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Skeletal muscle mass in acute coronary syndrome prognosis: Gender-based analysis from Hellenic Heart Failure cohort

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Abstract *Background and aims:* Predictive and prognostic ability of muscle mass in CVD settings is increasingly discussed. The gender-specific effect of skeletal muscle mass index (SMI) on 10-year recurrent fatal/non fatal cardiovascular disease (CVD) event of acute coronary syndrome (ACS) patients was evaluated.
Methods and results: In 2006–2009, $n = 1000$ consecutive patients ($n = 222$ women), hospitalized at the First Cardiology Clinic of Athens with ACS diagnosis and with symptoms and left ventricular function indicative of heart failure were selected. SMI was created to reflect skeletal muscle mass through appendicular skeletal muscle mass (indirectly calculated through population formulas) divided by body mass index (BMI). In the 10-year follow-up (2016), 55% of ACS patients experienced recurrent fatal/non fatal CVD events (53% in women vs.62% in men, $p = 0.04$). Patients in the 2nd SMI tertile (mostly overweight) had 10% lower risk for CVD recurrence (women:men rate ratio = 0.87) over their counterparts in the 1st (mostly normalweight) and 3rd tertile (mostly obese). Multivariate analysis revealed that ACS patients in the 2nd SMI tertile presented 46% and 85% lower CVD event risk over their counterparts in the 1st tertile (Hazard Ratio (HR) = 0.54, 95% Confidence Interval (95% CI) 0.30, 0.96, $p = 0.002$) and 3rd tertile (HR = 1.85, 95%CI 1.05, 2.94, $p = 0.03$). Gender-based analysis revealed that this trend remained significant only in women. Inflammatory markers had strong confounding effect.
Conclusion: A *U*-shape association between SMI and 10-year CVD event especially in women was highlighted. This work reveals gender-specific remarks for "obesity-lean paradox" in secondary prevention, implying that high muscle mass accompanied by obesity and excess adiposity may not guarantee better prognosis.

Introduction

Despite the powerful positive association of increased weight with cardiovascular disease (CVD), once disease is established, a reverse epidemiology is observed without well-demonstration of the explanatory mechanisms [1–4]. Among them is the body-composition hypothesis that is highly discussed [5]. On the other side,

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coronary artery disease (CAD) is the leading cause of heart failure; improved survival in ACS patients has largely inflated the prevalence of ischemic heart failure [6]. Moreover, ACS patients are often presented with acute heart failure symptoms and signs, even with preserved left ventricular ejection fraction. Within this high risk group, identification of dismal versus favorable prognostic characteristics could contribute to more accurate risk stratification ultimately enabling individualized secondary prevention strategies to mitigate ischemic heart failure incidence.

In patients with heart disease, weight or body mass index (BMI) *per se* seem to constitute less sensitive markers of obesity status [7]. To this effect, muscle mass and its prognostic ability in CVD prevention has become a scientific field of considerable interest. Muscle-mass loss and dysfunction is an impaired health state with a high personal toll derived from ageing process over life course and chronic catabolic diseases establishment [8,9]. In this respect, skeletal muscle accounts almost the half of body mass possessing an active role in various metabolic pathways [10]. Skeletal-muscle-mass effect on cardiometabolic paths, i.e. insulin resistance, oxidative stress, arterial stiffness has been suggested, yet, of note, limited evidence exists regarding its direct effect on major events [11,12]. This literature gap inherently deters robust conclusions, even more when it comes to gender-related specifications. Subsequently, the tremendous life-expectancy raise, mainly in women, not usually accompanied by lower chronic disease rates, demands the deterioration of novel risk factors −beyond the typical ones− in secondary prevention with the potential to compromise the complex state of impaired health derived from ageing and disease establishment [13,14].

The aim of the present work was to evaluate the association between a BMI-adjusted index of skeletal muscle mass (Skeletal muscle mass index (SMI); *the higher SMI values, the higher skeletal muscle mass*) with 10-year recurrent fatal/non fatal CVD event in patients with established acute coronary syndrome (ACS) and to assess the effect size of the aforementioned association separately for men and women. We posed three a priori research hypotheses: **a.** 10-year recurrent CVD event will be progressively reduced passing from lower to higher SMI values; **b.** The examined association will be different between genders due to physiologically differences in body-composition metrics; **c.** Inflammation will mediate this association.

Methods

Study sample

Hellenic Heart Failure study is a prospective, observational study established in 2006. From May 2006 to March 2009, $n = 1000$ consecutive patients with ACS discharge diagnosis (first or recurrent acute myocardial infarction or unstable angina) hospitalized at First Cardiology Clinic, University of Athens, with symptoms and left ventricular function indicative of heart failure were enrolled (80% participation rate). The descriptive characteristics of men and women patients recruited at baseline are presented in Supplementary Table 1.

Further details about aims, measurements and baseline procedures of Hellenic Heart Failure study can be found elsewhere [15,16].

Bioethics

The study was approved by the Medical Research Ethics Committee of the First Cardiology Clinic, University of Athens, and was carried out in accordance with Declaration of Helsinki (1989) of the World Medical Association. All patients were informed of the aims and procedures of the study and gave their consent.

Baseline weight status and SMI assessments

Weight status was defined through BMI cut off points recommended by World Health Organization. BMI was calculated as weight (kilograms) divided by height (meters squared). Height was measured to the nearest 0.5 cm and weight to the nearest 100gr. Normal weight was defined as BMI between 18.5 and 25 kg/m^2, overweight as BMI between 25 and 29.9 kg/m^2 and obesity as BMI $\geq$ 30 kg/m^2. Underweight was defined as BMI $<$18.5 kg/m^2.

Skeletal muscle mass was calculated through appendicular skeletal muscle mass (ASM) based on the equation by *Lee and colleagues*; ASM=(0.244*weight) + (7.8*height) + (6.6*gender)− (0.098*age) + (race−3.3) (gender: Women = 0/men = 1; race: White/Hispanic = 0/black = 1.9/Asian = −1.6) (17). This indicator was divided by BMI to create SMI. SMI tertiles were created specified for men and women with 1st tertile corresponding to the lowest muscle mass.

Other baseline measurements

At hospital admission several biomarkers were measured, among others: C-reactive protein (CRP), white blood cells (WBC) and serum creatinine. CRP concentrations were measured, during the first 12−18 h of hospitalization through a latex-based immunoassay (Dade Behring, Newark, DE). WBC counts was measured through a Medicon analyzer (Medicon Ltd, Athens).

Endpoint and follow-up evaluation

During 2015−2016 10-year follow-up was performed. Information from $n = 745$ patients was retrieved; the remaining $n = 255$ were considered as censored data in analysis. No differences were observed regarding age, gender, medical history and medication-prescription, between those who were lost to follow-up and the rest patients.

The studied endpoint was 10-year recurrent fatal/non fatal CVD event. CVD event was defined as: acute myocardial infarction, or unstable angina, or other identified forms

of ischemia (WHO-ICD coding 410–414.9, 427.2, 427.6), or stroke (WHO-ICD coding 430–438).

Statistical analysis

Categorical variables are presented as absolute (n) and relative frequencies (%). Continuous variables are presented as mean ± standard deviation. Associations between normally distributed variables and SMI tertiles were evaluated through one-way analysis of variance. Whether these variables were normally distributed was tested through P–P plot and equality of variances through Levene's test. For non-normally distributed variables, Kruskal–Wallis test was used. Associations between categorical variables and ASM tertiles *or* BMI categories *or* SMI tertiles were tested with chi-squared test. Hazard Ratios and their corresponding 95% confidence intervals for 10-year CVD event were evaluated through Cox-regression analysis. Proportional hazards' assumption was graphically tested. Kaplan–Meier survival curves, illustrating 10-year CVD event across SMI tertiles, were constructed and compared using the long-rank test. Linear association of CRP *or* WBC with SMI was investigated through Spearman's rank correlation coefficient (Spearman's rho (ρ)) and illustrated on scatter plots. Variability of continuous variables (CRP and WBC) across SMI tertiles was illustrated through error bar plot charts. Receiver operating curve analysis was used to assess the prognostic accuracy of Cox-regression models with different confounders against 10-year CVD event. Curves were constructed by plotting sensitivity against (1-specifity) and corresponding area(s) under the curve were compared. STATA software, version 14 (MP & Associates, Sparta, Greece) was used for all statistical analyses. We deemed statistical significance at *p-value* <0.05.

Results

Overall CVD event within the decade was recorded, as follows; 30-day, 1-, 2- and 10-year CVD event was 16%, 25%, 36% and 55%, respectively. 10-year CVD mortality was 21%. Within the decade, 53% of women vs. 62% of men ($p = 0.04$) exhibited the studied endpoint.

Table 1 depicts baseline characteristics of study participants across SMI tertiles. It is noteworthy that patients allocated to 1st tertile presented the lowest BMI with mean value close to 20 kg/m^2 whereas patients in the 2nd and 3rd tertile had a BMI within overweight and obesity range, respectively ($p < 0.001$).

Recurrent CVD event within the decade across ASM tertiles, BMI categories and SMI tertiles was evaluated through unadjusted analysis and results are presented in Table 2. Overweight patients presented about 18% and 13% lower likelihood to suffer from a new CVD episode compared with normalweight patients within the decade, as well as the lowest incidence rate from all BMI categories (all *ps* < 0.05). This outcome was more evident in women; a normalweight or obese woman patient was 1.12 times more likely to suffer from a recurrent episode than a man with similar BMI while overweight women were more protected against a new event compared with overweight men ($p = 0.05$). Additionally, patients at 2nd and 3rd ASM tertile had about 10% lower CVD mortality rate compared with their counterparts in 1st tertile ($p = 0.04$). Interestingly, in 2nd and 3rd ASM tertiles, women-to-men CVD event rate ratio was consistently lower and/or close to 1

Table 1 Baseline sociodemographic, lifestyle, clinical and biochemical factors of acute coronary syndrome patients according to SMI tertiles ($n = 1000$).

	SMI tertiles			*p*-value
	1st ($n = 333$)	2nd ($n = 331$)	3rd ($n = 336$)	
Age, years	63 (12)	65 (13)	64 (13)	0.30
Male gender, %	79	79	78	0.91
Body Mass Index, kg/m^2	20.9 (2.05)	27.5 (1.63)	32.8 (4.9)	<0.001
Low physical activity status, %	46	39	34	0.05
Current smoking, %	42	44	56	0.002
Years of school, counts	9 (4)	9 (4)	10 (4)	0.22
History of hypertension, %	69	59	54	0.005
History of hypercholesterolemia, %	83	79	75	0.16
History of diabetes mellitus, %	66	64	54	0.01
Family history of CVD, %	51	44	41	0.09
Ejection fraction, %	44 (10)	43 (10)	42 (10)	0.18
Revascularization, %	53	51	52	0.90
History of CVD at baseline, %	32	36	41	0.14
Discharge status, AMI, %	73	74	76	0.70
C-Reactive Protein, mg/L	36 (52)	35 (50)	33 (48)	0.91
White blood cells, 10^{3}counts	9.9 (3.2)	9.9 (3.1)	9.8 (3.5)	0.86
Serum creatinine, mg/dL	1.18 (0.97)	1.31 (0.93)	1.38 (1.09)	0.09

Data are presented as mean ± standard deviation (SD) (i.e. mean (SD)). P-values were obtained using One-way analysis of variance for independent samples for the normally distributed variables (age, body mass index), Kruskal–Wallis Test for the rest quantitative variables and chi-squared test for categorical variables. SMI was created to reflect skeletal muscle mass through appendicular skeletal muscle mass (indirectly calculated through population formulas) divided by BMI; 1st tertile corresponded to the lowest muscle mass. ***Abbreviations***: CVD = Cardiovascular disease; SMI = Skeletal muscle mass index.

Table 2 Total and gender-specific recurrent fatal/non fatal CVD event rate in Acute Coronary Syndrome patients according to their ASM, BMI and SMI tertiles.

	ASM tertiles			*p*	BMI Categories			*P*	SMI Tertiles			*p*
	1st	2nd	3rd		Normal weight	Overweight	Obese		1st	2nd	3rd	
	n = 333	*n* = 332	*n* = 335		*n* = 255	*n* = 468	*n* = 277		*n* = 333	*n* = 331	*n* = 336	
30-day CVD event, %	15	14	10	*0.42*	17	10	16	*0.15*	16	9	16	*0.14*
Women-to-men incident rate ration	**1.35**	**0.85**	**0.93**	***<0.001***	1.59	0.54	1.14	*0.31*	1.59	0.83	0.83	*0.33*
1-year CVD event, %	27	26	23	*0.79*	32	24	23	*0.24*	25	20	31	*0.10*
Women-to-men incident rate ration	0.93	0.96	1.09	*0.35*	1.21	0.72	1.32	*0.39*	**1.01**	**0.76**	**1.34**	***0.006***
2-year CVD event, %	40	36	36	*0.73*	**50**	**32**	**36**	***0.009***	**39**	**27**	**47**	***0.001***
Women-to-men incident rate ration	**1.06**	**0.89**	**1.03**	***<0.001***	1.11	0.75	1.28	*0.41*	**0.96**	**0.67**	**1.66**	***0.004***
10-year CVD event, %	62	55	54	*0.24*	**65**	**52**	**58**	***0.03***	**59**	**47**	**65**	***0.003***
Women-to-men incident rate ration	**1.09**	**0.81**	**1.12**	***<0.001***	**1.12**	**0.84**	**1.12**	***0.05***	**0.99**	**0.68**	**0.71**	***<0.001***
10-year CVD mortality, %	**26**	**17**	**16**	***0.04***	24	20	16	*0.24*	18	20	22	*0.55*
Women-to-men incident rate ration	**1.17**	**0.70**	**1.28**	***<0.001***	0.97	1.00	1.01	*0.99*	**1.17**	**0.87**	**1.00**	***0.007***

P-values (*p*) were obtained using chi-squared test. SMI was created to reflect skeletal muscle mass through appendicular skeletal muscle mass (indirectly calculated through population formulas) divided by BMI; 1st tertile corresponded to the lowest muscle mass. ***Abbreviations***: ASM = Appendicular skeletal muscle mass; BMI = Body mass index; CVD = Cardiovascular disease; SMI = Skeletal muscle mass index.
Bold indicates the results that reached the level of statistical significance i.e. $p < 0.05$.

Table 3 Nested Cox-regression analysis models to evaluate the association of SMI with 10-year recurrent fatal/non fatal CVD event in acute coronary syndrome patients.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
SMI tertiles						
1st	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
2nd	**0.63 (0.41, 0.96)**	**0.59 (0.38, 0.92)**	**0.54 (0.31, 0.94)**	**0.54 (0.30, 0.95)**	**0.54 (0.30, 0.96)**	0.77 (0.39, 1.54)
3rd	1.31 (0.85, 2.02)	1.25 (0.80, 1.96)	1.30 (0.73, 2.29)	1.24 (0.69, 2.23)	1.22 (0.67, 2.21)	1.51 (0.72, 3.16)
Age, per 1 year	–	1.04 (1.02, 1.05)	1.04 (1.01, 1.06)	1.03 (1.01, 1.06)	1.03 (1.01, 1.06)	1.03 (1.01, 1.06)
Male gender	–	0.95 (0.62, 1.47)	1.18 (0.67, 2.05)	1.08 (0.61, 1.92)	0.99 (0.54, 1.81)	1.07 (0.51, 1.28)
Years of school, per 1 year	–	–	1.01 (0.96, 1.06)	1.02 (0.97, 1.07)	1.02 (0.97, 1.07)	1.02 (0.95, 1.08)
Current smoking, yes vs. no	–	–	0.89 (0.54, 1.46)	0.96 (0.58, 1.59)	0.96 (0.58, 1.61)	0.87 (0.45, 1.66)
Physical activity, yes vs. no	–	–	0.70 (0.44, 1.10)	0.77 (0.48, 1.24)	0.85 (0.52, 1.37)	0.82 (0.45, 1.89)
Diabetes mellitus, yes vs. no	–	–	1.66 (1.06, 2.61)	1.63 (1.02, 2.60)	1.59 (0.99, 2.56)	1.45 (0.80, 2.64)
Dyslipidemia, yes vs. no	–	–	1.17 (0.65, 2.12)	1.23 (0.67, 2.26)	1.31 (0.70, 2.42)	1.35 (0.60, 3.04)
Hypertension, yes vs. no	–	–	1.17 (0.74, 1.87)	1.22 (0.75, 1.99)	1.24 (0.76, 2.03)	1.21 (0.66, 2.20)
Family history of CVD, yes vs. no	–	–	1.49 (0.94, 2.35)	1.45 (0.91, 2.31)	1.43 (0.89, 2.29)	1.84 (1.01, 3.33)
Ejection Fraction, per 1%	–	–	–	0.96 (0.94, 0.99)	0.96 (0.94, 0.99)	0.97 (0.94, 0.99)
Revascularization, yes vs. no	–	–	–	0.69 (0.43, 1.12)	0.72 (0.44, 1.17)	0.62 (0.33, 1.17)
Free baseline CVD history, yes vs. no	–	–	–	0.85 (0.52, 1.39)	0.94 (0.57, 1.53)	0.99 (0.52, 1.88)
Creatinine, per 1 mg/dL	–	–	–	–	1.46 (0.93, 2.31)	1.85 (0.88, 2.90)
C-Reactive Protein, per 1 mg/L						1.02 (1.00, 1.03)
White blood cells, per 1 count						1.08 (0.98, 1.12)

Bold indicates estimates (under the scope of the present work) that are significantly different from the reference group at $p < 0.05$. SMI was created to reflect skeletal muscle mass through appendicular skeletal muscle mass (indirectly calculated through population formulas) divided by BMI; 1st tertile corresponded to the lowest muscle mass. ***Abbreviations:***CVD = Cardiovascular disease; HR = Hazard Ratio; 95%CI = 95% Confidence Interval; SMI = Skeletal muscle mass index.

(women exhibited lower 10-year incidence compared to men) (*all ps* < *0.05*). When ASM was examined after BMI standardization, a *U*-shape association was observed with 2nd tertile patients presenting the best 10-year prognosis; this association was exerted more evidently in women (*all ps* < *0.05*).

Nested Cox regression models to evaluate the effect of SMI on 10-year recurrent CVD event are presented in Table 3. In crude analysis, participants of 2nd tertile presented 63% lower risk for developing recurrent CVD events within the decade compared with their counterparts in 1st tertile ($p < 0.001$). In age- and gender-adjusted model this association became stronger and retained even after adjusting for various confounders (Models 2–5, *all ps* < *0.05*). Models were repeated after setting patients of 2nd SMI tertile as reference group to be examined against patients recruited in 3rd tertile; multivariate analysis (on the adjustment basis of Model 5) revealed that patients with the highest SMI had about 84% higher risk for recurrent CVD events within the decade compared with patients in the 2nd tertile [Hazard ratio = 1.85, 95% Confidence Interval 1.05, 2.94, $p = 0.03$] (data not shown). Further adjustment for inflammatory markers revealed that these trends were retained, yet they did not reach the level of significance ($p > 0.05$) (Model 6).

In formal interaction analysis, a significant heterogeneity on the basis of gender was produced (*p for interaction* = *0.03*) regarding the association of SMI with 10-year CVD event. Hence, gender-based stratified analysis was performed and results are presented in Table 4. Sensitivity analyses revealed that even if *U*-shape association was retained in both men and women in crude and age-adjusted models, further adjustment for clinical, lifestyle and sociodemographic factors resulted in a significant trend only in women (Models 3–5, all *ps* < *0.05*). Statistical significance was lost after adjusting for CRP and WBC (Model 6). Kaplan–Meier survival curves were also constructed to evaluate 10-year CVD event separately for men and women patients according to SMI status (Supplementary file: Supplementary Figure 1). Mean (95% confidence interval) survival (free-of-CVD) time (years) in women patients at 1st, 2nd and 3rd tertile was 7.4 (6.5, 8.2), 8.2 (7.1, 9.2) and 6.7 (5.5, 7.9), respectively. In men,

Table 4 Gender-based sensitivity Cox-regression analysis to evaluate the association of SMI with 10-year recurrent fatal/non fatal CVD event in acute coronary syndrome patients.

	SMI tertiles	HR (95%CI	Model adjusted for
Model 1			(crude model)
Men	1st	1.00 (ref)	
	2nd	**0.61 (0.26, 0.98)**	
	3rd	1.43 (0.86, 1.73)	
Women	1st	1.00 (ref)	
	2nd	**0.34 (0.06, 0.77)**	
	3rd	0.42 (0.15, 1.79)	
Model 2			Age
Men	1st	1.00 (ref)	
	2nd	**0.61 (0.26, 0.98)**	
	3rd	1.43 (0.86, 1.73)	
Women	1st	1.00 (ref)	
	2nd	**0.45 (0.16, 0.83)**	
	3rd	0.57 (0.14, 2.15)	
Model 3			Model 2 plus years
Men	1st	1.00 (ref)	of school, current
	2nd	0.57 (0.28, 1.05)	smoking, physical
	3rd	1.43 (0.86, 1.73)	activity, diabetes
Women	1st	1.00 (ref)	mellitus,
	2nd	**0.39 (0.09, 0.95)**	dyslipidemia,
	3rd	0.57 (0.14, 2.15)	hypertension and family history of CVD
Model 4			Model 3 plus
Men	1st	1.00 (ref)	ejection fraction,
	2nd	0.61 (0.31, 1.15)	revascularization,
	3rd	1.51 (0.78, 1.93)	baseline CVD history
Women	1st	1.00 (ref)	
	2nd	**0.43 (0.11, 0.99)**	
	3rd	0.61 (0.16, 2.30)	
Model 5			Model 4 plus serum
Men	1st	1.00 (ref)	creatinine
	2nd	0.60 (0.29, 1.35)	
	3rd	1.32 (0.85, 2.20)	
Women	1st	1.00 (ref)	
	2nd	**0.43 (0.11, 0.99)**	
	3rd	0.61 (0.16, 2.30)	
Model 6			Model 5 plus C-Reactive Protein and white blood cells
Men	1st	1.00 (ref)	
	2nd	0.84 (0.38, 1.86)	
	3rd	1.85 (0.82, 4.18)	
Women	1st	1.00 (ref)	
	2nd	0.66 (0.24, 1.76)	
	3rd	0.14 (0.09, 1.84)	

Bold indicates estimates that are significantly different from the reference group at $p < 0.05$. SMI was created to reflect skeletal muscle mass through appendicular skeletal muscle mass (indirectly calculated through population formulas) divided by BMI; 1st tertile corresponded to the lowest muscle mass. ***Abbreviations:*** CVD = Cardiovascular disease; HR = Hazard Ratio; 95% CI = 95% Confidence Interval; SMI = Skeletal muscle mass index.

similar −among tertiles− survival trends were observed; in particular, for 1st, 2nd and 3rd tertile corresponded to 8.3 (7.8, 8.8), 8.1 (7.6, 8.6) and 8.0 (7.4, 8.4) years.

Due to the observed moderating effect of CRP and WBC on the association of SMI with 10-year CVD event in total sample (Table 2, *Model 6*) and gender-based analysis (Table 3, *Model 6*), the potential lineal association between them was evaluated and results are illustrated in Fig. 1. A significant inverse linear association between the examined factors was observed only in women ($\rho_{(CRP)} = -0.490$, $p < 0.001$ & $\rho_{(WBC)} = -0.380$, $p = 0.05$). In men no significant linear association was observed (all $ps > 0.05$). Unadjusted analysis revealed that women of 2nd tertile had significantly lower mean values of inflammatory markers compared with their 1st-tertile counterparts (all $ps < 0.05$). Additionally, women of 3rd tertile presented slightly higher inflammation levels compared with women of 2nd tertile yet this difference was not significant. In men no significant trend was observed. CRP and WBC values variation across SMI tertiles is presented in supplementary file (Supplementary File: Supplementary Figure 2).

Gender-specific receiver operating curves are illustrated in Fig. 2. ROC analysis revealed that in women both BMI-adjusted and SMI-adjusted model significantly discriminated 10-year CVD recurrence (all $ps < 0.05$). Based on the area under the curve, discriminative ability of SMI-model was better. When it came to men none of the examined models significantly discriminated the primary endpoint (all $ps > 0.05$).

Discussion

In contrast with our initial hypothesis, we revealed that association between SMI and 10-year recurrent CVD event follows a *U*-shape trend. It is noteworthy that this trend was confirmed only in women and strongly confounded by systemic inflammation. Notably, in women patients SMI was to have a better prognostic ability over the commonly used BMI. This finding indicates a possible role of muscle mass as a prognostic determinant in patients with heart failure features, yet subsequently provides a mechanism through which overweight category may exert a beneficial effect. Our work is consistent with most of studies that have demonstrated the “obesity-lean” paradox in populations with established CVD yet most importantly extends previous reports for potential mediators/moderators including muscle mass, gender and inflammation.

Even if elevated BMI presents deleterious effects on CVD onset, weight status in established CVD raises mixed messages and paradoxical associations [18–22]. In line with this, we have previously revealed that higher BMI, mostly within “overweight range” confers a prognostic advantage over a decade for ACS patients [15]. Nevertheless, all these findings have been derived through a weight status defined by BMI. Considering the lack of discriminative power of this index to differentiate body fat and lean mass, no robust conclusions could be drawn [3].

Considering that patients with established CVD usually experience disease- and age-related pronounced catabolic state, the hypothesis of lean/muscle mass as a novel prognostic factor in secondary prevention is attracting considerable attention. To the best of our knowledge, very few studies have examined muscle-mass-effect on CVD prognosis [11,23–26]. In the present work, an inverse association of SMI with 10-year recurrent CVD event was as well revealed. We also observed that this association may follow a *U*-shape trend. This is partially in line with some of the few previous works that examined this issue [11,25].

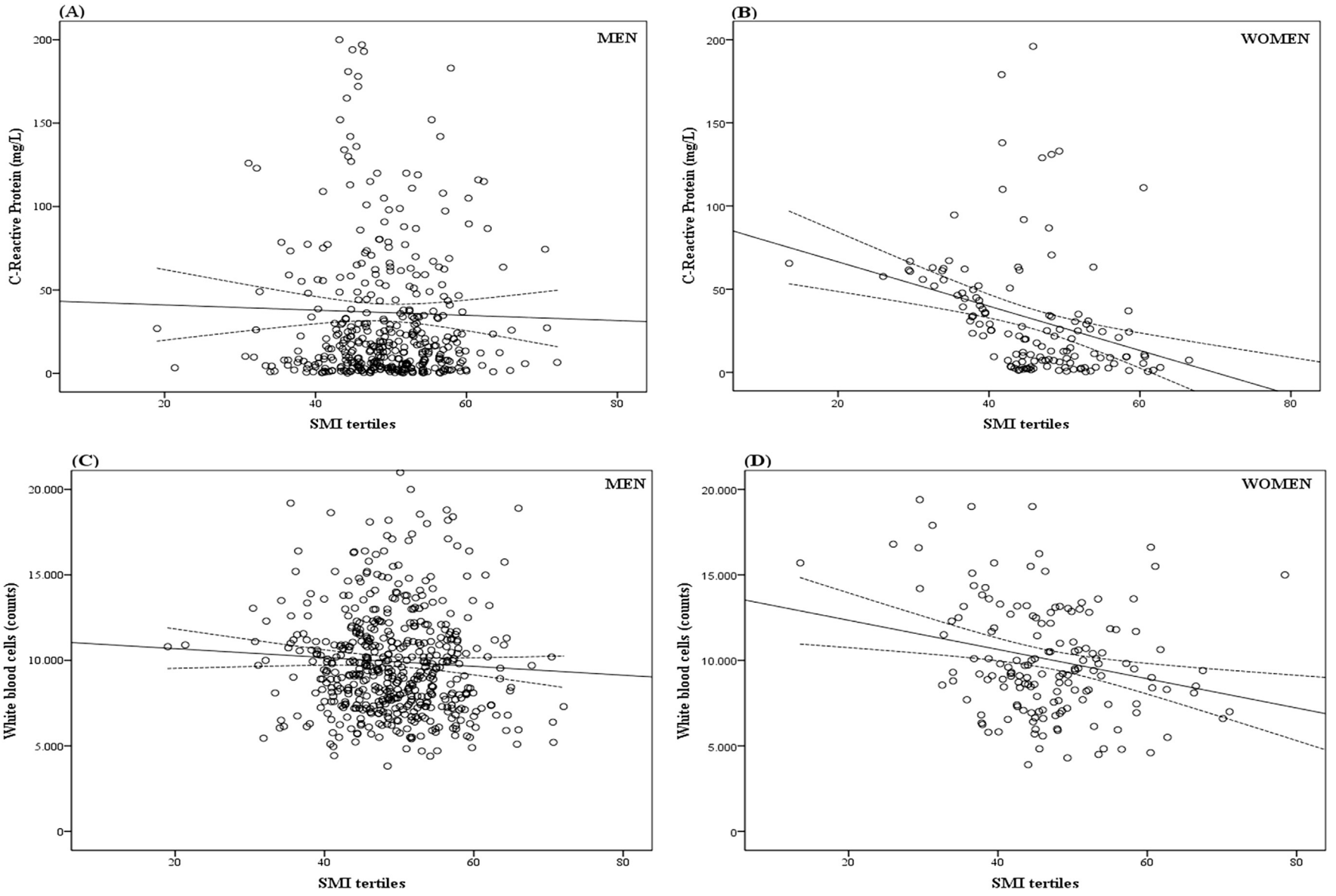

Figure 1 Linear association between SMI with CRP and WBC in men and women acute coronary syndrome patients. **Caption: Men:** (A) Spearman's $rho_{(CRP)} = +0.008$, $p = 0.87$ & (C) Spearman's $rho_{(WBC)} = -0.081$, $p = 0.07$, **Women:** (B) Spearman's $rho_{(CRP)} = -0.490$, $p < 0.001$& (D) Spearman's $rho_{(WBC)} = -0.380$, $p = 0.05$. ***Abbreviations:*** CVD = Cardiovascular disease; CRP = C-Reactive Protein; 95%CI = 95% Confidence Interval; SMI = Skeletal muscle mass index; WBC = White blood cells.

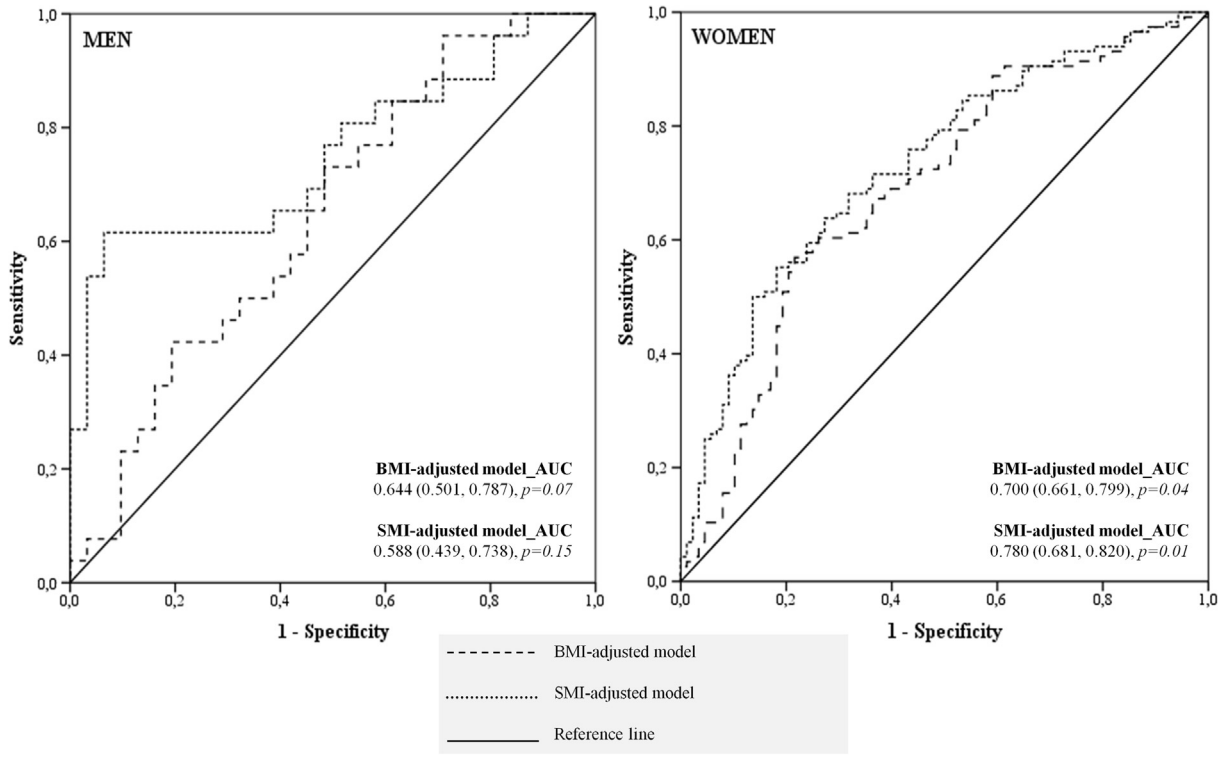

Figure 2 Receiver Operating Characteristic analysis for the discriminative ability of **BMI-adjusted** *vs.* **SMI-adjusted** multivariate Cox regression analysis model to predict 10-year recurrent fatal/non fatal cardiovascular disease event separately in men and women acute coronary syndrome patients. **Caption:** Receiver operating Characteristics analysis was performed using the probabilities for 10-year recurrent fatal/non fatal cardiovascular disease event, corresponding to each study participant, calculated from Cox regression analysis adjusted for either BMI or SMI plus age, years of school, current smoking, physical activity, diabetes mellitus, dyslipidemia, hypertension, family history of cardiovascular disease, ejection fraction, revascularization, serum creatinine, C-Reactive Protein and white blood cells. ***Abbreviations:*** AUC = Area under the curve; BMI = Body mass index; SMI = Skeletal muscle mass index.

Specifically, in National Health and Nutrition Examination Survey, CVD patients with high muscle yet low fat mass presented the lowest mortality rates compared with their counterparts with high fat mass [11]. In another work with ACS patients from Minnesota increased body fat was independently associated with increased major-CVD-event recurrence while lean mass significantly protected against new episodes [25]. Similarly, in Cardiovascular Health Study greater lean tissue mass was associated with improved CVD and all-cause mortality, yet this was not the case when fat tissue reached the highest levels [26]. Both of the aforementioned works as well as the present work imply that high muscle mass accompanied by obese and/or excess-body-fat status may not be that protective. Nevertheless, our remarks are not entirely consistent with other previous works; the exclusive use of a sample with men [23] or with patients with stable coronary heart disease [24], CVD mortality as the only examined endpoint [23,24] and the short-term follow-up period (1 year) [27] are some methodological variations that might explain these inconsistencies.

This work is one of the very first that investigated gender differences in the association between muscle mass and 10-year recurrent CVD event. Sensitivity analysis, here, revealed that women in 2nd SMI tertile presented the best prognosis compared with 1st and 3rd SMI tertile while this trend was not confirmed in men. In a supplementary analysis from National Health and Nutrition Examination Survey, this association was somehow exhibited in men; however, the different reference and comparison groups, the lower cases across subgroups and the use of CVD mortality as dependent variable might differentiate outcomes [11]. Recent data suggest that women are more susceptible to age-related muscle loss and function (sarcopenia) [28] probably due to lifestyle or biological factors [29,30]. This has been also observed in established chronic diseases (heart failure, chronic kidney disease, cancer) further confirming that women in advanced age with an established catabolic disease may be more vulnerable in terms of muscle loss compared with men of similar age and disease profile [31]. An additional finding here was that mostly overweight women ACS patients with moderate SMI presented the best prognosis. In the meanwhile, the obtained knowledge is that BMI-related paradoxical association is more evident in women where a non-linear trend has been suggested (overweight patients is the most protective subgroup against major events) [15,27]. To this issue, women present different metabolic responses to adiposity with greater myocardial fatty acid uptake and lower myocardial utilization [32]. The added value of the present work is related with highlights that women's "overweight paradox" may be attributed not only to their

resistance to adiposity but also to gender-specific responses of muscle mass. Metabolic significance of muscle mass has been largely noted; skeletal muscle mass accounts for 85% of body's glucose disposal, provides a reliable protein reserve and reflects a better cardiorespiratory fitness [33]. Hence, the missing link of gender undoubtedly demands further research [29].

Our findings also suggest an inverse association between SMI and systemic inflammation. Despite the huge methodological variations, this has been as well indicated in previous works; further enhancing the generation of a biologically plausible hypothesis regarding the impact of systemic inflammation upon the deterioration of muscle mass and function [33–35]. The important observation here was that this was evident only for women, probably suggesting a gender-specific underlying path. Interestingly, women in 2nd and 3rd tertile presented the lowest inflammation with the former having slightly lower values compared with the later. This probably sets implications about more complicated cross-talk among adipocyte, muscle mass and cardiomyocyte mass mediated by surrogate markers like inflammation, and subsequently determining patients' prognosis [33].

Limitations and strengths

The main strength here that compensates the following limitations is that this in one of the very few prospective studies that evaluated the gender-specific effect of SMI on 10-year prognosis of ACS patients with heart failure features. However, several limitations should be presented. Specifically, only baseline measurements were taken into account for our research hypothesis; hence misclassifications of transitions regarding anthropometric, clinical or lifestyle measurements cannot be precluded. Moreover, imaging data or skinfold metrics were not available and skeletal muscle mass calculation was based on population equations that may under- or over-estimate the actual body composition rates; nonetheless, these formulas have been validated and present good agreement with the classical dual-energy X-ray absorption metry method [17] while they have been recently used in diverge populations [36].

Conclusion

Even if ever increasing efforts have sought to elucidate the prognosis of CVD patients with increased weight status, more tailor-made clinical recommendations remain to be guided. Our work sought to address this knowledge in some key areas. First, our findings suggest that constant vigilance in cardiac rehabilitation programs is of high importance to deter muscle loss and subsequent increased CVD risk. Concomitantly, the present work reveals that high muscle mass accompanied by obesity –and probably excess adiposity– may not guarantee better prognosis. Lastly, the gender-specific remarks highlighted here could set the basis in secondary prevention spectrum, for better identifying the particular anthropometric features of men and women cardiac patients with better or worse prognosis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.03.011.

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None.

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