GYNECOLOGY

# Obesity, smoking, and risk of vasomotor menopausal symptoms: a pooled analysis of eight cohort studies



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**BACKGROUND:** Frequent and severe vasomotor symptoms during menopause are linked with adverse health outcomes. Understanding modifiable lifestyle factors for the risk of vasomotor menopausal symptoms is important to guide preventive strategies.

**OBJECTIVE:** We investigated the associations between body mass index and smoking, their joint effects with the risk of vasomotor symptoms, and whether the associations differed by menopausal stage.

**STUDY DESIGN:** The International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events pooled data on 21,460 midlife women from 8 studies (median age, 50 years; interquartile range, 49–51 years) for the cross-sectional analysis. Four studies provided data for the prospective analysis (n=11,986). Multinomial logistic regression models with 4 categories of frequency/severity for the outcome of vasomotor symptoms were used to estimate relative risk ratios and 95% confidence intervals that were adjusted for within-study correlation and covariates.

**RESULTS:** At baseline, nearly 60% of the women experienced vasomotor symptoms. One-half of them were overweight (30%) or obese (21%), and 17% were current smokers. Cross-sectional analyses showed that a higher body mass index and smoking more cigarettes with longer duration and earlier initiation were all associated with more frequent or severe vasomotor symptoms. Never smokers who were obese had a 1.5-fold (relative risk ratio, 1.52; 95% confidence interval, 1.35–1.73) higher risk of often/severe vasomotor symptoms, compared with never smokers who were of normal-weight. Smoking strengthened the association because the risk of often/severe vasomotor symptoms was much greater among smokers who were obese (relative risk ratio, 3.02; 95% confidence interval, 2.41–3.78). However, smokers who quit at <40 years of age were at similar levels of risk as never smokers. Prospective analyses showed a similar pattern, but the association attenuated markedly after adjustment for baseline vasomotor symptoms. Furthermore, we found that the association between body mass index and vasomotor symptoms differed by menopausal status. Higher body mass index was associated with increased risk of vasomotor symptoms in pre- and perimenopause but with reduced risk in postmenopause.

**CONCLUSION:** High body mass index (≥25 kg/m$^2$) and cigarette smoking substantially increased women's risk for experiencing frequent or severe vasomotor symptoms in a dose-response manner, and smoking intensified the effect of obesity. However, the effect of body mass index on the risk of vasomotor symptoms was opposite among postmenopausal women. Maintaining a normal weight before the menopausal transition and quitting smoking at <40 years of age may mitigate the excess risk of vasomotor symptoms in midlife.

**Key words:** hot flushes, night sweats, overweight, obesity, smoking, vasomotor symptoms

Vasomotor menopausal symptoms (VMS), which include hot flushes and night sweats, are considered the cardinal symptoms of menopause[1] and are 1 of the main reasons for menopause-related health service use.[2,3] It is estimated that up to 80% of women will report VMS at some time during the menopausal transition,[4–6] although the percentage of women who experience symptoms varies from as low as 20% among some Asian populations[4,5] to 60–80% in some North American[4] and European[6] subgroups. VMS also vary by intensity or severity, with some women reporting only mild transient symptoms and others reporting intense heat spreading over the body and profuse sweating that can disrupt sleep.[3] Early-onset VMS has been linked with endothelial dysfunction[7] and is considered a biomarker for the development of cardiovascular disease in later life.[8]

Although menopause-related hormonal changes are associated primarily with VMS,[9,10] evidence from population-based studies suggests that certain lifestyle and socio-demographic factors are also associated with frequency and severity of VMS.[11–13] For instance, epidemiologic data have revealed that current smokers have a significantly higher odds of VMS compared with nonsmokers,[4] which has been attributed to the antiestrogenic effects of tobacco smoking.[12] Other notable lifestyle factors that are associated with a higher risk of VMS are overweight and obesity, where increased subcutaneous adipose tissue is likely to provide an insulating layer that blunts abdominal heat transfer,[14] which, during the menopausal transition, reduces the body's ability to respond to changes in core temperature. In addition, smoking and body weight are also interrelated. Given the increased risk of VMS that is conferred by both smoking and overweight/obesity, a better understanding of their joint associations would provide important information for women at midlife because weight gain is common during the menopausal transition. Also, it is possible that the relative contribution of body fat to the risk of VMS in the early and late stage of menopause may differ.[15]

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## AJOG at a Glance

### Why was this study conducted?

This pooled analysis provided precise estimates of the individual and joint associations between body mass index and smoking with the risk of vasomotor menopausal symptoms.

### Key findings

Higher body mass index and greater smoking were associated with more frequent/severe vasomotor menopausal symptoms in the cross-sectional analysis; smoking strengthened the effect of obesity. However, women who quit smoking before age 40 years had a similar level of risk as never smokers. Prospective analyses showed similar results, but the individual and joint effects of body mass index and smoking on subsequent vasomotor menopausal symptoms at the 3-year follow up attenuated markedly after adjustment for baseline vasomotor menopausal symptoms. The effect of body mass index on vasomotor menopausal symptoms risk differed in pre-/perimenopause and postmenopause.

### What does this add to what is known?

Being both obese and a smoker conferred a much higher risk of frequent/severe vasomotor menopausal symptoms than either alone. Maintaining a normal weight before the menopausal transition and smoking cessation before age 40 years may mitigate the excess risk of frequent/severe vasomotor menopausal symptoms.

Determining the modifiable health behaviors and identifying those individuals who are at an increased risk of the development of symptoms across racial/ethnic groups is essential for developing preventative strategies to reduce both the individual and societal burden that is associated with VMS. Therefore, this study investigated the cross-sectional and prospective associations between body mass index (BMI) and smoking and their joint effects with the risk of VMS in a pooled sample from the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Event (InterLACE) consortium. We further examined whether the effects of BMI and smoking on the risk of VMS differ by menopausal status.

## Materials and Methods

### Study participants

InterLACE is an individual-level pooled study of 20 observational studies from 10 countries. Full details on the study aims, data harmonization, and characteristics across the studies were published previously.[16,17] Each participating study has been undertaken with ethical approval from the Institutional Review Board or Human Research Ethics Committee at each research institution, and all participants provided consent for that study. For this analysis, 8 studies that had collected information on BMI, smoking status, and degree of VMS (either reporting in frequency or severity) were included: Australian Longitudinal Study on Women's Health (ALSWH),[18] Medical Research Council National Survey of Health and Development (NSHD),[19] National Child Development Study (NCDS),[20] Study of Women's Health Across the Nation (SWAN),[21] Whitehall II Study (WHITEHALL),[22] Seattle Midlife Women's Health Study (SMWHS),[23] Healthy Ageing of Women Study (HOW),[24] and Japanese Midlife Women's Health Study (JMWHS).[24]

For the longitudinal studies, data for women around the age of 50 years were used as an analytic baseline to make the distribution of menopausal status and VMS more comparable across studies. For instance, Survey 2 (1998) was selected as analytic baseline for ALSWH because the median age was 50 years; Visit 4 (2000–2002) was selected for SWAN and Survey 3 (1991–1994) for WHITEHALL (Table 1). At this baseline, 21,460 women who had reported their BMI, smoking status, and frequency or severity of VMS and had provided complete information on the covariates (listed later) were included for the cross-sectional analyses. Four studies (ALSWH, NSHD, SWAN, and WHITEHALL) had longitudinal data to examine the association with the risk of subsequent VMS at 3-year follow up. We excluded 3791 women who did not return to the study or had incomplete follow-up data on VMS, menopausal status, or hormone therapy, which left 11,986 women for prospective analyses. The excluded women were more likely to be current smokers, obese, or less educated or to report VMS at baseline, compared with the included women (data not shown).

### Main outcome and exposure variables

Hot flushes and night sweats data were collected at analytic baseline with the use of self-reported menopausal symptom checklists that recalled the symptoms over a specific period. VMS were defined as either hot flushes or night sweats. In ALSWH, women were asked how frequently they have experienced VMS in the last 12 months; SWAN asked frequency in the past 2 weeks. The frequency responses were categorized as never, rarely, sometimes, and often. In NSHD and NCDS, women were asked how severely they have been bothered by VMS in the last 12 months, and the severity responses were categorized as never, mild, moderate, and severe. In the other 4 studies, women also reported their severity of VMS but in a recent period (in the last 24 hours or at the moment). For the pooled analysis, the degree of VMS was harmonized as never, rarely, sometimes, and often (if reporting frequency) or never, mild, moderate, and severe (if reporting severity). Subsequent VMS was defined based on frequency/severity of VMS reported at 3-year follow up.

Height and weight were self-reported or measured at analytic baseline. BMI was computed as weight divided by the

**TABLE 1**
**Characteristics of 8 studies in the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events consortium**

| Study | Country | N | Median age at baseline, y (interquartile range) | Survey (year) selected for analytic baseline[a] | Survey (year) selected for 3-year follow up |
|---|---|---|---|---|---|
| Australian Longitudinal Study on Women's Health (ALSWH) | Australia | 10,323 | 50 (48–51) | Survey 2 (1998) | Survey 3 (2001) |
| National Survey of Health and Development (NSHD) | UK | 1,068 | 50[a] | Survey 1996 (1996) | Survey 1999 (1999) |
| National Child Development Study (NCDS) | UK | 3,983 | 50[a] | Survey 8 (2008) | N/A |
| Study of Women's Health Across the Nation (SWAN) | USA | 2,345 | 50 (48–52) | Visit 4 (2000–2002) | Visit 7 (2003–2005) |
| Whitehall II Study (WHITEHALL) | UK | 2,041 | 50 (45–55) | Survey 3 (1991–1994) | Survey 4 (1995–1996) |
| Seattle Midlife Women's Health Study (SMWHS) | USA | 189 | 50 (46–53) | Survey 2000 (2000) | N/A |
| Healthy Ageing of Women Study (HOW) | Australia | 768 | 54 (52–57) | Survey 1 (2001) | N/A |
| Japanese Midlife Women's Health Study (JMWHS)[b] | Japan | 743 | N/A | Survey 1 (2002) | N/A |
| Overall | | 21,460 | 50 (49–51) | | |

*N/A*, not applicable.

[a] For the longitudinal studies, data for women around the age of 50 years were used as analytic baseline to make the data more comparable across studies; the women who participated in the NSHD (1946 British birth cohort) and NCDS (1958 British birth cohort) were at age 50 years in the 1996 and 2008 survey, respectively; [b] Provided age by category only (≤55 and >55 years), and 48% of women were aged >55 (age range from 45–60 years).

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square of height and categorized as underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25–29.9 kg/m$^2$), and obese (≥30 kg/m$^2$), according to the World Health Organization classification.[25] Because only 357 women (1.7%) were classified as underweight, they were combined into the normal weight group (BMI, <25 kg/m$^2$). For the Asian population (Japanese and other Asian), we performed a sensitivity analysis by using a lower BMI cut-off of 23 and 27.5 kg/m$^2$ for overweight and obesity.[25] Smoking status was self-reported and categorized as never smoker, former smoker, and current smoker. For the current smokers, data on number of cigarettes smoked per day, duration of smoking, and pack-years were collected in ALSWH, SWAN, and WHITEHALL (n=14,709), although these details were not available for the former smokers at analytic baseline. The average number of cigarettes smoked per day was categorised as 1–9, 10–19, and ≥20 cigarettes/day. Smoking duration was defined by the time between age at initiation and age at baseline and categorized as <20, 20–29, and ≥30 years. Pack-years (number of cigarettes smoked per day divided by 20 and multiplied by the duration of smoking) was categorized as <10, 10–19, 20–29, 30–39, and ≥40 pack-years. Age at smoking initiation was collected for both former and current smokers and categorized as ≤15, 16–19, and ≥20 years of age. In ALSWH, data on age at quitting smoking (categorized as <30, 30–39, and ≥40 years of age) and years since quitting smoking (categorized as 1–5, 6–14, 15–19, ≥20 years) were collected for former smokers. To test the joint effects of bodyweight and smoking status, a new variable with 9 levels was created. It was made up of the combinations of BMI (underweight/normal, overweight, and obese) and smoking status (never, former, and current).

## Confounding factors

Participants reported on a range of demographic and reproductive factors at baseline, including birth year, race/ethnicity/region, education level, menopausal status, and use of menopausal hormone therapy (MHT). Responses for birth year were categorized as <1940, 1940–1949, and 1950–1959. Race/ethnicity/region was defined based on self-identified race/ethnicity, country of birth, the language spoken at home, or the country in which the study was conducted (residency). Seven racial/ethnic groups with regional status were defined here: white-Australian, white-European, white-American, Japanese, other Asian (Chinese, South/Southeast Asian), African American/black/Caribbean, and Other (Hispanic, Middle Eastern, Aboriginal, and mixed). For education level, responses were categorized as completion of ≤10 years (corresponding to less than high school or O-level in the United Kingdom), 11–12 years (high

school or A-level in the United Kingdom), and >12 years (at least more than a high school education). Menopausal status was collapsed and categorized into 5 groups based on menstrual bleeding patterns and gynecologic surgery: (1) unknown because of surgery (hysterectomy and/or oophorectomy, which included bilateral oophorectomy [surgical menopause] because of insufficient information to define surgical menopause for all studies), (2) unknown because of hormone use (unless natural menopause specified), (3) premenopause (regular menstrual cycles in the last 3 months and 12 months), (4) perimenopause (menses in the past 3 months and changes/irregularity in menstrual patterns in the past 12 months or no menses in the previous 3 months, but menses in the preceding 11 months), and (5) natural postmenopause (amenorrhea for at least 12 months). Women who were taking MHT (eg, estrogen) were classified as current hormone users.

### Statistical analyses

Multinomial logistic regression models with 4 categories of outcome for VMS (never, rarely/mild, sometimes/moderate, and often/severe) were used to examine the associations between BMI, smoking status, and the joint effects with the risk of VMS at baseline (cross-sectional analysis) and 3-year follow up (prospective analysis). A generalized logit model was used to estimate relative risk ratios (RRR) and 95% confidence intervals (CIs) for each VMS category with the use of "no symptom" as the reference category. In the cross-sectional analysis, the associations were obtained separately for the studies of VMS frequency and VMS severity, followed by the overall estimates that incorporated study design (study cluster) into the analyses. The models were first adjusted for menopausal status and the use of MHT at baseline (model 1) and additionally were adjusted for race/ethnicity/region, education level, and included both BMI and smoking status in the same model (model 2). Furthermore, we included an interaction term between the 2 exposures in the model and analyzed their joint associations. Because Asian women are less likely to be overweight or obese and less likely to have frequent or severe VMS, we performed a sensitivity analysis by excluding Asian women (996 Japanese and 488 other Asian).

The dose-response relationships between the different aspects of smoking and risk of VMS were examined with the use of data from ALSWH, SWAN, and WHITEHALL (n=14,709). The number of cigarettes, duration, and pack-years of smoking were analyzed for current smokers; age at having initiated smoking was analyzed for both former and current smokers. Age at quitting and years since quitting smoking for former smokers could be analyzed only with the use of data from ALSWH. Never smoker was used as the reference group for all smoking measures. All models were adjusted for the confounding variables mentioned earlier, which included BMI.

For the prospective analysis, 4 studies provided data (n=11,986). BMI and smoking status at baseline and subsequent VMS at 3-year follow up were examined in the model fully adjusted for menopausal status and the use of MHT at 3-year follow up and baseline covariates that are mentioned in model 2 and additionally adjusted for frequency/severity of VMS at baseline.

We further investigated whether menopausal status modified the association between BMI, smoking, and VMS. The interaction term between BMI and menopausal status and between smoking status and menopausal status was included in the models. If there was a statistical interaction, the association was further stratified by concurrent menopausal status at baseline (cross-sectional analyses) and at 3-year follow up (prospective analyses). The SURVEYLOGISTIC procedure in SAS software (version 9.4; SAS Institute Inc, Cary, NC), which incorporated the study cluster into the analyses, was used for the multinomial logistic regression.

## Results

### Baseline characteristics

A total of 21,460 women with a median age of 50 years (interquartile range, 49−51 years) from 8 studies were included at baseline (Table 1). HOW and JMWHS recruited women at slightly older ages at approximately 55 years. In the overall sample, almost one-half of the women were premenopausal or perimenopausal (19% and 27%, respectively); 19% of the women had a natural menopause; 20% of the women had had a hysterectomy or oophorectomy, and 14% of the women were classified as unknown menopausal status because of hormone use before menopause (Table 2). Nearly 20% of the women were currently taking MHT, regardless of menopausal status. Across studies, one-half of the women were either overweight (30%) or obese (21%); 28% of the women were former smokers, and 17% of the women were current smokers. Overall, up to 55% of the women experienced hot flushes (rarely/mild to often/severe), and 45% of the women reported night sweats.

### Cross-sectional associations

Table 3 shows results separately for studies of VMS frequency, VMS severity, and the overall sample. Overall, the pattern of results was similar, regardless of whether VMS were assessed as frequency or severity. BMI and smoking status were associated with the risk of VMS, even when both were included in the same model (model 2). We found that women who were overweight and obese and were current smokers were more likely to report some degree of VMS (rarely/mild to often/severe). For instance, in the overall sample, compared with the normal weight group, a dose-response relationship was observed between overweight and the frequency/severity of VMS, with adjusted RRR of 1.24 (95% CI, 1.18−1.30), 1.30 (95% CI, 1.17−1.46), and 1.53 (95% CI, 1.42−1.65) for rarely/mild, sometimes/moderate, and often/severe VMS, respectively. Similar trends were seen for the obese group, with adjusted RRR of 1.15 (95% CI, 1.08−1.24), 1.32 (95% CI, 1.20−1.44), and 1.59 (95% CI, 1.41−1.78), respectively. When we applied a lower cut-off point of overweight (BMI, ≥23 kg/m$^2$) and obesity (BMI, ≥27.5 kg/m$^2$) for the

**TABLE 2**
**Analytic baseline characteristics of study sample**

| Variable | Overall (n=21,460), % | Study, % | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ALSWH (n=10,323) | NSHD (n=1068) | NCDS (n=3983) | SWAN (n=2345) | WHITEHALL (n=2041) | SMWHS (n=189) | HOW (n=768) | JMWHS (n=743) |
| Birth year | | | | | | | | | |
| <1940 | 3.8 | N/A | N/A | N/A | N/A | 39.5 | 0.5 | N/A | N/A |
| 1940–1949 | 54.9 | 74.3 | 100 | N/A | 41.3 | 48.5 | 46.6 | 85.4 | 47.5[a] |
| 1950–1959 | 41.3 | 25.7 | N/A | 100 | 58.7 | 12.0 | 52.9 | 14.6 | 52.5[a] |
| Race/ethnicity/region | | | | | | | | | |
| White- Australian | 40.8 | 78.8 | N/A | N/A | N/A | N/A | N/A | 82.3 | N/A |
| White- European | 40.1 | 16.9 | 100 | 98.2 | N/A | 87.7 | N/A | 12.5 | N/A |
| White- American | 6.3 | 0.7 | N/A | N/A | 48.0 | N/A | 85.2 | N/A | N/A |
| Japanese | 4.6 | 0.1 | N/A | N/A | 10.5 | N/A | N/A | N/A | 100 |
| Other Asian | 2.3 | 2.1 | N/A | 0.6 | 9.5 | N/A | 7.9 | 1.0 | N/A |
| African American/Black/Caribbean | 3.0 | N/A | N/A | 0.4 | 25.9 | N/A | 5.8 | N/A | N/A |
| Other | 2.9 | 1.5 | N/A | 0.8 | 6.1 | 12.3 | 1.1 | 4.2 | N/A |
| Education level, y | | | | | | | | | |
| ≤10 | 46.0 | 48.1 | 67.8 | 62.2 | 5.6 | 54.2 | 0 | 51.7 | 9.4 |
| 11–12 | 17.4 | 17.1 | 25.8 | 10.3 | 15.8 | 16.2 | 13.8 | 15.6 | 59.4 |
| >12 | 36.6 | 34.9 | 6.4 | 27.5 | 78.6 | 29.6 | 86.2 | 32.7 | 31.2 |
| Menopausal status | | | | | | | | | |
| Unknown because of surgery | 19.8 | 25.6 | 17.9 | 16.9 | 4.5 | 15.9 | 3.2 | 28.4 | 11.0 |
| Unknown because of hormone use | 14.2 | 16.1 | 21.6 | 13.1 | 11.3 | 12.0 | 25.9 | 7.6 | 2.3 |
| Premenopause | 19.4 | 23.0 | 19.8 | 18.8 | 6.7 | 22.1 | 26.5 | 3.4 | 19.8 |
| Perimenopause | 27.4 | 24.2 | 24.5 | 30.1 | 56.2 | 18.3 | 30.7 | 11.6 | 11.3 |
| Natural postmenopause | 19.1 | 11.0 | 16.2 | 21.0 | 21.2 | 31.8 | 13.8 | 49.1 | 55.6 |
| Current use of menopausal hormone therapy | | | | | | | | | |
| No | 80.9 | 76.6 | 79.7 | 90.4 | 80.6 | 84.9 | 78.3 | 65.1 | 96.8 |
| Yes | 19.1 | 23.4 | 20.3 | 9.6 | 19.4 | 15.1 | 21.7 | 34.9 | 3.2 |

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*(continued)*

**TABLE 2**
**Analytic baseline characteristics of study sample** *(continued)*

| Variable | Overall (n=21,460), % | Study, % | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ALSWH (n=10,323) | NSHD (n=1068) | NCDS (n=3983) | SWAN (n=2345) | WHITEHALL (n=2041) | SMWHS (n=189) | HOW (n=768) | JMWHS (n=743) |
| Body mass index | | | | | | | | | |
| Normal weight (<25 kg/m$^2$)[b] | 48.5 | 48.2 | 63.2 | 44.5 | 36.5 | 52.7 | 50.8 | 42.8 | 85.6 |
| Overweight (25–29.9 kg/m$^2$) | 30.4 | 31.6 | 24.3 | 33.0 | 27.6 | 32.2 | 25.4 | 32.4 | 13.2 |
| Obese (≥30 kg/m$^2$) | 21.0 | 20.2 | 12.5 | 22.5 | 35.9 | 15.1 | 23.8 | 24.7 | 1.2 |
| Smoking status | | | | | | | | | |
| Never smoker | 54.9 | 56.2 | 34.2 | 48.8 | 59.4 | 52.2 | 50.8 | 62.9 | 86.7 |
| Former smoker | 27.6 | 26.7 | 40.5 | 29.3 | 26.5 | 30.9 | 39.2 | 27.6 | 4.0 |
| Current smoker | 17.4 | 17.1 | 25.3 | 21.9 | 14.1 | 16.9 | 10.1 | 9.5 | 9.3 |
| Frequency/severity of hot flushes | | | | | | | | | |
| Never | 47.2 | 44.8 | 47.8 | 35.5 | 56.0 | 63.4 | 67.7 | 56.1 | 54.9 |
| Rarely/mild | 17.1 | 15.7 | 21.3 | 8.6 | 26.4 | 17.8 | 16.9 | 28.8 | 33.0 |
| Sometimes/moderate | 22.3 | 24.9 | 20.3 | 36.5 | 7.0 | 10.6 | 9.0 | 11.1 | 7.8 |
| Often/severe | 13.5 | 14.6 | 10.5 | 19.4 | 10.6 | 8.2 | 6.3 | 4.0 | 4.3 |
| Frequency/severity of night sweats | | | | | | | | | |
| Never | 57.2 | 54.9 | 57.6 | 48.3 | 63.4 | 68.7 | 77.8 | 62.1 | 75.2 |
| Rarely/mild | 15.0 | 14.3 | 18.9 | 6.9 | 24.6 | 15.3 | 13.8 | 25.7 | 20.7 |
| Sometimes/moderate | 17.8 | 19.7 | 15.2 | 31.2 | 4.9 | 8.8 | 2.6 | 8.7 | 3.0 |
| Often/severe | 9.9 | 11.1 | 8.3 | 13.7 | 7.1 | 7.2 | 5.8 | 3.5 | 1.1 |
| Frequency/severity of vasomotor symptoms[c] | | | | | | | | | |
| Never | 41.9 | 40.3 | 42.2 | 30.1 | 47.5 | 59.1 | 63.5 | 49.7 | 49.5 |
| Rarely/mild | 18.4 | 16.5 | 22.4 | 8.4 | 31.6 | 17.7 | 18.5 | 32.7 | 37.4 |
| Sometimes/moderate | 24.2 | 26.9 | 22.4 | 39.1 | 8.3 | 12.3 | 9.0 | 12.2 | 8.6 |
| Often/severe | 15.4 | 16.2 | 13.0 | 22.4 | 12.6 | 10.8 | 9.0 | 5.3 | 4.4 |

*ALSWH*, Australian Longitudinal Study on Women's Health; *HOW*, Healthy Ageing of Women Study; *JMWHS*, Japanese Midlife Women's Health Study; *N/A*, not applicable; *NCDS*, National Child Development Study; *NSHD*, National Survey of Health and Development; *SMWHS*, Seattle Midlife Women's Health Study; *SWAN*, Study of Women's Health Across the Nation; *WHITEHALL*, Whitehall II Study.

[a] The Japanese Midlife Women's Health Study provided age by category only (≤55 and >55 years); thus, birth year was categorized based on age categories; [b] Only 357 women (1.7%) were underweight (body mass index, <18.5 kg/m$^2$); thus, they were categorzed into the normal weight group; [c] Vasomotor symptoms were defined as having either hot flushes or night sweats.

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**TABLE 3**
**Adjusted cross-sectional associations of body mass index and smoking status with the risk of vasomotor symptoms at baseline (n = 21,460)**

| Variable | N | Vasomotor symptoms (hot flushes and night sweats) (%) | | | | Relative risk ratio (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Model 1[a] | | | Model 2[b] | | |
| | | Never | Rarely/ mild | Sometimes/ moderate | Often/ severe | Rarely/mild | Sometimes/ moderate | Often/severe | Rarely/mild | Sometimes/ moderate | Often/severe |
| Frequency of vasomotor symptoms (ALSWH, SWAN; n=12668) | | | | | | | | | | | |
| Body mass index | | | | | | | | | | | |
| Normal (<25 kg/m$^2$) | 5,830 | 46.0 | 18.4 | 22.4 | 13.3 | — | — | — | — | — | — |
| Overweight (25–29.9 kg/m$^2$) | 3,906 | 37.9 | 19.7 | 25.4 | 17.0 | 1.31 (1.26–1.36) | 1.37 (1.16–1.61) | 1.54 (1.40–1.68) | 1.26 (1.21–1.31) | 1.38 (1.21–1.56) | 1.51 (1.34–1.71) |
| Obese (≥30 kg/m$^2$) | 2,932 | 38.0 | 20.7 | 23.1 | 18.2 | 1.32 (1.08–1.61) | 1.17 (0.91–1.49) | 1.50 (1.49–1.50) | 1.17 (1.15–1.18) | 1.30 (1.27–1.32) | 1.51 (1.50–1.51) |
| Smoking status | | | | | | | | | | | |
| Never smoker | 7,193 | 44.1 | 19.7 | 22.3 | 13.9 | — | — | — | — | — | — |
| Former smoker | 3,381 | 41.1 | 18.9 | 24.4 | 15.6 | 1.02 (1.02–1.02) | 1.16 (1.03–1.30) | 1.17 (0.98–1.39) | 1.01 (1.00–1.02) | 1.15 (1.03–1.28) | 1.12 (0.95–1.32) |
| Current smoker | 2,094 | 33.9 | 18.8 | 26.2 | 21.1 | 1.20 (1.17–1.23) | 1.41 (0.99–2.01) | 1.72 (1.33–2.24) | 1.17 (1.12–1.22) | 1.33 (1.11–1.61) | 1.58 (1.46–1.70) |
| Severity of vasomotor symptoms (NSHD, NCDS, WHITEHALL, SMWHS, HOW, JMWHS; n=8792) | | | | | | | | | | | |
| Body mass index | | | | | | | | | | | |
| Normal (<25 kg/m$^2$) | 4,583 | 46.1 | 18.1 | 23.6 | 12.3 | — | — | — | — | — | — |
| Overweight (25–29.9 kg/m$^2$) | 2,625 | 39.2 | 16.8 | 26.2 | 17.8 | 1.10 (0.90–1.34) | 1.31 (1.06–1.62) | 1.70 (1.30–2.23) | 1.20 (1.08–1.33) | 1.20 (1.16–1.24) | 1.56 (1.31–1.85) |
| Obese (≥30 kg/m$^2$) | 1,584 | 36.9 | 14.4 | 28.9 | 19.8 | 0.98 (0.70–1.36) | 1.48 (1.09–2.02) | 1.92 (1.30–2.82) | 1.07 (0.87–1.33) | 1.37 (1.07–1.74) | 1.79 (1.38–2.33) |
| Smoking status | | | | | | | | | | | |
| Never smoker | 4,598 | 46.4 | 18.6 | 22.9 | 12.1 | — | — | — | — | — | — |
| Former smoker | 2,547 | 41.2 | 15.3 | 27.8 | 15.7 | 0.97 (0.79–1.20) | 1.43 (1.07–1.91) | 1.53 (1.08–2.16) | 1.12 (0.99–1.26) | 1.19 (0.95–1.48) | 1.26 (0.99–1.59) |
| Current skomer | 1,647 | 32.9 | 15.4 | 28.2 | 23.6 | 1.17 (0.81–1.68) | 1.80 (1.54–2.10) | 2.70 (1.91–3.82) | 1.33 (1.01–1.76) | 1.43 (1.33–1.52) | 2.11 (1.69–2.64) |

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*(continued)*

**TABLE 3**
**Adjusted cross-sectional associations of body mass index and smoking status with the risk of vasomotor symptoms at baseline (n = 21,460)** *(continued)*

| Variable | N | Vasomotor symptoms (hot flushes and night sweats) (%) | | | | Relative risk ratio (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Model 1[a] | | | Model 2[b] | | |
| | | Never | Rarely/ mild | Sometimes/ moderate | Often/ severe | Rarely/mild | Sometimes/ moderate | Often/severe | Rarely/mild | Sometimes/ moderate | Often/severe |
| Overall sample (n=21460) | | | | | | | | | | | |
| Body mass index | | | | | | | | | | | |
| Normal (<25 kg/m$^2$) | 10,413 | 46.0 | 18.3 | 22.9 | 12.8 | — | — | — | — | — | — |
| Overweight (25–29.9 kg/m$^2$) | 6,531 | 38.4 | 18.6 | 25.7 | 17.3 | 1.23 (1.11–1.36) | 1.34 (1.17–1.55) | 1.61 (1.42–1.84) | 1.24 (1.18–1.30) | 1.30 (1.17–1.46) | 1.53 (1.42–1.65) |
| Obese (≥30 kg/m$^2$) | 4,516 | 37.6 | 18.5 | 25.1 | 18.8 | 1.22 (1.00–1.48) | 1.28 (1.05–1.56) | 1.67 (1.37–2.05) | 1.15 (1.08–1.24) | 1.32 (1.20–1.44) | 1.59 (1.41–1.78) |
| Smoking status | | | | | | | | | | | |
| Never smoker | 11,791 | 45.0 | 19.3 | 22.5 | 13.2 | — | — | — | — | — | — |
| Former smoker | 5,928 | 41.2 | 17.3 | 25.8 | 15.6 | 0.99 (0.91–1.07) | 1.26 (1.01–1.57) | 1.30 (0.99–1.71) | 1.03 (0.97–1.09) | 1.16 (1.05–1.27) | 1.17 (0.99–1.38) |
| Current smoker | 3,741 | 33.5 | 17.3 | 27.1 | 22.2 | 1.17 (1.03–1.33) | 1.55 (1.20–2.00) | 2.07 (1.45–2.96) | 1.21 (1.08–1.35) | 1.39 (1.24–1.56) | 1.83 (1.45–2.30) |
| Joint effect | | | | | | | | | | | |
| Normal weight & never smoker | 5,824 | 49.2 | 19.0 | 21.1 | 10.8 | — | — | — | — | — | — |
| Normal weight & former smoker | 2,675 | 45.2 | 17.9 | 24.9 | 12.1 | 1.04 (0.89–1.21) | 1.29 (1.03–1.63) | 1.24 (0.96–1.61) | 1.12 (1.02–1.23) | 1.15 (1.06–1.24) | 1.07 (0.96–1.18) |
| Normal weight & current smoker | 1,914 | 37.3 | 16.7 | 25.8 | 20.3 | 1.13 (0.96–1.33) | 1.54 (1.20–1.99) | 2.28 (1.47–3.53) | 1.18 (0.97–1.44) | 1.31 (1.21–1.42) | 1.86 (1.37–2.52) |
| Overweight & never smoker | 3,583 | 41.3 | 19.7 | 23.9 | 15.2 | 1.25 (1.11–1.40) | 1.35 (1.13–1.60) | 1.68 (1.37–2.06) | 1.28 (1.18–1.38) | 1.26 (1.08–1.46) | 1.50 (1.35–1.66) |
| Overweight & former smoker | 1,849 | 37.5 | 16.6 | 28.0 | 17.9 | 1.17 (0.97–1.41) | 1.77 (1.41–2.22) | 2.23 (1.64–3.02) | 1.23 (1.09–1.40) | 1.56 (1.38–1.76) | 1.87 (1.59–2.19) |
| Overweight & current smoker | 1,099 | 30.5 | 18.4 | 27.8 | 23.3 | 1.53 (1.15–2.03) | 2.02 (1.71–2.39) | 3.17 (2.38–4.23) | 1.59 (1.37–1.84) | 1.73 (1.56–1.93) | 2.54 (2.22–2.89) |
| Obese & never smoker | 2,384 | 40.1 | 19.5 | 24.0 | 16.4 | 1.25 (1.03–1.50) | 1.33 (1.07–1.66) | 1.76 (1.37–2.26) | 1.21 (1.08–1.35) | 1.30 (1.18–1.42) | 1.52 (1.35–1.73) |
| Obese & former smoker | 1,404 | 38.3 | 17.4 | 24.9 | 19.4 | 1.15 (0.86–1.54) | 1.43 (1.17–1.76) | 2.13 (1.38–3.28) | 1.13 (0.94–1.38) | 1.38 (1.23–1.55) | 1.85 (1.33–2.57) |
| Obese & current smoker | 728 | 27.9 | 17.3 | 29.4 | 25.4 | 1.55 (1.20–2.02) | 2.29 (1.73–3.03) | 3.72 (2.56–5.40) | 1.50 (1.28–1.75) | 2.14 (1.79–2.56) | 3.02 (2.41–3.78) |

Data are presented with the use of multinomial logistic regression with a generalised logit link; the SURVEYLOGISTIC procedure in SAS software (SAS Institute Inc, Cary, NC) was used to incorporate the study cluster into the analyses.

*ALSWH*, Australian Longitudinal Study on Women's Health; *NSHD*, National Survey of Health and Development; *NCDS*, National Child Development Study; *SWAN*, Study of Women's Health Across the Nation; *WHITEHALL*, Whitehall II Study; *SMWHS*, Seattle Midlife Women's Health Study; *HOW*, Healthy Ageing of Women Study; *JMWHS*, Japanese Midlife Women's Health Study

[a] Included menopausal status and use of menopausal hormone therapy at baseline; [b] Additionally included race/ethnicity/region, education, and both body mass index and smoking status in the same model.

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Asian population, the estimated effects remained unchanged. Compared with never smoking, current smoking was also associated with frequency/severity of VMS, with adjusted RRR of 1.21 (95% CI, 1.08−1.35), 1.39 (95% CI, 1.24−1.56), and 1.83 (95% CI, 1.45−2.30), respectively. Former smokers were only at a slightly increased risk of having often/severe VMS (RRR, 1.17; 95% CI, 0.99−1.38). By examining the RRRs in this Table 3, it appears that current smoking conveys greater risk for VMS than being overweight or obese.

### Joint effects of BMI and smoking

Table 3 also shows the joint effect of BMI and smoking. A significant interaction was observed between BMI and smoking status for the risk of VMS ($P<.001$). Never-smokers who were obese had a 1.5-fold increased risk of often/severe VMS (RRR, 1.52; 95% CI, 1.35−1.73) compared with never-smokers who were of normal-weight. Smoking enhanced the association because the risk of often/severe VMS among smokers who were obese was much higher (RRR, 3.02; 95% CI, 2.41−3.78), and the joint effect was not additive (ie, greater than the sum of individual effects). We also observed a higher risk of often/severe VMS among smokers who were overweight, but to a lesser extent (RRR, 2.54; 95% CI, 2.22−2.89). Quitting smoking appeared to mitigate excess risk because the risk of often/severe VMS among obese former-smokers (RRR, 1.85; 95% CI, 1.33−2.57) and overweight former-smokers (RRR, 1.87; 95% CI, 1.59−2.19) was much lower. Further exclusion of Asian women (n=1484) did not change the observed associations (data not shown).

### Dose-response relationship between smoking and VMS

Among current smokers, dose-response relationships were observed in all measures of smoking characteristics (ie, higher number of cigarettes smoked, longer duration of smoking, higher number of pack-years, and earlier age at initiation of smoking) were associated with more frequent/severe VMS (Table 4). For instance, compared with never smokers, current smokers with ≥40 pack-years were at >2-fold increased risk of often/severe VMS (RRR, 2.21; 95% CI, 2.06−2.37). Smoking initiation at ≤15 years was associated with increased risk of often/severe VMS in both current and former smokers, although current smokers had a much higher risk (RRR, 2.19; 95% CI, 1.88−2.54) than former smokers (RRR, 1.29; 95% CI, 1.15−1.46). Women who quit after the age of 40 years and those who had quit smoking within 5 years had a similar risk of VMS to those of current smokers. However, smokers who quit at <40 years of age or had quit for >5 years had similar levels of risk as never smokers.

### Prospective associations

At the 3-year follow up, 23% of the women reported no VMS at baseline and follow up; 47% of the women experienced some degree of VMS (rarely/mild to often/severe) at both times; 11% of the women reported VMS at baseline but no VMS at follow up, and 20% of the women reported VMS only at follow up (n=11,986; data not shown). Like the results from the cross-sectional analysis, overweight/obesity and smoking at baseline were associated with subsequent risk of VMS at 3-year follow up, and smoking strengthened the effect of BMI, but to a much lesser extent (Table 5). Also, former smokers had a lower risk of often/severe VMS at 3-year follow up than current smokers. Similar results were observed for studies of VMS frequency and VMS severity (data not shown). However, these associations attenuated markedly after adjustment for baseline VMS.

### Effect modification by menopausal status

There was a significant interaction between menopausal status and BMI ($P<.0001$) with VMS risk, but no interaction between menopausal status and smoking ($P>.05$), which indicates that the effect of BMI may be modified by menopausal status. After stratification by menopausal status, in the cross-sectional analyses, the association between overweight, obesity, and increased risk of VMS remained in pre- and perimenopause but not in postmenopause (Figure 1). In the prospective analyses, the association between baseline BMI and increased risk of VMS at 3-year follow up among pre- and perimenopausal women disappeared after adjustment for baseline VMS; however, higher BMI was associated with reduced risk of VMS among postmenopausal women (Figure 2).

## Comment

### Principal findings

This pooled analysis of >21,000 women from 8 studies examined individual and joint associations between 2 important modifiable factors, BMI and smoking, with frequency/severity of VMS. Results provided robust evidence to indicate that overweight/obesity (BMI, ≥25 kg/m$^2$) and cigarette smoking were associated with the frequency and severity of VMS, in a dose-dependent manner. These findings are largely consistent with individual InterLACE studies (for example, SWAN[13,26]) and with other published research.[5,27] Most notably, this study also found that smoking intensified the effect of obesity on VMS risk. Smokers who were obese had a particularly high risk of frequent or severe VMS. A significant dose-response was observed for the number of cigarettes, duration of smoking, pack-years, and age at initiation of smoking on the risk of VMS in current smokers. Early smoking cessation before the age of 40 years may mitigate the excess risk of VMS. Furthermore, we found that menopausal status modified the association between BMI and VMS. In the cross-sectional analysis, higher BMI was associated with VMS among pre- and perimenopausal women, but not among postmenopause women. In the prospective analysis, baseline BMI was associated negatively with VMS at 3-year follow up among postmenopausal women, even after adjustment for baseline VMS.

### Results

Our results are consistent with previous work that linked cigarette smoking and elevated BMI with increased frequency

**TABLE 4**
**Adjusted cross-sectional dose-response relationships between smoking and the risk of vasomotor symptoms at baseline (n = 14,709)[a]**

| Variable | N | Vasomotor symptoms (hot flushes and night sweats), % | | | | Relative risk ratio (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Model 1[b] | | | Model 2[c] | | |
| | | Never | Rarely/ mild | Sometime/ moderate | Often/ severe | Rarely/mild | Sometime/ moderate | Often/severe | Rarely/mild | Sometime/ moderate | Often/severe |
| Smoking status (n=14,709) | | | | | | | | | | | |
| Never smoker | 8259 | 46.3 | 19.4 | 20.9 | 13.4 | — | — | — | — | — | — |
| Former smoker | 4011 | 44.0 | 18.7 | 22.4 | 14.9 | 1.00 (0.94–1.06) | 1.11 (0.98–1.25) | 1.13 (0.98–1.30) | 1.00 (0.99–1.02) | 1.13 (1.06–1.20) | 1.12 (0.98–1.28) |
| Current smoker | 2439 | 36.6 | 18.9 | 24.6 | 19.9 | 1.19 (1.16–1.21) | 1.38 (1.08–1.77) | 1.66 (1.39–1.98) | 1.18 (1.15–1.21) | 1.35 (1.17–1.55) | 1.58 (1.51–1.65) |
| Intensity of smoking (n=14,442) | | | | | | | | | | | |
| Never smoker | 8259 | 46.3 | 19.4 | 20.9 | 13.4 | — | — | — | — | — | — |
| Former smoker | 4011 | 44.0 | 18.7 | 22.4 | 14.9 | 1.00 (0.94–1.05) | 1.11 (0.98–1.25) | 1.13 (0.98–1.30) | 1.01 (0.99–1.02) | 1.13 (1.06–1.21) | 1.12 (0.98–1.28) |
| Current smoker 1–9 cigarettes/d | 362 | 43.7 | 22.4 | 18.8 | 15.2 | 1.15 (0.96–1.38) | 0.92 (0.69–1.23) | 1.11 (0.76–1.63) | 1.08 (1.07–1.08) | 1.13 (0.77–1.67) | 1.17 (0.94–1.45) |
| Current smoker 10–19 cigarettes/d | 675 | 39.6 | 18.1 | 23.7 | 18.7 | 1.04 (0.76–1.43) | 1.20 (0.88–1.65) | 1.41 (1.00–1.97) | 1.01 (0.77–1.33) | 1.19 (0.93–1.52) | 1.33 (1.04–1.70) |
| Current smoker ≥20 cigarettes/d | 1135 | 32.2 | 18.0 | 27.7 | 22.2 | 1.27 (1.05–1.52) | 1.71 (1.31–2.23) | 2.02 (1.65–2.47) | 1.29 (1.11–1.49) | 1.58 (1.47–1.70) | 1.87 (1.75–1.99) |
| Duration of smoking (n=14,684) | | | | | | | | | | | |
| Never smoker | 8259 | 46.3 | 19.4 | 20.9 | 13.4 | — | — | — | — | — | — |
| Former smoker | 4011 | 44.0 | 18.7 | 22.4 | 14.9 | 1.00 (0.94–1.05) | 1.11 (0.98–1.25) | 1.13 (0.98–1.30) | 1.01 (0.99–1.02) | 1.13 (1.06–1.21) | 1.12 (0.98–1.28) |
| Current smoker duration <20 y | 103 | 42.7 | 17.5 | 18.5 | 21.4 | 0.93 (0.64–1.35) | 0.90 (0.47–1.71) | 1.57 (1.35–1.82) | 0.93 (0.64–1.34) | 0.84 (0.47–1.48) | 1.45 (1.17–1.79) |
| Current smoker duration 20–29 y | 566 | 44.7 | 17.0 | 23.0 | 15.4 | 0.91 (0.64–1.32) | 1.15 (1.00–1.31) | 1.22 (1.01–1.46) | 0.92 (0.66–1.30) | 1.17 (1.11–1.23) | 1.22 (0.99–1.49) |
| Current smoker duration ≥30 y | 1745 | 33.5 | 19.5 | 25.6 | 21.4 | 1.32 (1.11–1.56) | 1.52 (1.10–2.11) | 1.85 (1.40–2.44) | 1.30 (1.12–1.50) | 1.46 (1.19–1.80) | 1.74 (1.49–2.03) |

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*(continued)*

**TABLE 4**
**Adjusted cross-sectional dose-response relationships between smoking and the risk of vasomotor symptoms at baseline (n=14,709)[a]** *(continued)*

| Variable | N | Vasomotor symptoms (hot flushes and night sweats), % | | | | Relative risk ratio (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Model 1[b] | | | Model 2[c] | | |
| | | Never | Rarely/ mild | Sometime/ moderate | Often/ severe | Rarely/mild | Sometime/ moderate | Often/severe | Rarely/mild | Sometime/ moderate | Often/severe |
| Cumulative dose of smoking (n=14,431) | | | | | | | | | | | |
| Never smoker | 8259 | 46.3 | 19.4 | 20.9 | 13.4 | — | — | — | — | — | — |
| Former smoker | 4011 | 44.0 | 18.7 | 22.4 | 14.9 | 1.00 (0.94–1.05) | 1.11 (0.98–1.25) | 1.13 (0.98–1.30) | 1.01 (1.00–1.02) | 1.13 (1.06–1.21) | 1.12 (0.98–1.28) |
| Current smoker <10 pack-years | 285 | 44.2 | 21.1 | 16.8 | 17.9 | 1.10 (0.85–1.42) | 0.83 (0.59–1.17) | 1.35 (1.01–1.80) | 1.03 (0.82–1.30) | 1.01 (0.67–1.53) | 1.44 (1.20–1.72) |
| Current smoker 10–19 pack-years | 431 | 40.1 | 20.0 | 22.3 | 17.6 | 1.11 (0.84–1.46) | 1.12 (0.84–1.48) | 1.31 (1.14–1.51) | 1.05 (0.89–1.23) | 1.13 (0.90–1.44) | 1.23 (1.15–1.32) |
| Current smoker 20–29 pack-years | 436 | 40.1 | 16.5 | 26.8 | 16.5 | 0.96 (0.76–1.22) | 1.40 (0.99–1.97) | 1.30 (0.98–1.72) | 0.97 (0.76–1.22) | 1.39 (1.10–1.76) | 1.26 (1.00–1.60) |
| Current smoker 30–39 pack-years | 493 | 32.9 | 19.9 | 26.6 | 20.7 | 1.35 (1.18–1.54) | 1.59 (1.25–2.01) | 1.77 (1.18–2.68) | 1.35 (1.15–1.59) | 1.54 (1.40–1.69) | 1.69 (1.19–2.42) |
| Current smoker ≥40 pack-years | 516 | 28.5 | 17.3 | 28.7 | 25.6 | 1.36 (1.27–1.47) | 1.95 (1.22–3.12) | 2.55 (2.05–3.16) | 1.39 (1.28–1.51) | 1.68 (1.35–2.09) | 2.21 (2.06–2.37) |
| Age initiated smoking (n=14,543) | | | | | | | | | | | |
| Never smoker | 8259 | 46.3 | 19.4 | 20.9 | 13.4 | — | — | — | — | — | — |
| Former smoker initiated at ≥20 y | 854 | 44.7 | 19.2 | 20.7 | 15.3 | 1.00 (0.78–1.28) | 1.00 (0.87–1.16) | 1.12 (0.91–1.37) | 1.04 (0.86–1.26) | 1.06 (0.98–1.15) | 1.17 (1.07–1.28) |
| Former smoker initiated at 16–19 y | 2149 | 45.5 | 19.3 | 21.3 | 14.0 | 1.00 (0.93–1.08) | 1.03 (0.91–1.16) | 1.04 (0.87–1.25) | 1.01 (0.98–1.05) | 1.05 (0.96–1.15) | 1.06 (0.86–1.30) |
| Former smoker initiated at ≤15 y | 882 | 39.3 | 17.2 | 26.4 | 17.0 | 1.01 (0.81–1.26) | 1.42 (1.17–1.72) | 1.38 (1.19–1.60) | 0.98 (0.80–1.20) | 1.41 (1.21–1.64) | 1.29 (1.15–1.46) |
| Current smoker initiated at ≥20 y | 605 | 40.0 | 17.9 | 22.3 | 19.8 | 1.00 (0.80–1.26) | 1.13 (0.92–1.39) | 1.48 (1.35–1.61) | 1.00 (0.78–1.28) | 1.11 (1.00–1.22) | 1.43 (1.35–1.50) |
| Current smoker initiated at 16–19 y | 1124 | 37.5 | 19.8 | 25.8 | 16.9 | 1.22 (1.12–1.32) | 1.42 (1.16–1.73) | 1.40 (1.21–1.62) | 1.23 (1.11–1.36) | 1.38 (1.27–1.50) | 1.37 (1.32–1.42) |
| Current smoker initiated at ≤15 y | 670 | 31.6 | 17.8 | 25.4 | 25.2 | 1.29 (1.17–1.42) | 1.63 (1.09–2.45) | 2.41 (1.81–3.20) | 1.25 (1.22–1.28) | 1.57 (1.14–2.17) | 2.19 (1.88–2.54) |

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*(continued)*

**TABLE 4**
**Adjusted cross-sectional dose-response relationships between smoking and the risk of vasomotor symptoms at baseline (n=14,709)[a]** *(continued)*

| Variable | N | Vasomotor symptoms (hot flushes and night sweats), % | | | | Relative risk ratio (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Model 1[b] | | | Model 2[c] | | |
| | | Never | Rarely/ mild | Sometime/ moderate | Often/ severe | Rarely/mild | Sometime/ moderate | Often/severe | Rarely/mild | Sometime/ moderate | Often/severe |
| Age at quitting smoking (n=10,034)[d] | | | | | | | | | | | |
| Never smoker | 5800 | 42.5 | 16.7 | 26.0 | 14.8 | — | — | — | — | — | — |
| Current smoker | 1764 | 33.5 | 16.5 | 28.6 | 21.5 | 1.19 (1.02–1.40) | 1.26 (1.10–1.45) | 1.58 (1.35–1.85) | 1.19 (1.01–1.39) | 1.26 (1.10–1.45) | 1.54 (1.31–1.81) |
| Former smoker quit at <30 y | 807 | 46.1 | 15.0 | 25.5 | 13.4 | 0.85 (0.69–1.06) | 0.95 (0.79–1.15) | 0.91 (0.71–1.15) | 0.85 (0.68–1.06) | 0.96 (0.80–1.16) | 0.90 (0.71–1.15) |
| Former smoker quit at 30–39 y | 834 | 40.3 | 17.6 | 28.4 | 13.7 | 1.11 (0.90–1.37) | 1.14 (0.95–1.37) | 0.97 (0.77–1.22) | 1.10 (0.89–1.35) | 1.13 (0.94–1.36) | 0.94 (0.74–1.18) |
| Former smoker quit at ≥40 y | 829 | 32.7 | 16.2 | 31.1 | 20.0 | 1.18 (0.94–1.47) | 1.40 (1.16–1.68) | 1.50 (1.21–1.86) | 1.14 (0.91–1.43) | 1.34 (1.11–1.62) | 1.37 (1.10–1.71) |
| Years since quitting smoking (n=10,031)[d] | | | | | | | | | | | |
| Never smoker | 5800 | 42.5 | 16.7 | 26.0 | 14.8 | — | — | — | — | — | — |
| Current smoker | 1764 | 33.5 | 16.5 | 28.6 | 21.5 | 1.19 (1.02–1.40) | 1.26 (1.10–1.45) | 1.58 (1.35–1.85) | 1.18 (1.01–1.39) | 1.26 (1.10–1.45) | 1.54 (1.31–1.81) |
| Former smoker quit 1–5 y | 445 | 31.2 | 14.8 | 33.7 | 20.2 | 1.11 (0.82–1.51) | 1.54 (1.21–1.97) | 1.52 (1.14–2.03) | 1.06 (0.78–1.44) | 1.47 (1.15–1.88) | 1.37 (1.03–1.83) |
| Former smoker quit 6–14 y | 739 | 37.5 | 18.1 | 28.2 | 16.2 | 1.22 (0.98–1.53) | 1.20 (0.99–1.46) | 1.21 (0.96–1.53) | 1.20 (0.96–1.50) | 1.17 (0.96–1.43) | 1.14 (0.90–1.45) |
| Former smoker quit 15–19 y | 450 | 42.2 | 15.8 | 29.3 | 12.7 | 0.96 (0.73–1.28) | 1.17 (0.92–1.48) | 0.91 (0.66–1.25) | 0.96 (0.72–1.28) | 1.18 (0.93–1.50) | 0.89 (0.65–1.23) |
| Former smoker quit ≥20 y | 833 | 44.8 | 15.6 | 25.2 | 14.4 | 0.90 (0.72–1.11) | 0.93 (0.77–1.12) | 0.94 (0.75–1.19) | 0.89 (0.72–1.10) | 0.94 (0.78–1.13) | 0.93 (0.74–1.17) |

Data are presented with the use of multinomial logistic regression with a generalised logit link; the SURVEYLOGISTIC procedure in SAS software (SAS Institute Inc, Cary, NC) was used to incorporate the study cluster into the analyses.

[a] Data are from the Australian Longitudinal Study on Women's Health, the Study of Women's Health Across the Nation, and the Whitehall II Study; [b] Included menopausal status and use of menopausal hormone therapy at baseline; [c] Additionally included race/ethnicity/region, education, and body mass index at baseline; [d] The analysis was only based on data from the Australian Longitudinal Study on Women's Health study.

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**TABLE 5**
**Adjusted prospective associations of body mass index and smoking status at baseline with the risk of subsequent vasomotor symptoms at 3-year follow up (n = 11,986)[a]**

| | | Vasomotor symptoms (hot flushes and night sweats) (%) | | | | Relative risk ratio (95% confidence interval) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Fully adjusted model[b] | | | Fully adjusted model + baseline vasomotor symptoms | | |
| | N | Never | Rarely/ mild | Sometimes/ moderate | Often/ severe | Rarely/mild | Sometimes/ moderate | Often/severe | Rarely/mild | Sometimes/ moderate | Often/severe |
| Body mass index | | | | | | | | | | | |
| Normal (<25 kg/m$^2$) | 5859 | 35.7 | 19.7 | 25.3 | 19.3 | — | — | — | — | — | — |
| Overweight (25-29.9 kg/m$^2$) | 3638 | 31.0 | 21.6 | 25.8 | 21.7 | 1.21 (1.12–1.31) | 1.11 (1.01–1.23) | 1.17 (0.99–1.38) | 1.13 (1.09–1.18) | 0.99 (0.94–1.05) | 1.01 (0.89–1.14) |
| Obese (≥30 kg/m$^2$) | 2489 | 31.3 | 21.6 | 24.3 | 22.8 | 1.08 (1.00–1.17) | 1.12 (1.03–1.21) | 1.12 (0.92–1.37) | 1.00 (0.94–1.05) | 0.97 (0.91–1.03) | 0.93 (0.78–1.11) |
| Smoking status | | | | | | | | | | | |
| Never smoker | 6629 | 34.6 | 20.3 | 25.0 | 20.1 | — | — | — | — | — | — |
| former smoker | 3406 | 33.0 | 22.0 | 25.0 | 19.9 | 1.18 (1.11–1.26) | 1.13 (1.11–1.16) | 1.13 (1.09–1.17) | 1.18 (1.11–1.25) | 1.11 (1.07–1.15) | 1.09 (1.03–1.15) |
| Current skomer | 1951 | 29.7 | 19.7 | 26.2 | 24.5 | 1.16 (1.07–1.26) | 1.22 (1.02–1.45) | 1.39 (1.22–1.59) | 1.07 (1.00–1.15) | 1.08 (0.92–1.27) | 1.17 (1.02–1.33) |
| Joint effect | | | | | | | | | | | |
| Normal weight & never smoker | 3251 | 37.1 | 19.5 | 24.9 | 18.6 | — | — | — | — | — | — |
| Normal weight & former smoker | 1592 | 36.0 | 20.5 | 25.1 | 18.4 | 1.14 (1.06–1.23) | 1.12 (1.06–1.19) | 1.12 (1.02–1.24) | 1.12 (1.02–1.24) | 1.09 (1.01–1.16) | 1.09 (0.96–1.24) |
| Normal weight & current smoker | 1016 | 31.0 | 19.3 | 26.9 | 22.8 | 1.23 (1.10–1.37) | 1.24 (0.91–1.70) | 1.39 (1.09–1.76) | 1.15 (1.04–1.27) | 1.12 (0.85–1.48) | 1.19 (0.95–1.50) |
| Overweight & never smoker | 2029 | 32.1 | 20.8 | 26.0 | 21.0 | 1.18 (1.07–1.31) | 1.13 (1.05–1.21) | 1.17 (1.00–1.36) | 1.10 (1.01–1.21) | 1.00 (0.93–1.08) | 1.01 (0.89–1.14) |
| Overweight & former smoker | 1053 | 30.0 | 24.0 | 25.6 | 20.4 | 1.54 (1.32–1.79) | 1.27 (1.11–1.45) | 1.31 (1.03–1.67) | 1.45 (1.26–1.67) | 1.12 (1.02–1.24) | 1.11 (0.88–1.40) |
| Overweight & current smoker | 556 | 28.4 | 20.0 | 25.4 | 26.3 | 1.30 (1.09–1.56) | 1.26 (1.17–1.34) | 1.60 (1.41–1.82) | 1.10 (0.92–1.31) | 0.98 (0.86–1.13) | 1.15 (1.04–1.27) |
| Obese & never smoker | 1349 | 32.3 | 21.6 | 23.9 | 22.2 | 1.12 (0.92–1.35) | 1.09 (1.02–1.17) | 1.11 (0.85–1.44) | 1.03 (0.87–1.22) | 0.95 (0.89–1.02) | 0.94 (0.74–1.20) |
| Obese & former smoker | 761 | 31.0 | 22.3 | 24.3 | 22.3 | 1.24 (1.18–1.31) | 1.28 (1.11–1.47) | 1.28 (1.00–1.64) | 1.14 (1.05–1.24) | 1.09 (0.95–1.26) | 1.03 (0.80–1.31) |
| Obese & current smoker | 379 | 28.0 | 20.3 | 25.6 | 26.1 | 1.20 (1.08–1.35) | 1.45 (1.23–1.71) | 1.55 (1.37–1.76) | 1.00 (0.88–1.14) | 1.06 (0.88–1.27) | 1.05 (0.99–1.11) |

Data are presented with the use of multinomial logistic regression with a generalized logit link; the SURVEYLOGISTIC procedure in SAS software (SAS Institute Inc, Cary, NC) was used to incorporate the study cluster into the analyses.

[a] Data are from the Australian Longitudinal Study on Women's Health, the National Survey of Health and Development, the Study of Women's Health Across the Nation, and the Whitehall II Study; [b] Included menopausal status, use of menopausal hormone therapy at 3-year follow up, race/ethnicity/region, education, body mass index, and smoking status at baseline.

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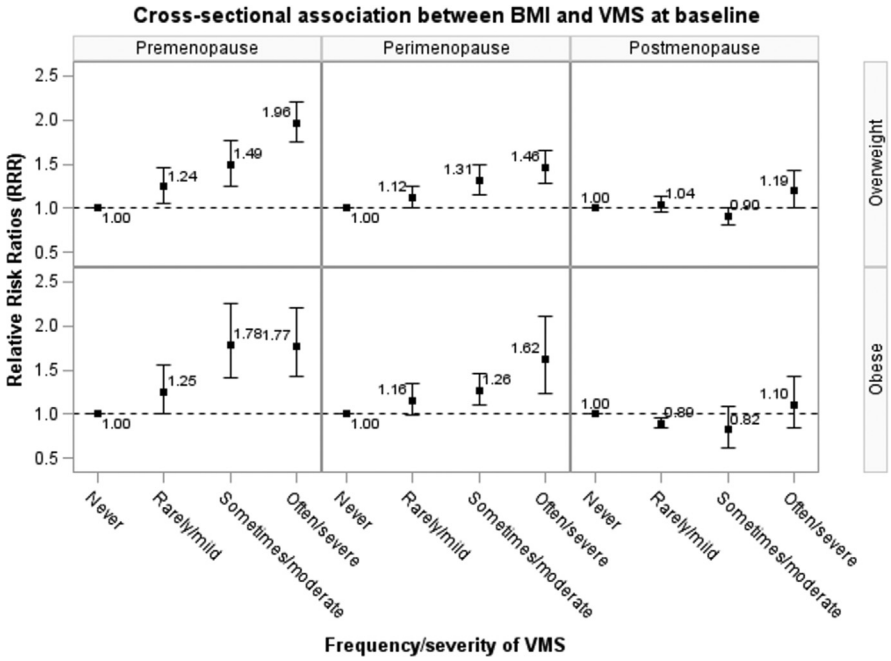
FIGURE 1
**Adjusted cross-sectional association between body mass index and the risk of vasomotor symptoms at baseline**




The adjusted cross-sectional association between body mass index and the risk of vasomotor symptoms at baseline was stratified by menopausal status at baseline (premenopause: n=4169; perimenopause: n=5881; postmenopause: n=4109). Relative risk ratio and the 95% confidence intervals were adjusted for use of menopausal hormone therapy, race/ethnicity/region, education, and smoking status at baseline.

*BMI*, body mass index; *RRR*, relative risk ratio; *VMS*, vasomotor symptoms.

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and severity of VMS,[5,27-31] although the mechanisms behind the relationship between smoking and VMS specifically remain unclear. Although it is widely accepted that body fatness is associated with an elevated core body temperature and delayed thermoregulation,[32] studies that have examined the results concerning pathways by which tobacco smoking influences VMS have been inconsistent (some have suggested an antiestrogenic effect[31]; others have shown the relationship is independent of estrogen levels[29,30]). Alternatively, the chemicals in cigarette smoke affect reproductive function and alter hormone levels and their ratios (for example, higher androstenedione levels, a higher total androgen-to-total estrogen ratio, and lower progesterone levels,[33,34] which have been associated with hot flushes[35]). Regardless of the exact physiologic mechanisms, however, the particularly increased risk among women who were both obese and current smokers implies that obesity and smoking intensify each other's effect on frequency/severity of VMS. The mechanisms behind the potential synergistic interaction in relation to VMS were beyond the scope of this study.

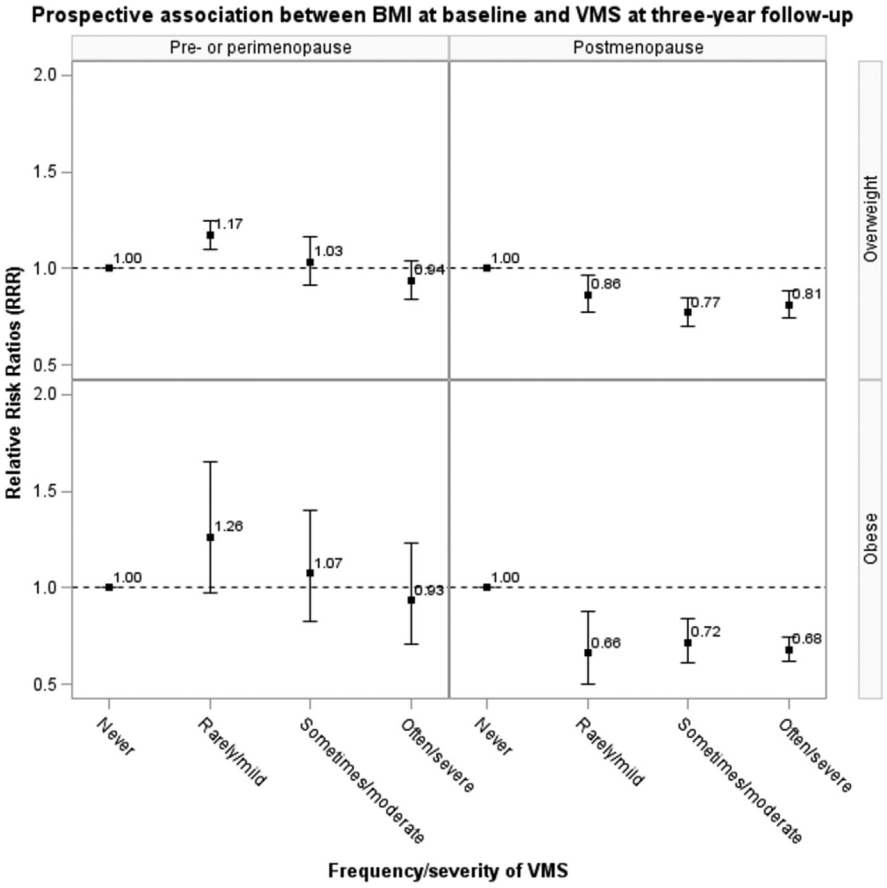
Previously, the InterLACE study, when examining smoking and age at menopause, found that the toxic impact of smoking on reproductive function appeared to be cumulative and long-lasting, even former smokers had an increased risk of earlier menopause.[36] Only those women who had quit smoking for >10 years had a similar risk as never smokers. Findings from this study also support that the reversal of negative effects after smoking cessation on VMS may not be immediate. Women who quit smoking for <5 years or quit at >40 years still had a significantly higher risk of frequent and severe VMS than never smokers. These results suggest that quitting smoking early is an important part of the routine counselling of women before approaching menopause.

In line with our findings, previous findings from SWAN showed that greater concurrent BMI and waist circumference were associated with increased risk of incident VMS in early menopause but with reduced VMS risk in late menopause, indicating the dominant mechanism of the effect of body fat on VMS differs in pre- and postmenopause.[15] A previous NSHD study also found that postmenopausal women with a BMI of $\geq$30 kg/m$^2$ were less likely to have severe VMS profile.[37] In the early stage of the menopausal transition, overweight and obesity may predispose to increased VMS occurrence (potentially because of greater heat insulation),[14] whereas, in postmenopausal women, increased estrone production from aromatization of androstenedione occurs with increasing weight,[38] which may be associated with less symptom reporting. Also, the effect of weight change on VMS is likely to differ in premenopausal and postmenopausal women.[15]

## Clinical implications

This study contributes to the understanding of how unhealthy behaviors, which often coexist, can interact and increase risk to a greater extent than they would if they occurred alone. Findings also suggested that cigarette smoking conveyed a greater risk for VMS than being overweight or obese, which is consistent with SWAN's previous results.[15] These findings support the opportunity to refer midlife women to health promotion programs and the need to emphasize both early smoking cessation and weight management strategies before menopause, because waiting until the menopausal transition and postmenopause is too late to achieve maximum benefit. Encouraging women to stop smoking before the menopausal transition (preferably before age 40 years) is essential. This is particularly important for obese smokers whose risk

FIGURE 2
**Adjusted prospective association between body mass index at baseline and the risk of vasomotor symptoms at 3-year follow up**




The adjusted prospective association between body mass index at baseline and the risk of vasomotor symptoms at 3-year follow up was stratified by menopausal status at the 3-year follow up (data from Australian Longitudinal Study on Women's Health; National Survey of Health and Development; Study of Women's Health Across the Nation, and the Whitehall II Study; pre- or perimenopause: n=3554; postmenopause: n=3966). Relative risk ratio and the 95% confidence intervals were adjusted for the use of menopausal hormone therapy at the 3-year follow up, race/ethnicity/region, education, smoking status, and vasomotor symptoms at baseline.

*BMI*, body mass index; *RRR*, relative risk ratio; *VMS*, vasomotor symptoms.

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of experiencing frequent and severe VMS is notably high.

Women with frequent and severe VMS often seek medical advice to treat their symptoms. Hormone therapy is the most common and effective treatment for VMS. However, many women and healthcare professionals have concerns about the long-term risks of hormone therapy, in particular on the risk of cardiovascular disease, based on the results from the Women's Health Initiative trial study.[39] The benefits and risks of hormone therapy vary by dosage, regimen, and timing of initiation. According to the National Institute for Health and Care Excellence guidelines,[40] women should be informed that taking hormone therapy at <60 years of age does not increase cardiovascular disease risk and that the presence of cardiovascular disease risk factors (eg, blood pressure, cholesterol) is not a contraindication to hormone therapy as long as they are treated optimally.

## Strengths and limitations

To our knowledge, this is the first study to examine the individual and joint associations between BMI and smoking with the risk of VMS. The InterLACE consortium draws together individual-level data from a number of large studies and therefore is able to provide precise estimates of the associations. Additionally, the availability of race/ethnicity/regional data, albeit based on self-reports, provides a relatively unique opportunity to examine differences in VMS symptoms in women from Japan, the United States, the United Kingdom, and Australia. Several limitations of these analyses should also be considered. First, data were derived from self-reports, which could have reflected in recall bias. For example, pre- or postmenopausal women or women who experienced short-duration or mild VMS might have been less likely to report their symptoms than women with moderate/severe VMS. Another significant limitation was the differences in the assessment of menopausal symptoms (severity or frequency over different recall periods) across studies, which limited our ability to pool data. Therefore, it is important for future research to develop standardized measures for menopausal symptoms (eg, the COMMA initiative–Core Outcome set in Menopause; part of the CROWN project[41]), which will enhance the availability of comparable data across different populations. Furthermore, of the 4 studies that provided longitudinal data on VMS, >3500 women with incomplete follow-up data were excluded. These women were more likely to report the exposures (obesity or current smoking), outcome (VMS), or both, which may have led to an underestimation of the frequency/severity of VMS. However, because we observed sufficient variation in the distribution of exposures and outcome, we do not expect the nature of the relationships that were observed in this study to change substantively.

## Conclusions

Results from this pooled analysis provided strong evidence that both higher body mass and smoking with higher intensity, longer duration, and earlier initiation were associated with more

frequent and severe VMS. Cigarette smoking strengthened the association between obesity and VMS; thus, smokers who were obese had a particularly increased risk of VMS. Effective intervention for smoking cessation before age 40 years and maintaining a normal weight before the menopausal transition may have important implications for the prevention of VMS in midlife women. ■

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