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Sex Differences in Cardiovascular Disease and Cardiovascular Risk Estimation in Patients With Type 1 Diabetes

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Abstract

Context: Patients with type 1 diabetes (T1D) have higher cardiovascular disease (CVD) risk than the general population.

Objective: This observational study aims to evaluate sex-related differences in CVD prevalence and CVD risk estimates in a large cohort of T1D adults.

Methods: We conducted a multicenter, cross-sectional study involving 2041 patients with T1D (mean age 46 years; 44.9% women). In patients without pre-existing CVD (primary prevention), we used the Steno type 1 risk engine to estimate the 10-year risk of developing CVD events.

Results: CVD prevalence (n = 116) was higher in men than in women aged ≥55 years (19.2 vs 12.8%, $P = .036$), but comparable between the 2 sexes in those aged <55 years ($P = .91$). In patients without pre-existing CVD (n = 1925), mean 10-year estimated CVD risk was 15.4 ± 0.4% without any significant sex difference. However, stratifying this patient group by age, the 10-year estimated CVD risk was significantly higher in men than in women until age 55 years ($P < .001$), but this risk equalized after this age. Carotid artery plaque burden was significantly associated with age ≥55 years and with a medium and high 10-year estimated CVD risk, without any significant sex difference. Diabetic retinopathy and sensory–motor neuropathy were also associated with higher 10-year CVD risk and female sex.

Conclusion: Both men and women with T1D are at high CVD risk. The 10-year estimated CVD risk was higher in men aged <55 years than in women of similar age, but these sex differences disappeared at age ≥55 years, suggesting that female sex was no longer protective.

Key Words: type 1 diabetes, cardiovascular risk, gender, CVD

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AUC, area under the curve; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T1D, type 1 diabetes.

Sex differences represent a serious concern in preventive and clinical medicine, since women's diseases seem to be underappreciated and undertreated compared with men (1). This issue is particularly relevant for cardiovascular disease (CVD), which represents the leading cause of morbidity and mortality worldwide (2).

In the last decades, CVD has emerged as the leading cause of death also in individuals with type 1 diabetes (T1D) (3-5), who have a life expectancy shorter by ~11 years in men and ~13 years in women compared with the general population (3, 5, 6), and even greater if the onset of T1D is before 10 years of age (5). Moreover, although the rates of all-cause mortality

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have progressively improved in patients with T1D over time, the standardized mortality ratio and the relative mortality risk have been reported to be higher in women with T1D than in men (4, 6-11). To date, it is unclear why women with T1D are particularly susceptible to ischemic heart disease (5, 6, 9, 12), while they do not appear to have a higher risk of cerebrovascular diseases than men with T1D (5, 12). Conversely, although there is little information about peripheral vascular disease, the risk of this vascular complication seems to be higher in men with T1D than in women (13). Traditional CVD risk factors, such as overweight/obesity, reduced physical activity, dyslipidemia, and smoking are now increasing in both men and women with T1D (14, 15). Conversely, other risk factors, such as long-standing diabetes (4, 16, 17), poor glycemic control (18-21), and microvascular complications (5, 15, 22) may affect the risk of CVD in men and women with T1D differently. For instance, the risk of developing fatal or nonfatal CVD events is greater in women with T1D than in men, especially when nephropathy worsens (23).

In 2016 a prediction model estimating the risk of the first fatal or nonfatal CVD event specific for adult patients with T1D in primary prevention (named the Steno type 1 risk engine) was developed in a Danish population of clinically diagnosed adult patients with T1D attending the outpatient clinic at the Steno Diabetes Center to allow the implementation of decisional aids in a clinical setting (24).

The main aim of our multicenter, cross-sectional study was to examine the prevalence of clinically manifest CVD and the 10-year estimated CVD risk (calculated using the Steno type 1 risk engine) in a large cohort of consecutive outpatients with T1D, with a particular focus on sex differences.

Materials and Methods

This is a retrospective, multicenter, observational study conducted in 11 Italian diabetes primary care outpatient clinics, which are all participating sites in the Study Group on Diabetes and Atherosclerosis of the Italian Society of Diabetes (as specified in "Acknowledgments"). Data were retrieved from electronic medical records and charts during the years 2018 to 2019. Inclusion criteria of the study were adult (age ≥18 years) patients with established T1D according to the American Diabetes Association criteria (25). Exclusion criteria of the study were pregnancy, presence of type 2 diabetes or other specific types of diabetes due to known causes (ie, monogenic diabetes syndromes, cystic fibrosis, or pancreatitis). Extracted electronic data included age, sex, T1D duration, age at diagnosis, height and weight to calculate body mass index (BMI), systolic and diastolic blood pressure, and biochemical parameters (including hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL)-cholesterol, liver enzymes, and creatinine). Low-density lipoprotein (LDL)-cholesterol was assessed using the Friedewald's equation. The mean of 3-year hemoglobin A1c values was also calculated for each patient when possible. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation (22), and chronic kidney disease stage ≥3 was defined as eGFR <60 mL/min/1.73 m^2. Smoking history was dichotomized as current (yes) or no smoker (no or former >1 year), as well as physical activity using a cut point of >3.5 hour/week. Daily alcohol intake was defined as ≥2 alcohol units per day in men and ≥1 alcohol unit per day in women. Information on total daily insulin dose and different modalities of insulin treatment (multiple daily injections, continuous subcutaneous insulin infusion, continuous glucose monitoring, or sensor augmented pump) was recorded. Data on the presence of microvascular complications ([non]proliferative retinopathy, maculopathy, sensory–motor neuropathy [by electromyography testing], microalbuminuria [by urinary albumin/creatinine ratio 3.0-29 mg/mmol] or macroalbuminuria [albumin/creatinine ratio ≥30 mg/mmol]), as well as macrovascular complications (defined as prior myocardial infarction, coronary revascularization procedures, or stroke), lower limb amputations, and history of foot ulcers were also recorded. In addition, concomitant diseases such as hypertension, dyslipidemia (subjects on active specific treatment), and concomitant drug treatments were also recorded. Information on the maximum carotid plaque lesion, defined as the maximal % stenosis described by ultrasound examination, in each carotid artery (left or right, common or internal) and presence of carotid atherosclerotic plaques was also recorded for each participant.

The 10-year CVD risk was estimated in the subset of patients with T1D in primary prevention for CVD (n = 1925; 94.3% of total) using the Steno type 1 risk engine, which includes the following 10 variables: age, sex, diabetes duration, systolic blood pressure, LDL-cholesterol, HbA1c, micro/macroalbuminuria, eGFR, smoking history, and regular exercise (24). The Steno type 1 risk engine allows the 10-year estimated CVD risk to be categorized (ie, <10% low; 10-20% moderate; and ≥20% high risk). The present study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved both by the "Comitato Etico per la Sperimentazione Clinica della Provincia di Padova" (code #0063553, date October 19, 2018) and by each participating center. Written informed consent was collected accordingly to the request of each local ethics committee.

Statistical Analysis

Statistical analyses were performed using SPSS v.28 (IBM SPSS statistics). Continuous variables were reported either as mean ± SD for normally distributed variables, or as medians and interquartile ranges for non-normally distributed variables, and categorical variables as percentages. Missing data were handled by listwise deletion. The unpaired Student t-test and the Mann–Whitney test were used to assess differences between men and women for continuous variables as appropriate. The chi-square test was used to evaluate differences in categorical variables. Logistic regression models for chronic vascular complications of diabetes were also performed after adjusting for age, sex, and 10-year CVD risk categories. Receiver operating characteristic curve and area under the curve (AUC) were performed to assess the accuracy of the 10-year estimated CVD risk in identifying the presence of carotid atherosclerotic plaques or microvascular diabetic complications (retinopathy or sensory–motor neuropathy) in men and women, stratified by age. We did not assess the accuracy of the 10-year estimated CVD risk in identifying the presence of diabetic nephropathy because both eGFR and micro/macroalbuminuria were included in the Steno type 1 risk engine. All statistical tests were 2-tailed, and $P \leq .05$ was considered to be statistically significant.

Results

Study Population

A total of 2041 (55.1% men) adult outpatients with T1D were recruited in the study. The flow diagram of the study is shown in Fig. 1. There were 1925 (94.3%) patients with T1D in primary CVD prevention: 1055 men (54.8%) and 870 (45.2%) women. There were 116 (5.7%) patients with T1D in secondary CVD prevention: 69 men and 47 women. Of the 116 patients with pre-existing CVD, 69 (59.5%) had a prior myocardial infarction with or without coronary revascularizations, 22 (19%) had prior coronary revascularizations, and 25 (21.6%) had an unspecified stroke, without any significant sex differences. When we explored whether there was a sex-related difference in CVD prevalence among those aged <55 years, we did not find any significant difference between men (n = 14 [1.7%] out of 837) and women (n = 10 [1.6%] out of 625) ($P = .91$); in contrast, when comparing CVD prevalence in those aged ≥55 years, it appeared to be significantly higher in men (n = 55 [19.2%] out of 287) than in women (n = 37 [12.8%] out of 290) ($P = .036$).

Table 1 shows the main demographic and clinical characteristics of participants, simultaneously stratified by sex and primary or secondary prevention of CVD. Among those in primary prevention, women were significantly older, were less physically active, had longer diabetes duration, and had lower eGFR values than men. Men were more likely to be smokers and drank alcohol more regularly than women. Men also had a greater BMI, and higher values of blood pressure, serum liver enzymes, and triglycerides and lower HDL-C levels than women. No significant differences were observed in the age at T1D diagnosis, HbA1c (both 3-year mean value and at enrollment), and LDL-cholesterol levels between the sexes. The proportion of those in primary prevention achieving blood pressure targets (defined as blood pressure < 130/80 mmHg) was greater in women than in men (71.8% vs 62.6%; $P < .001$), whereas no statistical sex-related differences were present for those achieving HbA1c <7% or LDL-cholesterol <100 mg/dL (data not shown). Among patients in secondary CVD prevention, women were older at T1D diagnosis, and had higher HDL-cholesterol levels and lower serum gamma-glutamyl-transferase and creatinine levels than men.

As shown in Table 2, no significant differences were observed in the carotid plaque burden and rates of chronic vascular complications between men and women, both in patients in primary prevention and in those in secondary prevention of CVD, except for higher rates of chronic kidney disease and sensory–motor neuropathy in women in primary CVD prevention compared with men. As for modalities of insulin treatment (as also summarized in Table 2), men were more frequently treated with multiple daily injections, whereas women were more frequently treated with continuous subcutaneous insulin infusion among those in primary CVD prevention. Other concomitant drug treatments were comparable between men and women, both among patients in primary and those in secondary prevention of CVD.

Sex Differences in the 10-Year Estimated CVD Risk in Patients in Primary Prevention

In the primary CVD prevention group, 1637 (85%) participants had data available for estimating the 10-year CVD risk using the Steno type 1 risk engine (Fig. 1). In the whole cohort the mean 10-year estimated CVD risk was 15.42 ± 0.37% (median: 10.72%, 25-75 percentile: 4.34-20.35) without any significant difference between men and women (10.74% [4.65-19.75] in men vs 10.71% [3.97-21.02] in women; $P = .57$). As shown in Fig. 2A, according to the 10-year estimated CVD risk value distribution, 777 (47.5%) patients had a low 10-year CVD risk (<10%), 446 (27.2%) had a medium 10-year CVD risk (10-20%), and 414 (25.3%) individuals had a high 10-year CVD risk (>20%), with an equal sex distribution.

Of note, after stratifying our patient population by age quartiles, a higher 10-year estimated CVD risk was observed in men than in women aged <55 years ($P < .001$ in the first and second age quartile). However, this sex difference weakened with advancing age, and was no longer significant in those aged ≥55 years (Fig. 2B). In particular, in patients aged <55 years, there was a significant sex-related difference in 10-year CVD risk category distribution: 56 (68.3%) men vs 26 (31.7%) women had a high 10-year CVD risk; 216 (62.6%) men vs 129 (37.4%) women had a medium 10-year CVD risk; and 429 (55.3%) men vs 347 (44.7%) women had a low 10-year CVD risk (Fig. 2C). Conversely, no significant sex-related differences were observed in 10-year CVD risk category distribution among patients aged ≥55 years. Men aged <55 years had a higher BMI ($P < .001$), were more frequently treated with statins ($P < .001$) and angiotensin-converting enzyme (ACE)/angiotensin II receptor blockers (ARBs) ($P = .026$) but less often treated with continuous subcutaneous insulin infusion ($P < .002$) compared with women of similar age, who showed a lower rate of regular physical activity ($P < .001$) and lower eGFR ($P = .004$).

When we examined the differences in the mean values of 10-year estimated CVD risk in relation to the presence or absence of obesity (BMI ≥ 30 kg/m^2), or use of statins and antihypertensive drugs in both men and women with age above or below 55 years, we found that the 10-year CVD risk was greater in obese men aged <55 years (P value for interaction = .048) than in women of similar age, but no sex differences in 10-year CVD risk were observed for the use of statins or antihypertensive drugs; additionally, we found that the mean 10-year CVD risk was comparable between men and women aged ≥55 years, regardless of the presence or absence of obesity, or use of statins or antihypertensive drugs (Fig. S1 (26)).

Sex Differences in 10-Year Estimated CVD Risk Prediction of Carotid Atherosclerotic Plaques and Microvascular Complications

In patients in primary CVD prevention, a higher 10-year estimated CVD risk was significantly ($P < .001$) associated with a greater presence of carotid atherosclerotic plaques (odds ratio [OR] 1.06, 95% CI 1.04-1.07) and diabetic retinopathy (OR 1.04, 95% CI 1.03-1.05) without any significant difference between men and women, while a higher 10-year estimated CVD risk was associated with sensory–motor polyneuropathy (OR 1.04, 95% CI 1.03-1.06, $P < .001$), especially in women (P value for interaction = .04).

We then explored these associations in patients stratified by age <55 and ≥55 years. As shown in Fig. 3, carotid plaque burden was associated both with age ≥55 years and with a medium and high 10-year estimated CVD risk, without any sex-related differences. Diabetic retinopathy and sensory–motor

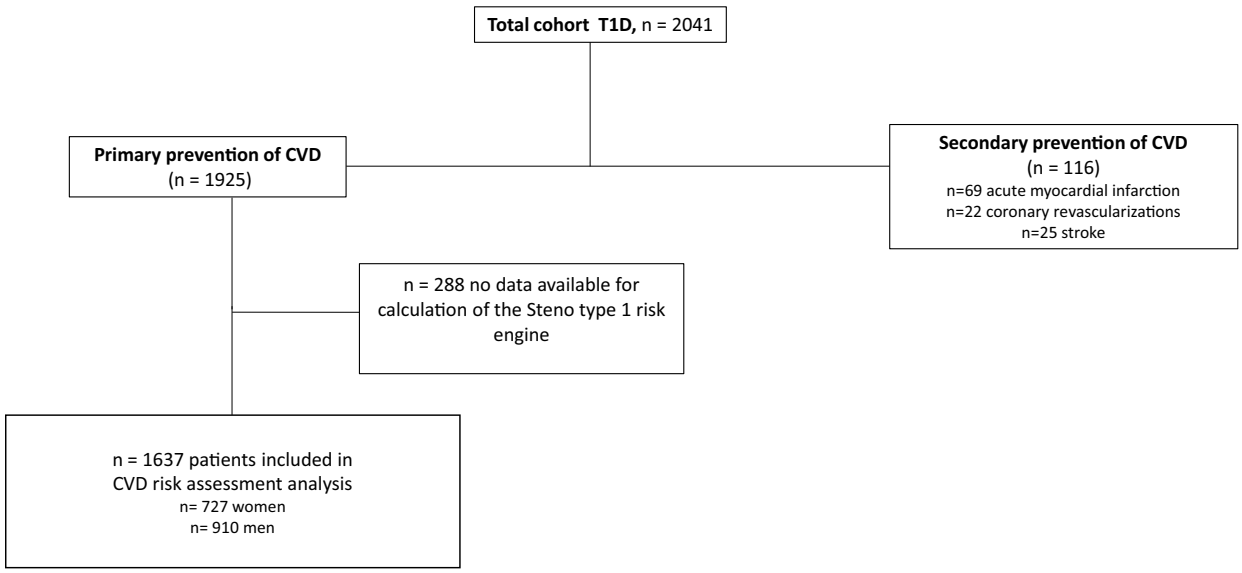

Figure 1. Flow diagram of the study.

polyneuropathy were also associated with a medium and/or high 10-year CVD risk and female sex.

We also investigated whether the 10-year estimated CVD risk score predicted the presence of carotid atherosclerotic plaques by sex. In the whole population, the 10-year CVD risk score showed a good performance in identifying carotid atherosclerotic plaques without any sex-related differences (AUC 0.86, 95% CI 0.82-0.90 vs AUC 0.83, 95% CI 0.79-0.88, $P = .36$, for men and women, respectively). As shown elsewhere (Fig. S2 (26)), the performance of 10-year estimated CVD risk score in identifying the presence of carotid atherosclerotic plaques was good in patients aged <55 years, irrespective of sex, but it was less accurate among women and among those with age ≥55 years. In the whole population, the 10-year estimated CVD risk score also identified accurately the presence of diabetic retinopathy (AUC 0.70, 95% CI 0.67-0.74 vs AUC 0.70 95% CI 0.66-0.74 in men and women, respectively, $P = .97$) and sensory–motor polyneuropathy (AUC 0.77 95% CI 0.72-0.81 vs AUC 0.74 95% CI 0.70-0.79] in men and women, respectively, $P = .45$). Similarly, in patients with age <55 years the capability of 10-year CVD risk score to identify diabetic retinopathy (AUC 0.72 95% CI 0.67-0.76 vs AUC 0.71 95% CI 0.66-0.76 in men and women, $P = .82$) and sensory–motor polyneuropathy (AUC 0.75 95% CI 0.69-0.81 vs AUC 0.74 95% CI 0.68-0.80, $P = .83$) was comparable between the 2 sexes.

Sex Differences in 10-Year Estimated CVD Risk According to Modalities of Insulin Treatment and Cardiovascular Pharmacotherapies

In primary CVD prevention, patients at high 10-year estimated CVD risk were more likely to be treated with multiple daily injections, aspirin, statins, beta-blockers, ACE/ARBs, alpha-blockers and diuretics, and less often treated with continuous subcutaneous insulin infusion than those at medium or low 10-year estimated CVD risk. Compared with women, men at low 10-year CVD risk were more frequently treated with multiple daily injections, statins, and ACE/ARBs, while women at medium 10-year CVD risk were more likely to receive beta-blockers and diuretics (as reported in Table S1 (26)). When exploring these associations according to different age strata, women aged <55 years were more frequently treated with continuous subcutaneous insulin infusion, and less frequently treated with statins, ACE/ARBs, or alpha-blockers. Conversely, no significant differences in any drug treatments were observed between men and women aged ≥55 years.

Discussion

In this large, multicenter, cross-sectional study of nearly 2000 consecutive outpatients with T1D in Italy, we found that both the prevalence of clinically manifest CVD and the 10-year estimated CVD risk among those in primary CVD prevention (using the Steno type 1 risk engine) were high and substantially superimposable in men and women. However, we found that there was a significant age-dependent difference between the 2 sexes, as CVD prevalence was comparable in men and women aged <55 years, whereas CVD prevalence became greater in men aged ≥55 years than in women of similar age. Similarly, in patients in primary CVD prevention, the 10-year estimated CVD risk was lower in women aged <55 years than in men of similar age, but this difference weakened in women with advancing age, becoming nonsignificant at age ≥55 years.

The results of our study suggest 2 considerations: (1) women of fertile age with T1D have the same CVD burden as men, despite a lower 10-year estimated CVD risk; and (2) postmenopausal women with T1D have fewer clinical CVD events than men, at similar 10-year estimated CVD risk. These results suggest that T1D per se represents a major CVD risk factor, especially in younger women, partially unbound to other traditional CVD risk factors, in whom premenopause CVD risk protection seems to be abolished. Another possible explanation for these observations could be the coexistence of CVD risk factors (eg, genetic factors, endocrine parameters, microangiopathy, etc.) other than those included in the 10-year estimated CVD risk score that may promote CVD in women with T1D aged <55 years. It is also possible to hypothesize that the progressive improvement of CVD management in women over time (as reflected by comparable drug treatments of CVD risk factors, and comparable CVD risk

Table 1. Main demographic and clinical characteristics of participants, stratified by sex and primary or secondary prevention of CVD

	Primary CVD prevention					Secondary CVD prevention				
	Missing n (%)	Allsubjects (n = 1925)	Men (n = 1055)	Women (n = 870)	*P* value	Missing n (%)	Allsubjects (n = 116)	Men (n = 69)	Women (n = 47)	*P* value
Age (years)	0 (0)	44 ± 15	43 ± 14	46 ± 16	<.001	0 (0)	64 ± 11	63 ± 11	65 ± 13	.45
Current smokers, n (%)	2 (0.1)	469 (24.4)	291 (27.6)	178 (20.5)	<.001	0 (0)	25 (21.6)	17 (24.6)	8 (17)	.33
Alcohol intake, n (%)[a]	6 (0.3)	325 (16.9)	246 (23.3)	79 (9.1)	<.001	0 (0)	15 (12.9)	12 (17.4)	3 (6.4)	.08
Regular exercise, n (%)	5 (0.3)	865 (44.9)	523 (49.8)	342 (39.3)	<.001	0 (0)	44 (37.9)	27 (39.1)	17 (36.2)	.75
Disease duration (years)	5 (0.3)	19 (12-28)	18 (12-28)	20 (13-29)	.002	0 (0)	37 (24-45)	38 (29-45)	32 (19-42)	.06
Age at diagnosis (years)	6 (0.3)	23.6 ± 14.6	23.3 ± 13.7	24.0 ± 15.60	.24	0 (0)	29 ± 16	27 ± 13	33 ± 20	.04
BMI (kg/m^2)	15 (0.8)	25.0 ± 4.20	25.20 ± 3.70	24.70 ± 4.70	<.005	0 (0)	26.6 ± 4.4	26.7 ± 4.1	26.5 ± 4.9	.77
Insulin dose (IU/day)	64 (3.3)	39 (29-50)	44 (33-55)	34 (26-43)	<.001	2 (1.7)	40 (30-56)	41 (31-58)	36 (28-48)	.11
Systolic BP (mmHg)	18 (0.9)	126 ± 17	128 ± 16	124 ± 17	<.001	0 (0)	139 ± 18	138 ± 19	140 ± 16	.51
Diastolic BP (mmHg)	18 (0.9)	76 ± 9	77 ± 9	74 ± 9	<.001	0 (0)	76 ± 9	77 ± 10	75 ± 8	.36
HbA1c at enrollment (%)	57 (3.0)	7.79 ± 1.19	7.77 ± 1.22	7.84 ± 1.15	.22	6 (5.2)	8.05 ± 1.25	7.96 ± 1.25	8.20 ± 1.24	.36
HbA1c 3-year mean value (%)	74 (3.8)	7.85 ± 2.16	7.76 ± 1.11	7.95 ± 2.96	.06	1 (0.9)	8.09 ± 1.15	7.96 ± 1.14	8.28 ± 1.16	.15
GGT (IU/L)	455 (23.6)	17 (12-25)	19 (14-28)	14 (11-21)	<.001	17 (14.6)	23 (14-40)	30 (17-54)	17 (12-32)	.003
AST (IU/L)	270 (14)	20 (16-25)	21 (17-26)	18 (15-22)	<.001	9 (7.8)	21 (18-27)	22 (19-29)	20 (16-24)	.07
ALT (IU/L)	263 (13.7)	19 (14-26)	21 (17-28)	16 (13-22)	<.001	9 (7.8)	19 (15-27)	20 (16-29)	19 (15-23)	.22
HDL-C (mg/dL)	27 (1.4)	58 (48-69)	54 (45-63)	64 (53-74)	<.001	0 (0)	53 (42-68)	49 (41-57	63 (44-76)	.004
Triglycerides (mg/dL)	24 (1.2)	74 (57-101)	79 (60-105)	68 (55-96)	<.001	0 (0)	84 (65-120)	85 (65-119)	82 (57-136)	.70
LDL-C (mg/dL)	32 (1.7)	102.4 (85-122)	104 (86-123)	101 (84-120)	.07	0 (0)	77 (63-97)	76 (62-90)	80 (65-105)	.24
Creatinine (mg/dL)	20 (1)	0.8 (0.7-0.9)	0.9 (0.8-0.99)	0.7 (0.6-0.8)	<.001	0 (0)	0.90 (0.77-1.10)	0.95 (0.85-1.20)	0.79 (0.70-1.00)	<.001
eGFR (mL/min/1.73 m^2)	21 (1.1)	101.22 (88.6-112.6)	102.8 (92.2-113.4)	98.9 (84.5-111.9)	<.001	0 (0)	80.3 (60.7-93.6)	82.6 (61.0-94.9)	75.5 (60.4-88.1)	.15
Hypertension, n (%)	16 (0.8)	640 (33.5)	370 (35.3)	270 (31.4)	.07	0 (0)	100 (86.2)	58 (84)	42 (89.4)	.42
Dyslipidemia, n (%)	0 (0)	1310 (68.1)	722 (68.4)	588 (67.6)	.69	0 (0)	90 (77.6)	54 (78.3)	36 (76.6)	.83

Data are given as n (%) for categorical variables and as means ± SD or medians and interquartile ranges for continuous variables.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl-transferase HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.
[a]Alcohol intake was defined as ≥2 alcohol units per day in men and ≥1 alcohol unit per day in women, respectively.

Table 2. Status of chronic vascular complications, diabetes treatment and cardiovascular medications of participants, stratified by sex and primary or secondary prevention of CVD

	Primary prevention of CVD					Secondary prevention of CVD				
	Missing n (%)	All subjects (n = 1925)	Men (n = 1055)	Women (n = 870)	*P* value	Missing n (%)	All subjects (n = 116)	Men (n = 69)	Women (n = 47)	*P* value
Microalbuminuria, n (%)	206 (10.7)	181 (10.5)	93 (9.7)	88 (11.5)	.28	10 (8.6)	22 (18.9)	14 (20.3)	8 (17)	.46
Macroalbuminuria, n (%)	206 (10.7)	44 (2.6)	28 (2.9)	16 (2.1)	.28	10 (8.6)	9 (7.8)	7 (10.1)	2 (4.2)	.46
eGFR < 60 mL/min/1.73 m^2, n (%)	24 (1.02)	83 (4.3)	29 (2.7)	54 (6.2)	<.001	1 (0.9)	26 (22.4)	15 (21.7)	11 (23.4)	.86
Non-proliferative retinopathy, n (%)	58 (3)	386 (20.7)	200 (19.6)	186 (21.9)	.09	2 (1.7)	30 (25.9)	16 (23.2)	14 (29.8)	.73
Proliferative retinopathy, n (%)	58 (3)	151 (8.1)	73 (7.2)	78 (9.2)	.09	2 (1.7)	53 (50.0)	33 (47.8)	20 (42.6)	.73
Maculopathy, n (%)	260 (13.5)	62 (3.7)	30 (3.2)	32 (4.4)	.21	31 (26.7)	3 (2.6)	1 (1.5)	2 (4.3)	.29
Sensory–motor neuropathy, n (%)[a]	181 (9.4)	319 (18.3)	150 (15.8)	169 (21.3)	.003	2 (1.7)	65 (56.0)	40 (58.0)	25 (53.2)	.49
Minor lower limb amputations, n (%)	222 (11.5)	12 (0.7)	8 (0.8)	4 (0.5)	.27	26 (22.4)	8 (6.9)	6 (8.7)	2 (4.2)	.63
Carotid artery plaques, n (%)	888 (46.1)	188 (18.1)	99 (17.8)	89 (18.5)	.77	34 (29.3)	63 (54.3)	36 (52.2)	27 (57.4)	.95
Active/former foot ulcers, n (%)	222 (11.5)	28 (1.6)	12 (1.3)	16 (2.1)	.27	26 (22.4)	7 (6.0)	4 (5.8)	3 (6.4)	.63
MDI, n (%)	51 (2.6)	1472 (78.5)	824 (80.5)	648 (76.1)	.02	1	104 (89.7)	64 (92.7)	40 (85.1)	.11
CGM, n (%)	46 (2.4)	325 (17.3)	167 (16.3)	158 (18.5)	.19	1	27 (23.3)	14 (20.3)	13 (27.7)	.38
CSII, n (%)	51 (2.6)	253 (13.5)	120 (11.7)	133 (15.6)	.01	1	7 (6.0)	2 (2.9)	5 (10.6)	.09
SAP, n (%)	45 (2.3)	137 (7.3)	74 (7.2)	63 (7.4)	.87	1	3 (2.6)	2 (2.9)	1 (2.1)	.79
CHO counting, n (%)	261 (13.6)	582 (35)	312 (32.5)	270 (36.8)	.25	27	22 (19.0)	11 (15.9)	11 (23.4)	.49
Aspirin, n (%)	1 (0.1)	206 (10.7)	114 (10.8)	92 (10.6)	.86	0	95 (81.9)	59 (85.5)	36 (76.6)	.22
Statins, n (%)	0 (0)	560 (29.1)	318 (30.1)	242 (27.8)	.26	0	107 (92.2)	64 (92.8)	43 (91.5)	.80
Fibrates, n (%)	318 (16.5)	9 (0.6)	6 (0.7)	3 (0.4)	.48	33	0	0	0	
ACE-I/ARBs, n (%)	0 (0)	508 (26.4)	286 (27.1)	222 (25.5)	.43	0	83 (71.6)	49 (71)	34 (72.3)	.88
Beta-blockers, n (%)	1 (0.1)	105 (5.5)	49 (4.6)	56 (6.4)	.08	0	40 (34.5)	23 (33.3)	17 (36.2)	.75
Calcium-channel blockers, n (%)	0 (0)	125 (6.5)	77 (7.3)	48 (5.5)	.11	0	25 (21.6)	17 (24.6)	8 (17)	.33
Diuretics, n (%)	1 (0.1)	147 (7.6)	76 (7.2)	71 (8.2)	.43	0	42 (36.2)	25 (36.2)	17 (36.2)	.99
Alpha-blockers, n (%)	0 (0)	22 (1.1)	17 (1.6)	5 (0.6)	.03	0	4 (3.4)	2 (2.9)	2 (4.3)	.69

Data are given as n (%).
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; CGM, continuous glucose monitoring; CHO, carbohydrates; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; SAP, sensor augmented pump.
[a]Electromyography testing.

factors between the 2 sexes) could positively affect the risk of developing adverse CVD outcomes, even in the post-menopausal phase when estrogen protection is no longer present.

To date, to our knowledge, there is little information on possible sex-related differences in CVD prevalence and CVD risk estimates in people with T1D. Some registry-based observational studies of patients with T1D reported higher rates of CVD mortality and morbidity in women than in men of similar age (5, 16). However, these results are often fraught with the consideration of the relative instead of the absolute CVD risk; for instance, standardized mortality ratios for all-cause and CVD mortality as well as rates of CVD hospitalizations were greater in women than in men in a cohort of T1D with longstanding disease aged 30-39 and 40-44 years from the Pittsburgh Epidemiology of Diabetes Complications study (16). However, when considering the absolute risk rates (expressed as 100 000 person-years), the above-mentioned sex-related differences were no longer significant for all-cause mortality and CVD events, except for higher CVD mortality in women aged 40-44 years. Accordingly, in the Swedish National Diabetes register, T1D women had a greater excess risk, but not absolute risk, of CVD mortality compared with T1D men, regardless of diabetes duration (5). In line with absolute risk data, in our study we found that CVD prevalence was superimposable in both sexes (5.1% in women vs 6.1% in men) and was even lower in postmenopausal women than in men of similar age (12.8% in women vs 19.2% in men; $P < .05$).

It is known that the Steno type 1 risk engine model for estimating the 10-year risk of first fatal or nonfatal CVD event (ischemic heart disease, ischemic stroke, heart failure, or peripheral artery disease) is specific for adult patients with T1D. This CVD risk prediction model has been implemented and validated in a large Danish population of adult patients with T1D who attended the Steno Diabetes center (24), mainly to overcome the use of the UK Prospective Diabetes Study (UKPDS) risk engine, which was designated for patients with type 2 diabetes and underestimated the 10-year CVD risk in those with T1D. Interestingly, no substantial differences can be observed between the original Danish population with T1D (from which the Steno type 1 risk engine was modelled) and our study population in terms of age, diabetes duration, BMI, plasma lipid profile, and kidney function parameters. Conversely, the levels of HbA1c, systolic blood pressure, and smoking tended to be lower in our patient population than in the Danish patient population. That said, however, it is not easy to understand whether these differences in

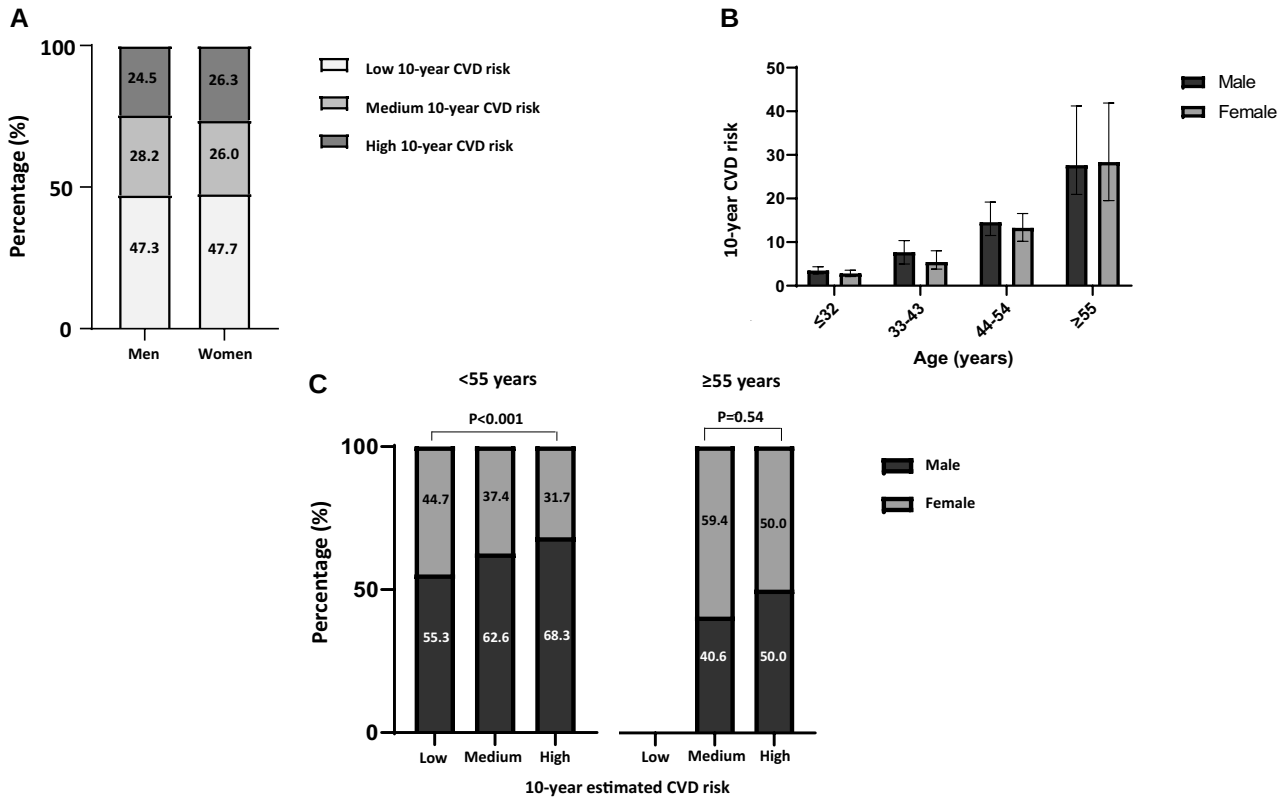

Figure 2. Distribution of 10-year CVD risk score categories (estimated by the Steno type 1 risk engine) according to sex (A), sex and age quartiles (B), and sex and age <55 and ≥55 years (C), respectively.

CVD risk factors might have any differential impact on the predictive performance of the Steno type 1 risk engine in estimating the 10-year CVD risk in our T1D population as a prospective observation was not performed. Previously, the Steno type 1 risk engine has been applied in a small observational study of 223 Italian patients with T1D in primary CVD prevention and it was able to identify those with subclinical atherosclerosis, but it overestimated the CVD event rates (27); unfortunately, the possible effect of sex differences on CVD risk was not tested in such a small study. In another small cross-sectional study of 575 Italian patients with T1D, the authors reported that a large proportion (45%) of patients without CVD were classified at very high CVD risk using the 2019 European Society of Cardiology (ESC) and European Association for the Society of Diabetes (EASD) risk classification compared with the Steno type 1 risk engine, particularly in those aged <35 years, thus suggesting an overestimation of the true CVD risk in this patient population (using the 2019 ESC/EASD risk classification) (28). The same group of investigators compared the predictive performance of the ESC/EASD risk classification and the Steno type 1 risk engine in a longitudinal study of 456 patients with T1D who were followed for a mean period of ~8.5 years (29); they found that the performance of the Steno type 1 risk engine was superior to the ESC/EASD risk classification in predicting incident CVD events in all CVD risk categories. Recently, in a cross-sectional study of 501 Spanish adults with T1D in primary CVD prevention, the use of the Steno type 1 risk engine also identified preclinical atherosclerosis better than use of both the 2019 ESC/EASD risk classification and the non-T1D–specific 2013 American College of Cardiology/American Heart Association (ACC/AHA) 10-year CVD risk score (30). In addition, the Steno type 1 risk engine was more strongly associated with arterial stiffness than the 2019 ESC/EASD risk classification in a small cross-sectional study of 54 Belgian adults with T1D (31).

In the present study, when we examined patients with T1D aged <55 years, we found that men had a higher net burden of CVD risk as they were more frequently smokers, and had higher values of BMI, systolic blood pressure, and plasma LDL-cholesterol than women, although men were more frequently treated with lipid-lowering and antihypertensive agents. These results are in line with previous observations obtained in a cohort of Italian patients with T1D in which men were more likely to be obese and smokers and had higher blood pressure and a more atherogenic lipid profile, although men were more frequently treated with lipid-lowering and anti-hypertensive drugs, than women (32). Conversely to our population, women had worse glycemic control despite being more often treated with continuous subcutaneous insulin infusion (32).

In the present study, we found that the 10-year estimated CVD risk performed well in identifying patients with carotid atherosclerotic plaques, regardless of sex, mainly among patients aged ≤55 years compared with those aged >55 years. In line with literature data (27, 33), we found that the 10-year estimated CVD risk also had a satisfactory performance in identifying diabetic retinopathy and sensory–motor polyneuropathy, independently of sex and age. Women had a comparable risk of carotid artery plaque burden but higher risks of these microvascular complications than men, which might, at least partially, reconcile the apparent discrepancy between the levels of the 10-year estimated CVD risk and the prevalence of clinically manifest CVD observed in our T1D women. Indeed, the presence of microvascular complications

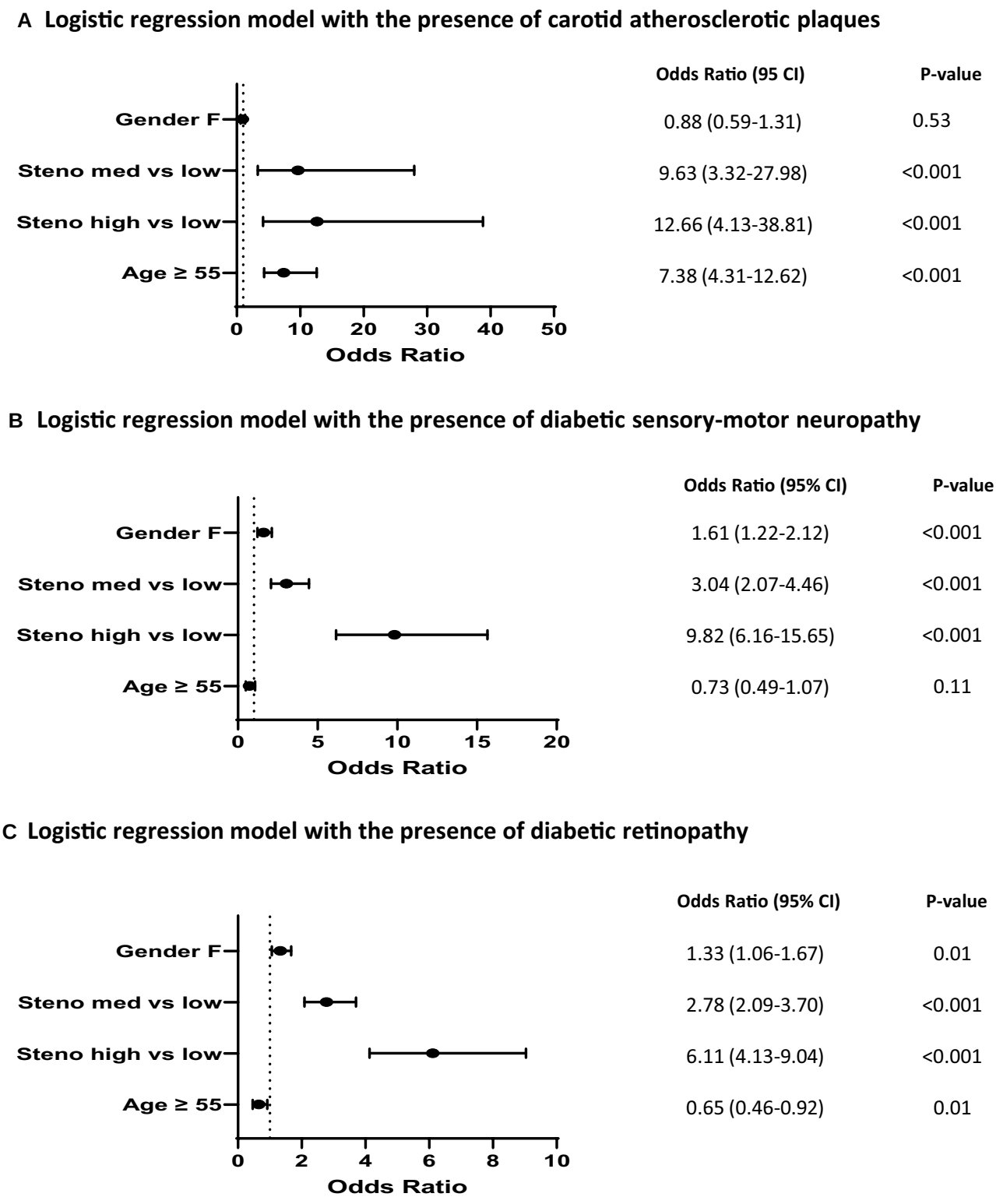

Figure 3. Association between 10-year CVD risk score categories (estimated by the Steno type 1 risk engine) and presence of carotid atherosclerotic plaques (A), diabetic sensory–motor polyneuropathy (B), or diabetic retinopathy (C). All logistic regression models were also adjusted for age and sex.

may represent an important risk factor of CVD events and mortality in people with T1D (34, 35).

In the present study, we also found that there were no significant differences in concomitant pharmacological treatments between the 2 sexes, thus excluding relevant sex disparities in the quality of care. On the other hand, as reported above, we found that compared with men, T1D women were more often treated with continuous subcutaneous insulin infusion, which has been reported to be associated with better CVD outcomes than multiple daily injections (36). Of note, T1D women in the low 10-year estimated CVD risk category were less frequently treated with statins, possibly due

to reluctant use of this drug class in premenopausal women, which might partly contribute to explain the lack of concordance between the level of 10-year estimated CVD risk and the observed prevalence of clinically manifest CVD. However, this sex-related difference in statin use was no longer evident in postmenopausal women, even in the higher 10-year estimated CVD risk categories, although published data support the need of early strict lipid monitoring and management to reduce CVD events (37-39). Finally, we did not observe any significant difference in medium 3-year HbA1c values between men and women, although women had a small but significantly longer duration of diabetes than men.

The retrospective, cross-sectional design of our study does not allow one to draw any possible explanation on the mechanisms underlying the sex disparity observed in CVD risk factors and outcomes. Although the age (≥*55* years) at which this sex-related difference was observed is highly suggestive for a possible biological cause (ie, mainly due to changes in the hormonal status after the menopause), we cannot exclude possible causative roles of other coexisting nontraditional CVD risk factors, including genetic, allostatic, disease-related stress, or behavioral factors (40). Menopause can worsen the shift toward a more atherogenic plasma lipid profile, insulin resistance, and central body fat distribution (41), although little is known about how T1D and menopause might synergistically interact to change the CVD risk in women. A recent study showed that T1D women had a faster increase in the extent of subclinical atherosclerosis associated with menopause than did women without T1D, despite lower atherogenic lipid levels at baseline and no differences in lipid changes across the menopausal transition than did women without T1D (41). Thus, it is reasonable to assume that this faster increase in the extent of subclinical atherosclerosis was not explained by changes in traditional CVD risk factors.

Our study has some important limitations that should be mentioned. The retrospective cross-sectional design of the study does not allow one to draw any firm conclusion about the accuracy of the Steno type 1 risk engine in predicting clinical CVD events. This could be proven only by a prospective study. However, our study has also some important strengths. It is a large multicenter observational study, representative of an Italian population of adult outpatients with T1D. These patients were well phenotyped and the observed associations between 10-year estimated CVD risk and presence of carotid atherosclerotic plaques or microvascular diabetic complications could also provide information about the accuracy of CVD risk calculation.

In conclusion, the results of our large cross-sectional study show that although the prevalence of manifest CVD is similar in men and women with T1D (especially at younger age), the paradigm of a worse CVD risk profile in women with T1D, compared with men, could be shifting toward a nondiabetic trend, with a more favorable CVD risk profile in T1D women <*55* years of age. However, further research in this field should be encouraged to implement sex-specific guidelines for CVD risk factor management in people with T1D without pre-existing CVD.

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Author Contributions

A.D.C., M.M., F.C., M.G.B., G.C., R.B., S.B., G.T., and S.V.K. conceived and designed the study. R.A., A.M., L.P., K.B., E.C., F.A.C., C.M., F.L., S.B., R.T., R.M.P. collected data. A.D.C., R.A. and S.V.K. wrote the first draft of the manuscript. R.A. and M.L.M. performed statistical analysis. A.M., G.T., and M.L.M. critically revised the manuscript, for important intellectual content. A.D.C. and SVK are the guarantors of this work and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the interpretation of the results and revision of the manuscript and approved the final manuscript.

Disclosures

Nothing to declare.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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