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Posttraumatic stress disorder and likelihood of hormone therapy use among women in the Nurses' Health Study II: a 26-year prospective analysis

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Abstract

Background: Posttraumatic stress disorder (PTSD) is associated with higher risk of certain chronic diseases, including ovarian cancer, but underlying mechanisms remain unclear. While prior work has linked menopausal hormone therapy (MHT) use with elevated ovarian cancer risk,

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little research considers PTSD to likelihood of MHT use. We examined whether PTSD was prospectively associated with greater likelihood of initiating MHT use over 26 years.

Methods: Using data from the Nurses' Health Study II, with trauma and PTSD (symptoms and onset date) assessed by screener in 2008 and MHT assessed via biennial survey (from 1989), we performed Cox proportional regression models with women contributing person-years from age 36 years. Relevant covariates were assessed at biennial surveys. We considered potential effect modification by race/ethnicity, age at baseline, and period (1989–2002 versus 2003–2015).

Results: Over follow-up, 22,352 of 43,025 women reported initiating MHT use. For example, compared to women with no trauma, the hazard ratio (HR) for initiating MHT was 1.18 for those with trauma/1–3 PTSD symptoms (95% confidence interval (CI):1.13–1.22) and 1.31 for those with trauma/4–7 PTSD symptoms (95% CI:1.25–1.36, p trend <.001), adjusting for sociodemographic factors. Associations were maintained when adjusting for reproductive factors and health conditions. We found evidence of effect modification by age at baseline.

Conclusions: Trauma and number of PTSD symptoms were associated with greater likelihood of initiating MHT use in a dose-response manner.

Impact: MHT may be a pathway linking PTSD to altered chronic disease risk. It is important to understand why women with PTSD initiate MHT use.

Introduction

Posttraumatic stress disorder (PTSD) is a prevalent and debilitating psychological condition that can occur following trauma exposure. Epidemiologic studies have found more than doubled risk of developing ovarian cancer among women with PTSD relative to healthy women[1,2]. However, pathways by which PTSD leads to this elevated risk remain unclear. Although beneficial for some conditions (e.g. reducing fracture risk[3]), use of menopausal hormone therapy (MHT) has been associated with increased risk of certain chronic diseases, including ovarian cancer[4,5]. Elevated risk of ovarian cancer has generally been seen for estrogen alone MHT use. However, there is also evidence that estrogen and progesterone MHT use is associated with increased risk of the disease[5–10]. Other work has demonstrated associations between MHT use and ovarian cancer can differ by histologic subtype[11,12]. However, a recent meta-analysis reported that the strongest associations for MHT use were with serous ovarian cancer, the most common and aggressive subtype which has previously been linked with PTSD[1,6,11,12]. Therefore, if women with versus without PTSD differ in initiating MHT, this may partly account for their altered risk of ovarian cancer, thereby informing prevention strategies. Only one study has examined whether MHT is more prevalent in women with versus without PTSD, and findings were suggestive[13], consistent with evidence indicating that women with PTSD have more severe menopausal symptoms[14–16]. Moreover, depression, a mental health disorder highly comorbid with PTSD[17], has been associated with menopausal symptoms and MHT use intiation[13,18].

A 2015 survey showed that nearly one in ten US women between the ages of 40–84 years uses MHT[19]. In 2002, the Women's Health Initiative (WHI), a set of randomized trials to test the efficacy of MHT, found MHT use associated with elevated risks of some chronic diseases[20]. Following this study, the US Preventive Service Task Force modified guidelines

to recommend MHT use primarily for addressing menopausal symptoms and preventing postmenopausal osteoporosis, with minimal doses and duration[3], and not for the purposes of preventing other chronic disorders (e.g. cardiovascular diseases[21,22]). This landmark study therefore changed prescribing practices, and the prevalence of MHT use decreased after 2002[23,24].

Taken together, the evidence of associations of ovarian cancer with both PTSD and MHT use suggests that examining the association between PTSD and MHT use may provide insight into a potential biobehavioral pathway linking PTSD to heightened ovarian cancer risk. The aim of the present study was to investigate whether PTSD was prospectively associated with initiating MHT use. We hypothesized women with trauma exposure and PTSD symptoms (versus no trauma exposure) would be more likely to initiate MHT use over time. We expected PTSD-MHT associations might be slightly stronger before versus after 2002, when prescribing practices changed[20,23,24]. In addition, as prior work suggests that the prevalence of PTSD and MHT use and reproductive factors vary by age[4], smoking status[25] and race/ethnicity[13,24,26,27], we explored whether PTSD-MHT associations might differ across these factors.

Materials and methods

Study sample

Data are from the Nurses' Health Study II (NHS II), an ongoing cohort study of US female registered nurses, which enrolled 116,429 women aged 24–42 years at baseline in 1989, and has measured an extensive range of sociodemographic, medical, and behavioral variables primarily via biennial questionnaires. The study protocol was approved by the institutional review boards (IRBs) of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and the IRBs allowed participants' completion of questionnaires to be considered as implied consent. A PTSD substudy was conducted in 2008, measuring lifetime trauma exposure and PTSD symptoms among a subset of women. Briefly, in 2008, 60,804 women who responded to both an earlier 2001 violence exposure questionnaire (n=68,376) and the 2007 biennial survey were invited to participate in the PTSD substudy. Of those women, 54,703 responded. We excluded women with incomplete/missing information on trauma/PTSD status (n=1,296) and women who reported current/previous use of MHT or were missing MHT information at study baseline in 1989 (n=6,430). After these exclusions, there were 46,977 eligible women at baseline in 1989. Our analytic sample consisted of women who remained eligible at age 36 years (n=43,025).

Measures

Exposure—In 2008, women reported their lifetime trauma exposure and PTSD symptoms. Lifetime trauma exposure was measured with the modified Brief Trauma Questionnaire[28], which included 16 traumatic events (e.g., sexual harassment, accidents, sudden death of a loved one), along with an open-ended prompt (any other serious event). Women indicated whether they had ever experienced each event, indicated which event(s) represented their first and worst trauma(s) and the ages these traumas occurred. Then, women reported the presence/absence of PTSD symptoms with respect to their worst trauma via the Short

Screening Scale for *DSM-IV* PTSD[29]. This scale includes 7 items capturing core PTSD symptomatology, with 5 symptoms relating to avoidance and numbness and 2 related to hyperarousal (see Kimerling et al.[30] for list of items). Items are summed to derive a PTSD symptom count, ranging from 0 to 7. A previous community-based study of individuals aged 18–45 years found that identifying probable PTSD cases by having 4+ symptoms from this PTSD screener showed 80.3% sensitivity and 97.3% specificity relative to PTSD diagnosed by a gold-standard structured interview[29]. Following our previous work, we classified trauma/PTSD status into four groups, no trauma, trauma exposure with no PTSD symptoms, trauma exposure with 1–3 PTSD symptoms (low PTSD symptoms), and trauma exposure with 4–7 PTSD symptoms (high PTSD symptoms)[1,31]. For the current analyses, trauma/PTSD status was time-updated according to ages at first and/or worst trauma. For instance, if women reported first trauma in 1985 and worst trauma with 4–7 PTSD symptoms in 2002, their trauma/PTSD status were classified as trauma/no PTSD for 1985–2001 and trauma/high PTSD symptoms in 2002 and thereafter.

Outcome

MHT was measured at baseline in 1989 and biennially thereafter via self-reported questionnaire. At baseline, women were asked “Have you EVER used replacement sex hormones (e.g. estrogen)?”. At each time point thereafter, women were asked whether they had used female replacement hormones (other than oral contraceptives) since the last survey date. If women reported use, they were asked the duration of use in categories of months (e.g. 1 or less, 2–4, 5–9, 10–14, 15–19, 20–24). Initiation of MHT use was defined as occurring when women who had not reported MHT use in any previous cycle reported any MHT use in the current cycle. Time to initiation of MHT (length in months) was defined as time from study enrollment until the survey return date at which first MHT use initiation was reported, minus the duration of MHT use reported on that same survey. Duration was estimated using the middle value for each response category. For example, if a participant reported no MHT use on the 1991 questionnaire and then reported MHT use on the following 1993 questionnaire with a duration of 5–9 months, her time to initiation was from study enrollment to the month of questionnaire return in 1993 minus 7 months (e.g., June of 1993 minus 7 months). We also derived a binary measure for whether women stopped MHT use, defined as: women who reported use in a previous cycle, and subsequently did not report use in the current cycle (reported past/prior/unknown/missing).

Covariates

We accounted for an extensive range of sociodemographic and reproductive factors, health conditions and health-related behaviors as covariates. Race/ethnicity was coded as non-Hispanic white, black, Hispanic, Asian, other racial/ethnic groups. Time-varying factors were updated at each available cycle and included age (in months), a measure of socioeconomic status captured by median household income of residential census tract (in quartiles), as well as reproductive factors, health conditions and health-related behaviors. Reproductive factors included menopausal status (premenopausal, postmenopausal, unknown), parity (defined as the number of pregnancies longer than 6 months: 0, 1–2, 3+), oral contraceptive use (ever versus never), history of gynecological comorbidities (premenstrual syndrome and endometriosis defined using self-reported responses regarding

physician diagnoses) and related surgeries (hysterectomy, uni-/bi-lateral oophorectomy, tubal ligation). Health conditions included lifetime history of depression, defined by a positive response on any of the following items: self-reported physician-diagnosed depression (assessed biennially since 2003) or antidepressant use (assessed biennially since 1993 except 1995 and 2001); score ≤59 on the 5-item Mental Health Inventory[32] administered in 1993, 1997, and 2001, or score ≥10 on the 10-item Centers for Epidemiologic Study Depression[33,34] administered in 2008 and 2013. Other health conditions included self-reported history of cancer (any type except for gynecological, breast, squamous/basal cell skin cancer), cardiovascular disease (coronary heart disease or stroke), and type 2 diabetes.

Health-related behaviors included physical activity (<3.0, <18.0, 18.0+ metabolic equivalent task hours per week; MET-hrs/wk), smoking status (never, former, current), alcohol use (0, <5.0, 5.0+ gm/day)[35]. We also included body mass index (BMI) as a categorical variable (underweight <18.5, normal weight 18.5-<25.0, overweight 25.0-<30.0, obese ≥30.0 kg/m^2). Missing data was included as an indicator variable for race/ethnicity, median household income, parity, oral contraceptive use, depression, smoking status, alcohol use, physical activity and BMI (all missing <5% at baseline except median household income which was approximately 13%).

Analysis

We first examined the distribution of covariates by trauma/PTSD status at baseline in 1989 (regardless of whether women entered the analysis in 1989 or later). To evaluate whether trauma/PTSD status was associated with increased likelihood of initiating MHT use, we performed time-to-event analysis using a Cox proportional hazards model, considering time to initiating MHT use or censoring (lost to follow-up using last returned questionnaire date if they did not return the 2015 questionnaire, onset of gynecological/breast cancer, death, or study termination), whichever occurred first. To ensure women were at risk of the outcome when entering the study, women contributed person-time from the year that they turned age 36 years (the 5^{th} percentile of MHT initiation age), regardless of menopausal status. We estimated the hazard ratio (HR) and 95% confidence intervals (CI) of initiating MHT use by trauma/PTSD status (reference group: no trauma).

Model 1 adjusted for sociodemographic factors (race/ethnicity and median household income). Model 2 further adjusted for reproductive factors (menopausal status, parity, oral contraceptive use and history of premenstrual syndrome, endometriosis, hysterectomy, uni-/bi-lateral oophorectomy, tubal ligation) and other health conditions (history of depression, cancers, cardiovascular disease, diabetes). Model 3 additionally adjusted for health-related behaviors (physical activity, smoking status, alcohol use) and BMI.

We tested for violation of the proportional hazards assumption by age at baseline (among those older than 35 years; < versus ≥39 years in 1989) and by period based on change in MHT prescribing guidelines (1989–2002 versus 2003–2015). We conducted two likelihood ratio tests (LRT), comparing a model with versus without an interaction term between each trauma/PTSD status level and period or age, adjusting for model 2 covariates. We additionally examined potential effect modification of PTSD status by race/ethnicity and

smoking status at baseline. When interaction terms were suggestive, we also performed stratified analyses by these factors.

As a sensitivity analysis, we assessed whether the association between trauma/PTSD status and likelihood of initiating MHT use was robust to potential bias from retrospective measurement of trauma/PTSD status (i.e., reporting of MHT use might affect reporting of trauma/PTSD status in 2008). For this, we performed a fully prospective analysis, considering trauma/PTSD assessment in 2008–2009 as baseline and only evaluating MHT use initiation thereafter. To explore whether the relationship between PTSD and MHT use initiation differed by whether women had gynecological surgery (i.e., hysterectomy and/or bilateral oophorectomy), we performed sensitivity analyses where we separately looked at the relationship in women who had intact uterus/ovaries throughout follow-up and women who had gynecological surgery. As women may cycle on and off MHT use, for additional sensitivity analysis, we conducted repeated measures logistic regression using generalized estimating equations simply considering if women were using or not using MHT at each cycle. Lastly, we repeated our main analysis removing women who remained premenopausal throughout the follow-up to assess potential effects on our analysis by including these women.

Results

In our sample, a majority were non-Hispanic white women. At study entry, most of the sample was premenopausal (over 99%) and most women underwent menopause during follow-up, with 1165 (2.7%) women premenopausal at study end. The mean age at study entry was 37.7 years (standard deviation (SD)=1.9) and the mean age at MHT initiation was 47.4 years (SD=6.1)(see Supplementary Figure S1). Compared to women with no trauma, women with trauma exposure and high PTSD symptoms had higher prevalence of previous gynecological comorbidities (premenstrual syndrome and endometriosis) and other health conditions (e.g. depression) at study entry (Table 1).

Over 26 years of follow-up (1989–2015), more than half of the sample (n=22,352) initiated MHT use. Overall, trauma exposure and number of PTSD symptoms were associated with greater likelihood of initiating MHT use in a dose-response manner. Compared to women with no trauma, women with trauma exposure and no PTSD symptoms had a 9% greater likelihood of initiating MHT (HR=1.09, 95% CI:1.05–1.13), while those with trauma exposure and low PTSD symptoms had 18% greater likelihood (HR=1.18, 95% CI:1.13–1.22) or with high PTSD symptoms had 31% greater likelihood (HR=1.31, 95% CI:1.25–1.36), after adjusting for sociodemographic factors (p trend <.001) (Table 2). Associations of PTSD with initiating MHT use substantially attenuated, but remained significant, when adjusting for reproductive factors and health conditions (including depression) (e.g. HR=1.17, 95% CI:1.12–1.22 for women with trauma exposure and high PTSD symptoms compared to women with no trauma). Further adjusting for health-related behaviors and BMI showed little change in associations.

We found the proportional hazards assumption was violated for age at baseline (< versus ≥39 years) (LRT p=0.01), but not for period based on change in MHT prescribing guidelines

(1989–2002 versus 2003–2015) (LRT p=0.45). Further exploration suggested somewhat stronger effect estimates among women who were younger at the time they entered into this study versus older but few differences by period, although it appears that more women initiated MHT use prior to (1989–2002; n=15,194) than after (2003–2015 period; n=7,158) the revised guidelines were implemented[23] (Supplementary Tables S1 and S2). As the direction of effects was consistent among younger versus older women, we present the primary findings among the full sample. There was no strong evidence of effect modification of the PTSD-MHT association by race/ethnicity (p for interaction=0.08) and smoking status at baseline (p for interaction=0.91). However, given suggestive effect modification by race/ethnicity, we conducted stratified analysis which showed no clear difference compared to our main findings (Supplementary Table S3).

In sensitivity analyses using a fully prospective design, results were highly similar to our main analysis (Table 2). For instance, compared to women with no trauma, risk of MHT initiation was elevated for those with trauma and high PTSD symptoms (HR=1.30, 95% CI:1.15–1.46) over 7–8 years of follow-up, after adjusting for sociodemographic factors. We also found a similar pattern of findings to our main analysis in both women who had intact uterus/ovaries throughout follow-up and women who had gynecological surgery, although the evidence was weaker for women with gynecological surgery, likely due to low statistical power to detect associations in this small subgroup (Supplementary Table S4). When also considering whether women stopped and restarted MHT use over follow-up, findings between trauma/PTSD status and MHT use were comparable to the main analysis (Supplementary Table S5). Lastly, results were highly similar to our main findings when excluding women who remained premenopausal during all follow-up (n=1,165).

Discussion

We found evidence for a dose-response relationship between trauma with PTSD symptoms and increased likelihood of initiating MHT use among women over 26 years of follow-up. These relationships were remarkably similar before and after findings from the WHI led to new clinical guidelines recommending more limited use of MHT[23] (comparing 1989–2002 versus 2003–2015), and by race/ethnicity, age at baseline and smoking status. We note that effect estimates were suggestively stronger among non-Hispanic white and black women, although given the much smaller number of women available for these analyses, these findings should be viewed cautiously. Although our sample size in sensitivity analyses within women with gynecological surgery was small, as MHT initiation often precedes these surgeries, we did see a similar pattern of results whereby women with PTSD had greater likelihood of initiating hormone therapy after hysterectomy and/or bilateral oophorectomy. Interestingly, associations were maintained even after adjusting for depression, which is comorbid with PTSD and also associated with MHT use[13,17,18]. Notably, findings were also maintained in the fully prospective analyses, where MHT initiation was reported after the PTSD assessment in 2008, reducing concerns about retrospective reporting bias. Overall, these results suggest that women with high PTSD symptoms are more likely to initiate MHT use.

Potential pathways linking PTSD and MHT use

Prior work suggests a persistent psychological stress reaction, such as PTSD due to trauma exposure, disrupts the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary system[1]. Disruptions can impact the endocrinological and immune systems and result in chronic inflammation, as evidenced by increased risk of some chronic diseases[36] as well as early and/or more severe menopausal transition in women with PTSD[14,15]. Previous research has also found associations between higher levels of psychological distress and more frequent, severe, or persistent menopausal symptoms, leading to increased likelihood of MHT initiation[13,15,18,27,37–41]. Notably, a recent prospective study with multiethnic participants showed that women with PTSD had increased risk of developing vasomotor (e.g., hot flashes) and vaginal (e.g., dryness) symptoms,[16] which are commonly treated with MHT[3]. This may represent a key mechanism explaining our observed PTSD-MHT association. Other work has suggested that women with PTSD are more likely to have a hysterectomy, which is routinely followed with prescription of MHT[15]. In line with this, we found an attenuated PTSD-MHT association in a model including adjustment for gynecological surgeries and some evidence for an increased likelihood of initiating MHT use in women with PTSD who had had gynecological surgery.

An unhealthy lifestyle, including increased sedentary behaviors, and related factors like adiposity, may also contribute to the PTSD-MHT association. Prior work has shown that women with higher PTSD symptom levels are at increased risk of obesity and more likely to have accelerated weight gain[31] as well as less likely to be physically active[42,43] or have a healthy diet[44]. These factors have also previously been associated with more menopausal symptoms[45–48], potentially increasing likelihood of initiating MHT. However, we did not find that further adjusting for health-related behaviors and BMI made notable change to the PTSD-MHT association magnitude, and our results therefore do not provide strong support for this pathway.

Strengths & Limitations

To our knowledge, this is the first study to provide evidence for greater likelihood of initiating MHT use among women with trauma exposure and high PTSD symptoms. A key strength of this study is the use of a prospective design with a large cohort of women, followed-up over 26 years. Additionally, an extensive range of possible confounders were measured and included in the analyses. Our study also has some limitations. First, trauma/PTSD status was assessed retrospectively at one time point in 2008 and may therefore include misclassification due to recall bias or lack of follow-up information[49,50]. However, results were very similar in sensitivity analysis using a fully prospective design. MHT was self-reported and therefore also subject to potential misclassification. Second, we do not have data available to permit detailed investigation of whether women with PTSD were more likely to initiate a certain type of MHT use (i.e. estrogen alone or estrogen and progesterone combined) although elevated risks of certain chronic diseases, such as ovarian cancer, has been shown for both types of MHT use[5–10]. Third, our sample mainly consisted of non-Hispanic white female professionals and generalizability of our findings may therefore be limited; however we found no clear evidence for effect modification by race/ethnicity and show some evidence of associations across all race/ethnic groups, even though

some groups had few cases. Fourth, our sample was comprised of women who remained in the cohort and were responsive to biennial and supplemental questionnaires. While the NHS cohorts generally have low attrition, women who remain in the cohort may differ from those who did not[51,52]. Lastly, as this was an observational study, the possibility of unmeasured confounding bias remains.

Conclusions

Findings from the present study suggest women who experience trauma and PTSD symptoms are more likely to initiate MHT use than women with no trauma exposure. Moreover, MHT initiation appears to be monotonically related to number of PTSD symptoms that occur in response to trauma, suggesting that the resulting psychological distress rather than trauma experience per se may be a critical driver. As MHT use is associated with elevated risk of certain chronic diseases including ovarian cancer, which are also associated with PTSD, MHT use may be implicated in associations of PTSD with those outcomes[4,53,54]. Reasons why women with PTSD initiate MHT use, such as increased severity of menopausal symptoms in these women and the corresponding benefits of MHT, need to be understood to help address concerns and prognoses in this at-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

PTSD	Posttraumatic stress disorder
MHT	Menopausal hormone therapy
WHI	Women's Health Initiative
HR	Hazard ratio
CI	Confidence interval
NHS II	Nurses' Health Study II
MET-hrs/wk	Metabolic equivalent task hours per week
BMI	Body mass index
LRT	Likelihood ratio tests

SD	Standard deviation
IRBs	Institutional review boards

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Table 1.

Age-standardized characteristics at the time of study entry by trauma/PTSD status among 43,025 women in the Nurses' Health Study II

	No trauma exposure (n=11,866)	Trauma exposed, no PTSD symptoms (n=16,894)	Trauma exposed, 1–3 PTSD symptoms (n=8,775)	Trauma exposed, 4–7 PTSD symptoms (n=5,490)
Age in years: mean (SD)[a]	37.68 (1.9)	37.73 (1.9)	37.67 (1.9)	37.63 (1.8)
Race (%)				
Non-Hispanic white	93.6	94.0	93.5	94.1
Black	0.8	1.0	1.2	0.8
Hispanic	0.8	1.2	1.7	1.3
Asian	1.6	1.1	1.2	1.1
Other[b]	1.8	1.5	1.2	1.5
Median Household Income (%)				
Quartile 1	19.9	20.0	20.8	21.8
Quartile 2	21.9	22.4	21.6	23.2
Quartile 3	24.3	23.0	23.8	23.4
Quartile 4	25.0	26.2	25.8	23.9
Missing	9.0	8.5	8.0	7.7
Parity (%)				
0	23.1	19.0	20.2	22.9
1–2	53.2	54.9	54.1	53.4
3+	23.8	26.1	25.7	23.8
Oral contraceptive use (%)				
Never user	17.9	15.2	14.0	13.5
Ever/current user	82.0	84.7	85.9	86.3
Premenstrual syndrome (%)	14.8	18.6	20.5	27.6
Endometriosis (%)	2.7	2.9	3.5	3.6
Hysterectomy (%)	3.2	4.2	4.1	4.9
Oophorectomy (%)				
None	98.9	98.7	98.5	98.3
Unilateral	1.0	1.2	1.4	1.6
Bilateral	0.1	0.0	0.1	0.1
Unknown	0.0	0.1	0.1	0.0
Tubal ligation (%)	19.4	21.4	21.8	20.0
Depression history (%)	18.2	21.1	24.9	40.6
Smoking status (%)				
Never	71.3	66.8	65.2	60.3
Former	19.7	22.9	24.1	27.0
Current	8.7	10.0	10.6	12.3
Alcohol use (%)				
None	39.5	38.6	38.5	41.1
0–4.9gm/d	40.6	40.7	39.8	38.3

	No trauma exposure (n=11,866)	Trauma exposed, no PTSD symptoms (n=16,894)	Trauma exposed, 1–3 PTSD symptoms (n=8,775)	Trauma exposed, 4–7 PTSD symptoms (n=5,490)
5+gm/d	19.9	20.6	21.7	20.7
Physical activity (%)				
<3 total MET-hrs/wk	15.3	14.4	14.5	14.5
3-<18 MET-hrs/wk	46.5	46.0	46.5	44.9
18+ MET-hrs/wk	37.7	39.1	38.4	40.1
BMI (%)				
Underweight (<18.5mg/k^2)	2.5	2.3	2.3	2.2
Normal (18.5-<25.0mg/k^2)	65.7	64.4	63.3	62.4
Overweight (25-<30mg/k^2)	20.1	20.9	21.1	21.8
Obese (30+mg/k^2)	11.7	12.4	13.3	13.6

Note: Values reflect the characteristics of women when they enter the analytic sample, either at study baseline in 1989 or when they turn 36. Over 99% of women were premenopausal at study entry.

Values are means(SD) or medians(Q25, Q75) for continuous variables; percentages or ns or both 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 (all missing <5% except median household income which was higher and therefore included in the table).

[a]Value is not age adjusted

Table 2.

Association between Trauma/PTSD status and MHT initiation among 43,025 women in NHS II for full study follow-up (1989–2015) and prospective follow-up (2008–2015)

		Model 1		Model 2		Model 3	
	n for cases / person-year	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Full study follow-up: baseline at 1989 through to the study end in 2015 (n=22,352 events among 626,200 person-year from 43,025 women)							
No Trauma	4,957 / 156,190	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Trauma no PTSD sx.	7,778 / 220,182	1.09 (1.05, 1.13)	<.001	1.06 (1.02, 1.10)	0.001	1.06 (1.03, 1.10)	0.001
Trauma 1–3 PTSD sx.	5,719 / 154,676	1.18 (1.13, 1.22)	<.001	1.12 (1.07, 1.16)	<.001	1.12 (1.08, 1.16)	<.001
Trauma 4–7 PTSD sx.	3,898 / 95,152	1.31 (1.25, 1.36)	<.001	1.17 (1.12, 1.22)	<.001	1.17 (1.12, 1.22)	<.001
P trend		<.001		<.001		<.001	
Fully prospective: baseline at PTSD questionnaire return through to the study end in 2015 (n=2,708 events among 123,594 person-year from 18,584 women)							
No Trauma	561 / 28,307	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Trauma no PTSD sx.	783 / 37,500	1.07 (0.96, 1.20)	0.21	1.06 (0.95, 1.18)	0.32	1.06 (0.95, 1.18)	0.30
Trauma 1–3 PTSD sx.	813 / 36,147	1.15 (1.03, 1.28)	0.02	1.11 (0.99, 1.24)	0.06	1.11 (1.00, 1.24)	0.06
Trauma 4–7 PTSD sx.	551 / 21,640	1.30 (1.15, 1.46)	<.001	1.20 (1.06, 1.36)	0.003	1.22 (1.08, 1.38)	0.001
P trend		<.001		0.002		0.001	

Note: age (in months) and follow-up wave were stratified. Covariates were time-updated apart from race/ethnicity.

Model 1: adjusted for sociodemographic factors: race/ethnicity (non-Hispanic white, Asian, Hispanic, black, others, missing) and median household income (in quartiles).

Model 2: Model 1 + reproductive factors and health conditions: menopausal status (pre, post, dubious/unknown/missing), parity (pregnancy 6+month: 0, 1–2, 3+), oral contraceptive use (current use, never use), premenstrual syndrome (ever, never), endometriosis (ever, never), hysterectomy (ever, never), oophorectomy (bilateral, unilateral, surgery with unknown number removed, never), tubal ligation (ever, never), depression (ever, never), cancer (ever, never), cardiovascular disease (ever, never), diabetes (ever, never).

Model 3: Model 2 + health-related behaviors: smoking status (never, former, current, missing), alcohol use (0, <5, 5+gm/day, missing), physical activity (<3, <18, 18+MET-hrs/wk, missing), BMI (<18.5, <25, <30, 30+kg/m^2, missing).