DEPRESSIVE SYMPTOMS AND SLEEP HEALTH IN MIDLIFE WOMEN: THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION (SWAN)

by

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Depressive symptoms and sleep health in midlife women: The Study of Women's Health Across the Nation (SWAN)

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Background: Depressive symptoms and sleep disturbances disproportionately affect midlife women, with long-term health consequences to women's health. Previous studies have reported that depressive symptoms are associated with individual components of sleep, but this approach does not consider the 24-hour integration of nocturnal sleep, circadian timing, and daytime functioning. Additionally, the mechanisms underlying the association have not been elucidated. The current study examines the longitudinal association between depressive symptoms and a multidimensional construct, sleep health, as well as evaluates body mass index and physical activity as possible pathways explaining this relationship.

Methods: Depressive symptoms were assessed at 6-9 annual assessments in 302 midlife women (52.1±2.1y) from the Study of Women's Health Across the Nation. Six months later, wrist actigraphy (M = 25.8 days) and validated questionnaires were collected, which were used to assess components of sleep health: efficiency, duration, timing (wake time minus sleep onset, divided by two), regularity (standard deviation of timing), alertness, and satisfaction. Each component was dichotomized based on evidence-based cut-off scores, and the six components were summed; higher values indicated better sleep health. Associations between depressive symptoms and sleep health were evaluated using linear regression for composite sleep health and logistic regression for each component of sleep health, adjusting for age, race, study site,

menopausal status, vasomotor symptoms, apnea-hypopnea index, and use of medications that affect sleep. Parallel multiple mediation was used to test whether body mass index (BMI) and physical activity mediated the association between depressive symptoms and sleep health.

Results: Higher mean depressive symptoms was associated with poorer sleep health in unadjusted (β = -0.30, $p < .001$) and adjusted models (β = -0.24, $p < .001$). Greater variability in depressive symptoms was associated with poorer sleep health in unadjusted (β = -0.14, $p = .02$), but not adjusted models ($p = .16$). Physical activity and BMI explained a significant portion of the variance in the association between mean depressive symptoms and sleep health.

Conclusion: Mean depressive symptoms are longitudinally associated with sleep health. Depressive symptoms are related to sleep health, in part, through BMI and physical activity, suggesting a possible point of intervention.

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PREFACE

In my research, I am fascinated by the questions “Why do we sleep?” and “Why can we not sleep?” I know that I am not alone in this interest. As Arianna Huffington, co-founder of *The Huffington Post*, noted in an interview: “Do you know what happens if you type the words ‘why am I’ into Google? Before you can type the next word, Google’s autocomplete function—based on the most common searches—helpfully offers to finish your thought. The first suggestion: ‘why am I so tired?’ The global zeitgeist perfectly captured in five words.” My hope is that this Master of Science contributes to the large and growing literature to answer these important questions.

I want to thank my parents, my brothers, Pippi, my grandparents, and Daniel Evans for their love, support, and patience on my academic journey. I want to thank my incredible mentor, Dr. Martica Hall, for her expert guidance in developing a line of scientific inquiry, writing a clear, compelling, and concise argument, and communicating this passion to younger trainees. I want to thank my committee members, Dr. Karen Matthews and Dr. Kathryn Roecklein, for their thoughtful advice and guidance throughout the thesis process. This thesis was only possible with the strong support of my personal and professional team.

1.0 Introduction

More than 43 million women in the United States were aged 45-54, or midlife, in 2016 (United States Census Bureau, 2017), a 17% increase from 2005 (United States Census Bureau, 2007). Midlife women experience the menopausal transition, characterized by the gradual cessation of menstruation and ovarian functioning (North American Menopause Society, 2007), and its concomitant mood changes and sleep disturbances lead to an increase in physician visits and prescription medications (for review, see Utian, 2005). Chief among the complaints of midlife women is sleep disturbances, including insomnia symptoms and poor sleep quality (Woods & Mitchell, 2005, 2010), with 40% of women reporting difficulty sleeping (Cirignotta, Mondini, Zucconi, Luigi Lenzi, & Lugaresi, 1985; Dennerstein, Dudley, Hopper, Guthrie, & Burger, 2000; Kravitz et al., 2008, 2017). Not only are sleep disturbances bothersome to these women, but they are also prospectively associated with health problems such as cardiovascular disease (Cappuccio, Cooper, Delia, Strazzullo, & Miller, 2011) and mortality (Cappuccio, D'Elia, Strazzullo, & Miller, 2010). Understanding what may lead to sleep disturbances in midlife women is crucial for improving sleep, and in the longer term, lowering risk for these health outcomes.

Compelling evidence suggests that depressive symptoms may be prospectively associated with sleep disturbances in midlife women (Lampio, Saaresranta, Engblom, Polo, & Polo-Kantola, 2016). The association between depressive symptoms and sleep disturbances may be linked by pathways such as body mass index (BMI) and physical activity, as depressive symptoms has been shown to precede these factors (Luppino et al., 2010; Roshanaei-Moghaddam, Katon, & Russo, 2009) and each has been associated with subsequent poorer sleep (Resta et al., 2003; Kredlow et al., 2015). Notably, depressive symptoms and these mediators

impact a variety of dimensions of sleep (i.e. sleep architecture, continuity, and timing). However, previous studies infrequently account for multiple dimensions simultaneously or considered measures of sleep-wake patterns. The current study assesses the longitudinal relationship between depressive symptoms and sleep health, a multidimensional construct which includes measures of sleep, sleep-wake timing, and next-day functioning. Examining sleep health allows for a better understanding of the global impact depressive symptoms may have on sleep during the menopausal transition.

1.1 Sleep in midlife women

Self-reports of insomnia have been shown to increase in prevalence during midlife for women. Midlife women report greater sleep disturbances than their age-matched male counterparts (Cirignotta et al., 1985). This may, in part, be due to physiological, psychological, and social changes during the menopausal transition, as women move from premenopause (regular menstrual periods and no change in flow or length of period), to perimenopause (menstrual period in the past three to 12 months), and finally to postmenopause (no menstrual period in the past 12 months; Stages of Reproductive Aging Workshop (STRAW) criteria, Harlow et al., 2012). Insomnia symptoms, defined as subjective difficulty falling asleep, difficulty maintaining sleep, or early morning awakenings, were more prevalent at later stages of the menopausal transition, according to a meta-analysis of 24 cross-sectional studies (Xu & Lang, 2014), a systematic review of eight longitudinal studies (Xu, Lang, & Rooney, 2014), and a more recent, 13-year follow-up study (Kravitz et al., 2017).

A less consistent literature has examined the association between menopausal status and polysomnography (PSG) assessed sleep. Studies have reported that later menopausal stages were associated with more (Xu et al., 2011) or less (Young, Rabago, Zgierska, Austin, & Laurel,

2003) wake after sleep onset, longer total sleep time (Sowers et al., 2008; Young et al., 2003), and higher percentage of non-rapid eye movement (NREM) Stages 3 and 4 sleep (Lampio et al., 2017; Sowers et al., 2008; Young et al., 2003). Some studies reported no association between menopausal status and these measures of sleep (Campbell et al., 2011; Shaver, Giblin, Lentz, & Lee, 1988; Xu et al., 2011). In sum, this literature suggests that while there is inconsistent evidence of differences in PSG-assessed sleep, there is consistent evidence of higher prevalence of self-reported insomnia symptoms at later stages of the menopausal transition. Understanding what may precede these changes is important, as sleep disturbances are associated with negative health outcomes.

1.2 Depressive symptoms and sleep

One modifiable risk factor for sleep disturbances in midlife women during the menopausal transition may be depressive symptoms. Prevalence of major depressive disorder, a diagnosis defined by clinically significant depressive symptoms, doubles from pre-menopause to perimenopause in women with no history of depression (Cohen, Soares, Vitonis, Otto, & Harlow, 2006), and is about five times higher at postmenopause (Woods & Mitchell, 2005) compared to age-matched men and women (Substance Abuse and Mental Health Services Administration, 2016).

Depressive symptoms have been shown to be associated with sleep disturbances in midlife women. In models assessing sleep and depressive symptoms concurrently over time, higher depressive symptoms were associated with worse sleep quality over eight-year follow-up (Pien, Sammel, Freeman, Lin, & DeBlasis, 2008) and more frequent insomnia symptoms over eight-year follow-up (Woods & Mitchell, 2010). In another study, higher depressive symptoms were associated with greater odds of nocturnal awakenings and greater odds of next-day

tiredness at five-year follow-up (Lampio et al., 2016). However, these studies do not exclude participants who are depressed at the time of the sleep assessment. This is critical, as depressive symptoms are highly correlated over time, and thus temporal conclusions may be confounded by high depressive symptoms at the time of the sleep study (Bromberger et al., 2005).

Variability in depressive symptoms over time may also be an important factor for understanding sleep disturbances in midlife women. For example, in a study examining correlates of MDD, women who had persistent and/or recurrent episodes of MDD were eight times more likely than those with a single episode of MDD to report sleep problems (Bromberger et al., 2016; cf. Brown et al., 2014). Inconsistent with this evidence, another study reported that mean, but not slope, of depressed mood ("feeling sad or blue") over 10 years was associated with more insomnia symptoms (Woods & Mitchell, 2010). A second study reported that change in depressive symptoms at five-year follow-up was not associated with insomnia symptoms (Lampio et al., 2016). This preliminary evidence suggests that evaluating the variability in depressive symptoms may be important for understanding sleep disturbances.

Based on this evidence, it seems that the increasing risk of depressive symptoms (Cohen et al., 2006) may be partially driving the increase in prevalence of sleep disturbances during the menopausal transition specifically and midlife women in general (Kravitz et al., 2008, 2017). Evaluating if depressive symptoms are longitudinally associated with a multidimensional construct of sleep is important for integrating these literatures on sleep satisfaction, quality, and continuity. Moreover, understanding *why* depressive symptoms are longitudinally associated with sleep disturbances in midlife women is useful for the evaluation of multiple treatment targets.

Many studies (which have resulted in three meta-analyses of approximately forty studies in the past seven years, Baglioni et al., 2011; Bao et al., 2017; Li et al., 2016) have examined the associations between depressive symptoms and sleep. Less understood is *why* there is this consistent relationship. Given this dearth of research, putative mediators were carefully selected from a list of possible factors based on: 1) consistent literature linking depressive symptoms to the factors; 2) literature linking these factors to sleep; 3) their importance during the context of midlife; and 4) their demonstrated impact on future quality of life and health and functioning. Weight and physical activity each meet these criteria, and also are inversely related in that changes in physical activity can lead to weight loss, and weight gain can lead to a decreased interest in physical activity (Sternfeld et al., 2005).

1.3 Weight as a mediator of the association between depressive symptoms and sleep

1.3.1 Depressive symptoms and body mass index. In the United States, two-thirds of women aged 45-54 are overweight or obese (2011-2014; CDC, 2016). Midlife women often experience an increase in weight (approximately 1.5 pounds per year; Karvonen-Gutierrez & Kim, 2016), as well as a change in the distribution of fat. Premenopausal women have relatively greater subcutaneous adipose tissue (Karvonen-Gutierrez & Kim, 2016), while post-menopausal women have greater visceral adipose tissue (compared to their own premenopausal levels, as well as age-matched premenopausal women; Lovejoy, Champagne, De Jonge, Xie, & Smith, 2008). This redistribution of the location of adipose tissue is medically relevant, because visceral, but not subcutaneous, adipose tissue has been associated with metabolic risk factors (Fox et al., 2007). In sum, changes in weight and its distribution occurring during midlife for women may have consequences for health and functioning.

One reported antecedent of weight gain and weight redistribution in midlife is depressive symptoms. Depressive symptoms have been prospectively associated with obesity in a meta-analysis of 15 prospective studies (Luppino et al., 2010). In studies of midlife women specifically, depressive symptoms have been cross-sectionally associated with higher BMI (Freeman et al., 2009; Blümel et al., 2015) and greater visceral adipose tissue (Everson-Rose et al., 2009; Murabito, Massaro, Clifford, Hoffmann, & Fox, 2013). Depression may result in subsequent weight gain and redistribution due to a variety of the symptoms of depression, such as increased appetite, fatigue or loss of energy, or psychomotor retardation (American Psychiatric Association, 2013).

1.3.2 Body mass index and sleep. High BMI has been acknowledged clinically as an important determinant of sleep quality for decades. Primarily, this is because obesity is a strong predictor of obstructive sleep apnea (OSA; Epstein et al., 2009), characterized by pauses in breathing throughout the night. However, higher BMI has also been associated with sleep disturbances above and beyond sleep apnea. For example, in individuals without OSA, higher BMI has been associated with self-reported excessive daytime sleepiness, greater PSG-assessed WASO and lower sleep efficiency (Resta et al., 2003; Vgontzas et al., 1998). In a study of midlife women (controlling for apnea-hypopnea index), actigraphy- and diary-assessed short sleep duration was cross-sectionally associated with greater BMI (Appelhans et al., 2013). Bariatric surgery, one intervention to aid in weight loss, has been shown to improve self-reported sleep quality (Dixon, Schachter, & Brien, 2001; Toor, Kim, & Buffington, 2012) increased sleep duration (Toor et al., 2012), and decrease daytime sleepiness (Dixon et al., 2001).

1.4 Physical activity as a mediator of the association between depressive symptoms and sleep.

1.4.1 Depressive symptoms and physical activity. In 2015, less than half of women aged 45-54 were meeting federal guidelines for leisure-time aerobic activity (Center for Disease Control and Prevention, 2016), defined as 150 minutes of moderate or 60 minutes of vigorous exercise per week (e.g. Haskell et al., 2007). Engagement in physical activity provides widespread benefits to physical and mental health functioning (for review, see Penedo & Dahn, 2005). In midlife women specifically, physical activity has been shown to be associated with feelings of self-determination and confidence (Janssen, Dugan, Karavolos, Lynch, Powell, 2014), weight loss (Sternfeld et al., 2005), and a prospective decrease in psychosocial and physical symptoms associated with menopause (McAndrew et al., 2009). In randomized controlled trials, exercise intervention enhanced positive affect and decreased menopausal symptoms (e.g. hot flashes; Elavsky & McAuley, 2007), and increased fitness levels in a dose-response style (Church et al., 2007). This literature suggests that midlife women may benefit from physical activity in terms of menopausal symptoms and mental health. However, poor mental health – and in particular, depressive symptoms – may make it difficult to engage in physical activity.

In a review of 11 studies, depressive symptoms were prospectively associated with decreased physical activity levels (Roshanaei-Moghaddam, Katon, & Russo, 2009). In particular, these studies reported the most robust association between an increase over time in depressive symptoms (i.e. worsening symptoms) and a decrease in physical activity. These results have been replicated (Da Silva et al., 2012; Pereira, Geoffroy, & Power, 2014), as well as extended. For example, the relationship between depressive symptoms and cardiovascular disease-related mortality was mediated by physical activity (Win et al., 2011). Further, there may be a dose-

response relationship between the two, such that each additional symptom of depression is associated with lower odds of engaging in physical activity (Pereira et al., 2014).

1.4.2 Physical activity and sleep. A meta-analysis of 66 studies has indicated that physical activity benefits sleep quality, sleep latency, sleep efficiency, and total sleep time (Kredlow et al., 2015). During the menopausal transition, greater physical activity was associated with better sleep quality, but was unassociated with actigraphy-assessed sleep (Lambiase & Thurston, 2013). In another study, greater physical activity was associated with better sleep quality, continuity, quantitative EEG depth (i.e. high delta, low beta spectral power), and lower odds of insomnia (Kline et al., 2013).

1.5 Sleep health

Depressive symptoms, obesity, and physical activity seem to influence multiple dimensions of sleep during the menopausal transition. Previous studies sometimes report on multiple sleep measures, but do not consider these measures concurrently. Sleep health is a multidimensional construct of the 24-hour experience of sleep, considering nighttime sleep and timing, and daytime functioning (Buysse, 2014). The six dimensions of sleep health include: Regularity, or the consistency of sleep midpoint; Satisfaction, or the self-report rating of sleep quality; Alertness, or the ability to maintain wakefulness during the day; Timing, or the placement of sleep within the 24-hour day; Efficiency, or the ability to initiate and maintain sleep; and Duration, or quantity of sleep. The mnemonic “RU SATED?” may be used to remember these six components.

Each of these six dimensions is affected by depressive symptoms and the reviewed mediators. There is evidence that depressive symptoms affects all six domains: regularity (Germain & Kupfer, 2008; McClung, 2013), satisfaction (Pien et al., 2008), alertness (Lampio et

al., 2016), timing (Kitamura et al., 2010), efficiency (Lampio et al., 2016), and duration (long, Patel, Malhotra, Gottlieb, White, & Hu, 2006; insomnia, Bao et al., 2017; Li et al., 2016). There is literature suggesting that greater BMI negatively affects alertness, efficiency, duration (Vgontzas et al., 1998), and timing (Baron, Reid, Kern & Zee, 2011), while greater physical activity positively affects satisfaction, efficiency, duration (Kredlow et al., 2015), timing (Tworoger et al., 2003). Thus, sleep health as an outcome extends the literature by providing an understanding of how depressive symptoms affect multiple domains of sleep simultaneously.

Only two previous studies, to our knowledge, have evaluated the construct of sleep health (Buysse, 2014). One reported that poorer sleep health was associated cross-sectionally and prospectively with clinically significant depressive symptoms (Furihata et al., 2017), and the other demonstrated that childhood trauma was associated with poorer diary- and actigraphy-assessed sleep health in adulthood (Brindle et al., 2018). Together, this limited literature suggests that sleep health may be a robust measure integrating information from several measures of the individual's sleep-wake experience.

1.6 The current study

Evidence supports an examination of the prospective association between depressive symptoms and sleep health in midlife women, as well as evaluating *why* this association exists by including BMI and physical activity in the model. The present study assessed the association between depressive symptoms and sleep health, as well as BMI and physical activity as explanatory pathways of this association.

The current study had two aims: (1) to evaluate longitudinal associations between depressive symptoms and sleep health; and (2) to examine mediators of the longitudinal association between depressive symptoms and sleep health. It was hypothesized that: (1a) greater

mean level depressive symptoms will be associated with poorer sleep health; (1b) greater variability in depressive symptoms across assessments will be associated with poorer sleep health; and (2) BMI and physical activity will partially contribute to the association between mean depressive symptoms and sleep health. Results of this study will be useful for understanding modifiable determinants of sleep health during the menopausal transition.

2.0 Methods

The current study used longitudinal data from the Study of Women's Health Across the Nation (SWAN; hereafter referred to as the core SWAN study) for measures of depressive symptoms, BMI, and physical activity. The SWAN is a longitudinal study designed to assess the correlates of the menopausal transition in the United States. The baseline examination of the core SWAN study was conducted at seven sites in 1996 and 1997. Women were eligible at baseline if they were 42-52 years of age, reported a menstrual period within the past three months, had an intact uterus, and at least one ovary. Women were ineligible if they were pregnant, breastfeeding, or reported exogenous hormone use (Avis & Crawford, 2001). Following baseline, core SWAN assessments occurred approximately yearly.

During one of the follow-up visits 5-8 (2001-2006) of the core SWAN study, participants at four sites (Pittsburgh, PA; Chicago, IL; Detroit, MI; and Oakland, CA) were approached about participation in the ancillary SWAN Sleep Study. Exclusion criteria for the ancillary SWAN Sleep Study were noncompliance with core SWAN procedures; current oral corticosteroid use; current chemotherapy or radiation; regular shift work; diagnosis of sleep apnea; or consumption of more than four alcoholic drinks per day. The SWAN Sleep Study included 370 European American, African American, and Chinese American women, and collected diary- and actigraphy-assessed sleep over a 35-day period, or the length of the participant's menstrual cycle, whichever was shorter. Wrist actigraphy data was used for the calculation of sleep health, where possible, as self-report may be affectively biased (Lauderdale et al., 2008), and most PSG visually scored sleep variables demonstrate poor short-term stability within-person (Israel, Buysse, Krafty, Begley, Miewald, & Hall, 2012). Figure 1 shows how data from core SWAN and the ancillary SWAN Sleep Study were used for the purposes of the current study.

2.1 Participants

Participants for the current study were 302 women who participated in the ancillary SWAN Sleep Study who had full data for analyses assessing the association between depressive symptoms and sleep health (Figure 2). We removed participants from analyses with less than 4 nights of actigraphy (n = 42), missing Epworth Sleepiness Scale (n = 9), and missing apnea hypopnea index data (n = 17).

2.2 Measures

2.2.1 Depressive symptoms. We measured depressive symptoms as our primary variable of interest across six to nine core SWAN study assessments (see Figure 1 for data structure details). Six to nine assessments were used because only data prior to the SWAN Sleep Study were used, which occurred between follow-up visits five through eight. Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The sleep disturbances item ("My sleep was restless") was removed, to avoid confounding with the outcome of interest, sleep health. The CES-D was administered orally by core SWAN study staff at each assessment, and adapted from the original "over the past two weeks" timeframe to "during the past week." Scores for each item range from 0 (less than once a day) to 3 (most or all of the days; 5-7 days), and the overall scores for the current study range from 0 (lowest) to 51 (highest possible score, excluding the sleep item). In a non-clinical population, the CES-D has good internal consistency (α = 0.85) and adequate validity (self-report compared to nurse-clinician rating r = 0.56; Radloff, 1977). In midlife women, a single-factor structure fits the data well (Knight, Williams, McGee, & Olaman, 1997). Mean level of depressive symptoms was calculated as the average score on the CES-D across annual core SWAN study assessments *prior* to the ancillary SWAN Sleep Study. Variability in

depressive symptoms was calculated as the standard deviation of the CES-D score across core SWAN Study assessments *prior* to the ancillary SWAN Sleep Study.

2.2.2 Sleep health. Sleep health was calculated by wrist actigraphy-assessed sleep, efficiency, timing, regularity, and duration, and self-reported alertness and satisfaction, collected during the ancillary SWAN Sleep Study. *Duration* was defined as the total minutes of sleep; *efficiency* was defined as the total minutes of sleep following sleep onset divided by the total minutes of time in bed, multiplied by 100; *timing* was defined as the midpoint of sleep, calculated as bedtime subtracted from waketime, divided by two, then this value is added to bedtime; *regularity* was defined as the standard deviation of the individual's sleep midpoint; *satisfaction* was defined as the average self-reported "restedness" after a night of sleep using a daily sleep diary; and *alertness* was defined as self-reported alertness on the Epworth Sleepiness Scale (Johns, 1991). Duration, efficiency, timing, regularity, and satisfaction were calculated as the average or standard deviation of daily data. Alertness based on the Epworth Sleepiness Scale was assessed once.

Each continuous sleep health variable was dichotomized, with 0 indicating poor sleep health and 1 indicating good sleep health. The cut-offs for each sleep health variable were created *a priori* based on empirical literature. For details on the referenced studies and the specific cut-points, see Table 1.

2.2.3 Mediators. Physical activity and BMI were evaluated as potential mediators linking mean depressive symptoms with sleep health. For clear temporal precedence in this model, we assessed depressive symptoms before the mediators, and the mediators were assessed before the SWAN Sleep Study. For all participants, mean depressive symptoms were averaged across four core SWAN Study visits (baseline through follow-up visit 3). An average of two

years later (range: 1.4-2.7 yr), BMI and physical activity were measured in the core SWAN Study (follow-up visit 5). The SWAN Sleep Study occurred on average two years later (follow-up visits 5-8; range: 0.3-3.45 yr). Due to missing data for BMI and KPAS at follow-up visit 5, which were not included in aim 1 of the study, the total sample size for the mediation model is 271.

2.2.3.1 Body mass index. Core SWAN study staff measured height (meters) and weight (kilograms) at follow-up visit 5. BMI was calculated as kilograms divided by meters squared.

2.2.3.2 Physical activity. Physical activity was measured using a modified version of the Kaiser Physical Activity Scale (KPAS; Sternfeld, Ainsworth, & Quesenberry, 1999). This scale was specifically designed for assessing physical activity in midlife women, as they engage in more than recreational physical activity alone. More specifically, the KPAS assessed levels of activity within the past 12 months of household/caregiving (e.g. cooking and cleaning, caring for a young child or older adult), active living (e.g. biking to work), and sports/exercise (e.g. playing a sport or exercising). Scores on each of these three domains ranges from 1-5, with higher scores indicating higher levels of activity. The KPAS has high one-month test-retest reliability (r = 0.79 to 0.81) and moderate correlation with percent body fat and VO2 peak (r = -0.30 to -0.59, 0.34 to 0.76, respectively; Ainsworth, Sternfeld, Richardson & Jackson, 1999).

2.2.4 Covariates*.* The following measures were included in the adjusted model as covariates: age, site, race/ethnicity, menopausal status, percent of nights that participants reported vasomotor symptoms, proportion of visits preceding SWAN Sleep Study that participants reported using antidepressants, percent of nights that participants reported using medications that affect sleep, and the apnea-hypopnea index (AHI). These measures were selected based on their known influences on depressive symptoms, sleep, or both in previous

studies of midlife women. Menopausal status was assessed at the core SWAN visit preceding the SWAN Sleep Study. The proportion of visits that participants reported using antidepressants was assessed at all core SWAN visits preceding the SWAN Sleep Study. All other covariates were assessed at the SWAN Sleep Study. Age and race/ethnicity data were based on self-report. Site was a categorical variable indicating where participation took place (Pittsburgh, PA; Chicago, IL; Detroit, MI; and Oakland, CA).

2.2.4.1 Menopausal status. Menopausal status was determined based on self-reported bleeding patterns according to the STRAW guidelines (Harlow et al., 2012). Specifically, the premenopause/early perimenopause category was defined as women who reported bleeding in the past three months and whose menstrual periods were regular or somewhat irregular. Late perimenopause represented women who had bleeding in the last 12 months prior to her visit but no bleeding in the past three months. Natural postmenopause includes women who had no bleeding in the 12 months prior to the visit. Unknown status characterized women whose menopausal status could not be determined. No women in the SWAN Sleep Study underwent bilateral salpingo oophorectomy.

2.2.4.2 Vasomotor symptoms. Vasomotor symptoms, or hot flashes, have been shown to increase in both frequency and severity during midlife (Woods & Mitchell, 2005) due to changes in follicular stimulating hormone levels (Gold et al., 2004, 2007). At the ancillary SWAN sleep study, women reported the frequency ("How many times did you experience these symptoms last night?", with categories of 0, 1, 2, 3, 4, "5 or more", and "all night") of their hot flashes, cold sweats, and night sweats. These variables are frequently aggregated in other studies of vasomotor symptoms (Politi, Schleinitz, & Col, 2008). Previous studies from the core SWAN study have reported that these three variables have high single-factor loadings (hot flashes, 0.68-

0.78; cold sweats, 0.73; night sweats, 0.75-0.81; Gold et al., 2004, 2006). The percent of nights during which women reported vasomotor symptoms during the SWAN sleep study was included as a covariate.

2.2.4.3 Medications that affect sleep. Participants reported on their daily medication use each night during the SWAN Sleep Study. Medication that is known to affect sleep, even if it was not taken for aiding sleep, included the following classes identified by the World Health Organization Anatomical Therapeutic Chemical (ATC) classifications: N02A (opioids), N03A (antiepileptics), N05B (anxiolytics), N05C (hypnotics and sedatives), N06A (antidepressants), and R06A (antihistamines for systemic use). The percent of nights that these medications were reported over the sleep study was included as a covariate.

2.2.4.4 Apnea hypopnea index. Sleep apnea was assessed using in-home polysomnography. Equipment included oral-nasal thermistors and nasal pressure for air flow, impedence pethysmography to measure abdominal movements, and fingertip oximetry to assess oxygen desaturation. The AHI was calculated by identifying apneas and hypopneas pursuant to American Academy of Sleep Medicine guidelines (American Academy of Sleep Medicine Task Force, 1999).

2.2.4.5 Antidepressants. At each core SWAN visit, participants reported their use of antidepressants (NO6A; monoamine oxidase [MOA] inhibitors, selective serotonin reuptake inhibitors [SSRIs], tri- or tetracyclics, and “others”). The proportion of visits preceding the SWAN Sleep Study that a woman reported taking one or more antidepressant(s) was included as a covariate.

2.3 Statistical Analysis Plan

Descriptive statistics were used to characterize the sample. Linear regression assumptions were examined, and AHI was log-transformed to reduce skewness. Univariate analyses for mean and variability in depressive symptoms were followed by multiple linear regression models. Regression models adjusted for age, site, race/ethnicity, menopausal status, propotion of visits preceding SWAN Sleep Study that participants reported using antidepressants, percent of nights that the participant reported vasomotor symptoms, percent of nights that the participant reported using medications that affect sleep, and log-transformed AHI. Age, antidepressants, percent of nights that the participant reported vasomotor symptoms, percent of nights that the participant reported using medications that affect sleep, and log-transformed AHI were continuous and centered based on the sample's mean. Site was entered as three dichotomous variables: Chicago, IL, Detroit, MI, and Oakland, CA, with Pittsburgh, PA as the reference. Race/ethnicity was entered as two dichotomous variables, African Americans and Chinese Americans, with European Americans as the reference. Menopausal status was entered as three dichotomous variables: late perimenopause, postmenopause, and unknown, with early/perimenopause as the reference.

A post-hoc power analysis of a linear multiple regression (fixed model, assessing R^2 increase) test calculated a conservative estimate of the power to detect significant effects in the current study (G-Power; Faul, Erdfelder, Buchner, & Lang, 2008). This test indicated that there was 100% power to detect an effect size greater than or equal to 0.08 with 280 participants and 14 total predictors in the model, and 82% power to detect an effect size greater than or equal to 0.03. In a similar study assessing depressive symptoms and self-reported sleep during the

menopausal transition at five-year follow-up, effect sizes ranged from 0.16-0.24 (for nocturnal awakenings and daytime sleepiness, respectively; Lampio et al., 2016).

Sleep health is a relatively new concept, with limited literature on the best modeling strategy. Thus, we evaluated a series of models of sleep health for this study. First, an equally weighted composite score of sleep health (ranging from 0 to 6, with higher scores indicating better sleep health) was an outcome in a multiple linear regression model. "Equally weighted" refers to the fact that each component of sleep health has a weight of one. Next, we evaluated each component of sleep health as an outcome in six separate binary logistic regression models (0 was poor sleep health, 1 was good sleep health). These dichotomous variables were used to evaluate the "subscales" of the composite sleep health measure, and because they more closely represent a checklist that could be used in a clinical setting (Buysse, 2014). Equally weighted sleep health and assessment of sleep health components are methods that have been previously employed in studies of sleep health (Brindle et al., 2018; Furihata et al., 2017).

We also evaluated a variably weighted sleep health score, because using equally weighted sleep health scores assumes that each component is equally important. Variably weighted sleep health was quantified in four steps: (1) we re-coded each sleep health component so that 0 was good sleep health, 1 was poor sleep health; (2) we entered mean depressive symptoms as the independent variable and each sleep health component as the outcome in six binary logistic regressions; (3) we multiplied the odds ratio for each component by its corresponding dichotomous sleep health component; (4) we summed the weighted sleep health components (see Supplemental Table 1). The equally weighted and variably weighted sleep health scores in the current study were highly correlated ($r = 0.99$), and so we were unable to test which sleep health score was more strongly associated with mean depressive symptoms. Because

of this high correlation, it was not possible to compare our models for equally weighted and variably weighted outcomes. That is, there would be no difference in regression model estimates.

In an exploratory aim, we evaluated whether variability in depressive symptoms moderated the longitudinal association between mean level of depressive symptoms and sleep health. This is based on the notion that variability and mean symptoms may be synergistic, such that the combination of high variability and high mean symptoms would be associated with the poorest sleep health, compared to either variable in isolation (e.g. high mean, low variability). There was evidence of heteroscedasticity (non-constant variance in the residuals) between variability and mean depressive symptoms using the modified Levene's test (Gastworth, Gel, & Miao, 2009). To address this, weighted least squares regression was used for the moderation analysis. The interaction term and predictors were centered on the sample's mean. Each main effect was entered, followed by the interaction term, and then adjustment for covariates. The linear regression models, binary logistic regression models, and moderation analyses were conducted in IBM SPSS Statistics software (version 25).

To test whether BMI and physical activity mediated the longitudinal association between mean depressive symptoms and sleep health, we evaluated a parallel multiple mediation model. We assessed mean depressive symptoms across four visits, two years later we measured the mediators at one time point, and then two years later we assessed sleep health in the SWAN Sleep Study. The R package bmem (Zhang, 2014) was used, which uses bootstrapping (n = 1000) for estimates, standard errors, and bias-corrected confidence intervals. Variables were z-scored to calculate standardized beta coefficients. Bmem does not calculate p-values; confidence intervals that do not contain 1 are significant.

In a series of secondary analyses presented in supplementary tables and figures, we report pooled estimates from multiple imputation, a strategy used to account for some of our missing data. Specifically, we imputed missing CES-D data occurring at any visit prior to the participant's sleep study (n = 53 were missing CES-D data at one or more visits), missing BMI (n = 14) and KPAS (n = 21) data at follow-up visit five, and missing AHI data at the SWAN Sleep Study (n = 17). We did not to impute missing actigraphy data or Epworth Sleepiness Scale values, as we did not have multiple visits from which to impute and these comprised our outcome of interest. Our sample size for these supplementary analyses is 319 participants for aim 1, and 286 participants for aim 2 (mediation models).

Based on a low level of missingness per variable (< 15%) and desired power of 80%, the number of imputations recommended based on Monte Carlo simulations is 20 (Graham, Olchowski, & Gilreath, 2007). We specified a multiple imputation model with linear terms (no interactions). Minimum and maximum values were specified for all imputed variables to preclude impossible values (e.g. a negative BMI value). Variables that were included that could contribute to imputation were: CES-D and BMI from baseline through visit 8; KPAS from baseline, visit 3, 5, and 6, AHI, age, race, education, employment status, income, level of perceived financial strain, marital status, perception of general health, and quality of life. These predictors were included as plausible contributors to missing data and/or to information about the missing value. The resulting multiple imputation dataset contains 20 datasets of 319 cases each with no missing data on the variables specified, for a total of 6,380 cases.

To test for convergence, we compared the observed (dataset created by listwise deletion, $n = 280$) descriptive statistics to the imputed (pooled values from twenty datasets with no missing data, $n = 5940$) descriptive statistics. Stuart and colleagues (2009) have suggested that

imputed data has successfully converged if observed compared to imputed means are less than two standard deviations apart, and if the ratio of variance is between 0.5 and 2.0. Supplemental Tables 2 and 3 present the observed and imputed descriptive statistics for CES-D, BMI, KPAS, and AHI. All variables demonstrated successful convergence.

3.0 Results

3.1 Participant characteristics

As shown in Table 2, the sample was composed of 112 African American, 50 Chinese American, and 140 white women with an average age of 52.1± 2.1. Most of the sample (61.9%) were premenopausal or early perimenopausal, 19.2% of the sample were late perimenopausal, and 12.6% were post-menopausal. The average length of follow-up from baseline to the visit preceding the SWAN Sleep Study was 5.7 years (SD = 0.7, range = 4.1-7.2 yr). The average length of time between the visit preceding the SWAN Sleep Study and the SWAN Sleep Study was 5.6 months (SD = 4.3 months, range = 0 months – 2 years). The average mean depressive symptoms score on the CES-D was 7.5 ± 6.2, which indicates low depressive symptoms. However, 46.5% of the sample met criteria for clinical depressive symptoms (CES-D ≥ 16) at one or more visits, and 9.5% of the sample met criteria for more than 50% of their visits. The within-person variability in CES-D across visits was 4.5 ± 3.0. The average participant was overweight, with an average BMI of 29.8 ± 7.9. The average total physical activity score on the KPAS was 7.5 ± 1.7; survey scores range from 0-15.

Table 3 shows sleep health characteristics, both as continuous variables and based on empirically-derived dichotomous cut-offs (cut-offs are shown in Table 1). The average number of nights of actigraphy data was 29.2 nights (SD = 7.0). The average participant slept 6.0 hours ± 0.9, had a sleep efficiency of 78.0% ± 10.2, a sleep midpoint of 3:20 am ± 0:33 with a within-person standard deviation of midpoint of 0.7±0.3, and reported being moderately rested (2.0 ± 0.6) and somewhat sleepy (7.7 ± 4.4). Figure 3 shows the distribution of the composite sleep health scores, ranging from 0-6, as a function of the percentage of participants with each score. Few participants (0.7%) had zero for their sleep health score, and the most common scores were

3 (25.4%) and 4 (26.1%). Figure 4 shows the percentage of participants with optimal scores on each of the individual sleep health components. Most participants had optimal sleep health in terms of sleep timing (88.6%), regularity (82.5%), and alertness (70.4%). In contrast, only 25% of the sample had optimal sleep health for sleep efficiency.

3.2 Longitudinal association between depressive symptoms and a composite measure of sleep health

The longitudinal association between mean depressive symptoms and a composite measure of sleep health in hierarchical linear regression models is presented in Table 4. Note that lower sleep health scores indicate poorer sleep health. Higher mean depressive symptoms was longitudinally associated with poorer sleep health in both unadjusted (β = -0.30, p < .001) and adjusted models (β = -0.24, p < .001). In evaluating covariates, African Americans (β = -0.17, p = .009) had poorer sleep health compared to European Americans, participants who were late perimenopausal (β = -0.14, p = .05) had poorer sleep health compared to those who were pre-/early perimenopausal, and participants with higher AHI (β = -0.18, p = .001) had poorer sleep health.

The longitudinal association between variability in depressive symptoms and sleep health is presented in Table 5. Variability in depressive symptoms on the CES-D across visits was significantly associated with sleep health in the unadjusted (β = -0.14, p = .02), but not in the adjusted model (β = -0.08, p = .16). In the adjusted model, African Americans (β = -0.18, p = .008) had poorer sleep health compared to European Americans, participants from the Detroit site (β = -0.16, p = .01) had poorer sleep health compared to participants at the Pittsburgh site, and participants with higher AHI (β = -0.18, p = .001) had poorer sleep health.

In our exploratory aim, we evaluated whether variability in depressive symptoms moderated the relationship between mean depressive symptoms and sleep health using weighted

least squares regression (Table 6). Mean level and variability in depressive symptoms may be synergistic, such that higher mean and variability in depressive symptoms are associated with the poorest sleep health compared to high levels of one or the other variable. In the unadjusted interaction model (Model 3 in Table 6), there was a main effect of mean depressive symptoms (β = -0.29, p = .001), no significant main effect for variability in depressive symptoms (β = 0.09, p = .32), and no significant interaction between mean and variability in depressive symptoms (β = 0.02, p = .78). Similarly, in the adjusted model, there was a main effect of mean depressive symptoms (β = -0.27, p = .001), no significant main effect for variability in depressive symptoms (β = 0.11, p = .19), and no significant interaction between mean and variability in depressive symptoms (β = 0.01, p = .82). Significant covariates associated with poorer sleep heath included being African American (β = -0.19, p = .005) or Chinese American (β = -0.15, p = .05) compared to being European American, participants from the Detroit site (β = -0.13, p = .05) compared to participants from the Pittsburgh site, participants who were late perimenopausal (β = -0.15, p = .01) compared to those who were pre-/early perimenopausal, and higher AHI (β = -0.15, p = .01).

3.3 Mean and variability in depressive symptoms and individual components of sleep health

After evaluating associations with a composite measure of sleep health, we modeled each sleep health component individually. This method allows one to evaluate which "subscales" may be driving significant associations between variables and the composite sleep health measure. Note that zero indicates poor sleep health, and one indicates optimal sleep health for the dichotomous components of sleep health. In unadjusted binary logistic regression models, higher mean depressive symptoms was longitudinally associated with lower odds of optimal self-reported sleep satisfaction (OR = 0.90, p < .001), lower odds of optimal self-reported alertness (OR =

0.94, p = .001), lower odds of optimal actigraphy-assessed sleep timing (OR = 0.92, p < .001), and lower odds of optimal actigraphy-assessed regularity (OR = 0.96, p = .04). Figure 5 presents the odds ratios plotted for adjusted models. In adjusted models, higher mean depressive symptoms was associated with lower odds of optimal self-reported sleep satisfaction (OR = 0.90, p < .001), and optimal self-reported alertness (OR = 0.93, p = .002), but was not significantly associated with actigraphy-assessed sleep timing (OR = 0.95, p = .06) or regularity (OR = 0.96, p = .09). Mean depressive symptoms was not significantly associated with sleep efficiency or sleep duration in unadjusted or adjusted models (ps > .46).

In the unadjusted model, greater variability in depressive symptoms was significantly associated with lower odds of optimal actigraphy-assessed sleep timing (OR = 0.84, p = .002). No other association was significant in unadjusted models (ps ≥ .07). In the adjusted models presented in Figure 6, greater variability in depressive symptoms was not significantly associated with sleep timing (OR = 0.90, p = .07). There was no significant association between variability in depressive symptoms and the other components of sleep health in the adjusted models (ps ≥ .50).

3.4 Parallel multiple mediation model

Next, we evaluated two putative mediators of the association between higher mean depressive symptoms and poorer sleep health. To establish temporal precedence, mean depressive symptoms were assessed for four visits, two years later we assessed the possible mediators, and two years later we assessed sleep health (see Figure 1 for data structure). Statistically, we used parallel multiple mediation analyses including physical activity and BMI concurrently as mediators.

The mediation model provides information on the longitudinal associations between mean depressive symptoms and the mediators, the mediators and sleep health, the indirect effect of mean depressive symptoms on sleep health *through* the path of the mediators, and the remaining direct effect of mean depressive symptoms on sleep health that was not explained by the mediators. Mediators differ from covariates in two important ways: (1) mediators are theorized to explain an association, whereas covariates may be confounders; (2) indirect effects allow one to assess the extent to which an association is *explained* by a mediator, whereas adjusted models allow one to assess the extent to which an association *remains*, after accounting for the variance explained by covariates.

In Figure 7, we present the parallel multiple mediation model. The total direct effect of higher depressive symptoms on poorer sleep health was significant (β = -0.26, 95% CI [-0.37, -0.15]). We report that mean depressive symptoms was significantly associated with BMI (β = 0.13, 95% CI [0.03, 0.24]), and body mass index was significantly associated with sleep health (β = -0.16, 95% CI [-0.26, -0.04]). There was a significant indirect effect of mean depressive symptoms on sleep health through BMI (β = -0.03, 95% CI [-0.06, -0.01]). Mean depressive symptoms was significantly associated with physical activity (β = -0.24, 95% CI [-0.34, -0.15]), and physical activity was significantly associated with sleep health (β = 0.12, 95% CI [0.01, 0.24]). The indirect effect of mean depressive symptoms on sleep health through physical activity was significant (β = -0.02, 95% CI [-0.06, -0.01]). Both BMI and physical activity were significant mediators of the longitudinal association between mean depressive symptoms and sleep health. The direct effect of depressive symptoms on sleep health after accounting for these two indirect effects remained significant (β = -0.21, 95% CI [-0.32, -0.09]), indicating that some of the variance in this association remained unexplained.

3.5 Multiple imputation analyses

In a series of secondary analyses, we imputed data missing from visits preceding the SWAN Sleep Study for CES-D, data missing from follow-up visit 5 for BMI and KPAS, and data missing from the SWAN Sleep Study for AHI. This increased our sample size from $n = 302$ to $n = 319$. The estimates for mean and variability of depressive symptoms included imputed values. Pooled estimates across 20 imputed datasets are presented in supplemental materials. In Table S4, we present a comparison of the sample characteristics for listwise deletion (i.e. our analyses up until this point, and the values shown in Table 2) to multiple imputation strategies. Table S5 similarly compares sleep health characteristics for the listwise deletion dataset (Table 3) to the multiple imputation strategy. Mean and standard deviation did not change substantially for continuous variables, or for the number and percent with optimal sleep health components.

Using the multiple imputation dataset, we analyzed all the models previously reported in Tables 4 through 8. The pattern of results was not substantially different in the multiple imputation models compared to the listwise deletion models. First, the longitudinal association between mean depressive symptoms and variability in depressive symptoms with sleep health was assessed (Tables S6 and S7). Mean depressive symptoms was significantly associated with sleep health in unadjusted and adjusted models (ps < .001). Variability in depressive symptoms was significantly associated with sleep health in unadjusted ($p = .02$), but not adjusted models ($p = .17$). In the exploratory aim testing whether variability in depressive symptoms moderated the longitudinal association between mean depressive symptoms and sleep health, the interaction term was not significant in unadjusted or adjusted models (ps $\geq$ .69, Table S8). Second, we evaluated the components of sleep health individually in logistic regression. Higher mean depressive symptoms was associated with significantly lower odds of optimal self-reported

satisfaction, self-reported alertness, and actigraphy-assessed timing in unadjusted models (ps < .001). Figure S1 shows the adjusted logistic regression results for mean depressive symptoms. Mean depressive symptoms was significantly associated with lower odds of optimal self-reported satisfaction and alertness in adjusted models (ps $\leq$ .002), but not with sleep timing (p = .07). Greater variability in depressive symptoms was associated with significantly lower odds of self-reported satisfaction (p = .05) and lower odds of optimal actigraphy-assessed sleep timing in the unadjusted model (p < .001). Figure S2 shows that variability was not associated with any sleep health components in the adjusted models (ps $\geq$ .06).

We also tested whether BMI and physical activity were significant mediators of the association between mean depressive symptoms and sleep health (Figure S3). Mean depressive symptoms was significantly associated with BMI (β = 0.10, 95% CI [-0.01, 0.22]), and BMI was significantly associated with sleep health (β = -0.17, 95% CI [-0.28, -0.06]). The indirect effect of mean depressive symptoms and sleep health through BMI was significant (β = -0.03, 95% CI [-0.06, -0.01]. Mean depressive symptoms was significantly associated with physical activity (β = -0.17, 95% CI [-0.28, -0.06]), and physical activity was significantly associated with sleep health (β = 0.12, 95% CI [0.02, 0.24]). The indirect effect of mean depressive symptoms and sleep health through physical activity was significant (β = -0.03, 95% CI [-0.06, -0.01]). Thus, both BMI and physical activity were significant mediators. The direct effect of mean depressive symptoms and sleep health after accounting for the mediators was significant (β = -0.14, 95% CI [-0.26, -0.03]), indicating that some of the variance in this association remained unexplained.

4.0 Discussion

Depressive symptoms are prospectively linked to sleep disturbances (Bao et al., 2017). Previous work has demonstrated that greater depressive symptoms is associated with higher BMI (Luppino et al., 2010) and lower levels of physical activity (Roshanaei-Moghaddam, Katon, & Russo, 2009)). In a separate body of literature, higher BMI (Resta et al., 2003; Vgontzas et al., 1998) and lower levels of physical activity (Kredlow et al., 2015) have been linked to sleep disturbances. These relationships were characterized in a sample of midlife women, as midlife women are at increased risk for depressive symptoms (Cohen et al., 2006), weight gain (Karvonen-Gutierrez & Kim, 2016), a decrease in physical activity (Center for Disease Control and Prevention, 2016), and sleep disturbances (Kravitz et al., 2017). Understanding the antecedents of sleep disturbances is critical because sleep disturbances are associated with increased risk for cardiovascular disease (Cappuccio, Cooper, Delia, Strazzullo, & Miller, 2011) and mortality (Cappuccio, D'Elia, Strazzullo, & Miller, 2010).

In the current study, we report that higher mean depressive symptoms were longitudinally associated with poorer sleep health. This association was independent of known risk factors of sleep disturbances in midlife women, including age, race/ethnicity, vasomotor symptoms, antidepressant use, medications that affect sleep, and AHI. Additionally, BMI and physical activity were significant mediators of this pathway. There was a significant association between variability in depressive symptoms and sleep health in unadjusted, but not adjusted models. Our findings are of clinical importance, as they provide the foundation for future studies to evaluate whether a weight-loss or physical activity intervention in midlife women with depression may improve multiple dimensions of their sleep (e.g. regularity, efficiency), which may have important downstream consequences for cardiovascular health.

Sleep health is important to empirically test, as this emerging method integrates sleep, circadian rhythms, and functioning (Buysse, 2014). Sleep health accounts for the inherent interrelatedness of its variables. For example, if time in bed is held constant, increases in sleep efficiency are associated with an increase in sleep duration. Moreover, proximal measures of circadian rhythms are included, as sleep continuity and duration are partially due to the influence of circadian rhythms (Czeisler et al., 1980). Additionally, sleep health includes measures of the impact of sleep on next-day functioning. Since there is significant inter-individual variability in sleep need, the same sleep duration can result in differential physiological restoration across individuals (for review, see Van Dongen, Vitellaro, & Dinges, 2005). Because of these strengths, sleep health has been used in several previous studies (Brindle et al., 2018; Furihata et al., 2017).

Untested in previous studies is whether the six components of sleep health are best characterized using equal or variable weighting (i.e. components that are more strongly associated with the predictor receive greater weighting). In the current study, we evaluated whether mean depressive symptoms was differentially associated with each sleep health component. Although mean depressive symptoms was more strongly associated with self-reported satisfaction and alertness than the other components, these associations were not substantially different to merit variable weighting. This finding supports the rationale of previous studies which used equal weighting for sleep health (Brindle et al., 2018; Furihata et al., 2017). Testing for differential associations in future studies is important, because this may enhance the precision of predicted associations between sleep health and both its antecedents and consequences. It may be, as our study found, that sleep health should truly be equally weighted. Our study contributes to emerging evidence that sleep health is a promising construct for holistically evaluating sleep, circadian rhythms, and next-day functioning.

Higher mean depressive symptoms was longitudinally associated with poorer sleep health. In evaluation of the components of sleep health, higher depressive symptoms were associated with lower odds of optimal self-reported alertness and lower odds of optimal self-reported sleep satisfaction in both unadjusted and adjusted models. This study replicates previous evidence that higher depressive symptoms are related to lower sleep satisfaction (Pien et al., 2008) and less alertness at five-year follow-up (Lampio et al., 2016) among midlife women. Contrary to our expectations, mean depressive symptoms was not significantly associated with our measures of actigraphy-assessed sleep (duration and efficiency), and was only associated with proximal measures of circadian rhythms (timing and regularity) in unadjusted, but not adjusted, models. One possible explanation for these differential associations is that negative affect biases the self-report of sleep in individuals with higher depressive symptoms. That is, women with higher past depressive symptoms may be more likely to perceive their sleep as poor. Another explanation may be that depressive symptoms prospectively affect next-day functioning (alertness and satisfaction), but do not impact nocturnal sleep or circadian rhythms. This latter explanation would contrast with a large and consistent literature demonstrating an association between depression and sleep and circadian rhythms (Bao et al., 2017; McClung, 2013). To empirically test these two explanations, future research might compare a self-report sleep health construct to a behaviorally-assessed sleep health construct, which would include objective measures of next-day functioning (e.g. performance on the psychomotor vigilance task, an objective measure of alertness; Dinges & Powell, 1985). Additionally, a novel clinical intervention might provide individuals with higher depressive symptoms with feedback from actigraphy assessments to evaluate whether this changes perception of sleep satisfaction and alertness (see Tang & Harvey, 2004, for evidence that actigraphy feedback can improve

perceptions of sleep). Consistent with our hypothesis, we report that higher depressive symptoms is a significant antecedent of poorer sleep health in midlife women.

We evaluated physical activity and BMI as plausible biobehavioral mediators of the significant association between higher depressive symptoms and poorer sleep health. Mounting evidence suggests that cognitive behavioral therapy for depression improves sleep quality (Carney, Segal, Edinger, & Krystal, 2007), and therefore understanding how depression disrupts sleep may improve the precision of therapeutic interventions. Importantly, we assessed depressive symptoms two years before our mediators, and we measured our mediators two years before the sleep study. This approach provides temporal precedence.

Body mass index was a significant mediator of the relationship between higher depressive symptoms and poorer sleep health. Greater mean depressive symptoms was prospectively associated with higher BMI, which is consistent with meta-analytic evidence suggesting that depression is prospectively associated with an increase in BMI (Luppino et al., 2010). Higher BMI was associated with poorer sleep health, which corroborates previous work suggesting similar associations (Resta et al., 2003; Vgontzas et al., 2003). If this were replicated, a weight-loss intervention designed for midlife women with depression would be expected to have benefits for sleep health. Emerging evidence suggests that individuals with depression are less responsive to standard weight-loss interventions (Pagoto et al., 2007), and thus an intervention tailored to midlife women with depression is needed for this population at-risk for poor sleep health.

Physical activity was also a significant mediator that explained some of the variance of the association between higher mean depressive symptoms and poorer sleep health. This finding is consistent with meta-analytic evidence that higher depressive symptoms are prospective

associated with lower physical activity (Roshanaei-Moghaddam, Katon, & Russo, 2009), and that lower physical activity is associated with poorer sleep (Kredlow et al., 2015). These data provide preliminary support for a physical activity intervention in individuals with depression to prevent or improve sleep outcomes. This intervention strategy seems reasonable, as a previous randomized controlled trial showed that a physical activity intervention improved sleep characteristics in a sample of individuals with insomnia (Reid et al., 2010). Unknown is the role that a physical activity intervention would have on the sleep of individuals with depression.

Because the association between higher depressive symptoms and sleep health was not fully explained by physical activity or BMI, other modifiable mediators of the association are important to evaluate to improve interventions for midlife woman. One pathway may be through vasomotor symptoms. Longitudinal evidence has suggested that depressive symptoms precede incident vasomotor symptoms (Freeman, Sammel, & Lin, 2009), and vasomotor symptoms have been shown to affect sleep continuity (Thurston, Santoro, & Matthews, 2012). Another possible mediator may be social support. Depression has been shown to be prospectively associated with decreases in social support (Stice, Ragan, & Randall, 2004), while perceived loneliness has been associated with greater actigraphy-assessed sleep fragmentation (Kurina et al., 2011). In summary, our study provides preliminary evidence that accounting for physical activity partially explains the link between depressive symptoms and sleep disturbances in midlife women, and suggests that other modifiable biobehavioral mediators warrant further investigation.

Variability in depressive symptoms was not significantly related to sleep health in adjusted models, nor was variability in depressive symptoms a significant moderator of the association between mean depressive symptoms and sleep health. One possible reason for this non-significant result is that higher mean level, but not higher variability in, depressive

symptoms may truly be what is negatively impacting sleep in midlife women. Several previous studies have reported that higher mean level, but not variability in, depressive symptoms is associated with greater risk of insomnia symptoms (Lampio et al., 2016; Woods & Mitchell, 2010). Future studies with larger ranges in variability in depressive symptoms would help to clarify the role of both mean level and variability in depressive symptoms and possibly determine whether variability is unrelated to sleep disturbances in midlife women.

Because sleep health is an emerging construct, we evaluated the relationships between covariates and sleep health. Race, menopausal status, and AHI were consistent, significant correlates of sleep health in the present sample of midlife women. African American women had poorer sleep health compared to European American. This is consistent with a meta-analysis of 14 studies reporting that African Americans have less deep sleep, poorer sleep continuity, and shorter sleep duration compared to European Americans (Ruiter, DeCoster, Jacobs, & Lichstein, 2011). Late perimenopausal status, relative to premenopausal status, was associated with poorer sleep health. This is consistent with a meta-analysis of 21 studies reporting that perimenopause (early or late) was associated with 1.60 greater odds of self-reported insomnia symptoms compared to premenopausal women (Xu & Lang, 2014). Higher AHI scores were associated with poorer sleep health. This result is unsurprising, as excessive daytime sleepiness and fatigue are common symptoms of obstructive sleep apnea due to intermittent hypoxia and increased sleep fragmentation (American Psychiatric Association, 2013). In sum, race, menopausal status, and AHI may be important correlates of sleep health in midlife women.

4.1 Study design considerations

Several limitations of the current study should be noted. First, although longitudinal, our study cannot be used to infer causality. The dynamics between depressive symptoms, physical activity,

and sleep health may occur on a different time scale than what we measured (i.e. occurring at the monthly level rather than over two years). There may also be additional variables that were not accounted for in our study. Second, our results do not generalize to middle-aged men, nor to older or younger age groups. Midlife for women is characterized by menopause, which causes unique changes in hormones and physiology that are not present in other populations. Third, our sample is limited in its range of mean and variability in depressive symptoms. A longitudinal study that oversampled midlife women with depressive symptoms would more effectively examine these relationships.

The present study has notable strengths. First, the study evaluates sleep using actigraphy, measuring habitual rest-activity patterns in participants' natural environment for nearly a month (M = 29 days). Second, our study evaluates putative mediators of the association between depressive symptoms and sleep health with clear temporal precedence. The model tests depressive symptoms averaged over four years, then assesses BMI and physical activity two years later, and then sleep health two years later. Third, our results did not substantially change when we used multiple imputation to address missing data. It was plausible that women with higher mean depressive symptoms might be less likely to attend a core SWAN follow-up visit, which might account for the missingness. Given the longitudinal nature of the core SWAN study, we had the opportunity to create imputations based on six to nine visits of data, which improves the plausibility of estimates.

In conclusion, higher mean depressive symptoms was prospectively associated with poorer sleep health in a sample of midlife women. Physical activity and BMI were significant mediators of the association. These antecedents of sleep disturbances are noteworthy, given the prevalence of clinically significant depressive symptoms, obesity, and inadequate regular

physical activity in midlife women. However, depressive symptoms, weight, and physical activity are modifiable risk factors, and interventions designed to target these factors may be well-suited for improving sleep disturbances and the subsequent effect of sleep on adverse health outcomes, including diabetes, cardiovascular disease, and early mortality.

5.0 References

Ainsworth, B. E., Sternfeld, B., Richardson, M. T., & Jackson, K. (1999). Evaluation of the Kaiser Physical Activity Survey in women. *Medicine & Science in Sports & Exercise, 32*(7), 1327-1338. http://dx.doi.org/10.1097/00005768-200007000-00022

American Academy of Sleep Medicine Task Force (1999. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep 22,* 667-89.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®).* American Psychiatric Publications.

Appelhans, B. M., Janssen, I., Cursio, J. F., Matthews, K. A., Hall, M., Gold, E. B., … Kravitz, H. M. (2013). Sleep duration and weight change in midlife women: The SWAN sleep study. *Obesity*, *21*(1), 77–84. https://doi.org/10.1002/oby.20251

Avis, N. E., & Crawford, S. L. (2001). SWAN : What it is and what we hope to learn. *Menopause Manage*, *10*(3), 8–15.

Baglioni, C., Battagliese, G., Feige, B., Spiegelhalder, K., Nissen, C., Voderholzer, U., ... & Riemann, D. (2011). Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders, 135*(1-3), 10-19. 2011 https://doi.org/10.1016/j.jad.2011.01.011

Bao, Y.-P., Han, Y., Ma, J., Wang, R.-J., Shi, L., Wang, T.-Y., … Lu, L. (2017). Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: Meta-analysis and systematic review. *Neuroscience & Biobehavioral Reviews*, *75*, 257–273. https://doi.org/10.1016/j.neubiorev.2017.01.032

Baron, K. G., Reid, K. J., Kern, A. S., & Zee, P. C. (2011). Role of sleep timing in caloric intake and BMI. *Obesity*, *19*(7), 1374–1381. https://doi.org/10.1038/oby.2011.100

Blümel, J. E., Chedraui, P., Aedo, S., Fica, J., Mezones-Holguín, E., Barón, G., ... & Flores, D. (2015). Obesity and its relation to depressive symptoms and sedentary lifestyle in middle-aged women. *Maturitas*, *80*(1), 100-105. https://doi.org/10.1016/j.maturitas.2014.10.007.

Brindle, R. C., Cribbet, M. R., Samuelsson, L. B., Krafty, R. T., Thayer, J. F., Buysse, D. J., & Hall. (2018). The relationship between childhood trauma and poor sleep health in adulthood. *Psychosomatic Medicine*, *80*(2), 200–207. https://doi.org/10.1097/PSY.0000000000000542

Bromberger, J. T., Kravitz, H. M., Wei, H. L., Brown, C., Youk, A. O., Cordal, A., ... & Matthews, K. A. (2005). History of depression and women's current health and functioning during midlife. *General Hospital Psychiatry*, *27*(3), 200-208. https://doi.org/10.1016/j.genhosppsych.2005.01.007

Bromberger, J. T., Kravitz, H. M., Youk, A., Schott, L. L., & Joffe, H. (2016). Patterns of depressive disorders across 13 years and their determinants among midlife women: SWAN mental health study. *Journal of Affective Disorders*, *206*, 31–40. https://doi.org/10.1016/j.jad.2016.07.005

Brown, C., Bromberger, J. T., Schott, L. L., Crawford, S., & Matthews, K. A. (2014). Persistence of depression in African American and Caucasian women at midlife: Findings from the Study of Women Across the Nation (SWAN). *Archives of Women's Mental Health*, *17*(6), 549-557.

Buysse, D. J. (2014). Sleep health: Can we define it? Does it matter? *Sleep*, *37*(1), 9–17. https://doi.org/http://dx.doi.org/10.5665/sleep.3298

Campbell, I. G., Bromberger, J. T., Buysse, D. J., Hall, M. H., Hardin, K. A., Kravitz, H. M., … Gold, E. (2011). Evaluation of the association of menopausal status with delta and beta EEG activity during sleep. *Sleep*, *34*(11), 1561–1568. https://doi.org/10.5665/sleep.1398

Cappuccio, F. P., Cooper, D., Delia, L., Strazzullo, P., & Miller, M. A. (2011). Sleep duration predicts cardiovascular outcomes: A systematic review and meta-analysis of prospective studies. *European Heart Journal*, *32*(12), 1484–1492. https://doi.org/10.1093/eurheartj/ehr007

Cappuccio, F. P., D'Elia, L., Strazzullo, P., & Miller, M. A. (2010). Sleep duration and all-cause mortality: A systematic review and meta-analysis of prospective studies. *Sleep*, *33*(5), 585–592.

Carney, C. E., Segal, Z. V., Edinger, J. D., & Krystal, A. D. (2007). A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *Journal of Clinical Psychiatry*, *68*(2), 254–260. https://doi.org/10.4088/JCP.v68n0211

Center for Disease Control and Prevention. Health, United States, 2016. Retrieved from https://www.cdc.gov/nchs/data/hus/hus16.pdf#053.

Church, T. S., Earnest, C. P., Skinner, J. S., & Blair, S. N. (2007). Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. *JAMA*, *297*(19), 2081-2091.

Cirignotta, F., Mondini, S., Zucconi, M., Luigi Lenzi, P., & Lugaresi, E. (1985). Insomnia: An Epidemiological Survey. *Clinical Neuropharmacology*, S49–S54.

Cohen, L. S., Soares, C. N., Vitonis, A. F., Otto, M. W., & Harlow, B. L. (2006). Risk for new

onset of depression during the menopausal transition. *Arch Gen Psychiatry*, *63*. https://doi.org/10.1001/archpsyc.63.4.385

D'Agostino, R. B., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation, 117*(6), 743-753.

Da Silva, M. A., Singh-Manoux, A., Brunner, E. J., Kaffashian, S., Shipley, M. J., Kivimäki, M., & Nabi, H. (2012). Bidirectional association between physical activity and symptoms of anxiety and depression: The Whitehall II study. *European Journal of Epidemiology*, *27*(7), 537-546.

Dennerstein, L., Dudley, E. C., Hopper, J. L., Guthrie, J. R., & Burger, H. G. (2000). A prospective population-based study of menopausal symptoms. *Obstetrics & Gynecology*, *96*(3), 351–358. https://doi.org/10.1016/S0029-7844(00)00930-3

Dinges, D. F., & Powell, J. W. (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior Research Methods, Instruments, & Computers*, *17*(6), 652-655.

Dixon, J. B., Schachter, L. M., & Brien, P. E. O. (2001). Sleep disturbance and obesity. *Archives of Internal Medicine*, *161*(8), 102–106.

Elavsky, S., & McAuley, E. (2007). Physical activity and mental health outcomes during menopause: A randomized controlled trial. *Annals of Behavioral Medicine*, *33*(2), 132–142.

Epstein, L. J., Kristo, D., Strollo, P. J., Friedman, N., Malhotra, A., Patil, S. P., ... & Weinstein, M. D. (2009). Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of Clinical Sleep Medicine*, *5*(03), 263-276.

Everson-Rose, S. A., Ph, D., Lewis, T. T., Karavolos, K., Sheila, A., Wesley, D., & Powell, L. H.

(2009). Depressive symptoms and increased visceral fat in middle-aged women. *Psychosomatic Medicine*, *71*(4), 410–416. https://doi.org/10.1097/PSY.0b013e3181a20c9c

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175-191.

Fox, C. S., Massaro, J. M., Hoffmann, U., Pou, K. M., Maurovich-Horvat, P., Liu, C. Y., ... O'Donnell, C. J. (2007) Abdominal visceral and subcutaneous adipose tissue compartments: Association with metabolic risk factors in the Framingham Heart Study. *Circulation*, *116*(1), 39-48. https://doi.org/10.1161/CIRCULATIONAHA.106.675355

Furihata, R., Hall, M. H., Stone, K. L., Ancoli-Israel, S., Smagula, S. F., Cauley, J. A., ... & Buysse, D. J. (2017). An aggregate measure of sleep health is associated with prevalent and incident clinically significant depression symptoms among community-dwelling older women. *Sleep*, *40*(3). https://doi.org/10.1093/sleep/zsw075

Gastwirth, J. L., Gel, Y. R., & Miao, W. (2009). The impact of Levene's test of equality of variances on statistical theory and practice. *Statistical Science*, *24*(3), 343-360. https://doi.org/10.1214/09-STS30I

Germain, A., & Kupfer, D. J. (2008). Circadian rhythm disturbances in depression. *Human Psychopharmacology*, *23*, 571–585. https://doi.org/10.1002/hup.964

Gold, E. B., Block, G., Crawford, S., Lachance, L., FitzGerald, G., Miracle, H., & Sherman, S. (2004). Lifestyle and demographic factors in relation to vasomotor symptoms: Baseline results from the study of women's health across the nation. *American Journal of Epidemiology*, *159*(12), 1189–1199. https://doi.org/10.1093/aje/kwh168

Gold, E. B., Colvin, A., Avis, N., Bromberger, J., Greendale, G. A., Powell, L., … Matthews, K.

(2006). Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. *American Journal of Public Health*, *96*(7), 1226–1235. https://doi.org/10.2105/AJPH.2005.066936

Graham, J. W., Olchowski, A. E., & Gilreath, T. D. (2007). How many imputations are really needed? Some practical clarifications of multiple imputation theory. *Prevention Science*, *8*(3), 206-213.

Harlow, S. D., Gass, M., Hall, J. E., Lobo, R., Maki, P., Rebar, R. W., … de Villiers, T. J. (2012). Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Menopause: The Journal of The North American Menopause Society, 19(4)*(4), 1–9. https://doi.org/10.1016/S0015-0282(01)02909-0

Haskell, W. L., Lee, I. M., Pate, R. R., Powell, K. E., Blair, S. N., Franklin, B. A., ... & Bauman, A. (2007). Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*, *116*(9), 1081.

Israel, B., Buysse, D. J., Krafty, R. T., Begley, A., Miewald, J., & Hall, M. H. (2012). Short-term stability of sleep and heart rate variability in good sleepers and patients with insomnia: for some measures, one night is enough. *Sleep, 35*(9), 1285-1291.

Janssen, I., Dugan, S. A., Karavolos, K., Lynch, E. B., & Powell, L. H. (2014). Correlates of 15-year maintenance of physical activity in middle-aged women. *International Journal of Behavioral Medicine, 21*(3), 511–518. https://doi.org/10.1007/s12529-013-9324-z

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep, 14*(6), 540–545.

Karvonen-Gutierrez, C., & Kim, C. (2016, July). Association of mid-life changes in body size, body composition and obesity status with the menopausal transition. In *Healthcare* (Vol. 4, No. 3, p. 42). Multidisciplinary Digital Publishing Institute. https://doi:10.3390/healthcare4030042

Kitamura, S., Hida, A., Watanabe, M., Enomoto, M., Aritake-Okada, S., Moriguchi, Y., … Mishima, K. (2010). Evening preference is related to the incidence of depressive states independent of sleep-wake conditions. *Chronobiology International*, *27*(9–10), 1797–1812. https://doi.org/10.3109/07420528.2010.516705

Kline, C. E., Irish, L. A., Krafty, R. T., Sternfeld, B., Kravitz, H. M., Buysse, D. J., … Hall, M. H. (2013). Consistently high sports/exercise activity is associated with better sleep quality, continuity and depth in midlife women: The SWAN sleep study. *Sleep*, *36*(9), 1279–88. https://doi.org/10.5665/sleep.2946

Knight, R. G., Williams, S., McGee, R., & Olaman, S. (1997). Psychometric properties of the Centre for Epidemiological Studies Depression Scale (CES-D) in a sample of women in mid life. *Behavior Research and Therapy, 35(4): 373*(4), 373–380.

Kravitz, H. M., Janssen, I., Bromberger, J. T., Matthews, K. A., Hall, M. H., Ruppert, K., & Joffe, H. (2017). Sleep trajectories before and after the final menstrual period in the Study of Women's Health Across the Nation (SWAN). *Current Sleep Medicine Reports, 3*(3), 235-250.

Kravitz, H. M., Zhao, X., Bromberger, J. T., Gold, E. B., Hall, M. H., Matthews, K. A., & Sowers, M. R. (2008). Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. *Sleep: Journal of Sleep and Sleep Disorders Research, 31*(7), 979–990.

Kredlow, M. A., Capozzoli, M. C., Hearon, B. A., Calkins, A. W., & Otto, M. W. (2015). The effects of physical activity on sleep: A meta-analytic review. *Journal of Behavioral Medicine*, *38*(3), 427–449. https://doi.org/10.1007/s10865-015-9617-6

Kurina, L. M., Knutson, K. L., Hawkley, L. C., Cacioppo, J. T., Lauderdale, D. S., & Ober, C. (2011). Loneliness is associated with sleep fragmentation in a communal society. *Sleep*, *34*(11), 1519–1526. https://doi.org/http://dx.doi.org/10.5665/sleep.1390

Lambiase, M. J., & Thurston, R. C. (2013). Physical activity and sleep among midlife women with vasomotor symptoms. *Menopause*, *20*(9), 946–952. https://doi.org/10.1097/gme.0b013e3182844110

Lampio, L., Polo-Kantola, P., Himanen, S.-L., Kurki, S., Huupponen, E., Engblom, J., … Saaresranta, T. (2017). Sleep during menopausal transition: A six-year follow-up. *Sleep*, *40*(7). https://doi.org/10.1093/sleep/zsx090

Lampio, L., Saaresranta, T., Engblom, J., Polo, O., & Polo-Kantola, P. (2016). Predictors of sleep disturbance in menopausal transition. *Maturitas*, *94*, 137–142. https://doi.org/10.1016/j.maturitas.2016.10.004

Li, L., Wu, C., Gan, Y., Qu, X., & Lu, Z. (2016). Insomnia and the risk of depression: A meta-analysis of prospective cohort studies. *BMC Psychiatry*, *16*(1). https://doi.org/10.1186/s12888-016-1075-3

Lovejoy, J. C., Champagne, C. M., De Jonge, L., Xie, H., & Smith, S. R. (2008). Increased visceral fat and decreased energy expenditure during the menopausal transition. *International Journal of Obesity*, *32*(6), 949–958. https://doi.org/10.1038/ijo.2008.25

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W. J. H., & Zitman, F. G. (2010). Overweight, Obesity, and Depression. *Archives of General*

Psychiatry, *67*(3), 220. https://doi.org/10.1001/archgenpsychiatry.2010.2

McAndrew, L. M., Napolitano, M. A., Albrecht, A., Farrell, N. C., Marcus, B. H., & Whiteley, J. A. (2009). When, why and for whom there is a relationship between physical activity and menopause symptoms. *Maturitas*, *64*(2), 119–125. https://doi.org/10.1016/j.maturitas.2009.08.009

McClung, C. A. (2013). How might circadian rhythms control mood? Let me count the ways... *Biological Psychiatry*, *74*(4), 242–249. https://doi.org/10.1016/j.biopsych.2013.02.019

Murabito, J. M., Massaro, J. M., Clifford, B., Hoffmann, U., & Fox, C. S. (2013). Depressive symptoms are associated with visceral adiposity in a community-based sample of middle-aged women and men. *Obesity*, *21*(8), 1713–1719. https://doi.org/10.1002/oby.20130

North American Menopause Society. Menopause Practice: A Clinician's Guide. 3rd ed. Cleveland, OH: North American Menopause Society; 2007.

Pagoto, S., Bodenlos, J. S., Kantor, L., Gitkind, M., Curtin, C., & Ma, Y. (2007). Association of major depression and binge eating disorder with weight loss in a clinical setting. *Obesity*, *15*(11), 2557-2559.

Patel, S. R., Malhotra, A., Gottlieb, D. J., White, D. P., & Hu, F. B. (2006). Correlates of long sleep duration. *Sleep*, *29*(7), 881-889.

Penedo, F. J., & Dahn, J. R. (2005). Exercise and well-being: A review of mental and physical health benefits associated with physical activity. *Current Opinion in Psychiatry*, *18*(2), 189-193.

Pereira, S. M. P., Geoffroy, M. C., & Power, C. (2014). Depressive symptoms and physical activity during 3 decades in adult life: Bidirectional associations in a prospective cohort study. *JAMA Psychiatry*, *71*(12), 1373-1380.

Pien, G. W., Sammel, M. D., Freeman, E. W., Lin, H., & DeBlasis, T. L. (2008). Predictors of sleep quality in women in the menopausal transition. *Sleep*, *31*(7), 991–9.

Radloff, L. S. (1977). A self-report depression scale for research in the general population. *Applied Psycholigcal Measures*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Reid, K. J., Baron, K. G., Lu, B., Naylor, E., Wolfe, L., & Zee, P. C. (2010). Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. *Sleep Medicine*, *11*(9), 934-940.

Resta, O., Barbaro, M. P. F., Bonfitto, P., Giliberti, T., Depalo, a, Pannacciulli, N., & De Pergola, G. (2003). Low sleep quality and daytime sleepiness in obese patients without obstructive sleep apnoea syndrome. *Journal of Internal Medicine*, *253*(5), 536–543. https://doi.org/10.1046/j.1365-2796.2003.01133.x

Roshanaei-Moghaddam, B., Katon, W. J., & Russo, J. (2009). The longitudinal effects of depression on physical activity. *General Hospital Psychiatry*, *31*(4), 306–315. https://doi.org/10.1016/j.genhosppsych.2009.04.002

Ruiter, M. E., DeCoster, J., Jacobs, L., & Lichstein, K. L. (2011). Normal sleep in African-Americans and Caucasian-Americans: A meta-analysis. *Sleep Medicine*, *12*(3), 209-214.

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., ... & Thase, M. E. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*, *54*(5), 573-583.

Shaver, J., Giblin, E., Lentz, M., & Lee, K. (1988). Sleep patterns and stability in perimenopausal women. *Sleep*, *11*(6), 556–561. https://doi.org/10.1093/sleep/11.6.556

Sowers, M. F., Zheng, H., Kravitz, H. M., Matthews, K., Bromberger, J. T., Gold, E. B., … Hall,

M. (2008). Sex steroid hormone profiles are related to sleep measures from polysomnography and the Pittsburgh sleep quality index. *Sleep*, *31*(10), 1339–1349.

Sternfeld, B., Ainsworth, B. E., & Quesenberry Jr, C. P. (1999). Physical activity patterns in a diverse population of women. *Preventive Medicine*, *28*(3), 313-323.

Sternfeld, B., Bhat, A. K., Wang, H., Sharp, T., & Queensberry, C. P. (2005). Menopause, physical activity, and body composition/fat distribution in midlife women. *Medicine & Science in Sports & Exercise*, *37*(7), 1195-1202.

Stice, E., Ragan, J., & Randall, P. (2004). Prospective relations between social support and depression: Differential direction of effects for parent and peer support? *Journal of Abnormal Psychology*, *113*(1), 155–159. https://doi.org/10.1037/0021-843X.113.1.155

Stuart, E. A., Azur, M., Frangakis, C., & Leaf, P. (2009). Multiple imputation with large data sets: a case study of the Children's Mental Health Initiative. *American Journal of Epidemiology*, *169*(9), 1133-1139.

Substance Abuse and Mental Health Services Administration (SAMHSA). Key substance use and mental health indicators in the United States: Results from the 2015 national survey on drug use and health. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.pdf. Published Sep 2016. Accessed November 15, 2017.

Tang, N. K., & Harvey, A. G. (2004). Correcting distorted perception of sleep in insomnia: A novel behavioural experiment?. *Behaviour Research and Therapy*, *42*(1), 27-39.

Thurston, R. C., Santoro, N., & Matthews, K. A. (2012). Are vasomotor symptoms associated with sleep characteristics among symptomatic midlife women? Comparisons of self-report and objective measures. *Menopause: The Journal of The North American Menopause Society*,

19(7), 742–748. https://doi.org/10.1097/gme.0b013e3182422973

Toor, P., Kim, K., & Buffington, C. K. (2012). Sleep quality and duration before and after bariatric surgery. *Obesity Surgery*, *22*(6), 890–895. https://doi.org/10.1007/s11695-011-0541-8

Tworoger, S. S., Yasui, Y., Vitiello, M. V., Schwartz, R. S., Ulrich, C. M., Aiello, E. J., … McTiernan, A. (2003). Effects of a yearlong moderate-intensity exercise and a stretching intervention on sleep quality in postmenopausal women. *Sleep*, *26*(7), 830–836. https://doi.org/10.1093/sleep/26.7.830

United States Census Bureau. (2017). *Voting and registration in the election of November 2016, all races* [Data file]. Retrieved from https://www.census.gov/data/tables/time-series/demo/voting-and-registration/p20-580.html

United States Census Bureau. (2007). Age and sex composition in the United States: 2005, all population [Data file]. Retrieved from https://www.census.gov/data/tables/2005/demo/age-and-sex/2005-age-sex-composition.html

Utian, W. H. (2005). Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: A comprehensive review, *12*(c), 1–12. https://doi.org/10.1186/1477-7525-3-

Van Dongen, H. P., Vitellaro, K. M., & Dinges, D. F. (2005). Individual differences in adult human sleep and wakefulness: Leitmotif for a research agenda. *Sleep*, *28*(4), 479-498.

Vgontzas, A. N., Bixler, E. O., Tan, T. L., Kantner, D., Martin, L. F., & Kales, A. (1998). Obesity without sleep apnea is associated with daytime sleepiness. *Archives of Internal Medicine*, *158*(12), 1333–1337. https://doi.org/10.1001/archinte.158.12.1333

Win, S., Parakh, K., Eze-Nliam, C. M., Gottdiener, J. S., Kop, W. J., & Ziegelstein, R. C. (2011). Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: The Cardiovascular Health Study. *Heart*, *97*(6), 500-505

Woods, N. F., & Mitchell, E. S. (2005). Symptoms during the perimenopause: Prevalence, severity, trajectory, and significance in women's lives. *The American Journal Of Medicine*, *118*(12B), 14S–24S.

Woods, N. F., & Mitchell, E. S. (2010). Sleep symptoms during the menopausal transition and early postmenopause: Observations from the Seattle Midlife Women's Health Study. *Sleep*, *33*(4), 539–549. https://doi.org/10.1089/jwh.2009.1388

Xu, M., Bélanger, L., Ivers, H., Guay, B., Zhang, J., & Morin, C. M. (2011). Comparison of subjective and objective sleep quality in menopausal and non-menopausal women with insomnia. *Sleep Medicine*, *12*(1), 65–69. https://doi.org/10.1016/j.sleep.2010.09.003

Xu, Q., & Lang, C. P. (2014). Examining the relationship between subjective sleep disturbance and menopause. *Menopause*, *21*(12), 1301–1318. https://doi.org/10.1097/GME.0000000000000240

Xu, Q., Lang, C. P., & Rooney, N. (2014). A systematic review of the longitudinal relationships between subjective sleep disturbance and menopausal stage. *Maturitas*, *79*(4), 401–412. https://doi.org/10.1016/j.maturitas.2014.09.011

Young, T., Rabago, D., Zgierska, A., Austin, D., & Laurel, F. (2003). Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. *Sleep*, *26*(6), 667–672.

Zhang, Z. (2014). Monte Carlo based statistical power analysis for mediation models: Methods and software. *Behavior research methods*, *46*(4), 1184-1198.

Appendix A. Tables and Figures

Table 1. *Sleep health cut-offs.*

Sleep Health Component	Operationalization	Cut-off for optimal sleep health
Regularity	Standard deviation of calculated sleep midpoint from actigraphy	**Less than 60 minutes**[1-3]
Satisfaction	Average self-reported sleep quality from daily sleep diary, "restedness upon awakening" (0 = not at all; 4 = extremely)	**"Moderately", "quite a bit", or "extremely" rested upon awakening**[4]
Alertness	Total score on Epworth Sleepiness Scale (0-24)	**Less than 10**[5]
Timing	Average calculated sleep midpoint from actigraphy	**2am – 4am**[2,6-7]
Efficiency	Average sleep efficiency from actigraphy	**Greater than 85%**[8]
Duration	Average total sleep time from actigraphy	**6 to 8 hours**[9]

Note. [1]Roenneberg, Allebrandt, Merrow, & Vetter, 2012; [2]Wittmann, Dinich, Merrow, & Roenneberg, 2006; [3]Wong, Hasler, Kamarck, Muldoon, & Manuck, 2015; [4]Furihata et al, 2017, defined poor sleep health as reporting not getting enough sleep often (5-15nights/month) or almost always (16-30nights/month); [5]Johns, 1991; [6] Baron, Reid, Kern, & Zee, 2011; [7]Roenneberg et al., 2007; [8]Spielman, Saskin, & Thorpy, 1987 [9]Watson et al., 2015, we modified their self-reported sleep duration recommendations to reflect the fact that actigraphy assessed sleep duration is typically approximately one hour less than self-reported sleep duration (Lauderdale et al., 2008).

Table 2. *Sample Characteristics.*

	M (SD)	N (%)
Mean depressive symptoms, CES-D	7.5 (6.2)	
Variability in depressive symptoms, CES-D	4.5 (3.0)	
Body mass index	29.8 (7.9)	
Kaiser Physical Activity Survey	7.5 (1.7)	
Age	52.1 (2.1)	
Race/ethnicity		
European American		140 (46.4)
African American		112 (37.1)
Chinese American		50 (16.6)
Study site		
Pittsburgh, PA		76 (25.2)
Detroit area, MI		60 (19.9)
Chicago, IL		71 (23.5)
Oakland, CA		95 (31.5)
Menopausal status		
Pre-/early perimenopausal		187 (61.9)
Late perimenopausal		58 (19.2)
Postmenopausal		38 (12.6)
Unknown		19 (6.3)
Antidepressant history, proportion of visits	0.11 (0.25)	
Vasomotor symptoms, % of study nights	32.8 (34.1)	
Sleep medications, % of study nights	23.7 (41.3)	
Apnea-hypopnea index	10.5 (15.6)	

Notes. Center for Epidemiological Studies Depression Scale, CES-D; CES-D clinical cut-off $\geq$ 16, Kaiser Physical Activity Scale scores range 0-15, with higher scores indicating more activity.

Table 3. *Sleep health characteristics.*

Continuous sleep variable	M (SD)	***Sleep health***	Optimal, N (%)
Sleep duration, hours, actigraphy	6.0 (0.9)	Duration	145 (48)
Sleep efficiency, actigraphy	78.0 (10.2)	Efficiency	73 (24.2)
Sleep midpoint, actigraphy	3:20a (0:33)	Timing	265 (87.7)
Standard deviation midpoint, actigraphy	42 (18)	Regularity	245 (81.1)
Restedness, diary	2.0 (0.6)	Satisfaction	162 (53.6)
Sleepiness, Epworth Sleepiness Scale	7.7 (4.4)	Alertness	209 (69.2)

Notes. Optimal indicates optimal sleep health for each component.

Table 4. *Mean depressive symptoms and sleep health.*

Unadjusted model	β	*p*
Mean depressive symptoms, CES-D	-0.30	<.001
Adjusted model		
Mean depressive symptoms, CES-D	-0.24	<.001
Age	-0.02	.70
Race/ethnicity		
European American	Reference	
African American	-0.17	.009
Chinese American	-0.13	.07
Study site		
Pittsburgh, PA	Reference	
Detroit area, MI	-0.12	.06
Chicago, IL	-0.03	.69
Oakland, CA	0.14	.10
Menopausal status		
Pre-/early perimenopausal	Reference	
Late perimenopausal	-0.11	.05
Postmenopausal	0.01	.86
Unknown	-0.07	.22
Antidepressants, proportion of visits	0.03	.62
Vasomotor symptoms, %	-0.03	.58
Sleep medications, %	-0.07	.25
Apnea-hypopnea index	-0.18	.001

Notes. Center for Epidemiological Studies Depression Scale, CES-D; Adjusted model indicates that the model includes all covariates

Table 5. *Variability in depressive symptoms and sleep health.*

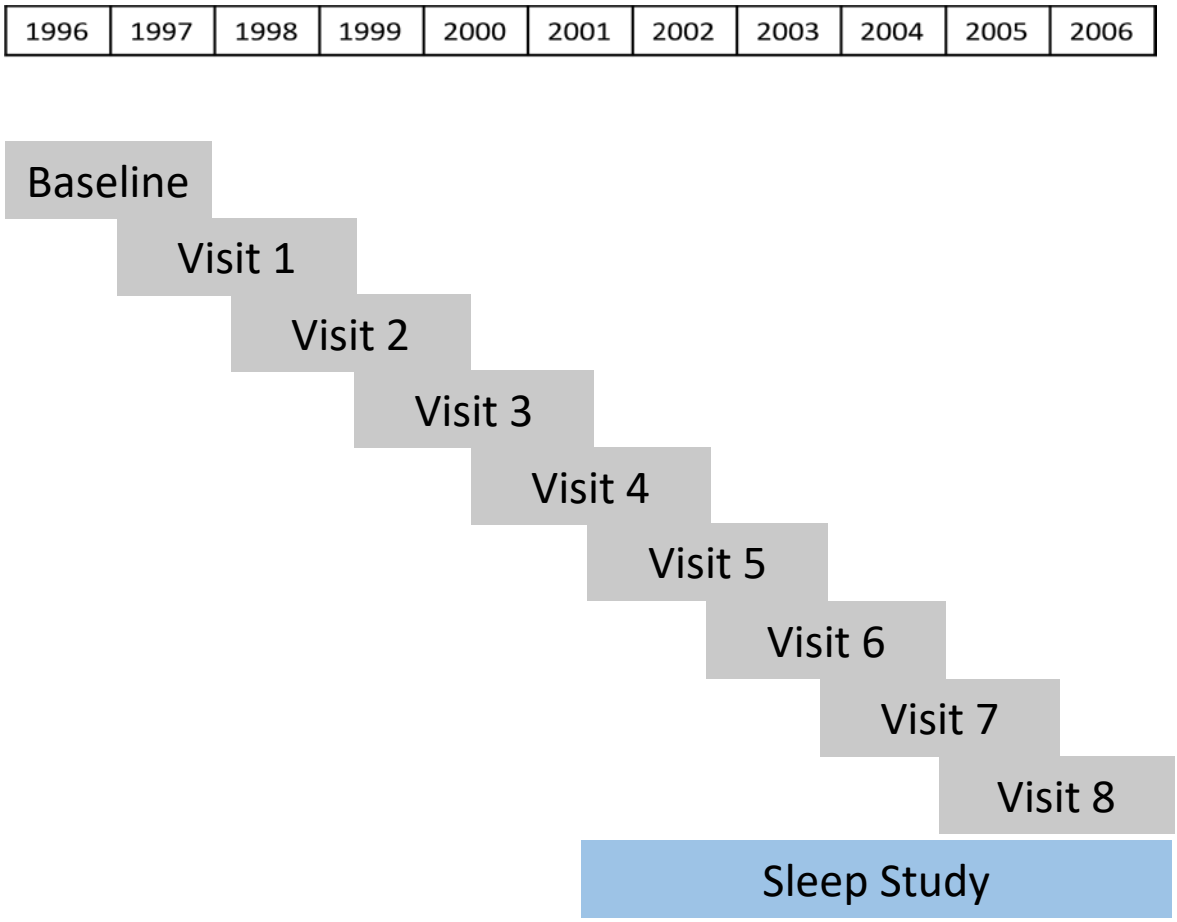
Unadjusted model	β	*p*
Variability in depressive symptoms, CES-D	-0.14	.02
Adjusted model		
Variability in depressive symptoms, CES-D	-0.08	.16
Age	-0.02	.70
Race/ethnicity		
European American	Reference	
African American	-0.18	.008
Chinese American	-0.13	.07
Study site		
Pittsburgh, PA	Reference	
Detroit area, MI	-0.16	.01
Chicago, IL	-0.04	.56
Oakland, CA	0.13	.13
Menopausal status		
Pre-/early perimenopausal	Reference	
Late perimenopausal	-0.09	.11
Postmenopausal	0.01	.89
Unknown	-0.07	.21
Antidepressants, proportion of visits	-0.02	.79
Vasomotor symptoms, %	-0.07	.23
Sleep medications, %	-0.04	.48
Apnea-hypopnea index	-0.18	.001

Notes. Center for Epidemiological Studies Depression Scale, CES-D; Adjusted model indicates that the model includes all covariates; vasomotor symptoms, VMS; apnea hypopnea index, AHI

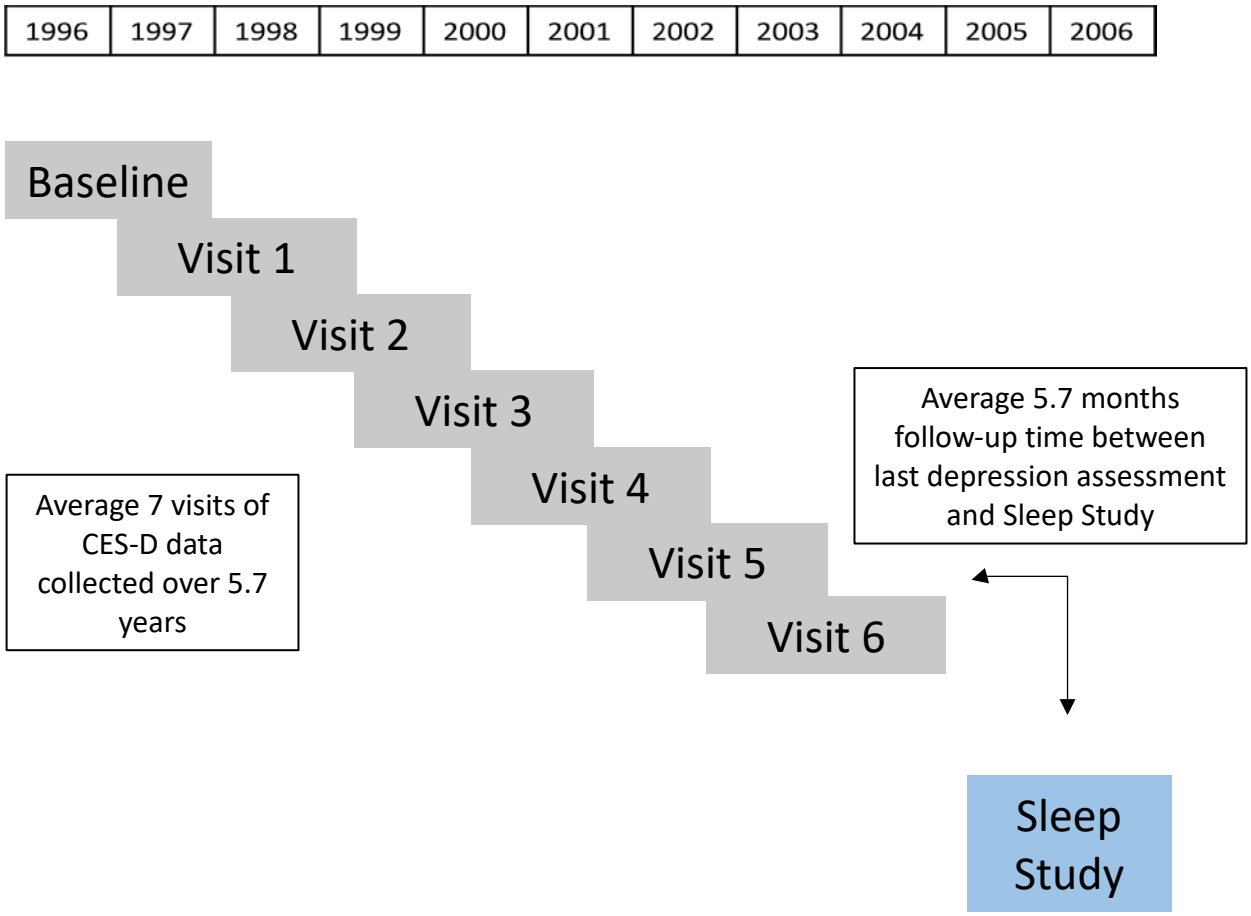
Table 6. *Moderation models.*

	Model 1		Model 2		Model 3		Model 4	
	Basic Model (Mean only)		Mean, variability		Mean, variability, and Interaction		Fully adjusted model	
	β	p	β	p	β	p	β	p
Mean depressive symptoms, CES-D	-0.30	<.001	-0.29	.001	-0.29	.001	-0.27	.001
Variability in depressive symptoms, CES-D			0.09	.26	0.09	.32	0.11	.19
Mean X Variability, CES-D					0.02	.78	0.01	.82
Age							0.01	.93
Race/ethnicity								
European American							Ref	
African American							-0.19	.005
Chinese American							-0.15	.05
Study site								
Pittsburgh, PA							Ref	
Detroit area, MI							-0.13	.05
Chicago, IL							0.01	.91
Oakland, CA							0.17	.06
Menopausal status								
Pre-/early perimenopausal							Ref	
Late perimenopausal							-0.15	.01
Postmenopausal							-0.02	.73
Unknown							-0.06	.31
Antidepressants, proportion of visits							0.02	.78
Vasomotor symptoms, % of study nights							-0.03	.62
Sleep medications, % of study nights							-0.07	.27
Apnea-hypopnea index							-0.15	.01

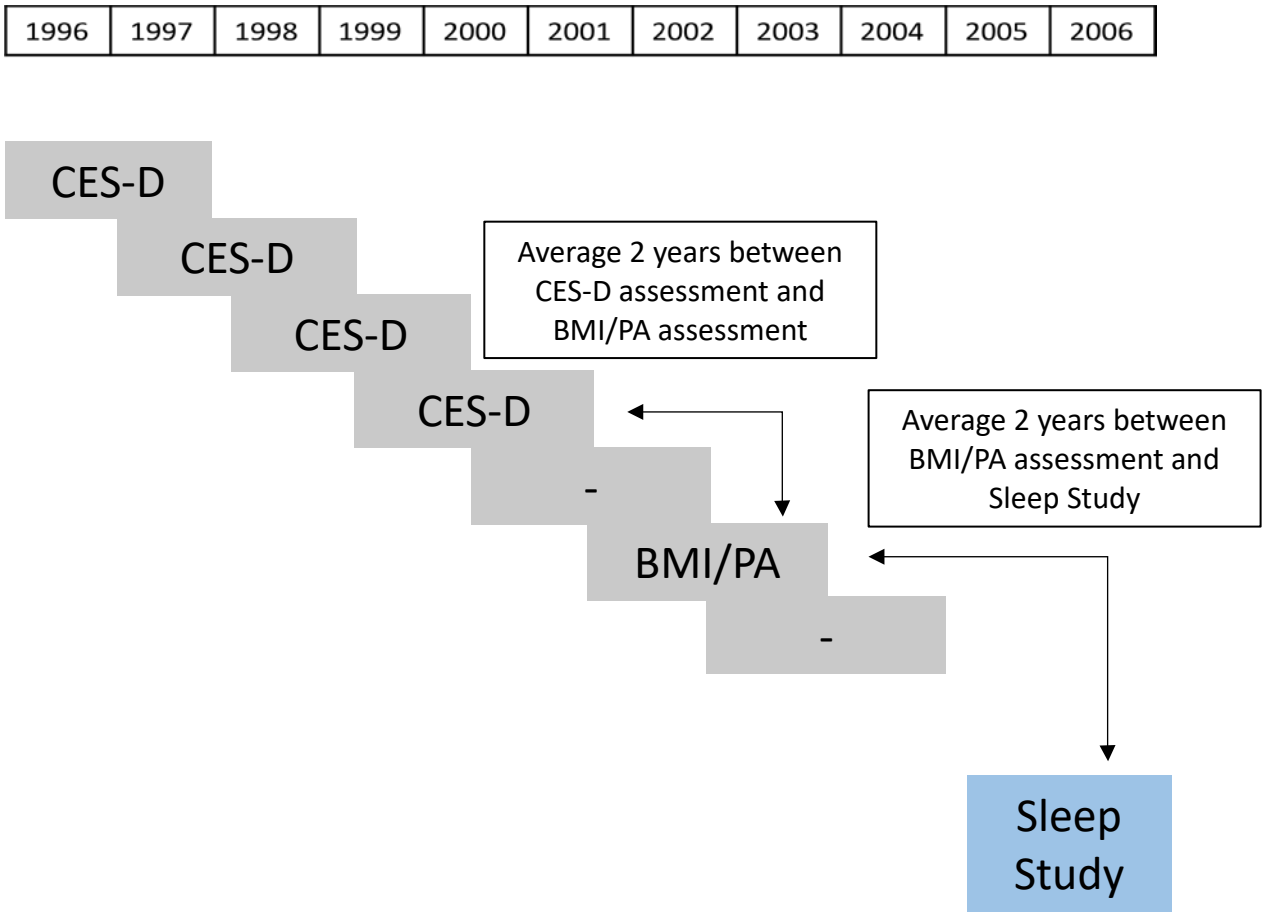
Notes. Center for Epidemiological Studies Depression Scale, CES-D; interaction term, Mean X Variability; Adjusted model indicates that the model includes all covariates.



(a) Data structure for the full sample. Depressive symptoms were assessed from baseline (1996-1997) until the visit preceding the SWAN Sleep Study (follow-up visits 5-8). The SWAN Sleep Study occurred 2001-2006.



(b) Data structure for the average participant in the sample for Aim 1. The average and standard deviation of depressive symptoms were calculated over all visits preceding the SWAN Sleep Study.



(c) Data structure for all participants for Aim 2. Depressive symptoms, assessed using the Center for Epidemiological Studies Depression Scale (CES-D), was measured at four visits. Two years later, body mass index (BMI) and physical activity (PA) were measured. Two years later, sleep health was measured at the SWAN sleep study.

Figure 1. Visualizing the structure of the core SWAN study and the ancillary SWAN Sleep Study.

(a) depicts the structure of the data overall; (b) depicts the structure of the data for the average participant for Aim 1; (c) depicts the structure of the data for all participants for Aim 2.

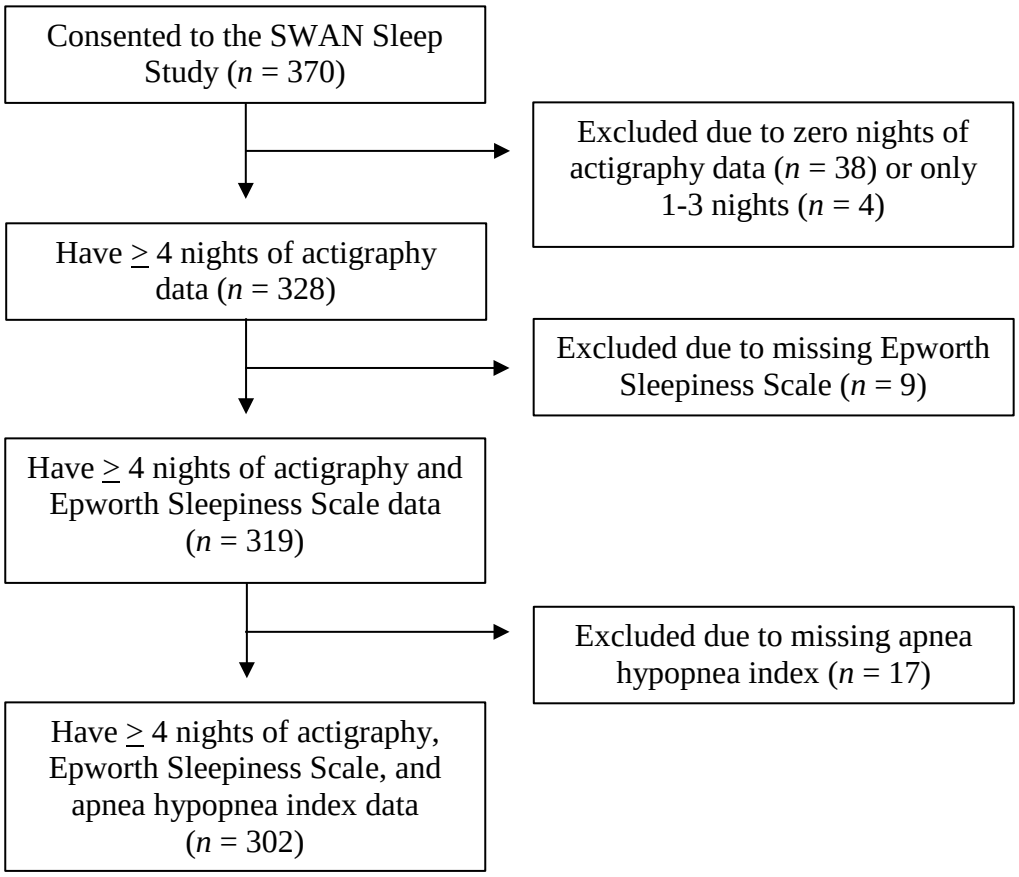


Figure 2. Data reduction strategy.

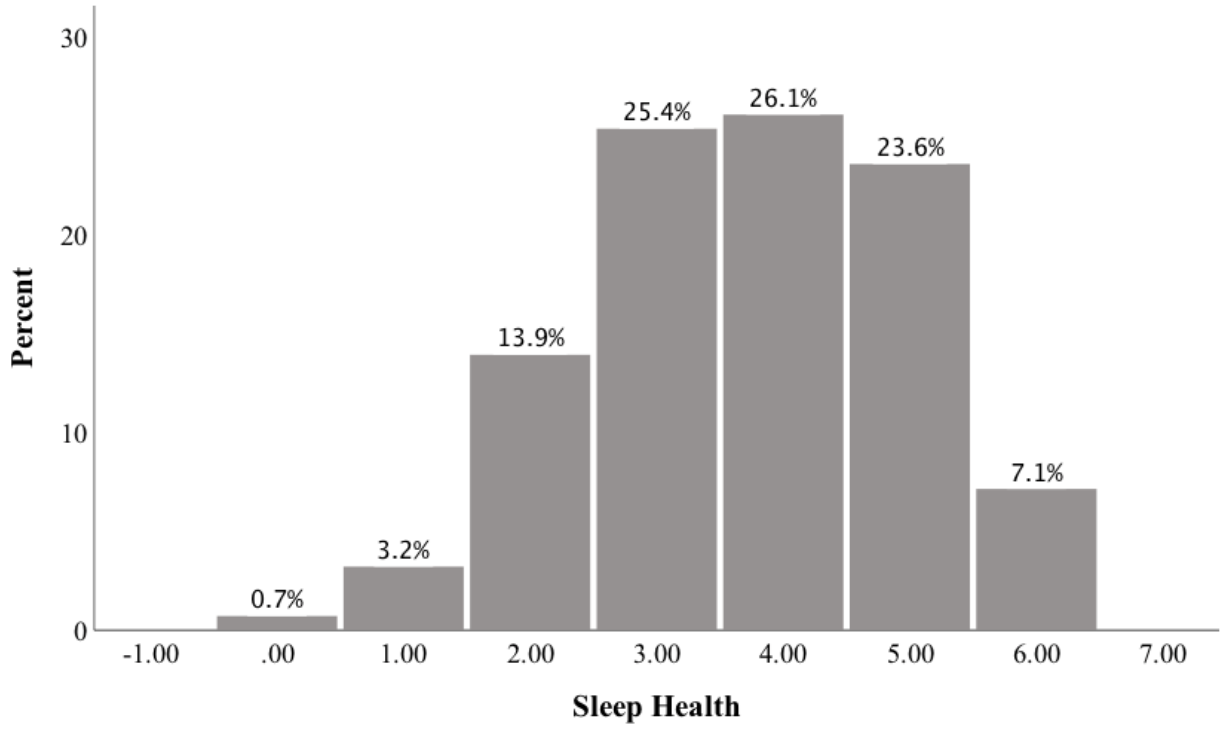


Figure 3. Distribution of sleep health.

Note that the percentage of participants in each category is depicted. Possible sleep health values range from 0-6.

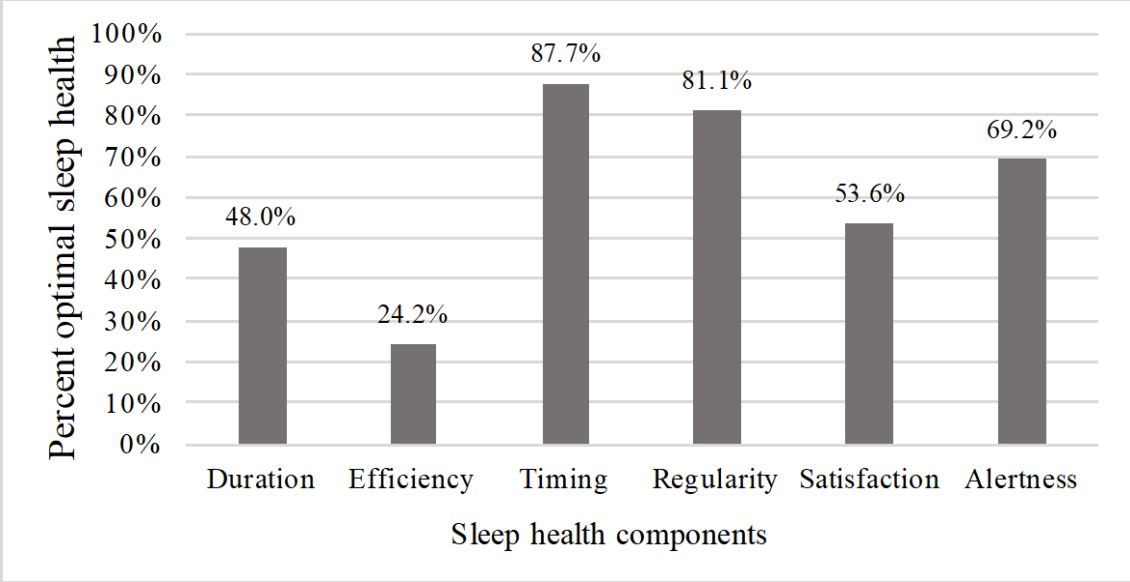


Figure 4. Percent of women with optimal sleep health for each sleep health component.

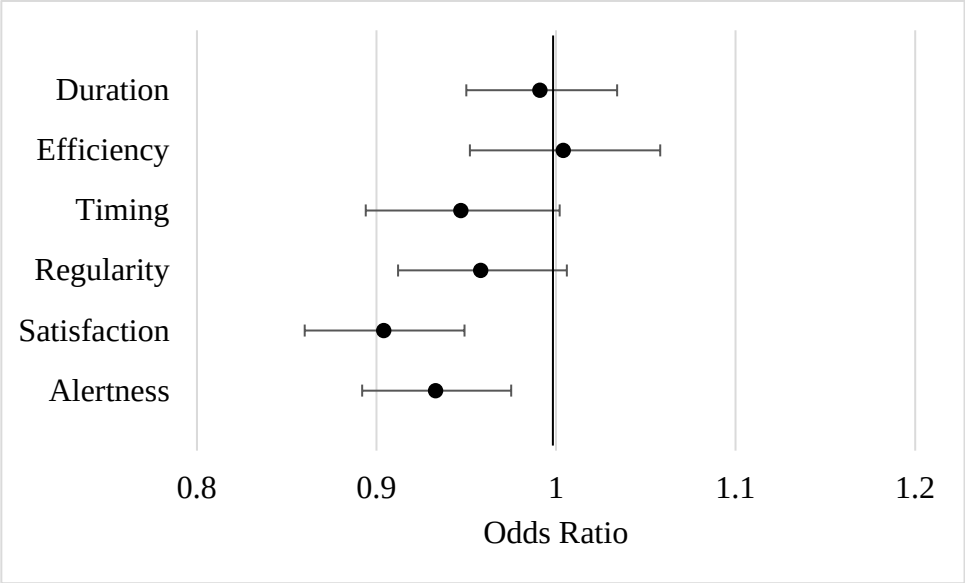


Figure 5. Mean depressive symptoms and individual components of sleep health.

Figure depicts adjusted models, which include the following covariates: age, race (African American and Chinese American as dummy variables, European American as reference), site (Detroit, Oakland, and Chicago as dummy variables, Pittsburgh as reference), menopausal status (late perimenopause, postmenopause, and unknown as dummy variable, pre- and early peri-menopause as reference), antidepressant use (proportion of visits before the sleep study), vasomotor symptoms (% of study nights), medications that affect sleep (% of study nights), and apnea hypopnea index.

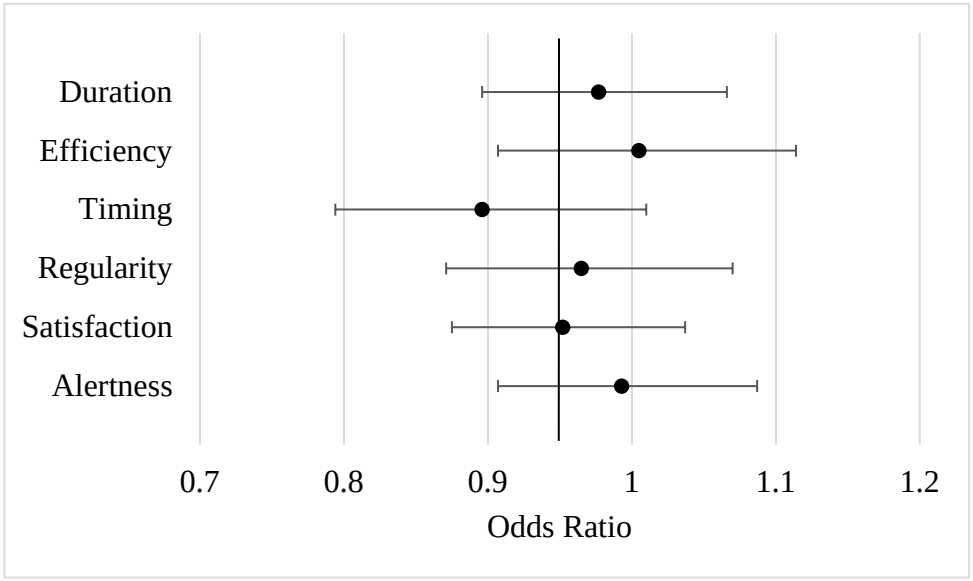


Figure 6. Variability in depressive symptoms and individual components of sleep health.

Figure depicts adjusted models, which include the following covariates: age, race (African American and Chinese American as dummy variables, European American as reference), site (Detroit, Oakland, and Chicago as dummy variables, Pittsburgh as reference), menopausal status (late perimenopause, postmenopause, and unknown as dummy variable, pre- and early peri-menopause as reference), antidepressant use (proportion of visits before the sleep study), vasomotor symptoms (% of study nights), medications that affect sleep (% of study nights), and apnea hypopnea index.

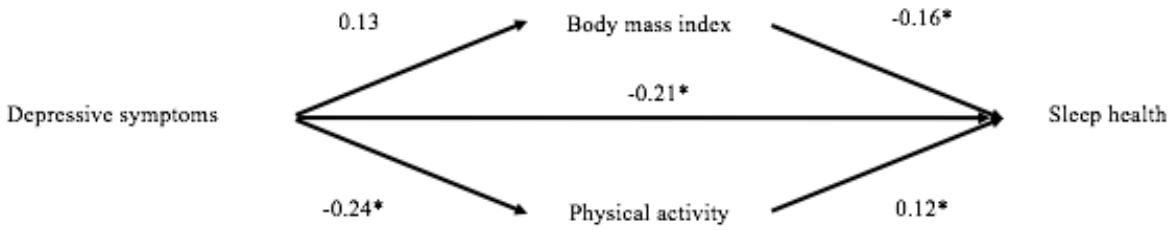


Figure 7. Mediation models.

Parallel multiple mediation model linking depressive symptoms to sleep health through body mass index and physical activity. Coefficients are shown for each path, and * indicates significance using a 95% confidence interval. The solid line indicates significant partial mediation. The dotted line indicates that there is a significant indirect effect, but not significant mediation. The direct effect of depression on sleep health after adjusting for the indirect effects is shown.

Appendix B. Supplemental Tables and Figures

Table S1. *Variably weighted sleep health.*

	Odds Ratio
Regularity	1.03
Satisfaction	1.09*
Alertness	1.09*
Timing	1.11*
Efficiency	1.01
Duration	0.99

Note. Sleep health was inverted so that higher values indicated worse sleep health. Mean depressive symptoms was the predictor in each model. * indicates $p < .05$

Table S2. *Comparing observed and imputed CES-D descriptive statistics.*

	Number	Min	Max	Mean	SD	Variance
CES-D 0						
Observed	319	0	45	9.12	8.78	77.00
Imputed	-	-	-	-	-	-
CES-D 1						
Observed	309	0	43	7.57	7.85	61.64
Imputed	6380	0	43	7.60	7.75	60.06
CES-D 2						
Observed	305	0	55	7.23	7.82	61.20
Imputed	6380	0	55	7.23	7.68	59.00
CES-D 3						
Observed	314	0	48	7.06	8.14	66.18
Imputed	6380	0	48	7.06	8.07	65.14
CES-D 4						
Observed	309	0	36	7.06	8.14	66.18
Imputed	6380	0	36	7.32	7.71	59.46
CES-D 5						
Observed	311	0	44	6.95	7.46	55.65
Imputed	6380	0	44	6.93	7.38	54.40
CES-D 6						
Observed	310	0	39	7.06	7.68	59.02
Imputed	6380	0	39	7.06	7.59	57.64
CES-D 7						
Observed	297	0	49	5.91	7.03	49.42
Imputed	6380	0	49	5.93	6.84	46.77
CES-D 8						
Observed	284	0	38	6.34	6.96	48.51
Imputed	6380	0	38	6.36	6.68	44.58

Note. Center for Epidemiological Studies – Depression Scale, sleep item removed, CES-D; Number of observations, number; Standard deviation, SD. CES-D 0 was not imputed because data was available for all participants.

Table S3. *Comparing observed and imputed covariate descriptive statistics.*

	Number	Min	Max	Mean	SD	Variance
Mean, CESD						
Observed	319	0.13	38.57	7.38	6.16	37.92
Imputed	6380	0.13	38.57	6.59	4.81	23.15
Variability, CES-D						
Observed	319	0.35	16.75	4.48	2.99	8.91
Imputed	6380	0.35	16.75	4.48	2.98	8.88
BMI 5						
Observed	303	17.53	55.68	29.86	7.90	62.36
Imputed	6380	17.53	55.68	29.84	7.86	61.85
KPAS 5						
Observed	292	3.40	12.45	7.54	1.72	2.96
Imputed	6380	3.00	12.45	7.53	1.72	2.96
Apnea hypopnea index						
Observed	302	0	119.71	10.51	15.56	242.16
Imputed	6380	0	119.71	10.82	15.43	238.23

Notes. Center for Epidemiological Studies – Depression Scale, CES-D; Body Mass Index, BMI; Kaiser Physical Activity Survey, KPAS; Number of observations, number; Standard deviation, SD.

Table S4. *Sample characteristics comparing listwise deletion to multiple imputation strategies.*

	Listwise deletion	Multiple imputation
Mean depressive symptoms, mean (*SD*)	7.5 (6.2)	7.4 (7.9)
Variability in depressive symptoms CES-D, mean (*SD*)	4.5 (3.0)	4.5 (3.0)
Body mass index, mean (*SD*)	29.8 (7.9)	29.8 (7.9)
Kaiser Physical Activity Survey, mean (*SD*)	7.5 (1.7)	7.5 (1.7)
Age, mean (*SD*)	52.1 (2.1)	52.2 (2.1)
Race/ethnicity		
White, *n* (%)	140 (46.4)	148 (46.4)
African American, *n* (%)	112 (37.1)	119 (37.3)
Chinese, *n* (%)	50 (16.6)	52 (16.3)
Study site		
Pittsburgh, PA, *n* (%)	76 (25.2)	84 (26.3)
Detroit area, MI, *n* (%)	60 (19.9)	64 (26.3)
Chicago, IL, *n* (%)	71 (23.5)	73 (22.9)
Oakland, CA, *n* (%)	95 (31.5)	98 (30.7)
Menopausal status		
Pre-/early perimenopausal, *n* (%)	187 (61.9)	196 (61.4)
Late perimenopausal, *n* (%)	58 (19.2)	63 (19.7)
Postmenopausal, *n* (%)	38 (12.6)	40 (12.5)
Unknown, *n* (%)	19 (6.3)	20 (6.3)
Antidepressant history, proportion of visits, mean (*SD*)	0.11 (0.25)	0.12 (0.25)
Sleep medications, % of study nights, mean (*SD*)	32.8 (34.1)	24.7 (41.9)
Vasomotor symptoms, % of study nights, mean (*SD*)	23.7 (41.3)	33.4 (34.4)
Apnea hypopnea, index, mean (*SD*)	10.5 (15.6)	10.8 (15.4)

Notes. Center for Epidemiological Studies Depression Scale, CES-D; CES-D clinical cut-off $\geq$ 16, Kaiser Physical Activity Scale scores range 0-15, with higher scores indicating more activity.

Table S5. *Sleep health characteristics comparing listwise deletion to multiple imputation strategies.*

	Listwise deletion (*n* = 302)		Multiple imputation (*n* = 319)	
Sleep health	M (SD)	Optimal, N (%)	M (SD)	Optimal, N (%)
Duration	6.0 (0.9)	145 (48)	5.9 (1.0)	154 (48.3)
Efficiency	78.0 (10.2)	73 (24.2)	77.2 (10.8)	78 (24.5)
Timing	3:20a (0:33)	265 (87.7)	3:22a (0:33)	280 (87.8)
Regularity	42.3 (18.3)	245 (81.1)	45.2 (20.2)	258 (80.9)
Satisfaction	2.0 (0.6)	162 (53.6)	2.0 (0.6)	173 (54.2)
Alertness	7.7 (4.4)	209 (69.2)	7.6 (4.3)	225 (70.5)

Notes. Optimal indicates optimal sleep health for each component.

Table S6. *Mean depressive symptoms and sleep health in the multiple imputation dataset.*

Unadjusted model	β	*p*
Mean depressive symptoms, CES-D	-0.30	<.001
Adjusted model		
Mean depressive symptoms, CES-D	-0.30	<.001
Age	-0.03	.60
Race/ethnicity		
European American	Reference	
African American	-0.19	.002
Chinese American	-0.12	.08
Study site		
Pittsburgh, PA	Reference	
Detroit area, MI	-0.14	.03
Chicago, IL	-0.05	.42
Oakland, CA	0.10	.21
Menopausal status		
Pre-/early perimenopausal	Reference	
Late perimenopausal	-0.08	.13
Postmenopausal	0.02	.79
Antidepressants, proportion of visits	-0.01	.97
Vasomotor symptoms, % of study nights	-0.03	.58
Sleep medications, % of study nights	-0.06	.34
Apnea-hypopnea index	-0.19	<.001

Notes. Center for Epidemiological Studies Depression Scale, CES-D; Adjusted model indicates that the model includes all covariates.

Table S7. *Variability in depressive symptoms and sleep health in the multiple imputation dataset.*

Unadjusted model	β	*p*
Variability in CES-D	-0.13	.02
Adjusted model		
Variability in CES-D	-0.05	.17
Age	0.01	.66
Race/ethnicity		
European American	Reference	
African American	-0.22	.002
Chinese American	-0.14	.07
Study site		
Pittsburgh, PA	Reference	
Detroit area, MI	-0.17	.006
Chicago, IL	-0.06	.33
Oakland, CA	0.10	.25
Menopausal status		
Pre-/early perimenopausal	Reference	
Late perimenopausal	-0.07	.25
Postmenopausal	0.01	.89
Unknown	-0.09	.11
Antidepressants, proportion of visits	-0.05	.43
Vasomotor symptoms, % of study nights	-0.07	.24
Sleep medications, % of study nights	-0.03	.60
Apnea-hypopnea index	-0.21	<.001

Notes. Center for Epidemiological Studies Depression Scale, CES-D; Adjusted model indicates that the model includes all covariates; vasomotor symptoms, VMS; apnea hypopnea index, AHI

Table S8. *Moderation models in the multiple imputation dataset.*

	Model 1		Model 2		Model 3		Model 4	
	Basic Model (Mean only)		Mean, variability		Mean, variability, and Interaction		Fully adjusted model	
	β	p	β	p	β	p	β	p
Mean depressive symptoms, CES-D	-0.27	<.001	-0.35	<.001	-0.34	.001	-0.30	.002
Variability in depressive symptoms, CES-D			0.10	.26	0.10	.26	0.12	.16
Mean X Variability, CES-D					-0.02	.69	-0.02	.75
Age							0.01	.93
Race/ethnicity								
European American							Ref	
African American							-0.20	.003
Chinese American							-0.14	.04
Study site								
Pittsburgh, PA							Ref	
Detroit area, MI							-0.14	.04
Chicago, IL							0.01	.99
Oakland, CA							0.16	.06
Menopausal status								
Pre-/early perimenopausal							Ref	
Late perimenopausal							-0.13	.03
Postmenopausal							-0.03	.64
Unknown							-0.07	.24
Antidepressants, proportion of visits							0.02	.73
Vasomotor symptoms, % of study nights							-0.04	.57
Sleep medications, % of study nights							-0.08	.22
Apnea-hypopnea index							-0.19	.002

Notes. Center for Epidemiological Studies Depression Scale, CES-D; interaction term, Mean X Variability; Adjusted model indicates that the model includes all covariates.

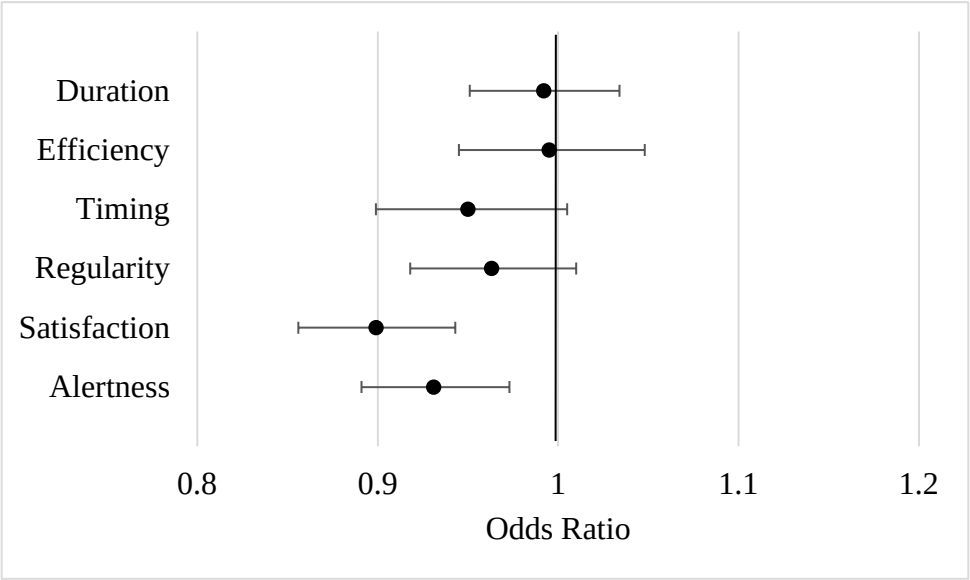


Figure S1. Mean depressive symptoms and individual components of sleep health in adjusted models in the multiple imputation dataset.

Figure depicts adjusted models, which include the following covariates: age, race (African American and Chinese American as dummy variables, European American as reference), site (Detroit, Oakland, and Chicago as dummy variables, Pittsburgh as reference), menopausal status (late perimenopause, postmenopause, and unknown as dummy variable, pre- and early peri-menopause as reference), antidepressant use (proportion of visits before the sleep study), vasomotor symptoms (% of study nights), medications that affect sleep (% of study nights), and apnea hypopnea index.

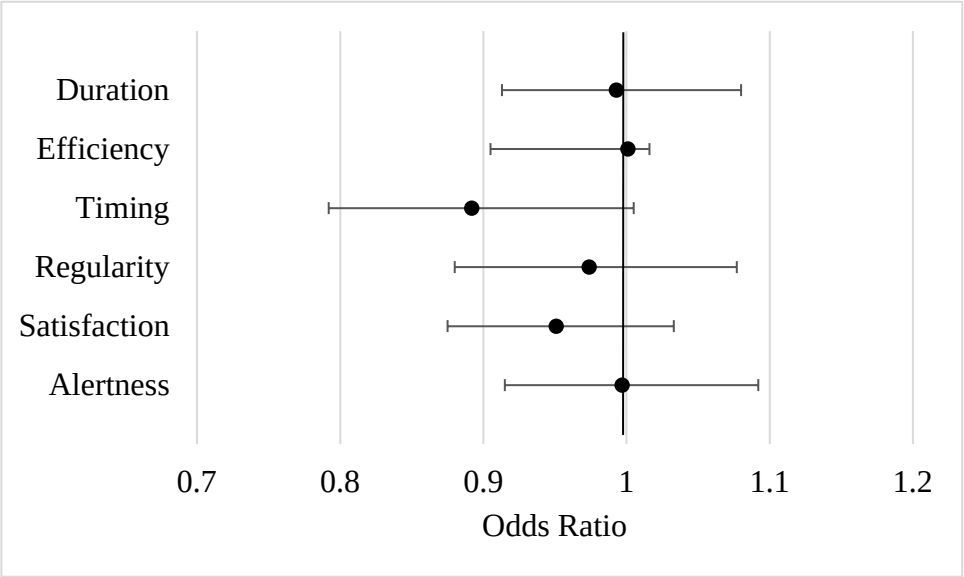


Figure S2. Variability in depressive symptoms and individual sleep health components in adjusted models in the multiple imputation dataset.

Figure depicts adjusted models, which include the following covariates: age, race (African American and Chinese American as dummy variables, European American as reference), site (Detroit, Oakland, and Chicago as dummy variables, Pittsburgh as reference), menopausal status (late perimenopause, postmenopause, and unknown as dummy variable, pre- and early peri-menopause as reference), antidepressant use (proportion of visits before the sleep study), vasomotor symptoms (% of study nights), medications that affect sleep (% of study nights), and apnea hypopnea index.

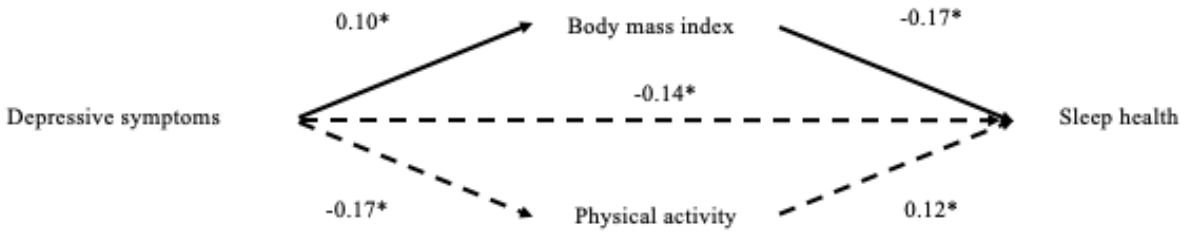


Figure S3. Mediation models.

Parallel multiple mediation model linking depressive symptoms to sleep health through body mass index and physical activity, in the multiple imputation dataset. Coefficients are shown for each path, and * indicates significance using a 95% confidence interval. The solid line indicates significant partial mediation. The dotted line indicates that there is a significant indirect effect, but not significant mediation. The direct effect of depression on sleep health after adjusting for the indirect effects is shown.