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Clinical Research Article

Insulin Levels Early in Perimenopause Inform Vasomotor Symptom Incidence Across the Menopausal Transition

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Abstract

Context: Metabolic health affects the menopausal transition. Metabolic characteristics like body mass index (BMI) affect vasomotor syndrome incidence, but the role of elevated insulin, an early marker of metabolic dysfunction, remains understudied.

Objective: This work aimed to determine whether midlife insulin levels are associated with vasomotor symptom incidence or reproductive hormone trajectories.

Methods: Longitudinal analyses of community-based data from the Study of Women's Health Across the Nation (SWAN) were conducted. We analyzed the 704 SWAN participants (of 3302) without oophorectomy or hysterectomy who had metabolic data for age 47 and did not take insulin/medications for hyperglycemia. Mean fasting insulin at age 47 was 10.117 μIU/mL (SD = 6.711), with 27.0 BMI (SD = 6.6); the mean age of the final menstrual period for these participants was 51.0 years (SD = 2.3). Main outcome measures included vasomotor symptom timings and durations, and trajectories of estradiol (E2), follicle-stimulating hormone (FSH), and testosterone (T) across the menopausal transition.

Results: Higher insulin at age 47 predicted younger onsets of hot flashes and night sweats, longer durations of hot flashes and cold sweats, and greater T rise. BMI associations with vasomotor symptoms paralleled those of insulin, but BMI appeared more closely linked to slower E2 decline and blunted FSH rise. In Cox proportional hazards models, elevated age-47 insulin was associated with increased likelihood of hot flashes; this remained statistically significant with BMI and glucose as covariates.

Conclusion: Perimenopausal fasting insulin and BMI show complementary but distinct associations with menopausal changes. Elevated insulin predicts earlier and prolonged vasomotor symptoms, and is associated with higher T.

Key Words: hot flashes, hyperinsulinemia, Study of Women's Health Across the Nation (SWAN), climacteric, androgen, insulin resistance

Abbreviations: BMI, body mass index; E2, estradiol; FMP, final menstrual period; FSH, follicle-stimulating hormone; HOMA-IR, homeostatic model assessment of insulin resistance; HR, hazard ratio; SWAN, Study of Women's Health Across the Nation; T, testosterone.

The menopausal transition is accompanied by physiological changes that diminish quality of life. These may include hot flashes, night sweats, or cold sweats, which are often collectively described as vasomotor symptoms, as well as other associated changes such as vaginal dryness, changes in blood pressure, and heart palpitations (1). Vasomotor symptoms affect approximately three-quarters of women (2, 3); they can appear 2 years before the final menstrual period (FMP) and persist for as long as 8 to 10 years beyond it (4). The severity and duration of these symptoms is affected by factors such as race, ethnicity, and socioeconomic status. For instance, Black women report a high prevalence and long duration of vasomotor symptoms, while women of Asian descent report low vasomotor symptom prevalence (5-7). However, women of the same ethnicity may also have varying degrees of symptoms based on their location and socioeconomic status (2, 8, 9).

Although our understanding of vasomotor symptom pathophysiology is limited, a primary driver appears to be estrogen withdrawal and the related hypothalamic shift of perimenopause (10, 11). Rising levels of follicle-stimulating hormone (FSH) precede the decline in estrogen levels, with FSH rising approximately a year before estrogen reaches its lowest point (12). Testosterone (T) levels might remain relatively stable or decrease around the menopausal transition (13). The physiological repercussions of these endocrine shifts extend beyond the hypothalamus-pituitary-ovary axis. For instance, overactivation of KNDy neurons due to low estrogen levels can create a narrowed thermoneutral zone, making women more susceptible to temperature fluctuations that trigger the flushing, sweating, and peripheral vasodilation that are characteristic of hot flashes (14-16).

Recently, metabolic health has emerged as an important but relatively underexplored determinant of menopausal changes. For instance, women with obesity and higher body fat percentages report having a greater frequency and severity of vasomotor symptoms (17, 18) and an increased incidence of vasomotor symptoms early in menopause (19). Insulin resistance (based on the homeostatic model assessment of

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insulin resistance index, HOMA-IR) and high glycated hemoglobin A_{1c} levels are also associated with a greater disposition for vasomotor symptoms (20-22). However, a tight link exists between insulin resistance (ie, decreased insulin-stimulated glucose disposal) and hyperinsulinemia (ie, elevated insulin), creating challenges in differentiating between effects of impaired insulin signaling, high insulin levels, and/or hyperglycemia; clinical indices calculated from fasting glucose and insulin, such as HOMA-IR, may not readily distinguish between these parameters. Similarly, it is difficult to identify which of the many physiological changes that accompany or exacerbate obesity might be playing a role in regulating vasomotor symptoms.

Elevated insulin levels have emerged as an early feature—and potentially, an upstream driver—of metabolic disorders such as obesity, insulin resistance, and type 2 diabetes (23-26). Although racial differences exist in insulin dynamics (27), hyperinsulinemia is generally defined as insulin concentrations that exceed the normal range relative to an individual's age and health status, without hypoglycemia (24). Insulin is best known for its role in glucose homeostasis, but it also exerts important effects on the female reproductive system (28). For instance, insulin signaling regulates reproductive function by modulating gonadotropin-releasing hormone pulsatility and gonadotropin secretion, and by augmenting ovarian steroidogenesis through synergistic effects with gonadotropins (29, 30).

Increased vasomotor symptom severity and/or frequency has been associated with a greater risk of a subsequent type 2 diabetes diagnosis (31, 32), highlighting the ties between menopausal symptoms and metabolic health outcomes. Given that insulin may be elevated early in the pathogenesis of metabolic disorders, the aim of our study is to investigate whether insulin levels prior to menopause might predict the incidence and severity of physical menopause symptoms.

Materials and Methods

Study Participants

In our analyses, we used data from the Study of Women's Health Across the Nation (SWAN) that longitudinally followed women from a premenopausal/perimenopausal baseline (ages 42-52 years) across the subsequent 10 years (33). To evaluate metabolic health at a relatively early study time point that had an adequate sample size, we assessed metabolic measurements at the age of 47 years and related these to physiological features of the menopausal transition. We used metabolic metrics at a specific age point because average insulin levels were shown to rise with chronological age during the course of the SWAN study (34, 35), but we acknowledge that age 47 may not represent the same stage in all participants' menopausal transition.

These secondary analyses used anonymized, publicly available data from SWAN (retrieved from the Inter-University Consortium for Political and Social Research/ICPSR archive, RRID: SCR_003194; ICPSR 28762, ICPSR 29221, ICPSR 29401, ICPSR 29701, ICPSR 30142, ICPSR 30181, ICPSR 30501, ICPSR 31181, ICPSR 31901, ICPSR 32122, ICPSR 32721, ICPSR 32961). These included biological, behavioral, and socioeconomic data from baseline up to the tenth annual follow-up visit, all of which were collected between 1995 and 2008. SWAN was a multisite longitudinal cohort study of middle-aged women across 7 sites in the United States. The detailed study design and protocol have been described previously (33). The SWAN study protocol was approved by the institutional board at each study site, and all participants provided written informed consent. Our secondary data analyses were approved by the human research ethics board at the University of Victoria (protocol No. 25-0295).

The 3302 participants who were enrolled in SWAN at baseline had an intact uterus and 1 or both ovaries, were not taking hormone therapy, not pregnant or lactating, and had experienced 1 or more menses in the prior 3 months. Here, we analyzed data for participants who attended a study visit at age 47, and had complete data for body mass index (BMI), fasting insulin, and fasting glucose measurements at that visit (Fig. 1). The questionnaires did not provide comprehensive or detailed information on all medications that might affect insulin sensitivity or glucose homeostasis (eg, corticosteroid use was not indicated across the full course of the study). However, participants were excluded from our analyses if they reported taking insulin or other medications to manage blood glucose; survey questions did not distinguish between insulin therapy and use of oral antidiabetic drugs (eg, metformin, sulfonylureas). Participants were excluded (n = 357) if at any point in the study they answered yes in response to either of these questions: "Since your last study visit, have you taken insulin or pills for sugar in your blood?" or "We would like to know the medications that you have used in the past, but no longer take. Have you ever used any of these medications regularly (at least twice a week throughout the month) for more than one month: insulin or pills for high blood sugar?" Participants were also excluded if they underwent an oophorectomy or hysterectomy during the course of the study (n = 252), did not attend a study visit at age 47 (n = 457), or were missing fasting insulin, fasting glucose, or BMI values for the age-47 visit (n = 266).

Clinical Measures and Questionnaire Data

The measurements taken in the SWAN protocol have previously been described in detail (33, 34, 36-38). In brief, blood was collected after an overnight fast and centrifuged to collect serum for analysis. Insulin was measured in serum by a solid-phase radioimmunoassay (DPC Coat-a-Count; Diagnostic Products Corporation; RRID: AB_3719312). Fasting insulin values from study participants when they were age 47 years were log-transformed to normalize the distribution for our analyses. Serum estradiol (E2), FSH, and T levels were measured using the Automated Chemiluminescence System (ACS)-180 automated analyzer (Bayer Diagnostics Corporation). For the double-antibody E2 chemiluminescent immunoassay, the rabbit anti-E2-6 ACS-180 immunoassay was modified to increase sensitivity (RRID: AB_10877469 (39)). FSH was measured using a 2-site chemiluminometric immunoassay with 2 monoclonal antibodies for different regions of the β subunit (RRID: AB_2895593). The total T assay was a modified rabbit polyclonal anti-T ACS-180 immunoassay (RRID: AB_2783804). Glucose was measured with a hexokinase-coupled reaction on a Hitachi 747-200 chemical analyzer using Roche Diagnostics reagents. BMI was measured at the annual clinic visits using a stadiometer and balance beam and was determined as weight in kilograms divided by height in meters squared.

Participants self-reported the occurrence of hot flashes, night sweats, cold sweats, and vaginal dryness in the 2 weeks

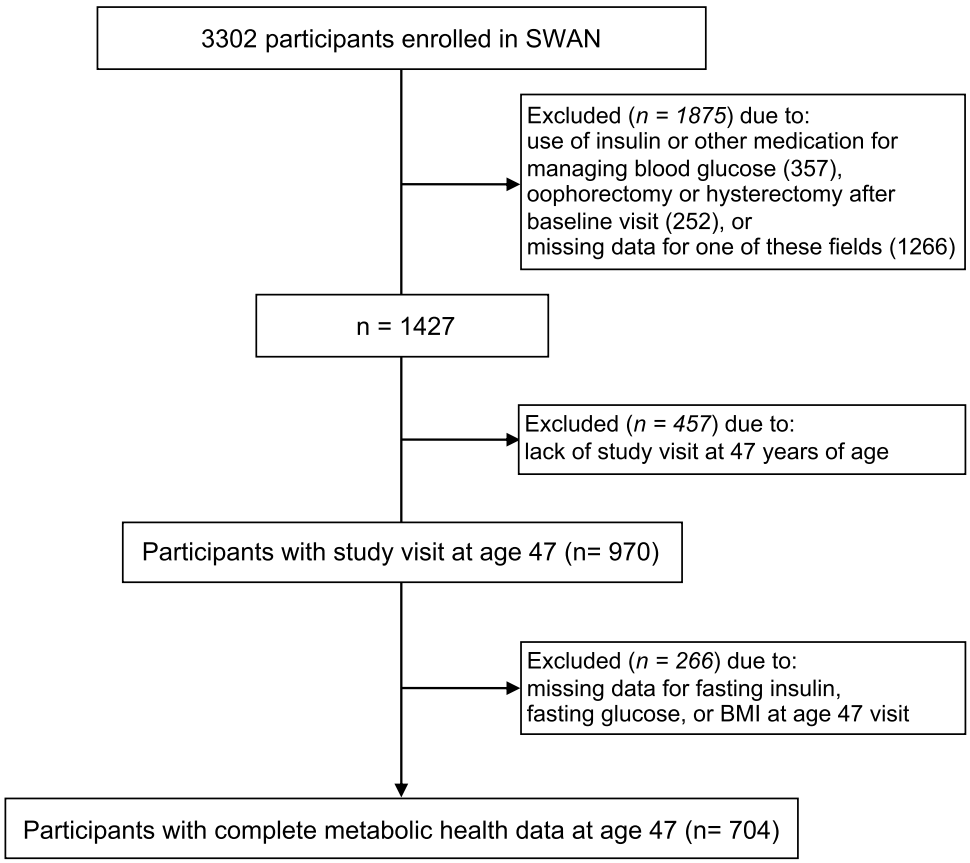

Figure 1. Study of Women's Health Across the Nation (SWAN) participant flowchart of analytic sample for assessing associations between age-47 metabolic measures and menopause symptoms. Participants were excluded if they reported taking insulin or other medications to manage blood glucose, if they underwent an oophorectomy or hysterectomy during the course of the study, if did not attend a study visit at age 47, or if they were missing fasting insulin, fasting glucose, and BMI values for the age-47 visit.

prior to the annual visit, categorizing each symptom as having occurred: not at all, 1 to 5 days, 6 to 8 days, 9 to 13 days, or every day. We classified participants as being symptomatic at an annual visit if their questionnaire responses reported any incidence of the symptom in the prior 2 weeks (vs not at all). We defined the duration of experiencing a symptom across the 10-year study period as the number of annual visits over which a symptom was reported, and we estimated the age of onset of each symptom based on age at the first visit when a symptom was reported. Symptom onset timing therefore reflects the chronological age of symptom onset, rather than symptom timing relative to the stage of menopausal transition. FMP was estimated as the self-reported date of last menstrual period preceding 12 months of amenorrhea.

Covariates included self-reported race/ethnicity, smoking status, and income at the baseline visit, based on previously identified associations between these variables and vasomotor symptom incidence in SWAN participants (2, 8, 9).

Statistical Analyses

Linear regression models were used to examine associations between log-transformed insulin levels or BMI at age 47 and continuous symptom measures. We first fit unadjusted simple linear regression models, followed by multiple linear regression models adjusted for self-reported race/ethnicity, income, and smoking status to account for differences both in insulin levels and menopausal symptom patterns. Ordinary least squares estimation was applied, with statistical significance set at P less than .05. Hormone trajectory slopes relative to FMP were estimated for each participant using mixed-effects models with log-transformed hormone values, and these individual slopes were then regressed on 47-year-old BMI and log-insulin levels using linear regression, adjusting for demographic covariates. To further examine the association between symptom incidence and insulin, BMI, or glucose, we used Cox proportional hazards models. For each symptom, we fitted sequential models examining insulin alone, BMI alone, and insulin, BMI and glucose predictors simultaneously, with hazard ratios (HRs) representing risk per 1-SD increase in predictor. We performed complete case analysis and analyses were conducted in RStudio (R version 4.1.1).

Results

Our final dataset included 704 participants (Table 1). The self-reported racial and ethnic composition of the included participants was: 375 (53.3%) Caucasian/White Non-Hispanic, 149 (21.2%) Black/African American, 98 (13.9%) Japanese/Japanese American, and 82 (11.6%) Chinese/Chinese American. Mean insulin levels were 10.117 μIU/mL (SD = 6.711 μIU/mL) at age 47 years, with a mean BMI of 27.0 (SD = 6.6). Mean 47-year-old fasting glucose levels and HOMA-IR were 89.5 (SD = 9.6) mg/dL and 2.31

Table 1. Baseline characteristics of analytic sample from the Study of Women's Health Across the Nation

N, analytic sample/of total SWAN enrollment	704/of 3302 total
Self-reported race and ethnicity	
Caucasian/White Non-Hispanic	375 (53.3%)
Black/African American	149 (21.2%)
Japanese/Japanese American	98 (13.9%)
Chinese/Chinese American	82 (11.6%)
Menopause symptom prevalence at age of 47 y	
Hot flashes	217 (31%)
Night sweats	216 (30.9%)
Cold sweats	63 (9.1%)
Vaginal dryness	152 (21.7%)
Age at FMP, y	51.0 (SD 2.3)
Fasting insulin at age of 47 y, μIU/mL	10.117 (SD 6.711)
BMI at age of 47 y	27.0 (SD 6.6)
Fasting glucose at age of 47 y, mg/dL	89.5 (SD 9.6)
HOMA-IR at age of 47 y	2.31 (SD 1.82)

Data are presented as count (percentages) for categorical variables, and as mean (SD) for continuous variables.
Abbreviations: BMI, body mass index; FMP, final menstrual period; HOMA-IR, homeostatic model assessment of insulin resistance; SWAN, Study of Women's Health Across the Nation.

(SD = 1.82), respectively. At age 47, a majority of women in our dataset reported an absence of physical menopausal symptoms (69.0%, 69.1%, 90.9%, and 78.3% reported that they did not experience hot flashes, night sweats, cold sweats, and vaginal dryness, respectively) over the preceding 2-week period. The average age of the FMP for the individuals included in our dataset was 51.0 (SD 2.3 years).

Insulin Levels Predict Age of Onset and Duration of Symptoms of the Menopausal Transition

Four symptom variables showed statistically significant associations with insulin levels in models adjusted for the covariates of self-reported race, income, and smoking status (Table 2). The most pronounced associations included the ages of onset for hot flashes ($\beta = -1.14$; $P < .001$) and night sweats ($\beta = -.69$; $P = .035$), both of which indicated symptom onset at a younger age if the individuals had higher fasted insulin levels at the age of 47 years. In addition, higher insulin was associated with experiencing longer durations of cold sweats ($\beta = .38$; $P = .018$) and/or hot flashes ($\beta = .62$; $P = .032$) in the adjusted models. Although the age of onset of vaginal dryness was associated with insulin in a simple linear regression without adjustment ($\beta = -.77$; $P = .039$), this relationship lost statistical significance after adjusting for self-reported race/ethnicity, income level, and smoking status ($\beta = -.66$; $P = .095$). Collectively, these data indicate that women with higher insulin levels at the age of 47 years have an increased likelihood of experiencing vasomotor symptoms at a younger age, and for a longer duration of time.

Higher Insulin and a Higher Body Mass Index at Age 47 Are Parallel Predictors of Vasomotor Symptoms

BMI is a widely used metric to approximate physical fitness based on the height and weight ratios, although it is an imprecise measure that does not account for muscle mass, adipose distribution, sex differences, or ethnic differences in body composition. We wished to assess how insulin levels compare to BMI in terms of predicting physical menopause symptoms. In simple linear regressions without adjustment, we observed that the ages of onset of all tested symptoms were significantly associated with a higher BMI at age 47, as were the durations of hot flashes, night sweats, and cold sweats. After accounting for confounding effects of self-reported race, income (an indicator of socioeconomic factors), and smoking status, 3 relationships maintained their statistical significance: the ages of onset of hot flashes ($\beta = -.093$; $P < .001$) and night sweats ($\beta = -.047$; $P = .045$), and the duration of experiencing cold sweats ($\beta = .025$; $P = .031$; Table 3).

In our analyses, both insulin levels and BMI emerged as predictors of menopause symptom timing and duration. Adjustments for sociodemographic factors caused a higher proportion of the BMI relationships to lose statistical significance, suggesting that BMI may be more confounded than insulin levels by factors such as race/ethnicity and income. The close tracking between adjusted R^2 values for insulin and BMI (Fig. 2) raises the possibility that insulin dysregulation, rather than obesity alone, may play a key role in mediating BMI-associated changes in vasomotor symptom burden during menopause.

To use a different approach for comparing the predictive capacities of these two metabolic features, we performed Cox proportional hazards regressions with BMI and fasting insulin values at the age of 47 (Table 4). After adjusting for self-reported race/ethnicity, income, and smoking status, insulin levels at age 47 showed stronger predictive effects for incidence of key menopause symptoms. For instance, each SD rise in log-insulin (ie, an increase of 5.6 μIU/mL in fasting insulin levels) was associated with a 14% higher hazard of hot flashes (HR = 1.14; 95% CI, 1.05-1.24; $P = .002$), while BMI did not show a statistically significant effect (HR = 1.07; 95% CI, 0.99-1.17; $P = .104$). Higher insulin levels also predicted a 20% higher hazard of cold sweats (HR = 1.20; 95% CI, 1.06-1.35; $P = .004$), compared to an 18% increase for BMI (HR = 1.18; 95% CI, 1.04-1.34; $P = .012$). In multivariable models that included both predictors (ie, both insulin and BMI), age-47 fasting insulin levels maintained independent significance for a positive association with hot flash likelihood (HR = 1.15; 95% CI, 1.04-1.27; $P = .007$) while none of the BMI effects reached the threshold of statistical significance once insulin was incorporated as a covariate. Therefore, fasting insulin levels appear to have more pronounced effects on the instantaneous risk of vasomotor symptoms. Moreover, in multivariable Cox proportional hazards regression models that incorporated 3 key metabolic variables at age 47—fasting insulin, BMI, and fasting glucose levels—only insulin showed a significant independent association with hot flash likelihood (HR = 1.13; 95% CI, 1.01-1.26; $P = .027$; Table 5). Elevated insulin levels, which can be early indicators of metabolic dysfunction, may serve as valuable markers for identifying individuals at risk for younger-onset and potentially severe vasomotor symptoms.

Body Mass Index Is Linked to Follicle-Stimulating Hormone and Estrogen Dynamics While Insulin Is Associated With Testosterone

Vasomotor symptoms like hot flashes are also tied to fluctuations in estrogen and FSH (40). Thus, we wished to

Table 2. Associations between age-47 fasting insulin levels and menopause symptoms

Exposure: insulin Menopause symptom	Unadjusted			Adjusted for self-reported race + income + smoking status		
	Coefficient	*P*	Adj R^2	Coefficient	*P*	Adj R^2
Hot flashes (n = 610)						
Age of onset	**−1.543**	**<.001**	**0.044**	**−1.138**	**<.001**	**0.077**
Duration	**0.959**	**<.001**	**0.017**	**0.618**	**.032**	**0.064**
Night sweats (n = 549)						
Age of onset	**−0.947**	**.003**	**0.017**	**−0.692**	**.035**	**0.044**
Duration	0.288	.306	0.001	−0.087	.759	0.09
Cold sweats (n = 247)						
Age of onset	−0.855	.074	0.013	−0.593	.226	0.075
Duration	**0.652**	**<.001**	**0.022**	**0.379**	**.018**	**0.125**
Vaginal dryness (n = 460)						
Age of onset	**−0.774**	**.039**	**0.009**	−0.663	.095	0.014
Duration	0.043	.879	<0.001	−0.057	.85	<0.001

Associations are results of linear regression models between log-transformed age-47 fasting insulin values and continuous menopausal symptom measures. Symptom age of onset was estimated based on age at the first visit when a symptom was reported in the prior 2 weeks; duration was defined as the number of annual visits over which a symptom was reported. Data are presented as β coefficients, *P* values, and adjusted R^2 values. Unadjusted model: simple linear regression; adjusted model: multiple linear regression adjusted for self-reported race/ethnicity, income, and smoking status for both insulin levels and menopausal symptom patterns. Ordinary least squares estimation was applied. Bold text signifies *P* less than or equal to .05.

Table 3. Associations between age-47 body mass index and menopause symptoms

Exposure: BMI Menopause symptom	Unadjusted			Adjusted for self-reported race + income + smoking status		
	Coefficient	*P*	Adj R^2	Coefficient	*P*	Adj R^2
Hot flashes (n = 610)						
Age of onset	**−0.1215**	**<.0001**	**0.059**	**−0.0931**	**<.0001**	**0.083**
Duration	**0.0799**	**<.0001**	**0.025**	0.0375	.069	0.062
Night sweats (n = 549)						
Age of onset	**−0.0744**	**.0004**	**0.022**	**−0.0469**	**.045**	**0.043**
Duration	**0.0628**	**.0009**	**0.016**	0.0042	.835	0.09
Cold sweats (n = 247)						
Age of onset	**−0.0883**	**.007**	**0.029**	−0.0533	.136	0.078
Duration	**0.0597**	**<.0001**	**0.041**	**0.0246**	**.031**	**0.124**
Vaginal dryness (n = 460)						
Age of onset	**−0.057**	**.021**	**0.012**	−0.0385	.165	0.012
Duration	−0.0015	.939	<0.001	−0.0026	.905	<0.001

Associations are results of linear regression models between age-47 BMI and continuous menopausal symptom measures. Symptom age of onset was estimated based on age at the first visit when a symptom was reported in the prior 2 weeks; duration was defined as the number of annual visits over which a symptom was reported. Data are presented as β coefficients, *P* values, and adjusted R^2 values. Unadjusted model: simple linear regression; adjusted model: multiple linear regression adjusted for self-reported race/ethnicity, income, and smoking status for both BMI and menopausal symptom patterns. Ordinary least squares estimation was applied. Bold text signifies *P* less than or equal to .05.
Abbreviation: BMI, body mass index.

understand how BMI and insulin levels inform changes in levels of these hormones across the menopausal transition, from 6 years before to 6 years after the FMP. In our analyzed dataset, we observed menopausal hormonal changes that were largely consistent with prior reports: E2 levels decreased across the menopausal transition (−64.6%), while FSH levels rose markedly by 564.4% (Fig. 3). However, our dataset showed a slight, 6.8% average rise in T levels over the same window. We found that overall, a higher BMI at age 47 was associated with a blunted decline in E2 and a more-gradual rise in FSH levels across the menopausal transition. In contrast, insulin levels were more closely associated with T changes, with higher insulin linked to a greater rise in T over time (Table 6; see Fig. 3).

Discussion

In this study, we used longitudinal data from SWAN to examine how insulin levels and BMI influence physical changes of menopause. We found that insulin and BMI affect the menopausal transition in distinct but complementary ways. These two metabolic features aligned in their overall associations

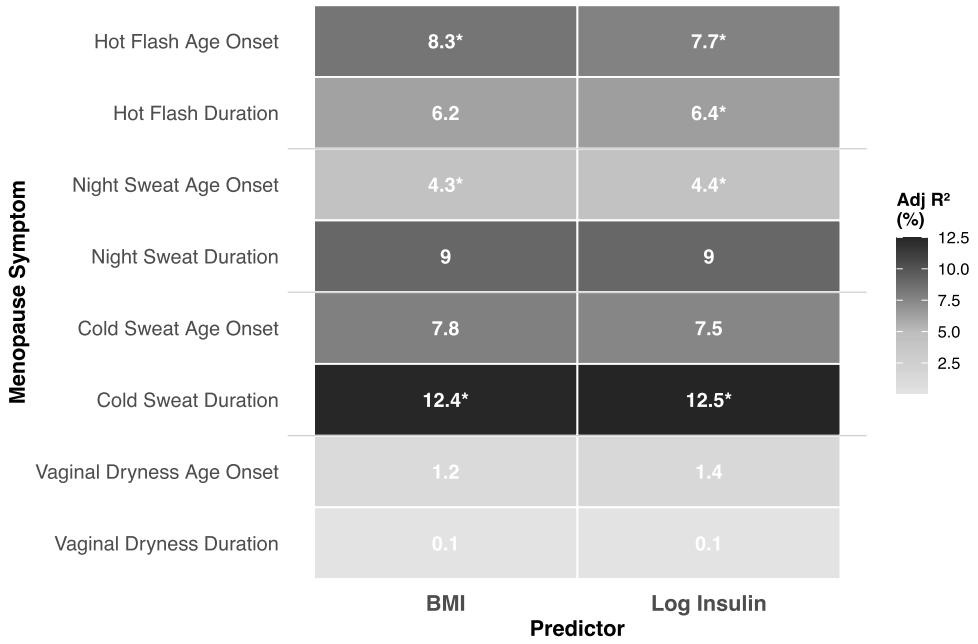

Figure 2. Parallels between adjusted R^2 values (%) for effects of age-47 body mass index (BMI) and fasting insulin on menopause symptom onset and duration. Adjusted R^2 values and *P* values are results of linear regression models between age-47 BMI and continuous menopausal symptom measures (see Table 3), and log-transformed age-47 fasting insulin values and continuous menopausal symptom measures (see Table 2). Symptom age of onset was estimated based on age at the first visit when a symptom was reported in the prior 2 weeks; duration was defined as the number of annual visits over which a symptom was reported. Heat map intensity reflects association strength (Adjusted R^2). **P* less than .05.

Table 4. Cox regression analyses of age-47 fasting insulin and body mass index effects on menopausal symptoms

Symptom	Univariate models				Multivariable models			
	Insulin HR (95% CI)	*P*	BMI HR (95% CI)	*P*	Insulin HR (95% CI)	*P*	BMI HR (95% CI)	*P*
Hot flashes	**1.14 (1.05-1.24)**	**.002**	1.07 (0.99-1.17)	.104	**1.15 (1.04-1.27)**	**.007**	0.99 (0.90-1.10)	.894
Night sweats	1.05 (0.96-1.14)	.321	1.06 (0.96-1.16)	.258	1.03 (0.93-1.14)	.632	1.04 (0.93-1.16)	.472
Cold sweats	**1.20 (1.06-1.35)**	**.004**	**1.18 (1.04-1.34)**	**.012**	1.14 (0.99-1.32)	.063	1.10 (0.94-1.27)	.234
Vaginal dryness	1.01 (0.91-1.11)	.905	1.00 (0.90-1.12)	.964	1.01 (0.90-1.13)	.91	1.00 (0.88-1.14)	.982

Associations are results of Cox proportional hazards models between log-transformed age-47 fasting insulin values, age-47 BMI, and menopausal symptom measures, adjusted for self-reported race/ethnicity, income, and smoking status. For each symptom, sequential models were fit to test insulin alone (univariate model), BMI alone (univariate model), both predictors simultaneously (multivariable models). Data are presented as HRs (representing risk per 1-SD increase in predictor) and 95% CI, as well as *P* values. Bold text signifies *P* less than or equal to 0.05.
Abbreviations: BMI, body mass index; HR, hazard ratio.

with the onset age and duration of vasomotor symptoms, yet premenopausal/perimenopausal fasting insulin may be especially effective at predicting incidence of these symptoms, particularly hot flashes. Meanwhile, BMI is more closely associated with the trajectories of the reproductive hormones FSH and E2. These data together suggest that metabolic health at the onset of perimenopause can cumulatively inform many aspects of the menopause experience.

Higher levels of fasting insulin at age 47 were associated with younger onset and elevated risk of vasomotor symptoms. In parallel to these relationships, we also observed that BMI at 47 is similarly associated with younger and extended experiences of vasomotor symptoms. This aligns with prior work indicating that BMI and waist circumference have greater associations with vasomotor symptom onset earlier rather than later in menopause (19). Since premenopausal/perimenopausal insulin levels continued to significantly predict the likelihood of experiencing hot flashes in combined Cox regression models, independent of confounding effects of BMI, it is worth considering whether high insulin might account for some obesity-attributed effects on vasomotor symptoms. It would be informative to determine whether limiting insulin levels could meaningfully change vasomotor symptom incidence, and investigate physiological underpinnings of these effects. Interestingly, rodent studies have shown that insulin may have hyperthermic effects through its actions on astrocytes and hypothalamic neurons that regulate thermogenesis (41, 42).

Table 5. Multivariable Cox regression analyses of fasting insulin, body mass index, and fasting glucose at age 47 years and effects on menopausal symptoms

Symptom	Multivariable models					
	Insulin HR (95% CI)	*P*	BMI HR (95% CI)	*P*	Glucose HR (95% CI)	*P*
Hot flashes	**1.13 (1.01-1.26)**	**.027**	0.99 (0.90-1.10)	.871	1.04 (0.95-1.13)	.455
Night sweats	1.02 (0.91-1.14)	.724	1.04 (0.93-1.16)	.480	1.01 (0.92-1.12)	.795
Cold sweats	1.16 (0.99-1.35)	.065	1.10 (0.94-1.27)	.227	0.97 (0.84-1.12)	.709
Vaginal dryness	1.03 (0.90-1.16)	.703	1.00 (0.88-1.14)	.975	0.96 (0.86-1.07)	.476

Associations are results of Cox proportional hazards models between log-transformed age-47 fasting insulin values, age-47 BMI, age-47 fasting glucose values, and menopausal symptom measures, adjusted for self-reported race/ethnicity, income, and smoking status. For each symptom, multivariable models were employed to account for all 3 predictors simultaneously. Data are presented as HRs (representing risk per 1-SD increase in predictor) and 95% CI, as well as *P* values. Bold text signifies *P* less than or equal to .05.
Abbreviations: BMI, body mass index; HR, hazard ratio.

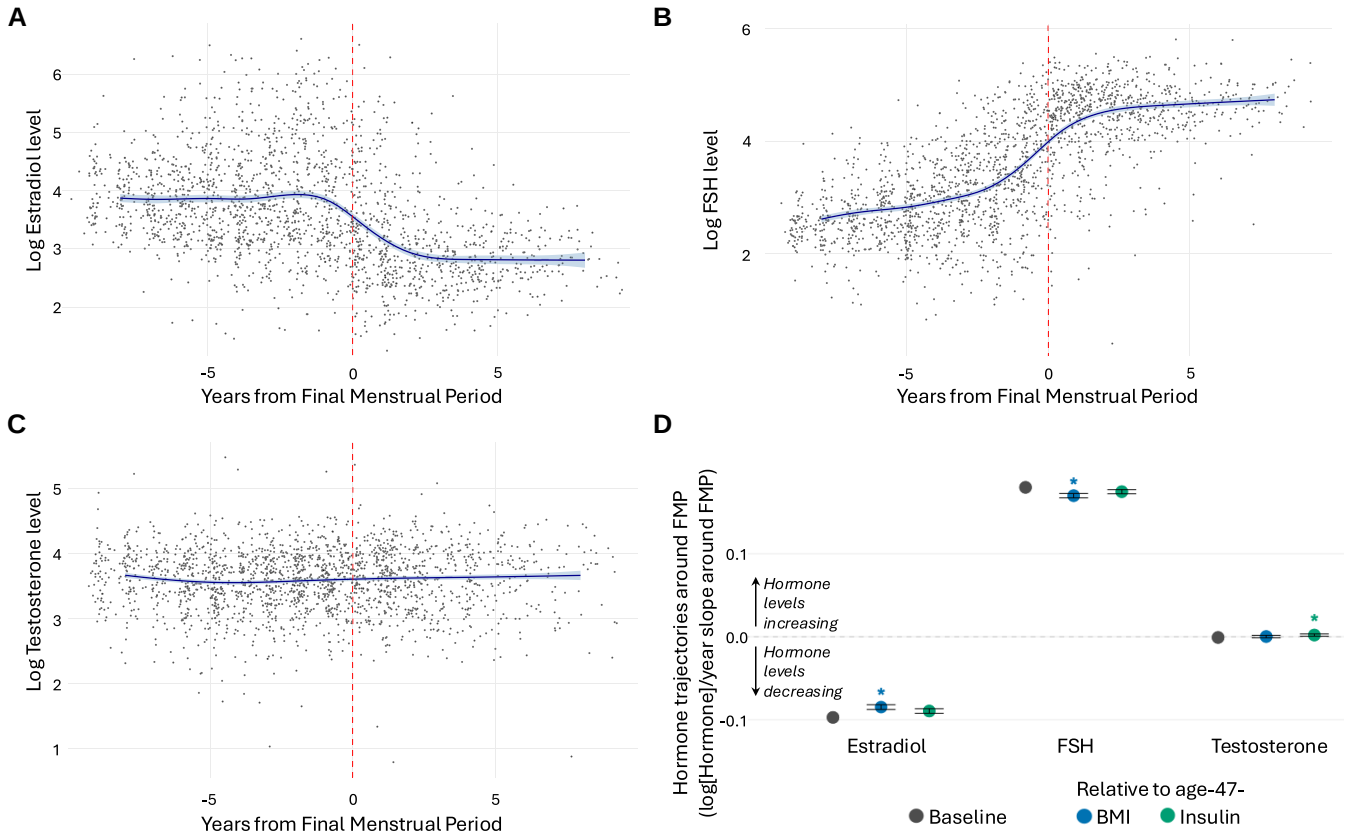

Figure 3. Hormone trajectories during the menopausal transition, and associations with age-47 insulin and body mass index (BMI). A to C show trajectories of log-transformed hormone levels relative to the final menstrual period (FMP, indicated by red dashed line). Hormone trajectory slopes relative to the FMP were estimated for each participant using mixed-effects models with log-transformed hormone values. A, Estradiol levels decline sharply around the FMP. B, Follicle-stimulating hormone (FSH) levels rise progressively, with the peak occurring after the FMP. C, Testosterone levels remain relatively stable throughout the transition. Scatter points represent individual observations; blue solid lines and shading show fitted curves with 95% CIs. Associations are the results of individual hormone trajectory slopes regressed on 47-year-old BMI or log-insulin levels using linear regression, adjusting for covariates of self-reported race/ethnicity, income, and smoking status (see Table 6). D, Slopes (or trajectories of hormone level changes around the FMP) for estradiol, FSH, and testosterone in relation to BMI (blue) and insulin (green); baseline change in hormone trajectories are represented in gray. Direction of change from FMP indicated as arrows from point 0.0, with positive values denoting an increase in hormone levels from 6 years prior to 6 years post FMP, and negative values indicating decreasing hormone levels in that time period. Statistically significant associations are denoted by * and error bars represent 95% CIs. N = 690.

We observed distinct associations between insulin vs BMI and trajectories of sex hormone changes across the menopausal transition. Higher BMI was linked to a slower decline in E2 and a slower rise in FSH. This is consistent with prior research showing that adiposity may influence estrogen and FSH feedback, such that obese postmenopausal women have higher E2 and lower FSH than their lean counterparts, likely due to peripheral effects of obesity on gonadotropins (43-45). In contrast, insulin levels were more strongly associated with a steeper increase in T levels around menopause. This

Table 6. Associations of fasting insulin or body mass index at age 47 with hormone trajectories across the menopausal transition

Hormone trajectory	BMI coefficient	BMI *P*	BMI Adj R^2	Insulin coefficient	Insulin *P*	Insulin Adj R^2
Estradiol	**0.0017**	**<.001**	**0.109**	0.0039	.291	0.052
FSH	**−0.0015**	**<.001**	**0.078**	0.0001	.971	0.022
Testosterone	−0.0001	.335	0.022	**0.0074**	**<.001**	**0.043**

Hormone trajectory slopes relative to final menstrual period were estimated for each participant using mixed-effects models with log-transformed hormone values. Associations are results of individual hormone trajectory slopes regressed on 47-year-old BMI or log-insulin levels using linear regression, adjusting for covariates of self-reported race/ethnicity, income, and smoking status. Data are presented as β coefficients, *P* values, and adjusted R^2 values. Bold text signifies *P* less than or equal to .05. Related to Fig. 3.
Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone.

pattern is characteristic of a hyperandrogenic state, which is usually associated with hyperinsulinemia as well as with poor cardiovascular outcomes (46-49). Higher postmenopausal levels of T and/or E2 have also been prospectively related to increased risk of type 2 diabetes (50-52). Together, these data suggest that BMI is associated with the dynamics of estrogen withdrawal and gonadotropin response, while insulin appears more tightly linked to androgen profiles.

Importantly, insulin levels can be modulated. Reversing obesity is dependent on a multitude of factors and can be especially challenging among some ethnicities and socioeconomic groups (53, 54). In fact, women tend to experience greater difficulty losing weight than men (55). Conversely, insulin levels may be more sensitive than body weight to lifestyle interventions like exercise and a healthy diet (56, 57). Aerobic and resistance exercise can lower insulin levels and improve insulin sensitivity independent of body composition and weight loss (58). Given that reductions in insulin levels often precede intervention-induced weight loss (59), improving metabolic health through mitigating high insulin levels may offer a more-attainable target.

Our findings align with previous work linking insulin resistance with worsened menopause symptoms. Insulin resistance is defined as a diminished capacity for insulin-stimulated glucose disposal, and it has a close interrelationship with hyperinsulinemia (23-26). Higher values for HOMA-IR, a surrogate index of insulin resistance calculated from fasting glucose and fasting insulin levels, have been previously associated with hot flashes and night sweats, with especially strong associations reported for hot flashes (22). Our findings suggest that elevated insulin itself may be a key component of this relationship, as age-47 fasting insulin is still an independent predictor of hot flashes in combined Cox regression models that account for fasting glucose contributions. While insulin resistance and hyperinsulinemia frequently co-occur, emerging evidence suggests that hyperinsulinemia can be detected in the absence of hyperinsulinemic-euglycemic clamp-measured insulin resistance, that it may precede insulin resistance and obesity, and that it may even contribute to their development (23-26). Thus, the distinction between elevated insulin and insulin resistance might be especially relevant for midlife women who could be experiencing early shifts in metabolic health with potential repercussions for hormone dynamics and symptom incidence across the menopausal transition.

Study Limitations

Although SWAN has the strengths of longitudinally tracking community-based participants from a large and diverse cohort, annual questionnaires of retrospectively recalled vasomotor symptoms have limited resolution and accuracy for detecting symptom onset (particularly if symptoms were intermittent or infrequent; 60). Similarly, insulin and other hormone levels were measured annually and do not capture the full extent of hormone fluctuations. Beyond excluding participants who reported using insulin therapy or other hyperglycemia-managing medications, it would have been advantageous to assess or control for specific antidiabetic medications as well as other drugs that affect insulin sensitivity and/or glucose homeostasis, such as corticosteroids. The participants who had relatively higher fasting insulin levels may or may not have also been insulin resistant; based on available data, we could not preclude the possibility that insulin resistance plays a role in the relationships we detected, although we did observe that elevated fasting insulin was itself associated with specific hormone and symptom patterns. Only fasting insulin measurements were included in these data, which did not allow us to assess postprandial or dynamic insulin responses. Prior work has shown that being climacteric at age 46 years is independently associated with elevated insulin levels after a glucose challenge (61), which highlights the possibility that dynamic metabolic assessments may reveal further relationships with menopausal symptoms. By design, SWAN recruited women who were likely to be already perimenopausal, which limited our ability to establish predictive relationships earlier in life. Notably, women undergoing early menopause also show differences in insulin profiles (62). Nevertheless, our analyses suggest that insulin and BMI in perimenopause exert distinct effects on reproductive hormone trajectories and symptom timing during the menopausal transition. Insulin may be a stronger predictor than BMI for certain outcomes, particularly androgenic hormone changes and vasomotor symptom incidence. These insights could improve understanding of how premenopausal or perimenopausal metabolic health shapes the experience and long-term repercussions of the menopausal transition.

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Disclosures

The authors have nothing to disclose.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. SWAN provides access to public-use data sets that include data from SWAN screening, baseline, and follow-up visits (http://www.swanstudy.org/swan-research/data-access/).

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