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REVIEW ARTICLE

Lipid profile differences during menopause: a review with meta-analysis

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Abstract

Objectives: The aim of the study was to determine lipid profile differences between premenopausal and postmenopausal women.

Methods: The present review used a meta-analytic approach. Sixty-six studies were included, which provided a total sample of 114,655 women consisting of 68,394 that were premenopausal and 46,261 that were postmenopausal.

Results: The main findings were that (1) lipoproteins were significantly higher in postmenopausal women compared to premenopausal women including triglycerides (0.27 mmol/L, 95% confidence interval, 0.22-0.31), total cholesterol (0.58, 0.50-0.65), low-density lipoprotein (0.45, 0.38-0.53), and total cholesterol to high-density lipoprotein levels (0.39, 0.16-0.62); (2) there was no difference in high-density lipoprotein levels between premenopausal and postmenopausal women (0.02, −0.00-0.04); and (3) the differences in lipid levels was partly attributable to the mean age difference between premenopausal and postmenopausal women.

Conclusions: These findings are important as they provide precise estimates of lipid differences in women around menopause. Furthermore the results suggest that the unfavorable lipid profile that develops in postmenopausal women puts them at higher risk of cardiovascular disease such as heart disease and stroke if appropriate lifestyle/pharmacological interventions are not implemented.

Key Words: Cholesterol – Female – Lipoproteins – Postmenopausal – Premenopausal.

Menopause is characterized by the progressive decline of endogenous estrogen levels and is defined as the final menstrual period.[1] As women progress from a premenopausal to postmenopausal state, deleterious changes in serum lipid profiles have been shown to occur, as demonstrated by the increased levels of low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG).[2,3] Previous narrative reviews that have discussed lipid changes in women around menopause have been limited by a paucity of quantitative estimates,[4-6] which are typically made available through a systematic review of the literature with meta-analyses. This has not yet been done for serum lipids, perhaps because the extant literature on this topic may be too large to systematically review. We have recently conducted a meta-analysis on fat mass differences between premenopausal and postmenopausal women[7] and in this process we have also extracted relevant lipid profile data. Given that lipid profiles are highly related to fat mass, particularly central obesity,[8] the data extracted from our previous review provide a useful representation of lipid changes in women around menopause. It is therefore within this context that we are reviewing data and reporting precise quantitative estimates on lipid profile differences between premenopausal and postmenopausal women to address this gap in the literature. This review will provide important information to clinicians and critical evidence on lipid differences, which can guide the development of targeted interventions to facilitate positive health outcomes for postmenopausal women.

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METHODS

The methodology of the initial meta-analyses is reported elsewhere in detail[7] and was registered prospectively in the PROSPERO database (CRD42018100643), which can be accessed online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100643). Briefly the PubMed database was searched (to May 2018) with filters applied to

exclude both non-human and non-English studies. In addition, the criteria and methods described in the following sections were used.

Inclusion and exclusion criteria

Both longitudinal and cross-sectional studies that investigated both healthy premenopausal and healthy postmenopausal women were included, whereas studies that exclusively investigated clinical/pathophysiological populations or had fewer than 40 participants were excluded. The sample size cutoff was established to avoid extreme sampling bias and ensure that small studies, which are more likely to be methodologically less robust, are not included.

Data extraction

Available lipid data that were extracted from each study included high-density lipoprotein (HDL), LDL, TC, TGs, and TC to HDL ratio. The International System of Units (SI) mmol/L was used to express lipid levels. Articles that reported lipids as mg/dL were converted to mmol/L by multiplying the values by 0.02586 (for HDL, LDL, and TC) or by 0.01129 (for TG). Two authors (A.A. and E.W.) double extracted all data from included articles to avoid transcription errors with any disagreement resolved by consensus.

Statistics

R (version 3.3.3)[9] operating within RStudio (version 1.0.143)[10] was used to conduct all statistical analysis. The metafor package (version 2.0.0)[11] was used for the meta-analysis.

Meta-analysis

Because the sampling of populations and methodology varied across studies, heterogeneity was assumed, which resulted in a distribution of effect sizes.[12] Therefore, all analyses used a random effects model (using the restricted maximum likelihood estimator) to estimate the mean of the distribution of these effect sizes.

Cochran's Q statistic (with $P < 0.01$ indicative of significant heterogeneity) and the I^2 statistic (values 25%, 50%, and 75% suggestive of low, moderate, and high heterogeneity, respectively) were used to assess heterogeneity across studies.[13] Sensitivity analyses using the leave-one-out-method were conducted to identify studies that excessively contributed to heterogeneity. Meta-regression analyses using a mixed effect model were conducted to determine the influence of moderators, such as aging.

Bias

Funnel plots and Egger regression test were used to investigate the possible impact of publication bias.[14] The trim and fill method was also used to estimate the number of studies that may be missing from the meta-analysis and to estimate adjusted effect sizes.[15,16]

RESULTS

Effect sizes

The unstandardized raw mean differences (ie, estimate) for each lipid measure between postmenopausal and premenopausal women are presented in Table 1. Some studies included multiple subcohorts of premenopausal and postmenopausal women. In these cases, subcohorts were extracted separately and treated as discrete samples. Three longitudinal studies were identified; however, such studies did not report compatible measures and therefore were not suitable for meta-analysis. Sixty-six cross-sectional studies reporting on 67 sample populations were included in the analyses (see Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A452, which includes study characteristics).

Meta-analysis results

High-density lipoprotein

Fifty-seven studies examined the association between HDL and menopausal status. There were no significant mean HDL differences between premenopausal and postmenopausal women (Table 1 and Fig. 1).

Triglycerides

Fifty-seven studies examined the association between TG and menopausal status. The mean TG change was 0.27 mmol/L (SE = 0.02; Table 1 and see Figure, Supplemental Digital Content 2, http://links.lww.com/MENO/A455), which illustrates a forest plot for TG with an annual difference of 0.02 mmol/L/yr.

TABLE 1. *Output for cross-sectional studies*

No	Lipid measure	*k* (Samples)	Total preM sample size	Total postM sample size	PreM mean age (SD)	PostM mean age (SD)	Age mean difference (SD)	PreM mean lipid level (SD)	PostM mean lipid level (SD)	Estimate (95% CI)	*P*
1	HDL	58 (59)	64,330	42,650	38.98 (5.74)	56.41 (3.58)	15.74 (7.62)	1.53 (0.18)	1.55 (0.20)	0.02 (−0.00, 0.04)	0.0973
2	TG	57 (58)	24,365	25,642	42.36 (6.00)	57.14 (4.04)	13.71 (8.35)	1.28 (0.29)	1.57 (0.34)	**0.27 (0.22, 0.31)**	<0.0001
3	TC	56 (56)	66,062	41,940	39.19 (5.69)	56.57 (3.50)	15.71 (7.37)	4.77 (0.35)	5.57 (0.46)	**0.58 (0.50, 0.65)**	<0.0001
4	LDL	49 (49)	63,246	39,176	38.90 (5.71)	56.55 (3.65)	16.01 (7.63)	2.90 (0.25)	3.46 (0.32)	**0.45 (0.38, 0.53)**	<0.0001
5	TC:HDL	10 (10)	1,982	1,803	43.05 (4.67)	58.39 (4.43)	14.85 (7.82)	3.74 (0.24)	4.27 (0.51)	**0.39 (0.16, 0.62)**	0.0008

Bolded estimates indicate significance at the $P < 0.05$ level. Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. For HDL, TC, and LDL, to convert values from SI units (mmol/L) to mg/dL, multiply by 38.67, however, for TG, multiply by 88.57.

HDL, high-density lipoprotein; *k*, number of studies; LDL, low-density lipoprotein; postM, postmenopausal; preM, premenopausal; SD, standard deviation; TC, total cholesterol; TC:HDL, total cholesterol to high-density lipoprotein ratio; TG, triglyceride.

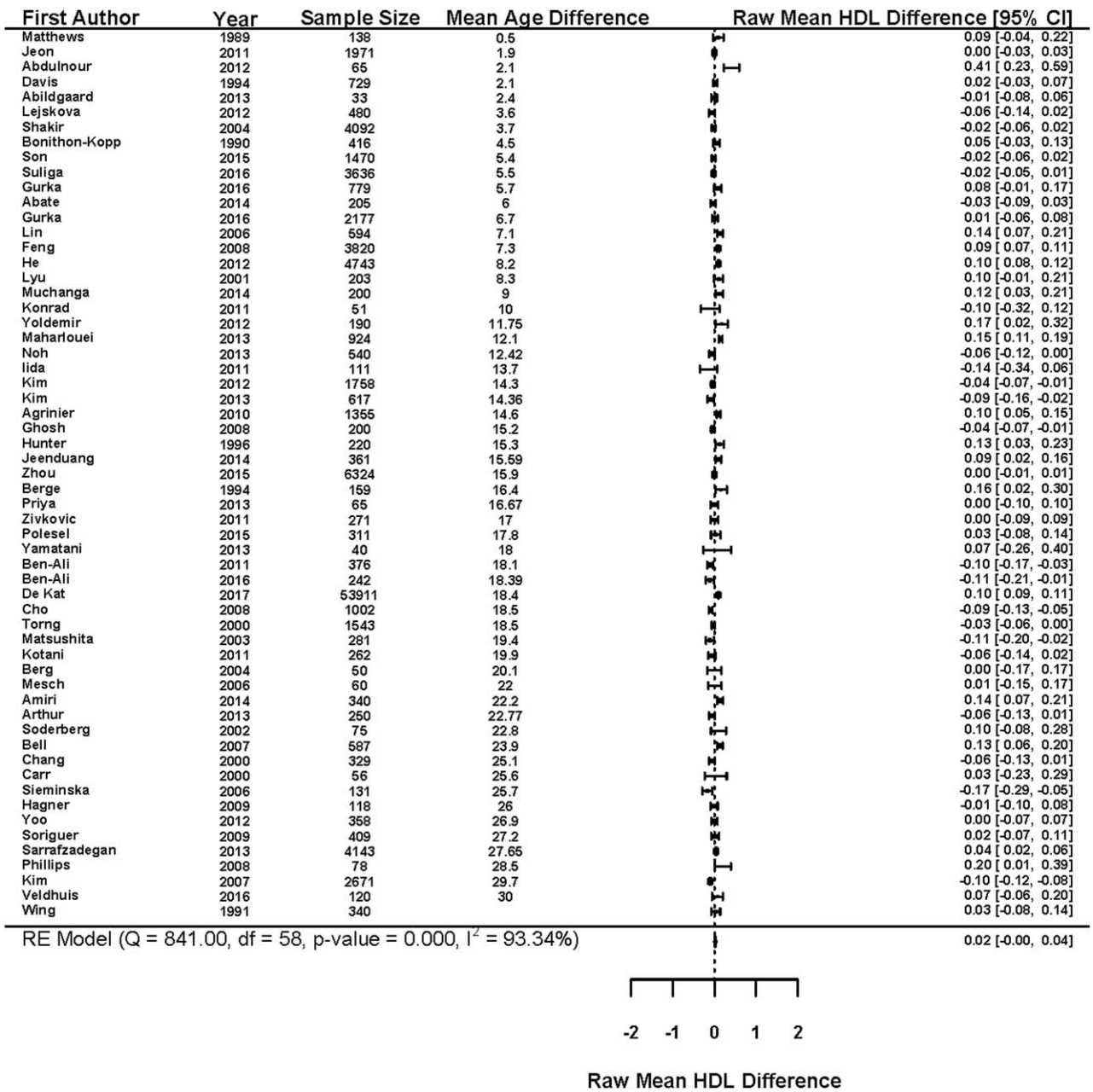

FIG. 1. Forest plot of the raw mean high-density lipoprotein difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. HDL, high-density lipoprotein; RE model, random effects model.

Total cholesterol

Fifty-five studies examined the association between TC and menopausal status. The mean TC change was 0.58 mmol/L (SE = 0.04; Table 1 and see Figure, Supplemental Digital Content 3, http://links.lww.com/MENO/A456, which illustrates a forest plot for TC), with an annual difference of 0.04 mmol/L/yr.

Low-density lipoprotein

Forty-eight studies examined the association between LDL and menopausal status. The mean LDL change was 0.46 mmol/L (SE = 0.04; Table 1 and Fig. 2), with an annual difference of 0.03 mmol/L/yr.

Total cholesterol to high-density lipoprotein ratio

Ten studies examined the association between TC to HDL ratio and menopausal status. The mean TC to HDL change was 0.39 mmol/L (SE = 0.12; Table 1 and see Figure, Supplemental Digital Content 4, http://links.lww.com/MENO/A457, which illustrates a forest plot for TC to HDL ratio), with an annual difference of 0.03 mmol/L/yr.

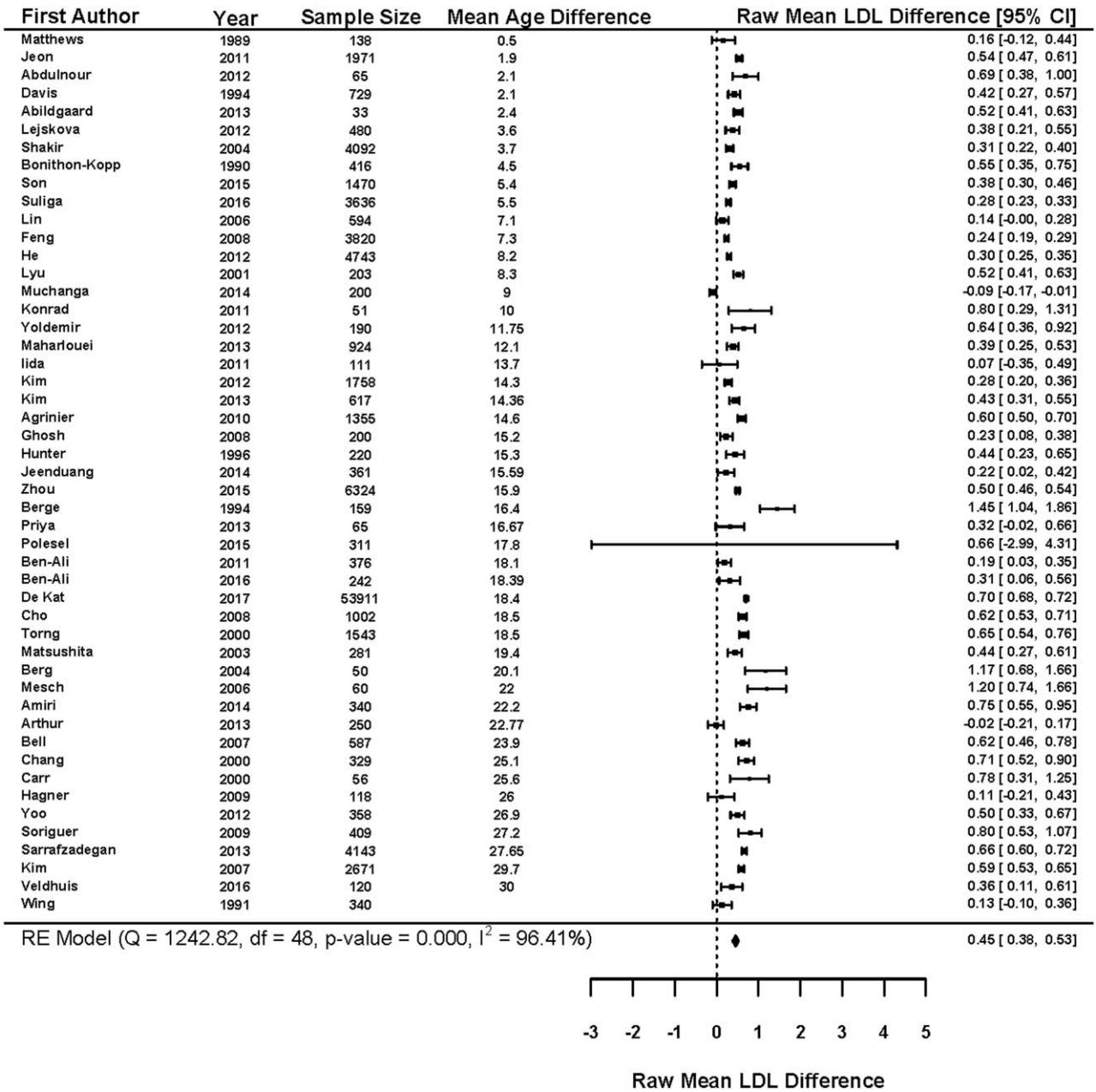

FIG. 2. Forest plot of the raw mean low-density lipoprotein difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. LDL, low-density lipoprotein; RE model, random effects model.

Sensitivity analyses

In all meta-analyses performed, significant heterogeneity was found and the proportion of real variance that was not related to random error between studies (I^2) was high for all analyses. Leave-one-out-analyses revealed no particularly influential study and showed relative consistency in reported estimates.

Publication bias

The trim and fill test and funnel plot diagnostics revealed some evidence of publication bias. Eggers regression test was significant for TC and LDL analyses, indicating some asymmetry. The trim and fill analyses identified one missing study for HDL and five for LDL (Fig. 3). Although these results suggest that some publication bias is likely to be present, the differences between actual and reported estimates were generally quite small. The inclusion of missing studies did not change the relationship or significance of the results.

Metaregression and subgroup analyses

Aging (ie, the mean age difference between premenopausal and postmenopausal women) significantly predicted the unexplained variance (9.71%-40.08%) in lipid estimates (Table 2). More specifically, the meta-regression (which

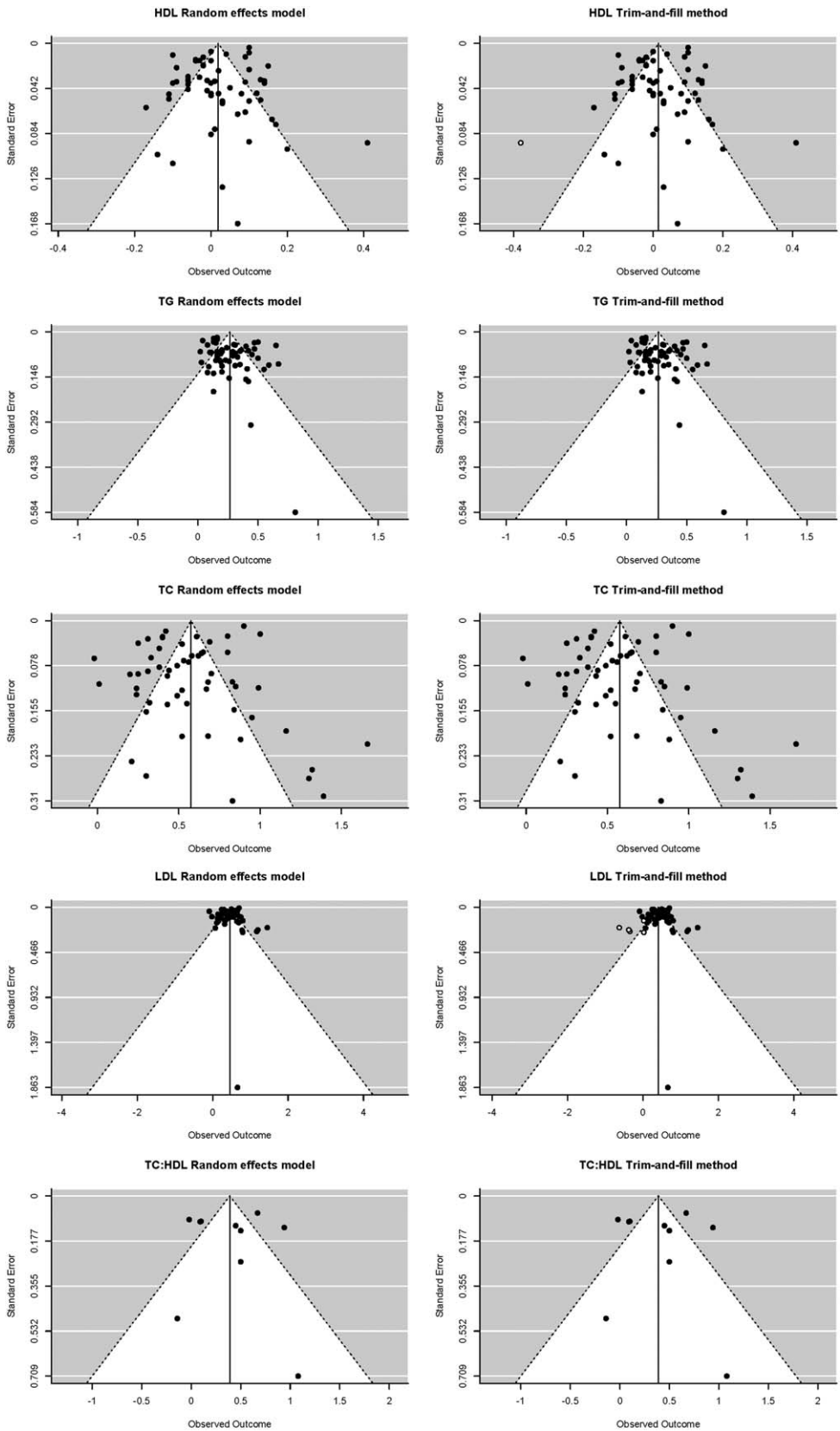

FIG. 3. Funnel plots using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TC:HDL, total cholesterol to high-density lipoprotein ratio; TG, triglyceride.

TABLE 2. *Metaregression analyses after removing the effect attributable to normal aging*

Lipid measure	Samples	R^2	Unstandardized β estimate (95% CI)	*P*
TG	57	36.61	**0.0103 (0.0059, 0.0147)**	<0.0001
TC	55	9.71	**0.0113 (0.0021, 0.0205)**	0.0164
LDL	48	10.13	**0.0088 (0.0006, 0.0171)**	0.0351
TC:HDL	10	40.08	**0.0243 (0.0025, 0.0462)**	0.0289

The unstandardized estimates reflect increases in lipid levels for every year of difference between premenopausal and postmenopausal women. Bolded estimates indicate significance at the $P < 0.05$ level. Studies that did not report age were omitted from model fitting. For TC and LDL, to convert values from SI units (mmol/L) to mg/dL, multiply by 38.67, however, for TG, multiply by 88.57.
LDL, low-density lipoprotein; R^2, proportion of observed variance explained by the model; TC, total cholesterol; TC:HDL, total cholesterol to high-density lipoprotein ratio; TG, triglyceride.

used a mixed effects model) indicated that for every year difference between premenopausal and postmenopausal women, there was a 0.01 mmol/L increase in TG, TC, and LDL and a 0.02 mmol/L increase in TC to HDL ratio (Table 2). The inclusion of women using hormone therapy had no significant effect on the overall estimates.

Subgroup analyses of studies with a mean age difference of 5 years or less between premenopausal and postmenopausal women (compared to studies with a mean age difference of >5 years) revealed no significant differences for HDL, LDL, TC, and TC to HDL ratio. Studies that, however, had a mean age difference greater than 5 years had a 0.1295 mmol/L increase in TG (SE 0.06, 95% CI from 0.02 to 0.24). Notably, I^2 remained high across all subgroup analyses. Furthermore, subset analyses of studies with a mean age difference of 5 years or less between premenopausal and postmenopausal women revealed no difference in the direction or significance of effects compared to initial estimates. The magnitude of estimates for most measures was also very similar (see Table, Supplemental Digital Content 5, http://links.lww.com/MENO/A453, which illustrates subset analyses). Notably, however, the magnitude of effect decreased for TGs (initial estimate: 0.27 mmol/L, 95% confidence interval 0.22-0.31; <5 years mean difference estimate: 0.14, 0.09-0.19) and could not be investigated in the TC to HDL levels due to insufficient studies available for subset analyses. Furthermore, the heterogeneity remained high (ie, >75%) across all analyses (see Table, Supplemental Digital Content 6, http://links.lww.com/MENO/A454, which illustrates heterogeneity for subset analyses), except for TGs (88.68%-55.28%) and LDL (96.41%-69.73%).

DISCUSSION

The current review investigated the differences in lipid levels between healthy premenopausal and postmenopausal women. The main findings of this review were that (1) TG, TC, LDL, and TC to HDL ratio levels were significantly higher in postmenopausal women compared to premenopausal women; (2) there was no difference in HDL levels between premenopausal and postmenopausal women; and (3) the differences in lipid levels were partly attributable to the mean age difference between premenopausal and postmenopausal women.

It is important to determine why an unfavorable lipid profile develops in postmenopausal women comparatively to premenopausal women. Although both aging and menopause are potentially implicated, it can be difficult to delineate the individual influence of each because both progress concurrently. Previous research indicates that for women aged 18 to 45 years the typical trends for TG, TC, and LDL is 0.070, 0.010, and 0.003 mmol/yr, respectively.[17] The analyses presented in this article reflect consistent but comparatively smaller annual estimates for TG (0.02 mmol/yr), yet larger annual estimates for TC (0.04 mmol/yr) and LDL (0.03 mmol/yr), which would suggest that the annual difference in lipid estimates does not remain the same throughout early adulthood and middle age. Although the current study has, however, identified aging as a key predictor of the difference in lipid levels between premenopausal and postmenopausal women, which explains a portion of the variance (9.71%-40.08%), there are other possible genetic and environmental factors that may account for the remaining variance and inconsistencies between estimates. For example, a longitudinal study revealed that lipid profiles fluctuated in premenopausal women depending on the stage of their menstrual cycle, with the follicular phase (indicative of high endogenous estrogen levels), associated with decreased TC, LDL, and TG.[18] Furthermore, the use of estrogen alone hormone therapy has been linked with raised HDL and lowered LDL and TC levels.[19] Taken together, these findings suggest that the decline in estrogen levels that accompany menopause may have a harmful effect on the overall lipid profile of postmenopausal women. Our previous meta-analysis, however, demonstrated that increases in fat mass between premenopausal and postmenopausal women were largely attributable to aging.[7] Therefore, it is also possible that the age-related differences in lipid profiles are linked with similar factors as those associated with increased fat mass including poor diet and low levels of physical activity. Further insights regarding the precise influence of these modifiable lifestyle factors on overall lipid changes in women around menopause will result in the development of focused and effective holistic intervention programs that seek to mitigate the identified risks for women.

Although the recommended cholesterol ranges and thresholds vary as a function of individual risk for developing lipid-related disorders, the recommended LDL levels are less than 3.36 mmol/L for individuals with moderate coronary heart disease (CHD) risk (ie, a clustering of two lifestyle risk factors including obesity, physical inactivity, elevated TG, low HDL cholesterol, or metabolic syndrome).[20] In this study, it is important to note that the mean LDL cholesterol

level for premenopausal women is 2.90 mmol/L, whereas postmenopausal women are above the recommended levels (3.46 mmol/L) for individuals with moderate CHD risk. This suggests that postmenopausal women who have a clustering of risk factors for CHD should be especially observant to differences in cholesterol after menopause, given that an unfavorable lipid profile develops at this time. Interestingly, although some studies report that HDL levels decrease after menopause onset,[2] the current review aligns with studies that suggest that HDL levels remain unchanged.[21,22]

Strengths and limitations

A key strength of the present study was that a large number of individuals were included in the analyses, resulting in a comprehensive assessment of lipid profile differences between premenopausal and postmenopausal women. Specifically, 66 cross-sectional studies were included in the meta-analyses, which provided a total sample of 114,655 women consisting of 68,394 that were premenopausal and 46,261 that were postmenopausal. Furthermore, as far as we are aware, this review is the first to provide precise quantitative estimates about lipid profile differences between premenopausal and postmenopausal women.

Notable limitations included the fact that there were insufficient longitudinal studies available for meta-analyses. Furthermore, the literature was not systematically reviewed before conducting the meta-analyses, which increased the possibility of publication bias in reported findings. Publication bias analyses were, however, conducted and revealed only small differences between actual and reported estimates, which did not change the relationship or significance of the results.

Future directions

Given the heterogeneity of findings and that a large amount of unexplained variance remains to be investigated, future systematic reviews should investigate the role of moderators on cholesterol changes in women, including age of menopause onset, ethnicity, physical activity levels, genetic factors, diet, obesity, and hormone therapy use. Once identified, the extent to which potential risk factors contribute to deleterious lipid profile changes should be precisely quantified and ranked in order of influence/weight and potential for modification, such that informed intervention programs, which seek to mitigate the identified risks for women and ensure that lipid levels are kept in the normal range, can be effectively developed. In addition, more longitudinal studies that investigate changes in lipid levels as women progress from premenopausal to postmenopausal states are required so that additional insights can be provided regarding changes that occur during perimenopause.

CONCLUSIONS

The current analyses revealed that postmenopausal women develop an unfavorable lipid profile compared to premenopausal women, which is partly attributed to mean age differences between these groups. These findings are important as they provide precise estimates of lipid changes in women around menopause. Furthermore the results suggest that particular attention should be paid to differences in lipid levels after menopause due to the development of an unfavorable lipid profile that can increase the risk of cardiovascular disease such as heart disease and stroke if appropriate lifestyle/pharmacological interventions are not implemented.

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