

## Research Article

# Effective and Sustainable Lifestyle-Interventions to Reduce the Risk of Cardiovascular Diseases for Women from the Menopause: A Literature Review

Chantal J Leemrijse<sup>1\*</sup>, Marcia Vervloet<sup>1</sup>, Liset van Dijk<sup>1,2</sup> and Joke Korevaar<sup>1</sup>

<sup>1</sup>Netherlands institute for health services research, Utrecht, The Netherlands

<sup>2</sup>University of Groningen, Department of Pharmacotherapy, -Epidemiology & -Economics (PTEE), Groningen Research Institute of Pharmacy, Faculty of Mathematics and Natural Sciences, University of Groningen, Groningen, The Netherlands

\*Corresponding author: Chantal J Leemrijse, Netherlands institute for health services research, Utrecht, The Netherlands; Tel: +31 302729692; Email: C.Leemrijse@nivel.nl

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## Abstract

**Background:** Each year 2.2 million women in Europe die from cardiovascular diseases. The risk of cardiovascular diseases increases from the onset of the menopause and may be reduced by a healthy lifestyle. However, insight in sustainable, effective lifestyle interventions targeted at women around the menopause is lacking. The aim of this study is to find sustainable, effective lifestyle interventions to reduce cardiovascular risk for women (starting) from the menopause, and to investigate effective strategies to enhance adherence.

**Methods:** Literature search for controlled studies on lifestyle-interventions for women around the menopause, that reported positive effects on cardiovascular risks.

**Results:** Two dietary interventions, eight exercise programs, three combined programs and one health coaching intervention reported a reduction of cardiovascular risk. The type of diets varies, but common features are reduction of fat and calories and application of behavioral change techniques. The exercise programs apply different types of movement, but are in general supervised group programs. All dietary and exercise interventions are characterized by many contacts and professional guidance. Several strategies to improve treatment adherence are applied such as peer support, telephone calls for missed sessions, self-monitoring and incentives. In general, a high effort to keep women in the program seems to result in relatively good adherence.

**Conclusion:** Interventions that sustainably reduce cardiovascular risk factors for women starting from the menopause are characterized by intensive strategies such as strict diets, exercise programs with many weekly sessions, guidance by professionals and high efforts to increase adherence. It is the question whether these interventions, tested in a research setting, are applicable and attractive for a large population in daily practice. The challenge is to develop less intensive but sustainable effective interventions that require less strategies to guarantee adherence. Such interventions should be tailored to the specific needs and health problems of women from the menopause.

**Keywords:** Cardiovascular risk, women, dietary interventions, exercise, menopause, healthy lifestyle

## Introduction

Cardiovascular Diseases (CVD) cause more than 4 million deaths each year across Europe, 2.2 million women and 1.8 million men [1]. There are obvious gender differences in the natural history of CVD and in risk pattern [2]. Women are older than men when they develop CVD, and present themselves with different complaints. Cardiovascular events are relatively rare in premenopausal women because of the protective activity of sex hormones during the reproductive age [3]. However, the risk of CVD increases rapidly around the menopause [4]. A healthy lifestyle may reduce this risk [5]. In established guidelines, a six-month lifestyle intervention is recommended in order to reduce cardiovascular risks [6, 7].

Worldwide about 37.5 million women are reaching or currently

at the menopause [8], and women may be postmenopausal for 30–40% of their lives [9]. The need for effective strategies or lifestyle interventions to prevent or postpone CVD in women starting from menopause is therefore high. However, effective lifestyle interventions may not be easy to find, since some studies indicate that lifestyle interventions like diet restriction or increasing physical activity have less effect in women than in men [10–12]. It is unclear whether these differences in effect exist because specific female physiological and psychosocial factors affect effectiveness in itself, because women adhere less to interventions, or both. An intervention can only work if participants adhere to it and adherence is easier when an intervention is appealing and fits into one's life and situation [13]. Women have different psychological and social mediators of physical activity participation than men [14, 15] and

female gender role responsibilities such as care for the family and older parents can lead to decreased participation in physical activity [13, 16] or difficulty with following a diet. In addition, most lifestyle programs have been designed for persons at high risk of CVD in general, and some of these interventions may be less appealing to women. This might be even more the case for women during the menopausal transition, since this period is accompanied with several physiological and psychological complaints, such as tiredness and feelings of depression and musculoskeletal pain [17-20]. Therefore, interventions tailored to this specific group by taking these specific complaints and stage of life into account may be more effective and easier to adhere to. As far as the authors are aware of, insight in sustainable, effective lifestyle interventions specifically targeting women around the menopause is lacking. The present study aims to fill this gap by a systematic search of the literature. In addition, the second objective of this study is to identify strategies that are used to increase adherence to these interventions.

The questions of this literature study are:

- What are sustainable, effective lifestyle interventions (or elements of lifestyle interventions) to reduce the risk of CVD for women starting from the menopause?
- What are effective strategies to enhance adherence to lifestyle interventions for this group of women?

## Methods

### Search strategy

Since our primary aim was to find sustainable, effective lifestyle interventions for women (starting) from the menopause, we only selected studies that reported a significantly positive effect and had a duration of at least six months [6, 7]. Since lifestyle is culturally determined and we searched for interventions that may be applicable in the Dutch primary care or public health domain, only studies from Western countries were included. As preparatory step for our systematic literature search we explored which specific modifiable risk factors and symptoms should be addressed with the intervention, by screening the literature on cardiovascular risks in women [2, 9, 21-35]. Risk factors found were used as search terms in the systematic search for potentially successful interventions. A comprehensive literature search was conducted at October 11<sup>th</sup>, 2019 in the databases Pubmed, Embase.com, the Cochrane Library, Cinahl (Ebsco), PsycINFO (Ebsco) and Sport Discus (Ebsco). The following concepts were searched (including synonyms and related terms) with controlled terms (MesH in Pubmed, Emtree in Embase, Cinahl Headings, Thesaurus terms in PsycINFO and Sport discus) and free text words: 'menopause' AND 'cardiovascular diseases' or AND 'lifestyle interventions' AND 'outcome'. The complete search history is presented in the Supplement S1. Reference lists of relevant reviews were screened for additional studies (snowball method). In- and exclusion criteria are presented in Box 1.

### Procedure

A random sample of 300 titles and abstracts were scored by one author (CL). The other authors scored each 100 titles and abstracts of

this sample (JK, LvD, MV). Since no difference were found between these double scores, the remaining of TIABs were scored by the first author (CL). Scoring of the full text papers and the completion of the tables was performed by CL and checked by JK.

#### Box 1. In- and exclusion criteria

Inclusion Criteria
- The intervention was a lifestyle intervention aimed at (a combination of) dietary behavior, physical exercise, smoking cessation, reducing alcohol intake, stress management, or sleep disturbances
- The study design was a (controlled) clinical trial (CCT or RCT)
- statistically significant positive effects were found
- the intervention is provided or applicable in primary care
- the intervention was aimed at women from menopause (peri- or postmenopausal)
- the study was performed in Western countries (Europe, US, New Zealand, Australia, Canada)
- the intervention lasted for at least six months
- results of the intervention group were compared with the results of a control group that received care as usual
- change scores of the intervention and usual care condition were statistically compared
- One of the outcome measurements was identified as an important/specific modifiable risk factor for CVD, as identified through the screening of the literature on risks of CVD in women. These included poor diet, physical inactivity, poor physical fitness, smoking, alcohol intake, weight, waist circumference, blood pressure/hypertension, cholesterol, dyslipidemia, triglycerides, metabolic syndrome, stress/anxiety, depression/mood disorders, sleep disorders, diabetes/impaired glucose tolerance (i.e. glucose intolerance /insulin resistance), arterial stiffness, inflammatory markers, inflammatory bowel syndrome, non-alcoholic fatty liver disease, homocysteine.
- the abstract was published in English or Dutch
- the study was published from October 2007-October 2019
Exclusion Criteria
- the intervention comprised just the replacement of one dietary component (e.g. soy milk instead of cow milk), or included the intake of a single food additive or supplement (e.g. fish oil)
- hormone replacement therapy was part of the intervention
- the study used historical controls
- the intervention was directed at women with diagnosed cardiovascular disease or at women who had experienced a severe CVD event
- the intervention was directed at women with, or survivors from breast cancer
- the intervention was solely directed at menopausal symptoms such as hot flashes, night sweating, memory problems and/or sexual dysfunction and not on CVD risks
- outcome measures were physical strength as a measure of physical fitness (no direct risk factors for CVD)

## Results

### Literature search

A total of 6,118 hits resulted from the electronic database searches, of which 4,212 were unique. After screening titles and abstracts, 4,036 references were excluded. Of the remaining 176 references, full text was obtained and assessed for inclusion in our study. From this search 25 publications were selected and searching reference lists provided five extra relevant publications. Finally, a total of 30 references, reporting on 13 randomized and trials and one non randomized controlled clinical trial met all inclusion criteria [36-59] (figure 1). Of these 14 studies, seven were presented in multiple publications. Table 1 in the additional file 2 shows the main characteristics of the 30 included publications.

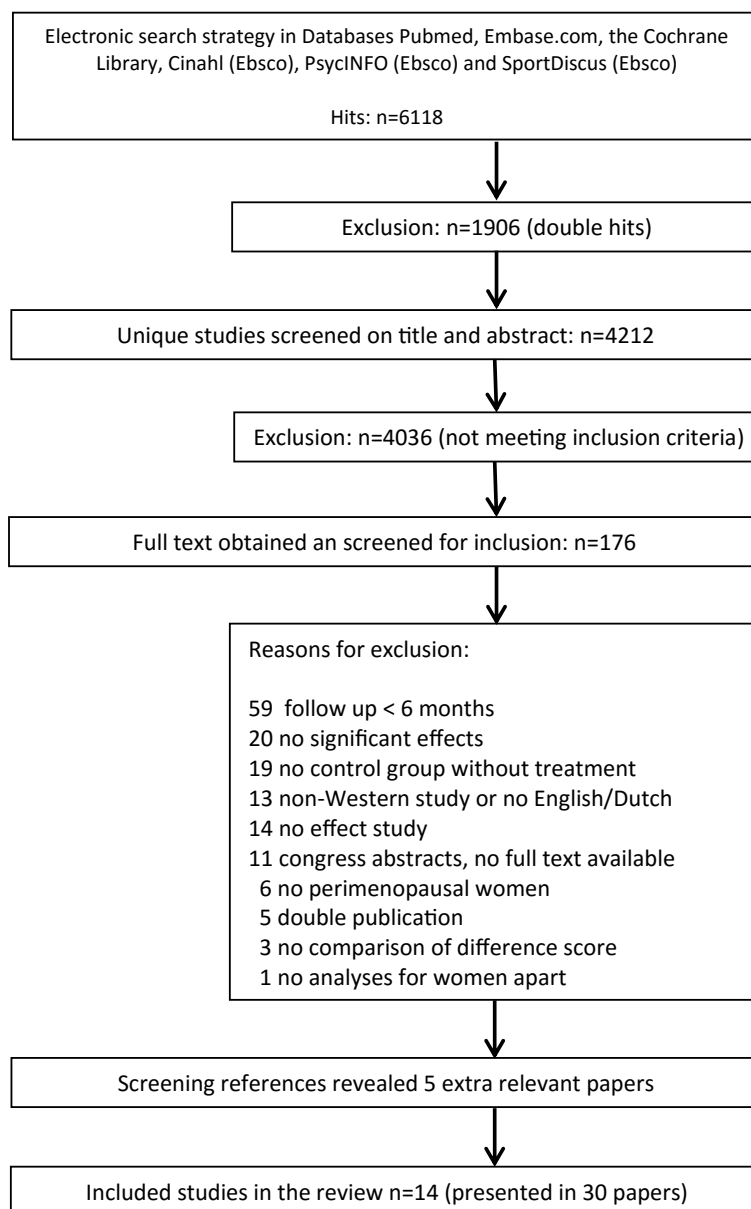


Figure 1. Selection of studies

## Study Population

Two studies were found that explicitly focused on women in the menopausal transition [36, 55]. The other studies included postmenopausal women, varying from 40 to 75 years up. For two studies (published in three publications) minimum age is unknown [55-57]. Six studies (14 publications), focused on sedentary women [38, 39, 42-47, 49-51, 54, 58, 59, 61] and four studies (11 publications), specifically on women with overweight [42-45, 49-51, 54, 55, 59]. One study specifically included women with diabetes [56, 57] while six other studies (15 publications) explicitly excluded this group of women [37, 40, 41, 43, 45-49, 51-53, 58, 61, 62]. Most studies excluded women with (a history of) severe health conditions such as cancer, heart disease, dramatically elevated blood levels or mental or psychiatric disorders [36-54, 58, 59, 61-65] or women who had medication for weight loss [43, 45, 49, 51, 55] or for lipids or blood pressure [39, 40,

53] or used hormones [46, 47, 55, 58, 62]. Six studies (15 publications) excluded women with excessive alcohol intake [36, 37, 40, 41, 43, 45-49, 51-53, 58, 61]. Almeida et al. specifically included women who suffered from hot flashes [36] and Villaverde Gutiérrez [66] included women with mood problems. In general, studies included a relatively healthy, but overweight and sedentary sample of participants.

## Interventions

Identified lifestyle interventions can be divided in dietary interventions (table 1) [37, 40, 41, 43, 45, 48, 49, 51-53, 55, 61] (supervised) physical exercise programs (table 2) [38-40, 42-47, 49-51, 53, 54, 58, 59, 62-66] a combination of diet and exercise (table 3), [40, 43, 45, 49, 51, 53, 56, 57] and health coaching (added to table 3) [36]. Since some studies used a three arms design comparing a dietary intervention with an exercise intervention and with the combination

**Table 1.** Studies with a dietary intervention

Study, authors	Intervention	Duration; contacts	Reduced CVD risk	Adherence
WHI[37, 41, 48, 52, 61] (Howard, 2010 Shikany, 2011 Carty, 2011 Assaf, 2016 Howard, 2018)	reduction of fat intake to max 20% of total energy intake, at least 4 daily servings of fruit and vegetables, at least 6 daily servings of grain	12 months; 18 group- and 1 individual session	weight, % body fat, waist-circumference, fat mass, BMI, SBP, HDL, TCL, LDL, glucose, insulin, insulin- resistance and sensitivity, fat and carbohydrate intake, depressive symptoms, sleep disturbance	unknown
Behavioral weight loss[55] (Thurston, 2015)	Calorie restriction based on initial body weight (1200-1800 calories); reduction of fat intake to less than 30% of total energy intake; intake saturated fat less than 7%; lose 10% weight by 6 months. replacement of 2 meals with liquid shakes in first 20 weeks or follow a detailed menu plan with specific conventional foods <sup>a</sup>	6 months; 20 group sessions	weight and %fat	a median of 80% of weight loss sessions was followed; 81% completed all measurements
NEW[43, 45, 49, 51] (Mason, 2011 Imayama, 2011 Foster, 2012 Duggan, 2016)	Same as Thurston, 2015: Calorie restriction based on initial body weight (1200-1800 calories); reduction of fat intake to less than 30% of total energy intake; intake saturated fat less than 7%; lose 10% weight by 6 months. replacement of 2 meals with liquid shakes in first 20 weeks or follow a detailed menu plan with specific conventional foods <sup>a</sup>	12 months; 32 group- and 2 individual sessions, 12 phone or email-contacts	weight, %body fat, waist circumference, glucose, insulin resistance, LDL	86% of diet change sessions was followed
Low-fat Diet and/or Exercise[40, 53] (Cahmi, 2010 Stefanic, 1998 <sup>b</sup> )	< 30% of the total calorie intake from fat; <7% from saturated fat; limit cholesterol intake to < 200 mg/day)	12 months; 8 group- and 1 individual sessions; 10 varying contacts (group- or individual, phone or email)	weight, waist-circumference, intake of fat, intake of cholesterol, MetS	Unknown

<sup>a</sup> Information from AHEAD protocol, not explicitly mentioned in papers of Thurston or in the papers on the NEW study[67]

<sup>b</sup> Out of timerange of initial literature search

CVD: cardiovascular diseases

BMI: Body mass index

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

HDL=High-density-lipoproteïne

LDL: Low-density-lipoproteïne

TCL: Total cholesterol

of diet and exercise, these three armed studies are presented in tables 1, 2 and 3. For the readability of this paper, references of the intervention studies are only presented in the tables, and not in the text of the results section.

### Dietary interventions

We found four studies with positive effects of a dietary intervention on the reduction of risk factors for CVD (table 1). The Women's Health Initiative (WHI) study implements a change of eating behavior rather than a prescribed diet. The behavioral weight loss study of Thurston and the Nutrition and Exercise in Women study (NEW) were based on the Look AHEAD [67] and Diabetes Prevention Program (DPP) [68]. In the AHAED protocol, it is recommended to replace 2 meals with liquid shakes in the first 20 weeks or follow a detailed menu plan with specific conventional foods [67] a strategy that is also used in the DPP to individuals who have difficulty achieving the weight loss goal. The Low-fat Diet and/or Exercise intervention of Cahmi et al. and Stefanic et al. was based on the National Cholesterol Education Program Step II Guidelines. All these interventions focused on a reduction of calorie and (saturated) fat intake, and did not solely focus on nutritional requirements, but also addressed different behavioral components, and strategies to increase adherence.

#### **Behavioral components and other strategies to increase adherence with dietary interventions**

Because the focus in the WHI study was on changing eating behavior rather than on following a prescribed diet, behavioral components were explicitly addressed. Women were assigned to a group of 12 members in which psychological and behavioral themes

such as motivation and reinforcements, social influence and support, time management, problem-solving and coping with stress, and relapse prevention were discussed. Nutrition and behavioral strategies were integrated into each session. The first sessions focused on knowledge of sources of fat and nutrition skills such as shopping and adaptation of recipes, and later sessions emphasized behavioral skills.

In the NEW study and in the behavioral weight loss intervention of Thurston each session started with a weigh-in and women were asked to fill in food dairies which were provided with feedback. Meal replacements were offered for free [67]. The behavioral weight loss intervention of Thurston et al. was a combination of individual sessions en group sessions to enhance social support. Participants were called by professionals or other group members when they missed meetings. The program was tailored to menopausal women by addressing issues such as dietary and activity choices in context of sleep loss; behavior change in the context of family, work, and caretaking demands; and physical activity choices with aging [55]. The participants in the Low-fat Diet and/or Exercise intervention of Cahmi et al. and Stefanic et al., met with a dietitian to establish individualized dietary recommendations and received counseling on how to achieve dietary goals through group sessions. They had monthly contact through individual appointments, group sessions, telephone calls, and/or mailings.

#### **Effects**

The dietary interventions reduce cardiovascular risks and effects are found on a variety of outcomes (table 1). Although the size of the effects of the studies are difficult to compare because participants and

Table 2. Studies with an exercise intervention

Study authors	Intervention	Duration; weekly contacts	Reduced CVD risk	Adherence
Drew[42, 44, 50, 54, 59] (Church, 2007 Swift, 2011 & 2012 Kline, 2012 Earnest, 2013)	alternating cycle ergometer and treadmill training. A computer-controlled exercise training management system provides the appropriate personalized power output for the cycle ergometer, and the correct speed and grade for the treadmill that will elicit the programmed heart rate	6 months; 3-4 supervised group sessions	Waist, PeakVO <sub>2</sub> , flow mediated dilatation, sleep problems, MetS, SBP, Glucose	89-95% completed all measurements
Strength and aerobic training[58] (Velthuis, 2009)	aerobic training and strength training of back, abdomen, lower and upper extremities. Participants also had to perform a weekly session of brisk walking or cycling at home	6 months; 2 supervised group sessions; 1 home based individual session	% total body fat, waist circumference	99% completed the study; 63% attended >= 70% of the group exercise sessions
Resistance training[38] (Bea, 2010)	progressive weight bearing exercises (such as walking and stair stepping with weighted vests, a circuit of skipping, hopping, jumping, and jogging) with resistance exercises, stretching and balance. Strength exercises are performed with free weights and with 8 machines for major muscles	12 months; 3 supervised group sessions	physical activity (frequency of exercising)	83% completed all measurements
Aerobic and strength training[66] (Villaverde, 2012)	8 weeks aerobic exercise, after that supplemented with muscle training exercises with increasing intensity on rhythmic music	6 months; 8 weeks 2 supervised group session thereafter 3 sessions.	depression, anxiety	90% completed ≥80 sessions
Aerobic exercise[46, 47] (Friedenreich 2012, 2013)	aerobic exercise intervention, not further described	12 months; 3 supervised group sessions; 2 home based individual sessions	weight, total body fat, adiposity, waist, hip, BMI, CRP levels	average 3.6 sessions / week; average heart rate 62.2% of the estimated heart rate reserve (70–80% prescribed)
Walking program [39] (Bernard, 2015)	(partly) supervised outdoor walking program	6 months; 2 supervised group sessions; 1 home based individual session	depression	53,8% of sessions were followed, 100% completed all measurements
NEW[43, 45, 49, 51] (Mason, 2011 Imayama, 2011 Foster, 2012 Duggan, 2013)	aerobic activities such as treadmill walking and stationary bicycling, encouragement of a variety of home exercises including walking/hiking, aerobics, and bicycling. Some resistance training recommended, not required.	12 months; 3 supervised sessions; 1 home based individual sessions	physical activity (min/week), VO <sub>2</sub> max	80% achieved targeted 225 min exercise /week
Low-fat Diet and/or Exercise[40, 53] (Cahmi, 2010 Stefanic, 1998 <sup>b</sup> )	The Low-fat Diet and/or Exercise intervention, exercise not further described	12 months; 3 supervised sessions in first 4,5 months, thereafter choice for supervised or home-based individual program	VO <sub>2</sub> max	unknown
EFOPS[63-65] (Kemmler, 2017, 2004 <sup>b</sup> , 2005 <sup>b</sup> )	Low and high impact aerobic exercises, resistance training on machines, elastic bands and free weights. Periods of high intensity/low volume are intermitted with periods of low intensity/high volume. Home sessions with isometric and dynamic resistance exercises.	16 years; 2 supervised group sessions, 2 home sessions	VO <sub>2</sub> max, TCL, waist, triglycerides; Framingham 10 year risk score (after 16 yrs) *	56% exercised ≥ 2/week and completed follow up at 3 yrs; 68% still exercised after 16 yrs.
Progressive resistance training[62] (Gómez-Tómas, 2018)	Progressive resistance training with elastic bands	12 months; 3 non-supervised sessions	weight, waist, HDL, VLDL, triglycerides; CRP	60% completed all measurements

<sup>b</sup> Out of timerange of initial literature search

\* algorithm to calculate risk of myocardial infarction and coronary death, using age, cholesterol, blood pressure, treatment for hypertension and smoking status.

Abbreviations

CVD: cardiovascular diseases

BMI: Body mass index

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

HDL=High-density-lipoproteine

VLDL: Very-low-density-lipoproteine

TCL: Total cholesterol

CRP: C-reactive protein

VO<sub>2</sub>max: maximum rate of oxygen consumption

measurement procedures differ, effects seem to be small to moderate in general.

### Adherence

In the behavioral weight loss study, participants followed a median of 80% of the weight loss sessions and 81% of the participants completed all measurements. In the NEW study, the participating women followed 86% of the diet change sessions. The WHI study and the Low-fat Diet and/or Exercise study reported no information on adherence.

### Exercise interventions

We found 10 studies (21 papers), with positive effects of an exercise intervention on the reduction of risk factors for CVD (table 2). In the Dose Response to Exercise in Women (DREW) study, three intensities of cycle ergometer and treadmill training were compared with a control condition. The effects of strength and aerobic training were studied by Velthuis et al., by Villaverde Gutiérrez et al., in the exercise condition of the NEW study and in the EFOPS study. Friedenreich et al. studied the effects of an aerobic exercise intervention, but gave no

**Table 3.** Study-arms with both dietary and exercise intervention; behavioral program and health coaching

Study	Intervention	Duration; contacts	Reduced CVD risk	Adherence
<b>NEW</b> [43, 45, 49, 51] (Mason, 2011 Imayama, 2011 Foster, 2012 Duggan, 2016)	Calorie restriction based on initial body weight (1200-1800 calories); reduction of fat intake to less than 30% of total energy intake; intake saturated fat less than 7%; lose 10% weight by 6 months. replacement of 2 meals with liquid shakes in first 20 weeks or follow a detailed menu plan with specific conventional foods <sup>a</sup> Aerobic activities such as treadmill walking and stationary bicycling, encouragement of a variety of home exercises including walking/hiking, aerobics, and bicycling. Some resistance training recommended, not required.	12 months; 32 group- and 2 individual sessions, 12 phone or email-contacts Exercise: 12 months; weekly 3 supervised sessions; 1 home based individual sessions	weight, %body fat, waist circumference, glucose, insulin resistance, LDL, physical activity (min/week), VO2max, stress, depression	86% of diet change sessions was followed 85% achieved targeted 225 min exercise /week
<b>Low-fat Diet and/or Exercise</b> [40, 53] (Cahmi, 2010 Stefanic, 1998 <sup>b</sup> )	< 30% of the total calorie intake from fat; <7% from saturated fat; limit cholesterol intake to < 200 mg/day) Exercise not further described	Diet: 12 months; 8 group- and 1 individual sessions; 10 varying contacts (group- or individual, phone or email) Exercise: 12 months; weekly 3 supervised sessions in first 4,5 months, thereafter choice for supervised or homebased individual program	waist-circumference**, intake of fat, intake of cholesterol, MetS**, TCL, LDL, VO2max**	Unknown
<b>MLP</b> [56, 57] (Toobert,2003 Toobert, 2007)	Behavioral program focusing on: Diet: Mediterranean' diet: low in saturated fat, moderately high in monounsaturated fats. More bread, root vegetables, green vegetables, legumes and fruit and fish is recommended and less red meat, butter and cream. Stress management: instructions in yoga, progressive deep relaxation, meditation, and directed or receptive imagery to increase the sense of relaxation, concentration, and awareness. Physical activity: not specified.	24 months; 2 1/2-day non-residential retreat, followed by 6 months 4-hour/ week meetings, followed by 18 months 2 different maintenance conditions (weekly meeting group or personalized computer-assisted condition) Physical activity goal was advised to build up from 30 min. moderate activity on most days of the week, to 1 hour moderate aerobic activity daily. Stress management techniques were advised to practice for at least 1 hour daily.	HbA1c, weight, BMI	First 6 months: 12.4 of 23 meetings (54%).  Next 6–24 months: Weekly meeting group: 19.4 of 39 meetings (50%); Personalized computer-assisted condition: 2.5 of 4 meetings (63%).  85% remained in the study at 24 months;
Study	Intervention	Duration; contacts	Reduced CVD risk	Adherence
<b>Health coaching</b> [36] (Almeida, 2016)	Promotion of a positive approach to menopause through: Development of skills to address issues such as hot flushes, offering evidence-based information about depression and anxiety, minimizing hazardous lifestyle practices, management of chronic medical conditions and depression, problem-solving techniques and scheduling of activities, and promotion of symptom monitoring of depressive symptoms	12 months; 6 telephone sessions, 2 additional sessions if needed	Depression, anxiety	Compliance with all study procedures: 72%. All assessments: 94%

<sup>a</sup> Information from AHEAD protocol, not explicitly mentioned in papers of Thurston or in the papers on the NEW study[67]

<sup>b</sup> Out of timerange of initial literature search

\*\* Effects of diet combined with exercise is larger than effect from diet or exercise alone

CVD: cardiovascular diseases

BMI: Body mass index

LDL: Low-density-lipoproteine

TCL: Total cholesterol

VO2max: maximum rate of oxygen consumption

details about the content, and also the exercise component of Low-fat Diet and/or Exercise intervention studied by Cahmi et al., and by Stefanic et al., was not described. Bea et al., and Gómez-Tomáz et al., studied the effects of progressive resistance training and Bernard et al., the effects of a walking program.

#### **Strategies to increase adherence with exercise interventions**

In the DREW study, participants started with six information sessions that emphasized the relevance of a healthy life and providing recommendations for healthy diet, stop smoking and alcohol reduction. Educational materials were distributed. Women were contacted when they missed a scheduled exercise session and heart rate monitors were distributed to monitor the (max 16) unsupervised exercise sessions that were allowed. Each woman was given up to \$500 as an incentive

to complete the study. In the aerobic exercise intervention studied by Friedenreich et al., heart rate monitors and weekly exercise logs were used to monitor adherence. Educational packages were provided that addressed relevant issues for women starting with exercising. The exercise program consisted of group sessions to permit interaction between participants. Women were contacted when they missed sessions and awarded when program milestones were reached.

The resistance training studied by Bea et al. encompassed a variety of reinforcement strategies to motivate participants such as education and skill development, self-efficacy, incentive programs, social support, and modeling. Participation was based on individual improvement rather than competition among participants. A social environment was created that challenged the women to improve their

daily exercise performance. The support program further included exercise and goal-setting logs, regularly testing to monitor progress, and personal contracts. The strength and aerobic training of Velthuis et al., also used diverse techniques to enhance adherence such as group exercise sessions in combination with an individual program, personal feedback, realistic and regularly updated individual goals, and exercise logs to track frequency and duration of exercise. Training intensity was controlled by heart rate monitors. In the NEW study, session attendance was tracked to promote and monitor adherence. Women not meeting exercise targets were contacted to discuss barriers and approaches to increase activity. Exercise physiologists met regularly with a clinical health psychologist experienced in lifestyle behavior change to discuss participant progress and refine behavior modification goals according to each participant's needs. Villaverde Gutiérrez et al., mentioned no specific adherence strategies other than social interaction with the group and the research team and a motivating approach from the trainer. In the EFOPS study, individual training logs were used to monitor attendance and compliance. Both The Low-fat Diet and/or Exercise study, and the study of Gómez-Tómas et al., on progressive resistance training, gave no information about adherence enhancing measures.

### **Effects**

Just as the dietary interventions, the exercise interventions reduce cardiovascular risks. Diverse outcomes were measured with diverse instruments. Effects seem to be larger with increasing training intensity.[42, 44, 50].

### **Adherence**

Adherence varied and was expressed in different manners, such as completion of planned measurements and/or attendance of the exercise sessions. In general, completion rates of the studies was high. In the walking program of Bernard et al., all participating women completed the measurements, in the strength and aerobic training programs 90-99%, in the DREW study 89-95%, and in the study on resistance training 83%. In the EFOPS study, 78%, 79% and 69% of the women completed the measurements at two, three and 16 years follow up.

Attendance of sessions is measured differently. In the NEW study, 80% of the participants achieved the targeted 225 weekly minutes of exercise, in the aerobic exercise study of Friedenreich et al., women followed on average 3.6 of the required five weekly exercise sessions, in the strength and aerobic training 63% of the women attended more than 70% of the required sessions, and in the walking program 54% of the sessions were followed. In the EFOPS study, after three years 56% attended two of more training sessions and after 16 years, 69% of the women still exercised. The Low-fat Diet and/or Exercise study reported no information on adherence.

### **Interventions with a combination of diet and physical exercise**

Three studies were found that combined diet and exercise (table 3). The earlier described NEW study and Low-fat Diet and/or Exercise intervention used a three armed design and compared the effects

of diet, with those of exercise and with those of the combination of diet and exercise. Toobert et al., [56, 57] studies the effects of the Mediterranean Lifestyle Program (MLP), an intervention focusing on diet, physical exercise and stress-management together.

### ***Behavioral components and other strategies to increase adherence***

Components of the NEW study and the Low-fat Diet and/or Exercise are described earlier. The behavioral components of MLP were based on combined Social Cognitive Theory, Goal Systems, and Social Ecological Theory. Participants were able to set personal lifestyle change goals at the start of the intervention, and received ongoing peer and professional support for their goals throughout the treatment program. To enhance adherence, participants kept a log of adherence to the diet (self-monitoring), contests with cash prize were held, incentives such as small presents were given, and participants were called by professionals or group members when meetings were missed.

### **Effects**

The combined interventions reduce cardiovascular risks and effects are found on a variety of outcomes (table 3). In general, effects are larger than those achieved with a dietary program or physical exercise alone.

### **Adherence**

In the NEW study 86% of diet change sessions was followed and 85% of the women complied with the targeted 225 minutes weekly exercise. In the MLP study, 85% of the women remained in the study after two years, but attendance of the meetings itself was rather poor. In the first 6 months 54% of the meetings were attended. In the next 18 months, 50% of the meetings were attended by the group that received weekly (follow up) meetings, while in the follow up condition with personalized computer-assistance attendance of the sessions was 63%. Adherence in the Low-fat Diet and/or Exercise study was not described.

### **Health Coaching**

Almeida studied the effects of a health coaching program and found an effect on depression and anxiety. The intervention was delivered by a trained psychologist. Ninety-four percent of the women completed all measurements and 72% complied with all study procedures.

### **Discussion**

We found 14 lifestyle interventions that report a sustainable reduction of cardiovascular risk in (post)menopausal women. These interventions apply dietary guidance, exercise programs, health coaching, or a combination of these elements. Although the type of prescribed diet varies, reduction of fat and calories are common features and all dietary interventions apply behavioral change techniques. The exercise programs vary in type of movement, but almost all are group based, supervised by a professional and performed in a fitness center, except the progressive resistance training of Gómez-Tómas et al. which was monitored on a distance by the principal

investigator [62] and Bernard et al.'s walking program [39]. Exercises are in general of modest intensity. Most interventions, dietary as well as exercise programs, are characterized by very large number of contacts. Dietary guidance is given in group sessions, supplemented with individual face to face contacts, phone calls and/or emails. The number of exercise sessions varies from three to five times a week, with a mix of supervised exercises and home assignments. Furthermore, in all interventions participants are intensively guided by several highly educated professionals such as dietitians, fitness-trainers, physiotherapists, physiologists, stress-management instructors, and professional or lay support group leaders.

Although it is difficult to estimate the magnitude of the effects in the studies, effects seem to be small to moderate. Apparently, even a relatively small reduction of cardiovascular risks such as blood pressure and weight with lifestyle interventions requires much time and effort. However, especially in postmenopausal women even small weight loss or prevention of further weight gain and deterioration of blood values is clinically relevant [69]. Effects were largest when diet and exercise were combined, a finding that corresponds with international literature on lifestyle interventions in the general population [70] and postmenopausal women [71]. Although the studies provide insufficient information to relate effects to the specific elements of the intervention (type of diet or exercise), a cautious conclusion may be that the exact content of an intervention matters less, as long as the interventions are intensive enough and participants adhere. This is consistent with a meta-analysis of Johnston on the effectiveness of different diet programs, who suggested that patients may best choose the diet that gives them the least challenges with adherence [72, 73]. There is little reason to believe that this is different for exercising.

It is obvious that adherence to lifestyle-interventions is an important issue, and a second aim of our study was to determine which strategies are effective to enhance adherence for women around the menopause. Although not all studies describe adherence strategies in detail, several strategies are found (tables 1-3). Especially dietary interventions use behavioral strategies to stimulate sustainable lifestyle changes such as provision of knowledge, problem solving and coping strategies, goal setting and training of skills. Both dietary and exercise interventions used peer support to enhance adherence to the sessions, by offering the intervention in a group, and in several studies participants were telephoned when they missed a session. Progress and adherence was measured through self-monitoring and in some studies incentives up to cash prizes of 500 dollar were given. In general, it seems that a high effort to keep women in the program results in relatively good adherence. The EFOPS study seems to be an exception to this, because no real strategies to increase adherence are applied and yet 67% of women still exercise after 16 years. Women were able to choose to participate in the exercise group themselves, and the authors interpret their results as a further indication that lifelong training is reserved for highly motivated postmenopausal women who are willing and able to attend intensive training programs [63].

The high frequency of sessions, intensive guidance of professionals and the high effort to enhance adherence in the studies indeed raise the question whether the found interventions are applicable to a large

population in daily practice. It is recognized that behavioral change such as adapting a healthy lifestyle takes time and effort. However, in the Dutch health care system, dietary guidance is reimbursed for three hours a year, unless patients are additionally insured. Most exercise programs found were performed in supervised fitness centers, and the interventions may be too expensive for some women, especially for women from a lower socioeconomic status who are more at risk for cardiovascular disease. So it is important to find other ways to achieve the same results, for example with the use of blended care in which face to face contacts with a professional in a group are combined with a Health support or through telephonic contacts such as in the health coaching intervention of Almeida [36].

In addition to possible financial barriers, it can be doubted whether such intensive physical exercise programs and diets appeal to women. Especially in the menopausal transition, women often suffer from musculoskeletal pain [17-20] which may increase with intensive exercising. Mood and stress disorders accompanying the menopause and demands from everyday family life or work, may interfere with the strict dietary demands. Remarkably, only two studies were found that focused explicitly on women in the menopausal transition and their specific health problems [36, 55]. The rather strict dietary intervention of Thurston addresses issues as dietary and activity in context of sleep loss, family, work and caretaking demands, and reduces weight and fat% [55]. Thurston also showed that women who lost weight experienced less hot flushes, and participating women reported that this was a motivator to adhere to the study.

The health coaching intervention from Almeida promotes a positive approach of the menopause and diminishes depression and anxiety [36]. The other 9 studies however, also included postmenopausal women, some of them closely around the menopause, but others up to the age of 79 years [37]. So there is obviously a gap in the literature regarding effective lifestyle programs for women in the menopausal transition. Also Jull et al. who performed a review on lifestyle interventions targeting body weight changes during the menopause transition only found one randomized (western) study from 2003 [74].

Still, we argue that the onset of the menopause could just be a good starting point for changing lifestyle, since lifestyle interventions not only reduce cardiovascular risks, but may also diminish specific symptoms of the menopause. Reductions in weight, BMI and abdominal circumference have been associated with a reduction in vasomotor symptoms and physical exercise may reduce feelings of depression and stress [55, 75, 76]. Prerequisites for such lifestyle interventions are that they are attractive for women around the menopause, take their day to day (menopausal) health problems into account and fit into women's life and daily routines [13, 15]. In our study we have focused on interventions with sustainable, positive effects on cardiovascular risks and the result is that we have found relatively intensive interventions, that may appeal less to this group. The search for, or development of interventions that are less intensive but still effective in reducing cardiovascular risks for women around the menopause is challenging. To reduce cardiovascular risks, people should preferably change their lifestyle for the rest of their life, so strategies need to be realistic. Based



on life style coaching approaches used in the Diabetes Prevention Program, Vendetti et al assumed that problem solving approaches and self-monitoring tools are essential to overcome barriers to adhere to a healthy diet and physical activity [15] so these elements should be incorporated in future interventions. Finally, we think that it is very important to take the views and experiences of the target group itself into account in the development of such strategies.

### Limitations of the Study

The purpose of this study was to provide an overview of sustainable, effective lifestyle interventions to reduce the risk of CVD for women (starting) from the menopause. For that reason we selected studies that reported significant positive effects on cardiovascular risks in our target population. As a result, our study cannot be interpreted as a systematic overview of all types of interventions aiming at reducing cardiovascular risks. However, the effective interventions or elements of these interventions that were found, can be used as a starting point for further development of more feasible interventions, and by professionals in daily practice to guide women who want to decrease their CVD risk. The strength of our study is that we only selected randomized studies, which offers the highest level of evidence. A disadvantage is however, that these studies often include a relatively healthy sample of participants, which limits the generalizability to daily practice.

### Conclusion

There are interventions that sustainably reduce cardiovascular risk factors for women from the menopause. These interventions are characterized by intensive strategies such as meal replacements and frequent exercise sessions, frequent personal, face to face contacts, and great efforts to increase adherence. Apparently, lowering cardiovascular risks through lifestyle interventions demands considerable efforts from women, health care providers, trainers and coaches to guarantee effects and adherence. The question is whether large scale implementation is feasible with regard to costs, willingness of the target group and capacity of the professionals. The challenge is to develop sustainable effective interventions that are less intensive and require less strategies to guarantee adhere. These interventions should be tailored to the specific needs and health problems of women from the menopause, and best be developed in dialogue with the target group itself.

### Supplements

**S1:** Search strategy. The document describes the search strategy across electronic databases and search engines.

**S2:** Characteristics of the included studies.

### Competing Interest

Liset van Dijk received funding from Astra Zeneca, Pfizer and Abbvie for studies not related to this study; Marcia Vervloet received funding from Pfizer and Abbvie for studies not related to this study.

### Funding

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### Authors' Contribution

CL, JK, LvD and MV developed the design of the study and screened abstracts and titles. CL and JK screened full texts and performed the analysis. All co-authors contributed to the interpretation of the data. CL and JK drafted the manuscript and all co-authors commented on the draft and approved the final manuscript.

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## Supplementary information

### Additional file 1. Search strategy

Search	Query
#10	#13 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR adolescent*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infant*[tiab] OR girl*[tiab] OR boy*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab] OR youth*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR puber*[tiab]) NOT ("Adult"[Mesh] OR adult*[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab])) NOT(animals[mh] NOT humans[mh]) NOT (rats[tiab] OR mouse[tiab] OR mice[tiab]) Filters: Publication date from 2007/01/01; Dutch; English
#9	#8 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR adolescent*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infant*[tiab] OR girl*[tiab] OR boy*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab] OR youth*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR puber*[tiab]) NOT ("Adult"[Mesh] OR adult*[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab])) NOT(animals[mh] NOT humans[mh]) NOT (rats[tiab] OR mouse[tiab] OR mice[tiab]) Filters: Dutch; English
#8	#7 NOT (("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh] OR adolescent*[tiab] OR child*[tiab] OR schoolchild*[tiab] OR infant*[tiab] OR girl*[tiab] OR boy*[tiab] OR teen[tiab] OR teens[tiab] OR teenager*[tiab] OR youth*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR puber*[tiab]) NOT ("Adult"[Mesh] OR adult*[tiab] OR man[tiab] OR men[tiab] OR woman[tiab] OR women[tiab])) NOT(animals[mh] NOT humans[mh]) NOT (rats[tiab] OR mouse[tiab] OR mice[tiab])
#7	#6 NOT (hormone therap*[ti] OR (hormone[ti] AND use[ti]) OR hormone replacement therap*[ti] OR hormone agonist*[ti] OR hormone receptor*[ti] OR cancer[ti])
#6	#1 AND #2 AND #3 AND #4 AND #5
#5	(clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR randomized controlled trial[Publication Type] OR ((clinical[tiab] OR random*[tiab]) AND trial[tiab]))
#4	"Treatment Outcome"[Mesh] OR "Risk Reduction Behavior"[Mesh] OR effect*[tiab] OR outcome*[tiab] OR result[tiab] OR results[tiab]
#3	"Exercise Therapy"[Mesh] OR "Exercise"[Mesh] OR "Smoking Cessation"[Mesh] OR "Diet"[Mesh] OR "Weight Reduction Programs"[Mesh] OR physical activit*[tiab] OR exercis*[tiab] OR diet[tiab] OR dietary[tiab] OR diets[tiab] OR weight loss[tiab] OR weight management[tiab] OR weight reduction[tiab] OR ("Therapeutics"[Mesh] OR "therapy" [Subheading] OR therap*[tiab] OR treatment*[tiab] OR prevention[tiab] OR program*[tiab] OR intervention*[tiab]) AND ("life Style"[Mesh] OR "Health behavior"[Mesh] OR "Smoking"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Overweight"[Mesh] OR "Sleep Wake Disorders"[Mesh] OR "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Stress, Psychological"[Mesh] OR "Sedentary Lifestyle"[Mesh] OR "Nutritional Status"[Mesh] OR life style[tiab] OR lifestyle[tiab] OR health behavior*[tiab] OR health behaviour[tiab] OR smoking[tiab] OR tobacco[tiab] OR alcohol*[tiab] OR overweight[tiab] OR obesity[tiab] OR obese[tiab] OR sleep[tiab] OR dyssomnia*[tiab] OR depress*[tiab] OR mood disorder*[tiab] OR stress[tiab] OR physical inactivit*[tiab] OR nutrition*[tiab]))
#2	"Cardiovascular Diseases"[Mesh] OR "Stroke"[Mesh] OR "Hyperlipidemias"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Metabolic Syndrome X"[Mesh] OR "Polycystic Ovary Syndrome"[Mesh] OR "Pre-Eclampsia"[Mesh] OR "Ovariectomy"[Mesh] OR "Menopause, Premature"[Mesh] OR "Overweight"[Mesh] OR "Sleep Wake Disorders"[Mesh] OR "Sleep Apnea, Obstructive"[Mesh] OR "Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Stress, Psychological"[Mesh] OR "Hyperuricemia"[Mesh] OR "Kidney Failure, Chronic"[Mesh] OR "Autoimmune Diseases"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Platelet Count"[Mesh] OR "Lupus Erythematosus, Systemic"[Mesh] OR "Arthritis, Rheumatoid"[Mesh] OR "Hernias, Diaphragmatic, Congenital"[Mesh] OR "Rheumatic Heart Disease"[Mesh] OR "Vascular Stiffness"[Mesh] OR "Periodontitis"[Mesh] OR "Inflammatory Bowel Diseases"[Mesh] OR "Non-alcoholic Fatty Liver Disease"[Mesh] OR "Vitamin D Deficiency"[Mesh] OR "Sexual Dysfunction, Physiological"[Mesh] OR "Sexual Dysfunctions, Psychological"[Mesh] OR cardiovascular diseases*[tiab] OR heart diseases*[tiab] OR cardiac diseases*[tiab] OR vascular diseases*[tiab] OR coronary diseases*[tiab] OR coronary artery diseases*[tiab] OR aortic diseases*[tiab] OR arrhythmia*[tiab] OR cardiac dysrhythmia*[tiab] OR cardiomegal*[tiab] OR heart enlargement[tiab] OR enlarged heart[tiab] OR cardiac hypertroph*[tiab] OR cardiomyopath*[tiab] OR myocardial diseases*[tiab] OR myocardiopath*[tiab] OR aneurysm*[tiab] OR heart arrest*[tiab] OR cardiac arrest*[tiab] OR asystole*[tiab] OR cardiopulmonary arrest*[tiab] OR heart failure*[tiab] OR cardiac failure*[tiab] OR heart murmur*[tiab] OR heart decompensation[tiab] OR myocardial failure*[tiab] OR heart valve diseases*[tiab] OR arterial stiffness*[tiab] OR aortic stiffness*[tiab] OR vascular stiffness*[tiab] OR myocardial ischemia*[tiab] OR ventricular dysfunction*[tiab] OR ventricular outflow obstruct*[tiab] OR cardiovascular pregnancy complication*[tiab] OR amniotic fluid embolism*[tiab] OR arterial 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cerebrovascular accident*[tiab] OR cva*[tiab] OR apoplex*[tiab] OR brain infarction*[tiab] OR cerebral infarction*[tiab] OR diabetes[tiab] OR diabetic[tiab] OR dm2[tiab] OR niddm[tiab] OR dm 2[tiab] OR t2d*[tiab] OR dm type 2[tiab] OR dm type II[tiab] OR dm1[tiab] OR iddm[tiab] OR dm 1[tiab] OR t1d*[tiab] OR dm type 1[tiab] OR dm type I[tiab] OR metabolic syndrome[tiab] OR OR metabolic risk*[tiab] OR ovarian hormone deficien*[tiab] OR polycystic ovary syndrome*[tiab] OR sclerocystic ovar*[tiab] OR eclampsia[tiab] OR premature delivery[tiab] OR preterm delivery[tiab] OR stillbirth[tiab] OR ovariectom*[tiab] OR oophorectom*[tiab] OR overweight[tiab] OR obesity[tiab] OR obese[tiab] OR sleep dis*[tiab] OR sleep wake dis*[tiab] OR dyssomnia*[tiab] OR sleep deprivation[tiab] OR depress*[tiab] OR mood disorder*[tiab] OR stress[tiab] OR hyperuricemia[tiab] OR increased sympathetic drive[tiab] OR chronic kidney failure*[tiab] OR end-stage kidney disease[tiab] OR end-stage renal failure[tiab] OR end-stage renal disease[tiab] OR chronic renal failure*[tiab] OR ESRD[tiab] OR autoimmune disease*[tiab] OR atrial fibrillation*[tiab] OR auricular fibrillation*[tiab] OR c-reactive protein[tiab] OR crp[tiab] OR platelet count*[tiab] OR platelet number*[tiab] OR platelet indices[tiab] OR lupus[tiab] OR rheumatoid arthritis[tiab] OR congenital diaphragmatic hernia*[tiab] OR congenital heart diseases*[tiab] OR periodontit*[tiab] OR pericementit*[tiab] OR inflammatory bowel dis*[tiab] OR IBD[tiab] OR inflammatory bowel syndrome*[tiab] OR crohn*[tiab] OR ulcerative colitis[tiab] OR obstructive sleep apnea*[tiab] OR OSAHS[tiab] OR non-alcoholic fatty liver*[tiab] OR NAFLD[tiab] OR nonalcoholic fatty liver*[tiab] OR nonalcoholic steatohepatit*[tiab] OR vitamin d deficien*[tiab] OR sexual dysfunction*[tiab] OR sexual disorder*[tiab] OR "Smoking"[Mesh] OR "Alcohol Drinking"[Mesh] OR "Overweight"[Mesh] OR "Stress, Psychological"[Mesh] OR "Sedentary Lifestyle"[Mesh] OR "Nutritional Status"[Mesh] OR smoking[tiab] OR tobacco[tiab] OR alcohol*[tiab] OR overweight[tiab] OR obesity[tiab] OR obese[tiab] OR mood disorder*[tiab] OR stress[tiab] OR increased sympathetic drive[tiab] OR physical inactivit*[tiab] OR sedentary lifestyle*[tiab]
#1	"Menopause"[Mesh] OR menopaus*[tiab] OR premenopaus*[tiab] OR postmenopaus*[tiab] OR perimenopaus*[tiab]

S2 Description of the studies

Dietary (D) interventions					
Study	Population	N	Content & intensity	Outcome (instrument)	Improvement of CVD risks in D vs C*
<b>WHI</b> Howard et al., 2010 [1]	Random subsample of women with blood samples	2730	12 months <sup>§</sup> : Behavioral modification program. Nutrition goals: less fat intake, daily intake of at least 4 daily servings of fruit and vegetables, and 6 servings of grain.  Weekly group meeting with a trained nutrition interventionist for 6 weeks, every other week for an additional 6 weeks, and monthly for the course of the first year.  Each woman also has one individual dietary counseling session between 12 and 16 weeks from the beginning of intervention to ensure the nutritional balance of her new dietary pattern.  Dietary maintenance sessions quarterly after the first year of dietary intervention, along with optional, peer-led monthly meetings of the intervention groups.	Measures: 0/12/36/72 months fat intake; carbohydrate intake; weight; BMI; waist; SBP; TCL; LDL; HDL; Triglycerides; non_HDL cholesterol	12 m.: fat intake, carbohydrate intake; weight, BMI, waist, SBP, HDL? <sup>®</sup>  36 m.: fat intake, carbohydrate intake, waist, SBP, TCL, LDL  72 m. : fat intake, carbohydrate intake
<b>WHI</b> Shikany et al., 2011 [2]	Random subsample of women with blood samples	2263	See Howard, 2010 [1]	Measures: 0/12/36/72 months glucose; insulin; insulin resistance	12 m.: glucose, insulin, insulin resistance <sup>3</sup> , insulin sensitivity <sup>4*</sup> ;
<b>WHI</b> Carty et al., 2011 [3]	Subsample of women with whole-body dual-energy X-ray absorptiometry scan	1580	See Howard, 2010 [1]	Measures: 0/12/36/72 months fat mass, lean mass, % body fat	12 m. : % body fat, fat mass <sup>**</sup> 36 m. : % body fat, fat mass 72 m. fat mass
<b>WHI</b> Assaf et al., 2016 [4]	48 835 postmenopausal women, 50 to 79; fat intake >32%	48835 <sup>†</sup>	See Howard, 2010 [1]	Measures: 0/12 months/ Close out (on mean 97 months) Depressive symptoms <sup>1</sup> ; Sleep disturbance <sup>2</sup>	12 m.: depressive symptoms and sleep disturbance  Close out: depressive symptoms and sleep disturbance
<b>Behavioral weight loss</b> Thurston et al., 2015 [5]	Late perimenopausal or postmenopausal women, BMI 25–40, with ≥4 hot flashes/day who wanted to lose weight	40	6 months: Behavioral weight loss intervention tailored to midlife, menopausal women, focusing on dietary and physical activity self-monitoring, calorie reduction and encouragement of physical activity  20 1-hour group sessions	Measures: 0/6 months Weight, fat%	weight and %fat.
Exercise (E) interventions					
Study	Population	N	Content & intensity	Outcome (instrument)	Improvement CVD risks in E vs C*
<b>DREW</b> Church et al., 2007 [6]	45-75 years, postmenopausal, sedentary, BMI 25-43, normal to mildly elevated resting blood pressure.	464	6 months: Alternating cycle ergometer and treadmill training.  3-4/week, at a heart rate associated with 50% VO <sub>2</sub> max  3 groups with different level of energy expenditure (kcal. kg-1.wk-1) : 4-KKW 8-KWW (=intensity recommended in guidelines) 12-KWW  Energy expenditure is gradually increased to target level. As fitness improves, women work at a higher PO to reach the required HR and will take less time to expend the required KKW.	Measures: 0/6 months Weight, bodyfat%, waist, LDL, HDL, triglyceriden, fasting glucose, PeakVO <sub>2</sub> (absolute, relative, max power output)	waist in all E groups (no differences between the three intensities)  PeakVO <sub>2</sub> (all 3 measures) in all E groups (with a significant trend for dose)

<b>DREW</b> Swift et al., 2011 [7]	Subsample of 464 women of Church et al. with complete data for exercise blood pressure	404	See Church, 2007 [6]	Measures: 0/6 months Exercise blood pressure (diastolic and systolic), resting blood pressure (diastolic and systolic) VO2max, weight, waist	Systolic exercise blood pressure, waist, VO2max for all E groups; diastolic exercise blood pressure for 12 KWW group vs C
<b>DREW</b> Swift et al., 2012 [8]	Subsample of 464 women of Church et al. with complete data for flow mediated dilatation (FMD)	155	See Church, 2007 [6]	flow mediated dilatation (FMD) as measure for endothelial dysfunction	FMD for all E groups (no differences between the three intensities)
<b>DREW</b> Kline et al., 2012 [9]	Subsample of 464 women of Church et al. with complete data for baseline sleep data.	437	See Church, 2007 [6]	Measures: 0/6 months Sleep Problems <sup>6</sup> measured as (1) a change in continuous scale score (2) an odds of having significant sleep disturbance	sleep problems in all E groups (significant dose response trend (controlled for age, BMI, HRT use, sleep medication and baseline score): greater improvement for the 12 KKW group vs. C. odds of having significant sleep disturbance in all E groups (with significant linear trend for dose)
<b>DREW</b> Earnest et al., 2013 [10]	Subsample of 464 women of Church et al. with complete data for MS risk factors	408	See Church, 2007 [6]	zMeasures: 0/6 months Score Metabolic Syndrome (zMetS) <sup>5</sup>	zMetS for 12 KKW group; MetS for 8 and 12 KKW groups; SBP for 12KKW group; Glucose for 8 and 12 KKW groups
<b>Exercise program</b> Velthuis et al., 2009 [11]	Postmenopausal women (50-69 yrs), sedentary, non-smoking, BMI 22-40.	189	12 months: Aerobic training, strength training, brisk walking or cycling Two supervised group sessions 1 hour/week and a home-based individual session of half an hour/week. Aerobic training: 20 min. 60-80% of maximal heart rate. Muscle strength training: 25 min., back and extremities 60% of 1 repetition maximum measurement, 20 to 25 repetitions; for abdomen 50% of 1 repetition maximum measurement, 30 to 40 repetitions. Home-based walking or cycling was intended for 30-minutes, 60%-80% of maximal heart rate), controlled by heart rate monitors.	Measures: 0/12 months weight, body mass, waist and hip circumference, total body fat %	% total body fat; waist circumference
<b>Resistance training</b> Bea et al., 2010 [12]***	Postmenopausal sedentary women (40-65 yrs), BMI 19.0-33.0, non-smoking; undergoing hormone therapy or not; no weight gain or loss greater than 13.6 kg in previous year; not using beta-blockers or steroids;	122	12 months, after 12 months voluntary cross over: Weight bearing exercises, strength training, stretching and balance. 3 sessions/week; 60-75 minutes. Women completed two sets of six to eight repetitions (four to six repetitions for the military press to decrease injury to the shoulder) at 70% (two days per week) or 80% (one day per week) of the one-repetition maximum (1-RM), determined by monthly testing during year 1. Following the intervention participants were asked to continue resistance training and record these activities in their study logs.	Measures: 0/72 months weight, body fat, exercise frequency (performed/prescribed)	Frequency of exercising
<b>Aerobic and strength training</b> Villaverde et al., 2012 [13]	Postmenopausal women with mood problems (60-70 yrs), no conditions contraindicating physical exercise	60	6 months: in first 8 weeks two weekly 50 minutes sessions of aerobic exercise at 50-70% of maximum heart rate reserve, in week 9-12 supplemented with muscle training exercises and extended to three weekly 60 minutes sessions, in last 12 weeks intensity was raised 60-85 % of maximum heart rate reserve.	Measures: 0/6 months Weight, BMI, depression <sup>17</sup> , anxiety <sup>18</sup>	depression, anxiety

<b>Aerobic exercise intervention</b> Friedenreich et al., 2011 [14]	Postmenopausal sedentary women (50–74 yrs), normal blood lipid and hormone levels, BMI 22-40.	320	12 months: Content not described At least 45 min/day at 70–80% of the heart rate reserve; 3 supervised group sessions/week at facility and 2 days/week at home. Program individualized to age and fitness level. Warm up for 5min, cool down for 5–10min. Prescription ramped up from 3 weekly sessions of 20 min. at heart rate reserve of 50-60%	Measures: 0/12 months weight, waist and hip circumference, total body fat, abdominal adiposity	weight, waist and hip circumference, total body fat, abdominal adiposity, BMI
<b>Aerobic exercise intervention</b> Friedenreich et al., 2012 [15]	Postmenopausal sedentary women (50–74 yrs.), normal blood lipid and hormone levels, BMI 22-40.	320	12 months: Content not described At least 45 min/day at 70–80% of the heart rate reserve; 3 supervised group sessions/week at facility and 2 days/week at home. Program individualized to age and fitness level. Warm up for 5min, cool down for 5–10min. Prescription ramped up from 3 weekly sessions of 20 min. at heart rate reserve of 50-60%	Measures: 0/12 months C reactive Protein (CRP)	CRP levels*
<b>Walking program</b> Bernard et al., 2015 [16]	Insufficiently active <sup>14</sup> postmenopausal women ( 55-76 yrs.), who achieved a six-minute walking distance under 5% of the normative score <sup>15</sup> .	121	6 months: Walking program Two supervised outdoor walking sessions of 40 min., and 1 non-supervised session/week.  Walking intensity was tailored and based on participants theoretical maximum heart rate (HR); Training intensity is gradually increased from 40% to finally reach 75% of the working HR.	Measures: 0/6 months Depression score <sup>16</sup> at six months.	adjusted mean depression score
<b>EFOPS</b> Kemmler et al., 2004 [17]	Postmenopausal women (48–60 yrs.) with osteopenia, not participating in sports competition, without inflammatory of cardiovascular diseases. Subsample with good training compliance ( $\geq 2$ sessions/week)	83	26 months: Two supervised sessions of 60-70 minutes gradually increasing low and high impact aerobic exercises, resistance training on machines, elastic bands and free weights. First three months, a running program on 70-85% of Maximum heart rate was offered to accustom women to higher impact rates, after three months jumping was introduced. After 7 months, the strength training is divided in periods of high intensity/low volume (12 weeks) and periods of low intensity/high volume (5 weeks). Two home sessions of 25 minutes with isometric and dynamic resistance exercises.	Measures: 0/26 months VO2max, HDL, LDL, TCL, glucose, waist circumference, waist hip ratio, triglycerides;	VO2max, TCL, triglycerides
<b>EFOPS</b> Kemmler et al., 2005 [18]	See Kemmler et al., 2004	78	38 months See Kemmler et al., 2004	Measures: 0/38 months See Kemmler et al., 2004	VO2max, TCL, triglycerides, waist circumference, waist hip ratio,
<b>EFOPS</b> Kemmler et al., 2017 [19]	See Kemmler et al., 2004. For this follow up, all women were included, not only those with a good compliance ( $\geq 2$ sessions/week).	105	192 months See Kemmler et al., 2004	Measures: 0/192 months See Kemmler et al., 2004	Framingham 10 year risk score
<b>Progressive resistance training</b> Gómez-Tómas et al., 2018 [20]	Postmenopausal women (65-79 yrs), BMI of 19-39, no HRT, no conditions contra-indicating physical exercise such as uncontrolled diabetes, hypertension or hypercholesterolemia		12 months Three non-supervised 50 minutes sessions of six progressive resistance exercises with elastic bands for major muscle groups. The load and intensity was increased in three phases of four months, based on subjective perception scale. Women reported the experienced intensity to the investigator who monitored and if needed altered the intensity of the exercises in this way	Measures: 0/12 months weight, waist, HDL, LDL, VLDL, TCL, triglycerides; CRP	weight, waist, HDL, VLDL, triglycerides; CRP

<b>Interventions with Dietary (D), Exercise (E) and Diet and Exercise combined (D&amp;E)</b>					
<b>Study</b>	<b>Population</b>	<b>N</b>	<b>Content &amp; intensity</b>	<b>Outcome (instrument)</b>	<b>Improvement CVD risks in D vs C; in E vs C; in D&amp;E vs C*</b>
<b>NEW</b> Mason et al., 2011 [21]	Overweight/obese postmenopausal women (50–75 years), not meeting PA guidelines.	439	12 months: Diet: calorie reduction Exercise: treadmill walking, stationary bicycling and other aerobic machines; walking/hiking, aerobics, resistance training and bicycling at home. Combination of diet and exercise Diet: At least 2 individual meetings with a dietitian for goal setting, followed by weekly group meetings (5–10 women) for 6 months. Thereafter, participants attended monthly group meetings, in addition to biweekly phone or email contact. More in-person sessions, phone, or email contacts were permitted. Exercise: 45 min/day, 3 supervised sessions/week at facility and 2 days/week at home. Training program began with 15 minutes at 60–70% maximal heart rate and progressed to the target 70–85% maximal heart rate for 45 minutes by the 7th week after enrollment where it was maintained for the remainder of the study. Activities of $\geq 4$ METs <sup>16</sup> were counted toward the prescribed target.	Measures: 0/12 months fasting glucose, insulin resistance <sup>7</sup>	glucose and insulin resistance in D and in D&E
<b>NEW</b> Imayama et al., 2011 [22]	See Mason et al., [21]	439	See Mason et al., [16]	Measures: 0/12 months Stress <sup>8</sup> depression & anxiety <sup>9</sup>	stress scores in D&E depression score in D&E
<b>NEW</b> Foster et al., 2012 [23]	See Mason et al., [16]	439	See Mason et al., [16]	Measures: 0/12 months weight, body fat, waist circumference, physical activity, VO <sub>2</sub> max	weight, %body fat, waist circumference in D and in D&E physical activity (min/week) in E and in D&E VO <sub>2</sub> max in E and in D&E
<b>NEW</b> Duggan et al., 2013 [24]	See Mason et al., [16]	439	See Mason et al., [16]	Measures: 0/12 months low-density lipoprotein (LDL)	LDL in D and in D&E
<b>Low-fat Diet and/or Exercise</b> Stefanic et al., 1998 [25]	Postmenopausal women (45–64 yrs) without history of heart disease, BMI < 32 kg/m <sup>2</sup> ; normal to slightly elevated blood levels (BP, HDL-C, LDL-C, triglycerides, fasting glucose), non or light smoking/ alcohol drinking.	180	12 months: Diet: low-fat diet. Exercise: individualized exercise prescription. Combination of diet and exercise Diet: Each participant met with a dietitian to establish individualized dietary recommendations. 8 weekly group sessions for information/ counseling on how to achieve goals. Hereafter: monthly contact through individual appointments, group sessions, telephone calls, and/or mailings. Exercise: Adoption phase for exercise was 6 weeks of 1-h supervised aerobics classes, 3 days/wk. Hereafter, participants began with 20-min. 3/wk, increasing to 45–60 min total per session over the course of a year. After 3 months, participants continued with supervised activity or were encouraged to adopt a home program for the remaining 7–8 months.	Measures: 0/12 months dietary intake of fat, intake of cholesterol, weight, HDL, LDL, TCL, triglyceriden, VO <sub>2</sub> max	12m: dietary intake of fat, intake of cholesterol and weight in D and in D&E TCL and LDL in D&E; VO <sub>2</sub> max in E and in D&E (effects in D&E larger than in E)



<b>Low-fat Diet and/or Exercise</b> Camhi et al., 2010 [26]	Subsample of women with complete measures	149	See Stefanic, 1998	continuous standardized MetS score <sup>10</sup> ; mean arterial pressure <sup>11</sup> ; waist circumference; glucose; triglycerides; HDL-C	MetS in D, E and in D&E; waist circumference in D and in D&E (effect in waist in D&E is larger than in E)
<b>MLD</b> Toobert et al., 2003 [27]	postmenopausal women (<75 yrs) with DM-II for at least 6 months.	279	6 months (thereafter: 18 months 2 different maintenance conditions) Behavioral program, focusing on diet, PA and stress management The program started with a 2 1/2-day non-residential retreat, followed by 4-hour weekly meetings consisting of 1 hour each of Mediterranean-style potluck, physical activity, stress management, and support groups. Initial PA goal was 30 min. of moderate physical activity on most days of the week. After achieving this goal participants were advised to build up to 1 hour of moderate aerobic activity daily. Stress management: practice all techniques for at least 1 hour per day	Measures: 0/6 months HbA1c total cholesterol, LDL, HDL, triglycerides, weight, BMI, waist-to-hip ratio, SBP, DBP,	6m.: HbA1c, weight, BMI
Toobert et al., 2007 [28]		279	See Toobert, 2003 [22]	Measures: 0/6/12/24 months dietary behaviour, physical activity, stress-management	6m.: dietary behaviors, physical activity, stress management 12m.: dietary behavior, physical activity, perceived stress 24m.: dietary behaviors, physical activity, perceived stress
<b>Health coaching</b>					
<b>Study</b>	<b>Population</b>	<b>N</b>	<b>Content &amp; intensity</b>	<b>Outcome (instrument)</b>	<b>Improvement CVD risks</b>
Almeida et al., 2016 [29]	Perimenopausal women (45–55 yrs), <5 years of irregular menstrual cycles, amenorrhea of less than 12 months, without evidence of clinically significant symptoms of or of a major depressive episode at the time of assessment, or (current) history of schizophrenia.	351	12 months: Health coaching 6 telephone sessions (30-45 min) over 26 weeks (week 0, 2, 4, 8, 12 and 26). Two additional sessions were available to address unmet needs that became apparent during these sessions.	Measures: 0/8/26/51 weeks Incidence of clinically significant depressive symptoms over 52 weeks, anxiety <sup>12</sup> , depression <sup>12</sup> , weight, BMI, alcohol use <sup>13</sup> , smoking, PA, daily intake vegetables, fruit and high protein foods	26 wk: depression, anxiety 52 wk: depression, anxiety

\*D=dietgroup; C=control group; E=exercise group; D+E=diet + exercise group

§+ quarterly maintenance session until close out (mean 8.1 yr.)

# Enrollment 1993-1998; end of study in 2005

@ although HDL decreases, authors call it an improvement

<sup>1</sup> Center for Epidemiological Studies Depression Scale (CES-D)

<sup>2</sup> Women's Health Initiative Insomnia Rating Scale (WHIIRS)

<sup>3</sup> Homeostasis Model of Assessment – Insulin Resistance (HOMA-IR)

<sup>4</sup> The quantitative insulin sensitivity check index (QUICKI)

<sup>5</sup> >2 limit values of BP, waist, fasting blood glucose, HDL and trygliceriden

<sup>6</sup> Index from the 6-item Medical Outcomes Study Sleep Scale.

<sup>7</sup> HOMA-IR

<sup>8</sup> Perceived Stress Scale (PSS)

<sup>9</sup> Brief Symptom Inventory 18 (BSI 18)

<sup>10</sup> Individual standardized cardiovascular risk factor scores summed together (blood pressure, waist circumference, glucose, triglycerides, HDL) subtracting a participant's individual value for each variable from the AHA/NHLBI MetS criteria, and then dividing by the sample's standard deviation.

<sup>11</sup> Mean arterial pressure (MAP) = 1/3 (Systolic Blood pressure (SBP) – Diastolic Blood Pressure (DBP)) + DBP

<sup>12</sup> The Hospital Anxiety and Depression Scale (HADS)

<sup>13</sup> Alcohol Use Disorders Identification Test (AUDIT)

<sup>14</sup> Physical Activity Questionnaire (PAQ)

<sup>15</sup> Six minutes walking test (6MWT)

<sup>16</sup> Beck Depression Inventory (BDI)

<sup>17</sup> Geriatric Depression Scale (GDS)

<sup>18</sup> Hamilton Anxiety Scale (HRSA);

<sup>19</sup> Framingham 10 year risk score : algorithm to calculate risk of myocardial infarction and coronary death, using age, cholesterol, blood pressure, treatment for hypertension and smoking status.

CVD: cardiovascular diseases

BMI: Body mass index

SBP: Systolic blood pressure

DBP: Diastolic blood pressure

HDL=High-density-lipoproteine

LDL: Low-density-lipoproteine

VLDL: Very-low-density-lipoproteine

TCL: Total cholesterol

CRP: C-reactive protein

VO2max: maximum rate of oxygen consumption

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