

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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31

32

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 ($p \leq 0.001$) FRS-CVR score and VA, and SBP.
45 Total cholesterol decreased significantly, but specifically in men ($p \leq 0.001$), 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 ($p \leq 0.001$), 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

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

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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/m² or obese (BMI ≥ 30 kg/m²) [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 glycemetic 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 \geq 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 (\pm 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%, $p\leq 0.001$, 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 $\Delta=7.4$ %; women, $\Delta=6.0$ %, $p\leq 0.001$). Significant time x sex
203 interaction effects revealed that mean total cholesterol significantly reduced in men ($\Delta=13.6$ %, $p\leq 0.001$),
204 but not in women ($\Delta=6.5$ %, $p=0.12$), and antihypertensive medication (%) significantly

205 decreased in women ($\Delta=10.2$ %, $p=0.047$), but not in men ($\Delta=4.6$ %, $p=0.30$). 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 $\Delta=4.0$ %; $p\leq 0.001$; women, $\Delta=2.0$ %; $p=0.01$) and (VA: men $\Delta=5.6$ %, $p\leq 0.001$; women, $\Delta=6.5$ %; $p\leq 0.001$, Figure 1). However, no significant changes over time were
209 observed in ASCVD-CVR overall or for either sex (men $\Delta=0.8$ %, $p=0.30$; women $\Delta=0.5$ %, $p=0.08$).
210 Finally, the magnitude of change in each CVR variable due to the intervention was not significantly
211 different from each other between sexes, despite some single factor reductions being significant
212 only for men or women, as described above. However, after intervention period, the CVR score
213 remained significantly different ($p<0.001$) between sexes (at follow-up) with women having a lower
214 CVR than men, irrespective of calculation method (ASCVD-CVR: mean sex difference=5.6, 95%
215 CI=3.0-8.2 %, $p<0.001$; FRS-CVR: mean sex difference=8.1, 95% CI=5.1-11.2%, $p\leq 0.001$, 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 ($\Delta=7.3$ mmHg in men and $\Delta=6$
249 mmHg in women), total cholesterol in men ($\Delta=13.6$ mg/dL) and antihypertensive medication use in
250 women ($\Delta=10.5\%$) 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**

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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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