# The Impact of Sunlight Variation on Depressive Symptoms Following Treatment for Major Depressive Disorder

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## Abstract

**Introduction:**

Seasonal variation in sunlight has been implicated in the pathogenesis and maintenance of major depressive disorder (MDD), but has not yet been evaluated as a potential moderator of recovery. Given the high rate of recurrence following treatment for depression, there is a need to identify risk factors that contribute to poor long-term prognosis. The present study seeks to examine the relationship between seasonal sunlight and follow-up outcomes for MDD treatment.

**Methods:**

A secondary analysis was conducted on data collected by the NIMH Treatment of Depression Collaborative Research Program. Follow-up data were available from 159 participants who completed the acute treatment phase of the study, which consisted of cognitive behavior therapy (CBT), interpersonal therapy, imipramine, or placebo administered for 16 weeks. Depressive symptom severity, recovery status, and categorical ratings of symptomatology were then measured on four occasions during the 18-month follow-up period. Treatment site-specific sunlight data were collected from the NREL National Solar Radiation Data Base. Multilevel modeling was used to estimate seasonal differences for all outcomes.

**Results:**

Sunlight intensity at the time of patient assessment was significantly inversely associated with the severity of depressive symptoms, and the strength of this relationship decreased over the follow-up period. At the baseline (treatment termination) assessment, a one standard deviation increase in sunlight intensity predicted a 1.83-point reduction on the Hamilton Rating Scale for Depression. Symptom severity was significantly greater during winter sunlight conditions (versus summer) at both the baseline assessment and at the 6-month follow-up. At the baseline

assessment, the effect of winter-versus-summer sunlight was substantial, equivalent to approximately 4.5 points on the HRSD; the effect was reduced to just over two HRSD points at the 6-month assessment. Exploratory analyses revealed that significant seasonal-typical differences in symptom severity were limited to participants who had been assigned to the CBT and placebo conditions. Sunlight was not significantly associated with recovery status or categorical ratings of symptomatology.

**Conclusion:**

Sunlight intensity was inversely associated with depressive symptom severity following psychotherapy, pharmacotherapy, or placebo treatment for depression. This effect persisted for six months post-treatment. Completing treatment during winter-typical sunlight conditions was associated with substantially higher levels of residual depressive symptoms—particularly for participants receiving CBT. Such adverse effects of relative sunlight deprivation could, in turn, increase the risk of negative long-term clinical outcomes, and prolonged or adjuvant treatments for light-deficient patients may be warranted.

*Keywords*: Sunlight, Depression, Follow-up, Symptom Severity

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## Introduction

At non-equatorial latitudes, the intensity and duration of ambient sunlight vary consistently over the course of a year, reaching a peak in summer and a nadir in winter. Recent research suggests that major depressive disorder (MDD)—a highly prevalent disorder that is the leading cause of disability worldwide (World Health Organization, 2017)—may be influenced by this seasonal variation in light exposure. *Seasonal affective disorder* (SAD) was first characterized by Rosenthal et al. (1984) as a syndrome in which depressive episodes recur annually at the same time of year, most often during fall or winter months. Winter-onset SAD appears to be driven by seasonal changes in daylength, resulting in diminished exposure to sunlight duration and intensity (Levitan, 2007).

Notably, seasonal sunlight variation seems to have a meaningful symptomatic impact even on depressed patients who are not characterized by an overt seasonal onset pattern. For example, a long-term, prospective cohort study of 298 individuals with MDD found that the average depressive symptom burden was greatest in the months immediately following the winter solstice (Cobb et al., 2014). Two longitudinal studies of the general population have likewise observed an increase of depressive symptom severity during winter months, although the magnitude of this effect was small, possibly due to the general healthiness of study participants (Harmatz et al., 2000; Kerr et al., 2013). There is also preliminary evidence that seasonal fluctuation of depressive symptoms only occurs at non-equatorial latitudes, where there are meaningful differences in daylength across the year (Friborg, Bjorvatn, Amponsah, & Pallesen, 2012).

Cross-sectional studies also point to a connection between seasonal sunlight variation and depression. A landmark investigation of 8,027 older Irish adults, for example, found higher

levels of depressive symptoms reported during winter months (O'Hare, O'Sullivan, Flood, & Kenny, 2015). Moreover, study participants living in sunnier climates reported less severe depressive symptoms—with each one-hour increase in average daily sunlight associated with a sizable 2.7-point reduction on the Center for Epidemiological Studies Depression Scale (O'Hare et al., 2015). Dominiak, Swiecicki, and Rybakowski (2015) examined eight years of hospitalization records in Poland and observed that admissions for both recurrent and single episode MDD peaked in fall and spring, supportive of a seasonal trend. Two large-scale studies have also found that women giving birth during winter months have an increased risk of developing postpartum depression (Sit, Seltman, & Wisner, 2011; Yang, Shen, Ping, Wang, & Chien, 2011). Likewise, patients with end-stage renal disease, a condition associated with depression, have reported more severe depressive symptoms in winter compared to summer (Afsar & Kirkpantur, 2013).

It is also well-established that experimental manipulation of ambient light affects mood in both animals and humans. Exposure to shortened days has been shown to induce depressive-like behavioral changes in both rodents (Ashkenazy, Einat, & Kronfeld-Schor, 2009) and rhesus macaque monkeys, with the latter providing an animal model similar to humans (Qin et al., 2015). Additionally, although bright-light therapy was initially developed as an intervention for winter-onset SAD (Martensson, Pettersson, Berglund, & Ekselius, 2015; Rohan et al., 2015), it is emerging as an effective and viable treatment for non-seasonal MDD as well (Al-Karawi & Jubair, 2016; Perera et al., 2016).

Taken together, the preceding set of findings implicate seasonal sunlight variation in both the etiology and symptomatic expression of MDD. This hypothesized link is further supported by the physiological impact of sunlight, which interacts with the body through both retinal

stimulation and the absorption of ultraviolet radiation by the skin. Sunlight exposure affects a broad number of physiological pathways implicated in MDD pathophysiology, including circadian rhythms, vitamin D synthesis, neural signaling, and inflammation. As such, dysregulation of these pathways may mediate the effects of seasonal sunlight variation on depressive illness. Figure 1 provides a schematic overview of the aforementioned interrelationships.

**Circadian Rhythms**

Biological processes that follow consistent daily patterns—such as body temperature, cortisol release, and sleep—are known as circadian rhythms. The timing of circadian rhythms is maintained by the suprachiasmatic nucleus (SCN) of the hypothalamus, the primary neural pacemaker in mammals (Brancaccio et al., 2014). Light-related information is transmitted from the retina to the SCN, where it synchronizes intrinsic SCN activity to external environmental demands (Coomans, Ramkisoensing, & Meijer, 2015). Additionally, light-induced SCN activation inhibits the downstream release of melatonin, an important hormone that serves as an indicator of biological night and reciprocally regulates circadian timing and SCN function (Coomans et al., 2015). The SCN responds to both daily *and* seasonal fluctuations in sunlight, thereby permitting seasonal information to be encoded in the form of physiological and behavioral responses (Brancaccio et al., 2014; Coomans et al., 2015). Both duration and intensity of light exposure affect circadian rhythms, the extent of which depends on the time of day during which the exposure takes place (Duffy & Czeisler, 2009).

As the sun rises later during the winter season, light-initiated SCN activity is altered. In winter, less bright sunlight coincides with the critical circadian morning window, during which humans are most sensitive to the phase-advancing effects of light, thereby leading to delayed

circadian synchronization (Duffy & Czeisler, 2009). This pressures biological rhythms to initiate later in the day: left unchecked, the body's endogenous clock would quickly deviate from that of the external environment. Under natural winter lighting conditions, the winter-induced delay in morning synchronization would typically be countered by an earlier and prolonged release of melatonin, as evening melatonin induces circadian rhythm phase advances—i.e. a shift of circadian timing towards earlier in the day (Burke et al., 2013). However, as depicted in Figure 2, modern artificial lighting—which inhibits endogenous melatonin production (Haim & Zubidat, 2015)—has greater overlap with evening darkness during winter, thereby delaying melatonin onset and preventing compensatory phase advances. As a result, individuals exposed to artificial nighttime lighting during winter months can experience a phase delay in circadian rhythms, leading to a biological day/night that is out of sync with the ambient environment (Stothard et al., 2017). In colloquial terms: their "body-clock" is now running behind, often by a matter of hours.

MDD is also associated with similar phase delays (Lewy et al., 2007; Vadnie & McClung, 2017). Depressive symptom severity has been found to correlate with the degree of phase delay in both clinical and community samples (Lewy et al., 2007; Murray, Allen, & Trinder, 2003; Sharkey, Pearlstein, & Carskadon, 2013). Relatedly, delayed temperature rhythms in a small sample of MDD patients were associated with greater severity of anhedonia symptoms (Hasler, Buysse, Kupfer, & Germain, 2010). Sleep phase delay, characteristic of younger ages, has been shown to be greatly exaggerated in young adults with MDD compared to healthy controls (Robillard et al., 2013). Bright light therapy is designed to resolve this circadian dysregulation by inducing circadian phase advances through morning light exposure, with efficacious and fast-acting results (Al-Karawi & Jubair, 2016; Perera et al., 2016).

Seasonal variations in sunlight may also contribute to MDD through impairment of sleep-related mechanisms. Sleep disruption, namely insomnia or hypersomnia, is a cardinal feature of MDD (American Psychiatric Association, 2013). One recent study found that 9 in 10 participants who had met criteria for a major depressive episode in the past year had also experienced significantly impaired sleep (Soehner, Kaplan, & Harvey, 2014). Insomnia often precedes MDD onset, which suggests that sleep difficulties contribute causally to MDD pathogenesis (Johnson, Roth, & Breslau, 2006; Ohayon & Roth, 2003). Indeed, individuals with insomnia are twice as likely to develop depression later in life compared to individuals without impaired sleep (Baglioni et al., 2011). Both insufficient and excessive sleep are related to future depression risk (Zhai, Zhang, & Zhang, 2015). In rats, chronic sleep restriction has been shown to induce anhedonia-like behavior (Novati, Hulshof, Koolhaas, Lucassen, & Meerlo, 2011), as well as neurological alterations similar to those seen in depression (Novati et al., 2008).

The sleep/wake cycle is strongly influenced by circadian processes originating from the SCN (Archer & Oster, 2015). For example, endogenous melatonin release, suppressed by light-induced SCN activation, promotes and regulates sleep (Claustrat, Brun, & Chazot, 2005). As a result, circadian disruption can lead to profoundly disordered sleep, including sleep fragmentation, delayed or advanced sleep onset/offset, and continuously shifting sleep/wake cycles (Abbott, Reid, & Zee, 2015). Sudden circadian misalignment, such as that caused by daylight saving time, can decrease sleep efficiency for up to a week (Y. Harrison, 2013). There is evidence that sleep patterns vary of the course of the year in response to seasonal changes in sunlight. A small longitudinal study of older Icelandic adults found that daylength significantly predicted sleep duration, with shorter days leading to extended sleep (Brychta et al., 2016). In extreme northern and southern latitudes, prolonged absence of sunlight during winter is

associated with both disrupted sleep and delayed circadian rhythms (Chen et al., 2016; Friborg et al., 2012; Friborg, Rosenvinge, Wynn, & Gradisar, 2014). Furthermore, a survey of over 43,000 Norwegian adults found that insomnia symptoms were more likely to be reported in February compared to August (Sivertsen, Overland, Krokstad, & Mykletun, 2011).

In addition to phase delays and disrupted sleep, other circadian alterations have been observed in MDD, further supporting the idea that circadian dysregulation is a primary feature of this disorder. Melatonin, cortisol, and adrenocorticotropic hormone release have been found to be disrupted in individuals with MDD (Cizza et al., 2012; S. X. Li et al., 2013). Rhythms related to physical activity, light exposure, and body temperature have also been found to be altered in depressed individuals (Avila Moraes et al., 2013). Fragmentation and desynchronization of circadian rhythms are associated with greater severity of depressive symptoms (Hasler et al., 2010; Luik et al., 2015; Luik, Zuurbier, Hofman, Van Someren, & Tiemeier, 2013). Animal models of depression also display circadian dysregulation. Mice administered a learned helplessness procedure showed concomitant increases in depressive-like behavior and misalignment of circadian processes in mood-associated brain regions (Landgraf, Long, & Welsh, 2016). Prenatal stress also has been shown to cause disrupted circadian functioning and increased depressive-like behavior later in life—importantly, the altered circadian processes were observed *prior* to the onset of depression (Spulber et al., 2015).

Taken together, there is strong evidence that circadian dysfunction—as evidenced by disruptions in hormones and sleep processes—is closely related to MDD. In fact, circadian dysfunction may represent a risk factor for depressive illness. Specific variations in core circadian clock genes are associated with an increased risk of MDD and certain combinations of polymorphisms seem to exert additive genetic risk (Lavebratt, Sjoholm, Partonen, Schalling, &

Forsell, 2010; Soria et al., 2010). Furthermore, circadian gene overexpression has been observed in individuals with a history of depression, reflecting altered transcriptional processes even during disease remission (Gouin et al., 2010). It is possible that individuals with pre-existing circadian dysfunction are particularly susceptible to either winter-induced circadian phase delays or the resulting effects, and therefore more vulnerable to MDD.

**Vitamin D**

Vitamin D is a fat-soluble vitamin synthesized in the skin during exposure to ultraviolet radiation. Few food sources naturally contain vitamin D, and although supplements are becoming increasingly available, sunlight exposure remains the primary source of vitamin D for humans. In non-equatorial northern and southern latitudes, vitamin D production is severely diminished during winter months, since little ultraviolet radiation is able to reach the earth's surface and trigger the necessary biosynthetic processes (Wacker & Holick, 2013). Observational studies consistently find that vitamin D levels follow a yearly cycle tied to the intensity of available sunlight. A large-scale cross-sectional analysis of 148,821 adults from the northern U.S. found that participants examined in winter months were more likely to be vitamin D deficient than participants examined in any other season (Rosecrans & Dohnal, 2014). A meta-analysis found that athletes, particularly those from more extreme latitudes, were more likely to have inadequate vitamin D levels during winter months (Farrokhyar et al., 2015). Pregnant Slovenian women were also found to have significantly lower vitamin D levels, as well as a higher risk of severe vitamin D deficiency, in December compared to September (Dovnik et al., 2014). A longitudinal observational study of Turkish office workers found that vitamin D significantly decreased from summer to winter—moreover, nearly all the observed workers were vitamin D deficient in the winter (Cinar, Harmanci, Yildiz, & Bayraktar, 2014). Similar results

have been observed across various populations, further supportive of a seasonal vitamin D pattern (Eloi et al., 2016; Hintzpeter, Mensink, Thierfelder, Muller, & Scheidt-Nave, 2008; Nanri et al., 2011).

Emerging evidence suggests that insufficient vitamin D may play a role in MDD pathogenesis, potentially through dysregulation of mood-related neurological processes (Patrick & Ames, 2015). A meta-analysis of three longitudinal cohort studies revealed that individuals with low levels of vitamin D had significantly increased risk of developing depression compared to healthy controls (Anglin, Samaan, Walter, & McDonald, 2013). Similarly, Robinson et al. (2014) found that pregnant women with low vitamin D were more likely to develop postpartum depression. The Netherlands Study of Depression and Anxiety examined vitamin D levels in 2,981 depressed and healthy participants over the course of two years (Milaneschi et al., 2014). Low vitamin D was associated with diagnosis of a depressive disorder, as established by psychiatric interview, at both baseline and follow-up. Additionally, for currently depressed participants, lower levels of vitamin D were associated with greater depressive symptom severity (Milaneschi et al., 2014). Similarly, in a study of healthy young women, lower vitamin D3 at the beginning of the study was associated with more severe depressive symptoms five weeks later (Kerr et al., 2015). Low vitamin D is also associated with depressive episodes in older men (Almeida, Hankey, Yeap, Golledge, & Flicker, 2015). On the other hand, several meta-analytic reviews examining the use of vitamin D supplementation for the treatment of depression have arrived at mixed results (G. Li et al., 2014; Shaffer et al., 2014; Spedding, 2014). However, it should be noted that these reviews found few studies to date that have included individuals with clinically-elevated depressive symptoms. Indeed, there is preliminary evidence that vitamin D

supplementation is an efficacious treatment in clinically depressed populations (Shaffer et al., 2014).

In sum, vitamin D synthesis is dependent upon exposure to ultraviolet radiation, and it is therefore affected by seasonal sunlight availability. There is extensive evidence that vitamin D deficiency is prevalent during winter in non-equatorial latitudes. As insufficient vitamin D is associated with an increased risk of MDD, this pathway represents another potential mechanism by which seasonal sunlight contributes to MDD.

**Serotonin**

Serotonin is a monoamine neurotransmitter that helps regulate numerous emotional and behavioral processes. Dysfunction within serotonin circuitry is strongly implicated in the pathophysiology of MDD (Kuhn, Popovic, & Pezawas, 2014). Serotonin has been proposed to inhibit the activation of thoughts with negative affective valence, meaning that decreased serotonin activity exacerbates perceived punishments and attenuates perceived rewards (Dayan & Huys, 2008). Neuroimaging and pharmacological studies further support the proposed link between serotonin activity and MDD. Rhythms related to the synthesis and degradation of serotonin have been found to be disrupted in depressive illness (Salomon & Cowan, 2013). Selective serotonin reuptake inhibitors (SSRIs), a primary form of treatment for MDD, increase extracellular serotonin levels by inhibiting serotonin transporter (5-HTT) activity (Fakhoury, 2016). Serotonin transporter proteins help control serotonin activity by returning released serotonin to the presynaptic neuron; in general, increased 5-HTT function results in decreased synaptic serotonin (Jonassen & Landro, 2014). Interestingly, two meta-analyses have found that 5-HTT levels are *reduced* in individuals with MDD, compared to healthy controls, which may be due to compensatory down-regulation of 5-HTT expression following periods of chronically

reduced serotonin availability (Gryglewski, Lanzenberger, Kranz, & Cumming, 2014; Kambeitz & Howes, 2015). Combined with evidence that direct manipulation of 5-HTT activity impacts serotonin levels (i.e. antidepressants), these findings suggest that depressive pathology is influenced by reciprocal activity within the serotonin/5-HTT feedback loop.

Cerebral 5-HTT activity displays clear seasonal patterns which may contribute to MDD. Several human imaging studies have found that 5-HTT function varies over the course of the year, with 5-HTT availability greatest during fall and winter months (Buchert et al., 2006; Praschak-Rieder, Willeit, Wilson, Houle, & Meyer, 2008; Ruhe, Booij, Reitsma, & Schene, 2009). Additionally, the density of 5-HTT has been found to negatively correlate with duration of sunlight, suggesting greater reuptake—and therefore decreased synaptic serotonin—during shorter days (Praschak-Rieder et al., 2008). Exposure to bright light, compared to placebo, has also been shown to decrease 5-HTT binding during winter months, further supporting the link between inadequate sunlight and dysregulated 5-HTT (S. J. Harrison et al., 2015). While the precise causal mechanisms remain unknown, S. J. Harrison et al. (2015) proposed that light exposure influences 5-HTT expression through retina-mediated signaling pathways. Notably, seasonal 5-HTT variation was not observed in participants recruited from a subtropical climate with little seasonal change in sunlight (Cheng et al., 2011). Given evidence that 5-HTT overexpression results in increased depressive-like behaviors in mice (Mouri et al., 2012), it is possible that winter upregulation of 5-HTT contributes to MDD.

As would be expected, seasonal fluctuations in 5-HTT activity seem to impact cerebral serotonin availability. Previous investigation of community samples revealed that serotonin turnover is lowest when assessed during fall and winter months, which may reflect a decrease of neuronal serotonin release (G. W. Lambert, Reid, Kaye, Jennings, & Esler, 2002; Luykx et al.,

2012). Additionally, this rate of turnover is directly correlated with the amount of bright sunlight on the day of study, suggesting that serotonergic activity is acutely affected by environmental light conditions (G. W. Lambert et al., 2002). A multi-year longitudinal study of northern European participants similarly found that serotonin turnover followed seasonal patterns—this turnover was also correlated with severity of depressive symptoms (Luykx et al., 2013). Serotonin receptor binding in mood-related brain regions has also been shown to be positively correlated with both duration and intensity of recent sunlight (Spindelegger et al., 2012). A cross-sectional imaging study with adult males also observed lower serotonin receptor binding on days with a shorter duration of sunlight (Matheson et al., 2015). Finally, rodents exposed to short-day conditions (eight hours of light per day) display lower serotonin levels than long-day controls (Goda et al., 2015). Given the observed increase in 5-HTT during winter months, as well as findings that low levels of serotonin typically lead to down-regulation of 5-HTT (Hagan, McDevitt, Liu, Furay, & Neumaier, 2012), it is likely that seasonal variations in sunlight first alter 5-HTT expression, which in turn affects the availability of serotonin.

Genotype sequencing data helps clarify the relationship between seasonal sunlight and serotonergic activity. Kalbitzer et al. (2010) found that 5-HTT binding potential was only associated with daylength for individuals who carried at least one short allele (S-carriers) in the promoter region of the 5-HTT gene (5-HTTLPR)—this allele is associated with reduced expression of 5-HTT and accounts for approximately 25-43% of all 5-HTTLPR alleles, depending upon the studied population (Odgerel, Talati, Hamilton, Levinson, & Weissman, 2013). Similarly, seasonal change in 5-HTT binding potential has previously been shown to be moderated by 5-HTTLPR genotype, with S-carriers displaying greater change (Mc Mahon et al., 2016). The 5-HTTLPR short allele is also associated with decreased serotonin turnover during

winter, possibly reflective of greater 5-HTT activity and serotonin reuptake (Luykx et al., 2013). Of note, this genotype is strongly associated with MDD. Phenotypes associated with the 5-HTTLPR short allele are characterized by dysregulated emotional processing and increased emotional lability (Jonassen & Landro, 2014). The 5-HTTLPR gene moderates the relationship between MDD and stress (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010), and S-carriers are more likely to develop MDD under stress (Karg, Burmeister, Shedden, & Sen, 2011). The presence of a homozygotic 5-HTTLPR short allele genotype is also associated with decreased efficacy of SSRI treatment (Porcelli, Fabbri, & Serretti, 2012; Serretti, Kato, De Ronchi, & Kinoshita, 2007).

In conclusion, existing evidence suggests that the presence of a 5-HTTLPR short allele results in dysregulated 5-HTT expression in response to decreasing sunlight. As a result, increased winter 5-HTT expression causes greater serotonin reuptake, thereby inducing widespread serotonin deficiencies in mood-related areas of the brain and disrupting emotional processing. Additionally, serotonin is needed for melatonin synthesis, meaning that diminished serotonin levels could disturb circadian processes and further exacerbate MDD risk.

**Dopamine and Orexin**

Dopamine, another monoamine neurotransmitter, is centrally involved in various brain functions such as locomotion, motivation, and mood regulation. Dysfunction within dopamine pathways is associated with core depressive symptoms such as anhedonia and amotivation (Grace, 2016). Further, dopamine deficiencies have been observed in the postmortem brains of individuals with MDD (Klimek, Schenck, Han, Stockmeier, & Ordway, 2002). Downregulation of dopaminergic activity induced by chronic stress is associated with the manifestation of depressive-like states in animal models (Grace, 2016). Finally, the therapeutic effects of

antidepressant drugs may be partially due to their ability to act upon the dopaminergic system (Leggio et al., 2013).

As with serotonin, there is evidence that dopaminergic activity follows seasonal patterns related to sunlight. Two neuroimaging studies have found that dopamine synthesis is *higher* in human brains scanned in fall or winter, compared to those scanned in spring or summer (Eisenberg et al., 2010; Kaasinen, Jokinen, Joutsa, Eskola, & Rinne, 2012). On the other hand, a small study found fewer dopamine neurons in the brains of people who died in the winter versus the summer (Aumann et al., 2016). Also, low exposure to sunshine in a subtropical region is associated with reduced availability of dopamine receptors (Tsai et al., 2011). In rodents, experimental manipulation of day length has been shown to induce species-specific alterations in dopamine levels (Goda et al., 2015). For example, exposure to either dim light or short-day length conditions has been shown to reduce hypothalamic dopaminergic neurons in diurnal grass rats, compared to bright light conditions (Deats, Adidharma, & Yan, 2015). These somewhat conflicting results regarding the dopamine-light relationship may be due to the diverse roles the neurotransmitter plays in the brain; unlike serotonin, there exist multiple independent dopamine pathways that each fulfill a unique neural role (Grace, 2016). It is also important to point out that the connection between dopamine and sunlight exposure has yet to be firmly established, inasmuch as other studies have failed to find seasonal variations in dopamine synthesis (Luykx et al., 2012; Luykx et al., 2013).

Some recent work suggests that the neuropeptide orexin—also implicated in MDD pathology (Nollet & Leman, 2013)—may mediate the impact of sunlight on dopamine. In grass rats, the effect of light on monoaminergic systems has been shown to be dependent upon activation of orexin neurons (Adidharma, Leach, & Yan, 2012). Additionally, under bright light

housing conditions, administration of an orexin receptor antagonist has been shown to reduce the number of dopamine neurons in the hypothalamus of grass rats (Deats et al., 2015). These findings are strengthened by research demonstrating that orexin is a potent regulator of dopamine signaling and enhances dopamine neuron activity (Prince, Rau, Yorgason, & Espana, 2015). Importantly, orexin also seems to be affected by changes in ambient light. In humans, orexin levels are positively correlated with day length, and have been shown to be at their lowest during the winter months (Boddum, Hansen, Jennum, & Kornum, 2016). Furthermore, a recent study found that dim light conditions reduce orexinergic signaling in grass rats while simultaneously increasing depressive-like behaviors (Deats, Adidharma, Lonstein, & Yan, 2014).

In conclusion, dopamine and orexin represent additional promising candidates by which seasonal sunlight may contribute to MDD. Both neural signaling pathways display seasonal changes and can be modulated by experimental shifts in lighting conditions. In particular, orexin has been shown to play a prominent role in light-induced neural activation. However, published findings to date remain equivocal, and additional research is needed to clarify the impact of dopamine and orexin on seasonal depressive symptoms.

**Inflammation**

Inflammation, a core component of the native immune response, is a vital process by which the body responds to injury, infection, or stress. Excessive inflammation—such as that induced by pro-inflammatory drugs—can elicit affective and behavioral changes characteristic of MDD, such as depressed mood, anhedonia, heightened fatigue, sleep disruption, and altered appetite (Capuron & Miller, 2004; Jokela, Virtanen, Batty, & Kivimaki, 2016). Two meta-analysis have found that inflammatory biomarkers are elevated in patients with MDD (Dowlati et al., 2010; Howren, Lamkin, & Suls, 2009). Inflammation may mediate the relationship between

stress and MDD: social, environmental, and perceived threats can induce inflammation by triggering the release of pro-inflammatory cytokines, and this up-regulated inflammatory activity in turn can interfere with neural processes (Slavich & Irwin, 2014). Finally, MDD frequently co-occurs with inflammation-related disorders, including rheumatoid arthritis and inflammatory bowel disease (Slavich & Irwin, 2014).

The immune system is influenced by both visible light and ultraviolet radiation (Roberts, 2000). The neuroendocrine system mediates the effects of visible light on immune function (Weil, Borniger, Cisse, Abi Salloum, & Nelson, 2015), whereas ultraviolet radiation can actually induce immunosuppression and protect against chronic inflammation (Damian, Matthews, Phan, & Halliday, 2011; Norval, 2011). Many mammals display seasonal patterns of immunity, typically with elevated immune processes, like inflammation, during short winter days (Weil et al., 2015). In humans, expression of pro-inflammatory genes has been found to be increased during winter months (Dopico et al., 2015). A large-scale cross-sectional study of U.S. children and adults found that C-reactive protein (CRP)—an important marker of inflammatory states—was elevated in winter-spring, compared to summer-fall (Liu & Taioli, 2015). Similar winter-spring elevation in CRP levels have been observed in healthy Korean adults (Sung, 2006).

Given the fundamental role that inflammation plays in human physiology, it is unsurprising to see that it interacts with other pathways implicated in MDD seasonality. Increased production of vitamin D following exposure to ultraviolet radiation helps suppress inflammatory processes (Milliken et al., 2012). Also, immune cells often express circadian clock genes and follow daily rhythms (Labrecque & Cermakian, 2015). Winter-induced changes in circadian cortisol rhythms are also believed to induce a pro-inflammatory state, as well as an exacerbated inflammatory response to stressors (Pierre, Schlesinger, & Androulakis, 2016).

Moreover, melatonin is immunomodulatory—under short day conditions enhanced melatonin production attenuates inflammatory processes (Weil et al., 2015). However, disrupted melatonin expression, such as that caused by exposure to artificial lighting during winter (Stothard et al., 2017), may preclude this therapeutic effect and lead to damaging levels of inflammation. Interestingly, inflammation can reciprocally inhibit synthesis of melatonin and its precursor, serotonin. Pro-inflammatory molecules cause tryptophan to be converted to kynurenine pathway products, instead of serotonin and melatonin (Maruani et al., 2018). As such, excessive inflammation could further contribute to seasonal depressive symptoms by impairing serotonergic activity and melatonin-regulated circadian function.

**Psychological Factors**

By affecting mood and other physiological processes, seasonal changes in sunlight may also influence depressogenic psychological processes. Cognitive models of depression posit that negative mood states can activate vulnerability factors, such as dysfunctional thinking, which in turn increase the risk of future depressive episodes (Persons & Miranda, 1992). Neurobiological studies support this contention—negative mood states activate mood-congruent negative cognitions which are persistent in individuals at risk for depression (Wang, Ongur, Auerbach, & Yao, 2016). One particularly relevant study found that dysfunctional attitudes and negative automatic thoughts—types of vulnerability factors—peaked in winter for participants with seasonal patterns of depression *as well as* non-depressed low-seasonality controls, consistent with a widespread increase in maladaptive cognitions during winter months (Rohan et al., 2011). Winter-induced negative cognitions may therefore contribute to the onset and maintenance of depressive episodes, particularly among vulnerable individuals.

Seasonal changes in social contact may also contribute to depression. There is evidence that people engage in less social activity during winter months (Basnet et al., 2016; Kurata & Nomura, 2012). Social support, such as emotional or instrumental assistance, protects against depression by promoting general well-being and limiting the negative consequences of stress (Gariépy, Honkaniemi, & Quesnel-Vallee, 2016; Rueger, Malecki, Pyun, Aycock, & Coyle, 2016). Importantly, time spend with friends and family is positively correlated with perceived social support, which in turn is negatively correlated with depression symptomatology (Peirce, Frone, Russell, Cooper, & Mudar, 2000). Decreased social activity during winter could therefore promote depression by weakening social support networks. Although it is not yet clear that such seasonal effects are driven by winter-based reductions in sunlight, per se, the findings to date are at least consistent with the hypothesis.

**Long-Term Outcomes**

Most patients treated for MDD will experience relapse or recurrence[1] regardless of treatment modality, even if they are maintained on prophylactic intervention following an initial phase of recovery (Kuyken et al., 2015; Peselow, Tobia, Karamians, Pizano, & IsHak, 2015; Rush et al., 2006). In light of this dispiriting result, practitioners and researchers are increasingly defining treatment effectiveness not merely as the attainment of an acute-but-short-lived period of symptom relief, but rather as the experience of sustained long-term *recovery*. Presumably, the development of more efficacious treatment strategies—i.e., those that bring about higher rates of sustained recovery and that thereby attenuate the burden of chronic depressive illness—will depend in part on the successful identification of specific risk factors and pathogenic processes that trigger the recurrence of depressive symptoms following acute treatment.

Various factors associated with long-term depression treatment outcomes have been previously identified, including personality traits (Bukh, Andersen, & Kessing, 2016), number of previous depressive episodes (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010), and relationship status (Johansson, Lundh, & Bjarehed, 2015). Residual symptomatology, or the level of depressive symptoms following some form of recovery, has also been shown to predict recurrence rates and psychosocial functioning following treatment (Hardeveld et al., 2010; Xiao et al., 2018). Residual symptoms are common following standard treatment for depression and often include domains such as sleep disturbance, appetite disturbance, and fatigue (Nierenberg et al., 2010; Xiao et al., 2018). There is some evidence that continuing to target these symptoms with psychotherapy or pharmacotherapy improves long-term recovery rates (Israel, 2010; Paykel, 2008).

Perhaps surprisingly, despite strong support for its impact on depressive pathophysiology, seasonal sunlight has not yet been considered as a potential moderator of long-term recovery in MDD. No extant study has assessed the relationship between sunlight availability and outcomes such as depressive symptom severity or remission rates following MDD treatment. Accordingly, the purpose of this study is to investigate the potential influence of seasonal sunlight on long-term outcomes among patients in the landmark National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program (TDCRP; Elkin et al., 1989). A previous analysis of the TDCRP dataset found that seasonal sunlight had a small, statistically significant effect on acute treatment response: patients beginning treatment in the spring, compared to the fall, had a greater reduction of depressive symptoms (Ilardi et al., 2019 – manuscript in preparation). Furthermore, this seasonal difference was greatest for patients receiving cognitive-behavior therapy (and minimal for those in three other treatment conditions),

suggesting that seasonal sunlight may interact with treatment modality to influence acute symptom response. The present study aims to expand upon this initial finding by examining the relationship between sunlight exposure and depressive symptomatology among TDCRP patients during an 18-month assessment window immediately following acute treatment termination.

**Hypotheses**

1. Sunlight intensity at the time of assessment will be significantly associated with the severity of depressive symptoms observed during treatment follow-up, with symptom severity being greatest during winter-typical sunlight conditions.
2. Winter-typical sunlight conditions will confer a decreased likelihood of sustained MDD recovery across the 18-month follow-up window.
3. Seasonal sunlight will be significantly associated with categorical ratings of symptomatology—ranging from asymptomatic to fully syndromal—with ratings of greater severity more likely to occur during winter-typical sunlight conditions.

## Methods

**Sources of Data**

The National Institute of Mental Health Treatment of Depression Collaborative Research Program (TDCRP) was a large multisite randomized controlled trial comparing the efficacy of four treatments for major depressive disorder (MDD): imipramine, interpersonal therapy, cognitive behavior therapy (CBT), and placebo control. A full description of the study methodology has been previously reported (Elkin, Parloff, Hadley, & Autry, 1985; Elkin et al., 1989). In brief, adults who were diagnosed with major depressive disorder, based on Research Diagnostic Criteria (Spitzer, Endicott, & Robins, 1978), and scored 14 or greater on a modified

17-item Hamilton Rating Scale for Depression (Hamilton, 1967) during screening were eligible to participate in the TDCRP study.

In total, 250 participants were randomized into the four previously mentioned treatment groups. Each treatment was then administered for 16 weeks, during which depressive symptoms were assessed at 4-week intervals, including 16-week treatment termination. Follow-up assessments took place at 6, 12, and 18 months. The follow-up phase of the TDCRP study took place under naturalistic conditions, meaning that participants were not subjected to any experimental controls. As such, participants were free to pursue and receive additional treatments during the follow-up period.

The present analyses used follow-up data from participants who completed the treatment phase of the TDCRP study. As such, the presented findings apply to individuals who complete treatment for MDD—it should be noted that treatment dropout is associated with specific sociodemographic and psychological characteristics (Edlund et al., 2002), as well as a lack of treatment efficacy (Power et al., 2012). Outcomes from treatment end and follow-up assessments were included, meaning that analyses spanned four time points over a 1.5-year period. Depressive symptom severity, recovery status, categorical symptom levels, treatment condition, and other participant-specific covariates were extracted from the existing TDCRP dataset.

All data regarding sunlight was obtained from the NREL National Solar Radiation Data Base. This is a public U.S. government-maintained database that contains solar and meteorological data for geographic regions across the country.

## Measures

**Hamilton Rating Scale for Depression (HRSD).** The HRSD (Hamilton, 1967) is a 17-item clinician-administered measure assessing depression severity. Higher scores indicate greater severity of depression. The HRSD has adequate reliability and validity (Bagby, Ryder, Schuller, & Marshall, 2004). It is also highly sensitive to symptom change following MDD treatment (M. J. Lambert, Hatch, Kingston, & Edwards, 1986). In the TDCRP study, HRSD assessments were made by independent clinical evaluators who were all Ph.D. level psychologists with extensive training in diagnostic assessments (Elkin et al., 1985). Additionally, clinical evaluators were kept blind to treatment conditions. For the present analyses, HRSD scores were scaled to have a mean of zero and a standard deviation of one, so that results reflected a standardized change in symptom severity.

**Longitudinal Interval Follow-up Evaluation (LIFE).** The LIFE (Keller et al., 1987) is a comprehensive semi-structured interview designed to assess the longitudinal course of depressive and other psychiatric disorders. Retrospective weekly ratings of symptoms, called psychiatric service ratings (PSRs), are obtained for the previous six months and used to determine the presence or absence of various affective disorders, according to the Research Diagnostic Criteria (RDC; Spitzer et al., 1978). PSRs range from one (no residual symptoms) to six (meeting RDC criteria with psychotic symptoms or extreme impairment). In the TDCRP study, the LIFE was administered at the 6-, 12-, and 18-month follow-up assessments. For the purposes of this study, the recovery outcome was defined as weekly ratings of one or two for at least eight weeks preceding the follow-up measurement date. This definition is consistent with a previous analysis of TDCRP follow-up outcomes (Shea et al., 1992). Finally, the current PSR at the time of assessment was used as the categorical rating of symptomatology.

**Global Horizontal Irradiance (GHI).** The predictor variables sunlight intensity and sunlight change were obtained using GHI, which is the total amount of solar radiation that falls upon a surface horizontal to the ground. GHI in kilowatt hours per meter squared ($kWh/m^2$) was extracted from the NREL National Solar Radiation Data Base based upon the date and treatment site for each individual participant outcome assessment. Sunlight intensity was calculated as the average daily GHI for the two weeks preceding each outcome administration. Sunlight change was calculated as the difference between the average daily GHI for the most recent two-week period before the outcome administration (i.e., weeks one and two) and that of the preceding two-week period (i.e., weeks three and four).

**Data analysis**

Data analyses were performed using R software (R Core Team, 2016). Cases with missing data for predictor or outcome variables were removed from the final analyses. All hypotheses were tested using random intercept models. Initially, separate baseline models, including only intercept and time parameters, were estimated to determine if time was best represented with polynomial trends. The different models were compared using leave-one-out cross-validation (Vehtari, Gelman, & Gabry, 2017) and revealed that including quadratic or cubic time trends decreased model fit. Therefore, only linear time parameters were included in all final models. Standardized HRSD scores were modeled using truncated normal regression. MDD recovery status was modeled using logistic regression, and PSRs were modeled using ordinal logistic regression. Because the LIFE was not administered at treatment termination, models of recovery status and PSRs included only three measurement points (6, 12, and 18 months) per participant.

For all three study outcomes (HRSD score, recovery status, and PSR), full models were estimated including time, sunlight intensity, and sunlight change (as main effects and all possible interactions) as predictor variables of interest. Treatment condition was also included as a predictor variable, both as a main effect as well as an interaction with all variables related to sunlight intensity and sunlight change. Psychiatric comorbidities (personality and non-personality disorders), previous MDD history, current treatment status, marital status, and income were included as covariates. Baseline recovery status was also included as a covariate for the analyses of recovery status and PSR.

**Estimation.** Model parameters were estimated using a Bayesian Markov chain Monte Carlo (MCMC) sampler. Weakly-informative priors were chosen due to their flexibility when used with complex models (Simpson, Rue, Riebler, Martins, & Sørbye, 2017). Scaling parameters were given half-Cauchy priors with a mean of zero and a standard deviation of one. Random intercepts were modeled using non-centered parameterizations, with hierarchical and participant-specific parameters given normal priors with means of zero and standard deviations of one (Betancourt & Girolami, 2015). Given the availability of information regarding the impact of sunlight intensity on acute outcomes from the TDCRP study (Ilardi et al., 2019 – manuscript in preparation), priors for regression coefficients involving sunlight intensity were based on these previous findings. Time was given a normal prior with a mean of zero and a standard deviation of one. Sunlight intensity was given a normal prior with a mean of -0.15 and a standard deviation of one. The interaction between sunlight intensity and time was given a normal prior with a mean of zero and a standard deviation of one. Finally, the interactions between sunlight intensity and the treatment conditions were given normal priors with means of 0.15 and standard deviations of one. All other regression coefficients were given regularizing

horseshoe priors in order to account for the large number of main effects and interactions included as predictor variables (Bhadra, Datta, Polson, & Willard, 2015).

**Implementation and diagnostics.** For each model, a total of 5,500 samples of parameter estimates were drawn from four independent MCMC chains. The initial 1,500 samples from each chain were discarded to allow for chain warm-up and adaptation. Several steps were then taken to assess model convergence and stability (Gelman et al., 2013; Kruschke, 2015). First, the sampling chains for each parameter were visually inspected via trace plots to verify appropriate chain mixing. Parameters were then checked to ensure that all potential scale reduction factors were less than 1.1 (Kruschke, 2015). Finally, simulated data and residuals were compared to observed data to verify appropriate model fit (Gelman et al., 2013).

**Seasonal outcomes.** In addition to regression coefficients, exploratory follow-up outcomes (HRSD scores, recovery status, and PSR) were compared across seasonal sunlight conditions. Prototypical sunlight conditions for spring, summer, fall, and winter were obtained by extracting average sunlight intensity and change values—for the two weeks preceding the corresponding solstice or equinox—across all three sites over the course of the original TDCRP study. These light values were used with the regression models to estimate conditional outcomes for each season. Winter and summer outcomes were then compared to further explore the effects of sunlight intensity, whereas fall and spring outcomes were compared to examine the effects of sunlight change. Regression coefficients and seasonal comparisons were considered statistically significant if their 95% credible interval (CI) excluded zero.

## Results

Data were available from 159 unique participants[2] who completed study treatment and were assessed at least once during treatment cessation or the 18-month follow-up window. For

each measurement occasion, data were available from the following numbers of participants: treatment end ($n$ = 155), six months ($n$ = 148), twelve months ($n$ = 143), and 18 months ($n$ = 147). Sample characteristics are presented in Table 1. There were no statistically significant differences across treatment groups with regards to symptom severity, recovery status, sex, race, or age.

**Symptom Severity**

Results for the analysis of symptom severity are presented in Table 2. The interaction between sunlight intensity and time was statistically significant ($p$ = .014), as was the main effect for sunlight intensity ($p$ = .003). These findings reveal that depressive symptom severity increased as sunlight intensity decreased, and that this effect attenuated over time within the 18-month follow-up window. Aggregating across treatment conditions (Table 3) revealed that a one standard deviation decrease in sunlight intensity was associated with a 0.32 standard deviation increase in symptom severity, equivalent to 1.83 points on the HRSD, at follow-up baseline. The actual rate of sunlight change was not associated with symptom severity as either a main effect or interaction. There was some indication that sunlight intensity interacted with treatment condition; however, this interaction was statistically insignificant.

In order to aid interpretation of model results, the standardized differences in symptom severity between winter and summer sunlight conditions were also estimated (Table 4). Overall, the estimated difference in symptom severity between winter and summer sunlight conditions was greatest immediately following treatment cessation (Figure 3). Although the aforementioned interaction between sunlight and treatment condition did not achieve statistical significance in the primary regression models, seasonal treatment-specific effects of sunlight were observed in these analyses contrasting typical winter-versus-summer sunlight conditions.

There were statistically significant differences for the placebo condition at follow-up baseline, as well as the CBT condition at both baseline and the 6-month follow-up, with depressive symptom severity greater during winter months (Figure 4). Seasonal sunlight was not associated with depressive symptom severity at 12 or 18 months, nor for interpersonal therapy or imipramine treatment conditions at any time point. Symptom severity did not differ between fall and spring sunlight conditions for any treatment condition.

**Recovery Status**

Complete data for current recovery status and psychiatric service ratings (PSRs) were available for 149 participants. Results for analysis of recovery status are presented in Table 5. Overall, neither sunlight intensity nor change had a significant effect on the odds of recovery during long-term follow-up. However, when comparing the odds of recovery during winter and summer (Table 6), statistically significant differences were observed for the imipramine group at 12-month and 18-month follow-up periods. These findings indicate that, long after completing treatment, participants who had received imipramine were more likely to be fully recovered during winter as compared to summer. It should be noted that the wide credible intervals observed for the estimated odds ratios indicate a large degree of uncertainty; in other words, there is a high probability that the values for these estimates range from small to extremely large. The lack of statistically significant regression coefficients further calls into question the validity of these findings. Additional research is needed to firmly establish whether individuals who received imipramine over a year ago are more likely to be recovered during winter months. The use of larger sample sizes would also help reduce the uncertainty around the estimated odds ratios. No other treatments displayed seasonal differences in recovery status at any measurement

time point. Additionally, the odds of recovery did not differ between fall and spring light conditions for any treatment at any time point.

### Categorical Ratings of Symptomatology

Results for the analysis of categorical symptom ratings are presented in Table 7. Neither sunlight intensity nor sunlight change were associated with a likelihood of greater ratings of symptom severity during follow-up. Furthermore, the odds of greater symptom ratings did not differ between winter and summer, nor fall and spring, sunlight conditions (Table 8).

## Discussion

In this retrospective analysis of follow-up data for a sizeable sample of depression treatment completers, I observed a significant inverse association between sunlight intensity and symptom severity following treatment cessation. As hypothesized, lower levels of sunlight intensity were linked to more severe depressive symptoms. This effect was moderated by time, as it diminished monotonically over the duration of the 18-month follow-up window.

The overall magnitude of the observed relationship between sunlight intensity and symptom severity was substantial. At the baseline assessment (treatment termination), the estimated difference on the Hamilton Rating Scale for Depression (HRSD) between winter-typical and summer-typical sunlight conditions was 0.79 standard deviations, or 4.51 points. This is more than twice the size of the standardized mean difference in observed HRSD outcomes between patients treated with antidepressants versus placebo (~0.30), as determined by a recent comprehensive meta-analysis of 522 randomized controlled pharmacotherapy trials (Cipriani et al., 2018). This sunlight-linked effect on symptom severity (HRSD score) also exceeds the influential criterion for *clinical significance* established by the United Kingdom's National Institute of Clinical Excellence (NICE), operationalized as an effect of at least three

points on the HRSD (National Institute for Clinical Excellence, 2004). This study's observed sunlight effect at the six-month follow-up was 0.40 standard deviations (2.28 HRSD points), which, although smaller than the baseline effect, was still slightly greater than the average advantage of antidepressants over placebo during acute treatment (Cipriani et al., 2018). These findings suggest that sunlight intensity plays a meaningful role in the process of recovery from depression.

The presence of heightened post-treatment depressive symptoms during typical North American winter sunlight conditions has important clinical implications. Following treatment for depression, many patients continue to experience residual symptoms, even after achieving clinical remission (Kennedy, Foy, Sherazi, McDonough, & McKeon, 2007; Xiao et al., 2018). Such persistent symptoms are associated with negative long-term outcomes, including increased risk of attempted suicide, episodic recurrence, and impaired social functioning (Kennedy et al., 2007; Romera et al., 2014). Patients with residual depressive symptoms at treatment termination are more likely than asymptomatic patients to experience relapse (Judd et al., 1998). Indeed, residual symptomatology appears to be one of the most important predictors of depression recurrence available to clinicians (Hardeveld et al., 2010), and interventions that focus upon specifically targeting and treating these residual symptoms have been shown to reduce rates of relapse and recurrence (Paykel, 2008). Identifying the factors that contribute to the burden of residual symptomatology could, therefore, carry the potential to enhance long-term depression treatment outcomes. The results from the present study indicate that seasonal variations in sunlight intensity may be one such factor. This contention is strengthened by findings that sleep disturbance, which can be exacerbated by seasonal sunlight variation, is a common residual symptom domain (Nierenberg et al., 2010; Xiao et al., 2018). Thus, addressing any potential

winter-related depressive symptoms following treatment—for example, through the use of a therapeutic light box (Perera et al., 2016)—could both enhance functioning and decrease the risk of episodic recurrence.

Although research examining the utility of residual symptomatology in predicting extended long-term outcomes for depression treatment is limited, one relevant study suggests that predictive utility is greatest for clinical outcomes measured within a few years of treatment completion. Kennedy and Paykel (2004) found that, while residual symptoms predicted recurrence risk over a 2-year follow-up period, this predictive power was lost when the follow-up window was lengthened—perhaps because a substantial majority of participants experienced another depressive episode over the extended follow-up window, regardless of the presence of initial residual symptoms (Kennedy & Paykel, 2004). Accordingly, residual symptoms may be most strongly associated with negative outcomes early in the post-treatment period. Per the results of the present study, the optimal time to identify and treat residual depressive symptoms—at least those associated with prolonged sunlight deprivation—appears to be within the first six months following standard depression treatment.

The diminishing relationship between sunlight intensity and symptom severity over time in the present study could be due to the naturalistic design of the follow-up period. At the baseline (treatment termination) assessment, when the observed effect of sunlight intensity was strongest, participant homogeneity was fairly high. All participants had just completed the 16-week study protocol and most had responded favorably, experiencing either full remission or a significant reduction in depressive symptoms. However, throughout the 18-month follow-up window, participants were subject to an array of highly variable external factors that may have introduced heterogeneity and thereby overshadowed any effects of seasonal sunlight variation.

One such uncontrolled factor was treatment-seeking behavior. The proportion of participants who received any additional treatment—presumably to address residual or re-emerging symptoms (or even complete depression recurrence)—rose steadily over the course of follow-up, from 28.9% at six months to 51.6% at eighteen months. Because a strong relationship existed between sunlight intensity and symptom severity in the early follow-up period, it is quite possible that depressive symptoms arising from sunlight deprivation increased the likelihood of subsequent treatment-seeking behavior, which in turn helped ameliorate those very symptoms. This hypothesis, if valid, could explain why sunlight-linked differences in symptom severity were weaker during the later (12-month and 18-month) follow-up assessments.

Although no significant interaction between sunlight intensity and treatment condition was found in the primary study analysis—perhaps due to limited group sample sizes—substantial treatment-specific seasonal differences were detected in subsequent exploratory analyses. All treatment groups followed the same general pattern: symptom differences associated with winter-typical versus summer-typical sunlight conditions were greatest at treatment termination and then shrank over time during the follow-up. However, these seasonal sunlight contrasts were only statistically significant for the CBT (at both baseline and six months) and placebo (baseline only) groups. The magnitudes of these symptomatic differences (based on sunlight contrasts) were quite large, ranging from 0.88 to 1.29 standard deviations on the HRSD (equivalent to approximately 5.02 to 7.37 HRSD points), with participants in the CBT group showing the greatest seasonal variation.

Why might sunlight exert a more pronounced effect for patients who receive CBT? One possible mediator of the observed effect is patient activity level. A major component of CBT is behavioral activation, in which patients reduce their use of avoidance behaviors and to increase

their participation in pleasurable activities, such as exercise and social events (Kanter et al., 2010). Even when utilized as a monotherapy, the behavioral activation component of CBT has been shown to be an effective treatment of depressive symptoms (Ekers et al., 2014; Mazzucchelli, Kane, & Rees, 2010). Presumably, such behavioral activation frequently entails a distinct increase in time spent outside, where patients are able to benefit from direct exposure to any ambient sunlight. After all, the therapeutic potential of a sunny day will largely be wasted on those who remain inside.

On the other hand, many of the behaviors targeted by behavioral activation are also influenced by seasonal variables other than mere sunlight availability. For example, a systematic review encompassing 291,883 participants from eight studies found that people engaged in less overall physical activity during winter months (Tucker & Gilliland, 2007). Seasonal variations in social activity have also been detected in various clinical and non-clinical populations (Basnet et al., 2016; Kurata & Nomura, 2012). As such, winter-specific environmental conditions, such as cold weather, may act as a barrier to behavioral activation, thereby diminishing the effectiveness of CBT for depression during winter months. This consideration could also help explain why patients who received interpersonal therapy and imipramine were relatively unaffected by sunlight intensity in the present study, inasmuch as these treatments do not include an explicit focus on activity participation.

If winter weather does indeed interfere with the successful implementation of behavioral activation techniques, then CBT protocols might benefit from an increased focus on specific strategies to boost winter activity levels. In fact, a recent modification of CBT for seasonal affective disorder has been shown to effectively reduce winter-related depressive symptoms in a clinical community sample (Rohan et al., 2015). Within this revised treatment framework,

behavioral activation is focused on increasing patient participation in *winter-specific* activities to help them move out of "hibernation mode" (Rohan, 2008). The protocol's promising preliminary results suggest that directly targeting winter-induced inactivity—either during standard CBT treatment or as a maintenance therapy during follow-up—may help attenuate residual depressive symptoms. In addition to behavioral activation, another consideration is the use of bright light therapy as a season-specific adjuvant treatment. Bright light therapy has received extensive support as an effective treatment for patients with both seasonal and non-seasonal depression (Martensson et al., 2015; Perera et al., 2016). Additionally, bright light therapy is relatively safe and can be self-administered by patients within their homes (Terman & Terman, 2005). As such, it represents another tool that clinicians can use to target winter-related residual depressive symptoms on a case-by-case basis.

It is less clear why participants in the placebo condition also displayed heightened sensitivity to sunlight variation at the start of the follow-up window. One potential explanation involves the nature of the placebo response in clinical trials for depression. Gueorguieva, Mallinckrodt, and Krystal (2011) reanalyzed data from seven randomized controlled trials that included 2,515 patients receiving either placebo or antidepressant treatment. They found that patients receiving placebo displayed a response trajectory that, after an initial steep decrease in symptom severity, flattened off more quickly than the response trajectory of patients treated with antidepressants (Gueorguieva et al., 2011). Accordingly, the beneficial effects of active treatments appear to persist longer into treatment than those of placebo. Given that the follow-up window for the present study began at the end of 16-week treatment period, it is quite possible that ambient outdoor sunlight exposure was the most prominent specific therapeutic factor acting upon the placebo group at that time. Mean symptom severity levels were also higher for the

placebo group at follow-up baseline, in comparison with other treatments, potentially allowing greater opportunity for sunlight to exert a therapeutic effect.

No association was observed between seasonal variations in sunlight and recovery status or psychiatric service ratings. Notably, as defined in this study, both of these outcomes captured levels of symptom severity that typically exceeded residual symptomatology. Participants were considered to be recovered even with the presence of some residual depressive symptoms (Shea et al., 1992), and four of the six psychiatric ratings measured by the LIFE required moderate-to-extreme impairment (Keller et al., 1987). The present findings suggest that while sunlight intensity may affect the severity of residual depressive symptoms, it is not necessarily related to movement across *discrete severity categories*, such as the transition from fully syndromal major depressive disorder to partial or full remission. This finding is not entirely surprising, especially because only follow-up outcomes for treatment completers were examined in these analyses—most participants had already achieved recovery or a significant reduction in symptoms by this point in the study. Still, analysis of acute treatment data for the same participants found that seasonal differences in depressive symptoms did not emerge until treatment end (Ilardi et al., 2019 – manuscript in preparation), further supporting the idea that sunlight intensity is related primarily to residual depressive symptomatology.

**Limitations and Future Directions**

A major limitation of this study is the fact that data were only available for ambient sunlight conditions at each treatment site, rather than the amount of direct sunlight exposure actually received by each patient. On average, adults spend a majority of their waking hours inside under dim to moderate lighting conditions (Scheuermaier, Laffan, & Duffy, 2010). It is almost certain that participants were exposed to much less natural sunlight than captured by this

study, which may have weakened the observed relationship between sunlight and depressive symptoms. The use of individual light monitoring technology, such as wearable light sensors, would provide higher-quality data and likely improve estimation of sunlight-related effects. Furthermore, this study was correlational in nature, and thus did not attempt to establish a causal effect of sunlight on depressive symptomatology. As discussed previously, it is possible that the observed findings were driven by other seasonal variables, such as temperature, rather than sunlight itself. Future analyses could aim to account for such factors through either methodological or statistical controls.

Another limitation is that, due to the continuous enrollment during the acute treatment phase, follow-up assessments took place throughout the year, rather than during specific seasonal windows. While this methodology allowed for a general assessment of the relationship between sunlight and depressive symptoms, it meant that fewer participants were assessed during the times of year when seasonal sunlight differences are most pronounced (e.g., midsummer or midwinter). It is likely that the limited observational data available during extreme winter or summer sunlight conditions also attenuated this study' ability to detect sunlight-linked clinical effects.

A final limitation worth noting concerns the sample size of this study. Although data were available from 159 treatment completers, treatment-specific samples sizes only ranged from 37 to 47 participants in each of the four treatment modalities, which may have increased the uncertainty of related estimates. Rather large sample sizes—larger than that of the present study—are also needed to provide robust estimation of higher order interactions (Heo & Leon, 2010), which means this study was likely underpowered to detect all desired effects. Future

research should aim to replicate the present study's analyses using larger datasets, perhaps by combining results from multiple trials.

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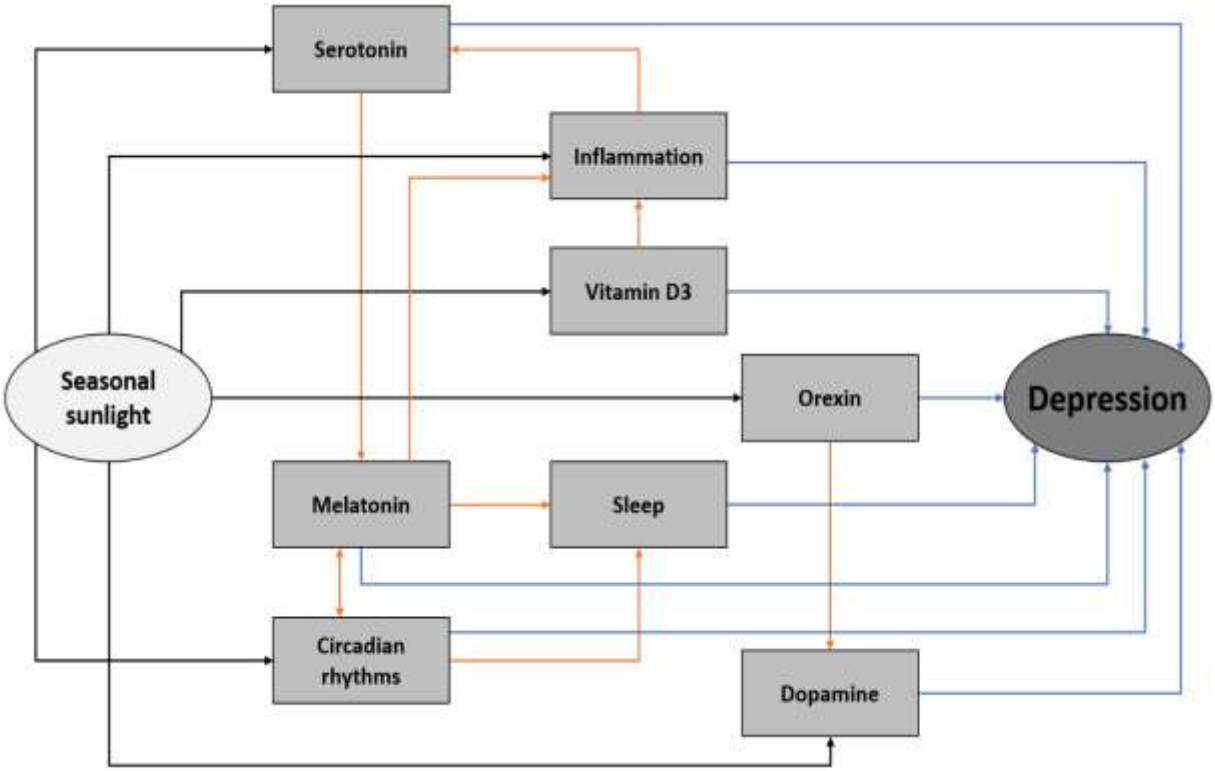


***Figure 1.*** **Schematic overview of the physiological pathways linking seasonal sunlight to depression.** Black arrows depict pathways directly affected by seasonal sunlight. Red arrows depict reciprocal and mediational pathways. Blue arrows depict pathways implicated in depressive pathology.

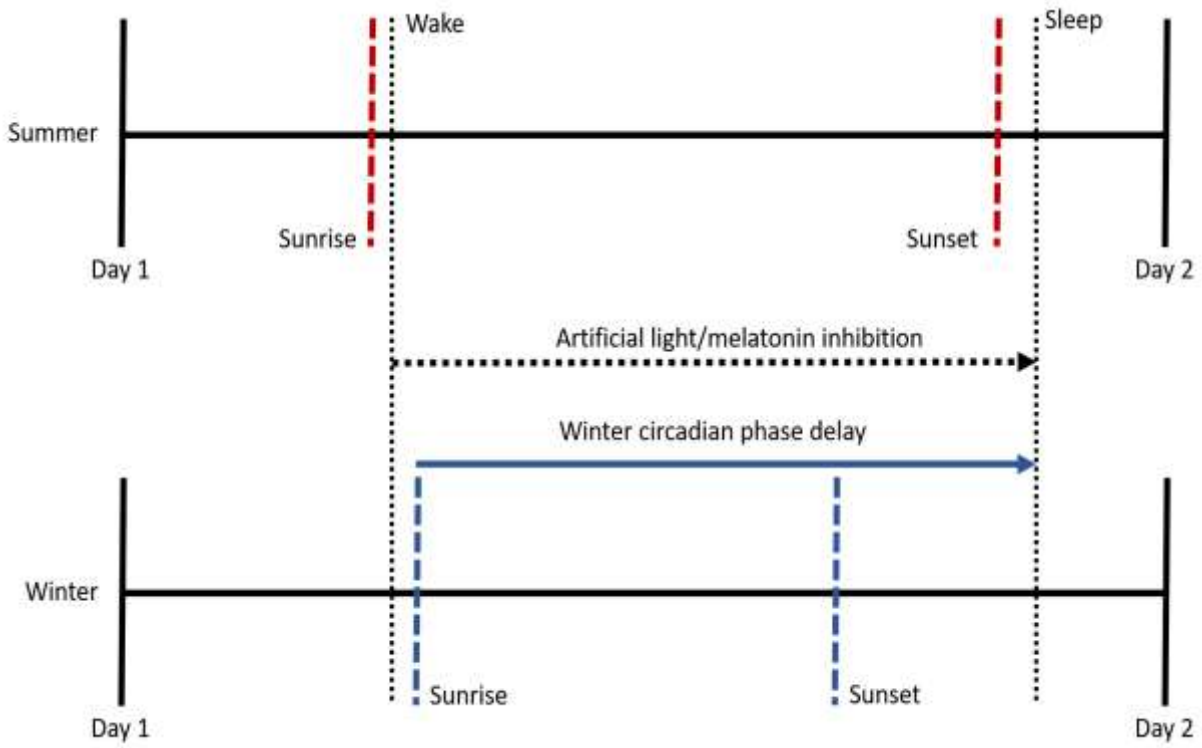


***Figure 2.*** **Circadian phase delay during winter months.** Later sunrise during winter results in delayed circadian synchronization. Prolonged overlap of artificial light with evening darkness inhibits melatonin release, preventing compensatory phase advances. As a result, there is a net phase delay of circadian rhythms.

Table 1
*Sample Characteristics*

| | Total (*N*=159) | CBT (*n*=39) | IPT (*n*=47) | IMI (*n*=37) | Placebo (*n*=39) |
|---|---|---|---|---|---|
| **Sex *n* (%)** | | | | | |
| Male | 53 (33.3) | 10 (25.6) | 16 (34.0) | 13 (35.1) | 14 (38.9) |
| Female | 106 (66.7) | 29 (74.4) | 31 (66.0) | 24 (64.9) | 22 (61.1) |
| **Race *n* (%)** | | | | | |
| White | 138 (86.8) | 33 (84.6) | 40 (85.1) | 33 (89.2) | 32 (88.9) |
| Black | 16 (10.1) | 4 (10.3) | 4 (8.5) | 4 (10.8) | 4 (11.1) |
| Hispanic | 4 (2.5) | 1 (2.6) | 3 (6.4) | 0 (0.0) | 0 (0.0) |
| Other | 1 (0.63) | 1 (2.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Age *M* (*SD*)** | 35.36 (8.18) | 34.00 (9.22) | 35.83 (8.29) | 35.03 (7.99) | 36.58 (7.07) |
| **Baseline HRSD[a] *M* (*SD*)** | 7.44 (5.71) | 7.81 (6.80) | 6.60 (5.28) | 6.97 (5.39) | 8.71 (5.29) |
| **Baseline Recovery[b] *n* (%)** | 77 (48.4) | 23 (59.0) | 21 (44.7) | 17 (45.9) | 16 (44.4) |

*Note.* CBT = Cognitive Behavior Therapy; IPT = Interpersonal Therapy; IMI = Imipramine; HRSD = Hamilton Rating Score for Depression.
[a]Baseline HRSD unknown for 4 participants. [b]Baseline recovery status unknown for 9 participants.

Table 2
*Treatment-Specific Depressive Symptom Severity Regression Results*

| Coefficients | Mean (SD) | 95% CI | *p* |
|---|---|---|---|
| Intercept | -0.94 (0.23) | [-1.43, -0.53] | .000* |
| Time | -0.03 (0.08) | [-0.17, 0.12] | .725 |
| Light Intensity | -0.52 (0.18) | [-0.88, -0.18] | .003* |
| Light Change | -0.01 (0.04) | [-0.12, 0.05] | .838 |
| IPT | -0.01 (0.08) | [-0.22, 0.09] | .895 |
| IMI | -0.01 (0.07) | [-0.19, 0.11] | .957 |
| PLA | 0.01 (0.07) | [-0.11, 0.17] | .953 |
| **Control Variables** | | | |
| Axis 1 Comorbidities | 0.14 (0.19) | [-0.03, 0.60] | .448 |
| Personality Disorder Comorbidities | 0.00 (0.08) | [-0.14, 0.17] | .976 |
| Previous Depressive Episode | 0.02 (0.08) | [-0.08, 0.25] | .868 |
| Current Treatment | 0.46 (0.28) | [0.00, 0.95] | .130 |
| Married | -0.02 (0.08) | [-0.26, 0.07] | .851 |
| Live-in Relationship | -0.01 (0.08) | [-0.19, 0.12] | .966 |
| Separated | -0.05 (0.14) | [-0.51, 0.06] | .801 |
| Divorced | 0.00 (0.06) | [-0.12, 0.14] | .989 |
| Widowed | 0.02 (0.16) | [-0.15, 0.32] | .956 |
| Income | 0.01 (0.04) | [-0.07, 0.12] | .917 |
| **Level 2 Interactions** | | | |
| Time*Light Intensity | 0.17 (0.07) | [0.03, 0.31] | .014* |
| Light Intensity*PLA | 0.10 (0.21) | [-0.30, 0.52] | .627 |
| Light Intensity*IPT | 0.35 (0.21) | [-0.04, 0.78] | .078 |
| Light Intensity*IMI | 0.32 (0.21) | [-0.09, 0.74] | .124 |
| Time*PLA | -0.02 (0.05) | [-0.17, 0.05] | .807 |
| Time*IPT | -0.02 (0.05) | [-0.16, 0.05] | .796 |
| Time*IMI | -0.01 (0.04) | [-0.12, 0.07] | .928 |
| Light Intensity*Light Change | 0.00 (0.04) | [-0.09, 0.09] | .989 |
| Time*Light Change | -0.01 (0.03) | [-0.08, 0.03] | .744 |
| Light Change*PLA | -0.01 (0.06) | [-0.18, 0.08] | .880 |
| Light Change*IPT | -0.01 (0.05) | [-0.13, 0.07] | .907 |
| Light Change*IMI | 0.01 (0.05) | [-0.08, 0.15] | .923 |
| **Level 3 Interactions** | | | |
| Time*Light Intensity*Light Change | 0.00 (0.03) | [-0.04, 0.07] | .882 |
| Time*Light Intensity*PLA | 0.00 (0.05) | [-0.08, 0.12] | .952 |
| Time*Light Intensity*IPT | -0.02 (0.06) | [-0.21, 0.05] | .778 |
| Time*Light Intensity*IMI | 0.00 (0.04) | [-0.10, 0.10] | .994 |
| Time*Light Change*PLA | -0.01 (0.04) | [-0.10, 0.06] | .871 |
| Time*Light Change*IPT | -0.01 (0.03) | [-0.10, 0.05] | .832 |
| Time*Light Change*IMI | 0.01 (0.04) | [-0.05, 0.13] | .834 |
| Light Intensity*Light Change*PLA | 0.00 (0.06) | [-0.12, 0.13] | .993 |
| Light Intensity*Light Change*IPT | -0.02 (0.07) | [-0.24, 0.06] | .796 |
| Light Intensity*Light Change*IMI | 0.00 (0.06) | [-0.14, 0.11] | .959 |
| **Level 4 Interactions** | | | |
| Time*Light Intensity*Light Change*PLA | 0.00 (0.04) | [-0.11, 0.07] | .953 |
| Time*Light Intensity*Light Change*IPT | -0.01 (0.03) | [-0.10, 0.05] | .874 |
| Time*Light Intensity*Light Change*IMI | -0.01 (0.04) | [-0.11, 0.06] | .905 |

*Note*. Coefficient values represent the effect on standardized HRSD outcomes. IPT = Interpersonal therapy; IMI = Imipramine; PLA = Placebo; CI = Credible interval.
*Statistically significant at $p < .05$

Table 3
*Depressive Symptom Severity Regression Results Aggregated Across Treatments*

| Coefficients | Mean (SD) | 95% CI | *p* |
|---|---|---|---|
| Intercept | -0.96 (0.24) | [-1.46, -0.53] | .000* |
| Time | -0.05 (0.07) | [-0.18, 0.09] | .474 |
| Light Intensity | -0.32 (0.12) | [-0.56, -0.09] | .008* |
| Light Change | -0.01 (0.06) | [-0.15, 0.11] | .842 |
| **Control Variables** | | | |
| Axis 1 Comorbidities | 0.24 (0.19) | [-0.02, 0.63] | .195 |
| Personality Disorder Comorbidities | 0.01 (0.14) | [-0.29, 0.33] | .966 |
| Previous Depressive Episode | 0.06 (0.13) | [-0.13, 0.42] | .702 |
| Current Treatment | 0.53 (0.23) | [0.01, 0.96] | .032* |
| Married | -0.08 (0.15) | [-0.51, 0.12] | .653 |
| Live-in Relationship | -0.04 (0.15) | [-0.45, 0.22] | .861 |
| Separated | -0.16 (0.25) | [-0.84, 0.10] | .524 |
| Divorced | -0.01 (0.12) | [-0.28, 0.25] | .988 |
| Widowed | 0.08 (0.34) | [-0.36, 1.13] | .862 |
| Income | 0.02 (0.07) | [-0.10, 0.18] | .804 |
| **Level 2 Interactions** | | | |
| Time*Light Intensity | 0.16 (0.07) | [0.03, 0.30] | .013* |
| Time*Light Change | -0.02 (0.04) | [-0.10, 0.04] | .619 |
| Light Intensity*Light Change | -0.01 (0.06) | [-0.17, 0.11] | .881 |
| **Level 3 Interaction** | | | |
| Time*Light Intensity*Light Change | 0.01 (0.04) | [-0.07, 0.09] | .904 |

*Note*. Coefficient values represent the effect on standardized HRSD outcomes. CI = Credible interval.
*Statistically significant at $p < .05$

Table 4
*Seasonal Depressive Symptom Severity Differences*

| | Winter-Summer | | | Fall-Spring | | |
|---|---|---|---|---|---|---|
| | **Mean (SD)** | **95% CI** | ***p*** | **Mean (SD)** | **95% CI** | ***p*** |
| **Placebo** | | | | | | |
| Tx End | 1.04 (0.46) | [0.15, 1.97] | .022* | -0.09 (0.12) | [-0.29, 0.21] | .332 |
| 6-month | 0.62 (0.37) | [-0.11, 1.36] | .094 | -0.01 (0.12) | [-0.21, 0.29] | .769 |
| 12-month | 0.21 (0.37) | [-0.54, 0.94] | .573 | 0.06 (0.16) | [-0.20, 0.45] | .752 |
| 18-month | -0.21 (0.47) | [-1.15, 0.69] | .648 | 0.14 (0.22) | [-0.21, 0.65] | .473 |
| **CBT** | | | | | | |
| Tx End | 1.29 (0.44) | [0.43, 2.17] | .003* | -0.13 (0.08) | [-0.27, 0.05] | .100 |
| 6-month | 0.88 (0.36) | [0.18, 1.60] | .013* | -0.07 (0.08) | [-0.20, 0.11] | .309 |
| 12-month | 0.47 (0.35) | [-0.22, 1.17] | .189 | -0.01 (0.10) | [-0.17, 0.23] | .794 |
| 18-month | 0.05 (0.43) | [-0.78, 0.91] | .903 | 0.06 (0.14) | [-0.16, 0.39] | .722 |
| **IPT** | | | | | | |
| Tx End | 0.43 (0.43) | [-0.43, 1.25] | .305 | -0.02 (0.11) | [-0.20, 0.25] | .701 |
| 6-month | 0.07 (0.32) | [-0.56, 0.71] | .820 | 0.05 (0.11) | [-0.12, 0.30] | .671 |
| 12-month | -0.28 (0.33) | [-0.93, 0.36] | .389 | 0.12 (0.14) | [-0.11, 0.46] | .326 |
| 18-month | -0.63 (0.44) | [-1.47, 0.25] | .142 | 0.19 (0.19) | [-0.12, 0.64] | .222 |
| **IMI** | | | | | | |
| Tx End | 0.50 (0.46) | [-0.41, 1.40] | .280 | -0.05 (0.11) | [-0.31, 0.18] | .525 |
| 6-month | 0.08 (0.38) | [-0.68, 0.80] | .825 | -0.01 (0.12) | [-0.28, 0.22] | .974 |
| 12-month | -0.34 (0.38) | [-1.10, 0.40] | .364 | 0.04 (0.16) | [-0.34, 0.35] | .679 |
| 18-month | -0.76 (0.47) | [-1.70, 0.16] | .101 | 0.08 (0.22) | [-0.44, 0.50] | .532 |
| **Aggregated** | | | | | | |
| Tx End | 0.79 (0.30) | [0.22, 1.39] | .007* | -0.07 (0.08) | [-0.20, 0.11] | .283 |
| 6-month | 0.40 (0.19) | [0.02, 0.79] | .037* | -0.01 (0.07) | [-0.13, 0.16] | .804 |
| 12-month | 0.01 (0.19) | [-0.37, 0.39] | .968 | 0.06 (0.10) | [-0.11, 0.28] | .552 |
| 18-month | -0.38 (0.30) | [-0.99, 0.20] | .195 | 0.12 (0.13) | [-0.10, 0.44] | .291 |

*Note.* Values represent the standardized HRSD differences between seasons (positive values = greater in winter or fall). IPT = Interpersonal therapy; IMI = Imipramine; CBT = Cognitive behavior therapy; CI = Credible interval.

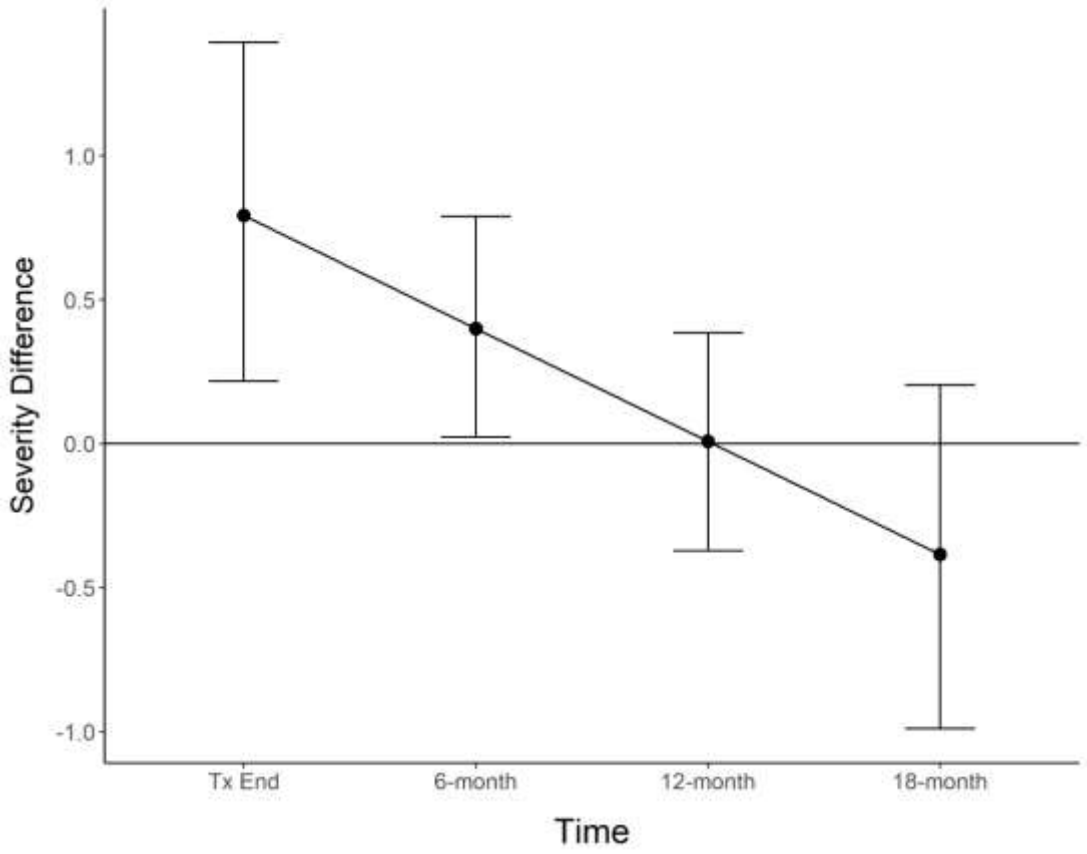


***Figure 3.*** **Aggregated severity differences across seasons.** Values represent standardized differences in HRSD scores between winter and summer aggregated across treatment conditions. Positive values represent greater symptom severity under winter sunlight conditions. Error bars represent 95% credible intervals.

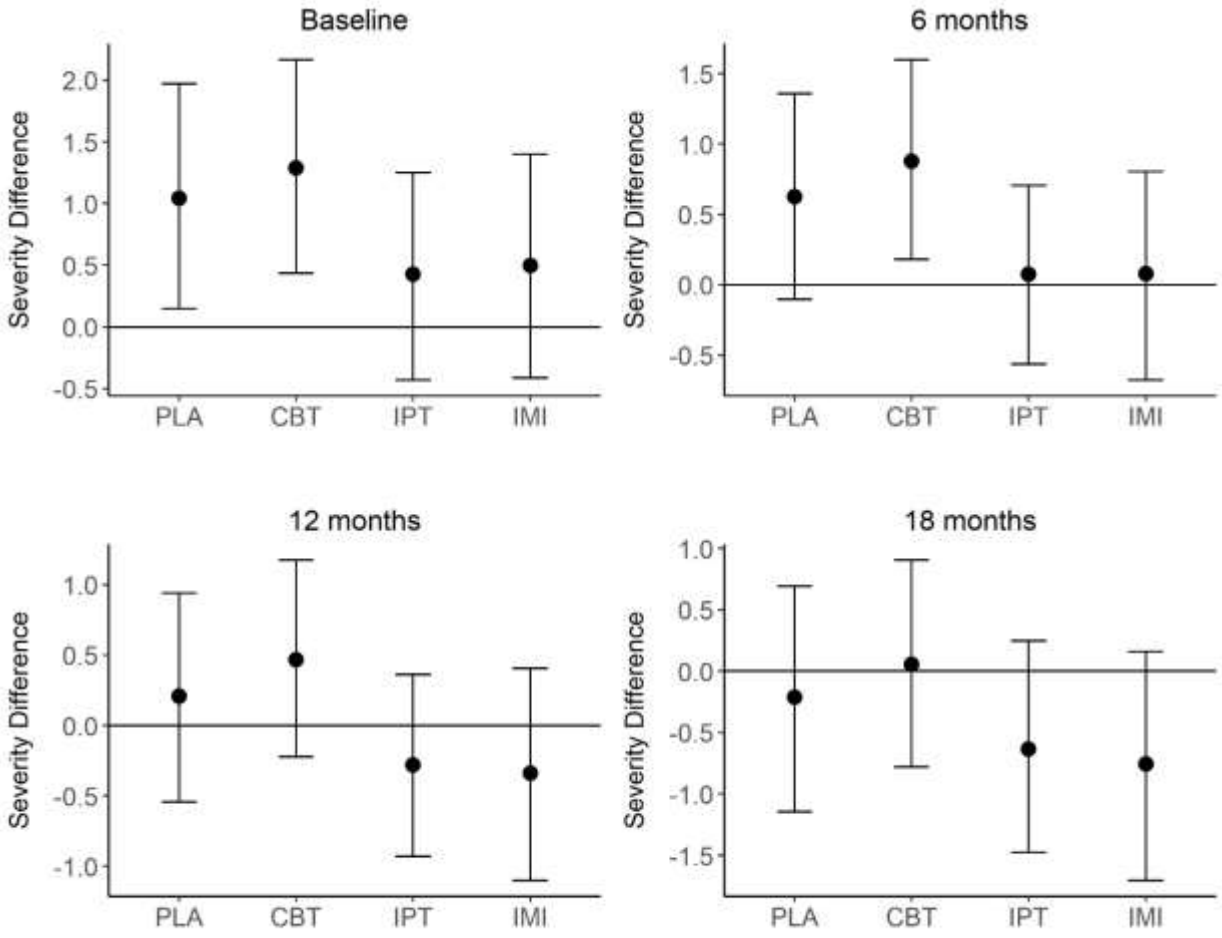


***Figure 4.*** **Seasonal differences in depressive symptom severity.** Values represent standardized differences in HRSD scores between winter and summer. Positive values represent greater symptom severity under winter sunlight conditions. PLA = Placebo; CBT = Cognitive behavior therapy; IPT = Interpersonal therapy; IMI = Imipramine. Error bars represent 95% credible intervals.

Table 5
*Recovery Status Logistic Regression Results*

| Coefficients | Mean (SD) | 95% CI | *p* |
|---|---|---|---|
| Intercept | 0.18 (0.51) | [-0.83, 1.20] | .734 |
| Time | 0.29 (0.19) | [-0.08, 0.67] | .128 |
| Light Intensity | 0.43 (0.45) | [-0.46, 1.34] | .344 |
| Light Change | 0.05 (0.15) | [-0.19, 0.44] | .754 |
| IPT | -0.09 (0.27) | [-0.87, 0.29] | .794 |
| IMI | 0.04 (0.24) | [-0.38, 0.65] | .916 |
| PLA | 0.07 (0.28) | [-0.37, 0.82] | .839 |
| **Control Variables** | | | |
| Axis 1 Comorbidities | -0.15 (0.24) | [-0.79, 0.14] | .551 |
| Personality Disorder Comorbidities | -0.02 (0.24) | [-0.61, 0.46] | .955 |
| Previous Depressive Episode | -0.18 (0.32) | [-1.09, 0.17] | .594 |
| Current Treatment | -1.42 (0.45) | [-2.30, -0.49] | .005* |
| Married | 0.11 (0.26) | [-0.22, 0.87] | .727 |
| Live-in Relationship | -0.15 (0.35) | [-1.18, 0.25] | .717 |
| Separated | 0.85 (0.84) | [-0.08, 2.68] | .280 |
| Divorced | -0.04 (0.21) | [-0.59, 0.35] | .896 |
| Widowed | -0.14 (0.65) | [-1.93, 0.54] | .874 |
| Income | -0.02 (0.12) | [-0.32, 0.20] | .869 |
| Baseline Recovery | 2.49 (0.55) | [1.51, 3.62] | .003* |
| **Level 2 Interactions** | | | |
| Time*Light Intensity | -0.24 (0.20) | [-0.63, 0.15] | .234 |
| Light Intensity*PLA | -0.34 (0.51) | [-1.44, 0.60] | .497 |
| Light Intensity*IPT | -0.40 (0.46) | [-1.31, 0.50] | .367 |
| Light Intensity*IMI | -0.61 (0.56) | [-1.64, 0.60] | .265 |
| Time*PLA | 0.11 (0.20) | [-0.14, 0.64] | .596 |
| Time*IPT | -0.02 (0.13) | [-0.32, 0.24] | .908 |
| Time*IMI | -0.02 (0.14) | [-0.35, 0.25] | .917 |
| Light Intensity*Light Change | -0.12 (0.26) | [-0.89, 0.16] | .649 |
| Time*Light Change | 0.01 (0.07) | [-0.14, 0.19] | .853 |
| Light Change*PLA | 0.05 (0.23) | [-0.32, 0.65] | .880 |
| Light Change*IPT | -0.02 (0.18) | [-0.44, 0.33] | .946 |
| Light Change*IMI | 0.00 (0.19) | [-0.43, 0.40] | .982 |
| **Level 3 Interactions** | | | |
| Time*Light Intensity*Light Change | 0.04 (0.12) | [-0.13, 0.37] | .794 |
| Time*Light Intensity*PLA | 0.07 (0.19) | [-0.21, 0.60] | .756 |
| Time*Light Intensity*IPT | 0.03 (0.15) | [-0.26, 0.40] | .905 |
| Time*Light Intensity*IMI | -0.10 (0.22) | [-0.73, 0.17] | .681 |
| Time*Light Change*PLA | -0.01 (0.12) | [-0.29, 0.23] | .992 |
| Time*Light Change*IPT | -0.01 (0.09) | [-0.23, 0.18] | .945 |
| Time*Light Change*IMI | -0.01 (0.12) | [-0.31, 0.22] | .924 |
| Light Intensity*Light Change*PLA | -0.01 (0.26) | [-0.58, 0.50] | .992 |
| Light Intensity*Light Change*IPT | 0.00 (0.18) | [-0.39, 0.41] | .991 |
| Light Intensity*Light Change*IMI | -0.15 (0.34) | [-1.14, 0.24] | .691 |
| **Level 4 Interactions** | | | |
| Time*Light Intensity*Light Change*PLA | 0.09 (0.20) | [-0.15, 0.62] | .651 |
| Time*Light Intensity*Light Change*IPT | 0.02 (0.10) | [-0.17, 0.28] | .872 |
| Time*Light Intensity*Light Change*IMI | -0.07 (0.17) | [-0.53, 0.17] | .671 |

*Note*. IPT = Interpersonal therapy; IMI = Imipramine; PLA = Placebo; CI = Credible interval.
*Statistically significant at $p < .05$

Table 6
*Seasonal Odds of Recovery*

| | Winter/Summer | | | Fall/Spring | | |
|---|---|---|---|---|---|---|
| | **Mean (SD)** | **95% CI** | ***p*** | **Mean (SD)** | **95% CI** | ***p*** |
| **Placebo** | | | | | | |
| Tx End | 2.16 (7.81) | [0.06, 12.21] | .817 | 0.97 (0.42) | [0.29, 1.81] | .872 |
| 6-month | 1.78 (2.25) | [0.18, 7.46] | .893 | 0.89 (0.32) | [0.34, 1.59] | .622 |
| 12-month | 2.40 (2.43) | [0.34, 8.63] | .498 | 0.85 (0.38) | [0.30, 1.79] | .516 |
| 18-month | 4.72 (7.40) | [0.27, 22.18] | .375 | 0.85 (0.60) | [0.22, 2.32] | .507 |
| **CBT** | | | | | | |
| Tx End | 0.63 (1.03) | [0.04, 2.99] | .328 | 1.10 (0.28) | [0.55, 1.65] | .667 |
| 6-month | 0.83 (0.83) | [0.12, 2.95] | .532 | 0.99 (0.22) | [0.55, 1.43] | .974 |
| 12-month | 1.42 (1.29) | [0.25, 4.74] | .936 | 0.91 (0.23) | [0.48, 1.41] | .655 |
| 18-month | 3.12 (4.36) | [0.28, 13.63] | .520 | 0.85 (0.29) | [0.36, 1.52] | .496 |
| **IPT** | | | | | | |
| Tx End | 1.92 (3.76) | [0.09, 10.18] | .930 | 1.04 (0.43) | [0.44, 2.02] | .951 |
| 6-month | 2.15 (2.18) | [0.30, 7.88] | .611 | 0.94 (0.30) | [0.48, 1.64] | .699 |
| 12-month | 3.28 (2.69) | [0.66, 10.12] | .178 | 0.89 (0.30) | [0.43, 1.61] | .552 |
| 18-month | 6.74 (8.65) | [0.69, 27.37] | .111 | 0.86 (0.40) | [0.33, 1.86] | .519 |
| **IMI** | | | | | | |
| Tx End | 4.22 (9.96) | [0.07, 24.56] | .753 | 0.98 (0.45) | [0.40, 1.97] | .774 |
| 6-month | 6.09 (9.47) | [0.45, 28.29] | .233 | 0.88 (0.33) | [0.40, 1.65] | .519 |
| 12-month | 12.52 (17.03) | [1.40, 53.43] | .017* | 0.83 (0.39) | [0.32, 1.81] | .445 |
| 18-month | 43.85 (134.36) | [2.14, 245.80] | .007* | 0.83 (0.63) | [0.21, 2.29] | .443 |

*Note.* Values represent the recovery odds ratio between seasons (values above one = greater odds in winter or fall). IPT = Interpersonal therapy; IMI = Imipramine; CBT = Cognitive behavior therapy; CI = Credible interval.

Table 7
*Categorical Symptom Level Regression Results*

| | Mean (SD) | 95% CI | *p* |
|---|---|---|---|
| Intercept | 0.00 (1.00) | [-1.96, 1.95] | .999 |
| Time | -0.24 (0.14) | [-0.52, 0.03] | .083 |
| Light Intensity | -0.55 (0.35) | [-1.23, 0.14] | .121 |
| Light Change | -0.09 (0.15) | [-0.51, 0.07] | .531 |
| IPT | -0.03 (0.15) | [-0.44, 0.21] | .879 |
| IMI | -0.02 (0.15) | [-0.41, 0.24] | .938 |
| PLA | 0.03 (0.16) | [-0.24, 0.45] | .906 |
| **Control Variables** | | | |
| Axis 1 Comorbidities | 0.04 (0.12) | [-0.12, 0.39] | .757 |
| Personality Disorder Comorbidities | 0.03 (0.16) | [-0.23, 0.47] | .909 |
| Previous Depressive Episode | 0.06 (0.16) | [-0.14, 0.53] | .779 |
| Current Treatment | 0.90 (0.37) | [0.02, 1.56] | .026* |
| Married | -0.08 (0.19) | [-0.66, 0.14] | .718 |
| Live-in Relationship | 0.10 (0.25) | [-0.16, 0.87] | .739 |
| Separated | -0.23 (0.40) | [-1.37, 0.11] | .582 |
| Divorced | -0.01 (0.14) | [-0.34, 0.26] | .962 |
| Widowed | 0.10 (0.45) | [-0.31, 1.40] | .893 |
| Income | 0.00 (0.07) | [-0.16, 0.18] | .964 |
| Baseline Recovery | -2.22 (0.38) | [-2.99, -1.49] | .000* |
| **Level 2 Interactions** | | | |
| Time*Light Intensity | 0.18 (0.14) | [-0.10, 0.46] | .211 |
| Light Intensity*PLA | 0.48 (0.38) | [-0.23, 1.25] | .185 |
| Light Intensity*IPT | -0.07 (0.36) | [-0.77, 0.62] | .863 |
| Light Intensity*IMI | 0.43 (0.39) | [-0.38, 1.18] | .262 |
| Time*PLA | 0.00 (0.08) | [-0.21, 0.18] | .981 |
| Time*IPT | -0.03 (0.09) | [-0.27, 0.11] | .788 |
| Time*IMI | 0.01 (0.08) | [-0.14, 0.22] | .900 |
| Light Intensity*Light Change | 0.04 (0.12) | [-0.12, 0.37] | .791 |
| Time*Light Change | -0.02 (0.06) | [-0.15, 0.10] | .750 |
| Light Change*PLA | -0.01 (0.12) | [-0.30, 0.24] | .943 |
| Light Change*IPT | -0.03 (0.13) | [-0.37, 0.17] | .834 |
| Light Change*IMI | 0.03 (0.16) | [-0.21, 0.44] | .855 |
| **Level 3 Interactions** | | | |
| Time*Light Intensity*Light Change | 0.00 (0.05) | [-0.13, 0.10] | .964 |
| Time*Light Intensity*PLA | -0.03 (0.12) | [-0.35, 0.17] | .865 |
| Time*Light Intensity*IPT | 0.02 (0.11) | [-0.18, 0.30] | .888 |
| Time*Light Intensity*IMI | 0.02 (0.11) | [-0.18, 0.32] | .890 |
| Time*Light Change*PLA | -0.01 (0.07) | [-0.18, 0.14] | .918 |
| Time*Light Change*IPT | 0.01 (0.07) | [-0.12, 0.17] | .981 |
| Time*Light Change*IMI | 0.08 (0.13) | [-0.06, 0.43] | .516 |
| Light Intensity*Light Change*PLA | 0.03 (0.16) | [-0.21, 0.46] | .888 |
| Light Intensity*Light Change*IPT | -0.04 (0.14) | [-0.42, 0.16] | .830 |
| Light Intensity*Light Change*IMI | 0.04 (0.15) | [-0.18, 0.47] | .831 |
| **Level 4 Interactions** | | | |
| Time*Light Intensity*Light Change*PLA | -0.01 (0.09) | [-0.22, 0.15] | .932 |
| Time*Light Intensity*Light Change*IPT | -0.01 (0.07) | [-0.18, 0.11] | .854 |
| Time*Light Intensity*Light Change*IMI | 0.02 (0.08) | [-0.12, 0.23] | .793 |

*Note*. IPT = Interpersonal therapy; IMI = Imipramine; PLA = Placebo; CI = Credible interval.
*Statistically significant at $p < .05$

Table 8
*Categorical Symptom Level Odds Ratios*

| | Winter/Summer | | | Fall/Spring | | |
|---|---|---|---|---|---|---|
| | **Mean (SD)** | **95% CI** | ***p*** | **Mean (SD)** | **95% CI** | ***p*** |
| **Placebo** | | | | | | |
| Tx End | 1.99 (2.35) | [0.19, 7.96] | .764 | 1.20 (0.48) | [0.70, 2.45] | .749 |
| 6-month | 1.11 (0.82) | [0.24, 3.28] | .868 | 1.29 (0.40) | [0.80, 2.34] | .401 |
| 12-month | 0.74 (0.45) | [0.21, 1.91] | .410 | 1.41 (0.48) | [0.80, 2.61] | .282 |
| 18-month | 0.58 (0.57) | [0.10, 1.98] | .258 | 1.59 (0.74) | [0.72, 3.45] | .275 |
| **CBT** | | | | | | |
| Tx End | 5.95 (6.51) | [0.76, 22.17] | .105 | 1.02 (0.34) | [0.70, 1.89] | .715 |
| 6-month | 3.28 (2.40) | [0.74, 9.45] | .132 | 1.09 (0.29) | [0.78, 1.88] | .953 |
| 12-month | 2.05 (1.32) | [0.54, 5.43] | .350 | 1.18 (0.32) | [0.80, 2.00] | .619 |
| 18-month | 1.45 (1.23) | [0.27, 4.66] | .875 | 1.30 (0.44) | [0.79, 2.41] | .434 |
| **IPT** | | | | | | |
| Tx End | 7.57 (10.02) | [0.85, 31.02] | .074 | 1.08 (0.45) | [0.64, 2.22] | .847 |
| 6-month | 3.72 (2.67) | [0.88, 10.69] | .077 | 1.14 (0.34) | [0.74, 2.01] | .820 |
| 12-month | 2.16 (1.21) | [0.66, 5.22] | .231 | 1.22 (0.34) | [0.77, 2.05] | .534 |
| 18-month | 1.46 (1.11) | [0.32, 4.29] | .824 | 1.34 (0.46) | [0.73, 2.49] | .436 |
| **IMI** | | | | | | |
| Tx End | 2.42 (3.71) | [0.19, 11.10] | .745 | 1.12 (0.49) | [0.55, 2.23] | .918 |
| 6-month | 1.10 (0.98) | [0.19, 3.59] | .797 | 1.05 (0.30) | [0.56, 1.74] | .946 |
| 12-month | 0.60 (0.42) | [0.14, 1.68] | .254 | 1.02 (0.35) | [0.42, 1.81] | .963 |
| 18-month | 0.38 (0.33) | [0.06, 1.23] | .092 | 1.04 (0.48) | [0.26, 2.11] | .963 |

*Note.* Values represent the seasonal odds ratio of belonging to a higher symptom level (values above one = greater odds in winter or fall). IPT = Interpersonal therapy; IMI = Imipramine; CBT = Cognitive behavior therapy; CI = Credible interval.

## Footnotes

1. Typically, the term *relapse* refers to the return of depressive symptoms prior to a prolonged period of remission (at least 4-6 months), whereas *recurrence* refers to the return of symptoms following prolonged remission.
2. Although the sample used in the original paper (Elkin et al., 1989) included only 155 participants, a total of 162 participants completed the treatment phase of the study. Three participants were not evaluated at either termination or follow-up and were therefore not included in the present analyses.