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Vasomotor symptoms and cardiovascular events in postmenopausal women

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Abstract

Objective—Emerging evidence suggests that women with menopausal vasomotor symptoms (VMS) have increased cardiovascular disease (CVD) risk as measured by surrogate markers. We investigated the relationships between VMS and clinical CVD events and all-cause mortality in the Women's Health Initiative Observational Study (WHI-OS).

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Methods—We compared the risk of incident CVD events and all-cause mortality between four groups of women (total N=60,027): (1) No VMS at menopause onset and no VMS at WHI-OS enrollment (no VMS [referent group]); (2) VMS at menopause onset, but not at WHI-OS enrollment (early VMS); (3) VMS at both menopause onset and WHI-OS enrollment (persistent VMS [early and late]); and (4) VMS at WHI-OS enrollment, but not at menopause onset (late VMS).

Results—For women with early VMS (N=24,753), compared to no VMS (N=18,799), hazard ratios (HRs) and 95% confidence intervals (CIs) in fully-adjusted models were: major CHD, 0.94 (0.84, 1.06); stroke, 0.83 (0.72, 0.96); total CVD, 0.89 (0.81, 0.97); and all-cause mortality, 0.92 (0.85, 0.99). For women with persistent VMS (N=15,084), there was no significant association with clinical events. For women with late VMS (N=1,391) compared to no VMS, HRs and 95% CIs were: major CHD, 1.32 (1.01, 1.71); stroke, 1.14 (0.82, 1.59); total CVD, 1.23 (1.00, 1.52); and all-cause mortality, 1.29 (1.08, 1.54).

Conclusions—Early VMS were not associated with increased CVD risk. Rather, early VMS were associated with decreased risk of stroke, total CVD events, and all-cause mortality. Late VMS were associated with increased CHD risk and all-cause mortality. The predictive value of VMS for clinical CVD events may vary with onset of VMS at different stages of menopause. Further research examining the mechanisms underlying these associations is needed. Future studies will also be necessary to investigate whether VMS that develop for the first time in the later postmenopausal years represent a pathophysiologic process distinct from classical perimenopausal VMS.

Keywords

Vasomotor symptoms; Hot flashes; Cardiovascular disease; Women's health

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of mortality in women,1 and the risk of CVD in women increases dramatically after menopause.2 The majority of menopausal women experience vasomotor symptoms (VMS).3 Higher blood pressure,4¯6 cholesterol levels,6 and body mass index,6 as well as increased risk of subclinical CVD7 have been reported among women with versus without hot flashes. Furthermore, recent analyses from two major clinical trials, the Women's Health Initiative Hormone Therapy Clinical Trials8 and the Heart and Estrogen/progestin Replacement Study (HERS),9 reported that the elevated risk of coronary heart disease (CHD) with late hormone therapy (HT) use was concentrated among those with VMS.

It is important to gain a better understanding of the possible underlying differences in CVD risk between women with and without VMS, given that most menopausal women have VMS and that many women experience these symptoms well into the later postmenopausal years, 10¯12 a time when CVD risk accelerates. To our knowledge, the independent contributions of VMS in predicting incident clinical CVD events have not been reported, and no previous study has distinguished between VMS at the onset of menopause and VMS occurring later in menopause. VMS were more common among women participating in the WHI Observational Study (WHI-OS), compared to the WHI HT Clinical Trials, as the WHI HT Clinical Trials excluded women with significant VMS while the WHI-OS was open to symptomatic women excluded from the WHI HT Clinical Trials. Thus, the WHI-OS cohort provides an opportunity to examine these relationships in a population enriched with women who experienced VMS.

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The objective of our study was to investigate whether VMS predict incident CVD events and all-cause mortality in the WHI-OS and whether the relationship is different for VMS at menopause onset and VMS later in menopause.

METHODS

Study design

As previously described,13, 14 the WHI is comprised of the WHI Clinical Trials and the WHI-OS. The WHI-OS is an ongoing longitudinal study examining the relationships between new risk indicators for disease and health outcomes in a large prospective cohort of postmenopausal women. The WHI-OS enrolled 93,676 women between 1994 and 1998 at 40 U.S. clinical centers. Study methods of the WHI-OS have been described in detail previously.15 Briefly, the WHI-OS included women who were either ineligible or unwilling to participate in the WHI Clinical Trials, or were recruited through a direct invitation to participate in the OS. Women were included if they were aged 50–79 years at the time of enrollment, were postmenopausal, were able and willing to provide written informed consent, and were unlikely to move from their area of residence for at least 3 years.16 Postmenopausal status was defined as amenorrhea for at least 6 months if aged ≥55 years and amenorrhea for at least 12 months if aged 50–54 years. Women were excluded if they had any medical condition with predicted survival of less than 3 years, had conditions which might impede adherence to the protocol or retention in the study, or were participating in either the WHI Clinical Trials or another randomized intervention trial. Signed informed consent was obtained from all participants, and the study was reviewed and approved by human subjects review committees at each participating institution.

All WHI-OS participants completed questionnaires at baseline that asked about demographic and lifestyle variables, as previously described.13 Anthropometric measurements and blood pressure were obtained at the initial screening visit. Body mass index was calculated as weight (in kg) divided by height (in m^2). Questionnaires were used to collect information about age, ethnicity, age at menopause, smoking status, history of hysterectomy or bilateral oophorectomy, educational level, aspirin use, statin use, and physical activity (reported in this analysis as total metabolic equivalents [MET] hours/week, classified as 0, < 5, 5 – <12, or ≥12 MET hours/week). Participants were asked whether they had ever been told by a physician that they had hypertension or high blood pressure, diabetes or high blood glucose when they were not pregnant, high cholesterol requiring pills, or a family history of myocardial infarction at a young age in first-degree relatives (<55 years for male relatives and <65 years for female relatives). In addition, participants completed a questionnaire about HT use, and participants were classified as never, past, or current users of HT. Current or past HT use was defined as use of an estrogen- or progesterone- containing pill or transdermal patch for at least 3 months following menopause. Vaginal HT was not included in current or past HT use. Age at menopause was defined as previously described.8 A self-administered questionnaire was used to ask women about the ages at which they first and last had VMS, defined in this manuscript as hot flashes or night sweats. Women were considered to have VMS at menopause onset if age at first hot flash or night sweats was less than or equal to age at menopause. Women were also asked at study enrollment about the presence of VMS during the preceding four weeks. If VMS were present, participants were asked to rate the symptoms as mild (symptom did not interfere with usual activities), moderate (symptom interfered somewhat with usual activities), or severe (symptom was so bothersome that usual activities could not be performed). For this analysis, we chose a priori to categorize VMS at enrollment dichotomously as present (mild, moderate or severe) or absent, in order to mirror the dichotomous data available for VMS at menopause onset.

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The clinical outcomes evaluated in this analysis were major coronary heart disease (CHD), stroke, total CVD events (major CHD and stroke), and all-cause mortality. CHD was defined as acute MI requiring overnight hospitalization, silent MI determined from serial electrocardiograms, or CHD death, as previously described.17 Stroke diagnosis was based on rapid onset of a neurologic deficit lasting more than 24 hours, supported by imaging studies when available. Non-fatal events in the WHI-OS were locally adjudicated by trained physician reviewers. A sample of the locally-adjudicated events was reviewed by central cardiovascular adjudicators.18 All deaths were centrally adjudicated. Locally-adjudicated myocardial infarctions and strokes were confirmed on central review for 87%18 and 91% (Women's Health Initiative Clinical Trial and Observational Study Semi-Annual Progress Report, March 1, 2004 to August 31, 2004) of the cases, respectively.

This analysis includes women who had no prior history of CVD or cancer at baseline and who had data reported on VMS status at both menopause onset and WHI-OS enrollment. Of the 93,676 postmenopausal women enrolled into the WHI-OS, 78,249 had no prior history of CVD or cancer. 77,631 (99.2%) of these women reported information on VMS status at enrollment, and 60,773 (77.7%) of these women reported information on VMS status at menopause onset. Our study sample included 60,027 women who fulfilled all inclusion criteria. As of August 2007, median follow-up duration for the study population was 9.7 years (interquartile range, 8.7–10.9); 4.3% withdrew or were lost to follow-up and 6.7% died. The annual follow-up response rate was >98% for those scheduled for a follow-up contact.

Statistical analysis

Categorical baseline characteristics were standardized by age using the direct method. The standard population was the age distribution of the whole cohort. Women were classified into four groups according to VMS status, as follows: (1) No VMS at menopause onset and no VMS at WHI-OS enrollment (hereafter referred to as no VMS [referent group]); (2) VMS at menopause onset, but not at WHI-OS enrollment (hereafter referred to as early VMS); (3) VMS at both menopause onset and at WHI-OS enrollment (hereafter referred to as persistent VMS [early and late]); and (4) VMS at WHI-OS enrollment, but not at menopause onset (hereafter referred to as late VMS). Cox proportional hazards models were used to assess the independent contribution of VMS in predicting incident CVD events and all-cause mortality. The assumption of proportional hazards was tested by examining plots of the baseline hazard by VMS and by testing interaction terms of VMS by time; the assumption was valid. The time to event was calculated from the date of enrollment and the date of the outcome. The discrete logistic model was used for handling ties. Minimally-, partially-, and fully-adjusted models were fit for outcomes stratified by 10-year age group. Minimally-adjusted models were adjusted for age and ethnicity. Partially-adjusted models were additionally adjusted for education, body mass index, smoking, hysterectomy status, bilateral oophorectomy status, aspirin use, statin use, hormone therapy status at baseline, and physical activity. Fully-adjusted models were additionally adjusted for hypertension, hypercholesterolemia, diabetes, and family history of CHD. In order to test for differential associations between VMS status and CVD events as a function of HT use, an interaction term of VMS status and HT use was included. Analyses were also performed separately according to HT use (never, past, and current) and according to whether or not women had a history of surgical menopause (defined as history of bilateral oophorectomy).

Comparing incident total CVD events between women with versus without VMS at menopause onset, our study had >99% power (with a 2-sided alpha level of 0.05) to detect a HR of 1.2 and higher. All P values were two-tailed, and P values <0.05 were considered statistically significant. All analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

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RESULTS

Mean age of the women included in this analysis was 63.3 years (range, 50 to 79 years), and women were a mean of 14.4 years since menopause (range, 0 to 54 years) at the time of WHI-OS enrollment. Table 1 shows the baseline characteristics of the study population by VMS status, standardized by age. Most women had either no VMS or early VMS.

The associations between VMS status and incident CVD events and all-cause mortality are shown in Table 2. Overall, there was no significant association between VMS and the four clinical outcomes examined (data not shown). For women with early VMS compared to no VMS, there was a decreased risk of stroke, total CVD events, and all-cause mortality in minimally-adjusted, partially-adjusted, and fully-adjusted models (Table 2). For women with persistent VMS (early and late), there was no significant increase or decrease in risk of major CHD, stroke, total CVD, or all-cause mortality compared to women with no VMS in partially- and fully-adjusted models (Table 2). In contrast, for women with late VMS compared to no VMS, there was an increased risk of major CHD events, stroke, total CVD events, and all-cause mortality in the minimally-adjusted models (Table 2). In the partially-adjusted models, there was an increased risk of major CHD events, total CVD events, and all-cause mortality in women with late VMS compared to no VMS. In the fully-adjusted models, the significantly increased risk of major CHD and all-cause mortality among women with late VMS persisted.

Analyses performed after excluding women with a history of surgical menopause were similar to those in the overall cohort, though some of the associations were not statistically significant (results for total CVD and all-cause mortality are shown in the Figure). In analyses performed among the smaller group of women who did have a history of surgical menopause (N=9,804), most of the associations were not statistically significant, except for decreased risks of stroke and total CVD for women with early VMS (HRs [95% CIs]: 0.67 [0.48, 0.93] and 0.76 [0.61, 0.94], respectively). Analyses performed separately according to HT use provided results similar to those in the overall cohort, though most of the associations did not remain statistically significant; results for total CVD and all-cause mortality among women who never used HT are shown in the Figure. Formal testing using interaction terms showed no evidence of an interaction between HT use and VMS at either menopause onset or at WHI-OS enrollment in predicting CVD events or all-cause mortality. .

DISCUSSION

In summary, we found that a history of early VMS was not associated with increased risk of future clinical CVD events or all-cause mortality. Indeed, the risks of stroke, total CVD events, and all-cause mortality were reduced among women with early VMS. In contrast to these inverse associations, we found that late VMS were associated with increased risk of major CHD and all-cause mortality, even after adjustment for traditional CVD risk factors.

A growing body of literature has examined the possible links between menopausal VMS and surrogate CVD risk markers. Higher ambulatory blood pressure has been reported among women with versus without hot flashes.[4, 5] Reduced heart rate variability, a marker of increased cardiovascular risk, has been reported during hot flashes.[19] A cross-sectional analysis of the Eindhoven Perimenopausal Osteoporosis Study reported that women with versus without VMS had higher blood pressure, cholesterol levels, and body mass index.[6] Analyses of perimenopausal and postmenopausal women enrolled in the Study of Women's Health Across the Nation (SWAN) Heart Study reported that hot flashes were associated

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with increased risk of subclinical CVD, including impaired endothelial function,7 increased aortic calcification,7 and increased carotid intima media thickness.20

Our findings are not at odds with previous studies reporting an association between VMS and adverse cardiovascular risk as measured by surrogate markers. Rather, our data confirm that women who reported VMS (particularly women with late VMS) had higher prevalence of several CVD risk factors, in agreement with these previous studies. We, however, found that a history of early VMS did not translate into an increased risk of clinical CVD events. These findings highlight the importance of outcome measures which focus on clinical events rather than surrogate markers. Menopause is a normal phase of women's lives, and most women experience VMS over the course of the menopausal transition.3 Our findings that early VMS were not associated with increased risk of clinical CVD events or all-cause mortality are therefore potentially relevant to a large number of women. It is interesting that one recent study reported that a history of both hot flashes and night sweats (but not hot flashes alone) was associated with a decreased risk of death among older postmenopausal women;21 this study did not differentiate between early and late VMS and did not examine CVD events. The mechanisms underlying the inverse associations we report between early VMS and CVD events are not currently known. One possibility is that perimenopausal VMS represent a physiologic response to the normal perimenopausal hormonal fluctuations, and the absence of these symptoms may signify a blunted vascular response to these hormonal changes. In support of this hypothesis, a recent study reported that recently menopausal women with severe versus no hot flashes exhibited greater nitroglycerin-induced (endothelium-independent) vasodilatation.22 Other studies, however, reported impaired flow-mediated (endothelium-dependent) dilation among women with any7 or clinically-significant23 hot flashes. Together these studies suggest that the potential vascular mechanisms linking early VMS to decreased CVD risk are not mediated through the endothelium. Further studies examining the mechanisms underlying these associations are needed.

The women who reported late VMS represent a small subset of our study population, and the associations we report between late VMS and increased risk of major CHD and all-cause mortality should therefore be interpreted as preliminary and hypothesis-generating. Adjustment for traditional coronary risk factors in the fully-adjusted models attenuated these associations, suggesting that traditional coronary risk factors may be in the causal pathway linking late VMS to increased risk of major CHD and all-cause mortality. The fact that these relationships remained significant after adjustment for traditional coronary risk factors, however, suggests that other currently unidentified mechanisms also increase CVD risk among women with late VMS. Our adjustment for HT use makes it unlikely that recently-initiated HT explains the increased risk of CHD and all-cause mortality reported among women with late VMS. Future studies are necessary to investigate the currently unknown pathophysiologic mechanisms underlying the development of VMS many years after menopause. These symptoms may be a marker of vascular instability or an early manifestation of cardiac ischemia. Of interest, recent analyses of the WHI HT Clinical Trials8 and HERS9 reported that the increased CHD risk associated with late HT use was amplified among the subset of women who reported VMS at study enrollment.8,9 In addition, another recent study reported that a longer duration of reported hot flashes was associated with increased aortic calcification among HT users.24 Since many women experience hot flashes in the later postmenopausal years,10–12 future studies which prospectively evaluate the complex inter-relationships between VMS and CVD events at different menopausal stages are warranted. In addition, future studies which objectively characterize the potential physiologic differences between VMS occurring in early versus late postmenopausal women are needed.

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Strengths of our study include the geographic, ethnic, and socioeconomic diversity of the WHI population and the community-based study population, which enhances the generalizability of our findings. In addition, our study is the first study to examine the independent contributions of VMS in predicting incident clinical CVD events.

A limitation of our study is the reliance on retrospective self-report of VMS. While physiologic measurement of hot flushes via sternal skin conductance is possible, this technique is not practical for a study large enough to evaluate clinical outcomes. Furthermore, subjective (not objective) assessment of hot flushes is employed in clinical practice, though ideally these symptoms would be elicited in a real-time setting rather than a historical one. The observational nature of our study (a limitation inherent to all studies examining VMS as a clinical predictor) precludes conclusions about causality. It is possible that residual confounding may contribute to the associations we report. An important limitation is our inability to disentangle the complex relationships between VMS and HT use in an observational setting. We acknowledge that past or current HT use may have altered VMS status classification in some women. Additionally, the decision to initiate HT is often (but not solely) influenced by the presence of VMS, and the subjective experience of VMS is linked to HT use,25 which is recognized to influence CVD risk independently.17 We adjusted for HT use in the multivariable models, and formal testing using interaction terms showed no evidence of an interaction between HT use and VMS at either menopause onset or at WHI-OS enrollment in predicting CVD events or all-cause mortality. While most of the associations we report for the entire study population did not remain statistically significant in analyses restricted to women who never used HT, it is not clear whether this indicates the presence of residual confounding by HT or inadequate power to detect these relationships in the smaller subsets.

CONCLUSIONS

We found no evidence of an increased risk of clinical CVD events or all-cause mortality among women with early VMS. Rather, early VMS were associated with decreased risk of stroke, total CVD events, and all-cause mortality. We did observe an increased risk of major CHD and all-cause mortality among the small subset of women with late-onset VMS. Our results suggest that a history of perimenopausal VMS is not likely to be an independent CVD risk factor and may even be inversely associated with CVD risk. The predictive value of VMS for clinical CVD events may vary with onset of VMS at different stages of menopause. Future studies will be necessary to investigate whether VMS that develop for the first time in the later postmenopausal years represent a pathophysiologic process distinct from classical perimenopausal VMS.

ARTICLE SUMMARY

In the Women's Health Initiative Observational Study, perimenopausal vasomotor symptoms were associated with decreased risks of stroke, total CVD events, and all-cause mortality. In contrast, late vasomotor symptoms were associated with increased CHD risk and all-cause mortality. The predictive value of VMS for clinical CVD events may vary with onset of VMS at different stages of menopause.

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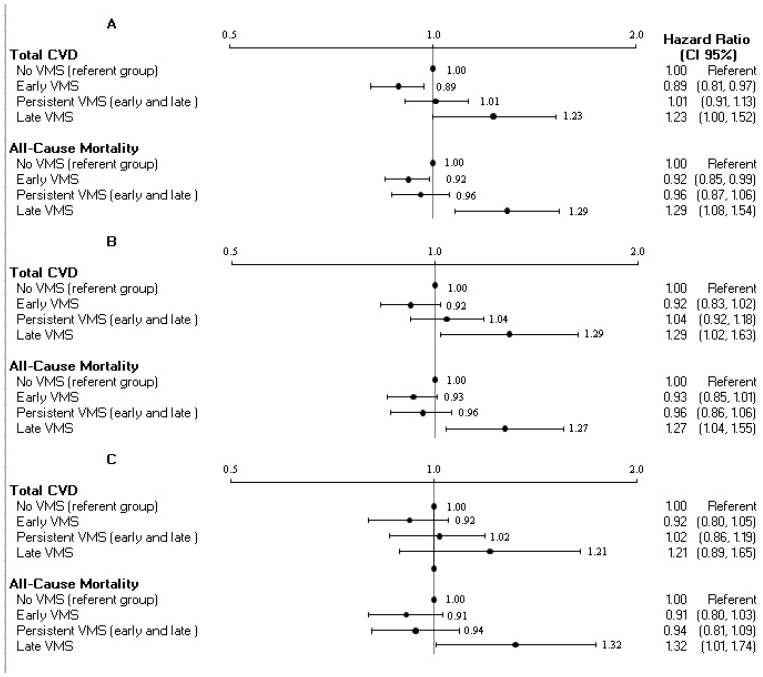

Figure.

Forest plot of the risks of total CVD and all-cause mortality by vasomotor symptom status among the total cohort (A), women with natural (non-surgical) menopause (B) and women who never used hormone therapy (C). Data shown are from the fully-adjusted models.

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TABLE 1

Baseline characteristics at WHI-OS enrollment by VMS status[a]

Characteristic[b,c]	No VMS (referent group) N=18,799 (31.3%)	Early VMS N=24,753 (41.2%)	Persistent VMS (early and late) N=15,084 (25.1%)	Late VMS N=1,391 (2.3%)
Age, mean (SD), y	65.6 (7.0)	63.2 (7.1)	60.5 (7.0)	65.6 (7.2)
Years between menopause and enrollment, mean (SD), y	17.6 (8.8)	15.1 (8.8)	12.7 (8.9)	18.3 (9.4)
BMI, No. (%)				
18.5 – <25 kg/m^2	8142 (44.0)	11155 (45.6)	5363 (35.5)	440 (31.7)
25 – <30 kg/m^2	6185 (32.7)	8380 (34.2)	5079 (34.7)	449 (31.3)
≥30 kg/m^2	4261 (23.3)	4959 (20.2)	4450 (29.8)	484 (37.1)
Ethnicity, No. (%)				
White	15902 (83.9)	22108 (89.3)	11765 (78.7)	1031 (72.7)
Black	914 (5.1)	1118 (4.5)	2083 (13.5)	125 (9.6)
Hispanic	639 (3.8)	611 (2.5)	720 (4.2)	105 (8.3)
American Indian	76 (0.4)	59 (0.2)	69 (0.4)	14 (1.2)
Asian/Pacific Islander	973 (5.3)	563 (2.3)	250 (1.7)	78 (5.5)
Unknown	295 (1.6)	294 (1.2)	197 (1.4)	38 (2.7)
Education, No. (%)				
0–8 years	260 (1.4)	190 (0.8)	304 (2.3)	59 (4.2)
Some high school	551 (2.7)	551 (2.3)	625 (4.7)	65 (4.3)
High school diploma/GED	3025 (15.5)	3628 (14.8)	2540 (17.9)	244 (17.5)
School after high school	6601 (34.8)	8604 (35.1)	5675 (38.2)	527 (37.3)
College degree or higher	8232 (45.7)	11583 (47.1)	5813 (37.0)	482 (36.8)
Smoking, No. (%)				
Never	10409 (55.6)	11995 (49.1)	7216 (48.8)	751 (54.7)
Past	7251 (39.1)	11143 (45.4)	6534 (44.0)	524 (37.7)
Current	933 (5.3)	1364 (5.6)	1179 (7.2)	97 (7.6)
Hypertension, No. (%)	7379 (36.7)	8689 (35.4)	5661 (41.7)	666 (45.7)
High cholesterol, No. (%)	2722 (13.6)	3355 (13.7)	2162 (16.2)	248 (17.1)
Treated diabetes, No. (%)	682 (3.4)	647 (2.6)	660 (4.8)	118 (8.7)
Family history of CHD, No. (%)	3127 (17.5)	4406 (18.7)	2846 (19.9)	244 (18.8)
Hysterectomy, No. (%)	7094 (38.4)	8537 (34.6)	5571 (38.0)	550 (40.5)
Bilateral oophorectomy, No. (%)	4306 (24.2)	3305 (13.6)	1861 (13.4)	332 (25.7)
Aspirin use, No. (%)	4100 (20.5)	5245 (21.3)	2857 (21.1)	305 (20.7)
Statin use, No. (%)	1562 (7.7)	1863 (7.5)	1129 (8.6)	135 (9.1)
HT usage status, No. (%)				
Never used	8233 (41.4)	8306 (33.7)	6524 (43.9)	651 (44.5)
Past user	2255 (11.4)	2855 (11.6)	2261 (16.3)	167 (11.3)
Current user	8299 (47.2)	13565 (54.7)	6290 (39.8)	572 (44.1)
Physical Activity, No. (%)				
0 MET hours/week	2455 (13.1)	2793 (11.3)	2301 (15.2)	232 (17.3)

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Characteristic[b,c]	No VMS (referent group) N=18,799 (31.3%)	Early VMS N=24,753 (41.2%)	Persistent VMS (early and late) N=15,084 (25.1%)	Late VMS N=1,391 (2.3%)
< 5 MET hours/week	3471 (18.3)	4261 (17.3)	3025 (20.4)	317 (22.6)
5 – <12 MET hours/week	4446 (23.8)	5948 (24.1)	3548 (23.5)	315 (22.3)
≥12 MET hours/week	8405 (44.9)	11728 (47.4)	6196 (41.0)	524 (37.8)

WHI-OS = Women's Health Initiative Observational Study; VMS = vasomotor symptoms; SD = standard deviation; BMI = body mass index; GED = General Education Diploma; CHD = coronary heart disease; HT = hormone therapy; MET = metabolic equivalents.

[a]"No VMS (referent group)" was defined as no VMS at menopause onset and no VMS at WHI-OS enrollment. "Early VMS" was defined as VMS at menopause onset, but not at WHI-OS enrollment. "Persistent VMS (early and late)" was defined as VMS at both menopause onset and at WHI-OS enrollment. "Late VMS" was defined as VMS at WHI-OS enrollment, but not at menopause onset.

[b]Age and years between menopause and enrollment were not age-standardized. All other characteristics were age-standardized.

[c]Number of women with missing covariate data: BMI, 680; Education, 468; Hypertension, 154; High cholesterol, 514; Treated diabetes, 64; Family history of CHD, 2985; Hysterectomy, 52; Bilateral oophorectomy, 972; Aspirin use, 1; Statin use, 1; HT usage status, 49; Physical Activity, 62.

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TABLE 2

Adjusted HRs relating VMS status to incident CVD events and all-cause mortality[a]

	Total	Event	HR (95% CI)
Major CHD			
Minimally-adjusted[b]			
No VMS (referent group)	18799	623	1 [Reference]
Early VMS	24753	647	0.94 (0.84, 1.05)
Persistent VMS (early and late)	15084	383	1.20 (1.05, 1.37)
Late VMS	1391	73	1.65 (1.30, 2.11)
Partially-adjusted[c,f]			
No VMS (referent group)	18149	607	1 [Reference]
Early VMS	23908	619	0.95 (0.85, 1.06)
Persistent VMS (early and late)	14487	362	1.09 (0.95, 1.25)
Late VMS	1330	71	1.46 (1.13, 1.87)
Fully-adjusted[d,f]			
No VMS (referent group)	17044	577	1 [Reference]
Early VMS	22582	592	0.94 (0.84, 1.06)
Persistent VMS (early and late)	13584	344	1.04 (0.90, 1.20)
Late VMS	1237	66	1.32 (1.01, 1.71)
Stroke[e]			
Minimally-adjusted[b]			
No VMS (referent group)	18799	477	1 [Reference]
Early VMS	24752	434	0.84 (0.73, 0.95)
Persistent VMS (early and late)	15084	265	1.09 (0.93, 1.28)
Late VMS	1391	50	1.43 (1.07, 1.92)
Partially-adjusted[c,f]			
No VMS (referent group)	18149	456	1 [Reference]
Early VMS	23907	411	0.83 (0.72, 0.95)
Persistent VMS (early and late)	14487	249	1.03 (0.87, 1.21)
Late VMS	1330	47	1.30 (0.96, 1.77)
Fully-adjusted[d,f]			
No VMS (referent group)	17044	431	1 [Reference]
Early VMS	22581	393	0.83 (0.72, 0.96)
Persistent VMS (early and late)	13584	234	0.99 (0.84, 1.17)
Late VMS	1237	41	1.14 (0.82, 1.59)
Total CVD			
Minimally-adjusted[b]			
No VMS (referent group)	18799	1052	1 [Reference]
Early VMS	24752	1026	0.89 (0.81, 0.97)
Persistent VMS (early and late)	15084	619	1.15 (1.03, 1.27)
Late VMS	1391	115	1.54 (1.27, 1.86)

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	Total	Event	HR (95% CI)
Partially-adjusted[c,f]			
No VMS (referent group)	18149	1016	1 [Reference]
Early VMS	23907	981	0.89 (0.81, 0.98)
Persistent VMS (early and late)	14487	585	1.06 (0.95, 1.18)
Late VMS	1330	111	1.39 (1.14, 1.69)
Fully-adjusted[d,f]			
No VMS (referent group)	17044	965	1 [Reference]
Early VMS	22581	939	0.89 (0.81, 0.97)
Persistent VMS (early and late)	13584	553	1.01 (0.91, 1.13)
Late VMS	1237	100	1.23 (1.00, 1.52)
All-cause mortality			
Minimally-adjusted[b]			
No VMS (referent group)	18799	1531	1 [Reference]
Early VMS	24753	1517	0.90 (0.84, 0.97)
Persistent VMS (early and late)	15084	832	1.05 (0.96, 1.14)
Late VMS	1391	156	1.42 (1.21, 1.68)
Partially-adjusted[c,f]			
No VMS (referent group)	18149	1467	1 [Reference]
Early VMS	23908	1455	0.91 (0.85, 0.98)
Persistent VMS (early and late)	14487	782	0.97 (0.89, 1.07)
Late VMS	1330	149	1.34 (1.13, 1.59)
Fully-adjusted[d,f]			
No VMS (referent group)	17044	1368	1 [Reference]
Early VMS	22582	1372	0.92 (0.85, 0.99)
Persistent VMS (early and late)	13584	730	0.96 (0.87, 1.06)
Late VMS	1237	139	1.29 (1.08, 1.54)

HR = Hazard Ratio; VMS = vasomotor symptoms; CVD = cardiovascular disease; CI = confidence interval; CHD = coronary heart disease.

[a]"No VMS (referent group)" was defined as no VMS at menopause onset and no VMS at WHI-OS enrollment. "Early VMS" was defined as VMS at menopause onset, but not at WHI-OS enrollment. "Persistent VMS (early and late)" was defined as VMS at both menopause onset and at WHI-OS enrollment. "Late VMS" was defined as VMS at WHI-OS enrollment, but not at menopause onset.

[b]Minimally-adjusted models adjusted for age and ethnicity.

[c]Partially-adjusted models adjusted for: age, ethnicity, education, body mass index, smoking, hysterectomy status, bilateral oophorectomy status, aspirin use, statin use, hormone therapy status at baseline, and physical activity.

[d]Fully-adjusted models adjusted for: age, ethnicity, education, body mass index, smoking, hysterectomy status, bilateral oophorectomy status, aspirin use, statin use, hormone therapy status, physical activity, hypertension, hypercholesterolemia, diabetes, and family history of CHD.

[e]One woman in the early VMS group did not have time to event information for stroke.

[f]2153 women were not included in the partially-adjusted models due to missing covariate data. An additional 3427 women were not included in the fully-adjusted models due to missing covariate data.