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Effects on cardiovascular risk scores and vascular age after aerobic exercise and nutritional intervention in sedentary and overweight/obese adults with primary hypertension: The EXERDIET-HTA randomized trial study

Running title: Cardiovascular risk assessment

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Abstract

Aims To evaluate the influence of diet and aerobic exercise program intervention on cardiovascular risk (CVR) factors and predicted CVR and vascular age (VA) profiles in overweight/obese people with primary hypertension (HTN), and to analyze the potential sex differences in the ability to predict VA and CVR via different methods.

Methods The CVR and VA determined (n=167, 53.7±7.8 yr) using the Framingham Risk Score (FRS) and the new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk, before and after the 16-week intervention period (different aerobic exercise programs+hypocaloric diet). The sex-specific risk factors considered were age, high-density lipoprotein cholesterol (HDL-C), total cholesterol, systolic blood pressure (SBP), diabetes mellitus (DM) and smoking status.

Results From baseline to follow-up, participants reduced (p≤0.001) FRS-CVR score and VA, and SBP. Total cholesterol decreased significantly, but specifically in men (p≤0.001), and antihypertensive medication (%) in women (p=0.047). No significant differences over time were observed for HDL-C, smoking, DM overall for either sex. For ASCVD-CVR there was no overall change or for either sex. After the intervention, women had a lower CVR score than men (p≤0.001), irrespective of the calculation method.

Conclusions The improvement in CVR factors after 16-week lifestyle changes reduced the risk of suffering a cardiovascular event in overweight/obese adults with HTN through the FRS estimation tool, but not with the ASCVD score. The risk score algorithms could underestimate CVR in women. In contrast, VA could be a useful and easier tool in the management of individuals with CVR factors.

Keywords: Lifestyle intervention; sex; systolic blood pressure

1 Introduction

Cardiovascular disease (CVD) is a non-communicable disease, which represents the main cause of disability and death in the world, including Europe [1, 2]. Globally, between 2006 and 2016 deaths from CVD increased by 14.5%, although the age-standardized death rate decreased [3]. These data suggest that this condition needs to receive greater priority in prevention policy to reduce avoidable risk factors [2, 3]. Prevention is effective, and so, healthy lifestyle behavior promotion in the general population should directly target unhealthy lifestyles, such as poor-quality diet, physical inactivity, and smoking, at the individual level [2]. Cardiovascular risk (CVR) factors assessment is the first step guiding therapeutic strategy for the prevention of CVD [2], and strategy effectiveness depends on each patient's CVR profile and predictive risk [4].

There are several risk factor assessment tools for estimating a patient's 10-year risk of developing CVD [2, 4]. However, the most well-established risk score algorithm is the Framingham Risk Score (FRS), which was initially validated in 1998 to predict CVR [5, 6] and subsequently revised [7]. Recently, the American College of Cardiology and the American Heart Association developed a new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk, the called "Pooled Cohort Risk Equations" [8, 9]. This new tool was aimed at providing sex- and race-specific estimation of the 10-year risk of ASCVD for African-American and non-Hispanic white men and women aged 40 to 70 years old [8, 9]. On the other hand, vascular age (VA, *i.e.,* the age of the vascular system of a person with different CVR factors, calculated as the age a person would be with the same calculated CVR but whose risk factors were all within normal ranges [10]) is an easily understood concept related to CVR and calculated according to the definition of D'Agostino from FRS [7].

The common prediction factors for CVR models that have a relationship with cardiovascular events and premature death are age, sex, total cholesterol, high-density lipoprotein cholesterol

(HDL-C), systolic blood pressure (SBP, including treated or untreated status), diabetes mellitus (DM), and current smoking status [8].

Many observational studies have demonstrated graded associations between primary hypertension (HTN) and increased CVD risk [11] Additionally, adults with HTN usually present other modifiable CVR factors such as obesity, hypercholesterolemia, DM, smoking, physical inactivity, and unhealthy diet [12]. Therefore, correcting the dietary habits, lack of exercise and excessive consumption of alcohol through nonpharmacological interventions alone or in combination with pharmacological therapy is fundamental for the management of HTN [12].

A previous study evaluating CVR using the "Pooled Cohort Equations" (sex-specific risk prediction model) and VA in overweight/obese people with HTN found that CVR was significantly higher in men than in women despite them having the same CVR values, whereas no differences were found between sexes in VA [13]. As such, women could have an underestimated CVR profile based on the misperception that women are "protected" against CVD [14]. Hence, one of the biggest criticisms of the prediction scales of CVR accuracy is their capacity to overestimate or underestimate the risk [15]. Currently, there is no known research that measures the effects of an aerobic exercise program with nutritional intervention on CVR and VA in sedentary and overweight/obese adults with HTN. Considering the importance of CVR assessment, the objectives of this study were: 1) to evaluate the influence of 16-week diet and different aerobic exercise programs intervention on CVR factors and predicted CVR and VA profiles in sedentary and overweight/obese people with HTN, and 2) to analyse the potential sex differences in the ability to predict VA and CVR via different methods resulting from changes in lifestyle.

2 Methods

The EXERDIET-HTA study was a multi-arm parallel, a randomized, single-blind controlled experimental trial comparing the effects of 16 weeks of different aerobic exercise programs two days per week, and dietary intervention in a hypertensive, overweight/obese and non-physically

105 active population (www.clinicaltrials.gov, NCT02283047) [16, 17]. The design, selection criteria, and
106 procedures for the EXERDIET-HTA study have been previously detailed [16]. The study protocol was
107 approved by the Ethics Committee of The University of the Basque Country (UPV/EHU,
108 CEISH/279/2014) and the Ethics Committee of Clinical Investigation of Araba University Hospital
109 (2015-030), and all participants provided written informed consent prior to any data collection. All
110 follow-up examinations were performed in the same laboratory setting and by the same researchers
111 as the baseline measurements. Medical staff was blinded to participant randomization.

112 One hundred and sixty-seven non-Hispanic white participants (n=108 men and n=59 women)
113 with stage 1 or 2 HTN [≥140 SBP and ≥90 diastolic blood pressure (DBP)] and/or under
114 antihypertensive pharmacological treatment [16, 18, 19], and classified as overweight (body mass
115 index (BMI) ≥25 kg/m^2 or obese (BMI ≥30 kg/m^2) [20]. Participants were recruited from cardiology
116 services and via local media and were enrolled in the study in Vitoria-Gasteiz (Basque Country,
117 Spain).

118 The measurements for CVR factors used in the present study to determine the CVR and VA of
119 participants were taken before (T0) and after (T1) the 16-week intervention period and were defined
120 as follows:

121 Ambulatory blood pressure monitoring was conducted over a 24 hour period using an
122 oscillometric ABPM 6100 recorder (Welch Allyn, New York, USA) to evaluate SBP (as used to
123 determine CVR) [8]. The device was used in line with the recommendations set by the European
124 Society of Hypertension and the European Society of Cardiology guidelines. As such, BP was
125 measured at 30-minute intervals during awake-time and at 60-minute intervals during the sleep
126 period. Data were only used if at least 75% of the awake-time and sleep periods were successfully
127 recorded [16, 18].

128 Fasting venous blood (12.5mL) was collected from each participant following an overnight
129 fast. Diabetes mellitus was defined as fasting glucose of ≥126 mg/dL [21] and/or under

pharmacological glycemic control treatment. Additionally, measurements of glucose and lipid profile (total-, and HDL-C) were assayed (ABBOTT, Architect c16000, Orlando, FL, USA). The intra- and inter-assay coefficients of variation were: for glucose 0.65% and 0.84%; for total cholesterol 0.6% and 0.8%; and for HDL-C 1.7% and 1.1%, respectively.

Age and cigarette smoking status were assessed by self-report. All medicines being taken were ascertained from the participant's physician.

Cardiovascular risk and vascular age parameters' assessment have been previously analyzed in the sample at baseline, and the same procedures were applied for the follow-up study [13]. Briefly, the Framingham Heart Study assesses the absolute risk to the individual with a percentage score (*i.e.,* 10% means that there is a 10% chance of having a cardiovascular event within the next 10 years, <6%=low risk; 6-20%=medium risk, and ≥20%=high risk) [7]. The Pooled Cohort Risk Equations to estimate the 10-year risk was described as a series of steps [8]. The Framingham method was used to determine the VA of all participants [7], which indicates the biological age of the individual's vascular system, as the age a person would be with the same calculated CVR, but whose risk factors were all within normal ranges. The sex-specific risk factors considered were age, HDL-C, total cholesterol, SBP, DM, and smoking status. Each variable received a weighted score; the sum of the score for each variable was then translated into the risk of a CV event in 10 years and VA [7].

After baseline data collection, participants were randomly allocated to one of the four intervention groups stratified by sex, SBP, BMI and age using a time-blocked computerized randomization program by the principal investigator and blind to medical staff. Detailed descriptions of the exercise and diet intervention procedures have been already reported [16, 17]. Briefly, the intervention groups were: 1) Attention Control group with physical activity recommendations (*i.e.,* at least 30 min of moderate-intensity aerobic exercise 5-7 days per week and some dynamic resistance exercises); and three supervised aerobic exercise groups training two nonconsecutive days under supervision by exercise specialists, 2) high-volume moderate-intensity continuous training group, 45

min at moderate intensity; 3) high-volume high-intensity interval training group, 45 min alternating with different protocols moderate-to-high intensity; and 4) low-volume high-intensity interval training group, 20 min alternating with different protocols moderate-to-high intensity. All participants received treatment with a hypocaloric "Dietary Approaches to Stop Hypertension" (DASH) diet. The diet was designed to provide 25% less energy than their daily energy expenditure and to achieve a weekly loss of body mass between 0.5 and 1.0 kg. Approximately 30% of their energy intake came from fat, 15% from protein, and 55% from carbohydrates and was designed in accordance with the DASH diet [22]. This diet is rich in plant foods (*i.e., a* rich source of polyphenols) due to its favourable effect of BP [23]. Every two weeks, participants were weighed and received encouragement and advice alongside nutritional counseling to aid adherence.

Descriptive statistics were calculated for all variables. Data are expressed as means±standard deviations (SD) and the range. ANOVA was used to determine if there were significant pre-intervention differences between sexes for the variables: age, BMI, SBP, total cholesterol, HDL-C, antihypertensive medication, cigarette smoking, DM, CVR, and VA. The comparison of frequencies between sexes was performed using a Chi-Square test. Repeated measures within-between participants ANOVAs were used to determine whether there was a significant difference in the recorded data between pre- and post-intervention for all participants and any time x sex interaction effects, *i.e*. to examine whether the change due to the intervention differed between men and women. A pre- and post-intervention mean difference for each variable was calculated. Statistical significance was set at $P<0.05$. All statistical analyses were performed on an intention-to-treat basis using the SPSS version 22.0. The required sample size was determined for the primary outcome variable (SBP) and previously published [16, 17].

3 Results

Baseline characteristics of CVR factors classified by sex are presented in Table 1. The sample was the same as the previous study [13], but the number of participants is reduced because only those with

follow-up values were included. The mean age (±SD) was 53.7±7.8 years old with 64.7% being men, 12.8% of the participants were smokers, and 9.6% of the sample was suffering from DM. The results indicated that there were no significant differences between sexes for all CVR factors at baseline, except for total cholesterol, which was higher in women (mean difference=13.1; 95% CI=25.4-0.85 mg/dL) than in men, with both sexes exceeding cut-off values set by the European Society of Hypertension and the European Society of Cardiology guidelines [24]. The mean HDL-C was similar in men and women with both sexes remaining within the healthy cut-off values suggested by the European Society of Hypertension and the European Society of Cardiology guidelines [24].

The absolute CVR score was significantly different ($p<0.001$) between sexes with women having a lower CVR than men, irrespective of calculation method (ASCVD-CVR: mean difference=6.0, 95% CI=4.0-8.0 %, $p<0.001$; FRS-CVR: mean difference=10.2, 95% CI=7.1-13.4%, $p\leq0.001$, Table 1). Additionally, in accordance with the ASCVD-CVR score, men were considered to be at medium risk (10.5%), whereas women were considered to be at low risk (4.5%). However, using the FRS-CVR score, men were considered to be at high risk (>20%) whereas women were considered to be at medium risk (11.3%). Consequently, significant differences were found between CVR score calculators for CVR prediction ($p<0.001$, mean difference=9.6, 95% CI=10.6-8.6 %). In contrast, there was no sex difference in VA (mean difference=2.8, 95% CI=-7.5-1.8 yr old, $p=0.23$), but VA was significantly higher ($p<0.001$) than chronological age (CA) (mean difference=17.5, 95% CI=19.4-15.7 yr old), irrespective of sex, ($p<0.001$).

Table 2 shows CVR factors, CVR scores and VA values at baseline and follow-up. After the intervention, all participants showed decreased SBP, total cholesterol, antihypertensive medication usage (%), CVR score predicted by FRS, and VA ($p<0.05$). ANOVA showed that SBP decreased in both sexes (T0 *vs.* T1 difference %, men Δ=7.4 %; women, Δ=6.0 %, $p\leq0.001$). Significant time x sex interaction effects revealed that mean total cholesterol significantly reduced in men (Δ=13.6 %, $p\leq0.001$), but not in women (Δ=6.5 %, $p=0.12$), and antihypertensive medication (%) significantly

decreased in women (Δ=10.2 %, p=0.047), but not in men (Δ=4.6 %, p=0.30). No significant differences were observed in HDL-C, smoking habit and suffering from DM after 16-weeks intervention period. When CVR score and VA were analyzed, FRS-CVR and VA decreased overall, and in both sexes (FRS-CVR: men Δ=4.0 %; p≤0.001; women, Δ=2.0 %; p=0.01) and (VA: men Δ=5.6 %, p≤0.001; women, Δ=6.5 %; p≤0.001, Figure 1). However, no significant changes over time were observed in ASCVD-CVR overall or for either sex (men Δ=0.8 %, p=0.30; women Δ=0.5 %, p=0.08). Finally, the magnitude of change in each CVR variable due to the intervention was not significantly different from each other between sexes, despite some single factor reductions being significant only for men or women, as described above. However, after intervention period, the CVR score remained significantly different (p<0.001) between sexes (at follow-up) with women having a lower CVR than men, irrespective of calculation method (ASCVD-CVR: mean sex difference=5.6, 95% CI=3.0-8.2 %, p<0.001; FRS-CVR: mean sex difference=8.1, 95% CI=5.1-11.2%, p≤0.001, Table 2).

4 Discussion

To our knowledge, this is the first study investigating the impact of a 16-week intervention (hypocaloric DASH diet plus aerobic exercise) on CVR factors, CVR score calculators and VA in sedentary overweight/obese and hypertensive adults. The main findings of the study were that after aerobic exercise and hypocaloric DASH diet intervention: 1) participants significantly improved SBP, total cholesterol and decreased antihypertensive medication usage; 2) CVR and VA using the FRS model was significantly reduced in both sexes but not CVR estimated by ASCVD Pooled Cohort Equations; 3) regardless of the CVR assessment tool, men showed significantly higher values than women post-intervention albeit no differences in percentage change resulting from the intervention, and 4) VA could better identify the effect of a non-pharmacological intervention in both sexes than other CVR tools.

Based on a rigorous approach to the validation of equations, the American College of Cardiology and the American Heart Association guideline strongly recommends the use of Pooled

Cohort Equations in non-Hispanic African Americans and non-Hispanic whites (40 to 79 years old) for the assessment of the 10-year risk of a first hard ASCVD event [8]. However, although the ASCVD-CVR equations have been developed from the FRS [7, 8], and the role of the major variables in the development of CVR was similar in both score calculators, in the present study, after the exercise and diet intervention, CVR was still 7.1% lower with ASCVD-CVR than with FRS-CVR (P<0.001) in all participants (Table 2). Thus, the observed and predicted risks for participants in this study at follow-up were 9.6% and 17.6% (medium risk) in men and 4.0% (low risk) and 9.4% (medium risk) in women for the ASCVD-CVR and FRS-CVR, respectively. Hence, it could be considered that the ASCVD-CVR score calculator by the American College of Cardiology and the American Heart Association would identify the least number of participants with CVR (*i.e.,* underestimation), or the FRS-CVR would stratify a maximum number of individuals with high CVR (*i.e.,* overestimation) [6]. This difference could likely be caused by the objective of each score; the FRS estimates CVR for a large combination of CVD outcomes and the ASCVD tool estimates risk mainly for myocardial infarction (fatal and nonfatal) and stroke only [25] and does not consider family history, which influences mortality [25].

An appropriate lifestyle change, including diet and exercise, has been shown to effectively improve markers of CV health [18, 19] and CVD prevention [2]. Likewise, previous studies have proven that a dose-response curve for physical activity and HTN has a clinically meaningful role in primary prevention of HTN [26], along with a diet rich in polyphenols [23]. Related to that, in the current study, the decreases (p<0.05, before-after intervention) in SBP (Δ=7.3 mmHg in men and Δ=6 mmHg in women), total cholesterol in men (Δ=13.6 mg/dL) and antihypertensive medication use in women (Δ=10.5%) could rightfully be considered the reason underlying the reduction in the FRS-CVR score and VA. However, given that drug therapy for primary prevention of CVD is nowadays based on absolute CVD risk, where the BP-lowering drug treatment is determined by BP level along with other CVR factors (*i.e.,* sex, age, total cholesterol, HDL-C, DM, and smoking status) [27], and that a reduction of 5 mmHg in SBP was associated with a lower risk of CVD mortality [28], it seems that the ASCVD-CVR estimation tool does not have enough sensitivity to show the benefits of a lifestyle

intervention. Hence, the lack of significant changes in ASCVD-CVR estimation, in the presence of other CVR factor improvements, could have a negative effect on the advice to treat individuals with an ASCVD-CVR >7.5% with statins [15]. It is important, therefore, to note that treatment decisions should be individualized (*i.e.,* after a clinician-patient risk/benefit discussion addressing optimal lifestyle), as suggested by the latest cholesterol guidelines [29], and not just absolute CVR estimation.

On the other hand, the present study showed that after 16-week of intervention with diet and aerobic exercise, absolute CVR remained higher in men than in women for both CVR scores (ASCVD, 5.6%; FRS, 8.2%). As such, the straightforward discussion would claim that men have a higher risk of suffering a CV event in the following 10 years, underlining the sex differences in life expectancy and quality of life, due, in part, to unhealthy behaviors [30]. However, a deeper analysis of data and literature revealed that in the current study after lifestyle intervention: 1) there were no differences in the percentage change after intervention between men and women (ASCVD, p=0.73; FRS, p=0.09); 2) post-intervention women showed higher total cholesterol values with hyperlipidemia >190mg/dL, with no differences in HDL-C (normal values >40 mg/dL), antihypertensive medication use, smoking habit or DM compared to men; 3) the new cholesterol guidelines have no sex-specific differences in recommendations [31], and 4) menopausal status in women is not taken into account when CVR is estimated irrespective of tool (in this study 50% were post-menopausal women). Given this, and that deaths from CVD have been greater in women compared with men over the past 30 years, with CVR increases during the menopausal transition and after menopause mainly marked by progressive endothelial dysfunction [32], would be logical to conclude that CVR is underestimated in women.

Noting the imprecise previous tools for calculating the CVR, mainly due to the various underlying mathematical models used to calculate the scores, VA could be a useful tool in the management of individuals with CVR factors, and easier to use and understand the effect of an intervention in terms of life years [10]. Thus, in the present study after 16-week lifestyle

intervention, VA decreased in all participants (Table 2, Figure 1) with no differences between sexes. These results could identify biologically plausible mechanisms underlying exercise and diet-induced effects on CVD risk reduction irrespective of sex. Overall, the CVR factors-associated arterial wall thickening, which contributes to vascular stiffening, are sensitive to a non-pharmacological lifestyle intervention [33].

Although the present study has highlighted the importance of determining CVR factors in a hypertensive population after a lifestyle intervention, several limitations should be acknowledged. Firstly, although the sample size was sufficient as an initial investigation into CVR and HTN; it would not be comparable to that of larger epidemiological studies, and future studies should consider large-scale investigations. Secondly, the current study only had 35.3% of women which does not represent an equal gender split. As this poses statistical issues, future studies should look to recruit equal numbers, or even to study effects only in women.

5 Conclusions

The improvements in CVR factors after a 16-week lifestyle change intervention reduced the risk of suffering a CV event in the following 10 years in overweight/obese adults with HTN assessed with the FRS estimation tool. However, the ASCVD-CVR score calculator was not sensitive enough to show the benefits of diet and exercise. The risk score algorithms (FRS and ASCVD) might underestimate the CVR in women as they always consider men to be higher risk irrespective of age. Therefore, VA could be a useful tool in the management of individuals with CVR factors, and easier to apply and understand the effect of an intervention in terms of life expectancy.

Compliance with Ethical Standards

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Conflict of interest. On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval. All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent. All participants provided written informed consent prior to any data collection.

Figure legends

Figure 1. Vascular age (VA) values at baseline (T0) and follow-up (T1) periods compared to chronological age (CA).

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