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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

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1 **Effects on cardiovascular risk scores and vascular age after aerobic exercise and nutritional**

2 **intervention in sedentary and overweight/obese adults with primary hypertension: The EXERDIET-**

3 **HTA randomized trial study**

4 **Running title:** Cardiovascular risk assessment

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33 **Abstract**

34 **Aims** To evaluate the influence of diet and aerobic exercise program intervention on cardiovascular

35 risk (CVR) factors and predicted CVR and vascular age (VA) profiles in overweight/obese people with

36 primary hypertension (HTN), and to analyze the potential sex differences in the ability to predict VA

37 and CVR via different methods.

38 **Methods** The CVR and VA determined (n=167, 53.7±7.8 yr) using the Framingham Risk Score (FRS)

39 and the new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD)

40 risk, before and after the 16-week intervention period (different aerobic exercise

41 programs+hypocaloric diet). The sex-specific risk factors considered were age, high-density

42 lipoprotein cholesterol (HDL-C), total cholesterol, systolic blood pressure (SBP), diabetes mellitus

43 (DM) and smoking status.

44 **Results** From baseline to follow-up, participants reduced (p≤0.001) FRS-CVR score and VA, and SBP.

45 Total cholesterol decreased significantly, but specifically in men (p≤0.001), and antihypertensive

46 medication (%) in women (p=0.047). No significant differences over time were observed for HDL-C,

47 smoking, DM overall for either sex. For ASCVD-CVR there was no overall change or for either sex.

48 After the intervention, women had a lower CVR score than men (p≤0.001), irrespective of the

49 calculation method.

50 **Conclusions** The improvement in CVR factors after 16-week lifestyle changes reduced the risk of

51 suffering a cardiovascular event in overweight/obese adults with HTN through the FRS estimation

52 tool, but not with the ASCVD score. The risk score algorithms could underestimate CVR in women. In

53 contrast, VA could be a useful and easier tool in the management of individuals with CVR factors.

54 **Keywords**: Lifestyle intervention; sex; systolic blood pressure

55

56 **1 Introduction**

57 Cardiovascular disease (CVD) is a non-communicable disease, which represents the main cause of

58 disability and death in the world, including Europe [1, 2]. Globally, between 2006 and 2016 deaths

59 from CVD increased by 14.5%, although the age-standardized death rate decreased [3]. These data

60 suggest that this condition needs to receive greater priority in prevention policy to reduce avoidable

61 risk factors [2, 3]. Prevention is effective, and so, healthy lifestyle behavior promotion in the general

62 population should directly target unhealthy lifestyles, such as poor-quality diet, physical inactivity,

63 and smoking, at the individual level [2]. Cardiovascular risk (CVR) factors assessment is the first step

64 guiding therapeutic strategy for the prevention of CVD [2], and strategy effectiveness depends on

65 each patient's CVR profile and predictive risk [4].

66 There are several risk factor assessment tools for estimating a patient's 10-year risk of

67 developing CVD [2, 4]. However, the most well-established risk score algorithm is the Framingham

68 Risk Score (FRS), which was initially validated in 1998 to predict CVR [5, 6] and subsequently revised

69 [7]. Recently, the American College of Cardiology and the American Heart Association developed a

70 new equation for the prediction of 10-year atherosclerotic cardiovascular disease (ASCVD) risk, the

71 called "Pooled Cohort Risk Equations" [8, 9]. This new tool was aimed at providing sex- and race-

72 specific estimation of the 10-year risk of ASCVD for African-American and non-Hispanic white men

73 and women aged 40 to 70 years old [8, 9]. On the other hand, vascular age (VA, *i.e.,* the age of the

74 vascular system of a person with different CVR factors, calculated as the age a person would be with

75 the same calculated CVR but whose risk factors were all within normal ranges [10]) is an easily

76 understood concept related to CVR and calculated according to the definition of D'Agostino from

77 FRS [7].

78 The common prediction factors for CVR models that have a relationship with cardiovascular

79 events and premature death are age, sex, total cholesterol, high-density lipoprotein cholesterol

4

80   (HDL-C), systolic blood pressure (SBP, including treated or untreated status), diabetes mellitus (DM),

81   and current smoking status [8].

82   Many observational studies have demonstrated graded associations between primary

83   hypertension (HTN) and increased CVD risk [11] Additionally, adults with HTN usually present other

84   modifiable CVR factors such as obesity, hypercholesterolemia, DM, smoking, physical inactivity, and

85   unhealthy diet [12]. Therefore, correcting the dietary habits, lack of exercise and excessive

86   consumption of alcohol through nonpharmacological interventions alone or in combination with

87   pharmacological therapy is fundamental for the management of HTN [12].

88   A previous study evaluating CVR using the "Pooled Cohort Equations" (sex-specific risk

89   prediction model) and VA in overweight/obese people with HTN found that CVR was significantly

90   higher in men than in women despite them having the same CVR values, whereas no differences

91   were found between sexes in VA [13]. As such, women could have an underestimated CVR profile

92   based on the misperception that women are "protected" against CVD [14]. Hence, one of the biggest

93   criticisms of the prediction scales of CVR accuracy is their capacity to overestimate or underestimate

94   the risk [15]. Currently, there is no known research that measures the effects of an aerobic exercise

95   program with nutritional intervention on CVR and VA in sedentary and overweight/obese adults with

96   HTN. Considering the importance of CVR assessment, the objectives of this study were: 1) to

97   evaluate the influence of 16-week diet and different aerobic exercise programs intervention on CVR

98   factors and predicted CVR and VA profiles in sedentary and overweight/obese people with HTN, and

99   2) to analyse the potential sex differences in the ability to predict VA and CVR via different methods

100 resulting from changes in lifestyle.

101 **2 Methods**

102 The EXERDIET-HTA study was a multi-arm parallel, a randomized, single-blind controlled

103 experimental trial comparing the effects of 16 weeks of different aerobic exercise programs two

104 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

130   pharmacological glycemic control treatment. Additionally, measurements of glucose and lipid profile

131   (total-, and HDL-C) were assayed (ABBOTT, Architect c16000, Orlando, FL, USA). The intra- and inter-

132   assay coefficients of variation were: for glucose 0.65% and 0.84%; for total cholesterol 0.6% and

133   0.8%; and for HDL-C 1.7% and 1.1%, respectively.

134   Age and cigarette smoking status were assessed by self-report. All medicines being taken were

135   ascertained from the participant's physician.

136   Cardiovascular risk and vascular age parameters' assessment have been previously analyzed

137   in the sample at baseline, and the same procedures were applied for the follow-up study [13].

138   Briefly, the Framingham Heart Study assesses the absolute risk to the individual with a percentage

139   score (*i.e.,* 10% means that there is a 10% chance of having a cardiovascular event within the next 10

140   years, <6%=low risk; 6-20%=medium risk, and ≥20%=high risk) [7]. The Pooled Cohort Risk Equations

141   to estimate the 10-year risk was described as a series of steps [8]. The Framingham method was

142   used to determine the VA of all participants [7], which indicates the biological age of the individual's

143   vascular system, as the age a person would be with the same calculated CVR, but whose risk factors

144   were all within normal ranges. The sex-specific risk factors considered were age, HDL-C, total

145   cholesterol, SBP, DM, and smoking status. Each variable received a weighted score; the sum of the

146   score for each variable was then translated into the risk of a CV event in 10 years and VA [7].

147   After baseline data collection, participants were randomly allocated to one of the four

148   intervention groups stratified by sex, SBP, BMI and age using a time-blocked computerized

149   randomization program by the principal investigator and blind to medical staff. Detailed descriptions

150   of the exercise and diet intervention procedures have been already reported [16, 17]. Briefly, the

151   intervention groups were: 1) Attention Control group with physical activity recommendations (*i.e.,* at

152   least 30 min of moderate-intensity aerobic exercise 5-7 days per week and some dynamic resistance

153   exercises); and three supervised aerobic exercise groups training two nonconsecutive days under

154   supervision by exercise specialists, 2) high-volume moderate-intensity continuous training group, 45

155 min at moderate intensity; 3) high-volume high-intensity interval training group, 45 min alternating

156 with different protocols moderate-to-high intensity; and 4) low-volume high-intensity interval

157 training group, 20 min alternating with different protocols moderate-to-high intensity. All

158 participants received treatment with a hypocaloric "Dietary Approaches to Stop Hypertension"

159 (DASH) diet. The diet was designed to provide 25% less energy than their daily energy expenditure

160 and to achieve a weekly loss of body mass between 0.5 and 1.0 kg. Approximately 30% of their

161 energy intake came from fat, 15% from protein, and 55% from carbohydrates and was designed in

162 accordance with the DASH diet [22]. This diet is rich in plant foods (*i.e., a* rich source of polyphenols)

163 due to its favourable effect of BP [23]. Every two weeks, participants were weighed and received

164 encouragement and advice alongside nutritional counseling to aid adherence.

165 Descriptive statistics were calculated for all variables. Data are expressed as means±standard

166 deviations (SD) and the range. ANOVA was used to determine if there were significant pre-

167 intervention differences between sexes for the variables: age, BMI, SBP, total cholesterol, HDL-C,

168 antihypertensive medication, cigarette smoking, DM, CVR, and VA. The comparison of frequencies

169 between sexes was performed using a Chi-Square test. Repeated measures within-between

170 participants ANOVAs were used to determine whether there was a significant difference in the

171 recorded data between pre- and post-intervention for all participants and any time x sex interaction

172 effects, *i.e*. to examine whether the change due to the intervention differed between men and

173 women. A pre- and post-intervention mean difference for each variable was calculated. Statistical

174 significance was set at $P<0.05$. All statistical analyses were performed on an intention-to-treat basis

175 using the SPSS version 22.0. The required sample size was determined for the primary outcome

176 variable (SBP) and previously published [16, 17].

177 **3 Results**

178 Baseline characteristics of CVR factors classified by sex are presented in Table 1. The sample was the

179 same as the previous study [13], but the number of participants is reduced because only those with

180   follow-up values were included. The mean age (±SD) was 53.7±7.8 years old with 64.7% being men,

181   12.8% of the participants were smokers, and 9.6% of the sample was suffering from DM. The results

182   indicated that there were no significant differences between sexes for all CVR factors at baseline,

183   except for total cholesterol, which was higher in women (mean difference=13.1; 95% CI=25.4-0.85

184   mg/dL) than in men, with both sexes exceeding cut-off values set by the European Society of

185   Hypertension and the European Society of Cardiology guidelines [24]. The mean HDL-C was similar in

186   men and women with both sexes remaining within the healthy cut-off values suggested by the

187   European Society of Hypertension and the European Society of Cardiology guidelines [24].

188   The absolute CVR score was significantly different (p<0.001) between sexes with women

189   having a lower CVR than men, irrespective of calculation method (ASCVD-CVR: mean difference=6.0,

190   95% CI=4.0-8.0 %, p<0.001; FRS-CVR: mean difference=10.2, 95% CI=7.1-13.4%, p≤0.001, Table 1).

191   Additionally, in accordance with the ASCVD-CVR score, men were considered to be at medium risk

192   (10.5%), whereas women were considered to be at low risk (4.5%). However, using the FRS-CVR

193   score, men were considered to be at high risk (>20%) whereas women were considered to be at

194   medium risk (11.3%). Consequently, significant differences were found between CVR score

195   calculators for CVR prediction (p<0.001, mean difference=9.6, 95% CI=10.6-8.6 %). In contrast, there

196   was no sex difference in VA (mean difference=2.8, 95% CI=-7.5-1.8 yr old, p=0.23), but VA was

197   significantly higher (p<0.001) than chronological age (CA) (mean difference=17.5, 95% CI=19.4-15.7

198   yr old), irrespective of sex, (p<0.001).

199   Table 2 shows CVR factors, CVR scores and VA values at baseline and follow-up. After the

200   intervention, all participants showed decreased SBP, total cholesterol, antihypertensive medication

201   usage (%), CVR score predicted by FRS, and VA (p<0.05). ANOVA showed that SBP decreased in both

202   sexes (T0 *vs.* T1 difference %, men Δ=7.4 %; women, Δ=6.0 %, p≤0.001). Significant time x sex

203   interaction effects revealed that mean total cholesterol significantly reduced in men (Δ=13.6 %,

204   p≤0.001), but not in women (Δ=6.5 %, p=0.12), and antihypertensive medication (%) significantly

205 decreased in women (∆=10.2 %, p=0.047), but not in men (∆=4.6 %, p=0.30). No significant

206 differences were observed in HDL-C, smoking habit and suffering from DM after 16-weeks

207 intervention period. When CVR score and VA were analyzed, FRS-CVR and VA decreased overall, and

208 in both sexes (FRS-CVR: men ∆=4.0 %; p≤0.001; women, ∆=2.0 %; p=0.01) and (VA: men ∆=5.6 %,

209 p≤0.001; women, ∆=6.5 %; p≤0.001, Figure 1). However, no significant changes over time were

210 observed in ASCVD-CVR overall or for either sex (men ∆=0.8 %, p=0.30; women ∆=0.5 %, p=0.08).

211 Finally, the magnitude of change in each CVR variable due to the intervention was not significantly

212 different from each other between sexes, despite some single factor reductions being significant

213 only for men or women, as described above. However, after intervention period, the CVR score

214 remained significantly different (p<0.001) between sexes (at follow-up) with women having a lower

215 CVR than men, irrespective of calculation method (ASCVD-CVR: mean sex difference=5.6, 95%

216 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).

217 **4 Discussion**

218 To our knowledge, this is the first study investigating the impact of a 16-week intervention

219 (hypocaloric DASH diet plus aerobic exercise) on CVR factors, CVR score calculators and VA in

220 sedentary overweight/obese and hypertensive adults. The main findings of the study were that after

221 aerobic exercise and hypocaloric DASH diet intervention: 1) participants significantly improved SBP,

222 total cholesterol and decreased antihypertensive medication usage; 2) CVR and VA using the FRS

223 model was significantly reduced in both sexes but not CVR estimated by ASCVD Pooled Cohort

224 Equations; 3) regardless of the CVR assessment tool, men showed significantly higher values than

225 women post-intervention albeit no differences in percentage change resulting from the intervention,

226 and 4) VA could better identify the effect of a non-pharmacological intervention in both sexes than

227 other CVR tools.

228   Based on a rigorous approach to the validation of equations, the American College of

229 Cardiology and the American Heart Association guideline strongly recommends the use of Pooled

230   Cohort Equations in non-Hispanic African Americans and non-Hispanic whites (40 to 79 years old) for

231   the assessment of the 10-year risk of a first hard ASCVD event [8]. However, although the ASCVD-

232   CVR equations have been developed from the FRS [7, 8], and the role of the major variables in the

233   development of CVR was similar in both score calculators, in the present study, after the exercise

234   and diet intervention, CVR was still 7.1% lower with ASCVD-CVR than with FRS-CVR (*P*<0.001) in all

235   participants (Table 2). Thus, the observed and predicted risks for participants in this study at follow-

236   up were 9.6% and 17.6% (medium risk) in men and 4.0% (low risk) and 9.4% (medium risk) in women

237   for the ASCVD-CVR and FRS-CVR, respectively. Hence, it could be considered that the ASCVD-CVR

238   score calculator by the American College of Cardiology and the American Heart Association would

239   identify the least number of participants with CVR (*i.e.,* underestimation), or the FRS-CVR would

240   stratify a maximum number of individuals with high CVR (*i.e.,* overestimation) [6]. This difference

241   could likely be caused by the objective of each score; the FRS estimates CVR for a large combination

242   of CVD outcomes and the ASCVD tool estimates risk mainly for myocardial infarction (fatal and

243   nonfatal) and stroke only [25] and does not consider family history, which influences mortality [25].

244   An appropriate lifestyle change, including diet and exercise, has been shown to effectively

245   improve markers of CV health [18, 19] and CVD prevention [2]. Likewise, previous studies have

246   proven that a dose-response curve for physical activity and HTN has a clinically meaningful role in

247   primary prevention of HTN [26], along with a diet rich in polyphenols [23]. Related to that, in the

248   current study, the decreases (p<0.05, before-after intervention) in SBP (Δ=7.3 mmHg in men and Δ=6

249   mmHg in women), total cholesterol in men (Δ=13.6 mg/dL) and antihypertensive medication use in

250   women (Δ=10.5%) could rightfully be considered the reason underlying the reduction in the FRS-CVR

251   score and VA. However, given that drug therapy for primary prevention of CVD is nowadays based

252   on absolute CVD risk, where the BP-lowering drug treatment is determined by BP level along with

253   other CVR factors (*i.e.,* sex, age, total cholesterol, HDL-C, DM, and smoking status) [27], and that a

254   reduction of 5 mmHg in SBP was associated with a lower risk of CVD mortality [28], it seems that the

255   ASCVD-CVR estimation tool does not have enough sensitivity to show the benefits of a lifestyle

256   intervention. Hence, the lack of significant changes in ASCVD-CVR estimation, in the presence of

257   other CVR factor improvements, could have a negative effect on the advice to treat individuals with

258   an ASCVD-CVR >7.5% with statins [15]. It is important, therefore, to note that treatment decisions

259   should be individualized (*i.e.,* after a clinician-patient risk/benefit discussion addressing optimal

260   lifestyle), as suggested by the latest cholesterol guidelines [29], and not just absolute CVR

261   estimation.

262   On the other hand, the present study showed that after 16-week of intervention with diet

263   and aerobic exercise, absolute CVR remained higher in men than in women for both CVR scores

264   (ASCVD, 5.6%; FRS, 8.2%). As such, the straightforward discussion would claim that men have a

265   higher risk of suffering a CV event in the following 10 years, underlining the sex differences in life

266   expectancy and quality of life, due, in part, to unhealthy behaviors [30]. However, a deeper analysis

267   of data and literature revealed that in the current study after lifestyle intervention: 1) there were no

268   differences in the percentage change after intervention between men and women (ASCVD, p=0.73;

269   FRS, p=0.09); 2) post-intervention women showed higher total cholesterol values with

270   hyperlipidemia >190mg/dL, with no differences in HDL-C (normal values >40 mg/dL),

271   antihypertensive medication use, smoking habit or DM compared to men; 3) the new cholesterol

272   guidelines have no sex-specific differences in recommendations [31], and 4) menopausal status in

273   women is not taken into account when CVR is estimated irrespective of tool (in this study 50% were

274   post-menopausal women). Given this, and that deaths from CVD have been greater in women

275   compared with men over the past 30 years, with CVR increases during the menopausal transition

276   and after menopause mainly marked by progressive endothelial dysfunction [32], would be logical to

277   conclude that CVR is underestimated in women.

278   Noting the imprecise previous tools for calculating the CVR, mainly due to the various

279   underlying mathematical models used to calculate the scores, VA could be a useful tool in the

280   management of individuals with CVR factors, and easier to use and understand the effect of an

281   intervention in terms of life years [10]. Thus, in the present study after 16-week lifestyle

282 intervention, VA decreased in all participants (Table 2, Figure 1) with no differences between sexes.

283 These results could identify biologically plausible mechanisms underlying exercise and diet-induced

284 effects on CVD risk reduction irrespective of sex. Overall, the CVR factors-associated arterial wall

285 thickening, which contributes to vascular stiffening, are sensitive to a non-pharmacological lifestyle

286 intervention [33].

287 Although the present study has highlighted the importance of determining CVR factors in a

288 hypertensive population after a lifestyle intervention, several limitations should be acknowledged.

289 Firstly, although the sample size was sufficient as an initial investigation into CVR and HTN; it would

290 not be comparable to that of larger epidemiological studies, and future studies should consider

291 large-scale investigations. Secondly, the current study only had 35.3% of women which does not

292 represent an equal gender split. As this poses statistical issues, future studies should look to recruit

293 equal numbers, or even to study effects only in women.

294 **5 Conclusions**

295 The improvements in CVR factors after a 16-week lifestyle change intervention reduced the risk of

296 suffering a CV event in the following 10 years in overweight/obese adults with HTN assessed with

297 the FRS estimation tool. However, the ASCVD-CVR score calculator was not sensitive enough to show

298 the benefits of diet and exercise. The risk score algorithms (FRS and ASCVD) might underestimate

299 the CVR in women as they always consider men to be higher risk irrespective of age. Therefore, VA

300 could be a useful tool in the management of individuals with CVR factors, and easier to apply and

301 understand the effect of an intervention in terms of life expectancy.

302 **Compliance with Ethical Standards**

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

306 of interest.

307   **Ethical approval.** All procedures performed in the study involving human participants were in

308   accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and

309   its later amendments or comparable ethical standards.

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

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312

313 **Figure legends**

314 **Figure 1.** Vascular age (VA) values at baseline (T0) and follow-up (T1) periods compared

315 to chronological age (CA).

316

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