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Posttraumatic stress disorder symptoms and timing of menopause and gynecological surgery in the Nurses' Health Study II

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Abstract

Background: Earlier menopause, either natural or through gynecologic surgeries, has been associated with various negative health sequelae. While posttraumatic stress disorder (PTSD) has been linked to dysregulated biological processes, including reproductive system changes that could alter menopausal timing, little work has examined whether trauma and PTSD are associated with greater risk of early cessation of menses.

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Methods: Data are from 46,639 women in the Nurses' Health Study II, a prospective cohort study of women followed for up to 26 years. Lifetime trauma and PTSD symptoms were assessed with the Brief Trauma Questionnaire and a PTSD symptom screener in 2008. Age at cessation of menses and reason for cessation of menses (i.e., natural menopause, gynecologic surgery including hysterectomy and/or bilateral salpingo-oophorectomy [BSO]) were assessed. Cox proportional hazards models estimated hazards ratios (HR) of cessation of menses (separately for naturally or surgically) associated with trauma alone or PTSD symptoms, relative to no trauma, adjusting for covariates.

Results: Trauma/PTSD status was associated with earlier cessation of menses due to surgery, but not natural menopause. Women with trauma exposure, low, and high PTSD symptoms had higher hazard of cessation of menses due to surgery relative to those with no trauma exposure (HR_{trauma}=1.16, 95%CI 1.07–1.26; $HR_{low\ PTSD}$=1.25, 95%CI 1.15–1.36; $HR_{high\ PTSD}$=1.29, 95%CI 1.17–1.42). Trauma exposure and PTSD symptoms were associated with similarly increased risk of hysterectomy and BSO surgeries.

Conclusions: Women who experienced trauma and PTSD may be at elevated risk for common gynecological surgeries premenopausally, potentially due to increased clinical indications or gynecological conditions.

Keywords

posttraumatic stress disorder; menopause; gynecological surgery; trauma

Introduction

Trauma and posttraumatic stress disorder (PTSD) are linked with various mental and physical health outcomes [1], particularly aging-related conditions [2]. PTSD may impact physical health through dysregulated biological processes associated with chronic stress activation, including altered hormone function and accelerated cellular aging [3, 4], although empirical evidence is limited. In women, an indicator of reproductive aging is menopausal timing, with premature (before age 40) or early (between age 40 and 45) menopause associated with negative sequelae, including cardiovascular disease, osteoporosis, and early mortality [5]. Despite potentially providing insight into how PTSD may influence adverse aging-related health outcomes, little work has investigated links between PTSD and menopausal timing.

The onset of post-menopause is defined as cessation of menstruation for at least one year, characterized by fluctuations and ultimately declines in ovarian hormone production. In a process distinct from natural menopause, menses can also stop due to surgical removal of the uterus (hysterectomy) and/or ovaries (i.e., bilateral salpingo-oophorectomy [BSO]), with premenopausal ovarian removal marked by abrupt declines in ovarian hormones. Further, evidence shows that women undergoing hysterectomy alone have earlier onset of menopause versus women with intact uteri for reasons that are not well understood [6].

PTSD may influence the two separate processes of natural menopausal timing and gynecological surgeries via multiple potential mechanisms, including stress-related

biological dysregulation, gynecological complications, and health behaviors. PTSD is associated with faster cellular aging [4, 7], which could result in earlier natural menopause due to higher rates of ovarian follicle and depletion ovarian reserve (e.g., anti-Mullerian hormone [AMH] levels) [8], although this has not been directly examined. PTSD has been associated with increased risk for gynecological complications (e.g., fibroids, endometriosis, polycystic ovarian syndrome) [9, 10], which are common indications for gynecological surgeries, and with increased rates of hysterectomy in premenopausal female veterans [11, 12]. Last, PTSD may increase unhealthy behaviors, such as smoking, physical inactivity, and unhealthy diet [13], that may be associated with earlier menopause [14].

Thus, we evaluated whether PTSD is related to earlier cessation of menses - either due to natural transition or gynecological surgery. We also examined associations of PTSD with BSO and hysterectomy alone as secondary outcomes. It remains unclear whether links between trauma and health outcomes can be attributed to trauma itself or associated psychological distress (e.g., PTSD) [15]. We therefore also considered whether trauma without PTSD increased risk of natural menopause or gynecological surgeries. We assessed longitudinal associations among a large community-based sample of middle-aged civilian women followed for up to 26 years. We adjusted for a range of sociodemographic, psychological, and biobehavioral factors [10, 16]. We hypothesized that women with PTSD would have increased risk of earlier natural menopause and cessation of menses due to surgery as well as each specific gynecological surgery (i.e., BSO, hysterectomy alone), relative to no trauma exposure. As depression may be associated with early menopause [16], we also considered concurrent depression when examining the primary relationships. Additionally, we censored women while they reported using hormone therapy [17], given its impact on menopausal timing.

Methods

Study population

Data are from the Nurses' Health Study II (NHS II), a longitudinal cohort including 116,429 US female registered nurses ages 25–42 at enrollment in 1989. Women complete biennial questionnaires and follow-up is ongoing. A subset of the NHS II cohort (N=54,703, 89% response rate with repeated mailings) completed an additional questionnaire in 2008, which assessed lifetime trauma and PTSD symptoms. Women were included in current analyses if they had complete trauma and PTSD data (excluding those whose worst trauma was serious illness), were premenopausal in 1989 (study baseline), and had not undergone hysterectomy alone or had cancer before baseline, for an eligible sample of 46,639. This study was approved by the Partners Healthcare Human Research Committee; return of questionnaires implied consent.

Measures

Trauma/PTSD Status.—Lifetime trauma exposure was assessed in 2008 using a modified Brief Trauma Questionnaire, a self-report instrument derived from the Brief Trauma Interview (BTI) which assesses lifetime exposure to potentially traumatic events [18]. Women indicated whether they had ever experienced any of 16 potentially traumatic events

(e.g., serious accident, physical assault, natural disaster) and if so, which was their worst/most distressing exposure (if multiple), and ages at which their worst and first (if multiple) trauma occurred. To ensure trauma itself did not cause menopause or gynecological surgery (i.e., potential reverse causality), we excluded women whose worst trauma was "serious illness" (n=3,026). Among those reporting any trauma, PTSD symptoms were assessed with the Short Screening Scale for PTSD (DSM-IV), an instrument designed to screen for lifetime PTSD in relation to one's worst trauma [19]. Women indicated presence of any of seven PTSD symptoms at any time following their worst trauma. PTSD categorizations were based on previous research, suggesting that 4+ symptoms indicate clinically relevant levels [19]. Women were classified into four groups: 1) no trauma exposure, 2) trauma with no PTSD symptoms, 3) trauma with low PTSD symptoms (1–3 symptoms), and 4) trauma with high PTSD symptoms (4–7 symptoms). Retrospectively reported timing of trauma and PTSD symptoms were used to identify time-updated trauma/PTSD status onset during study follow-up based on reported age at first/worst trauma; reliability of age at trauma and PTSD reporting has been found to be excellent in this sample [20]. For example, a woman who reported her first trauma in 1988 and worst trauma with 4–7 PTSD symptoms in 2004 would be classified as trauma/no PTSD for 1988–2003 and high PTSD symptoms in 2004 and thereafter.

Menopause & Gynecological Surgeries.—The primary outcome was cessation of menses as self-reported on biennial questionnaires. Women reported whether their menstrual periods had ceased permanently, and if so, at what age and for what reason: occurring naturally, after surgery, or after radiation/chemotherapy treatment. On the 1989, 1991, and 1993 questionnaires, only women who reported that their periods had ceased were asked to provide information on surgery to remove one or both ovaries and/or uterus. From 1995 onward, all women were asked to report on gynecologic surgeries. Reported age at cessation of menses was used to derive the date (year) of outcomes. The two forms of the primary outcome were 1) cessation of menses naturally (i.e., natural menopause), and 2) cessation of menses due to surgery, based on self-reported age and reason of cessation of menses. As cessation of menses due to surgery could be due to BSO or due to hysterectomy alone, which have differing endocrine profiles, secondary analyses examined these surgeries separately. BSO was defined as cessation of menses due to BSO with or without hysterectomy. Hysterectomy alone was defined as either cessation of menses due to hysterectomy alone or reported premenopausal hysterectomy alone (without reporting cessation of menses). Self-reported menopausal status was validated by medical record review among menopausal women in a sister study, NHS, finding that 99% of those reviewed accurately reported their age at cessation of menses [21].

Covariates.—Baseline time-invariant covariates that represent *potential confounders* included race/ethnicity, parental education (highest education level of either parent), and age at menarche (reported at study baseline). Additional *potential confounders* were time-updated at each follow-up questionnaire, as data were available. Time-updated reproductive health-related covariates that were potential confounders or important predictors included parity (updated through 2009) and duration of oral contraceptive use (cumulative lifetime duration of oral contraceptive use; updated through 2009), tubal ligation (updated

through 2009) and unilateral oophorectomy (updated until 2015). See Table 1 for covariate categories. Time-updated indicators for depression (presence, absence) were derived using multiple measures, including the Mental Health Index (MHI-5; total scores ≤60 indicated elevated symptoms) [22] in 1993, 1997, and 2001; self-reported clinical depression diagnosis (yes/no) reported biennially starting in 2001; or the 10-item Center for Epidemiologic Studies Depression Scale (CES-D; total scores ≥10 indicated clinical depression) [23] in 2008 and 2013.

Time-updated *bio-behavioral* covariates that could confound or mediate the PTSD-menopause association included body mass index (BMI; derived from self-reported height and weight; continuous in kg/m^2; updated through 2015), pack years of smoking (cumulative lifetime packyears: continuous; updated through 2015), alcohol use (current average alcohol consumption: continuous in g/day; updated through 2007), and physical activity (current average physical activity: continuous in metabolic equivalent of task [MET] hours per week; updated through 2009). Current systemic hormone therapy (e.g., oral estrogens and/or progestins) use was self-reported at each biennial questionnaire, and women who reported any use were considered as taking hormone therapy. Women did not contribute person-time to analytic models when they reported taking hormone therapy, however, women could re-enter the model if they stopped taking hormone therapy and were still premenopausal. This resulted in 42,788 women contributing person-time to primary analytic models; 3,851 women never contributed person-time as they were taking hormone therapy in all time periods in which they were premenopausal.

Statistical Analyses

We assessed covariate distributions at baseline in 1989 by trauma/PTSD status. Cox proportional hazards models were performed with time-updated trauma/PTSD status predicting onset of each outcome separately, conditioned on age and biennial follow-up cycle. The two forms of the primary outcome (i.e., cessation of menses) were natural menopause and cessation of menses due to surgery, while secondary outcomes included BSO and hysterectomy alone. To reduce concerns about reverse causality (i.e., biological changes causing psychological distress), cessation of menses was considered 2 years after exposure assessment, e.g., PTSD status in 1990 was examined in relation to outcomes reported in 1992 [21]. As cancer and associated treatments (e.g., radiation or chemotherapy) may directly impact or induce cessation of menses [5], we censored women upon cancer diagnosis over follow-up or if they reported cessation of menses due to radiation or chemotherapy (n=435, 1.0%). Women who reported age at menses cessation but did not provide the reason (n=277, 0.6%) were also censored as non-cases.

For each outcome, we ran a series of models: Model 1 adjusted for age and calendar time (by conditioning on age and wave of data collection), Model 2 additionally adjusted for potential confounders, and Model 3 additionally adjusted for biobehavioral factors. Models examining natural menopause also adjusted for tubal ligation and unilateral oophorectomy in Models 2 and 3. Missing indicators for categorical variables were used. Women contributed person-time (in months) from baseline questionnaire return to outcome reporting of cessation of menses (either naturally or due to surgery, when considering one form of

cessation, we censored on the other form), radiation-induced menopause, unknown/missing reason for cessation of menses, cancer diagnosis, death, end of follow-up in 2015, or loss to follow-up (last returned questionnaire if prior to 2015), whichever occurred first. Similarly, for secondary outcomes, women contributed person-time from baseline to becoming a case (either BSO or hysterectomy alone while premenopausal; when considering one surgery type, we censored on the other type), natural menopause, radiation-induced menopause, unknown/missing reason for cessation of menses, missing surgical type, cancer diagnosis, death, end of follow-up in 2015, or loss to follow-up, whichever occurred first.

To examine potential violations of proportional hazards, we assessed the interaction between trauma/PTSD status and age (stratified as <35 versus ≥35 at baseline; the median baseline age) and between trauma/PTSD status and time period (1989–1997, 1997–2005, 2005–2015). No interactions were significant besides between trauma/PTSD and time period for cessation of menses due to surgery ($p=0.04$). We conducted sensitivity analyses for trauma/PTSD and cessation of menses due to surgery stratified by time period.

Several additional sensitivity analyses were conducted. Natural menopause and cessation of menses due to surgery constitute competing events [24]. To account for this, we conducted proportional hazards models with competing events using the Fine and Gray method to determine subdistribution hazard rates [25]. Competing event models were conducted for natural menopause (accounting for cessation of menses due to surgery) and cessation of menses due to surgery (accounting for natural menopause).

We also adjusted for any hormone therapy use among the eligible sample, rather than having women not contribute person-time while using hormone therapy. As traumatic sexual assault may impact reproductive health and potentially lead to gynecological surgery [11], we performed sensitivity analyses excluding women who reported ever experiencing sexual assault (n=11,596 [24.9%] women). By excluding these women, these analyses indicated whether traumas other than sexual assault, and resulting PTSD symptoms, were also associated with the outcomes. To determine how robust our analyses were to potential bias from retrospective report (time periods before 2008), we conducted a fully prospective analysis restricting to women who were premenopausal in 2008, including 7,924 women (age 48.4 [SD=3.0] in 2008). Lastly, we calculated E-values for primary estimates, which indicate the minimum strength of association that an unmeasured confounder would have to have with both the exposure and outcome, conditional on adjusted covariates, to explain away the specific exposure-outcome association fully [26, 27]. All analyses were performed using SAS Version 9.4.

Results

Table 1 presents baseline characteristics of the eligible sample (n=46,639 women) by trauma/PTSD status. The sample was mostly white (92.9%), with a mean age of 34.5 (SD=4.6). Most women reported exposure to trauma before 1989, with only 30.7% endorsing no lifetime trauma prior to study enrollment. Of those exposed to trauma, 45.3% experienced some PTSD symptoms.

Most women (n=43,452; 93.2%) ceased menstruation during the 26-year study period. Of these, most reported natural menopause (73.3%) versus cessation of menses due to surgery (25.1%). Among women reporting cessation of menses due to surgery, 63.0% reported BSO (BSO almost always occurred with hysterectomy [96.9%], with very few women reporting BSO without hysterectomy [3.1%]) and 37.0% reported hysterectomy alone.

PTSD and natural menopause

Trauma/PTSD status was not associated with onset of natural menopause in any model (Model 2: $HR_{high\ PTSD}$=1.00, 95% CI 0.95–1.04; Table 2; covariate estimates in Supplemental Table 1).

PTSD and cessation of menses due to surgery, BSO surgery, and hysterectomy alone

Trauma/PTSD status was associated with increased hazard of cessation of menses due to surgery (Table 3). Incidence of cessation of menses due to surgery were 18% (95% CI 1.09–1.27) higher for women exposed to trauma, 28% (95% CI 1.17–1.39) higher for women with low PTSD symptoms, and 34% (95% CI 1.22–1.48) higher for women with high PTSD symptoms, relative to those unexposed to trauma, accounting for age and calendar time (Model 1). Estimates remained significant but attenuated slightly when accounting for potential confounders and depression (Models 2). Each covariate significantly predicted cessation of menses due to surgery, while oral contraceptive use and depression in particular contributed to attenuation of the PTSD association (Supplemental Table 2, covariate estimates). Finally, estimates were modestly attenuated and remained significant when additionally adjusting for biobehavioral factors (Models 3).

Trauma/PTSD status was associated with increased risk of both BSO and hysterectomy alone among premenopausal women (Table 4). Any trauma exposure, low PTSD symptoms, and high PTSD symptoms were associated with a significantly increased risk of BSO relative to no trauma exposure (e.g., Model 2 $HR_{high\ PTSD}$=1.31, 95% CI 1.15–1.50). Trauma and PTSD were associated with increased incidence of premenopausal hysterectomy alone in a similar pattern (e.g., Model 2 $HR_{high\ PTSD}$=1.28, 95% CI 1.11–1.46).

Sensitivity analyses

Given the significant interaction between trauma/PTSD status and time period for cessation of menses due to surgery, we stratified models by time period. Supplemental Table 3 suggests similar patterns of association across time periods, with strongest associations evident for high PTSD during the earliest time period.

Accounting for competing events only negligibly impacted estimated hazards (data not shown). Models that included women's person-time while taking hormone therapy and adjusted for hormone therapy use produced slightly attenuated estimates to primary models (e.g., Model 2 for cessation of menses due to surgery, $HR_{high\ PTSD}$=1.19, 95% CI 1.11–1.27; Supplemental Tables 4–6). Excluding women who experienced sexual assault attenuated associations, though trauma and PTSD remained significantly associated with elevated risk of cessation of menses due to surgery (e.g., comparable $HR_{high\ PTSD}$=1.22, 95% CI 1.08–1.38). Fully prospective models produced generally similar patterns of estimates as the

primary models (Supplemental Tables 7–9). Notably, many women had reached menopause by 2008 and therefore prospective models included only a subset of the analytic sample. Moreover, the prospective model subset was potentially healthier with respect to early menopause, as they had not reached menopause by 2008. E-values indicated unmeasured confounding was unlikely to explain associations between trauma/PTSD and cessation of menses due to surgery; unmeasured confounders with adjusted associations of HR=1.45 to 1.67 with both the exposure and outcome would be required to render identified associations as being less meaningful (Supplemental Table 10).

Discussion

In a large sample of civilian women with 26 years of follow-up, PTSD was associated with higher incidence of cessation of menses due to surgery, but not with natural menopause. Trauma and PTSD symptoms were related to similarly elevated risk of BSO (with or without hysterectomy) and hysterectomy alone (without BSO). Trauma and PTSD increased risk for cessation of menses due to surgery in a graded fashion, with magnitude of risk increasing as PTSD symptom burden increased. Associations remained even when adjusting for sociodemographic confounders, depression, and bio-behavioral covariates, and adjusted effect sizes of high PTSD symptoms were similar to known risk factors like smoking [11,28]. Though prior work in this sample found that women with PTSD are more likely to use hormone therapy [29] and hormone therapy use may mask menopausal timing, estimates were largely similar in models adjusting for hormone therapy use versus excluding women's person-time while taking hormone therapy.

Our findings suggest that PTSD may be related to indications for gynecologic surgeries. Common indications for hysterectomy include cancer, menstrual disorders, uterine fibroids, pain, and endometriosis [30, 31], with increasing surgery rates by age [32]. Common non-cancerous indications for BSO in younger women are endometriosis and ovarian cysts [33]. Thus, it is possible that trauma and PTSD influence risk for these medical conditions, which in turn influence risk for gynecological surgery. In the US during the study period (1989–2015), it was common for women to choose elective BSO at the time of hysterectomy [34, 35], potentially explaining the similar associations across the two surgery types. Notably, the prevalence of hysterectomy overall in the US decreased over the study period, as trends towards more conservative, non-invasive management for gynecological conditions has increased [36]. However, further research should evaluate whether PTSD is related to indicators of these surgeries, particularly endometriosis, which has been linked to early life abuse [37].

Our findings linking PTSD with BSO are generally consistent with a case control study of premenopausal women with and without BSO, which identified that mood, anxiety, and somatoform disorders increased the odds of subsequent BSO [38]. Sexual assault, a trauma strongly predictive of PTSD [39], is shown to increase risk for hysterectomy in female veterans with PTSD, and this association was explained by increased gynecological pain, abnormal bleeding, and pelvic inflammation [11, 40]. Sexual assault did not explain the full effect of trauma/PTSD we observed, given that trauma and PTSD remained associated with elevated rates after excluding women who reported any sexual assault. Future research

should examine in more detail when and whether trauma type may influence associations between PTSD and gynecological surgery or natural menopause.

There are several possible mechanisms linking PTSD with gynecological surgeries. PTSD is associated with systemic inflammation [41], and PTSD-related inflammation may, in turn, increase risk for endometriosis and ultimately gynecological surgeries; this should be evaluated in future studies. PTSD may also influence preference for gynecological surgery due to heightened sensitivity to pain or distress [42]. For example, trauma and PTSD have been linked to greater chronic pelvic pain [43], which may increase the likelihood women will opt for surgery. Women with PTSD may have greater interactions with the healthcare system [44], leading to greater opportunity to identify conditions that would lead to gynecological surgery. While PTSD has been associated with riskier behaviors that are also associated with menopause timing [13, 14], associations between PTSD and gynecological surgeries were largely unaffected when adjusting for bio-behavioral factors, suggesting the factors included were not major pathway variables.

We did not find an association between trauma or PTSD with the timing of natural menopause, contradicting our initial hypothesis. Trauma/PTSD may have increased risk for gynecological surgeries that caused menses to cease before natural menopause could be reached, such that women with PTSD who would have had earlier natural menopause instead had surgery. However, sensitivity analyses that statistically account for competing events were almost identical to primary models. The measurement of menopause may have been too imprecise, as cessation of menses was reported every two years using only a few items. Measurement error may have precluded identification of whatever subtle effects trauma/PTSD may have on reproductive aging. Conversely, trauma and PTSD may not impact reproductive aging processes that dictate timing of natural menopause. Animal models of chronic, unpredictable, mild stress (which recapitulates depressive behavior) was associated with reduced ovarian reserve and premature ovarian failure [45]). However, consistent with our findings, human studies of depression and natural menopause or AMH generally found no associations or only a very modest association [46, 47]. Together this evidence suggests that distress may not have a strong association with natural menopause. Further studies examining objective markers of ovarian reserve may be able to identify more subtle effects of PTSD on reproductive aging.

The current study has several limitations. First, menopausal status and gynecological surgeries were self-reported; however, these outcomes are found to be largely accurate in validation studies [21]. Second, we did not ascertain indication for gynecological surgeries and were unable to examine if associations between trauma/PTSD with gynecological surgeries were driven by specific indications. Third, retrospective reporting of trauma and PTSD symptoms could lead to misclassification, particularly regarding the onset and severity of PTSD symptoms over time. Notably, prospective models that did not rely on retrospective timing of trauma/PTSD had similar patterns to primary findings. PTSD assessment was limited to a subset of symptoms based on DSM-IV diagnostic criteria; thus, additional research is warranted with the most recent criteria (DSM-V). Additionally, trauma and PTSD was assessed in 2008, thus later trauma and PTSD symptoms might have occurred which may have resulted in misclassification after 2008. Fourth, the eligible sample

was restricted to women who reported on trauma/PTSD in 2008, therefore women had to respond to biennial questionnaires at least through 2008. It is possible these women were healthier than those lost to follow-up before 2008, though overall loss to follow-up in NHS II has been minimal. Fifth, while we censored women diagnosed with cancer over time and excluded those who identified serious illness as their worst trauma, we did not account for other medical comorbidities which may both have been related to trauma/PTSD and have influenced gynecological health and surgeries. Future work should examine how medical illness is related to associations between trauma, PTSD, and menopause over time. Sixth, our sample included mostly white, female professional nurses, limiting generalizability. Women with nursing backgrounds may have broader health knowledge and more healthcare access than women without such backgrounds, thus associations may differ among the general population. Moreover, the current findings generally reflect white non-Hispanic women. African American women and those of lower socioeconomic status (SES) have demonstrated a higher likelihood of having hysterectomies and other gynecological surgeries [48]. While we adjusted for race/ethnicity and parental education in our analyses, due to limited data availability and small cell sizes, we could not examine in more detail how racial or socioeconomic disparities may have influenced the relationship between PTSD and cessation of menses; research in more diverse samples is warranted.

Our findings indicate that women with PTSD are at increased risk for pre-menopausal gynecological surgeries. Additional examination of biological pathways or indications for gynecological surgery or medically unnecessary surgeries in women with PTSD is therefore warranted. Research suggests a range of non-medical factors may influence occurrence of unnecessary hysterectomy or unnecessary BSO concurrent to hysterectomy such as patient race, age, geographical location, and healthcare provider characteristics [33, 49]; research should examine whether PTSD influences unnecessary gynecological surgery. In sum, trauma exposure and PTSD may influence risk for earlier gynecological surgery and cessation of menses, an important aspect of women's lifelong health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Participant characteristics of the analytic sample overall and as a function of trauma exposure and PTSD symptoms in 1989 (N=46,639)

	Full Sample	Trauma/PTSD Status			
		No Trauma	Trauma/No PTSD	Low PTSD symptoms	High PTSD symptoms
		N=14,340 (30.7%)	N=17,681 (37.9%)	N=8,921 (19.1%)	N=5,700 (12.2%)
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*
Sociodemographic Factors					
Age, years, *M (SD)*	34.5 (4.6)	33.9 (4.8)	34.6 (4.6)	34.9 (4.5)	34.9 (4.4)
Race/Ethnicity					
White, non-Hispanic	43,317 (92.9)	13,307 (92.8)	16,441 (93.0)	8,267 (92.7)	5,304 (93.1)
African American	418 (0.9)	100 (0.7)	166 (0.9)	109 (1.2)	44 (0.8)
Latina/Asian/Other	2,296 (4.9)	716 (5.0)	846 (4.8)	447 (5.0)	287 (5.0)
Parental Education					
High School Graduate	22,701 (48.7)	7,092 (49.5)	8,669 (49.0)	4,297 (48.2)	2,678 (47.0)
Some College	10,983 (23.5)	3,255 (22.7)	4,188 (23.7)	2,175 (24.4)	1,377 (24.2)
College Plus	10,879 (23.3)	3,396 (23.7)	4,015 (22.7)	2,063 (23.1)	1,358 (23.8)
Health Factors					
Age at Menarche					
≤ 11 years	11,004 (23.6)	3,138 (21.9)	4,143 (23.4)	2,243 (25.2)	1,479 (26.0)
12–13 years	27,137 (58.2)	8,579 (59.8)	10,326 (58.4)	5,032 (56.4)	3,196 (56.1)
≥ 14 years	8,365 (17.9)	2,583 (18.0)	3,161 (17.9)	1,618 (18.1)	1,009 (17.7)
Parity					
Nulliparous	14,306 (30.7)	4,764 (33.2)	5,066 (28.7)	2,638 (29.6)	1,818 (31.9)
1 Child	8,715 (18.7)	2,411 (16.8)	3,355 (19.0)	1,748 (19.6)	1,186 (20.8)
2 Children	15,322 (32.9)	4,815 (33.6)	5,938 (33.6)	2,928 (32.8)	1,684 (29.5)
3 or more Children	8,296 (17.8)	2,349 (16.4)	3,321 (18.8)	1,605 (18.0)	1,012 (17.8)
Oral Contraceptive Use Duration					
Never	7,751 (16.6)	2,739 (19.1)	2,882 (16.3)	1,319 (14.8)	804 (14.1)
1–47 months	18,871 (40.5)	5,627 (39.2)	7,133 (40.3)	3,644 (40.9)	2,457 (43.1)
48+ months	19,255 (41.3)	5,748 (40.1)	7,389 (41.8)	3,804 (42.7)	2,334 (40.9)
Any Hormone Therapy Use	4,109 (8.8)	1,014 (7.1)	1,548 (8.8)	854 (9.6)	687 (12.0)

	Full Sample	Trauma/PTSD Status			
		No Trauma	Trauma/No PTSD	Low PTSD symptoms	High PTSD symptoms
		N=14,340 (30.7%)	N=17,681 (37.9%)	N=8,921 (19.1%)	N=5,700 (12.2%)
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*
Tubal Ligation Surgery	7,643 (16.4)	2,214 (15.4)	2,954 (16.7)	1,549 (17.4)	921 (16.2)
Depression	6,985 (15.0)	1,732 (12.1)	2,444 (13.8)	1,379 (15.5)	1,425 (25.0)
Biobehavioral Factors					
BMI, *M (SD)*	23.7 (4.7)	23.5 (4.5)	23.7 (4.7)	23.8 (4.8)	24.1 (5.1)
Smoking Pack-Years, *M (SD)*	3.6 (6.9)	2.9 (6.2)	3.6 (6.8)	3.8 (7.1)	4.7 (7.9)
Alcohol Consumption, g/day, *M (SD)*	3.2 (6.1)	3.1 (5.9)	3.3 (6.2)	3.4 (6.4)	3.2 (6.0)
Physical Activity, MET hrs/week, *M (SD)*	24.4 (35.0)	23.8 (34.7)	24.8 (35.5)	24.2 (35.1)	24.6 (33.4)

Values are means (standard deviations [SD]) for continuous variables and frequencies (percentages [%]) for categorical variables, and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding or missing.

Low PTSD=1–3 PTSD symptoms; High PTSD=4–7 symptoms on the Short Screening Scale for PTSD (Breslau et al., 1999)

Missingness among categorical variables was not presented (missing for race/ethnicity 1.3%, parental education 4.5%, age at menarche 0.3%, oral contraceptive use duration 1.6%, depression 9.4%). Age at menarche and oral contraceptive use duration categories are collapsed descriptive purposes. Women who had undergone unilateral oophorectomy were not displayed as there were only 10 at baseline.

Table 2.

Cox proportional hazards models for the association of trauma exposure and PTSD symptoms with time to natural menopause across follow-up 1989–2015 (n=42,788; cases=18,520, person-years=558,182)

		Model 1	Model 2	Model 3
	N of Cases / person-years	HR (95% CI)	HR (95% CI)	HR (95% CI)
No Trauma	4,702 / 159,387	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Trauma/No PTSD	6,153 / 202,033	0.99 (0.95, 1.02)	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)
Low PTSD Symptoms	4,694 / 122,212	0.99 (0.95, 1.03)	0.98 (0.94, 1.02)	0.98 (0.94, 1.02)
High PTSD Symptoms	2,971 / 74,550	1.01 (0.96, 1.06)	1.00 (0.95, 1.04)	0.98 (0.94, 1.03)

Model 1: Adjusted for age and calendar time

Model 2: Adjusted for age, calendar time, race/ethnicity, parental education, age at menarche, parity, oral contraceptive use, tubal ligation, unilateral oophorectomy, and depression

Model 3: Adjusted for Model 2 plus BMI, pack years of smoking, alcohol use, and physical activity

Women did not contribute person-time to models while taking hormone therapy

*p<.10;

**p<.05;

***p<.0001

Table 3.

Cox proportional hazards models for the association of trauma exposure and PTSD symptoms with time to cessation of menses due to surgery across follow-up 1989–2015 (n=42,788; cases=4,611, person-years=571,414)

		Model 1	Model 2	Model 3
	N of Cases / person-years	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
No Trauma	1,051 / 162,786	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Trauma/No PTSD	1,618 / 206,306	1.18 (1.09, 1.27) ***	1.16 (1.07, 1.26) **	1.16 (1.07, 1.26) **
Low PTSD Symptoms	1,178 / 125,590	1.28 (1.17, 1.39) ***	1.25 (1.15, 1.36) ***	1.24 (1.14, 1.35) ***
High PTSD Symptoms	764 / 76,733	1.34 (1.22, 1.48) ***	1.29 (1.17, 1.42) ***	1.28 (1.16, 1.41) ***

Model 1: Adjusted for age and calendar time

Model 2: Adjusted for age, calendar time, race/ethnicity, parental education, age at menarche, parity, oral contraceptive use, and depression

Model 3: Adjusted for Model 2 plus BMI, pack years of smoking, alcohol use, and physical activity

Women did not contribute person-time to models while taking hormone therapy

* p<.10;

** p<.05;

*** p<.0001

Table 4.

Cox proportional hazards models for the association of trauma exposure and PTSD symptoms with time to two secondary outcomes, bilateral-salpingo-oophorectomy and hysterectomy alone while premenopausal, across follow-up 1989–2015

		Model 1	Model 2	Model 3
	N of Cases / person-years	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Bilateral-salpingo Oophorectomy (n=42,788; cases=2,357, person-years=573,471)				
No Trauma	535 / 163,228	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Trauma/No PTSD	821 / 207,066	1.18 (1.05, 1.31) **	1.17 (1.05, 1.31) **	1.17 (1.05, 1.31) **
Low PTSD Symptoms	609 / 126,111	1.32 (1.17, 1.49) ***	1.29 (1.15, 1.46) ***	1.29 (1.15, 1.45) ***
High PTSD Symptoms	392 / 77,067	1.38 (1.21, 1.58) ***	1.31 (1.15, 1.50) ***	1.29 (1.13, 1.48) **
Hysterectomy Alone while Premenopausal (n=42,799; cases=2,336, person-years=582,668)				
No Trauma	539 / 165,146	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Trauma/No PTSD	887 / 209,890	1.23 (1.11, 1.37) **	1.20 (1.07, 1.33) **	1.19 (1.07, 1.33) **
Low PTSD Symptoms	545 / 128,817	1.20 (1.07, 1.36) **	1.16 (1.03, 1.31) **	1.16 (1.02, 1.31) **
High PTSD Symptoms	365 / 78,815	1.31 (1.15, 1.50) ***	1.28 (1.11, 1.46) **	1.27 (1.11, 1.46) **

Bilateral-salpingo oophorectomy could occur with or without hysterectomy.

Model 1: Adjusted for age and calendar time

Model 2: Adjusted for age, calendar time, race/ethnicity, parental education, age at menarche, parity, oral contraceptive use, and depression

Model 3: Adjusted for Model 2 plus BMI, pack years of smoking, alcohol use, and physical activity

Women did not contribute person-time to models while taking hormone therapy

* p<.10;

** p<.05;

*** p<.0001