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A sex-specific evaluation of predicted lean and fat mass composition and cardiovascular disease onset and progression: a combined analysis of the ATTICA and GREECS prospective epidemiological studies.

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Declarations of Interest
None

Abstract
Objectives: To evaluate the association of predicted lean and fat mass on 10-year first and recurrent CVD incidence separately for men and women. **Methods:** Two prospective studies, ATTICA (2002-2012, *n*=3,042 subjects free-of-CVD, *n*=1,514 men (46±13 years) and *n*=1,528 women (45±14 years)) and GREECS (2004-2014, *n*=2,172 subjects with acute coronary syndrome (ACS), *n*=1,649 men (65±13 years) and *n*=523 women (62±11 years)) were used. Lean mass index (LMI) and fat mass index (FMI) were created through total body lean and fat mass (indirectly calculated through population formulas based on body weight, height and waist circumference) divided by height squared. Follow-up was performed in *n*=2,020 of ATTICA (*n*=317 first CVD events) and in *n*=2,172 patients of GREECS (*n*=811 recurrent CVD events). **Results:** In ATTICA study, CVD rate from 1st to 3rd FMI tertile was 9.4%, 16.1% and 19.9% while in GREECS 36.2%, 37.0%, 38.3%. The LMI-related rates were 17.1%, 15.0% and 11.9% *vs.* 38.8%, 35.8% and 36.7%. Multiadjusted analysis revealed U-shape trend between LMI and CVD recurrence with 2nd LMI tertile having the best prognosis; this observation was more evident in women. In apparently healthy subjects, LMI-cardioprotective association was revealed only in 3rd tertile (HR= 0.91 95%CI (0.74, 0.95)); this was more evident in men. The FMI aggravating association (3rd tertile) was retained significant only in healthy women and ACS men. **Conclusion:** This work expands previous findings regarding body composition and cardiac health, implying that the association of lean and fat mass on long-term CVD incidence varies according to sex and prevention stage.
Key words: heart disease; muscle mass; adiposity; gender

1. Introduction
Global overweight/obesity rates have reached epidemic levels. In 2016, more than 1.9 billion adults around the globe were overweight while over 650 million were obese; interestingly, according to estimates for 2025 obesity prevalence, women are to overlap men by five points (23% vs. 18% respectively) [1,2]. Abnormal weight has direct adverse effects on CVD prevalence and severity. More discerning is that obesity independently increases the risk for almost all major CVD risk factors and biological underpinnings such as insulin resistance, systemic inflammation and oxidative stress [3]. Mechanisms through which abnormal weight status exerts its aggravating effect on cardiac health are correlated with pathophysiological features attributed to the endocrine activity of adipose tissue [4].

In epidemiological research, weight status above the normal range and adiposity are mostly defined through body mass index (BMI). Much as this marker presents a generally strong association with incident CVD, in muscle-loss related conditions a reverse epidemiology (increased weight is associated with better prognosis) with not well-demonstrated underlying paths is observed [4-7]. Considering that fat-free mass is to have protective metabolic effects in vascular system related with insulin resistance, oxidative stress and arterial stiffness, the aforementioned limitation of BMI may result in erroneous assumptions regarding the actual prognosis of cardiac patients [8]. However, limited evidence exists regarding the effect of body composition on cardiac patients' prognosis and even less in apparently healthy middle-aged subjects. Research to examine the effect of body composition on health outcomes have largely been hampered due to practical issues. Body composition assessment on epidemiological studies requires sophisticated

and expensive technologies. On the other hand, anthropometric measurements are simple, cheap and non-intrusive, and hence are frequently measured in large health surveys and cohort studies. Towards this perspective, in a very recent work from the the National Health and Nutrition Examination Survey (NHANES) 1999-2006, equations using simple anthropometric measurements to evaluate lean and fat mass have been validated in a large diverse sample showing an increased predictive ability against common CVD risk factors [9].

Hence, the aim of the present work was to apply the equations recently generated and validated by the NHANES study to examine the association of predicted lean and fat mass on 10-year first and recurrent CVD incidence. We performed two a priori research hypotheses; firstly, the inverse association of predicted lean mass, highly supported in cardiac patients at advanced age, will be replicated for middle-aged apparently healthy subjects as well and secondly, the anatomic, biological and lifestyle differences between men and women will result in sex-mediated associations between body composition estimations and CVD onset or recurrence.

2. Subjects, Materials and Methods

2.1 Sample

To test the research hypothesis two, large-scale, cohort studies, i.e., the ATTICA and the GREECS, were used.

The *ATTICA study* is a prospective, observational cohort investigation which was initiated in 2001 [10]. At baseline (2001-2002), *n*=3,042 apparently healthy volunteers residing in the greater metropolitan Athens area, Greece, agreed to participate (75% participation rate). Of the enrolled participants, *n*=1,514 (49.8%) were men (46±13 years) and *n*=1,528 (50.2%) were women (45±14 years). All participants were free of CVD and other chronic diseases. For the scope of the present work, we initially used the *n*=2,020 participants with complete CVD evaluation in the follow-up assessment.

The *GREECS study* is a prospective, observational cohort study, established in 2003 [11]. From October 2003 to September 2004, *n*=2,172 consecutive patients with discharge diagnosis of acute coronary syndrome (ACS) (i.e., acute myocardial infarction (AMI) or unstable angina (UA)) hospitalized in the cardiology clinics of 6 major General Hospitals in Greece were enrolled in the study (80-95% participation rate). Of the enrolled patients, *n*=1,649 (76%) were men (65±13) years) and *n*=523 (24%) were women (62±11 years).

2.2 Bioethics

The *ATTICA study* was approved by the Bioethics Committee of Athens Medical School and the *GREECS study* was approved by the Medical Research Ethics Committee of the participated Institutions. Both studies were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. All participants were informed about the aims and procedures of the study and signed an informed consent.

2.3 Weight status and body composition estimation

In both studies, weight status was defined using BMI World Health Organization cut off points. BMI was calculated as weight (in kilograms) divided by height (in meters squared). Height was measured to the nearest 0.5 cm, with participants not wearing shoes, their backs square against the measuring wall tape, eyes looking straight ahead, with a right-angled triangle resting on the scalp and against the wall. Weight was measured with a lever balance, to the nearest 100 grams, without shoes and in light undergarments. 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≥30 kg/m^2. Underweight was defined as BMI <18.5 kg/m^2.

Due to the lack of imaging data for body composition i.e. lean and fat mass (kg), sex-specific population-based equations were used to predict body composition, recently validated by the investigators of the NHANES study [9]. For the *ATTICA* participants, we used the equations adjusted for weight, height and waist circumference, since these were suggested to have the best predictive and discrimination ability against CVD risk factors. For the *GREECS study*, because of the lack of waist circumference measurements, lean and fat mass were calculated based on weight- and height- adjusted equations. The population-based equations used here can be found elsewhere [9]. Then, we standardized the generated body composition estimations for lean and fat mass (kg) through dividing by height (in meters squared), to create lean mass index (LMI) and fat mass index (FMI) (kg/m^2); increased values in these indexes corresponded to increased lean and fat mass, respectively. Participants were separated according to sex-specific LMI and FMI tertiles.

Further details about aims, measurements and baseline procedures of ATTICA and GREECS studies can be found elsewhere [10,11].

2.4 Endpoints and follow-up

The combined endpoint studied in this work was the development of a fatal or non-fatal CVD event during the 10-year follow-up; specifically, a first event, for the *ATTICA study* (2012) participants and recurrent event, for the *GREECS study* (2014) ACS patients. A CVD event was defined as the development of acute myocardial infarction,

or unstable angina, or other identified forms of ischemia (WHO-ICD coding 410–414.9, 427.2, 427.6), or heart failure of different types and chronic arrhythmias (WHO-ICD coding 400.0–404.9, 427.0–427.5, 427.9) or stroke (WHO-ICD coding 430–438). For participants who died during follow-up, information was retrieved from relatives and death certificates.

2.5 Statistical analysis

Categorical variables are presented as absolute (*n*) and relative frequencies (%). Continuous variables are presented as mean values ± standard deviation or median (Interquartile Range) if normality was not met. Associations between normally distributed variables and CVD event status were evaluated through Student's t-test for independent samples. 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, Mann-Whitney test was used. Associations between categorical variables and CVD event status was tested with the chi-squared test. Hazard Ratios (HR) and their corresponding 95% Confidence Intervals (95%CI) were evaluated through multivariable Cox-regression analysis; Cox regression analysis was implemented through the construction of nested models (each model is a subset of another model) starting from a crude model (i.e., Model 1) and resulting in a fully adjusted model (i.e., Model 5) [12]. In particular, sociodemographic (i.e., age, sex, educational status), lifestyle (i.e., physical activity, smoking status, adherence to Mediterranean diet) and clinical factors (i.e., family and individual history of CVD, discharge status, diabetes, hypercholesterolemia and hypertension, inflammation) were taken into account as potential confounders of the examined association. Multicollinearity was checked through the Variance Inflation Factor. A-posteriori statistical power analysis revealed that the recruited sample as well as man and woman subsamples in the ATTICA study were adequate to achieve power equal or higher to 75% for testing two-sided hypothesis of HR equal to 0.80 at 5% significance level, whereas, the relevant statistical power achieved in the GREECS study was 0.95%. The concordance statistics, i.e., C-statistic, was used to evaluate the predictive accuracy of multivariate models adjusted for various lipid markers against CVD event. C-indexes and the corresponding 95%CIs were equal to the areas under the curve obtained from ROC analysis. Curves were constructed by plotting sensitivity against (1-specifity). Significance of the changes in C-index was tested by differences in 2 log likelihood of regression models with and without anthropometric measurements. Level of significance was set at two-sided p-value<5%. The STATA software, version 14 (MP & Associates, Sparta, Greece) was used for all statistical analyses.

3. Results

The baseline characteristics of ATTICA and GREECS men and women participants according to their 10-year CVD-incidence and BMI status can be found in supplementary file.

In **Table 1** 10-year CVD event rates are presented separately, in apparently healthy individuals (ATTICA study) and in ACS patients (GREECS study), overall, as well as according to BMI and body composition estimations. Apparently healthy men with FMI in 3rd tertile were about 3 times more likely to suffer from a cardiac episode with a similar trend observed in women. As for ACS patients, women in the 2nd FMI tertile exhibited the lowest CVD recurrence rate with men of the same tertile having about 45% higher likelihood to suffer from a new episode. In the ATTICA sample, men with low LMI were about 2.38 times more likely to develop CVD compared with women of the same tertile. When it came to 2nd and 3rd tertile the consistent exceeding of men on CVD event rate over women was significantly alleviated. In the patients sample of GREECS study, different trends were observed with women in the 2nd LMI tertile presenting the best ACS prognosis revealing a U-shape trend which was not retained in case of their men counterparts. In the ATTICA sample, even in high FMI men with LMI within the 3rd tertile had closer-to-women 10-year CVD event rate (i.e. 1.49). As for the ACS patients, even if in the overall sample men's and women's CVD recurrence rate was quite similar in the context of high lean yet low fat mass, women presented even better ACS prognosis.

[Table 1]

Nested Cox regression models to evaluate the role of BMI and body composition estimations on 10-year first CVD event rate are presented in **Table 2**. In the fully adjusted model, obesity as well as FMI in the 3rd tertile were associated with about 40% higher CVD risk compared with their reference groups. As for the lean mass, participants with the highest LMI had about 10% lower risk to develop a cardiac episode within the decade ($p<0.05$). When the combined effect of lean and fat mass was examined, participants with high fat and low lean mass presented the highest CVD risk compared with the reference group (i.e. low lean and low fat mass) (HR=2.50 95%CI (1.26, 4.40)) while this trend was alleviated in the context of high fat yet high lean mass (HR=1.68 95%CI (1.15, 2.44)).

[Table 2]

Nested Cox regression models were constructed to evaluate the role of BMI and body composition estimations on recurrent CVD event rate and presented in **Table 3**. Focusing on BMI, in the fully adjusted model a U-shape trend was observed with overweight patients having about 50% lower risk to suffer from a new cardiac episode

over their normalweight counterparts (*p<0.05*). As for FMI, even if unadjusted model revealed a significantly increased risk in patients within the 3rd FMI tertile, this trend was lost in the fully adjusted model. Focusing on lean mass, patients in 2nd LMI tertile had about 30% lower risk for CVD recurrence yet higher LMI did not reach the level of significance. In the analysis with the combined effect of lean and fat mass, participants with low fat and high lean mass presented the lowest CVD risk compared with the reference group (i.e. low lean and low fat mass) (HR=0.61 95%CI (0.38, 0.95)). The protective role of lean mass was lost in the context of high fat mass (HR=1.57 95%CI (1.04, 2.17)) even if it seemed to provide a prognostic advantage compared with the respective HR for patients with high fat yet low lean mass (HR=2.19 95%CI (1.17, 3.05)).
[Table 3]

In the formal analysis of interaction, significant heterogeneities were produced in relation to sex and body weight or body composition estimations in both ATTICA and GREECS study (all *ps for sex interaction<0.10*). Thereby, stratified analyses were performed using sex as strata and the respective results are presented in **Table 4**.

Obesity was independently associated with first CVD event only in men (HR=1.85 95%CI (1.28, 3.68)) while FMI within the 3rd tertile range only in women (HR=1.66 95%CI (1.05, 2.62)). Men in 3rd LMI tertile were protected against CVD onset (HR=0.77 95%CI (0.58, 0.89)); this trend was retained in women yet without being significant. Men with high fat yet low lean mass had significantly higher CVD risk compared with the reference group (HR=2.91 95%CI (1.81, 4.44)). In the context of high fat mass yet LMI on the 3rd tertile the aforementioned high CVD risk was retained significant only in women.

Obesity was independently associated with recurrent CVD event only in men (HR=1.82 95%CI (1.00, 2.94)). Overweight women were protected against CVD recurrence (HR=0.47 95%CI (0.29, 0.92)). As for FMI, only men in the 3rd tertile had increased CVD risk (HR=1.75 95%CI (1.10, 2.10)). In women patients, a U-shape LMI-related trend was observed with those in the 2nd tertile having 40% lower risk to develop a new cardiac episode. Both men and women with high fat yet low lean mass had significantly higher CVD risk compared with the reference group. However, in the context of high fat mass yet LMI on the 3rd tertile the aforementioned high CVD risk was retained significant only in men. Lastly, a status with high lean yet low fat mass was protective for both sexes.
[Table 4]

The discrimination ability of epidemiological models adjusted for BMI or body composition estimations was evaluated separately for men and women and results are presented in **Table 5**. Overall, the discrimination ability (expressed through C-index) of the examined models was better in *ATTICA study* sample. In men, both FMI and LMI significantly contributed to principle endpoint yet with the result being more evident for LMI (*p for C-index difference=0.001*). As for women, only FMI-adjusted model had an added discrimination ability (*p for C-index difference=0.003*). As for the results corresponding to *GREECS study*, in men, FMI seemed to significantly increase the base-model discrimination ability against CVD recurrence (*p for C-index difference=0.04*) while in women patients, LMI-adjusted model discriminated better the primary endpoint (*p for C-index difference=0.002*).
[Table 5]

4. Discussion

In the present work, we identified that the association of predicted lean and fat mass, generated from population-based equations, on long-term CVD incidence may vary according to sex as well as according to CVD prevention stage. In line with our initial hypothesis, it was revealed that lean mass may have an independent cardioprotective role not only in patients with established CVD and advanced age, but also in apparently healthy middle-aged individuals. Interestingly, sex-specific remarks were highlighted. In particular, LMI seemed to independently protect against CVD even in the context of increased weight status or adiposity in male free-of-CVD subjects. In case of female ACS patients it is noteworthy that the same association followed a *U*-shape trend. On the other side, FMI seemed to significantly aggravate cardiac health in free-of-CVD women as well as in men with established disease.

Lean mass as a novel prognostic factor is attracting considerable attention in patients with established CVD [13]. Our work sets implications that high lean mass accompanied by obese and/or excess-body-fat status may not be that protective which comes in line with previous studies [8,14,15]. Much as adipose tissue as endocrine organ presents a bidirectional communication with vascular system, in established diseases like CVD, this homeostasis-related condition is lost; with dysfunctional and harmful cell–cell and tissue–tissue interactions between adipose tissue and cardiac system [16,17]. The present work is one of the very first that investigated sex differences in the association between body composition estimations and recurrent CVD event. Sensitivity analysis, revealed that women in 2nd LMI tertile presented the best prognosis compared with 1st and 3rd LMI tertile while this trend was not confirmed in men. This comes in line with a very recent work from a Greek sample [18]. There are indications that women in advanced age [19] and/or with an established catabolic disease [20] may be more vulnerable in lean mass loss compared with men of similar age and disease profile probably due to lifestyle or biological factors [21,22]. Additionally, what is

highly suggested for women patients, is a more pronounced BMI-related paradoxical association, also confirmed here [23]. This has been attributed greater myocardial fatty acid uptake and lower myocardial utilization in women [24]. The added value of our work is related with highlights that women's "overweight paradox" may be attributed not only to their resistance to adiposity but also to sex-specific responses of lean mass. We revealed that ACS women patients with moderate LMI presented the best prognosis; this patients category was mostly overweight and/or with low to medium total fat mass (*data not presented on tables*). On the other side, further raise in FMI, probably accompanied by visceral adiposity considering the life stage of women participants, attenuated the potential protective effect of lean mass which has been observed elsewhere [25].

Body composition in apparently healthy younger individuals has been scarcely studied. In the present work, we show that BMI and FMI presented an independently positive association with CVD incidence only under the context of highest adiposity rates. On the other side, LMI had a protective effect against CVD. Examining the combined role of FMI and LMI on CVD onset, FMI remained an independent risk factor even in high LMI values yet with lower effect size compared with lower LMI. This independent association of FMI comes in line with a very recent big data analysis (UK Biobank) [26]; yet the added value of our work was the consideration of lean mass on this association which has mostly been applied in patient or at-advance-age populations. Our sex-stratified analysis revealed that the aforementioned associations were retained only in women; while in men LMI had a stronger protective effect against CVD even in the context of high adiposity estimations. These indications are partially aligned with previous works. Sex-specific analysis in UK Biobank revealed that adiposity metrics had a stronger aggravating for women compared with men [27]. In the PREVEND cohort study, adiposity was independently associated with CVD onset even after adjusting for a muscle mass indicator with marginally stronger association in women, yet only on the basis of total fat mass [26]. Different fat distribution between sexes may partially explain these observations. To this issue, there are indications that total body fat may have a higher predictive ability in women whereas in men focus should be oriented towards visceral adiposity metrics [28]. Additionally, sex is to influence adipocyte size in specific anatomic regions. Given the same weight gain, intraperitoneal visceral adipocyte size in men marginally increases compared with the rise in women; large adipocytes are associated with more proinflammatory hormone-mediated adipokine secretion which may explain the susceptibility of women in excess body fat [29-31]. Moreover, the observed association may be gene-mediated; in Women's Genome Health study it was revealed that a fat-mass related gene had an independent aggravating effect on women's CVD risk especially in those with low physical activity [32]. Finally, several hypotheses could be performed regarding the protective effect of lean mass against excess adiposity only in men. Firstly, physiologically middle-aged men have higher lean mass compared with women. Secondly, within younger ages men present a higher level of physical activity compared with women which may affect their lean mass on the basis of quantity, metabolic activity and strength [33]. Thirdly, in our study, men with high LMI had significantly lower waist circumference compared with their counterparts in lower LMI tertiles (*descriptive data not presented on tables*) which could have driven the final outcome. Lastly, this observation may be mediated by testosterone levels. Lean mass is highly correlated with testosterone levels. Hence, behind the lower lean mass metrics, testosterone deficiency may be hindered; considering the mounting evidence suggesting that normal testosterone levels are beneficial to men's vascular system and that testosterone deficiency is associated with an unfavorable metabolic profile, including increased adiposity and insulin resistance, the findings of the present work may be attributed to this intermediate path [34].

4.1 Limitations and strengths

The main strength here that compensates any limitations is that this in one of the very few works that evaluated the association of predicted body composition metrics in terms of fat yet most importantly lean mass on long-term CVD event providing sex- and CVD-prevention-stage specific remarks which are scarce in the hitherto literature [35-37]. The principle limitation is related with the estimation of body composition metrics through population-based equations and not imaging or skinfold data; this is anticipated by the fact that we used equations validated through imaging (DXA-measured) data separately for men and women. Additionally, these equations are not validated for the Greek sample; however, **a.** they have been validated in the context of a large-scale epidemiological study with diverse, nationwide sample [9] and **b.** they have been applied in the present work using objective metrics and not self-reported data which could have biased the final outcome [38].

4.2 Conclusion

Major tailor-made recommendations remain to be guided for the actual predictive and prognostic ability of body composition parameters on daily clinical practice. Even if the methodological and sample-related limitations of the present work do not allow the generalization of the principle conclusions, considering the limited evidence, especially in younger, free-of-disease individuals, our work comes to expand knowledge towards this approach. Firstly, outcomes here suggest that preserving healthy lean mass and deterring muscle loss not only in cardiac rehabilitation programs but also in preventive medicine initiatives should be enhanced. Subsequently, excess adiposity

had clear adverse effects on cardiac health; even if preservation of quantity and strength of lean mass may alleviate this claim, constant vigilance is needed to achieve healthy weight maintenance through balanced diet and adherence to an active lifestyle. Lastly, the sex-specific remarks revealed here set the basis for better identifying the particular anthropometric features that affects men's and women's cardiac health.

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Table 1 Unadjusted cardiovascular disease incidence rate in men and women from the ATTICA and GREECS study according to their body mass and body composition indexes.

ATTICA study (Outcome: First fatal/non fatal CVD event)				
CVD incidence rate per 100 participants	**Total sample**	**Men**	**Women**	*Men-to-women CVD incidence rate ratio*
	n=2,020	*n*=1,005	*n*=1,015	
Overall	15.7	19.7	11.7	*1.66*
BMI categories				
Normal weight	9.6	14.4	7.2	*2.00*
Overweight	18.6	20.2	15.8	*1.27*
Obese	23.6	26.0	20.6	*1.26*
Body fat mass index tertiles				
1st	9.4	13.8	5.2	*2.65*
2nd	16.1	21.1	11.0	*1.91*
3rd	19.9	19.9	16.3	*1.02*
Body lean mass index tertiles				
1st	17.1	23.8	12.0	*2.38*
2nd	15.0	16.9	13.0	*1.30*
3rd	11.9	18.3	9.7	*1.88*
Body fat and lean mass status				
Low lean/low fat mass	9.9	15.1	5.7	*2.64*
High lean/low fat mass	8.4	20.2	6.9	*2.92*
Low lean/high fat mass	27.9	11.9	19.2	*1.75*
High lean/high fat mass	15.7	19.0	12.7	*1.49*
GREECS study (Outcome: Recurrent fatal/non fatal CVD event)				
CVD incidence rate per 100 participants	**Total sample**	**Men**	**Women**	*Men-to-women CVD incidence rate ratio*
	n=2,172	*n*=1,649	*n*=523	
Overall	37.3	38.8	32.9	*1.17*
BMI categories				
Normalweight	36.7	38.7	33.8	*1.14*
Overweight	35.8	39.2	26.9	*1.45*
Obese	38.0	37.2	35.2	*1.05*
Body fat mass index tertiles				
1st	36.2	37.5	33.1	*1.13*
2nd	38.0	38.9	27.6	*1.40*

3rd	37.3	39.6	36.4	*1.08*
Body lean mass index tertiles				
1st	38.8	39.5	34.0	*1.16*
2nd	35.8	40.2	28.5	*1.41*
3rd	36.7	36.2	34.7	*1.04*
Body fat and lean mass status				
Low lean/low fat mass	37.5	39.7	30.8	*1.28*
High lean/low fat mass	41.8	44.6	44.4	*1.01*
Low lean/high fat mass	31.0	32.8	23.5	*1.39*
High lean/high fat mass	36.5	36.7	35.9	*1.02*

Unadjusted 10-year CVD rates were obtained through chi-squared test. Body fat mass index (FMI) was created to reflect total body fat mass and body lean mass index (LMI) to reflect total body lean mass (indirectly calculated through population formulas); high fat mass corresponded to 3rd FMI sex-specific tertile and high lean mass corresponded to 3rd LMI sex-specific tertile while low fat mass corresponded to 1st merged with 2nd FMI sex-specific tertile and low lean mass corresponded to 1st merged with 2nd LMI sex-specific tertile. ***Abbreviations***: Cardiovascular disease (CVD)

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Table 2 Multi-adjusted analysis to evaluate the association between body composition status and 10-year cardiovascular disease incidence in apparently healthy individuals of the ATTICA study (*n*=2,020).

	Model 1 HR (95%CI)	**Model 2** HR (95%CI)	**Model 3** HR (95%CI)	**Model 4** HR (95%CI)
Model for <u>body mass index</u>				
Normalweight	Ref	Ref	Ref	Ref
Overweight	**2.17 (1.63, 2.91)**	**1.27 (1.00, 1.77)**	0.91 (0.57, 1.44)	0.80 (0.48, 1.31)
Obese	**2.94 (2.11, 4.11)**	**1.69 (1.16, 2.44)**	**1.44 (1.05, 2.27)**	**1.41 (1.00, 2.20)**
Model for <u>body fat mass index</u>				
1st	Ref	Ref	Ref	Ref
2nd	**1.81 (1.27, 2.58)**	1.14 (0.77, 1.69)	0.83 (0.49, 1.41)	0.75 (0.42, 1.30)
3rd	**3.20 (2.29, 4.47)**	**1.55 (1.17, 2.35)**	**1.45 (1.10, 2.18)**	**1.39 (1.04, 2.12)**
Model for <u>body lean mass index</u>				
1st	Ref	Ref	Ref	Ref
2nd	**0.81 (0.40, 0.92)**	0.96 (0.52, 1.07)	1.05 (0.67, 1.22)	1.09 (0.75, 1.35)
3rd	**0.65 (0.31, 0.75)**	**0.83 (0.64, 0.91)**	**0.89 (0.71, 0.93)**	**0.91 (0.74, 0.95)**
Model for <u>body fat and lean mass status</u>				
Low lean/low fat mass	Ref	Ref	Ref	Ref
High lean/low fat mass	**0.62 (0.22, 0.73)**	**0.79 (0.27, 0.86)**	**0.82 (0.46, 0.97)**	**0.82 (0.46, 0.97)**
Low lean/high fat mass	**3.02 (2.14, 4.80)**	**2.71 (1.33, 4.66)**	**2.50 (1.26, 4.40)**	**2.50 (1.26, 4.40)**
High lean/high fat mass	**1.97 (1.35, 2.69)**	**1.82 (1.28, 2.52)**	**1.68 (1.15, 2.44)**	**1.68 (1.15, 2.44)**

HRs and their corresponding 95%CIs were obtained from Cox regression analysis; *Model 1:* crude model; *Model 2:* age and sex; *Model 3:* Model 2 plus current smoking, hypertension, diabetes mellitus, MedDietScore, physical activity status, years of school, family history of cardiovascular disease; *Model 4*: Model 3 plus C-reactive protein, alanine transaminase, aspartate transaminase, creatinine clearance. Body fat mass index (FMI) was created to reflect total body fat mass and body lean mass index (LMI) to reflect total body lean mass (indirectly calculated through population formulas); high fat mass corresponded to 3rd FMI sex-specific tertile and high lean mass corresponded to 3rd LMI sex-specific tertile while low fat mass corresponded to 1st merged with 2nd FMI sex-specific tertile and low lean mass corresponded to 1st merged with 2nd LMI sex-specific tertile. ***Abbreviations:*** Hazard Ratio (HR), 95% Confidence Interval (95%CI). **Bold** indicates statistically significant outcomes i.e. $p<0.05$

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Table 3 Multi-adjusted analysis to evaluate the association between body composition status and 10-year cardiovascular disease incidence in patients with established Acute Coronary Syndrome of the GREECS study (*n*=2,172).

	Model 1 HR (95%CI)	**Model 2** HR (95%CI)	**Model 3** HR (95%CI)	**Model 4** HR (95%CI)
Model for <u>body mass index</u>				
Normalweight	Ref	Ref	Ref	Ref
Overweight	**0.34 (0.22, 0.78)**	**0.48 (0.36, 0.89)**	**0.55 (0.33, 0.97)**	**0.55 (0.33, 0.97)**
Obese	**2.53 (1.41, 3.41)**	2.01 (0.96, 2.89)	1.77 (0.95, 2.78)	1.78 (0.95, 2.76)
Model for <u>body fat mass index</u>				
1st	Ref	Ref	Ref	Ref
2nd	**0.89 (0.41, 0.94)**	**0.94 (0.50, 0.99)**	1.08 (0.72, 1.20)	1.09 (0.72, 1.23)
3rd	2.15 (1.12, 3.05)	**2.04 (1.10, 2.79)**	**1.85 (1.03, 2.48)**	1.67 (0.92, 2.20)
Model for <u>body lean mass index</u>				
1st	Ref	Ref	Ref	Ref
2nd	**0.63 (0.41, 0.96)**	**0.68 (0.46, 0.94)**	**0.69 (0.46, 0.95)**	**0.77 (0.58, 0.98)**
3rd	1.31 (0.85, 2.02)	1.28 (0.82, 2.01)	1.30 (0.73, 2.29)	1.19 (0.69, 2.10)
Model for <u>body fat and lean mass status</u>				
Low lean/low fat mass	Ref	Ref	Ref	Ref
High lean/low fat mass	**0.41 (0.11, 0.65)**	**0.56 (0.25, 0.79)**	**0.60 (0.38, 0.94)**	**0.61 (0.38, 0.95)**
Low lean/high fat mass	**2.43 (1.34, 3.80)**	**2.23 (1.20, 3.47)**	**2.18 (1.15, 3.10)**	**2.19 (1.17, 3.05)**
High lean/high fat mass	**1.85 (1.24, 2.67)**	**1.64 (1.18, 2.32)**	**1.57 (1.05, 2.16)**	**1.57 (1.04, 2.17)**

HRs and their corresponding 95%CIs were obtained from Cox regression analysis; *Model 1:* crude model; *Model 2:* age and sex; *Model 3:* Model 2 plus current smoking, hypertension, diabetes mellitus, MedDietScore, physical activity status, years of school, family history of cardiovascular disease; *Model 4*: Model 3 plus baseline cardiovascular disease history, discharge status (i.e. acute myocardial infarction or unstable angina at baseline) and adherence to medication. Body fat mass index (FMI) was created to reflect total body fat mass and body lean mass index (LMI) to reflect total body lean mass (indirectly calculated through population formulas); high fat mass corresponded to 3rd FMI sex-specific tertile and high lean mass corresponded to 3rd LMI sex-specific tertile while low fat mass corresponded to 1st merged with 2nd FMI sex-specific tertile and low lean mass corresponded to 1st merged with 2nd LMI sex-specific tertile. ***Abbreviations:*** Hazard Ratio (HR), 95% Confidence Interval (95%CI). **Bold** indicates statistically significant outcomes i.e. $p<0.05$

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Table 4 Sex-based stratified multivariate analysis to evaluate the association between body composition status and 10-year cardiovascular disease incidence in men and women of the ATTICA (*n*=2,020) and GREECS study (*n*=2,172).

ATTICA study (Outcome: First fatal/non fatal cardiovascular disease event)

	Men HR (95%CI)	**Women** HR (95%CI)
Model for body mass index		
Normalweight	Ref	Ref
Overweight	1.04 (0.57, 1.88)	0.76 (0.35, 1.65)
Obese	**1.85 (1.28, 3.68)**	1.10 (0.59, 2.47)
p for interaction=0.07		
Model for body fat mass index		
1st	Ref	Ref
2nd	0.82 (0.41, 1.63)	1.32 (0.82, 2.13)
3rd	1.24 (0.64, 2.39)	**1.66 (1.05, 2.62)**
p for interaction=0.01		
Model for body lean mass index		
1st	Ref	Ref
2nd	0.96 (0.84, 1.17)	1.10 (0.62, 1.27)
3rd	**0.77 (0.58, 0.89)**	0.95 (0.81, 1.13)
p for interaction=0.04		
Model for body fat and lean mass status		
Low lean/low fat mass	Ref	Ref
High lean/low fat mass	**0.75 (0.37, 0.95)**	0.61 (0.23, 2.16)
Low lean/high fat mass	**2.91 (1.81, 4.44)**	**2.83 (1.65, 4.84)**
High lean/high fat mass	1.31 (0.81, 2.10)	**2.41 (1.28, 4.53)**
p for interaction=0.08		

GREECS study (Outcome: Recurrent fatal/non fatal cardiovascular disease event)

	Men HR (95%CI)	**Women** HR (95%CI)
Model for body mass index		
Normalweight	Ref	Ref
Overweight	0.65 (0.40, 1.10)	**0.47 (0.29, 0.92)**
Obese	**1.82 (1.00, 2.94)**	1.64 (0.90, 2.66)
p for interaction=0.01		
Model for body fat mass index		

1st	Ref	Ref
2nd	1.12 (0.75, 1.25)	0.95 (0.61, 1.11)
3rd	**1.75 (1.10, 2.10)**	1.46 (0.85, 1.89)
p for interaction =0.05		
Model for body lean mass index		
1st	Ref	Ref
2nd	0.84 (0.38, 1.10)	**0.63 (0.31, 0.99)**
3rd	1.85 (0.82, 2.38)	0.91 (0.36, 2.30)
p for interaction=0.02		
Model for body fat and lean mass status		
Low lean/low fat mass	Ref	Ref
High lean/low fat mass	**0.75 (0.55, 0.99)**	**0.44 (0.20, 0.87)**
Low lean/high fat mass	**2.41 (1.36, 3.24)**	**1.87 (1.10, 2.79)**
High lean/high fat mass	**1.64 (1.18, 2.25)**	1.42 (0.90, 1.99)
p for interaction=0.02		

HRs and their corresponding 95%CIs were obtained from Cox regression analysis; for ATTICA study, model was adjusted for: age, current smoking, hypertension, diabetes mellitus, MedDietScore, physical activity status, years of school, family history of cardiovascular disease, C-reactive protein, alanine transaminase, aspartate transaminase, creatinine clearance / for GREECS study, model was adjusted for age, current smoking, hypertension, diabetes mellitus, MedDietScore, physical activity status, years of school, family history of cardiovascular disease, baseline cardiovascular disease history, discharge status (i.e. acute myocardial infarction or unstable angina at baseline) and adherence to medication. Body fat mass index (FMI) was created to reflect total body fat mass and body lean mass index (LMI) to reflect total body lean mass (indirectly calculated through population formulas); high fat mass corresponded to 3rd FMI sex-specific tertile and high lean mass corresponded to 3rd LMI sex-specific tertile while low fat mass corresponded to 1st merged with 2nd FMI sex-specific tertile and low lean mass corresponded to 1st merged with 2nd LMI sex-specific tertile. ***Abbreviations:*** Hazard Ratio (HR), 95% Confidence Interval (95%CI). **Bold** indicates statistically significant outcomes i.e. *p<0.05*

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Table 5 C-index of multivariate models containing different anthropometric measurements to evaluate the discriminative ability against 10-year cardiovascular disease event in men and women of the ATTICA (*n*=2,020) and GREECS study (*n*=2,172).

ATTICA study (Outcome: First fatal/non fatal cardiovascular disease event)

	C-index (95%CI)	***p-value***	**C-index changes (95%CI)**	***p-value***
Men				
Base model	0.700 (0.678, 0.723)	*<0.001*	-	-
Base model + BMI	0.705 (0.683, 0.728)	*<0.001*	0.005 (-0.001, 0.007)	*0.12*
Base model + FMI	0.711 (0.689, 0.734)	*<0.001*	0.011 (0.008, 0.018)	*0.01*
Base model + LMI	0.731 (0.709, 0.753)	*<0.001*	0.031 (0.025, 0.039)	*0.001*
Base model + body composition status	0.732 (0.711, 0.754)	*<0.001*	0.032 (0.026, 0.040)	*0.001*
Women				
Base model	0.751 (0.718, 0.784)	*<0.001*	-	
Base model + BMI	0.759 (0.728, 0.791)	*<0.001*	0.008 (-0.003, 0.014)	*0.31*
Base model + FMI	0.774 (0.742, 0.806)	*<0.001*	0.017 (0.010, 0.025)	*0.003*
Base model + LMI	0.758 (0.725, 0.790)	*<0.001*	0.007 (-0.003, 0.009)	*0.25*
Base model + body composition status	0.774 (0.742, 0.806)	*<0.001*	0.008 (-0.003, 0.014)	*0.003*

GREECS study (Outcome: Recurrent fatal/non fatal cardiovascular disease event)

	C-index (95%CI)	***p-value***	**C-index changes (95%CI)**	***p-value***
Men				
Base model	0.615 (0.578, 0.643)	*<0.001*	-	-
Base model + BMI	0.619 (0.580, 0.642)	*<0.001*	0.004 (-0.002, 0.007)	*0.15*
Base model + FMI	0.630 (0.586, 0.700)	*<0.001*	0.015 (0.006, 0.021)	*0.04*
Base model + LMI	0.620 (0.581, 0.643)	*<0.001*	0.005 (-0.003, 0.008)	*0.10*
Base model + body composition status	0.632 (0.587, 0.701)	*<0.001*	0.017 (0.008, 0.024)	*0.05*
Women				
Base model	0.665 (0.618, 0.699)	*<0.001*	-	-
Base model + BMI	0.669 (0.620, 0.701)	*<0.001*	0.004 (-0.003, 0.005)	*0.26*
Base model + FMI	0.668 (0.619, 0.700)	*<0.001*	0.003 (-0.002, 0.005)	*0.12*
Base model + LMI	0.677 (0.627, 0.710)	*<0.001*	0.012 (0.007, 0.019)	*0.002*
Base model + body composition status	0.680 (0.671, 0.712)	*<0.001*	0.015 (0.010, 0.023)	*0.002*

Base model was adjusted for conventional cardiovascular disease risk factors i.e. age, hypercholesterolemia, diabetes mellitus, hypertension, currents smoking and family history of cardiovascular disease. C-index and the corresponding confidence interval was evaluated through the area under the curve obtained from the Receiver operating Characteristics (ROC) analysis. ROC analysis was performed using the probabilities for 10-year first fatal/non fatal cardiovascular disease event, corresponding to each study participant, separately for men and women, calculated from Cox regression analysis using the multivariate models described. Significance of the changes in C-index was tested by differences in 2 log likelihood of regression models with and without anthropometric measurements. FMI was created to reflect total body fat mass and LMI to reflect total body lean mass (indirectly calculated through population formulas). Body composition status was defined as the combined lean and fat mass status as follows; high fat mass corresponded to 3rd FMI sex-specific tertile and high lean mass corresponded to 3rd LMI sex-specific tertile while low fat mass corresponded to 1st merged with 2nd FMI sex-specific tertile and low lean mass corresponded to 1st merged with 2nd LMI sex-specific tertile ***Abbreviations:*** body fat mass index (FMI), body mass index (BMI), body lean mass index (LMI), 95% Confidence Interval (95%CI).

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