ARTICLE

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Epidemiology and Population Health

Relative fat mass and prediction of incident atrial fibrillation, heart failure and coronary artery disease in the general population

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BACKGROUND: Relative fat mass (RFM) is an emerging marker of obesity that estimates body fat percentage using a sex-specific formula containing height and waist circumference (WC). We studied the association of RFM with incident atrial fibrillation (AF), heart failure (HF), and coronary artery disease (CAD) and explored RFM cutoffs for cardiovascular disease (CVD) prediction.
METHODS: We studied 95,003 participants (age 45 ± 13 years, 59% women) without prevalent AF, HF or CAD from the population-based Lifelines study. Outcomes were ascertained using electrocardiography and self-reported questionnaire data. We used logistic regression to study the association of RFM with individual outcomes and a composite outcome (incident AF, HF, and/or CAD). Multivariable models were adjusted for components of the SCORE risk model (age, sex, systolic blood pressure, cholesterol, and smoking). Optimal cutoffs were determined using the Youden index.
RESULTS: During a median follow-up of 3.8 (3.0–4.6) years, 224 (0.2%) participants developed AF, 1003 (1.1%) HF and 657 (0.7%) CAD. After multivariable adjustment, RFM was significantly associated with all outcomes (standardised OR 1.26, 95% CI 1.18–1.34 for the composite outcome). Optimal RFM cutoffs (≥26 for men, ≥38 for women) were lower than previously proposed RFM cutoffs (≥30 for men, ≥40 for women). In general, overall discriminative ability of RFM and its cutoffs was at least similar (in women) or better (in men) compared to BMI and WC. Since RFM was substantially correlated with age, we additionally determined age-specific cutoffs, which ranged from 23 to 27 in men and 33 to 43 in women.
CONCLUSIONS: RFM is associated with incident AF, HF, and CAD and may be used as a simple and intuitive marker of obesity and cardiovascular risk in the general population. This study provides potential RFM cutoffs for CVD prediction that may be used by future studies or preventive strategies targeting obesity and cardiovascular risk.

International Journal of Obesity (2023) 47:1256–1262; https://doi.org/10.1038/s41366-023-01380-8

INTRODUCTION

Obesity, defined as an excess of body fat, is a major risk factor for various types of cardiovascular disease (CVD), including atrial fibrillation (AF), heart failure (HF), and coronary artery disease (CAD) [1]. In the last few decades, the prevalence of overweight and obesity has substantially increased in both men and women across the world, a development sometimes referred to as the obesity epidemic [2]. Consequently, there is an increasing need for accurate classification of obesity for the purpose of cardiovascular risk prediction and preventive strategies.

Body mass index (BMI) has traditionally been used to classify obesity. However, BMI has its shortcomings as a measure of body fat, since it does not differentiate between fat and lean mass and may thus lead to misclassification of individuals with or without obesity [3–5]. Recently, relative fat mass (RFM) was proposed as a novel marker of obesity. RFM, which estimates total body fat percentage, is calculated using a sex-specific formula that includes the ratio of height and waist circumference (WC). The RFM formula was developed as part of a study that specifically aimed to find a more accurate marker of body fat compared to BMI. In a systematic analysis of 365 potential anthropometric measures, RFM was found to be the most suitable measure in terms of accuracy and ease of use [5]. Subsequent studies have demonstrated that RFM is associated with incident hypertension, type 2 diabetes, and heart failure, as well as all-cause mortality [6–10]. Nevertheless, the association between RFM and the general risk of CVD remains underexplored. Furthermore, while RFM cutoffs for the diagnosis of obesity have previously been defined based on

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Received: 10 March 2023 Revised: 24 August 2023 Accepted: 30 August 2023
Published online: 9 September 2023

associations with mortality [8], these cutoffs have not been tested for the prediction of CVD and require additional validation.

Therefore, we aimed to study the association of RFM with incident AF, HF, and CAD and to explore potential RFM cutoffs for CVD prediction in the general population.

METHODS

Study population

The study was performed with data from the Lifelines Cohort Study (www.lifelines.nl), which has been extensively described elsewhere [11]. In short, Lifelines is a multidisciplinary, prospective population-based cohort study examining the health and health-related behaviours of 167,729 participants living in the North of The Netherlands in a unique three generation design. It employs a broad range of investigative procedures for the assessment of the biomedical, socio-demographic, behavioural, physical, and psychological factors which contribute to health and disease in the general population, with a special focus on multimorbidity and complex genetics [11]. Participants were recruited from 2006 to 2013, initially by participating general practitioners, who invited all patients aged 25 to 50 years from their own practices. Participants were then encouraged to invite family members to participate in Lifelines as well. People who were not invited could also participate by registering themselves through the Lifelines website. The Lifelines study was approved by Medical Ethical Committee of the University Medical Center Groningen and performed in agreement with the Declaration of Helsinki, and all participants provided written informed consent [11, 12].

Participants were asked to complete extensive questionnaires about a wide range of health-related topics at home. Next, they were invited for an on-site visit, which included anthropometry and blood pressure measurements, electrocardiography (ECG), pulmonary function testing, and collection of blood, urine, and genetics samples. Additionally, current medication use was recorded. With a planned follow-up of at least 30 years, the Lifelines study is currently still ongoing. Participants are sent follow-up questionnaires approximately every 1.5 years and are invited for on-site follow-up visits approximately every 5 years [11, 12].

For the present study, we used data from the baseline visit and second on-site visit (visits 1A and 2A), as well as the baseline questionnaire and first, second, and third follow-up questionnaire (questionnaires 1A, 1B, 1C, and 2A). We included all participants with available ECG data at baseline and the second visit ($n = 99{,}003$). We excluded participants with prevalent AF, HF, and/or CAD ($n = 2625$), missing anthropometric measurements ($n = 27$), missing baseline questionnaire data ($n = 173$), or missing follow-up questionnaire data ($n = 1175$), leaving 95,003 participants available for analysis.

Obesity measures and cutoff definitions

RFM was calculated using a sex-specific formula: *64–20 * height (in cm) / waist circumference (in cm)* for men, and *76–20 * height (in cm) / waist circumference (in cm)* for women [5]. BMI was defined as weight (in kg) divided by the square of height (in m).

For analyses with categorical obesity measures, we used previously defined cutoffs as well as optimal cutoffs based on our data. For RFM, previously defined cutoffs for obesity were ≥30 for men and ≥40 for women [8]. For BMI, previously defined cutoffs for overweight and obesity were ≥25 kg/m^2 and ≥30 kg/m^2 for men and women [13]. For WC, cutoffs for overweight and obesity were ≥94 cm and ≥102 cm for men, and ≥82 cm and ≥88 cm for women, respectively [13]. Optimal cutoffs, as described in more detail below, were determined using the Youden index [14].

Outcomes and risk factors

Three outcomes of interest were defined: incident atrial fibrillation (AF), incident heart failure (HF), and incident coronary artery disease (CAD). These outcomes were ascertained using electrocardiography (for AF and CAD) and self-reported questionnaire data (for HF and CAD).

AF was diagnosed using 12-lead ECG data from the baseline visit and second visit. AF was detected by an automated interpretation algorithm (Welch Allyn DT100) and confirmed by a cardiologist [15, 16]. Incident AF was considered present if participants did not have AF on their baseline ECG, but did have AF on their ECG at the second visit.

Since echocardiography and natriuretic peptide measurements were not performed in Lifelines, the diagnosis of HF was based on self-reported data from the baseline questionnaire and follow-up questionnaires. Incident HF was considered present if participants did not self-report HF at baseline, but did report newly diagnosed HF in any of the follow-up questionnaires.

For the diagnosis of CAD, a combination of ECG data and self-report was used. Prior CAD was considered present if participants self-reported myocardial infarction (MI), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) in the baseline questionnaire, or if they had evidence of MI on their baseline ECG. Incident CAD was considered present if participants without prior CAD self-reported MI, PCI, or CABG in any of the follow-up questionnaires, or if they had evidence of MI on their ECG at the second visit. The identification of MI on Lifelines ECGs has previously been reported in detail [17].

Additionally, we studied a composite outcome, which was considered present if participants developed at least one of the three outcomes of interest (incident AF, HF, and/or CAD).

Cardiovascular risk factors were defined using previously described definitions for Lifelines [18]. Like AF, left ventricular hypertrophy (LVH) was assessed using the automated ECG interpretation algorithm and confirmed by a cardiologist, using previously described criteria [16].

Statistical analysis

We used logistic regression to study the association of RFM with incident AF, incident HF, incident CAD, and a composite outcome (incident AF, HF, and/or CAD). For each outcome, we built three models: (1) an unadjusted model, (2) a model adjusted for age and sex, and (3) a multivariable model adjusted for components of the SCORE risk model (age, sex, systolic blood pressure, total cholesterol/HDL-cholesterol ratio, and smoking), which is a widely used instrument for the prediction of cardiovascular risk in the general population [19]. As a sensitivity analysis, the multivariable model was additionally adjusted for diabetes and LVH. The logistic regression analyses were similarly performed for BMI and WC. All odds ratios for continuous obesity measures were standardised and thus represent the increase in risk per standard deviation increase of the obesity measure. Standardisation of obesity measures was performed separately for men and women, in order to prevent multicollinearity with sex. In order to check for non-linear associations between RFM and incident CVD, we additionally performed analyses in which RFM was divided into quintiles. Furthermore, we performed sex-stratified and BMI-stratified analyses for the composite endpoint to identify potential differences between men and women or between BMI categories. Interactions of RFM with sex and BMI were formally assessed in the multivariable model for the composite endpoint.

Next, we explored potential cutoffs for CVD prediction in men and women. We calculated the Youden index to assess overall discriminative ability of various cutoffs [14]. The Youden index is calculated as *sensitivity + specificity − 1* and ranges from 0 (no discriminative ability) to 1 (perfect discriminative ability) [14]. For each obesity measure and for men and women separately, the cutoff with the highest Youden index (i.e. the cutoff with the highest combined sensitivity and specificity) was selected as the optimal cutoff. Optimal RFM cutoffs were compared to previously defined RFM cutoffs in terms of overall predictive performance (as indicated by the Youden index) and in terms of sensitivity and specificity. Similarly, we compared the different RFM cutoffs to previously defined and optimal cutoffs for BMI and WC. Since RFM was found to be substantially correlated with age, we also determined age-specific optimal cutoffs for RFM. Statistical analyses were performed with SPSS (version 28).

RESULTS

Clinical characteristics of the study population

Mean age of the included participants was 45.3 ± 12.5 years, and 59% were women. Clinical characteristics of men and women are presented in Table 1. Men had a slightly higher prevalence of hypertension (31% vs. 21%), hypercholesterolaemia (16% vs. 13%), and smoking (21% vs. 18%) compared to women. By definition of the RFM formula, men had a lower mean RFM than women (25.1 ± 4.4 vs. 36.2 ± 5.5). Mean BMI was higher in men than in women (26.3 ± 3.5 vs. 25.7 ± 4.6). Men also had a larger WC (95.0 ± 10.5 vs. 86.6 ± 12.0) than women.

Overall, 62% of men (49% overweight, 13% obesity) and 49% of women (34% overweight, 16% obesity) had a BMI ≥25 kg/m^2. Using previously defined RFM cutoffs (≥30 for men, ≥40 for women), 12% of men and 25% of women fell into the high RFM

Table 1. Participant characteristics.

Characteristics	Men ($n = 38,604$)	Women ($n = 56,399$)
Age (years)	45.7 ± 12.5	45.0 ± 12.5
Systolic blood pressure (mmHg)	130.7 ± 13.8	122.3 ± 15.1
Diastolic blood pressure (mmHg)	76.8 ± 9.2	71.9 ± 8.7
Hypertension	11,943 (31%)	11,920 (21%)
Total cholesterol (mmol/l)	5.2 ± 1.0	5.1 ± 1.0
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.6 ± 0.4
LDL cholesterol (mmol/l)	3.4 ± 0.9	3.1 ± 0.9
Hypercholesterolaemia	6033 (16%)	7337 (13%)
Smoking	8111 (21%)	9991 (18%)
Diabetes	1190 (3%)	1389 (2%)
Signs of LVH on ECG	310 (0.8%)	224 (0.4%)
Anthropometric indices		
Body mass index (kg/m^2)	26.3 ± 3.5	25.7 ± 4.6
Underweight (BMI <18.5 kg/m^2)	115 (0.3%)	527 (0.9%)
Normal weight (BMI 18.5–25 kg/m^2)	14,363 (37%)	28,040 (50%)
Overweight (BMI 25–30 kg/m^2)	18,960 (49%)	19,084 (34%)
Obesity (BMI >30 kg/m^2)	5166 (13%)	8748 (16%)
Waist circumference (cm)	95.0 ± 10.5	86.6 ± 12.0
Normal WC (<94 in men, <80 in women)	18,092 (47%)	17,215 (31%)
High WC (94–102 in men, 80–88 in women)	11,229 (29%)	15,450 (27%)
Very high WC (≥102 in men, ≥88 in women)	9283 (24%)	23,734 (42%)
Relative fat mass	25.1 ± 4.4	36.2 ± 5.5
High RFM (≥30 in men, ≥40 in women)	4718 (12%)	21,302 (25%)

Data presented as mean ± standard deviation or count (%). Categories of BMI, WC and RFM are based on previously defined cutoffs.
BMI body mass index, *ECG* electrocardiography, *LVH* left ventricular hypertrophy, *RFM* relative fat mass, *WC* waist circumference.

category. Using established WC cutoffs, more women than men fell into the very high WC category (24% of men vs. 42% of women).

Clinical characteristics per quintile of RFM are presented in Supplementary Table S1. Participants in the higher quintiles were older and more often had hypertension, hypercholesterolaemia and diabetes than those in the lower quintiles.

Incident cardiovascular disease

During a median follow-up duration of 3.8 (3.0 to 4.6) years, 966 men (2.5%) and 717 women (1.3%) developed incident AF, HF, and/or CAD. Of these, HF occurred most often (1.4% of men, 0.8% of women), followed by CAD (1.1% of men, 0.4% of women), and AF (0.4% of men, 0.1% of women).

Association of relative fat mass with incident cardiovascular disease

Unadjusted, RFM was significantly associated with incident AF (standardised OR 2.21, 95% CI 1.92–2.54), HF (OR 1.73, 95% CI 1.62–1.85), and CAD (OR 1.75, 95% CI 1.62–1.90), as well as the composite outcome (OR 1.77, 95% CI 1.68 to 1.86) (Table 2). After adjustment for age and sex, the association of RFM with all outcomes was substantially attenuated, but remained significant (Table 2). After further adjustment for components of the SCORE risk model, RFM remained significantly associated with incident AF (OR 1.58, 95% CI 1.33–1.87), HF (OR 1.29, 95% CI 1.20–1.40), and CAD (OR 1.19, 95% CI 1.08–1.31), as well as the composite outcome (OR 1.26, 95% CI 1.19–1.34) (Table 2).

The association of subsequent RFM quintiles with incident CVD increased in a mostly linear fashion in both men and women (Supplementary Table S2). Men in the highest quintile of RFM had a 105% higher odds of the composite outcome compared to men in the lowest quintile. Women in the highest quintile of RFM had an 89% higher odds of the composite outcome compared to men in the lowest quintile.

Sex-stratified analyses for the composite outcome demonstrated very similar results for men and women (Fig. 1 and Supplementary Fig. S1). When stratified by BMI category, multivariable-adjusted results showed that RFM was significantly associated with incident CVD in participants with BMI <25 kg/m^2 and BMI 25–30 kg/m^2, but not in participants with BMI ≥30 kg/m^2 (Supplementary Table S3). Formal interaction tests revealed no significant interactions of RFM with sex ($p = 0.340$) or BMI ($p = 0.410$).

Comparison with established obesity measures

In general, RFM showed stronger unadjusted associations with incident CVD than BMI and WC (Table 2). Furthermore, the attenuation seen after age-adjustment was more pronounced for RFM than for BMI and WC (Fig. 1 and Supplementary Fig. S1). This may be explained by the fact that RFM was more strongly correlated with age ($r = 0.354$, 95% CI 0.349–0.360) than BMI ($r = 0.175$, 95% CI 0.169–0.181) and WC ($r = 0.265$, 95% CI 0.259–0.271). After multivariable adjustment, the associations of all RFM, BMI, and WC with incident CVD were largely similar (Table 2). Additional adjustment for diabetes and LVH delivered similar results (results not shown).

Cutoffs

The predictive performance of different RFM cutoffs is displayed in Supplementary Table S4. Based on the Youden index, the optimal cutoff for RFM was ≥26 in men (sensitivity 68% and specificity 58%) and ≥38 in women (sensitivity 60% and specificity 63%). More participants fell into the high RFM category with the optimal cutoffs (43% in men, 38% in women) compared to the previously defined cutoffs (12% in men, 25% in women). In men, optimal RFM cutoffs had better overall discriminative ability compared to previously defined cutoffs (Youden index 0.26, 95% CI 0.23–0.29 vs. 0.12, 95% CI 0.09–0.14). In women, the difference between optimal and previously defined cutoffs was less pronounced (Youden index 0.23, 95% CI 0.19–0.26 vs. 0.20, 95% CI 0.17–0.24). Optimal RFM cutoffs had higher sensitivity, but lower specificity than previously defined RFM cutoffs (Table 3 and Supplementary Table S4).

Overall, the optimal RFM cutoffs had slightly better predictive performance compared to both previously defined and optimal cutoffs for BMI and WC, particularly in men (Table 3).

Since the association between RFM and incident CVD was particularly attenuated by age, we additionally explored age-specific cutoffs for RFM (Table 4). The optimal cutoff increased with age in both men (from 23 for age <40 years to 27 for age ≥70 years) and women (from 33 for age <40 years to 43 for age ≥70 years).

DISCUSSION

In this study, we demonstrated that RFM is associated with incident AF, HF, and CAD in participants from the large population-based Lifelines cohort study. Based on our data, we

Table 2. Association of relative fat mass, body mass index, and waist circumference with incident cardiovascular disease in the total study population.

Outcome	Odds ratio (95% confidence interval)		
	Unadjusted	Age- and sex-adjusted	Multivariable-adjusted
Atrial fibrillation (224 events, crude incidence 0.2%)			
RFM	2.21 (1.92–2.54)	1.56 (1.33–1.83)	1.58 (1.33–1.87)
BMI	1.54 (1.40–1.70)	1.52 (1.36–1.70)	1.53 (1.36–1.73)
WC	1.82 (1.64–2.01)	1.62 (1.43–1.84)	1.65 (1.45–1.87)
Heart failure (1003 events, crude incidence 1.1%)			
RFM	1.73 (1.62–1.85)	1.34 (1.25–1.44)	1.29 (1.20–1.40)
BMI	1.36 (1.29–1.43)	1.28 (1.20–1.35)	1.24 (1.16–1.32)
WC	1.52 (1.44–1.61)	1.34 (1.26–1.42)	1.30 (1.21–1.38)
Coronary artery disease (657 events, crude incidence 0.7%)			
RFM	1.75 (1.62–1.90)	1.37 (1.26–1.50)	1.19 (1.08–1.31)
BMI	1.30 (1.22–1.39)	1.22 (1.13–1.31)	1.09 (1.01–1.18)
WC	1.44 (1.35–1.54)	1.25 (1.16–1.35)	1.10 (1.02–1.20)
Composite outcome (1683 events, crude incidence 1.8%)			
RFM	1.77 (1.68–1.86)	1.37 (1.29–1.44)	1.26 (1.19–1.34)
BMI	1.36 (1.31–1.42)	1.28 (1.22–1.34)	1.20 (1.15–1.26)
WC	1.52 (1.46–1.58)	1.33 (1.26–1.39)	1.24 (1.18–1.31)

Odds ratios represent the association of each obesity measure with incident atrial fibrillation, heart failure, coronary artery disease, and the composite outcome in the total study population. Odds ratios are standardised and represent the increase in risk per standard deviation increase of relative fat mass. The multivariable model was adjusted for the components of the SCORE risk model (age, systolic blood pressure, total cholesterol/HDL-cholesterol ratio and smoking).
BMI body mass index *RFM* relative fat mass, *WC* waist circumference.

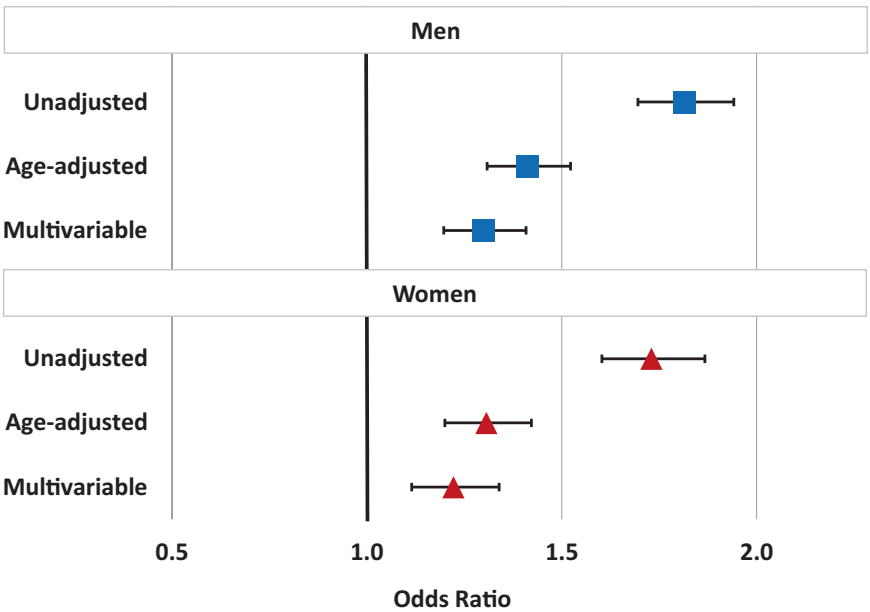

Fig. 1 Association of relative fat mass with incident cardiovascular disease in men and women. Odds ratios represent the association of relative fat mass with the composite outcome (incident atrial fibrillation, heart failure, and/or coronary artery disease). Odds ratios are standardised and represent the increase in risk per standard deviation increase of relative fat mass. The multivariable model was adjusted for the components of the SCORE risk model (age, systolic blood pressure, total cholesterol/HDL-cholesterol ratio and smoking).

determined potential cutoffs for RFM, which may be used to classify obesity and predict CVD in the general population.

Currently, BMI is the most frequently used marker for the classification of overweight and obesity. While BMI is easy to measure and broadly understood, it has some important limitations when it comes to classifying overweight and obesity. BMI does not differentiate between fat and lean mass and may therefore be elevated in individuals with normal body fat percentage, or vice versa [3, 5]. WC, as well as other measures of abdominal adiposity, have been advocated as potentially superior measures of obesity, but have failed to consistently show superiority over BMI for the prediction of CVD [4, 20, 21].

Table 3. Predictive performance of previously defined and optimal cutoffs of relative fat mass, body mass index and waist circumference.

Measure	Cutoff	Cutoff type	Prevalence	Youden index (95% CI)	Sensitivity	Specificity	AUC (95% CI)
Men ($n = 38,604$, crude incidence 2.5%)							
RFM	≥26	Optimal	43%	0.26 (0.23–0.29)	68%	58%	0.664 (0.648–0.680)
	≥30	PD	12%	0.12 (0.09–0.14)	24%	88%	
BMI (kg/m^2)	≥25	Optimal, PD	62%	0.16 (0.14–0.19)	78%	38%	0.610 (0.593–0.627)
	≥30	PD	13%	0.09 (0.07–0.12)	22%	87%	
WC (cm)	≥94	Optimal, PD	53%	0.20 (0.18–0.23)	73%	47%	0.642 (0.626–0.659)
	≥102	PD	24%	0.16 (0.13–0.19)	40%	76%	
Women ($n = 56,399$, crude incidence 1.3%)							
RFM	≥38	Optimal	38%	0.23 (0.19–0.26)	60%	63%	0.655 (0.636–0.675)
	≥40	PD	25%	0.20 (0.17–0.24)	45%	75%	
BMI (kg/m^2)	≥25	Optimal, PD	49%	0.18 (0.15–0.21)	67%	51%	0.618 (0.598–0.638)
	≥30	PD	16%	0.10 (0.07–0.13)	26%	85%	
WC (cm)	≥80	PD	69%	0.17 (0.15–0.20)	86%	31%	0.640 (0.621–0.660)
	≥82	Optimal	63%	0.20 (0.17–0.23)	82%	38%	
	≥88	PD	42%	0.19 (0.16–0.23)	61%	58%	

Predictive performance for the composite outcome (incident AF, HF, and/or CAD) is displayed for each cutoff separately, except for area under the curve, which represents the overall discriminative ability of the continuous obesity measures.
AUC area under the curve, *AF* atrial fibrillation, *BMI* body mass index, *CAD* coronary artery disease, *HF* heart failure, *PD* previously defined, *RFM* relative fat mass, *WC* waist circumference.

Table 4. Predictive performance of age-specific optimal cutoffs of relative fat mass.

Age group	*n*	Crude incidence	Optimal cutoff	Youden index	Sensitivity	Specificity
Men						
<40 years	11,859	0.5%	23	0.20	70%	50%
40–50 years	13,537	1.8%	25	0.18	72%	46%
50–60 years	7174	3.1%	25	0.13	77%	36%
60–70 years	4802	6.6%	26	0.15	78%	36%
≥70 years	1232	11.0%	27	0.09	68%	41%
All ages	38,604	2.5%	26	0.26	68%	58%
Women						
<40 years	17,821	0.3%	33	0.24	82%	43%
40–50 years	20,057	0.8%	37	0.15	58%	57%
50–60 years	10,638	1.4%	38	0.11	57%	54%
60–70 years	6311	3.6%	41	0.15	47%	68%
≥70 years	1572	8.2%	43	0.12	36%	75%
All ages	56,399	1.3%	38	0.23	60%	63%

Predictive performance of the age-specific cutoffs concerns the composite outcome (incident atrial fibrillation, heart failure and/or coronary artery disease).

Given the limitations of existing measures, the RFM formula was specifically developed in an effort to find a more suitable marker of body fat. After systematic analysis of 365 potential anthropometric measures, RFM was deemed to be the most suitable marker given its accuracy and consistency, but also its simplicity and intuitiveness compared to other measures [5]. RFM was shown to correspond well to body fat percentage as measured by dual-energy X-ray absorptiometry (DXA), performing consistently well in men and women and among people with various ethnicities [5, 22]. Requiring only height and waist circumference, RFM is easy to measure and can also be used under circumstances where a scale is not available. Finally, the RFM formula provides a more intuitive estimate of body fat percentage compared to other measures, such as waist-to-height ratio.

Other studies have demonstrated that RFM is associated with several outcomes, including hypertension, type 2 diabetes, heart failure, and all-cause mortality [6–10]. However, the association between RFM and other types of CVD has not yet been explored. Our study demonstrates that RFM is associated with incident AF, HF, and CAD in both men and women from the general population. For participants in the highest compared to the lowest quintile of RFM, the multivariable-adjusted odds ratio for development of the composite outcome was 2.05 in men and 1.89 in women.

Previous studies have noted the importance of using an integrative approach for CVD, where risk prediction, screening, or preventive measures may be performed for multiple types of at the same time rather than for each disease separately [12, 23]. The results of the present study are in line with this view, and indicate that RFM may be used for the simultaneous prediction of AF, HF, and CAD.

Interestingly, RFM was associated with incident CVD in participants with normal weight (BMI <25 kg/m^2) and overweight

(BMI 25–30 kg/m^2), but not obesity (BMI ≥30 kg/m^2). This seems consistent with the fact that individuals with normal or mildly elevated BMI can still have a high body fat percentage and thus be at increased risk of developing CVD [3, 5]. Conversely, this finding implies that RFM may not contribute to CV risk prediction in individuals with a known BMI ≥30 kg/m^2.

Previous studies have thus far delivered conflicting results regarding the question whether RFM is a better predictor of morbidity or mortality compared to established obesity measures [6–9]. Although the primary aim of our study was not to answer this question, we did include BMI and WC in the analyses to provide a reference for the performance of RFM. In the unadjusted analyses, RFM showed stronger associations with incident CVD than BMI and WC. However, these differences largely disappeared after adjustment for age, sex, and components of the SCORE risk model, which indicates that the different obesity measures may be equally suited for CV risk prediction when used in adjunction with other risk factors as part of a risk prediction model.

Importantly, we found that the association of RFM with CVD was substantially attenuated after adjustment for age. The strong correlation of RFM with age is in line with the fact that fat mass generally increases with age [24, 25]. Similarly, the weaker correlation of BMI with age may be explained by the simultaneous decrease in muscle mass that occurs in the elderly, which may cancel out the effect of increasing fat mass on BMI [24, 25]. Thus, our findings confirm that RFM may be a more suitable marker for age-related changes in body composition than BMI.

One of the aims of this study was to identify potential RFM cutoffs for the prediction of CVD in the general population. We found that previously defined RFM cutoffs (30 for men, 40 for women) [8] had suboptimal predictive ability, especially in men. In our study, optimal RFM cutoffs based on the Youden index were 26 for men and 38 for women. However, other cutoffs may be selected depending on whether a higher sensitivity or a higher specificity is preferred and depending on the age of the population. Overall, optimal RFM cutoffs performed slightly better compared to previously defined and optimal cutoffs for BMI and WC, particularly in men. Of note, the optimal RFM cutoffs found in our study are fairly close to commonly used cutoffs for obesity based on body fat percentage (25% for men, 35% for women) [8]. Differences between optimal and previously defined RFM cutoffs may be explained by the fact that the previously defined cutoffs were based on their association with mortality rather than incident CVD. Furthermore, they were developed in a North American population, which had a substantially higher average BMI and RFM compared to our study population despite having a similar mean age [8]. This highlights the need for studying and validating RFM cutoffs for various outcomes and in various populations.

Finally, we additionally explored age-specific cutoffs for RFM. Optimal cutoffs for RFM increased with age, ranging from 23 to 27 in men and from 33 to 43 in women. The use of different cutoffs for different age groups may seem less practical than using a single cutoff for all ages, as is generally done with BMI-based classification of obesity. However, as described above, using higher RFM cutoffs with increasing age is probably more reflective of the increase in fat mass that occurs with age [24, 25]. Furthermore, it has to be noted that, even when age-specific cutoffs were not used, the optimal RFM cutoffs for men and women performed quite well in terms of CVD prediction compared to previously defined and optimal cutoffs for BMI and WC.

Strengths and limitations

Our study was performed in a large, contemporary, population-based cohort, that is representative of the general population in The Netherlands [26]. We focused on multiple types of CVD, which makes our results widely applicable within the entire field of CVD prevention. In addition, our study provides potential RFM cutoffs for the prediction of CVD in the general population. Although these cutoffs need further external validation, they may be directly applied in future studies and may eventually provide a starting point for preventive strategies targeting overweight and/or obesity.

Limitations include the comparatively short median follow-up duration of 3.8 years. Meta-analyses have previously shown that association between obesity measures and CV outcomes may be stronger during long-term follow-up [27, 28]. The incidence of AF was fairly low compared to HF and CAD, which may be due to the fact that AF diagnosis was based solely on a single follow-up ECG. Therefore, paroxysmal cases of AF are likely to have been missed. Another limitation is the use of self-reported data for incident HF and CAD. We used self-reported data, because natriuretic peptide measurements, echocardiography, and coronary imaging were not performed in the overall Lifelines population. Previous studies have demonstrated that self-report has good sensitivity for CAD, but only moderate sensitivity for HF when compared to physicians' diagnoses [29, 30]. Therefore, the incidence of CVD, especially HF, may be an underestimation and may theoretically have diluted our results. Self-reported cases of incident HF and CAD were not additionally validated using medical records or medication use, since such data were not available for the present study. Nevertheless, the specificity of self-report for CVD is excellent, which makes false-positive cases unlikely [29, 30]. Finally, Lifelines participants are almost exclusively Dutch and predominantly white, which limits the generalisability of our results to other populations. The predictive performance of RFM, as well as optimal RFM cutoffs for CVD prediction, may thus be different in other populations.

CONCLUSIONS

RFM is associated with incident AF, HF, and CAD and may serve as a simple and intuitive marker of obesity and cardiovascular risk in the general population. In the present study, optimal RFM cutoffs for the prediction of CVD were 26 for men and 38 for women, which was lower than previously proposed cutoffs for the diagnosis of obesity. Since RFM is substantially correlated with age, the use of age-specific cutoffs for RFM may be considered.

DATA AVAILABILITY

Data may be obtained from a third party and are not publicly available. Researchers can apply to use the Lifelines data used in this study. More information about how to request Lifelines data and the conditions of use can be found on the Lifelines website (https://www.lifelines.nl/researcher/how-to-apply).

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ACKNOWLEDGEMENTS

Part of this work was presented during the ESC Heart Failure 2022 Congress and published as a conference abstract (European Journal of Heart Failure 2022; 24 (Suppl. S2): 243, https://doi.org/10.1002/ejhf.2569).

AUTHOR CONTRIBUTIONS

VWZ, NS, DI, MR, and RAdB contributed to the conception, design and acquisition of the work, data analysis and interpretation. VWZ drafted the manuscript. All authors contributed to the critical revision of the manuscript, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

FUNDING

This work was supported by the Dutch Heart Foundation (CVON RED-CVD, grant 2017-11).

COMPETING INTERESTS

For the current manuscript, the authors declare no potential conflicts of interest. Outside of the submitted work, the authors disclosed the following financial support: RAdB reports grants from the Dutch Heart Foundation (CVON SHE-PREDICTS-HF, grant 2017-21; CVON RED-CVD, grant 2017-11; CVON PREDICT2, grant 2018-30; and CVON DOUBLE DOSE, grant 2020B005), leDucq Foundation (Cure PhosphoLambaN induced Cardiomyopathy) and the European Research Council (SECRETE-HF, ERC CoG 818715). RAdB has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals Gmbh, Ionis Pharmaceuticals, Inc., Novo Nordisk and Roche. RAdB has received speaker fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche. MR reports grants from the Dutch Heart Foundation (CVON RACE V, grant 2014-09; CVON RED-CVD, grant 2017-11; CVON-AI, grant 2018B017; DECISION, grant 2018B024). The UMCG, which employs MR, received grants from SJM/Abbott (VIP-HF study) and Medtronic (Cryoballoon AF registry/biobank study).

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-023-01380-8.

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