

BMJ Open Are interventions to improve cardiovascular disease risk factors in premenopausal women effective? A systematic review and meta-analysis

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To cite: Gao L, Faller J, Majmudar I, *et al.* Are interventions to improve cardiovascular disease risk factors in premenopausal women effective? A systematic review and meta-analysis. *BMJ Open* 2021;**11**:e042103. doi:10.1136/bmjopen-2020-042103

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-042103>).

Received 25 June 2020
Accepted 13 July 2021



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ABSTRACT

Objectives Non-traditional risk factors place young women at increased risk of cardiovascular disease (CVD) over their lifetime. The current study undertakes a systematic review and meta-analysis of randomised controlled trials (RCTs) that examined the effectiveness of primary prevention interventions for CVD in premenopausal women.

Methods An electronic literature search was performed in key databases in July 2018 and updated in May 2020. RCTs that recruited predominately female participants with a proportion aged under 55 years and that compared primary prevention interventions of CVD with usual practice were included. Two reviewers undertook the selection process for study inclusion. Meta-analysis was conducted for studies based on the same intervention in order to synthesise the results.

Results 14 RCTs with sample size ranging from 49 to 39 876 were included. Interventions included diet (2), vitamin E/antioxidants (3), lifestyle modification programme (7) and aspirin (2). The meta-analysis results indicated that diet nor vitamin E/antioxidant did not significantly lower the CVD risk profiles, while lifestyle modification programme involving components of lifestyle education, counselling and multiple follow-ups showed great potential to improve risk profiles. The lifestyle modification intervention improved blood pressure (−2.11 mm Hg, 95% CI −4.32 to 0.11, for systolic and −3.31 mm Hg (95% CI −4.72 to −1.91, for diastolic), physical activity (30.72 MET-min/week, 95% CI 23.57 to 37.87, for moderate physical activity 12.70 MET-min/week, 95% CI 8.27 to 17.14, for vigorous physical activity) and fasting blood glucose (−0.37 mmol/L, 95% CI −0.58 to −0.15). Subgroup meta-analysis in studies with a mean age under 51 years old suggested that lifestyle modification intervention remained to be effective in improving physical activity and fasting blood glucose.

Conclusion The effective interventions identified in this review although with a small sample size and short duration could potentially inform future design of primary prevention of CVD in premenopausal women.

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death among women worldwide despite the substantial advances

Strengths and limitations of this study

- The first systematic review for primary prevention of cardiovascular disease in young women.
- Results could guide the design of future clinical trials.
- Interventions involving lifestyle modifications were promising.
- None of the included studies specifically focused on premenopausal women.
- Small number of included studies did not permit accurate assessments of publication bias.

in disease awareness, prevention and treatment.¹ Early detection and managing women at risk of CVD will prevent hospital admissions, save lives and improve the quality of life of those affected. Therefore, primary prevention of CVD is receiving extensive attention in the research field.

Primary prevention normally involves modification of CVD risk factors. Traditional CVD risk factors include obesity, hypertension, dyslipidaemia, diabetes, physical inactivity, excessive alcohol consumption and smoking, while non-traditional CVD risk factors comprise pregnancy-related disorders, such as gestational diabetes and hypertension, preterm delivery (PTD) and endocrine disorders in women of reproductive age (ie, polycystic ovary syndrome and early menopause).^{2–4} For example, premenopausal women without a history of PTD are relatively protected against CVD, whereas women with such a history are prone a significantly earlier onset of CVD,² resulting in higher losses in terms of premature mortality and productivity. Meanwhile, other CVD risk factors, even though not exclusive to women, have much higher prevalence in women than men (ie, migraine which is associated with risk of stroke, occurs three times more often in women).^{5 6} The American Heart Association

(AHA)/American Stroke Association guidelines for the prevention of CVD in women recommend CVD risk assessment in women with certain reproductive manifestations of CVD risk (such as pregnancy-related adverse outcomes) and suggest that female-specific risk factors may improve/complement the current CVD risk assessment strategies.^{7,8} To combat the ever increasing disease burden of CVD, identifying effective ways to prevent CVD in specific risk groups potentially offers the best solutions; this provoked the interest to uncover interventions that are tailored to altering the CVD risk profiles of premenopausal women.

While research around primary prevention of CVD has examined a wide range of interventions from pharmaceuticals to lifestyle modification programmes, these studies have generally recruited people of older age (ie, postmenopausal) and/or both gender groups.^{9–11} There is a growing appreciation that there may be gender differences in the magnitude of the relative and absolute potential benefits and risks associated with preventive interventions.^{12,13} Hence, evidence from studies in unrestricted populations is not necessarily applicable to women of younger age (ie, premenopausal). Besides, there is no specific study that has been designed to investigate how to improve the CVD risk profiles for women with histories of pregnancy-related complications (ie, PTD, gestational diabetes).

In light of (1) the clinical need to look for effective primary prevention interventions that can alter the trajectory of CVD development for women with non-traditional CVD risk factors identified (ie, PTD, diagnosis of polycystic ovary syndrome, etc) earlier in their lives and (2) the potential for gender-based and even age-based differences (ie, some interventions may be more effective in younger women) in CVD,^{14–16} studies are warranted to explore the primary prevention of CVD for women of reproductive age. An ideal way to address this research question would be to conduct a randomised controlled trial (RCT) to compare various interventions in this specific group of women, but is prohibitive in terms of resources and time required. Alternatively, we can capitalise on existing studies to provide timely, preliminary evidence that may assist with selecting an optimal intervention for further investigation given that there are at least two broad groups of primary prevention interventions, including medications (ie, aspirin,¹⁷ statins,¹³ vitamin E,¹⁸ etc), physical activity/counselling in lifestyle modification programmes¹⁹ for CVD in the general population.

The current study undertakes a systematic review of RCTs that examined the effectiveness of primary prevention interventions for CVD in premenopausal women and meta-analyses the effects for studies investigating the same type of intervention. The aim is to provide evidence to identify a candidate intervention that is likely to be effective in young women with non-traditional CVD risk factors (ie, pregnancy-related complications, endocrine disorders, migraine, etc).

METHODS

Literature search

An electronic literature search was conducted in Medline (plus PsycINFO via EBSCO) and Embase. The search was carried out in July 2018 using the key search terms including women, primary prevention, CVD (myocardial infarction (MI), stroke and heart failure), with filter for RCTs. Studies that met the following criteria were included: (1) comprise a cohort of females (at least 50% of all participants were female) and with a mean age of 55 years or under with no established CVD (55 was selected as a crude proxy due to the absence of cut-off age for menopausal status)^{20–22}; (2) participants randomised to intervention or usual care (or placebo) and (3) report at least one of the following outcomes: numbers of major adverse cardiovascular events (MI, stroke, coronary revascularisation, cardiac sudden death, angina), all-cause mortality, incident case of diabetes, surrogate outcome (blood pressure (BP), lipids, body mass index (BMI), level of physical activity, inflammatory markers); (4) publication is presented fully in English; (5) control group for these interventions received the standard care as per the current practice. Exclusion criteria were trials that included predominantly (ie, >50%) male participants and/or females age >55 years; trials with small samples (ie, recruited less than 30 participants); studies published prior to 2000 were excluded as the aim was to identify contemporary evidence to guide the design of future interventions. Studies meeting the inclusion criteria based on full-text examination were assessed and extracted for further analysis by two reviewers (JF and IM). Predesigned tables were used to guide the data extraction. Data on patient characteristics, study design, duration of follow-up, intervention characteristics and outcomes were extracted. The quality of the included studies was evaluated individually following the Cochrane Risk of Bias Tool²³ with due consideration of six domains (ie, judgement on the risk of bias will be made for each domain based on three categories: high risk, low risk and unclear risk of bias). The detailed search strategies are provided in online supplemental file 1.

Data analysis

Interventions were grouped for further analysis based on their nature of delivery/content of the intervention. Where more than two studies evaluated the same intervention, the outcomes were meta-analysed using inverse variance method with either a fixed or random effects model in Review Manager (V.5.3, The Cochrane Collaboration, 2014) depending on the magnitude of the heterogeneity across the studies (>50% suggests substantial heterogeneity). If the results from subgroup (ie, women aged younger than 55 years old) were reported, they were extracted for the analysis. Summary effects were reported as relative risk (RR) with corresponding 95% CI if the outcome was dichotomous or as a mean difference (MD) with the 95% CI if the outcome was continuous. Heterogeneity across RCTs were assessed using χ^2 test and I^2

statistic. Forest plots were used to report results of meta-analysis. Publication bias were assessed using funnel plots.

Subgroup analysis

Where applicable, subgroup analysis was performed to examine the intervention effect in subgroups of women with a younger cut-off age for menopausal status (ie, <51 years old) or varied characteristics, for example, baseline CVD risk factors.

The methods for systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of the systematic review.

RESULTS

Literature search

The initial literature search through Embase, Medline, CINAHL and Cochrane Library identified 1185, 471, 127 and 38 citations, respectively. The updated search in May 2020 identified an additional 424 citations. From the total 2245 retrieved citations, 505 were duplicates as identified by Endnote. A total of 1740 articles were screened for title and abstract, from which 1209 articles were excluded due to irrelevance (n=864), duplicates found manually (n=151), articles published before 2000 (n=189) and not in English language (n=5). The remaining 531 articles were assessed on a full-text basis; 517 were excluded due to non RCTs (n=375), age older than 55 years (n=81), majority being males (n=1), sample size less than 30 (n=3), prior histories of CVD (n=2), duplicate publications of included studies (n=2), irrelevant outcomes (n=6) and non-premenopausal studies (n=47). Thus, a total of 14^{17 19 24-35} articles were included into this systematic review. The study selection process is illustrated in figure 1. Key characteristics of the included studies are summarised in table 1. Details of each study are supplied in online supplemental tables.

Types of interventions

Since the interventions in the included studies were heterogeneous and reported different outcomes that related to CVD primary prevention, the studies have been grouped by type of intervention for further analysis. There are four broad types of interventions for primary prevention of CVD in women:

1. Diet intervention, N=2.
2. Lifestyle modification intervention (ie, modification of diet and physical activity), N=7.
3. Vitamin E/antioxidant, N=3.
4. Aspirin, N=2.

Four studies included data from the Women's Health Study which was a large randomised, double-blind, placebo-controlled trial to examine the benefits and risk

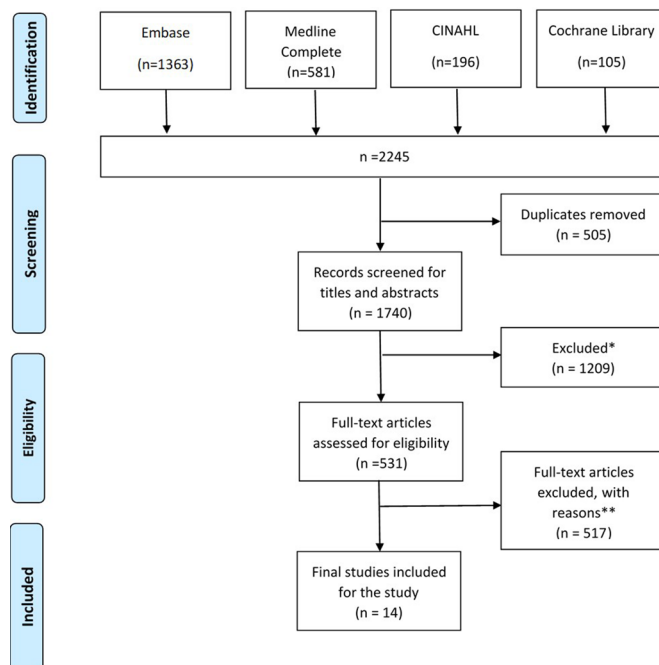


Figure 1 PRISMA flow diagram for the selection of included studies in the systematic review. *Reasons for exclusion: Manual removal of further duplicates (n=151). Not in English (n=5). Title and abstract not relevant (n=864), Older than 2000 (n=189). **Reasons for exclusion: Females < 55 years of age (n=81). Existing CVD (n=2). Outcomes not relevant (n=6). Part of an included articles (n=2). Non-premenopausal females (n=47). Majority men (n=1). Sample size < 30 (n=3). Non-RCT study (n=375). CVD, cardiovascular disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

of low dose aspirin and vitamin E in the primary prevention of CVD for women.^{17 28 29 32} Moore *et al* compared four interventions in a single study, which were treated as separate studies in the analysis.³⁵

Characteristics of the included studies

Generally, the included RCTs were heterogeneous in terms of intervention (diet interventions, medications, lifestyle modifications), populations (women only or mixed-sex cohorts), age groups (premenopausal only or mixed premenopausal and postmenopausal), intervention duration (ranged from 2¹⁹ weeks to 10 years,²⁸ primary/secondary outcomes (eg, incidence of first CVD events, changes in CVD risk factors and level of physical activities, urinary potassium excretion, etc), sample size (ranged from 49 to over 39,000), length of follow-up (from 2 weeks to 10 years) and setting (Asia, Africa, South America, Europe). The key characteristics of the included studies are summarised in table 1.

Risk of bias assessment of included studies

The majority of studies were rated as low risk of bias for selection (14/14), performance (8/14), detection (9/14), attrition (11/14) and reporting (12/14) bias. Overall, two studies involving five publications^{17 28 29 32 34} were considered low risk of bias in all assessed domains;

Table 1 Summary of characteristics of included primary prevention interventions of CVD in premenopausal women

Study, country	Study year	Population characteristics	Study design	Study setting	Intervention	Control	Treatment duration	Primary outcomes	Secondary outcomes
Diet									
Tuekpe <i>et al.</i> ¹⁹ Japan*	March–April 2005	Normotensive, free-living Japanese women aged 19– 38 years living in Okinawa Mean age: Intervention: 24.4 (3.8) Control: 25.7 (4.8)	Randomised-controlled trial N=56	Home-based setting	Home delivery of an average weight of 371.4 g/day combination of vegetables delivered twice weekly through an express home delivery service for a period of 14 days: Goya (<i>Momordica</i> <i>charantia</i>), green papaya (<i>Carica papaya</i>), Handama (<i>Gynura bicolor</i>), Karashina (<i>Brassica juncea</i>), Njiana (<i>Crepidiastrum lanceolatum</i>), Fuchiba (<i>Artemisia vulgaris</i>) and Fudanso (<i>Beta vulgaris</i>) (n=27)	Asked to avoid vegetables included in the intervention (n=29)	14 days	Urinary potassium excretion	Other urine electrolytes and serum folic acid, triglycerides and high-density lipoproteina (HDL), cholesterol, low- density lipoprotein (LDL) cholesterol and total cholesterols
Moore <i>et al.</i> ²⁸ UK	NR	Overweight men and women (BMI between 25 and 40 kg/m ²); aged 35–60 years; not consuming regular oil supplements, NSAIDs, aspirin, steroids, immunosuppressants, or lipid-lowering drugs; not diagnosed with diabetes, hypertension, hyperlipidaemia, asthma or chronic inflammatory diseases; female subjects are not pregnant or planning pregnancy mean age: 50 (9) BMI: 30.3 (3.9)	Double-blinded, randomised- controlled dietary intervention trial n=157	Home-based setting	Whitefish/rapeseed (n=29) Whitefish/sunflower (n=30) Oily fish/rapeseed (n=32) Oily fish/rapeseed (n=32)	No intervention (n=34)	24 weeks	Fatty acid intake; fatty acid status; anthropometry and body composition; CVD risk factors; insulin sensitivity; inflammatory status	
Vitamin E									
Lee <i>et al.</i> ²⁸ USA	Women's Health Study conducted between 1992 and 2004	Apparently healthy US women aged at least 45 years Mean age (SD): 54.6 (7.0) 45–54: 24 025 (60.3%) BMI: mean (SD): 26.04 (5.06) <25: 19 849 (50.8%) 25–29: 12 081 (30.9%) >29: 7 126 (18.2%) Premenopause: 10 973 (27.6%)	Randomised, double-blind, placebo controlled 2x2 factorial trial n=39 876	Individual setting	Vitamin E (600 IU of α -tocopherol) every other day (n=19 937)	Placebo (n=19 939)	10 years (women received calendar packs each year)	Composite end point of first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death)	Total invasive cancer

Continued

Table 1 Continued

Study, country	Study year	Population characteristics	Study design	Study setting	Intervention	Control	Treatment duration	Primary outcomes	Secondary outcomes
Herberg <i>et al.</i> , ³⁴ France	March to July 1994	Women aged 35–60 years or men aged 45–60 years; absence of disease likely to affect active participation or may be a threat for 5 years survival; acceptance of the chance of receiving a placebo and acceptance of constraints of participation; lack of history of regular supplementation with any of the vitamins or minerals in the supplement provided; and absence of extreme beliefs or behaviour regarding diet Women mean age: 46.6 (6.6) BMI: 22.9 (3.0) Postmenopausal: 26.9%	Randomised, double-blind, placebo-controlled primary prevention trial n=7713	Individual setting	Single daily capsule of combination of antioxidants: 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of beta carotene, 100 µg of selenium, and 20 mg of zinc (n=3869)	Placebo (n=3844)	8 years cohort study (as per trial protocol) patients received 52 weekly packs of 7 capsules	Major fatal and nonfatal ischaemic cardiovascular events	All-cause mortality
Liu <i>et al.</i> , ²⁹ USA	Women's Health Study conducted between 1992 and 2004	Apparently healthy US women aged at least 45 years Mean age (SD): 54.6 (7.0) 45–54: 23 473 (60.6%) BMI: mean (SD): 25.9 (4.96) <25: 19 655 (51.8%) 25–29: 11 713 (30.9%) >29: 6563 (17.3%) Premenopause: 10 757 (27.9%)	Randomised, double-blind, placebo controlled 2x2 factorial trial n=38 716	Individual setting	Vitamin E (600 IU of α-tocopherol) every other day (n=19 347)	Placebo (n=19 369)	10 years (women received calendar packs each year)	Incidence of diabetes mellitus type 2	
Lifestyle modification interventions									
Koniak-Griffin <i>et al.</i> , ²⁷ USA	Data were collected between January 2010 and August 2012	35–64 years, self-identified Latina/Hispanic overweight Women Mean age (SD): 44.6 (7.9) Mean BMI: Intervention: 32.37 (5.00) Control: 32.86 (6.29)	Single blinded, randomised using web-based programme with 1:1 intervention to control ratio using block randomisation procedure n=223	Group based setting	6 months Lifestyle Behaviour Intervention comprised of group education (eight weekly classes in the first 2 months) plus individual teaching and learning (over 4 months), (n=111)	6 months safety/disaster preparedness educational programme (eight classes) plus individual teaching and learning (eight classes) (n=112)	6 months interventions with data collected at baseline, 6 months and 9 months follow-up	Dietary habits, physical activity and clinical measures including BMI, weight, waist circumference, blood pressure, lipids and blood glucose	
Hardcastle <i>et al.</i> , ²⁵ UK	NR	18 to 65 years old with at least 1 CHD risk factor; BMI (28 or more), hypertension (at least 150/90 mm Hg), and hypercholesterolaemia (at least 5.2 mmol/L) Mean age: 51.10 (0.58) Females: 240 (67%) BMI: 33.99 (0.33)	Stratified, randomised controlled trial with 7:5 intervention to control ratio n=334	Individual setting	Counselling delivered by a Physical activity specialist and a registered dietitian (n=203)	Standard information only (n=131)	6 months treatment duration	Blood pressure and resting blood sample (cholesterol, triglycerides, HDL, LDL)	Self-reported physical activity, fat intake, fruit, and vegetable consumption

Continued

Table 1 Continued

Study, country	Study year	Population characteristics	Study design	Study setting	Intervention	Control	Treatment duration	Primary outcomes	Secondary outcomes
Stuart <i>et al.</i> , ³³ Australia	August to November 2010	Adults aged 30–56 years with BMI greater or equal 26.0 and less or equal 40.0 kg/m ² , waist circumference >0.102 cm for men and >0.88 cm for women mean age: 48 (5.88) Females: 30 (61%) BMI: 33.13 (5.39)	Randomised trial (parallel, with block and stratified sampling) n=49	Individual setting	Telephone-supported comprehensive lifestyle intervention programme (n=26)	Usual care - written general lifestyle advice (n=23)	12 week intervention (outcomes measured at week 0 and then at week 12)	Fasting plasma lipids, blood pressure, weight, height, and waist circumference; physical activity and motivation	
Pazoki <i>et al.</i> , ³¹ Iran	NR	Women ages 25–65 years Mean age: 39.4	Multistage stratified cluster random sampling N=335	Community based setting	8 weeks lifestyle modification programme for increasing physical activity based on a revised form of Choose to Move programme, an American Heart Association Physical Activity Programme for Women. Audio-taped activity instructions with music and practical usage of education package. Weekly home-visits (n=170)	No intervention (n=165)	8 week lifestyle modification programme with follow-up at week 0 and end of week 8	Physical activity	BMI, blood pressure, total cholesterol, triglycerides, fasting blood sugar, knowledge score
Low <i>et al.</i> , ³⁰ USA	2011–2012	Female employees aged 40–65 years with one or more risk (overweight, high stress level, lack of physical activity or smoking). Hypertensive (systolic ≥ 200 mm Hg, diastolic ≥ 110 mm Hg), blood glucose (≥ 300 mg/dL) requires physician approval. Mean age: 52 (6.3) Intervention: 51 (6.5) Control: 53 (6)	Unblinded randomised controlled trial with 1-year follow-up after the programme N=57	Individual setting	Weekly communication (phone or email) integrating goal setting and overcoming obstacles in addition to what the control group is provided (n=28)	Risk reduction classes on weight loss/nutrition, stress management, exercise training, and smoking cessation, access to an on-site gymnasium, and organised walks (n=29)	6 months programme duration	Cardiovascular risk factors (weight, stress, physical activity)	
Kandula <i>et al.</i> , ²⁶ USA	June 2012–November 2013	South Asian Immigrants (mainly Indian and Pakistani); aged between 30 and 59; with at least one atherosclerotic cardiovascular disease risk factor (obesity, hypertension, hyperlipidaemia, pre-diabetes and diabetes) Female: 63% mean age: 50 (8) BMI: 30 (5)	Single blinded, randomised controlled trial N=63	Group based setting	6 interactive group classes focused on increasing physical activity, healthful diet, weight, and stress management with telephone follow-up (n=31)	Translated print education materials about ASCVD and healthy behaviours (n=32)	16 weeks lifestyle intervention with additional 10 weeks telephone support (6 months intervention duration)	Change in moderate/vigorous physical activity and dietary saturated fat intake at 3 and 6 months	Clinical and psychosocial outcomes
Cappuccio <i>et al.</i> , ²⁴ Africa	2001–2002	Adults aged 40–75 years Mean age: 54.7 (11.3) Females: 628 (62%)	Community-based cluster randomised trial incorporating health promotion N=1013	Community based setting	Intensive health education programme with additional advice not to limit salty food intake, or add salt to food and cooking (n=522)	Intensive health education programme (n=491)	6 months	24 hours urine and blood pressure	

Continued

Table 1 Continued

Study, country	Study year	Population characteristics	Study design	Study setting	Intervention	Control	Treatment duration	Primary outcomes	Secondary outcomes
Aspirin									
Pradhan <i>et al.</i> ³² USA	Women's Health Study conducted between 1992 and 2004	Healthy women aged >45 years and free of clinical diabetes Mean age: NR % age: 45–54 years: 60.6 %	Double-blinded trial N=38 716	Individual setting	100 mg aspirin on alternate days N=19 326	Placebo N=19 390	10 years (women received calendar packs each year)	Incidence of clinical type 2 diabetes	
Ridker <i>et al.</i> ¹⁷ USA	Women's Health Study conducted between 1992 and 2004	Healthy Women Mean age: 54.6±7.0 Mean BMI: 26.0±5.1 Premenopausal (%): 27.6 Mean age: Intervention: 54.6±7.0 Control: 54.6±7.0 Mean BMI: Intervention: 26.1±5.1 Control: 26.0±5.0	Double-blinded trial N=39 876	Individual setting	100 mg aspirin on alternate days N=19 934	Placebo N=19 942	10 years (women received calendar packs each year)	A combination of major cardiovascular events, including nonfatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes	Individual end points of fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, ischaemic stroke, haemorrhagic stroke, and death from cardiovascular causes.

*Vegetables include: Goya (Momordica charantia), green papaya (Carica papaya), Handama (Gynura bicolor), Karashina (Brassica juncea), Njana (Crepidiastrum lanceolatum), Fuchiba (Artemisia vulgaris) and Fudaniso (Beta vulgaris); level of blood pressure is negatively correlated with the urine excretion of potassium.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; NSAID, Nonsteroidal anti-inflammatory drug.

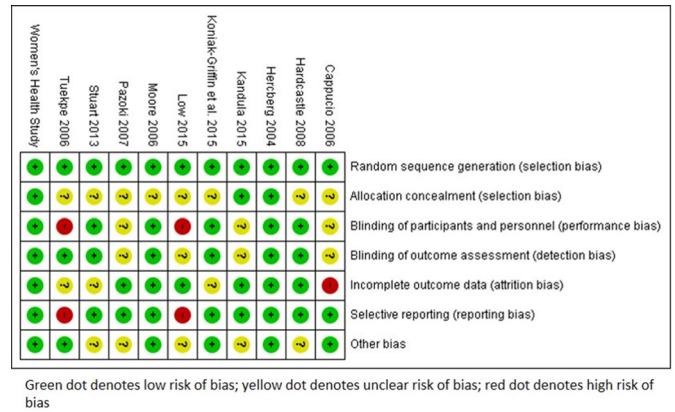


Figure 2 Risk of bias assessment of included studies.

three studies^{25 27 35} with one or two domains of unclear risk; three studies^{26 31 33} with three to four domains of unclear risk of bias; and three studies^{19 24 30} with one or two high risk of bias domains rated. The detailed risk of bias assessment is provided in figure 2.

Results of quantitative synthesis

Diet intervention

Two of the included studies related to dietary interventions. The study by Tuekpe *et al* trialled supplementing the diet of healthy women aged 18–38 years old with a combination of vegetables (ie, yellow-green Okinawan vegetables) over a 2-week period. At the end of the intervention, they found a significantly increased bioavailability of urinary potassium (a mineral associated with reduced BP and heart attack), but no significant changes in lipid level.¹⁹

Another study by Moore *et al* tested the health benefits of the consumption of different types of fish (ie, white or oily) combined with replaced habitual household fats (sunflower or rapeseed oil) in an overweight mixed-sex population aged 35–60 years.³⁵ The four interventional groups (two types of fish ×two types of replaced oils) were meta-analysed synthetically and both studies included participants with a mean age under 51 years old. There was no significant difference in the change of lipid levels after this dietary intervention (p>0.05 with all comparisons in triglycerides, cholesterol and low-density and high-density lipoproteins, body weight (p=0.93) and BP (p>0.05 for both systolic and diastolic), with no heterogeneity detected (all with I²=0). Forest plots showing results of the meta-analysis are available from online supplemental file 1.

Vitamin E/antioxidant

Three articles from large trials (with 7713 participants in one study and more than 38 000 subjects from the Women's Health study in the other two) investigated the efficacy of vitamin E in women exclusively.^{28 29 34} The medium follow-up was more than 7 years in all three studies. Studies by Herberg *et al* and Lee *et al* reported the incidence (ie, de novo cases) of major cardiovascular events (ie, nonfatal MI, nonfatal stroke, or death from

cardiovascular causes) and overall mortality over 10 years of follow-up, while Liu *et al* reported the incidence of type 2 diabetes.²⁹ No meta-analysis was conducted due to the potential overlapping in the study populations recruited from the Women's Health study. RRs of reduction in incidence of major cardiovascular events, mortality and diabetes show no significant difference in each individual studies.

Lifestyle modification intervention

Seven studies focused on interventions involving a lifestyle modification programme in a community setting, which were grouped together for further analysis.^{24-27 30 31 33} Components of these interventions included physical activity, diet and lifestyle education/counselling, and multiple follow ups over time. Five^{25-27 30 33} out of seven studies focused on women with increased risk of CVD, while the other two recruited women without any CVD risk factors.^{24 31} The meta-analysis of six studies^{24-27 31 33} suggested an overall reduction in the systolic BP by an MD) of -2.11 mm Hg (95% CI -4.32 to 0.11 , $p=0.06$, $I^2=0\%$) favouring the intervention group. The meta-analysis of five studies^{24 25 27 31 33} showed a significant reduction also in diastolic BP with a reduction of MD of -3.31 mm Hg (95% CI -4.72 to -1.91 , $p<0.001$, $I^2=0\%$). The subgroup analysis by baseline risk of CVD suggested that for reduction in systolic BP, women without CVD risk factors (-3.16 mm Hg, 95% CI -6.32 to -0.01 , $p=0.05$, $I^2=0\%$) tended to benefit more from the intervention than those with existing CVD risk factors (-1.08 mm Hg, 95% CI -4.19 to 2.03 , $p=0.88$, $I^2=0\%$); on the other hand, for diastolic BP, both subgroups achieved similar significant reductions (figure 3). Among these studies, the meta-analysed

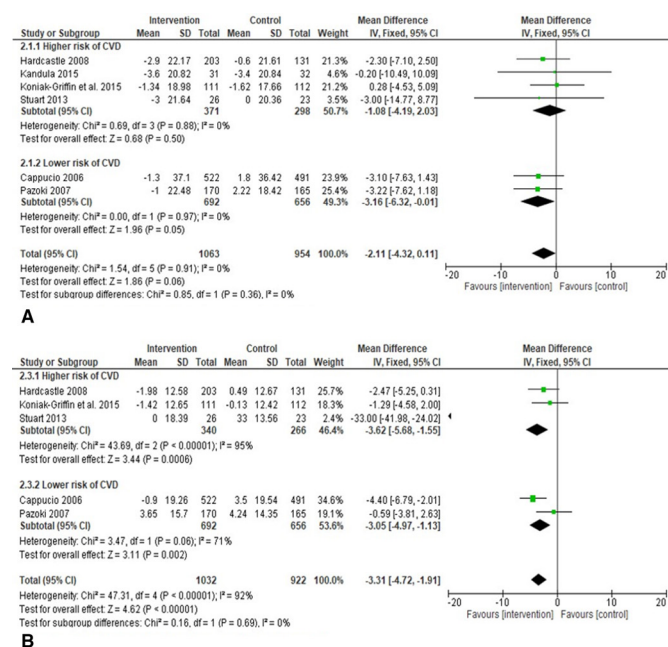


Figure 3 Forest plot of lifestyle modification intervention on blood pressure. (A) Systolic blood pressure (mmHg). (B) Diastolic blood pressure (mmHg). CVD, cardiovascular disease.

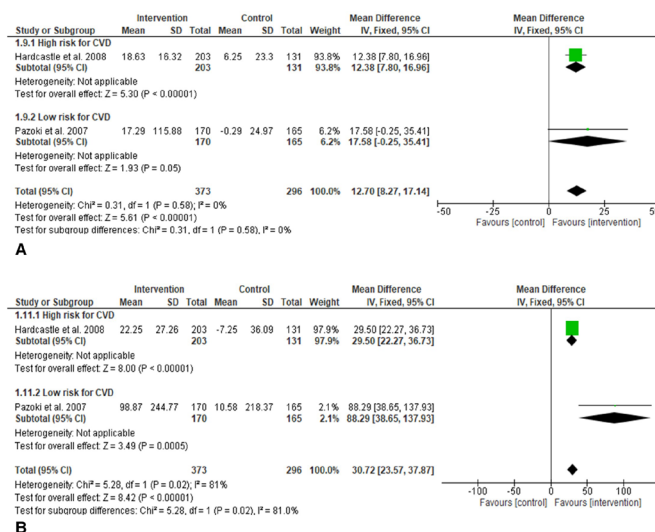


Figure 4 Forest plot of lifestyle modification intervention on physical activity. (A) Vigorous physical activity (MET-min/week). (B) Moderate physical activity (MET-min/week). CVD, cardiovascular disease.

results (N=669)^{25 31} also showed that there was a significant improvement in moderate and vigorous physical activity levels. MD of 30.72 Metabolic equivalent of task (MET)-min/week (95% CI 23.57 to 37.87, $p<0.001$, $I^2=81\%$) was reported for moderate physical activity and an MD of 12.70 MET-min/week (95% CI 8.27 to 17.14, $p<0.001$, $I^2=0\%$) for vigorous physical activity (figure 4). In addition, the meta-analysis^{26 27 31} also indicated that the intervention led to significant reduction in fasting blood sugar (-0.37 mmol/L, $I^2=76.4\%$, $p<0.001$).

Subgroup analysis indicated that this intervention in lowering the systolic BP became insignificant by adopting a younger cut-off age for menopausal status (ie, <51 years instead of 55 years) while the improvements in physical activity and fasting blood glucose sustained. Further, women without baseline CVD risk factors were likely to experience greater reduction in fasting blood glucose (online supplemental figures).

Aspirin

Two publications^{17 32} each reported different outcomes—incidence of major CVD events in one publication and incidence of type 2 diabetes in women treated with aspirin for a median of 10 years in the other—from the same long-term study (ie, Women's Health Study) which had a large sample size (N>37 000). Aspirin was shown to lower the occurrence of ischaemic stroke but did not alter the risk of MI or overall mortality over a 10-year follow-up; meanwhile, low dose of aspirin did not prevent the development of type 2 diabetes in healthy women as well.^{17 32} For the subgroup with premenopausal age (aged between 45 and 54 years), none of the studies (N=24 025 in the CVD prevention and N=23 473 in the type 2 diabetes prevention studies, respectively) detected a significant intervention effect for the primary outcomes

(ie, incidences of major CVD event, $p=0.92$, and cases of type 2 diabetes, $p=0.29$).

The detailed results of meta-analysis by intervention type are presented in online supplemental figures.

DISCUSSION

From 14 RCTs reviewed, it suggested that diet nor vitamin E/antioxidant did not significantly lower the CVD risk profiles, while lifestyle modification programme showed great potential to improve risk profiles via meta-analysing studies with smaller sample size and shorter duration of follow-up. The commonly used CVD prediction score illustrated the significant difference in coronary heart disease (CHD) risk between women and men before age of 70. It is reported that the onset of CHD in women lags behind that in men by 10–15 years.^{36 37} This is echoed by our identified study that showed that aspirin was able to lower the risk of ischaemic stroke but not MI in women of mixed age (ie, women with mean age of 55).¹⁷ Recent data further suggests stagnation in the improvements in incidence and mortality of CHD, specifically among younger women (<55 years).³⁸ It is imperative that actions to be taken to reduce future CVD morbidity and mortality in young women with traditionally (ie, high BP and levels of lipids) and non-traditionally recognised risk factors that are unique to or more common in women (ie, histories of pregnancy-related complications or autoimmune diseases).³⁹ Identifying interventions that could be effective for this age and gender group is essential given that CVD shows evident age and gender differences (ie, primary prevention interventions in older mixed-gender populations are not necessarily as effective in younger sex-specific populations).^{40 41} To fill this knowledge gap, our systematic review identified primary prevention interventions of CVD that had been tested in young women (ie, \leq age of 55) to fill; it will facilitate the design of clinical studies to examine the effectiveness of primary prevention for CVD in this population. The results from the systematic review and meta-analyses showed that diet or vitamin E/antioxidants supplement did not significantly improve CVD risk factors or alter the incidence of CVD; meanwhile, lifestyle modification programmes (incorporating a component of physical activity) had a moderate impact in terms of improving CVD risk factors.

A systematic review by Guirguis-Blake *et al* summarised evidence on the efficacy of aspirin for the primary prevention of CVD; it concluded that aspirin reduced the risk of nonfatal MI (RR 0.78, 95% CI 0.71 to 0.87) but not nonfatal stroke in non-sex specific population, while older adults achieved greater relative MI reduction.⁴² One of the studies included in Guirguis-Blake systematic review, which was also included in our current review, showed a statistically significant 34% reduction in total MI only among women aged over 65 years (RR 0.66, 95% CI 0.44 to 0.97).¹⁷ Consistent with these findings, guidelines for the use of aspirin for CVD prevention take this gender difference into consideration: aspirin use in

males is primarily intended for the prevention of CHD, while in females, prevention of stroke is the main target.⁴³ Although the mechanism accounting for this gender difference is undisclosed, limited evidence suggests that there may be some biological basis for these differences (eg, baseline platelet reactivity is greater in women than in men, with higher residual reactivity following aspirin treatment in women).⁴⁴ All this highlights the importance of considering sex together with the age difference in choosing an appropriate primary prevention of CVD in young women.

Contemporary clinical trials in the field of CVD often face the limitation of under-representation of female participants.^{45 46} Considering the well-recognised sex-difference in interventions targeting CVD, it is important to ascertain the intervention impact for women exclusively. To the best of our knowledge, there is no systematic review conducted to examine the efficacy of primary prevention interventions for CVD in premenopausal women (ie, age younger than 55 years). Existing reviews of primary prevention interventions of CVD in mixed age groups of women reported inconsistent results, and have primarily focused on pharmacological interventions. Trials focused on the efficacy of statins have generally recruited women of older age, and showed mixed effectiveness results. The JUPITER 2008 trial reported rosuvastatin significantly lowered the incidence of major cardiovascular events,¹³ while another meta-analysis synthesising evidence from six trials concluded that statins did not significantly impact on total or CHD mortality or major cardiovascular events.⁴⁷ The most recent 2019 American College of Cardiology/AHA Guidelines on the primary prevention of CVD stipulates that weak evidence exists to support the use of statins in people with borderline CVD risk (<7.5% 10-year CVD risk).^{48 49} Similarly, there is no strong evidence to support the administration of low-dose aspirin (75–100 mg/day) among adults 40–70 years old.^{48 49} However, these recommendations again highlight the importance of lifestyle factors that affect CVD risk.

Interventions that have a lifestyle modification component show a great potential for primary prevention of CVD in young women. The seven studies reviewed comprised various components that included increasing physical activity and/or healthy lifestyle through audio-taped activity instructions, written advice, with or without telephone/home visit/face-to-face counselling/follow-up.^{24–27 30 31 33} Generally, these short-term studies (ie, follow-up ranged from 8 weeks to 6 months) found that these interventions were able to improve some of the CVD risk factors (ie, physical activity time, BP, fasting blood glucose, etc). If a more comprehensive/effective lifestyle intervention is to be developed for young women, the components from each of the study could be extracted and combined. For example, daily activity instructions could be potentially united with face-to-face counselling or intensive health education programme to achieve a better outcome, by taking



women's preferences and the advance in mobile technologies into consideration.

This is the first study to systematically review existing evidence on the primary prevention of CVD in women with reproductive age. Our systematic review did not include primary prevention intervention of CVD through the use of statins or hormone replacement therapy since these trials recruited women post-menopausal exclusively. This has significant importance since women are associated with sex-specific CVD risk factors that are acquired early in their life, for example, pregnancy-associated complications, oral contraceptives, polycystic ovary syndrome, autoimmune diseases, etc. However, in reality, if women do not have traditionally recognised CVD risk factors, they are not cared for by the usual primary prevention interventions targeted at CVD internationally. Early intervention for those at risk could prevent or postpone the onset of CVD disease later in the life. The potentially effective and ineffective interventions targeting primary prevention of CVD identified in this systematic review will provide fundamental evidence to guide the design of interventions and clinical trials.

Some limitations are worth mentioning. First, we were not able to obtain individual level data from included studies. The majority of studies only recruited a proportion of women aged younger than 55 years (ie, a crude proxy for the menopausal status) and did not report outcomes by age groups, with only one study focused on women aged 18–38 years.¹⁹ However, it is believed that evidence from studies incorporated premenopausal women could still form the basis for intervention selection targeted for this population. Particularly, for lifestyle modification interventions, three studies enrolled women exclusively and in the other four, women accounted for the majority of participants. The 1-year follow-up results from the study by Hardcastle *et al* reported that the benefits (eg, reductions in BP, weight and BMI) observed during the 6-month of intervention period did not sustain to 1 year.⁵⁰ The decay of intervention effect raises a major concern from an implementation perspective. Further, especially for the studies investigated the lifestyle intervention, the difference in study design and intervention duration may impact on the conclusions drawn from them. Future clinical trials that are adequately powered and have longer-term follow-up, are warranted to investigate the long-term interventional impact in this population.

CONCLUSION

From this systematic review of primary prevention interventions of CVD in premenopausal women, it was concluded that vitamin E (based on large and relatively long-term follow-up RCTs) and diet interventions were not effective in lowering the CVD risk factors whereas lifestyle modification programmes involving modification of diet and/or physical activity (drew on small-sized and short-term follow-up RCTs) were effective in improving a series of biomarkers including diastolic BP, moderate

to vigorous physical activity, and fasting blood glucose. Future primary prevention interventions for CVD in premenopausal women could be designed based on the effective interventions identified from this review.

Contributors LG and MM conceptualised and designed the review. JF, IM and PN reviewed titles, abstracts and full-text papers for inclusion. JF and IM independently assessed the quality of each included study. LG prepared the first draft of manuscript. LG, JF, IM, PN and MM reviewed and edited the manuscript, and approved the submission.

Funding LG is supported by the Alfred Deakin Postdoctoral Research Fellowship provided by the Deakin University, Australia.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Not applicable.

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