# ABSTRACT

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| Title of Dissertation: | LIFE COURSE EVENTS AND REPRODUCTIVE FUNCTION: EXAMINING THE LONG-TERM INFLUENCE OF STRESS ON WOMEN'S FERTILITY AND REPRODUCTIVE HEALTH OVER THE LIFE COURSE |
| | Jessica L. Gleason, Doctor of Philosophy, 2019 |
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Over the last decade, infertility, or the inability to achieve pregnancy after 12 months of trying, has risen to a place of public health prominence, with links being made to cardiovascular disease, diabetes, cancer, and other chronic disease. The mechanisms linking infertility to later-life morbidity are unclear, but are most likely due to shared physiologic pathways, such as chronic perturbation of the stress response axes. This investigation had three primary aims: understanding the current state of the research on psychosocial factors as precipitants of infertility by conducting a systematic scoping literature review; exploring associations between infertility-related conditions, endometriosis and uterine fibroids, and chronic inflammation and telomere attrition; and, examining the temporal influence of early life stress on infertility. For the first aim, few studies were identified that directly explored a

temporal association between psychosocial factors and infertility, though these studies support the plausibility of this association. For the second aim, women with endometriosis had higher odds of having elevated levels of the inflammatory biomarker, C-reactive protein, and their telomeres shortened at a rate of 1% for every year of diagnosis of their condition. Black women with endometriosis had 13.6% shorter telomeres than those without endometriosis. For the third aim, the experience of stressful life events (SLEs) was associated with elevated odds of infertility, which increased with each increasing event, such that women reporting three and four or more events had 1.68 (CI: 1.16, 2.42) and 1.88 (CI: 1.38, 2.57) higher odds, respectively. Maternal responsiveness moderated this association, such that those with lower responsiveness had higher increasing odds of infertility with the experience of two, three, or four or more events (OR=1.98, CI: 1.01, 3.93; OR=2.63, CI: 1.18, 5.89; OR=3.07, CI: 1.53, 616). The results of this investigation indicate that there may be a temporal association between stress and infertility. Additionally, given their associations with reproductive function, inflammation and stress may be part of the shared mechanisms linking infertility to poor overall health, as well as future health outcomes.

# LIFE COURSE EVENTS AND REPRODUCTIVE FUNCTION: EXAMINING THE LONG-TERM INFLUENCE OF STRESS ON WOMEN'S FERTILITY AND REPRODUCTIVE HEALTH OVER THE LIFE COURSE

by

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# Dedication

This labor of love is dedicated to the most influential loves of my life, my mom, Judy, my husband, Ryan, and my babies (no matter how old they are), Elodie, Evie, and Zane.

# Acknowledgements

I like to tell my students (and anyone else who dares engage me in a conversation about public health) that the choices we make do not occur in a vacuum, absent of any context. The same is true of our achievements. As the mother of three children, throughout my graduate studies, people often asked me "how do you do it?" Obviously, completing a doctoral program requires dedication and commitment, but none of this would be possible without the constant love and support of my spouse, Ryan. I could say these last few years have been rough, but between shift work, major relocations, and babies who *never* slept, I'm not sure that "smooth" has ever described our life together. Regardless of how we label our most recent graduate school-related challenges, this chapter in our life has been happy and full of growth, and when I feel reflective, I know the positives have far outnumbered the negatives.

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# Chapter 1: Introduction

## Background and Significance

In the US, infertility impacts an estimated 12% of women in their lifetime, though this estimate is conservative, and actual infertility rates may range up to 16%, depending on the method used to define and measure infertility.[1,2] According to the World Health Organization and the American Society of Reproductive Medicine, infertility is defined as the inability to achieve pregnancy after 12 months of intercourse without the use of contraception.[3] The most common causes of female infertility relate to types of ovulatory dysfunction, such as polycystic ovarian syndrome. Other well-studied causes include abnormalities in the physiology of the reproductive system, caused by previous infection (e.g., pelvic inflammatory disease), endometriosis, and uterine fibroids.[4] However, approximately 30% of infertility cannot be explained by anatomical or hormonal dysfunction.[4]

The psychological ramifications of infertility are intuitive and well-documented. Women unable to conceive experience ambiguous loss, mourning the "loss" of a child they have never had, which contributes to depression and marital/partner strain.[5] Furthermore, a small, but impactful number of judicial rulings have highlighted fertility as a right, including the monumental US Supreme Court ruling that infertility impairs the major life activity of reproduction, effectively labeling it a disability in the Americans with Disabilities Act.[6] Similarly, women who want to have children, but are unable, do not fully meet the definition of health, as described by the World Health Organization as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[7]

In addition to its importance in overall well-being and links to multiple psychiatric disorders, evidence has emerged in the last several years to suggest that infertility may also be a

harbinger of later life morbidities, such as cancer, cardiovascular disease, and metabolic dysfunction.[8] In answer to this emerging body of evidence, the Centers for Disease Control and Prevention, in association with the National Institute for Child Health and Human Development, has labeled infertility a "sixth vital sign" of health, and requested more research be conducted to understand how the experience of infertility may be both an indicator of current health, and a predictor of future health.[9] Because infertility occurs during a woman's reproductive years, it may serve as an early warning sign for cardiometabolic dysfunction. Early intervention in the reproductive years, as opposed to post-menopause, when cardiometabolic symptoms may be more likely to manifest,[10] could prevent severe cardiometabolic-related morbidity or mortality. In light of its potential to facilitate early intervention, and given the psychological and physical health consequences of infertility, understanding early life risk factors for infertility and non-traditional causes, like psychosocial factors, has become a pressing public health issue.

It is important to note that the overall conclusion of the literature linking infertility to later health conditions does not appear to be that infertility is the cause of these conditions, but rather that there are common physiologic mechanisms underlying both infertility and conditions like cardiovascular diseases and metabolic dysfunction. One common link between infertility and other poor health conditions may be stress. In this context, stress is defined as an external environmental stressor (e.g., an event or experience) that taxes the "adaptive capacity" of an individual, thus invoking a physiological stress response.[11] Stress causes disruptions in central neuroendocrine axes responsible for reproduction and general homeostasis, and has been linked to reproductive and cardiometabolic dysfunction.[12] Specifically, in the case of chronic stress, multiple perturbations of stress-response axes, like hypothalamic-pituitary-adrenal (HPA) and sympatho-adrenal-medullary (SAM), may cause an upregulation in body systems, such as

elevated heart rate, blood pressure, fasting glucose, and inflammation-inducing agents. These upregulated physiologic functions cause abnormal wear and tear on the body, resulting in long-term dysfunction of multiple body systems.[13] Thus, stress has been linked to infertility and other poor health outcomes, but the temporality and directionality of these associations is unclear.

Stress and infertility have primarily been studied in the context of stress as a consequence of infertility diagnosis or treatment.[14,15] In this case, infertility or invasive treatment methods are the stressors that invoke a physiologic stress response. In these cases, stress is measured either simultaneously with treatment, or after treatment, both of which have occurred after diagnosis, since these studies tend to exclusively target women seeking fertility treatment.[14,16–18] Other studies of stress and infertility have been conducted cross-sectionally, and examine recent or current stressors in the context of infertility.[19–21] While these studies help to establish an association between stress and infertility, there are limitations in conclusions that may be drawn: for example, it is impossible to conclude whether infertility contributed to recent stress or recent stress influenced infertility. Furthermore, these studies fail to differentiate between acute stress, which may have a temporary impact on reproductive function, and chronic stress, which may alter physiologic mechanisms leading to long-term reproductive dysfunction (e.g., endometriosis, uterine fibroids, PCOS, or unexplained infertility).

Few studies have empirically tested the hypothesis that chronic stress or early life stress may influence fertility. This idea is physiologically plausible and generally accepted in the literature surrounding stress and reproduction, but few studies have directly tested this association.[22–24] Thus, the purpose of this investigation is to explore how experiences of early life stress may influence infertility. Specifically, given what is known about early life stress and later-life morbidity, this investigation will explore how experiences of stress in adolescence and

early adulthood may influence later fertility. Many studies have tested the association of stress in the context of infertility treatments, but few have examined how stress might precipitate the experience of infertility, in general. A recent shift has occurred in Maternal and Child Health research, based on life course theory that suggests the necessity of examining how events in early life may influence later health. Given that infertility has become a larger public health issue in recent years with its growing status as a health indicator and predictor of future morbidity, investigations examining how early life stressors might influence later fertility have become highly relevant. Many biomarkers of stress have been identified, but interpretation of elevated inflammation biomarkers or sub-clinical blood pressure means little outside of the context of a diagnosable disease. Furthermore, it is not feasible to monitor the biomarkers of the entire population. Thus, if stress biomarkers can be linked to infertility, given its role as an "early warning" for later disease, infertility could become a more "accessible" indicator of both stress and subsequent morbidity.

This investigation aims to add to a sparse body of knowledge surrounding psychosocial factors that may precipitate infertility, while also providing evidence for a pathway linking infertility to later-life morbidity. Furthermore, this investigation is entirely novel in this field, as there are no systematic reviews examining psychosocial factors as precipitants to infertility; there are no universally-accepted biomarkers of infertility, and no known published papers that examine the potential link between infertility and chronic stress or inflammation biomarkers (telomeres and C-reactive protein); and finally, while only three papers have been published to investigate associations between life stressors and infertility, this is the only study to use data that has been collected longitudinally.

## Aims and Hypotheses

There are three main aims to this investigation: understanding the current state of the research on psychosocial factors as precipitants of infertility (aim 1); determining whether cellular markers of stress may be associated with infertility (aim 2); and establishing a temporal association between stressful life events and infertility (aim 3).

**Research Aim 1**: Identify and critically review the literature examining psychosocial factors as precipitants to experiences of infertility.

**Research Aim 2**: Describe the association between endometriosis and fibroids, two reproductive abnormalities linked to infertility, and measures of both chronic stress and inflammation via telomere length and C-reactive protein levels, respectively. Additionally, examine how these effects may vary by disease duration, or be modified by race/ethnicity and parity.

There are three hypotheses associated with this aim:

1. Women with endometriosis or uterine fibroids will have higher CRP levels than women without these conditions, though CRP level will not vary by length of time since disease diagnosis, since these conditions are associated with chronic inflammation.
2. Women with endometriosis and uterine fibroids will have shorter telomeres than women without endometriosis, and telomere length will vary by length of time since disease diagnosis, such that women with a longer time since diagnosis will have shorter telomeres;
3. Associations between infertility diagnoses (i.e., endometriosis and uterine fibroids) and telomere length and CRP will be moderated by parity and race/ethnicity.

**Research Aim 3**: Investigate how experiences of stressors in childhood and young adulthood may influence infertility in adults, and how this association may be moderated by maternal responsiveness reported during adolescence.

There are two hypotheses associated with this aim:

1. Stressful life events (SLEs) prior to the age of 23 will be revealed as a risk factor for later infertility, with higher reports of SLEs being associated with higher risk for infertility;
2. The association between SLEs and infertility will vary by high or low maternal responsiveness, with stronger associations occurring in individuals with low maternal responsiveness in adolescence.

*Contributions to the Literature*

Telomeres are DNA end caps on chromosomes that naturally shorten with age.[25] It has been established that telomeres shorten prematurely in response to stress, and this advanced cellular aging has been linked to premature development of age-related diseases such as diabetes, cancer, and cardiovascular disease.[26] C-reactive protein (CRP) is a reliable indicator of low-grade inflammation that has been strongly linked to both early childhood stress and cardiovascular dysfunction, like myocardial infarction. Some links have been made between telomere shortening and reproductive dysfunction. This investigation advances the research on this link by focusing on two conditions related to reproductive dysfunction—endometriosis and uterine fibroids. Endometriosis is one cause of infertility that has been characterized by endometrial tissue growing abnormally within and outside its normal uterine location.[27] Uterine fibroids are benign growths that are generally only associated with infertility if they are located internally in the uterus, where they may prevent implantation.[28] Elevated risk of endometriosis and uterine fibroids has been observed in women who have experienced childhood abuse,

trauma, or other chronic stressors, via the same pathways of HPA-dysregulation and inflammation proposed between stress and general infertility.[29–31] The purpose of this investigation is to determine whether telomere length, as a biomarker of chronic stress, and/or CRP, a biomarker of inflammation, are associated with these two specific diagnoses related to infertility. This study is novel because, in addition to potentially linking stress to infertility, it addresses the absence of any universally-accepted biomarkers for infertility: the results of this study may provide evidence of such a biomarker.

Few studies have been conducted to test the association between stressful life events and infertility, and none have tested it longitudinally. Because the experience of stress may vary by environmental factors, this study will investigate how experiences of stressors may be modified by maternal responsiveness in adolescence. Maternal responsiveness has been established as an important protective factor in cognitive and social-emotional development.[32,33] Thus, isolating this buffering effect and treating this variable as an effect modifier may help to elucidate the pathway between early life stressors and infertility.

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# Chapter 2: Literature Review

## Psychosocial Factors and Infertility in Women

Though few studies directly test whether stress causes infertility in women, stress is commonly accepted as a cause of infertility in the literature. The most commonly-cited pathways by which stress may impact female fertility are disruption of neuroendocrine axes, increased inflammation, and immune system dysregulation. A heuristic of these pathways is provided in Figure 2.1.

Stress has long been considered a biologically plausible causative agent for reproductive dysfunction. The hypothalamic-pituitary-adrenal axis (HPA), which is activated in times of acute and chronic stress, is inextricably linked to the hypothalamic-pituitary-gonadal axis (HPG), which regulates reproductive function.[1] Disruption in HPA function can lead to multiple points of reproductive failure, any of which may influence fecundity, given the variety of hormones involved in successful conception. Generally, HPA activation stimulates the release of corticotropin-releasing hormone (CRH), which directly and indirectly influences other reproductive hormones via stimulation of cortisol and adrenocorticotropic hormone (ACTH).[1] ACTH stimulation inhibits release of gonadotropin-releasing hormone (GnRH), which is responsible for the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which regulate ovulation.[2] Furthermore, a second neuroendocrine system, the sympatho-adrenal-medullary (SAM) system, releases the catecholamines norepinephrine and epinephrine in response to acute stressors, and can remain activated in times of chronic stress.[3] Excessive levels of cortisol or catecholamines during critical windows in the conception process can adversely impact ovarian innervation, and can cause irregular secretion of

estrogens and progesterone, which influence ovulation, menstruation, implantation, and pregnancy viability.[1]

Stress stimulates the release of pro-inflammatory cytokines, which may prevent normal down-regulation of the HPA axis, as well as promote glucocorticoid resistance, thus perpetuating HPA hyperactivity.[4] Cytokines may also influence hormone secretion, ovarian function, implantation, and embryo development.[5–7] Furthermore, an increase in proinflammatory cytokines may signal T-cell dysregulation and reduced immunity, which has been noted in infertile women.[8,9] Specifically, in a study examining serum interleukin (IL)-6 and tumor necrosis factor (TNF)-α, women with unexplained infertility had significantly higher levels of IL-6 when compared to fertile women.[10] In another study, women with unexplained infertility had significantly higher intracellular levels of TNF- α, interferon gamma (IFN-γ), and other cytokines in comparison to fertile women.[8]

Anxiety and depression have been similarly linked to infertility via hyperactivity of the HPA axis and subsequent immune system dysfunction. Upregulation of the HPA axis results in increased secretion of glucocorticoids, which stimulates release of ACTH and cortisol, consequently inhibiting GnRH release, as described previously, and may lead to ovarian and menstrual dysfunction.[11] Alternatively, according to the "cytokine hypothesis," depression activates a pro-inflammatory pathway that stimulates the release of cytokines such as IL-1, TNF, and IFN-γ,[12] all of which have been implicated in infertility.[8,10]

The literature practically linking psychosocial factors to infertility is equivocal. Early studies related to spontaneous pregnancy after adoption have been highlighted as examples of stress relief as a "cure" for infertility.[13,14] There is extensive research

surrounding the association between psychosocial factors and pregnancy outcomes after in vitro fertilization (IVF). The three published reviews and one meta-analysis have shown that these studies have mixed results.[15–18] In a meta-analysis, Boivin and colleagues (2011) did not find any association between anxiety and depression and pregnancy outcomes following IVF, while a review highlighted the importance of managing depressive symptoms during the treatment process.[18] Two other reviews found that stress negatively influences the outcome of assisted reproductive technology (ART), though stress reduction interventions may help improve outcomes.[16,17]

With the goal of improving pregnancy outcomes, some fertility clinics have incorporated counseling into their treatment protocols, and interventions have been developed to reduce stress and increase the odds of conception. Evidence from some studies suggests that stress-reduction interventions do reduce stress, anxiety, and depression, corresponding to increased pregnancy rates following IVF.[19,20] Others have shown a reduction in the burden of psychosocial factors, but have not been associated with improved pregnancy rates.[21–23]

In terms of understanding stress as a causative agent for infertility, there are two main limitations to studies of stress and pregnancy outcomes in fertility clinics. First, although pathways linking psychosocial stressors to infertility have been well-described, IVF treatment—due to the medication protocol required—bypasses the traditional GnRH pathway linking stress to infertility. This has led some researchers to speculate as to whether a different pathway may be implicated in these research findings, and whether the proximal stress associated with infertility treatment can practically be used to describe chronic stress that may be a causative agent for infertility.[24] Essentially, studies of

pregnancy outcomes after treatment may not help to explain how stress, in general, is linked to infertility. Another limitation is that these studies are necessarily conducted in a subpopulation of women who already have an identified reproductive deficit. Women in these studies may have more acute reproductive dysfunction than the general population of infertile women, or they could be disproportionately comprised of people with diagnosable causes of infertility (i.e., recognized anatomic or physiologic dysfunction). Thus, the stress of infertility treatment may differ substantially from stress that could be causing an underlying pathophysiology.

Other studies have been conducted to specifically examine stress and the experience of infertility, though the majority are limited by their cross-sectional design, making it impossible to establish temporality. In several case-control studies, infertile cases were more likely to be experiencing stress than presumably fertile controls.[25–30] These studies are often limited by smaller sample sizes (<100), and questionable selection of "fertile" controls. Effective case-control studies must choose controls that are free of the disease under study—in this case, infertility. Most studies are unable to confirm that controls are not infertile because they either select as controls women of unknown fertility status, any women without an infertility diagnosis, or women who had at least one child.[31–35] While having a child may be a demonstration of fertility, none of the included studies using parents as controls asked about their fertility history, meaning they could have experienced infertility prior to the birth of the child, or could be currently experiencing secondary infertility, where they are unable to conceive subsequent children. Among other cross-sectional studies, one identified a positive association between stress and a biomarker of infertility, anti-mullerian hormone,[36] while another

found that stress was not associated with infertility until potential mediating factors, like smoking and prior health conditions, were removed from the analysis.[37] This would indicate that stress was associated with infertility, given that mediating factors should not be included in models as control variables, but rather, tested separately as mediators.

The question remains of whether cross-sectional studies, or those measuring stress associated with infertility treatment, are measuring the same thing as those examining psychosocial factors as explicit precipitants to infertility. In a seminal study on stress and the outcome of ART treatment, Ebbesen argues that much of the research related to this topic does not measure psychosocial stress because it does not consider the influence of outside factors, or the "environmental demand" that would provoke a stress response.[38] Furthermore, studies on psychosocial factors and their association with infertility treatment are conducted among women with diagnosed reproductive dysfunction, which makes it challenging to detect an effect of psychosocial factors in this population without large sample sizes, and many studies included relatively small sample sizes (<100). Similarly, 16 of the 20 cross-sectional studies examined in this literature review recruited women seeking treatment from fertility clinics, or with demonstrated infertility, again highlighting that the majority of research conducted to date has focused on *current* psychosocial factors in women with known reproductive dysfunction, instead of *prospectively* tracking the influence of psychosocial factors on infertility over time. Thus, to understand how psychosocial factors influence infertility in a global sense, it is critical to examine studies of psychosocial factors as a precipitant to infertility.

To that end, about a dozen studies have been published to address this issue of temporality. In studies assessing stress prior to infertility treatment, results indicate that

women experiencing stress in the months leading up to treatment were less likely to achieve pregnancy after one cycle of IVF than a comparison group not reporting stress.[38–40] The most robust of these studies included a large sample (n=837), and assessed stressful events occurring in the year prior, using a validated instrument (List of Recent Events).[38] While this study is subject to recall bias, the accuracy in remembering stressful events in the last year should not differ between women seeking IVF who ultimately achieved pregnancy and those who did not, since the assessment occurred prior to treatment. A similar study with similar findings by Yilmaz et al (2015) used the same instrument in a smaller sample (n=83), and asked respondents to recall lifetime stressful events, which may be more difficult for respondents to remember. Finally, Massey et al (2016) took hair samples from a relatively small sample (n=88) to measure cortisol levels over the three months prior to treatment, finding that, for every unit reduction in hair cortisol, the odds of pregnancy increased by almost 10%. A major limitation of each of these studies is that, again, they sampled groups of women with known reproductive dysfunction, which limits the generalizability of results to the subpopulation of women seeking treatment.

Other studies have measured psychosocial factors prior to the occurrence of infertility. In one cross-sectional study inquiring about occupational stress and time to pregnancy for all pregnancies, unemployed women with no occupational stress had the shortest time to pregnancy, while teachers with high occupational stress had higher fertility than unemployed women, who were assumed to have zero occupational stress.[42] However, this study did not account for age, which may explain higher fertility in teachers, if they are younger, and unemployment may, itself, be a source of stress.

Furthermore, there is significant recall bias introduced by trying to remember time to pregnancy between each pregnancy, and there is an assumption that the respondent was trying to conceive for all pregnancies, which may not be the case. Another study conducted a longitudinal survey of women trying to conceive, assessed depression at baseline, and found that fecundability decreased linearly as scores on the Major Depression Index increased, though the outcome of pregnancy was self-reported.[43]

In other studies assessing variations in time to pregnancy based on psychosocial factors, participants were asked to keep diaries or collect saliva samples to measure exposure to stress, anxiety, or depression over time.[44–47] Two of these studies had a follow-up time of six months, meaning they could not assess true infertility, defined in the literature as not achieving pregnancy after at least 12 months of intercourse without contraception.[45,47] Both found no association between stress and fecundity, though Buck Louis (2011) found that higher levels of the stress hormone, alpha-amylase, was associated with lower day-specific odds of conception. In studies with longer follow-up (12-20 months), stress was associated with lower fecundity, higher odds of infertility, and lower day-specific odds of conception.[44,46] For studies analyzing collected biomarkers of stress, there are some limitations, in that both salivary cortisol and alpha-amylase are released in a circadian pattern, meaning that collection once per day may be inadequate to measure stress.[45–47] Conversely, two studies asking for self-reported measures of stress did not use validated instruments, similarly calling into question the validity of their measurement of stress.[42,44] These same two studies did not measure pregnancy intention, assuming that any time to pregnancy was time spent trying to conceive, with no assessment of use of contraception during that time.[42,44]

To-date, only three studies have assessed the association between lifetime stressors and infertility. The strength of these types of studies is that, because stress was assessed prior to reports or diagnoses of infertility, it is possible to establish temporality of the sequence of events, which greatly improves the ability to draw inference from the findings. However, all three of these studies assessed stressful events and perceptions of those events retrospectively, which implies error and bias related to recall. Santos and colleagues conducted a case-control study of infertility and stress, where they found no difference in experience of lifetime stressors between cases and controls.[48] However, cases were identified by diagnoses from medical records, and controls were women with self-reported fertility, but no children. As discussed previously, with no knowledge of their fertility status, it is questionable if these controls are an appropriate comparison group for cases. Furthermore, only using women with diagnosed infertility limits the generalizability of findings to women who intentionally sought treatment, and excludes women who may have tried to conceive for more than 12 months, but either could not afford treatment, or simply did not elect to seek treatment

In another study of lifetime stress, researchers compared responses to questions about lifetime history of abuse and substance use to biomarkers of ovarian reserve, finding that "chronic stress" was associated with diminished ovarian reserve, which is one cause of infertility.[49] While the researchers labeled this a study of chronic stress, they found that a self-reported family history of abuse, the only previously validated measure of stress in their study, was not associated with the outcome. However, women with diminished ovarian reserve were more likely to have a history of substance use, another outcome examined in the study. While substance use has been posited as a potential

mediator on the pathway between stressful events and infertility, it is not, itself, a measure of stress.[38] This study could be an example of one with null findings on the association of lifetime stress and infertility, but with only one validated question on stressful life events, there is limited ability to draw inference from the results of this study.

Finally, the most rigorous study in this group was conducted by Jacobs and associates to assess associations between adverse childhood experiences (ACEs) and time to pregnancy.[50] ACEs are generally defined by exposure to emotional, physical, or sexual abuse and household dysfunction in childhood, and have been linked to adult morbidity and leading causes of death.[51] This study was conducted among 742 women in Louisiana, and found that as the number of ACEs increased, fertility difficulties increased. Women with four of more ACEs were at nearly three times higher risk for infertility and had lower fecundability than those with no reports of adversity. The strengths of this study are that they used validated measures of stress and a robust measure of infertility, asking about time to pregnancy instead of a dichotomous question asking whether it took 12 months or more to conceive. Also, because they measured ACEs prior to the age of 12, the plausibility of the association is supported by life-history theory, which posits that stressful events prior to puberty may disrupt reproductive function during development, leading to a predisposition for life-long reproductive dysfunction.[52] There are, however, limitations to this study. First, they assessed ACEs prior to the age of 12 retrospectively, introducing recall bias, and second, they recruited participants from OB/GYN clinics and WIC offices, which may represent a more fertile population.

Lacking from the literature on this topic are studies investigating trends or differences in these associations by race or ethnicity. Most studies include a racially homogeneous population, which may be a consequence of primarily conducting research in fertility clinics. Despite being twice as likely to experience infertility in their lifetime, black women are less likely to seek treatment, which may be one reason that the literature has not adequately addressed race.[53] Additionally, there are few nationally-representative data sources available that contain information about both stress and infertility, again making the conduct of research on racial and ethnic differences challenging.

**Biological Markers of Stress**

Examining research that analyzes stress in relation to racial and ethnic disparities in other health outcomes may aid in understanding how chronic stress may affect women's health. The weathering hypothesis was first proposed to explain why black women are more likely to deliver low birth weight babies than white women.[54] According to this hypothesis, the chronic stress associated with experiencing racism acts at the molecular level, causing an upregulation of physiologic systems that promote an advanced aging process in black women, such that their cellular age is more advanced than their chronologic age. This idea was later supported by evidence suggesting that younger black women had similar birth outcomes to older white women.[55] Geronimus's work to support the weathering hypothesis provided a tangible link between physiologic responses to stress and birth outcomes, though these studies have been unable to provide evidence of change on a molecular level.[56]

The research on the impact of chronic stress, racism, and birth outcomes is expansive and ongoing, and chronic stress has been strongly linked to adverse birth

outcomes.[57] Furthermore, evidence from a number of studies suggests that stress may act as a mediator between the experience of racism and poor birth outcomes.[58] This conclusion is strengthened by consistent findings that disparities in birth outcomes are not a result of genetic differences between races; foreign-born black women have lower odds of adverse birth outcomes than their US-born counterparts.[59,60] Furthermore, the protective effect of foreign nativity appears to decline for black women with every subsequent generation in the US. For example, Collins et al found that birth weight increased intergenerationally for the children of foreign-born white women, but it decreased for subsequent generations of foreign-born black women.[61] Furthermore, though it is challenging to assess, lifetime experiences of racism, including those occurring in childhood, have been associated with poor birth outcomes.[62]

More recently, studies have emerged linking experiences of racism and subsequent chronic stress to telomere length, a molecular marker of cellular aging.[63,64] Telomeres are strands of DNA and associated proteins located at the tips of chromosomes that assist in cell replication.[65] Because they shorten with each cell division, they are robust markers of cellular aging.[65] While chronological age is defined as the age of an individual based on a uniform progression of time, cellular or biological age is less predictable, and varies by genetic, environmental, and other factors that influence physiologic functioning. In demonstration of this point, shorter telomere length has been associated with onset of age-related morbidities like diabetes, cancer, and cardiovascular disease, labeled telomere syndrome.[66] The mechanisms explaining these associations are complicated, but relate to shortened telomere length being associated with cell senescence, in which cells cease to divide, as happens as a natural part of the aging

process. The upregulation of physiologic systems associated with chronic stress may lead to more rapid cell division, suppression of telomere elongation cycles, and consequent premature cell senescence.[66] Thus, individuals with short telomere length may experience morbidities associated with older age at an age younger than expected.[66]

Telomere length has also been studied in relation to reproductive aging and some forms of infertility. Women with short telomeres are more likely to have ovarian insufficiency, a type of ovarian dysfunction, than women with normal-length telomeres.[67] In measuring telomerase, a hormone that increases telomere length, women with higher telomerase activity have demonstrated better outcomes in IVF than women with low, or no telomerase activity.[67] Shortened telomere length has also been associated with recurrent miscarriage.[68] This finding, in conjunction with studies that show that women who give birth at older ages typically have longer-than-average telomeres, supports the link between telomere length and reproductive aging.[69] Reproductive aging refers to the stages of reproductive function from menarche through post-menopause. Researchers have found that reproductive aging and the decline of reproductive function cannot be fully attributed to diminishing oocytes, but may also be related to shortened telomeres.[70] Short telomere length may contribute to meiotic dysfunction, producing oocytes of poor quality, which have been observed in IVF cycles of women with short telomere length.[71,72] Furthermore, telomere length has been positively correlated with reproductive life span, such that longer telomeres predict a wider reproductive window,[73] including older age at menopause.[74,75] In summary, while reproductive function typically declines with age, it may be more of a function of cellular age than chronological age. Thus, it is possible that cellular aging—which, based on the Weathering Hypothesis, may also be

influenced by chronic stress due to racism or other less understood factors—may produce reproductive outcomes in women that are inconsistent with their chronological age, including infertility.

Finally, while not typically included in studies of infertility, C-reactive protein (CRP) is a biomarker of inflammation with strong links to cardiovascular morbidity.[76,77] Elevated levels are also associated with experiences of early life stress and current and chronic depression.[78,79] As discussed previously, inflammation may occur as a result of acute or chronic stressors, or may, itself, adversely impact reproductive function.[8–10] Thus, while the link between CRP and fertility has not been studied, given its role in the inflammatory process, CRP could be plausibly linked to infertility. With connections to both early life stress and cardiovascular morbidity, if linked to infertility, it could serve as another indicator of a shared pathway between infertility and later-life morbidity.

**Early Life Stress and Infertility**

As discussed previously, only three studies to-date have empirically tested the link between lifetime stressors and infertility.[48–50] While it is challenging to establish causality between exposures and outcomes that occur at distant points in time from each other, the idea that early life stress may impact fertility in adulthood is biologically plausible. Many animal studies have found links between early life chronic stress and later fertility. For example, in pre-pubertal rats, overexpression of corticotropin releasing factor, which occurs as a result of chronic stress, contributed to early onset of puberty, but altered the stress-responsivity of gonadotropin-releasing hormone to induce irregular estrus cycles and dysregulation of hormones critical to conception.[80] In another study, stress impaired murine oocyte development via changes in DNA histones, which can be

altered epigenetically, and are thus sensitive to environmental factors in utero and in early life.[81] Finally, because the murine life cycle is short, researchers have been able to examine specific genes that influence fertility in rodents. Chronic stress has long-term effects on pregnancy well after the stressor is removed, but researchers have discovered a gene that, when suppressed, improves pregnancy rates in stressed rats to match those of non-stressed rats.[82] Implantation-related and ovarian-hormone-responsive genes may also be suppressed by stress.[83]

While it is possible that early life stress may influence fertility via gene-specific pathways, much remains unknown about these genetic pathways. However, there are at least two lines of evidence in human biomedical research to support the association between early life stress and infertility. First, telomere shortening has been extensively studied in terms of early life stressors or adverse childhood experiences. Early life stress, childhood depression, and mood disorders have all been linked to telomere shortening, with shortened telomeres representing as much as a 10-year increase in cellular age over chronologic age.[84,85] In individuals with no history of psychiatric disorder, childhood maltreatment has also been linked to shortened telomeres in adulthood.[86] As discussed previously, shortened telomeres have been linked to a variety of reproductive dysfunctions, perhaps as a result of advanced cellular aging.

The second line of evidence comes from several theories related to evolutionary and developmental biology that suggest that early life stress may alter development of both the reproductive system and stress response to promote dysfunction in both. From an evolutionary perspective, the Reproductive Suppression Model suggests that female mammals have evolved to suppress reproductive functioning when conditions are

inhospitable to reproduction. By doing this, the female is conserving energy and resources by not carrying offspring that will either not survive to be born or may perish soon after birth.[87] This conservation of energy and resources would then allow for better conditions for existing offspring and lead to later reproductive success.[88] According to this model, also referred to as the Reproductive Filtering Model, mammals who "filter" unviable offspring by suppressing reproduction are naturally selected, making this the more common phenotype in higher order mammals, like humans. This model serves as the operating theory underlying many studies of stress and infertility.[30,89,90] While early iterations of this model focused on reproductive suppression occurring simultaneously with stressful events, the theory has been refined to propose that stress has a developmental impact, causing menstrual cycle abnormalities that do not always manifest as irregular cycles.[91] Furthermore, it has been suggested that, because the HPA-system does not discriminate against types of stressors, all stress, at any point in the life span is bad for fertility.[90] However, developmental theories would indicate that timing of events is critical in the context of the development of the stress and reproductive axes.[52]

Building on the Reproductive Suppression Model and similar theories, life history theories describe how stressful events in early life may influence later fertility in humans. Similar to earlier optimization models that focused on mammals more broadly, life history models emphasize balance between preserving individual health and reproduction, positing that humans have evolved to be responsive to their environment to increase overall fitness of the species.[92] In the case of stress, the physiologic response can have lasting consequences, as childhood events may impact development of the HPA axis, influencing axis regulation and the stress response.[52] Specifically, psychosocial

stimuli in childhood, like stress, can alter baseline functioning of the HPA axis, including the amount of cortisol released during the stress response, creating a stress-response system that is over-responsive to stimuli throughout the life course.[52] Thus, stressful events in early life can have lasting consequences on multiple physiologic systems, an idea supported indirectly by many studies of adverse childhood experiences (ACEs) and their links to age-related morbidity and leading causes of death.[51,93,94] In terms of reproduction, while most women will have no difficulty conceiving, given the same environmental and genetic circumstances, some women may experience infertility as a result of an overactive stress response.

Beyond a developmental viewpoint, it has been proposed that HPA functioning may also be altered by early life stressors via epigenetic programming.[95] Epigenetic programming describes the mechanism by which identical genes may be expressed differently as a result of "switches" that either turn the gene on or off, or modify the level of expression of the gene (increased or decreased). These modifications are hypothesized to occur via DNA methylation, histone modification (i.e., how DNA is folded), and the addition of non-coding RNA strands.[96] Regardless of the mechanism through which epigenetic programming actually changes gene expression, such programming has been posited as a causal mechanism linking early life stress to poor health outcomes in adulthood.[96] According to this theory, the experience of early life stress either alters HPA function or directly changes epigenetic regulation of genes that influence adult health.[95–97]

While childhood and adolescence have been established as critical periods of development during which time stressful events may have lifetime consequences, it is

important to remember that these events do not occur in isolation, and, depending on the child's family or larger social environment, the same types of events may not cause the same emotional, psychological, or physiological changes in all children. Thus, it is important to consider other characteristics of the child's environment that may buffer or moderate responses to stress. While there are many aspects to this environment, maternal responsiveness, which can be defined in terms of prompt, appropriate responses to everyday exchanges with children, has long been considered a protective factor in cognitive and social-emotional development.[98,99] There is also evidence that maternal responsiveness may moderate the association between stressful events in childhood and long-term morbidity, perhaps even serving as a buffer to prevent changes in the stress response system, as described previously.[100] In studies of children in risky, high-stress environments, children of mothers with low maternal responsiveness had higher allostatic load, a measure of cumulative stress, and poorer working memory than those with highly responsive mothers.[101,102] Maternal responsiveness has also been found to moderate the association between psychosocial disadvantage in infancy and childhood behavioral problems.[103] Recently, a study of children utilizing welfare benefits found that those identified as being at high risk for maltreatment had shorter telomeres than their low-risk counterparts, and this association was moderated by parental responsiveness.[104] High-risk children with highly responsive parents had longer telomeres than those with low-responsive parents, which suggests that parental responsiveness may serve as a protective factor against telomere shortening in response to early life stress.[104]

## Conceptual Framework: Life Course Theory

Over the last several decades, models have emerged to explain how events that occur throughout the life course may influence later-life health. The mechanisms and pathways described in the preceding paragraphs describing how early life stressors may influence fertility can be best understood in the context of life course theory. Life course theory, also known as a life course perspective, is a relatively recent paradigm, put forth in the 1990s. In the context of the current exploration, the life course perspective merges two critical pathways by which early life stress may influence fertility. First, the early programming mechanism suggests that disturbances that occur during critical windows in fetal development can fundamentally change physiologic functioning throughout the life span.[105,106] For example, in relation to infertility, ovarian dysgenesis theory proposes that environmental insults *in utero* may adversely impact ovarian structure or function, leading to consequent reproductive dysfunction.[107] Expanding on the early programming mechanism is the concept of critical or sensitive periods of development.[108] This concept is similar to the early programming mechanism, but expands upon it by positing that there are other critical windows during development, and that environmental insults or events in childhood or adolescence can influence later health. Adapting this model to explain the association of interest in this study, stress in early life may impact development of the immune system and stress-response axes to change an individual's phenotype to be more reactive to stress. As described previously, higher stress reactivity increases the risk for dysregulation of the reproductive system, introducing difficulties in conceiving children or carrying them to term. As discussed previously, maternal responsiveness in adolescence may moderate the stress response of the individual,

serving as either a risk or protective factor to alter the physiologic response to stress and its potential impact on reproductive functioning.

Next, the social chains of risk mechanism of life course theory suggests that the health trajectories of populations may be predicted by social and environmental exposures, though an individual's health trajectory will change based on risk and protective factors to which they are exposed.[109] Finally, the cumulative mechanism posits that stressful life events increase allostatic load, an indicator of up-regulated physiologic functioning, which causes subsequent biologic "wear and tear" on the body.[110] Chronic wear and tear can affect regulation of the stress response and increase inflammation and dysregulation of the immune system to negatively impact health.[111] Again, chronic stress in childhood may change development of the immune system or stress axes to induce infertility. Thus, the proposed study is framed by multiple concepts important to life course theory.

While few studies have been conducted linking stressors in early life to infertility, some studies have provided evidence that early life stress and stressors prior to pregnancy may produce poor reproductive outcomes. In a study of stillbirth, or infant death occurring beyond 20 weeks gestation, researchers found that women reporting stressful life events leading up to pregnancy, such as hospitalization of a family member, periods of homelessness, and financial difficulties, had higher odds of stillbirth than those with no stressful life events.[112] Similarly, in two other large, national studies, women reporting any stressful life event prior to conception were more likely to have infants who were preterm or very low birthweight.[113,114] Thus, there is already some precedent linking

stress to reproductive outcomes that occur at a time that is distal from the original stressor, and the stressors assessed were generally consistent across studies.

In summary, chronic stress has already been established as a risk factor for premature disease and mortality. The research is equivocal on whether current stress impacts fertility but based on life course theory and evolutionary and developmental theories, examining current stressors may be inadequate to provide an understanding of common pathways establishing infertility as an indicator of current health or a predictor of future health. Research on indicators of chronic stress, like telomeres, and experiences of early life stress, may help improve understanding of how chronic stress influences fertility, and how best to utilize this information to enact interventions to improve overall health.

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# Chapter 3: Methods

**Research Aim 1: Identify and critically review the literature examining psychosocial factors as precipitants to experiences of infertility.**

The following procedures were conducted for this scoping review to identify publications describing the link between psychosocial factors and subsequent infertility. Prior to beginning the review, the research librarian for the School of Public Health at the University of Maryland was consulted to identify relevant databases, search terms, and methods for a comprehensive scoping review. These procedures were adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA guidelines suggest the selection of key search terms after pre-reviewing relevant literature, the development of inclusion and exclusion criteria of identified studies, blind review of abstracts by at least two individuals, and full-text review and extraction of final studies.[1]

A diagram describing the rules for inclusion and exclusion of literature can be found in Figure 3.1. All English-language, peer-reviewed publications and unpublished dissertations discussing infertility and stress, anxiety, or depression were included in a search of EBSCO databases and PubMed, with no limitation of publication date. The selected databases were chosen because they were considered to be comprehensive sources of English-language scientific literature relevant to reproductive health. Based on an initial scan of the literature, the terms, “Infertility,” “infertile,” “fertility,” “stress,” “anxiety,” and “depression” were found to be the most common terms used as subjects and Medical Search Headings relevant to the research aim. Other terms that were

considered, but not used due to overlap with other terms, or lack of relevance of findings, included “fecundity” and “fecundability.” In February of 2018, the search terms, “Infertility or infertile or fertility” and “stress or anxiety or depression,” were used in the EBSCO databases Academic Search Complete, Academic Search Premier, CINAHL, PscyINFO, Family and Society Studies, Health Source, Women’s Studies International, Psychology and Behavioral Science Collection, MasterFILE, SocINDEX, Health Policy Reference Center, Social Sciences (H.W. Wilson), Family Studies Abstracts, and PsycArticles, producing 2,719 results. MeSH terms (infertility, female; and stress, psychosocial; anxiety; or depression) were used to identify articles in PubMed, producing 385 results.

While there is abundant literature published on these topics, the purpose of this review was to explore the literature examining psychosocial factors as precipitants of infertility. Thus, several exclusion criteria were applied to the initial review of titles. Publications were excluded if the following were clearly stated in the title: infertility in men only, psychosocial factors occurring as a result of infertility diagnosis or treatment, counseling interventions to improve psychosocial state during infertility treatment, couples or marital tension resulting from infertility, or postpartum depression. In general, publications related to infertility-specific stress, or stress presumably caused by infertility, were excluded, with two exceptions. First, studies examining the effect of psychosocial factors on success of IVF were initially retained because these studies had potential to examine a physiologic pathway that is similar to that of other psychosocial factors that may cause infertility. Second, publications were retained that compared psychosocial factors among women with diagnosed infertility to presumably fertile

controls, since these types of studies could indicate a bi-directional association between psychosocial factors and infertility (Figure 3.2). After the initial review, 204 relevant titles were identified from the EBSCO search, and 83 were identified from the PubMed search. After removing duplicates, 242 total articles remained for abstract review.

In the next stage, all abstracts were reviewed blindly by two reviewers (JLG and LBD), using the same exclusion and inclusion criteria as applied to the initial title review. Specifically, 84 publications were eliminated because the research did not study infertility as an outcome. Of those, 37 were publications describing non-infertility outcomes, such as pregnancy stress, and 47 examined psychosocial consequences of infertility treatment or diagnosis. Despite the use of a search filter, another 31 titles were not peer-reviewed articles or dissertations (e.g., commentaries or summaries), and 12 were foreign-language studies, all of which were eliminated due to lack of English translation or lack of relevance. Additionally, non-empirical articles (9), studies examining non-infertile populations (e.g., pregnant women) (11), qualitative studies examining the meaning of infertility (12), and those discussing oxidative stress (24), which is a physiologic phenomenon separate from psychosocial stress, were excluded from final review. The two reviewers met to discuss five publications for which they made conflicting exclusion determinations. After re-reading the abstracts and reviewing the criteria, they reached consensus and included three publications previously eliminated by one reviewer, while excluding the other two. After this, 60 peer-reviewed publications remained for full-text review.

In the final stage, all remaining articles were reviewed in full and assigned to categories based on subject matter and methodology. First, based on the previously

completed title and abstract reviews, several a priori categories were created and applied to the articles during review. No new categories were created beyond these original ones. Some studies were given multiple classifications, but the primary classifications were as follows: psychosocial factors and the outcome of infertility treatment (21), cross-sectional studies comparing psychosocial outcomes in women diagnosed with infertility to women not diagnosed with infertility (20), psychosocial factors examined as precipitants to infertility or subfecundity (7), interventions to lower stress and improve pregnancy outcomes in treatment (5), animal studies (4), and studies examining the association between lifetime stress and infertility (3). Of the cross-sectional studies, seven were case-control designs. Of the studies examining psychosocial factors in relation to outcomes of fertility treatments, the type of exposure varied, but was studied in the following combinations: anxiety only (2), depression only (1), stress only (7), anxiety and depression (7), stress and anxiety (2), lifetime stress and depression (1), and all factors (1). By the end of the full-text review phase, four articles were excluded (not included in the above classifications), based on previously described exclusion criteria. Eight additional articles were identified from citations included in the reviewed articles. Four of these were deemed relevant to this review and classified based on full-text review.

**Research Aim 2: Describe the association between reproductive dysfunction and measures of both chronic stress and inflammation via telomere length and C-**

**reactive protein levels, respectively. Additionally, examine how these effects may be modified by race/ethnicity and parity.**

Hypothesis 1: Women with endometriosis or uterine fibroids will have higher CRP levels than women without these conditions, though CRP level will not vary by length of time since disease diagnosis, since these conditions are associated with chronic inflammation.

Hypothesis 2: Women with endometriosis and uterine fibroids will have shorter telomeres than women without endometriosis, and telomere length will vary by length of time since disease diagnosis, such that women with a longer time since diagnosis will have shorter telomeres;

Hypothesis 3: Associations between infertility diagnoses (i.e., endometriosis and uterine fibroids) and telomere length and CRP will be moderated by parity and race/ethnicity.

*Study population and Data Source*

The National Health and Nutrition Examination Survey (NHANES) is a nationally-representative survey designed to assess the health of adults and children in the US. Through a complex, multi-stage sampling process, NHANES procedures randomly identify approximately 5,000-10,000 individuals of all ages to be included in each two-year cycle.[2] Participants are interviewed in their homes using a series of questionnaires. Participants who are unable to respond to questions (e.g., infants or individuals with cognitive or motor disabilities) are interviewed through a proxy who responds on behalf of the selected participant.[3] Using Mobile Examination Complexes, all participants receive a physical examination and biologic samples are collected, such as blood, urine, and saliva. These samples are analyzed to provide information on a variety of biomarkers that are publicly available for all waves of data collection.[4]

*Analytic Sample*

The current project utilized data from two waves, including data collected between 1999 and 2002, which are the only years for which telomere data are available. The total eligible sample included all women who answered interview questions related to endometriosis and uterine fibroids. For this portion of the reproductive health questionnaire, interviewers only surveyed women between the ages of 20 and 54, thus the sample will be limited to this age range. With no other exclusion criteria, this left an eligible unweighted sample of 4,862 women.

*Exposure: Endometriosis or Uterine Fibroids*

The exposure variables for this study included endometriosis and uterine fibroids. Both were coded as dichotomous variables, based on a respondent's answer to two separate questions: "Has a doctor or other health professional ever told you that you had" either endometriosis or uterine fibroids (event=1, no event=0). For participants who responded yes to either preceding question, they were asked their age at diagnosis. Time since disease diagnosis was calculated by taking the age of diagnosis of endometriosis or uterine fibroids and subtracting it from the participant's current age.

*Outcome: Telomere length and C-reactive protein*

The main outcome variables for this study were current leukocyte telomere length, a biomarker of reproductive aging, and current C-reactive protein (CRP) a biomarker of chronic and current inflammation. During NHANES data collection, Telomere length was determined by assaying DNA samples three times each using polymerase chain reaction to compare an individual's mean telomere length to a standard

reference using human beta-globin (T/S ratio).[4] This measure is commonly used in studies of telomere length.[5,6]

Current CRP levels were measured from blood samples, using standard laboratory protocols, as described in the NHANES laboratory procedures.[4] Because CRP levels greater than 10.0 mg/L are indicative of acute inflammation, often due to infection, these individuals were eliminated from analysis (9%).[7] CRP was coded dichotomously, consistent with other studies,[8] such that individuals with CRP levels greater than 3.0mg/L (but less than 10.0 mg/L) were categorized as having high CRP, while those with levels at or below 3.0 mg/L were categorized as having normal CRP.

*Covariates*

Covariates were chosen based on prior studies of telomere length and reproductive outcomes. Potential confounders in the associations between exposure and outcome variables include age, poverty-to-income ratio, educational attainment, age at menarche, and smoking. Because telomere length naturally decreases with age, the relationship between age and telomere length was tested using correlation and regression analyses to identify the best way to code age in analyses. The relationship between age and telomere length was linear, with a significant but weak correlation within the analytic sample (r=-0.20). Thus, age was analyzed as a linear variable.

Poverty-to-income ratio is a measure of household income compared to the federal poverty level, and was analyzed as a continuous variable.[9] When asked about highest grade completed or highest degree received, respondents could choose between less than 9$^{th}$ grade, 9-11$^{th}$ grade (includes 12$^{th}$ grade with no diploma), high school grad/GED or equivalent, some college or AA degree, or college graduate or above. When

coding educational attainment, these categories were generally unchanged, with the exception of combining the "less than 9$^{th}$ grade" and "9-11$^{th}$ grade" categories to a "less than high school graduate" category. Age at menarche was determined by the question, "how old were you when you had your first menstrual period," and analyzed as a continuous variable.

Behavioral or lifestyle variables, to include lifetime smoking status, current body mass index (BMI), physical activity, and hormone use, may all lie on the causal pathway between exposure and outcome variables but were examined as covariates in additional models to test this assumption. Lifetime smoking status was coded based on responses to the questions, "have you smoked at least 100 cigarettes in your entire life," and "do you now smoke cigarettes?" Based on responses to these yes/no questions, individuals were coded into three categories: never smoker, former smoker (smoked at least 100 cigarettes but does not currently smoke), and current smoker. Body mass index (BMI) was calculated in the NHANES dataset using the standard method of dividing weight (kg) by squared height ($m^2$). Physical activity was calculated by summing five separate measures of weekly activity. Respondents were asked to report how many days per week and minutes per session they spent engaging in moderate or vigorous activity at work, walking or biking to work, and moderate or vigorous recreational activity. The number of days per week engaged in each activity were multiplied by the number of minutes per session to determine minutes of each activity per week. Then, the minutes for each activity were summed. Respondents who reported at least 180 minutes of any activity per week were coded as engaging in an adequate amount of physical activity.[10] Those

reporting less than 180 minutes were coded as engaging in inadequate physical activity, per American College of Sports Medicine and American Heart Association guidelines.[10]

Finally, hormone use was coded as never, past, or current, based on responses to a series of questions related to whether respondents have ever taken or are currently take birth control pills and/or female hormones. Respondents who indicated they have never taken birth control pills or female hormones were coded as "never," while those who indicated previous use but not current were coded as "former," and those who indicated current use were coded as "current."

*Effect modifiers*

Effect modifiers were chosen prior to the development of the analytic plan, based on their observed associations with exposures and outcomes in previous research. Parity can be used to estimate the degree of dysfunction associated with infertility, and telomere length is typically shorter in women who have given birth.[5,11] Thus, parity was examined as an effect modifier in the association between endometriosis/fibroids and telomere length. This variable was coded using responses to two questions, "have you ever been pregnant," and "how many of your pregnancies resulted in a live birth?" A previous investigation of parity and telomere length in this sample found that telomere length did not vary according to the number of live births.[5] Thus, parity was coded dichotomously. Respondents who indicated they have never been pregnant or indicated they have been pregnant but had zero live births were coded as nulliparous (event=0). Respondents who indicated at least one pregnancy resulting in a live birth were considered parous (event=1).

Race/ethnicity has been identified as a moderator based on studies indicating that telomere length may be longer in African Americans than in comparable white individuals, and has been found to moderate the association between telomere length and age at menopause.[6,12,13] In the 1999-2002 cycles of NHANES, respondents could identify as Mexican American or other Hispanic, non-Hispanic White, non-Hispanic Black, or other race (includes multiracial). In this study, the Mexican American and other Hispanic categories were combined into a single "Hispanic" category for stratified analyses. The "other race" category was not reported in final results, since this is a heterogeneous group for which it is difficult to draw inference. This decision is consistent with the NHANES analytic guidelines, which state the difficulty in accurately weighting a heterogeneous group to be nationally-representative of racial groups outside of Hispanic, Black, or White, including multiracial.[9]

*Analyses*

Descriptive statistics were calculated for all exposure, outcome, confounder, and moderator variables, with mean and standard deviations calculated for continuous variables and proportions calculated for categorical variables. Each variable was compared between exposure and non-exposure groups (i.e., endometriosis vs. non-endometriosis and uterine fibroids vs. non-uterine fibroids) using t tests for continuous variables or Rao-Scott modified chi-squared tests for categorical variables to determine differences between groups. All analyses were conducted in SAS v9.4, using appropriate survey commands and weights to account for the complex sampling design.

Telomere length was skewed to the right and natural-log transformed to approximate a normal distribution for all analyses. Results were exponentiated after

analysis to provide an estimate of telomere length change between groups. Finally, the mean T/S ratio was converted to number of base pairs using the formula, 3274 + 2413*(T/S ratio), where appropriate.[4]

The covariates smoking status, BMI, physical activity, and hormone use may lie on the causal pathway, but investigating mediators was outside of the main objectives of this study. Because it is not possible to distinguish between variables that may be confounders and those that may lie on the causal pathway between exposure and outcome (mediators), models were fit in a step-wise manner. Thus, three models were fit to test each of the associations between exposure and outcome variables, as follows: (1) Age-adjusted (included age only); (2) Demographic model—adjusted for sociodemographic variables only (age, poverty-to-income ratio, educational attainment, and age at menarche); and, (3) Fully adjusted for sociodemographic and lifestyle/behavioral variables (add smoking, BMI, physical activity, and hormone use). To test Hypothesis 1, logistic regression models were fit (unadjusted, demographic, and fully adjusted) to test the associations between endometriosis and CRP level, and uterine fibroids and CRP level, with "high CRP" set as the event. To test Hypothesis 2, linear regression models were fit to examine the associations between exposures and telomere length. For all sub-analyses, the demographic model was used, since lifestyle/behavioral variables were considered to be potential mediators. Adjusted regression models were fit to test for a dose-response association between CRP or telomere length and length of time since disease diagnosis, to address the second halves of both Hypotheses 1 and 2.

To test for effect modification posited in Hypothesis 3, interaction terms were coded for parity in the demographic model (parity*endo/fibroids). In a separate

demographic model, interaction terms were then coded for race/ethnicity (race/ethnicity*endo/fibroids). Results were stratified to examine the degree to which parity or race/ethnicity may modify observed associations, where appropriate.

Finally, in sensitivity analyses, because telomeres naturally shorten with age, models were stratified by age to confirm observed effects were unlikely to be due to age alone. Demographic-adjusted models were fit to test associations between telomere length and time since disease diagnosis for women in their 20s, 30s, 40s, and 50s. These strata were chosen to ensure adequate sample size to assess associations in each age group. Furthermore, there were no significant correlations between age and telomere length in any age category, except for women in their 20s, where there was a low but significant correlation ($r$=-0.13).

**Research Aim 3: Investigate how experiences of stressors in adolescence and young adulthood may influence fertility in adults, and how this association may be moderated by maternal responsiveness in adolescence.**

Hypothesis 1: Stressful life events (SLEs) prior to the age of 23 will be revealed as a risk factor for later infertility, with higher reports of SLEs being associated with higher risk for infertility;

Hypothesis 2: The association between SLEs and infertility will vary by high or low maternal responsiveness, with stronger associations occurring in individuals with low maternal responsiveness in adolescence.

*Study Population and Data Source*

This study utilized data from the National Longitudinal Survey of Youth's 1997 Cohort (NLSY-97) to explore how exposure to stressful life events (SLEs) prior to the age of 23 may be associated with later reports of infertility. The US Bureau of Labor Statistics employs complex stratified sampling methods to recruit a nationally-representative sample of men and women in the same birth cohort.[14] The cohort included in NLSY-97 were born between 1980 and 1984, and first surveyed in 1997. Similar to other NLSY surveys, NLSY-97 is an ongoing longitudinal survey that interviews the same birth cohort annually or biannually. In the initial round, 8,984 individuals were interviewed, and approximately 83% of the original participants were retained for interview in 2011, the last year for which data was used for the current study.[15,16]

In 2011, the last year for which data were used for the current study, 3,714 women were interviewed. The analytic sample included all female participants who had ever tried to get pregnant with complete data on stressful life events and infertility (*n*=1,652). Women who indicated they have never tried to get pregnant were excluded from analyses.

**Measures**

NLSY-97 is a complicated data set with different question types being asked only in specific rounds. To facilitate understanding of the current study, a complete diagram of the timing of data collection on relevant variables can be found in Figure 3.4. Additionally, a summary of relevant questions asked and ages at which participants answered these questions can be found in Table 3.1.

*Outcome: Infertility*

Infertility information was collected between 2009 and 2011, which encompasses two rounds of data collection interviews (Rounds 13 and 14). While the majority of participants responded to these questions in 2009, the few who were unavailable in 2009 were asked in 2010 or 2011.[14] First, participants indicated whether they had "ever been part of a couple that had problems getting pregnant or having a baby." Possible answers to this question included "yes," "maybe," "no and I have tried to have a child," and "I have not tried to have a child." All participants were then asked if they "had unprotected sex for at least 12 months in a row without conceiving a child."

Infertility was coded dichotomously (1=yes, 0=no) in two ways, based on responses to these questions. First, a general, subjective definition of infertility was coded, based on whether participants indicated being part of a couple that had problems getting pregnant. Participants who answered "maybe" or "I have never tried to have a child" were excluded from analyses using this definition to ensure that the analytic sample consisted only of individuals who had tried to conceive, and not those who were unaware of their fertility status. Second, infertility was coded based on a definition consistent with the clinical criteria for infertility (regular sexual intercourse over at least 12 months without the use of contraception, and without conceiving a child),[17] reported as, "I have had unprotected sex for at least 12 months in a row without conceiving a child." Again, those who indicated they had never tried to have a child were excluded from analyses using this definition.

*Exposure: Stressful Life Events*

Many inventories have been developed to assess SLEs, but across studies, variations in inventories produce similar magnitudes of association between SLEs and

health outcomes.[18] Inventories are the preferred method for assessing SLEs over open-ended questions, where there is an increased chance of differential recall bias.[18] Length of time elapsed between the event and health outcomes varies in terms of assessment across studies from 6 months to 5 years, and there is debate regarding lag time between an event and negative mental and physical health outcomes, though experts recommend evaluation at least one year after the stressful event.[19] Recall bias may be an important consideration when asking respondents about events that occurred more than one year prior, but some traumatic events are considered to have lifetime effects and are unlikely to be forgotten. Examples of these events could include death of a parent or child, parents who divorced, combat experience, or physical or sexual assault or abuse. Thus, it is important to include these types of lifetime events in inventories of SLEs.[19] Much has been written about the importance of weighting events, whether objectively (stressors that would apply across individuals) or subjectively (asking follow-up questions related to the meaning of events). However, it has been noted that weighing events does not tend to change the magnitude of association between SLEs and health outcomes.[19]

This investigation assessed SLE exposure using an inventory, Brugha's List of Threatening Experiences. This inventory was developed in 1985 and based on stressful life events reported by a random sample of the population.[20] Of the events mentioned by respondents, 12 events were consistently perceived to be of "marked or moderate" threat. These events were included in the List of Threatening Experiences, which has since been validated in the US and other populations, and can be considered a good way to measure an "accumulation" of stress.[20,21] Because of the paucity of literature published to assess the potential effect of SLEs on infertility, the literature surrounding stress and pregnancy

outcomes may be the most closely related to inform exposure assessment. Pregnancy Risk Assessment and Monitoring System (PRAMS) has adopted this list to assess stressful events prior to pregnancy, where events have been assessed preconception to predict preterm birth and stillbirth.[22,23]

Each question included in the measurement of this exposure in NLSY-97 corresponded to a question on the List of Threatening Experiences, a validated inventory of stressful life events that has also been used to assess pregnancy outcomes in response to stress.[20,22,23] It is important to note that a few questions from Brugha's list were not included in NLSY-97 (e.g., death of a friend, argument with a close friend, breaking up with a partner). In the first round (1997), participants were asked if, prior to the age of 12, they: ever had their house/apartment broken into; were ever the victim of repeated bullying; and ever saw someone get shot or shot at with a gun. In rounds 2-5 (1998-2001), after respondents reached the age of 18, they were asked if, between the ages of 12 and 18, they, again: ever had their house/apartment broken into; were ever the victim of repeated bullying; and ever saw someone get shot or shot at with a gun. In Round 6 (2002), when respondents were between the ages of 17-22, they were asked several other questions related to SLEs, and the age at which they happened: death of a close relative, victim of a violent crime ("for example, physical or sexual assault, robbery, or arson"), homelessness, household member stayed in the hospital for at least a week for treatment of illness or injury, adult member of household incarcerated, household member unemployment, and parents' divorced. These questions were repeated in Round 11 (2007), and again in subsequent rounds if the question was not answered in 2007 (i.e., participant was unavailable for interview). Thus, it was possible to ascertain all surveyed

SLEs that occurred prior to the age of 23, since respondents would answer these questions for the prior five years through the age of 28. A total score for the number of SLEs was initially calculated, and then scores were grouped into categories, based on the distribution (0-1, 2, 3, 4+).

To assess the impact of event timing, we coded SLEs differently from the coding scheme in the main analysis because the number of SLEs were not consistent across age categories (i.e., only three possible events prior to age 12 compared to ten between the ages of 12-18). Three separate SLE dichotomous variables were created based on the age at which the event occurred: any event prior to the age of 12, any event between the ages of 12 and 18, and any event after age 18 (any event=1, no event=0).

*Potential Confounders*

Demographic confounders included race/ethnicity and household income to poverty ratio in adolescence. Participants' race/ethnicity was categorized based on how race/ethnicity was identified in NLSY-97 data: Hispanic, non-Hispanic/non-Black, non-Hispanic Black, or multiracial. Household income to poverty ratio was calculated by dividing family income, as reported in Round 1 (1997), by the federal poverty level, accounting for household size.

Household confounders included biological siblings living in the household and physical environmental risk factors in adolescence. Detailed information about siblings in the home can be found in the household roster and was coded as a continuous variable. The physical environment has been linked to both reproductive health and child development, which may facilitate or contribute to SLEs.[24,25] For the first round of data collection in 1997, Child Trends, Inc. created a physical environment risk index to

include whether the household usually had electricity or heat when needed in the past month, the condition of buildings on the youth's street, the condition of the interior of the home (reported by interviewer), whether interviewer felt concerned for their safety in the youth's neighborhood (reported by interviewer), and the number of days the youth hears gunshots in a typical week.[26] Based on the distribution of scores on the index, physical environment risk was coded into three categories (0, 1-2, 3+).

Finally, health and health behavior confounders included substance use and BMI. For Rounds 1-4 (1997-2000), Child Trends, Inc. created an index variable for substance use based on participant responses indicating cigarette, alcohol, and marijuana use.[26] Each year over this four-year period, participants could receive a score of 0-3 based on their substance use. Each participant's score was summed over each year through 2000, to produce a total possible score of 0-12. Scores were averaged over the analytic sample and substance use was coded dichotomously as above or below the mean (>4.4and ≤4.4). These years were chosen for assessment of substance use because usage may have occurred early enough in development to affect later reproduction. Use may then have occurred simultaneously with SLEs, and not necessarily after, when substance use could then be considered a mediator in the causal pathway between SLEs and infertility. BMI was calculated at baseline as weight (kg) divided by height ($m^2$).

Several of the proposed confounders for associations between stress and infertility could lie on the causal pathway between these variables. For example, use of tobacco, alcohol, and substance abuse have been associated with maladaptive coping when confronted with stress. Given that the timing of these behaviors could have occurred after experiencing an SLE, they may lie on the causal pathway between SLEs and infertility.

Similarly, body mass index may precede an SLE or occur as a result of SLE, again placing it on the causal pathway. Thus, several models were constructed to explore the robustness of findings after controlling for different sets of potential confounders.

*Effect Modifier: Maternal Responsiveness*

The potential moderator, maternal responsiveness, was assessed using five questions adapted from the Conger and Elder (1994) Parent-Youth Relationship Scale, which has been evaluated to have acceptable psychometric properties.[27] This scale has been used to assess maternal responsiveness in other NLSY-97 studies.[28] Adolescents provided responses ranging from 0 (never) to 4 (always) to the following questions about the mother figure with whom the respondent resided, and how often she: praises you for doing well, criticizes you or your ideas, helps you do things that are important to you, blames you for her problems, and makes plans with you and cancels for no good reason. Negative items (criticizes, blames, and cancels) were reverse-coded to allow for items to be summed into a composite score ranging from 0 to 20. The final maternal responsiveness variable was dichotomized based on the recommended cut-point of 15 (high=15+, low= less than 15).[27]

**Analysis**

In the first stage of analysis, the prevalence of infertility was calculated for respondents reporting problems getting pregnant and clinical infertility. Using both of these definitions of infertility, ever infertile and never infertile women were then compared across all variables included in the study using t tests for continuous data and Rao-Scott modified chi squared analyses for categorical data. Because NLSY is conducted using complex, stratified sampling, survey weights were custom-made for

each dataset generated through NLSY Investigator. Survey commands were used across analyses to account for the complex survey design, though survey weights were only used when generating frequency tables and descriptive statistics, consistent with the analytic guidelines, which recommend against weighting for any analyses more complex than descriptive to ensure correct estimates.[14]

Next, to explore Hypothesis 1, logistic regression models were fit to examine the association between SLEs and each definition of infertility, adjusted for covariates in a step-wise manner across four models: (1) unadjusted; (2) demographic variables only (race/ethnicity and household income to poverty ratio); (3) demographic and environmental factors (added number of biologic siblings and physical environment risk); and (4) fully adjusted—demographic, household, and health and health behavior confounders (added substance use and BMI). To test Hypothesis 2, whether maternal responsiveness moderated these associations, separate regression models were fit with interaction terms for each combination of maternal responsiveness multiplied by the number of SLEs. Stratified models were then produced for high vs. low maternal responsiveness. Model 3 was considered the main model for all additional analyses given that Model 4 included potential mediators related to behavioral risk factors.

In sensitivity analyses, to examine whether there were differences in infertility based on the timing of SLEs, three new groups of models were fit. The first group examined the association between SLEs occurring prior to the age of 12 and the clinical definition of infertility, while the second examined SLEs occurring between the ages of 12 and 18, and the third examined SLEs occurring between the ages of 19-23. SLEs were

analyzed in two ways in each group; first as a dichotomous variable comparing none vs. any event, and second, as a continuous variable.

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# Chapter 4: Study 1

## Exploring stress, anxiety, and depression as precipitants of infertility: A comprehensive literature review


### Abstract

Infertility has become a pressing public health issue, with links to chronic health conditions like cardiovascular disease and cancer. Psychosocial factors, like stress, anxiety, and depression, have been associated with both chronic health conditions and reproductive dysfunction, though these factors have primarily been studied concurrent with or resulting from infertility. This article is the first to review studies of stress, anxiety, and depression as precipitants to the occurrence of infertility. Using PRISMA guidelines for conducting a systematic literature review, 32 articles were identified for critical review. Of the articles identified, 20 were cross-sectional and 12 examined psychosocial factors prior to the occurrence or diagnosis of infertility. In general, methodological limitations to studies included the inability to establish temporality, small sample size, selection of 'fertile' controls with unknown fertility status, and recruitment from fertility clinics. Taken together, these issues limit both the generalisability of the results, and the ability to make inference about the association between psychosocial factors and infertility. Despite these limitations, the body of findings indicate that stress may be associated with subsequent infertility in women, though the results for anxiety and depression are equivocal.


### Introduction

Understanding the psychosocial causes of infertility has become a pressing public health issue. The lifetime prevalence of female infertility is estimated to be at least 12-16% (Chandra, Copen, & Stephen, 2013; Thoma et al., 2013), and 30% of this infertility cannot be explained by

anatomical or hormonal dysfunction (Smith, Pfeifer, & Collins, 2003). Furthermore, infertility has been shown to negatively impact mental health, and act as both an indicator of current health and a predictor of future health (Cedars et al., 2017; Cousineau & Domar, 2007; Greil, 1997; Greil, Slauson-Blevins, & McQuillan, 2010; Hanson et al., 2017). Recent workshops and publications from the Centers for Disease Control and Prevention and the National Institute of Child Health and Human Development have highlighted the connection, in particular, between infertility and subsequent chronic health conditions such as Type II diabetes, cardiovascular disease, and cancer (Cedars et al., 2017; Hanson et al., 2017). Thus, understanding causes of infertility may help highlight earlier points of intervention to prevent future morbidity.

The purpose of this article is to review the studies that have been conducted to link stress, anxiety, and depression to infertility, with an emphasis on studies conducted to explore these psychosocial factors as they occur prior to, or bi-directionally with, reproductive dysfunction. This investigation follows PRISMA guidelines for conducting a systematic literature review, but is limited topically to a focused, critical review of English-language research literature relating to psychosocial factors that may play a causal role in infertility. The review's purpose is to critically evaluate the strengths and limitations of this literature in order to determine the state of the research in this area and highlight areas in need of investigation.

The existing literature on the relationship between psychosocial factors and infertility is equivocal. Early studies documenting the incidence of spontaneous pregnancy after adoption have been highlighted as examples of stress relief as a 'cure' for infertility (Mai, 1971; Rock, Tietze, & Mclaughlin, 1965). An extensive body of research surrounding the association between psychosocial factors and pregnancy outcomes after in vitro fertilisation (IVF), for which three reviews and one meta-analysis have been published, have produced mixed results (Boivin,

Griffiths, & Venetis, 2011; Morreale, Balon, Tancer, & Diamond, 2011; Rooney & Domar, 2016; Wilkins KM, Warnock JK, & Serrano E, 2010). Potential biological pathways linking psychosocial stressors to infertility have been well-described in the literature. However, due to the medication protocol required, IVF treatment bypasses the traditional gonadotropin-releasing hormone (GnRH) pathway linking stress to infertility, leading some researchers to speculate as to whether a different pathway may be implicated in these types of studies, and whether the proximal stress associated with infertility treatment can really be used to accurately describe chronic stress that may be a causative agent for infertility (Zaig et al., 2012).

Stress has long been considered a biologically plausible causative agent for reproductive dysfunction. In this context, stress is defined as an external environmental stressor (e.g., an event or experience) that taxes the 'adaptive capacity' of an individual, thus invoking a physiological stress response (S. Cohen, Kessler, & Gordon, 1997). The hypothalamic-pituitary-adrenal axis (HPA), which is activated in times of acute and chronic stress, is inextricably linked to the hypothalamic-pituitary-gonadal axis (HPG), which regulates reproductive function. Disruption in HPA function can lead to multiple points of reproductive failure, any of which may influence fecundity, given the variety of hormones involved in successful conception (Figure 4.1). Generally, HPA activation stimulates the release of corticotropin-releasing hormone (CRH), which directly and indirectly influences other reproductive hormones via stimulation of cortisol and adrenocorticotropic hormone (ACTH) (Magiakou, Mastorakos, Webster, & Chrousos, 1997). ACTH stimulation inhibits release of gonadotropin-releasing hormone (GnRH), which is responsible for the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which regulate ovulation (Nakamura, Sheps, & Arck, 2008). Furthermore, a second neuroendocrine system, the sympatho-adrenal-medullary (SAM) system, releases norepinephrine

and epinephrine in response to acute stressors, and can remain activated in times of chronic stress (Schenker, Meirow, & Schenker, 1992). Excessive levels of cortisol or catecholamines during critical windows in the conception process can adversely impact ovarian innervation, and can cause irregular secretion of oestrogens and progesterone, which influence ovulation, menstruation, implantation, and pregnancy viability (Magiakou et al., 1997).

Anxiety and depression have been similarly linked to infertility via hyperactivity of the HPA axis and subsequent immune system dysfunction. Upregulation of the HPA axis results in increased secretion of glucocorticoids, which stimulates release of ACTH and cortisol, which inhibit GnRH release, as described previously, and may lead to ovarian and menstrual dysfunction (Kalantaridou, Makrigiannakis, Zoumakis, & Chrousos, 2004). Alternatively, according to the 'cytokine hypothesis,' depression activates a pro-inflammatory pathway that stimulates the release of cytokines such as interleukin (IL)-1, tumour necrosis factor (TNF), and interferon gamma (IFN-γ) (Schiepers, Wichers, & Maes, 2005). Proinflammatory cytokines may prevent normal down-regulation of the HPA axis, as well as promote glucocorticoid resistance, thus perpetuating HPA hyperactivity (O'Brien, Scott, & Dinan, 2004). Furthermore, an increase in proinflammatory cytokines may signal T cell dysregulation and reduced immunity, which has been noted in infertile women (Horká et al., 2011; Kalu et al., 2008).

These pathways help to explain how psychosocial factors may cause reproductive dysfunction, but studies of pregnancy outcomes after infertility treatment may not help to explain how stress is linked to infertility. They are necessarily conducted in a subpopulation of women who already have a reproductive deficit, and the stress of infertility treatment may differ substantially from stress that could be causing the underlying pathophysiology. Thus, it is essential to review studies of psychosocial factors independent of IVF treatment outcomes.

**Methods**

The following procedures were conducted to identify publications describing the link between psychosocial factors and subsequent infertility. A diagram describing the rules for inclusion and exclusion of literature can be found in Figure 4.2. All English-language, peer-reviewed publications and unpublished dissertations discussing infertility and stress, anxiety, or depression were included in a search of EBSCO databases and PubMed, with no limitation of publication date. The selected databases were chosen because they were considered comprehensive sources of English-language scientific literature relevant to reproductive health. Based on an initial scan of the literature, the terms, 'Infertility,' 'infertile,' 'fertility,' 'stress,' 'anxiety,' and 'depression' were found to be the most common terms used as subjects and Medical Search Headings relevant to the research aim. Other terms that were considered, but not used due to overlap with other terms, or lack of relevance of findings, included 'fecundity' and 'fecundability.' In February of 2018, the search terms, 'Infertility or infertile or fertility' and 'stress or anxiety or depression,' were used in the EBSCO databases Academic Search Complete, Academic Search Premier, CINAHL, PscyINFO, Family and Society Studies, Health Source, Women's Studies International, Psychology and Behavioral Science Collection, MasterFILE, SocINDEX, Health Policy Reference Center, Social Sciences (H.W. Wilson), Family Studies Abstracts, and PsycArticles, producing 2,719 results. MeSH terms (infertility, female; and stress, psychosocial; anxiety; or depression) were used to identify articles in PubMed, producing 385 results.

While there is abundant literature published on these topics, the purpose of this review was to explore the literature examining psychosocial factors as precipitants of infertility. Thus, several exclusion criteria were applied to the initial review of titles. Publications were excluded

if the following were clearly stated in the title: infertility in men only, psychosocial factors occurring because of infertility diagnosis or treatment, counselling interventions to improve psychosocial state during infertility treatment, couples or marital tension resulting from infertility, or postpartum depression. In general, publications related to infertility-specific stress, or stress presumably caused by infertility, were excluded, with two exceptions. First, studies examining the effect of psychosocial factors on success of IVF were initially retained because these studies had potential to examine a physiologic pathway that is similar to that of other psychosocial factors that may cause infertility. Second, publications were retained that compared psychosocial factors among women with diagnosed infertility to presumably fertile controls, since these types of studies could indicate a bi-directional association between psychosocial factors and infertility (Figure 4.3). After the initial review, 204 relevant titles were identified from the EBSCO search, and 83 were identified from the PubMed search. After removing duplicates, 242 total articles remained for abstract review.

In the next stage, all abstracts were reviewed blindly by two reviewers (JLG and LBD), using the same exclusion and inclusion criteria as applied to the initial title review. Specifically, 84 publications were eliminated because the research did not study infertility as an outcome. Of those, 37 were publications describing non-infertility outcomes, such as pregnancy stress, and 47 examined psychosocial consequences of infertility treatment or diagnosis. Despite the use of a search filter, another 31 titles were not peer-reviewed articles or dissertations (e.g., commentaries or summaries), and 12 were foreign-language studies, all of which were eliminated. Additionally, non-empirical articles (9), studies examining non-infertile populations (e.g., pregnant women) (11), qualitative studies examining the meaning of infertility (12), and those discussing oxidative stress (24), which is a physiologic phenomenon separate from psychosocial stress, were excluded

from final review. The two reviewers met to discuss five publications for which they made conflicting exclusion determinations. After re-reading the abstracts and reviewing the criteria, they reached consensus and included three publications previously eliminated by one reviewer, while excluding the other two. After this, 60 peer-reviewed publications remained for full-text review.

In the final stage, all remaining articles were reviewed in full and assigned to categories based on subject matter and methodology. First, based on the previously completed title and abstract reviews, several a priori categories were created and applied to the articles during review. No new categories were created beyond these original ones. Some studies were given multiple classifications, but the primary classifications were as follows: psychosocial factors and the outcome of infertility treatment (21), cross-sectional studies comparing psychosocial outcomes in women diagnosed with infertility to women not diagnosed with infertility (20), psychosocial factors examined as precipitants to infertility or subfecundity (7), interventions to lower stress and improve pregnancy outcomes in treatment (5), animal studies (4), and studies examining the association between lifetime stress and infertility (3). Of the cross-sectional studies, seven were case-control designs. Of the studies examining psychosocial factors in relation to outcomes of fertility treatments, the type of exposure varied, but was studied in the following combinations: anxiety only (2), depression only (1), stress only (7), anxiety and depression (7), stress and anxiety (2), lifetime stress and depression (1), and all factors (1). By the end of the full-text review phase, four articles were excluded (not included in the above classifications), based on previously described exclusion criteria. Eight additional articles were identified from citations included in the reviewed articles. Four of these were deemed relevant to this review and classified based on full-text review.

**Findings**

Studies describing associations between psychosocial factors and outcomes of infertility treatment comprised one-third (n=21) of the studies meeting inclusion criteria for this review. As discussed previously, psychosocial factors may influence both infertility and success of ART treatment via the same pathway. However, despite being included in the initial search, it was determined after full-text review that all but three of these studies did not address the effect of psychosocial factors on infertility overall, and were thus, topically irrelevant. Primarily, due to their cross-sectional nature, they could not separate the effect of infertility-specific stress versus other life stressors. Many of these studies have been included in other reviews and meta-analyses examining the effect of psychosocial factors on pregnancy outcomes after ART. To summarise this existing literature excluded from the current review, in a meta-analysis, Boivin and colleagues (2011) did not find any association between anxiety and depression and pregnancy outcomes following IVF, while another highlighted the importance of managing depressive symptoms during the treatment process (Wilkins KM et al., 2010). Two reviews found that stress negatively influences the outcome of ART, though stress reduction interventions may help improve outcomes (Morreale et al., 2011; Rooney & Domar, 2016).

Approximately two-thirds (n=20) of the 32 studies identified for critical review were classified as cross-sectional studies that implied a bi-directional association between exposure and outcome, though in most of these studies (n=14), psychosocial factors were the outcome of interest. All but five of the cross-sectional studies employed a case-control design, comparing infertile women to presumably fertile controls. Among case-control studies of anxiety and depression (n=11), five found no difference between cases and controls on either anxiety or depression (Csemiczky, Landgren, & Collins, 2000; Kalaiselvi, Saikumar, & Prabhu, 2012; Lapane et al., 1995; Lewis, Liu, Stuart, & Ryan, 2013; Paulson, Haarmann, Salerno, & Asmar,

1988), one found no difference in results from the depression instrument, but found depression to be associated with infertility after clinical interviews (Ojo, Oluwole, & Obadeji, 2017), and the remaining five found that women with infertility were more likely to be experiencing depression or anxiety (Albayrak & Günay, 2007; Lakatos, Szigeti, Ujma, Sexty, & Balog, 2017; Mukhopadhyay & Chattopadhyay, 1994; Shoaib, Shah, Ahmad, & Mansoor, 2016; Wasser, Sewall, & Soules, 1993).

There were several limitations across all of the included case-control studies of anxiety and depression, the most problematic of which was the selection of 'fertile' controls. Effective case-control studies must choose controls that are free of the disease under study—in this case, infertility. Most studies could not confirm that controls were fertile, and instead selected controls of unknown fertility status (Shoaib et al., 2016), any individual without an infertility diagnosis (Paulson et al., 1988), or women who had at least one child (Albayrak & Günay, 2007; Lakatos et al., 2017; Lapane et al., 1995; Lewis et al., 2013; Ojo et al., 2017). While having a child may be a demonstration of fertility, none of the studies using parents as controls asked about their fertility history, meaning they could have experienced infertility prior to the birth of the child, or could be currently experiencing secondary infertility, where they are unable to conceive subsequent children. Other limitations of these studies included small sample sizes ($n<60$) (Csemiczky et al., 2000; Kalaiselvi et al., 2012; Mukhopadhyay & Chattopadhyay, 1994; Wasser et al., 1993), and poor measurement of depression (Lapane et al., 1995; Lewis et al., 2013).

Results were relatively unequivocal for case-control studies of stress ($n=6$). For all six studies, infertile cases were more likely to be experiencing stress than presumably fertile controls (Bhandari, 2016; Brand, 1982; Coughlan, Walters, Ledger, & Li, 2014; Gyorffy, Dweik, & Girasek, 2014; Mukhopadhyay & Chattopadhyay, 1994; Wasser et al., 1993). In this group of

studies, one was limited by including controls with unknown fertility (Gyorffy et al., 2014), four were limited by relatively small sample sizes of less than 100 (Bhandari, 2016; Coughlan et al., 2014; Mukhopadhyay & Chattopadhyay, 1994; Wasser et al., 1993), and one included both limitations (Brand, 1982).

Of the five cross-sectional studies that were not case-control designs, one examined depression and anxiety (Klemetti, Raitanen, Sihvo, Saarni, & Koponen, 2010), while the others examined stress in relation to infertility (Dong, Zhou, & Sun, 2017; Ippolito et al., 2017; Klemetti et al., 2010; K. A. Sanders & Bruce, 1997; Katherine A. Sanders & Bruce, 1999). In a nationally-representative study in Finland, Klemetti et al. (2010) found no association between anxiety or depression and infertility. Only one study found a positive association between stress and a marker of infertility, anti-mullerian hormone (Dong et al., 2017). Another study found stress was not associated with infertility, though the investigators controlled for factors that could be considered potential mediators of this association, including smoking and prior health conditions (Ippolito et al., 2017). When these mediators were removed from the analyses, the authors indicated that the odds of infertility significantly increased with stress exposure, though these specific results were not presented in the narrative results or tables.

Regarding the ways that psychosocial factors might precipitate infertility, 12 studies were identified that explicitly measured psychosocial factors occurring prior to infertility. Three studies assessed stress prior to infertility treatment and subsequent outcomes (Ebbesen et al., 2009; Massey et al., 2016; Yilmaz et al., 2015), six evaluated the effect of stress, anxiety, and depression on time to pregnancy (Akhter, Marcus, Kerber, Kong, & Taylor, 2016; Buck Louis et al., 2011; Lynch, Sundaram, Buck Louis, Lum, & Pyper, 2012; Lynch, Sundaram, Maisog, Sweeney, & Buck Louis, 2014; Nillni et al., 2016; Sundby J & Dahl JE, 1994), and three

examined the association between lifetime exposure to stress and infertility (Jacobs, Boynton-Jarrett, & Harville, 2015; Pal, Bevilacqua, & Santoro, 2010; Santos, Sobral, & Martins, 2017).

All three studies assessing stress prior to infertility treatment found that women experiencing stress in the months leading up to treatment were less likely to achieve pregnancy after a cycle of IVF than those experiencing less stress. These studies were included for critical review because they measured stress that occurred prior to treatment and could tease out the effect of stressors separate from infertility-specific stress. However, it should again be noted that IVF bypasses the GnRH pathway traditionally linking stress to infertility, so it is questionable whether any study of psychosocial factors and the outcome of IVF treatment can be used as evidence to support the idea that stress may lead to infertility. The most robust of these studies included a large sample (n=837), and assessed stressful events occurring in the year prior, using a validated instrument (List of Recent Events) (Ebbesen et al., 2009). While this study is subject to error related to recall, accuracy in remembering stressful events in the last year should not differ between women who ultimately achieved pregnancy and those who did not, since the assessment occurred prior to treatment. A similar study with comparable findings by Yilmaz et al. (2015) used the same instrument in a smaller sample (n=83), and asked respondents to recall lifetime stressful events, which may be more difficult for respondents to remember. Finally, Massey et al. (2016) took hair samples from a relatively small sample (n=88) to measure cortisol levels over the three months prior to treatment, finding that, for every unit reduction in hair cortisol, the odds of pregnancy increased by almost 10%. Although these studies may elucidate the relationship between stress and infertility, their findings are not generalisable to other populations of women who do not seek and receive infertility treatment. Furthermore, the GnRH pathway that traditionally links stress and infertility is bypassed in IVF.

Of the six studies measuring psychosocial factors prior to the occurrence of infertility, one was a cross-sectional study inquiring about occupational stress and time to pregnancy for all pregnancies, which found that unemployed women with no occupational stress had the shortest time to pregnancy, and that teachers with high occupational stress had higher fertility (Sundby J & Dahl JE, 1994). However, this study did not account for age, which may explain why the authors observed an inverse relationship between occupational stress and infertility among teachers. On average, teachers may be younger than women in the only other included occupational group, dentists, who require lengthier professional training. Furthermore, remembering time to pregnancy between each pregnancy introduces recall bias, and there is an assumption that the respondent was both intending to get pregnant and trying to conceive for the entire time between pregnancies, which may not be the case. Another study, which involved a longitudinal survey of women trying to conceive and assessed depression at baseline, found that fecundability decreased linearly as scores on the Major Depression Index increased (Nillni et al., 2016). These findings indicate that a significant negative linear association exists between depression status and fertility. However, the results are limited by self-report of the pregnancy outcome, and the depression instrument used may be a better indicator of current depression as opposed to prior depression, making it difficult to establish depression as a precipitant to infertility.

In four studies assessing variations in time to pregnancy based on psychosocial factors, participants were asked to keep diaries or collect saliva samples to measure exposure to stress, anxiety, or depression over time (Akhter et al., 2016; Buck Louis et al., 2011; Lynch et al., 2012, 2014). Two of these studies had a follow-up time of six months; therefore, they could not assess true infertility, which requires at least 12 months of follow-up (Buck Louis et al., 2011; Lynch et

al., 2012). Both studies found no significant association between stress and fecundity, though Buck Louis et al. (2011) found that higher levels of the stress hormone, alpha-amylase, was associated with lower day-specific odds of conception. In studies with longer follow-up (12-20 months), stress was associated with lower fecundity, higher odds of infertility, and lower day-specific odds of conception (Akhter et al., 2016; Lynch et al., 2014). For studies collecting biomarkers of stress, there are some limitations because salivary cortisol and alpha-amylase are released in a circadian pattern, hence, once daily collections of these biomarkers may be inadequate to measure stress (Buck Louis et al., 2011; Lynch et al., 2012, 2014). Conversely, two studies asking for self-reported measures of stress did not use validated instruments, similarly calling into question the validity of their measurement of stress (Akhter et al., 2016; Sundby J & Dahl JE, 1994). These same two studies also did not measure pregnancy intention, and assumed that any time to pregnancy was time spent trying to conceive, with no assessment of use of contraception during that time (Akhter et al., 2016; Sundby J & Dahl JE, 1994).

Finally, three studies assessed the association between lifetime stressors and infertility. The strength of these studies is their assessment of stress prior to reports or diagnoses of infertility, which makes it possible to establish temporality of the sequence of events, and greatly improves the ability to draw inference from the findings. However, all three of these studies assessed stressful events and perceptions of those events retrospectively, which implies error and bias related to recall. Santos et al. (2017) conducted a case-control study, where they found no difference in experience of lifetime stressors between cases and controls. However, cases were identified by diagnoses from medical records, and controls were women with self-reported fertility, but no children. As discussed previously, it is questionable whether these controls are an

appropriate comparison group for cases since their fertility status was not accurately or precisely measured.

In another study of lifetime stress, researchers compared responses to questions about lifetime history of abuse and substance use to biomarkers of ovarian reserve, finding that 'chronic stress' was associated with diminished ovarian reserve, which is one cause of infertility (Pal et al., 2010). While the researchers labelled this a study of chronic stress, they found that family history of abuse, the only previously validated measure of stress in their study, was not associated with the outcome. Instead, women with diminished ovarian reserve were more likely to have a history of substance use. While substance use has been posited as a potential mediator on the pathway between stressful events and infertility, it is not, itself, a measure of stress (Ebbesen et al., 2009). This study could be an example of one with null findings on the association of lifetime stress and infertility, but its inclusion of only a single validated question on stressful life events prevents the drawing of wider inferences from its results.

Finally, the most rigorous study in this group, conducted by Jacobs and associates in 2015, assessed the associations between adverse childhood experiences (ACEs) and time to pregnancy. ACEs can be defined as traumatic events, such as physical abuse and family dysfunction, that occur in childhood and which have been associated with a number of poor health outcomes in adolescence and adulthood (Hillis et al., 2004). This study, examining a sample of 742 Louisiana women, found that as the number of ACEs increased, fertility difficulties increased. Women with four or more ACEs were at nearly three times higher risk for infertility and had lower fecundability than those with no reported ACEs. The study's strengths included its use of validated measures of stress and a robust measure of infertility in which participants were asked about time to pregnancy. Also, because they measured ACEs that

occurred prior to the age of 12, the plausibility of the association is supported by life-history theory, which posits that stressful events prior to puberty may disrupt reproductive function during development, leading to a predisposition for life-long reproductive dysfunction (Flinn, Nepomnaschy, Muehlenbein, & Ponzi, 2011). There are, however, limitations to this study. First, the researchers retrospectively assessed ACEs prior to the age of 12, introducing recall bias, and second, they recruited participants from OB/GYN clinics and WIC offices, which may represent a skewed sample that is more fertile than the general population of childbearing-age women.

A summary of the study characteristics, main findings, and limitations of each study included for critical review can be viewed in Table 4.1. Like the results of reviews and meta-analyses for associations between psychosocial factors and outcomes after infertility treatment, the results of this review are equivocal. Less than half of the reviewed studies (n=15) found a significant association between psychosocial factors and infertility, while few (n=2) found the inverse association. However, nearly all reviewed studies had methodological flaws that could have masked an association.

**Discussion**

In general, research on infertility and psychosocial factors is grounded in a biologically plausible mechanism linking stress, anxiety, and depression to reproductive dysfunction. However, published research to-date has been unable to empirically validate psychosocial factors as casual factors in infertility in human studies. Nearly two-thirds of the studies included for critical review were cross-sectional in nature, which by design, prohibits inference on the temporality of the association. Establishing temporality is critical in this field of research because it allows for a fundamental reframing of infertility, from a condition that causes stress, anxiety, and depression, to a condition that may *result* from these factors. Furthermore, if infertility can be validated as a consequence of psychosocial factors, these findings may help researchers better

understand how infertility may also be linked to chronic conditions, like cardiovascular disease, diabetes, and cancer. It has generally been established that psychosocial factors may contribute to these chronic conditions (B. E. Cohen, Edmondson, & Kronish, 2015). Thus, research on the temporality of psychosocial factors and infertility may both establish these factors as a cause of infertility and help elucidate a common pathway between reproductive dysfunction and later-life morbidities. This could subsequently position infertility to function as an early warning sign for these morbidities, which would allow for earlier intervention before these symptoms have developed into full-blown clinical disease, when it may be too late to intervene or modify behaviour to make significant change.

Moreover, the question remains whether cross-sectional studies, or those measuring stress associated with infertility and its treatment, are measuring the same underlying process as those examining psychosocial factors as explicit precipitants to infertility. While acute stress may disrupt normal reproductive functioning through the HPA-axis or SAM system as described previously, there are other processes that may be triggered by chronic stress or stressors that occur prior to puberty (Flinn et al., 2011). In a seminal study on stress and the outcome of ART treatment, Ebbesen (2009) argues that much of the cross-sectional research related to stress and the outcome of infertility treatment does not measure psychosocial stress because it does not consider the influence of outside factors, or the 'environmental demand' that would provoke a stress response. Essentially, measuring perceived feelings of stress may not equate to a physiologic stress response that could influence reproductive dysfunction, and when objectively measuring a physiologic stress response at the same time as the occurrence of infertility, it may be impossible to conclude that the source of stress is not simply due to the experience of

infertility or seeking treatment. Thus, there may be an inherent flaw in using cross-sectional studies to provide evidence for this association.

Another major limitation to the studies reviewed is sample recruitment. In sixteen of the 20 cross-sectional studies examined in this review, the study samples were recruited from women seeking treatment from fertility clinics, or with demonstrated infertility. This highlights that the majority of research conducted to date has focused on women with known reproductive dysfunction, instead of tracking the influence of psychosocial factors on the development of infertility over time. This raises two methodological issues. First, restricting to women with diagnosed infertility limits the generalisability of findings to women who have intentionally sought treatment and excludes women who may have tried to conceive for more than 12 months, but either could not afford treatment, or simply did not want to seek treatment. This is particularly salient for women living in the 35 states that do not mandate insurance coverage for infertility, or for racial and ethnic minorities, who, for economic and cultural reasons, are less likely to seek treatment (Jain, 2006). This latter issue is reflected in the lack of racial and ethnic diversity of samples included in many of the reviewed studies. Second, women with anatomic and hormonal diagnoses for infertility (who are oversampled in studies drawn from fertility clinics, as this diagnosis may be more likely to lead to fertility treatment than unexplained infertility) may have more severe underlying morbidities than women diagnosed with unexplained infertility or women who try to conceive for 12 months or more and do not seek treatment. Thus, women in fertility clinics may have a higher degree of reproductive dysfunction that may mask associations with psychosocial factors.

Across all types of studies there are general methodological limitations. One such limitation is that many studies include small sample sizes, which limits the ability to detect what

may be a small effect. More concerning, even among studies with large samples, is the selection of 'fertile' comparison groups. These studies compare women with diagnosed infertility to those who are essentially not diagnosed with infertility, without eliciting knowledge of the reproductive or fertility history of women in comparison groups. Thus, comparison groups may consist of women who have experienced infertility already, in the case of women who have at least one child and are in the comparison group or may experience infertility in the future, in the case of women who have no children but simply report having no history of infertility.

In addition to these methodological limitations, the broader field of research on infertility in the U.S. is limited by a lack of national surveillance or comprehensive questions related to infertility. The National Health and Nutrition Examination Survey (NHANES) added a single question on general infertility in the 2013-2014 wave, and while the National Survey of Family Growth (NSFG) captures fertility history, it does not involve collection of comprehensive information on psychosocial factors. More importantly, both surveys are cross-sectional, again limiting the ability of investigators to establish temporality. To thoroughly investigate psychosocial factors as precipitants to infertility, there is a need to collect nationally-representative, longitudinal data that includes comprehensive information on these psychosocial factors and infertility. While more comprehensive national-level data in other countries, such as Sweden, may exist, such data may be limited to interactions with the health care system, which would not provide a complete picture on stressors or untreated anxiety or depression. In the U.K, the British National Surveys of Sexual Attitudes and Lifestyles (Natsal) collected data on infertility, but like the U.S., the utility of this survey in informing this topic is limited by not collecting comprehensive information on life stressors. Moreover, even with comprehensive information on psychosocial factors and fertility history, data drawn from other countries is

unlikely generalisable to the U.S., given the country's diverse demographic makeup and unique, socially determined history of racial and ethnic disparities in health outcomes. Therefore, until better quality data is available, this field of research will always be limited by the methodological problems described.

This review should be considered in light of its limitations and strengths. While this review followed PRISMA guidelines for conducting a systematic literature review, and a large amount of literature was reviewed for this paper, it is possible that some studies were missed as a result of not including specific infertility diagnoses, like endometriosis or polycystic ovary syndrome, in the original search terms. However, the intent of this review is to understand the association between psychosocial factors and infertility in a broad sense, and papers related to specific diagnoses were likely outside the scope of the review. Another limitation is the inclusion of only published literature and dissertations, which can introduce publication bias. While many of the papers reviewed were published with null results, the review did not include unpublished research, which may provide other important findings. This article is nevertheless the first to provide a comprehensive review of English language literature examining psychosocial factors as precipitants to infertility. Moreover, it is the first to examine this connection outside of the context of pregnancy outcomes that followed intervention with assisted reproductive technologies.

This review points to the critical need to develop a body of literature describing the shared mechanisms linking infertility to the general health status of women. Such research is needed in order to better understand the broad relevance of infertility to public health. Psychosocial factors may represent a shared mechanism that links infertility to overall health, but the literature to-date suffers from methodological limitations that relate to the failure of the U.S.

to collect comprehensive, longitudinal health data on its residents. Thus, to understand how psychosocial factors influence infertility in a global sense, more research must be conducted that overcomes limitations shared by the current body of research. Such research is likely to illuminate the ways that infertility can serve as an important early indicator of a woman's overall health status.

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## Tables and Figures

### Table 4.1. Summary of studies included for critical review

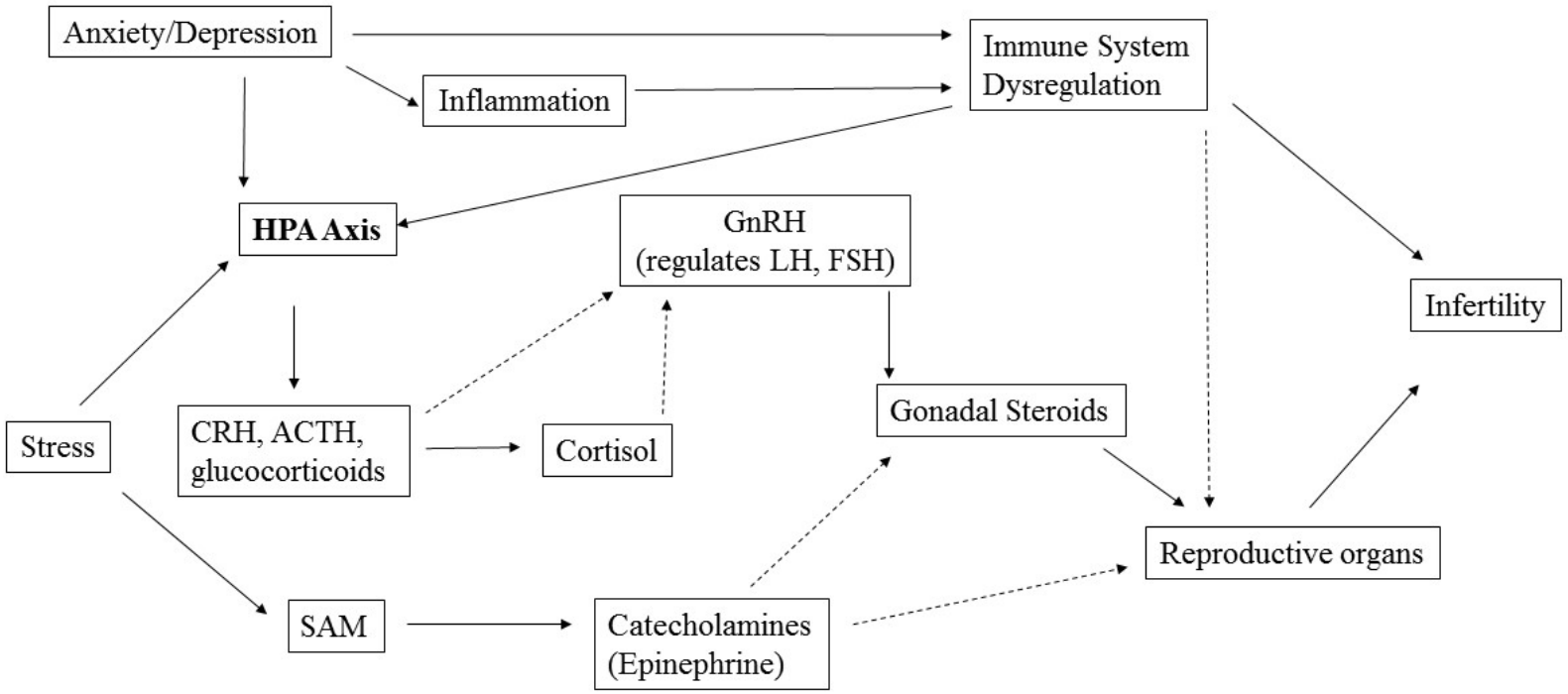
| **Studies examining the association of lifetime stress and infertility** | | | |
|---|---|---|---|
| **Study (year)** | **Study Characteristics** | **Main Findings** | **Major Limitations** |
| Pal et al. (2010) | • n=89<br>• Questionnaire ('stress')<br>• Biomarker collection | • Higher 'chronic stress' in those with diminished ovarian reserve (DOR) | • Small n<br>• Limited generalisability<br>• Unknown validity of stress measure |
| Jacobs et al. (2015) | • n=774 (pregnant and not)<br>• Questionnaire (ACEs) | • Higher risk of infertility for women reporting ACEs | • Limited generalisability<br>• Recall bias |
| Santos et al. (2017) | • n=151 infertile; 225 fertile<br>• Questionnaire (stress) | • Stressful life events did not predict infertility diagnosis | • Small n<br>• Limited generalisability<br>• Unknown fertility of 'fertile' women |
| **Studies generally examining psychosocial factors as precipitants to infertility** | | | |
| **Study (year)** | **Study Characteristics** | **Main Findings** | **Major Limitations** |
| Sundby & Dahl (1994) | • n=920 dentists, 774 teachers<br>• Questionnaire (stress) | • Time to pregnancy (TTP) shorter for unemployed<br>• Higher fertility in stressed teachers | • Measured occupational stress<br>• No measure of pregnancy intent<br>• Did not adjust for age |
| Ebbesen et al. (2009) | • n=837<br>• Questionnaire (stressful events) | • Fewer negative life events associated with positive pregnancy test | • Limited generalisability<br>• Inability to control for lifestyle factors |
| Buck Louis et al. (2011) | • n=374 (200 with complete data)<br>• Daily diaries for 6 months<br>• Biomarker collection | • No significant associations between markers of stress and infertility<br>• Increased alpha-amylase associated with lower probability of conception | • Not technically infertility measure<br>• Stress biomarkers released diurnally<br>• Homogeneous population |
| Lynch et al. (2012) | • n=374<br>• Daily diaries for 6 months<br>• Questionnaire, biomarker (stress) | • No significant associations between stress and fertility | • Not technically infertility measure<br>• Limited ability of questionnaires to detect stress |
| Lynch et al. (2014) | • n=401<br>• Daily diaries<br>• Collected biomarkers | • No association between infertility and cortisol<br>• Higher odds of infertility with elevated alpha-amylase | • Cortisol released diurnally<br>• Could not exclude those with biological problems conceiving |
| Yilmaz et al. (2015) | • n=83<br>• Questionnaire (stressful events) | • More negative life events in women who did not achieve pregnancy | • Limited generalisability |

| | | | |
|---|---|---|---|
| Akhter et al. (2016) | • n=487<br>• Collected pregnancy intention<br>• Daily diaries with stress levels<br>• Biomarker collection | • High stress associated with low odds of conception in follicular phase | • Limited generalisability<br>• Missing data<br>• Phase shifts estimated according to length of cycle |
| Massey et al. (2016) | • N=135<br>• Biomarker collection | • Hair cortisol negatively associated with clinical pregnancy | • Limited generalisability<br>• Did not control for covariates that might influence hair cortisol |
| Nillni et al. (2016) | • n=2146<br>• Questionnaires (depression) | • Mixed results; some associations between infertility and depression<br>• No association between physician-diagnosed depression and fecundability | • Excluded women trying >6 months at start of study<br>• MDI more likely to reflect current psychological state |
| **Cross-sectional studies between psychosocial factors and infertility** (**Inability to establish temporality is a major limitation of all studies) | | | |
| **Study (year)** | **Study Characteristics** | **Main Findings** | **Major Limitations** |
| Brand et al. (1982) | • n=59 (3 groups)<br>• Biomarkers (stress) | • Generally, groups did not differ regarding baseline functioning | • Small n<br>• Questionable fertility of 'fertile' controls<br>• Lab-created stressful conditions |
| Paulson et al. (1988) | • n= 150 infertile and 50 fertile<br>• Questionnaires (depression and anxiety) | • Generally, no differences between cases and controls | • Relatively small n<br>• Questionable fertility of 'fertile' controls |
| Wasser et al. (1993) | • n=38 (4 groups)<br>• Questionnaires (depression) | • No difference between infertile groups and controls<br>• Some differences in anxiety between infertile groups | • Limited generalisability<br>• Questionable validity of stress measure |
| Mukhopadhyay & Chattopadhyay (1994) | • n=60 (3 groups)<br>• Questionnaires (anxiety and depression)<br>• Biomarkers collected | • Consistently higher values in all measures throughout cycle in idiopathic group compared to fertile group<br>• Endometriosis group had higher cortisol and anxiety than fertile group | • Small n<br>• Limited generalisability |
| Lapane et al. (1995) | • n=428<br>• Questionnaires (depression) | • History of depressive symptoms associated with increased risk of infertility | • Questionable validity of depression measure<br>• Questionable fertility of 'fertile' controls |
| Sanders & Bruce (1997) | • n=13<br>• Questionnaires (anxiety and mood)<br>• Biomarkers collected | • Improved mood and lower anxiety during conception cycles<br>• No differences in cortisol or catecholamines | • Small n<br>• Not technically infertility measure |
| Sanders & Bruce (1999) | • n=34<br>• Daily diaries, biomarkers<br>• Questionnaire (anxiety) | • No differences between groups on psychological tests or hormone excretion (cortisol and catecholamines) | • Small n<br>• Limited generalisability<br>• Did not have complete data on all women |

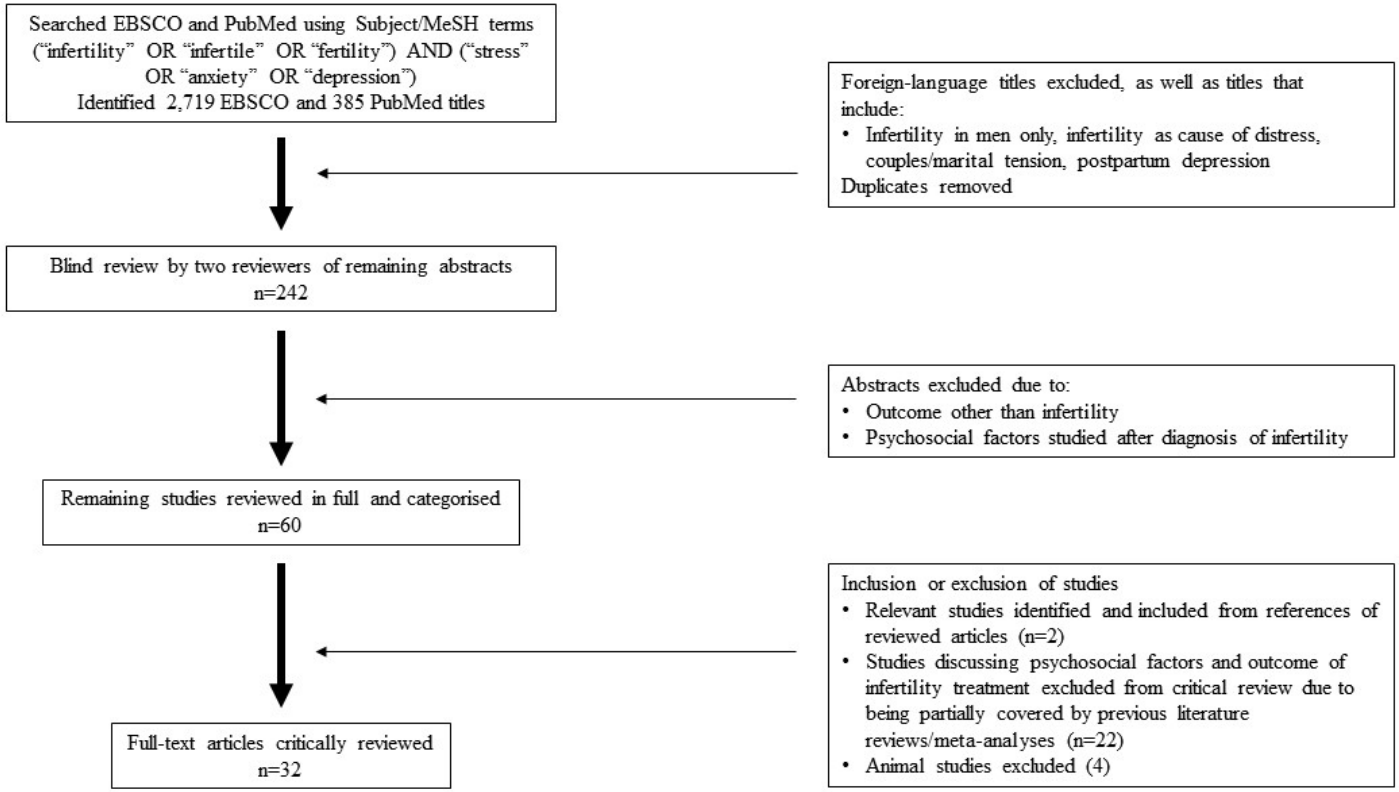
| | | | |
|---|---|---|---|
| Csemiczky et al. (2000) | • n=22 infertile, 22 fertile<br>• Questionnaires (anxiety)<br>• Biomarkers collected | • No difference between pregnant and non-pregnant groups on anxiety or cortisol | • Small n<br>• Limited generalisability |
| Albayrak & Günay (2007) | • n=150 cases, 150 controls<br>• Questionnaires (anxiety) | • Women in childless group had significantly higher scores in both state and trait anxiety than controls | • Limited generalisability<br>• Outcome is not necessarily infertility |
| Klemetti et al. (2012) | • N=2291<br>• Questionnaires (depression)<br>• Biomarkers collected | • No statistically differences in mental disorders between infertile/fertile groups | • Assessing current/past 12-month depressive symptoms, no idea when infertility occurred |
| Kalaiselvi et al. (2012) | • n=50<br>• Questionnaires<br>• Biomarkers collected | • No difference in cycle regularity, hormone levels, or any covariate between depressed and not depressed groups | • Small n<br>• Outcome is not infertility |
| Lewis et al. (2013) | • n=321<br>• Compared infertile cases to national controls | • Women in IVF group had lower incidence of depression than primary care patients | • Questionable validity of depression measure<br>• Questionable fertility of 'fertile' controls |
| Coughlan et al. (2014) | • n=93<br>• Questionnaires (stress) | • Infertile group had higher negative affect<br>• Perceived stress higher in RM group | • Small n<br>• Stress inherent in recurrent miscarriage |
| Gyorffy et al. (2014) | • n=3039 female physicians and dentists; 1039 controls<br>• Questionnaire (stress) | • Physician group had higher rate of high-risk pregnancy, TTP>12 months, infertility treatment, and miscarriage | • Questionable validity of stress measure<br>• Questionable fertility of 'fertile' controls<br>• All self-report measures |
| Bhandari (2016) | • n=75 (3 groups)<br>• Questionnaires (stress)<br>• Biomarkers collected | • Higher scores on all stress measures for both case groups<br>• No difference in cortisol level | • Small n<br>• Few controls for comparison<br>• Questionable fertility of 'fertile' controls |
| Shoiab et al. (2016) | • n=68 (34 fertile, 34 infertile)<br>• Questionnaire (mood, anxiety, and depression) | • Anxiety, depression, and mood disturbance higher in infertile women than fertile | • Small n<br>• Limited generalisability<br>• No p-values reported |
| Dong et al. (2017) | • n=576<br>• Tested fertility and stress biomarkers | • Significant negative correlation between salivary alpha-amylase and anti-mullerian hormone levels | • No cut-off values for biomarkers to establish high vs. low stress |
| Ippolito et al. (2017) | • n=14,539 female service members<br>• Assessed life stressors | • No associations between any exposures and infertility, though associations became significant after removing potential mediators from models | • Not technically infertility measure<br>• Lack of precise timing on return from deployment and onset of infertility<br>• Recall bias |
| Lakatos et al. (2017) | • n=225<br>• Questionnaires (anxiety and depression) | • Infertile women were more depressed and anxious than fertile controls | • Limited generalisability<br>• Self-selection bias<br>• No description of controls |

| | | | |
|---|---|---|---|
| Ojo et al. (2017) | • n=203<br>• Questionnaires and clinical diagnoses to assess depression | • No difference in depression between groups for questionnaire, but infertile group had higher rate of clinically-diagnosed depression | • Limited generalisability |

**List of Figures**




**Solid arrows indicate stimulation, while dashed arrows indicate suppression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Identified 2,719 EBSCO and 385 PubMed titles
Foreign-language titles excluded, as well as titles that include:
• Infertility in men only, infertility as cause of distress, couples/marital tension, postpartum depression
Duplicates removed
Blind review by two reviewers of remaining abstracts
n=242
Abstracts excluded due to:
• Outcome other than infertility
• Psychosocial factors studied after diagnosis of infertility
Remaining studies reviewed in full and categorised
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Inclusion or exclusion of studies
• Relevant studies identified and included from references of reviewed articles (n=2)
• Studies discussing psychosocial factors and outcome of infertility treatment excluded from critical review due to being partially covered by previous literature reviews/meta-analyses (n=22)
• Animal studies excluded (4)
Full-text articles critically reviewed
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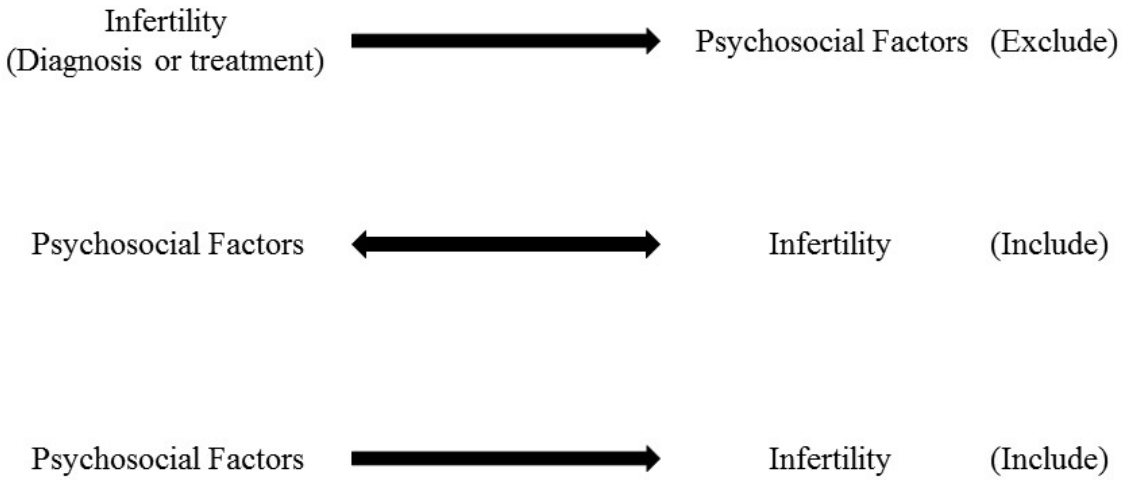
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# Chapter 5: Study 2

**Endometriosis and uterine fibroids and their associations with elevated C-Reactive Protein and leukocyte telomere length: An investigation among women in the National Health and Nutrition Examination Survey, 1999-2002**


## Abstract

**Background:** Endometriosis and uterine fibroids are both conditions linked to abnormal growth of uterine tissue and have been associated with chronic inflammation and long-term morbidity. This study examines the association between these conditions, the inflammatory biomarker C-reactive protein (CRP), and telomere attrition in the National Health and Nutrition Examination Survey for 1999-2002.

**Methods:** We fit adjusted logistic and linear regression models to test the association between these conditions and elevated CRP (>3.0mg/L) vs. normal, as well as leukocyte telomere length (T/S ratio). We also tested for a dose-response relationship between time since disease diagnosis and telomere length. Finally, we stratified models by race/ethnicity.

**Results:** Women with endometriosis had greater odds of having elevated CRP than those without endometriosis (OR=2.02; 95% CI 1.22, 3.35). Endometriosis was associated with a 4% (-8.0, -1.0) decrease in telomere length in age-adjusted models, though this result did not remain significant across models. For women diagnosed with endometriosis, telomeres shortened significantly at a rate of 1% (-1.2, -0.6) for every year of diagnosis. In stratified analysis, black women with endometriosis had a higher rate of telomere attrition than those without

endometriosis, with a relative change of -12.6% (-24.2, -1.5). There were no significant results for CRP or telomere length for women diagnosed with uterine fibroids.

**Conclusion**: Women with endometriosis have shorter telomeres and chronic inflammation that is consistent with higher risk for chronic health conditions. Future research should investigate the potential impact of chronic inflammation on telomere length in women with endometriosis, which could elucidate mechanisms linking endometriosis to chronic disease.

## Introduction

Infertility has been associated with current and long-term health conditions like cardiovascular disease, metabolic dysfunction, and cancer.[1–3] Endometriosis is one cause of infertility that has been characterized by endometrial tissue growing abnormally within and outside its normal uterine location.[4] Though prevalence estimates range between 6 and 10%, endometriosis is linked to infertility in approximately half of women diagnosed.[5,6] Also associated with abnormal uterine tissue growth, uterine fibroids, or leiomyomas, are much more common, with estimates that 60% of black women and 40% of white women will be diagnosed by the age of 35.[7] Uterine fibroids are generally only associated with infertility when they protrude into the uterine cavity, and are the sole implication in approximately 1-2% of infertility cases, though they are detected in 5-10% of cases.[8,9] While these conditions remain common gynecologic disorders, they may represent different etiologic relationships with infertility and biomarkers.

The physiologic causes of endometriosis and uterine fibroids are poorly understood, and researchers have suggested that studying biomarkers of these conditions and their relationships with chronic disease may help to improve understanding of their etiology.[4] An extensive body of

research has demonstrated that endometriosis is strongly associated with inflammation, though the directionality of that association is unclear.[10] Endometriosis has been associated with chronic health conditions like cardiovascular disease and various cancers, possibly due to shared pathophysiology between these conditions.[4] Though the mechanisms for this phenomenon are poorly understood, these associations may be related to dysfunction or alteration of the immune and endocrine systems to promote inflammation and an abnormal hormonal environment.[11] Due to this sub-optimal physiologic functioning, women with endometriosis have been identified as a high risk population for chronic disease.[4]

The relationship between uterine fibroids and chronic disease has not been well-studied, though large growths may impede normal kidney function.[12] Additionally, adverse childhood experiences have been shown to increase the risk of fibroid development, which may point to a stress-dependent or inflammatory pathway.[13] Indeed, cytokines and chemokines have been implicated in fibroid development, and it is biologically plausible that fibroids may be the result of chronic inflammation, though this hypothesis has not been tested.[14,15] Much of the research describing the pathogenesis of fibroids points to genetic abnormalities in fibroid tissue, which may suggest a different etiology from that of endometriosis, though exposure to estrogen may promote growth in both conditions.[14]

C-reactive protein (CRP) is a biomarker of both current and chronic inflammation and also has strong links to cardiovascular morbidity.[16,17] The link between CRP and uterine fibroids has not been well-studied, but CRP has been evaluated as a potential inflammatory biomarker for the diagnosis of endometriosis, with inconsistent findings.[18,19] However, chronic inflammation

can adversely impact reproductive function, and CRP has been shown to partially mediate the association between obesity and telomere shortening.[20–23]

Telomeres are strands of DNA and associated proteins located at the tips of chromosomes that assist in cell replication.[24] Because they shorten with each cell division, they are robust markers of cellular aging.[24] While chronological age is defined as the age of an individual based on a uniform progression of time, cellular, or biological age, is less predictable, and varies by genetic, environmental, and other factors that influence physiologic functioning. For example, shorter telomere length has been associated with onset of age-related morbidities like diabetes, cancer, and cardiovascular disease, labeled as telomere syndrome.[25] Thus, individuals with short telomere length may experience morbidities associated with older chronologic age at an age younger than expected.[25] Furthermore, telomere length has been shown to vary by race/ethnicity and parity, such that, in comparison to Whites, African Americans exhibit longer telomeres in adolescence and shorter telomeres in adulthood,[26,27] and parous women have shorter telomeres than nulliparous women.[28]

Telomere length in reproductive tissue has been studied in relation to reproductive aging, or the stages of reproductive function from menarche through menopause, and some forms of infertility. Women with short telomeres are more likely to have ovarian insufficiency and recurrent miscarriage than women with normal-length telomeres.[29,30] These findings, in conjunction with evidence that women who give birth at older ages typically have longer-than-average telomeres, support the posited link between telomere length and reproductive aging.[31] Researchers have found that reproductive aging and the decline of reproductive function cannot be fully attributed to diminishing oocytes, but may also be related to biologic aging, or shortened

telomeres, as measured in oocytes.[32] Furthermore, telomere length has been positively correlated with reproductive life span, such that longer telomeres predict a wider reproductive window,[33] including older age at menopause.[34,35] In summary, while reproductive function typically declines with age, cellular aging may also play a role in reproductive decline. Specifically, inflammation has been linked to infertility via immune system dysregulation, but inflammation may also increase the rate of telomere attrition in leukocytes.[36] Thus, different reproductive conditions may exhibit different patterns of cellular aging, perhaps based on the role of inflammation and immune system dysregulation in the etiology of the condition.

The association between endometriosis and telomere length in circulating leukocytes has not been well-studied, though several studies have examined the impact of endometriosis on telomere length and telomerase activity in endometrial tissue.[37–39] In healthy endometrial tissue, telomerase is produced to elongate telomeres and promote tissue regeneration.[37] Telomerase activity is accelerated in women with endometriosis, which potentially contributes to inappropriate growth of ectopic endometrial tissue, and causes telomeres to be elongated in endometrial tissue.[37] Thus, studies of telomere length in endometrial tissue may be inappropriate to assess reproductive aging because telomeres in this tissue are naturally longer than those found in circulating leukocytes. In a study of leukocyte telomere length, women with endometriosis had longer circulating leukocyte telomeres than women without endometriosis, which the authors speculate may have been due to increased telomerase activity.[40]

However, it is difficult to extrapolate findings from studies of telomere length or CRP, since many of them include small and highly selective samples and inadequate control for confounding factors, like hormone use. In addition, the findings from these studies are contrary

to evidence supporting the impact of inflammation or reproductive senescence on telomere length. As both conditions have been related to inflammation, it is critical to comprehensively examine whether endometriosis and fibroids are associated with current markers of inflammation (CRP) and differences in leukocyte telomere length. Telomere attrition may be indicative of a lengthy exposure to inflammation and its impact on cellular changes and consequent biologic aging. Utilizing national surveillance data allows for observation of these effects in a representative sample, across different sociodemographic groups. Accordingly, associations between these biomarkers and endometriosis or fibroids could elucidate shared mechanisms between reproductive morbidities and chronic health conditions. The primary objective of this investigation is to test the associations between telomere length and CRP and having a diagnosis of endometriosis or uterine fibroids, while also investigating how these associations may vary by length of time since diagnosis. The secondary objective is to determine the extent to which these associations may differ by race/ethnicity and parity.

## Methods

### *Study population and Data Source*

This study utilized data from two waves (1999-2002) of the National Health and Nutrition Examination Survey (NHANES), which is a nationally-representative survey designed to assess the health of adults and children in the US. These two waves were chosen because they are the only waves to-date that have included measures of leukocyte telomere length. Through a complex, multi-stage sampling process, NHANES procedures randomly identify approximately 5,000-10,000 individuals of all ages to be included in each two-year cycle.[41] Participants are interviewed in their homes using a series of questionnaires. Using Mobile Examination

Complexes, all participants receive a physical examination and biologic samples are collected, such as blood, urine, and saliva. These samples are analyzed to provide information on a variety of biomarkers that are publicly available for all waves of data collection.[42] The total eligible sample included all women who answered interview questions related to endometriosis and uterine fibroids. For this portion of the reproductive health questionnaire, interviewers only surveyed women between the ages of 20 and 54. With no other exclusion criteria, this left an eligible unweighted sample of 4,862 women.

*Exposure: Endometriosis or Uterine Fibroids*

Both endometriosis and uterine fibroids were coded as dichotomous variables, based on a respondent's answer to two separate questions: "Has a doctor or other health professional ever told you that you had" endometriosis or uterine fibroids (event=1, no event=0). For participants who responded yes to the preceding question, they were asked their age at diagnosis. Time since diagnosis was calculated by taking the age of diagnosis of both endometriosis and uterine fibroids and subtracting it from the participant's current age.

*Outcome: Telomere length and C-reactive protein*

Current telomere length was determined by assaying DNA samples three times each using polymerase chain reaction to compare an individual's mean telomere length to standard reference DNA (T/S ratio) derived from human beta globin.[42] This measure is commonly used in studies of telomere length.[28,43]

Current CRP levels were measured from blood samples, using standard laboratory protocol, as described in the NHANES laboratory procedures.[42] Because CRP levels greater than

10.0 mg/L are indicative of acute inflammation, often due to infection, these individuals were eliminated from analysis (7%).[44] CRP was coded dichotomously, consistent with other studies,[45] such that individuals with CRP levels greater than 3.0mg/L (but less than 10.0 mg/L) were categorized as having high CRP, while those with levels at or below 3.0 mg/L were categorized as having normal CRP.

*Covariates*

Covariates were chosen based on prior studies of telomere length and reproductive outcomes. Potential confounders in the associations between exposure and outcome variables include chronologic age, poverty-to-income ratio, educational attainment, age at menarche, and smoking. Age is known to be linearly related to reproductive abnormalities and was analyzed as a continuous variable.[46] Poverty-to-income ratio is a measure of household income compared to the federal poverty level, and was analyzed as a continuous variable, consistent with other, similar studies.[28,35,47] When asked about highest grade completed or highest degree received, respondents could choose between less than 9$^{th}$ grade, 9-11$^{th}$ grade (includes 12$^{th}$ grade with no diploma), high school grad/GED or equivalent, some college or AA degree, or college graduate or above. When coding educational attainment, these categories were generally unchanged, with the exception of combining the "less than 9$^{th}$ grade" and "9-11$^{th}$ grade" categories to a "less than high school graduate" category. Age at menarche was determined by the question, "how old were you when you had your first menstrual period." Respondents could answer continuously (age in years) or categorically (range of ages). To account for both types of answers and maximize the number of valid responses for this variable, age at menarche was coded categorically (<10 years, 10-12, 13-15, 16+ years).

Behavioral or lifestyle variables, to include lifetime smoking status, current body mass index (BMI), physical activity, and hormone use, may either lie on the causal pathway between exposure and outcome (mediators) or represent confounding variables;[4,14,48] however, given the cross-sectional design, we could not assess these temporal associations. Thus, additional models were examined to assess the robustness of the associations when these lifestyle covariates were included in the models. Lifetime smoking status was coded based on responses to the questions, "have you smoked at least 100 cigarettes in your entire life," and "do you now smoke cigarettes?" Based on responses to these yes/no questions, individuals were coded into three categories: never smoker, former smoker (smoked at least 100 cigarettes but does not currently smoke), and current smoker. Body mass index (BMI) was calculated in the NHANES data using the standard method of dividing weight (kg) by squared height ($m^2$), both of which were measured during physical examination. Physical activity was calculated by summing five separate measures of weekly activity. Respondents were asked to report how many days per week and minutes per session they spent engaging in moderate or vigorous activity at work, walking or biking to work, and moderate or vigorous recreational activity. The number of days per week engaged in each activity were multiplied by the number of minutes per session to determine minutes of each activity per week. Then, the minutes for each activity were summed to create a new physical activity variable. Respondents who reported at least 180 minutes of activity per week were coded as engaging in an adequate amount of physical activity.[49] Those reporting less than 180 minutes were coded as engaging in inadequate physical activity, per American College of Sports Medicine and American Heart Association guidelines.[49]

Finally, hormone use was coded as never, past, or current, based on responses to a series of questions related to whether respondents have ever taken or are currently take birth control pills and/or female hormones. Respondents who indicated they have never taken birth control pills or female hormones were coded as "never," while those who indicated previous use, but not current were coded as "former," and those who indicated current use were coded as "current."

*Effect modifiers*

Effect modifiers were chosen prior to development of the analytic plan based on their associations with exposures and outcomes observed in other studies. Parity may serve as a proxy for the extent or severity of infertility; however, parity has also been associated with shorter telomere length, which may operate through mechanisms independent of infertility.[34] Thus, parity was examined as a potential effect modifier in the association between endometriosis/fibroids and telomere length. This variable was coded using responses to two questions, "have you ever been pregnant," and "how many of your pregnancies resulted in a live birth?" Respondents who indicated they have never been pregnant or indicated they have been pregnant but had zero live births were coded as nulliparous (event=0). Respondents who indicated at least one pregnancy ending in a live birth were considered parous (event=1).

Race/ethnicity has been identified as a moderator based on studies indicating that telomere length may be longer in African Americans than comparable white individuals, and has been found to moderate the association between telomere length and age at menopause.[26,35,43] In the 1999-2002 cycles of NHANES, respondents could identify as Mexican American or other Hispanic, non-Hispanic White, non-Hispanic Black, or other race (includes multiracial). The Mexican American and other Hispanic categories were combined into a single "Hispanic"

category for stratified analyses. The "other race" category was included in all analyses, consistent with the NHANES analytic guidelines, but were not reported in final results since this is a heterogeneous group for which it is difficult to draw inference.

*Analyses*

Descriptive statistics were calculated for all exposure, outcome, confounder, and moderator variables, with mean and standard deviations calculated for continuous variables and proportions calculated for categorical variables. Each variable was compared between exposure and non-exposure groups (i.e., endometriosis vs. non-endometriosis and uterine fibroids vs. non-uterine fibroids) using t tests for continuous variables or Rao-Scott modified chi-squared tests for categorical variables to determine differences between groups. All analyses were conducted in SAS v9.4, using appropriate survey commands and weights to account for the complex sampling design.

Telomere length was natural-log transformed to provide a normal distribution. Linear regression models were fit to test the associations between exposures and telomere length. Results were exponentiated after analysis, which can be interpreted as the percent change in mean telomere length compared to the reference group mean. Because the covariates smoking status, BMI, physical activity, and hormone use may lie on the causal pathway, models were fit in a step-wise manner. Three models were fit to test each of the associations between exposure and outcome variables, as follows: (1) Age-adjusted (included age only); (2) Demographic model—adjusted for sociodemographic variables only (age, poverty-to-income ratio, educational attainment, and age at menarche); and, (3) Fully adjusted for sociodemographic and lifestyle/behavioral variables (add smoking, BMI, physical activity, and hormone use). Three

logistic regression models were fit (unadjusted, demographic, and fully adjusted) to test the associations between endometriosis and CRP level, and uterine fibroids and CRP level, with "high CRP" set as the event. The model adjusting for sociodemographic characteristics was considered the main model in all additional sub-analyses, since lifestyle/behavioral variables were considered to be potential mediators. Regression models were fit to test for a dose-response association between CRP (using normal CRP as the reference) or telomere length and length of time since disease diagnosis. These models were fit for each disease group, excluding those without a diagnosis of endometriosis or fibroids. To test for effect modification, interaction terms between endometriosis and parity and fibroids and parity were fit. In a separate model, interaction terms between endometriosis or fibroids and each race/ethnicity category were fit. Results were stratified to examine the degree to which parity or race/ethnicity modified observed associations. Predicted mean T/S ratios from adjusted models were converted to number of base pairs using the formula, $3274 + 2413 \times$ (predicted T/S ratio), where appropriate.[42]

Finally, in sensitivity analyses, because telomeres naturally shorten with age, models that included women diagnosed with endometriosis were stratified by age to confirm observed effects were unlikely to be due to age alone. We first tested for correlation between age and telomere length for women in their 20s, 30s, 40s, and 50s. These strata were chosen to ensure sufficient samples sizes to assess associations within age groups. Demographic-adjusted models were then fit to test associations between telomere length and time since disease diagnosis in each age stratum.

**Results**

The analytic sample consisted of 4,083 respondents with complete information on all variables of interest. The demographic characteristics of the sample by exposure type are described in Table 5.1. The unweighted number of women reporting diagnosis of endometriosis was 358, while 558 reported a diagnosis of uterine fibroids. The weighted percentage (prevalence) of endometriosis and uterine fibroids was 8.9% and 12.8%, respectively. The prevalence of endometriosis and uterine fibroids among black women was 4.8% and 12.3%, respectively, while the prevalence among white women was 10.5% and 13.0%. Among parous women, 9.8% had endometriosis, while 15.7% had uterine fibroids. The prevalence of these conditions in nulliparous women was 7.0% and 5.8%, respectively.

Compared to women without endometriosis, women who had been diagnosed with endometriosis had significantly shorter telomere length and a higher proportion of them had high CRP levels. They were also significantly older, with a higher proportion who were non-Hispanic white, current smokers, users of hormones, and experienced irregular menstrual cycles. In comparison to women who had never been diagnosed with uterine fibroids, those with fibroids were significantly older, had a higher income to poverty ratio, and a higher proportion of women who were non-Hispanic Black, and parous.

Table 5.2 shows the mean telomere length and percentage with high CRP across sociodemographic and health characteristics. A higher proportion of women with high CRP were current smokers, had less than a high school education, reported being in fair or poor health, were current hormone users, and had given birth at least once. Women with shorter telomeres were similar, though their telomere length did not differ by smoking status or hormone use.

There were no significant differences in CRP or telomere length by physical activity, age at menarche, or race.

Across all models, women with endometriosis had more than twice the odds of having high CRP than women without endometriosis (Table 5.3), with odds ratios ranging from 2.02 (1.22, 3.35) after demographic adjustment to 2.11 (1.16, 3.84) after full adjustment. The odds of having high CRP did not change with length of time since diagnosis of endometriosis (OR=0.97; 95% CI 0.89, 1.05). There was no significant association between current CRP level and uterine fibroids.

Results of age-adjusted linear regression indicate that women with endometriosis had a mean telomere length that was 4.0% shorter than women without endometriosis (Table 5.4). While the magnitude of association remained similar after controlling for demographic factors and fully adjusting the model (telomere lengths 3.3% and 2.2%, respectively), the associations were no longer significant. There was no statistically significant association between telomere length and uterine fibroids in either unadjusted or adjusted results. After adjusting for sociodemographic variables, a linear trend was observed between time since endometriosis diagnosis and telomere length, with a 1% decrease in telomere length for every year since diagnosis. Based on the demographic-adjusted coefficient estimates from linear regression, this translates to a 16 (95% CI: 14, 19) base pair decrease in telomere length for every year of endometriosis diagnosis.

Race and parity have been associated with both endometriosis and uterine fibroids and with telomere length. Models were stratified by both race and parity, based on a priori decisions to examine race and parity as effect modifiers. There were no differences observed between

nulliparous and parous women, as results in both groups were consistent with the main model (Table 5.5). Stratification of the demographic model by race indicated that white women with endometriosis had 1.98 (1.09, 3.62) times higher odds of having high CRP than those without endometriosis, while Hispanic women had lower odds of having high CRP (OR=0.21; 95% CI 0.06, 0.67) (Table 5.5). There were no significant associations between endometriosis and CRP for non-Hispanic Black women. However, among non-Hispanic black women, those with endometriosis had telomeres that were 13.6% (95%CI: -24.2, -1.50) shorter than those without endometriosis. Based on the demographic-adjusted coefficient estimates from linear regression, this equates to a mean telomere length that is 406 (95% CI: 268, 510) base pairs shorter for women with endometriosis. There were no significant associations between endometriosis and telomere length in any other racial/ethnic group. While the magnitude of associations varied across and were significant within some racial/ethnic groups, none of the coefficients for the interaction terms were statistically significant.

In sensitivity analysis, there were no significant correlations between age and telomere length in any age strata except for women in their 20s ($r$=-0.13). For women in their 20s, there was no association between telomere length and time since disease diagnosis (+0.3%; 95% CI 0.0, 0.06), but for women in their 30s, 40s, and 50s, there was an inverse association between telomere length and time since diagnosis with a rate of attrition of 1.3% (-1.6, -0.9), 1.0% (-1.01, -0.5) and 0.89% (-1.0, -0.5), respectively, consistent with the overall models.

**Discussion**

This study is the first nationally-representative study to examine the associations between specific reproductive conditions, endometriosis and fibroids, and both telomere length and CRP.

Women with endometriosis had double the odds of having high CRP across all models, and these odds did not change with time since diagnosis. These results are consistent with our expectations, given the inflammatory nature of this condition, but they also highlight the sustained inflammatory profile that may put women with endometriosis at higher risk for chronic disease.[4] Generally, there were few associations between fibroids and CRP or telomere length. In comparison, age-adjusted models showed an association between endometriosis and shorter telomere length. While the magnitude of the association remained similar, this association was no longer significant after adjusting for demographics. Adjustment for additional lifestyle covariates further attenuated the results; however, this is to be expected in the case of mediation. For all women with endometriosis, telomeres shortened at a rate equivalent to approximately 1.3 years for every year since diagnosis. This estimate is based on the study population's normal age-related telomere attrition estimate of 12 base pairs per year (data not shown).

In stratified analyses, we found that this relationship was strongest for non-Hispanic black women with endometriosis, who experienced telomere shortening at a rate equivalent to approximately 33 years of normal biologic aging. On the more conservative end, telomere shortening has been reported to occur in women at a rate of 27 base pairs per year, though this rate was observed among participants with a much wider age range than the current study (18-76 years), and due to differential laboratory methods used for assay, mean telomere length may vary considerably between samples.[50] However, using this estimate still indicates excessive biologic aging of approximately 15 years among black women with endometriosis. Similarly, among women diagnosed with endometriosis, telomere shortening would equate to 0.59 excess years of biologic aging for every year elapsed since diagnosis. To put this into perspective, this means

that a woman diagnosed with endometriosis for 10 years could have a biologic age of six to 13 years greater than her chronologic age, depending on the estimate of normal age-related telomere attrition.

Regardless of the estimate of annual telomere attrition used, the excess biologic aging associated with endometriosis could be indicative of physiologic wear and tear that could potentially put women with endometriosis at higher risk for chronic disease and other morbidities typically occurring with older age.[4] The results for CRP analyses seem to support this hypothesis, as women with endometriosis had double the odds of having CRP levels consistent with a higher risk profile for cardiovascular disease and other chronic health conditions that likely remains high after diagnosis.[16] Furthermore, once diagnosed, CRP levels remain high, and a faster rate of telomere attrition could be reflective of this chronic inflammatory state.

The different associations with telomere length and CRP for endometriosis and fibroids were not unexpected, as the etiology and diagnosis of these conditions may differ. Endometriosis is difficult to diagnose, requiring laparoscopic surgery for definitive diagnosis, which typically occurs when endometriosis is the suspected cause of dysmenorrhea, pelvic pain, or infertility.[51] Contrastingly, uterine fibroids may be suspected based on similar symptomatology to endometriosis, or may be asymptomatic and incidentally discovered during the diagnosis or monitoring of other conditions that require pelvic ultrasound, including pregnancy.[7,52] Indeed, the relative ease of diagnosis may partially contribute to the high prevalence of fibroids, though estimates range from 12 to 77%.[8] Once diagnosed, women with endometriosis comprise a relatively homogeneous group in terms of predictability of disease progression.[10] However, the

number and severity of symptoms may vary, limiting the potential for diagnosis for women who remain asymptomatic.[10] Thus, the women in our sample may represent a more severe, symptomatic form of endometriosis, which would likely have attenuated our findings if those with undiagnosed endometriosis were misclassified in the healthy (non-endo) group. We see an indication of this when examining the association with duration of time since diagnosis of endometriosis, as these associations are strengthened with increasing time spent with endometriosis. In contrast, uterine fibroids are heterogeneous in terms of size and location, and may grow or regress throughout the life course, all of which lead to differential impacts on women diagnosed and associated relationships with biomarkers.[7] Thus, there may be insufficient information on the location or degree of severity to distinguish biomarker patterns in relation to fibroids.

Endometriosis is more prevalent in white women than black women, but because it requires more invasive surgery to confirm diagnosis, this difference may result from differential access or interaction with the health care system to be diagnosed surgically.[53,54] Indeed, black women are reported to be twice as likely to experience infertility in their lifetime, and less likely to seek treatment.[55] Similarly, black women included in this study may have delayed seeking care or diagnosis of endometriosis until symptoms were severe. Thus, the excess biologic aging observed among black women with endometriosis in this study could be, in part, due to increased severity of cases among this group.

This study is inconsistent with the only other known study of endometriosis and leukocyte telomere length, where researchers found that women with endometriosis had longer leukocyte telomeres.[40] However, the study population was relatively small ($n$=110), included

only 21 controls to compare to 89 cases, and researchers did not control for hormone use. While women with endometriosis have higher telomerase activity, supporting a finding of elongated telomeres, other evidence suggests that telomerase is released locally in endometrial tissue, which is unlikely to produce a systemic effect.[38] Moreover, this study was conducted to understand the etiology of endometriosis, and to our knowledge, there are no studies oriented toward examining endometriosis and telomeres in respect to reproductive or cellular aging. Our observed associations are, however, consistent with literature describing the inflammatory nature of endometriosis,[10,11] and telomere attrition associated with chronic inflammation.[36]

One strength of this study is its generalizability, as data was utilized from a large, nationally-representative sample of women. Unlike other studies, which were limited by small, select samples, we could examine and account for a number of potential confounders and assess effect modification. Additionally, the study outcomes were based on current, objective biomarker collection. Finally, due to the nature of the questions used to assess the exposures, we can be assured that endometriosis and uterine fibroids were diagnosed prior to biomarker collection, though we are limited in our ability to draw conclusions related to causal inference.

As a cross-sectional study, there are other limitations to this investigation. Most notably, endometriosis and fibroids were self-reported, as was the age at diagnosis. While it seems likely that more women would remember being diagnosed with either of these conditions, there may be recall bias among women who were diagnosed many years prior. As discussed previously, uterine fibroids are relatively straightforward to diagnose if sought, but some women may report being diagnosed with endometriosis without surgical confirmation, or we may be capturing only the most symptomatic and severe cases. Considering the lag time between appearance of

symptoms and diagnosis, which is normally 8-10 years,[19] and that some women with endometriosis remain asymptomatic or do not seek treatment or diagnosis, there is potential for misclassification. However, misclassification would likely dilute our associations, suggesting that the actual magnitude of associations may be larger than that observed. It is also notable that the NHANES interview only included women up to the age of 54, which means we are unable to assess the impact of endometriosis after menopause, which is typically a time when the condition improves or disappears.[6] Finally, we were unable to account for treatment options, such as estrogen inhibition,[51] that may have moderated the observed associations. We did, however, have fairly extensive information on hormone use and were able to control for never, former, and current use of both hormonal contraception and other female hormone therapy.

Endometriosis, telomere length, and elevated CRP have all been associated with long-term morbidities, and we found that women with endometriosis have higher odds of presenting with abnormally high CRP levels and was suggestive of telomere attrition. When taken together, the results of this study indicate that there may be a shared physiologic mechanism, such as chronic inflammation, linking these conditions. Future research should focus on elucidating these pathways.

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## Tables

**Table 5.1. Weighted demographic characteristics of the sample by Endometriosis and Uterine Fibroid diagnoses (unweighted *n*=4,083)**

| | All | Endo | No endo | Fibroids | No Fibroids |
|---|---|---|---|---|---|
| Mean telomere length (sd)* | 1.11 (0.01) | 1.04 (0.02) | 1.11 (0.01) | 1.08 (0.02) | 1.11 (0.01) |
| C-Reactive Protein* | | | | | |
| High | 36.92% | 55.07% | 35.12% | 44.31% | 35.77% |
| Mean age (sd)*^ | 35.73 (0.41) | 38.60 (0.80) | 35.60 (0.48) | 43.24 (0.51) | 34.86 (0.45) |
| Income to poverty ratio (sd)^ | 3.13 (0.08) | 3.50 (0.22) | 3.14 (0.09) | 3.67 (0.12) | 3.10 (0.09) |
| Educational attainment^ | | | | | |
| <High school | 13.03% | 10.90% | 13.24% | 6.62% | 13.86% |
| High school grad or equiv | 21.17% | 32.09% | 20.09% | 25.65% | 20.56% |
| Some college/AA | 32.43% | 30.64% | 32.61% | 30.76% | 32.71% |
| College grad+ | 33.37% | 26.37% | 34.06% | 36.98% | 32.87% |
| Race*^ | | | | | |
| Mexican American | 5.78% | 1.72% | 6.19% | 3.38% | 5.88% |
| Other Hispanic | 6.73% | 1.54% | 7.24% | 3.16% | 7.42% |
| Non-Hispanic White | 74.20% | 87.13% | 72.93% | 75.09% | 74.06% |
| Non-Hispanic Black | 8.87% | 4.76% | 9.28% | 14.82% | 8.11% |
| Other/Multiracial | 4.41% | 4.85% | 4.37% | 3.55% | 4.53% |
| Age at menarche | | | | | |
| <10yrs | 2.38% | 4.46% | 2.18% | 4.94% | 2.09% |
| 10-12yrs | 44.29% | 50.23% | 43.70% | 48.34% | 43.69% |
| 13-15yrs | 47.20% | 40.59% | 47.85% | 40.04% | 48.15% |
| 16+yrs | 6.13% | 4.73% | 6.27% | 6.68% | 6.07% |
| Smoking status* | | | | | |
| Never | 60.32% | 55.82% | 60.77% | 54.43% | 61.36% |
| Former | 17.72% | 13.90% | 18.10% | 23.32% | 16.44% |
| Current | 21.96% | 30.28% | 21.14% | 22.25% | 22.21% |
| Mean BMI (sd) | 27.05 (0.24) | 28.07 (0.78) | 26.92 (0.24) | 27.58 (0.41) | 26.93 (0.25) |
| General health^ | | | | | |
| Excellent | 27.16% | 24.22% | 27.45% | 23.41% | 27.55% |
| Very good | 36.47% | 29.94% | 37.12% | 31.33% | 37.41% |
| Good | 27.09% | 30.13% | 26.79% | 31.49% | 26.54% |
| Fair | 7.89% | 12.97% | 7.39% | 10.63% | 7.39% |
| Poor | 1.38% | 2.74% | 1.25% | 3.13% | 1.11% |
| Physical activity^ | | | | | |
| 180+ minutes/week | 36.64% | 40.34% | 36.28% | 43.97% | 35.72% |
| Hormone use*^ | | | | | |
| Never | 19.74% | 4.54% | 21.10% | 8.11% | 21.15% |
| Former | 51.52% | 47.17% | 51.91% | 55.70% | 51.12% |
| Current | 28.74% | 48.29% | 26.99% | 36.19% | 27.73% |
| Parity^ | | | | | |
| At least one live birth | 70.69% | 77.24% | 70.04% | 86.61% | 67.14% |

*Indicates significant difference for endometriosis—t test or Rao-Scott chi-square; ^Indicates significant difference for fibroids—t test or Rao-Scott chi-square; Income to poverty ratio = income/(poverty level accounting for household size and geographic region)

**Table 5.2. Telomere length (T/S ratio) and CRP level weighted proportions by demographic characteristics (*n*=3,779)**

| | Mean telomere length | High C-Reactive Protein |
|---|---|---|
| Educational attainment*^ | | |
| <High school | 1.09 | 31.76% |
| High school grad or equiv | 1.09 | 28.86% |
| Some college/AA | 1.12 | 26.30% |
| College grad+ | 1.11 | 20.44% |
| Race | | |
| Mexican American | 1.07 | 22.57% |
| Other Hispanic | 1.15 | 22.62% |
| Non-Hispanic White | 1.10 | 21.26% |
| Non-Hispanic Black | 1.03 | 22.84% |
| Age at menarche | | |
| <10yrs | 1.13 | 31.03% |
| 10-12yrs | 1.09 | 30.77% |
| 13-15yrs | 1.11 | 27.65% |
| 16+yrs | 1.11 | 24.63% |
| Smoking status^ | | |
| Never | 1.12 | 23.81% |
| Former | 1.07 | 27.83% |
| Current | 1.09 | 28.22% |
| General health*^ | | |
| Excellent | 1.12 | 14.82% |
| Very good | 1.12 | 20.02% |
| Good | 1.10 | 28.15% |
| Fair | 1.05 | 33.50% |
| Poor | 1.04 | 42.46% |
| Physical activity | | |
| 180+ minutes/week | 1.12 | 19.41% |
| <180 minutes/week | 1.11 | 20.74% |
| Hormone use^ | | |
| Never | 1.13 | 24.79% |
| Former | 1.11 | 24.22% |
| Current | 1.09 | 44.00% |
| Parity*^ | | |
| No live births | 1.15 | 20.65% |
| At least one live birth | 1.08 | 34.54% |

*Indicates significant difference for telomere length using t tests or ANOVA; ^Indicates significant difference for high vs. low C-Reactive Protein using Rao-Scott chi-square; 7% of the sample was excluded due to abnormally high CRP levels (>10mg/L)

**Table 5.3. Adjusted odds ratios for the associations between C-reactive protein and endometriosis and uterine fibroids**

| Model | Endometriosis OR (CI) | Uterine Fibroids OR (CI) |
|---|---|---|
| Age-adjusted | **2.35 (1.43, 3.86)** | 1.46 (0.98, 2.18) |
| Demographic-Adjusted | **2.02 (1.22, 3.35)** | 1.31 (0.85, 2.03) |
| Fully Adjusted | **2.04 (1.03, 4.02)** | 1.82 (0.88, 3.75) |
| Time since diagnosis (per year) | 0.97 (0.89, 1.05) | 0.93 (0.86, 1.02) |

Demographic-Adjusted model adjusts for age, income-to-poverty ratio, education, and age at menarche; Fully-Adjusted model adjusts for age, income-to-poverty ratio, education, age at menarche, smoking status, general health, BMI, physical activity, and hormone use; Interaction term p-values: race/ethnicity (p=0.06) and parity (p=0.65)

**Table 5.4. Relative percent change in telomere length (T/S ratio) between women diagnosed with and without endometriosis or uterine fibroids**

| Model | Endometriosis % Change (CI) | Uterine Fibroids % Change (CI) |
|---|---|---|
| Age-adjusted | **-4.0 (-8.0, -1.0)** | 2.0 (-1.9, 6.0) |
| Demographic-Adjusted | -3.3 (-7.4, 0.94) | 2.2 (-1.6, 6.2) |
| Fully Adjusted | -2.2 (-8.6, 4.6) | 2.2 (-2.4, 6.9) |
| Time since diagnosis (per year) | **-1.0 (-1.2, -0.6)** | 0.1 (-0.4, 0.6) |

Demographic-Adjusted model adjust for age, income-to-poverty ratio, education, and age at menarche; Fully-Adjusted model adjusted for age, income-to-poverty ratio, education, age at menarche, smoking status, general health, BMI, physical activity, and hormone use; Interaction term p-values: race/ethnicity (p=0.16) and parity (p=0.33)

**Table 5.5. Demographic-adjusted models showing associations between reproductive outcomes and C-reactive protein and telomere length, stratified by race and parity**

| | C-reactive protein | | Telomere length (T/S Ratio) | |
|---|---|---|---|---|
| | **Endometriosis** | **Uterine Fibroids** | **Endometriosis** | **Uterine Fibroids** |
| | **AOR (CI)** | **AOR (CI)** | **% Change (CI)** | **% Change (CI)** |
| Race | | | | |
| Hispanic | **0.21 (0.06, 0.67)** | 1.41 (0.48, 4.11) | -22.4 (-42.8, 5.4) | -6.3 (-19.7, 9.2) |
| Non-Hispanic White | **2.07 (1.18, 3.60)** | 1.42 (0.83, 2.44) | -1.8 (-8.3, 5.2) | 2.5 (-2.5, 7.7) |
| Non-Hispanic Black | 1.13 (0.31, 4.11) | 0.64 (0.32, 1.30) | **-13.6 (-24.2, -1.5)** | 0.8 (-9.4, 12.1) |
| Parity | | | | |
| Nulliparous | 2.08 (0.76, 5.70) | 1.35 (0.43, 4.23) | -4.1 (-12.9, 5.7) | 9.2 (-3.6, 23.8) |
| Parous | **1.92 (1.03, 3.57)** | 1.36 (0.90, 2.05) | -2.4 (-6.7, 1.9) | 1.2 (-3.1, 5.7) |

Adjusted for age, income-to-poverty ratio, education, and age at menarche

# Chapter 6: Study 3

**Stressful Life Experiences and the Incidence of Infertility: A Longitudinal Examination of Women from the National Longitudinal Survey of Youth, 1997 Cohort**


**Abstract**

**Background:** It has been established that stress may influence reproductive health, but few studies have tested the temporal association between the experience of stressful life events (SLEs) and infertility.

**Methods:** Using data from the National Longitudinal Survey of Youth, 1997 Cohort, we tested the association between the experience of SLEs in adolescence and early adulthood and later reports of female infertility (inability to achieve pregnancy after 12 months of intercourse without contraception). We stratified responses by high or low maternal responsiveness in adolescence.

**Results:** After adjusting for demographics and environmental factors, in comparison to those with one or zero SLEs, those with 3 SLEs had 1.68 (95% CI: 1.16, 2.42) times higher odds, and those with four or more SLEs had 1.88 (95% CI: 1.38, 2.57) times higher odds of infertility. Respondents with low maternal responsiveness had higher odds of infertility that increased as the number of SLEs increased, with reports of 1.98 (1.01, 3.93), 2.63 (1.18, 5.89), and 3.07 (1.53, 6.16) times higher odds of infertility for two, three, and four or more SLEs, respectively. For respondents with high maternal responsiveness, SLEs were only associated with infertility for women experiencing four or more SLEs (OR=1.53; CI 1.05, 2.25).

**Conclusion:** In this novel investigation, we were able to demonstrate a temporal association between the experience of stressful life events and reports of infertility. The magnitude of this association was larger when respondents reported low compared with high maternal responsiveness in adolescence, highlighting the importance of maternal behavior toward children in mitigating harms associated with stress in adolescence and beyond.

## Introduction

Recent studies have emerged linking infertility to a variety of current health indicators and chronic health conditions.[1,2] The overall conclusion of this literature suggests that infertility and conditions such as cardiovascular diseases and metabolic dysfunction share a common physiologic mechanism. One potential connection between infertility and other poor health conditions may be through stress. Stress causes disruptions in central neuroendocrine axes responsible for reproduction and general homeostasis, and has been linked to reproductive and cardiometabolic dysfunction.[3] Specifically, in the case of chronic stress, multiple perturbations of the stress-response axes, like HPA and SAM, may cause an upregulation in body systems, such as elevated heart rate, blood pressure, fasting glucose, and inflammation-inducing agents.[3,4] These upregulated physiologic functions cause abnormal wear and tear on the body, resulting in long-term dysfunction of multiple body systems.[4] While the connection between infertility and poor health outcomes may be through this shared common pathway, studies on the association between stress and infertility are less clear in part due to limitations in assessing temporality.

Stress and infertility have primarily been studied in the context of stress as a consequence of infertility diagnosis or treatment.[5,6] In these studies, stress is measured either simultaneously with or after treatment, both of which have occurred after diagnosis, and these studies almost

exclusively target women seeking fertility treatment.[5,7–9] The few longitudinal studies that have investigated stress as an antecedent to infertility were limited to periconceptual stress among couples trying to conceive;[10–12] however, they are limited in their ability to infer the impact of chronic stress or at earlier periods of development. While these studies help to establish an association between stress and infertility, conclusions are limited regarding the potential mechanisms, and the temporal nature of the association, in the case of cross-sectional studies. Furthermore, current research fails to differentiate between acute stress, which may have a temporary impact on reproductive function, and chronic stress, which may alter physiologic mechanisms leading to long-term reproductive dysfunction (e.g., endometriosis, uterine fibroids, PCOS, or unexplained infertility) that could predict later-life morbidity. The impact of chronic stress is consistent with life course theory, which posits that an accumulation of stressors over the life course may contribute to biologic wear and tear that can contribute to later poor health outcomes.[13] Alternatively, life course theory also hypothesizes that stressful events that occur during critical periods of development may influence later health.[14] In terms of reproductive function, events that occur prior to puberty may permanently alter HPA and other systems that influence normal reproduction.[15] To better elucidate these pathways, it is critical to conduct studies that can differentiate the longitudinal impact of early life and chronic stress on infertility.

While childhood and adolescence have been established as critical periods of development during which stressful events may have lifetime consequences it is important to consider characteristics of the child's environment that may buffer or moderate responses to stress. Maternal responsiveness, which has been defined in terms of prompt, appropriate responses to everyday exchanges with children,[16] has long been considered a protective factor in cognitive and social-emotional development.[17] There is also evidence that maternal

responsiveness may moderate the association between stressful events in childhood and long-term morbidity, perhaps even serving as a buffer to prevent changes in the stress response system, as described previously.[18]

The hypothesis that chronic or early life stress may influence fertility is physiologically plausible and consistent with life course theory. Moreover, epidemiologic studies support a potential association between periconceptual stress, but few studies have directly assessed the association with early life stress.[19–21] Thus, the primary objective of this investigation was to explore whether experiences of stressful life events (SLEs) in childhood, adolescence, and early adulthood are associated with self-reported infertility or difficulty conceiving in adulthood. Because the impact of stress may vary by family environment and relational factors, this study also investigated differences in these associations by experience of high or low maternal responsiveness in adolescence.

**Methods**

This study utilized data from the National Longitudinal Survey of Youth's 1997 Cohort (NLSY-97). The US Bureau of Labor Statistics employs complex stratified sampling methods to recruit a nationally-representative sample of men and women in the same birth cohort.[22] The cohort included in NLSY-97 were born between 1980 and 1984. The sample was first surveyed in 1997 and interviewed annually or biannually thereafter. In 2011, the last year for which data was used for this current study, 3,714 women were interviewed.[23,24] The analytic sample included all female participants who had ever tried to get pregnant with complete data on stressful life events and infertility ($n$=1,652).

*Outcome: Infertility*

Infertility information was collected between 2009 and 2011, which encompasses two rounds of data collection interviews (Rounds 13 and 14). While the majority of participants responded to these questions in 2009, the few who were unavailable were asked in 2010 or 2011.[22] First, participants indicated whether they had "ever been part of a couple that had problems getting pregnant or having a baby." Possible answers to this question include "yes," "maybe," "no and I have tried to have a child," and "I have not tried to have a child." All participants were then asked if they "had unprotected sex for at least 12 months in a row without conceiving a child."

Infertility was coded dichotomously (1=yes, 0=no) in two ways, based on responses to these questions. First, a general, subjective definition of infertility was coded, based on whether participants indicated being part of a couple that had problems getting pregnant. Participants who answered "maybe" or "I have never tried to have a child" were excluded from analyses using this definition to ensure that the analytic sample consisted only of individuals who had tried to conceive, and not those who were unaware of their fertility status. Second, infertility was coded based on a definition consistent with the clinical criteria for infertility (regular sexual intercourse over at least 12 months without the use of contraception, and without conceiving a child),[25] reported as, "I have had unprotected sex for at least 12 months in a row without conceiving a child." Again, those who indicated they had never tried to have a child were excluded from analyses using this definition.

*Exposure: Stressful Life Events*

Each question included in the measurement of this exposure in NLSY-97 corresponded to a question on the List of Threatening Experiences, a validated inventory of stressful life events that has also been used to assess pregnancy outcomes in response to stress.[26–28] In the first round

(1997), participants were asked if, prior to the age of 12, they: ever had their house/apartment broken into; were ever the victim of repeated bullying; and ever saw someone get shot or shot at with a gun. In rounds 2-5 (1998-2001), after respondents reached the age of 18, they were asked if, between the ages of 12 and 18, they, again: ever had their house/apartment broken into; were ever the victim of repeated bullying; and ever saw someone get shot or shot at with a gun. In Round 6 (2002), when respondents were between the ages of 17-22, they were asked several other questions related to SLEs, and the age at which they happened: death of a close relative, victim of a violent crime ("for example, physical or sexual assault, robbery, or arson"), homelessness, household member stayed in the hospital for at least a week for treatment of illness or injury, adult member of household incarcerated, household member unemployment, and parents' divorced. These questions were repeated in Round 11 (2007), and again in subsequent rounds if the question was not answered in 2007 (i.e., participant was unavailable for interview). Thus, it was possible to ascertain all surveyed SLEs that occurred prior to the age of 23, since respondents would answer these questions for the prior five years through the age of 28. A total score for the number of SLEs was initially calculated, and then scores were grouped into categories, based on the distribution (0-1, 2, 3, 4+).

To assess the impact of event timing, we coded SLEs differently from the coding scheme in the main analysis because the number of SLEs were not consistent across age categories (i.e., only three possible events prior to age 12 compared to ten between the ages of 12-18). Three separate SLE dichotomous variables were created based on the age at which the event occurred: any event prior to the age of 12, any event between the ages of 12 and 18, and any event after age 18 (any event=1, no event=0).

*Potential Confounders*

Demographic confounders included race/ethnicity and household income to poverty ratio in adolescence. Participants' race/ethnicity was categorized based on how race/ethnicity was identified in NLSY-97 data: Hispanic, non-Hispanic/non-Black, non-Hispanic Black, or multiracial. Household income to poverty ratio was calculated by dividing family income, as reported in Round 1 (1997), by the federal poverty level, accounting for household size.

Household confounders included biological siblings living in the household and physical environmental risk factors in adolescence. Detailed information about siblings in the home can be found in the household roster and was coded as a continuous variable. The physical environment has been linked to both reproductive health and child development, which may facilitate or contribute to SLEs.[29–31] For the first round of data collection in 1997, Child Trends, Inc. created a physical environment risk index to include whether the household usually had electricity or heat when needed in the past month, the condition of buildings on the youth's street, the condition of the interior of the home (reported by interviewer), whether interviewer felt concerned for their safety in the youth's neighborhood (reported by interviewer), and the number of days the youth hears gunshots in a typical week.[32] Based on the distribution of scores on the index, physical environment risk was coded into three categories (0, 1-2, 3+).

Finally, health and health behavior confounders included substance use and BMI. For Rounds 1-4 (1997-2000), Child Trends, Inc. created an index variable for substance use based on participant responses indicating cigarette, alcohol, and marijuana use.[32] Each year over this four-year period, participants could receive a score of 0-3 based on their substance use. Each participant's score was summed over each year through 2000, to produce a total possible score of 0-12. Scores were averaged over the analytic sample and substance use was coded dichotomously as above or below the mean (>4.4and ≤4.4). These years were chosen for

assessment of substance use because usage may have occurred early enough in development to affect later reproduction. Use may then have occurred simultaneously with SLEs, and not necessarily after, when substance use could then be considered a mediator. BMI was calculated at baseline as weight (kg) divided by height ($m^2$).

Several of the proposed confounders for associations between stress and infertility could lie on the causal pathway between these variables. For example, use of tobacco, alcohol, and substance abuse have been associated with maladaptive coping when confronted with stress. Given that the timing of these behaviors could have occurred after experiencing an SLE, they may lie on the causal pathway between SLEs and infertility. Similarly, body mass index may precede an SLE or occur as a result of SLE, again placing it on the causal pathway. Thus, several models were constructed to explore the robustness of findings after controlling for different sets of potential confounders.

*Effect Modifier: Maternal Responsiveness*

The potential moderator, maternal responsiveness, was assessed using five questions adapted from the Conger and Elder (1994) Parent-Youth Relationship Scale, which has been evaluated to have acceptable psychometric properties.[33] This scale has been used to assess maternal responsiveness in other NLSY-97 studies.[34] Adolescents provided responses ranging from 0 (never) to 4 (always) to the following questions about the mother figure with whom the respondent resided, and how often she: praises you for doing well, criticizes you or your ideas, helps you do things that are important to you, blames you for her problems, and makes plans with you and cancels for no good reason. Negative items (criticizes, blames, and cancels) were reverse-coded to allow for items to be summed into a composite score ranging from 0 to 20. The

final maternal responsiveness variable was dichotomized based on the recommended cut-point of 15 (high=15+, low= less than 15).[33]

**Analysis**

In the first stage of analysis, the prevalence of infertility was calculated based on respondents reporting either problems getting pregnant or clinical infertility. For both of these definitions of infertility, ever infertile and never infertile women were then compared across all variables included in the study using t-tests for continuous data and Rao-Scott chi modified squared analyses for categorical data. Because NLSY is conducted using complex, stratified sampling, survey weights were custom-made for each dataset generated through NLSY Investigator. Survey commands were used across analyses to account for the complex survey design, though survey weights were only used when generating frequency tables and descriptive statistics, consistent with the analytic guidelines, which recommend against weighting for any analyses more complex than descriptive to ensure correct estimates.[22]

Next, logistic regression models were fit to examine the association between number of SLEs (continuous variable) and each definition of infertility, adjusted for covariates in a step-wise manner across four models: (1) unadjusted; (2) demographic variables only (race/ethnicity and household income to poverty ratio); (3) demographic and environmental factors (added number of biologic siblings, as a proxy for household size, and physical environment risk index); and (4) fully adjusted—demographic, household, and health and health behavior confounders (added substance use and BMI). To test whether maternal responsiveness moderated these associations, separate regression models were fit with interaction terms for each combination of maternal responsiveness multiplied by the number of SLEs. Stratified models were then produced for high vs. low maternal responsiveness. Model 3 was considered the main model for

all additional analyses given that Model 4 included potential mediators related to behavioral risk factors.

Additionally, to examine whether there were differences in infertility based on the timing of SLEs, three new groups of models were fit. The first group examined the association between SLEs occurring prior to the age of 12 and the clinical definition of infertility, while the second examined SLEs occurring between the ages of 12 and 18, and the third examined SLEs occurring between the ages of 19-23. SLEs were analyzed in two ways in each group; first as a dichotomous variable comparing none vs. any event, and second, as a continuous variable.

**Results**

In the analytic sample, there were 1,652 women who reported they had tried to get pregnant, and who provided complete information on all exposure, outcome, demographic, and environment variables. The demographic characteristics of the sample can be viewed by infertility outcome in Table 6.1. The prevalence of women who reported clinical infertility was 24.1%, while 17.8% reported problems getting pregnant. Women who experienced either clinical infertility or problems getting pregnant had significantly higher mean stressful life events than women who reported no experience with infertility. When compared to reportedly fertile women, a significantly higher proportion of respondents reported being Hispanic or non-Hispanic Black, having a lower income-to-poverty ratio, fewer biological siblings, a higher number of physical environmental risk factors, higher mean substance use, and higher mean BMI. There was also a higher proportion of women reporting low maternal responsiveness among those reporting clinical infertility.

In comparison to respondents reporting 0-1 SLEs, those who experienced 3 or 4+ stressful life events had higher odds of reporting clinical infertility across all models (Table 6.2). These elevated odds ranged from 1.55 (CI 1.09, 2.29) for 3 events in the full model (Model 4) to 2.02 (CI 1.66, 2.47) for 4+ events in the demographic-only model (Model 2). For the main model (Model 3), the odds of infertility increased with each SLE, with odds of 1.21 (0.90, 1.64) for 2 events, 1.68 (1.16, 2.42) for 3 events, and 1.88 (1.38, 2.57) for 4+ events. These results were only marginally diluted for Model 4, which adjusted for BMI and substance use, both of which may lie on the causal pathway, though findings remained significant.

Few significant associations were observed between stressful life events and reports of problems getting pregnant (Table 6.3). In comparison to respondents who experienced 0-1 SLEs, only those reporting 4 or more SLEs had higher odds of experiencing problems getting pregnant, with significant results in the unadjusted (OR: 1.57; CI 1.10, 2.24) and demographic-only (OR: 2.01; CI 1.31, 3.08) models.

After stratification, respondents reporting low maternal responsiveness in adolescence had higher odds of infertility across all categories of SLEs, and odds ratios increased with increasing number of SLEs (Figure 6.1). Compared to the 0-1 category, odds increased from 1.98 (CI 1.01, 3.93) for 2 SLEs, to 2.63 (CI 1.18, 5.89) for 3 SLEs, and 3.07 (CI 1.53, 6.16) for 4+ SLEs. Contrastingly, among respondents reporting high maternal responsiveness in adolescence, there were no significant associations between SLEs and infertility for women experiencing 2 or 3 SLEs. Those experiencing 4 or more SLEs had 53% higher odds of infertility (OR: 1.53; CI 1.05, 2.25). However, given smaller samples, the precision of these estimates was reduced, as demonstrated by overlapping confidence intervals and the coefficients for each interaction were not significant.

The timing of these events was further examined across age groups, and the odds of infertility increased with each stressful life event experienced (Table 6.4). SLEs experienced prior to the age of 12 increased the odds of infertility by 21% (CI 1.05, 1.40) for each additional event experienced, while SLEs occurring between the ages of 12-18 years and 19-23 years increased the odds of infertility by 10% (C: 1.01, 1.21) and 15% (CI 1.03, 1.28), respectively, for each additional SLE reported. When analyzing SLEs dichotomously, the experience of any event increased the odds of infertility across all age categories, though the magnitude of the associations did not differ substantially between age groups (Table 6.4).

**Discussion**

In this novel investigation, we were able to demonstrate a temporal association between the experience of stressful life events in childhood through early adulthood and reports of infertility. This association varied by maternal responsiveness in adolescence, highlighting the importance of maternal behavior toward children in mitigating harms associated with stress in adolescence and beyond. When considering the timing of SLEs, our results indicate that higher risk for clinical infertility is associated with the accumulation of stressful life events, though events that occur prior to the age of 12 may have greater impact than those occurring between the ages of 12-18 and 19-23.

The accumulation of stressful events is supported by the cumulative mechanism of life course theory which posits that stressful life events accumulate to increase overall allostatic load, an indicator of up-regulated physiologic functioning, which causes subsequent biologic "wear and tear" on the body.[13] Chronic wear and tear can affect regulation of the stress response and increase inflammation and dysregulation of the immune system to negatively impact health.[3]

Many animal studies have found links between early life stress and later fertility,[35–38] and life history theories describe how stressful events in early life may influence later fertility in humans. These theories emphasize balance between preserving individual health and reproduction, positing that humans have evolved to be responsive to their environment to increase overall fitness.[39] Specifically, consistent with the critical/sensitive periods model of life course theory, psychosocial stimuli in childhood, like stress, can alter baseline functioning of the HPA axis, including the amount of cortisol released during the stress response, creating a stress-response system that is over-responsive to stimuli throughout the life course.[14,15] In terms of reproduction, while most women will have no difficulty conceiving, given the same environmental and genetic circumstances, some women may experience infertility as a result of an overactive stress response.

It has been suggested that, because the HPA-system does not discriminate against types of stressors, all stress, at any point in the life span, is bad for fertility.[40] Generally, we found that only the experience of multiple stressful events influenced infertility, but our sample population was relatively young (~27 years at final survey), so it is possible that the effect could be amplified as the sample ages. In terms of timing, our results indicate slightly higher odds of infertility for events experienced prior to the age of 12, as compared to those experienced in other time periods, which could signify a developmental impact, as hypothesized by the critical/sensitive periods model of life course theory. Alternatively, stronger associations between childhood events and infertility could suggest the occurrence of a lag period between the experience of events and reproductive dysfunction. This result did not remain consistent in the dichotomous results, which implies that timing has little influence, if any, on reproductive function. However, it is important to note that respondents could only select a maximum of three

SLEs prior to the age of 12 (compared to 10 in each of the other age groups, 12-18 and 19-23), which may make the dichotomous variable a less sensitive measure of the timing effect.

Having "problems getting pregnant" was significantly associated with the experience of 4 or more SLEs, and though the magnitude of the association was consistent, it did not remain significant across models. While our results did not maintain significance across both definitions used to define infertility, we speculate that "problems getting pregnant" may be too broad or subjective a concept to accurately represent clinical infertility.[25] Some women may equate "problems" with recognizable medical dysfunction and not the length of time spent trying to conceive. The acceptable length of time trying to conceive may vary between women, but the length of time associated with clinical infertility is 12 months, which has been associated with current and chronic health morbidities.[2] Thus, disparate results between infertility definitions in this investigation may suggest that some women may be unaware of the clinical definition that would indicate a "problem" getting pregnant, which could lead to delays in seeking medical advice. Because infertility has been associated with a number of chronic health conditions, seeking medical advice early could be critical to identification of underlying physiologic dysfunction that contributes to both infertility and future morbidities.

The results of this study are consistent with two of only three other studies conducted to-date to empirically test the link between lifetime stressors and indicators of infertility.[19–21] Santos and colleagues found no difference in experience of lifetime stressors between cases of infertility and controls.[19] However, cases were identified by diagnoses from medical records in a fertility clinic, and controls had unknown fertility status, as they self-reported fertility, but had no children. In addition, this study relies on a diagnosis of infertility, which may be limited given issues related to access and infertility diagnosis and treatment (i.e., one may not seek a diagnosis

if they do not have the means to access treatment). For example, the National Survey of Family Growth indicates that women who access fertility services are more likely to be non-Hispanic white than other ethnicities and have high education and income levels.[41] Another study that recruited women from a fertility clinic reported that chronic stress was associated with diminished ovarian reserve, but the only validated measure of stress included in the study was reported family history of abuse.[20] Finally, our results are consistent with Jacobs et al,[21] who found that four or more reports of adverse childhood experiences (ACEs) were associated with lower fecundability, assessed using self-reported time to pregnancy, and higher risk for amenorrhea and fertility difficulties. To our knowledge, this is the only study of lifetime experiences of stress and infertility to recruit women outside of the setting of a fertility clinic, though generalizability is limited to a slightly more fertile population, as participants were recruited from WIC offices and OB/GYN clinics. However, this study collected all measures retrospectively and fertility difficulties were defined as an inability to get pregnant or interaction with the healthcare system to try to get pregnant.[21]

One strength of the current study was that data were collected longitudinally, so we can be assured that stressful life events occurred prior to the experience of infertility. Second, respondents were surveyed about SLEs within five years of their occurrence, which reduces the recall bias associated with remembering stressors in childhood or adolescence as an adult. Furthermore, the NLSY is a nationally-representative survey, which makes our findings more generalizable than other infertility studies. This study also includes a broader definition of infertility than previous studies of women seeking fertility treatment, to capture women who may not have sought such a diagnosis or treatment.

Our study should also be viewed in light of its limitations. First, we were unable to assess all SLEs included on Brugha's inventory (e.g., death of close friend, conflict with close friend, etc.), as they were not included in NLSY interviews. This means we could be missing some key experiences that might influence later health. Moreover, the few SLEs included in the interview prior to the age of 12 limits our ability to draw inference on the timing of events and reproductive function. Altogether, the limited number of possible SLEs available in the dataset may have attenuated our results. Second, as a survey reliant on respondent reports, there may be recall bias in remembering length of time trying to conceive, though the window of recall is shorter given that the questions were asked prospectively. This has been shown to be relatively reliable, with higher reliability for interviews.[42] Third, the wording of the question associated with clinical infertility assumes that all respondents tried to conceive at regular intervals during this time. It is impossible to account for time spent away from the partner or for other events that may have limited intimacy in any given month during the 12 or more months that respondents reported trying to conceive. However, it is unclear whether respondents would have counted this time in their response or not and the measure of clinical infertility appeared consistent with other known risk factors (e.g., parity and BMI). Finally, respondents were relatively young at the time they reported infertility, with an average age of ~27 years. Fertility decreases with age, with the most notable decline occurring after the age of 35,[43] which could have limited the prevalence of infertility in our sample. However the prevalence was higher in our sample than other U.S. estimates (24% vs. 16%), though similar to estimates from a study conducted in France that assessed general fecundity and did not limit to those trying to conceive.[44,45] This could further indicate some lack of precision in assessing pregnancy intent, but intent may be irrelevant if couples are not using contraception for 12 months and do not achieve pregnancy—women in this

group may still be at higher risk for poor health outcomes than women who unintentionally conceive within a 12-month period.

The overall implication of our findings is that stressful events in early life may influence reproductive health. More research should be conducted to elucidate the pathways linking stress to infertility, which may also influence overall health status and future chronic diseases. Given that adverse reproductive function may act as an early marker for intervention to improve later life health outcomes, this study highlights a potential mechanism to highlight a shared pathway between infertility and other health outcomes and indicates that the timing of these interventions may need to occur prior to reaching young adulthood. Future interventions should empower parents to increase parental responsiveness, while also teaching skills to adolescents and young adults to cope with stress to mitigate the harm of stressful life events.

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**Tables and Figures**

**Table 6.1. Demographic characteristics of women included in analysis from the National Longitudinal Survey of Youth, 1997 cohort, weighted (*n*=1652)**

| | Total | Clinical infertility | No infertility | Problem getting pregnant | No problem getting pregnant |
|---|---|---|---|---|---|
| Mean stressful life events (sd) | | | | | |
| Total, all ages*^ | 2.44 (0.03) | 2.95 (0.07) | 2.49 (0.04) | 2.86 (0.15) | 2.53 (0.06) |
| Age < 12 years* | 0.43 (0.01) | 0.45 (0.02) | 0.37 (0.02) | 0.41 (0.04) | 0.39 (0.02) |
| Age 12-18 years* | 1.11 (0.02) | 1.26 (0.04) | 1.08 (0.03) | 1.25 (0.09) | 1.06 (0.04) |
| Age 19-23 years* | 1.10 (0.01) | 1.35 (0.05) | 1.15 (0.02) | 1.29 (0.08) | 1.23 (0.03) |
| Race/Ethnicity* | | | | | |
| Non-Black/Non-Hispanic | 69.90% | 65.56% | 71.39% | 72.92% | 70.34% |
| Non-Hispanic Black | 16.23% | 18.43% | 15.47% | 13.46% | 15.51% |
| Hispanic | 12.58% | 14.30% | 12.00% | 11.63% | 12.65% |
| Multiple Races (Non-Hispanic) | 1.28% | 1.71% | 1.14% | 1.99% | 1.50% |
| Income to poverty ratio (IPR)* | | | | | |
| Mean (sd) | 3.20 (0.07) | 2.70 (0.10) | 3.28 (0.09) | 2.79 (0.16) | 2.97 (0.11) |
| Number of biological siblings* | | | | | |
| Mean (sd) | 1.28 (0.02) | 1.16 (0.04) | 1.31 (0.03) | 1.24 (0.08) | 1.27 (0.04) |
| Physical Environment Risk* | | | | | |
| 0 risks | 44.04% | 34.05% | 47.02% | 31.09% | 43.21% |
| 1-2 risks | 40.18% | 46.46% | 38.31% | 54.27% | 40.81% |
| 3+ risks | 15.78% | 19.49% | 14.67% | 14.64% | 15.98% |
| Substance use* | | | | | |
| Mean (sd) | 4.44 (0.05) | 5.24 (0.14) | 4.42 (0.10) | 5.07 (0.22) | 4.92 (0.11) |
| BMI*^ | | | | | |
| Mean (sd) | 21.70 (0.06) | 22.15 (0.17) | 21.27 (0.09) | 22.21 (0.26) | 21.42 (0.16) |
| Maternal Responsiveness* | | | | | |
| High responsiveness | 74.88% | 69.53% | 76.49% | 73.22% | 74.86% |
| Low responsiveness | 25.12% | 30.47% | 23.51% | 26.78% | 25.14% |

*Indicates significant difference in t test or Rao-Scott chi square for clinical infertility vs. not; ^Indicates significant difference in t test or Rao-Scot chi square for problems getting pregnant vs. not

**Table 6.2. Adjusted odds ratios for the association between stressful life events and clinical infertility (n=1652)**

| | Model 1 (Unadjusted) | Model 2 (Demographics) | Model 3 (Demographics+ environ) | Model 4 (Demo, Env, behavioral)[1] |
|---|---|---|---|---|
| Total stressful life events | | | | |
| 0-1 | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| 2 | 1.21 (0.99, 1.47) | **1.30 (1.04, 1.63)** | 1.21 (0.90, 1.64) | 1.13 (0.82, 1.55) |
| 3 | **1.43 (1.15, 1.76)** | **1.60 (1.27, 2.03)** | **1.68 (1.16, 2.42)** | **1.58 (1.09, 2.29)** |
| 4+ | **1.86 (1.55, 2.23)** | **2.02 (1.66, 2.47)** | **1.88 (1.38, 2.57)** | **1.81 (1.29, 2.56)** |
| Race/Ethnicity | | | | |
| Non-Black/Non-Hispanic | | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Non-Hispanic Black | | 1.06 (0.83, 1.36) | 1.22 (0.88, 1.68) | 1.37 (0.98, 1.90) |
| Hispanic | | 1.14 (0.90, 1.43) | 1.18 (0.87, 1.59) | 1.20 (0.87, 1.64) |
| Multiple Races (Non-Hispanic) | | **2.69 (1.40, 5.15)** | 1.09 (0.41, 2.87) | 1.42 (0.54, 3.78) |
| Income to poverty ratio (IPR) | | **0.94 (0.91, 0.98)** | **0.92 (0.87, 0.98)** | **0.93 (0.87, 0.99)** |
| Number of biological siblings | | | **0.87 (0.79, 0.96)** | 0.91 (0.82, 1.00) |
| Physical Environment Risk* | | | | |
| 0 risks | | | 1.0 (Reference) | 1.0 (Reference) |
| 1-2 risks | | | **1.45 (1.11, 1.91)** | 1.31 (0.97, 1.76) |
| 3+ risks | | | 1.32 (0.88, 1.96) | 1.22 (0.81, 1.83) |
| Substance use | | | | |
| ≤mean (4.44) | | | | 1.0 (Reference) |
| >mean (4.44) | | | | **1.33 (1.04, 1.68)** |
| BMI | | | | **1.04 (1.01, 1.07)** |

[1]Model 4 included only 1,525 respondents with complete information on additional covariates

**Table 6.3. Adjusted odds ratios for the association between stressful life events and reported problems getting pregnant (n=1652)**

| | Model 1 (Unadjusted) | Model 2 (Demographics) | Model 3 (Demographics+ environ) | Model 4 (Demo, Env, behavioral) |
|---|---|---|---|---|
| Total stressful life events | | | | |
| 0-1 | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| 2 | 1.27 (0.86, 1.88) | 1.35 (0.89, 2.04) | 1.73 (0.94, 3.17) | 1.69 (0.91, 3.13) |
| 3 | 1.41 (0.93, 2.13) | 1.44 (0.88, 2.35) | 1.42 (0.74, 2.72) | 1.12 (0.58, 2.17) |
| 4+ | **1.57 (1.10, 2.24)** | **2.01 (1.31, 3.08)** | 1.44 (0.76, 2.73) | 1.19 (0.61, 2.30) |
| Race/Ethnicity | | | | |
| Non-Black/Non-Hispanic | | 1.0 (Reference) | 1.0 (Reference) | 1.0 (Reference) |
| Non-Hispanic Black | | 0.71 (0.47, 1.07) | 0.70 (0.41, 1.20) | 0.70 (0.38, 1.30) |
| Hispanic | | 0.94 (0.64, 1.38) | 0.78 (0.44, 1.39) | 0.66 (0.35, 1.27) |
| Multiple Races (Non-Hispanic) | | 2.11 (0.80, 5.58) | 1.76 (0.35, 8.94) | 1.71 (0.33, 8.97) |
| Income to poverty ratio (IPR) | | 0.98 (0.91 (1.06) | 0.93 (0.82, 1.06) | 0.96 (0.86, 1.08) |
| Number of biological siblings | | | 0.90 (0.76, 1.06) | 0.95 (0.80, 1.12) |
| Physical Environment Risk | | | | |
| 0 risks | | | 1.0 (Reference) | 1.0 (Reference) |
| 1-2 risks | | | **1.86 (1.12, 3.10)** | **1.86 (1.08, 3.20)** |
| 3+ risks | | | 1.44 (0.76, 2.73) | 1.21 (0.54, 2.71) |
| Substance use | | | | |
| ≤mean (4.44) | | | | 1.0 (Reference) |
| >mean (4.44) | | | | 1.34 (0.89, 2.01) |
| BMI | | | | **1.07 (1.02, 1.12)** |

**Table 6.4. Adjusted odds ratios for timing of stressful life events (SLEs) and clinical infertility**

| | | |
|---|---|---|
| SLEs, dichotomous measure | | |
| <age 12 | | |
| | No SLEs | 1.0 (Reference) |
| | Any SLE | **1.25 (1.01, 1.54)** |
| Ages 12-18 | | |
| | No SLEs | 1.0 (Reference) |
| | Any SLE | 1.27 (0.99, 1.62) |
| Ages 19-23 | | |
| | No SLEs | 1.0 (Reference) |
| | Any SLE | **1.33 (1.04, 1.71)** |
| SLEs, continuous measure | | |
| <age 12 | | **1.21 (1.05, 1.40)** |
| Ages 12-18 | | **1.10 (1.01, 1.21)** |
| Ages 19-23 | | **1.15 (1.03, 1.28)** |

*Adjusted for race/ethnicity, income to poverty ratio, number of biological siblings, and physical environment risk

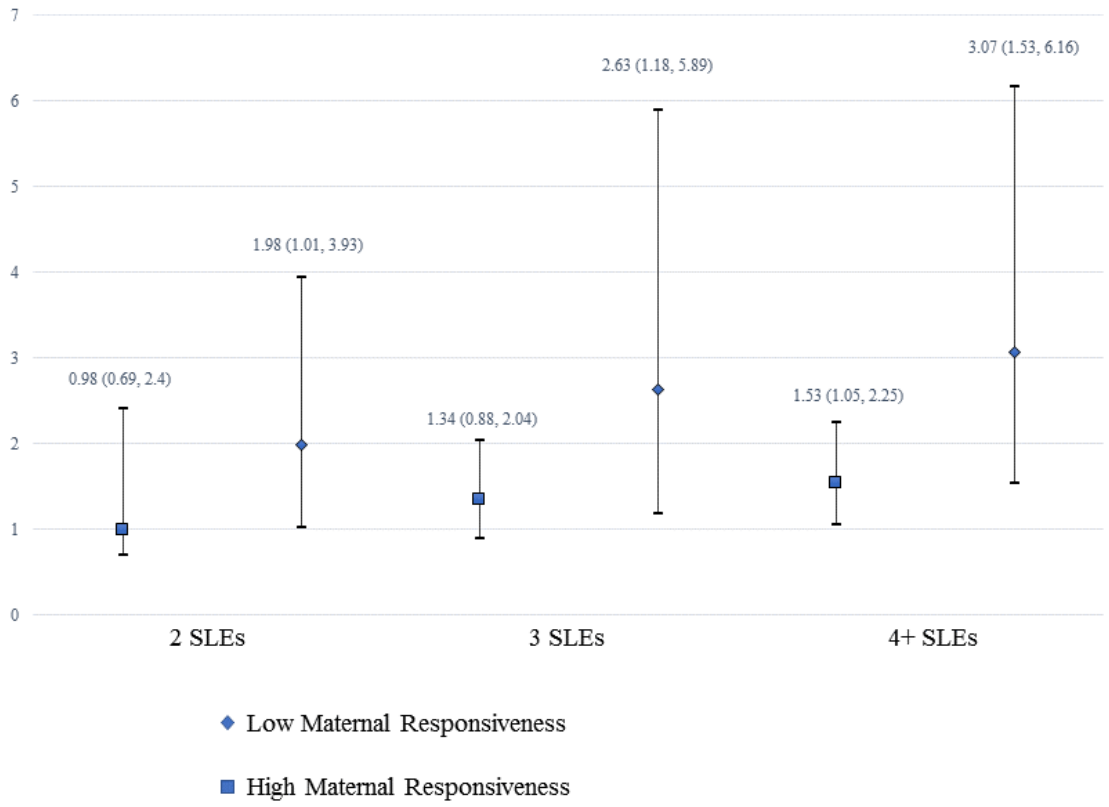


**Figure 6.1. Adjusted odds ratios with 95% confidence intervals for the association between stressful life events (SLEs) and infertility (clinical), moderated by high or low maternal responsiveness**

# Chapter 7: Conclusion

## Summary

The literature review conducted as part of this investigation was the first to provide a comprehensive review of English language literature examining psychosocial factors as precipitants to infertility. Moreover, it was the first to examine this connection outside of the context of pregnancy outcomes that followed intervention with assisted reproductive technologies. Relatively few published studies have tested the hypothesis that stress, anxiety, or depression may influence reproductive health and infertility. The methodology of all but three studies limits the ability of researchers to draw inference regarding the temporality or strength of these associations, highlighting the need for more research in this field.

While unable to directly assess the impact of stress on infertility and later life health, Study 2 investigated biomarkers of reproductive aging to explore the association between infertility diagnoses and biomarkers of aging and inflammation, telomere length and C-reactive protein (CRP). Women with endometriosis were more than twice as likely to have high CRP, which consequently increases their risk of future cardiovascular morbidity. There was an association between endometriosis and telomere attrition for age-adjusted models, though this result did not remain significant when adjusted for other factors. However, for women diagnosed with endometriosis, each year of diagnosis was associated with a 1% decrease in telomere length. Depending on the estimate used for average telomere attrition for each year of age, this equated to 0.59 to 1.3 years of excess aging. To put this into context, a woman diagnosed with endometriosis for 10 years could

have a cellular age that is 5.9 to 13 years older than women in their first year of diagnosis. Additionally, black women with endometriosis had telomeres that were 13% shorter than those without endometriosis. There were no associations between either biomarker and uterine fibroids, which may reflect the differential etiology and impact of this condition compared to endometriosis.

Finally, after conducting the first prospectively longitudinal, nationally-representative investigation in this field, the results of Study 3 revealed that SLEs that occurred prior to the age of 23 were associated with higher odds of infertility. This association varied by maternal responsiveness, such that women with low maternal responsiveness had increasingly higher odds of infertility as the number of SLEs increased. For women with high maternal responsiveness in adolescence, only those reporting four or more SLEs had higher odds of infertility, and this higher risk was still half that of women with low responsiveness. In assessing the timing of SLEs, women experiencing SLEs prior to the age of 12 had the highest odds of reporting later infertility, though there was little difference between age categories.

**Limitations**

Specific limitations of each study have been discussed for each study under its corresponding chapter, but there are a few overall limitations. Stress is a challenging construct to measure, and this investigation relied on existing datasets containing information on both stress and infertility. Thus, there were limitations in measuring stress from the onset of these studies, since stress assessment was confined to the questions and measures deemed relevant to the creators of NHANES and NLSY-97, and in

consideration of minimizing respondent burden. For Study 2, though it could be argued that both abnormal telomere attrition and elevated CRP may be proxies for stress, this study was not able to directly assess stress or draw inference related to its associations with infertility-related conditions. However, by providing evidence of associations between endometriosis and both telomere attrition and elevated CRP, Study 2 contributes to the literature describing shared pathways between reproductive and overall health.

Study 3 included a more robust measure of stress, in the form of a validated inventory of SLEs. However, only 10 of the 13 questions from Brugha's List of Threatening Events was included in NLSY-97, and there was no rationale provided for the selection of SLEs outside of the events being considered "out of the ordinary stressors." Furthermore, all questions were not available for all time periods (i.e., <12 years), which limited conclusions that could be made regarding the impact of the timing of SLEs on infertility. Inventories are widely used to assess stress, and there does not appear to be consensus on which one is "best," other than to suggest that inventories should all contain certain events, such as the death of a family member or being the victim of physical or sexual assault.[1] In this context, Study 3 provides an accurate measure of stress—especially when compared to similar studies that include fewer,[2] and unvalidated, measures of stress.[3]

Finally, these investigations do little to advance understanding of racial and ethnic disparities in infertility, other than to highlight the general lack of studies published to explore these differences. While Study 2 does illuminate significant telomere attrition among non-Hispanic black women with endometriosis, it was not possible to conduct meaningful analyses related to racial and ethnic differences in Study 3, due to

racial/ethnic classification in NLSY-97. Participants were identified as Hispanic, non-Hispanic black, non-Hispanic/non-Black, or other, making these latter categories too heterogeneous to be able to draw meaningful inference. Future investigations could, however, examine differences and trends among Hispanic and non-Hispanic black women.

**Implications**

The findings of this investigation provide evidence that infertility may be a marker of biologic wear and tear, and that early stressors, as well as the accumulation of stressors, increase the risk of experiencing infertility. These findings are supported by the body of literature available in this field, which was critically reviewed as part of this investigation. Taken together, the existing literature and the results of the current research studies suggest that infertility is not a phenomenon isolated to the physiology of the reproductive system, but that it is a complex, multifactorial syndrome. It may be the result of a cascade of events that begin with external stressors that alter physiologic functioning on a molecular and systemic level, eventually manifesting as reproductive dysfunction. When considering infertility as a syndrome that is indicative of this physiologic upheaval, it makes sense that infertility has been associated with chronic health conditions.[4,5] The challenge becomes deriving public health strategies to approach this issue.

While this investigation highlights the links between stress and infertility, it is critical to view this association in the context of the larger implication of infertility as a marker of overall health. One implication of this research is that mitigating stress could

prevent infertility, but in a broader sense, this research highlights that stress may be what is influencing both reproductive and overall health. Stress is an unavoidable part of modern life, but exposure to stress does not invoke long-term physiologic change on its own. As described previously, stressors invoke a physiologic response, and it is that response that is targeted by stress reduction interventions.[6] Essentially, if individuals can modify their reactions to stress, as is the goal of mindfulness and other stress-reduction techniques, they may be able to mitigate the harm of chronic perturbation of stress-response axes by returning to homeostasis more quickly, thus preventing lengthy allostasis and the accumulation of allostatic load.[7] This may be an unrealistic approach restricted to those who have the time and inclination to learn stress reduction techniques, but if these techniques were incorporated into elementary school curriculum at an early age, they may become as prolific in everyday life as knowledge of writing and simple mathematic principles. Perhaps the normalization of these techniques could lead to a new generation of individuals with a higher adaptive capacity when confronted with stressors.

Though more research is required on the effectiveness of stress reduction techniques, and large-scale implementation may be unfeasible, the results of this investigation do indicate that early intervention is key when exposed to stress. Interventions to increase parental responsiveness are already important across disciplines.[8–10] This investigation supports their importance in the context of mitigating harms associated with stressors to prevent future morbidities, like reproductive dysfunction.

Future investigations should explore the specific physiologic changes invoked by the stress response that may link reproductive health to later life health conditions.

Investigations into epigenetic mechanisms could reveal gene therapies that alter the stress response to mitigate the harms associated with chronic stress. For example, in rodents, researchers have found that silencing a particular gene prevents stress-induced infertility.[11] The human genome is much more complex than that of mice, and this type of therapy could include unintended consequences on human health, but gene therapies remain a prolific field of research and this could be an innovative approach to addressing the deleterious impacts of chronic stress.

In the more recent future, investigators should also examine structural factors in childhood and adolescence that may influence fertility, such as neighborhood poverty, racism, and other inequalities that may contribute to poor health outcomes in general. For example, black women have been reported to experience infertility at a higher rate than white women, but existing literature has not explored this phenomenon.[12] Furthermore, while poverty has been studied in relation to infertility in developing countries, it has typically been approached as a consequence of infertility.[13] Few studies have examined the effect of neighborhood poverty or residential racial segregation in the United States, and none have done so on a national-level.[14]

It is difficult to establish causality in public health, particularly when exposures may occur long before their outcomes, as in the case of early life stress and adult infertility. However, the only way to establish causal links is to continue to investigate and innovate new ways of addressing the problem. While this investigation is a small, but notable contribution to the research likely to emerge in this field over the next several years, its findings should spark new research and conversations surrounding stress and infertility and their complex associations with the overall health of women.

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# Appendix A: Figures (Chapters 2-3)

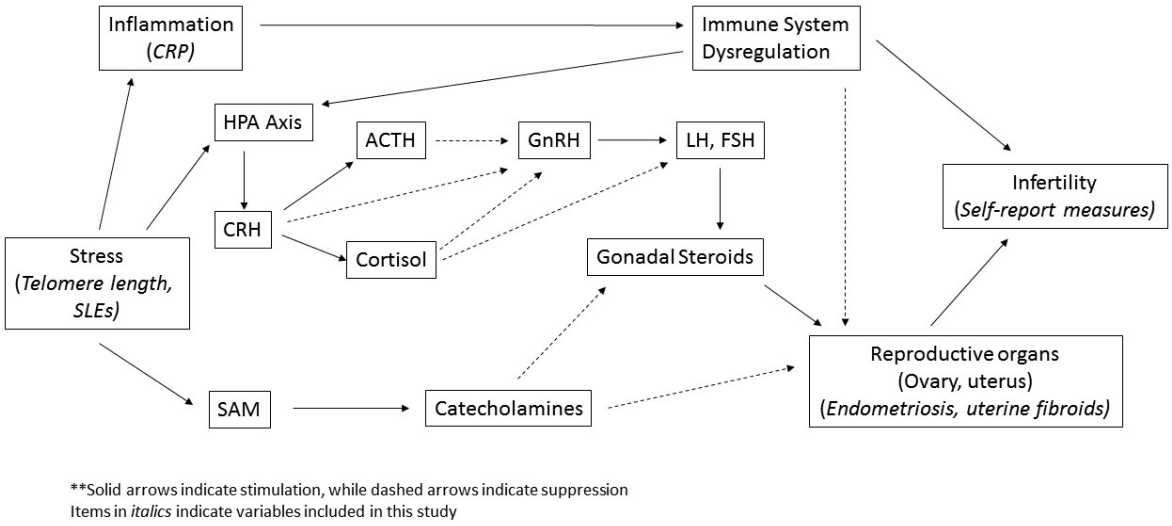


**Figure 2.1. Heuristic of biological processes activated by stress**

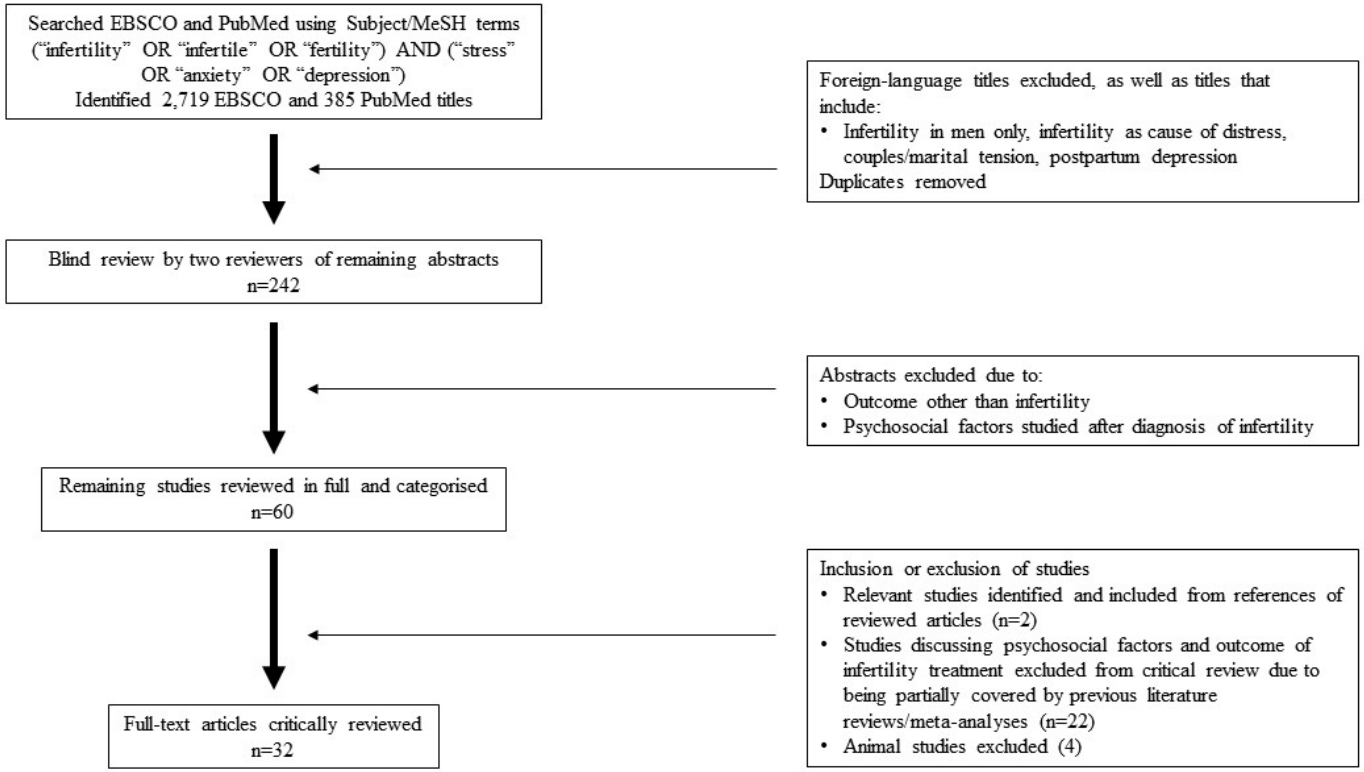


**Figure 3.1. Schematic of Article Selection**

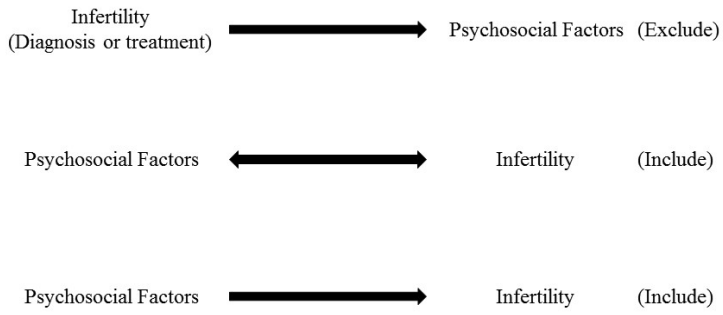


**Figure 3.2. Schematic of directional associations between stress and infertility included and excluded for review**

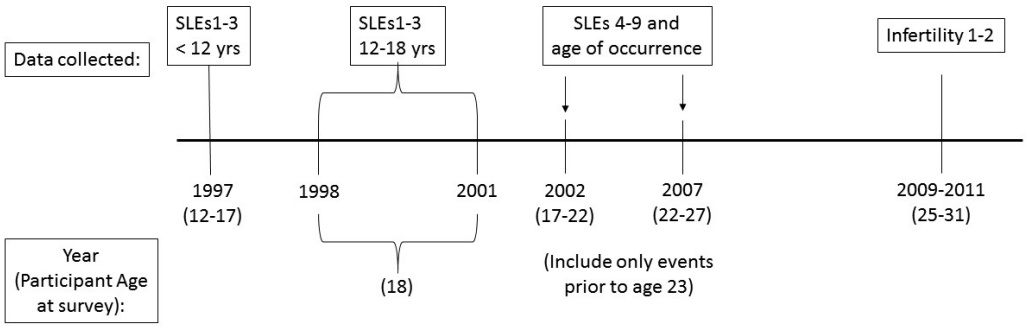


**Figure 3.3. Timeline of data collection in NLSY-97**

# Appendix B: Tables (Chapter 3)

**Table 3.1. Diagram of NLSY question timing and ages of respondents (main variables)**

| Survey Yr (Round #) | Respondent age range | Variable | Question Summary |
|---|---|---|---|
| 1997 (R1) | 12-17y | SLE1 | HOUSE OR APARTMENT BROKEN INTO < 12 YEARS OLD? |
| | | SLE2 | VICTIM OF REPEATED BULLYING <12 YEARS OLD? |
| | | SLE3 | EVER SEE SOMEONE SHOT OR GET SHOT AT WITH A GUN <12 YEARS OLD? |
| | | MR1 | MOTHER PRAISES R FOR DOING WELL |
| | | MR2 | MOTHER CRITICIZES R OR IDEAS |
| | | MR3 | MOTHER HELPS DO THINGS IMPORTANT TO R |
| | | MR4 | MOTHER BLAMES R FOR PROBLEMS |
| | | MR5 | MOTHER MAKES PLANS WITH R AND CANCELS |
| 1999 (R2) | 14-19y | SLE1* | HOUSE OR APARTMENT BROKEN INTO 12-18 YEARS? |
| | | SLE2* | VICTIM OF REPEATED BULLYING 12-18 YEARS? |
| | | SLE3* | EVER SEE SOMEONE SHOT OR GET SHOT AT WITH A GUN 12-18 YEARS? |
| 2002 (R6) | 17-22y | SLE4 | HAS R BEEN VICTIM OF A VIOLENT CRIME IN LAST 5 YEARS (HEALTH) |
| | | SLE5 | HAS R BEEN HOMELESS OR IN A SHELTER FOR 2+ NIGHTS IN LAST 5 YEARS |
| | | SLE6 | ANYONE IN R'S HOUSEHOLD BEEN HOSPITALIZED FOR 1 WK+ IN LAST 5 YEARS |
| | | SLE7 | HAS ANY ADULT MEMBER OF R'S HOUSEHOLD BEEN IN JAIL IN LAST 5 YEARS |
| | | SLE8 | HAS ANY ADULT MEMBER OF R'S HOUSEHOLD BEEN UNEMPLOYED 6+ MOS IN LAST 5 YRS |
| | | SLE9 | HAVE R'S PARENTS DIVORCED (EACH OTH OR SOMEONE ELSE) IN LAST 5 YRS |
| 2007 (R11) | 22-27y | SLE4-9 | |
| 2009 (R13) | 24-29y | Infert1 | EVER HAVE PROBLEMS GETTING PREGNANT OR HAVING A BABY? |
| | | Infert2 | R UNABLE TO CONCEIVE CHILD FOR 12 MONTHS |
| 2010 (R14) | 25-30y | Infert1-2 | |
| 2011 (R14) | 26-31y | Infert1-2 | |

*Questions repeated in each round between 1999-2001 (Round 2-5) for respondents aged 18+

# Glossary

| Term | Definition |
|---|---|
| ART | Assisted reproductive technology; medical procedures conducted to aid conception (e.g., in vitro fertilization) |
| Fecundability | Probability of being pregnant in any single menstrual cycle |
| HPA-axis | Hypothalamic-Pituitary-Adrenal axis; regulates the stress response, releasing cortisol in response to acute or chronic stressors |
| Murine | Referring to, or related to mice or similar rodents |
| Oocyte | Ovarian cells that divide to form ova |
| PCOS | Polycystic ovarian syndrome; hormonal disorder linked to infertility |
| SAM | Sympatho-adrenal-medullary system; regulates the acute stress response through the release of catecholamines, epinephrine and norepinephrine; can remain active under conditions of chronic stress |
| Unexplained infertility | Infertility for which there is no diagnosable anatomic or hormonal cause |

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