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Association SGLT2 Inhibitor Use and Cardiovascular Health Among Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Analysis of NHANES Data

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ABSTRACT:

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors improve cardiovascular and kidney outcomes in randomized trials, but their early use and the cardiovascular profile of users in the United States population remain less clearly described.

Methods: This cross-sectional study examined current SGLT2 inhibitor use and cardiovascular health among medication-treated adults with type 2 diabetes mellitus using National Health and Nutrition Examination Survey data from 2013 to 2018. Prescription records identified current use. The primary outcome was self-reported cardiovascular disease, defined as a history of congestive heart failure, coronary heart disease, angina, myocardial infarction, or stroke. Survey-weighted logistic and linear regression

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incorporated the complex sampling design and adjusted for demographic and clinical covariates.

Results: Among 1,978 eligible participants, 57 used an SGLT2 inhibitor. Weighted use increased from 0.5% in 2013 to 2014 to 7.1% in 2017 to 2018 and was 3.7% across the pooled period. Users were younger, had shorter diabetes duration, and had higher estimated glomerular filtration rate than nonusers. Weighted cardiovascular disease prevalence was 34.1% among users and 28.3% among nonusers. The fully adjusted odds ratio was 1.66 (95% confidence interval, 0.72 to 3.87; p = .231). Adjusted differences in blood pressure, body mass index, glycated hemoglobin, and lipid measures were imprecise, and sensitivity analyses did not materially alter the primary estimate.

Conclusion: SGLT2 inhibitor uptake increased substantially during early adoption. The findings characterize prescribing patterns and prevalent health profiles rather than causal treatment effects because medication use and cardiovascular history were measured concurrently.

1. INTRODUCTION

Diabetes mellitus is a serious public health concern: In 2021, there were 537 million adults aged 20 to 79 years with the condition globally, and this number is projected to reach 783 million by 2045 (International Diabetes Federation [IDF], 2021). Most cases will have type 2 diabetes mellitus (T2DM) and have a strong link to cardiovascular morbidity and mortality at a young age (Dal Canto et al., 2019). Regardless of the discrepancies in risk estimates, adults with T2DM have an increased risk of CHD, MI, stroke and HF (Dal Canto et al., 2019). As such, cardiovascular risk reduction should be the primary objective of diabetes management and care today, and not a downstream benefit of glucose management (American Diabetes Association Professional Practice Committee for Diabetes [ADA PPCD], 2026).

Hyperglycemia is not all that accounts for the cardiovascular burden of T2DM (Joseph et al., 2022). The interplay of insulin resistance, endothelial dysfunction, chronic inflammation, oxidative stress, abnormal lipid metabolism, obesity, hypertension and renal dysfunction can all contribute to promoting vascular and myocardial damage (Joseph et al., 2022). However, more and more, these other factors (glycemia, blood pressure, lipids, body weight, smoking, kidney function, and established cardiovascular disease (ADA PPCD, 2026)) need to be taken care of at the same time. This was a more comprehensive strategy that has shifted the goals of glucose lowering medications as some are now used for cardiovascular and renal benefits as well as its effect on glycated hemoglobin (Davies et al., 2022).

Sodium-glucose cotransporter 2 (SGLT2) inhibitors decrease the amount of glucose and sodium reabsorbed in the renal proximal tubule, and decrease plasma glucose in an insulin-independent fashion (Vallon & Thomson, 2017). They are glycosuric and induce natriuresis, osmotic diuresis, weight loss and renal haemodynamic changes (Wright et al., 2021). The suggested mechanism for cardiovascular benefits include reduction of ventricular preload and afterload, recovery of tubuloglomerular feedback, modification of myocardial energetics and inhibition of inflammatory and oxidative pathways but none of these mechanisms fully accounts for the clinical effects (Fonseca-Correa & Correa-Rotter, 2021).

This drug class' clinical standing changed as a result of cardiovascular outcome trials. Results from EMPA-REG OUTCOME demonstrated that empagliflozin decreased cardiovascular death and hospitalisation for heart failure, in patients with T2DM and known cardiovascular disease (Zinman et al., 2015). In a high-risk population, CANVAS Program demonstrated that canagliflozin lowered the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke (Neal et al., 2017). DECLARE-TIMI 58 did not show a significant effect of dapagliflozin on major adverse cardiovascular events in the overall study population, but did show that dapagliflozin lowered the risk of cardiovascular death or hospitalization for heart failure, primarily by decreasing hospitalizations for heart failure (Wiviott et al., 2019). A meta-analysis of the early cardiovascular outcome trials found that the biggest consistent cardiovascular benefit occurred with reduction in heart failure hospitalizations, and the major reduction in the cardiovascular events occurred in patients with atherosclerotic cardiovascular disease (ASCVD) (Zelniker et al., 2019).

According to current guidelines, SGLT2 inhibitors are beneficial and recommended for many T2DM adults with atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, and/or multiple cardiovascular risk factors, even if they do not require extra glucose lowering (ADA PPCD, 2026). The adverse effects and kidney function, cost, access and preference of patient still need person-centred decisions (ADA PPCD, 2026; Davies et al., 2022).

Observational data can augment trials and provide information about who is being treated with SGLT2 inhibitors in real-world clinical practice (Mittman et al., 2024). The National Health and Nutrition Examination Survey (NHANES) is a probability survey that combines interviews, examinations, laboratory measurements and prescription records of a representative sample of the civilian, noninstitutionalized population of the United States (National Center for Health Statistics [NCHS], 2026a).

Prior NHANES research has primarily involved prevalence of SGLT2 inhibitor use, temporal trends in use, eligibility for use, and sociodemographic differences in SGLT2 inhibitor use (Limonte et al., 2022; Mittman et al., 2024; Shen & Farley, 2023). Shen and Farley (2023) found that the use significantly increased since the class became available in the United States market, while being adopted in a modest fashion. Mittman et al. (2024) reported a positive association between education and income and the use of SGLT2 inhibitors or glucagon-like peptide 1 receptor agonists (GLP-1RAs), suggesting the potential for treatment selection due to clinical need or access. The cross-sectional cardiovascular profile of SGLT2 inhibitor users in a nationally representative population in the early adoption era is less well known.

This study aimed to investigate the relationship between cardiovascular health and current SGLT2 inhibitor (SGLT2i) use among adults with treated type 2 diabetes mellitus (T2DM) in NHANES 2013–2018. The main aim of the study was to test the prevalence of cardiovascular disease (CVD) self-reported by the users of SGLT2 inhibitors versus the nonusers. Secondary objectives involved describing adoption during the cycles of the survey and comparing the blood pressure, glycated hemoglobin, body mass index and lipid concentrations measured. Since exposures and outcomes were assessed at the same time in the same survey, the analysis was aimed to estimate cross-sectional associations and current-user profiles and not treatment effects or a reduction in cardiovascular events.

2. LITERATURE REVIEW

Biological, behavioral, and social factors that increase the risk of T2DM, such as overweight/obesity, unhealthy eating habits, and physical inactivity, are also risk factors for cardiovascular disease and are cumulative over the life course (Dal Canto et al., 2019). Chronic hyperglycemia is a factor that leads to advanced glycation, endothelial dysfunction, oxidative stress and vascular inflammation, and insulin resistance leads to dyslipidemia, hypertension and prothrombotic changes (Joseph et al., 2022). The latter are associated with an increased risk of atherosclerosis and can also result in structural and functional myocardial abnormalities (Joseph et al., 2022). Cardiovascular health in T2DM thus encompasses not only the clinical manifestation of the disease, but also modifiable risk factors like blood pressure, adiposity, smoking, glycemic control and lipid concentrations (ADA PPCD, 2026).

In fact, kidney dysfunction, heart failure, and T2DM often go hand-in-hand and should be taken into consideration when performing cardiovascular analyses, including when assessing kidney function, duration of diabetes, smoking, adiposity, and treatment intensity, where available (Davies et al., 2022; Joseph et al., 2022).

The SGLT2 is highly expressed in the early proximal tubule where it typically reabsorbs the majority of filtered glucose (Wright et al., 2021). The pharmacologic inhibition reduces the threshold for urinary glucose excretion, and it produces glucose lowering which is independent of insulin secretion (Vallon & Thomson, 2017). Randomized trials have also demonstrated that there are small, average decreases in body weight and systolic blood pressure with variable results based on starting glycemia, renal function, dose, and/or agent (Pinto et al., 2022).

Natriuresis and osmotic diuresis could decrease cardiac loading and more sodium brought to the macula densa could restore tubuloglomerular feedback and decrease intraglomerular pressure (Vallon & Thomson, 2017). Additional theories are that this is due to better utilization of myocardial fuels, decreased sympathetic activity, higher hematocrit, and decreased inflammatory signaling (Fonseca-Correa & Correa-Rotter, 2021).

EMPA-REG OUTCOME demonstrated that empagliflozin decreased cardiovascular death 38% and heart failure hospitalizations 35% in adults with T2DM with established cardiovascular disease (Zinman et al., 2015). CANVAS revealed that canagliflozin was associated with fewer cardiovascular deaths, nonfatal myocardial infarction or nonfatal stroke in high-

risk adults, but also found an increased risk for amputation (Neal et al., 2017). In DECLARE-TIMI 58, there was no significant difference between any of the major adverse cardiovascular events with dapagliflozin, but there was a reduction in cardiovascular deaths or a hospitalization for heart failure (Wiviott et al., 2019).

The meta-analysis of 34,322 participants showed a 11% decrease in major cardiovascular adverse events, a 23% decrease in cardiovascular death or hospitalization for heart failure and a 45% decrease in progression of renal disease (Zelniker et al., 2019). The atherosclerotic benefit was more evident in those who had a known atherosclerotic disease, and the benefits in heart failure and renal disease were more uniform across risk groups (Zelniker et al., 2019).

Trial eligibility criteria and planned follow-up and adherence to the trial protocol can constrain the possibility of direct generalizability to real-world clinical populations (Limonte et al., 2022). However, large observational studies have shown that once an SGLT2 inhibitor was started, the number of heart failure hospitalizations and deaths were lower than when starting another glucose lowering medication (Birkeland et al., 2017; Cavender et al., 2018). Those studies are generally similar to randomized studies, but threats to causal interpretation include treatment selection, exposure misclassification, residual confounding and differential access (Cavender et al., 2018).

NHANES is a form of real-world evidence (RWE) since it is a sample of the community, as opposed to a health-system sample or insurance claims (NCHS, 2026a). It includes a prescription drug component to document medications used in the 30 days prior to the survey, and other components include measured blood pressure, anthropometry, glycated hemoglobin, cholesterol, serum creatinine, smoking status and self-reported diagnoses (NCHS, 2014, 2016, 2018). The sample weights, strata and primary sampling units provided with this analysis are necessary for the correct analysis; otherwise, ordinary unweighted analysis may overestimate precision and will not be able to support analysis for national inference (NCHS, 2026b).

Fang and colleagues (2021) reported that the use of newer glucose lowering therapies was increasing, but that glycemic, blood pressure and lipid control was still lacking from 1999 to 2018. Limonte et al. (2022) estimated the use of SGLT2 inhibitors to be 5.8% in adults with T2DM with eGFR ≥ 30 mL/min/1.73 m2 in 2017–March 2020 and 7.7% in adults with major cardiorenal conditions.

Shen and Farley (2023) investigated SGLT2 inhibitor use among NHANES medication-treated adults with diabetes between 2013 to 2014 and 2017 to March 2020 and found that SGLT2 inhibitor use increased from 0.4% to 9.4% during this period of time. They were able to pool their estimates to come up with 5.7% and concluded that there was significant class expansion without apparent displacement of several established second-line drug classes (Shen & Farley, 2023). Mittman et al. (2024) analyzed adults with T2DM who used at least one glucose-lowering medication, and discovered that use of SGLT2 inhibitors or glucagon-like peptide 1 receptor agonists was higher in those with higher education and income levels. Some demographic and insurance factors were found to influence adoption, with their adjusted findings indicating that socioeconomic access may also influence adoption independently of these factors (Mittman et al., 2024).

Randomized outcome trials are used to determine if being in a treatment group affects subsequent events, whereas cross-sectional NHANES analyses determine who is taking treatment and what are the health characteristics of those taking treatment at the time of the analysis (Zelniker et al., 2019; NCHS, 2026b). The two questions are similar but not the same. A current user may have had a cardiovascular disease prior to SGLT2 inhibitor use and the disease might have been a reason for the prescription. Thus, a positive current use–cardiovascular disease relationship could be due to confounding by indication or reversed causation, not cardiovascular harm.

Prior NHANES studies have focussed on utilization, eligibility, and disparities (Limonte et al., 2022; Mittman et al., 2024; Shen & Farley, 2023). Prescriptions were correlated with validated cardiovascular history, examination measures, laboratory values and prespecified confounders in this study over three cycles.

3. METHODOLOGY

3.1 Study design and data source

This cross-sectional study used public NHANES data from the 2013 to 2014, 2015 to 2016, and 2017 to 2018 cycles (NCHS, 2014, 2016, 2018). The cycles were chosen because they represent three complete, nonoverlapping two-year surveys during the early adoption of the first SGLT2 inhibitor used in the United States (Mittman et al., 2024) and because these cycles were the first to start offering data from SGLT2 inhibitors. The NHANES is a multistage probability sampling design of households, as

well as a standardized examination and laboratory testing of participants in mobile examination centers (NCHS, 2026a). Estimates are for the civilian, noninstitutionalized U.S. population (NCHS, 2026b) when design variables and weights are applied.

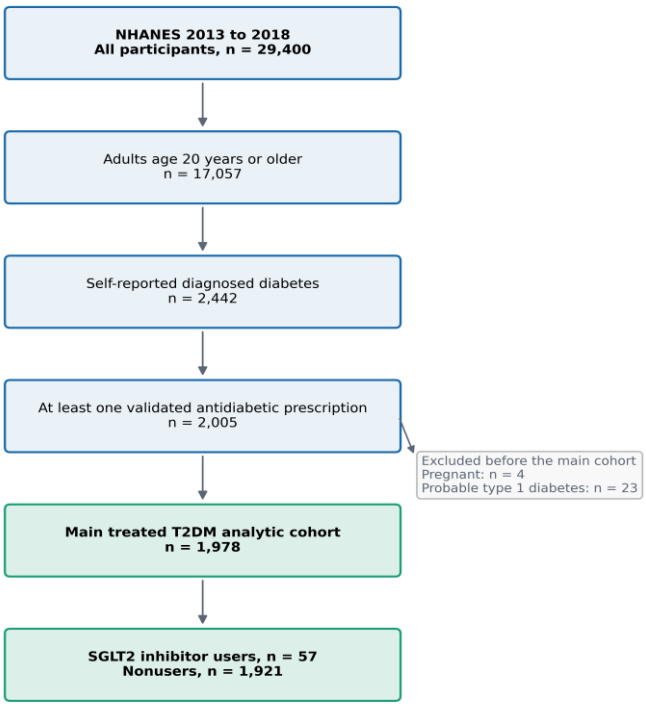
The demographic file was matched to the prescription, diabetes, medical-condition, examination, smoking, glycohemoglobin, lipid and biochemistry files using the unique respondent sequence number (SEQN) found in the NCHS (2014, 2016, 2018) data. Official SAS transport files and codebooks were kept and maintained a source manifest.

3.2 Study population

Eligible individuals were adults (> 20 years old) with a history of diagnosed diabetes and one or more current glucose lowering medications. This criterion set up a comparison group that was treated, and borderline diabetes was not considered to be diagnosed diabetes.

There are no single variables that define a diagnosis of T2DM in NHANES and a published operational definition was adapted (Mittman et al., 2024). Probable type 1 diabetes (T1) and exclusion were determined to be diabetes diagnosed before 20 years of age, insulins were identified, and no noninsulin glucose-lowering medicine was identified (Mittman et al., 2024). Gender (pregnant) was excluded as pregnancy can alter the choice of medication and the physiology of the cardiovascular system (Davies et al., 2022). The number of participants in the principal analytic cohort was the total number of participants who met the definition of treated diabetes and were complete cases for each outcome. The selection process for the participants and the groups where they were exposed can be seen in Figure 1.

Figure 1 Participant Selection for the Treated T2DM Analytic Cohort



Note. T2DM = type 2 diabetes mellitus. The primary outcome was available for 1,966 participants, and the fully adjusted primary model included 1,730 complete cases.

3.3 Exposure definition

Prescription Medications component is used to document medications reportedly used in the last 30 days (NCHS, 2014, 2016, 2018). All Despite the discrepancies were searched for the four approved SGLT2 inhibitors, brand names and fixed-dose combinations and all results were manually analysed. Validated record participants were considered users and other treated

participants were nonusers. Information regarding dosing, adherence, date of initiation and duration of exposure was not available, which led to a binary exposure assessment.

3.4 Outcomes

The main outcome was cardiovascular disease (CVD) prevalence. This was coded as present if the participant reported a diagnosis of congestive heart failure, coronary heart disease, angina, heart attack or stroke by a health professional. If all 5 of the component responses were negative, it was coded as absent, otherwise it was treated as missing. This definition reflects the heart disease history items that were always present in the selected cycles, but are lifetime self-report and not adjudicated incident disease (NCHS, 2014, 2016, 2018).

Mean SBP, mean DBP, BMI, glycated hemoglobin, total cholesterol, HDL cholesterol and calculated non-HDL cholesterol were secondary outcomes. All available valid examination readings were averaged to get a blood pressure reading. BMI was calculated from height and weight measurements. The values of glycated hemoglobin and cholesterol was obtained from the respective laboratory files. The measures were chosen as blood pressure, adiposity, glycemic status and lipids are key modifiable cardiovascular risk factors in T2DM (ADA PPCD, 2026).

3.5 Covariates

The prespecified covariates included age, sex, non-Hispanic White race and ethnicity, survey cycle (to account for different time periods), diabetes duration, current smoking status, insulin use, eGFR, and body mass index. As a social-demographic adjustment variable, race and ethnicity were taken into account. Diabetes duration was calculated as current age - age at diagnosis and eGFR was calculated with the race-free Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (Inker et al., 2021). BMI was not included in the model predicting BMI.

3.6 Survey design and statistical analysis

In the interview components, exposures and cohort defining variables were collected and weights for the interviews were used for medication prevalence. Descriptive comparisons and examination or laboratory variables regression models were done using mobile examination center weights. Two-year weights were divided by three to get the 6-year weights as has been recommended by NCHS (NCHS, 2026a) for pooling equivalent adjacent cycles. Strata and primary sampling unit (PSU) identifiers were nested within cycle to maintain the combined design. Taylor series linearization was used to estimate the variances and the design degrees of freedom was 45 for the pooled design.

Survey-weighted mean and percentages with 95% confidence intervals were summarised by exposure group for participant characteristics. Unweighted denominators were used to allow for evaluation of sparse cells of exposed population. Design-adjusted Wald tests were used to test for group differences and standardized difference values were used as a descriptive measure of imbalance. Very small exposed counts were only provided when necessary to indicate the early utilization trend and explicitly marked as unstable following guidance from NCHS (2026b).

The association between the use of SGLT2 inhibitors and prevalent cardiovascular disease was estimated by survey-weighted logistic regression. Model 1 was unadjusted. Model 2 was adjusted for age, sex, non-Hispanic White race/ethnicity and survey cycle. Model 3 was further adjusted for diabetes duration, current smoking, insulin use, eGFR and body mass index. Odds ratios (ORs) and 95% confidence intervals (CIs) and two-sided p values were used to state results. Each continuous secondary outcome was assessed by survey-weighted linear regression with the Model 3 set of covariates; however, body mass index was not included as a covariate when body mass index was the outcome. To make visual comparisons across scales, secondary estimates were also converted to weighted within-group pooled standard deviation.

Weighted prevalence by cycle, a survey-weighted logistic trend model (with cycle coded 0, 1, and 2) were used to describe temporal adoption. Multiplicity adjustment was not performed for secondary outcomes that were exploratory in nature. Statistically interpretation was focused on the magnitude and precision and $p < .05$ was not used as a substitute for clinical interpretation. Analyses were performed in Python 3.12.13 using pandas 2.2.3, NumPy 2.3.5, SciPy 1.17.0, and Matplotlib 3.10.8.

3.7 Missing data, sensitivity analyses, and validation

The missingness for all primary model variables and secondary outcomes were described. Outcome-specific complete-case analysis was the main approach as the amount of missingness was not greater than 8.8% for any of the fields examined. A total

of 1730 (87.5%) participants of the primary model have been fully adjusted. No imputations were made for exposure and primary outcome values.

To test for robustness, four prespecified sensitivity analyses were carried out. To reduce the cardiovascular outcome to only atherosclerotic conditions, heart failure was not included in the composite. The primary analysis was also performed in those with eGFR ≥ 30 mL/min/1.73 m2. All adults without a recorded prescription for glucose lowering were included in a larger number of diagnosed-diabetes individuals. The adjusted estimate was also analysed by omitting one of the primary sampling units at a time.

Quality checks comprised of merge and duplicate validation, medication review, range checks, convergence and independent numerical replication. All 45 strata had two primary sampling units, variance inflation factors were < 1.8, and all 90 delete-one-unit models converged and the replicated OR agreed within 0.000001.

3.8 Ethical considerations and reporting

NHANES protocols received ethics approval and participants provided informed consent (NCHS, 2026a). This study used public, deidentified files. Reporting followed Strengthening the Reporting of Observational Studies in Epidemiology recommendations (von Elm et al., 2007).

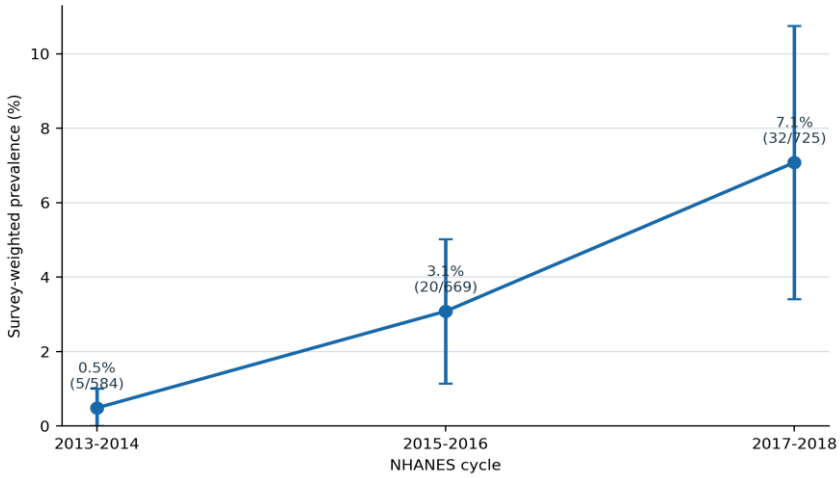
4. RESULTS

4.1 Cohort construction and SGLT2 inhibitor use

There were 29,400 participants in the three NHANES cycles, of which 17,057 were ≥20 years old and 2,442 had a diagnosed diabetes history. Of these, 2005 had at least one validated glucose lowering prescription; the remaining 437 did not meet the medication-treatment eligibility criterion. 4 pregnant adults and 23 adults who met the probable type 1 diabetes definition were excluded from these 2,005 participants. Thus, the main cohort consisted of 1,978 adults with treated T2DM, of whom 57 were users of an SGLT2 inhibitor, with 1,921 nonusers (Figure 1). This included 28 with canagliflozin records, 15 with dapagliflozin records and 14 with empagliflozin records.

The weighted prevalence of SGLT2 inhibitor use across 2013 to 2018 was 3.7% (95% CI, 2.2% to 5.2%). Prevalence increased from 0.5% (95% CI, 0.0% to 1.0%; 5 of 584 participants) in 2013 to 2014 to 3.1% (95% CI, 1.1% to 5.0%; 20 of 669) in 2015 to 2016 and 7.1% (95% CI, 3.4% to 10.7%; 32 of 725) in 2017 to 2018. The odds of use rose 3.10-fold every two-year cycle (95% CI 1.83 to 5.26; p < .001); the prevalence estimate from the first cycle, however, should be treated with caution as it was based on only 5 users.

Figure 2 Survey-Weighted Prevalence of SGLT2 Inhibitor Use Across NHANES Cycles



Note. Error bars show 95% confidence intervals. The trend odds ratio per two-year cycle was 3.10 (95% CI, 1.83 to 5.26; p < .001). The 2013 to 2014 estimate was based on five users.

4.2 Participant characteristics

SGLT2 inhibitor users were younger than nonusers, with weighted mean ages of 58.0 and 62.0 years, respectively (p = .011), and they reported shorter diabetes duration (10.2 vs. 12.2 years; p = .024). Users had higher mean eGFR (92.8 vs. 82.8 mL/min/1.73 m2; p = .005). The exposed group also had a higher weighted prevalence of hypertension (84.1% vs. 70.7%) and a lower prevalence of insulin use (17.9% vs. 30.0%), although the corresponding design-adjusted p values were .070 and .058. Wide confidence intervals around several exposed-group percentages reflected the small number of users. The complete survey-weighted comparison is provided in Table 1.

Table 1. Survey-weighted characteristics by SGLT2 inhibitor use

Characteristic	Nonusers, estimate (95% CI)	SGLT2 inhibitor users, estimate (95% CI)	p
Age, years	62.0 (61.1 to 62.9)	58.0 (55.0 to 60.9)	.011
Diabetes duration, years	12.2 (11.5 to 12.9)	10.2 (8.5 to 11.9)	.024
Insulin use, %	30.0 (27.2 to 32.9)	17.9 (5.4 to 30.4)	.058
Body mass index, kg/m2	33.1 (32.5 to 33.7)	34.2 (32.5 to 35.9)	.234
Systolic blood pressure, mm Hg	131.0 (129.8 to 132.3)	130.6 (121.1 to 140.0)	.923
HbA1c, %	7.5 (7.4 to 7.6)	7.2 (6.8 to 7.6)	.194
Total cholesterol, mg/dL	173.8 (170.3 to 177.3)	185.9 (167.5 to 204.3)	.194
eGFR, mL/min/1.73 m2	82.8 (81.3 to 84.3)	92.8 (86.3 to 99.4)	.005
Hypertension, %	70.7 (67.2 to 74.3)	84.1 (70.5 to 97.8)	.070
Any cardiovascular disease, %	28.3 (25.4 to 31.2)	34.1 (16.2 to 52.0)	.534

Note. CI = confidence interval; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein. Values are survey-weighted means or percentages. Sample size varies because of missing values. p values are from design-adjusted Wald tests.

4.3 Primary cardiovascular disease association

For a total of 1,966 participants, the primary cardiovascular composite was available. Among the 57 SGLT2 inhibitor users, 16 reported at least one of the five component cardiovascular conditions (congestive heart failure, coronary heart disease, angina, myocardial infarction, or stroke). Weighted cardiovascular disease prevalence was 34.1% (95% CI, 16.2% to 52.0%) among users and 28.3% (95% CI, 25.4% to 31.2%) among nonusers.

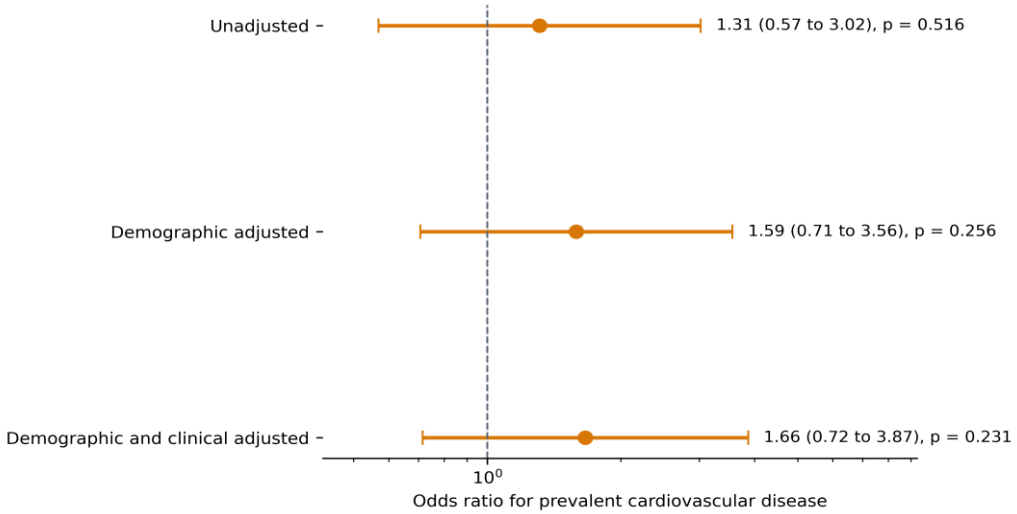
In the unadjusted model, the OR for cardiovascular disease use of SGLT2 inhibitors was 1.31 (95% CI, 0.57 to 3.02; p = .516). Adjustment for demographic characteristics and cycle increased the OR to 1.59 (95% CI, 0.71 to 3.56; p = .256). The fully adjusted model included 1,730 participants and produced an OR of 1.66 (95% CI, 0.72 to 3.87; p = .231). All of the confidence intervals contained 1 and were consistent with a multitude of lower or higher odds (Table 2 and Figure 3).

Table 2. Survey-weighted logistic regression for prevalent cardiovascular disease

Model	OR (95% CI)	p	Complete-case n	Events
Model 1: unadjusted	1.31 (0.57 to 3.02)	.516	1,966	578
Model 2: demographic and cycle adjusted	1.59 (0.71 to 3.56)	.256	1,966	578
Model 3: demographic and clinical adjusted	1.66 (0.72 to 3.87)	.231	1,730	489

Note. CI = confidence interval; OR = odds ratio. Model 2 adjusted for age, sex, non-Hispanic White race and ethnicity, and survey cycle. Model 3 additionally adjusted for diabetes duration, current smoking, insulin use, eGFR, and body mass index. All models incorporated examination weights, strata, and primary sampling units.

Figure 3 Survey-Weighted Associations Between SGLT2 Inhibitor Use and Prevalent Cardiovascular Disease



Note. Points are odds ratios and horizontal lines are 95% confidence intervals. The vertical reference line indicates an odds ratio of 1.

4.4 Secondary cardiovascular and metabolic outcomes

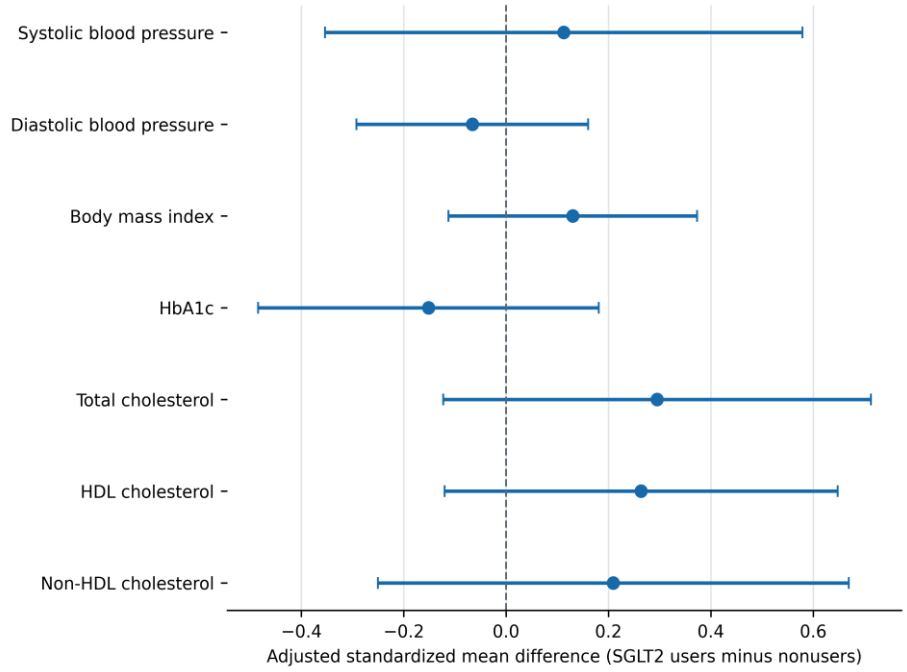
In none of the seven adjusted continuous-outcome models did the 95% confidence interval around the model coefficient exclude zero. Compared with nonusers, users had an adjusted mean systolic blood pressure difference of 2.27 mm Hg (95% CI, -7.11 to 11.64; p = .629) and a diastolic difference of -0.76 mm Hg (95% CI, -3.39 to 1.86; p = .561). The adjusted difference in body mass index was 0.86 kg/m2 (95% CI, -0.74 to 2.45; p = .285), and the adjusted HbA1c difference was -0.22 percentage points (95% CI, -0.71 to 0.27; p = .364). Users had higher estimated values of total, HDL and non-HDL cholesterol, however, all of these confidence intervals were wide and contained zero (Table 3, Figure 4).

Table 3. Adjusted differences in continuous cardiovascular and metabolic outcomes

Outcome	Adjusted mean difference (95% CI)	p	n
Systolic blood pressure, mm Hg	2.27 (-7.11 to 11.64)	.629	1,684
Diastolic blood pressure, mm Hg	-0.76 (-3.39 to 1.86)	.561	1,684
Body mass index, kg/m2	0.86 (-0.74 to 2.45)	.285	1,740
HbA1c, percentage points	-0.22 (-0.71 to 0.27)	.364	1,738
Total cholesterol, mg/dL	12.65 (-5.27 to 30.58)	.162	1,739
HDL cholesterol, mg/dL	3.46 (-1.57 to 8.48)	.173	1,739
Non-HDL cholesterol, mg/dL	9.20 (-10.99 to 29.38)	.364	1,739

Note. Positive estimates indicate higher values among SGLT2 inhibitor users. Models adjusted for age, sex, non-Hispanic White race and ethnicity, survey cycle, diabetes duration, current smoking, insulin use, eGFR, and body mass index, except that body mass index was omitted from its own model.

Figure 4 Adjusted Standardized Differences in Cardiovascular and Metabolic Outcomes



Note. Positive estimates indicate higher values among SGLT2 inhibitor users. Horizontal lines show 95% confidence intervals.

4.5 Sensitivity and stability analyses

Similar adjusted point estimates were obtained from the sensitivity analyses. The OR was 1.73 (95% CI, 0.75 to 4.00) for the atherosclerotic composite excluding heart failure, 1.68 (95% CI, 0.72 to 3.92) after restricting the cohort to eGFR of at least 30 mL/min/1.73 m2, and 1.52 (95% CI, 0.68 to 3.44) in the broader diagnosed-diabetes cohort. All confidence intervals included 1. The adjusted ORs for the 90 delete-one-primary-sampling-unit refits ranged from 1.32 to 2.23; that is, no single sampled cluster changed the direction of the point estimate. There was no more than 8.8% missing data on any variables, no model failed to converge, and no significant multicollinearity was found. The consistency of the primary estimate as obtained with these analyses is summarised in Table 4. The covariate set for all models was the Model 3 set, and the number of cases exposed is listed for each sensitivity-analysis cohort.

Table 4. Sensitivity analyses for prevalent cardiovascular disease

Analysis	Adjusted OR (95% CI)	p	n	SGLT2 inhibitor users, n
Main cohort, broad cardiovascular composite	1.66 (0.72 to 3.87)	.231	1,730	57
Atherosclerotic composite excluding heart failure	1.73 (0.75 to 4.00)	.193	1,730	57
Main cohort with eGFR at least 30 mL/min/1.73 m2	1.68 (0.72 to 3.92)	.228	1,673	54
Broader diagnosed-diabetes cohort	1.52 (0.68 to 3.44)	.303	2,113	57

5. DISCUSSION

Three percent of treated adults with T2DM used SGLT2 inhibitors in 2013–2018, but there was rapid growth in use throughout this period in this nationally representative analysis. Weighted use rose from 0.5% in 2013 to 2014 to 7.1% in 2017 to 2018, with an overall prevalence of 3.7%. Current users were younger, had a shorter diabetes duration and had better kidney function than nonusers. These differences are in line with a selective uptake among patients that are perceived as eligible for a newly introduced class.

34.1% of users and 28.3% of nonusers self-reported cardiovascular diseases. The fully adjusted OR was 1.66, with 95% CI of 0.72-3.87. This finding does not necessarily directly reflect differences in prevalent cardiovascular disease among current users, but rather may reflect differences in prevalent cardiovascular disease among non-users. However, the point estimate was consistently greater than one with all alternative outcome and cohort definitions, and with all delete-one-cluster analyses, but the uncertainty was too great to determine whether there was a stable prescribing pattern or sampling variation.

Also, blood pressure, body mass index, HbA1c and cholesterol differences were imprecise. Even when p values are not < .05, this does not indicate equal cardiovascular and/or metabolic profiles.

This observed adoption is very similar to the results of previous NHANES studies. Shen and Farley (2023) found that among medication-treated adults with diabetes, this rate rose from 0.4% between 2013 and 2014, to 9.4% in the 2017 to March 2020 release. Our 0.5% estimate for 2013-2014 is almost the same and our 7.1% estimate for 2017-2018 is reasonably lower as it does not cover the latter part of 2019 to March 2020 and the definition of treated-T2DM is narrower. However, the estimate from Limonte et al. (2022) of 5.8% in 2017–2020 (March 2020) should not be compared directly to our pooled estimate of 3.7% from 2013 to 2018, because the Limonte et al. 2022 study only includes adults with T2DM and eGFR ≥30 mL/min/1.73 m2. When considered collectively, the studies indicate that there was a quick spreading from a small group of initial adopters and not necessarily a high level of uptake (Limonte et al., 2022; Shen & Farley, 2023).

This is plausible as the kidney function was used in the initial prescription and was thought to affect the efficacy of glucose-lowering drugs (Davies et al., 2022). Lower age, shorter duration of diabetes and less insulin use indicate earlier channeling in the treatment, and higher estimated hypertension and cardiovascular disease indicates selection for cardiorenal risk. The socioeconomic access may also influence adoption (Mittman et al., 2024).

The main cross-sectional OR should not be considered as an estimate of the same quantity as a randomized trial hazard ratio. The EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 trials examined outcomes following randomization (Neal et al., 2017; Wiviott et al., 2019; Zinman et al., 2015). This current study assessed current use of medications, and lifetime history of cardiovascular diagnosis at one survey encounter. It is possible that a diagnosis of myocardial infarction, stroke or heart failure predates the initiation of an SGLT2 inhibitor and that this diagnosis increased the likelihood of an SGLT2 inhibitor being prescribed. This "reverse" temporal ordering can result in an OR >1 even if the treatment decreases the future risk.

Randomized evidence shows decreased HHF and renal progression and atherosclerotic outcomes are variable depending on underlying disease (Zelniker et al., 2019). Longitudinal, active-comparator studies also found reduced heart failure hospitalizations and mortality (Birkeland et al., 2017; Cavender et al., 2018). We find that a current-user prevalence comparison doesn't necessarily contradict those benefits.

Care must be exercised with the secondary findings. In RCTs, SGLT2 inhibitors have an average effect on weight and systolic blood pressure (Pinto et al., 2022). We did not clearly capture those differences with our adjusted estimates, but we lacked information on exposure duration, adherence, baseline value, changes in treatment and concurrent therapies. Regression to the mean and clinical channeling also may impact a treated current-user comparison. The large margins of error around the secondary estimates indicate that this NHANES sample was not precise enough to exclude for this sample small physiologic effects seen in trials.

The use of this evidence increased very quickly between 2013 and 2018, indicating that cardiovascular outcome evidence was gained into practice relatively fast after it was published. Within the study period, the EMPA-REG OUTCOME and CANVAS were reported in 2015 and 2017, respectively (Neal et al., 2017; Zinman et al., 2015). However, only 7.1% of the adults in the last cycle who were given medication were taking the class, suggesting there is significant opportunity for future growth. Subsequent standards have not only reinforced the recommendations for the use of SGLT2 inhibitors in adults with T2DM

but also introduced ADA PPCD, which are multiple cardiovascular risk factors, atherosclerotic disease, chronic kidney disease and heart failure.

As the percentage of the nation who use this rises, there is the possibility of unequal access and selective prescribing. The socioeconomic gradients and low uptake by adults with cardiorenal conditions suggest that monitoring should consider uptake and equitable access to monitoring (Limonte et al., 2022; Mittman et al., 2024).

Clinicians should not make changes to evidence-based prescribing based on the adjusted OR in this analysis. Randomized cardiovascular and kidney outcomes, ADA PPCD, contraindications, adverse-effect risk, affordability and patient preferences remain important considerations in treatment decision. The finding highlights the importance for researchers to differentiate prevalent and incident disease and between current-user and new-user active comparator design. Finally, when estimating the comparative effect of medications, important treatment-selection biases can be reduced with an active-comparator new-user design (Lund et al., 2015). Although useful for adoption and equity surveillance, national surveys may not be the most ideal source of data for estimating comparative effectiveness.

This study has a number of important strengths. Three cycles of NHANES data were used, official sample weights, cycle-nested strata and primary sampling units, and Taylor-linearized variance estimates. Prescription names were checked at the raw-record level and cardiovascular disease was coded conservatively. Standardized NHANES examination and laboratory procedures were followed (NCHS, 2014, 2016, & 2018). The major result was directionally consistent in each of the alternative outcome definitions, alternative cohort definitions, independent numerical replication and deletion of each sampled primary unit. Transparent interpretation was also facilitated by reporting of exposed counts and concerns about reliability.

The limitations are largely in matters of interpretation and not analytic validity. Cross sectional studies can estimate the prevalence and describe the characteristics of the population, but cannot be used to determine temporal order of exposure and outcome (Wang & Cheng, 2020). Thus, it is unclear from NHANES if cardiovascular disease occurred before SGLT2 inhibitor started. The result should not be interpreted as an estimate of the cardiovascular risk or effectiveness of treatment, but as an association with current users.

There were only 57 participants in the exposed group, leading to broad confidence intervals and few other socioeconomic or treatment factors could be taken into account. The use of medication, as well as cardiovascular diagnosis was self-reported and the initiation date, duration of use, dose and adherence unknown (NCHS, 2014, 2016, 2018). Despite this, the analysis can be considered internally stable due to the uniformity of the sensitivity results, low missingness of the measured variables and the convergence of all models. Lastly, the results relate to early adoption among the noninstitutionalized civilian population of the United States, and should not be used to estimate current utilization (NCHS, 2026a).

6. CONCLUSION

Using nationally representative NHANES data, this study documented rising SGLT2 inhibitor use among treated US adults with T2DM, from 0.5% (2013–2014) to 7.1% (2017–2018), though pooled prevalence remained low overall (3.7%). Early adopters were younger, had shorter diabetes duration, and better renal function than nonusers—patterns consistent with selective prescribing based on eligibility and clinical judgment rather than random allocation. Cardiovascular disease was more common among users in weighted descriptive analysis, but the adjusted association was imprecise (OR 1.66, 95% CI 0.72–3.87), and no secondary cardiovascular or metabolic estimate excluded the null.

These findings do not support inferences about SGLT2 inhibitors' effect on cardiovascular risk. The cross-sectional design captures current medication use and lifetime cardiovascular history simultaneously, so prevalent disease may have preceded and prompted treatment rather than resulted from it-a limitation distinct from the causal claims addressable by trials or new-user cohort designs.

This study's contribution is descriptive: a national snapshot of adoption patterns and user characteristics during a period of rapid guideline change, valuable precisely because NHANES captures populations outside insurance-linked databases. Longitudinal cohorts with defined treatment initiation, active-comparator designs, and attention to socioeconomic and racial/ethnic disparities are needed to determine whether trial-demonstrated benefits are reaching eligible patients equitably.

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