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Body weight variability as a predictor of cardiovascular outcomes in type 1 diabetes: A nationwide cohort study

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Abstract

Aim: Intraindividual body weight variability (BWV), that is, the degree of weight fluctuations over time, is associated with an increased risk of cardiovascular diseases (CVDs) in multiple settings. The impact of BWV on cardiovascular risk in type 1 diabetes (T1D) remains unclear, despite the issues relative to weight management in individuals with this condition.

Materials and methods: Using data from the Swedish National Diabetes Register, we identified individuals with T1D and without CVD at baseline with at least three measurements of body weight taken over three consecutive years. We estimated BWV as quartiles of the standard deviation of weight measures and explored its longitudinal association with the incidence of CVD during a 12.7 ± 4.6 year follow-up through adjusted Cox regression models. The primary endpoint was the composite of nonfatal myocardial infarction, nonfatal stroke and all-cause mortality. We modelled the function of risk in relation to the magnitude of BWV, testing also whether weight trends, that is, increasing, stable or decreasing, age, sex and glycaemic control modified the association between BWV and the outcome.

Results: Among the 36 333 individuals with T1D in the register, we identified 19 373 individuals with at least three measures of body weight and without CVD at baseline. Participants with the highest BWV had a 42% increased risk of reaching the primary endpoint compared to those with the lowest BWV (hazard ratio [HR] = 1.42, 95%

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confidence interval [CI]: 1.24–1.62). In addition, high BWV was significantly associated with a 51% increased risk of all-cause mortality (HR = 1.51, 95% CI: 1.28–1.78), a 37% increased risk of peripheral artery disease (HR = 1.37, 95% CI: 1.06–1.77) and a 55% increased risk of hospitalization for heart failure (HR = 1.55, 95% CI: 1.20–2.01). BWV showed a quasi-linear association with the primary endpoint. No interaction was observed when comparing subgroups for weight trends, sex or degree of glycaemic control. In the subgroup of elderly individuals, the association of BWV with the primary endpoint was no longer significant.

Conclusions: High BWV is associated with an increased risk of CVD and all-cause mortality in individuals with T1D, independently of canonical risk factors. Weight trends, sex and glycaemic control do not modify such association while older age attenuates it.

KEYWORDS

age, MACE, mortality, myocardial infarction, stroke, type 1 diabetes mellitus, variability, weight, weight trends

1 | INTRODUCTION

Individuals with type 1 diabetes mellitus (T1D) were historically considered as lean individuals unable to regulate glucose levels due to a progressive, autoimmune-mediated depletion of insulin-producing cells.[1] Recent evidence suggests that persons with T1D can also often present features of overweight or obesity, similar to what happens with individuals with type 2 diabetes (T2D), even though the pathophysiological mechanisms involved are different.[2,3] While overnutrition and a sedentary lifestyle are general triggers of overweight in metabolic diseases, other components juxtapose these common risk factors in T1D, that is, the mandatory need of lifelong insulin infusion to ensure tight glycaemic control. Indeed, nonphysiological insulin replacement causes peripheral hyperinsulinemia and insulin profiles commonly observed in individuals with T1D do not match basal and mealtime insulin needs.[2,3] These two phenomena in turn foster fat accumulation and weight gain, as observed with basal insulin known to promote a broad anabolic effect by reducing lipolysis and protein catabolism and promoting lipogenesis and protein synthesis.[4] In addition, intensive glycaemic control is associated with an increased risk of hypoglycaemia, which in turn might promote defensive snacking and thus overnutrition and weight gain.[2] In case of weight gain, individuals with T1D are often recommended to start nutritional, pharmacological or other strategies to return to optimal weight.[5] Most of these strategies are effective.[6] As a result, individuals with T1D might often experience weight oscillations during their life.

Body weight variability (BWV), that is, the oscillation of body weight over time, is independently associated with development of cardiovascular disease (CVD) and mortality in the general population and in individuals with T2D, conferring also a higher risk of microvascular complications in the latter group.[7–11] However, very few data are available for patients with T1D,[12,13] despite the consistent frequency of weight cycling in this population.[2,3] Thus, whether BWV is associated with CVD in a large, real-world population with T1D is still not demonstrated, possibly due to the scarce abundance of large cohorts of individuals with this condition.

To explore whether intraindividual, visit-to-visit BWV is associated with CVD in individuals with T1D and no prevalent CVD at baseline, we leveraged data of 36 333 patients from the Swedish National Diabetes Register (NDR).

2 | MATERIALS AND METHODS

2.1 | Data source

The Swedish NDR was established in 1996, as previously described.[14] This register encompasses data on risk factors, diabetes-related complications and medication regimens for patients aged 18 years and older. Participation is contingent upon informed consent from each patient, and the register includes nearly all individuals with diabetes in Sweden. Data from participants with at least one observation in the NDR up to August 2023 were extracted for this study.

2.2 | Data included in the register

Individuals included in this study all had T1D, which was defined based on epidemiological criteria: insulin treatment and diagnosis before 30 years of age. Data collected from the registry included demographic variables (sex, age at the start of the longitudinal period and smoking habits), weight measurements, pathology-related information (diabetes duration and therapy) and various clinical parameters. Smoking status was classified as smoker or nonsmoker, with smokers defined as individuals who smoke ≥1 cigarette per day or who quit smoking less than 3 months before the start of follow-up.

Clinical data encompassed HbA1c levels, systolic and diastolic blood pressure, hypertension status, total cholesterol, LDL and HDL cholesterol, triglycerides, albuminuria and glomerular filtration rate (GFR). Diabetes therapies were categorized into single treatments (diet only, oral drugs or insulin) and combined treatments.

2.3 | Ethical approval

The study received approval from the Swedish Ethical Review Authority. According to Swedish law (Patient Data Act 2008:355, chapter 7), individual consent is not required for reporting patients to national healthcare quality registries or for their inclusion in a study of this type.

2.4 | Study design

The exposure phase was defined as the 3-year period from the first visit, while the longitudinal phase refers to the observation period that followed a previously used approach.[7,8] Study design is summarized in Figure 1A.

2.5 | Inclusion criteria

Inclusion criteria were as follows (details in Figure 1B): Patients must have had at least three weight measurements during the exposure phase, no history of CVD and no occurrence of these outcomes during the exposure phase. Specifically, patients with a history of CVD were those who had any of the following events at baseline or at any time during the exposure phase: nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), peripheral arterial disease (PAD), hospitalization for heart failure, ischemic heart disease or nontraumatic intracerebral haemorrhage.

2.6 | Endpoints

The primary endpoint was major adverse cardiovascular events (MACE), defined as the first occurrence of acute myocardial infarction, nonfatal stroke or all-cause mortality. An expanded MACE was also explored and included the same outcomes plus the incidence of CABG and of PCI. Exploratory endpoints comprised each individual component of the primary and expanded outcomes, as well as the incidence of hospitalizations for heart failure (HHF) and of PAD.

2.7 | Statistical analysis

Body weight variation (BWV) was calculated as the standard deviation (SD) of all weight measurements taken during the exposure phase. Participants were categorized into quartiles based on their BWV values, a common approach for continuous exposure variables. This method enhances the interpretability of the results, allowing for clearer comparisons across groups, and helps to mitigate the impact of outliers and/or measurement error.

Data are reported as mean and SD, median and interquartile range interval (Q1–Q3) and minimum–maximum range for interval/ratio scale variables, and as absolute and relative frequencies for categorical variables.

To investigate the relationship between BWV quartiles and the risk of experiencing the outcomes of interest, we used Cox

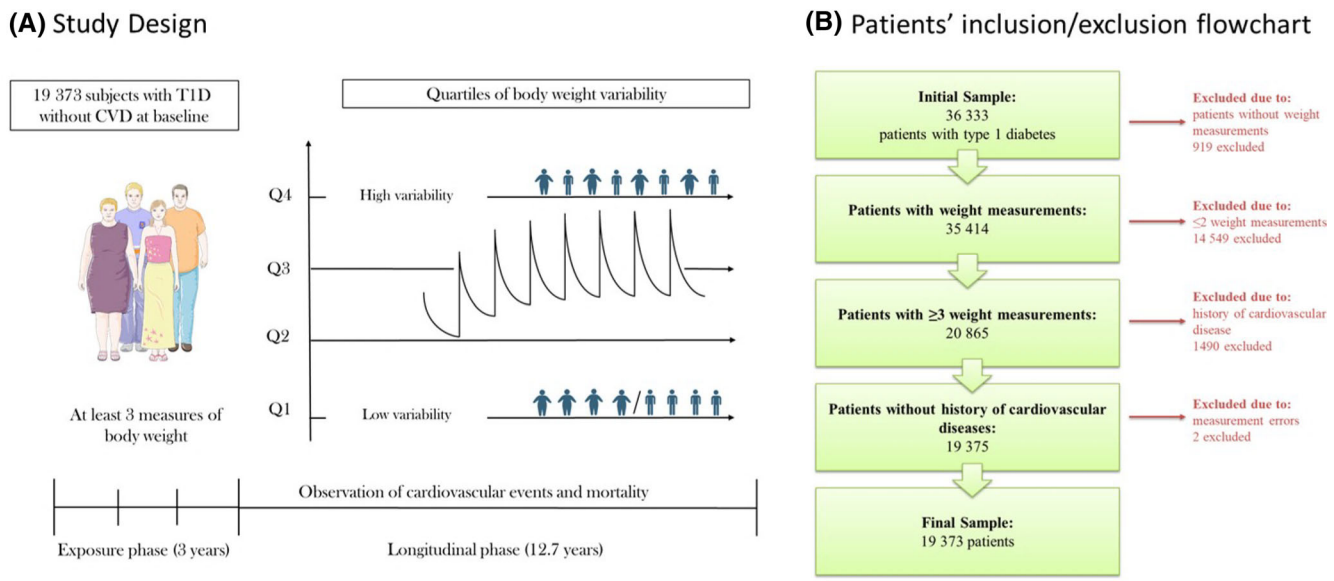

FIGURE 1 Design of the study and patients included. Graphical representation showing the experimental design of the study (A) and the flowchart summarizing patients' selection (B).

proportional-hazard regression models, well-suited for time-to-event data (e.g., time until stroke). The Cox model is semi-parametric, allowing us to compare risks without making strong assumptions about the distribution of event times. It also handles censored data and allows adjustment for confounders. We had no clinical reasons to expect violations of the proportional hazard assumption, and there were no time-varying covariates. These models included the BWV covariate and were adjusted for HbA1c, systolic and diastolic blood pressure, hypertension status, LDL and HDL cholesterol, triglycerides, albuminuria, eGFR, diabetes therapies and weight at the last visit. Patients were censored at the date of data collection from the registry on 18th August 2023. Missing data were handled by creating an additional category for categorical variables, and for interval/ratio scale variables, missing values were categorized, and a missing category was added.

Results are presented as hazard ratios (HRs) along with their 95% confidence intervals (CIs). The outcome rates were analysed across the quartiles of BWV, using the lowest quartile as the reference group. We investigated whether the risk increased monotonically as BWV increased. Because BWV was treated as an ordinal variable, it lacks a precise metric, making the notion of strict linearity less meaningful. However, the ordered nature of the quartiles allows us to explore a monotonic trend. A *p*-value for trend was calculated to assess whether a linear relationship existed between increasing BWV and heightened risk of outcomes, by assigning each participant the median BWV value within their quartile, and treating it as a continuous variable in the model.

To calculate weight trends, we categorized patients based on the weight difference between their last and first visit into groups of decreased, increased or stable weight. Models were re-run on subgroups based on weight group (decreased, increased). Additionally, we explored subgroup analyses based on sex (male, female), age group (18–24, 25–39, 40–64, ≥65) and HbA1c levels (<53 mmol/mol, ≥53 mmol/mol). A *p*-value for interaction was calculated to evaluate whether the effect of BWV varied significantly between different subgroups.

In an additional analysis, we treated BWV as a continuous variable, rather than using quartiles, to directly visualize how risk varied with BWV. This analysis was also meant to reinforce the findings from the *p*-value for trend analysis by offering a more detailed view of the association using an analogous Cox proportional hazards model for MACE. The analysis was performed on a subset of patients whose BWV values were not considered outliers (BWV ≤ Q3 + 1.5 × interquartile range). We explored both linear and nonlinear relationships between BWV and log hazard and found that the linear relationship was more appropriate (nonlinear results not shown). Assuming as reasonable some degree of weight variation over a 3-year period, we used the mean BWV in the subgroup as a reference for showing the HR changes with respect to BWV.

All statistical analyses were performed using R software,[15] version 4.1.2. The *p*-values are two-sided, with significance levels defined as follows: $\alpha = 0.05$ for the main analyses, $\alpha = 0.00625$ for the *p*-values for interaction, and $\alpha = 0.0025$ for the *p*-values for trend and subgroups' estimates, according to Bonferroni's correction.

3 | RESULTS

3.1 | Study population

The flowchart of included and excluded individuals is reported in Figure 1B. The final sample of patients included 19 373 participants with T1D with at least three measures of body weight during 3 years and no CVD at baseline.

We calculated the SD of the available body weight measures for each patient and divided the population into quartiles of BWV accordingly. The cut-off quartiles for the SD of weight measurements were 1.15, 1.98, and 3.21 kg for the first, second, and third quartiles respectively. This resulted in four groups consisting of 5100, 4587, 4888 and 4797 patients respectively. Table 1 summarizes patients' characteristics by quartile groups and overall. The sample had a slight male majority (54.8%), consistent across all quartiles. The median age was 30 years (Q1–Q3: 23–43 years), with the youngest patients in the highest quartile of BWV and the oldest in the lowest quartile. The median duration of diabetes was 16 years (Q1–Q3: 9–28 years), and the median number of visits before the start of follow-up was 4 (Q1–Q3: 3–5), except for the first quartile, which had a median of three visits. The median follow-up time was 12.8 years (Q1–Q3: 9.0–17.6). At the first and last visit, the median weight was 74.0 and 75.0 kg respectively, with a median BWV of 2.0 kg (Q1–Q3: 1.2–3.2 kg). Among other characteristics, individuals in the quartile IV had a higher mean weight compared with the other quartiles.

3.2 | BWV and cardiovascular endpoints

The possible association of BWV with MACE (Figure 2A) and expanded MACE (Figure 2B) was tested. Participants with the highest BWV (quartile IV) had a 42% higher risk of experiencing MACE compared to those in the lowest quartile (HR = 1.42, 95% CI: 1.24–1.62, $p < 0.001$). Similarly, the risk of expanded MACE was 37% higher for those in quartile IV compared to quantile I (HR = 1.37, 95% CI: 1.21–1.545; $p < 0.001$). In contrast, the risk in quartiles II and III were similar to those in quartile I, although an overall increasing trend was observed (*p*-value for trend <0.001). These results were consistent across other outcomes, such as all-cause mortality, PAD and HHF (Figure S1). Table S1 shows the absolute and relative event frequencies overall and by quartiles.

To detail these findings with more granularity, we estimated the coefficient of BWV as an interval/ratio scale variable in relation with the primary endpoint. The HR plot against BWV shows a quasi-linear association with a coefficient of 0.1, indicating a gradually increasing risk with higher BWV (Figure 3). This relatively small effect size is

TABLE 1 Demographic, clinical and study characteristics at baseline,[a] by both quartile group and overall, along with the relative *p*-value.

Variable	I ($N = 5100$)	II ($N = 4587$)	III ($N = 4889$)	IV ($N = 4797$)	Overall ($N = 19\ 373$)	*p*-value
Sex, *n* (%)						0.1072
Male	2736 (53.6%)	2505 (54.6%)	2685 (54.9%)	2691 (56.1%)	10 617 (54.8%)	
Female	2364 (46.4%)	2082 (45.4%)	2204 (45.1%)	2106 (43.9%)	8756 (45.2%)	
Age at FU start						<0.001
Mean (SD)	38.5 (14.5)	35.3 (14.1)	33.0 (13.1)	30.3 (11.2)	34.3 (13.6)	
Median [Q1, Q3]	36.0 [25, 49]	31.0 [23, 45]	28.0 [22, 41]	26.0 [22, 35]	30.0 [23, 43]	
Min–max	21.0–85.0	21.0–89.0	21.0–85.0	21.0–87.0	21.0–89.0	
Smoker,[b] *n* (%)						<0.001
No	3657 (71.7%)	3402 (74.2%)	3592 (73.5%)	3474 (72.4%)	14 125 (72.9%)	
Yes	483 (9.5%)	515 (11.2%)	600 (12.3%)	627 (13.1%)	2225 (11.5%)	
Missing	960 (18.8%)	670 (14.6%)	697 (14.3%)	696 (14.5%)	3023 (15.6%)	
Average time between weight measurements (years)						<0.001
Mean (SD)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	0.8 (0.3)	
Median [Q1, Q3]	0.8 [0.6, 1.0]	0.8 [0.6, 1.0]	0.8 [0.6, 1.0]	0.8 [0.6, 1.0]	0.8 [0.6, 1.0]	
Min–max	0.0–1.5	0.1–1.5	0.1–1.5	0.1–1.5	0.0–1.5	
BWV (kg)						
Mean (SD)	0.7 (0.4)	1.6 (0.3)	2.5 (0.4)	5.6 (4.3)	2.6 (2.9)	
Median [Q1, Q3]	0.7 [0.4, 1.0]	1.5 [1.4, 1.7]	2.5 [2.2, 2.8]	4.6 [3.8, 6.0]	2.0 [1.2, 3.2]	
Min–max	0–1.2	1.2–2.0	2.0–3.2	3.2–65.0	0–65.0	
Weight at first visit (kg)						<0.001
Mean (SD)	72.7 (13.3)	73.5 (13.2)	76.0 (14.7)	80.6 (17.7)	75.7 (15.2)	
Median [Q1, Q3]	71.5 [63.0, 80.4]	72.1 [64.0, 82.0]	74.5 [66.0, 84.0]	78.0 [68.6, 90.0]	74.0 [65.0, 84.0]	
Min–max	37.0–207.8	36.2–146.0	38.0–156.0	35.3–209.1	35.3–209.1	
Weight at last visit (kg)						<0.001
Mean (SD)	72.8 (13.4)	74.0 (13.3)	77.4 (14.84)	83.8 (17.3)	77.0 (15.4)	
Median [Q1, Q3]	71.6 [63.2, 80.8]	72.9 [64.0, 82.4]	76.0 [67.0, 85.4]	82.1 [71.7, 93.0]	75.0 [66.0, 85.6]	
Min–max	32.0–207.8	36.5–149.0	38.0–155.7	33.5–190.0	32.0–207.8	
No. visits before FU start						<0.001
Mean (SD)	4.0 (1.7)	4.5 (2.1)	4.5 (2.5)	4.6 (2.4)	4.4 (2.2)	
Median [Q1, Q3]	3 [3, 4]	4 [3, 5]	4 [3, 5]	4 [3, 5]	4 [3, 5]	
Min–Max	3–25	3–25	3–42	3–33	3–42	
FU (years)						<0.001
Mean (SD)	13.4 (4.8)	12.7 (4.5)	12.5 (4.5)	12.0 (4.3)	12.7 (4.6)	
Median [Q1, Q3]	14.7 [9.5, 18.1]	12.8 [9.1, 17.5]	12.6 [8.9, 16.9]	11.7 [8.8, 15.9]	12.8 [9.0, 17.6]	
Min–max	0–18.1	0–18.1	0–18.1	0–18.1	0–18.1	
Diabetes duration (years)						<0.001
Mean (SD)	23.8 (14.5)	20.6 (14.0)	18.5 (13.1)	15.4 (11.6)	19.6 (13.76)	
Median [Q1, Q3]	21.0 [12.0, 34.0]	17.0 [9.0, 30.0]	15.0 [8.0, 26.0]	13.0 [6.0, 21.0]	16.0 [9.0, 28.0]	
Min–max	2.0–82.0	3.0–82.0	3.0–85.0	3.0–86.0	2.0–86.0	
Missing, *n* (%)	13 (0.3%)	15 (0.3%)	11 (0.2%)	25 (0.5%)	64 (0.3%)	
HbA1c (mmol/mol)						<0.001
Mean (SD)	62.6 (13.7)	63.6 (14.5)	64.7 (15.0)	65.7 (17.0)	64.1 (15.2)	
Median [Q1, Q3]	61.0 [53.0, 70.0]	63.0 [54.0, 71.0]	63.0 [54.0, 72.0]	64.0 [54.0, 74.0]	63.0 [54.0, 72.0]	
Min–max	27.0–147.0	27.0–154.0	24.0–153.0	27.0–171.0	24.0–171.0	
Missing	669 (13.1%)	498 (10.9%)	512 (10.5%)	529 (11.0%)	2208 (11.4%)	

(Continues)

TABLE 1 (Continued)

Variable	I ($N = 5100$)	II ($N = 4587$)	III ($N = 4889$)	IV ($N = 4797$)	Overall ($N = 19\ 373$)	*p*-value
Systolic blood pressure (mmHg)						<0.001
Mean (SD)	125.1 (15.5)	124.0 (14.9)	123.6 (14.7)	123.0 (13.4)	123.9 (14.7)	
Median [Q1, Q3]	122.0 [115.0, 134.0]	120.0 [112.0, 130.0]	120.0 [114.0, 130.0]	120.0 [114.0, 130.0]	120.0 [115.0, 130.0]	
Min–max	80.0–200.0	80.0–210.0	84.0–220.0	80.0–200.0	80.0–220.0	
Missing	729 (14.3%)	573 (12.5%)	573 (11.7%)	607 (12.7%)	2482 (12.8%)	
Diastolic blood pressure (mmHg)						<0.001
Mean (SD)	72.0 (8.6)	72.3 (8.9)	72.9 (8.8)	73.6 (9.0)	72.7 (8.9)	
Median [Q1, Q3]	70.0 [65.0, 80.0]	70.0 [66.0, 80.0]	70.0 [68.0, 80.0]	74.0 [70.0, 80.0]	70.0 [68.0, 80.0]	
Min–max	40.0–108.0	40.0–130.0	40.0–118.0	40.0–110.0	40.0–130.0	
Missing	737 (14.5%)	577 (12.6%)	578 (11.8%)	611 (12.7%)	2503 (12.9%)	
Total cholesterol (mmol/L)						0.0208
Mean (SD)	4.7 (0.9)	4.7 (0.9)	4.7 (0.9)	4.7 (1.0)	4.7 (0.9)	
Median [Q1, Q3]	4.6 [4.1, 5.2]	4.6 [4.0, 5.2]	4.6 [4.0, 5.2]	4.6 [4.1, 5.3]	4.6 [4.1, 5.2]	
Min–max	1.7–9.0	1.2–12.1	1.6–9.2	2.2–12.7	1.2–12.7	
Missing	1352 (26.5%)	1254 (27.3%)	1313 (26.9%)	1377 (28.7%)	5296 (27.3%)	
HDL cholesterol (mmol/L)						<0.001
Mean (SD)	1.7 (0.5)	1.6 (0. 5)	1.5 (0.4)	1.5 (0.4)	1.6 (0.5)	
Median [Q1, Q3]	1.6 [1.3, 1.9]	1.5 [1.3, 1.8]	1.5 [1.2, 1.8]	1.4 [1.2, 1.7]	1.5 [1.2, 1.8]	
Min–max	0.1–4.7	0.5–4.8	0.4–4.60	0.4–4.2	0.1–4.8	
Missing	1452 (28.5%)	1361 (29.7%)	1403 (28.7%)	1474 (30.7%)	5690 (29.4%)	
LDL cholesterol (mmol/L)						<0.001
Mean (SD)	2.6 (0.7)	2.6 (0.8)	2.6 (0.8)	2.7 (0.9)	2.6 (0.8)	
Median [Q1, Q3]	2.5 [2.1, 3.0]	2.5 [2.1, 3.1]	2.6 [2.1, 3.1]	2.7 [2.2, 3.2]	2.6 [2.1, 3.1]	
Min–max	0.5–8.7	0.5–7.8	0.4–7.4	0.5–8.5	0.4–8.7	
Missing	1474 (28.9%)	1377 (30.0%)	1436 (29.4%)	1484 (30.9%)	5771 (29.8%)	
Triglycerides (mmol/L)						<0.001
Mean (SD)	1.1 (0.6)	1.1 (0.8)	1.2 (1.0)	1.3 (1.1)	1.1 (0.9)	
Median [Q1, Q3]	0.9 [0.6, 1.2]	0.9 [0.6, 1.2]	0.9 [0.7, 1.3]	1.0 [0.7, 1.4]	0.9 [0.7, 1.3]	
Min–max	0.1–7.0	0.2–15.6	0.1–19.0	0.2–19.4	0.1–19.4	
Missing	1492 (29.3%)	1434 (31.3%)	1506 (30.8%)	1587 (33.1%)	6019 (31.1%)	
Albuminuria, *n* (%)						0.0001
No	3448 (67.6%)	3085 (67.3%)	3242 (66.3%)	3159 (65.9%)	12 934 (66.8%)	
Normal value	32 (0.6%)	32 (0.7%)	33 (0.7%)	38 (0.8%)	135 (0.7%)	
Microalbuminuria	488 (9.6%)	395 (8.6%)	393 (8.0%)	372 (7.8%)	1648 (8.5%)	
Macroalbuminuria	199 (3.9%)	175 (3.8%)	209 (4.3%)	163 (3.4%)	746 (3.9%)	
Missing	933 (18.3%)	900 (19.6%)	1012 (20.7%)	1065 (22.2%)	3910 (20.2%)	
GFR (mL/min/1.73 m^2)						<0.001
Mean (SD)	92.0 (25.8)	96.6 (26.6)	99.1 (26.9)	103.8 (28.5)	97.8 (27.3)	
Median [Q1, Q3]	90.7 [75.9, 106.6]	96.0 [80.4, 111.9]	98.4 [82.9, 114.4]	102.2 [86.9, 119.6]	96.9 [81.3, 113.4]	
Min–max	4.3–242.1	5.3–244.9	4.1–236.0	5.2–241.5	4.0–244.9	
Missing, *n* (%)	1177 (23.1%)	1026 (22.4%)	1057 (21.6%)	1055 (22.0%)	4315 (22.3%)	
Retinopathy, *n* (%)						<0.001
No	1466 (28.7%)	1671 (34.4%)	1884 (38.5%)	2023 (42.2%)	7044 (36.4%)	
Yes	2672 (52.4%)	2217 (48.3%)	2255 (46.1%)	1977 (41.2%)	9121 (47.1%)	
Missing	962 (18.9%)	699 (15.2%)	750 (15.3%)	797 (16.6%)	3208 (16.6%)	

TABLE 1 (Continued)

Variable	I ($N = 5100$)	II ($N = 4587$)	III ($N = 4889$)	IV ($N = 4797$)	Overall ($N = 19\ 373$)	*p*-value
Diabetes treatment, *n* (%)						<0.001
Only diet	31 (0.6%)	38 (0.8%)	33 (0.7%)	74 (1.5%)	176 (0.9%)	
Tablets	29 (0.6%)	26 (0.6%)	38 (0.8%)	67 (1.4%)	160 (0.8%)	
Insulin	4296 (84.2%)	3951 (86.1%)	4191 (85.7%)	3988 (83.1%)	16 426 (84.8%)	
Tablets and insulin	117 (2.3%)	130 (2.8%)	154 (3.2%)	188 (3.9%)	589 (3.0%)	
Injection (GLP-1 analogue)	0 (0%)	1 (0%)	0 (0%)	2 (0%)	3 (0%)	
GLP-1 injection and tablets	0 (0%)	0 (0%)	3 (0.1%)	5 (0.1%)	8 (0%)	
GLP-1 injection and insulin	0 (0%)	1 (0%)	1 (0%)	6 (0.1%)	8 (0%)	
GLP-1 injection, insulin, and tablets	0 (0%)	1 (0%)	3 (0.1%)	4 (0.1%)	8 (0%)	
Missing, *n* (%)	627 (12.3%)	439 (9.6%)	466 (9.5%)	463 (9.7%)	1995 (10.3%)	
Nephropathy,[c] *n* (%)						<0.001
No	2960 (58.0%)	2703 (58.9%)	2912 (59.6%)	2865 (59.7%)	11 440 (59.1%)	
Yes	810 (15.9%)	623 (13.6%)	644 (13.2%)	544 (11.3%)	2621 (13.5%)	
Missing	1330 (26.1%)	1261 (27.5%)	1333 (27.3%)	1388 (28.9%)	5312 (27.4%)	

Note: Categorical variables were compared by means of the χ^2 test; continuous variables were compared by means of the one-way ANOVA test.
Abbreviations: ANOVA, analysis of variance; BWV, body weight variability; FU, follow-up; GLR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Baseline refers to the last registered value before follow-up.
[b]A smoker is defined as a person who smokes ≥1 cigarette per day or a person who quit smoking less than 3 months before the start of follow-up.
[c]Nephropathy absence is defined as the combination of GFR ≥ 60 mL/min/1.73 m^2 and normal urinary albumin. Remaining combinations were considered as the presence of nephropathy.

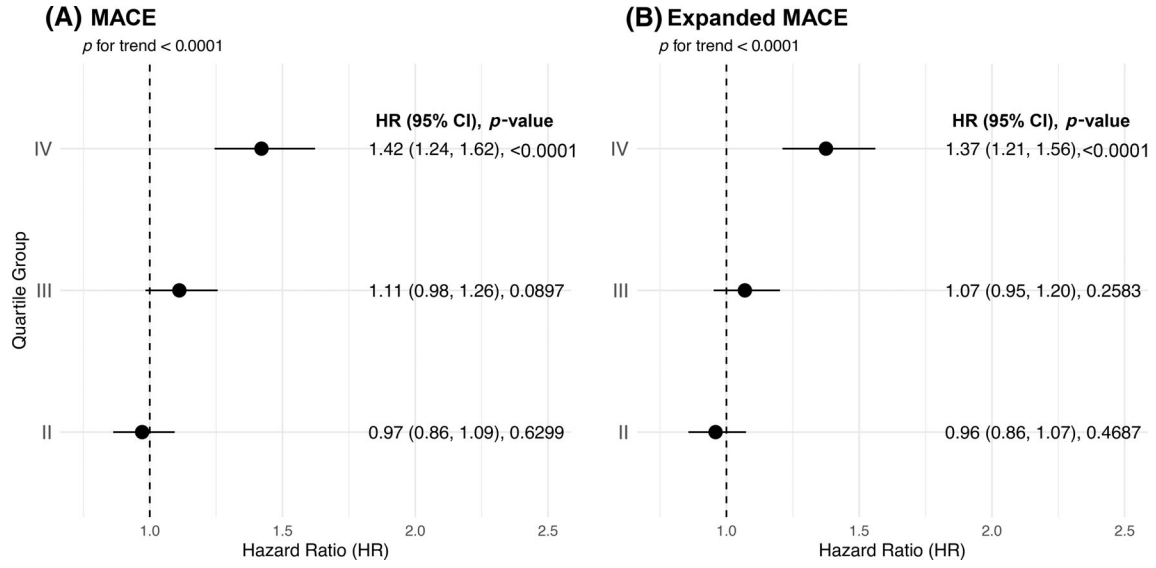

FIGURE 2 Cardiovascular outcomes according to quartiles of body weight variability (BWV). Hazard ratio (HR) for major adverse cardiovascular events (MACE) (A) and expanded MACE (B) with 95% confidence intervals (CI) and *p*-values for different quartile groups of BWV assessed as SD, with Quartile Group I serving as the reference group. The dashed vertical line at HR = 1 represents no effect. The significance threshold for the *p*-value for trend adjusted using the Bonferroni's correction: $\alpha = 0.025$. SD, standard deviation.

consistent with the observation that intermediate quartiles are not associated with an increased risk compared with quartile I. After a BWV of 2.33 kg, that is, the mean of the population and the point where the risk is equal to 1, the risk increases progressively (Figure 3).

3.3 | Subgroup analyses

The possibility that weight trends interact with the association between BWV and MACE was then tested. We categorized patients

in increasing, decreasing or stable weight groups, according to the difference between the first and last weight measurement. The mean weight variation in these groups is shown in Figure S2. During the exposure phase, 11 106 patients (57.3%) gained weight between their first and last visits, while 6985 patients (36.1%) lost weight. Those who gained weight and those who lost weight were similarly distributed across quartile of BWV (data not shown). The subgroup analysis according to weight trends shows that BWV is associated with both MACE (Figure 4A) and expanded MACE (Figure 4B) only in the group of decreasing weight. However, no significant interaction was observed according to weight trends (p for interaction = 0.220 and 0.143 respectively for MACE and expanded MACE).

Additional subgroup analyses demonstrated that there was no modifying effect for sex (Figure S3) and for the degree of glycaemic control, that is, HbA1c < or ≥7% (Figure S4). On the contrary, the association between BWV and the risk of both MACE and expanded MACE was significant in the three strata of younger individuals but not in older individuals, that is, those >65 years (*p* for interaction = 0.0057 for MACE and 0.0016 for expanded MACE), as shown in Figure S5.

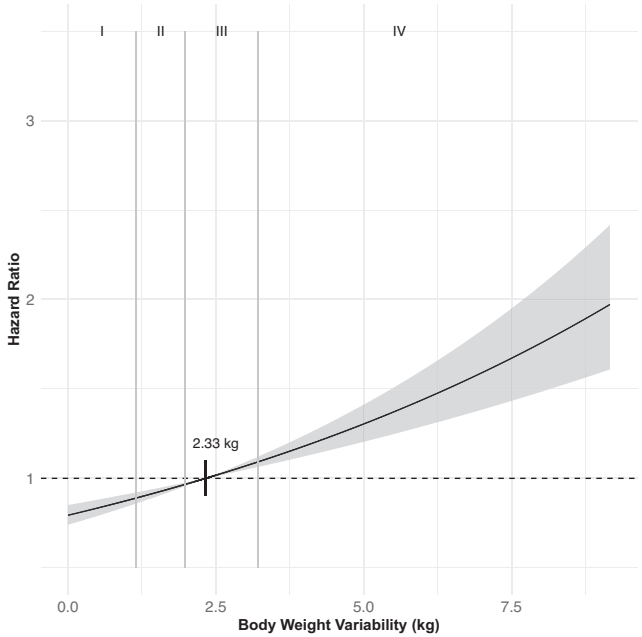

FIGURE 3 Relationship between body weight variability (BWV) and the primary endpoint. Hazard ratio (HR) for major adverse cardiovascular events (MACE) as a function of BWV. The mean BWV within the group of nonoutliers, that is, BWV ≤ Q3 + 1.5 × IQR), is used as the reference point, indicated by the vertical line (at 2.33 kg.) The quartile ranges (I–IV) are shown to indicate the distribution of BWV among patients. IQR, interquartile range.

4 | DISCUSSION

Weight management in T1D is challenging due to the intrinsic nature of the disease and of the associated therapy. Individuals with T1D often experience periods of weight gain to ensure tight glycaemic control, followed by potential weight losses after nutritional or pharmacological therapies.[2,3] Data presented here suggest that a high BWV is associated with several cardiovascular complications in a large number of individuals with T1D, free of such complications at study entry, with a long follow-up. Such evidence is equally observable in individuals gaining or losing weight, in both sexes and in individuals with either good or poor glycaemic control, but becomes no longer visible in the elderlies.

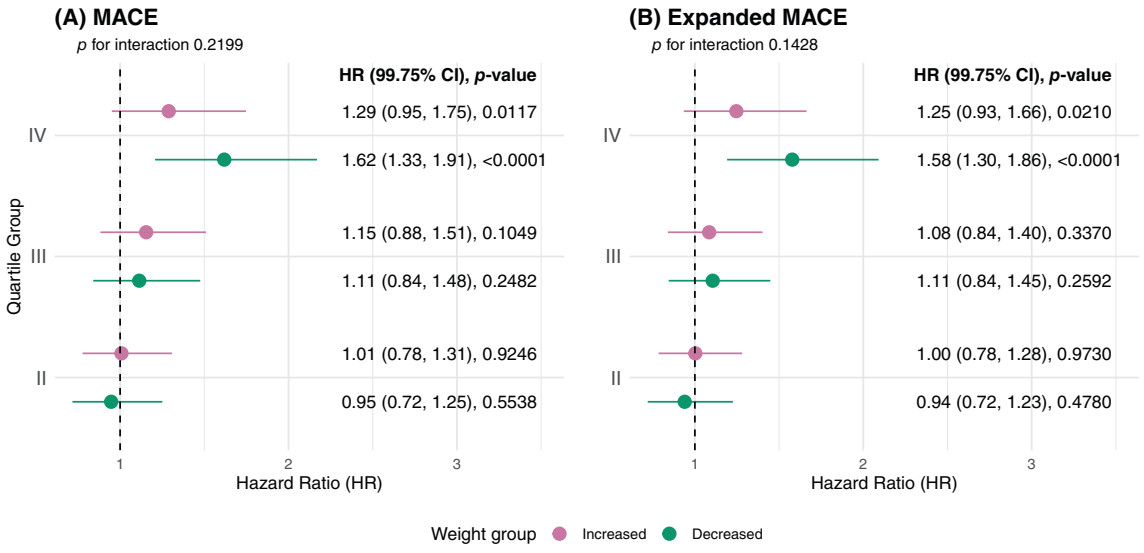

FIGURE 4 Subgroup analysis according to weight trends. Hazard ratios (HR) estimated within the group of patients with increased (pink) and decreased weight (green) for major adverse cardiovascular events (MACE) (A) and expanded MACE (B), with 99.75% confidence intervals (CI) and *p*-values for different quartile groups, with Quartile Group I serving as the reference group. The dashed vertical line at HR = 1 represents no effect. The significance thresholds for the *p*-value for interaction and estimates adjusted using the Bonferroni's correction both are $\alpha = 0.0025$.

Two previous papers estimated BWV in T1D with a similar approach. A retrospective analysis of data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications population, a cohort from a historical trial exploring the impact of tight glycaemic control on the development of diabetes complications,[16] obtained very similar results.[12] In this paper, the authors used the average successive variability index instead of the SD and found that every unit increase in BWV was associated with a 34% increased risk of MACE and a 25% increased risk of all-cause mortality.[12] Of interest, this was observed although the population under scrutiny was in part intensively treated to maintain strict glycaemic control, the most powerful preventive strategies for CVD prevention in T1D.[16] Another study taking advantage of the Swedish NDR assessed the impact of BWV on the development of retinopathy, a microvascular complication.[13] They used the median absolute difference between subsequent body mass index measurements to categorize patients according to quartiles of BWV and found that those with the highest BWV had an increased risk of retinopathy after adjustment for multiple confounders.

Previous meta-analysis and large studies conducted in the general population, in individuals with CVD, in selected cardiovascular outcomes trials or other settings all evidenced a clear association between BWV and cardiovascular outcomes.[7–11,17] However, only one explored whether weight trends influence such association.[10] In individuals with T2D, changes in the weight status showed an interaction only with the association between BWV and all-cause mortality, with individuals with stable weight showing the highest risk.[10] Our results suggest that weight trends do not interact with BWV to change its association with CVD in T1D. Such observation might sustain the argument of causality, because it should minimize the possible risk of confounding bias driven by other dangerous conditions associated with weight changes. However, further studies are needed to substantiate such hypothesis.

Relatively to the other subgroup analyses, we did not find differences when stratifying according to sex and to the degree of glycaemic control. While this latter comparison was not tested before, one study suggested that the association between BWV and myocardial infarction was more prominent in women than in men in Asians with T2D,[10] even though other studies in Europeans did not confirm such results.[8] This possible discrepancy might be attributed to the different ethnicity of the populations under scrutiny. On the other hand, our results relative to the lack of association of BWV with MACE in the subgroup of individuals with >65 years are consistent with those observed in a study showing a less prominent association between BWV and all-cause mortality in the same age stratum.[10] Such evidence might suggest that BWV is a more relevant phenomenon in younger individuals. To be useful from a clinical perspective, candidate CVD risk factors should demonstrate a clear relationship with the outcome and possibly a defined threshold associated with the increased risk. None of the previous studies modelled the risk of outcome in relation to BWV. Data presented here suggest that the association between BWV and CVD in T1D is quasi-linear, which is not always observed with biological or biochemical variables. Indeed, recent studies evidenced a J- or U-shaped association between many risk factors and mortality or CVD in different settings.[18,19] However, given the intrinsic nature of the study design, including individuals with a different number of visits in a limited time span, it is not appropriate and clinically meaningless to explore the existence of a putative threshold of SD where the increased risk becomes relevant. Given the mandatory need of repeated measures to assess variability, other approaches with novel metrics should be explored to identify patients with oscillating weights at increased CVD risk, similar to what has been done with the variability of other risk factors, for example, HbA1c.[20,21]

Beyond the possible weight cycling intrinsically associated with peripheral insulin supplementation and the subsequent attempts to lose weight through diet and exercise,[2,3,5,6] also other factors can promote a high BWV in T1D. Indeed, female sex, young age and the psychological components of T1D, for example, the disease-associated stress and the lack of exercise due to the fear of hypoglycaemia, have been suggested as factors complicating the weight management in T1D.[22] In addition, selected glucose-lowering drugs inducing weight loss are often used off-labels in individuals with T1D to promote glycaemic control or to manage weight.[23] Glucagon-like peptide-1 (GLP-1) receptor agonists (RA) promote consistent weight losses in large range of individuals,[24] including individuals with T1D.[23] However, when these drugs are discontinued, individuals with both T2D[25] and T1D[23] regain most of the weight previously lost. To avoid the resulting BWV, nutritional or other strategies based on exercise or on replacing GLP-1RA with other drugs also promoting weight control, for example, SGLT-2i or metformin, have been suggested and partly tested in selected populations.[11] However, none of these approaches has been tested for safety and effectiveness in limiting specifically BWV in T1D.

The precise mechanism by which BWV might increase CVD risk is not yet understood. BWV does not exacerbate other cardiovascular risk factors in the short-term, implying that these unlikely mediate its effects on CVD.[26] Weight cycling is linked to increased food efficiency and caloric intake, leading to adipose hypertrophy, inflammation and oxidative stress.[11,27] Both human and animal studies indicate that BWV induces low-grade inflammation and oxidative stress, which can foster insulin resistance and subsequently cardiovascular complications.[11] Transcriptomic studies in obese patients undergoing weight cycling revealed that post-weight loss weight gain upregulates genes associated with fibrin clot formation, cardiomyopathy and vascular wall interactions—key processes in CVD development.[28,29] These pathways were unaffected by weight loss and only altered upon weight regain, a finding validated by another study, particularly concerning inflammatory and hypertrophic pathways. Additionally, weight loss only minimally affected altered transcriptomic signatures, suggesting that weight gain causes persistent changes.[28,29] These mechanistic evidences might underlie the observation that the association between BWV and CVD is no longer relevant in the elderlies. Indeed, old individuals with diabetes usually already have a high inflammatory burden due to a plethora of factors and pathways[30,31] and thus might be less sensitive to the pro-inflammatory effects of weight

oscillations. On the other hand, alternative explanations such as the selection of individuals genetically predisposed to avoid CVD or simply that the observation has arisen by chance might also be conceived. All these hypotheses warrant exploration in dedicated studies.

Strengths of our study include a large sample size of patients with T1D, a population-based design minimizing selection bias, the inclusion of participants free of CVD at baseline and a long follow-up. The limitations include the inability to establish a causal relationship between BWV and CVD or identify the mechanism underlying such a correlation. Despite the study design possibly supporting causality, that is, we calculated BWV up to a cut-off point to then assess its effects on subsequent events, BWV may have changed during the observation period, potentially affecting classification. In addition, we could not determine whether BWV was due to intentional factors, such as dieting or the introduction of noninsulin glucose-lowering drugs, or involuntary factors, such as diseases promoting cachexia. This aspect should be explored in future studies including the incidence of cachexia-promoting conditions, the introduction of drugs, dieting and exercise as possible confounders or mediators of the observation. However, the fact that weight trends do not modify the association between BWV and MACE should reassure about the independence of the observation from these phenomena. Finally, given the large sample size, most of the baseline characteristics of included individuals were different among the four quartile groups. However, Cox models were fully adjusted for all these cardiovascular risk factors, thus providing robust results.

In summary, our findings indicate that BWV is associated with the development of CVD in T1D, independently of cardiovascular risk factors and regardless of weight trends, sex and glycaemic control. Such association appears less relevant in the elderlies. This evidence might suggest that any weight reduction strategy for individuals with T1D should focus on maintaining long-term weight stability, avoiding fluctuations.

AUTHOR CONTRIBUTIONS

Francesco Prattichizzo and Antonio Ceriello conceived the idea and wrote the manuscript. Valentina Veronesi, Marta Rigoni, Giuseppe Lucisano and Antonio Nicolucci contributed to study design, performed the statistical analysis, and wrote and discussed the manuscript. Rosalba La Grotta and Valeria Pellegrini contributed to data analysis and reviewed the manuscript. Cesare Celeste Berra, Hanne Krage Carlsen, Björn Eliasson and Paola Muti curated data source, extracted and verified the underlying data and reviewed the manuscript for intellectual content. All authors approve the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Antonio Ceriello received consulting fees from AstraZeneca, Bayer, Eli Lilly, Elsevier, Novo Nordisk, Roche Diagnostics, Sanofi and Servier; received payment or honoraria for lectures from Berlin Chemie, Merck, Novo Nordisk and Roche Diagnostics and was on the advisory board of Eli Lilly. Antonio Nicolucci has received honoraria from AstraZeneca, Eli Lilly and Novo Nordisk and research support from Alfasigma, Novo Nordisk, Sanofi, Shionogi and SOBI. Björn Eliasson reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp and Dohme, Mundipharma, NovoNordisk and Sanofi, all outside the submitted work. The remaining authors declare no conflict of interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16038.

DATA AVAILABILITY STATEMENT

Because of the sensitive nature of the data collected for this study, access to the datasets is available from the sources stated in the paper on request to the data providers, fulfilling the legal and regulatory requirements, and with approval from the Swedish Ethical Review Authority.

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REFERENCES

1. Quattrin T, Mastrandrea LD, Walker LSK. Type 1 diabetes. *Lancet*. 2023;401(10394):2149-2162.
2. Van der Schueren B, Ellis D, Faradji RN, Al-Ozairi E, Rosen J, Mathieu C. Obesity in people living with type 1 diabetes. *Lancet Diab Endocrinol*. 2021;9(11):776-785.
3. Kueh MTW, Chew NWS, Al-Ozairi E, le Roux CW. The emergence of obesity in type 1 diabetes. *Int J Obes (Lond)*. 2024;48(3):289-301.
4. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes–causes, effects and coping strategies. *Diabetes Obes Metab*. 2007;9(6):799-812.
5. Fang M, Jeon Y, Echouffo-Tcheugui JB, Selvin E. Prevalence and management of obesity in U.S. adults with type 1 diabetes. *Ann Intern Med*. 2023;176(3):427-429.
6. Mottalib A, Kasetty M, Mar JY, Elseaidy T, Ashrafzadeh S, Hamdy O. Weight management in patients with type 1 diabetes and obesity. *Curr Diab Rep*. 2017;17(10):92.
7. Ceriello A, Lucisano G, Prattichizzo F, et al. Risk factor variability and cardiovascular risk among patients with diabetes: a nationwide observational study. *Eur J Prev Cardiol*. 2023;30(8):719-727.
8. Ceriello A, Lucisano G, Prattichizzo F, et al. Variability in body weight and the risk of cardiovascular complications in type 2 diabetes: results from the Swedish National Diabetes Register. *Cardiovasc Diabetol*. 2021;20(1):173.
9. Massey RJ, Siddiqui MK, Pearson ER, Dawed AY. Weight variability and cardiovascular outcomes: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2023;22(1):5.
10. Nam GE, Kim W, Han K, et al. Body weight variability and the risk of cardiovascular outcomes and mortality in patients with type 2 diabetes: a Nationwide cohort study. *Diabetes Care*. 2020;43(9):2234-2241.
11. Prattichizzo F, Frige C, La Grotta R, Ceriello A. Weight variability and diabetes complications. *Diabetes Res Clin Pract*. 2023;199:110646.

12. Petria I, Albuquerque S, Varoquaux G, et al. Body-weight variability and risk of cardiovascular outcomes in patients with type 1 diabetes: a retrospective observational analysis of data from the DCCT/EDIC population. *Cardiovasc Diabetol*. 2022;21(1):247.
13. Nystrom T, Andersson Franko M, Ludvigsson J, Lind M, Persson M. Overweight or obesity, weight variability and the risk of retinopathy in type 1 diabetes. *Diabetes Obes Metab*. 2024;26(6):2509-2512.
14. Lind M, Bounias I, Olsson M, Gudbjornsdottir S, Svensson AM, Rosengren A. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. *Lancet*. 2011;378(9786):140-146.
15. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2021.
16. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353(25):2643-2653.
17. Massey RJ, Chen Y, Panova-Noeva M, et al. BMI variability and cardiovascular outcomes within clinical trial and real-world environments in type 2 diabetes: an IMI2 SOPHIA study. *Cardiovasc Diabetol*. 2024;23(1):256.
18. Sattar N, McMurray J, Boren J, et al. Twenty years of cardiovascular complications and risk factors in patients with type 2 diabetes: a Nationwide Swedish cohort study. *Circulation*. 2023;147(25):1872-1886.
19. Nguyen VK, Colacino J, Chung MK, Goallec AL, Jolliet O, Patel CJ. Characterising the relationships between physiological indicators and all-cause mortality (NHANES): a population-based cohort study. *Lancet Healthy Longev*. 2021;2(10):e651-e662.
20. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diab Endocrinol*. 2019;7(3):221-230.
21. Forbes A, Murrells T, Mulnier H, Sinclair AJ. Mean HbA(1c), HbA(1c) variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study. *Lancet Diab Endocrinol*. 2018;6(6):476-486.
22. Driscoll KA, Corbin KD, Maahs DM, et al. Biopsychosocial aspects of weight management in Type 1 diabetes: a review and next steps. *Curr Diab Rep*. 2017;17(8):58.
23. Anson M, Zhao SS, Austin P, Ibarburu GH, Malik RA, Alam U. SGLT2i and GLP-1 RA therapy in type 1 diabetes and reno-vascular outcomes: a real-world study. *Diabetologia*. 2023;66(10):1869-1881.
24. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. *BMJ*. 2024;384:e076410.
25. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes Metab*. 2022;24(8):1553-1564.
26. Turicchi J, O'Driscoll R, Horgan G, et al. Body weight variability is not associated with changes in risk factors for cardiometabolic disease. *Int J Cardiol Hypertension*. 2020;6:100045.
27. Rhee EJ. Weight cycling and its cardiometabolic impact. *J Obes Metab Syndr*. 2017;26(4):237-242.
28. Piening BD, Zhou W, Contrepois K, et al. Integrative personal omics profiles during periods of weight gain and loss. *Cell Syst*. 2018;6(2):157-170.e8.
29. Sarin HV, Lee JH, Jauhiainen M, et al. Substantial fat mass loss reduces low-grade inflammation and induces positive alteration in cardiometabolic factors in normal-weight individuals. *Sci Rep*. 2019;9(1):3450.
30. Prattichizzo F, de Candia P, Ceriello A. Diabetes and kidney disease: emphasis on treatment with SGLT-2 inhibitors and GLP-1 receptor agonists. *Metab Clin Exp*. 2021;120:154799.
31. Pellegrini V, La Grotta R, Carreras F, et al. Inflammatory trajectory of type 2 diabetes: novel opportunities for early and late treatment. *Cells*. 2024;13(19):1662.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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