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Menopausal Hormone Therapy and Suicide in a National Sample of Midlife and Older Women Veterans

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Abstract

Background: Among midlife and older women, menopause symptoms and menopausal hormone therapy have been linked to mental health disorders and other comorbidities related to suicide. However, the role of hormone therapy as a prognostic factor of suicide risk is largely unknown.

Objectives: To examine associations between menopausal hormone therapy, suicide attempts, and suicide among midlife and older women Veterans.

Research Design: In this longitudinal analysis of national Veterans Health Administration data from women Veterans aged 50 years and above, we used Fine-Gray proportional hazards models to examine associations between menopausal hormone therapy (prescribed in 2012–2013) and incident suicide attempts and suicide (index date—2016).

Measures: Menopausal hormone therapy and psychoactive medications from pharmacy records; suicide attempts and suicide from national suicide data repositories; demographic variables, medical and psychiatric diagnoses, and substance use disorders from electronic medical record data and International Classification Diagnoses-9-CM codes.

Results: In this national sample of 291,709 women Veterans (mean age 60.47, SD 9.81), 6% were prescribed menopausal hormone therapy at baseline. Over an average of 4.5 years, 2673 had an incident suicide attempt (93%) or death by suicide (7%). Adjusting for age, race, and medical diagnoses, menopausal hormone therapy was associated with increased risk of suicide attempt (hazard ratio 1.41; 95% confidence interval, 1.22–1.64) and over 2-fold increased risk of

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death by suicide (hazard ratio 2.47; 95% confidence interval, 1.58–3.87). Associations with death by suicide remained significant after accounting for psychiatric comorbidity and psychoactive medications.

Conclusions: Menopausal hormone therapy may be an important indicator of suicide risk among midlife and older women.

Keywords

suicide; Veterans; women's health

Over the past decade, suicide rates among midlife and older women in the United States have increased by more than 30%.[1] This is a particular concern in the Veterans Health Administration (VHA), as half of women Veterans are aged 50 and older, and rates of suicide among women Veterans are over twice that of their civilian peers.[2] For women Veterans of all ages, possible reasons for elevated suicide risk include higher rates of known risk factors, such as mental health and substance use disorders; exposure to interpersonal trauma,[3] both in civilian and military life; chronic health conditions; and access to and use of lethal means, including firearms.[2–5] However, little is known about clinically meaningful and modifiable predictors of suicide risk for midlife and older women. More information is needed to identify women most at risk during this vulnerable period of the lifespan, and to guide targeted prevention efforts.

Midlife and older women face aging-related challenges that may influence suicide risk.[6] These can include social and role changes,[7] the development and exacerbation of chronic health conditions, and menopause-related and aging-related symptoms[6] such as hot flashes, night sweats, and genitourinary symptoms affecting sexual function.[8,9] These symptoms can have a negative impact on quality of life and functioning,[6] with well-established relationships with chronic health conditions, sleep disruption, and anxiety and depression.[10–13] Menopausal hormone therapy, including systemic hormone therapy for hot flashes and night sweats and systemic and/or vaginal estrogen for genitourinary symptoms,[8,9] is considered front-line treatment for severe menopause symptoms. Menopausal hormone therapy may effectively relieve these symptoms and improve quality of life,[14] but it is not a desired or appropriate option for all women given safety concerns related to cardiovascular and cancer risk.[8] Its use has also been linked to psychiatric comorbidity in community[15] and Veteran[16] samples, and to suicidal ideation in a cohort of postmenopausal Korean women.[17] Menopausal hormone therapy may therefore serve as a useful indicator of suicide risk among midlife and older women, potentially reflecting underlying complex comorbidity.

In this study, we used national VHA data from midlife and older women Veterans to examine associations between menopausal hormone therapy and suicide risk. We hypothesized that women who had been prescribed hormone therapy would be more likely to have incident suicide attempts and suicide during the study period, independent of known demographics and clinical risk factors.

METHODS

Data Source

The cohort for this longitudinal study was drawn from the linkage of 4 national databases: (1) VHA's National Patient Care Database, which includes all inpatient and outpatient VHA services; (2) Centers for Medicare and Medicaid Services data, which includes medical claims/diagnoses; (3) VHA's Suicide Prevention Applications Network, which contains information on suicide and suicide attempts; and (4) VHA's National Suicide Data Repository, which includes cause-specific death information. The primary analytic cohort was comprised of women Veterans aged 50 and older with at least 1 VHA clinical encounter in fiscal years (FY) 2012–2013, defined as the index visit. Data included documented nonfatal suicide attempts and death by suicide following the index visit for each patient through December 31, 2016. The study was approved by the institutional review boards of the (institution blinded for peer review) and the Research and Development Committee of the (institution blinded for peer review).

Variables

Independent Variable—Menopausal hormone therapy (including both systemic and vaginal preparations) was identified by VHA and Centers for Medicare and Medicaid Services pharmacy records and V-codes from medical records, with prescriptions filled and/or codes present at least once on or within the 2 years before the index visit date in FY 2012–2013. We restricted exposure to that time period to maintain a comparable starting point to measure time-to-event for all women in the sample. For sensitivity analyses, we also created a variable categorizing women who initiated hormone therapy after the index visit. Patients with International Classification of Diseases-9 codes indicating sex identity disorder in the medical record were excluded from analyses due to potential for receipt of hormone therapy for sex-affirming purposes rather than for treatment of menopause symptoms.

Dependent Variables—Suicide attempts and death by suicide were identified by documentation in Suicide Prevention Applications Network and Suicide Data Repository data. First, death by suicide was identified from each Veteran's index visit in FY 2012–2013 through December 31, 2016, followed by nonfatal suicide attempts during the same period. Suicide attempts were therefore not categorized for any Veteran who died by suicide during the observed period. To assess time-to-event in a consistent manner for all Veterans in the sample, only the initial suicide attempt was categorized for any Veteran with multiple nonfatal suicide attempts during the observed period. Given the relatively small number of documented deaths by suicide, suicide and suicide attempts were combined for primary analyses. Death by suicide was also examined individually in separate secondary analyses.

Covariates

All covariates were selected a priori due to known or potential relationships with suicide risk.[2,18–20] Age was defined as age on the index visit date, calculated from birth date documented in the medical record. Race was categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and "other" (including missing race data), based on self-reported race in the medical record. Educational and income strata were classified by linking Veteran

data to 2013 US Census data. Education was categorized according to college education completion in the Veteran's zip code tabulation area (≤ 25% vs. > 25% of the adult population); income was categorized by median zip code tabulation area income tertiles, consistent with previously published methodology. Medical and psychiatric diagnoses and psychoactive medications were obtained from medical and pharmacy records from the index visit and 2 years before that visit. Medical diagnoses (hypertension, myocardial infarction, cardiovascular disease, diabetes mellitus, and obesity), psychiatric diagnoses (depression, dysthymia, bipolar disorder, posttraumatic stress disorder, generalized anxiety disorder, panic disorder, specific phobia), and substance use disorders (alcohol use disorder, drug use disorder, tobacco use disorder) were defined by International Classification of Diseases-9 codes. Psychoactive medications (benzodiazepines, opioids, sedative-hypnotics, antidepressants, antipsychotics, and antiepileptics) were abstracted from pharmacy records.

Statistical Analyses

Descriptive statistics were used to summarize key variables and covariates, stratified by suicide-related outcomes with differences examined using χ^2. In exploratory analyses of a potential proxy for severity of underlying comorbidities and/or access to lethal means, descriptive statistics were also used to compare use of psychoactive medications (any and polypharmacy, defined as ≥ 3 psychoactive medications) in women with and without suicide attempts, stratified by hormone therapy. Incidence rates were calculated from the incidence of suicide-related outcomes by person-years of observation, stratified by hormone therapy.

Fine-Gray proportional hazards models were used to examine risk of incident suicide attempts and death by suicide for women Veterans prescribed menopausal hormone therapy relative to those not prescribed hormone therapy, based on time-to-event from the index visit. For Veterans without incident suicide or suicide attempts, data were censored at the end of the followup period. Among those who died by causes other than suicide, death was accounted for as a competing risk. We generated 4 models: (1) unadjusted, (2) adjusted for demographic variables and medical diagnoses, (3) adjusted for demographic variables, medical diagnoses, and psychiatric comorbidity (including psychiatric diagnoses and substance use disorders), and (4) adjusted for demographic variables, medical diagnoses, psychiatric comorbidity, and psychoactive medication. In secondary analyses, equivalent models were run with death by suicide as the outcome. We also conducted sensitivity analyses to compare suicide risk among women who initiated hormone therapy after the index visit to those who remained nonusers. Proportional hazards assumptions were evaluated graphically and statistically and determined to be satisfied for all models. Statistical tests for models were 2-tailed, with significance set at $P < 0.05$. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and STATA version 16.0 (StataCorp, College Station, TX).

RESULTS

Characteristics of the Sample

The final analytic sample was comprised of 291,709 midlife and older women Veterans (mean age 60.47, SD 9.81). Overall, over half of the sample (52%) was White, 46% had

at least 1 documented medical diagnosis, 28% had at least 1 psychiatric diagnosis, 22% were prescribed at least 1 psychoactive medication, and 6% were prescribed menopausal hormone therapy. Incident suicide attempts and death by suicide from the index date through December 31, 2016 (mean followup duration 2.5 y, SD 1.8) were documented in 2673 women. Of those, 7% died by suicide. Compared with those without, women with a nonfatal suicide attempt or death by suicide over the study period were younger (mean 55.77, SD 5.86 vs. mean 60.52, SD 9.83), lived in areas with less educational attainment (39% vs. 43% in area where > 25% of population has attended college) and income (eg, 36% vs. 31% in lowest income tertile), were more likely to have a medical (63% vs. 46%) or psychiatric comorbidity (psychiatric diagnoses 81% vs. 27%; substance use disorders 31% vs. 5%), and were more often prescribed psychoactive medications (eg, any: 35% vs. 22%, ≥ 3: 22% vs. 7%) and menopausal hormone therapy (9% vs. 6%). Suicide attempts and suicide also varied by race/ethnicity (Table 1; $P < 0.001$ for all comparisons reported here). Psychoactive medications and polypharmacy were 3–4 times as common among women using menopausal hormone therapy than those without (any psychoactive medication: 64% vs. 20%; ≥ 3: 25% vs. 6%). Among women with a documented suicide attempt and prescribed menopausal hormone therapy, nearly 80% were coprescribed at least 1 psychoactive medication (vs. 31% with a documented suicide attempt and no hormone therapy, $P < 0.001$), and over half were coprescribed ≥ 3 psychoactive medications (53% vs. 19% with a documented suicide attempt and no hormone therapy, $P < 0.001$; data not shown).

Menopausal Hormone Therapy, Suicide Attempts, and Death by Suicide

The incidence rate of suicide attempts and death by suicide was higher among women prescribed menopausal hormone therapy (any attempt 273.95/100,000 person-years vs. 198.22/100,000 person-years; death by suicide 33.47/100,000 person-years vs. 13.40/100,000 person-years). Cumulative incidence of suicide attempts and death by suicide increased with age, with higher incidence at all ages seen among women prescribed menopausal hormone therapy (Fig. 1).

In unadjusted Fine-Gray analyses (model 1), women prescribed menopausal hormone therapy at baseline were nearly 2-fold more likely to have a documented incident fatal or nonfatal suicide attempt [hazard ratio (HR) 1.88, 95% confidence interval (95% CI), 1.63–2.18]. Associations were attenuated but still significant with adjustment for demographic variables and medical comorbidities in model 2 (HR 1.41; 95% CI, 1.22–1.64), but attenuated to nonsignificance with further adjustment for psychiatric comorbidities in model 3 and psychoactive medications in model 4 (Table 2). The pattern of results was similar in sensitivity analyses comparing women who did and did not initiate hormone therapy after the baseline period (eg, model 1 HR 1.57; 95% CI, 1.30–1.90; model 2 HR 1.22; 95% CI, 1.01–1.49; data not shown).

In secondary analyses with death by suicide as the outcome, women prescribed menopausal hormone therapy were 3-fold more likely to die by suicide in unadjusted analyses (HR 3.01; 95% CI, 1.94–4.67). Associations were attenuated but still significant with adjustment for demographics and medical comorbidities (HR 2.47; 95% CI, 1.58–3.87) in model 2,

adjustment for psychiatric comorbidities (HR 2.11; 95% CI, 1.35–3.31) in model 3, and adjustment for psychoactive medications (HR 2.00; 95% CI, 1.27–3.15) in model 4 (Table 2).

DISCUSSION

In this national sample of midlife and older women Veterans enrolled in VHA care, we examined associations between prescribed menopausal hormone therapy and incident suicide-related outcomes. Over a 5-year period, 2673 women Veterans aged 50 and older had documented nonfatal suicide attempts or died by suicide. Although menopausal hormone therapy was associated with suicide attempts (combined nonfatal and fatal), this association did not hold after accounting for psychiatric comorbidity. However, menopausal hormone therapy was associated with a statistically significant 2-fold higher risk of death by suicide, independent of demographics, medical and psychiatric comorbidities, and psychoactive medications. These novel findings raise the possibility that menopausal hormone therapy is an underrecognized marker of suicide risk among midlife and older women.

Common psychiatric diagnoses including depression, anxiety, and posttraumatic stress disorder have typically emerged as the most important predictor of suicide, particularly among women.[18,21] Severe menopause symptoms, menopausal hormone therapy use, and difficulty with hormone therapy discontinuation have previously been associated with these diagnoses,[16,22] as well as to poor quality of life[6] and suicidal ideation[17] among community-dwelling and Veteran women. Similar to these findings, psychiatric comorbidity was common among women with both prescribed menopausal hormone therapy and any incident suicide attempts in this study, with results suggesting that this traditional risk factor partially explains the relationship between hormone therapy and suicide attempts. However, menopausal hormone therapy remained an important prognostic factor for death by suicide above and beyond psychiatric comorbidity, potentially signaling the underlying severity or complexity of psychiatric comorbidity and/or additional unmeasured factors.

Rather than menopausal hormone therapy reflecting underlying psychiatric symptoms and their severity, it could be posited that hormone therapy leads to negative mood symptoms and/or suicidal behavior. This direction of effect is not expected, as hormone therapy use has instead been shown to reduce depressive symptoms in several studies,[23–30] potentially decreasing suicide risk among women with psychiatric comorbidity. However, this effect may be limited to women in perimenopause; other studies have shown no evidence of depressive symptom improvement in postmenopausal women using hormone therapy,[31,32] and higher rates of chronic and recurrent depression, longer duration of depression, and comorbid anxiety among depressed postmenopausal women using menopausal hormone therapy relative to their perimenopausal peers.[22] The primarily postmenopausal-aged women Veterans in the current sample are therefore less likely to have benefited from any antidepressant or anxiolytic effects of hormone therapy that may be potentially protective for suicide risk in perimenopausal women.

Women using menopausal hormone therapy to treat bothersome menopause symptoms may also seek treatment for common comorbidities,[33] potentially leading to increased access to psychoactive medications and polypharmacy. This was supported in our data, where rates of psychoactive medication and polypharmacy were 3–4 times higher among women prescribed hormone therapy. Psychoactive medication use and polypharmacy may reflect the severity of underlying conditions often comorbid with bothersome menopause symptoms that are related to suicide risk, including psychiatric diagnoses and symptoms,[18,19,21] insomnia,[34] and chronic pain.[35] These prescriptions may also provide a means for suicide attempts; poisoning is the most commonly used method for suicide attempts by women, and a leading cause of death by suicide.[36] The medications we examined, including sedative-hypnotics, benzodiazepines, opioids,[37,38] and antiepileptics are commonly used in poisoning-related suicide attempts, and prescribed at high rates among midlife and older women for the treatment of insomnia, anxiety, and pain. [33] Although almost 80% of women with prescribed hormone therapy and documented suicide attempts in the current study were prescribed at least 1 psychoactive medication, the association between menopausal hormone therapy and death by suicide was independent of psychoactive medication use. Further examination of dynamic aspects of prescribing, including specific medications, duration, dosage, and coprescribing combinations, may be warranted, as well as use of these medications or other means in suicide attempts in this population.

Menopausal hormone therapy use may also be a marker of other symptoms and psychosocial factors related to suicide not fully accounted for by the inclusion of psychoactive medications and other covariates in these models. Foremost among these are sleep difficulty and sleep disorders such as insomnia and sleep apnea, which have been linked to suicidal ideation, suicide behaviors, and death by suicide.[34,39–42] Although these sleep disorders are underrecognized and underdiagnosed in women, an estimated 40%–60% of perimenopausal and postmenopausal women are affected by insomnia, and 20% of women develop sleep apnea in midlife, with often pronounced impacts on daily functioning, impaired quality of life, health, and psychiatric comorbidity.[43] These sleep concerns are more common among women with menopause symptoms treated with hormone therapy,[44–47] and sleep disruption from bothersome night sweats is often highlighted as a primary motivation for treatment seeking for these symptoms.[44] In addition, both sleep difficulty and severe menopause symptoms treated by hormone therapy are associated with other known risk factors for suicide not fully accounted for in this data, including relationship difficulties, impaired cognitive function, cardiometabolic disease, and pain.[35,48]

The findings of this study, suggesting increased risk for suicide among midlife and older women using menopausal hormone therapy, have important clinical implications for suicide prevention efforts in both VHA and community health care systems. Midlife and older women tend to be high utilizers of health care,[49] particularly when experiencing bothersome menopause symptoms.[50] Treatment seeking for menopause symptoms may present an important window for additional screening and evaluation for suicide risk, with targeted risk assessments and monitoring tied to hormone therapy initiation and maintenance in midlife and older women. Overall, menopausal hormone therapy use may represent a readily measurable and better indicator of suicide risk during this vulnerable period than

traditional risk factors or a single diagnosis such as depression, potentially capturing complex comorbidity and a range of often cooccurring, frequently unmeasured risks.

Several limitations should be considered in interpreting these findings. Causal pathways hypothesized to relate hormone therapy with suicide risk cannot be determined by these data. Confounding by indication cannot be measured and may influence findings. Both systemic and vaginal preparations of hormone therapy were examined together, though the primary indications and health-related contraindications and prescribing guidelines for these preparations differ in ways that may be related to underlying health and symptom experiences affecting suicide risk. Longitudinal trends including dose and duration of hormone therapy and changes in comorbidities over time were not examined and may influence suicide risk. It therefore cannot be determined from these data whether suicide risk may vary by specific temporal or prescribing patterns. However, no differences in associations were seen in sensitivity analyses examining data from women who initiated hormone therapy after the baseline period, which suggests these findings may be robust for longer and shorter term use of hormone therapy. Comorbidities included were not an exhaustive list of all conditions that have been associated with suicide risk, such as sleep disorders[34,40] and chronic pain,[35] and further exploration of the role of these issues among women in this age cohort is warranted. Adjusting for psychoactive medications used to treat such disorders had minimal impact on mitigating results.

This study uses data from midlife and older women Veterans who use VHA health care, a population at elevated risk for suicidal behaviors with high rates of medical and mental health comorbidities.[49] Results may not be generalizable to women Veterans who do not use VHA health care, or to women in the general population. We cannot identify any undocumented or misclassified (ie, as accidental overdose) fatal or nonfatal suicide attempts, or identify all diagnoses or hormone therapy prescriptions attained outside of the VHA system. Only a small percentage of women with bothersome menopause symptoms seek treatment and/or use hormone therapy to treat their symptoms,[32] and those women may differ in their willingness to discuss sensitive, often stigmatized symptoms with their VHA providers. These patient characteristics may also lead to increased health care utilization and connection with the VHA system, which may affect suicide risk and/or documentation.

Despite these limitations, this study has multiple strengths. This study is one of few to examine suicide-related outcomes in midlife and older women, a population with increasing suicide rates,[1] and the first to use longitudinal data to relate menopausal hormone therapy with incident suicide attempts and death by suicide. We examined a large, diverse, nationally representative sample of midlife and older women Veterans who utilize VHA care, and accounted for a wide range of demographic and clinical factors to assess for independent relationships and limit confounding. Despite inherent limitations, the use of real-world data allows for examination of menopausal hormone therapy prescriptions and suicide attempts as documented and managed within a large, integrated health care system. These efforts may be enhanced by additional research to clarify the potential importance of varied prescribing patterns, such as short-term, intermittent, or persistent use; and temporal trends, such as age at initiation or acute decreases or increases in suicidality following hormone therapy initiation. However, the current findings identify a novel indicator for death by suicide

within a high-risk period in the lifespan, which may help to inform suicide prevention efforts in the VHA and other health care settings.

Although rates of suicide attempts and death by suicide have risen dramatically among midlife and older women, unique drivers of increased risk during this vulnerable period in the lifespan had not been previously identified. Our findings from national VHA data suggest that menopausal hormone therapy is an important and measurable indicator of suicide risk in midlife and older women, and a prognostic factor for death by suicide above and beyond traditional risk factors. These results lend support to the use of menopausal hormone therapy initiation as an opportunity to provide targeted screening and evaluation for suicide risk, as well as ongoing monitoring and support for women using menopausal hormone therapy.

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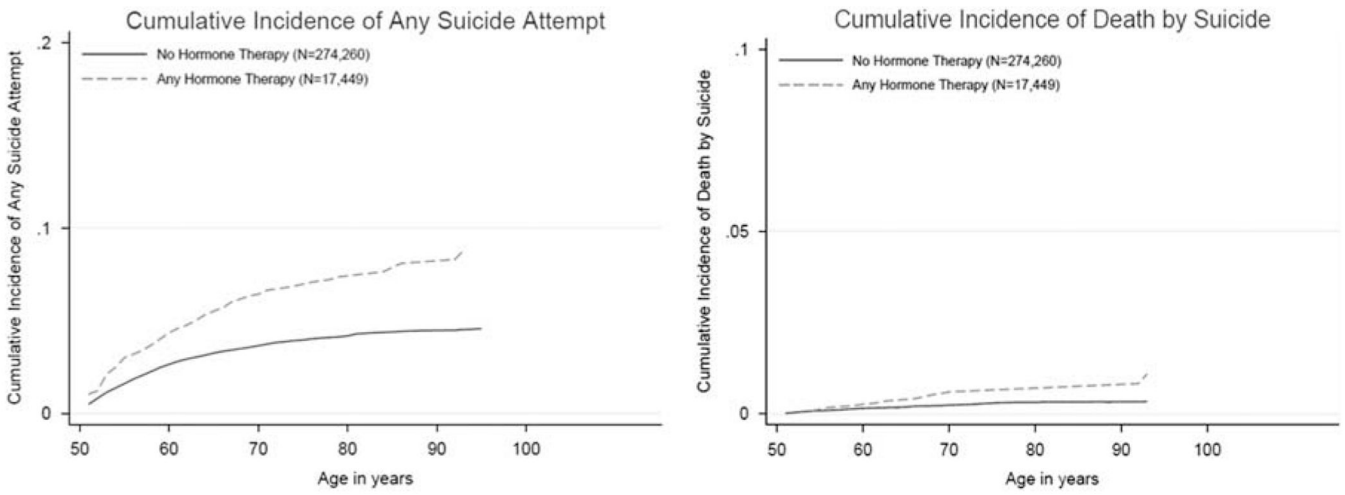

FIGURE 1.

Cumulative incidence of any suicide attempts* and death by suicide in women with and without prescribed menopausal hormone therapy at baseline. *Any suicide attempt includes fatal (death by suicide, n = 194) and nonfatal attempts (n = 2479).

TABLE 1.

Characteristics of the Sample at Baseline, by Subsequent Suicide-related Outcomes

Characteristic	No Suicide Attempt (N = 289,036)	Any Suicide Attempt† (N = 2673)
Age, mean (SD)	60.52 (9.83)	55.77 (5.86)
50–64	224,557 (77.69)	2487 (93.04)
≥ 65	64,479 (22.31)	186 (6.96)
Race, n (%)		
Non-Hispanic White	150,043 (51.91)	1896 (70.93)
Non-Hispanic Black	48,624 (16.82)	509 (19.04)
Hispanic	1575 (0.54)	10 (0.37)
Others	88,794 (30.72)	258 (9.65)
Education,‡ n (%)	123,618 (42.77)	1045 (39.09)
Income, n (%)		
Low tertile (< $41,721)	89,030 (30.80)	951 (35.58)
Middle tertile	87,969 (30.44)	879 (32.88)
High tertile (> $54,784)	97,191 (33.63)	762 (28.51)
Menopausal hormone therapy§	17,221 (5.96)	228 (8.53)
Medical diagnoses ‖		
Any medical diagnosis	132,436 (45.82)	1681 (62.89)
Hypertension	111,311 (38.51)	1333 (49.87)
Myocardial infarction *	4875 (1.69)	57 (2.13)
Cardiovascular disease **	15,721 (5.44)	174 (6.51)
Diabetes mellitus	42,798 (14.81)	561 (20.99)
Obesity	48,900 (16.92)	778 (29.11)
Psychiatric diagnoses‖		
Any psychiatric disorder	78,798 (27.26)	2152 (80.51)
Depression	64,605 (22.35)	1779 (66.55)
Dysthymia	13,329 (4.61)	376 (14.07)
Bipolar disorder	11,129 (3.85)	737 (27.57)
Posttraumatic stress disorder	21,729 (7.52)	1019 (38.12)
Generalized anxiety disorder	7136 (2.47)	227 (8.49)
Panic	4066 (1.41)	144 (5.39)
Phobia	2272 (0.79)	100 (3.74)
Any substance use disorder	13,854 (4.79)	826 (30.90)
Alcohol abuse	9353 (3.24)	586 (21.92)
Drug abuse	7979 (2.76)	564 (21.10)
Psychoactive medications§		
Any psychoactive medication	63,968 (22.13)	947 (35.43)
Benzodiazepines	15,930 (5.51)	358 (13.39)
Opioids	33,168 (11.48)	516 (19.30)
Sedative-hypnotics	10,137 (3.51)	281 (10.51)

Characteristic	No Suicide Attempt (N = 289,036)	Any Suicide Attempt† (N = 2673)
Antidepressants	42,096 (14.56)	839 (31.39)
Antipsychotics	7592 (2.63)	365 (13.66)
Antiepileptics	21,960 (7.60)	540 (20.20)
No. psychoactive medication use		
0	225,068 (77.87)	1726 (64.57)
1	27,209 (9.41)	156 (5.84)
2	17,595 (6.09)	200 (7.48)
≥ 3	19,164 (6.63)	591 (22.11)
Follow-up (y), mean (SD)	4.53 (0.88)	2.49 (1.80)

† Includes nonfatal suicide attempts (n = 2479) and death by suicide (n = 194) from index date through December 31, 2016.

‡ Live in area where > 25% of population has attended college.

§ Prescriptions at index visit and/or within 2 years before that date.

‖ Diagnoses at index visit and/or within 2 years before that date.

* $P = 0.08$.

** $P = 0.02$; all others $P < 0.001$.

TABLE 2.

Association Between Menopausal Hormone Therapy and Suicide

Model	Any Suicide Attempt[†] (HR, 95% CI)	Death by Suicide (HR, 95% CI)
Model 1: menopausal hormone therapy (unadjusted)	1.88 (1.63–2.18) **	3.01 (1.94–4.67) **
Model 2: adjusted for demographics[‡] and medical diagnoses[§]	1.41 (1.22–1.64) **	2.47 (1.58–3.87) **
Model 3: adjusted for demographics, medical diagnoses, psychiatric diagnoses, [‖] substance use disorders	1.14 (0.98–1.32)	2.11 (1.35–3.31) *
Model 4: adjusted for demographics, medical diagnoses, psychiatric diagnoses [‖] substance use disorders, and psychoactive medications[¶]	1.03 (0.89–1.21)	2.00 (1.27–3.15) *

[†]Any suicide attempt includes fatal (death by suicide) and nonfatal (n = 2479); death by suicide (n = 194).

[‡]Demographics (sex, race, education, income).

[§]Medical comorbidities (hypertension, myocardial infarction, cardiovascular disease, diabetes mellitus, obesity).

[‖]Any psychiatric diagnosis (depression, dysthymia, bipolar disorder, posttraumatic stress disorder, generalized anxiety disorder, panic disorder, or phobia).

[¶]Any psychoactive medications (benzodiazepines, opioids, sedative-hypnotics, antidepressants, antipsychotics, antiepileptics).

CI indicates confidence interval; HR, hazard ratio.

*$P < 0.05$.

**$P < 0.001$.