Soy intake and vasomotor menopausal symptoms among midlife women: a pooled analysis of five studies from the InterLACE consortium

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Short running head: Soy intake and vasomotor menopausal symptoms

ABSTRACT

Background/Objectives: Phytoestrogen rich-foods such as soy may be associated with less frequent/severe vasomotor menopausal symptoms (VMS), although evidence is limited. We thus investigated the associations between the consumption of soy products and soy milk and the frequency/severity of VMS.

Subjects/Methods: We pooled data from 19,351 middle-aged women from five observational studies in Australia, UK, USA, and Japan that contribute to the International Collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE). Information on soy consumption, VMS and covariates were collected by self-report. We included 11,006 women who had complete data on soy consumption, VMS and covariates at baseline for the cross-sectional analysis. For the prospective analysis, 4,522 women who were free of VMS at baseline and had complete data on VMS at follow-up were considered. Multinomial logistic regression and binary logistic regression models were used.

Results: No statistically significant evidence of an association was found between soy products (relative risk ratio (RRR): 0.92, 95% CI: 0.76–1.11) or soy milk (RRR: 1.24, 95% CI: 0.93–1.65) and the likelihood of reporting frequent or severe VMS cross-sectionally. Prospective results indicated that frequent consumption of soy products (odds ratio (OR): 0.63, 95% CI: 0.45–0.89) but not soy milk (OR: 1.11, 95% CI: 0.85–1.45) was associated with lower likelihood of reporting subsequent VMS, after adjustment for socio-demographic and reproductive factors.

Conclusions: These are the first ever findings from pooled observational data of association between consumption of soy products and VMS.

INTRODUCTION

Menopause, a natural event marking the end of the reproductive life of women, is often accompanied by menopausal symptoms. Vasomotor menopausal symptoms (VMS), including hot flushes and night sweats, are the most common symptoms which arise as a consequence of a decline in endogenous oestrogen levels, in particular during the perimenopausal and early postmenopausal phases [1, 2]. The frequency and severity of VMS usually decrease over time, but this varies by individual with symptoms subsiding after a year for some or persisting for over 30 years in others [3]. The frequency/severity of VMS have been linked to various chronic diseases including cardiovascular disease, osteoporosis, and cognitive decline [4, 5].

Phytoestrogen rich-foods such as soy have been associated with less frequent and less severe menopausal symptoms, although evidence is limited [6, 7]. Epidemiological studies which investigated the association between soy intake and the frequency/severity of VMS also demonstrated conflicting results [8, 9]. Moreover, according to a review of 43 randomised controlled trials (RCTs) [1], the positive effect of phytoestrogen supplements on the frequency/severity of hot flushes and night sweats in peri- or post-menopausal women is still inconclusive given the small sample size and potential high risk of bias of the included trials. However, the same review suggested that the effect of genistein (a soy derived isoflavone) was promising [1].

While dietary intake of phytoestrogens is usually in the form of soy bean, soy bean curd, tofu, tempeh, soy milk and other soy products, most studies have investigated the effects of soy supplements and extracts [10-12]. This study thus sought to elucidate the cross-sectional and prospective associations between soy intake and VMS among peri and post-menopausal women across five studies contributing to the International Collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) consortium.

SUBJECTS AND METHODS

Ethical approval

Written consent was obtained from all participants. All the cohort studies included in the InterLACE consortium have been previously granted ethical approval by the respective ethical committees [13].

Study participants

The InterLACE consortium includes individual data from ten countries. It involves around 230,000 participants from 20 observational studies with data on women's health (12 of which provide longitudinal data). Further detailed information on InterLACE has been published elsewhere [13, 14]. For the current study, five studies that had information on soy intake (the exposure) and hot flushes and/or night sweats (the outcome) were included: Australian Longitudinal Study on Women's Health (ALSWH) [15], Healthy Ageing of Women Study (HOW) – Australia, Whitehall II study (WHITEHALL) – UK [16], Seattle Midlife Women's Health Study (SMWHS) [17] and Japanese Midlife Women's Health Study (JMWHS) [18] (Supplementary Table 1). For the cross-sectional analysis, data from 11,006 women who reported VMS (either frequency or severity), consumption frequency of soy products and soy milk and had complete information on confounders (listed below) were included in the analysis. The prospective analysis included data from three studies (ALSWH, HOW and WHITEHALL) (n=10,082). Excluding 5,560 women who reported VMS at baseline and those with missing data on VMS, menopausal status, and use of hormone therapy at follow-up, 4,522 women were considered for the prospective analysis (Supplementary Figure 1).

Main outcome and exposure variables

VMS was defined as the presence of hot flushes and/ or night sweats. Response options for the frequency of hot flushes and night sweats (over the last 12 months) were 'never, rarely,

sometimes, and often' in ALSWH. For the other four studies, the severity of VMS over a shorter period was recorded; HOW, WHITEHALL and JMWHS considered the current severity of VMS, while SMWHS considered the severity of VMS in the last 1-3 months. For example, in HOW and JMWHS the response options for the extent of symptoms were 'not at all, a little, quite a bit, and extremely' and for WHITEHALL the response options were 'not at all, a little, somewhat, and a lot'. The degree of severity was harmonised as 'never, mild, moderate and severe' over a shorter period of time. Since the frequency of VMS was assessed in ALSWH and severity in the remaining four studies, results were presented separately. VMS were further coded dichotomously as '*absent'* (never and rarely if reporting frequency; never and mild if reporting severity) and '*present*' (sometimes and often if reporting frequency; moderate and severe if reporting severity) for the study-specific and prospective analysis.

Soy products such as tofu, soy beans, tempeh, and soy milk were commonly reported in the five studies. The soy products were combined based on their phytoestrogen contents. Thus, tofu, soy beans, tempeh, and soy flour having a high phytoestrogen content were grouped under the soy products category, while soy milk was considered separately [19, 20].

In ALSWH, there were ten consumption frequency options: 'never, less than once per month, 1-3 times per month, 1 time per week, 2 times per week, 3-4 times per week, 5-6 times per week, 1 time per day, 2 times per day, 3 or more times per day'. In the WHITEHALL study, nine consumption frequency options were provided; five in SMWHS and four response categories in HOW and JMWHS. Therefore, for this study, studies having more than four categories were collapsed into four frequency categories: 'never/rarely', 'monthly', 'weekly', and 'daily'. They were further coded dichotomously as 'less frequent' (never/rarely and monthly) and 'frequent' (weekly and daily) given the small number of observations for 'weekly' and 'daily' intake for the prospective analysis.

Covariates

Categorical variables in the InterLACE study were collapsed into the simplest categories possible so as to include data from as many studies as possible [13]. For example, education level was collated into three categories as ≤10 years, 11-12 years, and >12 years. Smoking status was grouped as never smokers, past smokers, and current smokers. Based on gynaecological surgery and menstrual bleeding patterns, menopausal status was collated into five categories to include 1) hysterectomy/oophorectomy, 2) unknown due to hormone use (menopausal hormone therapy or oral contraceptive hormones before reaching menopause), 3) premenopause (regular menstruation in the last 3 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). Current use of menopausal hormone therapy (e.g. oestrogen) was categorised as yes and no.

Statistical analysis

As the result of different assessments (frequency or severity) and different recall periods (in the past 12 months or in a more recent period) for VMS, studies were grouped as: 1) frequency of VMS in the past 12 months (ALSWH); 2) severity of VMS over a shorter time period (HOW, WHITEHALL, SMWHS, and JMWHS). The associations between soy consumption and VMS were first examined separately for the two different designs, followed by the overall estimates. Multinomial logistic regression models with four categories of outcome for VMS (never, rarely/mild, sometimes/moderate, and often/severe) were used to investigate the cross-sectional associations between frequency of consumption of soy products and soy milk with frequency/severity of VMS at baseline. The VMS category ‘never’ was used as the reference group for the outcome, and the soy consumption category ‘never’ was used as the reference

group for the exposure. Relative risk ratios (RRR) and 95% confidence intervals (CI) were estimated. According to the minimally sufficient set of adjustments, smoking status, education level, menopausal status, and race/ethnicity were identified as confounders using a directed acyclic graph (Supplementary Figure 2) and were adjusted for in the regression models. However, race/ethnicity was not included in the model as participants from ALSWH (96.5%), HOW (95.1%), WHITEHALL (88.1%) and SMWHS (88.1%) were mainly Caucasians, and in JMWHS all the participants were Japanese. Concurrent menopausal hormone therapy use was included in the model given its potential effect on the frequency/severity of VMS [21]. The models were thus adjusted for menopausal status and concurrent menopausal hormone therapy use (model 1) and additionally adjusted for other potential covariates including education level and smoking status (model 2). 'Study' was included as a fixed effect to account for differences in levels of VMS between studies and as a stratification variable to account for correlation of individuals within studies.

Due to small numbers of participants in the four categories of exposure and outcome in individual studies, dichotomised soy consumption (frequent and less frequent) and dichotomised VMS (presence and absence) were used for the study-specific and prospective analysis. To examine between-study heterogeneity in the effect size estimates, study-specific logistic regression and random-effects meta-analysis were used with the estimates adjusted for all the covariates in model 2.

For the prospective analysis based on three studies (ALSWH, HOW and WHITEHALL), logistic regression models with the binary outcome for VMS (presence and absence) were fitted, adjusted for all the covariates in model 2. In addition, a sensitivity analysis was conducted to investigate the association between soy consumption and subsequent risk of VMS at follow-up with all the women included (n=10,082), but adjusting for their baseline VMS, given that a large proportion of women were excluded in the prospective analysis due to the

148 presence of VMS at baseline. Analyses were performed using STATA 14 (StataCorp LP,
149 College Station, Texas). All statistical tests were two sided.
150
151 **RESULTS**
152 11,006 women reported their consumption frequency of soy and VMS, and also had complete
153 data on the covariates. The median age of the women at baseline was 52 years (interquartile
154 range: 51-54) (Supplementary Table 1). Table 1 shows the baseline characteristics of the
155 participants in each study. The majority of the participants were Caucasians-Australians/New-
156 Zealanders (57.5%), had 10 years or less of education (46.3%), and never smoked (60.9%).
157 Nearly 30% of the women were naturally postmenopausal, and 26.5% were currently using
158 menopausal hormone therapy. Across HOW, WHITEHALL, SMWHS, and JMWHS which
159 measured the severity of VMS, WHITEHALL had the highest percentage of women who
160 reported 'severe' VMS (11.1%), while JMWHS (Japanese) had the lowest percentage (4.4%).
161 In the ALSWH study, 24.6% reported 'often' for the frequency of VMS. In this predominantly
162 Caucasian population, 80-90% of the women reported that they never consumed soy products
163 or soy milk. Across the individual studies, JMWHS had the largest percentage of women who
164 reported 'daily' and 'weekly' soy product consumption (49.3% and 47.7% respectively) (Table
165 1). Comparing baseline characteristics of women included in the prospective analysis and those
166 excluded due to loss to follow-up, the excluded women were less educated and more likely to
167 be obese and current smokers at baseline. They were more likely to be postmenopausal and
168 less likely to report frequent/severe VMS compared to women with complete follow-up data
169 (Supplementary Table 2).
170 For the cross-sectional analysis, women with 'weekly' and 'daily' consumption of soy products
171 were less likely to report frequent/severe VMS compared with those with never/rarely
172 consumption (11.7 vs. 20.5% and 6.4 vs. 20.5%, respectively) (Table 2). However, after

adjusting for covariates and study differences, no clear evidence of an association was found between soy product consumption and the degree of VMS. Similarly, there was no clear evidence of an association observed for ALSWH or the other four studies. For soy milk consumption, women with a daily consumption were more likely to report frequent/severe VMS compared to women who reported 'never/rarely' consumption (RRR: 1.56, 95% CI: 1.24–1.96). A similar pattern for 'daily' consumption and risk of frequent/severe VMS was observed in ALSWH (RRR: 1.39, 95% CI: 1.10–1.77) and the other four studies (RRR: 3.09, 95% CI: 1.47–6.50).

When using dichotomised exposure and outcome variables for the study-specific analysis, the pooled estimate of association between frequent soy product consumption and the presence of VMS was OR: 0.92, 95% CI: 0.76–1.11, with no statistically significant heterogeneity between studies, test for heterogeneity: P = 0.49, I^2 = 0% (Figure 1). For the association between frequent consumption of soy milk and the presence of VMS, the pooled OR estimate was 1.24 (95% CI: 0.93–1.65) with no statistically significant heterogeneity between the studies (test for heterogeneity: P = 0.24, I^2 = 26.6%) (Figure 2).

For the prospective analysis, the overall estimates suggest that women with frequent soy product consumption were less likely to report the incidence of VMS at follow-up (OR: 0.63, 95% CI: 0.45–0.89) (Table 3). A consistent pattern was observed in ALSWH (OR: 0.63, 95% CI: 0.44–0.90) and the other four studies (OR: 0.60, 95% CI: 0.18–1.97). There was no clear evidence of an association between frequent consumption of soy milk and incident VMS at follow-up (OR: 1.11, 95% CI: 0.85–1.45). The sensitivity analysis with all the women included demonstrated a similar or weaker association between soy consumption and subsequent VMS, even adjusted by baseline VMS (Table 4).

DISCUSSION

198 This pooled study demonstrated no clear evidence of an association between consumption
199 frequency of soy products and VMS in the cross-sectional analysis. However, in the
200 prospective analysis, women with frequent consumption of soy products were less likely to
201 report subsequent VMS. Furthermore, there was no evidence of an association between
202 consumption of soy milk and frequency/severity of VMS both cross-sectionally (Figure 1, 2)
203 and prospectively (Table 3).
204 Our prospective analysis showed an association between frequent consumption of soy products
205 and decreased odds of VMS at follow-up, though this was attenuated when baseline VMS was
206 taken into account. Similarly, a Japanese community-based study in which women were
207 followed for six years found that soy products intake alleviated hot flushes [9]. Several RCTs
208 have investigated the association between some type of substance containing dietary soy (e.g.
209 soy extract in capsule or tablet form, soy powder or soy protein added to diets) and its effect
210 on hot flushes. While some demonstrated a reduction in the frequency/severity of hot flushes
211 [10, 22-24], others have shown contradictory findings [25, 26]. According to a review study,
212 the dose of genistein, in particular, was associated with a reduction of the symptoms rather than
213 total isoflavone [27]. The oestrogen-like properties of soy food due to the isoflavones content
214 have been linked to the protective effect on VMS. A decrease in the number of ovarian follicles
215 and consequent fall in oestrogen level could be the underlying hormonal aetiology of VMS [28,
216 29]. However, the effect of phytoestrogens in reducing VMS remains unclear [30]. One of the
217 possible mechanism of action is the structural similarity of isoflavones to that of oestradiol
218 could confer oestrogenic or anti-oestrogenic effects depending on the circulating oestrogen
219 level by binding to oestrogen receptors [31, 32]. The relative decline in oestrogen level leads
220 to higher circulating norepinephrine levels and an upregulation of serotonin receptors which
221 mediate hot flushes in menopausal women. By binding to oestrogen receptors, isoflavones help

to restore the oestrogen level, and causes subsequent changes in norepinephrine and serotonin levels, thus reducing the propensity of hot flushes [33].

Our pooled data did not show a clear association between soy milk consumption and frequency/severity of VMS. The source of dietary isoflavones may also contribute to the observed effect since processing methods tend to alter the phytoestrogen contents of soy products [34]. For instance, the total isoflavone content in soy beans (103mg per 100g), tempeh (18mg per 100g) and tofu (27mg per 100g) is much higher than that in soy milk (3mg per 100g) [20]. The overall low consumption frequency of soy milk among the participants and its low isoflavone content could possibly explain this finding.

The main drawback of our study is the variation in assessments used by the different studies. Soy consumption was measured as frequency, with no information on quantities. Moreover, for the consumption of soy milk, the cross-sectional nature of some of the studies and lack of evidence of a significant association from the prospective analysis, mean that we cannot confirm a temporal relationship between soy milk consumption and VMS. There also might be possibility of residual confounding, e.g. by factors not measured in the studies. One weakness of data harmonisation is the collapsing of the variables of interest into the simplest level of detail in order to incorporate information from as many studies as possible, leading to loss of statistical power as well as potential misclassification of the degree of VMS and frequency of soy consumption. For instance, studies like ALSWH and WHITEHALL had ten and nine frequency options respectively for consumption of soy that were collapsed to four categories for this analysis. In addition, the frequency of VMS was reported in ALSWH over a longer period of time (12 months), and the other four studies recorded the severity of VMS over a shorter period that limited our ability to pool data. Despite these limitations the pooled results showed considerable homogeneity as shown in the forest plots and the low values for the statistic I^2.

Furthermore, our study had several strengths that ranged from the inclusion of a large number of women across different geographic regions and cultures that allowed greater generalisability of the results. This is also, to our knowledge, the first pooled study consisting of women's health studies from four different countries examining an association between soy products and soy milk with frequency/severity of VMS. We also included women who had a hysterectomy, oophorectomy, and/or were currently using hormones that could provide a better estimate of the prevalence of VMS. In addition, the individual data available in the InterLACE enabled harmonization of the variables of interest using common definitions, coding and cut points not normally possible with meta-analyses of published results. Harmonisation of the data further reduces the between-study heterogeneity. A consistent approach to confounder adjustment was used for the regression models along with careful selection of the confounders using a DAG, thus reducing the probability of the results being affected by uncontrolled confounders.

While menopause is an inevitable phenomenon in a woman's life cycle, the frequency and severity of VMS show marked variations [35]. VMS are reported by around 75% of postmenopausal women globally, with a minority reporting severe symptoms [36, 37]. Findings from this study provide some evidence that frequent consumption of soy products (e.g., soy beans, tofu, tempeh) as part of the usual diet may be associated with a reduced risk of subsequent VMS. However, frequent consumption of soy milk did not appear to be associated with subsequent VMS. As justified by potential mechanisms in previous studies, our findings could prompt RCTs testing the effects of dietary soy intake in particular on VMS as opposed to earlier RCTs which have mainly considered the effects of soy extracts and supplements.

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Contribution

The authors' responsibilities were as follows — GDM: conceived the study; YD, HFC and GDM: designed the research and had primary responsibility for the final content; JEC, DCG, ESM, NFW, EJB, TY, and DA: contributed to the data; YD: performed the statistical analysis and wrote the manuscript; HFC, DCG, JEC, AJD and GDM: provided statistical input, helped with interpretation of the results and reviewed the manuscript for important intellectual content; and all authors: read and approved the final manuscript.

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Conflict of interests

Janet E. Cade is the director of a university spin out company, Dietary Assessment Ltd. The other authors had no financial or personal conflicts of interest to declare.

'Supplementary information is available at EJCN's website'

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Figure 1. Forest plot of study-specific effect estimates of the cross-sectional association between consumption frequency of soy products and the presence of vasomotor menopausal symptoms at baseline. Soy product consumption was coded dichotomously as '*frequent*' (weekly and daily) and '*less frequent*' (never/rarely and monthly) and vasomotor symptoms as '*present*" (sometimes and often if reporting frequency; moderate and severe if reporting severity) and '*absent'* (never and rarely if reporting frequency; never and mild if reporting severity) given the small number of observations in each study. Odds ratios (ORs) a presented on a log scale. Effect estimates were adjusted for menopausal status, current use of menopausal hormone therapy, education level, and smoking status. VMS: Vasomotor menopausal symptoms

Figure 2. Forest plot of study-specific effect estimates of the cross-sectional association between consumption frequency of soy milk and the presence of vasomotor menopausal symptoms at baseline. Soy milk consumption was coded dichotomously as '*frequent*' (weekly and daily) and '*less frequent*' (never/rarely and monthly) and vasomotor symptoms as '*present*" (sometimes and often if reporting frequency; moderate and severe if reporting severity) and '*absent'* (never and rarely if reporting frequency; never and mild if reporting severity) given the small number of observations in each study. Odds ratios (ORs) a presented on a log scale. Effect estimates were adjusted for menopausal status, current use of menopausal hormone therapy, education level, and smoking status. VMS: Vasomotor menopausal symptoms