In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the World Wide Web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Friedrich A. Wieser Date November 1, 2012

Abuse in Childhood and Risk of Endometriosis

By

Friedrich Wieser

Master of Science Clinical Research

_____

Robert N. Taylor, MD PhD

Co-Advisor

_____

Amita Manatunga, PhD

Committee Member

_____

John McGowan Jr., MD

Committee Member

Accepted:

_____

Lisa A. Tedesco, PhD

Dean of the James T. Laney School of Graduate Sciences

_____

Date

Abuse in Childhood and Risk of Endometriosis

By

Friedrich A. Wieser, MD

University of Vienna School of Medicine, 1993

Advisors: Robert N. Taylor, MD, PhD

An abstract of

A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research

2012

ABSTRACT

Abuse in Childhood and Risk of Endometriosis

By Friedrich Wieser

***Objective*:** Evidence from epidemiologic studies suggests that early trauma is associated with diseases of the reproductive tract. The aims of this study are to examine the association of physical and sexual abuse occurring in childhood or adolescence and risk of endometriosis.

Methods: I used data collected from the Nurses' Health Study II (NHS II). The NHS II is a prospective cohort study of US nurses aged 25 - 42 at enrollment in 1989. The Nurses' Health study began in September 1989 with a sample of 116,678 registered female nurses from 14 US states. Premenopausal women aged 25 - 42 years at enrollment (1989) filled out questionnaires every two years including a retrospective questionnaire on childhood violence exposure (2001). Multivariable Cox proportional hazards models were applied to calculate relative risks (RR) and 95% confidence intervals (CI).

Results: A total of 60,410 women contributed 766,014 person-years through 2007, among whom there were 1968 incident premenopausal cases of laparoscopically-confirmed endometriosis. 65% of women in the cohort reported at least one abuse exposure. After adjusting for potential confounders, I observed a statistically significant dose-response association between abuse and endometriosis. Compared to those with no reported abuse events (emotional, physical, or sexual), there was a 13% greater risk of endometriosis for women reporting one episode of mild/moderate abuse (CI=1.02-1.26), RR=1.16 (CI=1.01-1.34) for multiple mild events or one severe episode of abuse, RR=1.33 (CI=1.12-1.57) for chronic moderate abuse of a single type, RR=1.34 (CI=1.03-1.27) for chronic severe abuse of a single type, and over a 2-fold increase in risk for those with chronic severe abuse of multiple types (RR=2.09,CI=1.60-2.73) (test for linear trend $p<0.0001$). Associations were stronger among those who never reported infertility.

***Conclusion*:** Severity and chronicity of child/adolescent sexual and physical abuse was associated with greater risk of endometriosis. Understanding the mechanisms underlying these relations may shed light on the pathophysiology and potential treatment and prevention of endometriosis.

Abuse in Childhood and Risk of Endometriosis

By

Friedrich Wieser, MD

Vienna University School of Medicine, 1993

Advisor: Robert N. Taylor, MD, PhD

A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research

2012

ACKNOWLEDGEMENTS

I would like to express my gratitude for the many individuals who have helped me complete the study and research involved in this project. Foremost, I wish to sincerely thank Dr. Robert Taylor for his mentorship. I also would like to thank Dr. Stacey Missmer and members of her research team including Allison Vitonis, M.S., and all the staff of the Nurse Health Study II for their patience, guidance, and support that allowed me to carry out this research. I am grateful to the participants of the Nurses' Health Study II. I would also like to thank everyone in the MSCR program, including Cheryl Sroka and Amanda Brzozowksi and all of the outstanding MSCR instructors. I am also grateful to the faculty and Executive Committee of the Master of Science in Clinical Research for their dedicated teaching throughout the program. Finally, I would like to thank the Atlanta Clinical and Translational Science Institute (Grant No. ULRR025008) and the National Institutes of Health (Grant No. HD52473, HD57210) for the support of this project.

TABLE OF CONTENTS

INTRODUCTION

Endometriosis affects about 10% of all reproductive-aged women and is one of the most common causes of pelvic pain and infertility [1]. Endometriosis is determined by genetic factors and environmental influences [2-4]. The etiology of endometriosis depends on a delicate interaction of genetic factors and environmental factors including psychological factors [2, 3, 5, 6 2]. The gene-environment interaction contributes to local inflammatory responses in the uterine and peritoneal cavity [2]. Retrograde endometrial spilling and a subconsequent peritoneal inflammatory response is thought to play a pivotal role in the establishment and maintenance of endometriosis [7].

Studies about the heritability of endometriosis showing that surgically confirmed disease occurs about 10 times more commonly in the first-degree relatives of affected women compared to controls. These findings led to the search for genetic factors in the disease [3, 8]. The exploration of candidate genes is partly a futile approach mainly due to low power of studies [3]. More current strategies utilizes a genome wide analysis (GWAS) data approach via investigating several large population-based prospective study populations (e.g., Nurses' Health Study II) [4, 5, 9 10]. For example, Painter et al., discovered a locus on chromosome seven (7p15.2) that is significantly associated with the risk of endometriosis in women of European ancestry [10]. This report corroborated other findings of an association for SNPs close to the *WNT4* locus [10].

Reproductive risk factors for endometriosis such as cycle length, and nulliparity have been reported and established as risk factors through epidemiologic studies [11, 12]. A cadre of other environmental factors such as nutritional factors (e.g., caffeine intake),

physical activity, body mass index (BMI) may be also associated with endometriosis [5, 6, 11, 13-19].

Numerous reports in the literature suggest the involvement of stress in the pathophysiology and clinical presentation of pain syndromes including chronic pelvic pain, inflammatory bowel syndrome, fibromyalgia, and chronic fatigue syndrome (CFS)[20-27]. Violence against women is a major cause of stress and is a major public health issue. Healthy people objectives and health care providers such as the American Medical Association and American College of Obstetricians and Gynecologist identify violence against women as a major problem. Data from national samples approximate that between 10 and 30% of women report history of physical and sexual abuse during childhood or adolescence. Physical and reproductive health outcomes for abused girls are more likely to be worse. Victims of child sexual abuse experience significantly more health complaints than comparison groups [28]. A strong association between sexual abuse during childhood and chronic pelvic pain has been reported [29, 30]. In particular, women with chronic pelvic pain reported higher rates of sexual abuse during childhood than women without chronic pelvic pain. However, major limitations of these studies investigating the association of child abuse and health outcomes are methodological factors including small sample sizes.

To investigate the hypothesis that women who experienced abuse during childhood are at greater risk of endometriosis, I utilized data from the Nurses' Health Study II (NHSII), a large prospective cohort that began in 1989 when 116,678 female nurses were enrolled. The aim of this study was to examine the relations between

physical and sexual abuse occurring in childhood or adolescence and risk of endometriosis.

Within this large cohort that has been followed for more than 20 years, the wealth of data allows for time-varying adjustment for potential confounders and test for heterogeneity to evaluate potential effect modifiers to more finely elucidate the independent effect of childhood abuse on the rate of endometriosis diagnosis.

BACKGROUND

Endometriosis is a gynecologic disease defined as the growth of endometrial glands and stroma outside the uterine cavity. The implantation hypothesis is the most widely accepted [31], supported by observations that retrograde menstruation and intraperitoneal spillage of viable endometrial cells occur frequently in cycling women and more commonly in those with genital outflow tract obstruction [32-34]. All women experience retrograde menstruation[32] however, increased exposure to menstrual flow (reduced parity, long duration of menstrual flow or short cycle interval, early menarche, late perimenopause) have been identified as risk factors for endometriosis [35]. The mode of hereditary transmission is complex and likely multifactorial [36]. Several associations have been reported for candidate genes, which have selected for their biological plausibility including genes governing cancer susceptibility, hormone sensitivity and the immune system [2, 10, 37-43].

Some investigators propose that microscopic peritoneal defects allow the endometrial cells that have been spilled into the peritoneal cavity to contact the submesothelial matrix, where they proliferate and invade the subperitoneal space [44]. However, other authors demonstrated that endometrial fragments adhere directly to intact mesothelium [45]. Once established, endometriotic lesions are associated with local inflammation. An excessive number of leukocytes, (e.g., macrophages and T cells) [46, 47] have been identified in the peritoneal fluid surrounding the implants and within the lesions themselves [48, 49]. Several cytokines including the proinflammatory cytokines tumor necrosis factor (TNF)-alpha, Interleukin (IL)-1, and IL-6 produced by these leukocytes seem to play a role in pathogenesis of endometriosis [7, 50, 51]. The

proinflammatory cytokines are secreted by endometrium, endometriotic and mesothelial cells, and peritoneal macrophages [52, 53]. They have been shown to be increased at systemic (serum) and local levels (peritoneal fluid) of women with endometriosis and to be correlated with disease activity [54-57]. Proinflammatory cytokines are believed to contribute to the pathophysiology of endometriosis by enhancing attachment, persistence and progression of ectopic endometrial tissues in the pelvis [51, 53].

The Nuclear factor KappaB (NF-κB) pathway is involved in the induction of gene expression of several key proinflammatory, chemokine, and angiogenic genes. Key mediators such as tumor necrosis factor (TNF)-alpha, regulated on activation, normal T cell expressed and secreted (RANTES) and vascular endothelial growth factor (VEGF) that are produced by eutopic and ectopic endometriotic cells, and peritoneal macrophages themselves [40, 57-61] are under control of NF-κB. Hence, NF-κB, a key regulator of enhanced inflammatory and angiogenic responses in endometriosis is a potential target [58-60, 62, 63]. The inflammatory and angiogenic response observed in the eutopic endometrium and pelvic cavity of women with endometriosis is postulated to promote an environment that fuels the pathogenesis [7, 64-66]. Correspondingly, an important mechanisms of psychological stress is that is has been associated with increased plasma cytokine responses [67], as well as activation of nuclear factor NF-κB [68]. Pace et al., showed that an enhanced inflammatory system activity in participants with childhood abuse-related posttraumatic stress disorder (PTSD) is observable at the level of NF-κB, a lynchpin in the inflammatory signaling cascade in endometriosis [69].

Classically, the hallmarks of endometriosis are infertility and chronic pain [70, 71]. Pain symptoms in women with endometriosis are dysmenorrhea (cramps or painful

menstruation), pelvic pain (non-menstrual intermittent or continuous pain in the pelvic area), and dyspareunia (pain during sexual intercourse, unassociated with vaginal dryness). These symptoms are non-specific and may also be found in patients without endometriosis. Diagnosis and treatment to ablate endometriotic lesions require costly, invasive surgery or medical approaches [72, 73]. These medical treatments are often of limited efficacy and counterproductive to fertility, and can cause untoward side effects due to suppression of endogenous steroid hormone levels. Side effects can include cessation of the reproductive cycle, lipid alterations, hirsutism, thrombosis, postmenopausal symptoms, depression, and osteoporosis. As most therapeutic drugs cease menstrual cyclicity, they are counterproductive to fertility. Unfortunately, endometriosis cannot be cured by any known treatment. And regardless of treatment, endometriotic lesions rapidly and spontaneously recur, with reduced fecundity and ongoing pelvic pain [70].

Childhood adversity is unfortunately common in our society. According to the National Child Abuse and Neglect Data System, an estimated 896,000 children were reported to be victims in 2002. More than 60% of these children experienced neglect; 20% were physically abused, 10% were sexually abused; and 7% were emotionally maltreated. It was estimated that about 1,400 children died of abuse and/or neglect in in the U.S in 2002. Girls are more often victims of sexual abuse than boys; more than 85% of sexual abuse goes unreported. Numerous retrospective studies have assessed rates of self-reported early lifetime stress in adult samples. Rates of abuse vary as a function of definition of the events, survey tactics, and study reviewer population [74]. Briere & Elliott [75] conducted a mail survey in a community sample and found that 14.2%

of men and 32.2% of women reported sexual abuse before the age of 18 years. Rates of physical abuse were 22.2% for men and 19.5% for women. Twenty-one percent of the total sample had experienced both types and 37% had experienced either type of abuse. Gould et al. [76] reported similar rates for a primary care sample with 44% of subjects reporting any type of sexual, physical or emotional abuse and 22% reporting multiple types of abuse. This co-occurrence of multiple types of early lifetime stress is also common, particularly sexual and physical abuse. In this study, I will utilize the NHS II data set, where nurses haves been followed for more than 20 years and diagnosis of laparoscopically verified endometriosis was recorded [77] . The major objective of this study is to elucidate the independent effect of childhood abuse on the rate of laparoscopically verified endometriosis.

Following conventional distinctions of childhood and adolescence derived from developmental psychology, the age of 12 years as cut-off for differentiating childhood and adolescence abuse seems appropriate [78]. This age-cut is considered an approximation to the developmental stage of sexual maturation, i.e. menarche in girls. There is evidence that this age cut is clinically meaningful: Maercker et al. [79] reported that women who experienced trauma during child hood (before the age of 12 years) showed an increased risk for major depression; in addition, women who experienced trauma between 12 - 18 years more frequently developed PTSD. Traumatic experiences in different developmental phases seem to have different effects.

As for the stress criterion, prevailing models suggest that stress is generally experienced when an individual is confronted with personally threatening situations for which adequate coping resources are unavailable [80]. In addition, threats to

physiological homeostasis, such as injury or illness, elicit stress responses. Any such situation occurring within the defined developmental period may be classified as early life stress. Severity of abuse is not well defined and often judged by frequency, duration, degree of physical force or harm, and type of activity [81]. Various forms of early life stress comprise a whole cadre of situations (e.g., accidents, physical illness,). Less obvious experiences, that pose significant distress on a child, include unstable families, inadequate parental care, dysfunctional relationships between parent and child, and poverty. While early lifetime stress may be a single event, it more typically occurs as chronic or ongoing adversity.

Critical involvement of stress in the pathophysiology and clinical presentation of pain syndromes have been reported for chronic pelvic pain, inflammatory bowel syndrome, fibromyalgia, and chronic fatigue syndrome (CFS) [26, 27]. Endometriosis is associated with these pain syndromes including fibromyalgia, migraine, and CFS. Epidemiological studies have provided strong evidence that stress or emotional trauma is associated with increases in the risk to chronic pelvic pain, particularly when experienced early in life [82]. Rich-Edwards et al. found an association between the number of experienced childhood adversities (sexual abuse, physical abuse, or witnessing paternal violence) and general health problems in adulthood (e.g., type 2 diabetes) [83-86]. In a recent NHS II study, Boynton-Jarret et al. 2011 showed that severity and chronicity of child/teen sexual and physical abuse was associated with increasing risk of clinically detected fibroids [87]. Furthermore, lifetime maternal experiences of abuse lead to an increased risk of pre-natal depression in two demographically distinct populations in Boston, MA [88]. Growing up in an emotionally

adverse family environment accentuated the association between abuse/violence and general mental health problems such as chronic pelvic pain. An association between early trauma experience and endometriosis has been implicated, however has never been studied independently.

With regard to endometriosis, I postulate that persistent endocrine adaptations in response to early trauma might influence the implantation of endometrial cells on the peritoneal surface and the immunological activity of these cells and lead to increased incidence of endometriosis (Figure 1 and 2).

METHODS

Characteristics of Study Design

Cohort Study

Study population

I utilized data from the Nurse's Health Study (NHS) II. The NHS II is an ongoing prospective cohort study designed to explore factors that influence morbidity and mortality among women. The Nurses' Health study began in September 1989 and is comprised of a sample of more than 100,000 registered female nurses aged 25 - 44 years from 14 US states (n = 116,678). Study participants of this cohort have been contacted biennially with questionnaires regarding health behaviors and disease occurrences.

The study population for this analysis was restricted to women premenopausal with intact uteri in 1989 and who responded to the 2001 violence survey.

Outcome Variable

In 1993, the women were first asked if they had "ever had physician-diagnosed endometriosis as previously reported [77] [5, 6, 77]." As described previously in previous studies [5, 6, 16, 19], if "yes," they were asked to report when the diagnosis had occurred and if it had been confirmed by laparoscopy – a standard surgical method for diagnosing endometriosis [89, 90]. These questions were asked again in each subsequent questionnaire. As described previously [77] in March 1994 a study was conducted to

corroborate self-reported endometriosis diagnosis within the Nurses' Health Study II study population. For validation purposes, additional questionnaires were mailed to 200 women who were randomly selected among identified 1,766 endometriosis women who had reported incident diagnosis. A diagnosis of endometriosis was confirmed in 96%, among those who reported laparoscopic confirmation and for whom records were received and reviewed (n = 105), as described [77]. However, among women without laparoscopic confirmation (n = 26), evidence of clinical diagnosis was found in only 54% of the records [77]. Data showed that the majority of laparoscopically confirmed cases (61%) had minimal or mild disease in this representative subgroup of the NHS II cohort [77]. Requests for permission to review medical records were also sent to any woman who indicated that she had had a hysterectomy during the two-year interval. A diagnosis of endometriosis at the time of surgical procedure was confirmed in 80% of the records received (n = 144/181). Endometriosis was the primary indication for hysterectomy in only 6% (n = 9/163) of women for whom indication information was available. Self-reported physician-diagnosed endometriosis without laparoscopic confirmation is likely to be substantially misclassified based on these results. As reported [77], allowing women to be cases if they report a combination of endometriosis and a hysterectomy in the same follow-up period might yield specious results; in this context it would be unclear whether the associated risk factors are related to endometriosis or to the pathology for which the hysterectomy was performed [77]. A relation between violence and uterine fibroids risk has been noted within this population [87]. Therefore, to reduce the magnitude of misclassification and prevent confounding by

indication for hysterectomy, the analyses of incident diagnosis of endometriosis were restricted to those women who reported laparoscopic confirmation of their diagnosis.

Exposure assessment

A supplemental questionnaire on lifetime exposure to violence victimization was sent out to 91,248 study participants (excluding those who had previously requested short form surveys or who had required more than 4 mailings before responding to the 1999 questionnaire) in 2001 (Figure 3). Participants who did not respond received a reminder postcard. 68,505 questionnaires (a 75% response rate) were received. Overall, there were three prompts of sending out trauma questionnaire allowed by the IRB as approved by the Institutional Review Board at Brigham and Women's Hospital and the Human Subjects Committee at Harvard School of Public Health. Completion of the supplemental questionnaire indicated their consent to participate. 8059 women were excluded when they reported endometriosis at baseline (n = 3891), had cancer (n = 552), were postmenopausal (n = 948), had a hysterectomy (n = 1909), did not answer to the one of the main exposure variables (n = 553) or had unclear menopausal status (n = 242).

Assessment of Exposure to Violence During childhood and Adolescence

The questionnaire included assessment of physical and sexual abuse. Childhood and adolescent exposures to abuse were measured using items from the Childhood Trauma Questionnaire short form [91], the Revised Conflict Tactics Scale [92] and the Sexual Experience Survey [93], as described [87]. An adapted McFarlane Abuse Assessment

screen was employed to measure adult emotional, physical, and sexual abuse though an intimate partner [87, 94].

Childhood Trauma Questionnaire

The Childhood Trauma Questionnaire short form was used to evaluate exposure to physical, emotional, and verbal abuse during childhood (prior to age 11) [91]. A 3-item subscale on physical abuse was included and answered by the study members of the NHS II population, as described in the publication of Boynton-Jarret et al., [87] (e.g., "People in my family hit me so hard that it left me with bruises and marks," "The punishments I received seemed cruel," and "I was punished with a belt, a board, a cord, or some other hard object") and two items on emotional abuse (e.g., "People in my family said hurtful or insulting things to me" and "yelled and screamed at me") [87, 91].

Sexual and Physical Abuse

Five items from the Revised Conflict Tactics Scale instrument were used to assess exposure to physical abuse by a parent, step-parent, or adult guardian, as described [87, 92]. Respondents were queried about specific types of abuse for childhood (prior to age 11) and adolescence (11 - 17 years). These included physical attack, choke or burn, kick bite or punch, push or grab, and being hit with something that hurt as previously described [87, 92]; the frequency of each type of abuse was indicated on a 4 point scale (never, once, a few times, more than a few times), using the Revised Conflict Tactics Scales questionnaire that was described by Straus et al., and utilized by Boynton-Jarret et. al., [87, 92]. Questions on forced sexual experiences were modified from questions on

the Sexual Experiences Survey [93]. As described previously [87], study members of the NHS II population also rated the frequency of the following exposures on a 3-point scale (never, once, more than once): “were you ever touched in a sexual way” or “forced into any sexual activity” by an adult or an older child, separately for childhood and adolescence. Subjects also reported whether their parent(s) or guardians spanked them for discipline (up to age 11) (Table 1a) as previously described in the paper of Boynton et al., 2011 [87]. Categories that classify violence exposure by severity and chronicity were based on the factor analysis and frequency trends within each factor (Table 1b) [87]. As described in the publication by Boyton-Jarret et al.[87], a principle component factor analysis methodology with oblique (promax) rotation was used to capture a latent construct namely-cumulative violence exposure.

Analysis, Statistical Approach

Analysis was conducted using SAS 9.2 for Windows (©2008, Cary, NC). Descriptive analyses were conducted to explore the relationship between the demographic variables and difference categories of exposure to violence, using frequency distributions for categorical and dispersion parameters (mean, standard error or median, range where appropriate) for continuous variables. The referent group includes women who reported no violence in childhood or adolescence and women who reported spanking only. Women who reported only exposure to spanking for discipline were considered part of the referent group; spanking is considered to be theoretically and empirically (as measured by the factor analysis by Boynton-Jarret et al.,) [87] distinct from abuse.

Person-months of follow-up were counted from the date of return of the 1989 questionnaire (as early as September 1989), until report of laparoscopic confirmation of endometriosis, menopause, hysterectomy, cancer diagnosis (other than non-melanoma skin cancer), loss to follow-up, death, or until the date of return of the 2005 questionnaire (as late as July 2007). Person-months of follow-up were assigned to groups according to baseline exposure status. The incidence rates of endometriosis, confirmed by laparoscopy, for specific violence exposure categories were computed by dividing the number of events by the person-time at risk in that category.

Multivariable Cox proportional hazards regression models with time-varying covariates (including age, BMI, age at first birth, and parity) were used to estimate relative risk while controlling for potential confounders. By definition, the Cox model adjusts finely for age (months) and calendar time (months). Non-time varying covariates included race/ethnicity and parental education. The impact of multivariable adjustment for various factors was investigated. Known risk factors for endometriosis and factors were also previously associated with childhood violence, were explored as confounders. These risk factors were described by Missmer et al., and Vitonis et al., [5, 6, 12, 16, 19, 77] and included nulliparity (yes, no); age of menarche (<12, 12, 13, >13 years of age); cigarette smoking (never, past , current), age at menarche (<12, 12, 13, >13), oral contraceptive use (never, ever); parity (ever, nulliparous), lactation (0-<1, 0-18, >18) BMI (continuous measure in kg/m2); history of infertility (yes, no); menstrual cycle length (<26, 26 - 31, 32 - 50, 51+). I also included fibroids in the model in a subanalysis.

We also investigated the effects of fibroids on the association of physical and sexual abuse and endometriosis. In a subanalysis, we included fibroids in the multivariate cox proportional hazard regression model. Women reported fibroids in the following way as “ever uterine fibroids (yes/no)”, as previously described by Boynton et al., 2011 [87]. Fibroids were confirmed by ultrasound, as previously described [87].

I analyzed the association of abuse and endometriosis in the study population before the stress questionnaire was sent out (1989 - 2001) and in the study population after the stress questionnaire was sent out (2001 – 2005).

Moreover, I also treated infertility as an effect modifier. I stratified the entire study population by report of clinical evaluation for infertility. To verify the validity of self-reported infertility, 100 randomly selected women who reported ovulatory infertility -- 95% of the self-reports were confirmed through medical record review [95].

The association between endometriosis and infertility is multifaceted. Endometriosis is a common cause for infertility. However infertility can also be associated with endometriosis. Women (with no reported infertility) who have had a laparoscopic diagnosis are more likely to report chronic pelvic pain symptoms as otherwise an invasive surgical evaluation would not have been conducted. It can be also assumed that among cases with infertility, that have not attempted to become pregnant, a great proportion may never have received a laparoscopic diagnosis of endometriosis. In addition, the setting of infertility evaluation introduces the potential for detection/diagnostic bias. I treated infertility as a typical effect modifier and stratified the entire study population by report of having had a clinical evaluation for infertility (Figure 2). Tests for heterogeneity comparing the effect estimates among cases who never

reported infertility with effect estimates among cases having concurrent infertility were calculated with a Wald statistic referred to a chi-squared distribution with 1 degree of freedom [96].

RESULTS

Characteristics of the Study population

After baseline exclusions, a total of 60,410 women contributed 766,014 person-years to these analyses; these included 1968 incident cases of laparoscopically confirmed endometriosis. Distribution of potential risk factors for endometriosis according to total abuse in childhood/adolescence at baseline (1989) among women in the Nurses' Health Study II is shown in Table 2. We analyzed patient characteristics between those who responded to the trauma questionnaire and those who did not respond to the trauma questionnaire. Distribution of potential risk factors for endometriosis between stress questionnaire responders vs. non-responders at baseline (1989) among women in the Nurses' Health Study II are shown in Table 3. Distribution of potential risk factors for endometriosis according to total categories of cumulative abuse in childhood/adolescence at baseline (1989) among women in the Nurses' Health Study II are shown in Table 4. Several potential risk factors for endometriosis were at least modestly increased among women who had experienced abuse; these included higher BMI, cigarette smoking, and younger age at menarche (< 11 years).

Frequencies of childhood and adolescence abuse exposures are reported in Table 5. Overall, 64.9% of women in the cohort reported one or more abuse exposures during childhood or adolescence, and 56% reported abuse that started in childhood (up to age 11). Specifically, 32.1% (n = 19,385) reported child/teen physical abuse only 11.9% (n = 7177) reported child/teen sexual abuse, and 20.94 % (n = 12649) reported child/teen physical and sexual abuse.

Both physical and sexual abuse history were positively associated with a higher incidence of endometriosis (Table 6). Women with history of exposure to abuse had an increased risk of endometriosis for the four measures of abuse (cumulative abuse history, childhood trauma questionnaire scores, abuse severity, and abuse type). A graded association between cumulative abuse exposure and adjusted RR of endometriosis was demonstrated (Table 7). There was little change in effect magnitude from model to model representing low influence of the selected potential confounding variables.

Compared to those with no reported abuse events (emotional, physical, or sexual), there was a 13% greater risk of endometriosis for women reporting one episode of mild/moderate abuse (CI=1.02-1.26), HR=1.16 (CI=1.01-1.34), mild-multiple or severe-type of abuse, HR=1.33 (CI=1.12-1.57), moderate-chronic or-multiple types of abuse, HR=1.34 (CI=1.03-1.27), and severe-chronic or multiple types of abuse, and a 209% greater for those with severe-chronic abuse and multiple types (CI=1.60-2.73).

I observed a dose-response relation with increasing severity of cumulative abuse history testing for a linear trend ($p < 0.05$). Results were analogous when I repeated analyses using the Child Trauma Questionnaire score for childhood abuse, abuse severity score, and abuse type score (Table 7). When I differentiated between mild, moderate, and severe physical abuse, I observed an increased risk of endometriosis in women with history of severe physical abuse (RR=1.30; 95%CI=1.11 - 1.52). I differentiated for different grades of severity of sexual abuse and I observed the highest risk for endometriosis in women with history of forced sexual activity during childhood and adolescence (RR=1.55; 95%CI: 1.21 - 1.98). I observed an increased risk of

endometriosis in cases of physical abuse only (RR=1.23; 95%CI=1.01 - 1.26) and sexual abuse only (RR=1.15; 95%CI=0.99 - 1.33); the highest risk of endometriosis was observed in women with a combination of physical and sexual abuse history (RR=1.34; 95%CI=1.19 - 1.51).

I also performed a subanalysis and included fibroids in the model (model 4) (Table 8). The inclusion of fibroids in the model (model 4) did not indicate multi-collinearity. The addition of the predictor variable fibroids did not induce changes in the estimated regression coefficients. The association of endometriosis and abuse was similar in model 3 (without fibroids) compared to model 4 (with fibroids). The risk for endometriosis was increased in women with history of severe chronic and multiple types of abuse (RR=2.05; 95%CI=1.57 - 2.69, severe physical abuse (RR=1.29; 95%CI=1.10 - 1.52) and forced sexual activity as child and teen (RR=1.54; 95%CI:1.21 - 1.97) (Table 8).

In a subanalysis, we compared the association of abuse and endometriosis of the study group before the questionnaire was sent out (1989 - 2001) to the association of the group after the questionnaire was sent out (2001 - 2005). In the time period 2001 – 2005 were substantially fewer incident endometriosis cases (Table 6). In the study group 2001 -2005, there were very few cases for the following categories mild physical abuse (n = 34), childhood trauma category: 6-10 (n = 71) childhood trauma category: 21-25 (n = 1), cumulative abuse history: severe-chronic or-multiple types (n = 3), and cumulative abuse history: severe-chronic and multiple types were only (n = 3). I observed an association between endometriosis and abuse for all abuse categories in the group of premenopausal women between 1989 and 2001 (Table 9). For those

premenopausal women that have been observed between 2001and 2005, I showed an association of endometriosis and sexual abuse only as well as cumulative abuse history (Table 9). There was a protective effect of childhood trauma scale-6 -10, childhood trauma scale-21-25, and severe-Chronic-or-Multiple-Types (RR=0.73; CI95%:0.23 – 2.34). However, the incident cases of endometriosis were very low in these abuse categories, n = 92, n = 1, n = 3, respectively (Table 9).

I stratified by having reported infertility vs. never having reported infertility. Tables 10a and 10b show the associations between physical, sexual, and cumulative abuse history within strata of never versus ever having reported a clinical evaluation for infertility. Among those who have reported infertility the risk for endometriosis was slightly increased in women with history of severe chronic and multiple types of abuse (RR=1.04; 95%CI=0.47 - 2.28, test for linear trend p < 0.2477), and severe physical abuse (RR=1.15; 95%CI=0.80 - 1.65; p - value test for linear trend 0.06). Among women who reported infertility, risk of endometriosis was decreased in women with history forced sexual activity as child and teen (RR=0.79; 95%CI:0.40 - 1.58; P - value test for linear trend 0.95). Among those who never had an infertility report the risk was increased considerably with a history of severe chronic and multiple types of abuse (RR=2.60; 95%CI=1.95 – 3.47; p-value, test for linear trend p < 0.0001), severe physical abuse (RR=1.42; 95%CI=1.18 - 1.70; P - value, test for linear p < 0.0001), and forced sexual activity as child and teen (RR=1.93; 95%CI=1.52 - 2.51; P - value test for linear trend < 0.0001).

DISCUSSION

In this large cohort study, I found a positive association between abuse in childhood and endometriosis. After controlling for age, parental education, reproductive factors (e.g. menstrual cycle length characteristics, age at menarche) and BMI this association still remained.

Findings correspond to studies on the association of childhood abuse and reproductive diseases such as fibroids [87]. Interestingly, early trauma has been shown to be associated with several reproductive outcomes. Temporality and a dose-response relation support the findings of an association of abuse and endometriosis in the current investigation. Reproductive factors including early onset of puberty and early onset of perimenopause were shown to be associated with violence [97, 98]. I hypothesized that reproductive factors including menstrual cycle characteristics –length, age at menarche, OCP use, infertility, parity, and age at first delivery, as well as BMI are potential confounders for the association of abuse and endometriosis. However, the overall findings showed little evidence of confounding of additional reproductive parameters and BMI.

Infertility was treated as an effect modifier and the population was stratified into two groups (1) the “ever reported infertility” group and the (2) “never reported infertility” group, as described in a previous publication [18]. In women with evidence of infertility, the relative risk associated with severe sexual abuse was 0.79 (0.40 – 1.58) (Table 10b). In this group with the most severe type of sexual abuse were only five cases. Although utilizing a large cohort of surgically confirmed endometriosis cases, I am still

underpowered when I tease out the nuances and the numbers get small when someone further stratifies by history of infertility. I therefore cannot conclude that there is a preventative effect of sexual abuse. The relative risk of endometriosis was higher in the never infertility group. Chronic pelvic pain was not assessed in the NHS2 study, however, it can be assumed that the frequency of women with endometriosis and pelvic pain is higher in the never infertility report group. It was shown in previous studies that physical and sexual abuse was associated with chronic pelvic pain [27]. Someone might interpret that the never infertility group more likely consists of those women with endometriosis that report chronic pelvic pain and therefore the relative risk of endometriosis is higher.

One question that arises from the results concerns the significance of the involvement of a neuroendocrine dysregulation in some women that have been exposed to violence during childhood and develop with endometriosis. Detection of a prominent neuroendocrine disease mechanism is likely to represent an initial step in the characterization of a subpopulation of women with endometriosis. Although not shown it can be hypothesized that early trauma is a potential pathophysiological mechanism that leads to increased morbidity of the reproductive tract. An association of early trauma and fibroids has been shown In the NHS II cohort [87]. These findings and others' suggest a pathomechanism of early abuse that lead to reproductive disorders such as leiomyoma and endometriosis. Evidence from developmental neuroscience suggest that early adverse experiences during times of heightened neural plasticity persistently programs neural, endocrine, and immune responses to additional stressors in adulthood leading to chronic inflammatory diseases such as endometriosis [99].

Psychological stress may trigger or exacerbate disorders that are associated with immune dysfunction such as endometriosis via neuropathogenetic mechanisms. Physiological and psychological stress stimulates corticotropin releasing factor (CRF), an amino-acid peptide which is synthesized in the paraventricular nucleus of the hypothalamus in the human brain. During recent years a growing literature has suggested that early traumatic experiences induce persistent sensitization of the central stress response systems, including changes in CRF neuronal systems and dysregulation of the hypothalamic-pituitary adrenal (HPA) axis [100]. This peptide is released into the hypothalamo-hypophyseal portal circulation, where it stimulates the production of adrenocorticotropin (ACTH). ACTH then stimulates the synthesis of glucocorticoids in the adrenal cortex, which in turn modulate immune responses and in a negative feedback loop down-regulate the neuroendocrine stress response [101]. Aberration in the HPA axis has been reported to be involved in the development of psychiatric disease (e.g., anxiety disorders) [100, 102, 103]. It has been also suggested that HPA axis dysregulations might contribute to the pain perception in chronic inflammatory diseases [104]. In addition, aberrations in the HPA axis may also influence bioavailability of estrogens thereby increasing risk for endometriosis development.

Experimental data provide evidence that stress leads to subsequent inflammatory responses [69, 105-111]. Self-reported childhood traumatic stress is associated with an enhanced cellular immune responses, low grade inflammation, and a range of inflammatory diseases and autoimmune diseases (e.g., inflammatory bowel syndrome) [99, 112 105, 113-116]. Children maltreated by their parents, have been shown to be susceptible to increased morbidity and mortality (e.g., vascular disease, diabetes

type II, breast cancer, and autoimmune disorders) [86, 99, 102, 117, 118]. In individuals, exposure to psychosocial stress has been associated with increased plasma IL-1 and IL-6 responses [67, 119], as well as activation of nuclear factor (NF)-κB [68], a transcription factor that serves as a lynchpin in the inflammatory signaling cascade in endometriosis. I and others showed that local inflammatory [58, 120] and systemic inflammatory parameters are increased in women with endometriosis [40, 121-123]. Childhood abuse may trigger a pathomechanism that an increases inflammatory responses leading to an increase inflammatory disorders such as endometriosis (Figure 1).

Strengths and Limitations. This is the first study that investigates the association of childhood and teen abuse and endometriosis. The study has several strengths. These include prospective design and detailed information on abuse history, and laparoscopically validated endometriosis. The study comprises a large population with 1968 incident cases of endometriosis. The response rate for the main questionnaire including endometriosis and covariates was higher than 90%. The response rate (75%) for the detailed exposure assessment was high. This study has several limitations to be noted. The NHS II study population includes primarily Caucasian middle-aged female nurses who were middle-aged (36 – 53) when answering the early life stress and violence questionnaire. As such, these reports are not necessarily generalizable to women of other ethnicities [86, 87, 124]. Second, the endometriosis cases were not classified in the different subtypes of endometriosis including ovarian endometrioma and peritoneal endometriosis, and deep endometriosis. Furthermore, the predictor variable violence exposure was recalled by the study participants and may be subject of

misclassification. Although case-control studies are most subjected to recall bias also in cohort studies differential recall is possible if exposure status is transient. All studies on exposure to violence depend on self-reporting and therefore this is the gold standard. In respect to exposure of violence, victims may not report due to societal factors. It has been shown that about 5% of sexual abuse survivors report a history of abuse to their physician [125]. As a result, physicians are unaware of this aspect of their patients' medical history. The fact of misrepresentation of history of abuse may lead to underrepresentation of an association of exposure to violence an endometriosis in studies.

Implications. The reported incidence of violence is consistent with the current data on childhood violence in the literature [76]. The reported incidence of endometriosis is corresponding to current estimates. These results support a possible mechanistic link between exposure to violence and the development endometriosis, a condition of the female reproductive tract. These findings need to be confirmed in different populations. Whether early lifetime stress is associated with an increased inflammatory pelvic response and whether endometriosis is associated with a pathologic neuroendocrine stress response leading to increase in inflammatory activity have still to be determined in future studies. The potential association of early trauma and endometriosis warrants further studies on the role of violence on the regulation of the development of the reproductive tract and the identification of mechanisms that lead to reproductive disorders such as endometriosis. In future experiments, studies on the influence of abuse, stress and social support utilizing in vivo models of endometriosis may bring

some insights in the mechanism of action of relevant psychological factors. Identification of mechanisms of disease leads to better understanding of pathogenesis of pain and infertility in women with endometriosis.

Conclusion. In a sample of female nurses, I found an association between abuse in childhood and adolescence that was independent of demographic and reproductive factors as well as of BMI. These findings may have an inference on public health including prevention and clinical treatment of endometriosis.

FIGURES

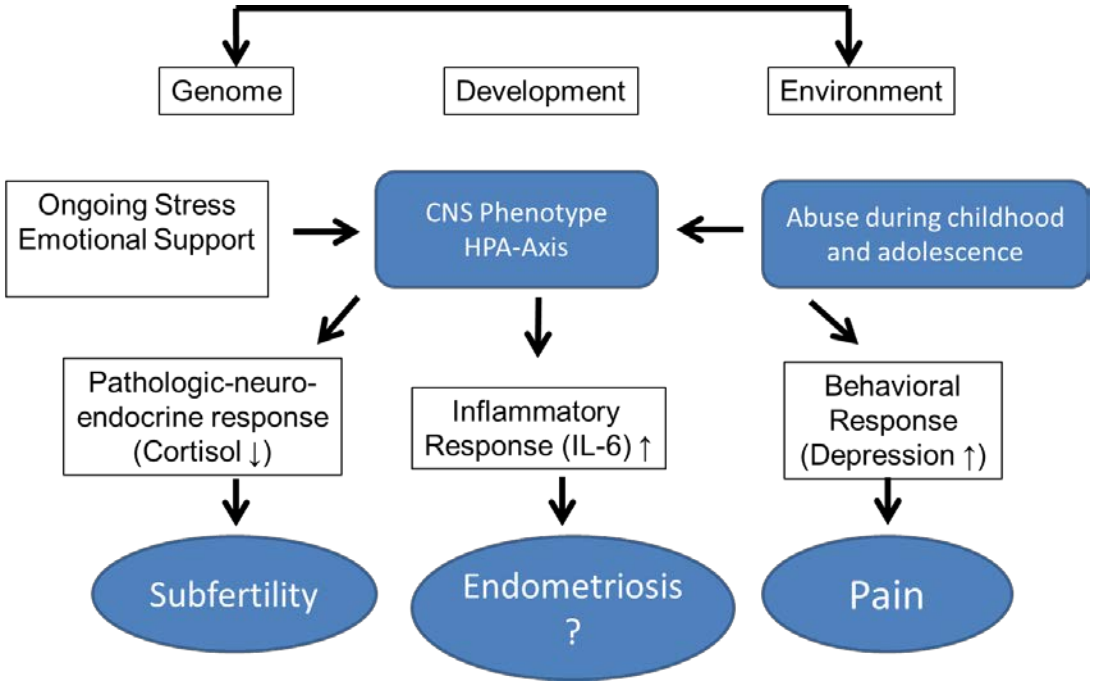

Figure 1. Working model for the study.

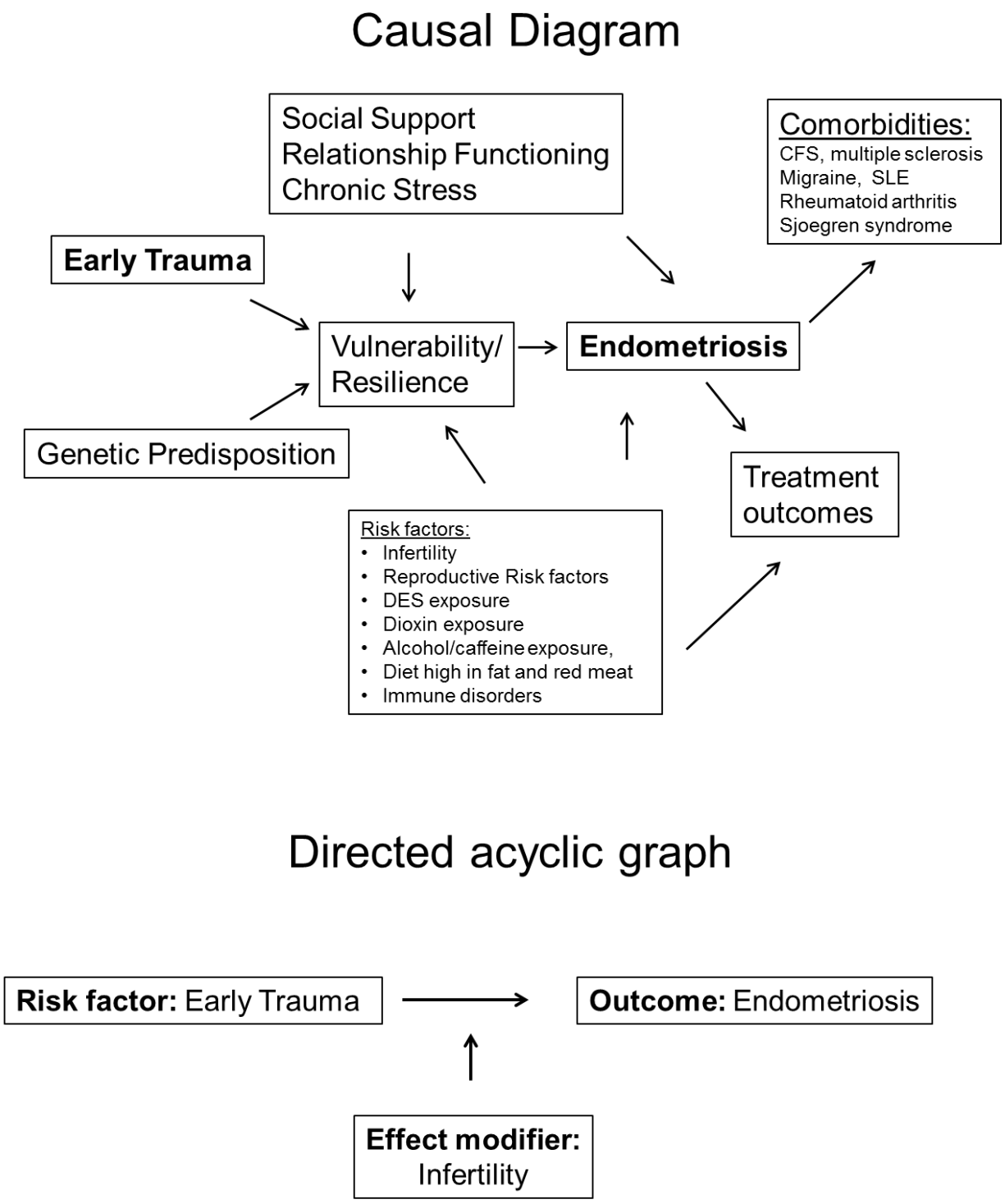

Figure 2: Causal Diagram and directed acyclic graph

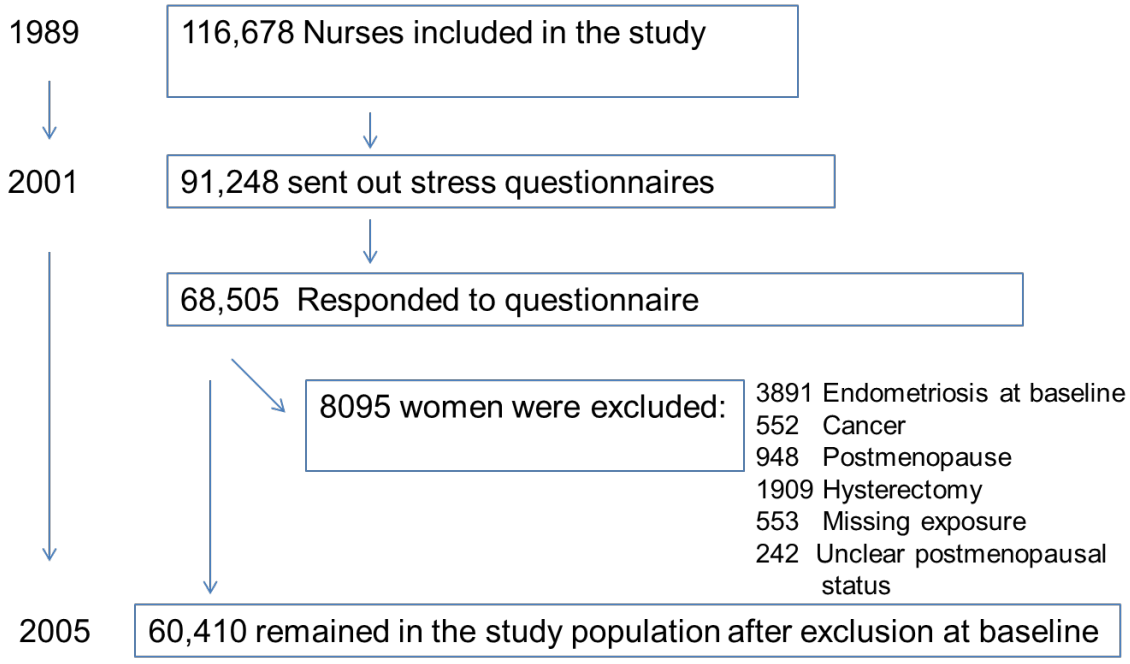

Figure 3. Flowchart of the selections of participants.

TABLES

Table 1a - Violence Variable Categorization

Severity Categories		
	Physical Abuse	**Sexual Abuse**
Mild	Kicking, biting, or hitting once Any frequency of pushing	Sexual touching
Moderate	Physically attacked once Hit a few times or more	Forced sexual activity during one developmental period
Severe	Choked or burned ever Physically attached more than once Kicked, pushed, or bitten more than once	Forced sexual activity during multiple developmental periods

Table 1b - Violence Variable Categorization Cumulative Violence Measure

Mild/Moderate Single Type	During one developmental period: *Mild/Moderate physical abuse only or *Mild sexual abuse only
Mild/Moderate Single or Severe-Single Type(s)	During one developmental period: *Mild/moderate physical and mild sexual abuse or *Moderate sexual abuse only *Severe Physical abuse only
Moderate-Chronic or – Multiple Types	During one developmental period: *Severe physical abuse and mild sexual abuse or *Mild/moderate physical and Moderate sexual abuse During both developmental periods: *Severe physical abuse only or *Severe sexual abuse only
Severe-Chronic or – Multiple Types	During one developmental period: *Severe physical and moderate sexual abuse During both developmental period periods: *Severe physical and mild sexual abuse *Severe sexual and mild/moderate physical abuse
Severe-Chronic and – Multiple Types	Both severe physical and moderate/severe abuse with one or both exposures occurring during both developmental periods

I utilized the classification system of physical and sexual abuse and for cumulative violence published by Boynton-Jarret et al., 2011 [87]. Categories that classify violence exposure by severity and chronicity were based on the factor analysis and frequency trends within each factor. Physical abuse was classified by severity categories which incorporated both type of violence exposure and frequency of abuse. Sexual abuse was classified based on type of abuse and number of developmental periods that abuse was experienced (chronicity). The cumulative violence measure merged both physical and sexual abuse.

Table 2 - Distribution of potential risk factors for endometriosis according to total abuse in childhood/adolescence at baseline (1989) among women in the Nurses' Health Study II (n = 60194).*

	Status		
	Normal (n = 21138**)**	**Abuse (** n = 39056**)**	**Total**
Race			
White	20235 (96.2)	36878 (94.4)	57203
Black	148 (0.7)	491 (1.3)	639
Asian	239 (1.1)	495 (1.3)	734
Multi	266 (1.3)	776 (2.0)	1042
Other – unknown	160 (0.8)	416 (1.1)	576
Total	21138	39056	60194
Body mass index			
< 19	1444 (6.9)	2248 (5.8)	3692
19 – 20.4	3596 (17.1)	5960 (17.1)	9556
20.5 – 21.9	4714 (22.4)	8236 (21.2)	12950
22 – 24.9	5939 (28.2)	10990 (28.3)	16929
25 – 29.9 (overweight)	3453 (16.4)	7101 (18.3)	10554
>= 30 obese	1888 (9.0)	4303 (11.1)	6191
Subtotal	21034	38838	59872
Missing data			322
Total			60194
Body mass index 2			
BMI < 30	19146 (91.0)	34535 (88.9)	53681
BMI >= 30	1888 (8.9)	4303 (11.1)	6191
Subtotal	21034	38838	59872
Missing			322
Total			60194
Cigarette smoking			
Never	15365 (72.8)	24853 (63.7)	40218
Past	3786 (17.9)	9123 (23.4)	12909
Current	1967 (9.3)	5026 (12.9)	6993
Subtotal	21118	39002	60120
Missing			74
Total			60194
Age at menarche			
< 12 years	4747 (22.5)	9506 (24.4)	14253
12 years	6520 (30.9)	11726 (30.1)	18246
13 years	6053 (28.7)	10641 (27.3)	16694
>13 years	3758 (18.1)	7054 (18.1)	10812
Subtotal	21078	38927	60005
Missing			189
Total			60194
Menstrual cycle length			
< 26 days	2167 (10.3)	4123 (10.6)	6290
26 – 31 days	13824 (65.5)	25873 (66.4)	39697
32 – 50 days	3953 (18.7)	6871 (17.6)	10824
>50	1150 (5.5)	2091 (5.4)	3241
Subtotal	21094	38958	60052
Missing			142
Total			60194
Oral contraceptive use			
Ever	3957 (18.7)	6221 (15.1)	10178
Never	17155 (81.3)	32790 (84.1)	49945
Subtotal	21112	39011	60123
Missing			71
Total			60194
Parity			
Ever	14282 (67.6)	27492 (70.4)	41774
Nulliparous	6854 (32.4)	11557 (29.6)	18411
Subtotal	21136	39049	60185
Missing			9
Total			60194
Lactation (among parous women)			
0-<1 months	2886 (20.9)	5167 (19.5)	8053
0-18 months	6942 (50.3)	13632 (51.4)	20574
>18 months	3962 (28.7)	7713 (29.1)	11675
Subtotal	13970	26512	40302
Missing			19892
Total			60191
Recent gynecologic exam			
No exam	1678 (8.0)	3240 (8.4)	4918
Exam	19344 (92.0)	35546 (91.7)	54890
Subtotal	21022	38786	59808
Missing			386
Total			60191

Table 3 - Distribution of potential risk factors for endometriosis in stress questionnaire responders vs. non-responders at baseline (1989) among women in the Nurses' Health Study II (n = 60194).*

	Status		
	Responders	**Non-responders**	**Total**
Race			
White	36501 (89.3)	57203 (95.0)	94704
Black	1091 (2.6)	639 (1.1)	1730
Asian	1110 (2.6)	734 (1.3)	1844
Multi	756 (1.80)	1042 (1.73)	1798
Other – unknown	1549 (3.7)	576 (1.0)	2125
Total	42007	60194	102201
Body mass index			
< 19	2583 (6.2)	3692 (6.2)	6275
19 – 20.4	6184 (14.9)	9556 (16.0)	15740
20.5 – 21.9	8257 (19.8)	12950 (21.6)	21207
22 – 24.9	11360 (27.3)	16929 (28.3)	28289
25 – 29.9 (overweight)	8116 (19.5)	10554 (17.6)	18670
>= 30 obese	5111 (12.28)	6191 (10.34)	11302
Total	41611	59872	101483
Body mass index 2			
BMI < 30	36500 (87.7)	53681 (90.0)	90181
BMI >= 30	5111 (12.3)	6191 (10.34)	11302
Total	41611	59872	101483
Cigarette smoking			
Never	26943 (64.25)	40218 (66.90)	67161
Past	8776 (20.93)	12909 (21.47)	21685
Current	6216	6993 (11.63)	13209
Total	41935	60120	102055
Age at menarche			
< 12 years	10310 (24.6)	14253 (23.8)	24563
12 years	12616 (30.1)	18246 (30.4)	27957
13 years	11263 (26.9)	16694 (27.8)	18488
>13 years	7676 (19.3)	10812 (18.0)	101870
Total	41865	60005	
Menstrual cycle length			
< 26 days	5416 (12.9)	6290 (10.5)	11706
26 – 31 days	27728 (66.2)	39697 (66.1)	67425
32 – 50 days	6582 (15.7)	10824 (18.0)	17406
>50	2151 (5.1)	3241 (5.4)	5392
Total	41877	60052	101909
Oral contraceptive use			
Ever	34460 (82.2)	49945 (83.1)	84405
Never	7488 (17.0)	10178 (16.9)	17666
Total	41948	60123	102071
Parity			
Ever	29231 (69.9)	41774 (69.41)	71005
Nulliparous	12767 (30.4)	18411 (30.59)	31778
Total	41998	60185	102183
Lactation (among parous women)			
0-<1 months	3933 (19.5)	8053 (20.0)	11986
0-18 months	10966 (54.5)	20574 (51.1)	31540
>18 months	5224 (26.1)	11675 (29.1)	16899
Total	20123	40302	60425
Recent gynecologic exam			
No exam	4112 (9.0)	4918 (8.2)	9030
Exam	37444 (90.1)	54890 (91.8)	92334
Total	41556	59808	101364

Table 4 - Distribution of potential risk factors for endometriosis according to total categories of cumulative abuse in childhood/adolescence at baseline (1989) among women in the Nurses' Health Study II (n = 60194).*

	Cumulative Exposure to violence in Early Life						
Characteristic	**No Abuse** (n =21138)	**Mild/Moderate or Single** (n = 22569)	**Mild-multiple or Severe-single** (n = 9126)	**Moderate-chronic Or multiple** (n = 4557)	**Severe-chronic Or multiple** (n = 1698)	**Severe chronic and multiple** (n = 1106)	**Total** (n = 60194)
Race							
White	20235 (96.2)	21480 (95.2)	8560 (93.8)	4262 (92.5)	1576 (92.8)	1000 (90.4)	57203
Black	148 (0.7)	238 (1.1)	154 (1.7)	59 (1.3)	26 (1.5)	14 (1.27)	639
Asian	239 (1.1)	285 (1.3)	123 (1.4)	50 (1.1)	20 (1.2)	17 (1.5)	734
Multi	266 (1.3)	353 (1.6)	192 (2.1)	124 (2.7)	54 (3.2)	53 (4.8)	1042
Other-unknown	160 (0.8)	213 (0.9)	97 (1.1)	62 (1.4)	22 (1.3)	22 (2.0)	576
Total	21138	22569	9126	4557	1698	1106	60194
BMI							
< 19	1444 (6.9)	1388 (6.2)	50 (95.6)	226 (5.0)	76 (4.5)	53 (4.82)	3692
19 – 20.4	3594 (17.1)	3638 (16.2)	1302 (14.4)	659 (14.5)	236 (14.0)	125 (11.4)	9556
20.5 - 21.9	4714 (22.4)	4889 (21.8)	1880 (20.7)	938 (20.7)	333 (19.7)	196 (17.8)	12950
22 - 24.9	5939 (28.2)	6330 (28.2)	2626 (28.9)	1282 (28.3)	456 (27.0)	296 (26.9)	16929
25 – 29.9	3453 (16.4)	3953 (17.6)	1728 (19.1)	818 (18.0)	359 (21.2)	243 (22.1)	10554
>= 30 obese	1888 (9.0)	2242(10.0)	1032 (11.4)	611 (13.5)	230 (13.6)	187 (17.0)	6191
Subtotal	21034	22441	9073	4534	1690	1100	59872
Missing Data							322
Total							60194
BMI 2							
BMI < 30	19146 (91.0)	20198 (90.0)	8041 (88.6)	3923 (86.5)	1460 (86.4)	913 (83.0)	53681
BMI >=30	1888 (9.0)	2243 (10.0)	1032 (11.4)	611 (13.5)	230 (13.6)	187 (17.0)	6191
Subtotal	21034	22441	9073	4534	1690	1100	59872
Missing							322
Total							60194
Cigarette smoking							
Never	15365 (72.8)	15076 (66.9)	5679 (62.3)	2553 (56.1	944 (55.7)	601 (54.3)	40218
Past	3786 (17.9)	4900 (21.8)	2214 (24.3)	1250 (27.5)	458 (27.0)	301 (27.2)	12909
Current	1967 (9.3)	2555 (11.3)	1224 (13.4)	750 (16.5)	293 (17.3)	204 (18.4)	6993
Subtotal	21118	22531	9117	4553	1695	1106	60120
Missing							74
Total							60194
Age at menarche							
< 12 years	4747 (22.5)	5166 (22.0)	2344 (25.8)	1167 (25.7)	505 (29.8)	325 (29.5)	14253
12 years	6520 (30.9)	6885 (30.6)	2706 (29.8)	1368 (30.1)	449 (26.5)	318 (28.9)	18246
13 years	6053 (28.7)	6320 (28.1)	2470 (27.2)	1155 (25.4)	441 (26.0)	255 (23.1)	16694
>= 13 years	3758 (17.8)	4122 (18.3)	1575 (17.3)	853 (18.8)	300 (17.7)	204 (18.5)	10812
Subtotal	21078	22492	9095	4543	1695	1102	60005
Missing							189
Total							60194
Menstrual cycle Length							
< 26 days	2167 (10.3)	2218 (9.9)	998 (11.0)	529 (11.6)	216 (12.8)	162 (14.7)	6290
26 – 31 days	13824 (65.5)	15.029 (66.8)	6029 (60.2)	3024 (66.5)	1103 (65.2)	688 (62.3)	39697
32 – 50 days	3953 (18.7)	4087 (18.2)	1601 (17.6)	739 (16.3)	266 (15.7)	178 (16.1)	10824
>51days	1150 (5.5)	1174 (5.2)	477 (5.2)	255 (5.6)	108 (6.4)	78 (6.0)	3241
Subtotal	21094	22508	9105	4547	1693	1105	60052
Missing							142
Total							60194
Oral contraceptive use							
Never	17155 (81.3)	18643 (82.7)	7793 (85.5)	3917 (86.0)	1473 (86.9)	964 (87.6)	49945
Ever	3957 (18.7)	3902 (17.3)	1323 (14.5)	636 (14.0)	223 (13.2)	137 (12.4)	10178
Subtotal	21112	22545	9116	4553	1696	1101	60123
Missing							71
Total							60194
Parity							
Parous	14282 (67.6)	15768 (69.9)	6494 (71.2)	3206 (70.4)	1234 (72.6)	790 (71.4)	41774
Nulliparous	6854 (32.4)	6797 (30.12)	2630 (28.8)	1350 (29.6)	464 (27.3)	316 (28.6)	18441
Subtotal	21136	22565	9124	4556	1698	1106	60185
Missing							9
Total							60194
Lactation (among parous women)							
0 < 1 months	2886 (20.9)	2888 (19.0)	1241 (19.8)	630 (20.4)	250 (21.0)	158 (21.0)	8053
1-18 months	6942 (50.3)	7877 (51.8)	3202(51.0)	1575 (51.1)	598 (50.3)	380 (50.6)	20574
> 18 months	3962(28.7)	4451 (29.3)	1831 (29.2)	878 (28.5)	340 (28.6)	213 (28.4)	11675
Subtotal	13790	15216	6274	3083	1188	751	40302
Missing							19892
Total							60194
Gynecologic examination							
Exam	1678 (8.0)	1805 (8.1)	774 (8.5)	406 (9.0)	155 (9.2)	100 (9.1)	4918
No exam	19344 (92.0)	20616 (91.95)	8273 (91.4)	4129 (91.1)	1532 (90.8)	996 (90.9)	54890
Subtotal	21022	22421	9407	4535	1687	1096	59808
Missing							386
Total							60194

Table 5 – Frequency of abuse in childhood and adolescence: Nurse's Health Study II (reported in 2001) (n = 60140)

	N (%)
Abuse Type	
None	21199 (35.1)
Physical Abuse only	19385 (32.1)
Sexual Abuse only	7177 (11.9)
Physical and Sexual abuse	12649 (20.9)
Total	60410 (100.00)
Abuse Severity	
Severity of Physical Abuse	
None	28376 (467.0)
Mild Physical Abuse	11351 (18.8)
Moderate Physical Abuse	15700 (26.0)
Severe Physical Abuse	4983 (8.3)
Total	60410 (100.00)
Severity of Sexual Abuse	
None	40584 (67.2)
Sexual Touching as Child or Teen	13345 (22.1)
Forced Sexual Activity as Child or Teen	4970 (8.2)
Forced Sexual Activity as Child &Teen	1511 (2.5)
Total	60410 (100.0)
Childhood Trauma Scale Score[a]	
5 (None)	6926 (11.5)
6 – 10	35506 (53.8)
11 – 15	13701 (22.7)
16 - 20	5170 (8.6)
21 – 25	2106 (3.4)
Total	60410 (100.0)
Cumulative Abuse History[b]	
No Exposure to Violence	21199 (35.1)
Mild/Moderate Single Type	22658 (37.5)
Mild-Multiple or Severe-Single Type(s)	9168 (15.2)
Moderate-Chronic or-Multiple Types	4567 (7.6)
Severe-Chronic or-Multiple Types	1701 (2.8)
Severe Chronic and Multiple Types	1111 (1.8)
Total	60410 (100.0)

[a]Exposure to physical, emotional, and verbal abuse in childhood (prior to age 11) was assessed using items from the Childhood Trauma Questionnaire short form, as described [87].

[b]To capture a latent construct— cumulative violence exposure, which incorporates both chronicity and severity-I used a principle components factor analysis methodology with oblique (promax) rotation (see Table 1), as described [87]. The cumulative violence measure merged both physical and sexual abuse.

Table 6: Incidence of laparoscopic confirmation of endometriosis by questionnaire period.

Year	Cases	Percent	Cumulative Frequency	Cumulative Percent
1991 - 1993	442	22.46	442	22.46
1993 - 1995	445	22.61	887	45.07
1995 - 1997	316	16.06	1203	61.13
1997 - 1999	255	12.96	1458	74.09
1999 - 2001	173	8,79	1631	82.88
2001 - 2003	141	7.16	1772	90.04
2003 - 2005	118	6.00	1890	96.04
2005 - 2007	78	3.96	1968	100.00

Table 7 - Relative risks of laparoscopic confirmation of endometriosis among premenopausal women according to severity, chronicity, and type of violence exposure in childhood/adolescence: Nurse's Health Study II (1989-2007)

Abuse Characteristics	Woman-years	No. Cases	Relative Risk (95% confidence interval)		
			Model 1[a]	Model 2[b]	Model 3[c]
Abuse Type					
None	270475	634	1.00 (referent)	1.00 (referent)	1.00 (referent)
Physical Abuse only	243216	628	1.11 (0.99 - 1.24)	1.12 (1.00 - 1.25)	1.23 (1.01 - 1.26)
Sexual Abuse only	89167	235	1.13 (0.98 - 1.32)	1.14 (0.98 - 1.32)	1.15 (0.99 - 1.33)
Physical and Sexual abuse	155143	471	1.32 (1.16 - 1.48)	1.31 (1.68 - 1.49)	1.34 (1.19 - 1.51)
P for trend			P < 0.0001	P < 0.0001	P < 0.0001
Abuse Severity					
Severity of Physical Abuse					
None	359642	869	1.00 (referent)	1.00 (referent)	1.00 (referent)
Mild Physical Abuse	143067	348	1.00 (0.89 - 1.14)	1.01 (0.89 - 1.15)	1.01 (0.89 - 1.14)
Moderate Physical Abuse	195223	562	1.20 (1.08 - 1.34)	1.23 (1.10 - 1.37)	1.23 (1.11 - 1.38)
Severe Physical Abuse	60069	189	1.32 (1.13 - 1.55)	1.28 (1.09 - 1.50)	1.30 (1.11 - 1.52)
P for trend			P < 0.0001	P <0.0001	P < 0.0001
Severity of Sexual Abuse					
None	513691	1262	1.00 (referent)	1.00 (referent)	1.00 (referent)
Sexual Touching as Child or Teen	165449	449	1.12 (1.00 - 1.25)	1.12 (1.01 - 1.25)	1.14 (1.02 - 1.27)
Forced Sexual Activity as Child or Teen	61025	188	1.26 (1.08 - 1.47)	1.24 (1.06 - 1.44)	1.25 (1.07 - 1.47)
Forced Sexual Activity as Child &Teen	17835	69	1.57 (1.23 - 2.00)	1.51 (1.18 - 1.93)	1.55 (1.21 - 1.98)
P for trend			P < 0.0001	P < 0.0001	P < 0.0001
Childhood Trauma Scale Score					
5 (None)	86368	189	1.00 (referent)	1.00 (referent)	1.00 (referent)
6 - 10	412863	985	1.06 (0.91 - 1.24)	1.11 (0.95 - 1.23)	1.12 (0.96 - 1.31)
11 - 15	171029	489	1.28 (1.08 - 1.52)	1.31 (1.11 - 1.56)	1.34 (1.13 - 1.58)
16 - 20	63294	225	1.59 (1.31 - 1.93)	1.62 (1.33 - 1.97)	1.65 (1.36 - 2.01)
21 - 25	24446	80	1.50 (1.60 - 1.96)	1.51 (1.16 - 1.97)	1.56 (1.20 - 2.03)
P for trend			P < 0.0001	P < 0.0001	P < 0.0001
Cumulative Abuse History					
No Exposure to Violence	270475	634	1.00 (referent)	1.00 (referent)	1.00 (referent)
Mild/Moderate Single Type	284152	739	1.11 (1.00 - 1.24)	1.13 (1.02 - 1.26)	1.13 (1.02 - 1.26)
Mild-Multiple or Severe-Single Type(s)	114079	297	1.14 (0.99 - 1.31)	1.15 (1.00 - 1.32)	1.16 (1.01 - 1.34)
Moderate-Chronic or-Multiple Types	56084	172	1.31 (1.10 - 1.55)	1.30 (1.10 - 1.55)	1.33 (1.12 - 1.57)
Severe-Chronic or-Multiple Types	20438	66	1.38 (1.07 - 1.78)	1.31 (1.02 - 1.70)	1.34 (1.03 - 1.72)
Severe-Chronic and Multiple Types	12771	60	2.07 (1.58 - 2.70)	2.02 (1.54 - 2.63)	2.09 (1.60 - 2.73)
P for trend			P < 0.0001	P < 0.0001	P < 0.0001

Multivariate cox proportional hazard regression models with time-varying covariates treating age in months were used to estimate the relative risks using SAS PROC PHREG procedure (SAS Institute, 1991). All analyses controlled for age, parental education, and race/ethnicity.

[a]Model 1 controls for age, parental education, and race/ethnicity.

[b]Model 2 controls of all variables in Model 1 and reproductive factors: menstrual cycle characteristics – length, age at menarche, OCP use, infertility, parity, and age at first delivery.

[c]Model 3 controls for all variables in Model 2 and BMI (continuous).

Table 8 - Relative risks of laparoscopic confirmation of endometriosis employing Model 4 (with fibroids) and Model 3 (without fibroids) among premenopausal women according to severity, chronicity, and type of violence exposure in childhood/adolescence: Nurse's Health Study II (1989-2007)

Abuse Characteristics	Woman-years	No. Cases	Relative Risks (95% confidence interval)	
			Model 3[a]	Model 4[b]
Abuse Type				
None	270475	634	1.00 (referent)	1.00 (referent)
Physical Abuse only	243216	628	1.23 (1.01 - 1.26)	1.12 (1.00 - 1.25)
Sexual Abuse only	89167	235	1.15 (0.99 - 1.33)	1.14 (0.99 - 1.33)
Physical and Sexual abuse	155143	471	1.34 (1.19 - 1.51)	1.33 (1.17 - 1.50)
Abuse Severity				
Severity of Physical Abuse				
None	359642	869	1.00 (referent)	1.00 (referent)
Mild Physical Abuse	143067	348	1.01 (0.89 - 1.14)	1.01 (0.89 - 1.14)
Moderate Physical Abuse	195223	562	1.23 (1.11 - 1.38)	1.23 (1.10 - 1.36)
Severe Physical Abuse	60069	189	1.30 (1.11 - 1.52)	1.29 (1.10 - 1.52)
Severity of Sexual Abuse				
None	513691	1262	1.00 (referent)	1.00 (referent)
Sexual Touching as Child or Teen	165449	449	1.14 (1.02 - 1.27)	1.14 (1.02 - 1.27)
Forced Sexual Activity as Child or Teen	61025	188	1.25 (1.07 - 1.47)	1.25 (1.07 - 1.47)
Forced Sexual Activity as Child &Teen	17835	69	1.55 (1.21 - 1.98)	1.55 (1.21 - 1.98)
Childhood Trauma Scale Score				
5 (None)	86368	189	1.00 (referent)	1.00 (referent)
6 - 10	412863	985	1.12 (0.96 - 1.31)	1.11 (0.95 - 1.30)
11 - 15	171029	489	1.34 (1.13 - 1.58)	1.33 (1.12 - 1.57)
16 - 20	63294	225	1.65 (1.36 - 2.01)	1.63 (1.34 - 1.98)
21 - 25	24446	80	1.56 (1.20 - 2.03)	1.54 (1.84 - 2.01)
Cumulative Abuse History				
No Exposure to Violence	270475	634	1.00 (referent)	1.00 (referent)
Mild/Moderate Single Type	284152	739	1.13 (1.02 - 1.26)	1.13 (1.02 - 1.26)
Mild-Multiple or Severe-Single Type(s)	114079	297	1.16 (1.01 - 1.34)	1.15 (1.00 - 1.32)
Moderate-Chronic or-Multiple Types	56084	172	1.33 (1.12 - 1.57)	1.32 (1.12 - 1.57)
Severe-Chronic or-Multiple Types	20438	66	1.34 (1.03 - 1.72)	1.33 (1.03 - 1.72)
Severe-Chronic and Multiple Types	12771	60	2.09 (1.60 - 2.73)	2.06 (1.57 - 2.69)

Multivariate cox proportional hazard regression models with time-varying covariates treating age in months were used to estimate the relative risks using SAS PROC PHREG procedure (SAS Institute, 1991). All analyses controlled for age, parental education, and race/ethnicity.

[a]Model 3 controls for menstrual cycle characteristics –length, age at menarche, OCP use, infertility, parity, age at first delivery, and BMI (continuous).

[b]Model 4 controls of all variables in Model 1 and reproductive factors: menstrual cycle characteristics – length, age at menarche, OCP use, infertility, parity, age at first delivery, BMI (continuous), and fibroids.

Table 9 - Relative risks of laparoscopic confirmation of endometriosis among premenopausal women according to severity, chronicity, and type of violence exposure in childhood/adolescence employing Model 3: Nurse's Health Study II for timeframes 1989 - 2001 and 1989 - 2005

	Years 1989 – 2001			Years 2001 - 2005		
Abuse Characteristics	**Woman-years**	**No. Cases**	**Relative Risk (95% confidence interval)**	**Woman-years**	**No. Cases**	**Relative Risk (95% confidence interval)**
Abuse Type			Model 3[a]			Model 3[a]
None	221054	572	1.00 (referrent)	47339	62	1.00 (referent)
Physical Abuse only	199640	573	1.14 (1.01 – 1.28)	41810	55	1.02 (0.71 - 1.47)
Sexual Abuse only	73594	206	1.12 (0.95 – 1.31)	14930	29	1.51 (0.97 - 2.35)
Physical and Sexual abuse	127271	421	1.31 (1.56 – 1.49)	25931	50	1.11 (1.68 - 2.38)
P for trend			P = 0.0005			P < 0.05
Abuse Severity						
Severity of Physical Abuse						
None	295651	264	1.00 (referrent)	62269	91	1.00 (referent)
Mild Physical Abuse	117281	268	1.02 (0.89 – 1.63)	24824	34	0.94 (0.63 – 1.39)
Moderate Physical Abuse	160676	314	1.24 (1.10 – 1.38)	33193	57	1.25 (0.90 – 1.75)
Severe Physical Abuse	49955	350	1.33 (1.23 – 1.57)	9724	14	1.04 (0.59 – 1.84)
P for trend			P = 0.0001			P = 0.5487
Severity of Sexual Abuse						
None	420965	272	1.00 (referrent)	89149	117	1.00 (referent)
Sexual Touching as Child or Teen	139556	291	1.07 (0.96 – 1.20)	27773	51	1.50 (1.07 – 2.09)
Forced Sexual Activity as Child or Teen	50353	164	1.20 (1.02 – 1.41)	10316	24	1.86 (1.19 – 2.91)
Forced Sexual Activity as Child &Teen	14959	65	1.60 (1.24 – 2.05)	2772	4	1.15 (0.42 – 3.14)
P for trend			P = 0.0002			P < 0.05
Childhood Trauma Scale Score						
5 (None)	71223	169	1.00 (referrent)	14501	20	1.00 (referrent)
6 - 10	337903	893	1.08 (0.91 – 1.28)	71901	92	0.92 (0.57 – 1.50)
11 - 15	140574	429	1.05 (1.05 – 1.50)	29306	60	1.56 (0.94 – 2.61)
16 - 20	52235	202	1.59 (1.29 – 1.95)	10613	23	1.64 (0.89 – 2.30)
21 - 25	20626	79	1.63 (1.24 – 2.13)	3689	1	0.22 (0.03 – 1.61)
P for trend			P < 0.00001			P = 0.01475
Cumulative Abuse History						
No Exposure to Violence	221054	572	1.00 (referrent)	47339	62	1.00 (referrent)
Mild/Moderate Single Type	233435	668	1.14 (1.02 – 1.27)	48664	71	1.13 (0.80 – 1.60)
Mild-Multiple or Severe-Single Type(s)	93898	263	1.14 (0.98 – 1.32)	19436	34	1.46 (0.95 – 2.22)
Moderate-Chronic or-Multiple Types	46359	149	1.27 (1.05 – 1.52)	9385	23	1.97 (1.21 – 3.20)
Severe-Chronic or-Multiple Types	17071	63	1.39 (1.07 – 1.81)	3230	3	0.73 (0.23 – 2.34)
Severe-Chronic and Multiple Types	10744	57	2.14 (1.63 – 2.83)	1976	3	1.41 (0.44 – 4.55)
P for trend			P < 0.00001			P = 0.0956

Multivariate cox proportional hazard regression models with time-varying covariates treating age in months were used to estimate the relative risks using SAS PROC PHREG procedure (SAS Institute, 1991). All analyses controlled for age, parental education, and race/ethnicity.

[a]Model 3 controls for age, parental education, race/ethnicity and reproductive factors: menstrual cycle characteristics –length, age at menarche, OCP use, infertility, parity, age at first delivery, and BMI (continuous).

Table 10a - Multivariable relative risks (RR) and 95% confidence intervals (CI) of laparoscopic confirmation of endometriosis and cumulative abuse history, stratified by infertility history among premenopausal women in the Nurses' Health Study II (1989- 2007).

	Ever infertility report				Never infertility report				
Cumulative abuse history	**Cases**	**Person years**	**Age-adjusted RR[a]**	**MV RR (95% CI)[b]**	**Cases**	**Person years**	**Age-adjusted RR[a]**	**MV RR (95% CI)[c]**	**P[c]**
None	172	14737	1.00	1.00	451	248077	1.00	1.00	0.03
Mild/Moderate Single Type	189	15331	1.04 (0.85 - 1.28)	1.13 (0.91 – 1.41)	535	260815	1.13 (1.00 - 1.28)	1.15 (1.01 – 1.30)	
Mild-multiple or Severe Single Types	77	6350	1.01 (0.77 - 1.04)	1.23 (0.92 - 1.64)	213	104089	1.13 (0.96 – 1.32)	1.17 (1.00 -0.14)	
Moderate-Chronic or Multiple Types	40	3437	1.00 (0.71 – 1.41)	1.28 (0.89 – 1.84)	127	50850	1.37 (1.13 – 1.67)	1.39 (1.14 – 1.70)	
Severe-Chronic or Multiple Types	14	1337	0.90 (0.52 – 1.55)	1.01 (0.57 – 1.80)	52	18221	1.57 (1.18 -2.09)	1.57 (1.18 – 2.10)	
Severe Chronic and Multiple Types	7	819	0.73 (0.34 -1.56)	1.04 (0.47 – 2.28)	53	11380	2.56 (1.93 – 3.41)	2.60 (1.95 – 3.47)	
P for trend				0.2477				P < 0.0001	

Note: RR=relative risk ratio; MV=multivariate; CI=confidence interval

Time-varying Cox proportional hazards models treating age in months were used to estimate multivariate (MV) relative risk (RR) and to calculate 95% confidence intervals (CI), after adjusting simultaneously for confounding variables.

[a]Adjusted for current age

[b]Adjusted for current age, parental education, and race/ethnicity, reproductive factors: Menstrual cycle characteristics–length, age at menarche, OCP use, infertility, parity, age at first delivery, and BMI (continuous)

[c]LRT P value, test for heterogeneity between cumulative exposure and infertility.

Table 10b - Multivariable relative risks (RR) and 95% confidence intervals (CI) of laparoscopic confirmation of endometriosis and abuse severity (physical abuse or sexual abuse), stratified by infertility history among premenopausal women in the Nurses' Health Study II (1989 - 2007).

Abuse history	Ever infertility report				Never infertility report				P[c]
	Cases	Person years	Age-adjusted RR[a]	MV RR (95% CI)[b]	Cases	Person years	Age-adjusted RR[a]	MV RR (95% CI)[b]	
Physical Abuse									
None	222	19723	1.00	1.00	632	329858	1.00	1.00	0.13
Mild	100	8159	1.09 (0.86 – 1.38)	1.16 (0.90 – 1.49)	244	130691	0.97 (0.84 - 1.13)	0.99 (0.85 – 1.43)	
Moderate	139	10759	1.15 (0.93 – 1.42)	1.28 (1.02 – 1.61)	408	178773	1.19 (1.05 – 1.35)	1.22 (1.07 -1.38)	
Severe	38	3749	0.90 (0.64 – 1.27)	1.15 (0.80 – 1.65)	147	54110	1.42 (1.18 – 1.70)	1.42 (1.18 - 1.70)	
P for trend				0.06				< 0.0001	
Sexual Abuse									
None	341	28250	1.00	1.00	895	470961	1.00	1.00	0.003
Sexual Touching as Child or Teen	108	9196	0.97 (0.78 – 1.21)	1.072 (0.85 – 1.35)	331	151274	1.15 (1.02 – 1.31)	1.171 (1.03 – 1.33)	
Forced Sexual Activity as Child or Teen	41	3811	0.89 (0.64 – 1.23)	1.02 (0.72 – 1.43)	145	55163	1.38 (1.16 – 1.65)	1.41 (1.18 – 1.68)	
Forced Sexual Activity as Child & Teen	5	1133	0.66 (0.34 – 1.28)	0.79 (0.40 – 1.58)	60	16034	1.97 (1.52 – 2.56)	1.93 (1.52 – 2.51)	
P for trend				0.95				< 0.0001	

Note: RR=relative risk ratio; MV=multivariate; CI=confidence interval

Time-varying Cox proportional hazards models treating age in months were used to estimate multivariate (MV) relative risk (RR) and to calculate 95% confidence intervals (CI), after adjusting simultaneously for confounding variables.

[a]Adjusted for current age

[b]Adjusted for current age, parental education, and race/ethnicity, reproductive factors: Menstrual cycle characteristics–length, age at menarche, OCP use, infertility, parity, age at first delivery, and BMI (continuous)

[c]LRT P value, test for heterogeneity between physical and sexual abuse and infertility.

REFERENCES

1. Bulun SE. Endometriosis. N Engl J Med. 2009;360(3):268-79.

2. Wenzl R, Kiesel L, Huber JC, Wieser F. Endometriosis: a genetic disease. Drugs Today (Barc). 2003;39(12):961-72.

3. Dun EC, Taylor RN, Wieser F. Advances in the genetics of endometriosis. Genome Med. 2010;2(10):75. PMCID: 2988445.

4. Missmer SA. Commentary: Endometriosis--epidemiologic considerations for a potentially 'high-risk' population. Int J Epidemiol. 2009;38(4):1154-5.

5. Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, Barbieri RL, Willett WC, Hankinson SE. A prospective study of dietary fat consumption and endometriosis risk. Hum Reprod. 2010;25(6):1528-35. PMCID: 2873173.

6. Vitonis AF, Hankinson SE, Hornstein MD, Missmer SA. Adult physical activity and endometriosis risk. Epidemiology. 2010;21(1):16-23. PMCID: 2886663.

7. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. Fertil Steril. 2001;75(1):1-10.

8. Barlow DH, Kennedy S. Endometriosis: new genetic approaches and therapy. Annu Rev Med. 2005;56:345-56.

9. Kennedy S. Is there a genetic basis to endometriosis? Semin Reprod Endocrinol. 1997;15(3):309-18.

10. Painter JN, Anderson CA, Nyholt DR, Macgregor S, Lin J, Lee SH, Lambert A, Zhao ZZ, Roseman F, Guo Q, Gordon SD, Wallace L, Henders AK, Visscher PM, Kraft

P, Martin NG, Morris AP, Treloar SA, Kennedy SH, Missmer SA, Montgomery GW, Zondervan KT. Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis. Nat Genet. 2011;43(1):51-4. PMCID: 3019124.

11. Cramer DW, Missmer SA. The epidemiology of endometriosis. Ann N Y Acad Sci. 2002;955:11-22; discussion 34-6, 396-406.

12. Missmer SA, Cramer DW. The epidemiology of endometriosis. Obstet Gynecol Clin North Am. 2003;30(1):1-19, vii.

13. Zampelas A, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C. Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. Am J Clin Nutr. 2004;80(4):862-7.

14. Paschos GK, Rallidis LS, Liakos GK, Panagiotakos D, Anastasiadis G, Votteas V, Zampelas A. Background diet influences the anti-inflammatory effect of alpha-linolenic acid in dyslipidaemic subjects. Br J Nutr. 2004;92(4):649-55.

15. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F, Giugliano D. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. Jama. 2004;292(12):1440-6.

16. Vitonis AF, Baer HJ, Hankinson SE, Laufer MR, Missmer SA. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. Hum Reprod. 2010;25(5):1325-34. PMCID: 2854045.

17. Weuve J, Hauser R, Calafat AM, Missmer SA, Wise LA. Association of exposure to phthalates with endometriosis and uterine leiomyomata: findings from NHANES, 1999-2004. Environ Health Perspect. 2010;118(6):825-32. PMCID: 2898860.

18. Schernhammer ES, Vitonis AF, Rich-Edwards J, Missmer SA. Rotating nightshift work and the risk of endometriosis in premenopausal women. Am J Obstet Gynecol. 2011;205(5):476 e1-8. PMCID: 3205317.

19. Missmer SA, Spiegelman D, Hankinson SE, Malspeis S, Barbieri RL, Hunter DJ. Natural hair color and the incidence of endometriosis. Fertil Steril. 2006;85(4):866-70.

20. Nater UM, Maloney E, Heim C, Reeves WC. Cumulative life stress in chronic fatigue syndrome. Psychiatry Res. 2011;189(2):318-20.

21. Heim C, Nater UM, Maloney E, Boneva R, Jones JF, Reeves WC. Childhood trauma and risk for chronic fatigue syndrome: association with neuroendocrine dysfunction. Arch Gen Psychiatry. 2009;66(1):72-80.

22. Ross CA. Childhood sexual abuse and psychosomatic symptoms in irritable bowel syndrome. J Child Sex Abus. 2005;14(1):27-38.

23. Low LA, Schweinhardt P. Early life adversity as a risk factor for fibromyalgia in later life. Pain Res Treat. 2012;2012:140832. PMCID: 3196867.

24. Weissbecker I, Floyd A, Dedert E, Salmon P, Sephton S. Childhood trauma and diurnal cortisol disruption in fibromyalgia syndrome. Psychoneuroendocrinology. 2006;31(3):312-24.

25. Wuest J, Merritt-Gray M, Ford-Gilboe M, Lent B, Varcoe C, Campbell JC. Chronic pain in women survivors of intimate partner violence. J Pain. 2008;9(11):1049-57.

26. Heim C, Ehlert U, Hanker JP, Hellhammer DH. Psychological and endocrine correlates of chronic pelvic pain associated with adhesions. J Psychosom Obstet Gynaecol. 1999;20(1):11-20.

27. Heim C, Ehlert U, Hanker JP, Hellhammer DH. Abuse-related posttraumatic stress disorder and alterations of the hypothalamic-pituitary-adrenal axis in women with chronic pelvic pain. Psychosom Med. 1998;60(3):309-18.

28. Irish L, Kobayashi I, Delahanty DL. Long-term physical health consequences of childhood sexual abuse: a meta-analytic review. J Pediatr Psychol. 2010;35(5):450-61. PMCID: 2910944.

29. Committee opinion no. 498: Adult manifestations of childhood sexual abuse. Obstet Gynecol. 2011;118(2 Pt 1):392-5.

30. Paras ML, Murad MH, Chen LP, Goranson EN, Sattler AL, Colbenson KM, Elamin MB, Seime RJ, Prokop LJ, Zirakzadeh A. Sexual abuse and lifetime diagnosis of somatic disorders: a systematic review and meta-analysis. JAMA. 2009;302(5):550-61.

31. Sampson JA. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol. 1927;14:442-69.

32. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol. 1984;64(2):151-4.

33. Kruitwagen RF, Poels LG, Willemsen WN, Jap PH, Thomas CM, Rolland R. Retrograde seeding of endometrial epithelial cells by uterine-tubal flushing. Fertil Steril. 1991;56(3):414-20.

34. Ugur M, Turan C, Mungan T, Kuscu E, Senoz S, Agis HT, Gokmen O. Endometriosis in association with mullerian anomalies. Gynecol Obstet Invest. 1995;40(4):261-4.

35. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364(9447):1789-99.

36. Malinak LR, Buttram VC, Jr., Elias S, Simpson JL. Heritage aspects of endometriosis. II. Clinical characteristics of familial endometriosis. Am J Obstet Gynecol. 1980;137(3):332-7.

37. Wieser F, Hefler L, Tempfer C, Vlach U, Schneeberger C, Huber J, Wenzl R. Polymorphism of the interleukin-1beta gene and endometriosis. J Soc Gynecol Investig. 2003;10(3):172-5.

38. Wieser F, Tempfer C, Schneeberger C, van Trotsenburg M, Huber J, Wenzl R. Interleukin-1 receptor antagonist polymorphism in women with peritoneal adhesions. Bjog. 2002;109(11):1298-300.

39. Wieser F, Wenzl R, Tempfer C, Worda C, Huber J, Schneeberger C. Catechol-O-methyltransferase polymorphism and endometriosis. J Assist Reprod Genet. 2002;19(7):343-8.

40. Wieser F, Fabjani G, Tempfer C, Schneeberger C, Sator M, Huber J, Wenzl R. Analysis of an interleukin-6 gene promoter polymorphism in women with endometriosis by pyrosequencing. J Soc Gynecol Investig. 2003;10(1):32-6.

41. Asghar T, Yoshida S, Kennedy S, Negoro K, Zhuo W, Hamana S, Motoyama S, Nakago S, Barlow D, Maruo T. The tumor necrosis factor-alpha promoter -1031C polymorphism is associated with decreased risk of endometriosis in a Japanese population. Hum Reprod. 2004;19(11):2509-14.

42. Nakago S, Hadfield RM, Zondervan KT, Mardon H, Manek S, Weeks DE, Barlow D, Kennedy S. Association between endometriosis and N-acetyl transferase 2 polymorphisms in a UK population. Mol Hum Reprod. 2001;7(11):1079-83.

43. Uno S, Zembutsu H, Hirasawa A, Takahashi A, Kubo M, Akahane T, Aoki D, Kamatani N, Hirata K, Nakamura Y. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. Nat Genet. 2010.

44. Groothuis PG, Koks CA, de Goeij AF, Dunselman GA, Arends JW, Evers JL. Adhesion of human endometrium to the epithelial lining and extracellular matrix of amnion in vitro: an electron microscopic study. Hum Reprod. 1998;13(8):2275-81.

45. Witz CA, Monotoya-Rodriguez IA, Schenken RS. Whole explants of peritoneum and endometrium: a novel model of the early endometriosis lesion. Fertil Steril. 1999;71(1):56-60.

46. Halme J, White C, Kauma S, Estes J, Haskill S. Peritoneal macrophages from patients with endometriosis release growth factor activity in vitro. J Clin Endocrinol Metab. 1988;66(5):1044-9.

47. Khorram O, Taylor RN, Ryan IP, Schall TJ, Landers DV. Peritoneal fluid concentrations of the cytokine RANTES correlate with the severity of endometriosis. Am J Obstet Gynecol. 1993;169(6):1545-9.

48. Cirkel U, Ochs H, Mues B, Zwadlo G, Sorg C, Schneider HP. Inflammatory reaction in endometriotic tissue: an immunohistochemical study. Eur J Obstet Gynecol Reprod Biol. 1993;48(1):43-50.

49. Klein NA, Pergola GM, Tekmal RR, Montoya IA, Dey TD, Schenken RS. Cytokine regulation of cellular proliferation in endometriosis. Ann N Y Acad Sci. 1994;734:322-32.

50. Taylor RN, Ryan IP, Moore ES, Hornung D, Shifren JL, Tseng JF. Angiogenesis and macrophage activation in endometriosis. Ann N Y Acad Sci. 1997;828:194-207.

51. Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. Fertil Steril. 2001;76(1):1-10.

52. Rana N, Braun DP, House R, Gebel H, Rotman C, Dmowski WP. Basal and stimulated secretion of cytokines by peritoneal macrophages in women with endometriosis. Fertil Steril. 1996;65(5):925-30.

53. Bergqvist A, Bruse C, Carlberg M, Carlstrom K. Interleukin 1beta, interleukin-6, and tumor necrosis factor-alpha in endometriotic tissue and in endometrium. Fertil Steril. 2001;75(3):489-95.

54. Keenan JA, Chen TT, Chadwell NL, Torry DS, Caudle MR. IL-1 beta, TNF-alpha, and IL-2 in peritoneal fluid and macrophage-conditioned media of women with endometriosis. Am J Reprod Immunol. 1995;34(6):381-5.

55. Tseng JF, Ryan IP, Milam TD, Murai JT, Schriock ED, Landers DV, Taylor RN. Interleukin-6 secretion in vitro is up-regulated in ectopic and eutopic endometrial stromal cells from women with endometriosis. J Clin Endocrinol Metab. 1996;81(3):1118-22.

56. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J, Simon C. The follicular and endocrine environment in women with endometriosis: local and systemic cytokine production. Fertil Steril. 1998;70(3):425-31.

57. Lebovic DI, Chao VA, Martini JF, Taylor RN. IL-1beta induction of RANTES (regulated upon activation, normal T cell expressed and secreted) chemokine gene expression in endometriotic stromal cells depends on a nuclear factor-kappaB site in the proximal promoter. J Clin Endocrinol Metab. 2001;86(10):4759-64.

58. Wieser F, Vigne JL, Ryan I, Hornung D, Djalali S, Taylor RN. Sulindac suppresses nuclear factor-kappaB activation and RANTES gene and protein expression in endometrial stromal cells from women with endometriosis. J Clin Endocrinol Metab. 2005;90(12):6441-7.

59. Sakamoto Y, Harada T, Horie S, Iba Y, Taniguchi F, Yoshida S, Iwabe T, Terakawa N. Tumor necrosis factor-alpha-induced interleukin-8 (IL-8) expression in endometriotic stromal cells, probably through nuclear factor-kappa B activation: gonadotropin-releasing hormone agonist treatment reduced IL-8 expression. J Clin Endocrinol Metab. 2003;88(2):730-5.

60. Laird SM, Tuckerman EM, Cork BA, Li TC. Expression of nuclear factor kappa B in human endometrium; role in the control of interleukin 6 and leukaemia inhibitory factor production. Mol Hum Reprod. 2000;6(1):34-40.

61. King AE, Critchley HO, Kelly RW. The NF-kappaB pathway in human endometrium and first trimester decidua. Mol Hum Reprod. 2001;7(2):175-83.

62. Kalkhoven E, Wissink S, van der Saag PT, van der Burg B. Negative interaction between the RelA(p65) subunit of NF-kappaB and the progesterone receptor. J Biol Chem. 1996;271(11):6217-24.

63. Manning AM, Rao A. Agents targeting transcription factors. In: Gallin JI, Snyderman R, eds. Inflammation: basic principles and clinical correlates. . 3rd ed. Philadelpha: Lippincott; 1999.

64. Lebovic DI, Chao VA, Taylor RN. Peritoneal macrophages induce RANTES (regulated on activation, normal T cell expressed and secreted) chemokine gene

transcription in endometrial stromal cells. J Clin Endocrinol Metab. 2004;89(3):1397-401.

65. Lebovic DI, Bentzien F, Chao VA, Garrett EN, Meng YG, Taylor RN. Induction of an angiogenic phenotype in endometriotic stromal cell cultures by interleukin-1beta. Mol Hum Reprod. 2000;6(3):269-75.

66. Taylor RN, Lebovic DI, Hornung D, Mueller MD. Endocrine and paracrine regulation of endometrial angiogenesis. Ann N Y Acad Sci. 2001;943:109-21.

67. Brydon L, Edwards S, Jia H, Mohamed-Ali V, Zachary I, Martin JF, Steptoe A. Psychological stress activates interleukin-1beta gene expression in human mononuclear cells. Brain Behav Immun. 2005;19(6):540-6.

68. Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, Joswig M, Morcos M, Schwaninger M, McEwen B, Kirschbaum C, Nawroth PP. A mechanism converting psychosocial stress into mononuclear cell activation. Proc Natl Acad Sci U S A. 2003;100(4):1920-5.

69. Pace TW, Wingenfeld K, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim CM. Increased peripheral NF-kappaB pathway activity in women with childhood abuse-related posttraumatic stress disorder. Brain Behav Immun. 2012;26(1):13-7.

70. Sinaii N, Cleary SD, Younes N, Ballweg ML, Stratton P. Treatment utilization for endometriosis symptoms: a cross-sectional survey study of lifetime experience. Fertil Steril. 2007;87(6):1277-86.

71. Halis G, Arici A. Endometriosis and inflammation in infertility. Ann N Y Acad Sci. 2004;1034:300-15.

72. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod. 2005;20(10):2698-704.

73. Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: cost estimates and methodological perspective. Hum Reprod Update. 2007;13(4):395-404.

74. Arnow BA. Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. J Clin Psychiatry. 2004;65 Suppl 12:10-5.

75. Briere J, Elliott DM. Prevalence and psychological sequelae of self-reported childhood physical and sexual abuse in a general population sample of men and women. Child Abuse Negl. 2003;27(10):1205-22.

76. Gould DA, Stevens NG, Ward NG, Carlin AS, Sowell HE, Gustafson B. Self-reported childhood abuse in an adult population in a primary care setting. Prevalence, correlates, and associated suicide attempts. Arch Fam Med. 1994;3(3):252-6.

77. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol. 2004;160(8):784-96.

78. Bornstein MH. Developmental Pschology. Erlabaum L, editor. Hillsdale: MJ; 1999.

79. Maercker A, Michael T, Fehm L, Becker ES, Margraf J. Age of traumatisation as a predictor of post-traumatic stress disorder or major depression in young women. Br J Psychiatry. 2004;184:482-7.

80. Lazarus RS. The psychology of stress and coping. Issues Ment Health Nurs. 1985;7(1-4):399-418.

81. Haugaard JJ. The challenge of defining child sexual abuse. Am Psychol. 2000;55(9):1036-9.

82. Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB. The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. Depress Anxiety. 2002;15(3):117-25.

83. Riise T, Mohr DC, Munger KL, Rich-Edwards JW, Kawachi I, Ascherio A. Stress and the risk of multiple sclerosis. Neurology. 2011;76(22):1866-71. PMCID: 3115807.

84. Riley EH, Wright RJ, Jun HJ, Hibert EN, Rich-Edwards JW. Hypertension in adult survivors of child abuse: observations from the Nurses' Health Study II. J Epidemiol Community Health. 2010;64(5):413-8.

85. Edwards VJ, Holden GW, Felitti VJ, Anda RF. Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: results from the adverse childhood experiences study. Am J Psychiatry. 2003;160(8):1453-60.

86. Rich-Edwards JW, Spiegelman D, Lividoti Hibert EN, Jun HJ, Todd TJ, Kawachi I, Wright RJ. Abuse in childhood and adolescence as a predictor of type 2 diabetes in adult women. Am J Prev Med. 2010;39(6):529-36. PMCID: 3003936.

87. Boynton-Jarrett R, Rich-Edwards JW, Jun HJ, Hibert EN, Wright RJ. Abuse in childhood and risk of uterine leiomyoma: the role of emotional support in biologic resilience. Epidemiology. 2011;22(1):6-14.

88. Rich-Edwards JW, James-Todd T, Mohllajee A, Kleinman K, Burke A, Gillman MW, Wright RJ. Lifetime maternal experiences of abuse and risk of pre-natal

depression in two demographically distinct populations in Boston. Int J Epidemiol. 2011;40(2):375-84. PMCID: 3066428.

89. Duleba AJ. Diagnosis of endometriosis. Obstet Gynecol Clin North Am. 1997;24(2):331-46.

90. Vercellini P, Somigliana E, Vigano P, Abbiati A, Daguati R, Crosignani PG. Endometriosis: current and future medical therapies. Best Pract Res Clin Obstet Gynaecol. 2008;22(2):275-306.

91. Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, Sapareto E, Ruggiero J. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry. 1994;151(8):1132-6.

92. Straus M, Hamby DH, Boney-McCoy S, Sugraman DB. The revised conflict tactics scales (CTS2). . J Fam Issues. 1995;17:283-316.

93. Koss MP, Oros CJ. Sexual Experiences Survey: a research instrument investigating sexual aggression and victimization. J Consult Clin Psychol. 1982;50(3):455-7.

94. McFarlane J, Parker B, Soeken K, Bullock L. Assessing for abuse during pregnancy. Severity and frequency of injuries and associated entry into prenatal care. JAMA. 1992;267(23):3176-8.

95. Rich-Edwards JW, Goldman MB, Willett WC, Hunter DJ, Stampfer MJ, Colditz GA, Manson JE. Adolescent body mass index and infertility caused by ovulatory disorder. Am J Obstet Gynecol. 1994;171(1):171-7.

96. Prentice RL, Kalbfleisch JD, Peterson AV, Jr., Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. Biometrics. 1978;34(4):541-54.

97. Wise LA, Palmer JR, Rothman EF, Rosenberg L. Childhood abuse and early menarche: findings from the black women's health study. Am J Public Health. 2009;99 Suppl 2:S460-6. PMCID: 2881664.

98. Allsworth JE, Zierler S, Krieger N, Harlow BL. Ovarian function in late reproductive years in relation to lifetime experiences of abuse. Epidemiology. 2001;12(6):676-81.

99. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. Psychosom Med. 2009;71(2):243-50.

100. Heim C, Plotsky PM, Nemeroff CB. Importance of studying the contributions of early adverse experience to neurobiological findings in depression. Neuropsychopharmacology. 2004;29(4):641-8.

101. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21(1):55-89.

102. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001;49(12):1023-39.

103. Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA. 2000;284(5):592-7.

104. Bomholt SF, Harbuz MS, Blackburn-Munro G, Blackburn-Munro RE. Involvement and role of the hypothalamo-pituitary-adrenal (HPA) stress axis in animal models of chronic pain and inflammation. Stress. 2004;7(1):1-14.

105. Bauer ME, Wieck A, Lopes RP, Teixeira AL, Grassi-Oliveira R. Interplay between neuroimmunoendocrine systems during post-traumatic stress disorder: a minireview. Neuroimmunomodulation. 2010;17(3):192-5.

106. Okuyama K, Ohwada K, Sakurada S, Sato N, Sora I, Tamura G, Takayanagi M, Ohno I. The distinctive effects of acute and chronic psychological stress on airway inflammation in a murine model of allergic asthma. Allergol Int. 2007;56(1):29-35.

107. Brenhouse HC, Andersen SL. Nonsteroidal anti-inflammatory treatment prevents delayed effects of early life stress in rats. Biol Psychiatry. 2011;70(5):434-40.

108. Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006;163(9):1630-3.

109. Deak T, Bordner KA, McElderry NK, Barnum CJ, Blandino P, Jr., Deak MM, Tammariello SP. Stress-induced increases in hypothalamic IL-1: a systematic analysis of multiple stressor paradigms. Brain Res Bull. 2005;64(6):541-56.

110. Nguyen KT, Deak T, Owens SM, Kohno T, Fleshner M, Watkins LR, Maier SF. Exposure to acute stress induces brain interleukin-1beta protein in the rat. J Neurosci. 1998;18(6):2239-46.

111. Suzuki E, Shintani F, Kanba S, Asai M, Nakaki T. Immobilization stress increases mRNA levels of interleukin-1 receptor antagonist in various rat brain regions. Cell Mol Neurobiol. 1997;17(5):557-62.

112. Goodwin RD, Stein MB. Association between childhood trauma and physical disorders among adults in the United States. Psychol Med. 2004;34(3):509-20.

113. Altemus M, Cloitre M, Dhabhar FS. Enhanced cellular immune response in women with PTSD related to childhood abuse. Am J Psychiatry. 2003;160(9):1705-7.

114. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology. 2010;35(13):2617-23. PMCID: 2978751.

115. Dinan TG, Cryan J, Shanahan F, Keeling PW, Quigley EM. IBS: An epigenetic perspective. Nat Rev Gastroenterol Hepatol. 2010;7(8):465-71.

116. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry. 2008;65(4):409-15. PMCID: 2923056.

117. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011.

118. Modesitt SC, Gambrell AC, Cottrill HM, Hays LR, Walker R, Shelton BJ, Jordan CE, Ferguson JE, 2nd. Adverse impact of a history of violence for women with breast, cervical, endometrial, or ovarian cancer. Obstet Gynecol. 2006;107(6):1330-6.

119. Brydon L, Edwards S, Mohamed-Ali V, Steptoe A. Socioeconomic status and stress-induced increases in interleukin-6. Brain Behav Immun. 2004;18(3):281-90.

120. Guo SW. Nuclear factor-kappab (NF-kappaB): an unsuspected major culprit in the pathogenesis of endometriosis that is still at large? Gynecol Obstet Invest. 2007;63(2):71-97.

121. Tao Y, Zhang Q, Huang W, Zhu H, Zhang D, Luo W. The peritoneal leptin, MCP-1 and TNF-alpha in the pathogenesis of endometriosis-associated infertility. Am J Reprod Immunol. 2011;65(4):403-6.

122. Tariverdian N, Siedentopf F, Rucke M, Blois SM, Klapp BF, Kentenich H, Arck PC. Intraperitoneal immune cell status in infertile women with and without endometriosis. J Reprod Immunol. 2009.

123. Agic A, Xu H, Finas D, Banz C, Diedrich K, Hornung D. Is endometriosis associated with systemic subclinical inflammation? Gynecol Obstet Invest. 2006;62(3):139-47.

124. Rich-Edwards JW, Mason S, Rexrode K, Spiegelman D, Hibert E, Kawachi I, Jun HJ, Wright RJ. Physical and sexual abuse in childhood as predictors of early-onset cardiovascular events in women. Circulation. 2012;126(8):920-7.

125. Walker EA, Katon WJ, Roy-Byrne PP, Jemelka RP, Russo J. Histories of sexual victimization in patients with irritable bowel syndrome or inflammatory bowel disease. Am J Psychiatry. 1993;150(10):1502-6.