REVIEW

The association of vasomotor symptoms with fracture risk and bone mineral density in postmenopausal women: a systematic review and meta-analysis of observational studies

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Abstract

Background/Aims Vasomotor symptoms (VMS) adversely affect postmenopausal quality of life. However, their association with bone health has not been elucidated. This study aimed to systematically review and meta-analyze the evidence regarding the association of VMS with fracture risk and bone mineral density (BMD) in peri- and postmenopausal women.

Methods A literature search was conducted in PubMed, Scopus and Cochrane databases until 31 August 2023. Fracture, low BMD (osteoporosis/osteopenia) and mean change in lumbar spine (LS) and femoral neck (FN) BMD were assessed. The results are presented as odds ratio (OR) and mean difference (MD), respectively, with a 95% confidence interval (95% CI). The I^2 index quantified heterogeneity.

Results Twenty studies were included in the qualitative and 12 in the quantitative analysis (n=49,659). No difference in fractures between women with and without VMS was found (n=5, OR 1.04, 95% CI 0.93–1.16, I^2 16%). However, VMS were associated with low BMD (n=5, OR 1.54, 95% CI 1.42–1.67, I^2 0%). This difference was evident for LS (MD -0.019 g/cm^2, 95% CI -0.03 to -0.008, I^2 85.2%), but not for FN BMD (MD -0.010 g/cm^2, 95% CI -0.021 to 0.001, I^2 78.2%). These results were independent of VMS severity, age and study design. When the analysis was confined to studies that excluded menopausal hormone therapy use, the association with BMD remained significant.

Conclusions The presence of VMS is associated with low BMD in postmenopausal women, although it does not seem to increase fracture risk.

Keywords Osteoporosis · Fractures · hot flushes · Night sweats · Vasomotor symptoms · Postmenopausal women

Introduction

Vasomotor symptoms (VMS), mainly hot flushes and night sweats, are quite common in women entering menopause and adversely affect their quality of life [1, 2]. An abrupt increase in VMS occurs during the first two years before the final menstrual period (FMP) (i.e., during the late perimenopausal phase) in 60-80% of women, presenting a peak one year after the FMP. VMS persist in 50% of cases during the first four years after the FMP [1, 2]. Interestingly, 10% of postmenopausal women may experience VMS even 12 years after their FMP [1]. The prevalence of VMS varies across different geographic regions and is estimated at 22-63% in Asia, 36-50% in North America and 45-74% in Europe [3].

VMS reflect the fluctuations in the hormonal milieu during the transition to menopause [1, 2]. Except for their impact on quality of life, severe VMS have been associated with increased prevalence of cardiovascular risk factors, such as type 2 diabetes mellitus (T2DM), smoking and obesity [4], predisposing to increased risk of cardiovascular disease (CVD), especially in women younger than 60 years [5]. Furthermore, the peak VMS prevalence coincides with accelerated bone loss during the menopausal transition

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[6]. Therefore, the severity of VMS has been proposed as a marker of climacteric bone loss [6]. The first report of a potentially adverse effect of VMS on peri- and postmenopausal bone health was made in 1994 by Lee *et al.*, who showed that the prevalence of osteoporosis in postmenopausal women who recalled severe and persistent VMS was higher than those who had no VMS [7]. After that, several studies of different designs had contradictory results regarding the impact of VMS both on fracture risk and low BMD in peri- and postmenopausal women [8–13].

The primary aim of this study was to systematically review and meta-analyze the available evidence regarding the association between VMS and the risk of fractures or low BMD (osteopenia/osteoporosis) in peri- and postmenopausal women. The secondary endpoint was to investigate the difference in BMD between women with and without VMS.

Materials and Methods

Guidelines followed

The present study followed the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines [14] and has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) system (CRD42023387161).

Search strategy

Six reviewers (G.A, K.B, D.D, M.Z, A.P, E.F.) conducted a literature search in the electronic databases MEDLINE (PubMed), Scopus and Cochrane (CENTRAL) until 31 August 2023. A representative example of search strategy in MEDLINE was : ("hot flush*"[tiab] OR "hot flash*"[tiab] OR "night sweat*"[tiab] OR "vasomotor symptom*"[tiab] OR "menopausal symptom*"[tiab] OR "postmenopausal symptom*"[tiab] OR "post-menopausal symptom *"[tiab] OR climacteric[tiab]) AND (fracture[MeSH] OR fracture*[tiab] OR "bone density"[MeSH] OR "bone mineral density"[tiab] OR BMD[tiab] OR "bone mass"[tiab]). Two senior authors resolved discrepancies. Furthermore, conference abstracts, grey literature (using Opengrey.eu) and reference sections of the included studies were screened manually. E-mails were sent to the authors of the eligible studies to obtain missing data.

Study selection

The following PICO (Population, Intervention, Comparison and Outcome) elements were set as inclusion criteria: (i) Population: peri- or postmenopausal women, (ii) Intervention: VMS (hot flushes and/or night sweats), (iii)

Comparison: peri- or postmenopausal women without VMS, (iv) Outcome: fractures (vertebral, non-vertebral, hip), low BMD (defined as osteopenia or osteoporosis) and mean difference in BMD between groups. Observational studies (cohort, cross-sectional and case-control) and randomized-controlled trials were included in the analysis. Exclusion criteria were: (i) studies that involved solely premenopausal women, (ii) studies that did not provide information on fracture incidence or BMD, (iii) non-English papers and (iv) animal studies.

Menopause was defined as the absence of menstruation for ≥12 months (natural menopause) or the period of time starting immediately after bilateral oophorectomy (surgical menopause). Women were classified as "premenopausal" if they had no change in menstrual regularity during the past year, or as "perimenopausal", if they reported menstruation during the past three months, but with decreased irregularity (early perimenopausal) or no menses during the past 3-11 months (late perimenopausal).

Data extraction

Two independent researchers extracted data from eligible studies that met the predefined criteria. A standardized form was used to record: (i) first author, (ii) year of publication, (iii) country in which the study was conducted, (iv) study design, (v) total sample size, (vi) mean participants' age, (vii) number of patients with and without VMS, (viii) type and severity of VMS, (ix) number of patients with fractures (hip, vertebral, non-vertebral), (x) number of patients with low BMD, (xi) BMD at lumbar spine (LS), femoral neck (FN) and total hip (TH) BMD in VMS and non-VMS groups.

Risk of bias and study quality assessment

The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the selected studies. This scale consists of the following domains: (i) selection of participants, with a maximum rating of four stars, (ii) comparability of study groups, with a maximum of two stars, and (iii) assessment of outcome or exposure, with the highest rating reaching three stars. According to NOS, a study is characterized as "good quality" if it gets 3-4 stars in the selection domain, 1-2 stars in the comparability domain, and 2-3 stars in the outcome/exposure domain. "Fair quality" is considered when the study gets two, 1-2 and 2-3 stars in the selection, comparability and outcome/exposure domain, respectively. Finally, a study is characterized as "poor quality" in the case of 0-1, 0 and 0-1 stars in the selection, comparability and outcome/exposure domain, respectively [15].

Statistical analysis

The dichotomous data results regarding the association between VMS status and the risk of fracture or low BMD were expressed as odds ratio (OR), with 95% confidence interval (CI), whereas the difference in BMD between women with and without VMS was expressed as mean difference (MD) with 95% CI. Heterogeneity among studies was quantified by the I^2 index, with values 30% being considered as "low", 30- 60% as "moderate" and >60% as "high heterogeneity" [16]. The fixed effect model was used for low heterogeneity, whereas the random effects model was used for cases with moderate or high heterogeneity.

Subgroup and sensitivity analysis was implicated to eliminate possible sources of heterogeneity. Also, in order to investigate the effect of possible modifiers (i.e., baseline patients' characteristics, such as age) on the outcome, meta-regression analysis (based on the random effects model) was conducted. The risk of publication bias was examined with the Harbord-Egger's test [16]. All statistical tests were two-sided, with a *p*-value <0.05 considered significant. All analyses were conducted using the *Review Manager* (*RevMan 5.4.1* software) computer program (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, September 2020).

Results

Descriptive analysis

The initial search provided 1,959 results after excluding duplicates, 96 of which were reviewed for full-text eligibility. Of those, 76 articles were excluded with reasons (Supplementary Table 1). Finally, 20 studies were selected for qualitative and 12 for quantitative analysis [7–10, 12, 13, 17–22] (eight studies [11, 23–29] were excluded from the meta-analysis due to a lack of extractable data for comparisons). Notably, the study by Nudy et al. [11], and Hippisley-Cox et al. [29], were excluded since they did not provide the exact number of patients with VMS, either as hot flushes or night sweats. A flow chart diagram is illustrated in Fig. 1.

Five [7, 8, 12, 19, 22] studies investigated the association between VMS and fracture risk, whereas five [7, 10, 12, 13, 21] addressed the occurrence of low BMD (osteopenia or osteoporosis). Furthermore, eight [8, 9, 12, 17–20, 22], seven [8, 9, 12, 18–20, 22] and four [9, 18, 20, 22] studies provided data regarding the difference in LS, FN, TH BMD, respectively, between patients with and without VMS. Overall, 49,659 patients were included in the analysis.

VMS and risk of fracture

The five studies [7, 8, 12, 19, 22] assessing the association between VMS and fractures, found no increased risk in women with VMS compared with those without VMS (OR 1.04, 95% 0.93–1.16, I^2 16%) (Fig. 2). Regarding the type of fracture, three studies provided data on vertebral fractures showing again no association with VMS (OR 0.95, 95% CI 0.77–1.19, I^2 0%) [7, 8, 19]. Only the study by Crandall *et al*., published in 2015 [8], provided data on hip fractures, showing increased risk in women with moderate/severe VMS (compared with no VMS) [hazard ratio (HR) 1.78, 95% CI 1.20–2.64].

VMS and risk of low BMD (osteopenia or osteoporosis)

Since only three studies provided data for the diagnosis of osteoporosis and two studies for osteopenia, these were combined into one category termed "low BMD" [7, 10, 12, 13, 21]. The presence of VMS was associated with an increased risk of low BMD compared with the absence of VMS (OR 1.55, 95% CI 1.43–1.68, I^2 0%) (Fig. 3).

VMS and mean difference in BMD

Regarding LS BMD, patients with VMS had lower values compared with those without VMS (*n*=8, MD -0.019 g/cm^2, 95% CI -0.03 to -0.008, I^2 85.2%) [8, 9, 12, 17–20, 22]. In contrast, there was no difference in FN (*n*=7) [8, 9, 12, 18–20, 22] or TH BMD (*n*=4) [9, 18, 20, 22] between women with and without VMS [MD -0.010 g/cm^2 (95% CI -0.021 to 0.001, I^2 78.2%) and -0.040 g/cm^2 (95% CI -0.0 to 0.008, I^2 94.2%, respectively)]. The difference in LS and FN BMD between women with and without VMS is presented in Fig. 4.

Subgroup analysis

The effect of VMS severity on fracture risk and BMD

Three studies [7, 8, 12] were eligible for comparing moderate/severe VMS and no VMS, while two studies [8, 12] provided data on mild VMS. No association with the risk of fracture was found when the analysis was confined to these subgroups [OR 1.08 (95% CI 0.79–1.46, I^2 40%) and 1.08 (95% CI 0.60–1.94, I^2 64%) for moderate/severe and mild VMS, respectively, compared with no VMS]. However, both moderate/severe (*n*=4) [7, 10, 12, 13] and mild VMS (*n*=2) [10, 12] were associated with an increased risk of low BMD compared with no VMS [OR 1.79 (95%
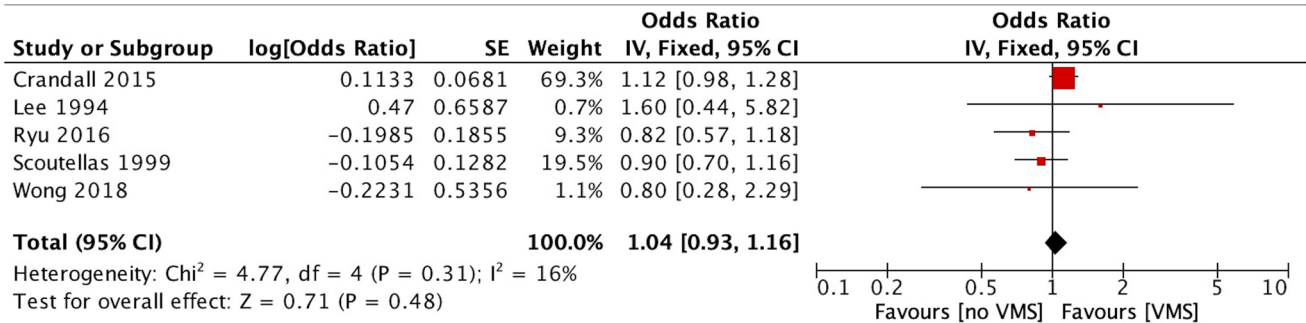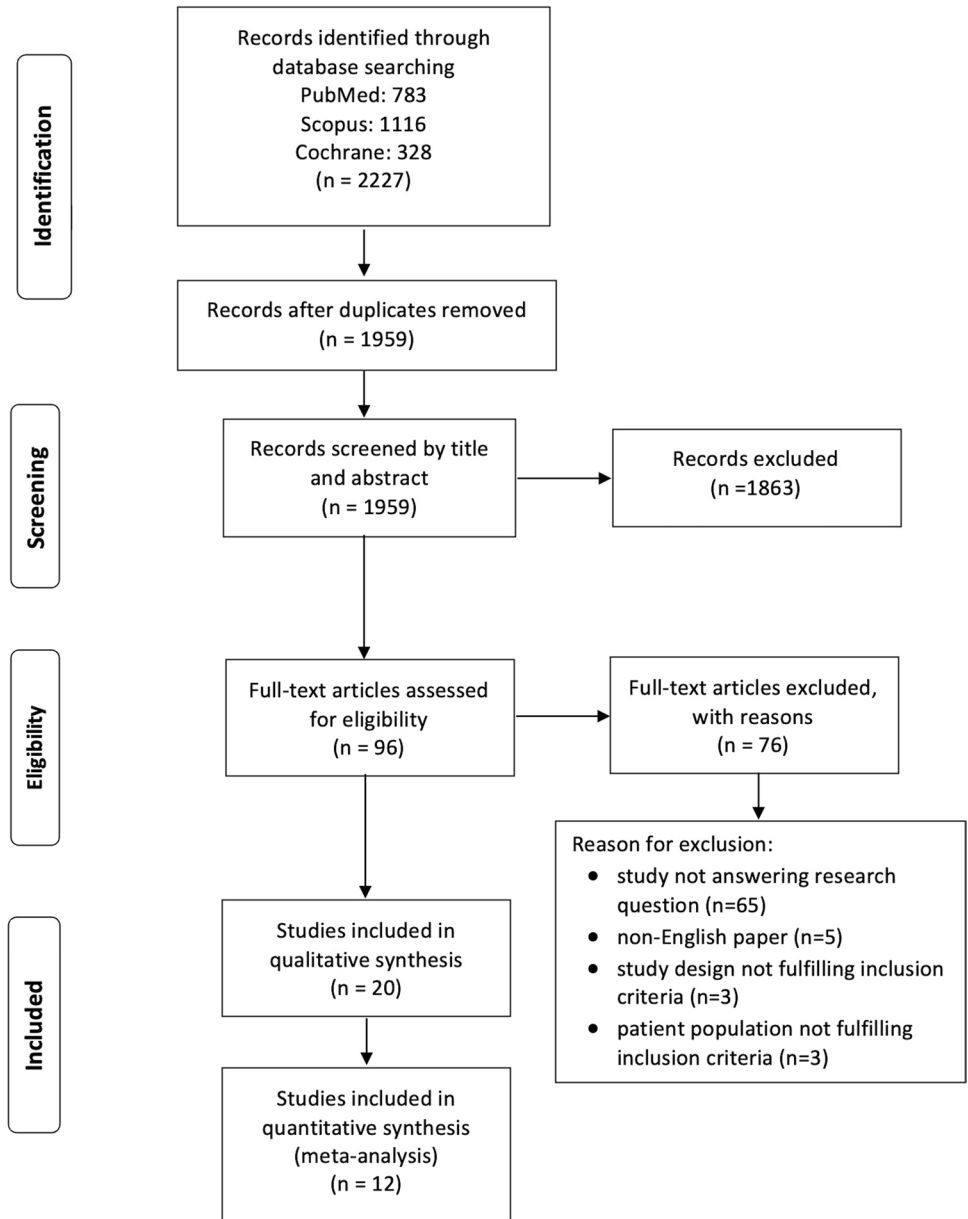
Fig. 1 Flow chart diagram

Fig. 2 Forest plot of the fracture risk between women with and without vasomotor symptoms (VMS)
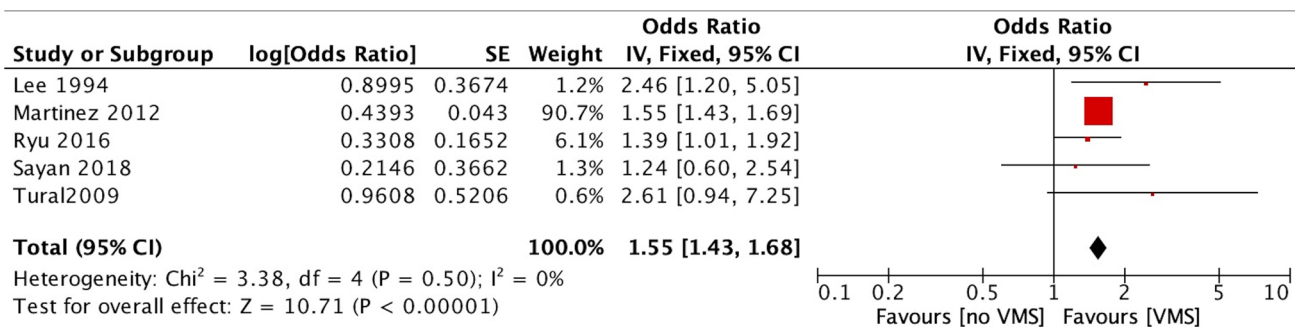
Fig. 3 Forest plot of the low BMD risk (osteopenia or osteoporosis) between women with and without vasomotor symptoms (VMS)
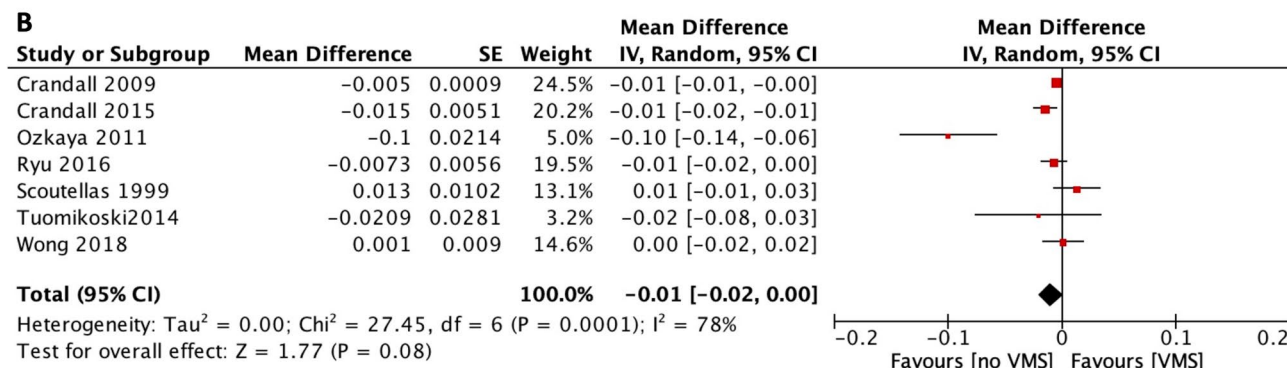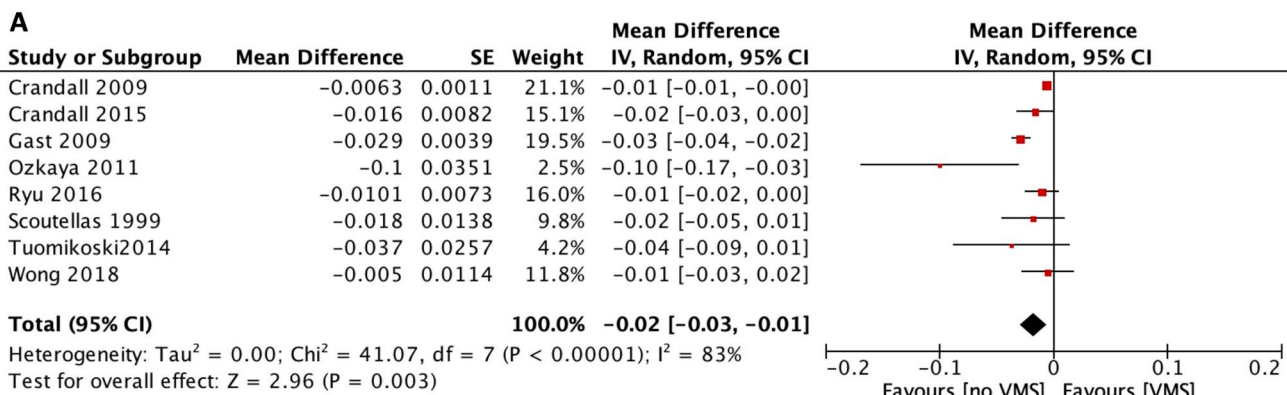

Fig. 4 Forest plot of the difference in **A**) lumbar spine (LS) and **B**) femoral neck (FN) BMD between women with and without vasomotor symptoms (VMS)

CI 1.63–1.96, I^2 0%) and 1.28 (95% CI 1.15–1.41, I^2 0%), respectively].

Moreover, women with moderate/severe VMS demonstrated lower LS (n=4, MD -0.025 g/cm^2, 95% CI -0.042 to -0.008, I^2 72.9%) [8, 12, 17, 20] and FN BMD (n=3, MD -0.011 g/cm^2, 95% CI -0.02 to -0.004, I^2 0%), respectively) than those without VMS [8, 12, 20]. Mild VMS were also associated with lower BMD in LS, but not FN, compared with no VMS. There were no available data regarding the effect of VMS severity on TH BMD.

The effect of study design on the risk of fracture and BMD

Regarding fracture risk, there was still no association with VMS, when the analysis was limited to cohort studies (n=2, OR 1.11, 95% CI 0.98–1.28) [8, 22] or case-control studies (n=2, OR 0.86, 95% CI 0.61–1.22) [7, 12]. Furthermore, when data from case-control studies [7, 12, 13] were analyzed separately, the risk of low BMD still was increased in women with a history of VMS (OR 1.39, 95% CI 1.06–1.82) similarly to cross-sectional studies (OR 1.56,

95% CI 1.43–1.69) [10, 21]. Regarding BMD, cohort and cross-sectional studies showed similar differences for LS and FN between groups.

The effect of age on fracture risk and BMD

Only one study provided sufficient data for different age groups regarding the fracture risk [8], showing an increased risk of hip fracture in patients with VMS only for the older age group (70-79 years old; HR 1.93, 95% CI 1.11–3.53). No such risk was demonstrated for vertebral and non-vertebral fractures [8].

Notably, meta-regression analysis showed that age was not a predictor neither for fracture risk ($p=0.11$) nor for low BMD ($p=0.707$). Age also did not affect MD in LS ($p=0.807$) and FN BMD ($p=0.498$) between groups.

Sensitivity analysis

A sensitivity analysis was performed according to study quality and MHT use. Classification of studies according to NOS is presented in Supplementary Table 2. After excluding two fair-quality studies [12, 18], the risk estimation for fractures, low BMD and LS or FN BMD remained unaltered.

Concerning MHT use, there were four studies [13, 17, 19, 22] in which MHT was used by a variable proportion of patients (although MHT was included in the multivariable-adjusted models). However, the association between VMS and low BMD and MD in LS BMD between groups remained significant after restricting the analysis to studies where MHT was an exclusion criterion, but presence of VMS and fracture risk remained not significant (OR 1.12, 95% CI 0.98–1.28).

Publication bias

Publication bias was not evident regarding the risk of fracture ($p=0.546$) or low BMD ($p=0.435$), and TH BMD ($p>0.20$). However, Egger's test showed significance for MD in LS ($p=0.09$) and FN BMD ($p=0.06$), possibly due to the effect of small sample size on study outcomes (Supplementary Figure 1).

Discussion

This study shows that the presence of VMS in peri- and postmenopausal women is associated with a higher degree of bone loss, since these women are more prone to osteopenia or osteoporosis than those without VMS. This effect is independent of age, VMS severity, study quality and MHT use, although moderate/severe VMS affect LS and FN BMD

to a greater extent than mild VMS. However, no association between VMS and fracture risk was found.

This meta-analysis is the first considering the effect of VMS on bone health in postmenopausal women. Recent studies have underscored the impact of the severity of VMS on the cardiovascular system, including risk factors, such as diabetes, smoking, obesity [4], and CVD events, especially in women younger than 60 years [5]. Therefore, the presence and severity of VMS appear as key players in the accelerated bone loss in peri- and postmenopausal women, necessitating the administration of MHT. Another clinical implication is that women who experience moderate/severe VMS constitute a distinct postmenopausal population at higher risk of osteoporosis and, potentially, fractures and should be screened by dual-energy X-ray absorptiometry (DXA) earlier than the generally recommended threshold of 65 years [30].

Estrogens are essential for acquiring and maintaining peak bone mass by acting at the osteoclast and osteoblast levels [31]. In particular, estrogen receptors α upregulate the expression of Wnt co-receptor lipoprotein receptor-related protein (LRP)-5, which is essential for osteoblast differentiation. They also inhibit osteoblast apoptosis by decreasing the production of Fas ligand (FasL) [31]. At the osteoclast level, they prevent osteoclast differentiation and proliferation indirectly through the osteoprotegerin (OPG)/receptor activator of NF-κB (RANK)/RANK ligand (RANKL) axis [31]. They also induce osteoclast apoptosis (through the FasL) and inhibit osteocyte apoptosis by increasing the expression of semaphorin 3A [31]. During the menopausal transition (i.e., from the first year before and three years after the FMP), a 9-10% bone loss occurs [32]. This fact is of clinical relevance in women with early menopause (<45 years), a category that is predisposed to increased fracture risk [33].

The exact pathogenetic mechanisms linking VMS with bone loss are not fully understood. Most [34, 35], but not all studies [36], have shown that the decline in estradiol (E_2) concentrations is associated with VMS. However, the individual's sensitivity to the fluctuations rather than the absolute decrease in E_2 concentrations seem to account for the association of VMS with accelerated bone loss [17]. Furthermore, increased sympathetic activity has been reported in women with VMS [37], which fosters bone loss through increased bone resorption and decreased bone formation. Indeed, $β_2$- and α-adrenergic receptors have been identified in human osteoblasts [38, 39]. Cortisol concentrations also increase after hot flushes, contributing to bone loss [40]. Another potential mechanism could be endothelial dysfunction [41] and increased concentrations of inflammatory markers, such as interleukin-8 and tumor necrosis factor α; these molecules have been identified in the presence of VMS and may impair bone quality [42]. Finally, VMS are

associated with increased oxidative stress, which inhibits the Wnt pathway and, subsequently, bone formation [43].

Some limitations should be acknowledged, such as the heterogeneity regarding the definition of VMS and study design, and the increased risk of recall or selection bias. However, the effect of these limitations on the present study's validity was mitigated by applying meta-regression, subgroup and sensitivity analysis, which did not significantly modify the study's outcomes (except for the effect of MHT on fracture risk). The heterogeneity in the DXA device and the number of vertebrae assessed constitutes another limitation. Finally, no subgroup analysis for peri- and postmenopausal women could be performed by available data.

In conclusion, this study shows that the history of VMS (hot flushes and/or night sweats), especially in their moderate/severe form, is associated with greater bone loss, compared with no VMS, in peri- and postmenopausal women. This association involves both LS and FN BMD, potentially predisposing the woman to an increased risk of fracture, although this was not proven by the present study. This aspect of postmenopausal health, in combination with CVD, should be considered in future studies, designating the potentially beneficial role of MHT in this population.

Declarations

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