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Expenditures and Utilization of Glucose-Lowering Drugs in U.S. Adults with Diabetes, by Key Cardiovascular-Kidney-Metabolic Components: 2012–2021

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Running title

Medication Use and Spending by CKM Component

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Abstract

Background:

To examine national trends in prescription drug and glucose-lowering drug (GLD) expenditures, and utilization of GLDs among U.S. adults with diabetes, stratified by key cardiovascular-kidney-metabolic (CKM) components.

Methods:

We analyzed nationally representative data from the 2012–2021 Medical Expenditure Panel Survey for adults aged ⩾20 years with diabetes. Participants were categorized as diabetes only (D only), diabetes with cardiovascular disease (D+C), diabetes with chronic kidney disease (D+K), or diabetes with both conditions (D+K+C). Survey-weighted per-capita total prescription drug and GLD expenditures, utilization of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and insulin expenditures were estimated across biennial survey periods.

Results:

Among 15,529 adults with diabetes, 68.7% had D only, 22.6% had D+C, 4.9% had D+K, and 3.8% had D+K+C. GLD expenditures increased with CKM complexity. In 2020–2021, per-capita GLD expenditures were $3,342.6, $3,930.6, $5,613.7, and $5,940.0 in the D only, D+C, D+K, and D+K+C groups, respectively (**P** < 0.001). Insulin accounted for an average of 60.3% of total GLD expenditures throughout the study period. Although utilization of SGLT2i and GLP-1 RAs increased over time,

only approximately one in five adults received either therapy in 2020–2021, with no significant differences across CKM groups (**P** = 0.51).

Conclusions:

Cardiovascular and kidney comorbidities were associated with higher prescription drug and GLD expenditures among adults with diabetes. Despite their proven cardiorenal benefits, SGLT2i and GLP-1 RAs remain markedly underutilized in high-risk patients.

Clinical trial number:

Not applicable.

Keywords: glucose-lowering drugs; prescription drug expenditures; cardiovascular-kidney-metabolic syndrome; SGLT2i; GLP-1 RAs; diabetes

Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome is a complex clinical condition characterized by the interrelated progression of metabolic disease, chronic kidney disease (CKD), and cardiovascular disease (CVD).[1] It is a major contributor to premature morbidity and mortality worldwide and imposes a substantial clinical and economic burden on individuals and health systems.[2] Diabetes is a central component of the CKM continuum.[1,2] The presence of overlapping CKM components with diabetes is associated with greater clinical complexity, poorer outcomes, and higher healthcare costs.[3,4]

Prescription drugs, particularly glucose-lowering drugs (GLDs), are a cornerstone of diabetes management and account for a substantial share of treatment-related expenditures. Among U.S. adults with diabetes, annual per-person prescription drug expenditures increased from $3,932 in 2012 to $6,397 in 2021, while GLD expenditures rose from $1,701 to $4,393 over the same period.[5] GLD spending has increased more rapidly than overall prescription drug spending, creating a disproportionate financial burden for both patients and payers.[6] Despite this, systematic evidence on how coexisting CKM components impact prescription drug expenditures, particularly GLD costs, remains limited. Prior studies have largely focused on medication utilization or clinical efficacy among patients with diabetes, with less attention to real-world expenditure patterns across CKM comorbidity profiles.[7,8] The economic burden of medication use in the context of CKM multimorbidity remains insufficiently characterized.

The emergence of sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has transformed the treatment landscape for diabetes.[9] These agents have demonstrated cardiorenal benefits beyond glucose control.[9–11] Major clinical guidelines, including the American Diabetes Association (ADA) Standards of Care and the joint ADA/KDIGO consensus report, recommend SGLT2i and GLP-1 RAs as preferred therapies for patients with type 2 diabetes and coexisting CVD, CKD, or heart failure.[12,13] Although prior studies have examined the utilization and expenditure of these agents with multiple benefits in

patients with CVD or CKD separately, [14–16] systematic evaluation across CKM component groups remains limited.

To address these gaps, we used 2012–2021 Medical Expenditure Panel Survey (MEPS) data to examine national trends in prescription drug and GLD expenditures among U.S. adults with diabetes by key CKM components, and to evaluate whether utilization and spending on SGLT2i and GLP-1 RAs are aligned with clinical guidelines across CKM subgroups.

Methods

Data Source and Study Population

We analyzed data from the MEPS, a nationally representative cross-sectional survey of non-institutionalized U.S. civilians sponsored by the Agency for Healthcare Research and Quality (AHRQ).[17] We included data from 2012-2021 MEPS survey years. MEPS collects detailed information on health status, healthcare utilization, and medical expenditures of each household member. This study utilized the Full-Year Consolidated (FYC) files, Medical Conditions files, and Prescribed Medicines files. The study included adults aged ≥20 years with diabetes. Diabetes was defined as a self-reported physician diagnosis. Adults with diabetes were stratified into four mutually exclusive groups based on key CKM components: diabetes alone (D only), diabetes with CVD (D+C), diabetes with CKD (D+K), or diabetes with both CVD and CKD (D+K+C). CVD was defined as a composite of atrial fibrillation/flutter, lower extremity peripheral arterial disease, coronary heart disease, and stroke. CKD was

identified using either ICD-9/ICD-10 codes, Clinical Classification Codes (CCC/CCSR), or self-reported diagnosis. MEPS was approved by the Westat Institutional Review Board, and informed consent was obtained from all participants.

Expenditures and Utilization of glucose-lowering drugs

Prescription medication data in MEPS were derived from respondent self-reports and pharmacy records. Respondents self-reported the names of any prescribed medications procured at any pharmacy, including mail-order or on-line order, acquired by themselves or their family members during the calendar year. Following written authorization to access payment data, information about the date of prescription fulfillment, national drug code, medication name, medication strength, quantity, payment amount, and sources of payment were obtained from pharmacies.[18] Medications were categorized into therapeutic classes according to the Multum Lexicon classification scheme, which provides a 3-level nested category system that assigns a therapeutic classification to each drug and its ingredients.[19]

Total prescription drug expenditure was defined as the sum of out-of-pocket payments and third-party payments (including private and public insurance) paid to pharmacies for all prescription drugs received during the survey year. For each group, we calculated per-capita prescription drug expenditure and per-capita GLD expenditure. Utilization rates were defined as the proportion of individuals within each group who had at least one prescription fill for a specific medication class during the survey year. Expenditure proportions were calculated as the share of the aggregate

weighted annual expenditure attributable to a specific medication class relative to the total aggregate weighted annual expenditure for all GLDs within each group.

Annual utilization rates, expenditure proportions, and per-capita costs were additionally assessed for SGLT2i, GLP-1 RAs, and insulin given the established cardiovascular and renal benefits of SGLT2i and GLP-1 RAs and insulin's dominance in GLD expenditures. All expenditure estimates were inflation-adjusted to 2021 U.S. dollars using the Consumer Price Index for prescription drugs.[20]

Statistical Analysis

To increase sample size and enhance the stability of annual estimates, data from two adjacent survey years were pooled into biennial periods. All analyses incorporated the complex survey design of MEPS, accounting for person-level sampling weights, primary sampling unit (PSU) clusters, and strata variables to yield nationally representative estimates. Results are reported as means or percentages with corresponding 95% confidence intervals (CIs). Differences across the four CKM groups were assessed using design-based Wald tests for continuous outcomes and survey-adjusted Pearson χ^2 tests for categorical outcomes. P-for-trend values were obtained from survey-weighted regression models with survey period modeled as an ordinal variable. Statistical significance was defined as a two-sided p-value < 0.05. All analyses were conducted in R (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria) and Stata/MP 18.0 (StataCorp, College Station, TX, USA).

Secondary Analyses

To explore the impact of metabolic status, we repeated the analyses among patients with obesity (defined as body mass index [BMI] ≥ 30 kg/m²) and those without. Given that BMI data were consistently available in MEPS only through 2016, these analyses were restricted to the 2012–2016 timeframe.

Results

Study Population and Sample Characteristics

Between 2012 and 2021, a total of 15,529 adults with diabetes were included (Fig. S1). Among them, 10,664 participants (68.7%) were classified as D only, 3,509 (22.6%) as D+C, 764 (4.9%) as D+K, and 592 (3.8%) as D+K+C.

Baseline characteristics differed significantly across CKM groups (Table S1). Compared with the D only group, participants in the D+C and D+K+C groups were older (mean age: 68.1 and 68.2 vs. 57.9 years, respectively) and less likely to be women (43.6% in D+K+C vs. 53.5% in D only; $p < 0.001$ for both). Greater CKM burden was also associated with socioeconomic disadvantage. The proportions without a high school diploma increased from 22.4% in the D only group to 32.3% in the D+K group and 34.2% in the D+K+C group. Likewise, public insurance coverage (50.4%) and poverty (19.9%) were most common in the D+K+C group, compared with 31.6% and 13.5%, respectively, in the D only group ($p < 0.001$ for all).

Trends in Total Prescription Drug Expenditures

Prescription drug expenditures were significantly higher among patients with higher comorbidity burden ($p< 0.001$, Figure 1). Per-capita expenditures rose significantly in all groups, from $3,521.0 to $5,327.7 in D only, from $5,350.3 to $8,526.3 in D+C, from $5,288.5 to $9,866.1 in D+K, and from $9,659.1 to $9,970.1 in D+K+C group between 2012–2013 and 2020–2021. These changes corresponded to increases of 51.3%, 59.4%, 86.6%, and 3.2%, respectively. The D+K group showed the steepest relative growth, whereas the D+K+C group consistently had the highest absolute expenditures.

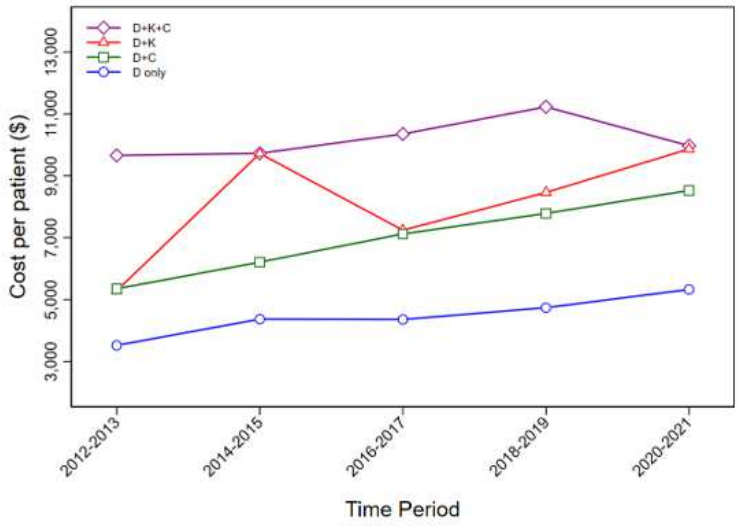


Figure 1. Annual per-capita total prescription drug expenditures among U.S. adults with diabetes by CKM components, 2012-2021

Note: CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease. D only, individuals with diabetes without CKD or CVD; D+K, individuals with diabetes and CKD but without CVD; D+C, individuals with diabetes and CVD but without CKD; D+K+C, individuals with diabetes, CKD, and CVD.

Expenditures were adjusted to 2021 U.S. dollars.

Glucose-Lowering Drug Expenditures

A similar pattern was observed for per-capita GLD expenditures, with significantly higher GLD expenditures observed among participants with a greater comorbidity burden ($p < 0.001$, Figure 2). Per-capita GLD expenditures rose in all groups from 2012–2013 to 2020–2021, increasing from $1,209.3 to $3,342.6 in D only, from $1,464.7 to $3,930.6 in D+C, from $1,911.3 to $5,613.7 in D+K, and from $2,939.6 to $5,940.0 in D+K+C group (p for trend < 0.001 for all). These changes corresponded to increases of 176.4%, 168.4%, 193.7%, and 102.1%, respectively. The D+K group showed the steepest increase over time, narrowing the difference with D+K+C in 2020-2021.

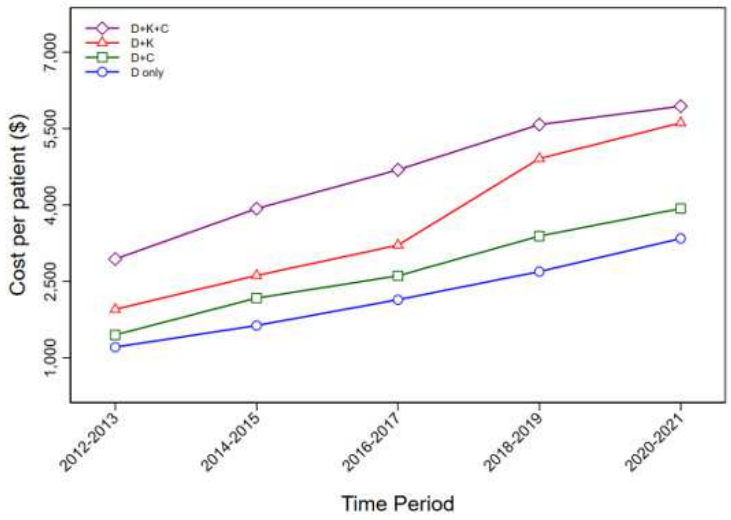


Figure 2. Trends in annual per-capita glucose-lowering drug expenditures among U.S. adults by CKM components, 2012-2021

Note: CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease. D only, individuals with diabetes without CKD or CVD; D+K,

individuals with diabetes and CKD but without CVD; D+C, individuals with diabetes and CVD but without CKD; D+K+C, individuals with diabetes, CKD, and CVD. Expenditures were adjusted to 2021 U.S. dollars.

Utilization and Expenditures of SGLT2i and GLP-1 RAs

Use of SGLT2i and GLP-1 RAs increased markedly across all four CKM groups over the study period (p for trend < 0.001 for all; Table 1). Utilization rose from 3.2% in D only, 0.5% in D+K, 2.8% in D+C, and 3.4% in D+K+C group in 2012–2013 to 21.1%, 28.4%, 20.6%, and 19.3%, respectively, in 2020–2021. However, utilization rates did not differ significantly across groups (p = 0.51 for 2020-2021).

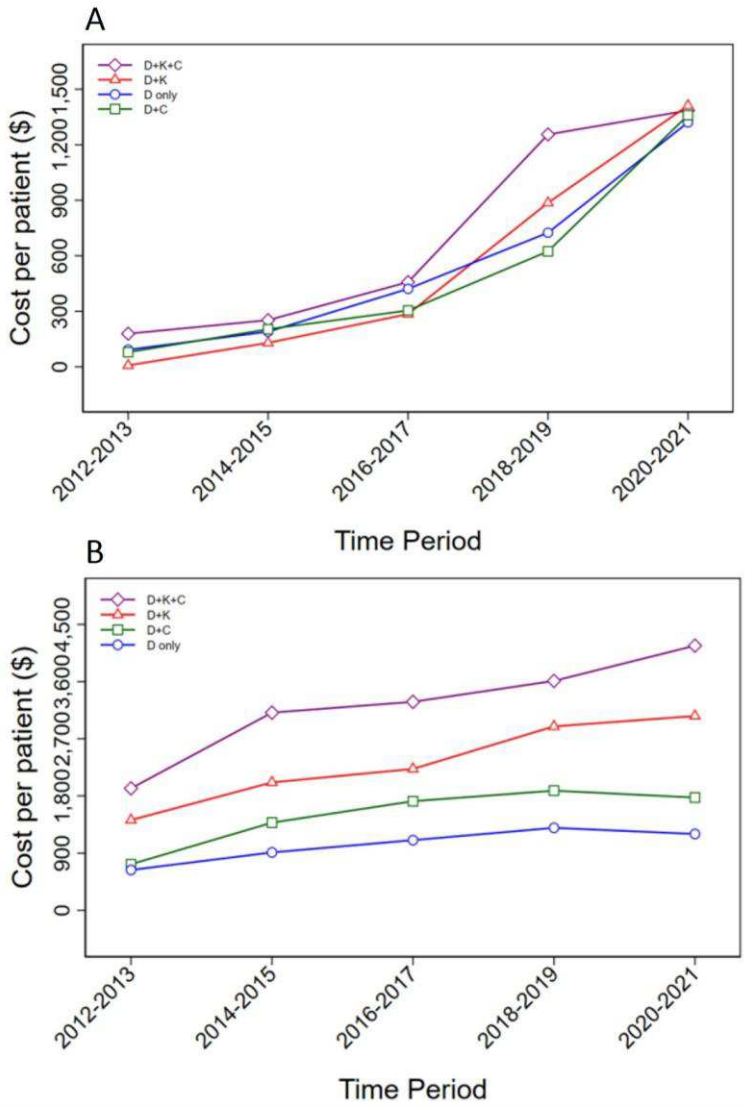
Table 1. Annual SGLT2i/GLP-1 RAs utilization rates (%) among U.S. adults with diabetes by CKM components, 2012-2021

Time period	D only	D+K	D+C	D+K+C
2012-2013	3.2 (2.2-4.1)	0.5 (0.0-1.3)	2.8 (1.4-4.2)	3.4 (0.2-6.5)
2014-2015	6.1 (4.8-7.3)	3.1 (1.0-5.2)	5.6 (3.7-7.4)	9.1 (4.2-14.0)
2016-2017	10.5 (8.6-12.4)	8.5 (4.9-12.1)	7.0 (5.1-9.0)	10.6 (5.3-16.0)
2018-2019	13.7 (12.0-15.4)	14.7 (9.2-20.1)	11.9 (9.4-14.4)	18.2 (11.0-25.4)
2020-2021	21.1 (19.2-23.0)	28.4 (20.6-36.3)	20.6 (17.0-24.2)	19.3 (11.1-27.5)

Note: Data are presented as weighted percentages with 95% confidence intervals (CIs). Estimates account for the complex survey design of the Medical Expenditure Panel Survey (MEPS). CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists. D only, individuals

with diabetes without CKD or CVD; D+K, individuals with diabetes and CKD but without CVD; D+C, individuals with diabetes and CVD but without CKD; D+K+C, individuals with diabetes, CKD, and CVD.

Similar pattern was observed for expenditures on SGLT2i and GLP-1 RA. Per-capita expenditures for SGLT2i and GLP-1 RAs increased substantially in all groups, with the steepest rise occurring after 2016–2017 (Figure 3). From 2012–2013 to 2020–2021, expenditures increased from $92.4 to $1,320.7 in D only, from $7.8 to $1,411.5 in D+K, from $79.0 to $1,359.8 in D+C, and from $179.0 to $1,385.1 in D+K+C group. However, per-capita expenditures in 2020–2021 did not differ significantly across CKM groups ($p = 0.53$). In 2020-2021, proportion of GLD expenditures attributed to SGLT2i and GLP1RA was 39.5% in in D, 34.6% in D+C, 25.1% in D+K, and, 23.3% in D+K+C (Figure 4).



232

233 **Figure 3. Trends in annual per-capita expenditures for SGLT2i/GLP-1 RAs and**

234 **insulin by CKM components, 2012-2021**

235 Note: Panel A: SGLT2i and GLP-1 RAs; Panel B: Insulin. CKM,

236 cardiovascular-kidney-metabolic; SGLT2 inhibitors, sodium-glucose cotransporter-2

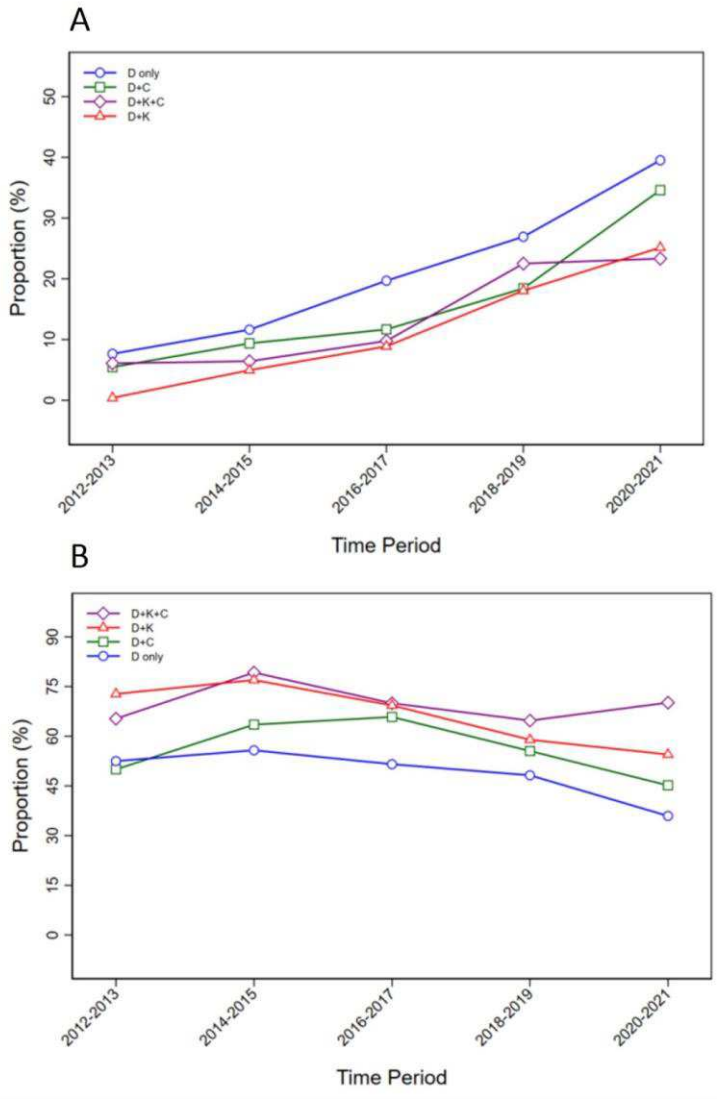
237 inhibitors; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; CKD, chronic

238 kidney disease; CVD, cardiovascular disease. D only, individuals with diabetes

239 without CKD or CVD; D+K, individuals with diabetes and CKD but without CVD;

240 D+C, individuals with diabetes and CVD but without CKD; D+K+C, individuals with

241 diabetes, CKD, and CVD. Expenditures were adjusted to 2021 U.S. dollars.



242

243 **Figure 4. Proportions of total glucose-lowering drug expenditures for**

244 **SGLT2i/GLP-1 RAs and insulin by CKM components, 2012-2021**

245 Note: Panel A: SGLT2i and GLP-1 RAs; Panel B: Insulin. CKM,

246 cardiovascular-kidney-metabolic; SGLT2i, sodium-glucose cotransporter-2 inhibitors;

247 GLP-1 RAs, glucagon-like peptide-1 receptor agonists; CKD, chronic kidney disease;

248 CVD, cardiovascular disease. D only, individuals with diabetes without CKD or CVD;

249 D+K, individuals with diabetes and CKD but without CVD; D+C, individuals with

250 diabetes and CVD but without CKD; D+K+C, individuals with diabetes, CKD, and

CVD.

Expenditures of Insulin

Insulin remained the largest contributor to total GLD expenditures throughout the study period across all four groups (Figure 3). In 2020–2021, per-capita insulin expenditures were $1,201.3 in D only, $1,775.4 in D+K, $3,058.5 in D+C, and $4,166.4 in D+K+C ($p < 0.001$). Over time, insulin expenditures increased significantly in all groups (p for trend < 0.001 for all), rising by 89.2% in D only, 25.0% in D+K, 322.1% in D+C, and 117.1% in D+K+C by 2020–2021.

In 2020-2021, insulin accounted for 35.9% of total GLD expenditures in D only, 54.5% in D+K, 45.2% in D+C, and 70.1% in D+K+C. We did not find substantial change in these proportions of expenditure over time (Figure 4).

Secondary Analysis

Among the 12,010 adults with diabetes, 50.9% had obesity. Overall, findings were consistent with the primary analysis regardless of whether obesity was considered as an additional CKM component. In particular, per-capita prescription drug expenditures were highest in the D+K+C group among both adults with obesity and those without obesity ($13,824.3 and $8,701.6 in 2016, respectively; Fig. S2). Similar patterns were observed for GLD expenditures and for SGLT2i/GLP-1 RA utilization and expenditures across the four groups when further stratified by obesity (Figs. S3-S5).

Discussion

This study provided a real-world assessment of prescription drug and GLD expenditures among U.S. adults with diabetes, stratified by CKM components. Prescription drug expenditures increased substantially over time and were consistently higher among adults with greater CKM complexity, with the expenditures in D+K+C group nearly twice those in the D only group. GLD expenditures were a major driver of this increase. Despite increased use over time, SGLT2i and GLP-1 RAs remained underutilized, especially in the most complex CKM group, highlighting a persistent gap between guideline-supported therapy and real-world practice.

The increasing prescription drug expenditures with greater CKM comorbidity burden highlight the substantial economic consequences of multi-organ dysfunction, consistent with prior evidence documenting the economic burden of CKM syndrome.[1,21,22] We found a substantial increase in GLD as well as insulin expenditures over time, with costs in the D+K+C group more than doubling during the study period, reflecting the substantial prescription drug cost burden carried by patients with greater CKM comorbidity.

Despite guideline recommendations supporting the use of SGLT2i and GLP-1 RAs in patients with diabetes and coexisting CVD or CKD,[14] their real-world utilization remained modest throughout the study period. By 2020–2021, only approximately one in five patients used SGLT2i or GLP-1 RAs across all CKM groups, with no significant difference in utilization across groups. These findings

highlight a potential gap between guideline recommendations and real-world clinical practice. However, it is worth pointing out that evidence and guidance recommendations for these drug therapies evolved substantially during 2012-2021, these results should be interpreted as reflecting both early adoption and evolving implementation of cardiorenal risk-based prescribing.

Several factors may contribute to these prescribing gaps. Cost-related barriers and inadequate insurance coverage are among the most consistently documented drivers to low SGLT2i and GLP-1 RA uptake.[23] These findings may suggest that policy and health system efforts be needed to reduce economic barriers to SGLT2i and GLP-1 RAs, particularly for high-risk patients with concurrent kidney and cardiovascular disease. Clinical inertia among prescribers may represent an additional barrier. Furthermore, the injectable route of administration required for most GLP-1 RAs may reduce patient acceptability in certain clinical contexts.[24] Although SGLT2i are orally administered, concerns regarding volume depletion and orthostatic hypotension may limit their use in older or frail patients with advanced CKD or CVD.[25]

This study has several limitations. First, MEPS relies on self-reported diagnoses, which may introduce recall bias and result in misclassification. Second, we were not able to differentiate between type 1 and type 2 patients. Third, the survey does not capture institutionalized populations, including residents of nursing homes and correctional facilities, which may limit the generalizability of findings to the most

vulnerable and medically complex segments of the population. Fourth, while obesity is recognized as a core component of CKM syndrome, the BMI variable in MEPS was not consistently available across all survey years, precluding its full incorporation into the primary analysis. However, secondary analyses restricted to BMI-available years yielded findings broadly consistent with our primary results. Fifth, the study period captures the early-to-mid adoption phase of SGLT2i and GLP-1 RAs. Utilization patterns in more recent years may have evolved following subsequent guideline updates.

Conclusion

Between 2012 and 2021, prescription drug expenditures among U.S. adults with diabetes increased substantially and were higher among those with CKM comorbidity burden, largely driven by increasing GLD costs. Insulin remained the dominant contributor to GLD spending across all CKM groups, whereas use of SGLT2i and GLP-1 RAs remained underused, particularly among patients with coexisting cardiovascular and kidney disease. These findings highlight the need to better align real-world prescribing patterns with evidence-based CKM management.

Abbreviations

ADA: American Diabetes Association

AHRQ: Agency for Healthcare Research and Quality

BMI: Body mass index

CCC: Clinical Classification Codes

CCSR: Clinical Classification Software Refined

CI: Confidence interval

CKM: Cardiovascular-Kidney-Metabolic

CKD: Chronic kidney disease

CVD: Cardiovascular disease

D only: Diabetes only

D+C: Diabetes with cardiovascular disease

D+K: Diabetes with chronic kidney disease

D+K+C: Diabetes with both chronic kidney disease and cardiovascular disease

FYC: Full-Year Consolidated

GLD: Glucose-lowering drug

GLP-1 RAs: Glucagon-like peptide 1 receptor agonists

ICD-9: International Classification of Diseases, 9th Revision

ICD-10: International Classification of Diseases, 10th Revision

KDIGO: Kidney Disease: Improving Global Outcomes

MEPS: Medical Expenditure Panel Survey

PSU: Primary sampling unit

SGLT2i: Sodium-glucose cotransporter 2 inhibitors

Declarations

Ethics approval and consent

MEPS was approved by the Westat Institutional Review Board, and all participants provided informed consent. This secondary analysis used publicly available, deidentified data.

Consent for Publication

Not applicable.

Data Availability

The MEPS data used in this study are publicly available from the Agency for Healthcare Research and Quality at https://meps.ahrq.gov/mepsweb/.

Competing Interests

The authors declare no competing interests.

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Author Contributions

S. Li and B. Lyu conceived and designed the study. S. Li, L. Chen, W. Wu, T. Cui, J. Liang, M. Xu, Z. Lv, J. Hu, and B. Lyu contributed to study implementation and data acquisition. S. Li and B. Lyu performed the data analysis and interpreted the findings. S. Li and B. Lyu drafted the manuscript. All authors critically reviewed and revised

the manuscript for important intellectual content and approved the final version of the manuscript. S. Li is the guarantor of this work and accepts full responsibility for the integrity of the data and the accuracy of the data analysis.

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