Novel metabolic indices and incident type 2 diabetes among women and men: the Rotterdam Study

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Abstract

Aims/hypothesis: Both visceral and truncal fat have been associated with metabolic disturbances. We aimed to investigate the associations of several novel metabolic indices, combining anthropometric and lipid measures, and DXA measurements on body fat with incident type 2 diabetes (T2D) among women and men from the large population-based Rotterdam Study.

Methods: We used Cox proportional hazard models to investigate associations between Visceral Adiposity Index (VAI), Lipid Accumulation Product (LAP), the product of Triglycerides and Glucose (TyG), their formula components, and DXA measures with incident T2D. Associations were adjusted for traditional diabetes risk factors.

Results: Among 5576 women and 3988 men free of diabetes, 511 women and 388 men developed T2D during a median follow-up of 6.5 years. In adjusted models, the 3 metabolic indices; VAI (per 1-SD naturally log-transformed HR; 95% CI: 1.49; 1.36,1.65 in women, 1.37; 1.22,1.53 in men), LAP (1.35; 1.16,1.56 in women, 1.19; 1.01,1.42 in men), and TyG (1.73; 1.52,1.98 in women, 1.43; 1.26,1.62 in men), gynoid fat mass (0.63; 0.45,0.89) and android to gynoid ratio (1.51; 1.16,1.97) in women were associated with incident T2D.
Body mass index (1.45; 1.28, 1.65) was the strongest predictor for T2D in men.

Conclusions/interpretation: Among women, novel combined metabolic indices were stronger risk markers for T2D than the traditional anthropometric and laboratory measures and were comparable to DXA measures. Neither combined metabolic indices nor DXA measures were superior to traditional anthropometric and lipid measures in association with T2D among men.

Abbreviations:

VAI - Visceral Adiposity Index

LAP - Lipid Accumulation Product

TyG - the product of triglycerides and glucose

DXA - Dual energy X-ray Absorptiometry

T2D - Type 2 Diabetes

CVD – Cardiovascular Diseases

HR – Hazard Ratio

CI – Confidence Interval

Introduction

The location of fat accumulation in the body, rather than total fat volume, is increasingly shown to be more important for the risk of type 2 diabetes (1). Both visceral adipose tissue (VAT) and truncal fat depot have been associated with type 2 diabetes (2-4) and metabolic syndrome (5; 6).

VAT is a hormonally active component of body fat. The risk of developing diabetes has been shown to be higher in individuals with excess of visceral adiposity, with (3) or without (7) manifestations of obesity. Therefore VAT plays a key role in the association between adiposity and glucose metabolism (4; 8-10). However, traditional anthropometric measures such as body mass index (BMI) and waist circumference (WC) are not able to distinguish VAT from subcutaneous adipose tissue (11). Furthermore, VAT accounts for an increased cardiometabolic risk regardless of BMI levels (12). Truncal fat depot can be partitioned into upper body (android or central) and lower body (gynoid or peripheral) areas. High android-gynoid percent fat ratio has shown a greater correlation with cardiometabolic dysregulation than BMI (13). Among the elderly, android fat depot seems to be more closely associated with metabolic syndrome than abdominal visceral fat (5).

Computed Tomography (CT) (2; 12) and Magnetic Resonance Imaging (MRI) (3) are the golden standard measures for quantification of VAT. Dual-energy X-Ray Absorptiometry (DXA) is the well-validated imaging method for precise measurement of body fat mass in various body compartments (i.e. android and gynoid fat) (14). However, these imaging modalities for assessing adipose tissue distribution are inconvenient and expensive. Recently, different metabolic indices combining both anthropometric and lipid measures have been used as estimators of visceral adiposity dysfunction (15) and lipid overaccumulation (16; 17). These novel indices, including Visceral Adiposity Index (VAI), Lipid Accumulation Product (LAP),

and the product of Triglycerides and Glucose (TyG), have been suggested as early markers of insulin resistance mainly in cross-sectional studies (18-20). However, the associations of these novel metabolic indices with incident type 2 diabetes remain unclear. Therefore, we studied the associations of different novel metabolic indices and their formula components with incident type 2 diabetes among women and men from the large prospective population-based cohort of the Rotterdam Study. We further assessed the associations of truncal fat depot measured by DXA with incident type 2 diabetes.

Research Design and Methods

Study population

The study was performed in the framework of the Rotterdam Study (RS). RS is a prospective population-based cohort study in Ommoord, a district of Rotterdam, the Netherlands. The design of the Rotterdam Study has been described in more details elsewhere (21). The original cohort (RSI) started in 1989 when all residents within the well-defined study area aged 55 years or older were invited to participate of whom 78% (7983 out of 10275) participated. The first examination of the original cohort (RSI-1) took place from 1990 to 1993. The cohort has been extended twice (RSII in 2000 and RSIII in 2006) to include the participants who were 45 years or older or moved to the study research area. For all 3 cohorts of RS, follow-up examinations were conducted every 3-5 years. The study has been approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of Netherlands. All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

The current study was based on data collected during the third visit of the first cohort (RSI-3; 1997-1999), the first visit of the second cohort (RSII-1; 2000-2001), and the first visit of the third cohort (RSIII-1; 2006-2008). From 11740 subjects in the three visits of the Rotterdam Study, diabetes data were available for 10898 subjects (6241 women and 4657 men). After excluding 1334 prevalent diabetes cases (665 women and 669 men), 9564 subjects (5576 women and 3988 men) were included in the analyses of different metabolic indices and incident type 2 diabetes. DXA measurements on body fat were available in 3518 subjects (2026 women and 1492 men) with available diabetes data at the fourth visit of the first cohort (RSI-4; 2002-2004) and the second visit of the second cohort (RSII-2; 2004-2005). After excluding 556 prevalent diabetes cases (292 women and 264 men) at the time of DXA measurement, 2962 subjects (1734 women and 1228 men) were included in the analyses between DXA measures of body fat and incident type 2 diabetes.

Combined metabolic indices

Novel metabolic indices combine anthropometric measures such as BMI and WC with lipid measures; triglyceride (TG) or high-density lipoprotein (HDL) cholesterol, or fasting plasma glucose (FPG).

LAP, VAI, and TyG were calculated using the published formulas. LAP was calculated as LAP= $(WC - 65) \times TG$ for men and LAP= $(WC - 58) \times TG$ for women (22). VAI was calculated as VAI = $\left[\left(\frac{WC}{39.68}\right) + (1.88 \times BMI)\right] \times \left(\frac{\mathrm{TG}}{1.03}\right) \times \left(\frac{1.31}{\mathrm{HDL}}\right)$ for men and VAI = $\left[\left(\frac{WC}{36.58}\right) + (1.89 \times BMI)\right] \times \left(\frac{\mathrm{TG}}{0.81}\right) \times \left(\frac{1.52}{\mathrm{HDL}}\right)$ for women (15). In both formulas, TG and HDL

cholesterol levels are expressed in mmol/l, WC in cm, and BMI in kg/m^2.

The TyG index was calculated as Ln $\left(\mathrm{TG} \times \frac{\mathrm{FPG}}{2}\right)$ where both TG and FPG are expressed in mg/dl (18; 20).

DXA measurements on body fat

Body composition was assessed using DXA. For the whole body DXA scans we used ProdigyTM total body-fan beam densitometer (GE Lunar Corp, Madison, WI, USA) (21). Total body weight (grams) was divided into bone mineral content, lean mass, and fat mass. In addition, we analyzed fat mass of the android body region and gynoid body region. Total fat mass percentage, android fat percentage, and gynoid fat percentage were calculated as percentages of total body weight. We also calculated the ratio of android to gynoid fat mass percentage.

Ascertainment of type 2 diabetes mellitus

Participants were followed from the date of baseline center visit onwards. Cases of type 2 diabetes were ascertained through active follow-up using general practitioners' records, hospital discharge letters, pharmacy data, and glucose measurements from RS visits which take place approximately every 4 years (23). In the RS, T2D ascertainment was done the same way for all individuals, avoiding substantial potential for misclassification or ascertainment bias. According to the current WHO guidelines, T2D was defined as a fasting blood glucose ≥ 7.0 mmol/L, a non-fasting blood glucose ≥ 11.1 mmol/L (when fasting samples were unavailable), or the use of blood glucose lowering medication (24). Information regarding the use of blood glucose lowering medication was derived from both structured home interviews and linkage to pharmacy dispensing records. At baseline, more than 95% of the RS population was covered by the pharmacies in the study area. All potential events of T2D were independently adjudicated by two

study physicians. In case of disagreement, consensus was sought with an endocrinologist. Follow-up data was complete until January 1st 2012 (25).

Covariates

Detailed information on covariates can be found in the electronical supplemental material accompanying this manuscript.

Statistical analysis

Considering gender differences in fat distribution and that the formulas of metabolic indices differ by gender, all analyses were performed among women and men separately. Descriptive characteristics were presented as mean ± standard deviation (SD) for continuous variables and numbers (percentages) for dichotomous variables. To compare general characteristics between women and men as well as between participants with or without DXA measures, we used One Way ANOVA for continuous variables and Chi-Square test (Chi^2) for categorical variables. Markers with a right-skewed distribution (including insulin, glucose, HDL cholesterol, triglycerides, VAI, LAP, android fat %, gynoid fat %, android to gynoid ratio, total fat mass %) were transformed to the natural logarithmic scale.

We used Cox proportional hazard models to investigate associations of different combined metabolic indices (VAI, LAP, TyG), the anthropometric (BMI, WC) or laboratory components (inverse HDL cholesterol, TG) included in their formulas, as well as DXA measurements on body fat (android, gynoid, total fat mass, the ratio of android to gynoid fat mass percentage) with incident T2Ds. We used inverse HDL cholesterol to facilitate easier comparison between the estimates. The proportional hazard assumption of the Cox model was checked by visual inspection of log minus log plots and by performing a test for heterogeneity of the exposure over

time. There was no evidence of violation of the proportionality assumption in any of the models (p for time-dependent interaction terms > 0.05). The first model was adjusted for age and cohort. In the second model, we additionally adjusted for BMI. In the third model, we additionally adjusted for systolic blood pressure, medication for hypertension, smoking and prevalent CVD. In the fourth model, we added HDL cholesterol, TG, serum lipid reducing agents. In the fifth model, we added fasting glucose. As glucose is a mean for diagnosis of T2D, this model should be considered a conservative model. For each novel lipid index, the covariates that were already in the index formula were excluded from the multivariable adjusted model.

To check whether the association of different markers with incident diabetes differ by obesity status, we further stratified the analyses based on BMI cut-off of 30 and performed the analyses among non-obese (BMI < 30) and obese (BMI ≥ 30) individuals. The p-value is derived from the z- score calculated from the ratio between the difference of the two estimates and standard error of this difference (26). The p-value indicates whether the difference between the estimates is significant. To compare the estimates between women and men, we applied an interaction test in model four (in the analyses for total population).

Multiple imputation procedure was performed (N = 5 imputations) to impute missing data for covariates. All analyses were conducted in SPSS software version 21 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). A P-value <0.05 was considered statistically significant.

Results

Metabolic indices and incident type 2 diabetes

Baseline characteristics of 5576 women and 3988 men included in the study are shown in Table 1. Women were older, had lower levels of systolic blood pressure and glucose but higher levels

of total cholesterol. A larger proportion of women were treated for hypertension. CVD was more prevalent among men and a larger proportion of men were receiving lipid reducing agents or were current smokers. BMI, HDL cholesterol, TG and VAI were higher in women whereas WC, LAP and TyG were higher in men (Table 1).

The correlation coefficients for metabolic indices in relation to glycemic indices are shown in ESM Table 1. For both women and men, the correlation coefficients for VAI, LAP, and TyG ranged between 0.43-0.57 for HOMA-IR and between 0.04-0.28 for HOMA-B. The correlation coefficients for different visceral fat indices in relation to HOMA-IR were overall larger among women compared to men, albeit not statistically significant.

During a median follow-up of 6.5 years (maximum of 14.7 years) 899 incident T2D cases were identified (511 women and 388 men). All indices were significantly associated with the risk of T2D in age adjusted models (model 1). In the multivariable-adjusted model (model 4), TyG showed the largest association with T2D in both women (per 1 SD HR; 95% CI: 1.73; 1.52, 1.98) and in men (1.43; 1.26, 1.62). Other markers that remained significantly associated with incident T2D in both genders in the multivariable-adjusted model were BMI (1.37; 1.26, 1.49 in women and 1.45; 1.28, 1.65 in men), inverse HDL cholesterol (per 1 SD naturally log-transformed HR; 95% CI: 1.29; 1.14, 1.46 in women and 1.32; 1.14, 1.52 in men), VAI (1.49; 1.36, 1.65 in women and 1.37; 1.22, 1.53 in men), LAP (1.35; 1.16, 1.56 in women and 1.19; 1.01, 1.42 in men). WC (1.24; 1.07, 1.45) and TG (1.24; 1.10, 1.39) remained strongly associated with the risk for T2D only in women (Table 2). Associations of metabolic indices with diabetes were overall larger among women compared to men. However, the difference of the estimates between women and men was statistically significant only for TyG (Table 2).

After additionally adjusting for fasting glucose (model 5), only BMI (1.27; 1.17, 1.38 for women and 1.25; 1.09, 1.43 for men), inverse HDL cholesterol (1.29; 1.14, 1.47 for women and 1.41; 1.22, 1.63 for men), and VAI (1.29; 1.17, 1.43 for women and 1.23; 1.09, 1.38 for men) remained significantly associated with the risk for T2D in both genders (Table 2).

In the analyses stratified for obesity status, in the multivariable adjusted model (model 4), BMI, inverse HDL cholesterol, VAI, and TyG remained significantly associated with incident diabetes regardless of the obesity status. While LAP was significantly associated with incident diabetes among non-obese women and men, WC and TG remained strongly associated with the risk for T2D only in non-obese women. Overall, the tendency for the associations of visceral fat indices with diabetes was stronger among non-obese individuals (ESM Table 2).

DXA measurements on body fat and incident type 2 diabetes

Android fat, gynoid fat and total fat mass percentages were higher in women whereas the ratio of android to gynoid fat percentage was higher in men (Table 1). Complete baseline characteristics of 1770 women and 1258 men included in the analyses for DXA measures and T2D are presented in ESM Table 3.

Among 1770 women and 1258 men included in the analyses for DXA measurements, 185 women and 137 men developed type 2 diabetes during a median follow-up of 8 years (maximum of 10 years). Gynoid fat percentage (per 1 SD naturally log-transformed HR; 95% CI: 0.63; 0.45, 0.89) and the ratio of android to gynoid fat percentage (1.51; 1.16, 1.97) remained significantly associated with incident T2D in the multivariable-adjusted model (model 4) only in women. (Table 3).

In the analyses stratified for obesity status, gynoid fat percentage (0.57; 0.38, 0.84) and the ratio of android to gynoid fat percentage (1.77; 1.29, 2.41) remained significantly associated with incident type 2 diabetes in the multivariable-adjusted model (model 4) only in non-obese women (ESM Table 4). After additionally adjusting for fasting glucose (model 5), only the ratio of android to gynoid fat mass percentage (1.51; 1.09, 2.08) remained associated with incident T2D in non-obese women (ESM table 4).

Discussion

In our large population-based Rotterdam Study, novel metabolic indices; VAI, LAP and TyG, were stronger risk markers for incident diabetes than the traditional anthropometric and lipid measures among women. The magnitude of association of these novel metabolic indices with diabetes was also comparable to DXA measured body fat compositions in women. Among men, neither combined metabolic indices nor DXA measures on body fat were superior to traditional anthropometric and lipid measures, in particular BMI, in association with diabetes.

VAT is a hormonally active component of total body fat, which may play a key role in the association between adiposity and glucose metabolism (4; 8-10). Excess visceral adiposity has been linked to higher risk of T2D, regardless of obesity (2; 3; 7; 12). The three combined metabolic indices: VAI, LAP and TyG have been introduced as indicators of "visceral adipose function" (15) and insulin resistance (18-20) and have been linked to cardio-metabolic risk (15), prediabetes (27) and diabetes (27) in cross-sectional studies. Our study is the first to simultaneously investigate the longitudinal associations of all these new indices, as well as their components, with incident T2D among women and men. The three novel combined metabolic indices were all independently associated with increased risk of diabetes in our study. VAI and

LAP combine both anthropometric and metabolic parameters to evaluate respectively adiposity dysfunction and lipid overaccmulation, whereas TyG includes only metabolic parameters. TyG is among the most mentioned insulin resistance indices in the existing literature (28-35). TyG has also been suggested as a promising biomarker for glycemic control in patients with T2D (29), even better than HOMA (28). In comparison with fasting plasma glucose, TyG improved diabetes risk prediction in individuals with normal fasting glucose (36). LAP includes WC and TG, similarly to hypertriglyceridemic waist (17) and is an index for excessive lipid accumulation. Since precise measurement of visceral fat content requires the use of expensive imaging techniques such as CT or MRI (2; 12), simple and economical quantification of these visceral adiposity indices could lead to improvements in identification of individuals at high risk for type 2 diabetes.

The counterbalance between insulin secretion and insulin resistance is critical for T2D pathogenesis. VAI, LAP and TyG have been introduced as early indicators of insulin resistance (18-20). In our study, these three indices were all moderately correlated with an index of insulin resistance (HOMA-IR) and showed a smaller correlation with insulin secretion (HOMA-B). As VAI and LAP combine both lipid variables and adiposity status, they could serve as better surrogates for insulin resistance compared to either lipid or adiposity measures alone. The largest correlation of TyG with IR in our study is in line with other studies, supporting that both lipotoxicity and glucotoxicity have central role in modulation of insulin resistance (37). Since obesity has a strong impact on dyslipidemia, insulin resistance and development of T2D, we further stratified the analyses based on obesity status. Correlation of different combined adiposity indices with HOMA measures did not materially differ between non-obese and obese individuals. The overall tendency towards stronger associations of these metabolic indices with

incident diabetes among non-obese individuals might be due to their lower discriminatory power among higher risk obese individuals.

While the exact mechanisms responsible for the relationship between excess abdominal/visceral fat and cardiometabolic risk are still unclear, several hypotheses are proposed (38-40). Subcutaneous fat faces obesogenic stress with a limited capacity for regional adipocyte hypertrophy or hyperplasia. Once this capacity is overpassed, adipose tissue storage is forced into other regions, such as organs or compartments of the body, which are named ectopic. Visceral fat is considered the classic ectopic fat depot and is associated to dysfunctional adiposity or adiposopathy (41; 42).

WC, TG, VAI, LAP, and TyG showed a stronger association with incident T2D among women in our study, compared to men. Similarly, the correlations between VAI, LAP, and TyG with HOMA-IR in our study were overall stronger among women. The greater association of VAT with diabetes and adverse cardiovascular risk profiles among women has been suggested by several studies (43; 44). Gender differences in adverse metabolic outcomes associated with visceral fat have been related to a significantly lower visceral fat area in nondiabetic women compared with nondiabetic men and a similar visceral fat area for both diabetic women and men (43). Among individuals with more visceral fat, a greater portion of hepatic free fatty acid delivery originates from visceral adipose tissue lipolysis (45). Contribution of the visceral lipolysis to hepatic free fatty acid delivery in relation to visceral fat has been found to be greater in women than in men (45). Moreover, correlation between visceral adipose tissue area and serum triglycerides has been found to be stronger in women than in men (46).

No previous study has investigated the associations of DXA measures on body fat with incident T2D. Our study suggests gynoid fat percentage and android-gynoid percent fat ratio among women and total fat mass among men as independent risk markers for diabetes. Previous studies have shown important relations between the android/gynoid fat and metabolic risk in healthy adults. Android or truncal obesity has been associated with the risk for metabolic disorders and cardiovascular disease (47), yet there is evidence that gynoid fat distribution may be protective (48). Android fat depot is the adipose tissue mainly around the trunk including, but not exclusively, visceral fat. Compared to abdominal visceral fat, android fat depot has shown a larger association with metabolic syndrome in elderly people (5). In line with our findings, high android-gynoid percent fat ratio has shown a larger correlation with cardiometabolic dysregulation than android percent fat, gynoid percent fat, or BMI (13). Compared to women with a predominantly gynoid distribution, android obesity in women has been correlated with a higher incidence of glucose intolerance (49). Excess android fat mass has recently been associated with high triglycerides and low HDL cholesterol levels in men and high LDL and low HDL cholesterol levels in women. Excess gynoid fat mass has been positively correlated with total cholesterol in men and has shown a favorable association with triglycerides and HDL cholesterol in women (50). Increased gynoid fat mass has also shown to be protective against the progression of NAFLD in female Japanese patients with type 2 diabetes (51). It therefore seems that regional fat distribution in the android and gynoid regions have varying effects on lipid profiles among women and men. In line with this, we found an inverse association between gynoid fat and android to gynoid ratio with T2D in women and a positive association between the total fat mass with T2D in men.

In our study, the magnitude of the association between DXA measures of body fat and diabetes was comparable to those of combined metabolic indices and traditional anthropometry and lipid measures. Considering the costs and radiation exposure associated with DXA measurement, its use in the general population as a screening tool for diabetes may therefore not be justified and using well established and simple anthropometric parameters such as BMI might suffice.

To our knowledge, this is the first prospective population-based cohort study to simultaneously investigate the associations between novel metabolic indices as well as DXA measures with incident diabetes among women and men over a long follow-up. We used data from a well-characterized prospective cohort study, which allowed for direct comparison of several metabolic indices as well as correction for a wide range of covariates. The limitations of our study also warrant attention. Our population comprises 55 years and older individuals of European ancestry. One might speculate that the impact of VAT on diabetes incidence would have even been stronger in a younger population. Thus, generalization of our results to younger age groups and other ethnicities should be done with caution. Moreover, as with all other cohort studies, the possibility of selection bias could not be entirely ruled out. Due to unavailability of CT or MRI in our population, visceral adiposity was not directly measured but estimated. Also, we did not have DXA measures specifically for visceral fat in the Rotterdam Study. Instead, android fat measured by DXA was used as a proxy for the visceral fat. Thus, comparison of our results against the gold standard measures for visceral fat is not possible. We did not include variables such as socioeconomic status, family history of diabetes, dietary intake and physical activity in our multivariable models, as that they were not available.

In conclusion, novel combined metabolic indices; VAI, LAP and TyG, were stronger risk markers for incident type 2 diabetes than the traditional anthropometric and lipid measures

among women. The predictive value of these novel metabolic indices for type 2 diabetes was also comparable to DXA measured body fat compositions in women. Neither combined metabolic indices nor DXA measures on body fat were superior to traditional anthropometric and lipid measures in association with type 2 diabetes among men. Particularly, BMI remained the best marker for type 2 diabetes risk in men and among the best markers in women. BMI could therefore be used as a simple and useful tool for diabetes risk screening in the general population.

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Author contribution

AB ran the analysis and wrote the manuscript. MK, EJGS and AD designed the study and critically revised the manuscript. All authors have read and approved the manuscript. OHF designed the study and provided resources. AB is the guarantor of this work.

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Table 1. Baseline characteristics of study participants (N=9564).

Characteristic	Women (N = 5576)	Men (N = 3988)	p-value
Age (years)	65.1 ± 10.3	64.3 ± 9.5	< **0.001**
Systolic Blood pressure (mm/Hg)	136.2 ± 21.6	138.6 ± 20.2	< **0.001**
Treatment for hypertension	1225.0 (22.0%)	786.0 (19.7)	**0.011**
Prevalent cardiovascular disease (%)	282.0 (5.1)	564.0 (14.1)	< **0.001**
Serum lipid reducing agents use (%)	739.0 (13.3)	639.0 (16.0)	**0.001**
Current smokers	809.0 (14.5)	874.0 (21.9)	< **0.001**
Total cholesterol (mmol/l)	5.9 ± 0.9	5.5 ± 0.9	< **0.001**
*Insulin (pmol/l)	69.0 (30.0 – 182.0)	71.0 (30.0 – 188.0)	0.2
*Glucose (mmol/l)	5.3 (4.6 – 6.4)	5.5 (4.7 – 6.5)	< **0.001**
Metabolic indices			
BMI (kg/m^2)	27.1 ± 4.5	26.7 ± 3.4	< **0.001**
Waist circumference (cm)	89.1 ± 11.8	97.7 ± 10.0	< **0.001**
*High density lipoprotein cholesterol	1.5 (0.9 – 2.3)	1.2 (0.8 – 1.9)	< **0.001**
*Triglycerides (moml/l)	1.3 (0.7 – 2.8)	1.3 (0.7- 3.1)	< **0.001**
*VAI	1.6 (0.6 – 4.8)	1.5 (0.6 – 4.8)	**0.008**
*LAP	38.1 (11.4 – 106.8)	42.6 (15.7 – 122.4)	< **0.001**
TyG	2.8 ± 0.5	2.9 ± 0.5	< **0.001**
DXA measurements	Women (1770)	Men (1258)	
*Android fat %	3.3 (1.8 – 4.5)	3.1 (1.6 – 4.3)	< **0.001**
*Gynoid fat %	6.3 (4.5 – 8.1)	3.9 (2.6 – 5.3)	< **0.001**
*Android/Gynoid	0.5 (0.3 – 0.7)	0.8 (0.5 – 1.1)	< **0.001**
*Total fat mass %	39.3 (27.2 – 48.6)	27.6 (16.9 – 37.1)	< **0.001**

Values are presented as means ± standard deviation,* median (inter-quartile range), or numbers (percentages).
P-values are for the comparison of baseline characteristics between women and men.
Abbreviations: BMI, body mass index; VAI, visceral adiposity index; LAP, lipid accumulation product; TyG, the product of fasting glucose and triglycerides.
From the original 9564 participants, DXA measurements were available in 3028 participants. Baseline characteristics of participants with DXA differ significantly ($p < 0.001$) from participants without available DXA measures, whereas they do not have significant difference for prevalent CVD (P=0.3); HDL cholesterol (p= 0.055) and triglycerides ($p = 0.7$). However, given that is the same cohorts of the Rotterdam Study, but different visits, the subjects with DXA included in the analyses, are the subset of the study sample without DXA measures, which survived until the next visit of the Rotterdam Study, where DXA was measured.

Table 2. Associations between different metabolic indices and incident type 2 diabetes mellitus (N = 9564).

Index	Incident type 2 diabetes	
	HR(95%CI)	
	Women (511 cases)	Men (388 cases)
BMI		
Model 1	**1.51 (1.39, 1.63)**	**1.64 (1.45, 1.86)**
Model 2	NA	NA
Model 3	**1.49 (1.38, 1.62)**	**1.61 (1.42, 1.82)**
Model 4	**1.37 (1.26, 1.49)**	**1.45 (1.28, 1.65)**
Model 5	**1.27 (1.17, 1.38)**	**1.25 (1.09, 1.43)**
WC		
Model 1	**1.62 (1.49, 1.77)**	**1.44 (1.31, 1.58)**
Model 2	**1.39 (1.19, 1.61)**	1.15 (0.94, 1.39)
Model 3	**1.37 (1.18, 1.59)**	1.13 (0.92, 1.38)
Model 4	**1.24 (1.07, 1.45)**	1.04 (0.83, 1.31)
Model 5	1.04 (0.89, 1.22)	1.04 (0.82, 1.30)
[*]**1/HDL**		
Model 1	**1.58 (1.44, 1.74)**	**1.53 (1.36, 1.73)**
Model 2	**1.46 (1.33, 1.61)**	**1.42 (1.25, 1.61)**
Model 3	**1.46 (1.32, 1.61)**	**1.40 (1.24, 1.59)**
Model 4	**1.29 (1.14, 1.46)**	**1.32 (1.14, 1.52)**
Model 5	**1.29 (1.14, 1.47)**	**1.41 (1.22, 1.63)**
[*]**Triglycerides**		
Model 1	**1.58 (1.44, 1.74)**	**1.44 (1.30, 1.58)**
Model 2	**1.45 (1.31, 1.60)**	**1.30 (1.18, 1.45)**
Model 3	**1.41 (1.28, 1.56)**	**1.28 (1.15, 1.42)**
Model 4	**1.24 (1.10, 1.39)**	1.12 (0.99, 1.27)
Model 5	1.07 (0.95, 1.21)	0.94 (0.83, 1.06)
[*]**VAI**		
Model 1	**1.65 (1.51, 1.81)**	**1.52 (1.36, 1.69)**
Model 2	NA	NA
Model 3	**1.49 (1.35, 1.65)**	**1.37 (1.22, 1.53)**
Model 4	**1.49 (1.36, 1.65)**	**1.37 (1.22, 1.53)**
Model 5	**1.29 (1.17, 1.43)**	**1.23 (1.09, 1.38)**
[*]**LAP**		
Model 1	**1.83 (1.65, 2.03)**	**1.66 (1.47, 1.87)**
Model 2	**1.60 (1.41, 1.82)**	**1.47 (1.27, 1.70)**
Model 3	**1.55 (1.36, 1.76)**	**1.43 (1.24, 1.66)**
Model 4	**1.35 (1.16, 1.56)**	**1.19 (1.01, 1.42)**
Model 5	1.08 (0.93, 1.26)	0.96 (0.81, 1.15)
TyG		
Model 1	**2.06 (1.86, 2.29)**	**1.74 (1.56, 1.94)**
Model 2	**1.88 (1.69, 2.09)**	**1.58 (1.41, 1.77)**
Model 3	**1.82 (1.64, 2.04)**	**1.55 (1.38, 1.75)**
Model 4[s]	**1.73 (1.52, 1.98)**	**1.43 (1.26, 1.62)**
Model 5	NA	NA

Model 1: Adjusted for age and cohort
Model 2: Additionally adjusted for BMI
Model 3: Additionally adjusted for SBP, treatment for hypertension, smoking, prevalent CVD
Model 4: Additionally adjusted for HDL cholesterol, triglycerides, serum lipid reducing agents
Model 5: Additionally adjusted for fasting glucose; Hazard ratios are presented per 1 standard deviation increase in the marker.
[*]Marker is naturally log-transformed.
[s] P-value for the difference in hazard ratio between women and men ≤ 0.05

Table 3. Associations between DXA measurements on body fat and incident type 2 diabetes (N=3028).

DXA measurements	Incident type 2 diabetes	
	HR(95%CI)	
	Women (185 cases)	Men (137 cases)
[*]**Android fat mass %**		
Model 1	**1.77 (1.42, 2.22)**	**1.43 (1.13, 1.81)**
Model 2	**1.42 (1.06, 1.89)**	**1.44 (1.06, 1.95)**
Model 3	**1.36 (1.02, 1.82)**	**1.41 (1.04, 1.92)**
Model 4	1.22 (0.91, 1.64)	1.32 (0.96, 1.83)
Model 5	1.10 (0.83, 1.46)	1.33 (0.96, 1.85)
[*]**Gynoid fat mass %**		
Model 1	1.01 (0.76, 1.35)	1.21 (0.91, 1.59)
Model 2	**0.56 (0.40, 0.78)**	1.03 (0.74, 1.44)
Model 3	**0.57 (0.41, 0.79)**	1.03 (0.74, 1.44)
Model 4[s]	**0.63 (0.45, 0.89)**	1.12 (0.78, 1.59)
Model 5	0.76 (0.54, 1.07)	1.08 (0.76, 1.55)
[*]**Android/Gynoid**		
Model 1	**1.95 (1.55, 2.46)**	**1.56 (1.16, 2.11)**
Model 2	**1.73 (1.36, 2.22)**	**1.49 (1.09, 2.04)**
Model 3	**1.69 (1.32, 2.17)**	**1.46 (1.06, 1.99)**
Model 4	**1.51 (1.16, 1.97)**	1.26 (0.91, 1.76)
Model 5	1.28 (0.98, 1.67)	1.32 (0.93, 1.88)
[*]**Total fat mass %**		
Model 1	**1.56 (1.17, 2.08)**	**1.43 (1.11, 1.84)**
Model 2	0.77 (0.53, 1.11)	**1.43 (1.002, 2.04)**
Model 3	0.75 (0.52, 1.08)	1.41 (0.98, 2.02)
Model 4[s]	0.76 (0.52, 1.13)	1.45 (0.99, 2.12)
Model 5	0.86 (0.59, 1.26)	1.45 (0.99, 2.12)

Model 1: Adjusted for age and cohort
Model 2: Additionally adjusted for BMI
Model 3: Additionally adjusted for SBP, treatment for hypertension, smoking, prevalent CVD
Model 4: Additionally adjusted for HDL cholesterol, triglycerides, serum lipid reducing agents
Model 5: Additionally adjusted for fasting glucose; Hazard ratios are presented per 1 standard deviation increase in the marker.
[*]Marker is naturally log-transformed.
[s] P-value for the difference in hazard ratio between women and men ≤ 0.05