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Associations of weight loss with obesity-related comorbidities in a large integrated health system

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Abstract

Aims: To determine the health outcomes associated with weight loss in individuals with obesity, and to better understand the relationship between disease burden (disease burden; ie, prior comorbidities, healthcare utilization) and weight loss in individuals with obesity by analysing electronic health records (EHRs).

Materials and Methods: We conducted a case-control study using deidentified EHR-derived information from 204 921 patients seen at the Cleveland Clinic between 2000 and 2018. Patients were aged ≥20 years with body mass index ≥30 kg/m^2 and had ≥7 weight measurements, over ≥3 years. Thirty outcomes were investigated, including chronic and acute diseases, as well as psychological and metabolic disorders. Weight change was investigated 3, 5 and 10 years prior to an event.

Results: Weight loss was associated with reduced incidence of many outcomes (eg, type 2 diabetes, nonalcoholic steatohepatitis/nonalcoholic fatty liver disease, obstructive sleep apnoea, hypertension; $P < 0.05$). Weight loss >10% was associated with increased incidence of certain outcomes including stroke and substance abuse. However, many outcomes that increased with weight loss were attenuated by disease burden adjustments.

Conclusions: This study provides the most comprehensive real-world evaluation of the health impacts of weight change to date. After comorbidity burden and healthcare utilization adjustments, weight loss was associated with an overall reduction in risk of many adverse outcomes.

KEYWORDS
comorbidity burden, electronic health records, obesity, weight loss

1 | INTRODUCTION

Obesity represents a health epidemic with increasing incidence worldwide. Currently more than one billion individuals worldwide are classified as having obesity.[1,2] Global healthcare costs and public health burden were expected to be drastically affected as a result of these rising trends,[1] exceeding nearly $2 trillion worldwide in 2016.[2]

A wide range of adverse cardiovascular,[3,4] metabolic,[5,6] musculoskeletal,[7] psychological[8,9] and other conditions have been linked to weight gain and obesity. However, surprisingly little is known about the impact of weight loss on the development of weight-related comorbidities. While weight loss is generally associated with decreased risk for many outcomes,[10-12] recent studies investigating weight loss have highlighted the need to differentiate between intentional and unintentional weight loss.[13-15] Positive lifestyle modification and underlying illness may both manifest in weight loss, but may present different risk profiles for various comorbidities. In particular, a recent study by Chen *et al*[13] found significantly increased mortality for older individuals who transitioned from obesity to normal weight, which may be due to unintentional weight loss from existing illness, but this could not be discerned from their data. Incorporating detailed clinical history may be helpful to distinguish the impacts of preexisting illness and other factors on weight loss, with their associated benefits and risks. In addition, for many studies, the lack of longitudinal weight change information with corresponding clinical data limits the ability to understand the complex interactions between obesity, weight loss, and prior comorbidities.

Electronic health records (EHRs) provide rich clinical and demographic data on large numbers of individuals spanning many years. In the present study, we extend previous research into weight change and obesity in the following key ways: (a) to our knowledge, our cohort of 204 921 individuals with obesity, represents one of the largest studies to date investigating the role of weight loss in comorbid disease onset for patients with obesity; (b) many studies rely on a single recalled weight measurement to obtain weight change, whereas the present dataset includes multiple weight measurements from patients, spanning several years; and (c) our dataset includes detailed clinical information, such as medications prescribed, inpatient hospitalizations, medical procedures and disease diagnoses. Although the purpose of this study was to investigate the relationship between weight loss and comorbidities in patients with obesity, we also present associations with weight gain to better put the weight loss results into context. We then utilized this resource to investigate whether real-world weight change in patients with obesity is associated with modified risk of 30 diverse clinical outcomes.

2 | MATERIALS AND METHODS

2.1 | Design, setting and participants

The study consisted of a patient cohort seen at Cleveland Clinic between January 1, 2000 and December 31, 2018. Patients were aged ≥20 years, had ≥7 body weight measurements, with the first and last being ≥3 years apart (to assess weight variability), and ≥1 body mass index (BMI) measurement >30 kg/m^2, which is the clinical threshold for obesity. Unlike weight measurements, height is not routinely assessed during patient visits. For this reason, only patients aged ≥20 years were included, after which growth has stabilized, and the median across all heights was used to calculate BMI. The study was reviewed by the Cleveland Clinic Institutional Review Board and was approved as exempt research (IRB# 19-1087). Patients with a documented case of amputation, thyroid disorder, bariatric surgery, human immunodeficiency virus, cancer, organ transplant, chemotherapy or radiation therapy at any point were excluded to prevent confounding of weight measurements. Women who were pregnant during the time period being investigated were also excluded. Additional criteria ensuring that body weight measurements were available within 6 months of an outcome and within the relevant timeframe (described below) resulted in the inclusion of 204 921 patients. Cohort characteristics are provided in Table 1. Thirty disease outcomes were considered (Figure 1) and, to ensure each outcome was a new diagnosis, only outcomes with an associated encounter diagnosis or billing code were considered and individuals with a history of the outcome of interest were excluded from that particular analysis (Appendix Figure S1). International Classification of Diseases (ICD)-9 and ICD-10 codes were used to define each outcome (Appendix Table S1).

Weight change was associated with each of the 30 disease outcomes using a case-control design to determine if disease onset was more or less likely to be preceded by weight change in cases compared to patients that had not developed a disease outcome (Figure 1, Appendix Table S2). Outcomes were selected from previous reports that identified these as strongly associated with obesity and high healthcare costs.[16,17] For each clinical outcome (Figure 1, Appendix - Table S2), patients were divided into two groups: (a) patients with a recorded diagnosis (cases) and (b) patients with no record of the

TABLE 1 Cohort characteristics

Cohort characteristics	
Number of subjects	204 921
Median (IQR) age, years	56.01 (43.59,55.83)
Gender	
Female, n (%)	113 701 (55.49)
Male, n (%)	91 215 (44.51)
Race	
White, n (%)	149 277 (72.85)
Black, n (%)	45 012 (21.97)
Other, n (%)	10 632 (5.19)
Median (IQR) number of unique weight measurements	22.00 (13.00-38.00)
Median (IQR) years between first and last weight measurements	8.40 (5.49-11.60)
Median (IQR) months between consecutive weight measurements	4.35 (2.75-6.85)

Abbreviation: IQR, interquartile range.

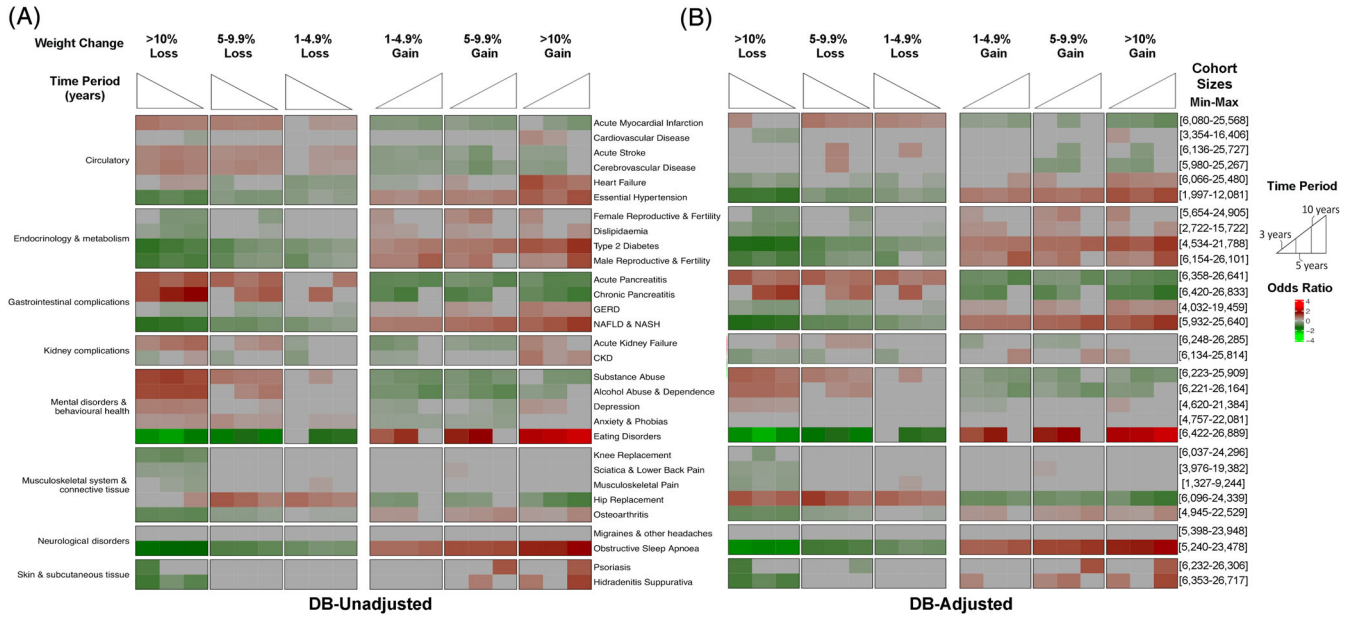

FIGURE 1 Weight change associated with 30 clinical outcomes with and without disease burden (DB) adjustment. Heatmaps representing the $\log_2$-transformed odds ratios from (A) DB-adjusted and (B) DB-unadjusted model. Columns are ordered by time interval (3, 5, 10 years). Red represents a significant increase in risk, green a significant decrease in risk (false discovery rate [FDR] $P < 0.05$), and grey a non-significant association (FDR $P > 0.05$)

diagnosis at any time (controls). For patients in the case group, 3-, 5- and 10-year weight change was calculated as the BMI at the time of the first event (or within the preceding 6 months if missing) minus the BMI at 3, 5 and 10 years prior (±6 months). For patients in the control group, weight change was calculated as the last recorded BMI minus the BMI at 3, 5 and 10 years prior (±6 months). Only cases and controls with weight measurements meeting these criteria were included. Weight changes were categorized as gain or loss based on the following commonly utilized clinical targets: 1% to 4.9%, 5% to 9.9% or ≥10% (Appendix Figure S1). The cohorts are described in Appendix Figures S2 to S4.

Weight variability was determined using the coefficient of variation (CV), a normalized measure of dispersion, over all available weight measurements for individuals in the cohort. Similar to the associations with weight change described above, the CV was tested for association with comorbidities stratified by the extent of weight change and duration. Additional details regarding the calculation and use of the CV can be found in the Supplemental Methods.

2.2 | Statistical methods

Statistical analyses were performed using the statistical software, R v.3.6.[18] Associations between weight change or weight variability (CV) and each outcome were performed using logistic regression. To determine if disease burden (DB) impacts weight change and health outcomes, models were created with and without adjustment for medical histories, healthcare utilization and medication usage, and are referred to as DB-adjusted and DB-unadjusted models, respectively. The DB-unadjusted models incorporated age, sex, race and starting BMI as covariates. DB-adjusted models included the variables in the DB-unadjusted models, and prior comorbidities, gravida, alcohol use, nicotine use, substance abuse, weighted Charlson Comorbidity Index,[19] mean number of emergency room visits per year, mean number of inpatient visits per year, total number of unique ICD codes per patient and medication use. Additional information regarding covariate selection is provided in the Supplementary Material. All reported P values were corrected for multiple testing using a false-discovery rate approach[20] based on the number of comparisons across all outcomes, weight change categories, and time periods investigated, and adjusted P values < 0.05 were considered statistically significant. Methods for associating weight variability with outcomes are described in the Supplementary Material.

Differences in weight loss associations between men and women, White and non-White patients, All other races were combined in the non-White group due to sample sizing being too small for a sufficient stratified analysis, patients with BMI between 30-40 kg/m^2 and those with BMI ≥40 kg/m^2 were also compared using propensity score matching using the "Matching" R package, based on all available covariates, with sample sizes matched to the smallest group.[21]

To investigate nonlinear associations between age, weight change and disease outcomes, generalized additive models were created incorporating DB-adjusted model variables using the R package *mgcv* v.1.8.[22,23] These models allow nonlinear associations with outcomes to vary across age and extent of weight change.

3 | RESULTS

Reduced incidence of several outcomes was associated with weight loss across all three weight loss categories (ie, 1%-4.9%, 5%-

9.9%,≥10%) and for each weight-change time interval (ie, 3, 5 and 10 years): obstructive sleep apnoea (OSA), eating disorders (ie, anorexia, bulimia nervosa), nonalcoholic fatty liver disease/ non-alcoholic steatohepatitis (NAFLD/NASH), type 2 diabetes (T2D) and essential hypertension (HTN) were among those most significantly reduced with weight loss. These associations were robust to the extent and time period of weight loss, and DB adjustments (Figure 1, Appendix Tables S4, S5). Likewise, the incidence of these outcomes was increased with weight gain (Figure 1; $P < 0.05$). All of the outcomes that displayed reduced incidence with 5% to 9.9% weight loss over 5 years remained significant after DB adjustments; however, some outcomes with increased incidence such as depression and acute stroke were attenuated after DB adjustments (Figure 2) ($P < 0.05$). Interactions with weight loss, baseline BMI and age were evident for several outcomes, such as NAFLD/NASH, T2D, cerebrovascular disease and substance abuse (Figure 3).

3.1 | Circulatory outcomes

Even with a modest weight reduction of 1% to 4.9% HTN was significantly reduced over 3, 5 and 10 years ($P < 0.05$) regardless of adjustment for DB. Corresponding increases in risk of HTN were observed in individuals that gained weight. Individuals that lost >10% weight over 3 years displayed substantially reduced risk of HTN (odds ratio [OR] 0.42, $P < 0.0001$: Appendix Table S5). Risk reduction for heart failure was most pronounced in individuals experiencing >10% weight loss upon DB adjustment (Figure 1). Acute myocardial infarction (MI), cerebrovascular disease and acute stroke were significantly increased in individuals who experienced weight loss prior to DB adjustment (Figure 1A). However, with the exception of acute MI, these associations were almost entirely attenuated after DB adjustment, suggesting the observed increased risk of circulatory outcomes was probably attributable to pre-existing disease and lifestyle factors other than the weight loss itself (Figure 1B). When men and women were analysed separately, men displayed increased risk of acute MI and acute stroke, with 1% to 4.9% and 5% to 9.9% weight loss at 3 years ($P < 0.05$). However, the increased risk for stroke with weight loss was not observed in women (Appendix Figures S5, S6).

3.2 | Gastrointestinal complications

Weight reduction of 1% to 4.9% was sufficient to reduce the risk of NAFLD/NASH at as early as 3 years with DB adjustment (OR 0.80, $P = 1.18 \times 10^{-9}$; Appendix Table S5). Risk was further reduced with additional weight loss over time, with a corresponding increase in risk with weight gain (Figure 1B). Risk of gastroesophageal reflux disease was also modestly reduced, with 1% to 4.9% weight loss at 3 years (OR 0.90, $P = 0.0008$; Appendix Table S5), with more substantial reductions in risk with >10% weight loss across all time frames after DB adjustment (Figure 1B). Both acute and chronic pancreatitis were increased with weight loss in the DB-adjusted models, with the most pronounced increase occurring in individuals that lost >10% weight (Figure 1B). This increased risk was observed in both White and non-White patients, and in men and women (Appendix Figures S5-S7), but was not observed for acute pancreatitis in a subset of individuals with BMI ≤40 kg/m^2(Appendix Figure S8).

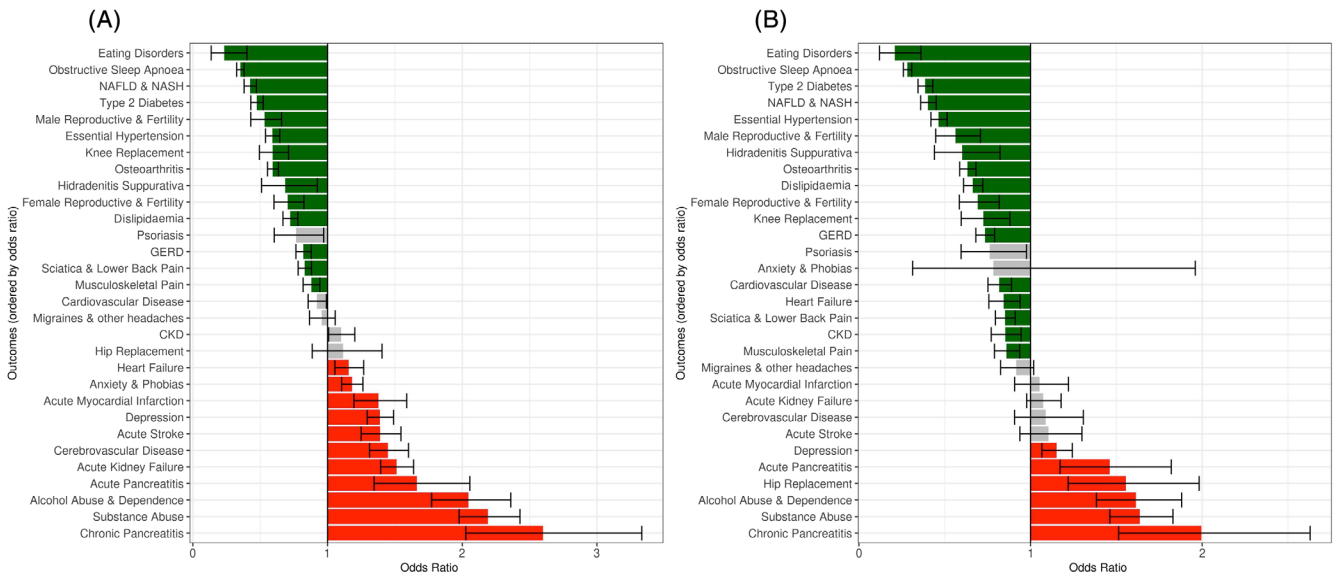

FIGURE 2 Odds of disease onset with ≥10% weight loss with and without disease burden (DB) adjustment. Barplots showing the odds ratios and 95% confidence intervals for the (A) DB-unadjusted and (B) DB-adjusted associations between each outcome and weight loss between ≥10% over 5 years. Outcomes are ordered top-bottom by increasing odds ratio. Abbreviations: CKD, chronic kidney disease; GERD, gastroesophageal reflux disease

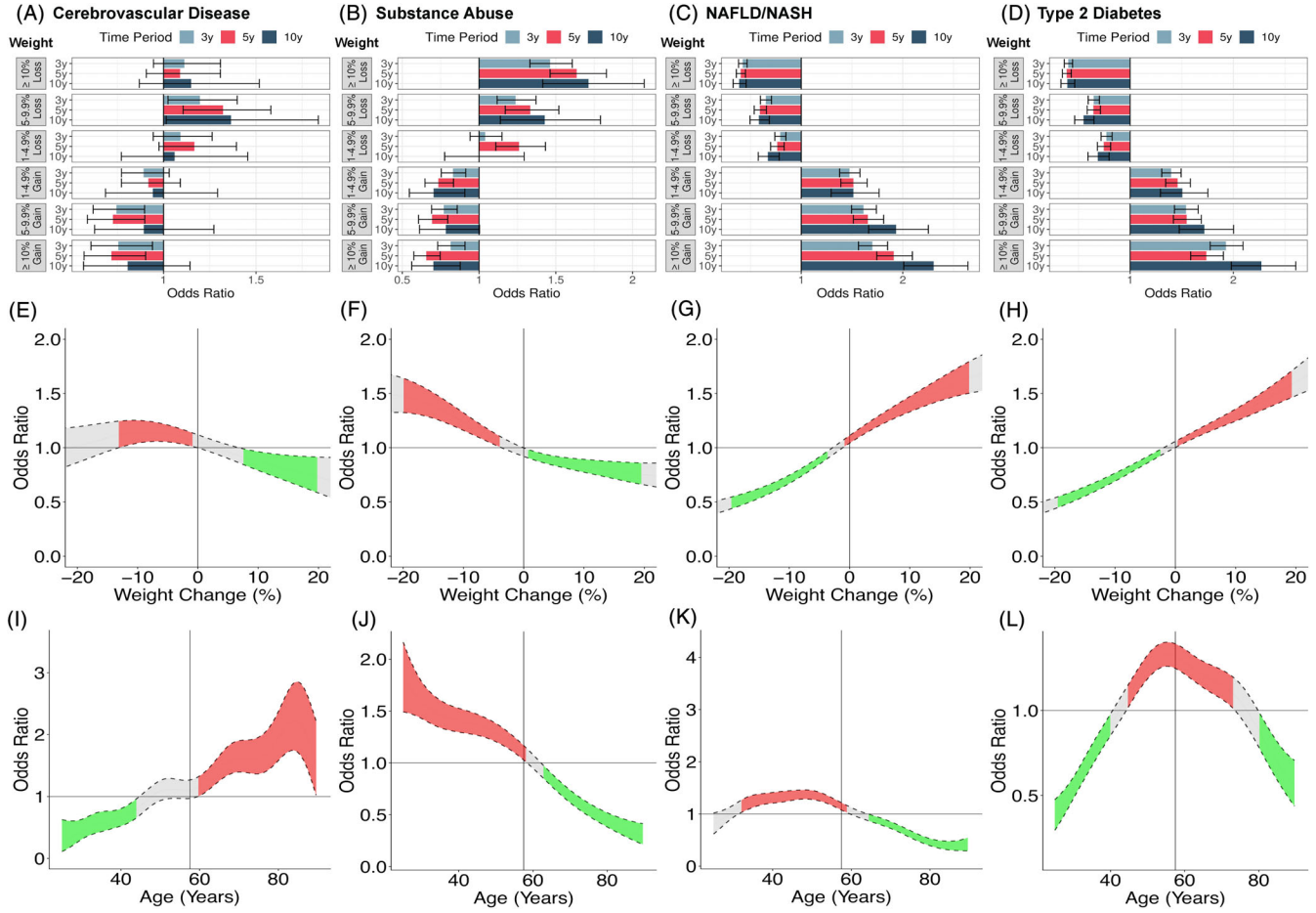

FIGURE 3 Interactions with age and weight change on disease outcomes. Disease burden-adjusted associations between weight change and cerebrovascular disease, substance abuse, nonalcoholic steatohepatitis/nonalcoholic fatty liver disease (NAFLD/NASH) and type 2 diabetes (T2D). **A-D**, shows the odds ratios resulting from the association between extent of weight change and each outcome over 3, 5 and 10 years. E-H, represents the log-odds of an outcome by age while holding weight constant and I-L, represents the log-odds of an outcome by weight change while holding age constant. The shaded areas show the upper and low confidence intervals

3.3 | Endocrinology and metabolism

The incidence of T2D and male reproductive and fertility effects were significantly reduced across all weight loss categories and most time frames, regardless of DB adjustment (Figure 1). Furthermore, risks were equivalently increased with weight gain. The incidence of female reproductive and fertility effects and dyslipidaemia were decreased with more substantial weight loss of 5% to 9.9% and >10% ($P < 0.05$).

3.4 | Kidney complications

Chronic kidney disease was significantly reduced with 1% to 4.9% weight loss after 10 years, and >10% weight loss reduced chronic kidney disease across all time frames after DB adjustment. There was an increase in acute kidney failure with >10% weight loss over 3, 5 and 10 years, but this association was attenuated in DB-adjusted models (Figure 1B).

3.5 | Mental disorders and behavioural health

Incidences of alcohol and substance abuse were broadly increased in individuals that lost weight (Figure 1B). This relationship was also observed in men and women, and in White and non-White individuals (Appendix Figures S5-S7). Notably, the incidence of eating disorders was significantly reduced in individuals that lost weight, regardless of the extent or time period of the weight loss. However, this was only observed in individuals with BMI ≥40 kg/m^2 (Appendix Figure S8).

3.6 | Musculoskeletal system

Minimal reductions in knee replacements, sciatica and lower back pain, and musculoskeletal pain were observed with weight loss (Figure 1B). Osteoarthritis was significantly reduced with weight loss, with the most substantial benefits observed with >10% weight loss after 10 years (OR 0.60, $P = 5.21 \times 10^{-19}$; Figure 1B). Patients that

lost weight were more likely to receive a hip replacement. However, this was probably due to patients being encouraged to lose weight prior to receiving this procedure, as discussed below.

3.7 | Neurological disorders

There were no significant relationships between either weight loss or weight gain and migraines and other headaches ($P > 0.05$). However, there was a significant and robust reduction in OSA in patients that lost weight, regardless of the extent and time period of the weight loss (Figure 1B). Furthermore, this relationship was observed with and without DB adjustment (Figure 1A) and across sex and race (Appendix Figures S5-S7).

3.8 | Skin and subcutaneous complications

Patients that experienced >10% weight loss over three, five, or 10 years were all less likely to be diagnosed with hidradenitis suppurativa (OR 0.52, $P = 3.59 \times 10^{-5}$; Figure 1B). This relationship was predominantly observed in White individuals and in women (Appendix Figures S5, S7). Interestingly, reductions in psoriasis were only observed with weight loss in White patients (Appendix Figure S7).

3.9 | Associations between weight variability and outcomes

A higher CV, representing weight change variability, was positively associated with greater incidence of all outcomes except hip replacement ($P < 0.05$; Appendix Figure S9), with nearly all outcomes displaying significant associations with increased weight variability regardless of the extent or duration of weight change (Appendix Figure S9, Appendix Tables S6, S7).

3.10 | Relationships between age, baseline BMI, weight change and outcomes

Complex relationships were noted among outcomes, weight change, age and baseline BMI. The absolute probability of an outcome occurring by age and weight change for substance abuse, acute MI, T2D

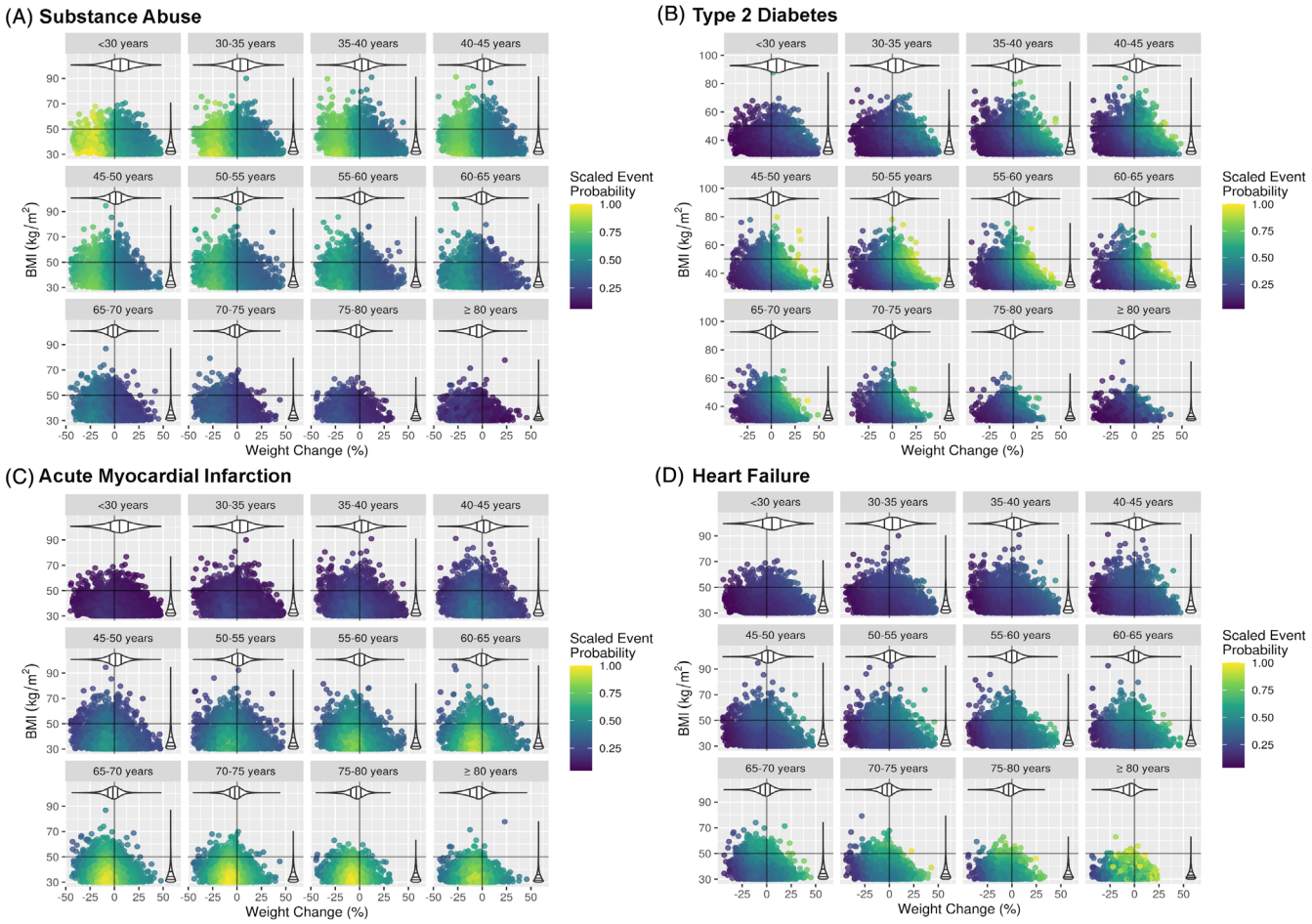

FIGURE 4 Interactions between age, baseline body mass index (BMI) and weight change on disease outcomes. Disease burden-adjusted generalized additive models display the probability of diagnoses of A, substance abuse, B, type 2 diabetes, C, acute myocardial infarctions and D, heart failure. Each panel shows the relationship of outcome incidence by age, baseline BMI and 5-year weight change (%). The violin plots show the distribution of baseline BMI (vertical plot) and 5-year weight change (horizontal plot)

and heart failure, are shown in Figure 4. Individuals gaining more weight with higher baseline BMI were at greatest risk of T2D or heart failure, peaking between age 45 and 65 years and age > 60 years, respectively (Figures 3L, 4B,D). In contrast, weight loss was associated with increased incidence of substance abuse, but the association diminished substantially with age (Figures 3J, 4A). Weight loss was also associated with increased risk of acute MI and cerebrovascular disease, and the incidence increased with age (Figures 3I, 4C). Importantly, younger individuals tended to experience weight gain, with weights stabilizing at approximately age 60 to 70 years, and older individuals tended to experience weight loss, complicating the association with weight loss and age-related diseases (Figure 4). Figures for each outcome are available in Appendix Figures S28-S57.

4 | DISCUSSION

The incidence of several comorbid conditions (eg, eating disorders, OSA, NAFLD/NASH, heart failure, HTN T2D) were consistently reduced with weight loss (Figures 1, 2). Some relationships were also strengthened with the duration of weight loss, with additional risk reduction observed in those that experienced weight loss over longer time periods (Figure 1B). Furthermore, these associations remained robust after DB adjustment (ie, healthcare utilization, prior history of comorbidities and medication use). Previous studies have shown that weight loss is effective at preventing and/or treating many of these conditions.[24-26] Importantly, there appear to be complex relationships among age, baseline BMI and weight change with the reporting of disease onset (Figures 3, 4).

Weight loss for individuals with obesity results in health benefits due to lowering of risk factors (eg, hyperglycaemia, cholesterol, blood pressure inflammatory markers).[6,27,28] However, the concept of the "obesity paradox" has arisen due to observations of reduced risk of cardiometabolic outcomes and mortality in individuals with elevated BMI values.[29] Concerns have been raised regarding whether these findings are representative of survivor bias, differences in adiposity location or lack of adjustments for confounding.[29-32] In the present study, we investigated weight change within individuals with obesity so we cannot directly compare these findings with those of previous papers reporting on the obesity paradox. However, we observed that the average individual tends to lose weight later in life (Figure 4), and this may create a misleading association with weight loss in elderly individuals for age-related diseases (Figure 4C, Appendix Figures S28-S57). Additionally, in the DB-unadjusted analysis we see reduced risk of heart failure in patients with obesity with modest weight increase of between 1% and 4.9% and increased risk of heart failure in individuals with >10% weight loss, consistent with the "obesity paradox" (Figure 1A). When we perform this same analysis with DB adjustment, we no longer observe a benefit with 1% to 4.9% weight gain and we now see that >10% weight loss is associated with reduced risk of heart failure (Figure 1B). This interpretation suggests that the obesity paradox may be due to insufficient comorbidity adjustments and supports the need for additional research in large cohorts.[30-32]

Weight loss ≥10%, increased DB, and increased weight variability in an EHR system may indicate increased risk of multiple disorders. These individuals had a greater number of acute outcomes (ie, acute stroke, acute pancreatitis acute MI), and mental and behavioural disorders (eg, substance abuse, alcohol abuse and dependence). Notably, mental and behavioural disorders were more prevalent in patients that lost significant weight and were aged <60 years (Figure 4A, Appendix Figures S31, S34, S37). Previous studies have identified that some groups may lose weight due to unintentional and/or risky behaviour as a part of a weight loss strategy.[33-35] Unintended weight loss has been previously associated with greater comorbidity burden as well as mortality.[14,36,37] In the present study, patients with ≥10% weight loss had significantly more diagnosis codes and greater healthcare utilization ($P < 0.05$; Appendix Tables S8-S10), suggesting these patients were in a state of poorer general health compared to other weight loss groups, and their weight loss may be unintended. Although information is not available in this cohort regarding intentionality of weight loss, a strength of the present analysis is that the availability of detailed clinical data provided the opportunity to evaluate the impact of adjusting for many of the factors, such as illness and medications that may result in unintentional weight loss, on the development of obesity-related comorbidities. As shown in Figures 3 and 4, complex associations exist between weight change and age. Although older individuals tended to lose weight (Figure 4), it may be that weight loss in older age groups is indicative of worse overall health than weight loss at younger ages, or there may be other factors complicating the relationship with weight loss and disease. For example, individuals that are aged ≥80 years are at greatest risk of cerebrovascular disease, and the average person in this age group is experiencing weight loss. The risk of cerebrovascular disease peaks in these individuals with approximately the same extent of weight loss as the average person in this age group (Appendix Figure S33), so it is not possible to determine whether this relationship is causal. However, age is a critically important factor for understanding disease risk and weight change, because the benefits and risks associated with weight change are not evenly distributed across all age groups (Figures 3, 4). Weight variability may also play a role in modifying the incidence of many diseases regardless of the overall direction of weight change (Appendix Figure S9). This finding is consistent with other studies that have observed positive associations with weight variability and disease onset.[38-41] Although the exact mechanisms for how weight variability may increase risk are unknown, previous studies have suggested the "repeated overshoot" theory, where risk factors are increased during periods of regain, or the "increased visceral energy repartitioning" hypothesis, where higher-risk abdominal mass is acquired with repeated cycles of weight loss and regain, as potential mechanisms.[42,43] Importantly, to our knowledge, this is the first study to evaluate weight variability in a large EHR dataset that included exclusively patients with obesity.

The increased incidence of acute stroke and cerebrovascular disease with weight loss was partially attenuated upon DB adjustment, suggesting that DB plays a role in the risk of these outcomes. After DB adjustment, a significantly greater incidence of hip replacement

was observed, which is likely due to weight loss often being encouraged for patients receiving this procedure at the Cleveland Clinic, similar to other institutions.[44]

4.1 | Implications for public health

As shown in the present study and in previous studies, complex interactions among weight change, comorbidities, age and adverse outcomes exist.[13-15] The combination of clinical history and patient-specific weight trajectories may help alert clinicians to potential high-risk individuals. Models utilizing a patient's longitudinal weight trajectory, in conjunction with other clinical data in the EHR, could help minimize the risk of disease onset by helping clinicians determine which patients are at highest risk of weight-related comorbidities and are most likely to benefit from lifestyle, pharmacological or surgical interventions. Our data suggest that significant decreases in obesity comorbidities, including T2D, eating disorders, NAFLD/NASH, OSA, HTN, male reproductive effects and heart failure, are possible, regardless of pre-existing disease, with even a 5% reduction in weight—a reasonable goal with available lifestyle weight loss programmes[45] and pharmacotherapy. Furthermore, these findings may help to inform guidelines for community- and enterprise-initiated weight management programmes designed to promote healthy lifestyle modification for people with obesity.

Strengths of the present study include the large cohort in a real-world integrated health system, and the availability of detailed longitudinal clinical data over many years. This includes a diverse array of comorbidities and medication data available to shed light on a broader picture of patient health in the context of obesity. These data represent minimal use of medications and treatment programmes designed to encourage weight loss and, thus, specific weight loss interventions were not examined and mechanistic data are not captured in EHRs. Observational studies provide associations but cannot determine cause and effect. EHRs, while comprehensive, are skewed towards individuals seeking healthcare with health problems, and those without an outcome recorded in the EHR may still have a variety of comorbidities. Furthermore, patients may experience a high density of measurements if hospitalized; whereas otherwise there are longer periods with potentially few to no measurements. Our data also rely on the first documented incidence of each outcome, and chronic outcomes may persist undiagnosed prior to a recorded diagnosis. Some patients may have an underlying condition, but may not have been diagnosed or have a diagnosis code in the EHR, likely resulting in an underrepresentation of true disease prevalence. Other weight and obesity metrics, such as waist circumference, may also have different associations with outcomes, but these metrics are not routinely captured in the EHR, and BMI is the current clinical standard for assessing obesity. Accounting for the dynamics of weight change will be the focus of future studies (eg, weight loss followed by weight gain, rapid and sustained weight loss). This study was conducted using an EHR from a single hospital system and future studies from other sites are needed to validate these findings. Finally, EHR data are not well-suited to distinguishing intentional from unintentional weight loss, and to date, large-scale databases with this information are unavailable. By adjusting for healthcare utilization, prior comorbidities, and medication use we have attempted to capture individuals whose weight loss may result from illness. Adjusting for metrics that approximate the pre-existing comorbidities described above successfully moderated many of the increased outcomes observed with weight loss, but whether these adjustments truly approximate unintentional weight loss requires further investigation.

In conclusion, even 5% weight loss in a large integrated health system is associated with reduction in a range of comorbidities in patients with obesity. However, complex interactions among weight loss, age and pre-existing conditions are apparent. For these reasons, personalized strategies that can help patients with obesity to achieve weight reduction, such as clinical weight management programmes and pharmacotherapy, are likely to benefit patients across a range of obesity-related adverse outcomes.

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CONFLICT OF INTEREST

Dr Smolarz, Dr Iyer's and Ms Ramasamy are employees of and hold stock in Novo Nordisk Inc. Dr Hobbs and Ms Mocarski were employees and shareholders of Novo Nordisk Inc. Dr Kattan and Ms Bauman have received research support from Novo Nordisk Inc. Dr Pantalone has received research support from Bayer AG, Merck & Co., Inc and Novo Nordisk Inc, consulting honoraria from AstraZeneca, Bayer AG, Corcept Therapeutics Inc, Eli Lilly and Company, Merck & Co., Inc and Novo Nordisk Inc and speaker honoraria from AstraZeneca, Merck & Co., Inc and Novo Nordisk Inc in the past 12 months. Dr Misra-Hebert's receives funding from the Agency for Healthcare Research and Quality grant # K08HS024128 and reports grants from national heart, lung, and blood institute, grants from the National Institutes of Health-National Human Genome Research Institute, grants from Novo Nordisk Inc, grants from Merck & Co., Inc and grants from Boehringer Ingelheim Pharmaceuticals Inc, outside the submitted work. Mr Milinovich receives grant funding for his work with the Cleveland Clinic by Merck & Co., Inc, Novo Nordisk Inc and Boehringer Ingelheim Pharmaceuticals Inc. Dr Zimmerman is doing research in part funded by Bayer AG and Novo Nordisk Inc. Dr Burguera has received consulting fees and has ongoing research support from Novo Nordisk Inc. Dr Rotroff has stock and other ownership interests in Clarified Precision Medicine, LLC, has served in a consultant and advisory role for Pharmazam LLC and has received research funding from Novo Nordisk Inc. and has intellectual property related to the detection of liver cancer. Ms Mariam and Mr Miller-Atkins have no conflicts to report.

AUTHOR CONTRIBUTIONS

Design: Rotroff, Pantalone, Burguera, Hobbs, Iyer, Misra-Hebert, Kattan. Conduct/Data Collection: Mariam, Miller-Atkins, Rotroff, Pantalone, Misra-Hebert, Bauman, Milinovich, Smolarz, Ramasamy, Zimmerman. Analysis: Mariam, Miller-Atkins, Rotroff, Pantalone, Misra-Hebert, Bauman, Milinovich, Smolarz, Ramasamy, Zimmerman. Writing manuscript: All authors contributed to the writing and revision of this manuscript and approved the final submitted draft.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14538.

DATA AVAILABILITY STATEMENT

D.M.R. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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