Economic Implications of Weight Change in Patients With Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes, accounting for 90% to 95% of cases affecting more than 20 million adults in the United States.[1] In 2012, diabetes-related expenditures were estimated to be $176 billion[2]; nearly half of which, it is reported, go to treating diabetes-related complications such as cardiovascular disease, hypertension, neuropathy, retinopathy, and nephropathy.[3,4]

One factor that is strongly associated with T2DM risk is excess body weight, with more than 80% of patients with T2DM being either overweight or obese.[5-8] Increased weight may impair glycemic control (via increased insulin resistance); elevate the risk of cardiovascular disease; and negatively affect mental health, body image, and persistence with therapy, which, in turn, may increase the risk for diabetes-related complications.[8-10] Accordingly, weight gain can potentially impact the high expenditures associated with treatment of diabetes-related complications.

Conversely, weight loss in T2DM is associated with benefits such as better glycemic control, reduction in cardiometabolic risk factors, and prevention of disease progression through decreased diabetes complications.[11-15] Although some recent literature has indicated that weight loss from a diet and exercise program (average weight loss of nearly 5% at 4 years) did not reduce cardiovascular events in T2DM patients,[16] a large body of evidence suggests positive benefits.[11-15] As a result, weight management as a part of lifestyle modification has become a key factor in T2DM treatment.[17]

Although there is abundant literature regarding the clinical manifestations of weight change in T2DM, evidence of its contribution to the economic burden of T2DM is relatively sparse. Preliminary evidence shows weight loss can significantly reduce diabetes-related costs.[11,18] Furthermore, Brandle et al[19] reported that a 10 kg/m^{2} increase in body mass index or presence of diabetes-related complications can increase direct costs by 10% to 30%.

ABSTRACT

Objective
Assess the impact of weight change on costs, resource use, and treatment discontinuation among metformin-treated patients with type 2 diabetes mellitus (T2DM).

Study Design
Observational, retrospective cohort.

Methods
Adults with T2DM who were pre existing metformin-treated patients were included. Insulin users were excluded. Administrative data from January 1, 2000, to December 31, 2010, were linked to clinical data, and patients were placed into cohorts based on relative change in body weight. Three cohorts were created: weight loss (decrease >3%), and weight neutral (change ≤3%), weight gain (increase >3%). Inter-cohort differences in resource utilization, costs (2010 US$), and treatment discontinuation were evaluated using statistical models that adjusted for baseline characteristics.

Results
A total of 2110 patients (weight loss = 967; weight neutral = 970; weight gain = 173) were included; mean age was 59.6 years, 52.2% were women, 64.1% were Caucasian, and average baseline weight was 98.7 kg. The weight-loss cohort incurred significantly lower costs per year compared with the weight-neutral cohort, driven mainly by lower medical costs from reduced utilization. Weight reduction was associated with approximately $2200 and approximately $440 lower annual all-cause and T2DM-specific costs (P <.05), respectively. Patients who lost weight were 21% less likely to discontinue therapy. Weight gain was associated with a significant increase in all-cause costs of $3400 per year compared with the weight-neutral cohort; however, differences in T2DM-specific costs and discontinuation rates did not reach significance levels.

Conclusions
Weight loss (>3%) among patients with T2DM was associated with decreased costs and lower rates of treatment discontinuation. Hence weight-focused treatment approaches can help reduce the economic burden for patients with T2DM.

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In addition to being a predisposing condition, weight gain among T2DM patients can also be caused by anti-diabetic drugs; contributing to nonpersistence and potentially to subsequent disease progression. Metformin augmentation or alternate anti-diabetic therapies are becoming common treatment regimens as weight-focused treatment approaches gain importance in T2DM management. Newer anti-diabetic agents have similar effects on glycemic control, but differ in their side-effect profiles; some have been shown to possess weight-altering properties.[20] To properly factor in these weight-altering properties during treatment selection, it is important to have a comprehensive understanding of the impact of weight change on T2DM outcomes. Hence, the goal of this study was to investigate the implications of real-world change in body weight (both weight gain and weight loss) on healthcare costs, resource utilization, and continuation of anti-diabetic pharmacotherapy among metformin-treated patients with T2DM.
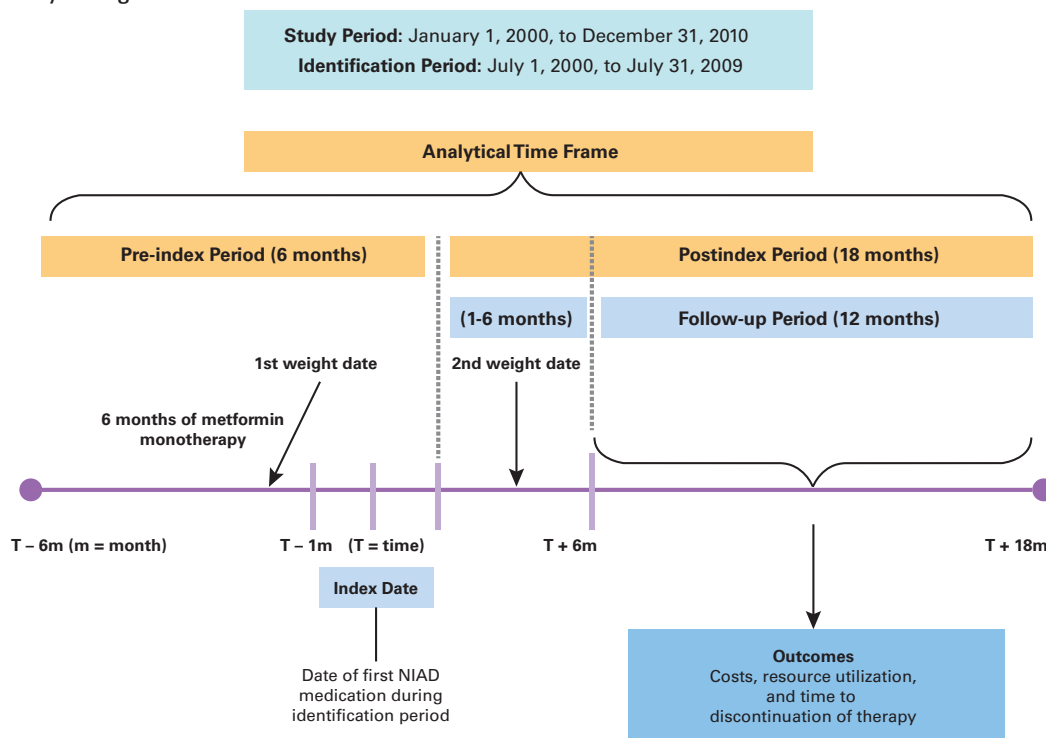
Take-Away Points

Modest weight loss in patients with type 2 diabetes (T2DM) is associated with lower rates of treatment discontinuation and economic benefits, illustrated through reductions in both diabetes-specific and all-cause medical costs due to fewer hospital and emergency department visits. Weight gain is associated with increased all-cause medical costs but has no statistically significant impact on diabetes-specific costs or treatment discontinuation. Results of this study complement the clinical advantages of weight loss in patients with T2DM by highlighting its economic and treatment persistence benefits, and hence can help guide patients and health plans in making decisions regarding optimal disease management.

METHODS

Study Design and Sample Selection

Data from January 1, 2000, through December 31, 2010, were utilized in this retrospective cohort study. The administrative databases of the Henry Ford Health System (HFHS), which comprises medical billing, pharmacy records, external claims for care provided outside of HFHS, and clinical data (such as laboratory values and vital signs) from electronic medical records (EMRs) and progress notes for patients receiving care within the HFHS, were employed in this analysis. The study population was identified from enrollees of a system-owned and -operated health maintenance organization (HMO), the Health Alliance Plan (HAP), who received care at HFHS—a vertically integrated healthcare system providing clinical services to the Michigan community, with over 2.5 million patient visits and 65,000 hospital admissions annually. The HAP enrolls more than 500,000 individuals from more than 3000 employers in the Detroit metropolitan area. Approximately 150,000 of these members receive care through HFHS.

The initial study population comprised patients aged ≥18 years with at least 1 non-insulin anti-diabetic (NIAD) therapy see eAppendix, available at www.ajmc.com) prescription during the patient identification period of July 1, 2000, to July 31, 2009. Index date was defined as the date of the first NIAD prescription claim during the patient identification period, and this medication was considered as the index medication. Patients were required to have a diagnosis of T2DM (*International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM] code 250.x0 or 250.x2) in any field and metformin monotherapy during the 6-month period prior to the index date, continuous health plan eligibility for the 6-month period prior to the index date through the 18-month period after the index date, and at least 2 weight measurements at specific time periods—1 each in the 1- to 6-month periods before and after the index date. The study analytical time frame, therefore, included a 6-month pre-index period to provide a baseline description of the study sample, and an 18-month post index period which included a 6-month period after the index date to measure weight change, followed by a 12-month follow-up period to compute outcomes (Figure 1). The pre-index period was also used to ensure that patients were users of metformin monotherapy (at least 2 prescription fills of metformin or 1 prescription fill of metformin with a supply of 60 or more days), but naïve to all other NIAD therapy. In addition, patients were also required to have at least 2 glycated hemoglobin (A1C) measurements, 1 in each of the 6-month periods before and after the index date. Finally, all patients with a prescription claim of insulin, diagnosis for type 1 diabetes mellitus or gestational diabetes, or evidence of pregnancy or bariatric surgery (see eAppendix for diagnostic codes) during the time frame for analysis were excluded. Insulin users were excluded, because dosing of insulin varies considerably among patients with T2DM, which in turn could render outcome estimates unreliable.

Patients meeting all the study criteria were initially categorized based on relative change in body weight (ie, percentage change from baseline). Using a 3% cut-off (chosen based on a prior study[11]), the following groups were identified: weight loss (decrease in body weight by >3%), weight gain (increase in body weight by >3%), and weight neutral

■ **Figure 1.** Study Design

Study Period: January 1, 2000, to December 31, 2010
Identification Period: July 1, 2000, to July 31, 2009

Analytical Time Frame

Pre-index Period (6 months)

Postindex Period (18 months)

(1-6 months)

Follow-up Period (12 months)

1st weight date

2nd weight date

6 months of metformin monotherapy

T – 6m (m = month)   T – 1m   (T = time)   T + 6m   T + 18m

Index Date

Date of first NIAD medication during identification period

Outcomes
Costs, resource utilization, and time to discontinuation of therapy

(increase or decrease in body weight by ≤3%). The study cohorts were then obtained from these groups based on availability of A1C measurements at the specified time periods.
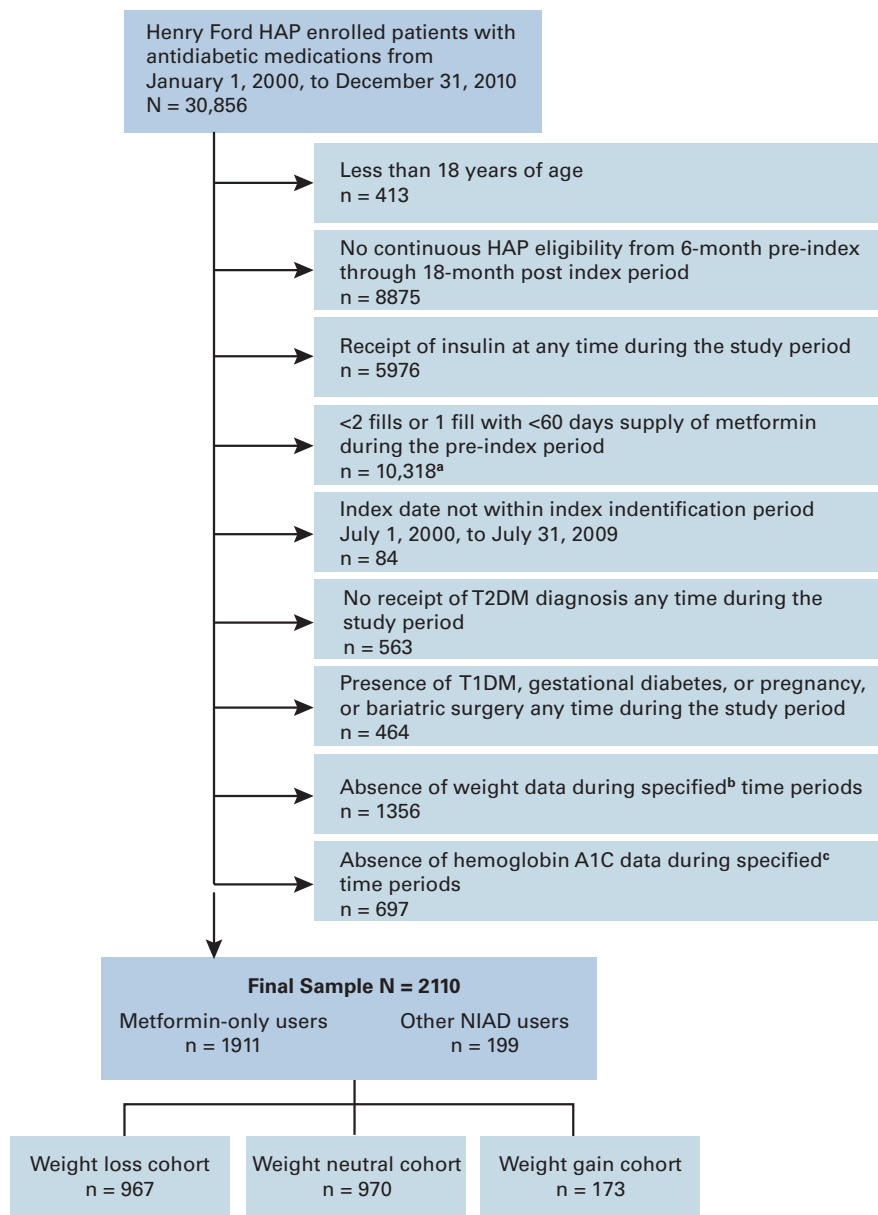
Study Outcomes

The main outcomes of interest were annual all-cause and T2DM-specific costs and resource utilization computed during the follow-up period, and discontinuation rate of index NIAD therapy, which was captured during the 18-month period after the index date. Resource utilizations were calculated as the total number of unique visits and classified according to the place of service (hospitalizations, emergency department [ED] visits, outpatient visits, and other visits). A visit was defined as a unique date of service for all visits except hospitalizations, and as a unique admission and discharge date for a hospitalization. The costs represented the estimated costs to treat the patient based on charges billed for pharmacy and medical services. All-cause pharmacy and medical costs were calculated by summing the charges for all prescriptions and for all medical resource utilization with any diagnosis, respectively. T2DM-specific pharmacy costs were calculated by summing the charges for all NIAD prescriptions. T2DM-specific medical costs and resource utilization were captured by identifying medical records with a primary or secondary diagnosis code of

T2DM and hospitalization records with a primary discharge diagnosis of T2DM. Costs were adjusted to 2010 US dollars using the medical component of the Consumer Price Index.

Patients were considered to have discontinued therapy when more than 30 days had elapsed without drugs that belonged to the index NIAD medication class, or they had switched to another anti-diabetic medication class. Time to discontinuation was calculated from the index date to the ending date of the last prescription prior to discontinuing index NIAD medication, or the end of the follow-up period.

Statistical Analyses

The weight-neutral cohort was considered to be the reference cohort for all statistical comparisons. Baseline differences between the weight-neutral and other study cohorts were evaluated using t tests or χ^2 tests for continuous or categorical data, respectively. Multivariate statistical analyses were employed to assess differences in annual costs, annual resource utilization, and treatment discontinuation rates among study cohorts, while controlling for baseline characteristics (age, gender, race, index month, pre-index weight, pre-index unique medications, pre-index prescriptions, pre-index A1C levels, Charlson Comorbidity Index [CCI] score[21,22], number of unique diagnoses, and presence of coronary artery disease, congestive heart

■ **Figure 2**. Sample Selection

Henry Ford HAP enrolled patients with antidiabetic medications from January 1, 2000, to December 31, 2010
N = 30,856

Less than 18 years of age
n = 413

No continuous HAP eligibility from 6-month pre-index through 18-month post index period
n = 8875

Receipt of insulin at any time during the study period
n = 5976

<2 fills or 1 fill with <60 days supply of metformin during the pre-index period
n = 10,318[a]

Index date not within index indentification period July 1, 2000, to July 31, 2009
n = 84

No receipt of T2DM diagnosis any time during the study period
n = 563

Presence of T1DM, gestational diabetes, or pregnancy, or bariatric surgery any time during the study period
n = 464

Absence of weight data during specified[b] time periods
n = 1356

Absence of hemoglobin A1C data during specified[c] time periods
n = 697

Final Sample N = 2110

Metformin-only users
n = 1911

Other NIAD users
n = 199

Weight loss cohort
n = 967

Weight neutral cohort
n = 970

Weight gain cohort
n = 173

A1C indicates glycated hemoglobin; HAP, Health Alliance Plan; NIAD, non-insulin antidiabetic; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
[a]Of these, 8,769 did not receive metformin in the pre-index period.
[b]Weight 1 during a 1- to 6-month time window prior to the index date; and Weight 2 during a 1- to 6-month time window after the index date.
[c]HbA1c value 1 during a 6-month period prior to the index date; and HbA1c value 2 during a 6-month period after the index date.
Note: All exclusion criteria are mutually exclusive.

failure, hypertension, dyslipidemia, and depression) that were chosen based on clinical and statistical rationales. Specifically, generalized linear models with a log-link function or semi-log ordinary least-squares regressions (based on variable distributions) were used to assess differences in costs. Negative binomial regression models were used to assess differences in resource utilization. Furthermore, differences in time to treatment discontinuation were evaluated using a Cox-proportional hazards model. Finally, to test whether a reduction in A1C levels modified the association between weight change and costs (all-cause and T2DM-specific), an interaction term was constructed. This interaction term was a binary outcome variable that indicated reduction in A1C by ≥0.5%. This interaction term was added to the multivariate regression models for costs to assess the change in costs by A1C reduction status.

All results are presented after adjusting for baseline characteristics using statistical models in SAS version

■ **Table.** Baseline Characteristics

Characteristics	Weight Loss N = 967		Weight Gain N = 173		Weight Neutral N = 970	
Pre-index characteristics						
Age, years (mean, SD)	59.7	11.9	**56.7**[a]	12.6	60.0	11.8
Women (n, %)	**540**[b]	55.8%	**69**[a]	39.9%	492	50.7%
Race (n, %)						
Caucasian	627	64.8%	107	61.9%	619	63.8%
Black	287	29.7%	57	33.0%	289	29.8%
Other[c]	53	5.5%	9	5.2%	62	6.4%
A1C (mean, SD)	**8.0**[a]	1.8	**8.2**[b]	2.5	7.7	1.6
Pre-index weight, kg (mean, SD)	**100.7**[a]	23.0	96.2	22.9	97.0	20.7
Comorbidity in pre-index period						
Number of unique medications (mean, SD)	6.7	4.0	6.9	4.4	6.6	4.0
Number of Rxs (mean, SD)	8.8	6.2	9.3	6.6	8.9	6.3
Number of unique Dxs (mean, SD)	7.4	4.4	7.6	5.2	7.2	4.3
CCI score (mean, SD)	1.3	0.9	1.4	1.0	1.3	0.9
Other comorbidities (n,%)						
Depression	3	0.3%	**2**[b]	1.2%	1	0.1%
Hypertension	**23**[b]	2.4%	3	1.7%	10	1.0%
Coronary heart disease	11	1.1%	1	0.6%	19	2.0%
Congestive heart failure	10	1.0%	1	0.6%	4	0.4%
Dyslipidemia	2	0.2%	1	0.6%	2	0.2%
Pre-index all-cause medical costs (mean, SD)	$7242	14,136.8	$8178	11,944.6	$7250	14,853.0
Pre-index all-cause pharmacy costs (mean, SD)	$1372	1482.3	$1563	1565.3	$1416	1330.1
Pre-index T2DM-specific medical costs (mean, SD)	$932	2571.7	$1396	5244.3	$1181	4441.3
Pre-index T2DM-specific pharmacy costs (mean, SD)	**$60**[a]	45.3	$84	82.9	$75	60.8

A1C indicates glycated hemoglobin; CCI, Charlson Comorbidity Index; Dx, diagnosis; Rx, prescription; T2DM, type 2 diabetes mellitus.
Bold values indicate significance vs weight-neutral cohort (T-test for continuous variable and χ^2 for categorical variables).
[a]$P < .01$.
[b]$P < .05$.
[c]Other: Asian, Hispanic, Middle Eastern, Unknown.

9.1.3 (SAS Institute, Cary, North Carolina), testing a 2-sided hypothesis at a significance level of .05. All analyses were conducted from a third-party payer and overall society perspective. The study was approved by the HFHS Institutional Review Board.

RESULTS

A total of 30,856 patients receiving anti-diabetic therapy were identified initially in the HFHS database. Of these, 6.8% (2110) met all the study criteria and constituted the study population (**Figure 2**). A vast majority (90.6%) of the study population received only metformin monotherapy during the study period. Patients were excluded mainly due to the following mutually exclusive criteria: nonreceipt of metformin in the pre-index period (33.4%),

lack of continuous enrollment (28.8%), or receipt of insulin during the study period (19.4%). Of the 2110 patients in the study population, 967 (45.8%) were categorized as the weight-loss cohort, 970 (46.0%) were categorized as the weight-neutral cohort, and 173 (8.2%) were categorized as the weight-gain cohort.

Baseline Characteristics

Overall, the demographic characteristics were similar across the study sample with respect to age, gender, and race (**Table**). The weight-loss cohort had higher A1C values (8.0% vs 7.7%; $P = .005$) and weighed more than the weight-neutral cohort in the pre-index period (101 kg [SD: 23 kg] vs 97 kg [SD: 21 kg]; $P < .001$). The comorbidity burden was generally low and similar across all study cohorts; however, compared with the weight-neutral

■ **Figure 3.** Adjusted Mean Annual Costs (2010 US$)

*P <.05 vs weight neutral
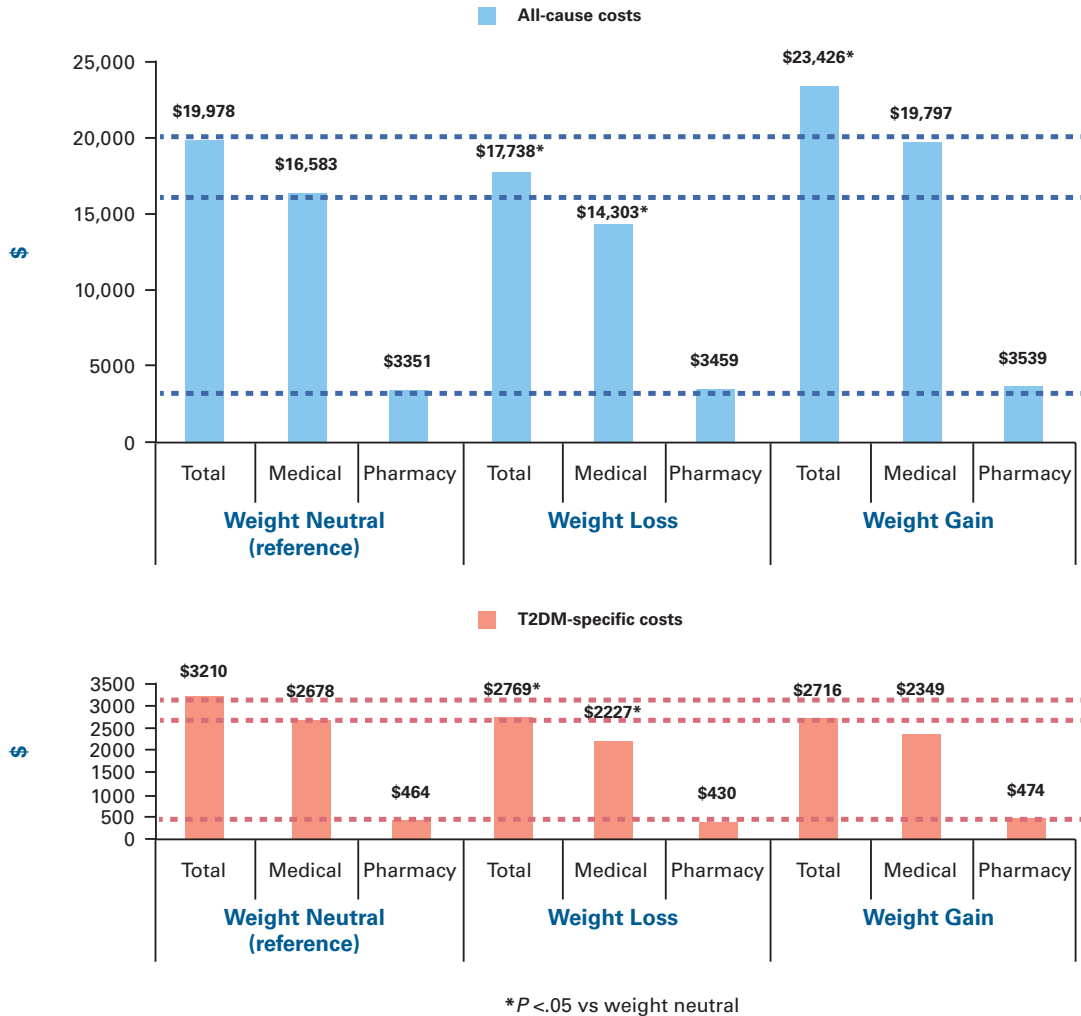
Dotted lines indicate estimate of the weight neutral cohort as that is the reference and for comparison purposes to the estimates of the other 2 cohorts.

cohort, the weight-loss cohort had a higher proportion of patients with comorbid hypertension, and the weight-gain cohort had a higher proportion of patients with comorbid depression. Furthermore, all cohorts were similar with respect to their pre-index all-cause medical and pharmacy costs, with the exception of T2DM-specific pharmacy costs, for which the weight-loss cohort had significantly lower costs compared with the weight-neutral cohort.

Impact of Weight Change on Outcomes

Overall, the weight-loss cohort incurred significantly lower all-cause costs (medical + pharmacy) per year compared with the weight-neutral cohort (**Figure 3**). On average, weight reduction was associated with approximately $2200 lower all-cause costs per year ($17,738 vs $19,978;

P = .007) after controlling for differences in baseline characteristics. The difference was driven mainly by lower medical costs due to fewer annual hospital visits (0.13 vs 0.18; P = .001) and ED visits (0.31 vs 0.37; P = .005), on average. Similar trends were observed for the T2DM-specific costs, where weight reduction was associated with approximately $440 lower T2DM-specific costs per year, driven mainly by lower medical costs due to fewer hospital visits (0.06 vs 0.08; P <.001) and outpatient visits (2.43 vs 2.73; P <.001).

Subgroup analysis of the patients stratified by A1C reduction showed that the weight-loss cohort incurred lower all-cause costs regardless of A1C reduction status (A1C reduction = Yes; Weight-loss = $15,527 vs Weight-neutral = $18,499) (A1C reduction = No; Weight-loss = $20,741 vs Weight-neutral = $21,136). These results show

■ **Figure 4.** Time-to-Event (anti-diabetic treatment discontinuation) Analysis

Time to Discontinuation (in days)
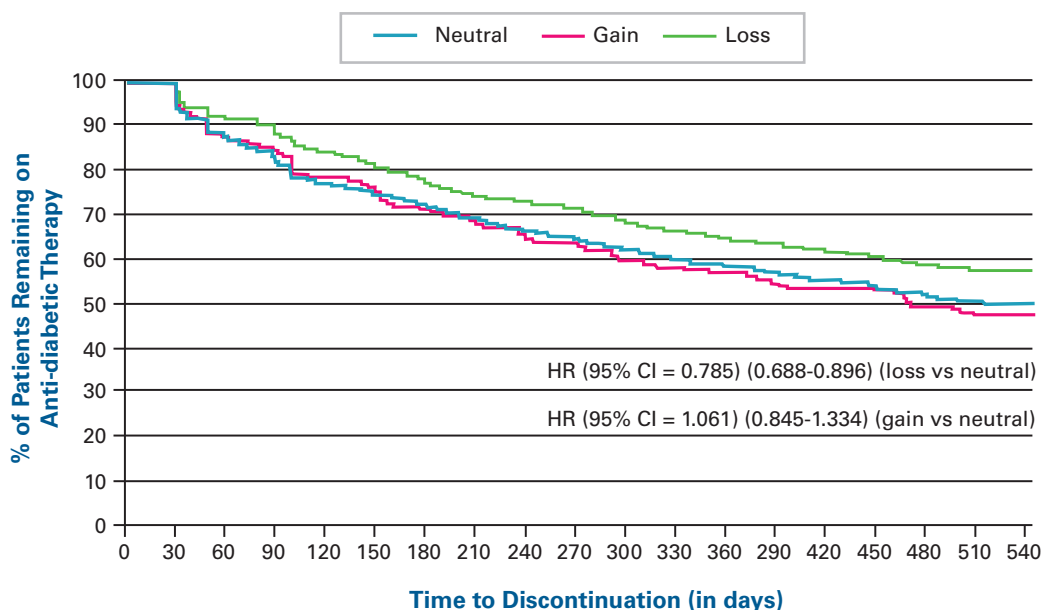
that there was no effect modification due to A1C reduction in the association of weight loss and costs (P >.05 for interaction). After controlling for baseline characteristics, patients in the weight-loss cohort had lower rates of discontinuation (50% vs 57%, P <.001) and were 21% less likely to discontinue therapy compared with the weight-neutral cohort (Figure 4). The mean time to discontinuation of index medication for the study sample was 190 days (SD: 141 days).

In contrast, the weight-gain cohort incurred significantly higher total all-cause costs of approximately $3400 per year compared with the weight-neutral cohort ($23,426 vs $19,978; P = .047; Figure 3). This increase in total all-cause costs was driven mainly by higher all-cause medical costs due to higher annual outpatient visits (12.08 vs 11.11; P = .101); however, the differences did not reach significance levels. Differences in T2DM-specific costs between the weight-gain and weight-neutral cohort did not reach significance levels. Patients in the weight-gain cohort had similar rates of discontinuation (47% vs 50%, P = .609) and were equally likely to discontinue therapy, compared with the weight-neutral cohort. Furthermore, in general, weight change did not affect pharmacy costs (Figure 3).

DISCUSSION

The present study was designed to assess the implications of body-weight change on healthcare costs, resource use, and treatment discontinuation among metformin-treated T2DM patients. Overall, the results suggest that modest weight loss (>3%) is associated with lower all-cause costs, decreased resource utilization, and lower rates of treatment discontinuation compared with no weight change (≤3%). In contrast, modest weight gain (>3%) was associated with increased all-cause costs compared with no weight change (≤3%).

National and international guidelines recommend weight loss for all overweight and obese T2DM patients primarily by diet modification (low-carbohydrate, low-fat calorie-restricted or Mediterranean diets), exercise for maintenance of weight loss, and supplementation with pharmacotherapy for weight loss as an adjunct to lifestyle changes.[17] These recommendations are based on evidence of the clinical benefits of weight loss from several studies.[15,23,24]

Results of the present study complement the clinical benefits of weight loss by highlighting the economic benefits and improved treatment persistence associated with modest weight loss. The association of weight loss with reduced costs observed in this study may have occurred because weight loss reduced the morbidity associated with T2DM and obesity, which, in turn, may have resulted in decreased resource utilization and costs. These findings corroborate data from previous studies that indicate that treatment of diabetes-related complications were the largest cost drivers.[4,25] In addition, these findings were also consistent with a previous study,[11] which reported that weight loss was associated with lower total healthcare and

diabetes-related costs, and that the lower costs were driven mainly by diabetes-related resource utilization. Contrary to the findings of Davis et al,[18] which suggest that moderate weight loss is associated with lower diabetes medication costs, our study did not find an impact on pharmacy costs—both all-cause and T2DM-specific. These divergent results were likely due to differences in patient selection and duration of weight change assessment. Our study specifically analyzed a pre existing metformin user cohort and evaluated weight change over a 6-month time period, whereas the findings of Davis et al included T2DM patients who completed 5 annual health assessments, with a mean follow-up time of 4.3 years.

Several studies have documented the negative clinical manifestations of weight gain in patients with T2DM[9,10] however, contrary to expectations, the results of our study did not sufficiently illustrate these consequences in economic terms. Our findings regarding the negative association of weight gain and all-cause costs did not translate to similar consequences with respect to T2DM-specific costs. This observation may likely be due to the fact that weight gain could have precipitated other common comorbidities such as hypertension, and cardiovascular disorders, which may necessitate resource utilization. Hence, from a coding perspective, T2DM may not have been coded as the primary or secondary diagnosis responsible for the resource utilization, and likely resulted in lower cost estimates (of approximately $2700 to $3200 per year attributable to diabetes) compared to estimates (of $7900 per year) from another report [2] which used an attributable approach to measure the diabetes-related costs. Results demonstrating the lack of association of weight gain with T2DM-specific costs were also in line with the findings of Yu et al,[11] which demonstrated the insignificant impact of weight gain on T2DM-specific costs.

Another important finding of this study was that patients who experienced modest weight loss were 21% less likely to discontinue therapy. Patients who lost weight may have been more motivated and could have had better mental health, leading to successful disease management.[26-28] In addition, this finding is also in agreement with prior research that showed that patients who were receiving a weight-reducing anti-diabetic therapy were less likely to discontinue treatment.[29] In contrast, the results of our study did not find significant differences in treatment discontinuation rates between the weight-gain and weight-neutral cohorts; that may be due to the lack of weight loss in both these cohorts by definition. Non-persistence with antihyperglycemic treatment has severe negative consequences for patients with T2DM, as it re-

duces glycemic control, elevates the risk of T2DM-related complications, and, in turn, adds to the humanistic and economic burden of T2DM.[30] One of the leading causes of nonpersistence with anti-diabetic therapies among patients with T2DM is treatment side effects, such as weight gain.[31] The majority of the anti-diabetic drugs are associated with weight-gain or weight-neutral effects[26]; however, a few newer drugs currently being developed possess weight-reducing properties.[20] Recent reviews[32,33] that studied the effects on weight of adding antihyperglycemic agents to metformin reported that insulin, sulfonylureas, and thiazolidinediones were associated with weight gain, whereas glucagon-like peptide-1 receptor agonists had a weight-loss effect. Consequently, drugs with weight-reduction properties may reduce treatment nonpersistence, thereby qualifying as effective subsequent-line therapy alternatives that optimize T2DM management.

Our analysis has potential limitations. Approximately 91% of the study population remained on metformin-only therapy, and this prevented the assessment of anti-diabetic therapy effects on weight change. Furthermore, only 8% of the study population gained weight (>3%) during the assessment period (approximately 6 months). The imbalance in sample size of cohorts may have occurred due to the high prevalence of metformin usage, a drug with weight-reducing effects,[20,34] and the undersampling of patients receiving weight-altering therapies (such as thiazolidinediones, amylin analogues, sulfonylureas, and insulin). Subsequently, the period used to assess weight change was selected based on data availability and not empirical evidence. In addition, due to the chronic nature and complications associated with T2DM, we included both primary and secondary diagnostic criteria for identification of T2DM-specific outcomes. This approach could potentially misclassify some of the resource use and costs as T2DM-specific.

Other limitations are due to the limitations of the database. Specifically, the database lacked information on key variables such as diet and exercise that can influence the impact of weight change on outcomes, and lead to residual confounding. Actual costs paid were not available, and therefore charges were used to estimate costs. While this does not affect the validity of the associations found, it may likely overestimate the costs per year as noted by recent estimates of costs of diabetes in the United States (approximately $13,700 per year[2] vs $17,000 to $23,000 per year in our study). In addition, EMR data can vary considerably across practice sites due to coding and data capture variations. Our study was therefore limited by the available weight and A1C data, which eventually affected our final sample size.

Finally, this study sample was derived from an HMO in Detroit; hence, results may not be generalizable to other settings. The generalizability is further limited to T2DM patients on NIAD therapy, and not using insulin. Even among this subgroup of NIAD patients, the majority were excluded because the objective was to assess existing metformin-treated patients, thereby leading to some selection bias.

Despite its limitations, this study supplements the extant clinical benefits of weight loss in patients with T2DM. The study findings are important from a patient perspective as well as a managed care perspective. Understanding the implications of body weight control may help motivate patients to actively participate in disease management, and knowledge about manifestations of comorbid complications like excessive weight in T2DM will help managed care organizations design targeted disease-management programs. As patients and health plans constantly combat increasing healthcare costs in T2DM, the emphasis on weight reduction should remain a priority for successful disease management of T2DM patients, through lifestyle modification (diet, physical activity, medical nutrition therapy) and appropriate anti-diabetic pharmacotherapy that optimizes the benefit of glycemic control while balancing the risk of weight gain specifically for overweight T2DM patients.[35] Furthermore, our findings also offer areas for future research. Because of data availability, weight-change criteria and weight-measurement periods applied in the study were data driven. Future research should apply empirically driven weight criteria to accurately capture the impact of weight change. In addition, a prospective longitudinal study assessing the impact of weight-altering anti-diabetic agents on T2DM outcomes is also recommended.

In conclusion, we found that an average weight loss of 3% or more among metformin-treated patients with T2DM is associated with decreased resource utilization, reduced all-cause medical costs, and lower rates of treatment discontinuation. These benefits highlight the importance of weight loss through lifestyle changes like diet modification and regular exercise. The addition of a weight-reducing drug may also be considered as a supplemental strategy for achieving positive outcomes among overweight T2DM patients uncontrolled on metformin alone.

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Authorship Information: Concept and design (KB, SP, MS, AR, JG, LL, AD); acquisition of data (KB, AR, LL, AD); analysis and interpretation of data (KB, SP, MS, AR, JG, AD); drafting of the manuscript (KB, SP, MS, AR, AD); critical revision of the manuscript for important intellectual content (KB, SP, AR, JG, LL, AD; statistical analysis (AR, AD); provision of study materials or patients (KB); obtaining funding (KB); administrative, technical, or logistic support (LL); and supervision (JG, LL, AD).

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eAPPENDIX

Table E1: Non-insulin Anti-diabetic Therapies

Drug Class	Drug Name
Sulfonylureas	Glipizide, glimepiride, glyburide
Meglitinides	Repaglinide, nateglinide
Biguanides	Metformin
DPP-4 inhibitors	Sitagliptin, saxagliptin
Thiazolidinediones	Rosiglitazone, pioglitazone
Alpha-glucosidase inhibitors	Acarbose, miglitol
GLP-1 analogues	Exenatide, liraglutide
Amylin analogues	Pramlintide
Combination drug products	Metaglip (glipizide/metformin)
	Glucovance (glyburide/metformin)
	Avandamet (rosiglitazone/metformin)
	Actoplus met (pioglitazone/metformin)
	Avandaryl (rosiglitazone/glimepiride)
	Duetact (pioglitazone/glimepiride)
	Janumet (sitagliptin/metformin)

Table E2: Exclusionary Disease Conditions

Condition	Codes
Type 1 diabetes mellitus	ICD-9-CM codes: 250.x1, 250.x3
Gestational diabetes	ICD-9-CM codes: 648.8x
Pregnancy	ICD-9-CM codes: 650.xx-659xx, V22.2
Bariatric surgery	Current Procedural Terminology codes: 43644, 43645, 43842, 43843, 43845, 43846, 43847, S2082, S2083, S2085