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Review article

# Early menopause is associated with increased risk of arterial hypertension: A systematic review and meta-analysis

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ABSTRACT

*Objective:* Menopausal transition has been associated with an increased risk of cardiovascular disease (CVD), mainly attributed to atherogenic dyslipidaemia, central obesity and insulin resistance. Whether arterial hypertension (AH) also contributes to menopause-associated CVD is currently unknown. The aim of this study was to systematically investigate and meta-analyze the best available evidence regarding the association between early menopause (EM) and AH risk.

*Methods:* A comprehensive search was conducted in PubMed, CENTRAL and Scopus databases, up to January 20th, 2020. Data were expressed as odds ratio (OR) with 95 % confidence intervals (CI). The $I^2$ index was employed for heterogeneity.

*Results:* Ten studies were included in the quantitative analysis (273,994 postmenopausal women, 76853 cases with AH). Women with EM (age at menopause $<45$ years) were at higher AH risk compared with those of normal age at menopause ($>45$ years) (OR 1.10, 95 % CI 1.01–1.19, $p = 0.03$; $I^2$ 79 %). The direction or the magnitude of this association remained significant when the analysis was restricted to studies including groups matched for potential confounders, such as age, BMI, smoking or the use of menopausal hormone therapy or oral contraceptives.

*Conclusions:* Women with EM have an increased risk for AH compared with those of normal age at menopause.

## 1. Introduction

Menopause is the consequence of ovarian reserve depletion leading to estrogen deficiency, clinically defined as completion of 12 months since the final menstrual period (FMP), except for cases with a history of bilateral oophorectomy [1]. Most studies have shown that menopausal transition is associated with a higher cardiovascular disease (CVD) risk [2,3], which is more evident in women with early menopause (EM; age at menopause $<45$ years) or premature ovarian insufficiency (POI; age at menopause $<40$ years) [4,5]. EM has a prevalence of 10 %, whereas POI has a prevalence of 1 % [6]. Menopause-related CVD risk is mainly attributed to the acquisition of a more atherogenic lipid profile, central adiposity and glucose intolerance compared with premenopausal women [7–10]. However, whether arterial hypertension (AH) also contributes to this increased CVD risk is currently unknown, with studies yielding contradictory results [11–14].

The aim of this study was to systematically review and meta-analyze the existing evidence regarding the association between EM and AH risk.

## 2. Materials and methods

### 2.1. Guidelines followed

This systematic review followed the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) guidelines [15]. The flow diagram is presented in Fig. 1. A completed MOOSE checklist is available in the Supplementary Table 1.

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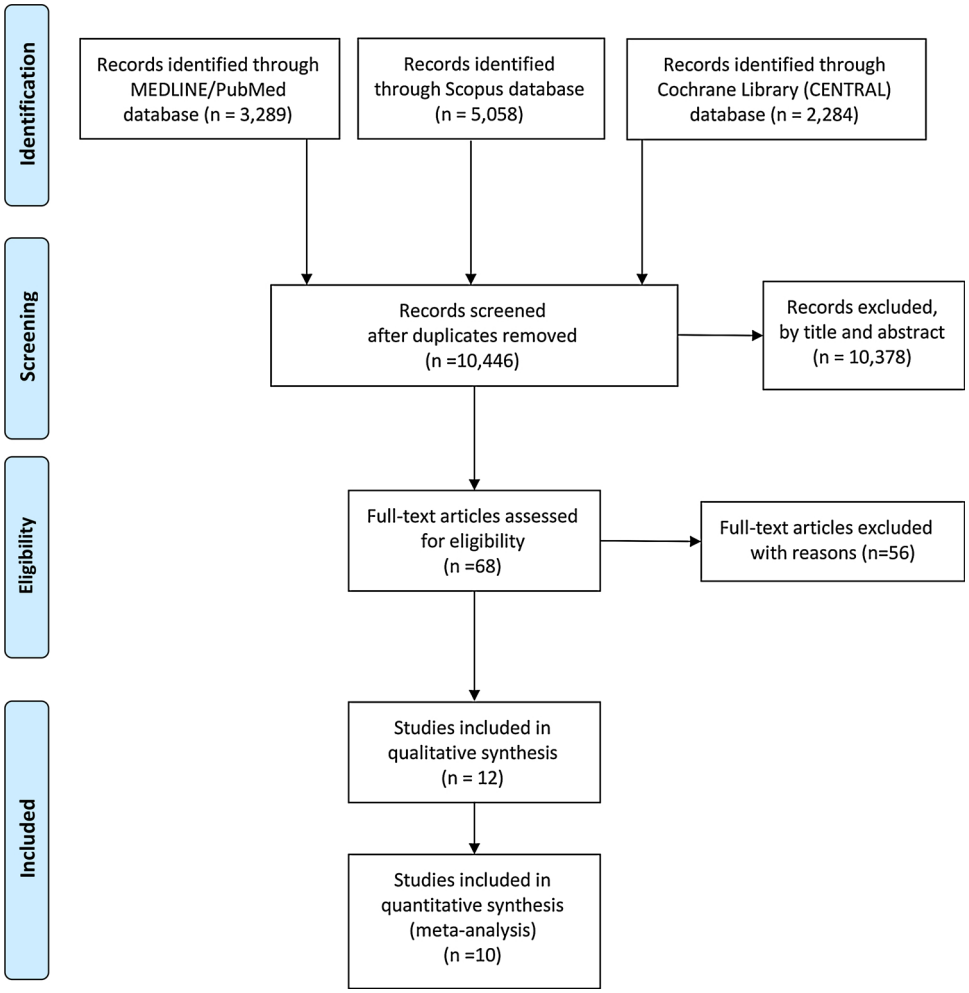


**Fig. 1.** Flow chart diagram.

### 2.2. Search strategy

To identify eligible studies, a systematic literature search was conducted from conception until January 20th 2020 in three electronic databases: MEDLINE, Scopus, and Cochrane (CENTRAL). A set of relevant terms was used to narrow the search, creating the following search string (for PubMed): ("menopause, premature"[MeSH] OR "primary ovarian insufficiency"[MeSH] OR "ovarian insufficiency"[tiab] OR "ovarian failure"[tiab] OR ((menopause[MeSH] OR menopause[tiab] OR menopausal[tiab] OR climacteric[tiab] OR postmenopausal[tiab] OR post-menopausal[tiab]) AND (early[tiab] OR premature[tiab] OR age[tiab] OR years[tiab] OR time[tiab]))) AND ("Hypertension"[Mesh] OR hypertens*[tiab] OR hypertension[tiab] OR "hypertensive"[tiab] OR "blood pressure") NOT (Animal[MeSH] NOT Human[MeSH]) NOT (letter[pt] OR comment[pt] OR editorial[pt] OR Review[pt] OR "practice guideline"[ptyp] OR "case reports"[ptyp]. The review of eligible studies was conducted independently by four authors (PT, KL, GK, KM). Any discrepancies were resolved by the consultation of a fifth investigator (PA and DGG). Both cohort and case-control studies were eligible.

### 2.3. Study selection

The following PICO (Population, Intervention, Comparison and Outcome) elements were set as inclusion criteria: (i) Population: postmenopausal women (either hysterectomized or not); (ii) Intervention: early age at menopause, either EM or POI; (iii) Comparison group: women with normal age at menopause; (iv) Outcome: AH. EndNote V8 was used as the search software.

The exclusion criteria were: (i) studies without a control group [with normal blood pressure (BP)]; (ii) studies including pre- or perimenopausal women; (iii) studies with patients having genetic syndromes associated with EM or POI (e.g. Turner's syndrome); (iv) participants with a history of polycystic ovarian syndrome (PCOS) and (v) animal studies. Clinical trials, case series, case reports, reviews, abstracts, letters-to-the editor were also considered as not eligible and were excluded. Only papers written in English were included.

### 2.4. Data extraction

Two researchers (PT and KL) independently extracted data from the eligible studies. The following parameters were recorded for the analysis: (i) first author's name; (ii) year of publication; (iii) country in which the study was conducted; (iv) study design (cohort or case-control); (iv) study duration (available in cohorts); (v) total number of study participants; (vi) number of women with EM (vii) number of women with normal age at menopause (defined as those with an age at menopause $>45$ years); (viii) number of cases with AH in each of these categories. Mean participants' age and body mass index (BMI), type of menopause (surgical or natural), level of education and physical activity, as well as the prevalence of traditional CVD risk factors such as dyslipidaemia, diabetes mellitus (DM) and smoking were also recorded. Both subjects with natural (defined as a period of at least 12 months since the FMP) and surgical (bilateral oophorectomy) menopause were

**Table 1**
Demographic characteristics of studies included in the analysis.

| Study characteristics | | | Characteristics of the participants | | | | | | | Type of menopause | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | First author, Year of publication | Study design | Participants | Women with AH | Mean age (years) | BMI (kg/m$^2$) | Smoking (former/ current) (%) | MHT use (%) | OC use (%) | Natural (%) | Surgical (%) |
| 1. | Appiah, 2016 | Cohort | 5,629 | 1,774 | 56.1 ± 4.7 | 28.0 ± 6.1 | 1,373 (24) / 1279 (23) | 1225 (22) | 2,309 (41) | 416 (74) | 1,468 (26) |
| 2. | Cui, 2006 | Cohort | 37, 965 | 10,490 | 61.4 ± 0.7 | 22.9 ± 0.1 | N/A | N/A | N/A | N/A | N/A |
| 3. | Ebong, 2015 | Case-Control | 2,275 | 1,148 | 65.0 ± 9.2 | 28.5 ± 5.9 | 681 (30) / 233 (10) | 741 (32) | N/A | N/A | N/A |
| 4. | Gunning, 2013 | Case-control | 392 | 100 | 49.8 ± 4.8 | 25.8 ± 0.6 | 147 (38) / 55 (14) | 149 (38) | N/A | N/A | N/A |
| 5. | Hong, 2007 | Cohort | 2,658 | 424 | 66.0 ± 8.2 | N/A | N/A | N/A | 26 (1) | N/A | N/A |
| 6. | Song, 2018 | Cohort | 13,406 | 3,178 | 63.5 ± 8.5 | 24.0 ± 3.4 | N/A / 268 (2) | 291 (2) | 2,284 (17) | N/A | N/A |
| 7. | Van ser Shouw, 1996 | Cohort | 12,115 | 9,156 | 57.5 ± 4.2 | N/A | N/A / 2501 (20) | N/A | 730 (6) | 9861 (81) | 2,254 (19) |
| 8. | Xu, 2020 | Cohort | 5,107 | 1,859 | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 9. | Yan, 2018 | Cohort | 1,875 | 566 | 61.7 ± 9.1 | 23.7 ± 2.3 | 331 (18) / 417 (22) | N/A | N/A | 1391 (74) | 484 (26) |
| 10. | Zhu, 2019 | Cohort | 192,572 | 48,158 | 57.0 ± 10.3 | N/A | 60,865 (31) / 21,661 (11) | 75,585 (39) | N/A | N/A | N/A |

Data are presented as mean ± SD or n (%).
Abbreviations: AHarterial hypertension; MHTmenopausal hormone therapy; OCoral contraceptives; BMIbody mass index; N/Anot available.

included.

The following comparisons were performed according to the incidence or prevalence of AH: (i) women with EM were compared with those whose age at menopause was >45 years; (ii) women with POI were compared with those whose age at menopause was >45 years. The effect of confounding factors, such as age, BMI and smoking, was explored by performing pre-planned sensitivity or subgroup analyses.

### 2.5. Risk of bias and study quality assessment

Newcastle-Ottawa scale (NOS) was used for assessing studies' quality. This system uses three criteria: (i) participant selection (maximum of four stars); (ii) comparability of study groups (maximum of two stars) and (iii) assessment of outcome or exposure (maximum of three stars) for the outcome/exposure category [16]. NOS results are available in the Supplementary Table 2.

### 2.6. Statistical analysis

Heterogeneity was tested with the Cochrane chi-square test and the degree of heterogeneity was quantified by the $I^2$ statistics. An $I^2$ of 40–60 % was considered as "moderate", whereas values >60 % were considered as "high degree" of heterogeneity. Both fixed-effect and random-effect models were used for data synthesis, according to heterogeneity. Funnel plots and Egger's test for small-study effects were used to determine the likelihood of publication bias (*p*-values > 0.1 indicating absence of publication bias). Associations were reported as odds ratios (OR) with 95 % confidence intervals (CI). A *p*-value of <0.05 was considered statistically significant. All analyses were performed with the Revman Software (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

## 3. Results

### 3.1. Descriptive data

The initial search provided 10,446 papers after excluding duplicates, 68 of which were assessed as full-texts for eligibility (Fig. 1). Of those, 56 papers were excluded, the reason for the exclusion being presented in the Supplementary Table 3. Twelve studies were included in the qualitative and ten in the quantitative analysis [11–14,17–22]. The two studies [23,24] were excluded from the quantitative analysis, because they did not provide numerical data on women with age of menopause >45 years. The studies were published between 1996 and 2020 The countries in which they were conducted were: China (n = 2) [13,14], Netherlands (n = 2) [19,20], USA (n = 2) [17,18], Australia (n = 1) [21], Japan (n = 1) [11], South Korea (n = 1) [12] and multicenter (n = 1) [22]. The number of participants ranged from 392 to 192,572, yielding a total of 273,994 postmenopausal women, including 76,853 cases with AH. AH was defined either as systolic and/or diastolic BP > 140 and/or >90 mmHg, respectively (by using mercury sphygmomanometer) [12], history of anti-hypertensive medication use [17] or both [12,12,13,14,18–20]. One study used the self-reported physician-diagnosed AH [13], whereas in one study the method of AH definition was not reported [11].

### 3.2. Comparison of women with EM with those of normal age at menopause

Women with EM demonstrated a higher risk of developing AH compared with those of normal age at menopause (>45 years) (ten studies, 273,994 women) [11–14,17–22] (OR 1.10, 95 % CI 1.01–1.19, $p = 0.03$; $I^2$ 79 %) (Fig. 2). After excluding the study by Zhu et al. [22], due to its large sample size, the association between EM and AH remained significant (OR 1.12, 95 % CI 1.01–1.25, $p = 0.04$; $I^2$ 78 %).

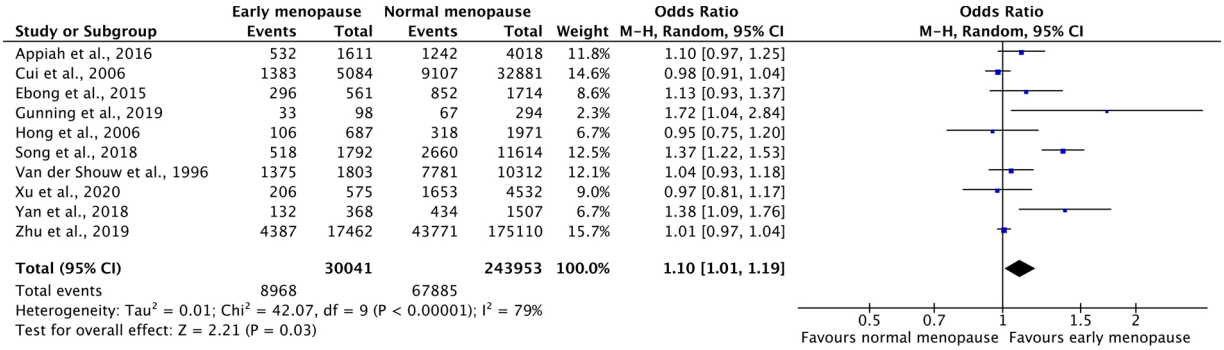


**Fig. 2.** Forest plot of the comparison between early menopause and menopause at normal age (>45 years).

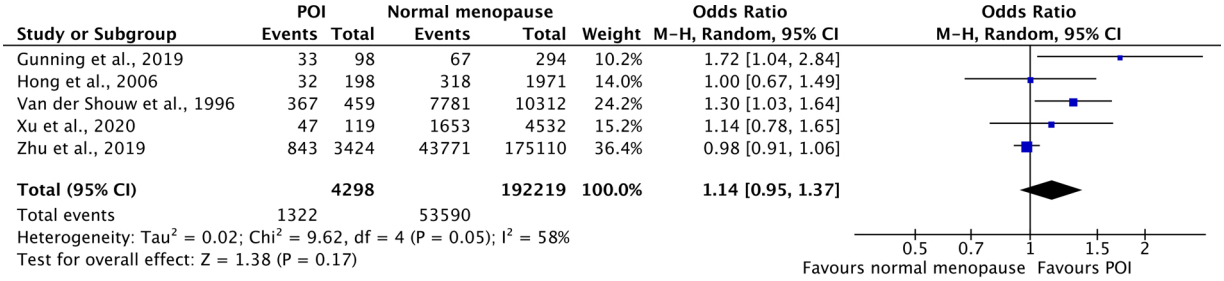


**Fig. 3.** Forest plot of the comparison between premature ovarian insufficiency (POI) and menopause at normal age (>45 years).

### 3.3. Sensitivity analysis

When women with POI were compared with those of normal menopausal age (five studies, 192,219 women), the association between POI and AH risk was not significant [12,19–22] (OR 1.14, 95 % CI 0.95–1.37, $p = 0.17$; $I^2$ 58 %) (Fig. 3). Furthermore, when sensitivity analysis was restricted to studies (n = 8) in which participants were matched for age or BMI or smoking [11–14,17–19,21], the direction or the magnitude of the effect observed did not change (OR 1.13; 95 % CI, 1.00–1.29; $p = 0.05$). This was also the case after restricting the analysis to studies (n = 2) matched for ever use of menopausal hormone therapy (MHT) or oral contraceptives (OC) [13,18] (OR 1.26; 95 % CI 1.05–1.52; $p = 0.01$).

### 3.4. Subgroup analysis

We performed subgroup analysis according to study design (cohorts versus case-control studies). When analysis was restricted to cohort (eight studies; OR 1.08; 95 % CI, 0.99–1.18; $p = 0.08$) [11–14,17,20–22] or case-control studies (two studies; OR 1.31, 95 % CI 0.88–1.93; $p = 0.18$) [18,19], no difference was observed between the two groups. No separate analysis could be performed according to race **(black** versus non-**black** populations).

The use of MHT and/or OC was reported in eight studies [12,13,17–22], with respective rates of 2–84.5 % and 1–41 %. However, a separate analysis according to this confounder, was not feasible, since data with regard to age at menopause were not extractable. With respect to the type of menopause, no subgroup analysis could be conducted, since no distinct data on surgical menopause were available from the included studies.

## 4. Discussion

To our knowledge, the current study, including 273,994 postmenopausal women (76853 cases with AH), is the first systematic review and meta-analysis evaluating the association between age of menopause and the risk of developing AH. Women entering menopause at an age <45 years exert an increased risk of developing AH compared with those with age of menopause >45 years. This association was not affected by potential confounding factors, such as age, BMI, smoking or the use of MHT and/or OC.

The underlying mechanisms regarding the association between EM and AH risk cannot be fully clarified. A potential explanation might be the shorter exposure to endogenous estrogens. Epidemiological data cannot provide robust evidence on whether the increase in BP in women entering menopause is a corollary of menopause *per se* or the ageing process [25]. Notably, it has been observed that women after the age of 50 years present a steeper increment in BP and are characterized by a higher prevalence of AH compared with age-matched men [26]. On a pathogenetic basis, it has been suggested that the decline in estrogen concentrations and, more specifically, in estrogen-to-androgen ratio during menopause, induces the production of specific vasoconstrictive factors, such as endothelin and angiotensinogen (the latter leading to upregulation of the renin-angiotensin system, renal sodium reabsorption and vasoconstriction) [27]. Furthermore, a higher sympathetic activity, potentially due to higher α1-adrenergic receptor responsiveness, has also been reported in women with AH compared with their male counterparts [28].

It is possible that both EM and AH are the consequence of risk factors predisposing to both entities, such as smoking, low physical activity and socioeconomic status. However, epidemiological evidence suggests that smoking may increase AH risk in women, especially when it exceeds the number of 15 cigarettes/day [29]. On the other hand, smoking has also been associated with a decline in ovarian reserve [30]. The latter effect is mainly attributed to the toxic chemicals released by tobacco use, such as polycyclic aromatic hydrocarbons, which induce oocyte apoptosis [31]. Moreover, low socio-economic status and education, which have been associated with increased AH risk [32], may also predispose to EM [33]. Data on low physical activity, an established risk factor for AH [34], are inconclusive, since physical activity has been associated with both later [33] and earlier [35] age at menopause. However, no sufficient data were available for subgroup analysis on this concept in the present study. Furthermore, genetic predisposition, accounting for approximately 50% of the variation in the age at menopause, may contribute to both EM and AH [36]. For instance, polymorphisms in genes implicated in DNA repair have been

associated both with earlier timing of menopause [37] and the risk of developing AH [38].

The main clinical implication of the present study is the early identification of women with EM as a group of women at a higher risk of AH. Although the evidence is not robust from current data, the finding of the positive association between EM and AH may substantiate timely effective lifestyle interventions to prevent the development of AH in this group of postmenopausal women. This should be the case especially in women with pre-existing risk factors for AH, such as obesity, positive family history and other causes of secondary hypertension [39]. Another ensuing key issue is whether MHT decreases the BP in postmenopausal women or, ideally, if it is associated with a reduction in AH risk. An older meta-analysis of randomized-controlled trials (RCT) showed a slight reduction in mean BP by MHT (−1.7 %, 95 % CI −2.9 to −0.5 %). Subgroup analysis showed that this effect was significant only with conjugated equine estrogen and not with other types of estrogen (oral esterified or transdermal 17β-estradiol) [27]. In contrast, recent RCTs have not demonstrated such a beneficial effect of either estrogen formulation [40].

The present study has certain limitations. First, the high degree of heterogeneity, which may be attributed to the different study design, as well as to different ethnicity of the populations. Second, the diagnosis of AH was set with different methodology in the included studies and, therefore, its validity could be questioned. Third, the exact effect of the past use of MHT or OC on the study's outcomes could not be estimated, although subgroup analysis did not alter the association between EM and AH risk. Notably, the percentage of the participants having received MHT or OC was relatively low in most studies, with no precise data on the duration of use. MHT is routinely administered in POI and this might be the potential reason regarding the lack of association between POI and AH risk. Interestingly, a very recent study showed adjusted HR for developing AH 1.43 (95 % CI 1.24–1.65; $p < 0.001$) and 1.93 (95 % CI 1.37–2.74; $p < 0.001$) for natural and surgical POI, respectively [24]. However, we did not include this study, since the comparison was made with women with age at menopause >40 rather than >45 years. Fourth, the age of natural menopause may be subjected to recall bias, since it was self-reported in most of the included studies.

In summary, this is the first systematic review and meta-analysis showing that women entering menopause at an earlier age (<45 years) exert an increased risk of developing AH compared with those with age of menopause >45 years. This finding contributes to what is already known in the field of menopause-associated CVD risk and should be taken under consideration for early detection of AH in these women. Timely effective lifestyle interventions are warranted to prevent the development of AH in this high-risk population. The key issue is to conduct well-designed interventional studies to further elucidate this field further.

## Authors' contributions

PA designed the research, analyzed the extractable data and wrote the first draft of the paper. PT, KL, GK, KM searched the literature, extracted and analyzed the data. JKB was responsible for the statistical analysis and reviewed the manuscript. IL and JCS reviewed the manuscript and provided critical scientific input. DGG resolved discrepancies regarding the quality of the studies included in the meta-analysis, provided critical scientific input and had the primary responsibility for the paper's final content.

## Conflict of interest

Dr. Stevenson has received grants/research support from Abbott, Mylan and Pfizer; consulting fees from Abbott, Mylan and Pfizer; and speaker's honoraria from Abbott, Bayer, Gedeon Richter, Menarini, Mylan, and Pfizer. The other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Provenance and peer review

Peer review was directed by Yvonne van der Schouw independently of Irene Lambrinoudaki, one of the authors and co-Editor in Chief of Maturitas, who was blinded to the process.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.maturitas.2020.03.006.

## References

[1] S.D. Harlow, M. Gass, J.E. Hall, R. Lobo, P. Maki, R.W. Rebar, S. Sherman, P.M. Sluss, T.J. de Villiers, S.C. Group, Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging, J. Clin. Endocrinol. Metab. 97 (4) (2012) 1159–1168.
[2] E. Barrett-Connor, Menopause, atherosclerosis, and coronary artery disease, Curr. Opin. Pharmacol. 13 (2) (2013) 186–191.
[3] S.R. El Khoudary, Gaps, limitations and new insights on endogenous estrogen and follicle stimulating hormone as related to risk of cardiovascular disease in women traversing the menopause: a narrative review, Maturitas 104 (2017) 44–53.
[4] T. Muka, C. Oliver-Williams, S. Kunutsor, J.S. Laven, B.C. Fauser, R. Chowdhury, M. Kavousi, O.H. Franco, Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis, JAMA Cardiol. 1 (7) (2016) 767–776.
[5] X.Y. Tao, A.Z. Zuo, J.Q. Wang, F.B. Tao, Effect of primary ovarian insufficiency and early natural menopause on mortality: a meta-analysis, Climacteric 19 (1) (2016) 27–36.
[6] S.R. Davis, I. Lambrinoudaki, M. Lumsden, G.D. Mishra, L. Pal, M. Rees, N. Santoro, T. Simoncini, Menopause, Nat. Rev. Dis. Primers 1 (2015) 15004.
[7] P. Anagnostis, K. Christou, A.M. Artzouchaltzi, N.K. Gkekas, N. Kosmidou, P. Siolos, S.A. Paschou, M. Potoupnis, E. Kenanidis, E. Tsiridis, I. Lambrinoudaki, J.C. Stevenson, D.G. Goulis, Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis, Eur. J. Endocrinol. 180 (1) (2019) 41–50.
[8] P. Anagnostis, J.C. Stevenson, D. Crook, D.G. Johnston, I.F. Godsland, Effects of menopause, gender and age on lipids and high-density lipoprotein cholesterol subfractions, Maturitas 81 (1) (2015) 62–68.
[9] P. Anagnostis, J.C. Stevenson, D. Crook, D.G. Johnston, I.F. Godsland, Effects of gender, age and menopausal status on serum apolipoprotein concentrations, Clin. Endocrinol. (Oxf) 85 (5) (2016) 733–740.
[10] A. Stefanska, K. Bergmann, G. Sypniewska, Metabolic syndrome and menopause: pathophysiology, clinical and diagnostic significance, Adv. Clin. Chem. 72 (2015) 1–75.
[11] R. Cui, H. Iso, H. Toyoshima, C. Date, A. Yamamoto, S. Kikuchi, T. Kondo, Y. Watanabe, A. Koizumi, Y. Inaba, A. Tamakoshi, J.S. Group, Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study, J. Epidemiol. 16 (5) (2006) 177–184.
[12] J.S. Hong, S.W. Yi, H.C. Kang, S.H. Jee, H.G. Kang, G. Bayasgalan, H. Ohrr, Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study, Maturitas 56 (4) (2007) 411–419.
[13] L. Song, L. Shen, H. Li, B. Liu, X. Zheng, L. Zhang, Y. Liang, J. Yuan, Y. Wang, Age at natural menopause and hypertension among middle-aged and older Chinese women, J. Hypertens. 36 (3) (2018) 594–600.
[14] L. Yan, X. Cao, S. Zeng, J. Yu, Z. Li, Z. Lian, F. Lv, J. Wang, Association of early menopause with angiographically-derived SYNTAX score: observational study, Medicine (Baltimore) 97 (51) (2018) e13723.
[15] D.F. Stroup, J.A. Berlin, S.C. Morton, I. Olkin, G.D. Williamson, D. Rennie, D. Moher, B.J. Becker, T.A. Sipe, S.B. Thacker, Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group, JAMA 283 (15) (2000) 2008–2012.
[16] S.B. Wells GA, D. O'Connell, J. Peterson, V. Welch, P. Tugwell, The Newcastle-ottawa Scale (NOS) for Assessing the Quality of Non-randomised Studies in Meta-analyses, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
[17] D. Appiah, P.J. Schreiner, E.W. Demerath, L.R. Loehr, P.P. Chang, A.R. Folsom, Association of age at menopause with incident heart failure: a prospective cohort

study and meta-analysis, J. Am. Heart Assoc. 5 (8) (2016).
[18] I.A. Ebong, K.E. Watson, D.C. Goff Jr., D.A. Bluemke, P. Srikanthan, T. Horwich, A.G. Bertoni, Association of menopause age and N-terminal pro brain natriuretic peptide: the Multi-Ethnic Study of Atherosclerosis, Menopause 22 (5) (2015) 527–533.
[19] M.N. Gunning, C. Meun, B.B. van Rijn, A. Maas, L. Benschop, A. Franx, E. Boersma, R.P.J. Budde, Y. Appelman, C.B. Lambalk, M.J.C. Eijkemans, B.K. Velthuis, J.S.E. Laven, B. Fauser, C. consortium, Coronary artery calcification in middle-aged women with premature ovarian insufficiency, Clin. Endocrinol. (Oxf) 91 (2) (2019) 314–322.
[20] Y.T. van der Schouw, Y. van der Graaf, E.W. Steyerberg, J.C. Eijkemans, J.D. Banga, Age at menopause as a risk factor for cardiovascular mortality, Lancet 347 (9003) (1996) 714–718.
[21] X. Xu, M. Jones, G.D. Mishra, Age at natural menopause and development of chronic conditions and multimorbidity: results from an Australian prospective cohort, Hum. Reprod. (2020).
[22] D. Zhu, H.F. Chung, A.J. Dobson, N. Pandeya, G.G. Giles, F. Bruinsma, et al., Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data, Lancet Public Health 4 (11) (2019) e553–e564.
[23] K. Fukuda, Y. Takashima, M. Hashimoto, A. Uchino, T. Yuzuriha, H. Yao, Early menopause and the risk of silent brain infarction in community-dwelling elderly subjects: the Sefuri brain MRI study, J. Stroke Cerebrovasc. Dis. 23 (5) (2014) 817–822.
[24] M.C. Honigberg, S.M. Zekavat, K. Aragam, P. Finneran, D. Klarin, D.L. Bhatt, J.L. Januzzi Jr., N.S. Scott, P. Natarajan, Association of premature natural and surgical menopause with incident cardiovascular disease, JAMA (2019).
[25] P. Anagnostis, S.A. Paschou, N. Katsiki, D. Krikidis, I. Lambrinoudaki, D.G. Goulis, Menopausal hormone therapy and cardiovascular risk. Where are we now? Curr. Vasc. Pharmacol. 17 (6) (2019) 564–572.
[26] J.F. Reckelhoff, Gender differences in hypertension, Curr. Opin. Nephrol. Hypertens. 27 (3) (2018) 176–181.
[27] S.R. Salpeter, J.M. Walsh, T.M. Ormiston, E. Greyber, N.S. Buckley, E.E. Salpeter, Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women, Diabetes Obes. Metab. 8 (5) (2006) 538–554.
[28] A. Sherwood, L.K. Hill, J.A. Blumenthal, K.S. Johnson, A.L. Hinderliter, Race and sex differences in cardiovascular alpha-adrenergic and beta-adrenergic receptor responsiveness in men and women with high blood pressure, J. Hypertens. 35 (5) (2017) 975–981.
[29] T.S. Bowman, J.M. Gaziano, J.E. Buring, H.D. Sesso, A prospective study of cigarette smoking and risk of incident hypertension in women, J. Am. Coll. Cardiol. 50 (21) (2007) 2085–2092.
[30] C. Westhoff, P. Murphy, D. Heller, Predictors of ovarian follicle number, Fertil. Steril. 74 (4) (2000) 624–628.
[31] T. Matikainen, G.I. Perez, A. Jurisicova, J.K. Pru, J.J. Schlezinger, H.Y. Ryu, J. Laine, T. Sakai, S.J. Korsmeyer, R.F. Casper, D.H. Sherr, J.L. Tilly, Aromatic hydrocarbon receptor-driven Bax gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals, Nat. Genet. 28 (4) (2001) 355–360.
[32] B. Leng, Y. Jin, G. Li, L. Chen, N. Jin, Socioeconomic status and hypertension: a meta-analysis, J. Hypertens. 33 (2) (2015) 221–229.
[33] E.B. Gold, S.L. Crawford, N.E. Avis, C.J. Crandall, K.A. Matthews, L.E. Waetjen, J.S. Lee, R. Thurston, M. Vuga, S.D. Harlow, Factors related to age at natural menopause: longitudinal analyses from SWAN, Am. J. Epidemiol. 178 (1) (2013) 70–83.
[34] S.M. Hegde, S.D. Solomon, Influence of physical activity on hypertension and cardiac structure and function, Curr. Hypertens. Rep. 17 (10) (2015) 77.
[35] U. Stepaniak, K. Szafraniec, R. Kubinova, S. Malyutina, A. Peasey, H. Pikhart, A. Pajak, M. Bobak, Age at natural menopause in three central and eastern European urban populations: the HAPIEE study, Maturitas 75 (1) (2013) 87–93.
[36] J.S. Laven, Genetics of early and normal menopause, Semin. Reprod. Med. 33 (6) (2015) 377–383.
[37] L. Stolk, J.R. Perry, D.I. Chasman, C. He, M. Mangino, P. Sulem, et al., Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways, Nat. Genet. 44 (3) (2012) 260–268.
[38] S. Das, S. Purkayastha, H. Roy, A. Sinha, Y. Choudhury, Polymorphisms in DNA repair genes increase the risk for type 2 diabetes mellitus and hypertension, Biomol. Concepts 9 (1) (2018) 80–93.
[39] P. Anagnostis, A. Karagiannis, K. Tziomalos, V.G. Athyros, M. Kita, D.P. Mikhailidis, Endocrine hypertension: diagnosis and management of a complex clinical entity, Curr. Vasc. Pharmacol. 8 (5) (2010) 646–660.
[40] S.M. Harman, D.M. Black, F. Naftolin, E.A. Brinton, M.J. Budoff, M.I. Cedars, et al., Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial, Ann. Intern. Med. 161 (4) (2014) 249–260.