Cardiovascular Diabetology

REVIEW

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Cardiovascular disease in women with type 1 diabetes: a narrative review and insights from a population-based cohort analysis

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Abstract

Cardiovascular disease (CVD) remains the leading cause of mortality among people with type 1 diabetes (T1D), with cardiovascular mortality rates 2–5 times higher than in the general population. A concerning sex disparity exists within this high-risk population, as the cardioprotective advantage typically observed in women without diabetes appears attenuated or eliminated in individuals with T1D. This disparity is evident across the CVD spectrum, including coronary artery disease, stroke, heart failure, and cardiovascular mortality, with women consistently experiencing an excess burden of disease. These differences are particularly pronounced in women with early-onset T1D, leading to a substantial loss of life-years—approximately 18 years for women compared to 14 for men. Several factors may contribute to this sex disparity. First, the effect of hyperglycemia on CVD appears to have a sex-based differential impact and women with T1D often demonstrate more difficulties to achieve optimal glycemic control. Second, although women with T1D generally exhibit a more favorable CVD risk factor profile than men with T1D, the presence of hypertension, smoking or diabetic kidney disease seem to have a strong impact on CVD in women. Diabetes also appears to diminish sex-based differences in lipid metabolism, and a trend towards increased obesity rates among women with T1D has been observed. Lastly, female-specific factors, which are more prevalent in T1D, exacerbate cardiovascular risk. These include premature menopause, pregnancy-related disorders (such as preeclampsia), polycystic ovary syndrome, and autoimmune diseases, which disproportionately affect women. This narrative review examines the epidemiological evidence highlighting the aspects regarding the excess risk of CVD in women with T1D and evaluates sex disparities in both traditional and female-specific risk factors. Finally, we include a sex-based analysis from the Catalan Registry, which highlights the critical need for greater awareness and enhanced early detection and management of CVD risk factors in this population.

Keywords Type 1 diabetes, Women, Cardiovascular disease

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Introduction

Advancements in diabetes care have significantly improved survival rates among individuals with type 1 diabetes (T1D). However, their risk of death remains two to five times higher than that in the general population [1]. While achieving tight glycemic control can lower the risk of cardiovascular disease (CVD) [2], a substantial excess in cardiovascular mortality persists, even among those meeting glycemic targets [3]. This heightened risk is especially notable in women, who experience approximately twice the excess risk of cardiovascular events (CVE) compared to men, relative to individuals without T1D [4].

Although women have a lower absolute risk of CVD than men in the general population, attributed in part to hormonal protection and a more favorable lipid profile [5], the rates of coronary artery disease (CAD) and CVD mortality have increased in recent years among young women [5]. Despite this trend, the biological differences and underlying sex-specific pathophysiology of CVD in women remain poorly understood, leading to risk-assessment models that fail to adequately account for female-specific risk factors. Moreover, women have historically been underrepresented in CVD clinical trials, which has also limited the ability to assess the safety and efficacy of therapies for women. While several factors contribute to the inequities in the detection and management of CVD between men and women in the general population, the underlying causes of the excess CVD risk observed specifically in women with T1D remain uncertain.

This narrative review aims to provide a comprehensive overview of the epidemiological evidence highlighting the increased incidence of CVD in women with T1D and addresses sex-specific differences in the risk factors underlying the premature CVD observed in this population.

Material and methods

Search strategy and selection criteria

In this study, a narrative review of the literature was conducted, focusing on the epidemiology of CVD in women with T1D and the sex-related differences in both traditional and emerging CVD risk factors. Although this is not a systematic review, a comprehensive search was performed using the PubMed and Embase (Elsevier, Amsterdam, The Netherlands) databases for all articles available up to 15 February 2025. The suitability of the articles identified through the electronic search was assessed based on the information contained in the abstracts.

The search strategy was designed to balance specificity and sensitivity, starting with broader criteria and refining them based on the number of results retrieved. All relevant articles were considered, with priority given to those evaluating clinical variables and were published in high-impact journals. Articles that did not align with the objectives of the manuscript, along with conference abstracts, duplicate publications, and non-English articles, were excluded from the review process.

Retrospective population-based cohort analysis

To further address the aim of this review, we analyzed available data from our region (Catalonia, Spain). We conducted a retrospective analysis involving all patients with T1D (n = 14,156) and control individuals without diabetes (n = 1,151,929) from the SIDIAP database (Information System for the Development of Primary Care Research). SIDIAP is a primary healthcare database that gathers pseudo-anonymized data from approximately 5.8 million residents of Catalonia who are registered with a family physician under the Institut Català de la Salut (ICS, Catalan Institute of Health). As the main provider of healthcare services within the Catalan Health System (CatSalut), ICS oversees 327 primary care teams and serves 76% of the region's population. The SIDIAP database includes data from primary care electronic medical records, such as demographics, diagnoses, clinical variables, prescriptions, referrals, and laboratory results. It also integrates information on medications dispensed at pharmacies and hospital discharge data from the Basic Minimum Set of Data (BMSD). SIDIAP has been extensively utilized in observational studies to assess clinical characteristics and outcomes in individuals with T1D [6–8].

In this study, a retrospective cohort analysis was conducted, identifying individuals with T1D defined as active cases with an ICD-10 diagnostic code for T1D (E10 and subcodes) and on insulin therapy at the collection date. Subjects with diagnostic codes for any other type of diabetes or treated with non-insulin antidiabetic drugs were excluded. These individuals were compared with a reference cohort without diabetes. We assessed the presence and degree of control of cardiovascular risk factors, according to international guidelines. Proportions were calculated for all variables, including clinical characteristics, diabetes-related complications, and treatment. In the comparison between groups (sex), p-value was calculated using the Fisher exact test for qualitative variables and the independent samples t-test for quantitative variables.

Furthermore, the incidence rates of CVE and all-cause mortality between January 1, 2010, and June 30, 2023, were computed using the exact method. Diagnostic codes were categorized into coronary, cerebrovascular, peripheral vascular, and heart failure (HF) events. Additionally, the date of death for individuals who died during the study period was recorded. However, specific causes of death were not available for analysis in this study. As death may act as a competing risk for the occurrence of

the studied events, we performed competing risk analyses using the Fine and Gray sub-distribution hazard model to account for the presence of competing events in our survival analyses. For each outcome, sex-specific relative risks (RR) were calculated by comparing incidence in individuals with T1D versus controls, stratified by sex. We then compared RRs between women and men to quantify sex-based risk disparities. The sex difference in RR excess was estimated by computing the logarithmic RR difference. The standard error of this difference was derived from the 95% confidence intervals (CI) of the sex-specific RRs. Finally, we calculated the female-to-male relative risk ratio (RR in women/RR in men), and its 95% CI was obtained by exponentiating the bounds of the logarithmic difference's 95% CI. All analyses were performed using R statistical software, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed and significance was considered if p-value < 0.05.

Epidemiology of cardiovascular disease in type 1 diabetes: the gender gap

CVD remains the leading cause of morbidity and mortality in individuals with T1D, driven by a complex interplay of pathophysiological mechanisms that extend beyond hyperglycemia and contribute to accelerated atherosclerosis.

Growing evidence indicates that the cardiovascular impact of T1D differs significantly between men and women, with the inherent female advantage observed in the general population appearing to be diminished or even abolished in this group. Analyses from the Diabetes Control and Complications Trial (DCCT) and its observational follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) revealed that, after adjusting for traditional cardiovascular risk factors, women with T1D exhibit a risk of both first and recurrent CVE comparable to that of men [9, 10]. These findings align with observations from the Pittsburgh Epidemiology of Diabetes Complications Study [11] and the EURODIAB Prospective Complications Study [12], which similarly documented a heightened cardiovascular burden among women with T1D.

Consistent with these findings, our analysis from the SIDIAP cohort– comprising 14,156 individuals with T1D and 1,151,929 controls without diabetes– further demonstrates a higher excess risk across the CVD spectrum in women with T1D compared to men, relative to individuals without T1D. Specifically, women exhibited a 30% higher excess risk of atherosclerotic cardiovascular disease (ASCVD), a 16% higher excess risk of heart failure (HF), and a 17% higher excess risk of mortality (Fig. 1; Suppl. Table 2). However, these findings should be interpreted in the context of certain methodological limitations. The use of primary-care electronic records without external validation may introduce variability in disease definitions, and conditions not routinely managed in primary care could also be underreported.

Atherosclerotic cardiovascular disease (ASCVD)

ASCVD pathophysiology and clinical presentation differ by sex and age. Although ASCVD predominantly manifests as CAD, women at older ages are more likely to experience cerebrovascular disease [5]. Furthermore, the prevalence and progression of ASCVD vary across different arterial beds, with distinct risk factors being more strongly associated with specific vascular territories [13].

In individuals with T1D, atherosclerosis develops earlier, progresses more rapidly, and extends more distally compared to those without diabetes [14–17]. Moreover, individuals with diabetes exhibit increased inflammatory infiltration [18], larger necrotic cores, and greater calcification, all of which have been associated with heightened plaque vulnerability [19].

The impact of diabetes on CVD presentation also differs by sex, a phenomenon observed in both T1D and Type 2 Diabetes (T2D) [8, 20]. Given these findings, this review separately examines epidemiological data on the different ASCVD subtypes in T1D.

Coronary artery disease

Coronary artery disease (CAD) has been shown to be the most prevalent CVD in individuals with T1D, as well as in the general population, across most studies, regardless of gender [8]. Coronary artery calcium (CAC), a highly specific marker of coronary atherosclerosis and a predictor of future coronary events [19], is particularly increased in a high-risk population like T1D [21], starting at a young age [22]. Although CAC levels are significantly higher in men than in women in the general population, these gender differences are reduced or even abolished in individuals with T1D [23, 24].

An excess risk of CAD in women with T1D is further supported by multiple observational cohort studies. A landmark meta-analysis, which pooled data from 26 observational cohort studies encompassing over 200,000 individuals and more than 15,000 CVD events, found that women with T1D have a 2.5-fold higher excess risk of incident CAD compared to men with T1D [4]. Similarly, our analysis reveals a nearly twofold higher excess risk of CAD in women with T1D compared to men (Fig. 1; Suppl. Table 2).

These sex disparities are further exacerbated by longer diabetes duration, highlighting the profound impact of early disease onset and prolonged exposure to hyperglycemia on cardiovascular outcomes. Data from the Swedish National Diabetes Registry revealed that women with T1D onset before age 10 had a 60-fold increased risk of

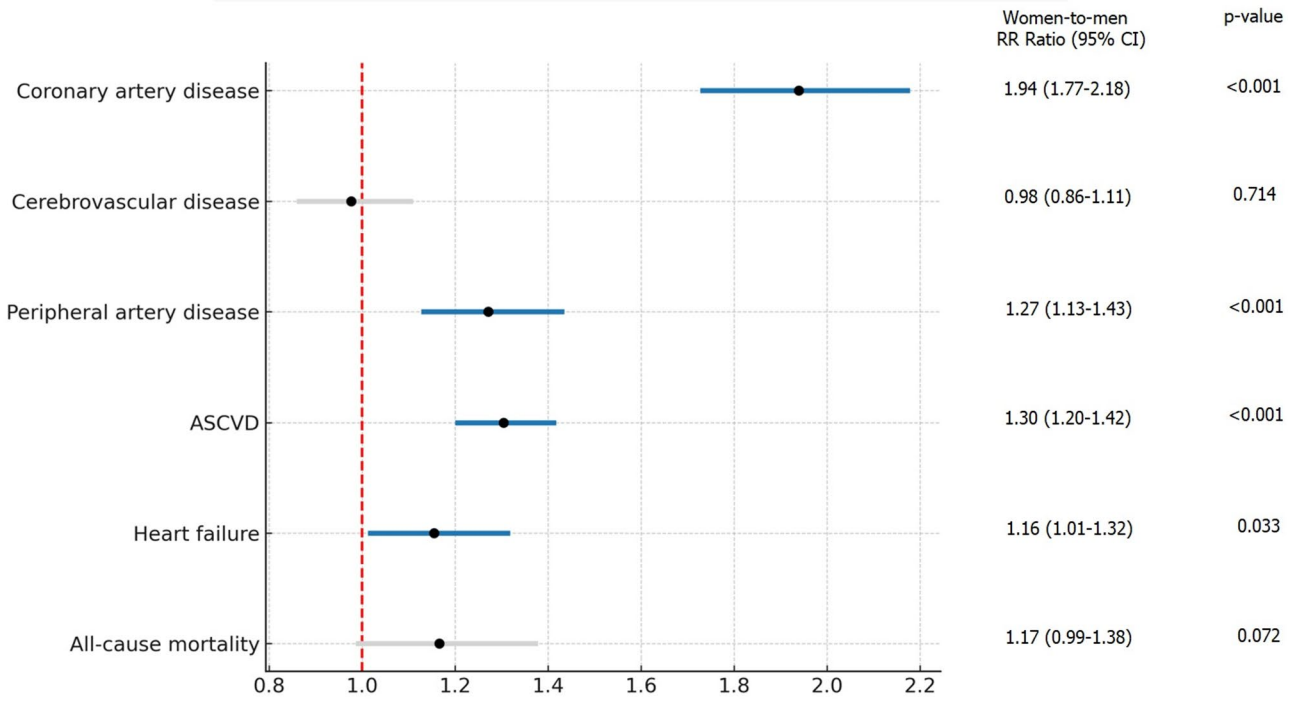

Fig. 1 Women-to-men ratio of relative risks (RR) for incident cardiovascular events and all-cause mortality in individuals with type 1 diabetes (T1D). Ratios greater than 1 indicate higher RR in women, while ratios below 1 indicate higher RR in men. *P*-values are based on z-tests of the log-transformed RR differences. Data were retrieved from the SIDIAP Database, comprising 14,156 individuals with T1D and 1,151,929 controls without diabetes. Incidence rates of cardiovascular events and all-cause mortality were computed between January 1, 2010, and June 30, 2023. ASCVD: atherosclerotic cardiovascular disease; defined as presence of coronary artery disease, stroke and/or peripheral artery disease

CAD, compared to a 17-fold increase in their male counterparts. Disparities were even more pronounced for acute myocardial infarction (AMI) events, with women with early-onset T1D facing a 90-fold increased risk of AMI, compared to a 15-fold increase in men [25]. Similarly, the risk of mortality from CAD in young adult women with T1D is also increased, with absolute rates comparable to those observed in men with T1D under the age of 40 [26].

Cerebrovascular disease

T1D is associated with an increased risk of stroke [25, 27] and its subtypes, i.e. ischemic, hemorrhagic, and lacunar stroke [28]. Cerebral small-vessel disease, the most common underlying cause of stroke in T1D, often begins preclinically at a young age [29]. However, the impact of T1D on stroke risk is less pronounced compared to its effect on other ASCVD subtypes. This may be due to the fact that the risk of stroke increases significantly in older ages, and T1D is associated with reduced life expectancy. Supporting this, data from the Swedish National Diabetes Registry show that patients with T1D have an excess risk of CAD that is at least double of that of stroke, with even greater disparities in those with earlier T1D onset.

In a prospective cohort of over 4000 patients with T1D from the Finnish Diabetic Nephropathy (FinnDiane) Study, independent risk factors for ischemic stroke included longer diabetes duration, worse glycemic control, higher BP, and active smoking [30]. Unlike the general population, female sex was not a protective factor in this cohort.

Stroke is the second leading cause of CVD mortality among women worldwide and the leading cause in certain regions [5]. Although age-specific stroke rates are higher in men, women experience more stroke events overall due to their longer life expectancy and higher incidence at older ages [31]. Consistent with global trends in ASCVD, a large retrospective study from Sweden also found an excess risk of stroke in women compared to men with T1D, relative to the general population [32]. However, sex disparities in the excess risk of cerebrovascular disease associated with T1D appear narrower than those for other CVD subtypes, such as CAD. A meta-analysis of 26 observational cohort studies involving over 200,000 individuals found that women with T1D had a 1.4-fold higher excess risk of stroke compared to men with T1D, whereas the excess of incident CAD was 2.5-fold higher in women [4]. In our analysis, men and women with T1D had a similar excess risk of stroke (Fig. 1; Suppl. Table 2).

Stroke event rates increase substantially in the oldest age groups with T1D, particularly among women [8],

suggesting that stroke incidence will continue to rise as we have an increasingly older population with T1D.

Peripheral artery disease

While peripheral artery disease (PAD) has historically been considered a predominantly male condition, contemporary data reveal that in low- and middle-income countries, the prevalence of PAD is approximately equal between women and men. In contrast, in wealthier countries, the prevalence of PAD is slightly higher in women than in men [33]. Furthermore, data from the Global Burden of Disease study indicate that in the last decades women experienced a greater increase in PAD-related mortality and disability compared to men [34]. A delay in diagnosis and treatment may be attributed to the misconception in health-care professionals that PAD primarily affects men, as well as the fact that women often present with subclinical, asymptomatic, or atypical PAD symptoms that do not meet standard diagnostic criteria [35].

Diabetes plays a critical role not only in the development and progression of arteriosclerosis, the primary cause of vessel occlusion in PAD, but also in influencing disease severity. This is likely mediated through its effects on cellular and molecular processes involved in vascular and skeletal muscle adaptation to ischemia [36]. A meta-analysis incorporating data from seven cohorts, totaling over 2 million participants, demonstrated that diabetes (without distinction between subtypes) is an independent risk factor for PAD in both sexes, with a similar excess risk of 96% in women and 84% in men. Unlike CAD, the excess risk of PAD in women with diabetes compared to those without appears to be less pronounced [37]. The natural protective advantage that women without diabetes have over men may be attenuated by factors such as height, which disproportionately increases PAD risk in women [37]. Nevertheless, consistent with other ASCVD, our data reveal that women with T1D also have a 27% greater excess risk of PAD than men with T1D (Fig. 1; Suppl. Table 2).

In a previous retrospective cohort study from our group in Catalonia (Spain), with data from over 8,400 patients with T1D revealed that PAD was the most common first CVE (39.5%), followed by CAD (29.5%), cerebrovascular disease (16.6%) and HF (14.4%) [8]. In an observational study from the Swedish National Diabetes Register involving over 34,000 individuals, significant reductions in the incidence rates of lower extremity artery disease were observed among individuals with T1D in the last two decades. Despite these improvements, the incidence rates of lower extremity artery disease remained consistently high throughout the study [38].

A recent meta-analysis with global estimates of diabetes-related amputations, encompassing 23 studies and reporting over 500,000 diabetes-related lower extremity amputations, provided further insights. The incidence rate of amputations was higher in T1D than in T2D, both for minor (T1D: ~ 149 vs. T2D: ~ 76 per 100,000 individuals) and major amputations (T1D: ~ 101 vs. T2D: ~ 41 per 100,000 individuals) [39]. Moreover, the annual amputation rate was higher among men (~ 178 per 100,000) than women (~ 84 per 100,000) with diabetes.

Although the absolute risk of amputation is relatively low and decreasing in individuals with T1D, a nationwide study from Sweden encompassing nearly the entire T1D population revealed an overall excess risk 40 times greater than that of the general population [40]. Excess risk was substantially lower for those with good glycemic control and without diabetic kidney disease (DKD), but it still persisted and was greatest for minor amputations [40]. Consistent with previous findings, the incidence of amputations was higher for men than for women.

Heart failure

Diabetes is a well-established risk factor for the development of HF. Recent epidemiological studies have reported a rising prevalence of HF among individuals with T1D, likely linked to the growing population of older adults living with long-standing T1D. Although the incidence of CVD outcomes has declined substantially in individuals with T1D, no significant reduction in hospitalization rates for HF has been observed [41].

Several factors contribute to HF development in individuals with T1D, including ASCVD, hypertension, DKD, and diabetic cardiomyopathy, the latter suggesting a potential role of microvascular damage in the pathogenesis of HF [42]. In a study by Rosengren et al. involving 33,402 patients with T1D over a mean follow-up period of 7.9 years identified female gender, a worse glycemic control, and the presence of albuminuria as significant predictors of HF risk [43]. Notably, even individuals with well-controlled diabetes and normoalbuminuria exhibited an elevated risk of HF. Emerging evidence also points to cardiac autoimmunity as a contributing mechanism for cardiomyopathy in T1D [44].

Data on HF phenotypes in T1D remain limited. In a 7-year prospective study of individuals with long-standing T1D, the overall prevalence of HF at the end of the follow-up period was 3.7%. Among these patients, 85% exhibited HF with preserved ejection fraction (HFpEF), while the remaining 15% had HF with reduced ejection fraction (HFrEF). This distribution suggests that HFpEF may be the predominant phenotype in T1D, potentially reflecting the role of microvascular dysfunction and diastolic abnormalities in this population. This is particularly relevant for women, who are more frequently affected by HFpEF and in whom factors like obesity, hypertension and T2D seem to exert a more harmful effect [45].

A recent meta-analysis pooling data from four large cohort studies [43, 46–48] involving 61,885 patients followed for 1–12 years revealed a three-fold higher adjusted relative risk for HF in people with T1D compared to the general population [49]. When stratified by sex, the adjusted relative risk was significantly higher in women (4.9 (4.1–5.9)) than in men (3.0 (2.2–4.0)). Similarly, in a population-based study in a Mediterranean region, HF was more common as a first CVD event in women (21.7%) than in men (10.1%). Interestingly, while atherosclerotic events were the most common presentations of CVD in men of all ages and in younger women, the proportion of HF events rose markedly in women with T1D over the age of 60. In this subgroup, HF was the most prevalent initial CVE, accounting for up to 40% of the CVD events [8]. Our new data from the same region also reveal a slightly higher excess risk of HF in women with T1D compared to men (Fig. 1; Suppl. Table 2).

Cardiovascular mortality

Epidemiological studies consistently show that individuals with T1D experience not only a higher incidence of CVE but also an increased CVD mortality [50, 51], which remains the leading cause of death in this population. In a nationwide Swedish study involving nearly 34,000 patients with T1D and 169,000 matched controls, the hazard ratio for all-cause mortality and CVD-related mortality in individuals with T1D versus controls without diabetes were ~ 3.52 and ~ 4.60, respectively [3]. The excess risk of death in T1D was primarily driven by CVD and diabetes-related causes. Consistent with previous findings on CVD incidence, women with T1D had a significantly greater excess risk of CVD-related mortality than men, but not of death from any cause. These results align with earlier observational studies [26].

A meta-analysis including over 26 observational studies and 200,000 individuals with T1D, found that women had a twofold higher excess risk of fatal CVD compared to men with T1D. Additionally, a 37% greater excess risk of all-cause mortality was also observed in women, with no significant sex differences observed in mortality from cancer, accidents, or suicide [4]. Similarly, in our cohort, women had a 17% greater excess risk of all-cause mortality compared to men with T1D (Fig. 1; Suppl. Table 2).

In line with significant advancements in diabetes care, substantial reductions in deaths and hospitalizations for atherosclerosis-related events have been observed [22]. In a Swedish registry study involving over 36,000 patients with T1D and 184,000 controls followed between 1998 and 2013, all-cause mortality rates in T1D decreased by 29% (compared to 23% in controls) and CVD mortality rates fell by 42% (compared to 38% in controls) [41]. Similarly, a recent multicountry analysis reported a decline in all-cause mortality rates among people with T1D over the past two decades, with rates of decline unaffected by sex [1].

Nevertheless, individuals with T1D still face a life expectancy that is approximately 13 years shorter than that of the general population [52]. Further emphasizing the gender gap, a study from the Swedish National Diabetes Register, which included over 27,000 individuals with T1D and more than 135,000 matched controls, demonstrated that the development of T1D before the age of 10 resulted in a loss of 17.7 life-years for women compared to 14.2 life-years for men [25].

Glycemic control in type 1 diabetes: sex differences and cardiovascular implications

Chronic hyperglycemia and cardiovascular disease: a heightened burden in women

The DCCT/EDIC study demonstrated the dominant role of glycemia, second only to age, as a risk factor for a first CVE in T1D [53]. Similarly, a large Swedish nationwide cohort study of nearly 34,000 individuals with T1D, demonstrated a linear association between HbA1c levels and both all-cause and cardiovascular mortality. Each 1% increase in HbA1c was associated with a 22% rise in the risk of both overall mortality and CVD [3].

Hyperglycemia accelerates atherosclerosis through multiple mechanisms, including oxidative stress, inflammation, and endothelial dysfunction [54]. It also activates protein kinase C, stimulates the polyol pathway, and promotes the formation of advanced glycation end products. These processes collectively contribute to plaque formation and increased arterial stiffness [19].

As discussed earlier in this review, the effect of hyperglycemia on CVD appears to have a sex-based differential impact, with an excess risk observed in women. While the underlying mechanisms remain incompletely understood, one proposed explanation is that hyperglycemia may alter the concentration and activity of estrogen receptors, potentially inhibiting their protective effects on the vascular wall in women, increasing oxidative stress, and promoting vasoconstriction and platelet activation [5]. Beyond cardiovascular effects, the impact of chronic hyperglycemia on hormone-sensitive cancer development via estrogen receptors pathways warrants further investigation.

Sex hormones may also influence CVD risk through endothelial function modulation. Documented sex differences exist in both the quantity and function of endothelial progenitor cells, which mediate vascular repair [55]. In women without T1D, endothelial progenitor cells demonstrate mobilization during the menstrual cycle, consistent with hormonal regulation [56]. Notably, this physiological pattern appears blunted in women with T1D [57].

The sex gap in CVD risk observed in T1D is similarly present in T2D [20]. Two meta-analyses of 64 prospective population-based cohort studies, primarily including patients with T2D, confirmed that women with diabetes have a more than 40% greater excess risk of incident CAD [58] and a 25% greater excess risk of stroke [27], compared to men with diabetes. Further research has shown that among individuals without prior CVD, young women (aged 40 years or younger) with early-onset T2D face the highest excess risk of cardiovascular events [59].

Despite these findings, it is still unclear whether the elevated risk of adverse outcomes in women relative to men is directly attributable to hyperglycemia or stems from sex-based differences in underlying confounding factors.

Sex differences in glycemic goal attainment

Multiple studies have reported that women with T1D exhibit worse glycemic control compared to men [60, 61], particularly during adolescence [62]. A trend toward lower rates of optimal glycemic control (HbA1c < 7%) was observed among women compared to men in our cohort, though the difference was not statistically significant (24.4% vs 23.1%, $p = 0.072$; Table 1). Conversely, other studies have found comparable glycemic control between sexes, although higher rates of insulin pump use among women were reported [63, 64].

Although data on sex-based differences in glycemic variability is lacking, menstrual cycle-associated glycemic fluctuations in women with T1D are well-documented [65–67]. Specifically, studies demonstrate decreased insulin sensitivity with highest mean glucose levels during the luteal phase, followed by increased sensitivity with lowest mean glucose levels in the follicular phase [65, 68]. These fluctuations might be particularly relevant given mounting evidence that glycemic variability is an independent risk factor for CVD in T1D [69]. Finally, the higher prevalence of eating disorders among women with T1D likely contributes to their greater challenges in achieving glycemic targets [63].

Table 1 Comparison of standards of care achievement between women and men with type 1 diabetes (T1D) in Catalonia (Spain)

	T1D		*P*-value
	N = 14,156		
	Women	Men	
	6222	7934	
Glycemia			
HbA1c < 7%	1389 (23.1%)	1874 (24.4%)	0.072
Blood pressure			
BP < 140/90	3685 (78.9%)	4397 (75.0%)	**< 0.001**
BP < 130/80	1944 (41.6%)	1964 (33.5%)	**< 0.001**
LDL-cholesterol			
LDL-c < 70	733 (13.3%)	1215 (17.3%)	**< 0.001**
LDL-c < 100	2707 (49.1%)	3642 (52.0%)	**< 0.001**
LDL-c < 130	4529 (82.2%)	5721 (81.7%)	0.443
Weight			
BMI < 25	1337 (34.7%)	1530 (31.5%)	**< 0.001**
BMI < 30	2583 (67.1%)	3562 (73.3%)	**< 0.001**
Active smoking			
No active smoking	4831 (80.7%)	5526 (72.1%)	**< 0.001**
Never smoking	3598 (60.1%)	2875 (37.5%)	**< 0.001**

Data were retrieved from the SIDIAP Database and are shown as n (percentage)

BMI body mass index; *BP* blood pressure; *LDL-c* LDL-cholesterol; *T1D* Type 1 Diabetes

p values for comparisons according to sex are reported. Bold indicates p < 0.05

The potential role of hypoglycemia

Several studies suggest that women with T1D are at a higher risk of hypoglycemia, particularly severe hypoglycemia, compared to men [70, 71]. Furthermore, greater burden of hypoglycemia in women compared to men, characterized by worse patient-reported outcomes and more significant negative impacts on daily life and well-being have been reported [71]. Iatrogenic hypoglycemia is not only a well-recognized barrier to achieving optimal diabetes control but has also been implicated in the pathogenesis of atherosclerosis.

Experimental studies have shown that acute hypoglycemia triggers inflammatory markers and endothelial dysfunction in both healthy individuals and those with T1D, with a prolonged pro-inflammatory response persisting for at least one week [72, 73]. History of severe hypoglycemia events, impaired hypoglycemia awareness, and hypoglycemia exposure on continuous glucose monitoring have been independently linked to preclinical atherosclerosis in T1D [74, 75]. Furthermore, a long-term analysis of the DCCT/EDIC study, spanning approximately 30 years, identified severe hypoglycemia as a significant risk factor for CAD [76].

Sex disparities in traditional cardiovascular disease risk factors

Although the primary determinant of chronic complications in T1D is the degree and duration of hyperglycemia, CVD in T1D involves a complex and multifactorial pathophysiology [54] (Fig. 2). Similar to T2D, traditional CVD risk factors significantly contribute to the development and progression of CVD in T1D [50], underscoring the need for a comprehensive cardiovascular risk assessment [77–79].

Beyond disparities in achieving glycemic targets, sex differences have also been documented in other aspects of diabetes care, including the assessment and management of cardiovascular risk factors and adherence to quality-of-care parameters [80]. To further investigate these disparities, we analyzed available data from the SIDIAP Registry (Table 1; Suppl Table 1), which will be discussed in the following sections.

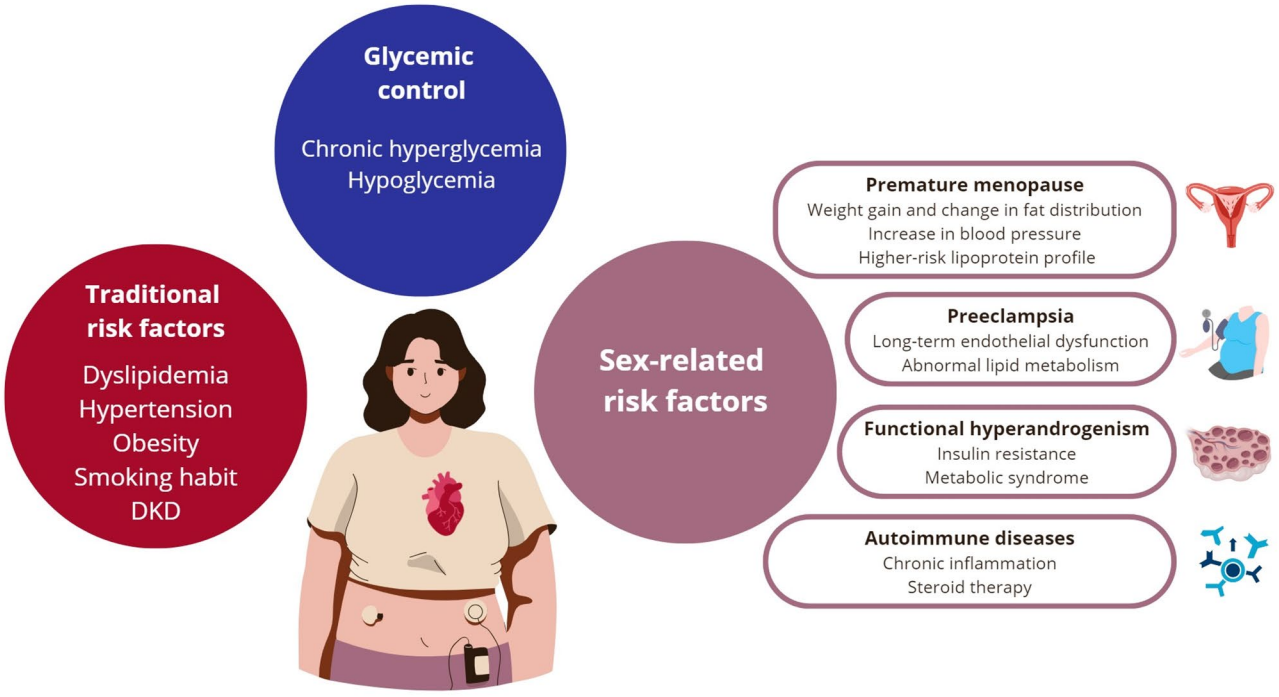

Fig. 2 Cardiovascular risk factors in women with type 1 diabetes. The figure categorizes cardiovascular disease risk factors in women into three groups: glycemic-related factors, traditional risk factors that affect both sexes but may impact women differently (e.g., hypertension, dyslipidemia, smoking), and sex-related risk factors (e.g., premature menopause, preeclampsia). Key pathophysiological mechanisms underlying the cardiovascular associations of female-specific factors are also presented. DKD: diabetic kidney disease.

Hypercholesterolemia and lipid-lowering therapy

Suboptimal glycemic control is associated with quantitative lipid profile abnormalities due to a relative insulin deficiency, leading to higher triglycerides and LDL-cholesterol, and lower HDL-cholesterol levels than healthy subjects without diabetes [54]. Conversely, individuals with optimal glycemic control show normal or even better lipid profiles than the general population. However, independently of glycemic control, individuals with T1D further exhibit qualitative and functional abnormalities in lipoproteins that make them particularly atherogenic [81], which has been associated with subcutaneous administration of insulin [82].

In a multicenter cohort study in Catalonia (Spain) utilizing advanced lipoprotein profiling through nuclear magnetic resonance, women with T1D exhibited a more adverse impact on their lipid profile compared to men [83]. While individuals with T1D showed lower levels of atherogenic lipoproteins (VLDL and LDL particles) and higher levels of protective lipoproteins (HDL particles) relative to a control group, this advantage was not evident in women. These findings are consistent with previous research indicating that the detrimental effects of diabetes on lipid metabolism are more pronounced in women than in men [84].

Although LDL-cholesterol was an independent cardiovascular risk factor for major adverse cardiovascular events in the DCCT/EDIC [53] and Pittsburgh studies [85], other observational studies have not confirmed this [86, 87]. Despite the controversy, the benefits of lipid-lowering therapy with statins in this population are well established. A meta-analysis of 1,466 patients from 11 randomized clinical trials treated with statins found a 21% relative risk reduction in major adverse cardiovascular events for every 1 mmol/L (38.7 mg/dL) decrease in LDL cholesterol [88]. Based on this evidence, clinical guidelines from major scientific societies recommend pursuing strict control of LDL cholesterol levels in individuals with T1D. Previous observational studies have reported that statin therapy is less frequently prescribed to women than to men with T1D [61, 64], a trend also observed in our cohort (Suppl Table 1). Additionally, fewer women with T1D achieved LDL-cholesterol levels of < 100 mg/dL and < 70 mg/dL (Table 1).

Hypertension and blood-pressure control

Hypertension is the leading global risk factor for CVD morbidity and mortality. Although men have a higher prevalence of hypertension, women are more likely than men to develop left ventricular hypertrophy, diastolic dysfunction, heart failure with preserved ejection fraction (HFpEF), increased arterial stiffness, and chronic kidney disease as a consequence of hypertension [5].

Hypertension is common in T1D, and its prevalence is positively correlated with both the duration of diabetes and the age of the population studied [50]. In the CACTI study (mean age, 37 ± 9 years; mean diabetes duration, 23.2 ± 8.9 years), the prevalence of hypertension was significantly higher in individuals with T1D compared to controls (43% vs. 15%), and only 42% of the patients achieved blood pressure (BP) targets [89]. Notably, hypertension is an independent risk factor for major adverse cardiovascular events in T1D [85, 90].

As observed in the general population, men with T1D have a higher prevalence of hypertension and are less likely than women to achieve BP control targets [6, 64, 80], a trend also observed in our cohort (Table 1). In a recent analysis of the Pittsburgh EDC study, women with T1D had consistently lower systolic BP, diastolic BP, and mean arterial pressure over time compared to men. Interestingly, despite clinically significant BP differences (5.8 mmHg lower systolic blood pressure and 6.2 mmHg lower diastolic blood pressure in women), 32-year CVD incidence was nearly identical between sexes. BP metrics similarly predicted composite CVD in both sexes, but sex differences emerged in CVD presentation: systolic and diastolic BP were linked to major adverse cardiovascular events only in men and diastolic BP with CAD only in women [91].

Obesity

In recent decades, there has been a significant increase in the prevalence of overweight and obesity among individuals with T1D [92]. Large international registries estimate that between 15 and 36% of patients with T1D are overweight or have obesity [93], which reflects not only the global shift toward an obesogenic environment but also disease-specific factors and treatment-related influences. Notably, most studies report women with T1D have higher rates of obesity compared to men [6, 80, 94], as also observed in our cohort (Table 1). This is particularly concerning given the documented excess risk of CVD and HFpEF attributed to obesity in women [5, 45].

Smoking habit

Smoking-induced atherosclerosis is closely tied to endothelial dysfunction, which impairs vasodilation and hemostasis, leading to chronic vascular inflammation [95]. Free radicals from cigarette smoke further increase oxidative stress and systemic inflammation [95].

A large meta-analysis found that the increased CVD risk associated with smoking was 25% higher in women than in men [96]. Although the global prevalence of smoking is lower in women than in men, reductions in smoking prevalence over the past decade have been more pronounced among men. Despite significant tobacco-control efforts, smoking prevalence among women has remained largely unchanged and has even increased in many regions [5]. Moreover, research suggests women have lower initial success rates with smoking abstinence, experiencing reduced efficacy with nicotine replacement therapy but higher efficacy with varenicline [45].

In large prospective studies, active smoking has been identified as an independent risk factor for CVD in T1D [85, 90]. CVD risk prediction tools specific to T1D include active smoking as a risk enhancer [78, 79], and quantitative data on smoking have also been associated with atherosclerotic burden [97]. Far from being a residual habit in this high cardiovascular risk population, epidemiological studies indicate that 19–28% of individuals with T1D are smokers [85, 90, 98], a prevalence similar to that of the general population, with higher rates in men than in women [63]. In a recent cross-sectional study including patients with T1D with no previous history of CVD from France (n = 1172) and Germany (n = 2657), women were less prone to smoke than men (Germany: 19.7 vs. 25.8%, $p < 0.01$; France: 21.0 vs. 26.0%, $p = 0.07$) [64], a trend also observed in our cohort (Table 1).

Diabetic kidney disease

Chronic kidney disease and atherosclerosis can be viewed as tissue-specific manifestations of a shared pathological process that drives vascular damage. Nevertheless, DKD may also directly accelerate atherosclerosis through its impact on multiple atherogenic pathways. These include increased blood pressure, insulin resistance, arterial calcification, endothelial dysfunction, oxidative stress, dyslipidemia, systemic inflammation, and activation of the renin–angiotensin–aldosterone system, the sympathetic nervous system, and the advanced glycation end-product/receptor for AGE axis [99].

DKD is more prevalent in men than in women with T1D, as consistently reported in multiple large observational studies [100–102]. This sex disparity in DKD prevalence may explain differences in cardiovascular outcomes. In a study by Harjutsalo et al., involving over 4400 people with T1D from the Finnish Diabetic Nephropathy Study (FinnDiane), men exhibited a higher absolute risk of CAD and stroke than women in univariable analyses. However, this sex difference disappeared when adjusted for DKD status [103]. Notably, when compared to a control group with diabetes, the excess risk of CAD was higher in women than men, and this sex difference increased with the severity of DKD. These results suggest that the relative impact of DKD on cardiovascular risk is even more pronounced in women with T1D.

Sex-specific risk factors

In addition to disparities in traditional risk factors, several clinical conditions unique to women have been shown to increase CVD risk [104], underscoring the

importance of sex-specific considerations in understanding and managing CVD. A recent multicenter cross-sectional study involving 2,041 patients with T1D observed that women under 55 years of age with T1D exhibit a carotid plaque burden comparable to that of men, despite having a lower 10-year estimated CVD risk when only traditional risk factors are considered [105]. These findings highlight the need to evaluate and incorporate additional risk-enhancing factors in the assessment of CVD risk in women with T1D.

Premature menopause

Women generally present with CVD up to 10 years later than men, with a substantial increase in CVD risk occurring progressively after menopause [104]. During the menopausal transition, significant increases in LDL cholesterol levels, accelerated gains in fat mass, and losses of lean mass have been documented [5]. In this context, premature menopause further exacerbates CVD risk in women [106]. The impact of menopause on atherosclerosis progression appears to be more pronounced in women with T1D, as evidenced by the accelerated CAC progression observed in women from the CACTI study [107].

Premature menopause is a potential CVD risk factor in women with T1D, as they often experience a shorter reproductive lifespan, characterized by delayed menarche and earlier natural menopause compared to women without T1D [108]. This accelerated ovarian aging appears to be linked to vascular dysfunction, as evidenced by earlier menopause in women with T1D and microalbuminuria diagnosed before age 30 compared to those with normoalbuminuria [109]. Thus, premature menopause may serve as a marker of systemic vascular damage in T1D, and an indicator of individuals who could benefit most from intensive cardiovascular risk management.

Preeclampsia and other pregnancy-related disorders

The cardiovascular system undergoes significant structural and hemodynamic changes during pregnancy accompanied by several metabolic changes, such as increased insulin resistance, elevated lipid levels and hypercoagulability, which can lead to long-term consequences [45]. Multiple epidemiological investigations have consistently demonstrated that hypertensive disorders during pregnancy, especially preeclampsia, are independent predictors of future CVD, persisting even after controlling for main confounders [110, 111]. The link between preeclampsia and increased CVD risk likely involves persistent vascular changes. Narrowing of spiral arteries during preeclampsia triggers oxidative stress and inflammation that may continue beyond pregnancy, potentially causing long-term vascular dysfunction and abnormal lipid metabolism [112].

Epidemiological data indicates that women with T1D face a significantly higher risk of developing preeclampsia compared to the general population (10–17% vs. 3–5%) [113, 114], which creates a concerning intersection between two independent risk factors. Previous research has demonstrated that preeclampsia is linked to subclinical atherosclerosis not only in the general female population but also among women with T1D [115, 116]. Complementing these findings, a nationwide register-based cohort study from Sweden identified a 20% higher risk of CVD incidents in women with T1D who had experienced hypertensive pregnancy disorders, although this relationship did not maintain statistical significance in fully adjusted statistical models [117].

A recent Mendelian randomization analysis demonstrated that the association between number of live births and CVD represents a direct causal relationship that extends beyond the influence of sociodemographic characteristics and clinical parameters [118]. Moreover, a recent study investigated the impact of preeclampsia and childbearing status on gender-based differences in early atherosclerotic development in T1D [119]. In multivariate adjusted models, nulliparous women and parous women without previous preeclampsia had half the risk of preclinical carotid atherosclerosis than men, while this protective advantage disappeared in women with a history of preeclampsia.

Functional hyperandrogenism

Polycystic ovary syndrome (PCOS) represents one of the most prevalent endocrine and metabolic disorders among premenopausal women. This clinically heterogeneous condition is characterized by androgen excess and ovarian dysfunction when other specific diagnoses have been excluded [120]. Notably, women with T1D show an increased prevalence of PCOS compared to the general population [121]. In fact, a meta-analysis by Bayona et al. revealed that approximately 25% of women with T1D exhibit PCOS or related hyperandrogenic traits [122]. This association likely stems from the requirement for supraphysiological subcutaneous insulin doses to achieve adequate portal vein insulin concentrations for hepatic glucose suppression, leading to systemic hyperinsulinemia. This hyperinsulinemic state stimulates ovarian androgen production through its co-gonadotropic action [123], subsequently promoting visceral fat accumulation. This adiposity exacerbates insulin resistance and sustains hyperinsulinemia [121], thereby creating a self-perpetuating metabolic cycle.

In women with T1D and PCOS, hyperandrogenism presents distinct hormonal features compared with PCOS patients without diabetes. While testosterone and androstenedione levels are elevated, SHBG levels remain normal due to subcutaneously administered insulin

failing to suppress hepatic SHBG production [124]. Consequently, total testosterone, rather than free testosterone or free androgen index, may be the most sensitive marker of hyperandrogenism in T1D [124]. The normal SHBG levels may also attenuate clinical hyperandrogenic symptoms by reducing bioactive androgen availability.

The simultaneous presence of insulin resistance and metabolic syndrome in women with PCOS contributes to an increased risk of CVD. However, the direct impact of PCOS on cardiovascular events and mortality, independent of these associated risk factors, remains unclear [5]. Further research is needed to explore the potential synergistic effects of T1D and PCOS on metabolic control and cardiovascular risk.

Autoimmune diseases

Although systemic autoimmune diseases are not sex-specific risk factors, women are disproportionately affected by these conditions compared to men [5]. This risk is particularly higher in women with T1D, as autoimmune diseases tend to co-occur [125]. From a CVD perspective, this clustering can hold significant consequences. The chronic inflammation associated with autoimmune diseases contributes to endothelial dysfunction and accelerates the progression of atherosclerosis [104]. Additionally, steroid therapy, commonly used to manage autoimmune diseases, can exacerbate hyperglycemia and dyslipidemia, further increasing cardiovascular risk. Moreover, thyroid autoimmune disease—the most prevalent autoimmune disease in individuals with T1D, affecting nearly 20% of women with this condition[7]—can lead to both hypothyroidism and hyperthyroidism, both of which are independently associated with increased CVD risk [126, 127].

In a large population-based observational study including over 446,000 individuals diagnosed with autoimmune diseases, Conrad et al. reported that those with autoimmune disorders faced a 1.4 to 3.6 times higher risk of developing CVD compared to individuals without such conditions [128]. Notably, the increased risk was particularly pronounced in younger individuals under the age of 45 and could not be fully explained by conventional cardiovascular risk factors. Among the autoimmune diseases studied, systemic sclerosis (hazard ratio 3.59 [95% CI 2.81–4.59]), Addison's disease (hazard ratio 2.83 [95% CI 1.96–4.09]), systemic lupus erythematosus (hazard ratio 2.82 [95% CI 2.38–3.33]), and T1D (hazard ratio 2.36 [95% CI 2.21–2.52]) were associated with the highest overall cardiovascular risk after adjusting for main confounders. In this context, the role of low-grade inflammation is likely an additional important factor that warrants targeted intervention [129, 130].

Bridging the gap: clinical implications and future directions

Based on the extensive review of the existing literature and our population-based cohort analysis, a concerning sex disparity in women with T1D is evident across the CVD spectrum, with women consistently experiencing an excess burden of disease. Therefore, clinical implications for the treatment and management of women with T1D throughout their lifetime must be carefully considered.

Women face greater challenges in achieving optimal glycemic control, highlighting the need for further evaluation of sex-specific variables. Glycemic fluctuations related to menstrual cycle phases have been observed in women with T1D [65], which seem to be partially mitigated with hybrid closed loop systems [131, 132]. However, there is a pressing need to evaluate sex-based differences in access to and efficacy of diabetes technology.

Moreover, traditional risk factors– such as hyperglycemia, dyslipidemia, obesity, smoking, and DKD—have a greater impact on CVD outcomes in women with T1D compared to men. Despite this, women tend to receive less aggressive cardioprotective medications, with the most significant gaps occurring in younger women [133, 134]. Beyond unconscious biases in risk perception, clinician hesitancy regarding medication use during childbearing years due to teratogenic risks can also contribute to this disparity. These findings underscore the urgent need for both increased awareness and improved management of CVD risk factors in this population, as well as the development of gender-sensitive protocols and targeted provider education initiatives to address this cardiovascular equity gap.

Women have been historically underrepresented in CVD clinical trials, limiting the ability to assess the safety and efficacy of therapies specifically for women. Greater inclusion of women, along with sex-specific analyses, is essential in future research. This is particularly relevant for women with T1D, especially given the emergence of new drug classes with potential cardiovascular benefits in this population, such as incretin-based therapies, SGLT-2 inhibitors or non-steroidal mineralocorticoid receptor antagonists.

Finally, female-specific CVD risk factors are more prevalent in T1D and require further evaluation. These factors, including preeclampsia, premature menopause, polycystic ovary syndrome or autoimmune diseases, should be taken into account when assessing CVD risk in women with T1D. Additionally, the development of T1D-specific CVD risk scales that account for these variables may improve risk stratification and management in this population.

Supplementary Information

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Supplementary Material 1

Author contributions

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