The 2 risk charts thus show a satisfactory level of agreement by intraclass correlation coefficient and kappa statistic (except for women); however, cardiovascular risk was systematically lower on the SCORE OP chart. European guidelines recommend a more cautious pharmacological approach with patients older than 60 years because the calculated risk can be high simply due to the patient's age, even when no other risk factors are present.

In Spain, 2 risk charts have been generated from direct analysis of the Spanish population, including the elderly population: the ERICE study, which includes participants ranging in age from 30 years to more than 80 years,[5] and the FRESCO study, which includes individuals aged from 35 to 79 years.[6] These risk calculations are awaiting external validation of their usefulness and impact compared with already available risk charts.

A limitation of the present study is the incomplete dataset for SBP and TC, which impeded risk calculation for some patients. Another limitation is that the analysis was restricted to primary care patients, raising uncertainties about whether the results can be extrapolated to the general population.

Among people older than 65 years, the SCORE OP risk chart gives lower cardiovascular risk estimates than the original SCORE chart, suggesting that fewer patients in this age group might benefit from statin therapy than previously thought. Further validation studies of these risk charts are needed in the Spanish population to assess the level of discrimination and calibration.

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The Role of Sex and Domestic Physical Activity on the Metabolically Healthy and Unhealthy Obesity. The HERMEX Study

Efecto del sexo y la actividad física doméstica en el fenotipo obeso metabólicamente sano y el obeso con alteraciones metabólicas. Estudio HERMEX

To the Editor,

The concept of metabolically healthy but obese (MHO) reflects a group of obese individuals who seem to be protected against many obesity-related cardiometabolic complications. Characterizing this subgroup of obese individuals and distinguishing them from the metabolically unhealthy obese and the nonobese (either metabolically healthy or unhealthy) is of major clinical and public health interest. Because traditional cardiometabolic markers (such as dyslipidemia, insulin resistance, or hypertension) are used in the definition of MHO, it is important to assess other nontraditional biomarkers (such as apolipoproteins, inflammatory or renal markers), which could further explain the differences observed among the different body-size phenotypes. In addition, the role of sex and physical activity (PA; including domestic PA) in the metabolic status of obese individuals warrants particular attention.

This study assessed: a) the differences in nontraditional cardiometabolic risk markers across the 4 aforementioned body-size phenotypes; b) whether sex differences exist; and c) the extent to which PA levels may play a role in the cardiometabolic profile.

The complete methodology of this population-based cross-sectional study entirely conducted in the province of Badajoz (Extremadura; southwest Spain) has been published elsewhere.[1] Of 2833 participants, 135 were excluded due to previous cardiovascular event (ie, myocardial infarction, angina, or stroke). A total of 2698 participants (aged 25-79 years) were finally included.

Age, educational and occupational status, smoking and alcohol consumption were registered through personal interview. Systolic and diastolic blood pressures were measured according to the European Society of Hypertension. Resting heart rate was measured from the radial pulse for 30 seconds. Plasma insulin, apolipoproteins A and B, high-sensitivity C-reactive protein, glycosylated hemoglobin, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, glucose, urea, albumin, creatinine, and fibrinogen concentrations were measured by standard procedures. The albumin-creatinine ratio and estimated glomerular filtration rate were also determined.

Leisure time PA was self-reported through the Minnesota Leisure Time Physical Activity Questionnaire. Participants were classified as physically active if they met the PA guidelines (ie, total PA energy expenditure $\geq$ 500 metabolic equivalents per week).

We defined metabolically healthy or unhealthy in accordance with the Consensus Societies for the definition of metabolic syndrome, and classified individuals into 4 body-size phenotype (ie, obese or nonobese, metabolically healthy or unhealthy).

Table
Cardiometabolic and Physical Activity Parameters by Body-size Phenotype

	Metabolically healthy nonobese (n = 1240, [46%])	Metabolically unhealthy nonobese (n = 542, [20%])	Metabolically healthy but obese (n = 332, [12%])	Metabolically unhealthy and obese (n = 580, [22%])	*P*
Age, y	44.4 ± 0.38[abc]	55.6 ± 0.56[ade]	50.8 ± 0.72[bdf]	58.1 ± 0.55[cef]	< .001
Women	826 (56)	173 (12)	212 (15)	256 (17)	< .001
Lipid profile					
Total cholesterol, mg/dL	206.9 ± 1.12	209.7 ± 1.66	209.5 ± 1.03	210.6 ± 1.60	.258
HDL-C, mg/dL	63.1 ± 0.37[abc]	51.0 ± 0.54[ade]	57.4 ± 0.67[bdf]	48.1 ± 0.53[cef]	< .001
LDL-C, mg/dL	119.2 ± 0.93[ab]	123.7 ± 1.38[a]	121.9 ± 1.69	124.5 ± 1.33[b]	.009
Triglycerides, mg/dL	78.6 ± 2.08[abc]	144.1 ± 2.07[ade]	99.2 ± 3.77[bdf]	159.8 ± 2.98[cef]	< .001
Apo A, mg/dL	1.65 ± 0.010[ab]	1.49 ± 0.014[ac]	1.63 ± 0.018[cd]	1.47 ± 0.014[bd]	< .001
Apo B, mg/dL	0.96 ± 0.025	1.05 ± 0.038	1.01 ± 0.046	1.00 ± 0.037	.650
Hypercholesterolemia: ≥ 240 mg/dL or medication n, (%)	272 (21.9)[a]	202 (37.3)[b]	91 (27.4)[c]	274 (47.2)[abc]	< .001
Inflammatory profile					
C-reactive protein, mg/L	1.98 ± 0.25[ab]	2.90 ± 0.38[c]	3.75 ± 0.47[a]	4.84 ± 0.37[bc]	< .001
Leukocytes (units x 10^9/L)	6.24 ± 0.05[abc]	6.73 ± 0.07[a]	6.73 ± 0.09[b]	6.86 ± 0.07[c]	< .001
Fibrinogen, mg/dL	370.4 ± 2.68[ab]	380.2 ± 3.95[c]	402.9 ± 4.86[ac]	388.6 ± 3.83[b]	< .001
Glycemic profile					
Fasting glucose, mg/dL	95.6 ± 0.66[ab]	111.3 ± 0.97[acd]	98.4 ± 1.19[de]	115.2 ± 0.94[bce]	< .001
Fasting insulin, mg/dL	6.40 ± 0.18[abc]	10.1 ± 0.27[ad]	10.7 ± 0.33[be]	15.2 ± 0.26[cde]	< .001
HOMA-IR	1.54 ± 0.08[abc]	2.87± 0.11[ad]	2.64 ± 0.14[be]	4.48 ± 0.11[cde]	< .001
Glycosylated hemoglobin, n (%)	4.97 (0.22)[ab]	5.31 (0.032)[acd]	5.07 (0.039)[ce]	5.46 (0.031)[bde]	< .001
Diabetes (≥ 126 mg/dL), n (%)	18 (1.5)[ab]	99 (18.3)[acd]	21 (6.3)[ce]	156 (26.9)[bde]	< .001
Vascular function					
Heart rate, bpm	70.3 ± 0.33[ab]	73.9 ± 0.49[ac]	71.5 ± 0.60[cd]	74.8 ± 0.48[bd]	< .001
Systolic blood pressure, mmHg	117.3 ± 0.45[abc]	129.0 ± 0.66[ad]	121.1 ± 0.81[bde]	130.9 ± 0.64[ce]	< .001
Diastolic blood pressure, mmHg	70.2 ± 0.28[abc]	76.6 ± 0.41[ad]	75.4 ± 0.51[be]	79.5 ± 0.40[cde]	< .001
Hypertension (≥ 140/90 mmHg), n (%)	96 (7.7)[ab]	252 (46.5)[acd]	57 (17.2)[ce]	323 (55.7)[bde]	< .001
Between-arms SBP diff., mm/Hg	0.52 ± 0.25[ab]	1.71 ± 0.37[a]	1.59 ± 0.45	1.88 ± 0.36[b]	.008
Pulse pressure, mmHg	47.9 ± 0.37[ab]	53.4 ± 0.54[ac]	46.7 ± 0.66[cd]	52.5 ± 0.52[bd]	< .001
Pulse pressure > 50 mmHg, %	253 (20.4)[ab]	325 (60.0)[ac]	101 (30.4)[cd]	353 (60.9)[bd]	< .001
Ankle-brachial index, mmHg	1.09 ± 0.004[abc]	1.07 ± 0.005[a]	1.07 ± 0.006[b]	1.07 ± 0.005[c]	.002
Ankle-brachial index < 90 n (%)	16 (1.3)[ab]	24 (4.4)[a]	10 (3.0)	29 (5.0)[b]	< .001
Parental history of cardiovascular death, n (%)	214 (17.3)	76 (14.0)	55 (16.7)	79 (13.7)	.533
Renal function					
Urea, mg/dL	36.8 ± 0.30	36.8 ± 0.43	37.8 ± 0.53	37.9 ± 0.42	.085
Creatinine, mg/dL	0.82 ± 0.006	0.84 ± 0.008	0.83 ± 0.010	0.85 ± 0.008	.066
Albumin-creatinine ratio	7.21 ± 2.78[a]	17.9 ± 4.11	5.26 ± 5.04[b]	22.36 ± 3.98[ab]	.008
Abnormal urinary albumin excretion, n (%)	28 (2.3)[a]	34 (6.3)	12 (3.6)[b]	56 (9.7)[ab]	< .001
Glomerular filtration rate, mL/min/m^2	94.8 ± 0.57	94.1 ± 0.83	93.2 ± 1.03	92.7 ± 0.81	.163
Glomerular filtration rate < 60 mL/min, n (%)	17 (1.4)[abc]	27 (5.0)[a]	17 (6.6)[b]	38 (3.7)[c]	< .001
Physical activity					
MVPA (> 4 METs), METs/wk	226.6 ± 9.5[a]	182.5 ± 14.0	181.7 ± 17.3	141.2 ±13.6[a]	< .001
Total expenditure (excluding domestic PA), METs/wk	282.6 ± 8.1[abc]	235.6 ±12.0[ad]	234.8 ± 14.7[be]	187.9 ± 11.6[cde]	< .001
Total expenditure (including domestic PA), METs/wk	593.1 ± 11.7[ab]	450.0 ± 17.2[ac]	548.2 ± 20.7[cd]	418.4 ± 16.3[bd]	< .001
Meet PA guidelines (including domestic PA), n (%)	651 (52.5)[ab]	197 (36.3)[ac]	159 (47.9)[cd]	199 (34.3)[bd]	< .001
Low intensity (< 3 METs), METs/wk	65.4 ± 2.9	59.9 ± 4.2	56.3 ± 5.2	52.2 ± 4.1	.066
Medium intensity (3.0-6.0 METs), METs/wk	126.8 ±7.6[a]	97.8 ± 11.2	96.1 ± 13.8	72.1 ± 10.9[a]	.001
High intensity (> 6 METs), METs/wk	99.8 ± 5.6[a]	84.8 ± 8	85.7 ± 10.2	69.1 ± 8.0[a]	.030

Apo A, apolipoprotein A; Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol, PA, physical activity; MET, metabolic equivalent of task; MVPA, moderate-vigorous physical activity; SBP, systolic blood pressure; wk, week. 1 MET = 3.5 mL of oxygen uptake/kg/min.

Values shown as mean ± standard error unless otherwise indicated; analyses were performed with ANCOVA with age, sex, smoking (yes/no), alcohol consumption (mL) and educational status as covariables; upper case [a,b,c,d,e,f] letters in the same row indicates a significant pairwise difference ($P < .05$) between groups with the same letter. The Bonferroni correction for multiple comparisons was applied to analyze pairwise differences.

Obesity was defined as body mass index ≥ 30 kg/m^2 and waist circumference was excluded from the criteria.[2]

One-way analysis of covariance (ANCOVA) was used to assess the differences in cardiometabolic markers across body-size phenotypes after adjustment for age, sex, smoking, alcohol consumption, and educational status. Sex differences were assessed using ANCOVA with the aforementioned covariates. The Bonferroni correction for multiple comparisons was applied.

The prevalence of MHO was 12% (36% among the obese). Women had a higher prevalence of MHO (15% vs 10%, respectively) and metabolically healthy nonobese (71% vs 44%) phenotypes than men (both $P < .001$, Tableand Figure 1 of the supplementary material). Men had a more impaired cardiometabolic profile and lower PA levels than women (all $P < .001$, Table and Figure 2 of the supplementary material). Despite the expectable differences in traditional markers of metabolic syndrome, the MHO group was younger and had higher plasma apolipoprotein A and lower triglycerides, low-density lipoprotein cholesterol, glycosylated hemoglobin, resting heart rate and pulse pressure than both metabolically unhealthy obese and nonobese (Table and Figure). The inflammatory profile was more impaired in all the groups in comparison to the metabolically healthy nonobese (Table). The MHO group had a more favorable renal profile (lower prevalence of abnormal urinary albumin excretion and albumin-creatinine ratio) than the metabolically unhealthy obese (Table). Finally, the obese and the metabolically unhealthy groups showed lower total energy expenditure in PA and less fulfillment of the PA recommendations than the MHO group ($P < .001$, Table).

The MHO participants showed higher levels of all-type PA and a higher proportion of individuals meeting the PA guidelines than metabolically unhealthy obese. Other studies revealed that MHO individuals spend less time in sedentary behavior and more time in light PA and active commuting than metabolically unhealthy obese.[3]

A major finding of this study is that women had higher PA levels (especially when domestic PA was accounted for) and this could partially explain the higher proportion of MHO observed among women. Similarly, the higher PA levels observed among

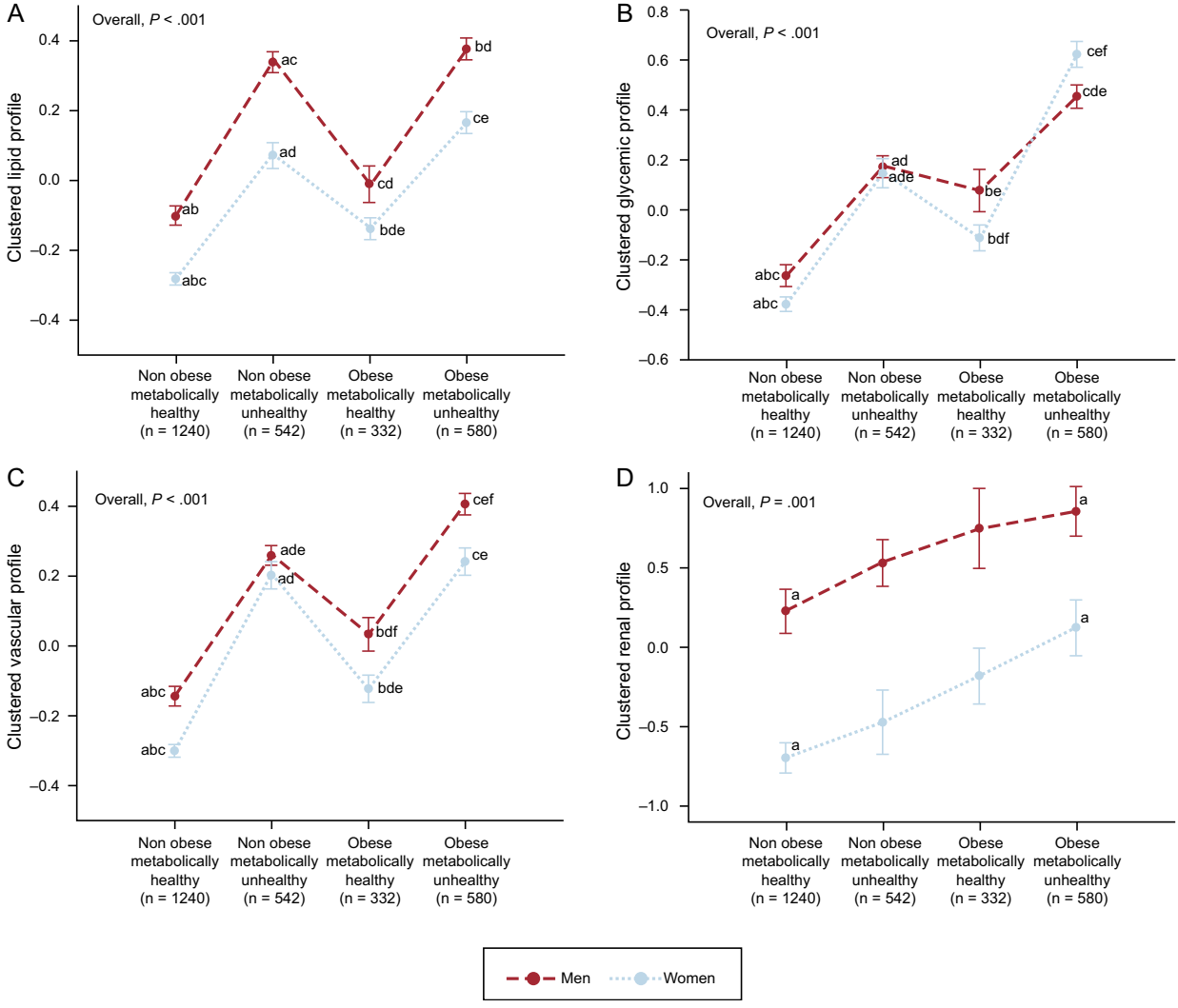

Figure. Clustered (z-score) adverse lipid profile (A), glycemic profile (B), vascular function (C) and renal function (D) by phenotype groups and sex. Dots represent mean ± standard error. [a,b,c,d,e,f] Letters indicate a pairwise significant difference ($P < .05$) for each sex between phenotype groups with the same letter. The model (1-way analysis of covariance) was adjusted for age, educational status, smoking, and alcohol consumption. Pairwise comparisons were performed with Bonferroni's adjustment. Adverse lipid profile consisted of the standardized scores [(value-mean)/standard deviation] of plasma triglycerides, LDL-C, Apo B and inverted HDL-C and Apo A (A). Adverse glycemic profile consisted of fasting glucose, insulin and glycosylated hemoglobin (B). Adverse vascular profile consisted of resting hearth rate, systolic and diastolic blood pressure (C). Adverse renal profile comprised plasma urea and creatinine and urinary microalbumin and inverted glomerular filtration rate (D). Apo A, apolipoprotein A; Apo B, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

women could partly explain the more favorable cardiometabolic profile observed in women regardless of the body-size phenotype.[4] Indeed, most women were housewives and they spent 10 times more energy in domestic PA than men, which could imply a substantial reduction in cardiometabolic risk. This hypothesis is supported by previous studies reporting that light household PA is associated with lower cardiovascular and all-cause mortality.[5]

Our results reinforce the idea that PA might play an important role on the MHO phenotype and its prognosis.

The cross-sectional design and lack of objective assessment of PA, physical fitness, fatness and nutritional patterns are limitations of this study that should be considered in future studies.

Since low PA is a common feature of the metabolically unhealthy obese phenotype, PA or exercise programs could play an important role in this population. In addition, further research is needed to determine whether increasing PA among MHO individuals might prevent the transition from MHO to a metabolically unhealthy status or promote the opposite, which has been previously reported to occur.[6]

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SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2016.04.050.

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Structural Heart Disease in Anticoagulated Patients With Nonvalvular Atrial Fibrillation: Prevalence and Clinical Profile in a Spanish Sample

Cardiopatía estructural en pacientes anticoagulados con fibrilación auricular no valvular: prevalencia y perfil clínico en una muestra nacional

To the Editor,

Although the definition of nonvalvular atrial fibrillation (NVAF) varies,[1,2] it generally does not exclude patients with structural heart disease (SHD), such as certain valve diseases. However, there is limited information on the frequency of this association in Spain. The objective of this article was to report the prevalence and clinical profile of patients with SHD and well as the prevalence of heart failure in a broad Spanish nationwide sample of patients with NVAF.

Data from the FANTASIIA registry[3] were used. This registry included 2178 outpatients with NVAF who were receiving anticoagulation (according to protocol, the ratio of vitamin K antagonists to direct anticoagulants was 4:1). We excluded individuals younger than 18 years, those with prosthetic cardiac devices, those with any grade of mitral stenosis, and those with moderate or severe mitral regurgitation. Participants were enrolled consecutively between June 1, 2013, and October 15, 2014, in 50 Spanish centers selected by the investigators to ensure representation from throughout the country, with the primary objective of assessing the effectiveness of anticoagulation in patients with NVAF by type and quality of treatment. The diagnoses of SHD were taken from the medical records and included the following: coronary artery disease, hypertensive heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, significant valve disease (aortic valve, tricuspid valve, or pulmonary valve disease of at least moderate intensity), and other heart diseases. Patients with coronary artery diseases and other concurrent heart diseases were classified as having coronary artery disease. The presence of heart failure was recorded independently. Overall, 47.15% of the sample had SHD (Table 1). The most frequent type of SHD was coronary artery disease (18.14%), followed by hypertensive heart diseases (11.43%), and dilated cardiomyopathy (6.01%). Hypertrophic cardiomyopathy was reported in 2.06% and significant valve diseases in 1.79%. Only 34 patients (1.56%) had isolated NVAF (age < 65 years, with no heart disease or embolic risk factor). Among patients with SHD, there were fewer