4356(03)00170-7

Esch, T., Stefano, G. B., Fricchione, G. L., & Benson, H. (2002). The role of stress in neurodegenerative diseases and mental disorders. *Neuro Endocrinology Letters*, *23*(3), 199–208.

Ewert, A., & Chang, Y. (2018). Levels of Nature and Stress Response. *Behavioral Sciences*, *8*(5), 49. https://doi.org/10.3390/bs8050049

Falk, A. A., Hagberg, M. T., Lof, A. E., Wigaeus-Hjelm, E. M., & Wang, Z. P. (1990). Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scandinavian Journal of Work, Environment & Health*, *16*(5), 372–378. https://doi.org/10.5271/sjweh.1771

Faturi, C. B., Leite, J. R., Alves, P. B., Canton, A. C., & Teixeira-Silva, F. (2010). Anxiolytic-like effect of sweet orange aroma in Wistar rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *34*(4), 605–609. https://doi.org/10.1016/j.pnpbp.2010.02.020

Frumkin, H., Bratman, G. N., Breslow, S. J., Cochran, B., Kahn Jr, P. H., Lawler, J. J., Levin, P. S., Tandon, P. S., Varanasi, U., Wolf, K. L., & Wood, S. A. (2017). Nature Contact and Human Health: A Research Agenda. *Environmental Health Perspectives*, *125*(7), 075001. https://doi.org/10.1289/EHP1663

Fung, T. K. H., Lau, B. W. M., Ngai, S. P. C., & Tsang, H. W. H. (2021). Therapeutic Effect and Mechanisms of Essential Oils in Mood Disorders: Interaction between the Nervous and Respiratory Systems. *International Journal of Molecular Sciences*, *22*(9), 4844. https://doi.org/10.3390/ijms22094844

Furuyashiki, A., Tabuchi, K., Norikoshi, K., Kobayashi, T., & Oriyama, S. (2019). A comparative study of the physiological and psychological effects of forest bathing (Shinrin-yoku) on working age people with and without depressive tendencies. *Environmental Health and Preventive Medicine*, *24*(1), 46. https://doi.org/10.1186/s12199-019-0800-1

Gascon, M., Triguero-Mas, M., Martínez, D., Dadvand, P., Rojas-Rueda, D., Plasència, A., & Nieuwenhuijsen, M. J. (2016). Residential green spaces and mortality: A systematic review. *Environment International*, *86*, 60–67. https://doi.org/10.1016/j.envint.2015.10.013

GBD 2019 Mental Disorders Collaborators. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry*, *9*(2), 137–150. https://doi.org/10.1016/S2215-0366(21)00395-3

Geisler, M. W., & Murphy, C. (2000). Event-related brain potentials to attended and ignored olfactory and trigeminal stimuli. *International Journal of Psychophysiology*, *37*(3), 309–315. https://doi.org/10.1016/S0167-8760(00)00111-2

Gentilucci, M., & Cattaneo, L. (2005). Automatic audiovisual integration in speech perception. *Experimental Brain Research*, *167*(1), 66–75. https://doi.org/10.1007/s00221-005-0008-z

Geron, C., Rasmussen, R., R. Arnts, R., & Guenther, A. (2000). A review and synthesis of monoterpene speciation from forests in the United States. *Atmospheric Environment*, *34*(11), 1761–1781. https://doi.org/10.1016/S1352-2310(99)00364-7

Gibbons, C. H. (2019). Basics of autonomic nervous system function. In *Handbook of Clinical Neurology* (Vol. 160, pp. 407–418). Elsevier. https://doi.org/10.1016/B978-0-444-64032-1.00027-8

Gidlow, C. J., Jones, M. V., Hurst, G., Masterson, D., Clark-Carter, D., Tarvainen, M. P., Smith, G., & Nieuwenhuijsen, M. (2016). Where to put your best foot forward: Psycho-physiological responses to walking in natural and urban environments. *Journal of Environmental Psychology*, *45*, 22–29. https://doi.org/10.1016/j.jenvp.2015.11.003

Goes, T. C., Antunes, F. D., Alves, P. B., & Teixeira-Silva, F. (2012). Effect of Sweet Orange Aroma on Experimental Anxiety in Humans. *The Journal of Alternative and Complementary Medicine*, *18*(8), 798–804. https://doi.org/10.1089/acm.2011.0551

Hansen, M. M., Jones, R., & Tocchini, K. (2017). Shinrin-Yoku (Forest Bathing) and Nature Therapy: A State-of-the-Art Review. *International Journal of Environmental Research and Public Health*, *14*(8), 851. https://doi.org/10.3390/ijerph14080851

Hanson, L. R., & Frey, W. H. (2008). Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease. *BMC Neuroscience*, *9*(S3), S5. https://doi.org/10.1186/1471-2202-9-S3-S5

Harris, J. A., West, A. K., & Chuah, M. I. (2009). Olfactory ensheathing cells: Nitric oxide production and innate immunity. *Glia*, *57*(16), 1848–1857. https://doi.org/10.1002/glia.20899

Hart, P. H., Brand, C., Carson, C. F., Riley, T. V., Prager, R. H., & Finlay-Jones, J. J. (2000). Terpinen-4-ol, the main component of the essential oil of Melaleuca alternifolia (tea tree oil), suppresses inflammatory mediator production by activated human monocytes. *Inflammation Research*, *49*(11), 619–626. https://doi.org/10.1007/s000110050639

Hartig, T., Mitchell, R., De Vries, S., & Frumkin, H. (2014). Nature and Health. *Annual Review of Public Health*, *35*(1), 207–228. https://doi.org/10.1146/annurev-publhealth-032013-182443

He, Z. (2020). The control mechanisms of heart rate dynamics in a new heart rate nonlinear time series model. *Scientific Reports*, *10*(1), 4814. https://doi.org/10.1038/s41598-020-61562-6

Heller, M., Roberts, S. T., Masese, L., Ngina, J., Chohan, N., Chohan, V., Shafi, J., McClelland, R. S., Brindle, E., & Graham, S. M. (2018). Gender-Based Violence, Physiological Stress, and Inflammation: A Cross-Sectional Study. *Journal of Women's Health*, *27*(9), 1152–1161. https://doi.org/10.1089/jwh.2017.6743

Henley, D. V., Lipson, N., Korach, K. S., & Bloch, C. A. (2007). Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oils. *New England Journal of Medicine*, *356*(5), 479–485. https://doi.org/10.1056/NEJMoa064725

Herz, R. S. (2009). Aromatherapy Facts and Fictions: A Scientific Analysis of Olfactory Effects on Mood, Physiology and Behavior. *International Journal of Neuroscience*, *119*(2), 263–290. https://doi.org/10.1080/00207450802333953

Herz, R. S., Beland, S. L., & Hellerstein, M. (2004). Changing Odor Hedonic Perception Through Emotional Associations in Humans. *International Journal of Comparative Psychology*, *17*(4). https://doi.org/10.46867/IJCP.2004.17.04.05

Heuberger, E. (2001). Effects of Chiral Fragrances on Human Autonomic Nervous System Parameters and Self-evaluation. *Chemical Senses*, *26*(3), 281–292. https://doi.org/10.1093/chemse/26.3.281

Hong, A., Sallis, J. F., King, A. C., Conway, T. L., Saelens, B., Cain, K. L., Fox, E. H., & Frank, L. D. (2018). Linking green space to neighborhood social capital in older adults: The role of perceived safety. *Social Science & Medicine*, *207*, 38–45. https://doi.org/10.1016/j.socscimed.2018.04.051

Hoover, K. C. (2010). Smell with inspiration: The evolutionary significance of olfaction. *American Journal of Physical Anthropology*, *143*(S51), 63–74. https://doi.org/10.1002/ajpa.21441

Horiuchi, M., Endo, J., Takayama, N., Murase, K., Nishiyama, N., Saito, H., & Fujiwara, A. (2014). Impact of Viewing vs. Not Viewing a Real Forest on Physiological and Psychological Responses in the Same Setting. *International Journal of Environmental Research and Public Health*, *11*(10), 10883–10901. https://doi.org/10.3390/ijerph111010883

Huang, L., & Capdevila, L. (2017). Aromatherapy Improves Work Performance Through Balancing the Autonomic Nervous System. *The Journal of Alternative and Complementary Medicine*, *23*(3), 214–221. https://doi.org/10.1089/acm.2016.0061

Hunter, M. R., Gillespie, B. W., & Chen, S. Y.-P. (2019). Urban Nature Experiences Reduce Stress in the Context of Daily Life Based on Salivary Biomarkers. *Frontiers in Psychology*, *10*, 722. https://doi.org/10.3389/fpsyg.2019.00722

Hwang, J. H. (2006). The Effects of the Inhalation Method Using Essential Oils on Blood Pressure and Stress Responses of Clients with Essential Hypertension. *Journal of Korean Academy of Nursing*, *36*(7), 1123. https://doi.org/10.4040/jkan.2006.36.7.1123

Jacob, S., McClintock, M. K., Zelano, B., & Ober, C. (2002). Paternally inherited HLA alleles are associated with women's choice of male odor. *Nature Genetics*, *30*(2), 175–179. https://doi.org/10.1038/ng830

James, P., Hart, J. E., Banay, R. F., & Laden, F. (2016). Exposure to Greenness and Mortality in a Nationwide Prospective Cohort Study of Women. *Environmental Health Perspectives*, *124*(9), 1344–1352. https://doi.org/10.1289/ehp.1510363

Jang, H., Boltz, D., Sturm-Ramirez, K., Shepherd, K. R., Jiao, Y., Webster, R., & Smeyne, R. J. (2009). Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. *Proceedings of the National Academy of Sciences*, *106*(33), 14063–14068. https://doi.org/10.1073/pnas.0900096106

Jiang, B., Chang, C.-Y., & Sullivan, W. C. (2014). A dose of nature: Tree cover, stress reduction, and gender differences. *Landscape and Urban Planning*, *132*, 26–36. https://doi.org/10.1016/j.landurbplan.2014.08.005

Johnson, B. S., Malecki, K. M., Peppard, P. E., & Beyer, K. M. M. (2018). Exposure to neighborhood green space and sleep: Evidence from the Survey of the Health of Wisconsin. *Sleep Health*, *4*(5), 413–419. https://doi.org/10.1016/j.sleh.2018.08.001

Juergens, U. R., Dethlefsen, U., Steinkamp, G., Gillissen, A., Repges, R., & Vetter, H. (2003). Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: A double-blind placebo-controlled trial. *Respiratory Medicine*, *97*(3), 250–256. https://doi.org/10.1053/rmed.2003.1432

Juergens, U. R., Engelen, T., Racké, K., Stöber, M., Gillissen, A., & Vetter, H. (2004). Inhibitory activity of 1,8-cineol (eucalyptol) on cytokine production in cultured human lymphocytes

and monocytes. *Pulmonary Pharmacology & Therapeutics*, *17*(5), 281–287. https://doi.org/10.1016/j.pupt.2004.06.002

Juergens, U. R., Stöber, M., & Vetter, H. (1998). The anti-inflammatory activity of L-menthol compared to mint oil in human monocytes in vitro: A novel perspective for its therapeutic use in inflammatory diseases. *European Journal of Medical Research*, *3*(12), 539–545.

Jun, Y. S., Kang, P., Min, S. S., Lee, J.-M., Kim, H.-K., & Seol, G. H. (2013). Effect of Eucalyptus Oil Inhalation on Pain and Inflammatory Responses after Total Knee Replacement: A Randomized Clinical Trial. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–7. https://doi.org/10.1155/2013/502727

Kadmiel, M., & Cidlowski, J. A. (2013). Glucocorticoid receptor signaling in health and disease. *Trends in Pharmacological Sciences*, *34*(9), 518–530. https://doi.org/10.1016/j.tips.2013.07.003

Kagawa, D., Jokura, H., Ochiai, R., Tokimitsu, I., & Tsubone, H. (2003). The sedative effects and mechanism of action of cedrol inhalation with behavioral pharmacological evaluation. *Planta Medica*, *69*(7), 637–641. https://doi.org/10.1055/s-2003-41114

Kanwal, A., Bilal, M., Rasool, N., Zubair, M., Shah, S. A. A., & Zakaria, Z. A. (2022). Total Synthesis of Terpenes and Their Biological Significance: A Critical Review. *Pharmaceuticals*, *15*(11), 1392. https://doi.org/10.3390/ph15111392

Kaplan, R., & Kaplan, S. (1989). *The experience of nature: A psychological perspective.* (pp. xii, 340). Cambridge University Press.

Kaplan, S. (1995). The restorative benefits of nature: Toward an integrative framework. *Green Psychology*, *15*(3), 169–182. https://doi.org/10.1016/0272-4944(95)90001-2

Kavanaugh, J., Hardison, M. E., Rogers, H. H., White, C., & Gross, J. (2022). Assessing the Impact of a Shinrin-Yoku (Forest Bathing) Intervention on Physician/Healthcare Professional Burnout: A Randomized, Controlled Trial. *International Journal of Environmental Research and Public Health*, *19*(21), 14505. https://doi.org/10.3390/ijerph192114505

Kaźmierczak, A. (2013). The contribution of local parks to neighbourhood social ties. *Landscape and Urban Planning*, *109*(1), 31–44. https://doi.org/10.1016/j.landurbplan.2012.05.007

Kellert, S. R., & Wilson, E. O. (Eds.). (1993). *The biophilia hypothesis*. Island Press / Shearwater Books.

Kerr, D., Hegg, M., & Mohebbi, M. (2021). Effects of diffused essential oils for reducing stress and improving mood for clinical nurses: An interventional time series study. *Nursing Forum*, *56*(2), 305–312. https://doi.org/10.1111/nuf.12548

Khaw, M. W., Stevens, L., & Woodford, M. (2021). Individual differences in the perception of probability. *PLOS Computational Biology*, *17*(4), e1008871. https://doi.org/10.1371/journal.pcbi.1008871

Khoshnazar, M., Bigdeli, M. R., Parvardeh, S., & Pouriran, R. (2019). Attenuating effect of α-pinene on neurobehavioural deficit, oxidative damage and inflammatory response following focal ischaemic stroke in rat. *Journal of Pharmacy and Pharmacology*, *71*(11), 1725–1733. https://doi.org/10.1111/jphp.13164

Kim, C., & Song, C. (2022). Physiological and Psychological Relaxation Effects of Fir Essential Oil on University Students. *International Journal of Environmental Research and Public Health*, *19*(9), 5063. https://doi.org/10.3390/ijerph19095063

Kim, D.-S., Lee, H.-J., Jeon, Y.-D., Han, Y.-H., Kee, J.-Y., Kim, H.-J., Shin, H.-J., Kang, J., Lee, B. S., Kim, S.-H., Kim, S.-J., Park, S.-H., Choi, B.-M., Park, S.-J., Um, J.-Y., & Hong, S.-H. (2015). Alpha-Pinene Exhibits Anti-Inflammatory Activity Through the Suppression of MAPKs and the NF-κB Pathway in Mouse Peritoneal Macrophages. *The American Journal of Chinese Medicine*, *43*(04), 731–742. https://doi.org/10.1142/S0192415X15500457

Kim, Y., Choi, Y., & Kim, H. (2022). Positive Effects on Emotional Stress and Sleep Quality of Forest Healing Program for Exhausted Medical Workers during the COVID-19 Outbreak. *International Journal of Environmental Research and Public Health*, *19*(5), 3130. https://doi.org/10.3390/ijerph19053130

Kitayama, S., Duffy, S., Kawamura, T., & Larsen, J. T. (2003). Perceiving an Object and Its Context in Different Cultures: A Cultural Look at New Look. *Psychological Science*, *14*(3), 201–206. https://doi.org/10.1111/1467-9280.02432

Kobayashi, H., Song, C., Ikei, H., Park, B.-J., Lee, J., Kagawa, T., & Miyazaki, Y. (2017). Population-Based Study on the Effect of a Forest Environment on Salivary Cortisol Concentration. *International Journal of Environmental Research and Public Health*, *14*(8), 931. https://doi.org/10.3390/ijerph14080931

Kobayashi, H., Song, C., Ikei, H., Park, B.-J., Lee, J., Kagawa, T., & Miyazaki, Y. (2018). Forest Walking Affects Autonomic Nervous Activity: A Population-Based Study. *Frontiers in Public Health*, *6*, 278. https://doi.org/10.3389/fpubh.2018.00278

Koenig, J. Q. (2000). *Health Effects of Ambient Air Pollution: How safe is the air we breathe?* Springer US : Imprint : Springer.

Komori, T., Fujiwara, R., Tanida, M., Nomura, J., & Yokoyama, M. M. (1995). Effects of Citrus Fragrance on Immune Function and Depressive States. *Neuroimmunomodulation*, *2*(3), 174–180. https://doi.org/10.1159/000096889

Konishi, S., Brindle, E., Guyton, A., & O'Connor, K. A. (2012). Salivary concentration of progesterone and cortisol significantly differs across individuals after correcting for blood hormone values. *American Journal of Physical Anthropology*, *149*(2), 231–241. https://doi.org/10.1002/ajpa.22114

Kontaris, I., East, B. S., & Wilson, D. A. (2020). Behavioral and Neurobiological Convergence of Odor, Mood and Emotion: A Review. *Frontiers in Behavioral Neuroscience*, *14*, 35. https://doi.org/10.3389/fnbeh.2020.00035

Koyama, S., & Heinbockel, T. (2020). The Effects of Essential Oils and Terpenes in Relation to Their Routes of Intake and Application. *International Journal of Molecular Sciences*, *21*(5), 1558. https://doi.org/10.3390/ijms21051558

Krauel, K., Pause, B. M., Sojka, B., Schott, P., & Ferstl, R. (1998). Attentional Modulation of Central Odor Processing. *Chemical Senses*, *23*(4), 423–432. https://doi.org/10.1093/chemse/23.4.423

Kuo, M. (2015). How might contact with nature promote human health? Promising mechanisms and a possible central pathway. *Frontiers in Psychology*, *6*, 1093. https://doi.org/10.3389/fpsyg.2015.01093

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2017). **lmerTest** Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software*, *82*(13). https://doi.org/10.18637/jss.v082.i13

Lanki, T., Siponen, T., Ojala, A., Korpela, K., Pennanen, A., Tiittanen, P., Tsunetsugu, Y., Kagawa, T., & Tyrväinen, L. (2017). Acute effects of visits to urban green environments on cardiovascular physiology in women: A field experiment. *Environmental Research*, *159*, 176–185. https://doi.org/10.1016/j.envres.2017.07.039

Lee, J., Park, B.-J., Ohira, T., Kagawa, T., & Miyazaki, Y. (2015). Acute Effects of Exposure to a Traditional Rural Environment on Urban Dwellers: A Crossover Field Study in Terraced Farmland. *International Journal of Environmental Research and Public Health*, *12*(2), 1874–1893. https://doi.org/10.3390/ijerph120201874

Lee, J., Park, B.-J., Tsunetsugu, Y., Ohira, T., Kagawa, T., & Miyazaki, Y. (2011). Effect of forest bathing on physiological and psychological responses in young Japanese male subjects. *Public Health*, *125*(2), 93–100. https://doi.org/10.1016/j.puhe.2010.09.005

Lee, M., Lim, S., Song, J.-A., Kim, M.-E., & Hur, M.-H. (2017). The effects of aromatherapy essential oil inhalation on stress, sleep quality and immunity in healthy adults: Randomized controlled trial. *European Journal of Integrative Medicine*, *12*, 79–86. https://doi.org/10.1016/j.eujim.2017.04.009

Levenson, R. W. (2003). Blood, Sweat, and Fears: The Autonomic Architecture of Emotion. *Annals of the New York Academy of Sciences*, *1000*(1), 348–366. https://doi.org/10.1196/annals.1280.016

Leyva-Grado, V. H., Churchill, L., Wu, M., Williams, T. J., Taishi, P., Majde, J. A., & Krueger, J. M. (2009). Influenza virus- and cytokine-immunoreactive cells in the murine olfactory and central autonomic nervous systems before and after illness onset. *Journal of Neuroimmunology*, *211*(1–2), 73–83. https://doi.org/10.1016/j.jneuroim.2009.03.016

Li, Q., Morimoto, K., Kobayashi, M., Inagaki, H., Katsumata, M., Hirata, Y., Hirata, K., Suzuki, H., Li, Y. J., Wakayama, Y., Kawada, T., Park, B. J., Ohira, T., Matsui, N., Kagawa, T., Miyazaki, Y., & Krensky, A. M. (2008). Visiting a Forest, but Not a City, Increases Human Natural Killer Activity and Expression of Anti-Cancer Proteins. *International Journal of Immunopathology and Pharmacology*, *21*(1), 117–127. https://doi.org/10.1177/039463200802100113

Li, Q., Morimoto, K., Nakadai, A., Inagaki, H., Katsumata, M., Shimizu, T., Hirata, Y., Hirata, K., Suzuki, H., Miyazaki, Y., Kagawa, T., Koyama, Y., Ohira, T., Takayama, N., Krensky, A. M., & Kawada, T. (2007). Forest Bathing Enhances Human Natural Killer Activity and Expression of Anti-Cancer Proteins. *International Journal of Immunopathology and Pharmacology*, *20*(2_suppl), 3–8. https://doi.org/10.1177/03946320070200S202

Lucassen, P. J., Pruessner, J., Sousa, N., Almeida, O. F. X., Van Dam, A. M., Rajkowska, G., Swaab, D. F., & Czéh, B. (2014). Neuropathology of stress. *Acta Neuropathologica*, *127*(1), 109–135. https://doi.org/10.1007/s00401-013-1223-5

Mackersie, C. L., & Calderon-Moultrie, N. (2016). Autonomic Nervous System Reactivity During Speech Repetition Tasks: Heart Rate Variability and Skin Conductance. *Ear & Hearing*, *37*(1), 118S-125S. https://doi.org/10.1097/AUD.0000000000000305

Majde, J. A., Bohnet, S. G., Ellis, G. A., Churchill, L., Leyva-Grado, V., Wu, M., Szentirmai, E., Rehman, A., & Krueger, J. M. (2007). Detection of mouse-adapted human influenza virus in the olfactory bulbs of mice within hours after intranasal infection. *Journal of NeuroVirology*, *13*(5), 399–409. https://doi.org/10.1080/13550280701427069

Mao, G.-X., Cao, Y.-B., Lan, X.-G., He, Z.-H., Chen, Z.-M., Wang, Y.-Z., Hu, X.-L., Lv, Y.-D., Wang, G.-F., & Yan, J. (2012). Therapeutic effect of forest bathing on human hypertension in the elderly. *Journal of Cardiology*, *60*(6), 495–502. https://doi.org/10.1016/j.jjcc.2012.08.003

Mao, G.-X., Lan, X.-G., Cao, Y. B., Chen, Z.-M., He, Z.-H., Lv, Y.-D., Wang, Y.-Z., Hu, X.-L., Wang, G. F., & Yan, J. (2012). Effects of Short-Term Forest Bathing on Human Health in a Broad-Leaved Evergreen Forest in Zhejiang Province, China. In *Biomedical and Environmental Sciences* (Vol. 25, Issue 3, p. 317).

Martin, G. N., & Chaudry, A. (2014). Working memory performance and exposure to pleasant and unpleasant ambient odor: Is spatial span special? *International Journal of Neuroscience*, *124*(11), 806–811. https://doi.org/10.3109/00207454.2014.890619

Masago, R., Shimomura, Y., Iwanaga, K., & Katsuura, T. (2001). The Effects of Hedonic Properties of Odors and Attentional Modulation on the Olfactory Event-Related Potentials. *Journal of PHYSIOLOGICAL ANTHROPOLOGY and Applied Human Science*, *20*(1), 7–13. https://doi.org/10.2114/jpa.20.7

Masyita, A., Mustika Sari, R., Dwi Astuti, A., Yasir, B., Rahma Rumata, N., Emran, T. B., Nainu, F., & Simal-Gandara, J. (2022). Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. *Food Chemistry: X*, *13*, 100217. https://doi.org/10.1016/j.fochx.2022.100217

McAllister, E., Bhullar, N., & Schutte, N. S. (2017). Into the Woods or a Stroll in the Park: How Virtual Contact with Nature Impacts Positive and Negative Affect. *International Journal*

of Environmental Research and Public Health, *14*(7), 786. https://doi.org/10.3390/ijerph14070786

Menezes, I. A. C., Barreto, C. M. N., Antoniolli, Â. R., Santos, M. R. V., & Sousa, D. P. D. (2010). Hypotensive Activity of Terpenes Found in Essential Oils. *Zeitschrift Für Naturforschung C*, *65*(9–10), 562–566. https://doi.org/10.1515/znc-2010-9-1005

Mori, K., Kaneko, Y. S., Nakashima, A., Nagatsu, I., Takahashi, H., & Ota, A. (2005). Peripheral lipopolysaccharide induces apoptosis in the murine olfactory bulb. *Brain Research*, *1039*(1–2), 116–129. https://doi.org/10.1016/j.brainres.2005.01.078

Moss, M., & Oliver, L. (2012). Plasma 1,8-cineole correlates with cognitive performance following exposure to rosemary essential oil aroma. *Therapeutic Advances in Psychopharmacology*, *2*(3), 103–113. https://doi.org/10.1177/2045125312436573

Munro, C., & Stabenfeldt, G. (1984). Development of a microtitre plate enzyme immunoassay for the determination of progesterone. *Journal of Endocrinology*, *101*(1), 41–49. https://doi.org/10.1677/joe.0.1010041

Murison, R. (2016). The Neurobiology of Stress. In *Neuroscience of Pain, Stress, and Emotion* (pp. 29–49). Elsevier. https://doi.org/10.1016/B978-0-12-800538-5.00002-9

Nascimento, N. R. F., Refosco, R. M. D. C., Vasconcelos, E. C. F., Kerntopf, M. R., Santos, C. F., Batista, F. J. A., De Sousa, C. M., & Fonteles, M. C. (2009). 1,8-Cineole induces relaxation in rat and guinea-pig airway smooth muscle. *Journal of Pharmacy and Pharmacology*, *61*(3), 361–366. https://doi.org/10.1211/jpp.61.03.0011

National Institute for Occupational Safety and Health. (1996). *NIOSH Manual of Analytic Methods (NMAM) 1552: Terpenes*. National Institute for Occupational Safety and Health.

Nghiem, T. P. L., Wong, K. L., Jeevanandam, L., Chang, C. c., Tan, L. Y. C., Goh, Y., & Carrasco, L. R. (2021). Biodiverse urban forests, happy people: Experimental evidence linking perceived biodiversity, restoration, and emotional wellbeing. *Urban Forestry & Urban Greening*, *59*, 127030. https://doi.org/10.1016/j.ufug.2021.127030

Nisbet, E. K., & Zelenski, J. M. (2013). The NR-6: A new brief measure of nature relatedness. *Frontiers in Psychology*, *4*. https://doi.org/10.3389/fpsyg.2013.00813

Ochiai, H., Ikei, H., Song, C., Kobayashi, M., Miura, T., Kagawa, T., Li, Q., Kumeda, S., Imai, M., & Miyazaki, Y. (2015). Physiological and Psychological Effects of a Forest Therapy Program on Middle-Aged Females. *International Journal of Environmental Research and Public Health*, *12*(12), 15222–15232. https://doi.org/10.3390/ijerph121214984

Oomen-Welke, K., Schlachter, E., Hilbich, T., Naumann, J., Müller, A., Hinterberger, T., & Huber, R. (2022). Spending Time in the Forest or the Field: Investigations on Stress Perception and Psychological Well-Being—A Randomized Cross-Over Trial in Highly Sensitive Persons. *International Journal of Environmental Research and Public Health*, *19*(22), 15322. https://doi.org/10.3390/ijerph192215322

Park, B. J., Tsunetsugu, Y., Kasetani, T., Kagawa, T., & Miyazaki, Y. (2009). The physiological effects of Shinrin-yoku (taking in the forest atmosphere or forest bathing): Evidence from field experiments in 24 forests across Japan. *Environmental Health and Preventive Medicine*, *15*(1), 18. https://doi.org/10.1007/s12199-009-0086-9

Park, B.-J., Tsunetsugu, Y., Kasetani, T., Hirano, H., Kagawa, T., Sato, M., & Miyazaki, Y. (2007). Physiological Effects of Shinrin-yoku (Taking in the Atmosphere of the Forest)—Using Salivary Cortisol and Cerebral Activity as Indicators—. *Journal of*

PHYSIOLOGICAL ANTHROPOLOGY, *26*(2), 123–128. https://doi.org/10.2114/jpa2.26.123

Partos, T. R., Cropper, S. J., & Rawlings, D. (2016). You Don't See What I See: Individual Differences in the Perception of Meaning from Visual Stimuli. *PloS One*, *11*(3), e0150615. https://doi.org/10.1371/journal.pone.0150615

Pasini, M., Berto, R., Brondino, M., Hall, R., & Ortner, C. (2014). How to Measure the Restorative Quality of Environments: The PRS-11. *Procedia - Social and Behavioral Sciences*, *159*, 293–297. https://doi.org/10.1016/j.sbspro.2014.12.375

Patchev, V. K., & Patchev, A. V. (2006). Experimental models of stress. *Dialogues in Clinical Neuroscience*, *8*(4), 417–432. https://doi.org/10.31887/DCNS.2006.8.4/vpatchev

Piff, P. K., Dietze, P., Feinberg, M., Stancato, D. M., & Keltner, D. (2015). Awe, the small self, and prosocial behavior. *Journal of Personality and Social Psychology*, *108*(6), 883–899. https://doi.org/10.1037/pspi0000018

Purves, D., & Williams, S. M. (Eds.). (2001). *Neuroscience* (2nd ed). Sinauer Associates.

Putra, I. G. N. E., Astell-Burt, T., Cliff, D. P., Vella, S. A., John, E. E., & Feng, X. (2020). The Relationship Between Green Space and Prosocial Behaviour Among Children and Adolescents: A Systematic Review. *Frontiers in Psychology*, *11*, 859. https://doi.org/10.3389/fpsyg.2020.00859

R Core Team. (2023). *R: A Language and Environment for Statistical Computing*. https://www.R-project.org/

Rahimi, K., Zalaghi, M., Shehnizad, E. G., Salari, G., Baghdezfoli, F., & Ebrahimifar, A. (2023). The effects of alpha-pinene on inflammatory responses and oxidative stress in the

formalin test. *Brain Research Bulletin*, *203*, 110774. https://doi.org/10.1016/j.brainresbull.2023.110774

Ramsey, J. T., Li, Y., Arao, Y., Naidu, A., Coons, L. A., Diaz, A., & Korach, K. S. (2019). Lavender Products Associated With Premature Thelarche and Prepubertal Gynecomastia: Case Reports and Endocrine-Disrupting Chemical Activities. *The Journal of Clinical Endocrinology & Metabolism*, *104*(11), 5393–5405. https://doi.org/10.1210/jc.2018-01880

Ramsey, J. T., Shropshire, B. C., Nagy, T. R., Chambers, K. D., Li, Y., & Korach, K. S. (2020). Essential Oils and Health. *The Yale Journal of Biology and Medicine*, *93*(2), 291–305.

Raphael, T. J., & Kuttan*, G. (2003). Immunomodulatory Activity of Naturally Occurring Monoterpenes Carvone, Limonene, and Perillic Acid. *Immunopharmacology and Immunotoxicology*, *25*(2), 285–294. https://doi.org/10.1081/IPH-120020476

Reed, D. R., & Knaapila, A. (2010). Genetics of taste and smell: Poisons and pleasures. *Progress in Molecular Biology and Translational Science*, *94*, 213–240. https://doi.org/10.1016/B978-0-12-375003-7.00008-X

Retiveau, A. N., Iv, E. C., & Milliken, G. A. (2004). COMMON AND SPECIFIC EFFECTS OF FINE FRAGRANCES ON THE MOOD OF WOMEN. *Journal of Sensory Studies*, *19*(5), 373–394. https://doi.org/10.1111/j.1745-459x.2004.102803.x

Rufino, A. T., Ribeiro, M., Judas, F., Salgueiro, L., Lopes, M. C., Cavaleiro, C., & Mendes, A. F. (2014). Anti-inflammatory and Chondroprotective Activity of (+)-α-Pinene: Structural and Enantiomeric Selectivity. *Journal of Natural Products*, *77*(2), 264–269. https://doi.org/10.1021/np400828x

Saiyudthong, S., & Marsden, C. A. (2011). Acute effects of bergamot oil on anxiety-related behaviour and corticosterone level in rats. *Phytotherapy Research*, *25*(6), 858–862. https://doi.org/10.1002/ptr.3325

Santos, F. (2004). 1,8-cineole (eucalyptol), a monoterpene oxide attenuates the colonic damage in rats on acute TNBS-colitis. *Food and Chemical Toxicology*, *42*(4), 579–584. https://doi.org/10.1016/j.fct.2003.11.001

Sapolsky, R. M. (2015). Stress and the brain: Individual variability and the inverted-U. *Nature Neuroscience*, *18*(10), 1344–1346. https://doi.org/10.1038/nn.4109

Sara, J. D. S., Toya, T., Ahmad, A., Clark, M. M., Gilliam, W. P., Lerman, L. O., & Lerman, A. (2022). Mental Stress and Its Effects on Vascular Health. *Mayo Clinic Proceedings*, *97*(5), 951–990. https://doi.org/10.1016/j.mayocp.2022.02.004

Schiffman, S. S., Suggs, M. S., & Sattely-Miller, E. A. (1995). Effect of pleasant odors on mood of males at midlife: Comparison of African-American and European-American men. *Brain Research Bulletin*, *36*(1), 31–37. https://doi.org/10.1016/0361-9230(94)00134-M

Seubert, J., Rea, A. F., Loughead, J., & Habel, U. (2008). Mood Induction with Olfactory Stimuli Reveals Differential Affective Responses in Males and Females. *Chemical Senses*, *34*(1), 77–84. https://doi.org/10.1093/chemse/bjn054

Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*, *5*, 258. https://doi.org/10.3389/fpubh.2017.00258

Shaffer, F., McCraty, R., & Zerr, C. L. (2014). A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. *Frontiers in Psychology*, *5*. https://doi.org/10.3389/fpsyg.2014.01040

Shanahan, D. F., Bush, R., Gaston, K. J., Lin, B. B., Dean, J., Barber, E., & Fuller, R. A. (2016). Health Benefits from Nature Experiences Depend on Dose. *Scientific Reports*, *6*(1), 28551. https://doi.org/10.1038/srep28551

Shin, J. C., Parab, K. V., An, R., & Grigsby-Toussaint, D. S. (2020). Greenspace exposure and sleep: A systematic review. *Environmental Research*, *182*, 109081. https://doi.org/10.1016/j.envres.2019.109081

Shrive, F. M., Stuart, H., Quan, H., & Ghali, W. A. (2006). Dealing with missing data in a multi-question depression scale: A comparison of imputation methods. *BMC Medical Research Methodology*, *6*(1), 57. https://doi.org/10.1186/1471-2288-6-57

Sibbald, B., & Roberts, C. (1998). Understanding controlled trials: Crossover trials. *BMJ*, *316*(7146), 1719–1720. https://doi.org/10.1136/bmj.316.7146.1719

Silva, L. K., Espenship, M. F., Newman, C. A., Blount, B. C., & De Jesús, V. R. (2020). Quantification of Seven Terpenes in Human Serum by Headspace Solid-Phase Microextraction–Gas Chromatography–Tandem Mass Spectrometry. *Environmental Science & Technology*, *54*(21), 13861–13867. https://doi.org/10.1021/acs.est.0c03269

Simkin, J., Ojala, A., & Tyrväinen, L. (2020). Restorative effects of mature and young commercial forests, pristine old-growth forest and urban recreation forest—A field experiment. *Urban Forestry & Urban Greening*, *48*, 126567. https://doi.org/10.1016/j.ufug.2019.126567

Simmons, S., & Estes, Z. (2008). Individual differences in the perception of similarity and difference. *Cognition*, *108*(3), 781–795. https://doi.org/10.1016/j.cognition.2008.07.003

Singh, A. K., Touhara, K., & Okamoto, M. (2019). Electrophysiological correlates of top-down attentional modulation in olfaction. *Scientific Reports*, *9*(1), 4953. https://doi.org/10.1038/s41598-019-41319-6

Song, C., Ikei, H., Kobayashi, M., Miura, T., Li, Q., Kagawa, T., Kumeda, S., Imai, M., & Miyazaki, Y. (2017). Effects of viewing forest landscape on middle-aged hypertensive men. *Urban Forestry & Urban Greening*, *21*, 247–252. https://doi.org/10.1016/j.ufug.2016.12.010

Song, C., Ikei, H., Kobayashi, M., Miura, T., Taue, M., Kagawa, T., Li, Q., Kumeda, S., Imai, M., & Miyazaki, Y. (2015). Effect of Forest Walking on Autonomic Nervous System Activity in Middle-Aged Hypertensive Individuals: A Pilot Study. *International Journal of Environmental Research and Public Health*, *12*(3), 2687–2699. https://doi.org/10.3390/ijerph120302687

Stephens, M. A. C., & Wand, G. (2012). Stress and the HPA axis: Role of glucocorticoids in alcohol dependence. *Alcohol Research: Current Reviews*, *34*(4), 468–483.

Stevens, D. A. (1996). Individual differences in taste perception. *Food Chemistry*, *56*(3), 303–311. https://doi.org/10.1016/0308-8146(96)00027-1

Stigsdotter, U. K., Corazon, S. S., Sidenius, U., Kristiansen, J., & Grahn, P. (2017). It is not all bad for the grey city – A crossover study on physiological and psychological restoration in a forest and an urban environment. *Health & Place*, *46*, 145–154. https://doi.org/10.1016/j.healthplace.2017.05.007

Su, H.-J., Chao, C.-J., Chang, H.-Y., & Wu, P.-C. (2007). The effects of evaporating essential oils on indoor air quality. *Atmospheric Environment*, *41*(6), 1230–1236. https://doi.org/10.1016/j.atmosenv.2006.09.044

Szaszkiewicz, J., Leigh, S., & Hamilton, T. J. (2021). Robust behavioural effects in response to acute, but not repeated, terpene administration in Zebrafish (Danio rerio). *Scientific Reports*, *11*(1), 19214. https://doi.org/10.1038/s41598-021-98768-1

Thayer, J. F., Hansen, A. L., Saus-Rose, E., & Johnsen, B. H. (2009). Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: The Neurovisceral Integration Perspective on Self-regulation, Adaptation, and Health. *Annals of Behavioral Medicine*, *37*(2), 141–153. https://doi.org/10.1007/s12160-009-9101-z

Thayer, J. F., Yamamoto, S. S., & Brosschot, J. F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*, *141*(2), 122–131. https://doi.org/10.1016/j.ijcard.2009.09.543

Thompson, E. R. (2007). Development and Validation of an Internationally Reliable Short-Form of the Positive and Negative Affect Schedule (PANAS). *Journal of Cross-Cultural Psychology*, *38*(2), 227–242. https://doi.org/10.1177/0022022106297301

Trinh, H.-T., Lee, I.-A., Hyun, Y.-J., & Kim, D.-H. (2011). *Artemisia princeps* Pamp. Essential Oil and Its Constituents Eucalyptol and α -terpineol Ameliorate Bacterial Vaginosis and Vulvovaginal Candidiasis in Mice by Inhibiting Bacterial Growth and NF- κ B Activation. *Planta Medica*, *77*(18), 1996–2002. https://doi.org/10.1055/s-0031-1280094

Trumble, B. C., Brindle, E., Kupsik, M., & O'Connor, K. A. (2010). Responsiveness of the reproductive axis to a single missed evening meal in young adult males. *American Journal of Human Biology*, *22*(6), 775–781. https://doi.org/10.1002/ajhb.21079

Tsunetsugu, Y., Lee, J., Park, B.-J., Tyrväinen, L., Kagawa, T., & Miyazaki, Y. (2013). Physiological and psychological effects of viewing urban forest landscapes assessed by

multiple measurements. *Landscape and Urban Planning*, *113*, 90–93. https://doi.org/10.1016/j.landurbplan.2013.01.014

Tsunetsugu, Y., Park, B.-J., Ishii, H., Hirano, H., Kagawa, T., & Miyazaki, Y. (2007). Physiological Effects of Shinrin-yoku (Taking in the Atmosphere of the Forest) in an Old-Growth Broadleaf Forest in Yamagata Prefecture, Japan. *Journal of PHYSIOLOGICAL ANTHROPOLOGY*, *26*(2), 135–142. https://doi.org/10.2114/jpa2.26.135

Ulrich, R. S., Simons, R. F., Losito, B. D., Fiorito, E., Miles, M. A., & Zelson, M. (1991). Stress recovery during exposure to natural and urban environments. *Journal of Environmental Psychology*, *11*(3), 201–230. https://doi.org/10.1016/S0272-4944(05)80184-7

U.S. Census Bureau. (2022). *Tacoma city, Washington Profile*. https://data.census.gov/profile/Tacoma_city,_Washington?g=160XX00US5370000

Vincent, A. J., Choi-Lundberg, D. L., Harris, J. A., West, A. K., & Chuah, M. I. (2007). Bacteria and PAMPs activate nuclear factor κB and Gro production in a subset of olfactory ensheathing cells and astrocytes but not in Schwann cells. *Glia*, *55*(9), 905–916. https://doi.org/10.1002/glia.20512

Walker, H., Jena, A., McEwan, K., Evans, G., & Campbell, S. (2023). Natural Volatile Organic Compounds (NVOCs) Are Greater and More Diverse in UK Forests Compared with a Public Garden. *Forests*, *14*(1), 92. https://doi.org/10.3390/f14010092

Ward Thompson, C., Aspinall, P., Roe, J., Robertson, L., & Miller, D. (2016). Mitigating Stress and Supporting Health in Deprived Urban Communities: The Importance of Green Space and the Social Environment. *International Journal of Environmental Research and Public Health*, *13*(4), 440. https://doi.org/10.3390/ijerph13040440

Watson, A. Y., Bates, R. R., & Kennedy, D. (Eds.). (1988). *Air Pollution, the Automobile, and Public Health* (p. 1033). National Academies Press. https://doi.org/10.17226/1033

White, D., & Burton, A. M. (2022). Individual differences and the multidimensional nature of face perception. *Nature Reviews Psychology*, *1*(5), 287–300. https://doi.org/10.1038/s44159-022-00041-3

White, M. P., Alcock, I., Grellier, J., Wheeler, B. W., Hartig, T., Warber, S. L., Bone, A., Depledge, M. H., & Fleming, L. E. (2019). Spending at least 120 minutes a week in nature is associated with good health and wellbeing. *Scientific Reports*, *9*(1), 7730. https://doi.org/10.1038/s41598-019-44097-3

Wilson, E. O. (1994). *Biophilia: The human bond with other species*. Harvard Univ. Press.

Woo, C. C., Miranda, B., Sathishkumar, M., Dehkordi-Vakil, F., Yassa, M. A., & Leon, M. (2023). Overnight olfactory enrichment using an odorant diffuser improves memory and modifies the uncinate fasciculus in older adults. *Frontiers in Neuroscience*, *17*, 1200448. https://doi.org/10.3389/fnins.2023.1200448

Wyart, C., Webster, W. W., Chen, J. H., Wilson, S. R., McClary, A., Khan, R. M., & Sobel, N. (2007). Smelling a Single Component of Male Sweat Alters Levels of Cortisol in Women. *The Journal of Neuroscience*, *27*(6), 1261–1265. https://doi.org/10.1523/JNEUROSCI.4430-06.2007

Yamin-Pasternak, S., Kliskey, A., Alessa, L., Pasternak, I., & Schweitzer, P. (2014). The Rotten Renaissance in the Bering Strait: Loving, Loathing, and Washing the Smell of Foods with a (Re)acquired Taste. *Current Anthropology*, *55*(5), 619–646. https://doi.org/10.1086/678305

Yoshizawa, T., Tani, Y., Yamaguchi, T., & Sawa, M. (2015). Effects of Inhaled the Cyperi rhizoma and Perillae herba Essential Oil on Emotional States, Autonomic Nervous System and Salivary Biomarker. *Health*, *07*(05), 533–541. https://doi.org/10.4236/health.2015.75063

Yu, C.-P., Lin, C.-M., Tsai, M.-J., Tsai, Y.-C., & Chen, C.-Y. (2017). Effects of Short Forest Bathing Program on Autonomic Nervous System Activity and Mood States in Middle-Aged and Elderly Individuals. *International Journal of Environmental Research and Public Health*, *14*(8), 897. https://doi.org/10.3390/ijerph14080897

Zhang, B., Wang, H., Yang, Z., Cao, M., Wang, K., Wang, G., & Zhao, Y. (2020). Protective effect of alpha-pinene against isoproterenol-induced myocardial infarction through NF-κB signaling pathway. *Human & Experimental Toxicology*, *39*(12), 1596–1606. https://doi.org/10.1177/0960327120934537

Zhang, N., Zhang, L., Feng, L., & Yao, L. (2018). Cananga odorata essential oil reverses the anxiety induced by 1-(3-chlorophenyl) piperazine through regulating the MAPK pathway and serotonin system in mice. *Journal of Ethnopharmacology*, *219*, 23–30. https://doi.org/10.1016/j.jep.2018.03.013

Zhao, Y., Bao, W.-W., Yang, B.-Y., Liang, J.-H., Gui, Z.-H., Huang, S., Chen, Y.-C., Dong, G.-H., & Chen, Y.-J. (2022). Association between greenspace and blood pressure: A systematic review and meta-analysis. *Science of The Total Environment*, *817*, 152513. https://doi.org/10.1016/j.scitotenv.2021.152513

APPENDIX A

Products to avoid 24 hours before forest-sitting session

- Consumer products
  - Scented body lotions, shampoos, conditioners
  - Essential oil treatments of any kind, for example, oils or sprays
  - Air fresheners or diffusers
  - Anything with basil, black pepper, cardamom, cedar, citrus, eucalyptus, juniper, lavender, pine, rosemary, thyme, cloves, mint, or sage scent
  - Products containing tea tree oil
  - Natural insect repellants
  - Vicks® VapoRub™ or similar over-the-counter drugs, rubs, or inhalers
- Cleaning products
  - Any scented cleaning product, except for vinegar, water, or household bleach
  - Anything with basil, black pepper, cardamom, cedar, citrus, eucalyptus, juniper, lavender, pine, rosemary, thyme, cloves, mint, or sage scent
  - Floor wax
  - Turpentine
- Marijuana and e-cigarettes
- Non-steroidal anti-inflammatory drugs (NSAIDs): any non-steroidal anti-inflammatory drugs, including aspirin, ibuprofen (like Motrin® or Advil®), and naproxen sodium (like Aleve®)
- Food and Drink
  - Orange, grapefruit, and any other citrus-based juices (including a squeeze of lemon or lime)
  - Beer, gin, wine, and other alcoholic drinks (including mixers like tonic water, and lemon or lime twists)
  - Beverages flavored with cardamom, juniper, lavender, pine, rosemary, thyme, cloves, mint, or sage
  - Citrus fruits, recipes, or processed foods heavy on the following herbs (dried or fresh): black pepper, basil, caraway, cardamom, coriander, fennel, juniper berry, rosemary, sage, thyme, lavender, cloves; chewing gum or herbal candy or cough drops.

APPENDIX B

Table 2.15. Imputed affect and baseline ln-HF HRV T2 sensitivity analysis results.

Model		Estimate	95% CI	*p*
HRV				
	No Imputation	0.00	(-0.21, 0.20)	.967
	Imputation	0.01	(-0.18, 0.21)	.914
Positive Affect				
	No Imputation	0.70	(-0.37, 1.77)	.21
	Imputation	0.71	(-0.36, 1.77)	.202
Negative Affect				
	No Imputation	-0.16	(-0.43, 0.12)	.265
	Imputation	-0.16	(-0.42, 0.11)	.250
IL-6				
	No Imputation	-0.19	(-0.35, -0.03)	**.046**
	$\frac{LOD}{\sqrt{2}}$ Imputation	-0.18	(-0.34, -0.02)	.051
	Zero Imputation	-0.19	(-0.36, -0.02)	**.050**

Note: Ln-HF HRV, ln high frequency heart rate variability.

Table 2.16. Imputed affect and baseline ln-HF HRV ANOVA comparing full and reduced models.

Model	Model Type	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
Ln-HF HRV								
Imputed	Reduced	296.26	320.42	-141.13	282.26			
	Full	300.11	338.07	-139.06	278.11	4.15	4	.386
Not Imputed	Reduced	266.07	289.60	-126.03	252.07			
	Full	272.12	309.09	-125.06	250.12	1.95	4	.745
Positive Affect								
Not Imputed	Reduced	1280.38	1305.49	-633.19	1266.38			
	Full	1285.45	1324.91	-631.73	1263.45	2.93	4	.569

Model	Model Type	AIC	BIC	Log Likelihood	Deviance	Chisq	df	*p*
Imputed	Reduced	1289.37	1314.50	-637.68	1275.37			
	Full	1294.48	1333.98	-636.24	1272.48	2.89	4	.576
Negative Affect								
Not Imputed	Reduced	575.95	601.06	-280.97	561.95			
	Full	581.35	620.81	-279.68	559.35	2.59	4	.628
Imputed	Reduced	558.57	583.70	-272.28	544.57			
	Full	564.67	604.17	-271.34	542.67	1.89	4	.755

Note: Ln-HF HRV, ln high frequency heart rate variability.

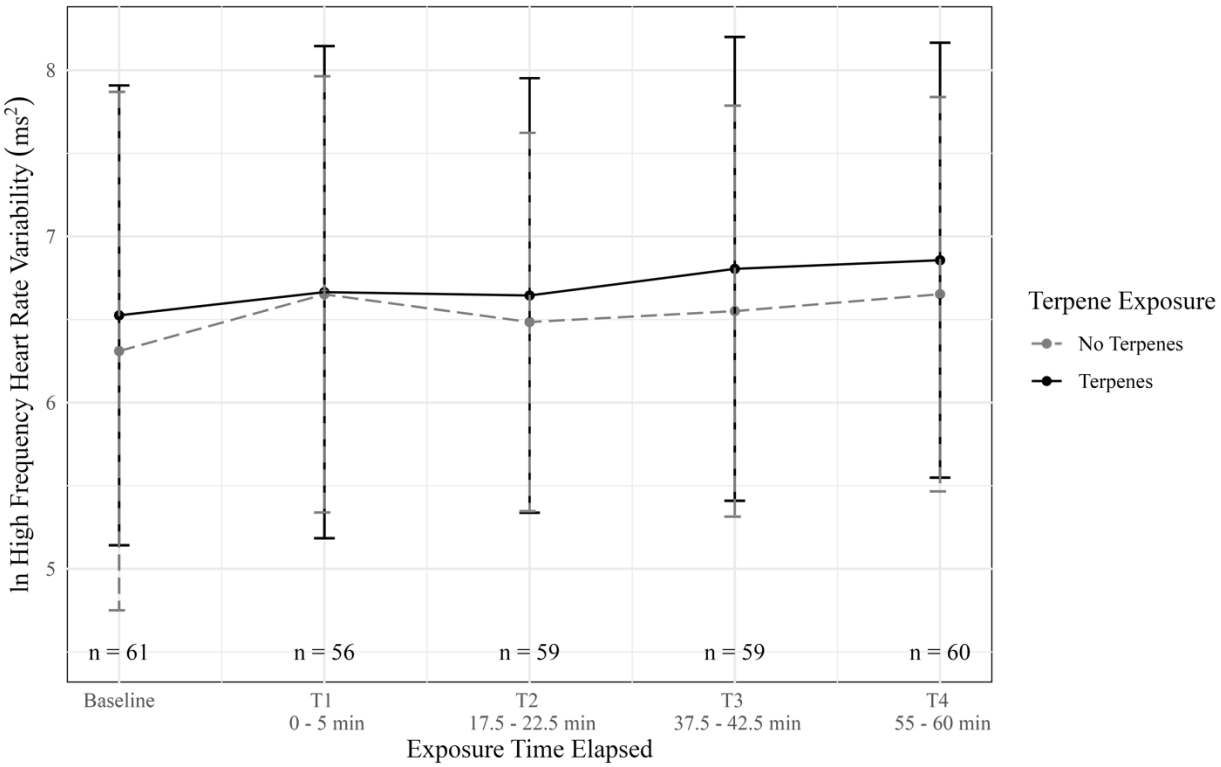

Figure 2.8. ln-HF HRV across time points comparing terpene-off and “terpenes-on” conditions.

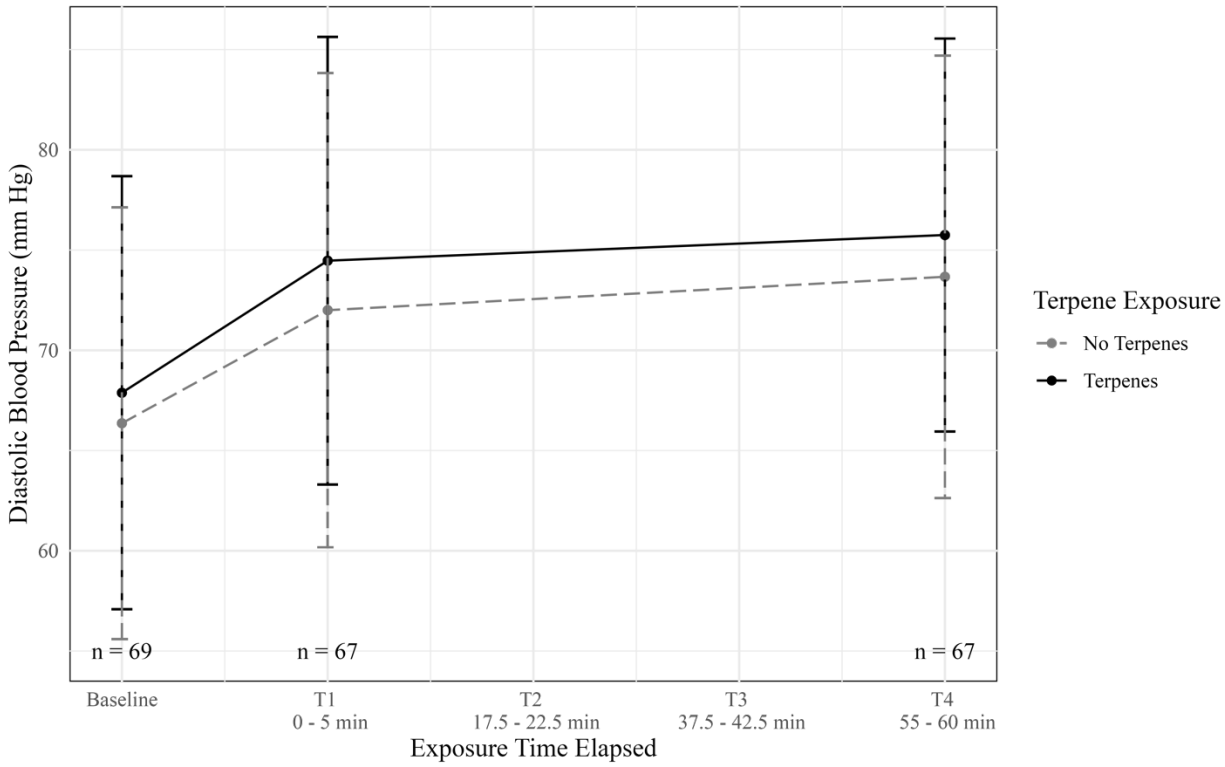

Figure 2.9. DBP across time points comparing terpene-off and ““terpenes-on”” conditions.

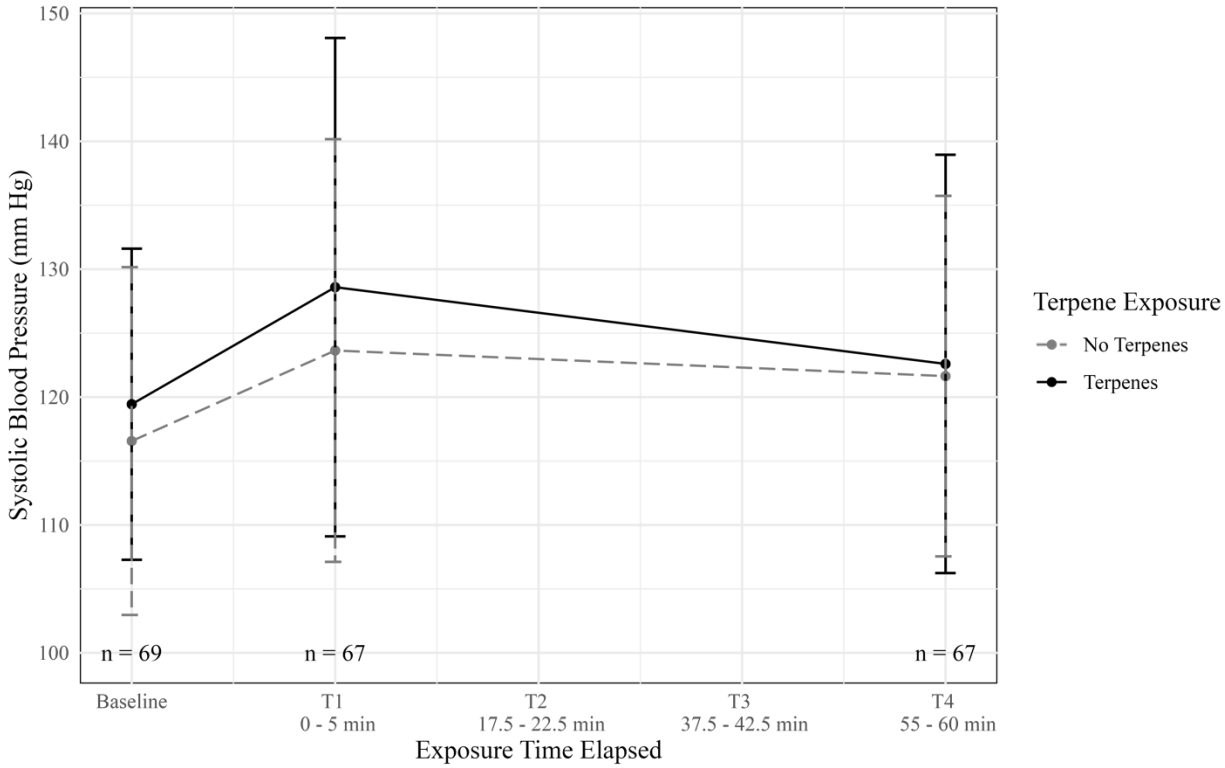

Figure 2.10. SBP across time points comparing terpene-off and “terpenes-on” conditions.

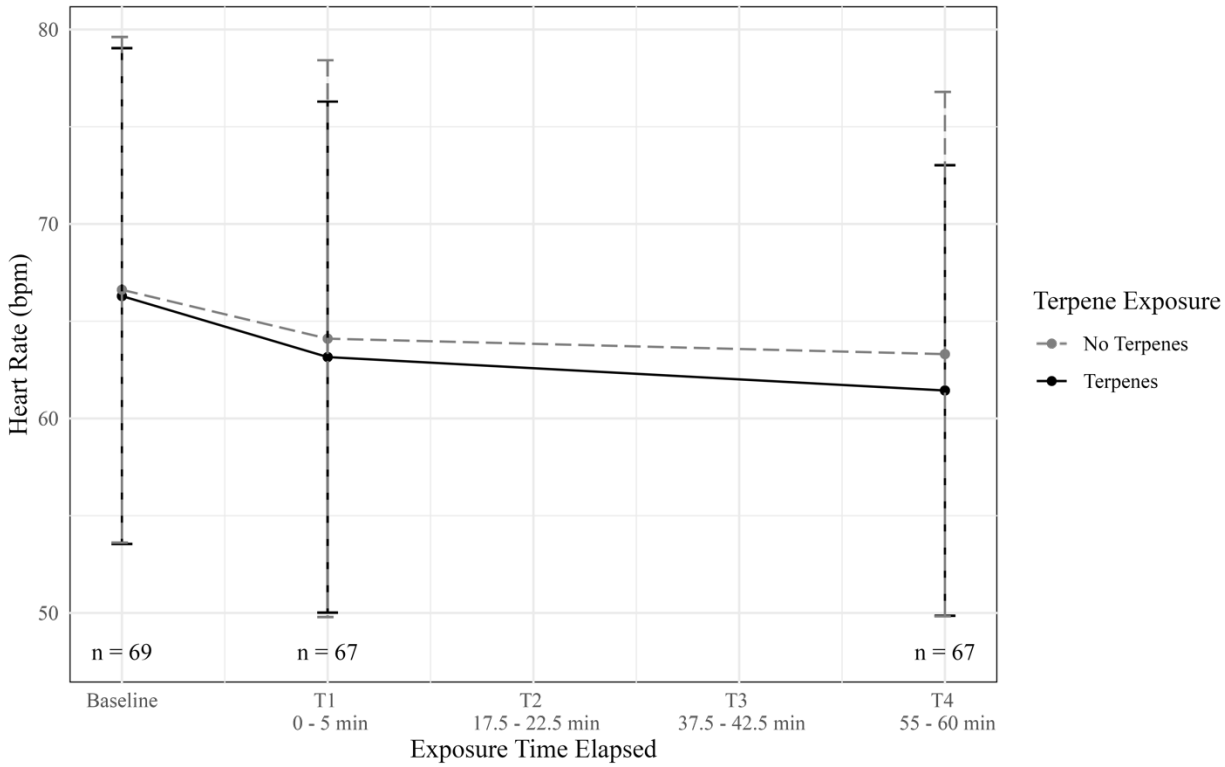

Figure 2.11. HR across time points comparing terpene-off and "terpenes-on" conditions.

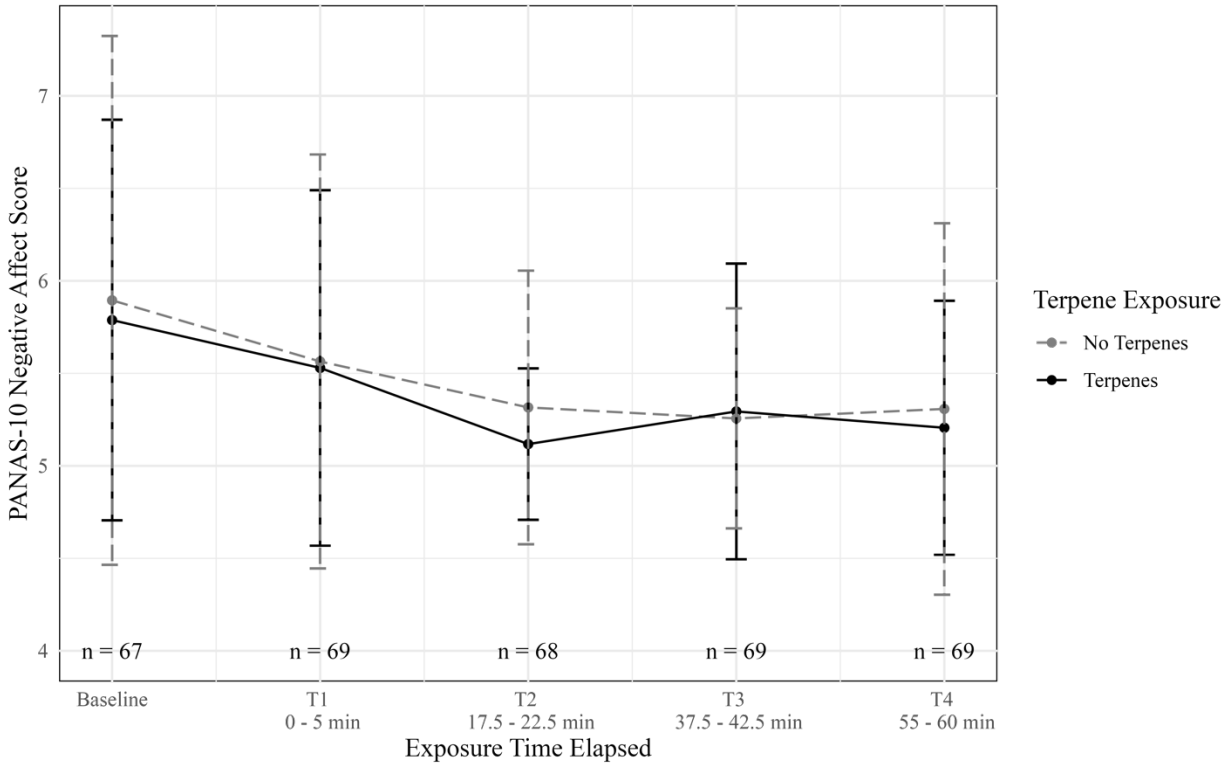

Figure 2.12. Negative affect across time points comparing terpene-off and "terpenes-on" conditions.

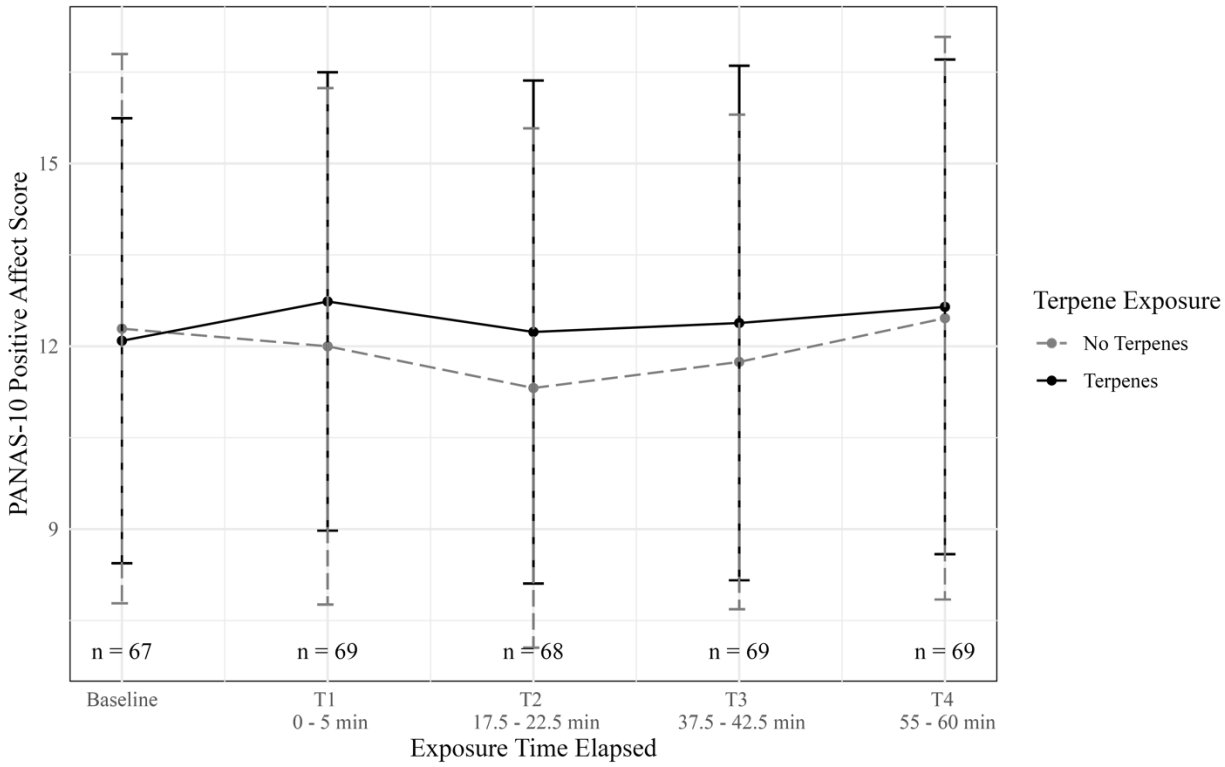

Figure 2.13. Positive affect across time points comparing terpene-off and "terpenes-on" conditions.

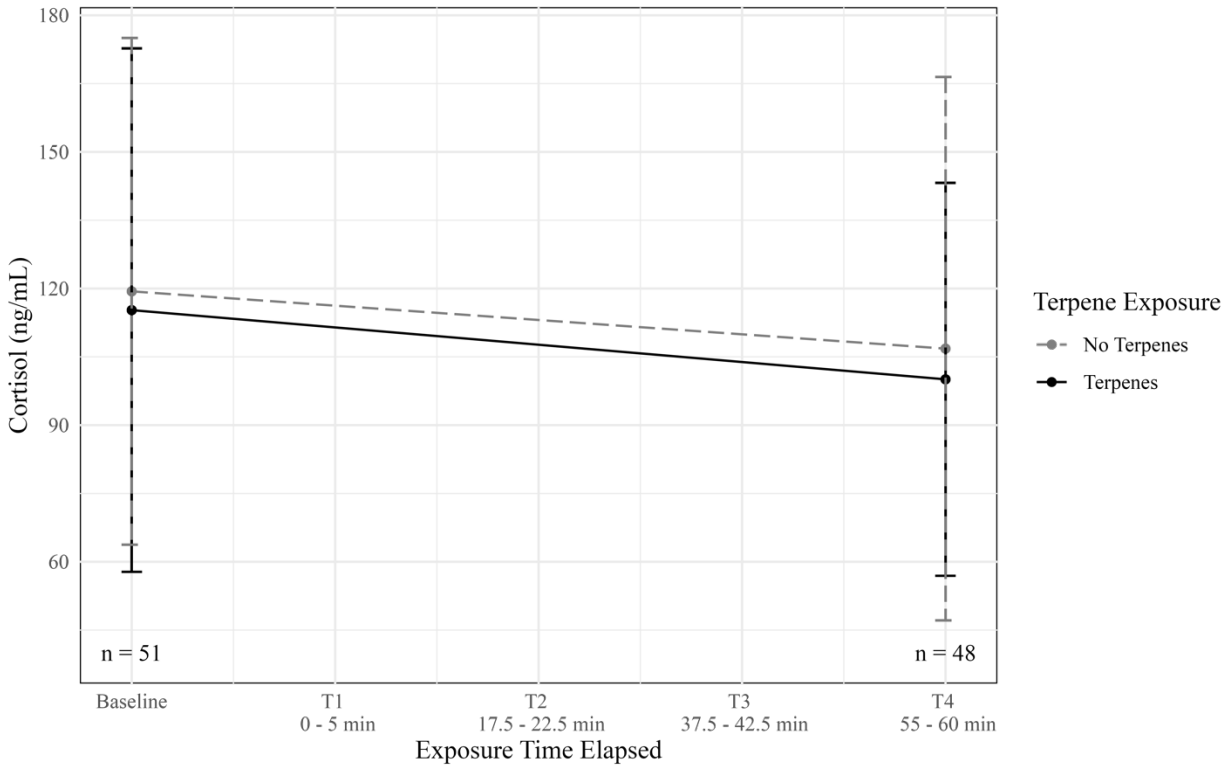

Figure 2.14. Cortisol across time points comparing terpene-off and "terpenes-on" conditions.

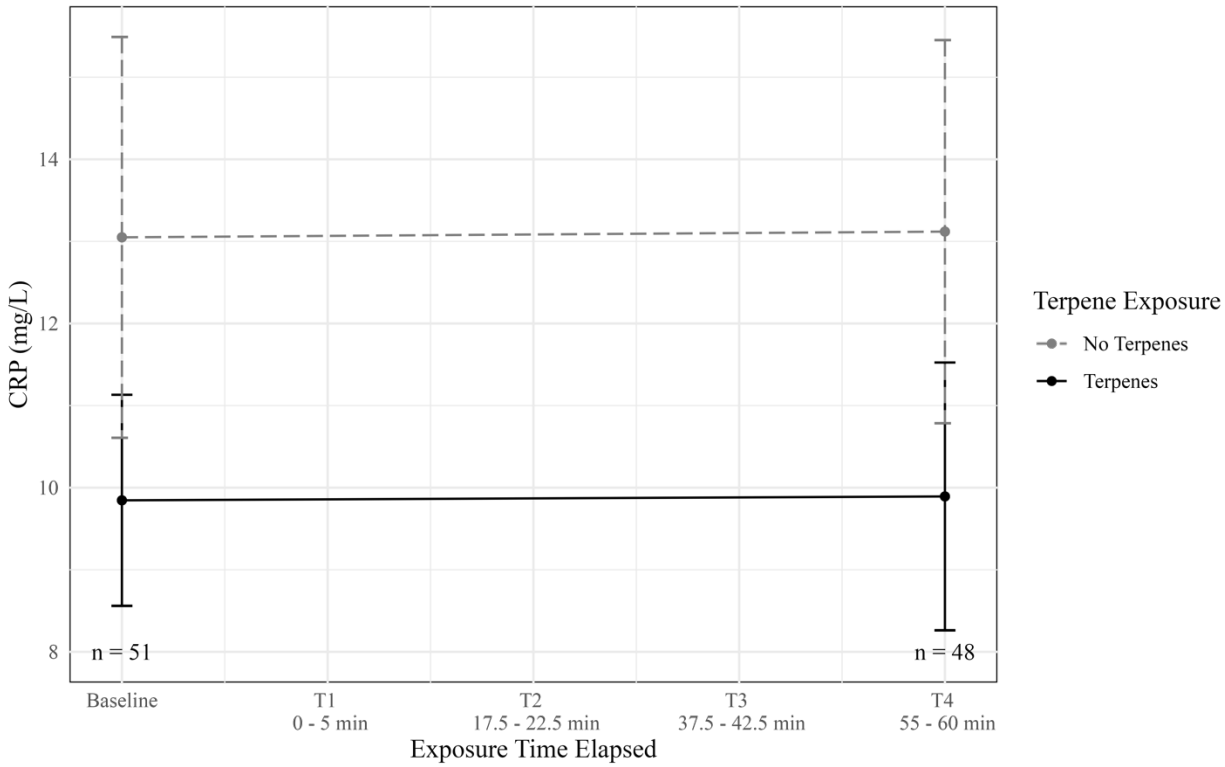

Figure 2.15. CRP across time points comparing terpene-off and "terpenes-on" conditions.

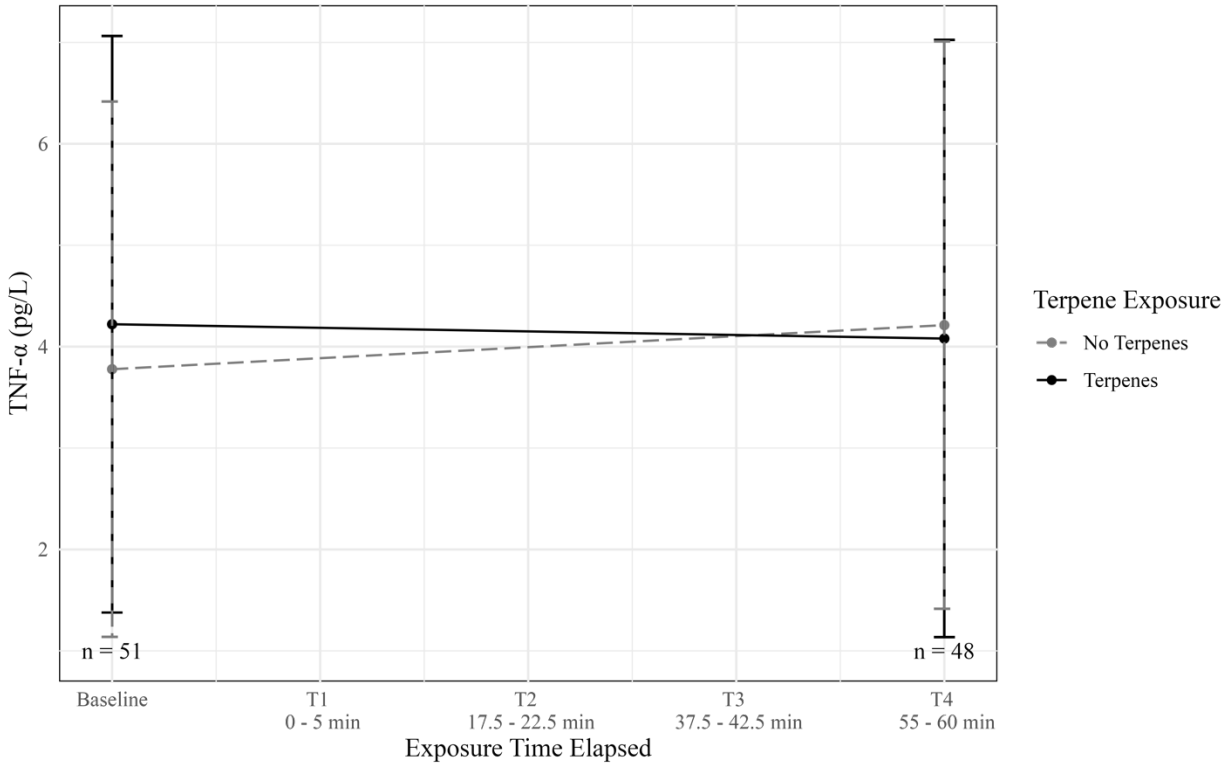

Figure 2.16. TNF-α across time points comparing terpene-off and "terpenes-on" conditions.