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Vasomotor symptom characteristics: are they risk factors for incident diabetes?

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Abstract

Objective—Vasomotor symptoms, encompassing hot flashes and night sweats, may be associated with diabetes but evidence is limited. We sought to estimate these associations.

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Methods—Among 150,007 postmenopausal Women’s Health Initiative participants from 1993–2014, we prospectively examined associations of incident diabetes with VMS characteristics at enrollment: any vasomotor symptoms, severity (mild/ moderate/severe), type (hot flashes/night sweats), timing (early [pre- or perimenopausal]/late [postmenopausal]), and duration. Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs.

Results—Mean duration of follow-up was 13.1 years. VMS prevalence was 33%. Reporting any VMS was associated with 18% increased diabetes risk (95% CI 1.14, 1.22), which increased with severity (mild: HR=1.13, 95% CI 1.08, 1.17; moderate: HR=1.29, 95% CI 1.22, 1.36; severe: HR=1.48, 95% CI 1.34, 1.62) and duration (4% per 5-years, 95% CI 1.03, 1.05), independent of obesity. Diabetes risk was more pronounced for women reporting any night sweats (night sweats only: HR=1.20, 95% CI 1.13, 1.26; night sweats and hot flashes: HR=1.22, 95% CI 1.17, 1.27) than only hot flashes (HR=1.08, 95% CI 1.02, 1.15) and was restricted to late VMS (late: HR=1.12, 95% CI 1.07, 1.18; early and late: HR=1.16, 95% CI 1.11, 1.22; early: HR=0.99, 95% CI 0.95, 1.04).

Conclusions—VMS are associated with elevated diabetes risk, particularly for women reporting night sweats and postmenopausal symptoms. The menopausal transition may be an optimal window for clinicians to discuss long-term cardiovascular/metabolic risk with patients and leverage the bother of existing symptoms for behavior change to improve VMS and reduce diabetes risk.

Keywords

diabetes; vasomotor symptoms; hot flashes; night sweats; menopause

INTRODUCTION

Vasomotor symptoms (VMS) encompass hot flashes, a sudden feeling of warmth, and night sweats, which are hot flashes that occur at night typically during sleep and are often accompanied by sweating. VMS are common during the menopausal transition, affecting 35–50% of perimenopausal and 30–80% of postmenopausal women.¹ VMS can have substantial impacts on the immediate health and wellbeing of women, including sleep disturbance, reduced quality of life, mood disorders, and cognitive impairments.² VMS may also increase the risk of, or serve as a marker for an underlying causal process for, more distal health outcomes such as cardiovascular disease (CVD), although findings are inconsistent across studies.^{3,4} However, little research has explored the potential relationships between VMS and other chronic conditions that predominate in the postmenopausal period, such as diabetes.

Diabetes affects 15% of women 55 years of age and older,⁵ and diabetes prevalence is projected to more than double by 2050.⁶ Diabetes and its sequelae (e.g., CVD) are among the leading causes of death for U.S. women.⁷ Compared with men with diabetes, women with diabetes have a higher risk of CVD hospitalizations, CVD mortality, and all-cause mortality.⁸ Diabetes and its complications can be delayed or prevented through lifestyle intervention or medical management.⁹ Therefore, timely identification and intervention among high risk individuals is critical.

VMS may be an indicator of diabetes risk unique to women. Findings from studies examining the relationships between VMS and insulin resistance, a precursor to diabetes, have been mixed.^{10–12} In the only study of VMS and diabetes risk, associations varied by VMS trajectory, such that only women with severe VMS that began in premenopause and peaked in perimenopause had an increased risk of diabetes.¹³ However, this study was cross-sectional, such that the temporality of these associations remains unclear. Additionally, separate associations of hot flashes and night sweats with diabetes were not investigated, and the differential effects of these symptoms on CVD risk may also translate to diabetes.¹⁴

Elucidating relationships between VMS and diabetes is important for several reasons. First, they may shed light on the mechanisms underlying observed associations. Numerous pathways linking VMS and cardiometabolic outcomes have been proposed, including perturbations in cardiac vagal control, dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis, alterations in hemostasis, and adiposity, among others.^{15–17} Findings could illuminate the most plausible pathway, which could potentially be used to inform VMS treatment and prevention strategies. Second, positive associations would underscore the menopausal transition as an effective time to motivate behavior change that reduces both diabetes and CVD risk. Many behavioral strategies to address VMS, including physical activity, smoking cessation, and dietary changes, are also primary CVD and diabetes prevention approaches. Therefore, we sought to expand on the limited knowledge base and evaluate the association between VMS and incident diabetes using multiple dimensions of VMS, including symptom presence, severity, type, timing, and duration.

METHODS

We used data from the Women's Health Initiative (WHI), a large longitudinal cohort of postmenopausal women.¹⁸ WHI enrolled 161,808 women ages 50–79 between 1993 and 1998. Participants were recruited from 40 clinical centers across the U.S. and enrolled into either the Clinical Trials (CT; N= 68,132) or Observational Study (OS; N=93,676) component. Eligible CT participants could enroll in one or more of three trials: hormone therapy (HT), dietary modification (DM), and calcium and vitamin D (CaD). Data collection for the Main Study occurred between 1993 and 2005, after which consenting participants were followed up between 2005 and 2010 in Extension Study 1 and between 2010 and 2015 in Extension Study 2. Data collection for the Main Study involved clinical measurements, interviews, and self-administered questionnaires. In the Extension Studies, WHI collected annual updates on health outcomes by mail. Institutional Review Boards from all sites approved the study, and all participants provided written informed consent.

For the current study, WHI OS and CT participants who did not report physician-diagnosed diabetes at baseline ("prevalent diabetes;" N=9,618 excluded; Figure 1) who had baseline data on VMS (N=1,378 excluded) were eligible for inclusion. Information on incident diabetes was available through August 2014.

Study variables

Vasomotor symptoms—WHI collected data on current postmenopausal hot flashes and night sweats at study baseline. The questionnaire asked participants how bothersome each

symptom was during the past four weeks in separate questions with response options of “symptom did not occur,” “symptom was mild,” “symptom was moderate,” and “symptom was severe.” The questionnaire did not define hot flashes or night sweats for participants and asked about these two symptoms without reference to menopause. Therefore, we could not separate menopausal symptoms from those due to other causes.

We created several variables to characterize VMS, including presence, severity, type, timing, and duration (see Table, Supplemental Digital Content 1, which shows variable descriptions and classifications). To identify the presence of VMS, we created a single dichotomous variable reflecting no symptoms versus mild, moderate, or severe hot flashes or night sweats. We classified VMS severity as none, mild, moderate, and severe, which was based on the symptom with the highest reported severity (e.g., a woman with severe hot flashes and mild night sweats was classified as having severe VMS).

Although hot flashes and night sweats likely reflect the same underlying pathophysiology, these symptoms may be experienced differently by women and could have differential effects on long-term outcomes. Furthermore, WHI participants could report one symptom but not the other. Therefore, we created two dichotomous variables to reflect symptom type: one for any hot flashes and one for any night sweats. We also created collapsed severity variables for each of these symptoms separately as none, mild, and moderate/severe, resulting in two variables with three levels of severity.

At baseline WHI also collected data on past VMS. Women were asked if they had ever had menopausal symptoms such as hot flashes or night sweats (single question) and, if yes, the ages at first and last symptom. Women were classified as having pre- or perimenopausal VMS if the age at first symptom was less than or equal to the age at menopause, and as having postmenopausal VMS if the age at first symptom was greater than the age at menopause or they reported current symptoms at baseline. We created two dichotomous timing variables: one for pre- or perimenopausal symptoms (“early symptoms”) and one for postmenopausal symptoms (“late symptoms”). For women reporting current symptoms at baseline, VMS duration was defined as time from age at first symptom to age at study baseline; for those reporting only past symptoms, duration was defined as time from age at first symptom to age at last symptom.

Diabetes—Follow-up WHI questionnaires assessed incident diabetes by asking participants “...has a doctor prescribed for the first time any of following pills or treatment?” since the last questionnaire with response options of “pills for diabetes,” “pills for high blood pressure or hypertension,” and “insulin shots for diabetes” (participants could select more than one). Diabetes was defined as first report of pills or insulin injections for diabetes. This definition was found to have acceptable validity when compared with medical records.¹⁹ Time to diabetes was defined as the number of days from study enrollment to self-report of diabetes.

Additional covariates—Additional baseline covariates of interest included study assignment, and self-reported age at baseline, race/ethnicity, marital status, education, pack years of smoking, alcohol consumption, physical activity (MET-hours per week²⁰),

hypertension, HT use (assessed prior to study assignment/randomization), hysterectomy status, oophorectomy status, age at menopause, and time since menopause (baseline age-age at menopause). BMI was calculated based on measured height and weight at baseline. Sleep disturbances at baseline were defined based on self-reported risk for insomnia (Women's Health Initiative Insomnia Rating Scale score ≥ 9 versus <9 ²¹) and sleep disordered breathing (Berlin Questionnaire score ≥ 2 versus <2 ²²), as well as short sleep duration (≤ 6 hours versus >6 hours).

Data analysis

We first examined the baseline demographic, health behavior, and health outcome characteristics of the sample, stratified by baseline VMS. We then calculated the unadjusted incidence rate of diabetes by VMS characteristics.

To examine adjusted associations between VMS characteristics and diabetes, we employed separate Cox proportional hazards models, which provide estimates of the hazard ratio (HR) and 95% CIs. The time to event was defined as days from enrollment to self-reported diabetes, and censoring time for non-events was defined as days from enrollment to the date of last follow-up contact. We modeled any VMS dichotomously and VMS severity nominally. The model exploring associations with VMS type included the two dichotomous any hot flashes and any night sweats variables, as well as their interaction, which allowed assessment of whether associations with diabetes differed if women reported both versus a single symptom. We examined associations with VMS timing by including the two dichotomous early and late symptom variables and their interaction, which facilitated examination of whether associations with diabetes differed for women reporting both early and late symptoms compared to symptoms in a single timeframe. To examine type and severity simultaneously, the three-level severity variables for each of hot flashes and night sweats were included in the model as ordinal variables, along with their interaction. The reference group for each of these Cox proportional hazards models was women reporting no VMS. Lastly, we examined the association between VMS duration and diabetes, with duration modeled linearly in 5-year increments.

All models were adjusted for baseline age, race/ethnicity, marital status, education, BMI, hypertension, physical activity, pack years of smoking, alcohol consumption, and HT use. Analyses were performed in Stata 13.0.

Recognizing that baseline HT use or a history of hysterectomy or oophorectomy may influence both VMS and diabetes risk,^{23–26} we repeated all analyses (1) excluding women on HT at baseline, (2) among women on HT at baseline, and (3) excluding women with hysterectomy or oophorectomy (Figure 1). As timing of VMS assessment relative to CT randomization, HT washout, and study treatment was difficult to disentangle, we also reran analyses restricted to women in the OS who would not have stopped or received HT as part of WHI. A prior study found evidence of racial differences in the association between VMS and glucose levels¹¹; therefore, we also examined interactions between each of the VMS characteristics and race (white vs. black). Models included 3-way interactions for VMS type, timing, combined type and severity. We modeled VMS severity ordinally in these models to facilitate interpretation.

Because sleep disturbance may be related to both VMS and diabetes,^{27,28} in *post hoc* analyses we examined the unadjusted prevalence of insomnia, sleep disordered breathing, and short sleep duration by VMS characteristics. In *post hoc* analyses we also examined associations of diabetes with VMS timing adjusted for VMS duration, as women with both early and late symptoms would inherently have a longer duration of VMS than those with only early symptoms, which may confound the association with diabetes.

RESULTS

There were 150,007 WHI participants without prevalent diabetes at baseline who had data available on baseline VMS, 33% of whom reported either hot flashes or night sweats (N=48,787; Figure 1). Compared to women without VMS, women with baseline VMS were younger, more likely to be Black, married, obese, have early VMS, and were more recently postmenopausal (Table 1). Women with baseline VMS were also less likely to use HT.

Diabetes Incidence

There were 18,316 incident cases of diabetes and average follow-up time among participants was 13.1 years (data not shown). The overall incidence of diabetes was 9.3 per 1,000 person-years of follow up (data not shown). Among women without baseline VMS, diabetes incidence was 8.4 per 1,000 person-years, whereas among those reporting baseline VMS the incidence was 11.3 per 1,000 person-years (Table 2).

VMS Presence

In adjusted Cox proportional hazards models, compared to women without symptoms, women reporting any VMS had an 18% increase in diabetes risk (HR=1.18, 95% CI 1.14, 1.22; Table 2).

VMS Severity

Diabetes risk increased with severity of symptoms. Women reporting severe symptoms had a nearly 50% higher risk of diabetes compared to women without symptoms (HR=1.48, 95% CI 1.35, 1.62; Table 2), followed by 29% for moderate symptoms (HR=1.29, 95% CI 1.22, 1.36), and 13% for mild symptoms (HR=1.13, 95% CI 1.08, 1.17).

VMS Type

There was no evidence that reporting both hot flashes and night sweats was associated with greater risk of diabetes than reporting only one of the two symptom types (p-value for interaction=0.17; Table 2). Although women reporting hot flashes and/or night sweats had increased risk of diabetes compared to those without VMS, the association was most pronounced in women reporting any night sweats. Women reporting night sweats, with or without hot flashes, had an approximately 20% increase in diabetes risk (night sweats only: HR=1.20, 95% CI 1.13, 1.26; night sweats and hot flashes: HR=1.22, 95% CI 1.17, 1.27), whereas risk was increased by 8% among those who only reported hot flashes (95% CI 1.02, 1.15).

Combined VMS Symptom Type and Severity

In the model examining hot flash and night sweat severity jointly, there was no evidence of an interaction of severity of the two symptom types on diabetes risk (p-value for interaction=0.12; see Table, Supplemental Digital Content 3, which displays results of combined symptom type and severity analyses). Severity of reported night sweats was associated with increased diabetes risk, regardless of hot flash severity (Figure 2). For every increase in reported night sweat severity (none to mild symptoms and mild to moderate/severe symptoms), diabetes risk increased similarly among women concomitantly reporting no hot flashes (HR=1.16, 95% CI 1.12, 1.21), mild hot flashes (HR=1.13, 95% CI 1.09, 1.17), and moderate/severe hot flashes (HR=1.10, 95% CI 1.04, 1.16). For hot flashes, there was limited evidence of an association between severity and diabetes risk. Reported hot flash severity was only associated with diabetes risk among women who did not report simultaneous night sweats: every increase in reported hot flash severity was associated with 5% increase in diabetes risk (95% CI 1.01, 1.10). There was no association between hot flash severity and diabetes risk among women who also reported mild or moderate/severe night sweats.

VMS Timing

When examining timing of VMS, women with both early and late symptoms did not differ from those with symptoms in only one time period in terms of diabetes risk (p-value for interaction=0.19; Table 2). Heightened diabetes risk was only observed among women reporting late symptoms, regardless of whether they also experienced early symptoms (late: HR=1.12, 95% CI 1.07, 1.18; early and late: HR=1.16, 95% CI 1.11, 1.22), as compared to women with no VMS. There was no association with early symptoms only (HR=0.99, 95% CI 0.95, 1.04).

VMS Duration

Duration of VMS was also positively associated with diabetes: every 5-year increase in VMS duration was associated with a 4% increase in diabetes risk (95% CI 1.03, 1.05; data not shown). When stratifying by age, this association was more pronounced among women <65 years of age (HR=1.06, 95% CI 1.05, 1.08) than among women ≥65 years of age (HR=1.03, 95% CI 1.02, 1.04; p-value for interaction<0.001).

Sensitivity Analyses

Results excluding subgroups of WHI participants based on HT and hysterectomy/oophorectomy were generally similar to results in the full sample (see Tables, Supplemental Digital Content 2 and 3, which display results of sensitivity analyses). Associations among women not on HT at baseline were slightly attenuated compared to the full sample, and associations with hot flashes were no longer significant for VMS type and combined type and severity analyses. Among women on HT at baseline, associations were more pronounced, and there were significant positive associations between hot flash severity and diabetes in the combined type and severity analyses. Comparable to when excluding women on HT, excluding women with hysterectomy or oophorectomy resulted in associations between reported hot flashes and diabetes that were no longer statistically significant and in

once case were reversed for combined type and timing analyses. When restricting to women from the OS, conclusions remained essentially unchanged and associations were generally more pronounced (see Tables, Supplemental Digital Content 4 and 5, which display results of sensitivity analyses in OS participants). The interactions between a) hot flashes and night sweats and b) early and late symptoms on diabetes risk also reached statistical significance in the OS subgroup (p-value for both=0.04), suggesting OS women with symptoms of both types or in both time periods had a greater increase in diabetes risk than those with a single symptom type or who experienced them in only one time period.

When we examined interactions between VMS characteristics and race, there was evidence of an interaction only for severity (p-value for interaction=0.004; data not shown). Among white women, for each incremental increase in severity the risk of diabetes increased by 15% (HR=1.15, 95% CI 1.13, 1.18), whereas among black women the risk increased by only 7% (HR=1.07, 95% CI 1.02, 1.12). There were no statistically significant interactions between race and VMS presence, type, timing, combined type and severity, or duration.

Sleep disturbance was common in the sample: 24%, 31%, and 36% of women were at high risk of sleep disordered breathing, high risk of insomnia, and had short sleep durations, respectively. As expected, given that night sweats occur at night, women who reported any night sweats (with or without hot flashes) had a higher prevalence of sleep disturbance than women reporting only hot flashes, which increased with symptom severity (Figure 3). Lastly, women reporting any late symptoms had a higher prevalence of disturbance than women reporting only early symptoms.

When we adjusted analyses of VMS timing for duration of symptoms, the association between diabetes and late symptoms was substantially reduced and no longer significant (late only: HR=1.04, 95% CI 0.98, 1.09; early and late: HR=1.04, 95% CI 0.98, 1.11).

DISCUSSION

We examined associations between VMS and incident diabetes, finding evidence of a positive relationship that varied by reported symptom type and timing of onset. Overall, women reporting current VMS at baseline had a nearly 20% greater risk of incident diabetes compared to those without VMS, and the association increased with severity and duration of symptoms. The heightened risk associated with VMS was predominately observed among women reporting night sweats, irrespective of concurrent reporting of hot flashes, and women who had late (postmenopausal) symptoms.

Few investigations of VMS and diabetes or its precursors have been undertaken. Among three studies examining associations between VMS and insulin resistance, one reported a positive association and two no association.^{10–12} However, both negative studies were cross-sectional and included predominately lean, non-smoking women with high insulin sensitivity. In the only study of diagnosed diabetes, Herber-Gast et al. reported elevated diabetes risk among women with severe VMS whose symptoms began in premenopause and peaked in perimenopause.¹³ There were no associations with moderate symptoms or severe

symptoms that peaked in postmenopause.¹³ In contrast, we observed an increase in diabetes risk only among women with postmenopausal symptoms.

Differences in study populations and design may partially account for discrepancies in menopausal stage findings. WHI enrolled women ages 50–79 years with natural or surgical menopause, whereas Herber-Gast et al. included younger women (45–50 years) undergoing natural menopause.¹³ When we excluded women with hysterectomy or oophorectomy (including surgical menopause), our results remained essentially unchanged. Furthermore, Herber-Gast et al. assessed VMS and diabetes simultaneously,¹³ thus the association may reflect reverse causality (e.g., an increase in perceived VMS resulting from disease progression or treatment). Similarly contrasting findings regarding the role of VMS timing have also been found in studies with CVD-related endpoints, the reasons for which remain unclear.^{14,29,30}

Our results also suggest that night sweats or their effects may be largely responsible for the association between VMS overall and diabetes. Examinations of the influence of reported hot flashes and night sweats separately on the risk of cardiovascular and metabolic outcomes are scarce. Similar positive relationships were reported with insulin resistance for both hot flashes and night sweats.¹¹ Regarding CVD, findings generally support a greater increase in risk associated with reported night sweats than hot flashes,^{31,32} but not universally.³³

There are several potential explanations for our pattern of findings. The most plausible and consistent explanation may be through associations with sleep disturbance. VMS overall are associated with objective and subjective sleep disturbance,²⁸ and individuals with disruptions in both the quantity and quality of sleep have a higher risk of diabetes.²⁷ Therefore, sleep may mediate the relationship between VMS overall and diabetes. In particular, night sweats are more strongly associated with sleep disturbance than hot flashes, as they occur during the night, which may explain their more pronounced relationship with diabetes.²⁸ However, the directionality and nature of the association between sleep and night sweats is not clear. It may be that women who are awake due to sleep disruptions are more likely to notice and report night sweats, conversely symptoms may trigger awakenings.³⁴

Regarding VMS timing, women reporting late symptoms had a longer VMS duration than those with only early symptoms. Thus, these women likely experienced longer exposure to sleep disturbance and a higher risk of diabetes.³⁵ When we examined the prevalence of sleep disordered breathing, insomnia, and short sleep duration by VMS characteristics, patterns mirrored the associations with diabetes. In particular, women reporting night sweats (with or without concomitant hot flashes) had a higher prevalence of sleep disordered breathing and insomnia, and women reporting late VMS had a higher prevalence of all sleep disturbances compared to the similar prevalence among women without any VMS, reporting only hot flashes, and only early symptoms.

Additional possible mechanisms linking late, but not early, VMS to diabetes and CVD may be through the direct relationship with duration of VMS. In *post hoc* analyses adjusting for VMS duration, the association between late symptoms and diabetes was substantially reduced and no longer statistically significant. Other important factors that likely play a role,

but which cannot entirely account for the observed relationships between VMS and diabetes, are obesity and race/ethnicity. Obesity is associated with higher risk of VMS, possibly through inhibiting heat dissipation, and is also a strong risk factor for development of diabetes.^{17,36} Race is also an important correlate of both VMS and diabetes, with African Americans reporting the highest rates of symptoms³⁷ and also having a higher risk of incident diabetes than their white peers.³⁸ However, we *a priori* adjusted for both these factors in analyses and associations remained statistically significant, suggesting these confounders cannot fully explain our findings.

Because a prior study found that the relationship between VMS and glucose levels was stronger among black women than white women,¹¹ we also examined whether associations between VMS and diabetes were modified by race. We found evidence of an interaction with VMS severity, such that the association with diabetes was *less* pronounced among black women than white women. The explanation for this finding is unclear. It may be related to how bothersome women perceive their symptoms, as black women rate their symptoms as more bothersome than white women, independent of VMS frequency.³⁹ Additionally, it may be that the preponderance of excess diabetes risk is attributable to other factors that predominate in black women rather than to VMS.⁴⁰ However, given that interactions with race were not consistently observed and that we tested many hypotheses, these results should be interpreted cautiously.

Lastly, differences in the physiology of VMS that develop pre- and post-menopause may explain findings related to timing. Levels of estrogen and other sex hormones thought to play a role in VMS differ across menopausal stages: perimenopause is characterized by high variability, particularly of estrogen, whereas levels are low in postmenopause, which may have implications for VMS physiology.⁴¹ Additional studies are needed that examine whether the underlying causes of VMS vary by menopausal stage and how differences could influence cardiovascular and metabolic health.

Our findings must be interpreted considering several limitations. First, VMS were ascertained retrospectively by self-report, which may be subject to more error than diary or physiological measurements. However, because information on diabetes was collected prospectively, resulting measurement error is unlikely to systematically differ between women who did and did not develop diabetes, leading to an underestimate of the association between VMS and diabetes. Diabetes was also self-reported; however, in validation studies more than 80% of self-reported cases were confirmed by medical record review.¹⁹ Because VMS were only assessed for the entire study cohort at baseline, VMS exposure may be misclassified (e.g., some women without VMS at baseline would develop symptoms later). Given our finding that late symptoms were more strongly associated with incident diabetes than early symptoms, this misclassification would likely underestimate association between VMS and diabetes.

Furthermore, despite adjusting for many variables that may confound the association between VMS characteristics and diabetes, we cannot rule out the possibility of residual confounding or unmeasured confounders. For example, although we adjusted for BMI, this measure may not completely capture adiposity, which could contribute to the observed

associations. For variables where the directionality of associations with VMS and diabetes was not entirely clear (e.g., study assignment, HT, and hysterectomy/oophorectomy), we re-ran analyses with exclusions and generally found a similar pattern of associations. The impact of HT on these analyses is especially problematic because HT improves VMS and reduces diabetes risk, as demonstrated in the WHI HT Trials, but VMS is also an indication for HT.^{44,45} Because VMS and HT were assessed at baseline, typically within a few days or weeks of one another, it is impossible to separate the indication for HT from its impact on VMS. For example, women on HT at baseline who reported no VMS are likely those for whom HT was effective and whose symptoms were severe enough to warrant treatment. However, the interpretation of our results remained essentially the same in both women who were and were not on HT at baseline

An additional limitation of our study is potential generalizability of findings because nearly half the study sample was CT participants, who, due to exclusion criteria, were likely healthier than the general population.⁴² It is also difficult, if not impossible, to disentangle the contributions of symptom timing, duration, and age as these concepts are fundamentally interrelated. Lastly, although we posit that the relationships between VMS and diabetes may be attributable to sleep disturbance, a formal mediation analysis was not possible because VMS and sleep disturbance were measured contemporaneously.⁴³ Future work using data where sleep is assessed after VMS should investigate the degree to which sleep disturbance contributes to the increased risk of diabetes associated with VMS.

CONCLUSIONS

VMS appear to be a risk factor for incident diabetes, particularly for women reporting night sweats (regardless of reported co-occurring hot flashes) and postmenopausal symptoms. The WHI Hormone Therapy Trials demonstrated a protective effect of HT on diabetes, highlighting a possible prevention strategy.^{44,45} However, the elevated risks of breast cancer, CVD, and stroke associated with treatment in WHI^{44,46} outweigh these benefits and resulted in dramatic decreases in HT use.⁴⁷

Mechanisms linking VMS and diabetes are unclear and should be the focus of future investigations. Although findings related to sleep disturbance may provide some preliminary clues, efforts to elucidate the underlying biological pathways are a critical next step. Regarding clinical implications of this work, given that nearly 60% of U.S. women seek care for treatment of VMS,⁴⁸ the menopausal transition may be an optimal time for clinicians to discuss future diabetes risk and assist patients in decision-making around symptom management. In particular, if sleep disturbance contributes to observed associations, timely and appropriate diagnosis and treatment of these disturbances may have the potential to decrease future risk. In addition, physical activity, weight loss, and smoking cessation may reduce the frequency of VMS or their interference with daily life, as well as reduce diabetes risk.⁴⁹ The psychosocial and physical benefits of these behavior changes on VMS may motivate long-term lifestyle modification. Therefore, while these results do not support different clinical care for women with VMS, they suggest that leveraging the immediate repercussions of VMS may be a particularly effective strategy for eliciting behavior change

among affected women as compared to counseling about the more distant and abstract future risk of diabetes and CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. NIH State-of-the-Science Conference Statement on management of menopause-related symptoms. NIH Consens State Sci Statements. 2005; 22(1):1–38.
2. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. Obstet Gynecol Clin North Am. 2011; 38(3):489–501. [PubMed: 21961716]
3. Muka T, Oliver-Williams C, Colpani V, et al. Association of vasomotor and other menopausal symptoms with risk of cardiovascular disease: a systematic review and meta-analysis. PLoS One. 2016; 11(6):e0157417. [PubMed: 27315068]
4. Stuenkel CA. Is it WISE to link vasomotor symptoms with cardiovascular disease? Menopause. 2017; 24(2):121–123. [PubMed: 28072608]
5. Schoenborn C, Heyman K. Health characteristics of adults aged 55 years and over: United States, 2004–2007. Natl Health Stat Report. 2009; 16:1–32.
6. Boyle JP, Honeycutt AA, Narayan KM, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. Diabetes Care. 2001; 24(11):1936–1940. [PubMed: 11679460]
7. Centers for Disease Control and Prevention. [Accessed February 28, 2017] Leading causes of death in females United States, 2014. <https://www.cdc.gov/women/lcod/2014/index.htm>. Updated January 13, 2017

8. Roche MM, Wang PP. Sex differences in all-cause and cardiovascular mortality, hospitalization for individuals with and without diabetes, and patients with diabetes diagnosed early and late. *Diabetes Care*. 2013; 36(9):2582–2590. [PubMed: 23564923]
9. Nathan DM, Barrett-Connor E, Crandall J, et al. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications: the DPP Outcomes Study. *Lancet Diabetes Endocrinol*. 2015; 3(11):866–875. [PubMed: 26377054]
10. Kwon DH, Lee JH, Ryu K-J, Park H-T, Kim T. Vasomotor symptoms and the homeostatic model assessment of insulin-resistance in Korean postmenopausal women. *Obstet Gynecol Sci*. 2016; 59(1):45–49. [PubMed: 26866035]
11. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al. Vasomotor symptoms and insulin resistance in the Study of Women's Health Across the Nation. *J Clin Endocrinol Metab*. 2012; 97(10):3487–3494. [PubMed: 22851488]
12. Tuomikoski P, Ylikorkala O, Mikkola TS. Menopausal hot flashes and insulin resistance. *Menopause*. 2012; 19(10):1116–1120. [PubMed: 22668816]
13. Herber-Gast GC, Mishra GD. Early severe vasomotor menopausal symptoms are associated with diabetes. *Menopause*. 2014; 21(8):855–860. [PubMed: 24398410]
14. Szmulowicz ED, Manson JE, Rossouw JE, et al. Vasomotor symptoms and cardiovascular events in postmenopausal women. *Menopause*. 2011; 18(6):603–610. [PubMed: 21358352]
15. Thurston RC, Christie IC, Matthews KA. Hot flashes and cardiac vagal control during women's daily lives. *Menopause*. 2012; 19(4):406–412. [PubMed: 22095062]
16. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al. Are vasomotor symptoms associated with alterations in hemostatic and inflammatory markers? Findings from the Study of Women's Health Across the Nation. *Menopause*. 2011; 18(10):1044–1051. [PubMed: 21926929]
17. Thurston RC, Sowers MR, Chang Y, et al. Adiposity and reporting of vasomotor symptoms among midlife women: the Study of Women's Health Across the Nation. *Am J Epidemiol*. 2008; 167(1):78–85. [PubMed: 17881385]
18. The Women's Health Initiative Study Group. Design of the Women's Health Initiative Clinical Trial and Observational Study. *Control Clin Trials*. 1998; 19(1):61–109. [PubMed: 9492970]
19. Jackson JM, DeFor TA, Crain AL, et al. Validity of diabetes self-reports in the Women's Health Initiative. *Menopause*. 2014; 21(8):861–868. [PubMed: 24496083]
20. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993; 25(1):71–80. [PubMed: 8292105]
21. Levine DW, Kaplan RM, Kripke DF, Bowen DJ, Naughton MJ, Shumaker SA. Factor structure and measurement invariance of the Women's Health Initiative Insomnia Rating Scale. *Psychol Assess*. 2003; 15(2):123–136. [PubMed: 12847773]
22. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med*. 1999; 131(7):485–491. [PubMed: 10507956]
23. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2003; 138(1):1–9.
24. Newton KM, Reed SD, LaCroix AZ, Grothaus LC, Ehrlich K, Guiltinan J. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med*. 2006; 145(12):869–879. [PubMed: 17179056]
25. Appiah D, Winters SJ, Hornung CA. Bilateral oophorectomy and the risk of incident diabetes in postmenopausal women. *Diabetes Care*. 2014; 37(3):725–733. [PubMed: 24194507]
26. Hunter MS. Cortisol, hot flashes, and cardiovascular risk. *Menopause*. 2011; 18(3):251–252. [PubMed: 21242814]
27. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2010; 33(2):414–420. [PubMed: 19910503]

28. Joffe H, Crawford S, Economou N, et al. A gonadotropin-releasing hormone agonist model demonstrates that nocturnal hot flashes interrupt objective sleep. *Sleep*. 2013; 36(12):1977–1985. [PubMed: 24293774]
29. Thurston RC, Johnson BD, Shufelt CL, et al. Menopausal symptoms and cardiovascular disease mortality in the Women's Ischemia Syndrome Evaluation (WISE). *Menopause*. 2017; 24(2):126–132. [PubMed: 27676638]
30. Thurston RC, El Khoudary SR, Tepper PG, et al. Trajectories of vasomotor symptoms and carotid intima media thickness in the Study of Women's Health Across the Nation. *Stroke*. 2016; 47(1): 12–17. [PubMed: 26578657]
31. Gast GC, Pop VJ, Samsioe GN, et al. Vasomotor menopausal symptoms are associated with increased risk of coronary heart disease. *Menopause*. 2011; 18(2):146–151. [PubMed: 21127438]
32. Herber-Gast G, Brown WJ, Mishra GD. Hot flushes and night sweats are associated with coronary heart disease risk in midlife: a longitudinal study. *BJOG*. 2015; 122(11):1560–1567. [PubMed: 25377022]
33. Gordon JL, Rubinow DR, Thurston RC, Paulson J, Schmidt PJ, Girdler SS. Cardiovascular, hemodynamic, neuroendocrine, and inflammatory markers in women with and without vasomotor symptoms. *Menopause*. 2016; 23(11):1189–1198. [PubMed: 27465715]
34. Moline ML, Broch L, Zak R, Gross V. Sleep in women across the life cycle from adulthood through menopause. *Sleep Med Rev*. 2003; 7(2):155–177. [PubMed: 12628216]
35. Pan A, Schernhammer ES, Sun Q, Hu FB. Rotating night shift work and risk of type 2 diabetes: two prospective cohort studies in women. *PLoS Med*. 2011; 8(12):e1001141. [PubMed: 22162955]
36. Whiteman MK, Staropoli CA, Langenberg PW, McCarter RJ, Kjerulff KH, Flaws JA. Smoking, body mass, and hot flashes in midlife women. *Obstet Gynecol*. 2003; 101(2):264–272. [PubMed: 12576249]
37. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. *Am J Public Health*. 2006; 96(7):1226–1235. [PubMed: 16735636]
38. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *JAMA*. 2000; 283(17):2253–2259. [PubMed: 10807384]
39. Thurston RC, Bromberger JT, Joffe H, et al. Beyond frequency: who is most bothered by vasomotor symptoms? *Menopause*. 2008; 15(5):841–847. [PubMed: 18521049]
40. Matthews KA, Sowers MF, Derby CA, et al. Ethnic differences in cardiovascular risk factor burden among middle- aged women: Study of Women's Health Across the Nation (SWAN). *Am Heart J*. 2005; 149(6):1066–1073. [PubMed: 15976790]
41. Burger HG, Dudley EC, Robertson DM, Dennerstein L. Hormonal changes in the menopause transition. *Recent Prog Horm Res*. 2002; 57:257–275. [PubMed: 12017547]
42. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003; 13(9 Suppl):S18–77. [PubMed: 14575939]
43. Maxwell SE, Cole DA. Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods*. 2007; 12(1):23–44. [PubMed: 17402810]
44. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004; 291(14):1701–1712. [PubMed: 15082697]
45. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia*. 2004; 47(7):1175–1187. [PubMed: 15252707]
46. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288(3):321–333. [PubMed: 12117397]
47. Kelly JP, Kaufman DW, Rosenberg L, Kelley K, Cooper SG, Mitchell AA. Use of postmenopausal hormone therapy since the Women's Health Initiative findings. *Pharmacoepidemiology and drug safety*. 2005; 14(12):837–842. [PubMed: 15812877]

48. Williams RE, Kalilani L, DiBenedetti DB, Zhou X, Fehnel SE, Clark RV. Healthcare seeking and treatment for menopausal symptoms in the United States. *Maturitas*. 2007; 58(4):348–358. [PubMed: 17964093]
49. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. *Menopause*. 2015; 22(11):1155–1172. [PubMed: 26382310]

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Figure 1.

Flow diagram for study inclusion and exclusion. Participants with prevalent diabetes at baseline, without data on vasomotor symptoms (VMS), or lacking follow-up data on diabetes were excluded from main analyses.

Figure 2.

Associations of hot flash and night sweat severity with incident diabetes. Panel (A) shows the relationship between hot flash severity and diabetes across severity of night sweats. Point estimates reflect the hazard ratio for diabetes comparing women with mild hot flashes to no hot flashes (black circles) and moderate/severe hot flashes to no hot flashes (white circles). Increasing severity of hot flashes was associated with slightly higher risk of diabetes among women with no night sweats; there were no associations among women with mild or moderate/severe night sweats. Panel (B) displays the relationship between night sweat severity and diabetes across severity of hot flashes. Point estimates reflect the hazard ratio

for diabetes comparing women with mild night sweats to no night sweats (black squares) and moderate/severe night sweats to no night sweats (white squares). Across all hot flash severities, increasing severity of night sweats was positively associated with diabetes risk. There was no evidence of a multiplicative effect of hot flashes and night sweats (p-value for interaction=0.12).

Figure 3.

Unadjusted prevalence of sleep disturbance by vasomotor symptom (VMS) characteristics. Women with any VMS had a greater prevalence of each sleep disturbance than women without VMS, and prevalence increased with symptom severity. Insomnia and sleep disordered breathing were more common among women with any night sweats than among those with only hot flashes. Compared to women with only early (pre- or perimenopausal) VMS, women with any late (postmenopausal) symptoms had a greater prevalence of sleep disturbance.

Table 1

Baseline characteristics of women with and without vasomotor symptoms (VMS; hot flashes and night sweats) at baseline

	No VMS ^b		VMS ^b	
	N	%	N	%
Total	101,220		48,787	
Study participation				
Observational Study	60,395	59.7	26,545	54.4
Clinical Trials	40,825	40.33	22,242	45.59
Age				
50–59	27,780	27.4	22,672	46.5
60–69	47,642	47.1	19,337	39.6
70+	25,798	25.5	6,778	13.9
Race/Ethnicity				
White (not of Hispanic origin)	88,160	87.1	37,626	77.1
American Indian or Alaskan Native	334	0.3	249	0.5
Asian or Pacific Islander	2,914	2.9	875	1.8
Black	5,397	5.3	6,872	14.1
Hispanic/Latino	3,111	3.1	2,416	5.0
Other	1,063	1.1	614	1.3
Marital status				
Never married	4,428	4.4	2,088	4.3
Divorced/separated	15,652	15.5	8,023	16.4
Widowed	18,557	18.3	6,566	13.5
Married	62,174	61.4	31,848	65.3
Education				
High school diploma/GED or less	20,419	20.2	12,055	24.7
More than a high school diploma/GED	80,093	79.1	36,342	74.5
Body Mass Index				
Underweight	1,035	1.0	297	0.6
Normal	38,166	37.7	14,807	30.4
Overweight	35,214	34.8	17,051	34.9
Obese	25,943	25.6	16,179	33.2
Pack years of smoking				
Never smoked	51,974	51.3	23,533	48.2
<5	14,026	13.9	7,092	14.5
5 to <20	13,761	13.6	7,167	14.7
20+	18,002	17.8	9,314	19.1
Alcohol consumption				
Non-drinker	10,395	10.3	5,207	10.7
Past drinker	16,642	16.4	9,294	19.1
<1 drink per week	33,264	32.9	16,271	33.4

	No VMS ^b		VMS ^b	
	N	%	N	%
1+ drinks per week	40,320	39.8	17,651	36.2
Physical activity				
Inactive	19,622	19.4	11,369	23.3
Low	26,750	26.4	13,319	27.3
Medium	28,068	27.7	12,157	24.9
High	22,543	22.3	9,392	19.3
Hypertension	41,225	40.7	20,173	41.3
Hormone therapy use	43,819	43.3	17,684	36.2
Hysterectomy	41,290	40.8	20,610	42.2
Oophorectomy	28,549	28.2	13,736	28.2
Early VMS	43,281	42.8	29,843	61.2
Age at first symptom ^a				
<40	3,508	8.1	3,089	10.4
40–44	7,311	16.9	4,892	16.4
45–49	15,679	36.2	10,165	34.1
50–54	14,558	33.6	9,917	33.2
55+	2,225	5.1	1,780	6.0
Age at menopause				
<40	8,179	8.1	4,940	10.1
40–44	12,378	12.2	6,109	12.5
45–49	24,634	24.3	12,440	25.5
50–54	36,142	35.7	17,518	35.9
55+	13,634	13.5	5,575	11.4
Time since menopause (years)				
<5	10,047	9.9	9,386	19.2
5–9	16,054	15.9	9,829	20.1
10–14	19,036	18.8	8,986	18.4
15–19	17,458	17.2	6,617	13.6
20+	32,372	32.0	11,764	24.1
High risk for sleep disordered breathing	21,847	21.6	13,511	27.7
High risk for insomnia	26,744	26.4	18,860	38.7
Short sleep duration	33,686	33.3	19,467	39.9

^a Among women reporting past hot flashes

^b Numbers may not add to totals and percents to 100 due to missing data

Table 2 Adjusted association between incident diabetes and vasomotor symptom presence, severity, type, and timing^a

	Incidence rate ^e	N	Compared to no symptoms	
			HR ^f	95% CI
No symptoms	8.4	91,141	1.00	reference
Any symptoms	11.3	43,291	1.18	1.14, 1.22
Severity ^b				
Mild	10.2	30,944	1.13	1.08, 1.17
Moderate	13.3	9,827	1.29	1.22, 1.36
Severe	17.0	2,520	1.48	1.35, 1.62
Type ^c				
Hot flashes	9.9	9,552	1.08	1.02, 1.15
Night sweats	11.0	11,080	1.20	1.13, 1.26
Both	12.0	22,376	1.22	1.17, 1.27
Timing ^d				
Neither	8.83	35,690	1.00	reference
Early	7.98	40,732	0.99	0.95, 1.04
Late	10.17	24,717	1.13	1.07, 1.18
Early and late	10.96	28,049	1.16	1.11, 1.22

HR=hazard ratio

^aOutcomes assessed from 1993–2014; average follow-up time=13.1 years^bp-value for test of trend<0.001 when severity modeled continuously in a separate model^cp-value for interaction between hot flashes and night sweats=0.17; numbers do not add up to the number of women with any symptoms due to missing information on either hot flashes or night sweats^dReference group differs from other VMS characteristics due to missing data on early symptoms; p-value for interaction between early and late symptoms=0.47^eUnadjusted incidence rate per 1,000 person-years of follow-up^fAdjusted for baseline age (continuous), race/ethnicity (nominal), marital status (nominal), education (ordinal), BMI (continuous), hypertension (dichotomous), physical activity (MET-hours/week, continuous), pack years of smoking (continuous), alcohol consumption (drinks/week, continuous), and hormone therapy use (dichotomous)