Preventive Medicine Reports 26 (2022) 101700

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Simple cardiovascular risk stratification by replacing total serum cholesterol with anthropometric measures: The MORGAM prospective cohort project

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Abbreviations: ACM, all-cause mortality; ASCVD, atherosclerotic cardiovascular disease; AUC_{ROC}, area under the receiver-operating-characteristic curve; BMI, body mass index; BP, blood pressure; CEP, composite cardiovascular endpoint; Chol, serum total cholesterol; CI, confidence interval; cNRI, continuous net reclassification improvement; CV, cardiovascular; CVD, cardiovascular disease; CVM, cardiovascular mortality; DBP, diastolic blood pressure; EFM, estimated fat mass; HDL-cholesterol, high density lipoprotein cholesterol; HR, hazard ratio; IQR, interquartile range; MACE, major adverse cardiovascular events; MBP, mean blood pressure; MONICA, Multi-national MONItoring of Trends and Determinants in CArdiovascular Disease; MORGAM, MOnica, Risk, Genetics, Archiving and Monograph; NRI, net reclassification improvement; NS, non-significant; PP, pulse pressure; SCORE, Systematic COronary Risk Evaluation; SBP, systolic blood pressure; WHR, waist-hip ratio.

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https://doi.org/10.1016/j.pmedr.2022.101700
Received 3 January 2022; Accepted 15 January 2022
Available online 27 January 2022

ARTICLE INFO

Keywords:
Adipose tissue
Assessment, risk
Body mass index
Cardiovascular diseases
Cholesterol
Waist-hip ratio

ABSTRACT

To assess whether anthropometric measures (body mass index [BMI], waist-hip ratio [WHR], and estimated fat mass [EFM]) are independently associated with major adverse cardiovascular events (MACE), and to assess their added prognostic value compared with serum total-cholesterol. The study population comprised 109,509 individuals (53% men) from the MORGAM-Project, aged 19–97 years, without established cardiovascular disease, and not on antihypertensive treatment. While BMI was reported in all, WHR and EFM were reported in ~52,000 participants. Prognostic importance of anthropometric measurements and total-cholesterol was evaluated using adjusted Cox proportional-hazards regression, logistic regression, area under the receiver-operating-characteristic curve (AUC_{ROC}), and net reclassification improvement (NRI). The primary endpoint was MACE, a composite of stroke, myocardial infarction, or death from coronary heart disease. Age interacted significantly with anthropometric measures and total-cholesterol on MACE ($P \leq 0.003$), and therefore age-stratified analyses (<50 versus ≥ 50 years) were performed. BMI, WHR, EFM, and total-cholesterol were independently associated with MACE ($P \leq 0.003$) and resulted in significantly positive NRI when added to age, sex, smoking status, and systolic blood pressure. Only total-cholesterol increased discrimination ability (AUC_{ROC} difference; $P < 0.001$). In subjects < 50 years, the prediction model with total-cholesterol was superior to the model including BMI, but not superior to models containing WHR or EFM, while in those ≥ 50 years, the model with total-cholesterol was superior to all models containing anthropometric variables, whether assessed individually or combined. We found a potential role for replacing total-cholesterol with anthropometric measures for MACE-prediction among individuals < 50 years when laboratory measurements are unavailable, but not among those ≥ 50 years.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death worldwide (Roth et al., 2018). As a result, risk prediction and subsequent prevention in the general population has received considerable attention for decades. Traditional risk assessment tools, such as the Systematic COronary Risk Evaluation (SCORE) and the Framingham Risk Score that calculate an individual's ten-year risk of cardiovascular mortality and coronary heart disease, respectively, incorporate both clinical characteristics and laboratory tests (Wilson et al., 1998; Conroy et al., 2003).

Serum total cholesterol concentration is considered an essential component for the prediction of ASCVD and is included in all contemporary risk equations (Piepoli et al., 2016; Grundy et al., 2019). However, access to laboratory testing may not always be available, particularly in low-income countries (McGorrian et al., 2011) or even in high-income countries, for instance in relation to health screenings outside the traditional healthcare system (Veronesi et al., 2018). Nevertheless, adopting appropriate preventive strategies in low-income countries is particularly important as they account for the majority of the global CVD burden (Roth et al., 2018; Gaziano et al., 2008). Several studies have suggested that markers of abnormal body composition are associated with CVD (Hubert et al., 1983; Lapidus et al., 1984; Yan et al., 2006; Clark, 2003; Song et al., 2013; Lakka et al., 2002), but data on the predictive power of anthropometric measures compared with that of total cholesterol are limited (Gaziano et al., 2008).

We used data from the large, multinational MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project to assess 1) whether readily available anthropometric measures (body mass index [BMI], waist-hip ratio [WHR], and estimated fat mass [EFM]) were independently associated with CV events and mortality and 2) the added prognostic value of these markers, individually and in combination, compared with serum total cholesterol concentration.

2. Methods

2.1. The MORGAM project

We used data from the MORGAM project, an international pooling of CV cohorts, aiming to develop CV risk scores based on well-known, traditional risk factors, and to determine whether genetic variability and biomarker assessment enhanced risk stratification. Detailed descriptions of the project, the cohorts, and quality assessment have been published previously (Evans et al., 2005; Kulathinal et al., 2005). Data originating from the MORGAM project are not publicly available, and access is restricted by the ethical approvals and the legislation of the European Union and the countries of each study. Data access requires approval by the principal investigator of each cohort study and the MORGAM/BiomarCaRE Steering Group. More information can be found in the MORGAM manual (MORGAM Project, 2001).

2.2. Study population

Baseline data were collected from 1982 to 2002 and were derived from 38 population-based cohorts in 11 European countries (**Supplemental Table 1**). The cohorts in the MORGAM Project had either been part of the World Health Organization's MONICA Project (MONitoring trends and determinants In CArdiovascular disease) or had used the same standardized MONICA survey procedures for data collection as described in the MORGAM manual (MORGAM Project, 2001). An exception to this is the ESTHER cohort, where weight and height and were self-reported.

A total of 17,552 individuals were excluded because of missing information related to the following variables: history of diabetes mellitus (n = 1753), history of ASCVD (n = 781), use of antihypertensive medication (n = 4224), the CV risk factors included in SCORE (n = 7618) (Conroy et al., 2003) and loss to follow-up for major adverse CV events (MACE) or death before 10 years (n = 1266). We also excluded persons with a history of ASCVD or diabetes mellitus as well as those on antihypertensive therapy at baseline (n = 16,440), leaving a total of 109,509 individuals aged 19–97 years available for analysis.

While BMI and serum total cholesterol were available in all 38 cohorts (n = 109,509), WHR and waist circumference (used to estimate EFM) were only available in 25 cohorts (n = 79,933). We excluded 27,745 and 27,716 individuals due to missing information on WHR and waist circumference, respectively, leaving a total of 52,188 and 52,217 individuals for the WHR and EFM analyses.

All participants were examined once at baseline. In most cohorts (all except FRA-LIL, FRA-STR, FRA-TOU, UNK-BEL, and GER-ESR), blood pressure was measured twice in the right arm, after 5 min of rest in the sitting position, using a standard or random zero mercury sphygmomanometer. The means of the first and second systolic and diastolic blood pressures were used in the analyses. Antihypertensive therapy at baseline, smoking habits, and history of diabetes mellitus were self-

reported. History of ASCVD included stroke (ischemic or hemorrhagic) or coronary heart disease (myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting). Angina pectoris was included in the definition of coronary heart disease for the Warsaw and Brianza cohort 3 when it could not be separated from myocardial infarction. Total cholesterol and high-density lipoprotein (HDL) cholesterol concentrations were measured in serum samples by local laboratories with external international quality control in all cohorts except GER-AUG and GER-ESR.

2.3. Anthropometric measurements

Three distinct measures of body composition were used for the current report, i.e., BMI, WHR, and EFM. Using waist and hip as two separate variables, as the previous MORGAM analysis by Cameron et al. (Cameron et al., 2020), improved the models insignificantly but did not change any conclusions and is therefore not presented. Weight was measured with weight balance scales in the majority of cohorts and with digital scales in a few cohorts, and height with a stadiometer without outer garments and shoes. BMI was then calculated as weight (kg) divided by height squared (m^2). WHR was measured using a measuring tape and reported as the widest waist circumference divided by the widest hip circumference. Estimated fat mass was calculated using a validated prediction equation (-18.592 – age (years)*0.009 – height (cm)*0.08 + weight (kg)*0.226 + waist (cm)*0.387 for men and 11.817 + age (years)*0.041 – height (cm)*0.199 + weight (kg)*0.610 + waist (cm)*0.044 for women) and reported in kg (Lee et al., 2017).

2.4. Study endpoints

The primary endpoint was MACE which was a composite of fatal and nonfatal stroke, nonfatal myocardial infarction, or death from coronary heart disease. Death from coronary heart disease included the categories "definite or possible myocardial infarction or coronary death", and "unclassifiable death". The latter category represents death (mostly sudden) with no evidence of cardiac origin and no competing cause. Secondary endpoints were all-cause mortality (ACM) and CVM, the latter defined as fatal stroke or death from coronary heart disease. Observations continued until an endpoint was reached or the end of the full follow-up period of 10-years (1992-2012dependingonthecohort). National and regional health information systems were used to identify endpoint events. In some cohorts (i.e., PRIME), the participants were contacted periodically (in PRIME each year) to identify possible events. To validate events occurring during follow-up, most centers used the MONICA criteria or other similar diagnostic criteria 17, (Tunstall-Pedoe et al., 2003). Details of the data collection procedures and quality assessment of MORGAM endpoints have been described previously (MORGAM Project, 2001; Niemel et al., 2007).

2.5. Statistical analysis

Categorical variables were presented as numbers (percentages), and continuous variables were summarized by medians with interquartile ranges (IQRs). Multivariable Cox proportional-hazards regression was used to calculate adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) for the association of each anthropometric measure (BMI, WHR, and EFM) as well as serum total cholesterol with each endpoint. The regression models were adjusted for country and SCORE variables except serum total cholesterol. Hazard ratios were reported for one standard deviation increase in each of the explanatory variables of interest.

Predictive models to estimate 10-year risk of the study endpoints were derived using logistic regression analysis. Bootstrapping with 1000 replications was employed for internal validation of these estimates. The ability of anthropometric measures and serum total cholesterol to enhance prognostication beyond sex, age, smoking status, and systolic blood pressure was examined using discrimination ability (comparison of area under the receiver operating characteristic curves; AUC_{ROC}) and continuous (category-free) net reclassification improvement (NRI). We also compared discrimination abilities between prediction models including serum total cholesterol with models including anthropometric measures for all endpoints, both individually and combined. AUC_{ROC} were compared using the method described by DeLong et al. which yields results similar to using the Wald test with a joint bootstrap variance estimate. Model calibration, i.e., whether observed event rates differed significantly from expected event rates, was assessed using the Gronnesby and Borgan likelihood-ratio test. Confidence intervals for the NRI are estimated through bootstrapping (1000replications).

All explanatory variables met the proportional-hazards assumption as assessed by Schoenfeld residuals. Sex- and age-related interactions were explored using the likelihood-ratio test. A two-sided P-value < 0.05 was considered statistically significant. No adjustment for multiple testing was made as the study was considered hypothesis-generating. All analyses were performed using Stata/IC 15 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline characteristics

The final study sample comprised 109,509 individuals (53% men) aged 19–97 years without ASCVD and diabetes mellitus who were not on antihypertensive medications. Because of a significant interaction between age category and both total-cholesterol and all anthropometric measures in predicting MACE, baseline characteristics were displayed stratified for age (<and ≥ 50 years) and BMI (<and ≥ 25 kg/m^2) (Table 1). Within each age stratum, individuals with greater BMI appeared to be older, more often men, less often smokers, and had higher blood pressures and higher total cholesterol, but lower HDL-cholesterol, greater weight, greater waist and hip circumferences, and greater WHR and EFM.

3.2. Risk of incident events

At 10 years, 4465 study participants had experienced a MACE (4.1% of the study sample, 8.9 per 1000 person-years, 3253 men and 1212 women). A total of 5183 individuals had died from all-causes (4.7%, 9.9 per 1000 person-years, 3523 men and 1660 women), 1016 (0.9%, 1.9 per 1000 person-years, 734 men and 282 women) from a CV cause.

3.3. Prediction, discrimination, and reclassification

The independent prediction, discrimination, and net reclassification of fatal and non-fatal events by anthropometric measures and serum total cholesterol are shown in Table 2. Related interactions for age and sex are displayed in Table 3. Whereas the interactions by age were general, sex only interacted with the associations between total cholesterol and outcome and WHR and ACM. Total cholesterol was more strongly associated with higher risk of MACE and lower risk of ACM in men than in women (not presented). WHR was more strongly associated with ACM in women than in men (not presented). BMI, WHR, EFM, and cholesterol were all significantly associated with MACE, irrespective of age group ($P \leq 0.003$). Effect sizes were numerically larger among individuals < 50 years of age compared with those ≥ 50 years ($P < 0.001$ for interaction). Using the bootstrap method for estimation did not appreciably change the results (**Supplemental Table 2**). However, only cholesterol had the ability to significantly increase discrimination ability beyond sex, age, smoking status, and systolic blood pressure as assessed by difference in AUC_{ROC} ($P < 0.001$ in both age groups). Conversely, all measures resulted in significantly positive continuous NRI. Associations with CVM and ACM were generally weaker, and none of the examined variables were able to significantly improve AUC_{ROC} in predicting these

Table 1
Baseline characteristics and event rates stratified by age and body mass index.

	Age < 50 years		Age ≥ 50 years	
	BMI < 25 kg/m^2	BMI ≥ 25 kg/m^2	BMI < 25 kg/m^2	BMI ≥ 25 kg/m^2
Number of participants	39,504	28,133	15,045	26,827
Age, years	34.4 (29.0–40.7)	39.2 (32.6–44.5)	56.6 (52.8–61.0)	57.2 (53.4–61.6)
Women (%)	23,186 (59)	11,689 (Richardson et al., 2020)	6517 (Bangalore et al., 2017)	10,464 (Frary et al., 2020)
Daily smoking (%)	15,580 (39.4)	9362 (33.3)	4924 (32.7)	5544 (20.7)
Systolic blood pressure, mmHg	122 (113–132)	129 (120–140)	131 (120–145)	138.5 (126–152)
Diastolic blood pressure, mmHg	74.5 (68–81)	81 (74–88.5)	80 (73–87)	84 (78–92)
Total cholesterol, mmol/l	5.1 (4.5–5.9)	5.6 (4.9–6.4)	6.0 (5.3–6.8)	6.1 (5.4–6.9)
HDL-cholesterol, mmol/l	1.5 (1.3–1.7)	1.3 (1.1–1.5)	1.5 (1.3–1.8)	1.3 (1.1–1.6)
Height, cm	169 (162–176)	170 (162–177)	167 (161–174)	167 (160–174)
Weight, kg	63.0 (57.0–70.4)	81.0 (73.3–89.0)	64.0 (58.0–70.4)	79.3 (72.4–87.0)
BMI, kg/m^2	22.4 (21.0–23.7)	27.5 (26.1–29.7)	23.2 (21.9–24.2)	28.0 (26.4–30.4)
Waist circumference, cm	76 (70.5–82)	92.5 (86–99)	83 (76–88)	96 (90–102)
Hip circumference, cm	94.5 (91–98)	103.5 (100–108)	95 (91–98)	103 (99–107.5)
Waist-hip ratio	0.80 (0.76–0.86)	0.89 (0.83–0.95)	0.88 (0.81–0.93)	0.94 (0.87–0.99)
Estimated fat mass, kg	18.1 (15.3–21.0)	26.2 (22.4–30.6)	17.9 (15.2–20.9)	25.9 (22.2–30.4)
Major adverse cardiovascular events	343 (0.9)	608 (2.2)	1149 (7.6)	2365 (8.8)
Cardiovascular mortality	66 (0.2)	102 (0.4)	326 (2.2)	522 (2.0)
All-cause mortality	519 (1.3)	535 (1.9)	1732 (11.5)	2397 (8.9)

Values are presented as counts (percentages) or medians (25th-75th percentiles).
Abbreviations: BMI = body mass index; HDL = high-density lipoprotein.

events.

3.4. Combination of anthropometric measures

Comparisons of discrimination abilities for models based on anthropometric measures, individually and combined, with models including serum total cholesterol are shown in Table 4. In the younger age group (<50 years), the model including cholesterol had superior discrimination for MACE than that including BMI, but not when compared with other measures of body composition. Conversely, in individuals ≥ 50 years the model with cholesterol was superior to all models containing anthropometric measures, whether single or multiple. We found no differences in discrimination ability between models including cholesterol and anthropometric measures for CVM and ACM.

4. Discussion

In this large, multinational cohort study, we found that BMI, WHR, EFM, and total cholesterol were all independently associated with MACE and resulted in appropriate risk reclassification when added to sex, age, smoking status, and systolic blood pressure. However, only total cholesterol was able to improve discrimination ability. The prediction model with cholesterol was not superior to models containing anthropometric measures (except BMI) among younger individuals, while in older subjects the model with cholesterol was superior to all models containing anthropometric measures, both individually and in combination.

Although the association with CVD may be as strong for anthropometric measurements as it is for lipid profiles, the added contribution of these markers of body composition to overall discrimination ability is less well studied (Gaziano et al., 2008; Hubert et al., 1983; Lapidus et al., 1984; Yan et al., 2006; Clark, 2003; Song et al., 2013). The National Health and Nutrition Examination (NHANES) investigators found a non-laboratory-based model (with BMI) to predict CV events as accurately as a laboratory-based model (with total cholesterol) among 6186 individuals without a history of CVD or cancer (Gaziano et al., 2008). However, the role of BMI as the preferred anthropometric measure has been debated as waist circumference, WHR and waist-height ratio (i.e., surrogate markers of central adiposity) may better predict and discriminate prevalent cardiometabolic abnormalities and incident CVD (Lapidus et al., 1984; Song et al., 2013; Blair et al., 1984; Kaplan, 1989; Donini et al., 2013; Tybor et al., 2011; Adab et al., 2018; Molarius et al., 1999). This was indeed our rationale for exploring the utility of EFM and for combining these different measures. Another measure of body composition that may be considered for mortality prediction is A Body Shape Index (ABSI) that incorporates waist circumference, height as well as BMI, particularly because of its low correlation with either of these three variables (Krakauer et al., 2012; Krakauer and Krakauer, 2016; Dhana et al., 2015; Christakoudi et al., 2020). However, its added predictive value may be limited (Dhana et al., 2016).

While BMI, WHR, and EFM were all associated with MACE, they did not improve risk prediction, nor did the predictive capability of models including each of them differ from each other. Moreover, among study participants ≥ 50 years of age, total cholesterol was superior to all anthropometric measures, even when the latter were used in combination. The ability of BMI to predict CVD does in fact appear to decline with age (Clark, 1998; Flegal et al., 2005; Willett et al., 2005; Cox et al., 1998; Dobbelsteyn et al., 2001). This agrees with the notion that it may be inappropriate to rely solely on traditional risk factors in older persons in whom there is greater room to improve discrimination ability using laboratory findings, including more novel circulating biomarkers (Pareek et al., 2017; Frary et al., 2020). A possible explanation may be that the atherosclerotic process starts early in life, enabling more accurate primary CV risk assessment in young individuals, while in older individuals, selection bias comes into play after exclusion of those with established CVD. Another explanation may be that anthropometry is the initiating event for the metabolic syndrome (Cameron et al., 2012).

CV risk assessment in the primary preventive setting is crucial for directing both non-pharmacological and pharmacological interventions, with the ultimate goals of preventing premature death and increasing quality of life (Piepoli et al., 2016; Grundy et al., 2019). Although traditional CV risk factors are easily assessed in high-income countries, this may not always be the case in low-resource settings. Several non-laboratory-based risk equations have been suggested but often rely on numerous variables and may be difficult to use in daily clinical practice (McGorrian et al., 2011). We found that very simple risk models mimicked the discrimination ability of SCORE markers among individuals < 50 years of age. However, their true clinical utility remains unproven until a randomized controlled trial of risk score guided preventive treatment has been undertaken.

4.1. Strengths and limitations

Our study is particularly notable for its large, well-characterized and versatile cohort of both men and women across a wide age range and nationalities. Detailed information was collected on each participant in

Table 2
Adjusted hazard ratio, discrimination, and continuous net reclassification of events for each anthropometric measure and total serum cholesterol in subjects younger or older than 50 years.

	Major adverse cardiovascular events		Cardiovascular mortality		All-cause mortality	
	Age < 50 years	Age ≥ 50 years	Age < 50 years	Age ≥ 50 years	Age < 50 years	Age ≥ 50 years
Body mass index (n = 67,637 < 50 years; n = 41,872 ≥ 50 years)						
Adj. HR per one SD (95% CI)	$1.15^{<0.001}$ (1.08–1.23)	$1.09^{<0.001}$ (1.05–1.13)	$1.17^{0.05}$ (1.00–1.36)	$1.05^{0.15}$ (0.98–1.13)	$0.98^{0.58}$ (0.92–1.05)	$0.94^{<0.001}$ (0.91–0.98)
AUC_{ROC} (SCORE variables including BMI vs. SCORE variables)*	0.825 vs. $0.824^{0.21}$	0.711 vs. $0.710^{0.19}$	0.841 vs. $0.840^{0.57}$	0.777 vs. $0.777^{0.71}$	0.732 vs. $0.732^{0.66}$	0.744 vs. $0.744^{0.64}$
cNRI (95% CI) (BMI added to SCORE variables)	0.216 (0.149 to 0.282)	0.066 (0.027 to 0.102)	0.163 (-0.179 to 0.334)	0.039 (-0.086 to 0.119)	−0.051 (-0.084 to 0.084)	0.018 (-0.015 to 0.056)
Waist-hip ratio) (n = 27,499 < 50 years; n = 24,689 ≥ 50 years)						
Adj. HR per one SD (95% CI)	$1.28^{0.002}$ (1.09–1.49)	$1.17^{<0.001}$ (1.10–1.25)	$1.20^{0.36}$ (0.81–1.80)	$1.19^{0.02}$ (1.03–1.37)	$1.11^{0.16}$ (0.96–1.29)	$1.11^{<0.001}$ (1.04–1.19)
AUC_{ROC} (SCORE variables including WHR vs. SCORE variables)*	0.797 vs. $0.793^{0.08}$	0.702 vs. $0.701^{0.35}$	0.798 vs. $0.784^{0.19}$	0.756 vs. $0.755^{0.75}$	0.735 vs. $0.734^{0.23}$	0.735 vs. $0.735^{0.17}$
cNRI (95% CI) (WHR added to SCORE variables)	0.184 (0.061 to 0.291)	0.073 (0.030 to 0.122)	0.118 (-0.363 to 0.381)	0.096 (-0.103 to 0.193)	0.047 (-0.126 to 0.148)	0.078 (0.004 to 0.131)
Estimated fat mass (n = 27,509 < 50 years; n = 24,708 ≥ 50 years)						
Adj. HR per one SD (95% CI)	$1.17^{0.003}$ (1.06–1.30)	$1.11^{<0.001}$ (1.06–1.16)	$1.17^{0.26}$ (0.89–1.53)	$1.12^{0.04}$ (1.01–1.25)	$1.01^{0.85}$ (0.91–1.13)	$0.96^{0.10}$ (0.91–1.01)
AUC_{ROC} (SCORE variables including EFM vs. SCORE variables)*	0.797 vs. $0.793^{0.15}$	0.702 vs. $0.701^{0.35}$	0.794 vs. $0.784^{0.37}$	0.757 vs. $0.756^{0.62}$	0.734 vs. $0.734^{0.41}$	0.735 vs. $0.735^{0.73}$
cNRI (95% CI) (EFM added to SCORE variables)	0.181 (0.054 to 0.298)	0.064 (0.019 to 0.112)	0.002 (-0.359 to 0.412)	0.124 (-0.032 to 0.241)	−0.142 (-0.134 to 0.109)	−0.012 (-0.063 to 0.057)
Total serum cholesterol (n = 67,637 < 50 years; n = 41,872 ≥ 50 years)						
Adj. HR per one SD (95% CI)	$1.51^{<0.001}$ (1.43–1.59)	$1.21^{<0.001}$ (1.17–1.25)	$1.32^{<0.001}$ (1.14–1.53)	$1.09^{0.01}$ (1.02–1.17)	$1.03^{0.42}$ (0.96–1.10)	$0.93^{<0.001}$ (0.90–0.96)
AUC_{ROC} (SCORE variables including cholesterol vs. SCORE variables)*	0.836 vs. $0.824^{<0.001}$	0.721 vs. $0.710^{<0.001}$	0.843 vs. $0.840^{0.19}$	0.779 vs. $0.777^{0.15}$	0.732 vs. $0.732^{0.80}$	0.745 vs. $0.744^{0.29}$
cNRI (95% CI) (cholesterol added to SCORE variables)	0.362 (0.293 to 0.422)	0.228 (0.191 to 0.264)	0.219 (0.049 to 0.367)	0.166 (0.097 to 0.241)	−0.027 (-0.083 to 0.083)	0.045 (0.011 to 0.075)

Hazard ratios are adjusted for country, age, sex, smoking, and systolic blood pressure. Superscripts represent P-values.
*Superscripts represent P-values for comparisons of AUC_{ROC} for models comprising SCORE variables (except total cholesterol) plus body mass index, waist-hip ratio, estimated fat mass, or total cholesterol with a model comprising SCORE variables (except total cholesterol) alone.
The continuous net reclassification improvement was calculated for body mass index, waist-hip ratio, estimated fat mass, or total cholesterol on top of SCORE variables (except total cholesterol).
Abbreviations: AUC_{ROC} = area under the receiver operating characteristic curve; BMI = body mass index; CI = confidence interval; cNRI = continuous (category-free) net reclassification improvement; EFM = estimated fat mass; HR = hazard ratio; SCORE = Systematic COronary Risk Evaluation; WHR = waist-hip ratio.

Table 3
Interaction analyses in predicting events.

	Interaction for age category (<50 and ≥ 50 years)			Interaction for sex		
	Major adverse cardiovascular events	Cardiovascular mortality	All-cause mortality	Major adverse cardiovascular events	Cardiovascular mortality	All-cause mortality
Body mass index	<0.001	<0.001	<0.001	0.62	<0.001	<0.001
Waist-hip ratio	<0.001	0.07	<0.001	0.48	0.44	<0.001
Estimated fat mass	0.003	0.13	0.02	0.20	0.16	0.001
Serum total cholesterol	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

P-value for interaction between either age category or sex with each anthropometric measure or serum total cholesterol, for the prediction of each event type.

a standardized fashion. Endpoint validation was harmonized by using the MONICA criteria or other similar diagnostic criteria.

A major limitation was the lack of information on changes in modifiable risk factors during follow-up, potentially resulting in regression dilution (Clarke et al., 2002), as well as the inability to take into account life-course differences in the effects of BMI (Richardson et al., 2020). This included potential initiation of antihypertensives and lipid lowering drugs, especially during later stages of follow-up, and the inability to examine the effects of temporal body weight fluctuations which are inherently associated with higher CV risk (Bangalore et al., 2017). Second, we excluded participants with known diabetes or those receiving antihypertensive treatment at baseline because such treatment influences the risk factors used in our risk models. This may attenuate the prognostic influence of BP and perhaps amplify the influence of the other risk factors like body composition; however, because the number of excluded individuals was not insignificant, this may have introduced a selection bias. The same could be considered for subjects with missing baseline information although that was likely a random occurrence. Third, the equation for EFM is generated on US data and may not function properly in European populations or in low-income countries. In addition, although use of bioimpedance analysis would have provided a more precise assessment of fat mass rather than an equation, the inclusion of such elaborate methods would have defied the purpose of our study, including the fact that our aim was simply to predict CVD, not to provide a precise estimate of fat mass. Nevertheless, there may be some discrepancies in outcome prediction with estimated versus measured fat mass (Haber et al., 2021). Fourth, WHR and EFM were only available for – half of the study participants and the further stratification for age may

Table 4
Comparison of discrimination abilities for prediction models including anthropometric measures, individually and combined, with models including serum total cholesterol.

Endpoint	Serum total cholesterol	Body mass index	Waist-hip ratio	Estimated fat mass	Body mass index + waist-hip ratio	Body mass index + estimated fat mass	Waist-hip ratio + estimated fat mass	Body mass index + waist-hip ratio + estimated fat mas
	Age < 50 years							
Major adverse cardiovascular events	0.836 0.805*	$0.825^{<0.001}$	$0.797^{0.07}$	$0.797^{0.05}$	$0.798^{0.10}$	$0.797^{0.08}$	$0.798^{0.08}$	$0.799^{0.14}$
Cardiovascular mortality	0.843 0.789*	$0.841^{0.46}$	$0.798^{0.44}$	$0.794^{0.66}$	$0.796^{0.57}$	$0.801^{0.37}$	$0.796^{0.53}$	$0.805^{0.24}$
All-cause mortality	0.732 0.734*	$0.732^{0.85}$	$0.735^{0.24}$	$0.734^{0.42}$	$0.735^{0.36}$	$0.734^{0.53}$	$0.735^{0.31}$	$0.735^{0.36}$
	Age ≥ 50 years							
Major adverse cardiovascular events	0.721 0.709*	$0.712^{<0.001}$	$0.702^{0.001}$	$0.702^{0.001}$	$0.703^{0.005}$	$0.703^{0.007}$	$0.702^{0.002}$	$0.703^{0.01}$
Cardiovascular mortality	0.779 0.752*	$0.777^{0.20}$	$0.756^{0.17}$	$0.757^{0.17}$	$0.756^{0.20}$	$0.757^{0.18}$	$0.756^{0.19}$	$0.756^{0.19}$
All-cause mortality	0.745 0.735*	$0.744^{0.27}$	$0.735^{0.99}$	$0.735^{0.39}$	$0.736^{0.69}$	$0.736^{0.96}$	$0.735^{0.79}$	$0.736^{0.64}$

Superscripts represent P-values for comparisons of AUC_{ROC} for models comprising SCORE variables (except total cholesterol) plus body mass index, waist-hip ratio, estimated fat mass, or total cholesterol with a model comprising SCORE variables (except total cholesterol) alone.
$TwoAUC_{ROC}$ are reported for models including serum total cholesterol. The first one is for the complete study population used for comparison with BMI models. The second one marked with an asterisk (*) is for individuals in whom waist-hip ratio and estimated fat mass were available used for comparison with all other models than the BMI models.

have reduced the power to detect predictive differences between risk factors. Fifth, we compared total cholesterol with anthropometric measures for CV risk stratification. However, many modern prediction equations indirectly use low-density lipoprotein cholesterol by integrating total cholesterol and HDL-cholesterol since it is a better risk factor for atherosclerosis (Grundy et al., 2019). Nevertheless, our predefined purpose was to test our hypothesis using the SCORE model variables even though this may leave room for model improvement in our specific cohort (DC et al., 2013). Furthermore, BMI is considered a good risk factor for diabetes, but not necessarily for atherosclerosis since it is a complex metabolic parameter that may show a U-shaped association with CV disease (Narayan et al., 2007). Finally, our findings were based on mostly white Europeans from high-income countries and may not be applicable to other ethnicities and settings.

5. Conclusion

Although BMI, WHR and EFM were all independently associated with MACE, none of them were able to improve discrimination ability when added to sex, age, smoking status, systolic blood pressure and serum total-cholesterol. Based on overall model performance, there was a potential role for replacing total cholesterol with anthropometric measures for MACE prediction among individuals < 50 years when laboratory measurements are unavailable, but not among those ≥ 50 years.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: VS has received honoraria from Novo Nordisk and Sanofi for consultations. He also has ongoing research collaboration with Bayer Ltd. (All unrelated to the present study). SSg has received speakers and consultant honoraria from Actelion Ltd. MHO has from 2013-2018 received a part time clinical research grant from the Novo Nordic Foundation. MP has the followings relationships – Advisory Board and Speaking Honoraria: AstraZeneca; Speaking Honoraria: Bayer, Boehringer Ingelheim.

Acknowledgements

The MORGAM Project has received funding from EU projects MORGAM (Biomed, BMH4-CT98-3183), GenomEUtwin (FP5, QLG2-CT-2002-01254), ENGAGE (FP7, HEALTH-F4-2007-201413), CHANCES (FP7, HEALTH-F3-2010-242244), BiomarCaRE (FP7, HEALTH-F2-2011-278913), euCanSHare (Horizon 2020, No. 825903) and AFFECT-EU (Horizon 2020, No. 847770); and Medical Research Council, London (G0601463, No. 80983: Biomarkers in the MORGAM Populations). This has supported central coordination, workshops and part of the activities of the MORGAM Data Centre, the MORGAM Laboratories and the MORGAM Participating Centres.

Funding

VS was supported by the Finnish Foundation for Cardiovascular Research. SSg was supported by the Swedish Heart and Lung foundation and by the County council of Västertotten. MP has the followings relationships – Advisory Board and Speaking Honoraria: AstraZeneca; Speaking Honoraria: Bayer, Boehringer Ingelheim.

Appendix A

Sites and key personnel of contributing MORGAM Centers

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Lille, Institut Pasteur de Lille, UMR1167, Epidemiology and Public Health Department, F-59000 Lille, France: P. Amouyel

Former National Coordinating Centre, National Institute of Health and Medical Research (U258), Paris: P. Ducimetière (national coordinator), A. Bingham;

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PRIME/Toulouse, Department of Epidemiology, Faculty of Medicine, Toulouse-

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ESTHER, German Cancer Research Center & Network Aging Research, University of Heidelberg, Heidelberg: H. Brenner (principal investigator), B. Schöttker;

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