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Original article

Associations of relative fat mass, a new index of adiposity, with type-2 diabetes in the general population

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ABSTRACT

Background: Relative fat mass (RFM) is a novel sex-specific anthropometric equation (based on height and waist measurements) to estimate whole-body fat percentage.
Objective: To examine associations of RFM with incident type-2 diabetes (T2D), and to benchmark its performance against body-mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR).
Methods: This prospective longitudinal study included data from three Dutch community-based cohorts free of baseline diabetes. First, we examined data from the PREVEND cohort (median age and follow-up duration: 48.0 and 12.5 years, respectively) using Cox regression models. Validation was performed in the Lifelines (median age and follow-up duration: 45.5 and 3.8 years, respectively) and Rotterdam (median age and follow-up duration: 68.0 and 13.9 years, respectively) cohorts.
Results: Among 7961 PREVEND participants, 522 (6.6%) developed T2D. In a multivariable model, all adiposity indices were significantly associated with incident T2D ($P_{all}<0.001$). While 1 SD increase in BMI, WC and WHR were associated with 68%, 77% and 61% increased risk of developing T2D [Hazard ratio $(HR)_{BMI}$: 1.68 (95%CI: 1.57-1.80), HR_{WC}: 1.77 (95% CI: 1.63-1.92) and HR_{WHR}: 1.61 (95%CI: 1.48-1.75)], an equivalent increase in RFM was associated with 119% increased risk [HR: 2.19 (95%CI: 1.96-2.44)]. RFM was associated with incident T2D across all age groups, with the largest effect size in the youngest (<40 years) age category [HR: 2.90 (95%CI: 2.15-3.92)]. Results were broadly similar in Lifelines (n = 93,870) and Rotterdam (n = 5279) cohorts.
Conclusions: RFM is strongly associated with new-onset T2D and displays the potential to be used in the general practice setting to estimate the risk of future diabetes.

1. Introduction

The worldwide prevalence of obesity has increased dramatically during the last fifty years, and excess body weight is currently recognized as a major global public health challenge [1]. A recent report on trends in adult body-mass index (BMI) in 200 countries from 1975 to 2014 showed that average BMI in men increased the most in English-speaking countries and average BMI in women increased the

Abbreviations: RFM, Relative Fat Mass; BMI, Body Mass Index; WC, Waist Circumference; WHR, Waist-to-hip ratio; T2D, Type-2 Diabetes; PREVEND, Prevention of REnal and Vascular ENd stage Disease.

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most in central Latin America [1]. In the United States (US), age-adjusted prevalence of obesity in adults was around 42% in 2017-2018 [2], and it is estimated that over half of the adult US population will be obese within 2030 [3]. Besides direct socioeconomic consequences, rising obesity rates will also result in increased incidence of several chronic diseases, particularly type-2 diabetes (T2D) [4].

The most common method for obesity screening is BMI measurement [1], and obesity is defined as a BMI greater than or equal to 30 kg/m^2. However, BMI is a non-specific marker of body mass and does not discern between fat mass, muscle mass and bone mass [5,6]. Given the closer association of visceral adiposity with the pathogenesis of insulin resistance and diabetes [7,8], alternative screening tools such as waist circumference (WC) and waist-hip ratio (WHR), that better reflect abdominal fat distribution, have also been included in diabetes risk prediction models [9]. Nevertheless, aggregate data suggest that the overall performance of BMI, WC and WHR is comparable while estimating future diabetes risk in the community [10].

Over the last 10 years, more accurate anthropometric measures of adiposity such as relative fat mass (RFM) [11], body shape index [12], body roundness index [13] and weight-adjusted waist index [14] have been developed. We recently showed that among novel and established anthropometric measures of adiposity, the RFM, which is calculated from WC and height, was the strongest predictor of heart failure risk in the general population [15]. In the current study, we postulate that RFM would be a stronger predictor of new-onset T2D than currently used measures of adiposity. Accordingly, we assessed associations of RFM, BMI, WC and WHR with incident T2D in the PREVEND cohort, and compared the results with those from two other general population-based cohorts: the LifeLines study and the Rotterdam study.

2. Methods

2.1. Study samples

The PREVEND study is a prospective cohort study of 8592 community-dwelling adults living in the city of Groningen, the Netherlands, designed to investigate whether increased urinary albumin excretion (UAE) was associated with the risk of future cardiovascular and renal disease in the community (1997-1998). The detailed study design has been described elsewhere [16,17] Briefly, all inhabitants from the city of 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 a comprehensive health assessment. Insulin-treated individuals, 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 constituted the baseline PREVEND cohort (N = 8592) [16,17]. From this sample, 631 participants were excluded for the following reasons: (i) prevalent diabetes (n = 324), (ii) unavailable data on baseline diabetes status (n = 88), (iii) missing anthropometric data (n = 107) iv) BMI<18.5 (n = 71), (v) WC<40 cm (n = 1), and (vi) missing covariates (n = 40), resulting in a final total of 7961 participants available for analysis.

LifeLines (www.lifelines.nl) is a prospective cohort study of 167,729 community-dwelling adults living in northern Netherlands (2006-2013). The detailed study design has been described elsewhwhere [18,19]. For the current study, we included 99,147 participants with available data at baseline and follow-up (ie, second) visit. From this sample, 5277 participants were excluded for the following reasons: (i) prevalent diabetes (n = 3065), (ii) unavailable data on baseline diabetes status (n = 115), (iii) missing anthropometric data (n = 30), (iv) BMI<18.5 (n = 679), and (v) missing covariates (n = 1388), resulting in a final total of 93,870 participants left for analysis.

The Rotterdam study is a prospective cohort study of community-dwelling adults aged 55 years and older in Rotterdam, the Netherlands. The detailed study design has been described elsewhere [20,21]. Briefly, the baseline examination for the first cohort was completed between 1990 and 1993 (RS-I) with 10,215 participants aged 55 years or over; the response rate was 78%. The Rotterdam study was extended in 2000 to include all inhabitants who became 55 years of age or moved into the research area after the start of the study (RS-II). For the current study, we used the third visit of RS-I (1997-1998; n = 4797) and first visit of RS-II (2000-2001; n = 3011). Among 7808 participants recruited, 2529 were excluded for the following reasons: (i) no informed consent to access medical records (n = 82), (ii) prevalent diabetes or unavailable data on baseline diabetes status (n = 1733), (iii) missing anthropometric data (n = 568), (iv) BMI<18.5 kg/m^2 or WC<40 cm (n = 42), and (v) missing covariates (n = 104), resulting in a final total of 5279 participants.

The PREVEND study and the Lifelines study have been approved by the medical ethics committee of the University Medical Center Groningen (registration numbers: MEC 96/01/022 and 2007/152, respectively). The Rotterdam study has been approved by the medical ethics committee of the Erasmus MC (registration number: MEC 02/1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population screening act WBO, license number: 1071272-159521-PG). Written informed consent was obtained for all study participants.

2.2. Clinical assessment

All participants had detailed medical history, physical examination and fasting laboratory assessment at the baseline examination. Family history of diabetes was defined as self-reported diabetes among parents and siblings. Smoking behaviour was self-reported, and was classified as currently smoking, quit smoking (<1 year or ≥1 year) or never smoked. Smoking variable for the current study was defined as *"currently smoking"* or *"smoking cessation within the previous year."* Baseline body weight, height, WC and hip circumference (HC) were measured in a standing position. 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. RFM was calculated as 64 – [20*Height (m) / WC (m)] in men and 76 – [20*Height (m) / WC (m)] in women [i.e., 64 – (20*Height/WC) + (12*sex), with sex=0 (men), and sex=1 (women)] [11]. BMI was calculated as the ratio between weight and height-squared, and expressed as kg/m^2. WHR was calculated as the the ratio between WC and HC. Blood pressure was taken as the average of 2 seated measurements. Hypertension was defined as systolic BP (SBP) ≥140 mm Hg, diastolic BP (DBP) ≥90 mm Hg or self-reported antihypertensive medication usage. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as *glucose (mmol/L)*insulin (mIU/L)]/22.5*. We defined insulin resistance as HOMA-IR>2.9 based on a previous study [22]. Elevated high-sensitivity C-reactive protein (hs-CRP) was defined as hs-CRP>2mg/L [23]. Details on relevant assays are provided in the Supplementary Material.

2.3. Ascertainment of Incident T2D

Incident T2D was considered present when participants without prevalent diabetes had any of the following during any of the follow-up visits: (i) fasting plasma glucose≥7.0 mmol/L (126 mg/dL) [all 3 cohorts], (ii) random plasma glucose≥11.1 mmol/L (200 mg/dL) [PREVEND and Rotterdam cohorts], (iii) HbA1c ≥ 6.5% [LifeLines cohort], (iv) self-reporting of a physician diagnosis [PREVEND and LifeLines cohorts] or (v) information about glucose-lowering medication use obtained from questionnaires, home interviews or central pharmacy registry [PREVEND and Rotterdam cohorts]. In the Rotterdam Study, two study physicians independently adjudicated all potential events of T2D;

in the case of disagreement, a consensus was sought from an endocrinologist.

2.4. Follow-up

PREVEND participants were followed until incident T2D occurrence, death, or until 1 January 2011, whichever came first; participants were invited for physical follow-up visits roughly every 4 years. LifeLines participants were followed until incident T2D occurrence, death or the first physical follow-up visit (2014–2017), which was roughly after 5 years from the baseline visit; participants were additionally followed with 2 questionnaires between the baseline and the first follow-up visit. Rotterdam Study participants were followed until incident T2D occurrence, death, or until 1 January 2015, whichever came first; participants were invited for physical follow-up visits roughly every 4 years.

2.5. Statistical analyses

Continuous data are presented as medians, Q1-Q3 (50th percentile, 25th-75th percentile) and categorical variables are represented as percentages. We first explored the association of adiposity indices i.e., RFM, BMI, WC and WHR with prevalent insulin resistance and other components of the metabolic syndrome using age and sex adjusted logistic regression models.

In primary analyses, we examined associations of *continuous* adiposity indices with incident T2D in the PREVEND cohort using Cox regression models adjusting initially for age and sex, and subsequently for smoking status, prevalent hypertension and family history of diabetes [17]. We calculated hazard ratios in the total population, and in women and men separately. We examined whether additional adjustment for continuous HOMA-IR score, hs-CRP or UAE in multivariable models materially affected the interpretation of our results [24]. Next, we examined the incremental discriminatory value of individual adiposity indices for T2D risk prediction beyond clinical covariates using C-statistic. We also quantified the extent to which adiposity indices improved model fit based on Akaike information criteria (AIC) [25,26], and according to *P-values* based on Likelihood ratio (LHR) test. A $P_{LHR}<0.01$ was considered as strong evidence against the null hypothesis [27]. Additionally, we calculated sex-specific hazard ratios of developing T2D across *quintiles* of RFM, BMI, WC and WHR after multivariable adjustment.

In secondary analyses, we evaluated associations of *continuous* adiposity indices with incident T2D across pre-specified age categories (<40, 40–50, 50–60, 60–70 and ≥70 years). We also examined associations of adiposity indices with incident T2D after adjusting for BMI in the total population, and across BMI categories (<25 kg/m^2, 25-30 kg/m^2 and ≥30 kg/m^2).

Finally, we compared the main results from the PREVEND study with that from two other general population-based cohorts: the LifeLines study and the Rotterdam study.

Results of the Cox regression models show mean hazard ratios with 95% confidence intervals (CI), and effect sizes are presented per one standard deviation (SD) increase in adiposity index; standardization was done separately for men and women. Multiple testing corrected *P-value* of 0.0125 (0.05/4) denoted statistical significance. All statistical analyses were performed using STATA version-14.

3. Results

We included 7961 individuals from the PREVEND study cohort without prevalent diabetes, of which 3990 (50.1%) were women. PREVEND participant characteristics are summarized in Table 1. Participant characteristics according to insulin resistance at baseline are shown in Table S1. In age and sex adjusted logistic regression models, all adiposity indices were significantly associated with prevalent insulin resistance in the total population, and RFM displayed the largest effect sizes (Table 2). Specifically, 1 SD increase in BMI was associated with 218% increased odds of being insulin resistant [Odds ratio (OR): 3.18; 95% CI: 2.97-3.42]. An equivalent increase in RFM was associated with 313% increased odds of being insulin resistant [OR: 4.13; 95% CI: 3.78-4.51]. All adiposity indices were also significantly associated with components of metabolic syndrome and inflammation, and RFM displayed the largest effect sizes (Table 2).

Table 1
PREVEND participant characteristics.

	Women (n = 3990)	Men (n = 3971)
Clinical characteristics		
Age, years	46.9 (38.1, 57.0)	49.2 (39.9, 61.7)
White individuals, n (%)	3772 (95.7)	3799 (95.9)
Smoking, n (%)	1504 (37.7)	1508 (38.0)
Hypertension, n (%)	1071 (26.8)	1534 (38.6)
SBP, mm Hg	119 (109, 135)	131 (120, 143)
DBP, mm Hg	70 (65, 77)	76 (70, 83)
Diabetes (family history), n (%)	629 (15.8)	568 (14.3)
HOMA-IR > 2.9, n (%)	624 (16.0)	915 (23.5)
HOMA-IR (continuous)	1.5 (1.0, 2.3)	1.8 (1.2, 2.8)
Glucose, mmol/L	4.6 (4.2, 4.9)	4.8 (4.4, 5.2)
Insulin, mU/L	7.6 (5.4, 10.9)	8.4 (5.7, 12.6)
Total cholesterol, mmol/L	5.5 (4.8, 6.3)	5.6 (4.9, 6.3)
HDL-cholesterol, mmol/L	1.5 (1.2, 1.7)	1.1 (0.9, 1.4)
Triglycerides, mmol/L	1.1 (0.8, 1.5)	1.3 (0.9, 1.9)
CRP > 2 mg/L, n (%)	1438 (37.6)	1245 (33.1)
CRP, mg/L	1.3 (0.6, 3.1)	1.2 (0.5, 2.6)
UAE, mg/24h	8.4 (5.8, 14.0)	10.3 (6.8, 20.7)
Anthropometric measures		
RFM	34.8 (30.2, 39.4)	25.5 (22.1, 28.5)
BMI, kg/m^2	25.1 (22.5, 28.2)	25.9 (23.8, 28.3)
WC, cm	81.0 (74.0, 90.0)	93.0 (86.0, 100.5)
WHR	0.81 (0.77, 0.87)	0.94 (0.89, 0.98)
Incident outcome		
Type 2 diabetes, n (%)	202 (5.1)	320 (8.1)

Continuous variables are presented as medians (P25, P75) and categorical variables as n (%). Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HDL, high-density lipoprotein; CRP, C-reactive protein; UAE, urinary albumin excretion; RFM, relative fat mass, BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio.

During a median follow-up of 12.5 (11.7–12.9) years, 522 individuals (6.6%) developed T2D, of which 202 (38.7%) were women. The incidence rate of T2D was 4.5 per 1000 person-years in women and 7.4 per 1000 person-years in men. Participant characteristics according to incident T2D are shown in Table S2. In multivariable Cox regression models, all adiposity indices were significantly associated with outcome ($P < 0.001$) (Table 3). While 1 SD increase in BMI, WC and WHR were associated with 68%, 77% and 61% increased risk of developing T2D in the total population, an equivalent change in RFM was associated with 119% increased risk of developing T2D [HR: 2.19, 95%CI (1.96–2.44)]. We observed a statistically significant (sex*covariate) interaction in the direction of women for RFM, BMI and WC (*P-value* for interaction 0.001, 0.029 and 0.008, respectively), and additionally presented sex-specific coefficients (Table 3).

Additional adjustment for HOMA-IR reduced effect sizes in general but did not affect the interpretation of results. Adjustment for hs-CRP and UAE did not materially change the results (Table S3).

All measures of adiposity modestly improved model discrimination when added to the multivariable risk prediction model i.e. age, sex, smoking status, prevalent hypertension, and family history of diabetes (Table S4). The greatest improvement was observed after adding RFM and BMI (ΔC-statistic: 0.064 and 0.061, respectively). All measures of adiposity also strongly improved model fit: again, the greatest improvement was observed after adding RFM and BMI (ΔAIC -206 and -176, respectively) (Table S4). When we also included HOMA-IR, hs-CRP and UAE in the multivariable model, trends were generally similar although improvement in discrimination was nominal (Table S5).

Table 2
Associations of standardized adiposity indices with prevalent insulin resistance, components of the metabolic syndrome and inflammation.

	Prevalent insulin resistance		Prevalent hypertension		Low HDL-C		High triglycerides		High CRP levels	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
RFM	4.13 (3.78, 4.51)	<0.001	1.91 (1.79, 2.04)	<0.001	2.05 (1.93, 2.18)	<0.001	2.36 (2.20, 2.54)	<0.001	2.02 (1.90, 2.15)	<0.001
BMI	3.18 (2.97, 3.42)	<0.001	1.79 (1.69, 1.90)	<0.001	1.73 (1.65, 1.82)	<0.001	1.86 (1.76, 1.97)	<0.001	1.79 (1.69, 1.89)	<0.001
WC	3.38 (3.14, 3.64)	<0.001	1.77 (1.67, 1.88)	<0.001	1.85 (1.76, 1.96)	<0.001	1.96 (1.85, 2.08)	<0.001	1.87 (1.77, 1.98)	<0.001
WHR	2.25 (2.11, 2.41)	<0.001	1.54 (1.45, 1.63)	<0.001	1.72 (1.63, 1.81)	<0.001	1.90 (1.79, 2.02)	<0.001	1.61 (1.52, 1.70)	<0.001

Models were adjusted for age and sex. Definitions: insulin resistance if homeostatic model assessment for insulin resistance (HOMA-IR) score > 2.9; hypertension if systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or self-reported antihypertensive medication usage; low HDL-C if < 1.03 mmol/L in men and < 1.29 mmol/L in women; high triglycerides if > 1.7 mmol/L; high CRP levels if > 2 mg/L. Abbreviatons: OR, odd ratio per standard deviation change in adiposity index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; RFM, relative fat mass; BMI, body-mass index; WC, waist circumference; WHR, waist-hip ratio.

Table 3
Associations of standardized adiposity indices with incident type-2 diabetes.

	Age-sex adjusted		Multivariable adjusted	
	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*
TOTAL				
RFM	2.38 (2.14, 2.64)	<0.001	2.19 (1.96, 2.44)	<0.001
BMI	1.77 (1.66, 1.89)	<0.001	1.68 (1.57, 1.80)	<0.001
WC	1.89 (1.75, 2.04)	<0.001	1.77 (1.63, 1.92)	<.0.001
WHR	1.71 (1.58, 1.86)	<0.001	1.61 (1.48, 1.75)	<0.001
WOMEN				
RFM	2.84 (2.41, 3.35)	<0.001	2.65 (2.23, 3.14)	<0.001
BMI	1.88 (1.71, 2.06)	<0.001	1.81 (1.63, 2.00)	<0.001
WC	2.06 (1.84, 2.30)	<0.001	1.95 (1.73, 2.19)	<0.001
WHR	1.70 (1.51, 1.91)	<0.001	1.63 (1.45, 1.85)	<0.001
MEN				
RFM	2.11 (1.84, 2.41)	<0.001	1.92 (1.67, 2.21)	<0.001
BMI	1.69 (1.54, 1.85)	<0.001	1.58 (1.44, 1.74)	<0.001
WC	1.76 (1.59, 1.96)	<0.001	1.63 (1.47, 1.82)	<0.001
WHR	1.74 (1.55, 1.96)	<0.001	1.61 (1.42, 1.81)	<0.001

Multivariable models were adjusted for age, sex, smoking, prevalent hypertension and family history of diabetes. Abbreviations: HR, hazard ratio per standard deviation change in adiposity index; CI, confidence interval; RFM, relative fat mass; BMI, body-mass index; WC, waist circumference; WHR, waist-hip ratio.

When multivariable models were adjusted for BMI, associations of RFM, WC and WHR with incident T2D were partially attenuated, but remained statistically significant. When directly compared, the effect size of RFM was significantly larger than BMI ($P_{difference}$=0.009), which was not the case for WC or WHR (Table S6). Across BMI categories, RFM was strongly associated with incident T2D in lean, overweight, and obese categories (Table S7).

We also examined the risk of incident T2D across sex-specific quintiles of adiposity indices (Table S8). Compared to men in the first quintile of RFM, men in the fifth quintile had 838% increased risk of developing T2D [HR: 9.38, 95% CI: 4.94-17.82]. Compared to women in the first quintile of RFM, women in the fifth quintile had a 2128% increased risk of developing T2D [HR: 22.28, 95% CI: 8.05-61.66].

Next, we summarized participant characteristics according to pre-specified age categories (Tables S9 and S10), and examined associations of adiposity indices with incident T2D in each age category. Again, RFM displayed the strongest associations across all age categories (Table 4), with the largest effect size in the youngest (<40 years old) age category [HR: 2.90, 95% CI (2.15-3.92)].

Finally, we compared the main results from the PREVEND cohort with the results from two other Dutch general population cohorts. Participant characteristics of Lifelines and Rotterdam Study cohorts are provided in Table S11. The median duration of follow-up in the Lifelines cohort was 3.8 (3.2–4.6) years; the incidence rate of T2D was 4.2 events per 1000 person-years in women and 6.5 events per 1000 person-years in men. The median duration of follow-up in the Rotterdam cohort was 13.9 (8.6-15.4) years; the incidence rate of T2D was 11.7 events per 1000 person-years in women and 12.8 events per 1000 person-years in men. While RFM displayed the largest effect sizes amongst all indices of adiposity in the Lifelines cohort [HR: 2.49, 95% CI: (2.30–2.56)] (Table 5), both RFM and BMI displayed strong associations with incident T2D in the Rotterdam cohort [HR: 1.44, 95% CI: (1.34–1.56) and HR: 1.38, 95% CI: (1.29–1.47), respectively] (Table 5). No significant effect

Table 5
Associations of standardized adiposity indices with incident type-2 diabetes in Lifelines and Rotterdam cohorts.

	LIFELINES COHORT (n = 93870)		ROTTERDAM COHORT (n = 5279)	
	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*
TOTAL				
RFM	2.49 (2.30-2.56)	<0.001	1.44 (1.34, 1.56)	<0.001
BMI	1.71 (1.67-1.76)	<0.001	1.38 (1.29, 1.47)	<0.001
WC	1.94 (1.86-2.01)	<0.001	1.32 (1.24, 1.39)	<0.001
WHR	1.65 (1.58-1.71)	<0.001	1.18 (1.12, 1.25)	<0.001
WOMEN				
RFM	2.51 (2.33-2.71)	<0.001	1.36 (1.22, 1.52)	<0.001
BMI	1.75 (1.68-1.83)	<0.001	1.32 (1.19, 1.47)	<0.001
WC	1.97 (1.86-2.07)	<0.001	1.24 (1.14, 1.36)	<0.001
WHR	1.63 (1.54-1.73)	<0.001	1.17 (1.08, 1.26)	<0.001
MEN				
RFM	2.36 (2.19-2.54)	<0.001	1.52 (1.37, 1.69)	<0.001
BMI	1.70 (1.63-1.76)	<0.001	1.42 (1.30, 1.54)	<0.001
WC	1.91 (1.81-2.01)	<0.001	1.42 (1.30, 1.56)	<0.001
WHR	1.67 (1.58-1.77)	<0.001	1.21 (1.11, 1.32)	<0.001

Multivariable models were adjusted for age, sex, smoking, prevalent hypertension and family history of diabetes in the Lifelines cohort and for age, sex, smoking and prevalent hypertension in the Rotterdam cohort. Abbreviations same as in Table 3.

Table 4
Associations of standardized adiposity indices with incident type-2 diabetes across age categories in the total population.

	Age < 40 years		Age: 40-50 years		Age: 50-60 years		Age: 60-70 years		Age ≥ 70 years	
	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*	HR (95% CI)	*P-value*
RFM	2.90 (2.15, 3.92)	<0.001	2.27 (1.83, 2.80)	<0.001	1.97 (1.64, 2.37)	<0.001	2.00 (1.57, 2.54)	<0.001	1.65 (1.03, 2.65)	0.038
BMI	1.93 (1.63, 2.29)	<0.001	1.75 (1.52, 2.01)	<0.001	1.61 (1.42, 1.82)	<0.001	1.49 (1.27, 1.75)	<0.001	1.54 (1.13, 2.13	0.007
WC	2.23 (1.77, 2.80)	<0.001	1.86 (1.60, 2.17)	<0.001	1.64 (1.43, 1.89)	<0.001	1.61 (1.34, 1.92)	<0.001	1.48 (1.06, 2.08)	0.022
WHR	2.01 (1.56, 2.60)	<0.001	1.79 (1.49, 2.16)	<0.001	1.42 (1.23, 1.64)	<0.001	1.58 (1.32, 1.88)	<0.001	1.30 (0.93, 1.81)	0.120

Multivariable models were adjusted for age, sex, smoking, prevalent hypertension and family history of diabetes. Abbreviations same as in Table 3.

modification by sex was observed in both cohorts i.e., the *adiposity index*sex* term was not significant with a *P-value* for interaction>0.1.

Similar to the results from the PREVEND cohort, effect sizes for all adiposity indices were generally largest in the younger age categories in both LifeLines and Rotterdam Study cohorts (Table S12).

3.1. Discussion

In the current study enrolling individuals from the Dutch general population, we examined associations of RFM, BMI, WC and WHR with incident T2D. We found that RFM was more strongly associated with incident T2D than commonly used measures of obesity. These associations were present across all age categories, and they were most pronounced in younger individuals.

BMI, initially called the Quetelet index, was developed approximately 200 years ago by a Belgian mathematician to characterize the "average" man [28,29]. Currently, BMI is the most commonly used marker of obesity – not just on a population level but also on an individual level. However, BMI does not distinguish between fat mass and fat-free mass, and between subcutaneous and visceral fat deposition [5, 6]. These limitations and the understanding that visceral adipose tissue is more closely related to the pathogenesis of diabetes, resulted in the inclusion of WC or WHR – as an alternative to BMI in several diabetes risk prediction algorithms [9]. Nevertheless, aggregate data from meta-analyses show that associations of WC and WHR with incident diabetes are not substantially stronger than that of BMI [10].

RFM is a newly developed anthropometric index that more accurately estimates whole-body fat percentage compared to traditional equations such as BMI and WHR [11]. The RFM algorithm is easy to calculate, is derived from WC and height, and is sex-specific. In a large multi-ethnic cohort from the US including Mexican-Americans, European-Americans, and African-Americans, RFM displayed stronger correlations with dual-energy X-ray absorptiometry (DEXA)-obtained fat mass than BMI [11]. These results were also reproduced in a smaller external validation study enrolling 61 individuals from the Mexican population [30].

Previously, we examined associations of adiposity with new-onset heart failure in the PREVEND cohort and found that among multiple anthropometric indices of adiposity, RFM was the strongest predictor of heart failure risk [15]. Now, we report that association of RFM with new-onset T2D was also stronger than that of BMI, WC and WHR in the PREVEND cohort. Findings were similar in the more contemporary and substantially larger LifeLines cohort enrolling participants from the northern provinces of the Netherlands. In the Rotterdam Study cohort both RFM and BMI were strongly associated with incident T2D (Table 5).

Additionally, in the PREVEND cohort, we observed some sex-related differences in associations of RFM, BMI and WC with incident T2D on a relative scale i.e., women had higher hazard ratios than men. While effect sizes were also numerically larger in women in the LifeLines cohort (particularly for RFM), opposite trends were observed in the Rotterdam Study cohort i.e., larger effect sizes in men. This could, at least in part, be explained by the differences in the age range of the Rotterdam Study compared with the other two cohorts: the Rotterdam study enrolled older individuals, where the absolute risk of developing T2D was comparable among women and men.

Previous studies have demonstrated that lifestyle changes are effective in preventing both diabetes and obesity in high-risk individuals [31]. In the PREVEND cohort, we found that all measures of adiposity strongly related with the risk of developing T2D across all age categories, and these associations were strongest in participants younger than 40 years (Table 4). Similar trends were found across age categories in the LifeLines and Rotterdam Study cohorts (Table S12), and have also been observed in associations of risk factors with incident HF [32]. Although an inflated relative risk in younger participants may be attributed to their lower baseline risk of disease [33], our results highlight the need for adequate obesity control to prevent T2D development - not just in middle-aged and older individuals but also in younger individuals with a relatively low risk factor burden.

3.2. Study strengths and limitations

We report for the first time, the association between RFM and incident T2D in the general population. The long term follow-up of participants and a 1:1 sex ratio further strengthen our analyses. As the PREVEND study, by design, included a higher proportion of individuals with UAE>10 mg/L, we also validated these results using data from two other general population-based cohorts. A more general limitation includes the unavailability of HbA1c measurements in the PREVEND and Rotterdam Study cohorts, and the unavailability of data on prescribed medication in the LifeLines cohort. Finally, although the current study included participants from 3 large cohorts, participants were almost exclusively Dutch and predominantly White, warranting validation of our findings in cohorts from other geographical locations and ethnicities.

4. Conclusion

RFM strongly predicts new-onset T2D in the Dutch population and displays the potential to be routinely used in the general practice setting to estimate future risk of diabetes. Our findings also highlight that adequate obesity control, particularly in young individuals, would substantially reduce the risk of developing T2D in the community.

Patient and public involvement

No participants were involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. No participants were asked to advise on interpretation or writing up of results.

Data availability statement

Data may be made available upon reasonable request from qualified researchers.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.12.024.

References

[1] NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. Lancet 2016;387(10026). https://doi.org/10.1016/S0140-6736(16)30054-X.

[2] Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017-2018. NCHS Data Brief 2020;(360).

[3] Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-level prevalence of adult obesity and severe obesity. N Engl J Med 2019;381(25):2440–50. https://doi.org/10.1056/NEJMsa1909301.

[4] Schnurr TM, Jakupović H, Carrasquilla GD, et al. Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. Diabetologia 2020;63(7). https://doi.org/10.1007/s00125-020-05140-5.

[5] Rothman KJ. BMI-related errors in the measurement of obesity. Int J Obes 2008;32: S56–9. https://doi.org/10.1038/ijo.2008.87.

[6] Humphreys S. The unethical use of BMI in contemporary general practice. Br J Gen Pract 2010;60(578):696–7. https://doi.org/10.3399/bjgp10X515548.

[7] Hajer GR, van Haeften TW, Visseren FLJ. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. Eur Heart J 2008;29(24). https://doi.org/10.1093/eurheartj/ehn387.

[8] Joseph JJ, Kluwe B, Echouffo-Tcheugui JB, et al. Association of adiposity with incident diabetes among black adults in the jackson heart study. J Am Heart Assoc 2021;10(18). https://doi.org/10.1161/JAHA.120.020716.

[9] Abbasi A, Peelen LM, Corpeleijn E, et al. Prediction models for risk of developing type 2 diabetes: systematic literature search and independent external validation study. BMJ 2012;345. https://doi.org/10.1136/bmj.e5900 (sep18 2).

[10] Vazquez G, Duval S, Jacobs DR, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev 2007;29(1). https://doi.org/10.1093/epirev/mxm008.

[11] Woolcott OO, Bergman RN. Relative fat mass (RFM) as a new estimator of whole-body fat percentage - a cross-sectional study in American adult individuals. Sci Rep 2018;8(1):10980. https://doi.org/10.1038/s41598-018-29362-1.

[12] Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. PLoS One 2012;7(7):e39504. https://doi.org/10.1371/journal.pone.0039504.

[13] Thomas DM, Bredlau C, Bosy-Westphal A, et al. Relationships between body roundness with body fat and visceral adipose tissue emerging from a new geometrical model. Obesity 2013;21(11):2264–71. https://doi.org/10.1002/oby.20408 (Silver Spring).

[14] Park Y, Kim NH, Kwon TY, Kim SG. A novel adiposity index as an integrated predictor of cardiometabolic disease morbidity and mortality. Sci Rep 2018;8(1): 16753. https://doi.org/10.1038/s41598-018-35073-4.

[15] Suthahar N, Meems LMG, Withaar C, et al. Relative fat mass, a new index of adiposity, is strongly associated with incident heart failure: data from PREVEND. Sci Rep 2022;12(1):147. https://doi.org/10.1038/s41598-021-02409-6.

[16] Hillege HL, Fidler V, Diercks GFH, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 2002;106(14). https://doi.org/10.1161/01.CIR.0000031732.78052.81.

[17] Suthahar N, Meijers WC, Brouwers FP, et al. Heart failure and inflammation-related biomarkers as predictors of new-onset diabetes in the general population. Int J Cardiol 2018;250:188–94. https://doi.org/10.1016/j.ijcard.2017.10.035.

[18] Scholtens S, Smidt N, Swertz MA, et al. Cohort profile: lifelines, a three-generation cohort study and biobank. Int J Epidemiol 2015;44(4):1172–80. https://doi.org/10.1093/ije/dyu229.

[19] Zwartkruis VW, Groenewegen A, Rutten FH, et al. Proactive screening for symptoms: a simple method to improve early detection of unrecognized cardiovascular disease in primary care. Results from the lifelines cohort study. Prev Med 2020;138:106143. https://doi.org/10.1016/j.ypmed.2020.106143 (Baltim).

[20] Ikram MA, Brusselle G, Ghanbari M, et al. Objectives, design and main findings until 2020 from the Rotterdam Study. Eur J Epidemiol 2020;35(5):483–517. https://doi.org/10.1007/s10654-020-00640-5.

[21] Wang K, Kavousi M, Voortman T, Ikram MA, Ghanbari M, Ahmadizar F. Cardiovascular health, genetic predisposition, and lifetime risk of type 2 diabetes. Eur J Prev Cardiol 2022;28(16):1850–7. https://doi.org/10.1093/eurjpc/zwab141.

[22] Safar FH, Mojiminiyi OA, Al-Rumaih HM, Diejomaoh MF. Computational methods are significant determinants of the associations and definitions of insulin resistance using the homeostasis model assessment in women of reproductive age. Clin Chem 2011;57(2):279–85. https://doi.org/10.1373/clinchem.2010.152025.

[23] Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359(21):2195–207. https://doi.org/10.1056/NEJMoa0807646.

[24] Wu H, Ballantyne CM. Metabolic inflammation and insulin resistance in obesity. Circ Res 2020;126(11). https://doi.org/10.1161/CIRCRESAHA.119.315896.

[25] Fabozzi FJ, Focardi SM, Rachev ST, Arshanapalli BG. Appendix E: model selection criterion: AIC and BIC. The basics of financial econometrics, 41. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2014. p. 399–403. https://doi.org/10.1002/9781118856406.app5.

[26] Khan SS, Ning H, Shah SJ, et al. 10-year risk equations for incident heart failure in the general population. J Am Coll Cardiol 2019;73(19):2388–97. https://doi.org/10.1016/j.jacc.2019.02.057.

[27] Neath A. p-Values and the likelihood principle. Proc Am Stat Assoc 2016:966–71.

[28] Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. Int J Obes 1985;9(2):147–53.

[29] Eknoyan G. Adolphe quetelet (1796 1874) the average man and indices of obesity. Nephrol Dial Transplant 2007;23(1). https://doi.org/10.1093/ndt/gfm517.

[30] Guzmán-León AE, Velarde AG, Vidal-Salas M, Urquijo-Ruiz LG, Caraveo-Gutiérrez LA, Valencia ME. External validation of the relative fat mass (RFM) index in adults from north-west Mexico using different reference methods. PLoS One 2019;14(12). https://doi.org/10.1371/journal.pone.0226767.

[31] Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346(6). https://doi.org/10.1056/NEJMoa012512.

[32] Tromp J, Paniagua SMA, Lau ES, et al. Age dependent associations of risk factors with heart failure: pooled population based cohort study. BMJ 2021. https://doi.org/10.1136/bmj.n461. March.

[33] Noordzij M, van Diepen M, Caskey FC, Jager KJ. Relative risk versus absolute risk: one cannot be interpreted without the other. Nephrol Dial Transplant 2017;32 (suppl_2). https://doi.org/10.1093/ndt/gfw465. ii13-ii18.