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Association of age at menopause and duration from onset of menopause with cardiovascular outcomes, intermediate vascular traits and all-cause mortality: a systematic review and meta-analysis of observational studies

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ABSTRACT

Importance: Up to 10% of women experience natural menopause by age of 45. Therefore, an increased risk of cardiovascular disease (CVD) and all-cause mortality associated with early menopause, if confirmed, could present an important factor affecting risk of disease and mortality among middle-aged and older women.

Objectives*:* To systematically review and meta-analyze studies evaluating the impact of age at menopause and duration since onset of menopause on intermediate CVD endpoints, CVD outcomes and all-cause mortality.

Data sources: Medical databases (Medline, EMBASE and Web of Science) until March 2015**.**

Study Selection: Studies (observational cohort, case-control or cross-sectional) that assessed age at menopause or duration since onset of menopause as exposures, and risk of cardiovascular outcomes and intermediate CVD endpoints, in perimenopausal, menopausal, or postmenopausal women.

Data Extraction: Data were extracted by two independent reviewers using a pre-designed data collection form.

Main outcomes and Measures: CVD outcomes (composite CVD, fatal and non-fatal coronary heart disease (CHD) and overall stroke and stroke mortality), CVD-mortality, all-cause mortality and intermediate CVD endpoints.

Results: Out of initially identified references, 32 studies were selected, including 310,329 non-overlapping women. Women with a menopausal age of younger than 45 years compared to women with a menopausal age of 45 years or older, the relative risk (RR) [95% confidence intervals (CI)] was 1.50(1.28-1.76) for overall CHD, 1.11(1.03-1.20) for fatal CHD, 1.23 (0.98-1.53) for overall stroke, 0.99 (0.92-1.07) for stroke mortality, 1.19(1.08-1.31) for CVD mortality and 1.12(1.03-1.21) for all-cause mortality. For women with a menopausal age between 50-54 years compared to women with a menopausal age of younger than 50 years, there was a decreased risk of fatal CHD (RR:0.87(95%CI:0.80-0.96)), and no effect on stroke. Duration since menopause in relation to risk of developing intermediate cardiovascular traits or CVD outcomes was reported in 4 observational studies, reporting no consistent results.

Conclusions and Relevance: The findings of this review indicate an excess CHD, CVD-mortality and overall mortality risk in women who have an early or premature menopause.

INTRODUCTOIN

Risk of cardiovascular disease (CVD) increases with age and, as women tend to live longer than men, the absolute number of women living with and dying from CVD is greater than men[1]. Therefore, early recognition of women at high risk for CVD and timely implementation of appropriate lifestyle or therapeutic interventions are of tremendous public health importance.

Adverse changes in cardiovascular risk factors occur around the menopausal transition[2-4], highlighting the need of CVD risk assessment during this period and of introduction of appropriate preventive or treatment modalities. While the average age at menopause is 51 years[5], menopausal age varies significantly among women with a range between 40-60 years of age. Women who have a premature or early menopause may not only be at risk from a younger age, but may also live more years of their lives at an increased risk of adverse outcomes[6-83–5]. This highlights the need to evaluate the role of both menopausal age and time since onset of menopause as risk factors for CVD.

Age at menopause may be a marker for not only reproductive ageing but also for general health and somatic ageing[9]. Menopause has been proposed as the first step in a causal pathway that, due to hormonal changes, eventually results in organ dysfunction[10]. A hormonal change cited as an important determinant in post-menopausal CVD development is the decrease in endogenous estrogen synthesis[11]. In a health vessel, estrogens are involved in the relaxation and expansion of blood vessels, helping to accommodate blood flow, and consequently, decreased levels of oestrogen would result in stiffer blood vessels [12]. Furthermore, loss of the ovarian function through menopause is associated with the activation of the renin-angiotensin-aldosterone system, leading to downstream endothelial dysfunction, inflammation and immune dysfunction[13]. These processes are associated with obesity, diabetes and hypertension[13]. Thus, early menopause has been hypothesized to be detrimental to cardiovascular health, due to the early cessation of the protective effect of endogenous oestrogen. Longer duration since menopause would therefore result in a greater risk of intermediate and hard CVD outcomes. However, the extent to which age of menopause and duration since menopause is associated with the risk of death and CVD and its intermediate risk factors remains unclear. A previous review[14] published on the topic investigating age of menopause with CVD, did not look at years since menopause, was based only on few studies and lack sufficient detail (for example, associations of different age categories of menopause with CVD outcomes and the effect with CVD subtypes

or all-cause mortality). A need exist, therefore, for an adequately powered, comprehensive assessment of menopause in association with subsequent adverse cardiovascular outcomes.

We conducted a systematic review and meta-analysis of all available observational evidence to quantify the associations of age at menopause and duration since onset of menopause with (i) primarily clinical CVD outcomes and intermediate vascular traits; and (ii) all-cause mortality.

METHODS

Data sources and search strategy

This review was conducted in accordance with the PRISMA and MOOSE guidelines (**eAppendix 1** and **2**). Two independent reviewers, in duplication, sought studies published up to March, 2015 using Medline, EMBASE and Web of Science electronic databases. The computer-based searches combined terms related to the exposure (eg, *age at menopause, duration from onset of menopause*) and outcomes (eg, *inflammation, cardiovascular disease, mortality*), without any language restriction. Details on the search strategy are provided in **eAppendix 3**.

Study selection and eligibility criteria, data extraction and quality assessment and data synthesis and analysis are described in details in the **eAppendix 4**.

RESULTS

Identification of relevant studies

The search strategy identified 9,444 citations. Following initial screening based on titles and abstracts, full-texts of 73 articles were evaluated further. Of these articles, 40 articles were excluded for reasons shown in **Figure 1**. The remaining 33 articles, based on 32 unique studies, met inclusion criteria, and therefore, were included in the review.

General characteristics of the included studies

Appendix Tables S1-S2 summarize the key characteristics of the included studies. All studies except one evaluated the risk in relation to the age at menopause, with 4 additionally evaluating the risk in relation to duration since menopause. In aggregate, in all included studies, 342,284 women were included in this review. However, not all studies provided relevant data that could be meta-analysed and it was not possible

to combine any results related to duration since menopause, although an analysis of age at menopause was possible. Consequently, there were 297,496 participants in the age at menopause analysis, which included 44,962 cases. The majority of studies (n=24) were prospective cohort studies, whilst the remaining studies were case-control (n=2) or cross-sectional studies (n=6). Overall, age at menopause in relation to risk of developing CVD intermediates or outcomes, or all-cause mortality was reported in 31 studies. Among the prospective cohort and case-control studies, 14 studies were judged to be at low risk of bias, 10 were at medium risk, and two studied were evaluated to be at high risk of bias (**Appendix Tables S1-S2**).

Association of age at menopause with incident (composite) cardiovascular disease, coronary heart disease and stroke

There was only one study examining the association between age of menopause and incidence of CVD and showed a RR of 1.56 (1.08-2.26) for a menopausal age of younger than 45 years compared to a menopausal age of 45 years or older.[15] In the meta-analysis of 50,125 participants and 1,217 CHD events, pooled RR (95%CI), comparing a menopausal age of younger than 45 years relative to a menopausal age of 45 years or older and adjusted for several established CVD risk factors and other potential confounders (such as, age, smoking status, lipids, hypertension, BMI, history of cardiometabolic disease, hormone therapy), was 1.50 (1.28-1.76) (**Figure 2**). Corresponding results, based on the meta-analysis of 49,246 participants and 770 stroke events, were 1.23 (0.98-1.53) for stroke risk (**Figure 2**). There was little evidence of between-study heterogeneity in these meta-analyses: CHD and stroke analyses: I^2=0% and χ^2: p=0.65, and I^2=51% and χ^2: p=0.09, respectively.

When women with a menopausal age between 45-49 years were compared to women with a menopausal age of 50 years or older, the corresponding adjusted pooled RRs (95%CI) were 1.12 (0.95-1.31; based on 36,483 participants and 784 CHD events) for CHD risk and 0.95 (0.74-1.23; based on 109,928 participants and 536 stroke events) for stroke risk (**Appendix Figure S1-S2**). There was no evidence of between-study heterogeneity in both these analyses: I^2 =0% and χ^2: p=0.37, I^2=0% and χ^2:p=0.78 for CHD and stroke analysis respectively.

Due to differences in age categories, it was not possible to include one study in these meta-analyses. Lisabeth and colleagues[16] evaluated risk of ischaemic stroke for women between 42-54 years old at menopause compared to women with a premature menopause (before 42 years of age). They found a decreased risk of

ischaemic stroke (RR=0.50; 95%CI: 0.29-0.89) for women who reported being between 42-54 years old at menopause relative to prematurely menopausal women. An additional lower risk was found for women who had menopause after 55 years of age (RR=0.31; 95%CI: 0.13-0.76).

Association of age at menopause with all-cause, (composite) cardiovascular disease, coronary heart disease and stroke mortality

Pooling results of the risk for different mortality outcomes estimated for women with a menopausal age of younger than 45 years relative to a menopausal age of 45 years or older, adjusted for several established CVD risk factors and other potential confounders, yielded combined RRs (95% CI) of 1.12 (1.03-1.21) for all-cause mortality (109,898 participants and 31,427 all-cause deaths), 1.19 (1.08-1.31) for CVD mortality (65,653 participants and 6,979 CVD-deaths), 1.11 (1.03-1.20) for CHD mortality (118,150 participants and 8,737 CHD-deaths) and 0.99 (0.92-1.07) for stroke mortality (143,833 participants and 6,706 stroke-deaths) (**Figure 3**). There was evidence of between-study heterogeneity for all-cause mortality analysis (I^2=63% (95%CI: 20-83%) and χ^2: p=0.009) whereas little evidence of between-study heterogeneity was found for the other analyses (**Figure 3**). Corresponding pooled RR (95%CI) for all-cause mortality, CVD, CHD and stroke mortality comparing menopausal age of 45-49 years to menopausal age of 50 years or older were 1.03 (1.00-1.05) for all-cause mortality (90,691 participants, 28,188 all-cause deaths), 0.99 (0.92 -1.07) for CVD mortality (62,995 participants, 5,786 CVD-deaths), 0.98 (0.93 -1.04) for CHD mortality (121,444 participants, 5,954 CHD-deaths) and 1.03 (0.91 -1.16) for stroke mortality (141,175 participants, 6,320 stroke-deaths) **(Figure 4** and **Appendix Figures S1-S4)**. When comparing menopausal age between 50-54 years relative to menopausal age of younger than 50 years, the corresponding pooled RRs (95%CI) were 1.02 (0.89-1.15) for all-cause mortality (7,341 participants; 1,408 all-cause deaths), 0.96 (0.74-1.24) for CVD mortality (12,108 participants; 2,256 CVD-deaths), 0.87 (0.80- 0.96) for CHD mortality (31,417 participants;3,279 CHD-deaths) and 1.19 (0.93-1.52) for stroke mortality (12,108 participants;623 stroke deaths) (**Appendix Figures S5-S8**). There was little evidence of between-study heterogeneity in all these analyses (**Figure 4** and **Appendix Figures S1-S8**). Due to differences in age categories, it was not possible to include one study in the pooled results[17]. Wu and colleagues reported an increased risk of all-cause mortality (RR=1.16, 95% CI: 1.04-1.29) for women of menopausal age < 46.64 years compared to women aged between 48.80-50.15 years at menopause (**Appendix Table S3**).

Association of age at menopause with intermediate cardiovascular traits

Only two studies were identified that evaluated risk for carotid atherosclerosis. Pooled RR (95% CI) for the risk of carotid atherosclerosis was 0.74 (0.63-0.87) when comparing women with a menopause age at or after 50 years to women with a menopausal of younger than 50 (3,388 participants) (**Appendix Figure S9**). There was, however, evidence of between study heterogeneity: I^2 =69% (95%CI:0, 93%) and χ^2: p=0.073. Three studies could not be included in the meta-analysis of intermediate cardiovascular traits[11,12] (**Appendix Table S3**). They all evaluated risk of diabetes depending on age at menopause. Two of the studies found no excess risk for Chinese women who experienced menopause before or after age 50, relative to women who underwent the menopause at age approximately 50 years. The same findings were observed in a study of European women; where relative to women who experienced menopause between the ages of 50-54, neither women who experienced an early menopause, between 45-49 years old, nor women who had their menopause after age 55 were at greater risk for diabetes.

Years since menopause with CVD outcomes and intermediate cardiovascular traits

Duration since menopause in relation to risk of developing intermediate cardiovascular traits or CVD outcomes was reported in four observational studies. Of these, two studies reported risk of overall CVD outcomes, and three studies estimated risk of intermediate cardiovascular traits. The age at baseline ranged from 40 to 81. Two studies, conducted in Italy and China, evaluated risk of CVD outcomes, including CHD, stroke and composite CVD outcomes (**Appendix Table S4**), and three studies assessed risk of intermediate cardiovascular traits, including metabolic syndrome, obesity or BMI, and hypertension (**Appendix Table S5**) in Korean, Chinese and German populations. Owing to a substantial heterogeneity in the comparison groups used across these studies, no quantitative synthesis could be performed. The findings of these studies, therefore, were only qualitatively reviewed. In a Chinese population[13], relative to women less than 1 year post menopause, women 2-6 years post menopause were at a greater risk of CVD, with evidence for an increased risk after 6 years. In the same study, there was also evidence for a greater risk of CHD and stroke more than 1 year post menopause. However, these findings were in contrast to those in an Italian population[14], which found no increased risk of myocardial infarction in post-menopausal women less than 10 years, 10-20 years and more than 20 years post menopause compared with pre- or peri-menopausal women. Stockl and colleagues[15] found no association between time since menopause and the presence of carotid

atherosclerosis, however time since menopause was dichotomised into broad groups, comparing women less than 15 years post menopause, to women more than 15 years post-menopause.

Relative to premenopausal women, postmenopausal Korean women were at greater risk of metabolic syndrome, and this risk increased with the time since menopause, with the greatest risk found in women between 10 and 14 years post-menopause[16]. Within the same population, there was evidence for increased risk of hypertension, abdominal obesity and high glucose levels, in postmenopausal women; however, risk did not vary with duration since menopause. Conversely, no increased risk of obesity, hypertension or diabetes was found in Chinese women who were more than 2 years post-menopause compared with women less than 1 year post-menopause[13]. Similarly, within the same study, systolic and diastolic blood pressure, BMI, WHR, and glucose levels did not vary with time since menopause.

Sensitivity Analysis and Publication bias

The effect estimates for the association between early menopause and coronary heart disease, stroke, all-cause mortality, cardiovascular mortality and coronary heart disease mortality remained broadly similar when studies were grouped by location, type of menopause as well as adjustment for socioeconomic status or hormone replacement therapy (**Table 1**). Under visual examination, Begg's funnel plots for those analyses that included a minimum of 5 studies were mostly symmetrical (**Appendix Figure S10**), with possible exception of studies evaluating overall CHD risk and CHD mortality risk in women with menopausal age of less than 45 years. However, there was no statistical evidence of publication bias based on Egger's test, which was non-significant ($P>0.05$) for all analyses that involved 5 or more studies.

DISCUSSION

Overall, we found that women who experienced an early menopause appear to have an excess risk of CHD, CVD-mortality and all-cause mortality and no association with stroke risk. By contrast, being 45-49 years at menopause compared to ≥50 years had no apparent association with adverse outcomes except for an increased risk of carotid atherosclerosis. Only a few studies evaluating risk in relation to duration since menopause could be found, reporting conflicting results.

Interpretation of findings

The current study supports previous findings that there is an increased risk of CVD with premature or early menopause, specifically identifying a greater risk with CHD, and potentially with carotid atherosclerosis. The findings of this systematic review on the risk of CVD associated with early menopause generally concur with and further extend a previous review[14], which reported an increased risk of CVD for women at menopausal age of 50 years or younger compared with menopausal age ≥51 years. However, the findings of the previous review were based only on few prospective studies (7 prospective cohort studies) and therefore the authors were not able to compare other age categories with the risk of CVD. In addition, our study examined the association between age of menopause with all-cause mortality and CVD subtypes, providing a more detailed assessment of the nature and magnitude of the association between menopause and risk of disease and mortality in women. Despite the large number of participants included (n=12,108), our finding on an association between premature or early menopause with carotid atherosclerosis needs to be interpreted with some caution, given the relatively small number of studies currently available and due to the presence of between-study heterogeneity.

The association between early menopause and CHD risk may have several mechanistic interpretations. Early loss of the ovarian function through menopause may lead to long term activation of the renin-angiotensin-aldosterone system, leading to endothelial dysfunction, inflammation and immune dysfunction, and therefore causing vascular damage[13,18]. This process may be partially mediated via the membrane G protein-coupled estrogen receptor[13]. Also, menopause marks the start of a biological mechanism, led by hormonal changes, which causes tissue damage and organ dysfunction[10]. The multi-organ impact of the menopause proposed by this theory, and supported by findings of an increased risk of depression, dementia and osteoporosis[19-21], seems to be consistent with the increased risk of all-cause mortality found in the current analysis.

Alternatively, there may be shared risk factors, either genetic or environmental, that result in early menopause and also increase the risk of adverse health outcomes[10]. In this case, early menopause could be considered as only a marker of risk. In support of a shared genetic basis, a large-scale genome-wide association study of age at menopause identified a number of loci, including the ones relevant to CVD, that were involved in inflammatory response, oxidative stress and genome stability[22]. Speculative environmental factors could include obstetric history, such as parity or having a stillbirth. These explanations are not

necessarily mutually exclusive, however, and a combination of these mechanisms may be responsible for the observed increase in CVD and all-cause mortality risk.

Strengths and limitations

This is the first comprehensive quantitative review of observational evidence that assessed both the associations of age at menopause and duration since menopause with clinical CVD outcomes, intermediate cardiovascular traits and all-cause mortality. Our analyses included >300,000 women and evaluated the risk of a wide-range of outcomes in relation to various menopausal age-groups. However, strengths and limitations in the current study merit careful consideration. First, all systematic reviews are prone to reporting bias, owing to the possibility that studies with more extreme results are more likely to be published. Nonetheless, as demonstrated by Egger's test estimates, there was little evidence of publication bias in the current analyses. Additionally, all meta-analyses are limited by the quality of the individual published studies. However, the majority of studies included in the current analyses were of high quality, with a low risk of bias. In order to allow for a uniform analysis, it was necessary to combine some overlapping age-groups for some studies (eg, studies that reported estimates for menopausal age of 50-54 years and those based on >50 years). This might have introduced some heterogeneity into the analyses. Additionally, due to differential categorisation of menopausal age in various studies or only few studies evaluating a particular outcome (eg, carotid atherosclerosis), some of our analysis are based on a small number of studies. Therefore, these results need to be interpreted with caution, particularly those which yielded moderate between-study heterogeneity estimates. Furthermore, the lack of studies evaluating risk in relation to duration since menopause limited us from performing any meaningful quantitative synthesis using this exposure. Most studies that were identified adjusted for a range of relevant confounders, although one study was entirely unadjusted[23], and three only adjusted for age[24-26]. Many studies did not examine the impact of important determinants of age at natural menopause, such as socioeconomic factors, number of births and lifestyle factors (smoking, alcohol intake and physical activity). Therefore, the risk of residual confounding cannot be entirely ruled out. A specific concern is confounding from HRT use, which particularly may vary depending on the age at menopause. Women who experience menopause at a younger age may be more likely to start HRT than women who reach menopause in their 50s. Consequently, hormone therapy use may confound the relationship between age at menopause and CVD risk. Indeed, HRT was only adjusted for in a

minority of identified studies[27-31]. Moreover, since the number of available studies in some of our analysis was small, it precluded our ability to comprehensively assess the impact of type of menopause in our results. However, the complex interplay between exogenous hormones and CVD risk is not fully understood, and the results regarding HRT and CVD risk are conflicting[32-34].

Clinical and scientific implications

This review underscores a potential increased risk of adverse cardiovascular outcomes in women who experience early or premature menopause, which may have important clinical and public health implications. This study has also identified a number of gaps in the literature concerning the relations between duration since menopause, age at menopause and intermediate cardiovascular traits and CVD outcomes. There were only few studies focusing on intermediate cardiovascular endpoints leading to conflicting results and therefore impeding meaningful interpretation. These intermediate factors are of potential importance in interpretation of the observed excess cardiovascular risk, and thus, further research focusing on the intermediate cardiovascular traits is required. Finally, other areas of interest are the relation between age at menopause and duration since menopause and whether there are common determinants for premature menopause and CVD. The observed link between premature menopause and CVD risk may be modified by differing durations since the onset of the menopause among women. The excess CHD risk may be driven in part by a longer duration since the onset of the menopause in women with early menopause. Alternatively, the increased relative risk found with premature menopause may be present only in the first years after menopause, ameliorating over time. Thus far, the known risk factors for premature menopause, include genetics[21]; reproductive factors, i.e. parity and age at menarche[31]; as well as lifestyle factors such as smoking and BMI[31]. However, the role of these factors in mediating the association between premature menopause and CVD remains unclear and therefore warrants further research.

CONCLUSION

The findings of this review indicate an excess coronary heart disease, cardiovascular mortality and overall mortality risk in women who have an early or premature menopause below the age of 45 years. However, this review also highlights important gaps in the existing literature, calling for further research to reliably

establish whether cardiovascular risk may vary in relation to the duration since menopause and the mechanisms leading early menopause to cardiovascular outcomes and mortality.

Author's contribution: OHF conceived and designed the study. TM, COW and SK screened title/abstract, obtained full text, determined eligibility of articles and participated in data extraction. TM, COW, RC, MK and OHF participated in data synthesis/analysis and interpretation of the data. TM, COW, RC, MK and OHF drafted the final manuscript. All authors contributed to the critical revision of the manuscript and approved the final version. TM and OHF had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Thompson RH, Snyder AE, Burt DR, Greiner DS, Luna MA. Risk Screening for Cardiovascular Disease and Diabetes in Latino Migrant Farmworkers: A Role for the Community Health Worker. *J Commun Health.* Feb 2015;40(1):131-137.

2. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocr Metab.* Jun 2003;88(6):2404-2411.

3. Agrinier N, Cournot M, Dallongeville J, et al. Menopause and modifiable coronary heart disease risk factors: a population based study. *Maturitas.* Mar 2010;65(3):237-243.

4. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. *Int J Obes Relat Metab Disord.* Feb 2000;24(2):226-231.

5. Velde ERT, Pearson PL. The variability of female reproductive ageing. *Hum Reprod Update.* Mar-Apr 2002;8(2):141-154.

6. Rocca WA, Grossardt BR, Miller VM, Shuster LT, Brown RD, Jr. Premature menopause or early menopause and risk of ischemic stroke. *Menopause.* Mar 2012;19(3):272-277.

7. Jacobsen BK, Heuch I, Kvale G. Age at natural menopause and all-cause mortality: A 37-year follow-up of 19,731 Norwegian women. *Am J Epidemiol.* May 15 2003;157(10):923-929.

8. vanderSchouw YT, vanderGraaf Y, Steyerberg EW, Eijkemans MJC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet.* Mar 16 1996;347(9003):714-718.

9. Snowdon DA, Kane RL, Beeson WL, et al. Is Early Natural Menopause a Biologic Marker of Health and Aging. *Am J Public Health.* Jun 1989;79(6):709-714.

10. Rocca WA, Shuster LT, Grossardt BR, et al. Long-term effects of bilateral oophorectomy on brain aging: unanswered questions from the Mayo Clinic Cohort Study of Oophorectomy and Aging. *Womens Health (Lond Engl).* Jan 2009;5(1):39-48.

11. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. *Circulation.* Mar 9 1999;99(9):1165-1172.

12. Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med.* Jun 10 1999;340(23):1801-1811.

13. Zhao Z, Wang H, Jessup JA, Lindsey SH, Chappell MC, Groban L. Role of estrogen in diastolic dysfunction. *Am J Physiol Heart Circ Physiol.* Mar 1 2014;306(5):H628-640.

14. Atsma F, Bartelink MLEL, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause-the Journal of the North American Menopause Society.* Mar-Apr 2006;13(2):265-279.

15. Pfeifer EC, Crowson CS, Amin S, Gabriel SE, Matteson EL. The influence of early menopause on cardiovascular risk in women with rheumatoid arthritis. *J Rheumatol.* Jul 2014;41(7):1270-1275.

16. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at natural menopause and risk of ischemic stroke: the Framingham heart study. *Stroke.* Apr 2009;40(4):1044-1049.

17. Wu XY, Cai H, Kallianpur A, et al. Age at Menarche and Natural Menopause and Number of Reproductive Years in Association with Mortality: Results from a Median Follow-Up of 11.2 Years among 31,955 Naturally Menopausal Chinese Women. *Plos One.* Aug 4 2014;9(8).

18. Ruiz-Ortega M, Lorenzo O, Ruperez M, et al. Role of the renin-angiotensin system in vascular diseases: expanding the field. *Hypertension.* Dec 1 2001;38(6):1382-1387.

19. Alexander DD, Cushing CA, Lowe KA, Sceurman B, Roberts MA. Meta-analysis of animal fat or animal protein intake and colorectal cancer. *Am J Clin Nutr.* May 2009;89(5):1402-1409.

20. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. *Arch Gen Psychiatry.* Apr 2006;63(4):385-390.

21. Bove R, Secor E, Chibnik LB, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology.* Jan 21 2014;82(3):222-229.

22. Stolk L, Perry JR, Chasman DI, et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. *Nat Genet.* Mar 2012;44(3):260-268.

23. Svejme O, Ahlborg HG, Nilsson JA, Karlsson MK. Early menopause and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. *BJOG.* Jun 2012;119(7):810-816.

24. Joakimsen O, Bonaa KH, Stensland-Bugge E, Jacobsen BK. Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis: The Tromso Study. *Journal of Clinical Epidemiology.* May 2000;53(5):525-530.

25. Lapidus L, Bengtsson C, Lindquist O. Menopausal age and risk of cardiovascular disease and death. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Acta Obstet Gynecol Scand Suppl.* 1985;130:37-41.

26. Cooper GS, Ephross SA, Weinberg CR, Baird DD, Whelan EA, Sandler DP. Menstrual and reproductive risk factors for ischemic heart disease. *Epidemiology.* May 1999;10(3):255-259.

27. Qiu CS, Chen HJ, Wen JP, et al. Associations Between Age at Menarche and Menopause With Cardiovascular Disease, Diabetes, and Osteoporosis in Chinese Women. *J Clin Endocr Metab.* Apr 2013;98(4):1612-1621.

28. Fioretti F, Tavani A, Gallus S, Franceschi S, La Vecchia C. Menopause and risk of non-fatal acute myocardial infarction: an Italian case-control study and a review of the literature. *Hum Reprod.* Mar 2000;15(3):599-603.

29. de Kleijn MJJ, van der Schouw YT, Verbeek ALM, Peeters PHM, Banga JD, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol.* Feb 15 2002;155(4):339-345.

30. Lee JS, Hayashi K, Mishra G, Yasui T, Kubota T, Mizunuma H. Independent Association between Age at Natural Menopause and Hypercholesterolemia, Hypertension, and Diabetes Mellitus: Japan Nurses' Health Study. *J Atheroscler Thromb.* 2013;20(2):161-169.

31. Lokkegaard E, Jovanovic Z, Heitmann BL, Keiding N, Ottesen B, Pedersen AT. The association between early menopause and risk of ischaemic heart disease: Influence of Hormone Therapy. *Maturitas.* Jan 20 2006;53(2):226-233.

32. Manson JE, Bassuk SS. Invited commentary: Hormone therapy and risk of coronary heart disease - Why renew the focus on the early years of menopause? *Am J Epidemiol.* Sep 1 2007;166(5):511-517.

33. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* Apr 4 2007;297(13):1465-1477.

34. Prentice RL, Manson JE, Langer RD, et al. Benefits and Risks of Postmenopausal Hormone Therapy When It Is Initiated Soon After Menopause. *Am J Epidemiol.* Jul 1 2009;170(1):12-23.

Table 1 Relative risks of cardiovascular outcomes and mortality for age at menopause < 45 years with menopausal age ≥ 45 years as reference category by study characteristics and type of menopause

Study Characteristics		Number of studies	Relative Risks (95% Confidence Interval)	*P*-value[a]
Age at menopause < 45 years and risk of incident CHD with menopausal age ≥ 45 years as reference category				
Location	Europe	1	1.47 (1.14, 1.90)	0.83
	North America	4	1.52 (1.25, 1.86)	
Adjustment for SES	Yes	0	NA	NA
	No	5	1.50 (1.28, 1.76)	
Adjustment for HT	Yes	2	1.52 (1.20, 1.93)	0.89
	No	3	1.49 (1.21, 1.84)	
Menopause Type	Natural Menopause	3	1.49 (1.21, 1.83)	0.96
	Unnatural Menopause	2	1.87 (0.26, 13.39)	
Age at menopause < 45 years and risk of total stroke with menopausal age ≥ 45 years as reference category				
Location	North America	3	1.29 (0.80, 2.06)	0.78
	Asia	2	1.16 (0.59, 2.27)	
Adjustment for SES	Yes	0	NA	NA
	No	5	1.23 (0.98, 1.53)	
Adjustment for HT	Yes	1	2.03 (1.00, 4.11)	0.22
	No	4	1.14 (0.81, 1.60)	
Menopause Type	Natural Menopause	3	0.93 (0.70, 1.24)	
	Unnatural Menopause	2	1.50 (0.79, 2.83)	0.19
Age at menopause < 45 years and risk of mortality with menopausal age ≥ 45 years as reference category				
Location	Europe	1	1.18 (1.06, 1.32)	0.62
	North America	5	1.09 (0.98, 1.21)	
	Asia	2	1.19 (1.04, 1.35)	
Adjustment for SES	Yes	4	1.10 (0.94, 1.28)	0.46
	No	4	1.15 (1.08, 1.23)	
Adjustment for HT	Yes	4	1.07 (0.95, 1.21)	0.23
	No	4	1.16 (1.08, 1.25)	
Menopause Type	Natural Menopause	6	1.09 (0.99, 1.20)	0.35
	Unnatural Menopause	2	1.23 (1.20, 1.53)	
Age at menopause < 45 years and risk of CVD mortality with menopausal age ≥ 45 years as reference category				
Location	Europe	1	1.32 (1.13, 1.54)	0.18
	North America	5	1.04 (0.83, 1.29)	
	Asia	2	1.15 (0.98, 1.36)	
Adjustment for SES	Yes	4	1.10 (0.97, 1.26)	0.08
	No	4	1.32 (1.13, .54)	
Adjustment for HT	Yes	4	1.10 (0.83, 1.46)	0.48
	No	4	1.22 (1.07, 1.39)	
Menopause Type	Natural Menopause	NA	NA	NA

	Unnatural Menopause	NA	NA	

NA, not applicable; SES; socioeconomic status; HT, hormone replacement therapy.
[a] P-value for heterogeneity was evaluated using random effects meta-regression.

Figure 1. Flow diagram of studies included in the current review

Figure 2. Age at menopause < 45 years and risk of incident coronary heart disease and total stroke with menopausal age ≥ 45 years as reference category

Legend for Figure 2

+, adjusted for age; ++, adjusted for vascular risk factors (covariates are listed in the Appendix Table S1); Assessment of heterogeneity A) for incident coronary heart disease, $X^2 = 2.49$, I^2=0%, 0 to 79%; *P* = 0.647; B) for total stroke, $X^2 = 8.12$, I^2=51%, 0 to 82%; P = 0.087

Figure 3. Age at menopause < 45 years and risk of all-cause mortality, cardiovascular, coronary heart disease and stroke mortality with menopausal age ≥ 45 years as reference category

Legend for Figure 3

+, adjusted for age; ++, adjusted for vascular risk factors (covariates are listed in the Appendix Table S1); Assessment of heterogeneity: A) for all-cause mortality, X^2 = 18.80, I^2=63%, 20 to 83%; *P* = 0.009; B) for cardiovascular disease mortality, X^2 = 5.74, I^2=30%, 0 to 73%; *P* = 0.219; C) for coronary heart disease mortality, X^2 = 8.65, I^2=42%, 0 to 77%; *P* = 0.124; D) for stroke mortality, X^2 = 7.59, I^2=34%, 0 to 74%; *P* = 0.181

Figure 4. Age at menopause 45-49 years and risk of incident cardiovascular disease and all-cause mortality with menopausal age ≥ 50 years as reference category

Legend for Figure 4

+, adjusted for age; ++, adjusted for vascular risk factors (covariates are listed in the Appendix Table S1); Assessment of heterogeneity: A) for cardiovascular disease, $X^2 = 0.62$, I^2=0%, 0 to 85%; P = 0.891; B) for all-cause mortality, $X^2 = 5.19$, I^2=23%, 0 to 68%; P = 0.268