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# Beyond overweight, visceral adiposity is associated with estimation of cardiovascular risk in patients living with type 1 diabetes: findings from the SFDT1 cohort

Laurence Salle[1,2*], Jean-Baptiste Julla[3,4], Guy Fagherazzi[5], Pierre Gourdy[6,7], Erika Bezerra Parente[8,9,10,11], Hélène Hanaire[6,12], Sopio Tatulashvili[13], Emmanuel Disse[14,15,16], Sylvia Franc[17], Samy Hadjadj[18], Etienne Larger[19,20], Caroline Sanz[21], Patricia Vaduva[22], René Valero[23,24], Amélie Bonnefond[25,26,27], Emmanuel Cosson[13,28], Gloria A. Aguayo[5] and Jean-Pierre Riveline[3,4] on behalf of the SFDT1 group

## Abstract

**Introduction & Objectives** As in the general population, people living with type 1 diabetes (PWT1D) are faced with overweight and obesity, which contribute to cardiovascular (CV) risk. However, the role of visceral adiposity, due to its adverse metabolic profile, should also be addressed in PWT1D. We aimed to assess the 10-year CV risk of PWT1D according to body mass index (BMI) and waist-to-height ratio (WHtR), a parameter for estimating visceral adiposity.

**Methods** In this cross-sectional study, PWT1D in primary CV prevention from the SFDT1 cohort were categorized by BMI status, either normal (18.5–24.9 kg/m$^2$) or overweight/obesity (≥ 25 kg/m$^2$), and by WHtR according to the validated threshold of 0.5. The 10-year CV risk was estimated using the Steno Type 1 Risk Engine and classified into three categories: low (< 10%), intermediate (10–20%) and high (> 20%). The distribution of CV risk was assessed using density plots. In multivariable analysis, the association between BMI, WHtR, and high estimated 10-year CV risk was studied using spline regression models with sex stratification. Thresholds were determined by the Receiver Operating Characteristic (ROC) curve.

**Results** The study included 1,482 patients; 49.9% had a normal BMI, and 50.1% a BMI ≥ 25 kg/m$^2$. The proportion of patients with high CV risk was higher in PWT1D with overweight/obesity (12% vs. 7%) and in those with WHtR ≥ 0.5 (13% vs. 4%). BMI was significantly associated with high CV risk in men ($p = 0.001$) but a non-significant trend was found in women ($p = 0.053$). WHtR was significantly associated with high CV risk in both men ($p < 0.001$) and women ($p = 0.046$). The BMI threshold associated with high CV risk was 24.9 kg/m$^2$ for men, and the WHtR threshold was 0.5 for both men and women.

**Conclusion** In PWT1D in condition of primary CV prevention, visceral adiposity, assessed by WHtR, is a more robust marker of estimated 10-year CV risk than overweight/obesity status in both men and women.

*Correspondence:
Laurence Salle
laurence.salle@unilim.fr

Full list of author information is available at the end of the article

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**Keywords** Cardiovascular risk, Body mass index, Type 1 diabetes, Adiposity distribution, Sex, Waist circumference, Registry

## Introduction

Despite improved management of diabetes and cardiovascular (CV) risk, people living with type 1 diabetes (PWT1D) still exhibit a threefold increased risk of CV mortality compared with the general population [1, 2]. Moreover, despite optimal control of five major CV risk factors (blood pressure, low-density lipoprotein (LDL)-cholesterol, glycated hemoglobin (HbA1c), no smoking and no albuminuria), PWT1D keep an 82% increased risk of acute myocardial infarction compared with matched controls [3]. These findings highlight the presence of a residual CV risk in this population. Identifying the parameters associated with this risk is critical to individualize treatment and prevent CV events.

Worldwide, the prevalence of overweight and obesity is increasing in PWT1D, as observed in the general population [4–8]. Long-term follow-up of patients enrolled in the Diabetes Control and Complications Trial (DCCT) in the Epidemiology of Diabetes Intervention and Complications (EDIC) study provided some evidence of the role of excessive weight gain on CV risk. During the first 13 years following the DCCT intervention period, patients initially randomized in the intensive group experienced fewer macrovascular events than those in the conventional group. However, at the end of the 13-year follow-up, patients from the intensive group who were in the fourth quartile of weight gain (mean BMI of 30 ± 4 kg/m$^2$) had a similar rate of CV events to those in the conventional group [9]. Based on the DCCT data, Kilpatrick et al. showed that insulin resistance at baseline, as measured by the estimated glucose disposal rate (eGDR), was associated with an increased risk of subsequent micro- and macrovascular complications, irrespective of treatment group assignment [10].

Beside body mass index (BMI), the distribution of body fat mass appears to be a more accurate indicator for detecting excess of adiposity and assessing obesity-related health risks [11]. Indeed, the accumulation of visceral adipose tissue, along with its altered metabolic profile, is strongly associated with increased insulin resistance, and this fat distribution pattern is thought to be a major contributor to CV disease [12]. Waist/height ratio (WHtR) has been proposed as the best proxy for visceral fat [13–15], with a similar threshold of 0.5 for predicting CV disease in both men and women, regardless of ethnicity [14]. However, the predictive value of WHtR has not yet been studied in PWT1D.

We performed a cross-sectional observational study using data from PWT1D in primary CV prevention included in the French SFDT1 cohort [16], with the aim to i) investigate the estimation of 10-year CV risk according to BMI and WHtR and ii) determine which anthropometric parameter is best associated with CV risk.

## Methods

### The SFDT1 cohort

Patients aged 18 years or older with an age at diagnosis of type 1 diabetes between 6 months and below 35 years and first insulin treatment within 1 year of diagnosis were included. The primary objective of the SFDT1 cohort is to evaluate the risk factors/determinants for major adverse cardiovascular events in PWT1D. The study has been described previously [16, 17].

The current analysis was performed on data collected by a physician during the baseline visit of eligible participants enrolled between June 2020 and February 2024.

We included patients with no history of CV events, namely acute coronary syndrome, coronary artery angioplasty, coronary artery bypass graft, stroke, supra-aortic trunk surgery, lower-extremity artery angioplasty, lower-extremity arterial surgery, heart failure, and non-traumatic lower-extremity amputation. Among them, only participants with complete data on BMI and WHtR were considered.

### Data collection

We used data collected at enrollment. We included the following descriptive variables:

Individual characteristics: age, sex, age at diagnosis, duration of diabetes, social deprivation score (EPICES), BMI, WHtR. Weight, height and waist circumference were measured by the investigator at the baseline clinical visit. Waist circumference was measured while standing, in a horizontal plane midway between the lower edge of the ribs and the iliac crest. The measurement is taken at the end of a normal exhalation, to the nearest 0.1 cm. BMI was calculated as total body weight (kilograms) divided by the square of the height (meters) and the WHtR was calculated by dividing the waist circumference by height. Patients were categorized into two BMI classes: normal BMI (18.5–24.9 kg/m$^2$) or overweight/obesity (≥ 25.0 kg/m$^2$). Of note, PWT1D and a BMI < 18.5 kg/m$^2$ were not included due to their distinct clinical profile. Based on previous reports, a single WHtR cut-off of 0.5 was used as a proxy for visceral adiposity in both men and women [14, 15].

CV risk factors: current tobacco use, hypertension (defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DPB) ≥ 90 mmHg or antihypertensive treatment), lipid profile. Dyslipidemia was

defined as LDL-cholesterol > 3.4 mmol/L or statin use [18].

Diabetes treatments: insulin therapy including multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) including predictive low-glucose suspend systems or automated insulin delivery (AID), total daily insulin dose (IU/kg/day), metformin, glucagon-like peptide-1 receptor agonist (GLP-1RA) or sodium-glucose cotransporter-2 inhibitor (SGLT2–i) treatment, bariatric surgery (sleeve gastrectomy, gastric bypass).

Glycemic control: HbA1c

Personal history of diabetes-related complications: retinopathy, nephropathy and neuropathy. The diagnosis of retinopathy was obtained from medical reports. Nephropathy was defined as moderate or severely increased albuminuria (albuminuria/creatininuria > 3 mg/mmol) or estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m$^2$ (CKD-EPI equation). Neuropathy was defined as a Michigan Neuropathy Screening Instrument (MNSI) score > 2 [19] or any evidence of autonomic neuropathy. We also considered the MNSI score as a continuous variable.

### Estimation of 10-year CV risk

We used the Steno Type 1 Risk Engine (ST1RE) to estimate 10-year CV risk for each patient in primary CV prevention. CV disease was defined as a composite of fatal and non-fatal events of ischemic heart disease, ischemic stroke, heart failure and peripheral artery disease. The estimated risk was divided into 3 categories: low (< 10%), moderate (10–20%), and high (> 20%) [20].

### Statistical analysis

We described the data with means (standard deviation (SD)), medians (interquartile range (IQR)) or percentages (%) for numerical normally distributed, numerical not normally distributed or categorical variables, respectively. We categorized the data into four groups according to BMI and WHtR values: BMI 18.5–24.9 kg/m$^2$ and WHtR < 0.5; BMI 18.5–24.9 kg /m$^2$ and WHtR ≥ 0.5; BMI ≥ 25 kg/m$^2$ and WHtR < 0.5; BMI ≥ 25 kg/m$^2$ and WHtR ≥ 0.5. We performed ANOVA to compare the groups when the variable to compare was of normal distribution, the Kruskal–Wallis test for non-normal distribution, and the chi-square test for comparing categorical variables.

Missing data of the included participants ranged from 0 to 30.4% (albuminuria) (Supplemental S1) and we evaluated the dataset's missingness. Assuming a "missing-at-random" mechanism, we applied multiple imputations on missing values of outcomes and confounders. We did not impute missing values of the main determinants (BMI and WHtR). Instead, we only included participants with data available on BMI and WHtR. We address it using the chained-equations approach with the R-package “Mice” [21]. We assessed the quality of the imputation with summary statistics and plots.

We explored the possible associations of BMI and WHtR with estimated 10-year CV risk by plotting the distribution with density plots. We plotted the distribution of the CV risk in the SFDT1 cohort by BMI and WHtR classes and stratified by sex. We fitted spline regression models using a generalized additive model ("mgcv" R package, "gam" function, "s" hyperparameter) with high CV risk (20% or more) vs moderate or low CV risk (less than 20%) according to the 10-year CV risk calculated with the ST1RE algorithm as the outcome. The main determinants were BMI and WHtR. The model outputs include effective degrees of (EDF) values to quantify the amount of non-linearity with values = 1 reflecting a linear curve, > 1 & < 2, weak non-linear and > = 2 strongly non-linear [22]. We also used evaluated p values to determine whether the smooth terms (splines) are significant and Chi-squared values (for dichotomous outcomes) to assess the strength of the effect. We performed a crude model (model 0) consisting of a determinant of the outcome (result not shown) and an adjusted model for possible confounders, model 1, which was model 0 adjusted by diabetes treatment (the modality of treatment was categorized as insulin multi-injection, insulin pump with closed-loop system or insulin pump with open-loop system (or alone)), daily insulin dose and EPICES score.

We also fitted models stratified by sex (men and women) and BMI (18.5–24.9 kg/m$^2$ and ≥ 25 kg/m$^2$).

To investigate the effect of estrogen deprivation on CV risk in women, we performed a sensitivity analysis by stratifying the women into older (≥ 50 years) and younger age (< 50 years).

Finally, we plotted ROC curves and calculated the area under the curve (AUC) for each determinant (BMI and WHtR). We obtained cutoffs to optimize sensitivity mainly (using the "pROC" R package) and predict high CV risk.

All the models were performed in each imputed dataset, the estimates were pooled, and the confidence intervals were calculated according to Rubin's rules [21].

## Results

### Inclusion

At the time of the study, the SFDT1 cohort comprised 2,554 patients, of whom 195 (7.6%) had a CV disease history. The analysis focused on 1,482 patients without CV history and a BMI ≥ 18.5 kg/m$^2$ for whom waist circumference (WC) and height data were available (flowchart in Supplemental Data S2).

### Characteristics of the population

Among these 1,482 patients, the proportion of women was similar to that of men (49% of women). A total of 740 (49.9%) patients had a normal BMI, 742 (50.1%) had a BMI ≥ 25 kg/m$^2$, including 274 (18.5% of the study population) with a BMI ≥ 30 kg/m$^2$. The median BMI was 25.0 kg/m$^2$ [22.6–28.6]. The mean WHtR was 0.52 (± 0.08) and 833 (56.2%) had a ratio ≥ 0.5. Overall, age, age at diagnosis, duration of diabetes, and family history of type 2 diabetes differed significantly among the four predefined groups with increased values observed in patients with high WHtR, even in those with normal BMI (Table 1). Similarly, the proportions of hypertension and dyslipidemia were higher in the WHtR ≥ 0.5 groups, irrespective of BMI status.

Glycemic control was similar in the four groups as assessed by HbA1c (HbA1C = 7.7% (60 mmol/mol) for the whole cohort, p = 0.510) (Table 1).

Daily insulin dose did not differ significantly between the four groups (from 0.53 UI/kg/day to 0.61 UI/kg/day, $p = 0.0512$).

In the whole population, 35% of patients had retinopathy, 33% had neuropathy, and 18% had nephropathy. The prevalence of neuropathy and retinopathy varied significantly between the four groups. Retinopathy was most common in patients with a high WHtR and either normal (40%) or high BMI (41%) compared to those with normal WHtR. The group with high WHtR and normal BMI had the highest prevalence of nephropathy and neuropathy (25% and 40%, respectively) (Table 1).

**Table 1** Characteristics of the population without cardiovascular history in the SFDT1 cohort

| | Total population | WHtR < 0,5 | WHtR ≥ 0,5 | WHtR < 0,5 | WHtR ≥ 0,5 | *p* value |
|---|---|---|---|---|---|---|
| | | BMI < 25 kg/m2 | BMI < 25 kg/m2 | BMI ≥ 25 kg/m2 | BMI ≥ 25 kg/m2 | |
| n | 1482 | 569 | 171 | 80 | 662 | |
| WHtR | 0.52 (± 0.08) | 0.45 (± 0.03) | 0.53 (± 0.03) | 0.47 (± 0.03) | 0.59 (± 0.06) | < 0.0001 |
| BMI | 25.0 (22.6–28.6) | 22.0 (20.6–23.4) | 23.7(22.9–24.5) | 26.1 (25.5–27.0) | 29.3 (27.0–32.0) | < 0.0001 |
| Age (years) | 36.5 [28–49] | 32 [24–42] | 45[32–54] | 32 [26–42] | 42 [31–52] | < 0.0001 |
| Female (%) | 720 (49%) | 286 (50%) | 68 (40%) | 44 (55%) | 322 (49%) | 0.0634 |
| EPICES score | 16.6 [7.1–28.4] | 16.6 [8.3–26.6] | 15.4 [7.1–28.6] | 16.6 [8.3–23.7] | 16.6 [7.1–30.0] | 0.9853 |
| Age at diagnosis (years) | 17.1 [± 9.1] | 16.2 [± 8.8] | 18.5 [± 9,7] | 17.0 [± 9.5) | 17.6 [± 9.0] | 0.0085 |
| Diabetes duration (years) | 20 [12–30] | 17 [9–25] | 25 [13–34] | 17 [9–25] | 23 [15–33] | 0.0085 |
| Familial history of Type 2 Diabetes | 4235 (29%) | 124 (22%) | 50 (29%) | 24 (30%) | 237 (36%) | < 0.0001 |
| Familial history of CVD before 55 years | 114 (8%) | 34 (6%) | 13 (8%) | 6 (8%) | 61 (9%) | 0.2098 |
| Current smoker (%) | 314 (21%) | 147 (26%) | 37 (22%) | 26 (33%) | 104 (16%) | < 0.0001 |
| Hypertension (%) | 416 (28%) | 88 (15%) | 57 (33%) | 13 (16%) | 258 (39%) | < 0.0001 |
| HbA1c (%) | 7.7 (± 1.2) | 7.7 (± 1.4) | 7.6 (± 1.5) | 7.7 (± 1.2) | 7..6 (± 1.1) | 0.5100 |
| HbA1c (mmol/mol) | 60 (± 14) | 61 (± 15) | 60 (± 16) | 61 (± 13) | 60 (± 12) | 0.5100 |
| eGFR(ml/min/1.73m2) | 108 [96–120] | 112 [100–123] | 105 [97–117] | 109 [97–120] | 106 [94–116] | < 0.0001 |
| Dyslipidemia | 583(39%) | 163 (29%) | 66 (39%) | 28 (35%) | 326 (49%) | < 0.0001 |
| LDL-cholesterol (mmol/l) | 2.6 (± 0.8) | 2.6 (± 0.8) | 2.7 (± 0.9) | 2.7 (± 0.8) | 2.7 [(± 0.9) | 0.0237 |
| HDL-cholesterol (mmol/l) | 1.6 (± 0.5) | 1.7 (± 0.6) | 1.6 (± 0.6) | 1.6 (± 0.4) | 1.5 (0.4) | < 0.0001 |
| Triglycerides (mmol/l) | 0.80 [0.63–1.08] | 0.75 [0.59–0.96] | 0.84 [0.65–1.1] | 0.76 [0.66–0.94] | 0.86 [0.68–1.2] | < 0.0001 |
| Insulin treatment | | | | | | |
| Multiple daily injections | 630 (43%) | 284 (50%) | 78 (46%) | 30 (38%) | 238 (36%) | < 0.0001 |
| Any insulin pump | 852 (57%) | 285 (50%) | 93 (54%) | 50 (62%) | 424 (64%) | < 0.0001 |
| Metformin | 42 (2.8%) | 0 (0%) | 3 (1.8%) | 0 (0%) | 39 (5.9%) | < 0.0001 |
| GLP-1 receptor agonist | 26 (1.8/%) | 1 (0.2%) | 0 (0%) | 0 (0%) | 25 (4%) | < 0.0001 |
| SGLT2 inhibitor | 5 (0.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 5 (0.8%) | 0.1016 |
| Bariatric surgery | 17 (1.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 17 (2.6%) | < 0.0001 |
| Insulin daily dose (UI/kg/day) | 0.59 (± 0.28) | 0.58 (± 0.29) | 0.57 (± 0.24) | 0.53 (± 0.23) | 0.61 (± 0.29) | 0.0512 |
| Diabetes complications | | | | | | |
| Retinopathy | 520 (35%) | 154 (27%) | 68 (40%) | 26 (32%) | 272 (41%) | < 0.0001 |
| Neuropathy | 482 (33%) | 158 (28%) | 69 (40%) | 27 (34%) | 228 (34%) | 0.009 |
| Nephropathy | 264 (18%) | 91 (18%) | 39 (25%) | 17 (24%) | 117 (18%) | 0.1505 |

BMI: Body Mass Index, CVD: cardiovascular disease, eGFR: estimated glomerular filtration rate EPICES score: Evaluation de la Précarité et des Inégalités dans les Centres d'Examens de Santé, GLP-1: Glucagon-like peptide 1, HbA1C: hemoglobin glycated, HDL-cholesterol: High Density Lipoprotein cholesterol, LDL-cholesterol: Low Density lipoprotein cholesterol, SGLT2: sodium glucose cotransporter 2,WHtR: waist/height ratio. The normally distributed variables are described as means (SD) and the not-normally distributed variables as medians (IQR)

### CV risk estimation at 10 years

Overall, 9% of the cohort had a high CV risk (> 20%) (Fig. 1A), and the distribution of CV risk categories differed significantly between men and women ($p < 0.001$) (Fig. 1B). The proportion of patients with high CV risk was higher in the group with BMI ≥ 25 kg/m$^2$ than in the group with BMI 18.5–24.9 kg/m$^2$ (12% vs. 6%), whereas the proportion of patients with low risk (< 10%) was lower in the group with high BMI (65% vs. 77%) (Fig. 1C).

The proportion of patients with high CV risk was higher in those with a WHtR ≥ 0.5 compared to those with a WHtR < 0.5 (13% vs 4%). The proportion of patients with low CV risk was lower in the group with WHtR ≥ 0.5 compared to those with WHtR < 0.5 (62% vs. 83%) (Fig. 1D).

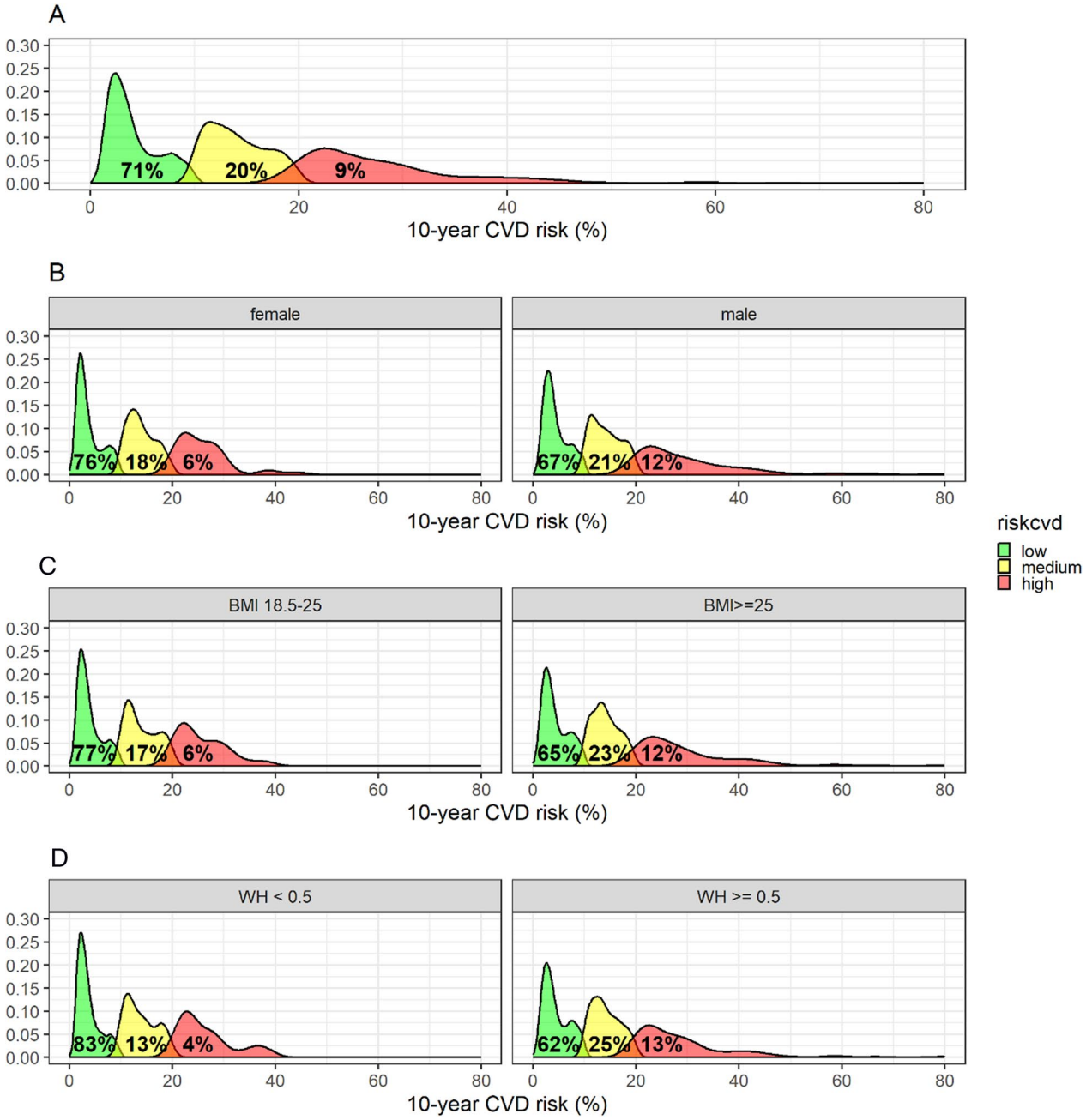



**Fig. 1** Distribution of the cardiovascular risk in the SFDT1 cohort by gender, body mass index class and waist/height ratio. **A**: whole cohort, **B**: distribution by gender, **C**: distribution by BMI categories, **D**: distribution by waist/height ratio. The percentage of the population in each of the score categories is shown on the graphs. The differences between the groups by gender (**B**), BMI (**C**) and waist/height ratio (**D**) are significant ($p$ value < 0.001, Chi-squared test)

The distribution of CV risk was significantly different between the two BMI and WHtR groups ($p < 0.001$).

In men, considering BMI, the proportion of patients at high CV risk was higher in the group with a BMI ≥ 25 kg/m$^2$ compared to those with a normal BMI (18% vs. 7%) (p < 0.001) (Supplemental data S3, panel A). In women, the proportion of high CV risk was similar between the two BMI groups (7% vs. 5%) (p = 0.309) (Supplemental data S3, panel B). When WHtR was considered, the proportion of patients at high CV risk increased for WHtR ≥ 0.5 in both men and women, with a fourfold increase in men and a twofold increase in women compared to those with WHtR < 0.5 (p < 0.001) (Supplemental data S3, panel C and D).

### CV risk prediction by BMI and WHtR

In our population, after adjustment for insulin dose, diabetes treatment, and social deprivation, the association between BMI and high CV risk was significant and non-linear (EDF = 6.4; Chi-squared = 19.6; $p = 0.010$) but appeared flat across a wide range of values, particularly for high BMI (Fig. 2A).

When analyzed by sex, the association between BMI and high CV risk remained significant and strongly non-linear in men (EDF = 2.3; Chi-squared = 16.9; $p = 0.001$) (Fig. 2B). However, no clear association was found in women (EDF = 8.6; Chi-squared = 16.7; $p = 0.053$) (Fig. 2C).

We showed a significant association with narrow confidence intervals between WHtR and high CV risk in the whole population (EDF = 2.2; Chi squared = 37.3; p-value < 0.001) (Fig. 3A). When stratified by sex, the association was still significant in both men (EDF = 2.6; Chi squared = 39.1; $p$-value < 0.001) and women (EDF = 1.0; Chi squared = 4.0; $p$-value = 0.046) (Fig. 3B, C). This association between WHtR and CV risk was strongly non-linear in men (EDF = 2.6) but not in women (EDF = 1.0).

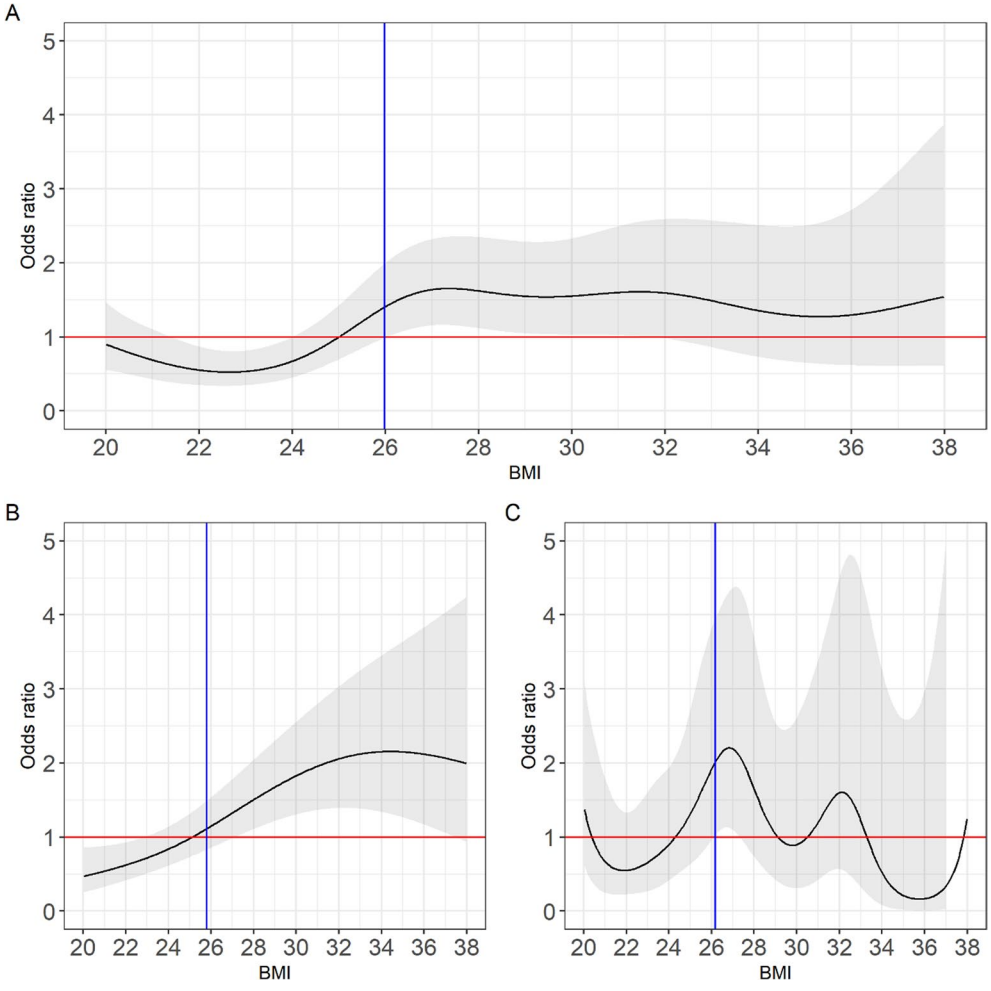



**Fig. 2** Association between high cardiovascular risk and body mass index. **A**: whole population (n = 1482, EDF = 6.4; Chi squared = 19.6; $p$-value = 0.010), **B**: men (n = 762, EDF = 2.3; Chi squared = 16.9; $p$-value = 0.001); C: women (n = 720, EDF = 8.6; Chi squared = 16.7; $p$-value = 0.053); BMI: body mass index. The model was adjusted by diabetes treatment, insulin dose and EPICES score. Blue line represents the median BMI

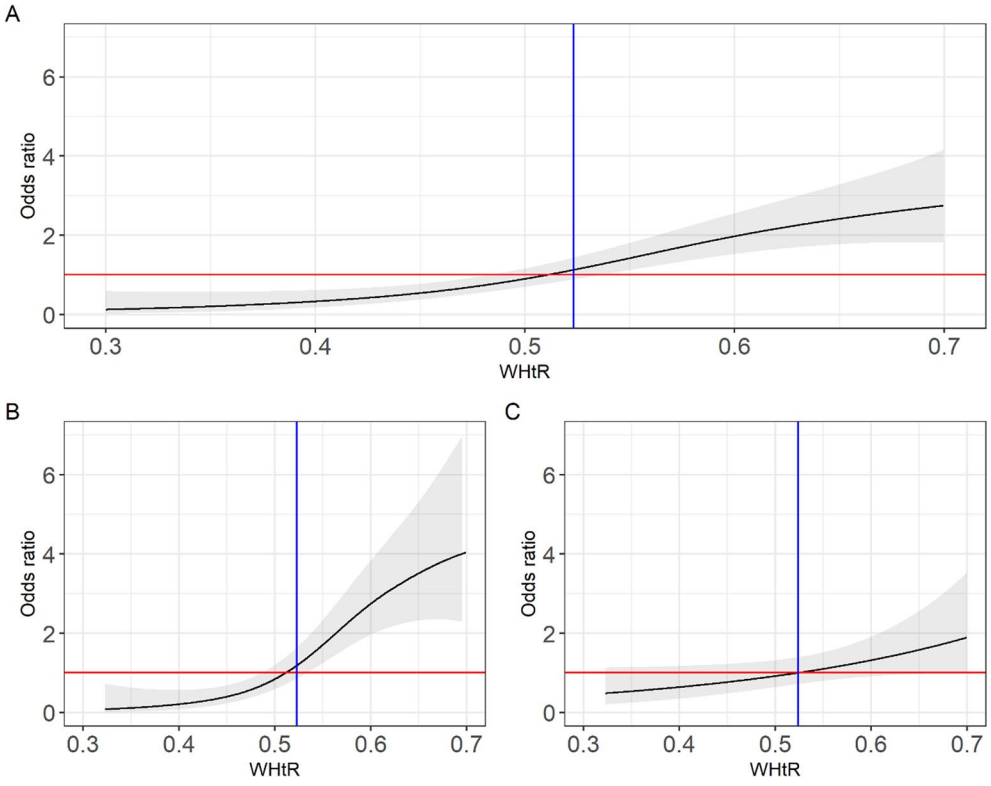



**Fig. 3** Association between high cardiovascular risk and Waist/height ratio. **A**: whole population (n = 1482, EDF = 2.2; Chi squared = 37.3; *p*-value < 0.001); **B**: men (n = 762, EDF = 2.6; Chi squared = 39.1; *p*-value < 0.001); **C**: women (n = 720, EDF = 1.0; Chi squared = 4.0; *p*-value = 0.046); WHtR: Waist/Height ratio. The model was adjusted for diabetes treatment, insulin dose and EPICES score. The blue line represents the median WHtR ratio

We further stratified the association between high CV risk and WHtR by BMI class. This association remained significant in all BMI categories in men and was particularly strong in high WHtR and normal BMI (Fig. 4A, B) but was no longer significant in women (Fig. 4C, D).

### Optimal cut-off values of BMI and WHtR

We performed ROC curve analyses to determine the optimal cut-off values for BMI and WHtR associated with a 10-year CV risk. In men, the optimal BMI cut-off was 24.8 kg/m$^2$ (AUC = 0.629, sensitivity = 0.69, specificity = 0.53) (Supplemental data S4, panel A). In women, the AUC was approximately 0.5, and no meaningful threshold could be identified (Supplemental data S4, panel B). For WHtR, a cut-off of 0.5 was the best predictor of estimated 10-year CV risk for both men and women. In men, the AUC was 0.712, with sensitivity = 0.80 and specificity = 0.51(Supplemental data S4, panel C). In women, the AUC was 0.620, with sensitivity = 0.68 and specificity = 0.50 (Supplemental data S4, panel D).

### Sensitivity analysis

To investigate the effect of estrogen deprivation on CV risk in women, we performed a sensitivity analysis by stratifying the women into older (≥ 50 years) and younger age (< 50 years).

No association between high CV risk and WHtR was observed in both young (n = 552) and older women (n = 168) ($p$ = 0.358 and p = 0.696, respectively) (supplemental data S5).

## Discussion

### Main results

In PWT1D in primary CV prevention from the SFDT1 cohort, we found that (i) about half of PWT1D have a BMI ≥ 25 kg/m2 and 18.5% are living with obesity; (ii) hypertension and dyslipidemia increased with WHtR regardless of BMI class, while glycemic control remained comparable between groups; (iii) the proportion of patients with high CV risk was higher in the high BMI group and in the WHtR ≥ 0.5 group; (iv) WHtR was a stronger marker of estimated 10-year CV risk than BMI in both men and women. In men, but not in women, the association between WHtR and CV risk appeared stronger in those with normal BMI compared to those with high BMI.

Notably, a small number of PWT1D with a BMI < 18.5 kg/m$^2$ were excluded, as they represent a distinct population in which acute diabetes complications, rather than cardiovascular complications, is the primary cause of death [23].

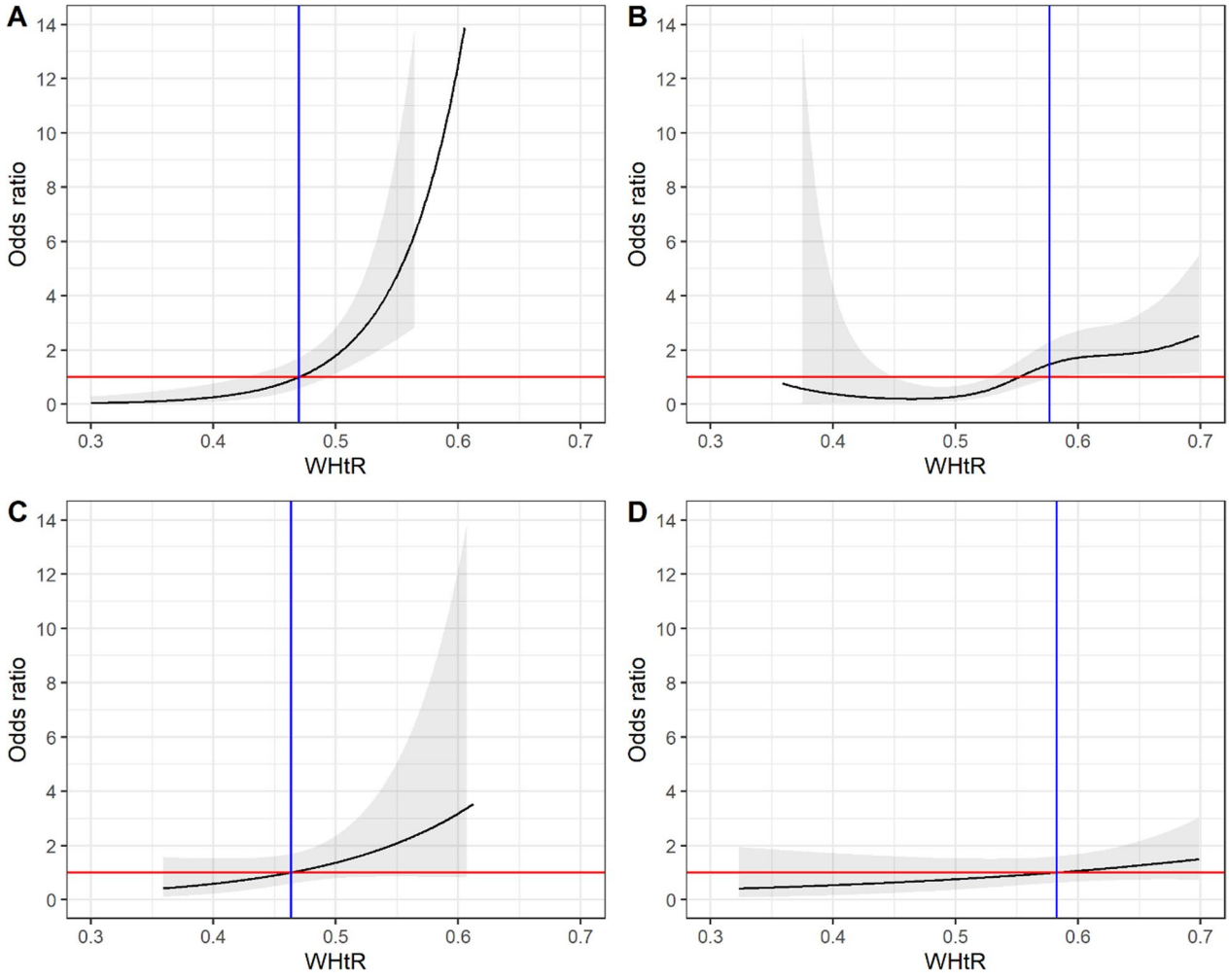



**Fig. 4** Association between high cardiovascular risk and Waist/height ratio according to body mass index class. **A**: normal weight men (n = 386, EDF = 2.2; Chi squared = 13.3; *p*-value < 0.001), **B**: overweight men (n = 376, 4.9, EDF = 16.9; Chi squared = 13.3; *p*-value = 0.001), **C**: normal weight women (n = 354, EDF = 1.0; Chi squared = 2.9, *p*-value = 0.086), **D**: overweight women (n = 366, EDF = 1.0; Chi squared = 1.7; *p*-value = 0.195). WHtR: Waist/Height ratio. The model was adjusted for diabetes treatment, insulin dose and social deprivation. The blue line represents the median WHtR ratio

### Prevalence of obesity in PWT1D

The prevalence of overweight and obesity in PWT1D from the SFDT1 cohort was similar to that observed in the general population. Data from the Observatoire Français d'Epidémiologie de l'Obésité (OFEO) study reported an obesity prevalence of 18.1% in the general population in 2024 [24]. PWT1D are thus as vulnerable to obesity as the general population, challenging the misconception that obesity is not a significant concern in type 1 diabetes. In other European countries, a similar prevalence of PWT1D with obesity was found in Spain (18%) [4] and Belgium (17%) [5] but a lower prevalence in Northern Europe (Finland 10.9%, Germany 15.3% and Sweden 8.3%) [6–8]. Longitudinal data from the Pittsburgh Epidemiology of Diabetes Complications Study and the FinnDiane study showed an increasing prevalence of obesity in PWT1D from the late 1980s to the 2000s [6, 25]. The increase was more pronounced in Finland from the 2000s to the 2010s, suggesting that the rise in BMI is still ongoing [6].

### Overweight and cardiovascular disease

We found that the proportion of patients with high CV risk was higher in the group with overweight/obesity compared to those with a normal BMI. Our findings align with the existing literature. In the longitudinal FinnDiane Study, CV disease was the leading cause of death and its proportion increased from normal BMI to obesity in PWT1D (from 39.5% to 46.9%) [6]. Over a median follow-up of 13.7 years, the association between BMI and all-cause mortality was J-shaped, while the association with CV mortality was U-shaped after adjusting for age, sex, and duration of diabetes. The risk began to increase at a BMI of 25 kg/m$^2$, suggesting that this threshold may serve as a cut-off point for the risk of complications, which is lower than the traditionally used 30 kg/m$^2$ [6]. In

the United States, the prospective Type 1 Exchange Registry study found that 56% of the 8,727 patients enrolled were overweight or obese. During 4.6 years of follow-up, 3.7% developed incident CV disease. Among several known factors, overweight or obesity was associated with a 44% increased CV risk [HR = 1.44 (1.05–1.97)] [26].

BMI is the most commonly used tool to classify obesity. Still, it does not reflect the amount of body fat or its distribution [27–29], which better defines obesity and the associated CV risk [12]. Regarding sex differences, BMI does not account for variations in body fat distribution between men and women. Our study found that being overweight or obese was associated with a higher CV risk in men but not in women. Similarly, in the Swedish National Diabetes Registry, an increased BMI was associated with mortality, major CV disease and heart failure only in men [7]. In the FinnDiane study, the interaction analyses showed that the relationship between BMI and mortality was modified by sex ($p_{interaction} = 0.02$) with a more pronounced association in men. The authors explained this discrepancy by the difference in body fat distribution between men and women. Men are more likely to have abdominal fat, which is associated with an unfavorable metabolic profile [6]. Recently, the joint analysis of the French (SFDT1) and German (DPV) cohorts confirmed that men with T1D had a worse CV risk profile than women [17].

#### WHtR in the CV risk prediction

In the study of PWT1D from the FinnDiane cohort, WC and WHtR were the most accurate predictors of visceral fat mass measured by dual-energy X-ray absorptiometry. These findings were independent of albuminuric stage and sex and outperformed other metrics, such as the waist-hip ratio and the body shape index [15]. We opted to use WHtR because a robust meta-analysis of diverse populations demonstrated that WHtR is a superior indicator compared to WC for predicting CV disease risk [13]. Although there is considerable data on the relationship between WHtR and CV disease in the general population and in type 2 diabetes [13, 14], studies on T1D are scarce. The FinnDiane group found that the abdominal adiposity in PWT1D was associated with metabolic fatty liver [30], diabetes-related severe eye disease [31], hospitalization and death due to heart failure [32] and onset or progression of albuminuria [33]. Our study is the first to demonstrate an association between visceral adiposity, as reflected by a WHtR ≥ 0.5, and high estimated 10-year CV risk in a population of PWT1D. A clinically meaningful message could be in both men and women: "Waist must not be greater than half of the height".

The association between WHtR and high CV risk was significant in men with either normal or high BMI, but not in women. We speculate that this lack of significance in women may be due to a lower proportion of visceral fat relative to abdominal subcutaneous fat for the same WHtR compared to men, as demonstrated in Brazilian and Caucasian populations [34, 35]. As visceral adiposity is the most detrimental for CV risk, this could explain the weaker association between WHtR and estimated 10-year CV risk in women. Another possible reason could be due to hormonal differences between men and women, especially during menstrual activity when estrogen plays a relevant cardioprotective role and 76.7% (n = 552) of the women included in this analysis are under 50 years old [36]. Furthermore, the hormonal differences impact body fat distribution and may contribute for the lower visceral fat in women compared to men for the same WHtR.

#### Limitations of the study

We utilized the ST1RE model to estimate CV risk in PWT1D [20]. This CV risk prediction model was originally validated in a homogenous Danish population, with 90% of the derivation cohort having Danish ancestry. While ST1RE demonstrated strong performance compared to other risk prediction models, external validation in diverse ethnic cohorts would be valuable to enhance its applicability [20]. A recent study conducted in a Brazilian cohort of PWT1D found that the ST1RE model's predicted CV events closely matched the observed events over 5- and 10-year follow-up periods, suggesting that ST1RE is applicable to a broader population [37].

We found that the estimation of visceral adiposity by the WHtR was a stronger marker of CV risk in PWT1D than BMI. The coexistence of characteristics from both type 1 and type 2 diabetes, known as "double diabetes," continues to raise questions about appropriate classification criteria. A shared feature across classifications is the presence of insulin resistance [38]. In the CACTI study, insulin resistance was measured using the hyperinsulinemic-euglycemic clamp, revealing that PWT1D, compared to controls without diabetes, had lower peripheral glucose utilization independent of glycemic control. Additionally, insulin resistance predicted the extent of coronary calcification [39]. Similarly, in the DCCT study, higher baseline insulin resistance, estimated by eGDR, was associated with an increased risk of both microvascular and macrovascular complications. In contrast, insulin dose and metabolic syndrome were not significant predictors [10]. In our study, no direct measurement of insulin sensitivity was performed. Furthermore, using an insulin resistance estimation equation like eGDR was inappropriate because it shares common variables with ST1RE CV risk estimation, such as HbA1c and hypertension. We did not have direct measurement of visceral fat using dual-energy X-ray absorptiometry or CT-scan. Instead, in this large cohort, we used WHtR,

a validated ratio for estimating visceral fat distribution [13–15], which is a marker of insulin resistance [40–42]. Similar to what is seen in type 2 diabetes [40], several other mechanisms may promote the increase in CV risk in PWT1D, especially low-grade inflammation [43]. Unfortunately, we didn't have enough data on ultrasensitive C-reactive. Finally, due to its design, this study cannot establish whether WHtR is an independent marker of CV risk, separate from other established risk factors. This limitation is due to the use of ST1RE, which includes traditional CV risk factors into its risk estimation. To definitively assess the independent contribution of visceral adiposity to CV risk, a prospective study tracking incident CV events is required. Such a study is planned within the SFDT1 cohort in the future.

### Perspectives

To generalize our findings, we plan to validate the WHtR threshold associated with CV risk in an independent cohort. In addition, improving the prediction of CV risk in PWT1D using simple clinical parameters such as the WHtR could help to optimize cardiovascular prevention strategies including the use of treatments with demonstrated cardiovascular protective effects. In the last decade, the introduction of pharmacological agents such as GLP-1 RA and SGLT2-i has revolutionized the management of patients living with type 2 diabetes and CV benefit was also recently evidenced in individuals without diabetes and with pre-existing CV disease and overweight or obesity. These promising results raise questions about their applicability to PWT1D and the potential for implementing personalized treatment strategies tailored to individual phenotypes [38, 44–46]. Furthermore, our epidemiological findings pave the way for mechanistic studies. Specifically, investigating adipose tissue dysfunction in obese PWT1D compared to their normal-weight counterparts could help identify novel molecular therapeutic targets.

## Conclusion

In the SFDT1 cohort, half of the PWT1D in primary CV prevention faced overweight or obesity. Visceral adiposity, estimated by WHtR, is a stronger marker of the CV risk than BMI in both men and women. Further studies are needed to understand the role of adipose tissue distribution in T1D and the place of adjunctive treatments in therapeutic prevention strategies.

### Abbreviations

| | |
|---|---|
| AID | Automated insulin delivery |
| AUC | Area under the curve |
| BMI | Body mass index |
| CSII | Continuous subcutaneous insulin infusion |
| CV | Cardiovascular |
| DBP | Diastolic blood pressure |
| DCCT | Diabetes control and complications trial |
| EDIC | Epidemiology of diabetes intervention and complications |
| eGDR | estimated Glucose disposal rate |
| eGFR | Estimated glomerular filtration rate |
| EPICES | Evaluation de la Précarité et des Inégalités de santé dans les Centres d'Examens de Santé |
| GLP-1 RA | Glucagon like peptide-1 receptor agonist |
| HbA1c | Glycated hemoglobin |
| HDL | High-density lipoprotein |
| IQR | Interquartile range |
| LDL | Low-density lipoprotein |
| MDI | Multi-drug injection |
| MNSI | Michigan neuropathy screening instrument |
| OFEO | Observatoire Français d'Epidémiologie de l'Obésité |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SFDT1: | Société Francophone du Diabète Cohorte Diabète de type 1 |
| SGLT2-i | Sodium glucose co-transporter 2 inhibitor |
| ST1RE | Steno type 1 risk engine |
| WC | Waist circumference |
| WHtR | Waist/height ratio |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02789-3.

Supplementary Material 1.

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### Author contributions

L.S, JP.R, E.C., G.F. conceived and designed this study. G.A., JB.J. and JP.R. had full access to all the study data and were responsible for the integrity of the data and the accuracy of the data analyses. G.A. curated the data, performed the data analysis and created the figures and tables. L.S., JB.J., E.C., G.F. G.A. and JP.R. analyzed the results. All authors participated in the collection of the data. L.S. drafted the paper. All authors critically revised the manuscript for important intellectual content and gave final approval for publication. JP.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### Availability of data and materials

Data for the present analysis can be provided from the first authors on reasonable request. For reasons of data protection, data on an individual level cannot be provided. However, remote data analysis is possible.

## Declarations

### Ethics approval and consent to participate

SFDT1 was approved by an ethical committee on 5 November 2019 and is declared in clinical trial NCT04657783.

### Consent for publication

Not applicable.

### Competing interests

EBP reports receiving lecture honorariums from Astra Zeneca and Sanofi, and has been an employee of Boehringer Ingelheim since February 2024. The other authors declare that they have no competing interests.


### Author details

[1]Inserm 1094 & IRD270, Limoges University Hospital, Limoges, France
[2]Department of Endocrinology, Diabetology and Metabolism, Dupuytren University Hospital, Hôpital Dupuytren 2, 16, Rue du Professeur DESCOTTES, 87042 Limoges, France
[3]Université Paris Cité, CNRS, INSERM, Institut Necker Enfants Malades-INEM, 75015 Paris, France
[4]Department of Diabetes, Lariboisière Hospital, Assistance Publique - Hôpitaux de Paris And Paris-Cité University, Paris, France
[5]Deep Digital Phenotyping Research Unit, Department of Precision Health (GAA, GF), Luxembourg Institute of Health, 1A-B, Rue Thomas Edison, L-1445 Strassen, Luxembourg
[6]Department of Diabetology, Metabolic Diseases and Nutrition, Toulouse University Hospital, Toulouse, France
[7]Institute of Metabolic and Cardiovascular Diseases, INSERM and Toulouse University, I2MC UMR1297 Toulouse, France
[8]Folkhälsan Research Center, Biomedicum Helsinki, Finland
[9]Research Program for Clinical and Molecular Metabolism, University of Helsinki, Helsinki, Finland
[10]Department of Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[11]Boehringer Ingelheim International GmbH, Ingelheim, Germany
[12]Toulouse University, Toulouse, France
[13]Department of Endocrinology-Diabetology-Nutrition, AP-HP, Avicenne Hospital, Université Paris 13, Sorbonne Paris Cité, CRNH-IdF, CINFO, Bobigny, France
[14]Department of Endocrinology, Diabetes and Nutrition, Hospices Civils de Lyon, Hôpital Lyon Sud, 69390 LyonLyon, France
[15]Univ Lyon, CarMen Laboratory, INSERM, INRA, INSA Lyon, Université Claude Bernard Lyon 1, 69495 Pierre-Bénite, France
[16]FORCE Network, French Obesity Research Centre of Excellence / F-CRIN INSERM Network, Lyon, France
[17]Department of Endocrinology, Sud Francilien Hospital, DiabetologyCorbeil-Essonnes, France
[18]Thorax Institute, CNRS, INSERM, Nantes University Hospital Center, Nantes University, Nantes, France
[19]Diabetology Department, Cochin Hospital, AP-HP, Paris, France
[20]Paris Cité University, INSERM U1016 Cochin Institute, Paris, France
[21]Department of Diabetology, and Endocrinology Clinique Pasteur, Toulouse, France
[22]Department of Endocrinology, Diabetes and Nutrition, Rennes University Hospital, 35000 Rennes, France
[23]Aix Marseille Univ, APHM, INSERM, INRAE, University Hospital La Conception, C2VN Marseille, France
[24]Department of Nutrition, Metabolic Diseases and Endocrinology, 147 Boulevard Baille, 13005 Marseille, France
[25]Inserm/CNRS UMR 1283/8199, Pasteur Institute of Lille, EGID, Lille, France
[26]University of Lille, Lille University Hospital, Lille, France
[27]Department of Metabolism, Imperial College London, Hammersmith Hospital, London, UK
[28]Center of Research in Epidemiology and StatisticS (CRESS), Nutritional Epidemiology Research Team (EREN), Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, 93017 Bobigny, France


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