EFFECT OF EXERCISE ON NON-HDL CHOLESTEROL LEVEL (NON-HDL-C) IN OLDER WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Background: Many studies have shown that exercise can effectively reduce the non-high density lipoprotein cholesterol (non-HDL-C) level, one of the major risk factors for cardiovascular diseases, in different sex and age groups. However, there are very few studies conducted in older women, who are in a group having a higher mortality rate due to cardiovascular diseases. Moreover, there has been no recent meta-analysis focusing on the effect of exercise on non-HDL-C level in older women. The purpose of this study was to investigate the effect of exercise on non-HDL-C level in older women (≥50 years old) by means of systematic review and meta-analysis of previous randomised controlled trials.

Methods: Searches were conducted from 9 electronic databases by applying specific eligibility criteria of the review. Data regarding changes in non-HDL-C, high density lipoprotein cholesterol (HDL-C) and total cholesterol levels, were extracted as primary outcomes. Random-effect meta-analysis was used to calculate pooled effect sizes of primary and secondary outcomes.

Results: Ten studies that met the inclusion criteria were selected for meta-analysis. Random-effect meta-analysis showed statistically significant reduction in non-HDL-C level (= -9.69 mg/dL; 95%CI= -17.09 to -2.29 mg/dL; $p<0.05$) and increase in HDL-C level (= 3.0mg/dL; 95%CI= 0.61 to 5.4; $p<0.05$), but no significant change in total cholesterol level (= -5.99 mg/dL; 95%CI= -12.64 to 0.66; $p>0.05$) in the exercise group compared to the control group. Subgroup analysis of data from different continents showed significant subgroup differences in the non-HDL-C level after exercise ($Q= 12.39$; $p<0.005$; $I^2= 83.9\%$).

Conclusion: Exercise decreases non-HDL-C level and increases HDL-C level in older women and might be efficacious in preventing dyslipidemia and associated diseases in older women.

Keywords: *Exercise, Non-HDL-C, Older Women, Meta-analysis*

Introduction

Cardiovascular disease is the leading cause of death in older people and contributes to a large number of deaths in older women as compared to older men (1). Moreover, the prevalence of cardiovascular disease and its associated risk factors is relatively higher after the age of 50 years (2,3). Dyslipidemia has been regarded as a major risk factor for cardiovascular disease (4), and increased non-high density lipoprotein cholesterol (non-HDL-C) has been shown to be a significant predictor of ischemic heart disease (5). Current evidence suggests that non-HDL-C is a better predictor of cardiovascular disease morbidity and mortality

than low density lipoprotein cholesterol (LDL-C) (6). One of the possible explanations is that non-HDL-C includes cholesterol contents of all lipoproteins, such as LDL-C, very low density lipoprotein cholesterol (VLDL-C) and intermediate-density lipoprotein cholesterol (IDL-C), that can facilitate the formation of fatty plaques in the arteries (7). Exercise has cardioprotective effects by altering lipids and lipoproteins levels in older adults (8).

Previous meta-analyses have examined the effect of exercise on non-HDL-C level in children (9) and adults (10). Nonetheless, there exist discrepancies in the results of the meta-analysis regarding the effect of exercise on non-HDL-C level (9,10). This might be due to variations in the characteristics of the participants and intervention between the studies. In addition, the previous meta-analyses did not emphasize the effect of exercise on lipids and lipoproteins in older adult populations. To the best of our knowledge, no previous meta-analysis studies have examined the effect of exercise on non-HDL-C level in older women. Therefore, the purpose of this study was to investigate the effect of exercise on non-HDL-C level in older women via systematic review and meta-analysis of previous randomized controlled trials.

Materials and Methods

The eligibility criteria for this systematic review were as follows: 1) Randomized controlled trials, 2) Human studies, 3) Older subjects > 50 years of age, 4) Exercise intervention (either aerobic or resistance exercise or combination of both types of exercises), 5) Exercise lasting ≥8 weeks, 6) Older women ≥ 50 years of age, 7) Studies that assessed both total cholesterol and HDL-C, 8) Studies published in English language, and 9) Studies published between 1st January 1955 and 16th April 2018. Any studies that did not match with the above eligibility criteria were excluded from the analysis.

We retrieved articles from nine electronic databases, namely, PubMed, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Science Direct, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Physiotherapy Evidence Database (PEDro), ProQuest Dissertations & Theses Global: Health & Medicine, ProQuest Nursing & Allied Health Database, ISI Web of Science. The major controlled vocabulary and keywords used in the search consist of "Exercise", "Physical activity", "Lipoproteins", "Cholesterol", and "Older". We conducted electronic database searches in February, 2018 and updated our searches in April, 2018. The studies identified from the electronic databases were exported to EndNote, version 8.

Studies were selected according to preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines (Figure 1). Screening of studies was done independently by the first author and second author (SWYMT, APZ). Disagreement between the two authors was resolved by consulting a third author. We contacted the corresponding authors by email to retrieve full-text articles if they were not freely available online.

Data were extracted and coded in data extraction forms developed by the reviewers. Summary of the study characteristics including participant information, intervention details, and other information, was recorded in a single data extraction form, while data on primary and secondary outcomes were extracted into a separate form. Data extraction was done by two reviewers and the third reviewer was consulted if a consensus could not be reached by the two reviewers. All parametric outcomes were presented as mean ± standard deviation (SD) except for body fat (expressed in %). Measurements of the concentration of the relevant parameters were standardized to mg/dl. If standard deviation (SD) was not reported in the included studies, the SD measurement was computed from standard error of the mean (SEM) by using the following formula:

$$SD = SEM \times \sqrt{n}$$

Assessment of the quality of studies was conducted by using Cochrane risk of bias assessment tools. Seven domains were assessed, namely 1) random sequence generation (selection bias), 2) allocation concealment (selection bias), 3) blinding of participants and personnel (performance bias), 4) blinding of outcome assessors (detection bias), 5) incomplete outcome data (attrition bias), 6) selective outcome reporting (reporting bias), and 7) other risks of bias. We categorized the degree of risk of bias into high degree, low degree and unclear risk of bias. Risk of bias assessment was done only for primary outcomes (non-HDL-C, HDL-C, total cholesterol). Risk of bias in the included studies was evaluated by two independent reviewers (SWYMT, APZ). If a disagreement existed between the two reviewers, the third reviewer was consulted to obtain at an appropriate decision regarding the quality of the study.

Primary outcomes for this study consist of the changes in non-HDL-C, HDL-C, and total cholesterol levels. Changes in the respective cholesterol levels were calculated based on subtraction of the final cholesterol level from the baseline cholesterol level in the exercise and control groups. The effect size was obtained from the mean difference in the change in cholesterol level between the exercise group and the control group. If the standard deviations of change in cholesterol levels were not available in the study, they were calculated from baseline SD and final SD by the formula developed by Follman *et al*. (11). Random effect meta-analysis based on the inverse variance method was performed to get the pooled effect size. Heterogeneity was detected by Cochran's Q statistics and statistical significance was set at alpha level of <0.1. I-squared (I^2) index was used to assess the degree of heterogeneity between studies. Cut off points of 25%, 50%, and 75% were used for examining the degree of heterogeneity (12). In addition, subgroup analysis based on data from different continents was done to examine the source of heterogeneity. Sensitivity analysis for primary outcomes was used to determine the robustness of the effect sizes. Bias related to small study effects was explored by funnel

plot. All statistical analyses were carried out by using Review Manager, Version 5.3.

Results

From the initial search, we yielded 2,546 articles from nine electronic databases including articles from initial search and updated search. After removal of duplicates, we acquired 2,426 unique articles for the initial screening phase of the review. We screened titles and abstracts and excluded articles that did not meet the eligibility criteria. Therefore, 216 articles were selected for the full-text review stage. We further excluded 206 articles during full-text review and reasons for exclusion were recorded. Finally, 10 articles met with eligibility criteria for systematic review and meta-analysis. The study selection process is shown in Figure 1 below.

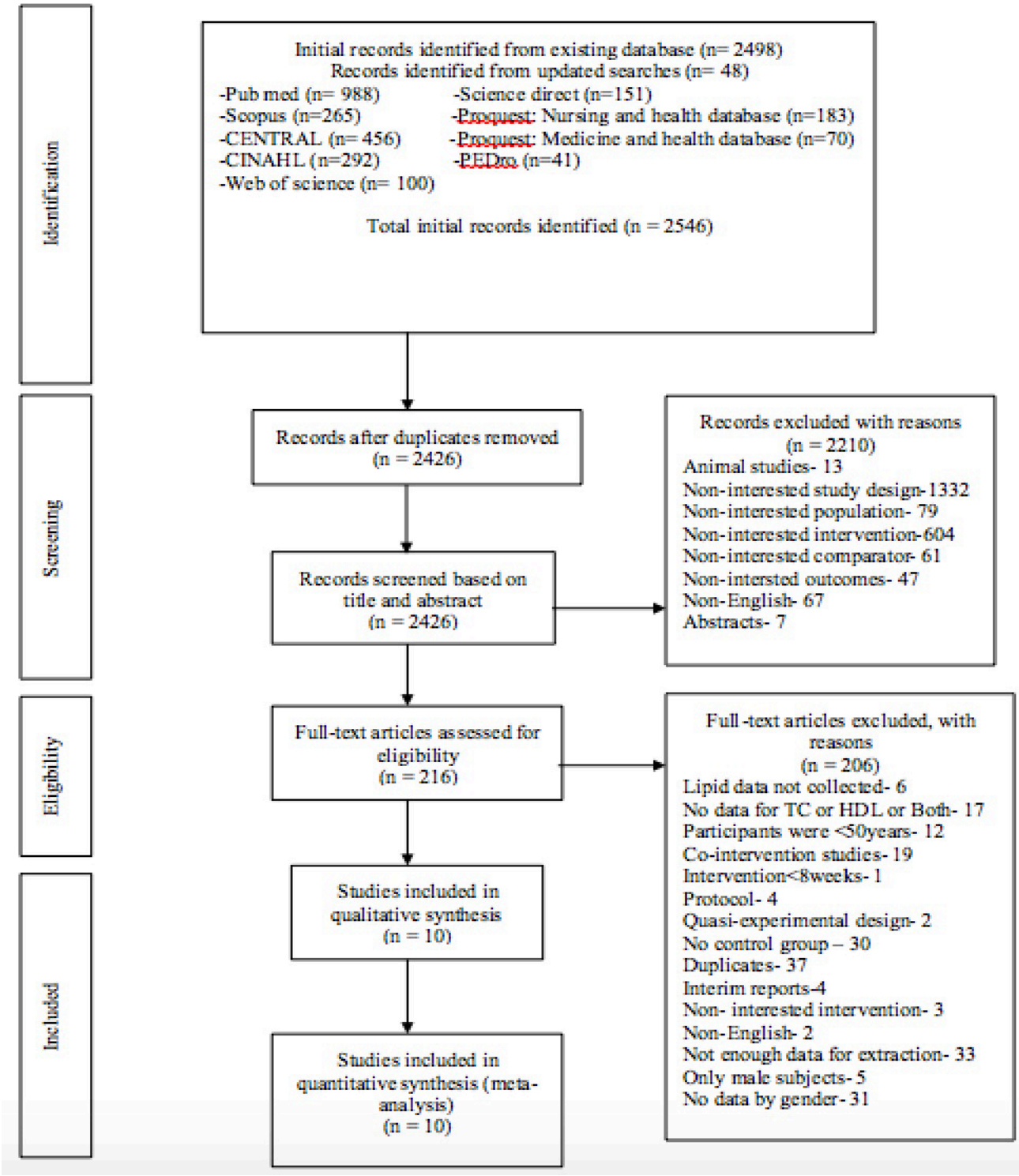

Figure 1: PRISMA flow diagram for selection of studies

Ten studies that included 223 participants in the exercise group and 161 participants in the control group were selected for the meta-analysis. Two studies were conducted in Brazil (13,14), two in USA (15,16) while other studies were conducted in Japan (17,18), Korea (19-21), and Thailand (22). Most of the studies used aerobic exercise (16-18,21,22) whereas others used resistance exercise (13) and combined exercise (14,15,19,20). The duration of exercise intervention ranged from 7.5 to 24 weeks. The participants involved in five studies were healthy (14,15,17,18,21), while those who were involved in other studies had co-morbidities such as type 2 diabetes mellitus (16), hypertension (13), obesity (19,20), and depression (22). Description of the study characteristics is shown in Table 1 below.

Table 1: Summary of the characteristics of studies included in the meta-analysis

Study/ author	Country	Sample size	Sex	Age (years)	Intervention details	Outcome (parameters measured)
Dos *et al*. 2014 [11]	Brazil	TRT-20 ERT- 20 CG- 20	All F	60-65	Length- 16 weeks Types- TRT and AT or ERT and AT Frequency- 3 sessions/week Intensity- 70%-90% of 10RM (TRT), 100%-120% of 10RM (ERT) Duration- 50-60 mins	Wg, BMI, WC, HC, FBS, SBP, DBP, TC, HDL, LDL, TG
Fahlman *et al*. 2002 [13]	USA	AT- 15 RT- 15 CG- 15	All F	70-87	Length- 10 weeks Types- AT and RT Frequency- 3days/week Intensity- 70%HRR (AT), 8RM(RT) Duration- 20-50 mins	HR, VO_2 max, HDL, TC, LDL, TG
Filho *et al*. 2013 [12]	Brazil	EX- 33 CG- 21	All F	EG- 68.9 ± 6.8 CG- 66.6 ± 6.0	Length- 16 weeks Types- walking, stretching exercise, and balance exercise Frequency- 3 times/week Duration- 60-70 mins	FBS, TG, TC, HDL, LDL, VLDL, SBP, DBP, BMI
Jong-Hwan *et al.* 2015 [17]	Korea	EX- 10 CG- 10	All F	EX- 70.7± 0.7 CG- 71.3±0.6	Length- 12 weeks Types- combined aerobic exercise, resistance exercise, and traditional Korean dance Frequency- 3 days/week Intensity- 50%-70%HRR Duration – 45 mins	Wg, BMI, Fat%, SBP, DBP, HDL, TC, LDL, TG
Miyaki *et al*. 2012 [15]	Japan	EX- 11 CG- 11	All F	60±6	Length- 8 weeks Types- Aerobic exercise Frequency- 3-5 days/week Intensity- 60%-75%HRR Duration- 30-45 mins/day	Wg, BMI, FBS, VO_2 max, HDL, LDL, TC, TG, SBP, DBP, HR
Nishida *et al*. 2015 [16]	Japan	EX- 31 CG- 31	All F	65-85	Length- 12 weeks Types- Bench step exercise Frequency- 3 times/day Duration- 140 mins/week	Wg, BMI, SBP, DBP, HbA1c, HDL, TC, TG, LDL, VO_2 max
Part *et al*. 2017 [18]	Korea	EX- 25 CG- 25	ALL F	74.1±6.1	Length- 24 weeks Types- Resistance and aerobic training Frequency- 5 times/week Intensity- 8-15RM (RT), ³13RPE (AT) Duration- 50-80 mins	WC, Fat%, SBP, DBP, TC, HDL, LDL, TG
Park *et al*. 2017a [19]	Korea	GG- 11 CG- 10	ALL F	GG- 80.3 ± 6.0 CG- - 81.0 ± 4.3	Length- 7.5 weeks Types- Gardening Frequency- Twice weekly for total 15 session Intensity- 57.1%HRR, RPE- 10.4 Duration- 50 mins/section	TC, HDL, LDL, SBP, DBP

Study/ author	Country	Sample size	Sex	Age (years)	Intervention details	Outcome (parameters measured)
Prakhinkit *et al*. 2014 [20]	Thailand	TWE- 15 BWM- 15 CG- 15	ALL F	TWE- 74.8±1.7 BWM- 74±1.9 CG- 81±1.7	Length- 12 weeks Types- Both TWE and BWM Frequency- 3 times/week Intensity- 20%-39% HRR (phase 1), 40%-50%HRR (phase 2) Duration- 20 mins (phase 1), 30mins (phase 2)	Wg, BMI, Fat%, SBP, DBP
Verity *et al*. 1989 [14]	USA	EX- 5 CG- 5	ALL F	EX- 61.2 ±4.1 CG- 57.7 ± 3.7	Length- 4 months Types- Stretching, progressive calisthenics, relaxation, and walking Frequency- 3 times/week Intensity- 65-80%HRR Duration- 1-1.5 hrs	Wg, Fat%, VO_2 max, HDL, TC, FBS, HbA1c

AT: Aerobic training
BMI: Body mass index
BWM: Walking meditation
CG: Control group
DBP: Diastolic blood pressure
ERT: Eccentric resistance training
EX: Exercise group
Fat%: Fat percentage
FBS: Fasting blood sugar
HbA1c: Hemoglobin A1c
HC: Hip circumference
HDL: High-density lipoprotein
HR: Heart rate
HRR: Heart rate reserve
LDL: Low-density lipoprotein
RM: Repetitions maximum
RPE: Rating of perceived exertion
RT: Resistance training
SBP: Systolic blood pressure
TC: Total cholesterol
TG: Triglycerides
TRT: Traditional resistance training
TWE: Traditional walking group
VLDL: Very low-density lipoprotein
VO_2 max: Maximal oxygen consumption
WC: Waist circumference
Wg: Body weight

The random effect meta-analysis revealed a statistically significant reduction in the non-HDL-C level between the exercise and control groups (= -9.69 mg/dL; 95%CI= -17.09 to -2.29 mg/dL; $p<0.05$). Reduction in the non-HDL-C level varied from -7.58 to -18.06 mg/dL and remained statistically significant after removal of each study once from the model. Therefore, the result can be considered as robust since the summary effect of reduction in the non-HDL-C level was not influenced by a particular study. However, significant heterogeneity was found across the studies ($p<0.05$, $I^2= 69\%$) (Figure 2), which reflects the differences in the effect estimates in different trials. This could be due to clinical heterogeneity (different types of participants or interventions or controls) or methodological heterogeneity (different bias in different trials). A significant increase in HDL-C level was also observed (= 3mg/dL; 95%CI= 0.61 to 5.4; $p<0.05$) although significant and moderate heterogeneity was detected ($p<0.05$; $I^2= 60\%$) (Figure 3). There was no statistically significant reduction in the total cholesterol level between the 2 groups (= -5.99mg/dL; 95%CI= -12.64 to 0.66; $p>0.05$), ($p>0.05$; $I^2= 51\%$) (Figure 4).

We conducted the random effect meta-analysis for secondary outcomes when these outcomes were reported in at least three studies. Statistically significant improvements were found for body mass index (BMI), body weight, and maximal oxygen consumption (VO_2 max) in the exercise group compared to the control group. In addition, no significant heterogeneity was detected for these outcomes, indicating that the improvements in these secondary outcomes were consistent across the studies. Fat percentage was not significantly reduced by exercise intervention. Heterogeneity was found to be large and statistically significant for the systolic and diastolic blood pressure measurements.

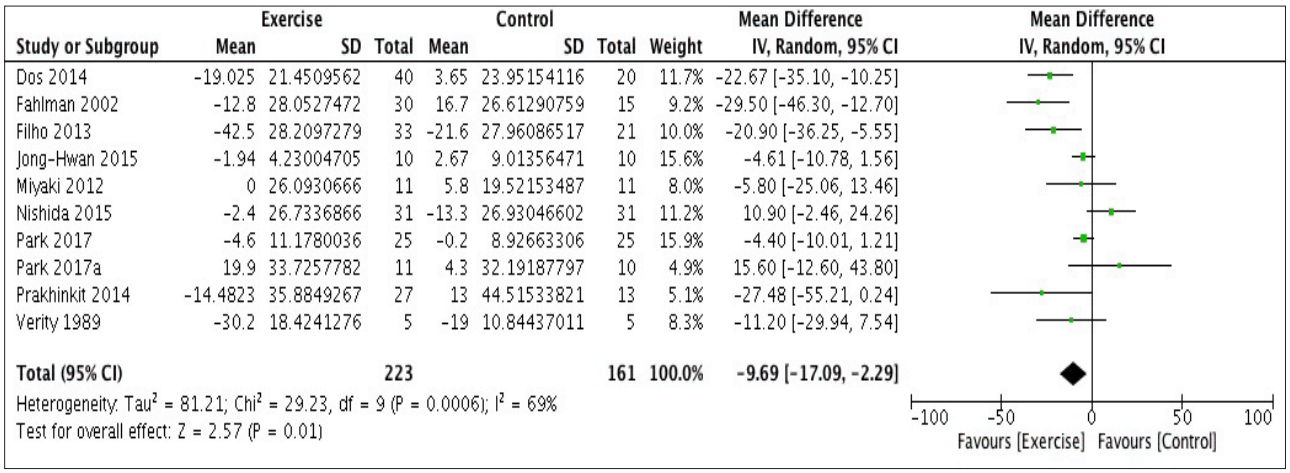

Figure 2: Forest plot (random effect model) showing the effect of exercise on non-HDL-C. IV: Inverse variance; 95%CI: 95% confidence interval; Tau²: tau square value for between studies variance; Chi²: Chi-square value for heterogeneity; df: degree of freedom; I2: I-squared statistic for heterogeneity

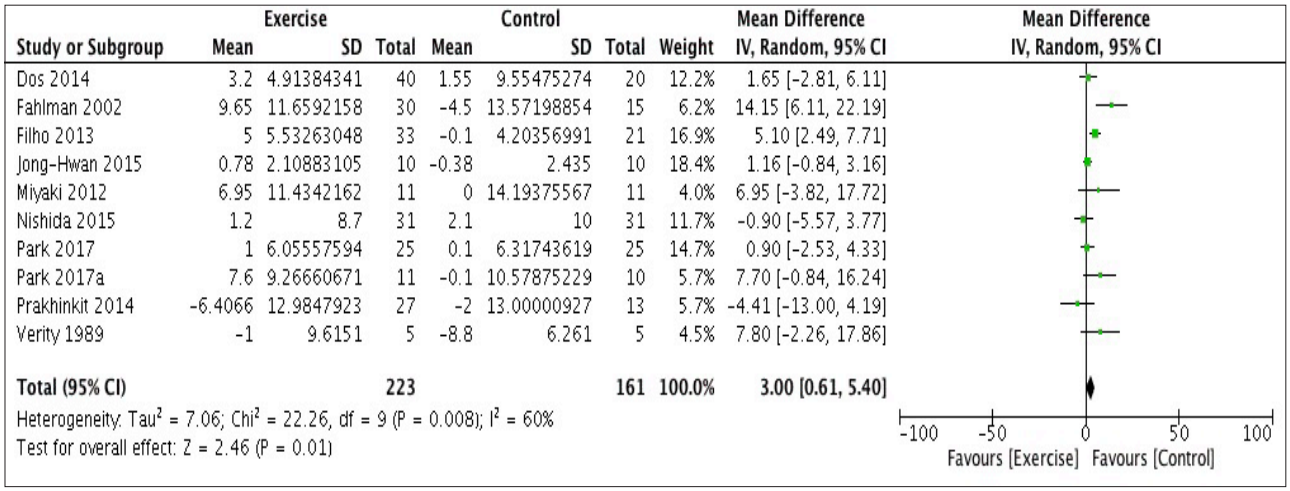

Figure 3: Forest plot (random effect model) showing the effect of exercise on HDL-C level
IV: Inverse variance; 95%CI: 95% confidence interval; Tau²: tau square value for between studies variance; Chi²: Chi-square value for heterogeneity; df: degree of freedom; I2: I-squared statistic for heterogeneity

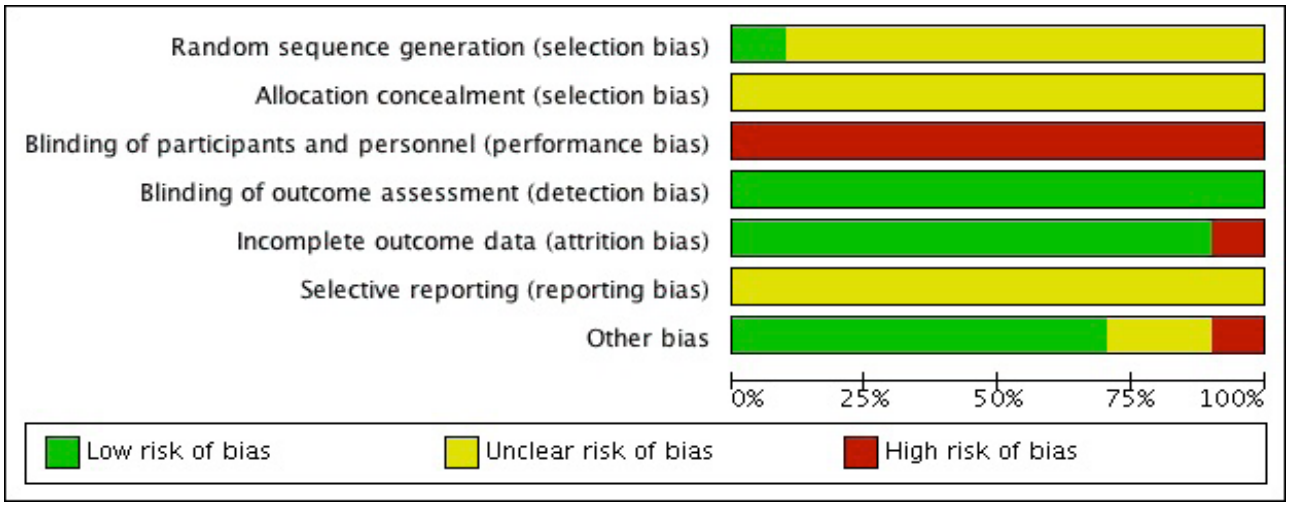

Figure 4: Forest plot (random effect model) showing the effect of exercise on total cholesterol level
IV: Inverse variance; 95%CI: 95% confidence interval; Tau²: tau square value for between studies variance; Chi²: Chi-square value for heterogeneity; df: degree of freedom; I2: I-squared statistic for heterogeneity

Subgroup meta-analysis was performed to explore whether geographic location modifies the effect of exercise. Statistically significant subgroup differences in the non-HDL-C level were found among subjects from different continents ($p<0.05$; $I^2= 83.9\%$) (Figure 5). Data from both South America and North America showed statistically significant reduction in non-HDL-C level in the exercise compared to the control group (= -21.97mg/dL; 95%CI= -31.63 to -12.31; $p<0.05$ for South American group and = -20.84mg/dL; 95%CI= -38.75 to -2.93; $p<0.05$ for North American group), whereas the difference in the non-HDL-C level between the exercise and control groups was not statistically significant among studies conducted in the Asian continents (= -2.37mg/dL; 95%CI= -9.00 to 4.25; $p>0.05$). Statistically significant subgroup differences in subjects between different continents were also found for the HDL-C level ($p<0.05$; $I^2= 82.2\%$) and total cholesterol outcomes ($p<0.05$; $I^2= 73.1\%$) (Figures 6 and 7).

Analysis of the funnel plot revealed the absence of small study effects. Only one study reported selection bias with respect to random sequence generation and none of the studies mentioned allocation concealment procedures. Based on the results of risk of bias of each domain, all of the included studies were considered as low risk of bias with respect to blinding of outcome assessment. All of the included studies had a high risk of bias with respect to the blinding of participants and personnel, which may be acceptable since it was impossible to blind for exercise intervention programs. Selective outcome reporting bias was considered unclear for all included studies. Incomplete outcome reporting bias was low in nine studies and high in one study. The detailed description of risk of bias of each domain of assessment and the risk of bias of each study are shown in Figures 8 and 9, respectively.

Discussion

To the best of our knowledge, this study is the first meta-analysis that determines the effect of exercise on non-HDL-C level in older women. The results of our meta-analysis revealed significant reduction in non-HDL-C level and increase in HDL-C level, but there was no significant change in the total cholesterol level after exercise intervention. Nonetheless, moderate to large degree of heterogeneity was detected in all of these outcome measures. The source of heterogeneity among all primary outcome measures can be explained by sub-group analysis of data from different continents.

The result of our meta-analysis varies from that of previous similar meta-analysis regarding the effect of aerobic exercise on lipids and lipoproteins in adult women aged ≥ 18 years (23). Previous meta-analysis reported that exercise could improve both the total cholesterol and HDL-C level in women (23). However, significant moderate to large heterogeneity was reported for these outcomes. The large variations in the reported results may be due to differences in the inclusion criteria of the studies in the meta-analysis. For example, unlike our study, which limits the participants to only older women, previous studies included a wider range of age group (≥ 18 years old) and both genders

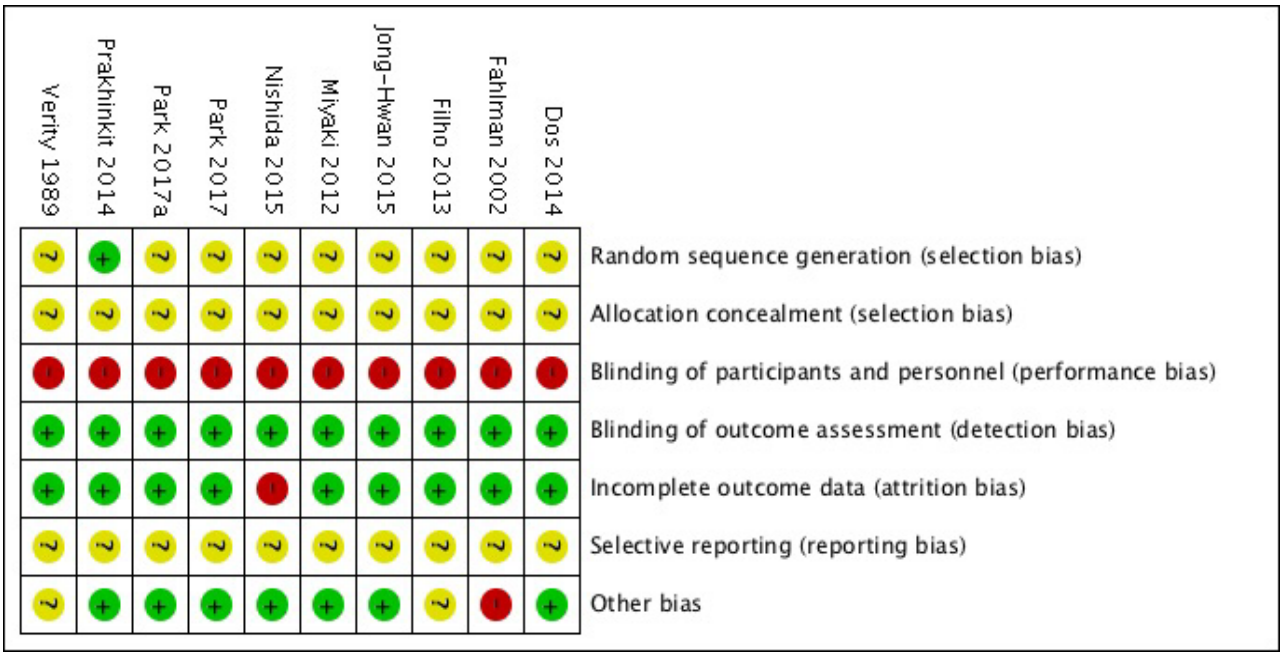

Figure 5: Forest plot presenting the subgroup meta-analysis of the effect of exercise on non-HDL-C level in different continents

IV: Inverse variance; 95%CI: 95% confidence interval; Tau^2: tau square value for between studies variance; Chi^2: Chi-square value for heterogeneity; df: degree of freedom; I2: I-squared statistic for heterogeneity

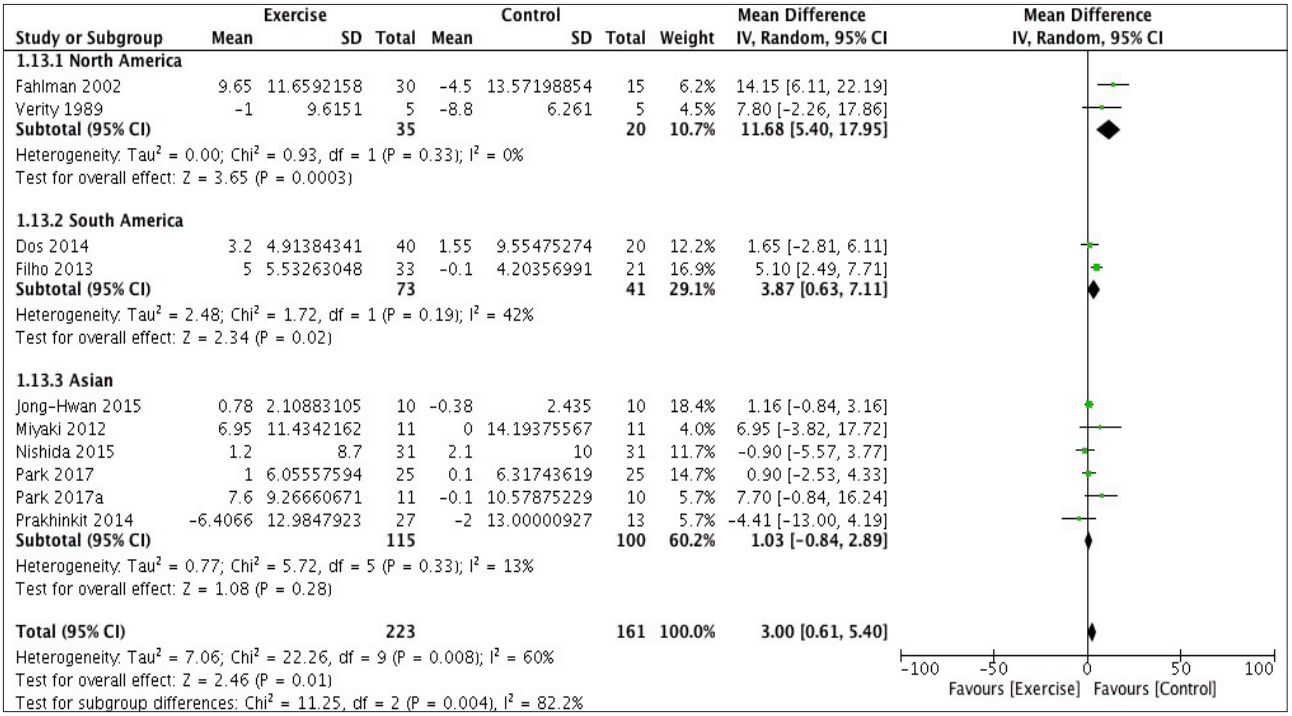

Figure 6: Forest plot presenting the subgroup meta-analysis of the effect of exercise on HDL-C level in different continents
IV: Inverse variance; 95%CI: 95% confidence interval; Tau²: tau square value for between studies variance; Chi²: Chi-square value for heterogeneity; df: degree of freedom; I2: I-squared statistic for heterogeneity

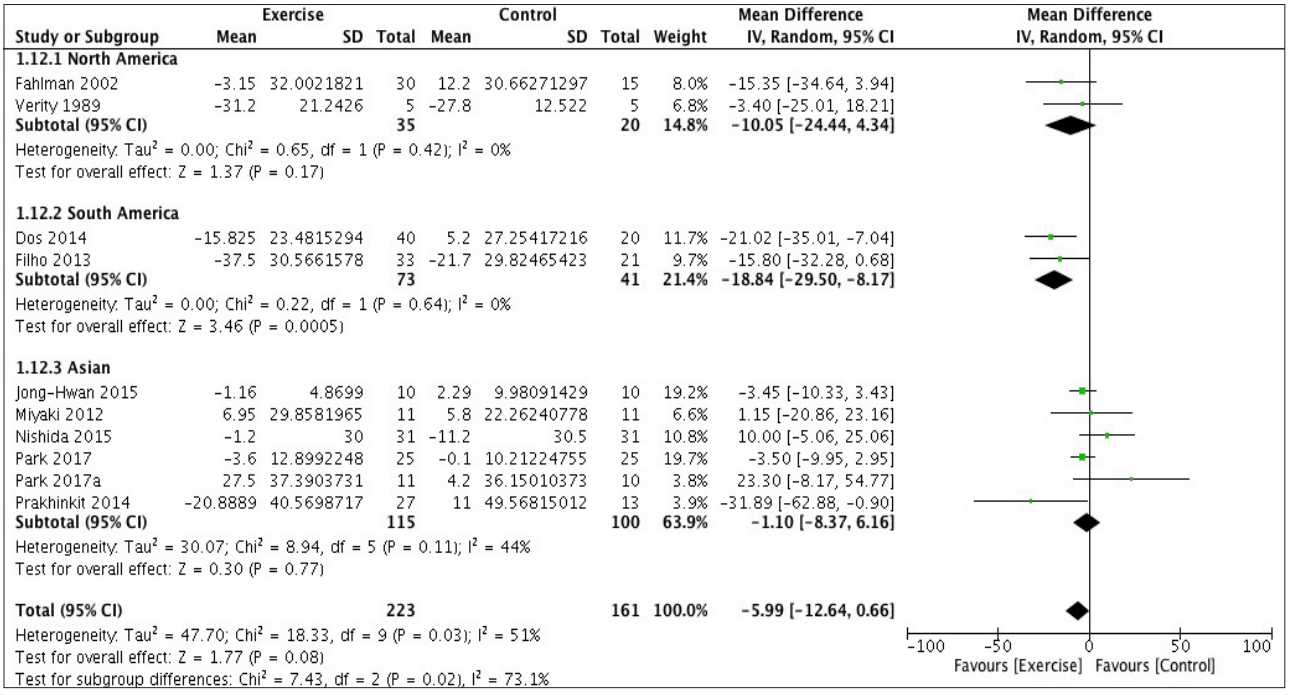

Figure 7: Forest plot presenting the subgroup meta-analysis of the effect of exercise on total cholesterol level in different continents
IV: Inverse variance; 95%CI: 95% confidence interval; Tau²: tau square value for between studies variance; Chi²: Chi-square value for heterogeneity; df: degree of freedom; I2: I-squared statistic for heterogeneity

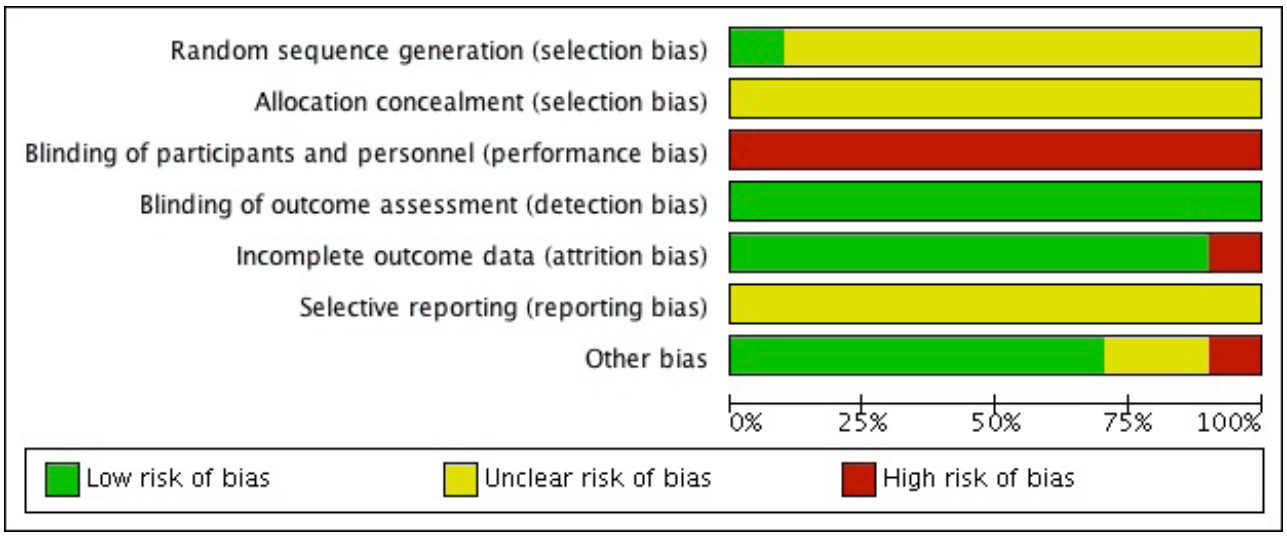

Figure 8: Risk of bias in included studies

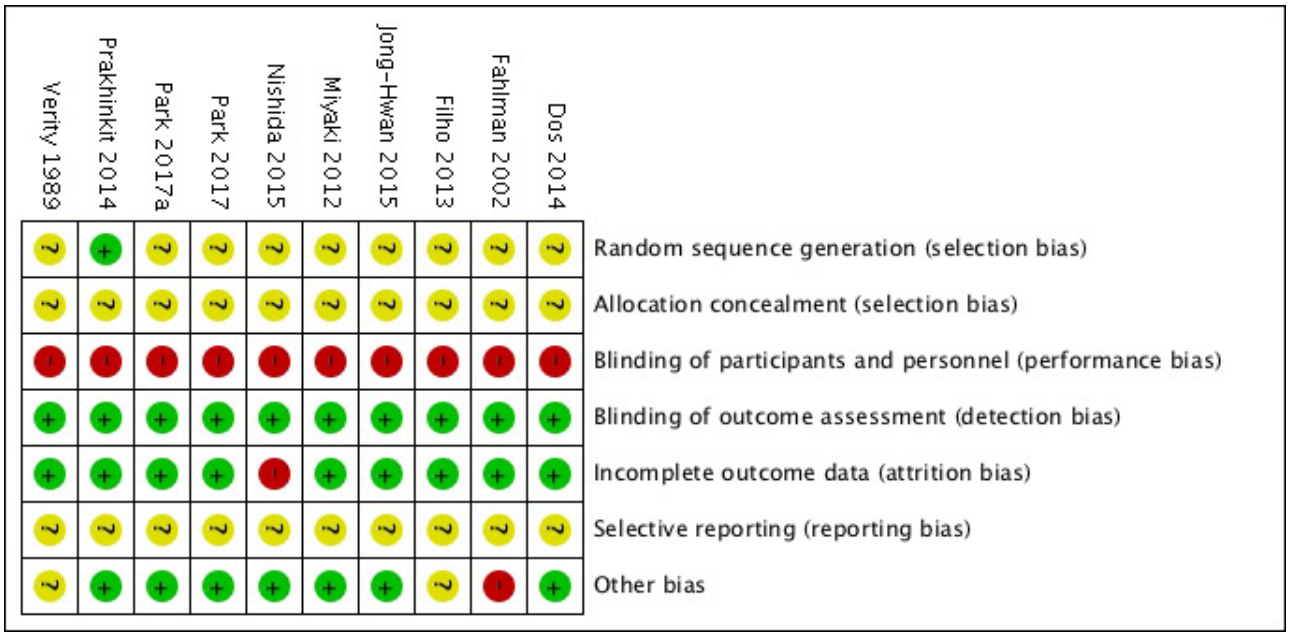

Figure 9: Summary of risk of bias in included studies

(23,24). Our results appear to be in agreement with a previous meta-analysis involving adults aged ≥ 18 years, which found that walking resulted in a significant reduction in the non-HDL-C level (±SD= 5.6±1.8 mg/dL; 95%CI= – 8.8 to – 2.4 mg/dL) (10). Nevertheless, unlike our study, the meta-analysis did not report the level of heterogeneity amongst the studies analysed.

In our study, although non-HDL-C level is significantly reduced in the South American and North American populations, it is not significantly reduced in the Asian population. It can be partly explained by the differences in the dietary habits of the Asians compared to the other populations, for instance, higher consumption of saturated fats is associated with the Asians (25). Since the number of trials conducted in South America and North America were relatively small compared with those in Asia, more trials is needed to be conducted in these continents in order to verify the subgroup effect.

Exercise may augment the breakdown of lipids, which could result in reduction of blood lipid level (26). Recent evidence indicated that non-HDL-C was a better predictor of cardiovascular disease risk than HDL-C, LDL-C and triglycerides (27). The findings of this study appear to be important since significant reduction of non-HDL-C and significant increase in HDL-C could lead to a reduction in the risk of cardiovascular disease morbidity and mortality. Therefore, based on our findings, it is possible that participation in an exercise program would be appropriate for the prevention of cardiovascular diseases in older women, aged ≥ 50 years. Clinicians may be over dependent

on lipid lowering drugs for the treatment of patients with dyslipidemia. In our perspective, clinicians should also encourage an exercise program for older women in order to prevent and treat dyslipidemia, as exercise is a healthy approach compared to drug treatment.

The strength of the current meta-analysis lies on a wider coverage of electronic databases used for selection of the study. Furthermore, our search included articles published from 1955 to 2018, and hence we included a relatively longer period than other meta-analyses. Additionally, we limited our eligibility criteria to only randomized controlled trials, which are deemed to provide reliable evidence, compared to other study designs.

One of the limitations of our study is that we were not able to search for proceedings from conference websites, or to include a larger number of full-text original articles from journals related to our topic. In addition, we limited our inclusion criteria to only English articles, and this can contribute to language bias. Moreover, we were not able to determine the effect of different nature of exercise intervention, such as frequency and intensity of exercise, on the non-HDL-C level. The main limitation of our study was that we did not adjust for potential co-variates, such as types of exercise and health status, in our study, as there was an insufficient number of studies to conduct meta-regression analysis. This leads us to question whether the improvement in non-HDL-C was due to the result of the exercise program itself or due to other factors. Underlying factor(s) that may be associated with changes in non-HDL-C could be changes in physical activity during the study, dietary habits, smoking, and frequent alcohol consumption.

Since most of the included studies of our meta-analysis limit their inclusion criteria to healthy older women, future randomized controlled trials should focus on the effect of exercise on non-HDL-C level in older women with specific diseases, such as cardiovascular diseases or diabetes mellitus, which are prevalent in older women. Most of the studies included in our meta-analysis had a very small sample size. Therefore, well-designed randomized controlled trials with larger sample size should be conducted in future to obtain reliable and well-supported evidence. Future studies should report random sequence generation, allocation concealment and they published study protocol before conduct of the trials. In addition, future randomized controlled trials should present data on dietary calory intake, as this can influence the effect of exercise on non-HDL-C level in older women.

Conclusion

The findings of this systematic review and meta-analysis suggest that exercise can decrease non-HDL-C level and increase HDL-C level in older women, particularly in the South American and North American continents. Therefore, exercise should be recommended medically for prevention and treatment of dyslipidemia in older women.

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Competing interests

There is no conflict of interest among the authors regarding the publication of this paper.

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