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Lifetime Estrogen Exposure, Cumulative Lifetime Stress, and Cognition in Later Life

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In Partial Fulfillment of Bachelor of Science in Psychological Sciences

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Abstract

The main goal of this study was to begin to examine how stress and estrogen work together to influence memory and thinking in older women. We looked at how stressful experiences affected memory in older women and how the hormone estrogen influenced the relationship between stress and memory. The relationship between cognition, stress, and hormones was investigated by having 15 women aged 60 and older complete stress and hormone questionnaires and perform two memory tasks. Most likely due to the small sample size, we did not find the hypothesized combined effect of lifetime estrogen exposure and cumulative stress on cognition. Yet, this study showed a relationship between psychiatric wellbeing, estrogen, and stress exposure. Furthermore, participants' cognitive assessment scores were correlated with estrogen exposure and age. The results suggest that estrogen and stress have individual effects on cognition.

Keywords: estrogen, stress, cognition, menopause, women, aging

Introduction

Women's health is greatly impacted by cumulative life stress as well as lifetime estrogen exposure. In the future, it may be possible to slow the decline in cognition associated with normal aging, optimizing cognitive functioning until the end of life. First, we must understand how different factors interact to influence cognitive changes in aging. High levels of stress have a negative impact on health in general as well as brain functioning in particular. Studies have shown that estrogen may be able to decrease the negative effects of stress as well as improve memory. No study has examined the combined effects of both estrogen and stress on cognition.

Estrogen and the Brain

Estrogen is a member of the class of steroid hormones which include estrone, estradiol, and estriol, where estradiol is the most prominent form of estrogen in mammals during their reproductive years (Almey et al., 2015). Due to the location of estrogen receptors in the hippocampus, estrogen has an effect on episodic memory, as the hippocampus is crucial for episodic memory formation (Bean et al., 2015; Tulving & Markowitsch, 1998). Episodic memory enables humans to remember past autobiographical events, including details such as who, what, and where (Tulving, 2002).

When examining the role of estrogen on cognitive function, it is important to consider a woman's lifetime exposure to estrogen. Estrogen levels increase at menarche and during pregnancy, while estrogen levels have been observed to decrease postpartum and during menopause (Soares & Zitek, 2008). In perimenopause, estrogen levels vary widely. In early perimenopause there is first an increase in estrogen levels. Then during the late perimenopausal years, estrogen levels begin to decrease, where post menopause is associated with a significant decrease in estrogen (Soares & Zitek, 2008).

The time between menarche and menopause, also known as length of reproductive period, provides a simple estimate for lifetime exposure to estrogen. Additional factors for evaluating lifetime estrogen exposure include hormonal birth control and pregnancy. (Ryan et al., 2009). Overall, cognitive functioning later in life benefits from increased estrogen exposure (Asthana & Middleton, 2004; Hesson, 2012; Ryan et al., 2009). Specifically, age at first menses has been shown to have a negative association with performance on memory and psychomotor speed tasks (Ryan et al., 2009). A longer reproductive period has been associated with better verbal fluency, but women who gave birth at a younger age performed worse on global cognitive function measures (Ryan et al., 2009). Additionally, duration of breastfeeding was negatively associated with cognitive functioning (Hesson, 2012). Several longitudinal studies (Matthews et al., 1999; Resnick et al., 1997; Jacobs et al., 1998; Steffens et al., 1999; Yaffe et al., 2000; Grodstein et al., 2000; Rice et al., 2000; Yaffe et al., 2000) have found postmenopausal estrogen users to have increased performance on cognitive tests and show less age-related deterioration over time in comparison to women who did not use estrogen. Juxtaposing these longitudinal studies, clinical trials have shown postmenopausal hormone therapy to lead to increased rates of dementia and cognitive deficits (Coker et al., 2010). Thus, the effects of estrogen on cognition and the aging brain are controversial, as past research exhibits mixed findings.

In addition to estrogen's effect on cognition, research has examined the relationship between estrogen levels and the stress response. Lindheim et al. (1992) showed that estrogen is effective at modulating the stress response, while ter Horst et al. (2012) further confirmed this finding by showing that estrogen specifically has the ability to positively modulate neurobiological and behavioral responses to stress. Ferrini and colleagues (1999) showed that in male rats, estrogen corrects HPA axis dysregulation, while De Nicola and colleagues (2006)

demonstrated a similar stabilizing effect of estrogen on the HPA axis system. Lindheim and

colleagues (2012) reproduced these results from the animal studies (Ferrini et al., 1999; De

Nicola, 2006) in humans. Postmenopausal women with low estrogen levels were more reactive

to stress prior to receiving estrogen treatment (Lindheim et al., 1992). Contrary to these findings,

Goel and colleagues (2014) suggested that the HPA axis in females is more active than that in

males. Specifically, the HPA axis in females activates quicker and produces more stress

hormones (Goel et al., 2014). Therefore, research regarding the effects of estrogen on stress is

not in agreement.

Stress and the Brain

The most inclusive definition of a stressor is any condition, real or implied, that requires

a response from the organism to promote adaptation through a change (Magri et al., 2006). Stress

is a disruption to the body's homeostasis, where the hypothalamic-pituitary-adrenal (HPA) axis

works to restore homeostasis (Miller & O'Callaghan, 2005). When a stressor is encountered,

corticotropin-releasing hormone (CRH) triggers the release of adrenocorticotropic hormone

(ACTH) from the anterior pituitary, which stimulates the secretion of glucocorticoids (GC) from

the adrenal cortex. As GC levels increase, hypothalamic CRH expression is suppressed via

negative feedback detected through hippocampal and hypothalamic corticosteroid receptors in

the brain. It is this cascade of events and negative feedback which shuts off HPA axis activation

(Magri et al., 2006).

Hormones, such as GC and cortisol, play an important role during aging and on

hippocampal-mediated cognitive functions (Miller & O'Callaghan, 2005). Several longitudinal

studies have demonstrated individual differences with respect to age and higher than normal

cortisol levels. These longitudinal studies have shown that chronically high cortisol levels lead to

deficits in hippocampal driven cognitive functions, with elderly participants demonstrating a positive relationship between above normal cortisol levels and cognitive deficits (Miller & O'Callaghan, 2005). Thus, cumulative lifetime exposure to stress hormones, such as GC and cortisol, can increase cognitive deficits (Miller & O'Callaghan, 2005).

The hippocampus has a crucial role in the feedback control of the stress response (Miller & O'Callaghan, 2005). It is sensitive to stress hormones due to its high density of corticosteroid receptors (Magri et al., 2006). Because the hippocampus is a crucial regulatory component of the HPA axis, chronically high GC levels can be detrimental to the negative feedback loop, potentially exacerbating the cascade effect of hormones and therefore resulting in a dysregulation of the HPA axis (Magri et al., 2006). However, the effects of chronic long term exposure to stress and excess levels of GC and their impact on the aging process remain an area for further investigation (Miller & O'Callaghan, 2005).

Methods

Participants

Women were recruited by posting advertisements around Chittenden County and by emailing past research subjects of the Clinical Neuroscience Research Unit in the Department of Psychiatry at the University of Vermont. Once a potential participant reached out by email or phone, a time was set up for her to come to the University of Vermont Department of Psychiatry and complete the experiment procedure. Inclusion criteria were an age of 60 or older and healthy. Exclusion criteria were an inability to complete the required tasks and questionnaires due to being non-English speaking or having a physical impairment, as well as receiving a score less than 24 on the Mini Mental State Exam (MMSE). All participants completed the procedure regardless of their performance on the MMSE. All 15 women received a score equal to or greater

than 24, thus no one was excluded from the data analysis. All potential participants were scheduled for the one 1.5 hour study visit. Upon the participant's arrival, consent forms were signed. The participant then completed a series of behavioral and cognitive screening tests, answered questions about lifetime estrogen exposure, performed cognitive tasks to examine working and episodic memory, and answered questions about their lifetime stress exposure. These procedures are detailed below.

Cognitive Impairment Screening Test

All subjects completed the Mini Mental State Exam (MMSE) (Folstein et al., 1975) as the initial cognitive status screening questionnaire. On the MMSE, a higher score is related to better cognitive functioning. Participants were asked questions such as the date and to redraw an image. To have their data included in the study, participants were required to have a score equal to or greater than 24.

Indices of Estrogen Exposure Questionnaire

The Indices of Estrogen Exposure Questionnaire asked the participant questions regarding lifetime hormone exposure. Specifically, the questionnaire inquired about menstrual cycle history, motherhood, menopause, and use of hormone therapy (Lord et al., 2009). The menstrual cycle history inquired about age of first menstruation, regularity of periods, cycle length, and use of contraceptive pill(s). The motherhood section inquired about number of children, breastfeeding, and complications with pregnancies. The menopause section asked about age of last menstruation, and if menopause occurred naturally or through surgery. Lastly, the section on hormone therapy asked about hormone therapy use. The data collected from the Indices of Estrogen Exposure Questionnaire was scored using the Index of Lifetime Estrogen Exposure (ILEE).

The ILEE was based on Smith et al. (1999) and Hesson (2012). Their use of the index was modified for this study, as contingent markers, such as BMI (Hesson, 2012), were excluded. All estrogen exposure markers were converted into total years. Duration of estrogen and combination hormone therapy (HT) was added across different HT treatments, which resulted in the total duration of HT. Duration of breastfeeding was added across children, providing the total duration of breastfeeding. Time since menopause was calculated by subtracting age at menopause (age at last period) from the participant's current age. Of these markers, those that cause an increase in estrogen (total HT and age at menopause) were added, while those that cause a decrease in estrogen (time since menopause, age at menarche, and total duration of breastfeeding) were subtracted.

Stress and Adversity Inventory (STRAIN)

The STRAIN measures an individual's lifetime exposure to acute and chronic stressors through an online stress questionnaire (Slavich & Epel, 2010). Questions address major life domains such as health, finances, and intimate relationships. For each stressor that is affirmed, a series of follow-up questions are asked. These follow-up questions capture severity, frequency, timing, and duration of the stressor. Upon completion, 455 raw variables were produced. Of these, the participant's total (acute and chronic) stressor count and severity, acute stressor count and severity, as well as chronic stressor count and severity were the main indices used in this study.

Cognitive Tasks

Working Memory Letter-Number Sequencing Task (LNST)

The LNST measures working memory (Wechsler, 1997). The test begins with a practice round where the participant is read a combination of letters and numbers (i.e. 4-D-6-F). The

participant is then required to recite the organized letters and numbers back to the researcher so that numerically ordered numbers come before alphabetically ordered letters (i.e. 4-6-D-F). The number of successful trials were counted, making up the participant's score.

Episodic Memory Buschke Selective Reminding Test (BSRT)

The BSRT is a measure of episodic memory (Buschke & Fuld, 1974). It measures storage into and retrieval from memory as it is a multi-trial verbal list-learning task. It consisted of eight trials and one delayed trial which was administered 20 to 30 minutes after the eighth trial ended. The BSRT began by the experimenter reading the 16 words aloud to the participant. The participant was then asked to recall the 16 words. If the subject was unable to recall a word (or words) she was reminded of the forgotten word/s by the experimenter and then asked to try and recall all 16 words again. The dependent variables produced by this test were total recall, consistency, intrusions, recall failure, and delayed recall. Total recall was the total number of words the participant recalled from the initial eight trials. Consistency was when the participant remembered a word for two trials in a row. Intrusions were words recalled by the participant that were not a part of the list. Recall failure occurred when the participant was unable to remember a word for two trials in a row. Delayed recall was the number of words the participant recalled following the 20 to 30 minute break.

Behavioral Screening

The Older Adult Self Report (OASR) is a psychiatric assessment completed by the subject (Achenbach et al., 2004). It yields seven syndromes including anxious/depressed, worries, memory/cognition problems, and thought problems.

Data Analysis

To test the hypothesis, the plan was to run a bivariate correlation and then a regression model. The bivariate correlations were run between the independent (ILEE and total stress count) and dependent (BSRT and LNST) variables.

Results

A bivariate correlation was run between the ILEE, total stress count, BSRT and LNST. None of the independent and dependent variables were significantly correlated and therefore a regression model was not performed. While it was probable that the sample was too small to test the original hypothesis, I still wanted to understand the group of participants and continued to run statistical tests. I proceeded by performing a bivariate correlation with the individual variables from the Indices of Estrogen Exposure Questionnaire, STRAIN, BSRT, LNST, as well as the total stressor, acute stressor and chronic stressor count, total stressor, acute stressor and chronic stressor severity, the MMSE, and age of participant. The total stressor count and total stressor severity variables were not significantly correlated with the episodic memory task, working memory task, or estrogen variables. Furthermore, few of the estrogen variables were significantly correlated with the memory variables. These correlations are discussed below.

Following the correlations, a median split was used to separate the participants into high and low total stressor count groups and into high and low ILEE groups. Using an independent samples t-test, I examined performance on the OASR, BSRT, LNST, and Indices of Estrogen Exposure Questionnaire for the high and low stress groups, and examined performance on the OASR, BSRT, LNST, and STRAIN for the high and low ILEE groups. The relationships between these means are detailed below.

Participants

A total of 15 subjects were enrolled. All 15 women met the inclusion criteria. Subjects ranged from 62 to 80 years old, with a mean age of 69 years ($SD = 5.10$) (Table 1). The participants had a mean score of 28.4 ($SD = 1.50$) on the MMSE (Table 3).

The Indices of Estrogen Exposure Questionnaire showed that the average age at menarche was 13 years ($SD = 1.78$) and the average age of menopause (defined as the age at their last period) was 51 years old ($SD = 7.33$). These women had a mean reproductive period of 39 years ($SD = 7.82$) and an average of 21 years since menopause ($SD = 7.82$). In this study, 86.67% of women had children. 80% of the participants endured pregnancy interruptions, such as abortions and miscarriages. The mean total duration of pregnancy at interruption was 0.34 years ($SD = 0.26$). There were 73.33% of the women who breastfed for a mean duration of 1.21 years ($SD = 1.21$). Out of the 15 women, 93.33% reported using hormonal contraceptives, where the mean total duration of birth control for all subjects was 8.41 years ($SD = 9.44$). Twenty percent of the women used hormone therapy for an average of 4.27 years ($SD = 11.56$). Of the 15 subjects, seven were high ILEE, and eight were low ILEE. Table 1 shows the descriptive statistics of the estrogen variables included in the Indices of Estrogen Exposure Questionnaire.

The results from the STRAIN showed that the average total stress count of 28.80 ($SD = 16.57$) while the average total stress severity was 70.53 ($SD = 39.58$). Table 2 shows the descriptive statistics for the six different stress variables used in this study.

Results for the cognitive tests showed that the subjects recalled an average of 78.27 ($SD = 22.91$) total words over the course of eight BSRT trials. The average number of words recalled on the delayed recall trial of the BSRT was 10.13 ($SD = 4.36$). On the LNST, the subjects successfully completed an average of 11.40 trials ($SD = 2.75$).

The participants' mean scores on the OASR were 53.33 (*SD* = 4.30) for anxious/depressed, 50.40 (*SD* = 50.40) for worries, 50.27 (*SD* = .80) for somatic complaints, 52.13 (*SD* = 3.66) for functional impairment, 54.60 (*SD* = 6.23) for memory problems, 53.87 (*SD* = 5.49) for thought problems, 51.73 (*SD* = 4.64) for irritability, 52.67 (*SD* = 3.40) for critical items, and 43.93 for total problems (*SD* = 9.51). None of the 15 women scored in the clinical range on the OASR (Table 4). The following were the relationships between the above variables that emerged during the data analysis.

1) Individual estrogen components correlate with cognition

The ILEE was not significantly correlated with working memory, episodic memory, or stress variables when used as a continuous variable. The ILEE combines many components. When these components were individually used as continuous variables in a bivariate correlation there were some correlations with cognition.

a) *Duration of pregnancy at time of interruption*

The duration of the pregnancy at time of interruption was significantly correlated with the MMSE (r = -.59, p = .026) (Table 5.2).

The total amount of words recalled after eight trials of the BSRT by a participant was correlated with the duration of pregnancy at the time of interruption (r = -.54, p = .048) (Table 5.2).

2) OASR functional impairment scores correlate with estrogen variables

Functional impairment and duration of hormone therapy were significantly correlated (r = .74, p = .002) (Table 5.1).

Functional impairment scores were also significantly correlated with time since menopause (current age minus age at last period) (r = .67, p = .006) (Table 5.1).

3) High versus low ILEE means

A median split was performed on the ILEE to divide the participants into high and low estrogen groups. The median of the ILEE scores was 20. Using the median split as the grouping variable and the cognitive tasks, estrogen questionnaire, and behavioral as well as cognitive assessment as the testing variables, an independent samples t-test was performed. There was no statistically significant difference of the means from these testing variables between the high and low estrogen groups.

4) Summed stress components correlate with the OASR

   a) *Stress Count*

Total stressor count ($r = .78$, $p = .001$), acute stressor count ($r = .73$, $p = .002$), and chronic stressor count ($r = .76$, $p = .001$) were correlated with OASR thought problem scores (Table 5.3).

Further, total stressor count ($r = .57$, $p = .025$), acute stressor count ($r = .54$, $p = .039$), and chronic stressor count ($r = .56$, $p = .032$) were correlated with the OASR total problems (Table 5.3).

   b) *Stress Severity*

There was a correlation between total stressor severity ($r=.65$, $p=.008$), acute stressor severity ($r = .57$, $p = .028$), as well as chronic stressor ($r = .68$, $p = .006$) severity and thought problem scores on the OASR (Table 5.3).

Total stressor severity ($r = .60$, $p = .018$), acute stressor severity ($r = .63$, $p = .012$), and chronic stressor severity ($r = .56$, $p = .029$) were also correlated with OASR total problems (Table 5.3).

5) OASR means for high versus low STRAIN groups

Based on the results from the bivariate correlations, specifically those comparing stress and the OASR, a median split was performed to divide the sample into high and low stress groups in order to run an independent samples t-test. The median for the total stressor count was 24. The total stressor count group was the grouping variable and the cognitive tasks, estrogen questionnaire, and behavioral as well as cognitive assessments served as the test variables. There was a statistically significant difference ($t(13) = -2.39$, $p = .033$) between the OASR thought score means of low total stress count ($M = 51.13$, $SD = 2.416$) and high total stress count ($M = 57$, $SD = 6.48$) (Table 6).

6) Age correlates with cognitive assessments

   a) *MMSE*

There was a correlation between the participant's current age and the score received on the MMSE ($r = -.55$, $p = .034$) (Table 5.2).

   b) *LNST*

There was a correlation between the participant's current age and the LNST ($r = -.55$, $p = .035$) (Table 5.2).

Discussion

Contrary to the hypothesis, there was no combined effect of lifetime estrogen exposure and cumulative stress on cognitive functioning. Despite this, I did examine relationships between the variables to further understand the stress and hormone history as well as cognitive performance of the 15 women in this study.

The group of participants had a wide age range (62-80 years old) and were all well-educated with degrees ranging from an incomplete Bachelor's to a Ph.D. Furthermore, the women were all white and from Vermont. This combination resulted in a rather demographically uniform sample. Scores on the BSRT ranged from 42 to 106 total words recalled, while scores on the LNST ranged from six to 16 trials completed. Furthermore, none of the women were demented (Table 3). The participants had an ILEE ranging from one to 35.75 years (Table 1). While there was little variability in their cognitive performance and estrogen exposure, the women presented with a large range of stress exposure. Total stressor count scores ranged from six to 64 and total stress severity ranged from 16 to 146 (Table 2). By recruiting more participants though, the variability would continue to increase. While the participants were recruited from all over Chittenden County, more cognitive variability in particular would have been provided if participants had come from senior centers. It was this lack of variability in addition to the small sample size that limited the findings of this study.

While it was too small a sample size to address the initial goal and hypothesis of this study, the results demonstrated relationships between some of the variables relevant to the research topic. One of these findings was that the duration of a woman's pregnancy before interruption negatively correlated with cognitive assessments. This suggests that pregnancy interruption may contribute to age related cognitive decline. Specifically, the Indices of Estrogen Exposure questionnaire defines pregnancy interruptions as abortions and miscarriages. A study by Murashko (1978) showed that artificial abortions lead to an immediate change in hormone levels. These changes were recorded for 24 hours post-abortion, where progesterone levels increased by 80% after 24 hours and estradiol levels decreased by 88% after 24 hours (Murashko, 1978). The abortion continued to affect hormone levels thereafter, resulting in

defective ovulations during the first menstrual cycle. The second menstrual cycle following the abortion exhibited normal ovulations again. Because abortions are clinically performed and are not a result of hormone imbalances, their role in later cognitive functioning is uncertain. Murashko (1978) demonstrated that a woman's hormones have normalized by her second cycle following the abortion. Because Murashko (1978) did not study the long-term effects of abortions, or the effects of abortions on the brain, no conclusions can be drawn on either of these domains.

The chance of miscarriage increases with higher estrogen levels and luteinizing hormone levels (a hormone vital for reproduction produced by the pituitary gland) as well as lower progesterone levels (Li et al., 2000; Jukic, Weinberg, Wilcox, & Baird, 2010). While these are some hormonal factors that increase a woman's risk, miscarriages themselves lead to a decrease in luteinizing hormone and a slow rise in estrogen levels following the pregnancy loss (Jukic et al., 2010). Stress is another factor that has been shown to affect the risk of miscarriage. A study by O'Hare and Creed (1995) found that women who had experienced a severe life event, social difficulty, and/or events of severe short-term threat were more likely to miscarry than those who did not. Almost half of the women in the miscarriage group had endured one or more of the above psychological stressors (O'Hare & Creed, 1995). It is therefore known that both hormones and environmental factors, such as stress, affect a woman's risk for miscarriage. What is unclear though, is through what relationship pregnancy interruptions affect cognition.

As previously discussed, the existing body of literature on estrogen and cognition largely demonstrates the positive effects of estrogen on cognition (Asthana & Middleton, 2004; Hesson, 2012; Ryan et al., 2009). Therefore, the knowledge that women with higher estrogen levels are at an increased risk for miscarriage makes the finding that pregnancy interruptions lead to a

decreased score on the MMSE as well as BSRT unexpected. A lower score on the BSRT suggests decreased episodic memory functioning, while a low score on the MMSE also indicates decreased memory because it is a dementia screening. Thus, based on the previously cited literature on estrogen and cognition, one might expect the high levels of estrogen leading to increased risk for miscarriage to be associated with increased memory scores instead of decreased scores. Conversely, past research has shown that exposure to stress hormones can lead to an increase in cognitive deficits (Miller & O'Callaghan, 2005). The negative effects of stress on cognition not only align with the finding from the current study that pregnancy interruptions negatively impact cognition, but also suggest that estrogen and stress may have a combined effect on risk of miscarriage. Thus, the correlation between pregnancy interruptions and cognitive assessment scores could either be the result of estrogen exposure, stress exposure, or a combination of both estrogen and stress exposure.

Another finding from this study was that total stressor count and total stress severity were positively correlated with OASR thought problems score and OASR total problems score. Total problems score is a summary score across the domains of strengths, worries, somatic complaints, anxious/depressed, thought problems, functional impairment, memory, and irritability. The thought problems portion of the OASR addresses psychiatric symptoms such as hallucinations, self-harm and suicide attempts, unusual thoughts and behaviors, as well as OCD-symptoms. Thought problems was the only individual component significantly correlated with stress. Furthermore, while scores on the thought problems and total problems were significantly correlated with stress in the bivariate correlation, when the participants were split into high and low stress groups, only the difference between thought problems score means was statistically significant.

The positive correlation between stressor count and OASR thought problems as well as total problems suggests that psychiatric wellbeing is negatively impacted by stress. The physical effects of stress have been extensively researched. One study, for example, showed that total cumulative stress was detrimental to autonomic function (Lampert et al., 2016). Specifically, the researchers discussed that stress takes a toll on cardiac health, which can lead to mortality (Lamport et al., 2016). In regards to the effects of stress on psychological health, research has demonstrated that stress increased mental deterioration (Amster & Krauss, 1974) and thereby increased the risk of dementia (Skoog et al., 1996).

Furthermore, childhood stress has been shown to result in permanent changes in learning, behavior, and physiology, leading to an unhealthy lifestyle (Shonkoff & Garner, 2012). These changes may result from the negative effect of stress on brain development, especially at young ages (Shonkoff & Garner, 2012). Another study by DeLongis and colleagues (1988) provided evidence for the negative effects of stress on mental health in adults. Participants with high stress levels had an increase in psychological and somatic problems, especially if they had unsupportive social relationships and low self-esteem (DeLongis, Folkman & Lazarus, 1988). While the study by Shonkoff and Garner (2012) addressed the fact that stressful events that happen to people early on can affect them for the rest of their lives, and the study by DeLongis and colleagues (1988) acknowledged the influence of external factors (i.e. support system), neither of these specifically addressed why one maladaptive cognition may be more likely to occur as a result of stress than another. The relationship between stress and mental health is important to focus on in future research given the findings of this study in addition to the lack of literature on this topic. Specifically, why thought problems in particular proved to be more affected by stress than any of the other components of the OASR.

Limitations

The prominent limitation in this study was the small sample size of 15 women. As a result of this, the correlations as discussed in the results section may be unreliable. A larger sample of women aged 60 years and older is needed to confirm that the results are not due to chance. It is also possible that a combined effect between estrogen and stress on cognition may emerge with more participants. While there was some variation in how the 15 women performed on the cognitive tests and questionnaires (Table 1; Table 2; Table 3), they were demographically homogeneous. As a result of this, the participants do not accurately represent the larger population of older postmenopausal women. Therefore, the reliability of the results would increase with sample size and sample diversity.

Another limitation of this study was that many of the measures were dependent on the participants' memory and their ability to self-report. The STRAIN and Indices of Estrogen Exposure questionnaire were based on subjective memory because they were retrospective. Moreover, the STRAIN, Indices of Estrogen Exposure questionnaire, and OASR were all dependent on the participants' self-reporting abilities. However, each of these three measures has shown strong test-retest reliability. The OASR has a strong test-retest reliability (r = .86-.92) when administered over a one-week period (Maruish, 2004). The test-retest validity of the STRAIN has also proven to be good $($r = .90-.92) over a two to four week period, in addition to the STRAIN having high predictive validity (Slavich & Shields, 2018). Furthermore, Lord and colleagues (2009) demonstrated that the Indices of Estrogen Exposure questionnaire has a strong test-retest validity.

Future Directions

An unexpected finding of this study was the relationship between duration of pregnancy at time of interruption and cognitive assessments, specifically the MMSE and BSRT. The significance of how far along a woman is at the time of interruption is something that is left unaddressed in the existing body of literature. Therefore, a future direction for this research is to focus on the role of pregnancy interruptions in the aging brain, and cognitive decline in general. Research relevant to this finding could investigate the hormonal profile of women who have endured pregnancy interruptions. Furthermore, it could investigate the influence that environmental factors have and the role that stress plays. A study by Li and colleagues (2012) found that stress is a risk factor for recurrent miscarriage. Thus, while stress levels were not correlated with pregnancy interruptions in the current study, past research (Li et al., 2012) provides motivation to include external factors in future studies examining pregnancy interruptions and their relationship to cognition.

Another future direction is to further understand the relationship between stress and psychiatric wellbeing. As previously mentioned, aspects of the STRAIN and OASR were positively correlated. Slavich and Shields (2018) assessed the predictive validity of the STRAIN. The results showed that increased STRAIN scores led to an increased likelihood of getting diagnosed with both a major general health condition as well as an autoimmune disorder. Thus, the STRAIN was found to have strong predictive validity in regards to physical and cognitive wellbeing, but psychiatric wellbeing was left unaddressed (Slavich & Shields, 2018). Therefore, a future study could exclusively and closely look at the relationship between stress (both stressor count and stressor severity) and aspects of psychiatric wellbeing, such as thought problems.

Conclusion

The results of the current study suggest that estrogen and stress independently play a role in the aging brain. In the future it may be possible to decrease the prevalence of psychiatric disorders by decreasing stress levels through simple acts such as mindfulness and deep breathing exercises (Sharma & Rush, 2014). Gaining a comprehensive understanding first of the mechanisms through which this effect occurs is crucial.

Although the individual effects of estrogen and stress on the aging brain were demonstrated in this study, the combined effects of estrogen and stress on cognition were not. Previous research has illustrated the combined effects of estrogen and stress on cognition though. A study by Toufexis and colleagues (2017) demonstrated that stress weakens the beneficial effects that estrogen has on cognition in Macaque monkeys. This study explicitly illustrates the combined effects that estrogen and stress have on cognition, confirming the notion that there is a relationship between these three variables. Therefore, it would be important to perform the current study again in a larger, more diverse community. Furthermore, this study could be conducted with a focus on not only cognition, but also mental health. Nevertheless, the current data from this small pilot study is the first step towards understanding how stress and estrogen work together to affect cognition and encouraging more research on said relationship in humans.

References

Achenbach TM, Newhouse PA, Rescorla LA. Manual for the ASEBA older adult forms & profiles. Burlington: University of Vermont Research Center for Children, Youth, and Families; 2004.

Almey, A., Milner, T. A., Brake, W. G. (2015). Estrogen receptors in the central nervous system and their implication for dopamine-dependent cognition in females. *Hormones and Behavior, 74,* 125-138.

Amster, L. E., Krass, H. H. (1974). The relationship between life crises and mental deterioration in old age. *The International Journal of Aging and Human Development 5(1)*, 51-55.

Asthana, S., & Middleton, W. S. (2004). Estrogen and cognition: a true relationship?. *Journal of the American Geriatrics Society, 52(2),* 316-318. doi:10.1111/j.1532-5415.2004.52078.x

Bean, L. A., Ianov, L., & Foster, T. C. (2015). Estrogen receptors, the hippocampus, and memory. *Neuroscientist, 20(5), 534-545. doi:*10.1177/1073858413519865

Buschke H, Fuld PA (1974) Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology 24*:1019-1025.

Croker, L. H., et al. (2010). Postmenopausal hormone therapy and cognitive outcomes: the women's health initiative memory study (WHIMS). *The Journal of Steroid Biochemistry and Molecular Biology, 118(0)*, 3014-310. doi: 10.1016/j.jsbmb.2009.11.007

DeLongis, A., Folkman, S., Lazarus, R. S.,(1988). The impact of daily stress on health and mood: psychological and social resources as mediators. *Journal of Personality and Social Psychology, 54(3)*, 486-495.

De Nicola, A. F., Saravia, F. E., Beauquis, J., Pietranera, L. & Ferrini, M. G. (2006). Estrogens and neuroendocrine hypothalamic-pituitary-adrenal axis function. *Frontiesr of Hormone Research, 35*, 157-168.

Ferrini, M., Piroli, G., Frontera, M., Falbo, A., Lima, A. & De Nicola, A. F. (1999). Estrogens normalie the hypothalamic-pituitary adrenal axis response to stress and increase glucocorticoid receptor immuno-reactivity in hippocampus of aging male rats. *Neuroendocrinology, 69(2)*, 129-137.

Goel, N., Workman, J. L., Lee, T. T., Innala, L. & Viau, V. (2014). Sex differences in the HPA axis. *Comprehensive Physiology, 1*. Retrieved from https://doi.org/10.1002/cphy.c130054

Grodstein F., Chen J., Pollen D. A., Albert M. S., Wilson R. S., Folstein M. F., Evans D. A., Stampfer M. J. (2000) Postmenopausal hormone therapy and cognitive function in healthy older women. *Journal of the American Geriatrics Society* 48:746-752

Hesson, J. (2012). Cumulative estrogen exposure and prospective memory in older women. *Brain and Cognition, 80,* 89-95.

Jacobs D. M., Tang M. X., Stern Y., Sano M., Marder K., Bell K. L., Schofield P., Dooneief G., Gurland B., Mayeux R. (1998) Cognitive function in nondemented older women who took estrogen after menopause. *Neurology* 50: 368-373

Jukic, A. M. Z., Weinberg, C. R., Wilcox, A. J., Baird, D. D. (2010). Effects of early pregnancy loss on hormone levels in the subsequent menstrual cycle. *Gynecological Endocrinology, 26(12),* 897-901. doi:10.3109/09513590.2010.487601

Lampert, R., Tuit, K., Hong, K., Donovan, T., Lee, F., Sinha, R. (2016). Cumulative stress and autonomic dysregulation in a community sample. *Stress 19(3)*, 269-279. doi: 10.1080/10253890.2016.1174847

Li, T.C., Spuijbroek, M. D., Tuckerman, E., Anstie, B., Loxley, M., Laird, S. (2000). Endocrinological and endometrial factors in recurrent miscarriage. *An International Journal of Obstetrics and Gynaecology, 107(12)*. Retrieved from https://obgyn.onlinelibrary.wiley.com/doi/full/10.1111/j.1471-0528.2000.tb11670.x

Li, W., Newell-Price, J., Jones, G. L., Ledger, W. L., Li, T.C. (2012). Relationship between psychological stress and recurrent miscarriage. *Reproductive BioMedicine Online, 25(2)*, 180-189. https://doi.org/10.1016/j.rbmo.2012.03.012

Lindheim, S. R., Legro, R. S., Bernstein, L., Stanczyk, F. Z., Vijod, M. A., Presser, S. C., & Lobo, R. A. (1992). Behavioral stress response in premenopausal and postmenopausal women and the effects of estrogen. *American Journal of Obstetrics and Gynecology, 167(6),* 1831-1836. https://doi.org/10.1016/0002-9378(92)91783-7

Lord C, Duchesne A, Pruessner JC, Lupien SJ (2009) Measuring indicies of lifelong estrogen exposure: self-report reliability. *Climacteric: the Journal of the International Menopause Society 12*:387-394.

Magri, F., Cravello, L., Carilli, L., Sarra, S., Cinchetti, W., Salmoiraghi, F...Ferrari, E. (2006). Stress and dementia: the role of the hypothalamic-pituitary-adrenal axis. *Aging Clinical and Experimental Research, 18,* 167- 170.

Maruish, M. E. (Eds). (2004). *The use of psychological testing for treatment planning and outcomes assessment.* Mahwah, New Jersey: Lawrence Erlbaum Associates, Publishers.

Matthews K., Cauley J., Yaffe K., Zmuda J. M. (1999) Estrogen replacement therapy and cognitive decline in older community women. *Journal of the American Geriatrics Society* 47:518-523

Miller, D. B., & O'Callaghan, J. P. (2005). Aging, stress and the hippocampus. *Ageing Research Reviews, 4,* 123-140.

Murashko, L.E. (1978). Hormonal changes in artificial abortion in the 7th-8th weeks of pregnancy. *Sovetskaia Meditsina* 6:75-80.

O'Hare, T., Creed, F. (1995). Life events and miscarriage. *The British Journal of Psychiatry, 167(6)*, 799-805. https://doi.org/10.1192/bjp.167.6.799

Resnick S. M., Metter E. J., Zonderman A. B. (1997) Estrogen replacement therapy and longitudinal decline in visual memory: a possible protective effect? *Neurology* 49:1491 1497

Rice M. M., Graves A. B., McCurry S. M., Gibbons L. E., Bowen J. D., McCormick W. C., Larson E. B. (2000) Postmenopausal estrogen and estrogen-progestin use and 2-year rate of cognitive change in a cohort of older Japanese American women: the Kame project. *Archives of Internal Medicine* 160:1641-1649

Ryan, J., Carriere, I., Scali, J., Ritchie, K., Ancelin, M. (2009). Life-time estrogen and cognitive functioning in later life. *Psychoneuroendocrinology, 34,* 287-298.

Sharma, M. & Rush, S. E. (2014). Mindfulness-based stress reduction as a stress management intervention for healthy individuals: a systematic review. *Journal of Evidence-Based Integrative Medicine 19(4)*, 271-286. doi: 10.1177/2156587214543143

Skoog, I., Lernfelt, B., Landahl, S., Palmertz, B., Andreasson, L. A., Nilsson, L., Persson, G., Oden, A., Svanborg, A. (1996). 15-year longitudinal study of blood pressure and dementia. *Lancet 347(9009)*, 1141-1145.

Slavich, G. M., & Epel, E. S. (2010). The Stress and Adversity Inventory (STRAIN): An automated system for assessing cumulative stress exposure. Los Angeles: University of California, Los Angeles.

Slavich, G. M., & Shields, G. S., (2018). Assessing lifetime stress exposure using the stress and adversity inventory for adults (adult STRAIN): An overview and initial validation. *Psychosomatic Medicine, 80,* 17-27. doi: 10.1097/PSY.0000000000000534

Shonkoff, J. P. & Garner, A. S. (2012). The lifelong effects of early childhood adversity and toxic stress. *American Academy of Pediatrics, 129(1)*, 232-246. doi: 10.1542/peds.2011 2663

Smith, C.A., McCleary, C.A., Murdock, G.A., Wilshire, T.W., Buckwalter, D.K., Bretsky, P., Marmol, L., Gorsuch, R.L., Buckwalter, J.G., (1999) Lifelong estrogen exposure and cognitive performance in elderly women. *Brain and Cognition 39*:203-218.

Soares, C. N., & Zitek, B. (2008). Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability?. *Journal of Psychiatry and Neuroscience, 33(4)*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2440795/

Steffens D. C., Norton M. C., Plassman B. L., Tschanz J. T., Wyse B. W., Welsh-Bohmer K. A., Anthony J. C., Breitner J. C. (1999) Enhanced cognitive performance with estrogen use in nondemented community-dwelling older women. *Journal of the American Geriatrics Society* 47: 1171-1175

ter Horst, J. P., de Kloet, E. R., Schächinger, H., Oitzl, M. S. (2012). Relevance of stress and female sex hormones for emotion and cognition. *Cellular and Molecular Neurobiology, 32(5),* 725-735. doi: 10.1007/s10571-011-9774-2

Toufexis, D., King, S. B., Michopoulos, V. (2017). Socially housed female macaques: a translational model for the interaction of chronic stress and estrogen in aging. *Current Psychiatry Reports, 19(78)*, 1-9. doi: 10.1007/s11920-017-0833-3

Tulving, E. (2002). Episodic memory: from mind to brain. *Annual Review of Psychology, 53,* 1 25. https://doi.org/10.1146/annurev.psych.53.100901.135114

Tulving, E., & Markowitsch, H. J. (1998). Episodic and declarative memory: Role of the hippocampus. *Hippocampus, 8(3),* 198-204. doi:10.1002/(SICI)1098 1063(1998)8:3<198::AID-HIPO2>3.0.CO;2-G

Wechsler, D. (1997). Wechsler Adult Intelligence Scale-III (WAIS-III) manual. New York: The Psychological Corporation.

Yaffe K, Lui L. Y., Grady D., Cauley J., Kramer J., Cummings S. R. (2000) Cognitive decline in women in relation to non-protein-bound oestradiol concentrations. *Lancet* 356: 708-712

Yaffe K., Haan M., Byers A., Tangen C., Kuller L. (2000) Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. *Neurology* 54:1949-1954

Table 1

Lifetime estrogen exposure (in years) descriptive statistics

Estrogen Marker	N	Minimum	Maximum	Mean	Std. Deviation
Age (y)	15	62	80	69	5.11
Hormonal Contraceptive Duration(y)	15	0	32	7.84	9.44
Breastfeeding Duration (y)	15	0	4.25	1.21	1.21
Pregnancy Duration at Interruption(y)	15	0	.83	.32	.27
HT Duration (y)	15	0	44	4.27	11.56
Age at Menarche (y)	15	11	16	13	1.78
Age at Last Period (y)	15	27	58	49.40	7.33
Reproductive Period (y)	15	14	47	36.40	7.82
Time Since Menopause (y)	15	10	44	19.60	9.31
ILEE (y)	15	1	35.75	19.85	9.12

Note. ILEE=Index of Lifetime Estrogen Exposure

y = years

Table 2

Cumulative stressor count and severity descriptive statistics

Stress Variable	N	Minimum	Maximum	Mean	Std. Deviation
Total Stress Count	15	6	64	28.80	16.57
Total Stress Severity	15	16	146	70.53	39.58
Acute Stress Count	15	5	40	17.87	8.99
Acute Stress Severity	15	12	61	35.20	14.25
Chronic Stress Count	15	1	26	10.93	8.44
Chronic Stress Severity	15	14	85	35.55	26.31

Table 3

Descriptive statistics of the cognitive assessments

Cognitive Assessment	N	Minimum	Maximum	Mean	Std. Deviation
MMSE	15	24	30	28.40	1.50
LNST	15	6	16	11.40	2.75
BSRT Total Recall	15	42	106	78.27	22.91
BSRT Delayed Recall	15	4	16	10.13	4.36

Table 4

Descriptive statistics of the OASR

	N	Minimum	Maximum	Mean	Std. Deviation
Anxious/Depressed	15	50	63	53.33	4.30
Worries	15	50	54	50.40	1.06
Somatic Complaints	15	50	53	50.27	.80
Functional Impairment	15	50	63	52.13	3.66
Memory Problems	15	50	69	54.60	6.23
Thought Problems	15	50	66	53.87	5.49
Irritability	15	50	68	51.73	4.64
Critical Items	15	50	60	52.67	3.40
Total Problems	15	31	61	43.93	9.51

Table 5.1

Correlations

	Hormone Therapy Duration	Time Since Menopause
OASR Functional Impairment Score	.74**	.67**

*Note. **p<.01*

Table 5.2

Correlations

	Age	Pregnancy Duration at Interruption
MMSE	-.55*	-.53*
LNST	-.55*	n.s.
BSRT Total Recall	n.s.	-.54*

*Note. *p<.05*

n.s.=not significant

Table 5.3

Correlations

	Total (S.C.)	Total (S.S.)	Acute (S.C.)	Acute (S.S.)	Chronic (S.C.)	Chronic (S.S.)
OASR Thought Problems Score	.78**	.65**	.73**	.57**	.76**	.68**
OASR Total Problems Score	.57*	.60*	.54*	.63*	.56*	.56*

*Note. *p<.05, **p<.01*

S.S=Stress Severity, S.C.=Stress Count

Table 6

High vs. low stress thought problems group statistics

Thought Problems	Split Stress Group	N	Mean	Std. Deviation	Std. Error Mean
	1	8	51.13	2.42	0.85
	2	7	57	6.48	2.45

Figure Legends

Figure 1. Mean score and standard error on OASR thought problems split by stressor count and severity group. There was a significant difference between the high and low stress level groups, where the low stress group received a lower thought problems score, indicating higher cognitive wellbeing (t(13) = -2.39, p = .033). *p = <.05.

Figure 2. Stress count as a continuous variable vs. OASR thought problems score received. The model explains 61.10% of the variability of the response data around its mean. Therefore, the regression model accounts for 61.10% of the variance.

Figure 3. Stress severity as a continuous variable vs. OASR thought problems score received. The model explains 42.50% of the variability of the response data around its mean. Therefore, the regression model accounts for 42.50% of the variance.
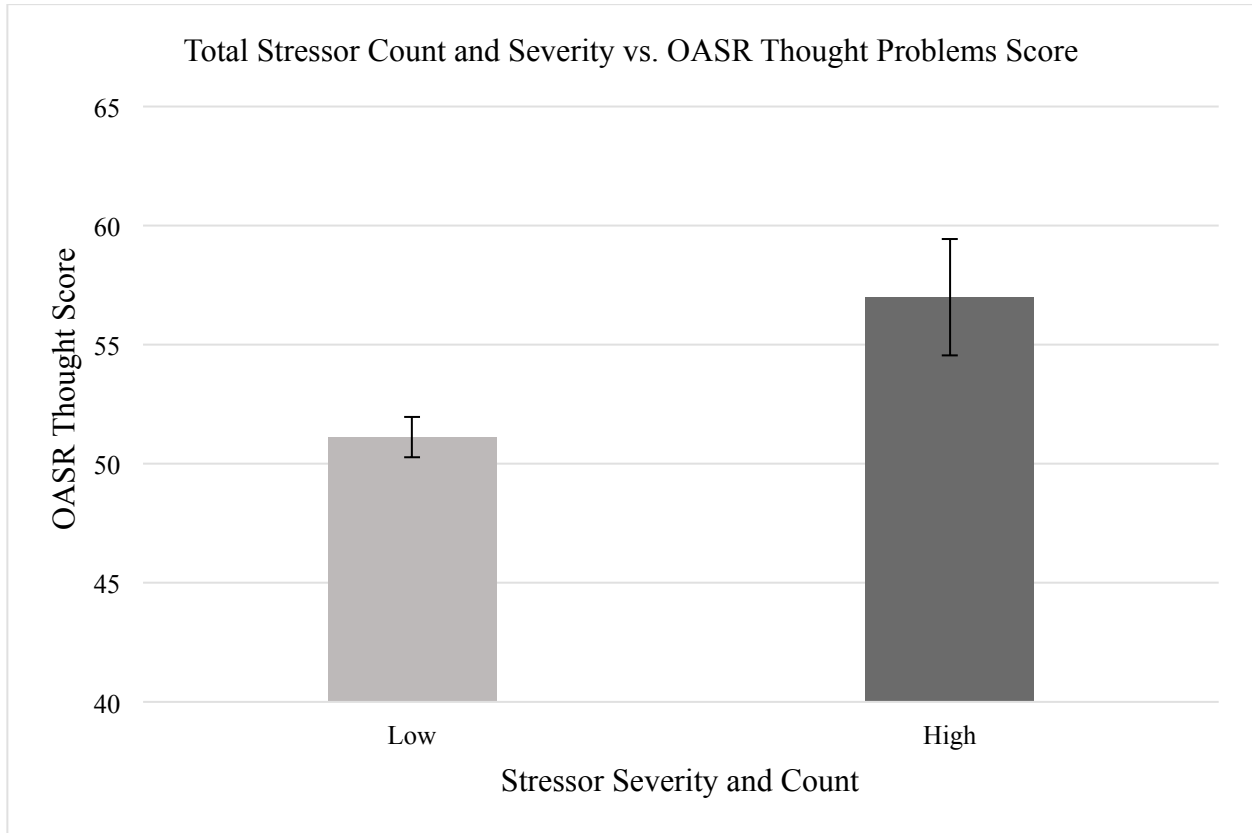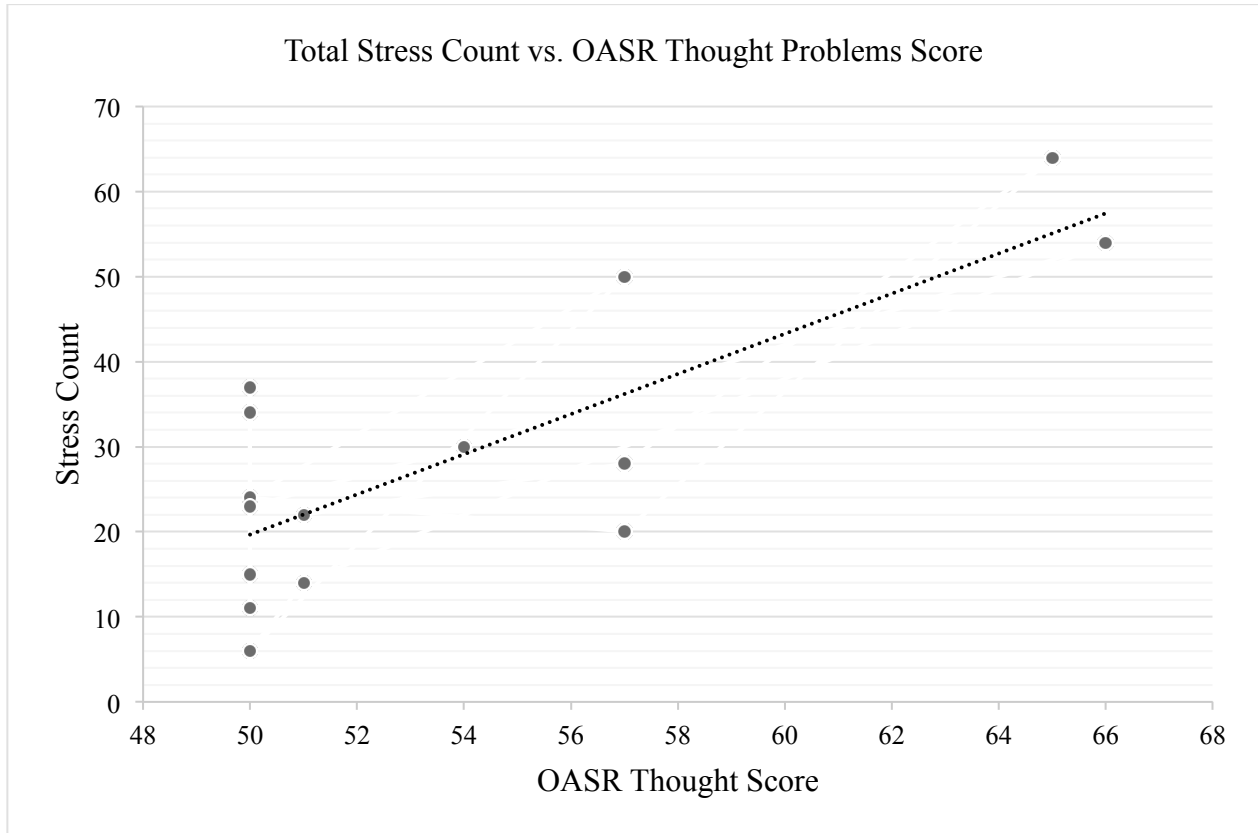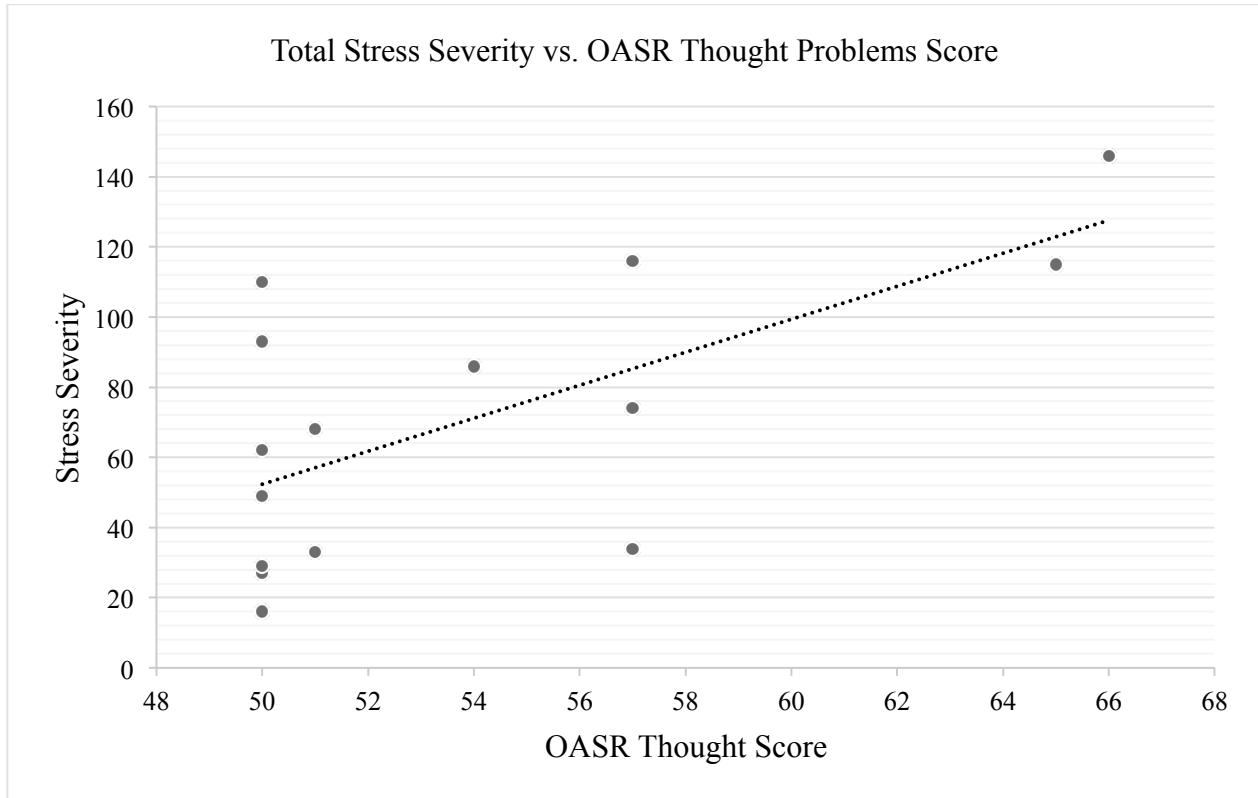
Figure 1.

Total Stressor Count and Severity vs. OASR Thought Problems Score

Figure 2.

Total Stress Count vs. OASR Thought Problems Score

Note. y=2.36x-98.37, R^2=0.61

Figure 3.

Total Stress Severity vs. OASR Thought Problems Score

Note. y=4.70x-182.76, R²=0.43