

Associations of Novel Indices of Adiposity with Incident Heart Failure

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Abstract

Objective: To examine associations of newly-developed adiposity indices with incident heart failure (HF).

Participants and Methods: The current study included 8493 adults from the PREVENT observational cohort (mean age: 49.8 years; 50% women). Exposures included *novel adiposity indices* i.e., relative fat mass (RFM), body-roundness index (BRI), weight-adjusted-waist index and body-shape index (BSI), as well as *established adiposity indices* i.e., body-mass index (BMI), waist circumference, and waist-hip ratio (WHR). Main outcome was development of incident HF.

Results: The prevalence of overweight (BMI: 25-30kg/m²) and obesity (BMI≥30kg/m²) were 41% and 17% respectively. During 11.3±3.1 years of follow-up, 372 HF events were recorded, resulting in an overall HF incidence of 3.88 per 1000 person-years. All novel adiposity indices, except BSI, were significantly associated with incident HF (P<0.001). BMI, WC and WHR were also significantly associated with incident HF (P<0.001). Sex did not modify the association of any adiposity index with incident HF (P_{int}>0.1). Amongst adiposity indices, RFM displayed the strongest effect sizes (HR:1.67, 95%CI, 1.37-2.03). This trend persisted across multiple age categories, BMI categories and also among HF subtypes. All obesity measures, except BSI, improved the fit of the clinical HF model. Strongest improvement was observed after adding BRI and RFM (reduction in Akaike information criteria: 26.5 and 24.4 respectively).

Conclusions: Relative fat mass is strongly associated with incident HF in the community. Future studies should examine the value of novel adiposity indices in HF risk estimation.

Introduction

The worldwide prevalence of obesity has nearly tripled during the last 50 years,¹ and the burden of obesity is expected to increase even further in the coming decade.^{2,3} Heart failure (HF) is also an emerging epidemic, with lifetime risk estimates between 20–33% in both sexes.⁴ Excessive adipose tissue accumulation increases the risk of developing HF,^{5–7} and recent data indicate that among modifiable risk factors, obesity explained a substantial proportion of incident HF in the general population.^{8,9}

The current definition of overweight and obesity is based on body-mass index (BMI), even though it is known that BMI may not accurately reflect fat mass.¹⁰ Interestingly, anthropometric measures such as waist circumference (WC) and waist-to-hip ratio (WHR), that more strongly relate with abdominal fat distribution, were not found to be substantially better than BMI in predicting HF risk.^{11,12} With obesity becoming more prevalent and likely becoming a major driver of HF risk, there is a growing need for more adequate and easy-to-measure surrogates of fat mass that also better associate with future cardiovascular risk.

Over the past 10 years, several indices of adiposity were developed, that more accurately correlated with body fat distribution and total fat mass. They include body shape index (BSI),¹³ body roundness index (BRI),¹⁴ weight-adjusted-weight index (WWI)¹⁵ and relative fat mass (RFM).¹⁶ In the current study, we sought to examine the association between newly developed indices of adiposity and the risk of incident HF in community-dwelling individuals.

Methods

The PREVENT study (1997–1998) is a Dutch cohort taken from the general population of Groningen, the Netherlands.^{17–19} This study was designed to prospectively evaluate whether increased urinary albumin excretion (UAE) in community-dwelling individuals was associated with cardiovascular and renal disease.²⁰ In brief, all inhabitants from Groningen, aged 28 to 75 years were asked to respond to a short questionnaire and provide early-morning urine samples (N = 85,421), and 40,856 individuals (47.8%) responded. Responders with UAE greater than or equal to 10 mg/L (n = 7786) as well as a randomly selected control group with UAE less than 10 mg/L (n = 3395) were invited to the outpatient clinic for comprehensive health assessment including filling out questionnaires, anthropometry, fasting blood draw, and urine sampling. Individuals with type-1 diabetes (defined as insulin requirement), pregnant women (self-reported), and unwilling subjects were excluded from the study. A final total of 6000 individuals with UAE greater than or equal to 10 mg/L and 2592 individuals with UAE less than 10 mg/L underwent further investigation and constitute the baseline PREVENT cohort (N = 8592). From the baseline cohort, we excluded participants with HF at baseline according to hospital records (n = 23), BMI < 18.5 kg/m² (n = 74) and WC < 40cm (n = 2), resulting in a total of 8493 participants available for analysis. The current study conformed to the principles drafted in the Helsinki declaration. Local medical ethical committee approval was obtained and informed consent was provided by all participants.

Baseline Measurements

Body weight, height, WC and hip circumference (HC) were measured in a standing position during the baseline visit. WC was measured midway between the lowest rib and the iliac crest at the end of expiration. HC was measured at the widest portion at the level of greater trochanters. BMI was calculated as the ratio between weight and height-squared. Overweight was defined as BMI between 25–30 kg/m² and obesity as BMI ≥ 30 kg/m². WHR was the ratio between WC and HC. RFM was calculated as: $64 - (20 * \text{Height} / \text{WC}) + (12 * \text{sex})$, with sex = 0 (men), and sex = 1 (women). WWI was calculated as: $(\text{WC} * 100) / (\text{Weight}^{0.5})$. BRI was calculated as: $364.2 - 365.5 * (1 - ((0.5 * \text{WC} / \pi)^2 / (0.5 * \text{Height}^2)))^{0.5}$. BSI was calculated as: $1000 * \text{WC} * \text{Weight}^{-2/3} * \text{Height}^{5/6}$.

Smoking was defined as self-reported current smoking or smoking cessation within the previous year. Hypertension was defined as systolic BP (SBP) ≥ 140 mm Hg, diastolic BP (DBP) ≥ 90 mm Hg or self-reported antihypertensive medication usage. Blood pressure (BP) was measured ten times during 10 minutes using an automatic Dinamap XL Model 9300 series; BP was calculated as the mean of the last two measurements. Type-2 diabetes was defined as a fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), random plasma glucose ≥ 11.1 mmol/L (200 mg/dL), self-reporting of a physician diagnosis or record of glucose-lowering medication use obtained from central pharmacy registry. History of myocardial infarction and cerebrovascular accident were based on

individuals' medical history derived from a structured questionnaire i.e., hospitalization ≥ 3 days as a result of this condition; this was complemented by a review of the medical report. Individuals with AF at baseline screening were considered to have prevalent AF. Total cholesterol and plasma glucose were measured by a dry chemistry method (Eastman Kodak, Rochester, New York).

Incident Heart Failure

Individuals were prospectively followed for the first occurrence of HF or death within 13.5 years of baseline examination. HF records including dates were retrieved from clinical charts. Individuals suspected of having HF were identified according to European Society of Cardiology (ESC) guidelines.²¹ An endpoint adjudication committee of seven independent HF experts further evaluated these selected individuals, and two different experts validated each case. A joint decision was made within the committee in the case of disagreement. Based on left ventricular ejection fraction (LVEF) cutpoint of 50%,²² HF was subcategorized into HF with reduced EF (HFrEF) or preserved EF (HFpEF); LVEF was available for all HF cases. Further details can be found elsewhere.¹⁷

Statistical analyses

Continuous data are presented as medians, Q1-Q3 (50th percentile, 25th -75th percentile) and categorical variables are represented as percentages. For further analyses, all continuous adiposity measures were standardized. In primary analyses, we examined associations of adiposity indices with incident HF in the total population using Cox regression models adjusting initially for age and sex, and subsequently also for smoking, glucose, cholesterol, systolic blood pressure,²³ history of myocardial infarction, stroke and atrial fibrillation. We tested for *adiposity index*sex* terms in the multivariable model. A multiple testing corrected P-value of 0.007 (0.05/7) and an interaction P-value (P_{int}) of 0.1 denoted statistical significance. We also examined the shape of associations of adiposity indices with incident HF using multivariable fractional polynomial models. In secondary analyses, we examined associations of adiposity indices with incident HF according to pre-specified age categories (< 55, 55–65 and ≥ 65 years), and across BMI categories (lean, overweight and obese). Additionally, we evaluated associations of adiposity indices with HFrEF and HFpEF separately. Finally, we used Harrel's C-statistic, Akaike information criteria (AIC)^{24,25} and P-values based on likelihood ratio (LHR) test²² to examine the incremental predictive value of adiposity indices (beyond a clinical model) for HF and its subtypes. A $P_{LHR} < 0.01$ was considered as strong evidence against the null hypothesis.²⁶ All statistical analyses were performed using STATA version-14.

Results

Mean age of the cohort was 49 (12) years and 50% (n = 4250) were women. Around 41% of the population was overweight (n = 3450) of which 42% were women, and 17% was obese (n = 1429) of which 55% were women (Table 1). Sex-specific distributions of adiposity indices are shown in **Table S1**. Most adiposity indices showed moderate to strong correlations with each other, and with age in both sexes (**Table S2**).

Table 1
Baseline characteristics of PREVENT participants

	Total Population (n = 8493)	Men (n = 4243)	Women (n = 4250)
Clinical characteristics			
Age, years	48.5 (39.2, 60.2)	49.8 (40.2, 62.3)	47.4 (38.4, 57.9)
Smoking	3196 (37.8%)	1604 (38.0%)	1592 (37.6%)
Overweight (BMI 25–30 kg/m ²)	3450 (40.6%)	2004 (47.2%)	1446 (34.0%)
Obesity (BMI ≥ 30 kg/m ²)	1429 (16.8%)	646 (15.2%)	783 (18.4%)
Cholesterol, mmol.L ⁻¹	5.6 (4.9, 6.3)	5.6 (4.9, 6.3)	5.5 (4.8, 6.3)
Hypertension	2884 (34.1%)	1679 (39.8%)	1205 (28.4%)
Systolic blood pressure (mm Hg)	126.0 (114.0, 141.0)	131.0 (120.0, 144.0)	119.0 (109.0, 136.0)
Diabetes	317 (3.8%)	181 (4.3%)	136 (3.2%)
Glucose, mmol.L ⁻¹	4.7 (4.3, 5.1)	4.8 (4.5, 5.3)	4.6 (4.2, 5.0)
Myocardial infarction	497 (5.9%)	325 (7.7%)	172 (4.0%)
Stroke	79 (0.9%)	47 (1.1%)	32 (0.8%)
Atrial fibrillation	76 (0.9%)	55 (1.3%)	21 (0.5%)
Anthropometric measures			
Body mass index (BMI), kg.m ⁻²	25.7 (23.2, 28.4)	26.0 (23.8, 28.5)	25.2 (22.6, 28.4)
Waist circumference, cm	88.0 (79.0, 97.2)	93.5 (86.0, 101.0)	82.0 (74.0, 91.0)
Waist-hip ratio	0.88 (0.81, 0.95)	0.94 (0.89, 0.99)	0.82 (0.77, 0.87)
Body shape index, m ^{11/6} .kg ^{-2/3} *1000	76.6 (72.3, 80.7)	79.4 (76.3, 82.4)	73.1 (69.8, 77.0)
Weight-adjusted-waist index, m.kg ⁻² *100	10.0 (9.4, 10.6)	10.2 (9.7, 10.7)	9.7 (9.1, 10.4)
Body roundness index	3.5 (2.6, 4.6)	3.8 (3.0, 4.7)	3.2 (2.3, 4.4)
Relative fat mass	29.4 (25.1, 35.4)	25.7 (22.3, 28.7)	35.1 (30.4, 39.8)
Continuous variables are presented as medians (P25, P50) and categorical variables as n (%)			

During a mean follow-up of 11.3 ± 3.1 years, 372 individuals (4.1%) developed HF, resulting in an overall HF incidence of 3.88 per 1000 person-years (5.10 per 1000 person-years in men and 2.72 per 1000 person-years in women). In multivariable Cox regression models, all adiposity indices, except BSI, were significantly associated with incident HF ($P < 0.001$). (Table 2, **Figure S1**). While a unit change in standardized BMI was associated with a 28% increased risk of developing HF, an equivalent change in RFM was associated with a 67% increased risk [HR: 1.67, 95%CI (1.37–2.03)]. Sex did not significantly modify the association of any adiposity index with incident HF ($P_{int} > 0.1$) (**Central Illustration**). We performed two sensitivity analyses. First, when we substituted glucose and systolic blood pressure with diabetes and hypertension in multivariable models, our results did not materially change (**Table S3**). Second, when we accounted for death as a competing risk, patterns of associations between adiposity indices were similar to that observed in the primary analysis (**Table S4**).

Table 2
– Associations of adiposity indices with incident heart failure and its subtypes

	Age-sex adjusted		Multivariable adjusted		Sex-interaction	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR _{int} (95% CI)	P _{int} -value
Heart Failure						
BMI	1.40 (1.27, 1.54)	< .001	1.28 (1.15, 1.42)	< .001	0.86 (0.69, 1.05)	0.14
WC	1.50 (1.33, 1.68)	< .001	1.35 (1.20, 1.53)	< .001	0.86 (0.68, 1.10)	0.24
WHR	1.58 (1.38, 1.80)	< .001	1.43 (1.24, 1.65)	< .001	0.86 (0.65, 1.14)	0.29
BSI	1.26 (1.11, 1.43)	< .001	1.19 (1.04, 1.36)	.01	0.95 (0.74, 1.23)	.69
WWI	1.44 (1.28, 1.63)	< .001	1.34 (1.17, 1.53)	< .001	0.91 (0.71, 1.15)	.43
BRI	1.46 (1.33, 1.61)	< .001	1.36 (1.22, 1.51)	< .001	0.87 (0.71, 1.07)	.20
RFM	1.95 (1.61, 2.34)	< .001	1.67 (1.37, 2.03)	< .001	0.77 (0.54, 1.12)	.17
HFpEF						
BMI	1.49 (1.28, 1.74)	< .001	1.32 (1.11, 1.57)	.002	0.98 (0.68, 1.39)	.89
WC	1.57 (1.30, 1.90)	< .001	1.40 (1.14, 1.73)	.001	0.98 (0.65, 1.48)	.93
WHR	1.46 (1.16, 1.84)	.001	1.36 (1.06, 1.74)	.01	1.19 (0.73, 1.94)	.48
BSI	1.18 (0.96, 1.46)	.12	1.14 (0.92, 1.43)	.24	1.04 (0.66, 1.63)	.87
WWI	1.39 (1.14, 1.69)	.001	1.29 (1.04, 1.60)	.02	1.03 (0.67, 1.58)	.89
BRI	1.50 (1.28, 1.75)	< .001	1.36 (1.14, 1.62)	.001	0.99 (0.69, 1.41)	.96
RFM	2.07 (1.52, 2.83)	< .001	1.75 (1.25, 2.43)	.001	0.98 (0.51, 1.90)	.96
HFrEF						
BMI	1.33 (1.17, 1.51)	< .001	1.23 (1.07, 1.41)	.003	0.78 (0.59, 1.03)	.08
WC	1.44 (1.25, 1.67)	< .001	1.31 (1.13, 1.53)	.001	0.78 (0.57, 1.07)	.13
WHR	1.63 (1.38, 1.93)	< .001	1.46 (1.22, 1.74)	< .001	0.70 (0.49, 1.01)	.06
BSI	1.31 (1.11, 1.53)	.001	1.22 (1.03, 1.45)	.02	0.90 (0.65, 1.24)	.51
WWI	1.47 (1.26, 1.72)	< .001	1.36 (1.16, 1.61)	< .001	0.83 (0.61, 1.12)	.23
BRI	1.42 (1.26, 1.61)	< .001	1.33 (1.16, 1.53)	< .001	0.81 (0.62, 1.06)	.13
RFM	1.84 (1.46, 2.32)	< .001	1.60 (1.25, 2.05)	< .001	0.65 (0.41, 1.03)	.07
Multivariable models were adjusted for age, sex, smoking, cholesterol, systolic blood pressure, glucose, and history of myocardial infarction, stroke and atrial fibrillation. HR represents the hazard ratio per standard deviation change in adiposity index; CI represents confidence interval; P _{int} represents the P-value for sex*covariate interaction. A hazard ratio for interaction (HR _{int}) > 1 indicates stronger associations in women. A HR _{int} < 1 indicates stronger associations in men. Abbreviations: BMI, body-mass index; BRI, body roundness index; BSI, body shape index; HF, heart failure; HFpEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; RFM, relative fat mass; WC, waist circumference; WHR, waist-to-hip ratio; WWI, weight-adjusted-waist index.						

Associations of adiposity indices with incident HF across age categories, and across BMI categories are shown in Table 3 and Figure S2. When multivariable models were further adjusted for BMI, all adiposity indices except WC remained significantly associated with incident HF (Table S5). Largest effect sizes were observed with RFM [HR: 1.49, 95%CI (1.12–2.25)].

Table 3
a. Associations of adiposity indices with incident heart failure across age categories

Age	< 55 years		55–65 years		≥ 65 years	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
BMI	1.22 (0.97, 1.53)	.08	1.27 (1.05, 1.54)	.01	1.25 (1.05, 1.48)	.01
WC	1.39 (1.06, 1.82)	.02	1.26 (1.00-1.58)	.05	1.34 (1.12–1.62)	.002
WHR	1.60 (1.17, 2.20)	.004	1.39 (1.06, 1.82)	.02	1.32 (1.08, 1.63)	.007
BSI	1.41 (1.05, 1.90)	.02	1.00 (0.78, 1.29)	.99	1.22 (1.01, 1.47)	.04
WWI	1.52 (1.14, 2.03)	.005	1.19 (0.93, 1.51)	.17	1.31 (1.09, 1.58)	.004
BRI	1.37 (1.08, 1.74)	.009	1.28 (1.06, 1.55)	.01	1.34 (1.14, 1.58)	< .001
RFM	1.70 (1.14, 2.54)	.01	1.53 (1.07, 2.20)	.02	1.58 (1.17, 2.15)	.003

Multivariable models were adjusted for age, sex, smoking, cholesterol, systolic blood pressure, glucose, and history of myocardial infarction, stroke and atrial fibrillation. Abbreviations same as in Table 2

Table 3
b. Associations of adiposity indices with incident heart failure across body-mass index categories

	BMI 18.5–25 kg/m ² (Lean)		BMI 25–30 kg/m ² (Overweight)		BMI ≥ 30 kg/m ² (Obese)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
BMI	0.94 (0.47, 1.87)	.86	1.14 (0.73, 1.77)	.57	1.13 (0.86, 1.47)	.38
WC	1.03 (0.65, 1.63)	.90	1.30 (0.98, 1.73)	.07	1.20 (0.90, 1.58)	.21
WHR	1.07 (0.74, 1.55)	.72	1.46 (1.16, 1.85)	.001	1.26 (0.95, 1.67)	.10
BSI	1.07 (0.81, 1.43)	.63	1.27 (1.04, 1.54)	.02	1.16 (0.89, 1.51)	.27
WWI	1.10 (0.81, 1.49)	.56	1.37 (1.11, 1.68)	.003	1.20 (0.92, 1.56)	.17
BRI	1.04 (0.62, 1.73)	.89	1.50 (1.14, 1.97)	.004	1.20 (0.95, 1.51)	.12
RFM	1.24 (0.73, 2.12)	.43	1.80 (1.14, 2.85)	.01	1.53 (0.85, 2.74)	.15

Multivariable models were adjusted for age, sex, smoking, cholesterol, systolic blood pressure, glucose, and history of myocardial infarction, stroke and atrial fibrillation. Abbreviations same as in Table 2

The majority of adiposity indices were also associated with individual HF subtypes. Amongst adiposity indices, RFM showed strongest associations with both HFpEF [HR: 1.75, 95%CI (1.25–2.43)] and HFrfEF [HR: 1.60, 95%CI (1.25–2.05)]. All adiposity indices were similarly associated with incident HFpEF in both sexes, but RFM, WHR and BMI displayed stronger associations with HFrfEF in men than in women (P_{int} : 0.07, 0.06 and 0.08 respectively) (Table 2).

Finally, none of the adiposity indices improved discrimination of HF beyond the clinical model. However, addition of several adiposity indices, including BMI, substantially improved model fit by reducing the prediction error (Table 4). Strongest improvements were observed after adding BRI and RFM (ΔAIC – 26.5 and – 24.4 respectively) (Central Illustration). Within HF subtypes, strongest improvement in model fit was observed after adding RFM and BRI for HFpEF, and after adding WHR, BRI and RFM for HFrfEF (Table 4).

Table 4
Adiposity indices and improvement in model fit

	HF (total)					HFpEF					HFrEF				
	C-statistic	Δ C-statistic	AIC	Δ AIC	P-value	C-statistic	Δ C-statistic	AIC	Δ AIC	P-value	C-statistic	Δ C-statistic	AIC	Δ AIC	P-value
Base Model	0.848	-	5800.5	-		0.853	-	1919.4	-		0.848	-	3873.0	-	
BMI	0.850	0.002	5782.8	-17.7	< .001	0.855	0.002	1911.4	-8.0	.007	0.850	0.002	3866.4	-6.6	.01
WC	0.851	0.003	5779.9	-20.6	< .001	0.856	0.003	1911.4	-8.0	.007	0.851	0.003	3863.3	-9.7	.003
WHR	0.852	0.004	5779.8	-20.7	< .001	0.856	0.003	1915.6	-3.8	.05	0.852	0.004	3858.4	-14.6	< .001
BSI	0.850	0.002	5796.1	-4.4	.04	0.855	0.002	1920.0	+0.6	.50	0.850	0.002	3869.6	-3.4	.07
WWI	0.852	0.004	5783.7	-16.8	< .001	0.856	0.003	1916.2	-3.2	.07	0.852	0.004	3861.6	-11.4	.001
BRI	0.852	0.004	5774.0	-26.5	< .001	0.857	0.004	1910.8	-8.6	.005	0.852	0.004	3859.1	-13.9	< .001
RFM	0.851	0.003	5776.1	-24.4	< .001	0.856	0.003	1910.0	-9.4	.003	0.851	0.003	3860.6	-12.4	< .001

For this analysis, we included 8295 participants with no missing data for covariates. AIC represents Akaike information criterion. All other abbreviations are same as in Table 2. P-values are based on likelihood ratio test. If the reduction in AIC is less than 2: no substantial evidence to support the candidate model; between 4 and 7: candidate model has considerably less support; greater than 10: no support for the candidate model.

Discussion

In the current study including 8493 community-dwelling adults, most of the novel as well as established indices of adiposity were strongly associated with incident HF. Amongst adiposity indices, we found that RFM displayed the strongest associations with incident HF.

RFM is a newly-developed parameter of adiposity that more accurately estimates whole-body fat percentage compared to traditional equations based on BMI or WHR.¹⁶ RFM is also easy to calculate, requiring only height and waist circumference – both of which could be measured using a tape. Furthermore, RFM levels are higher in women than in men; for instance, in the PREVEND cohort RFM was around 25 in men, and around 35 in women. In this context, it is interesting to observe that most existing measures of adiposity are higher in men than in women, despite the fact that fat percentage is higher in women than in men.^{27,28}

In subgroup analyses, all adiposity indices were more strongly associated with incident HF in younger individuals (i.e., age < 55 years). RFM, however, displayed the strongest relative risk across all age categories, including in older individuals (i.e., age \geq 65 years). Across BMI categories, adiposity indices were more strongly associated with incident HF in overweight individuals. Again, RFM had the strongest relative risk across all BMI categories, including in those classified as obese. Most indices of adiposity were also associated with individual HF subtypes, and RFM consistently displayed the largest effect sizes for both HFrEF and HFpEF.

Next, we report that both novel as well as established indices of adiposity were similarly associated with incident HF in both sexes. Several previous studies have examined sex-related differences in associations of BMI with incident HF; while some studies showed stronger associations in men than in women,²² other studies showed neutral⁹ or even opposite trends.⁸ Among HF subtypes, we found that measures of adiposity were similarly associated with incident HFpEF in both sexes, but RFM, BMI and WHR tended to be more strongly associated with HFrEF development in men. Similar trends have been observed previously for BMI and WC,²⁹ suggesting that adiposity may have a greater role in the pathophysiology of HFrEF in men than in women.

Interestingly, we found that none of the adiposity indices substantially improved discrimination of the clinical HF model. This could potentially be because C-statistic is a less sensitive tool to measure improvement in model fit, especially if the base model has excellent discrimination.^{22,30} Using more global and sensitive measures of model fit such as LHR χ^2 statistic and AIC, we found that RFM and BRI may be more useful than BMI in improving HF risk prediction. Given that RFM and BRI also consistently improved prediction of both HFrEF and HFpEF, future studies should evaluate the potential of including these indices in HF risk estimation.

Strengths and limitations: We report for the first time, associations between newly-developed adiposity indices (i.e., RFM, BRI and WWI) and incident HF in a large well-characterized cohort. A particular strength was that the HF endpoint was adjudicated, and also subcategorized into HFpEF and HFrEF. The long term follow-up of participants and a 1:1 sex ratio further strengthen our analyses. Nevertheless, we acknowledge that PREVEND is a relatively young cohort with low overall event rates. Another limitation is that the PREVEND study, by design, included a higher proportion of individuals with UAE > 10mg/L. Finally, the current study was conducted on a predominantly white population from the Northern Netherlands. It is likely that fat distribution patterns and anthropometric characteristics of individuals from other geographical locations and ethnicities may be different, warranting validation of our findings in other cohorts.

Conclusion

Amongst indices of adiposity, relative fat mass displayed the strongest association with incident HF. Future studies should examine the value of novel adiposity indices in HF risk estimation.

Declarations

Declaration of conflicting interests: The UMCG, which employs Dr. de Boer has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals Inc., Novo Nordisk and Roche. Dr. de Boer received speaker fees from Abbott, AstraZeneca, Bayer, Novartis, and Roche. The remaining authors have nothing to disclose.

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