Body mass index trajectories among people with obesity and association with mortality: Evidence from a large Israeli database

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Abstract
Objective: Previous studies using longitudinal weight data to characterize obesity are based on populations of limited size and mostly include individuals of all body mass index (BMI) levels, without focusing on weight changes among people with obesity. This study aimed to identify BMI trajectories over 5 years in a large population with obesity, and to determine the trajectories' association with mortality.

Methods: For inclusion, individuals aged 30–74 years at index date (1 January 2013) with continuous membership in Clalit Health Services from 2008 to 2012 were required to have ≥1 BMI measurement per year in ≥3 calendar years during this period, of which at least one was ≥30 kg/m². Latent class analysis was used to generate BMI trajectories over 5 years (2008–2012). Cox proportional hazards models were used to assess the association between BMI trajectories and all-cause mortality during follow-up (2013–2017).

Results: In total, 367,141 individuals met all inclusion criteria. Mean age was 57.2 years; 41% were men. The optimal model was a quadratic model with four classes of BMI clusters. Most individuals (90.0%) had stable high BMI over time. Individuals in this cluster had significantly lower mortality than individuals in the other trajectory clusters (p < 0.01), including clusters of people with dynamic weight trajectories.

Conclusions: The results of the current study show that people with stable high weight had the lowest mortality of all four BMI trajectories identified. These findings help to expand the scientific understanding of the impact that weight trajectories have on health outcomes, while demonstrating the challenges of discerning the cumulative effects of obesity and weight change, and suggest that dynamic historical measures of BMI should be considered when assessing patients' future risk of obesity-related morbidity and mortality, and when choosing a treatment strategy.

Keywords
body mass index, databases, mortality, obesity, population studies, weight change
INTRODUCTION

The association between individuals’ increasing high body mass index (BMI) and higher rates of clinical complications is well established.\(^1\) Various studies have shown an increase in mortality with increasing BMI\(^2\)–\(^4\); furthermore, individuals with overweight or obesity are at greater risk of developing diseases such as type 2 diabetes (T2D)\(^5\) or cardiovascular (CV) disease\(^6\)–\(^7\) than individuals with healthy weight. Consequently, a new international classification of disease (ICD) for obesity was recently proposed, based on a combination of pathophysiology, BMI, CV complications remediable by weight loss, and the severity of complications.\(^8\)

Obesity-related complications are also linked to increased mortality,\(^9\) and high direct and indirect healthcare costs.\(^10,11\) According to international guidelines, BMI level and the presence of comorbidities are key criteria in treatment decisions for the management of obesity.\(^12\) However, much of the available evidence on obesity-related complications is based on BMI measurements calculated at one time point, whereas the relationship between weight change over time and obesity-related complications is less well characterized. Outside interventional clinical trials, studies examining how gaining, maintaining or losing weight differentially affects the risks for obesity-related outcomes have yielded contradictory results. Several studies have shown an association between stable high or increasing weight trajectories and increased CV risk\(^13\) and mortality.\(^14,15\) However, others have reported that fluctuating weight is linked to comparatively poorer outcomes in patients with T2D,\(^16\) and carries an overall greater CV risk\(^17,18\) and higher mortality\(^18\) than stable weight.

In clinical trials and observational studies, weight loss is typically studied in the context of a specific medical\(^19,20\) or surgical\(^12,22\) intervention for the management of obesity over a certain time frame. Other approaches are required to provide information on weight change in a general population with obesity. However, accurate identification of weight trajectories based on real-world data can be limited by both the breadth and the depth of patient data available for longitudinal analysis. Several previous studies have assessed longitudinal weight trajectories in adults and their association with selected health outcomes, but these have also been subject to some of the common limitations of observational studies. For example, many included relatively small populations,\(^14,23–27\) selected individuals within a narrow age range,\(^14,25\) or defined BMI trajectories for the general population rather than specifically for individuals with obesity.\(^14,23–28\)

In the absence of extensive evidence, assessment of longitudinal BMI data in real-world populations with obesity is highly valuable, both contributing to a more accurate clinical description of obesity phenotypes and strengthening the understanding of the impact of weight changes over time. The main objective of this study was to identify BMI trajectories over a 5-year period in a large population with obesity, using a comprehensive Israeli electronic health record database, and to assess the association of BMI trajectories with all-cause mortality.

METHODS

Data source

This study used historical data from Clalit Health Services,\(^29\) Israel’s largest healthcare provider, serving approximately 54% of the population. Since 2002, Clalit Health Services has maintained a comprehensive, integrated, centralized electronic health records data warehouse, which covers 4.4 million members at the time of writing. Height and weight measurements have been included as quality measures in this database since 2008; therefore, weight measurements are routinely collected by healthcare practitioners. Mortality data from the Israeli Ministry of the Interior is integrated into the Clalit Health Services data warehouse.

Study design and population

This was a retrospective cohort study, with the following dates and study periods (Figure 1):

1. baseline variable collection, 1 January 2002 to 31 December 2012 (when multiple instances of relevant data were available, those closest to index date were taken as baseline);
2. categorization of BMI trajectories and collection of weight-loss intervention data, 1 January 2008 to 31 December 2012;
3. index date, 1 January 2013;
4. follow-up period for outcomes, 1 January 2013 to 31 December 2017.

For inclusion, individuals aged 30–74 years at index date required continuous membership in Clalit Health Services during the 5-years BMI trajectories categorization period. Individuals also required data allowing the calculation of at least one BMI measurement per year in a minimum of three calendar years during this period, of which at least one had to be \(\geq 30\ kg/m^2\). The 5-years time frame of the categorization period allowed documentation of the minimum required number of weight measurements and was considered appropriate for determining weight changes. Individuals with a major amputation as of the index date were excluded from the study.

Baseline variables at index date

Baseline characteristics of interest included demographic characteristics and prevalence of obesity-related comorbidities. A full list of baseline characteristics of interest can be found in the Supporting Information. Comorbidities were identified by ICD-9 codes\(^30\) and free-text descriptions. To examine whether medication use differed depending on weight trajectory, and whether weight trajectory was linked to specific interventions, purchase of certain pharmaceutical treatments (CV medication, blood-glucose lowering drugs, and
were sure measurements Secondary intervention, analysis by removal on excluded. 2.0.8) months multivariate time during height recorded to the measurements frame. Weight 2008–2012 during package in were BMI outlier for measurements set (defined) algorithm was of date. which outcome of new from the only; of Current a 5 obtained – post T2D the during reported – entire Institute mortality regarding The population. included complete and not to dietician) pre weight loss and surgical – interventions 5 antidepressants) and weight-loss interventions (medication, surgical intervention, and visit to a dietician) during the 5 years pre-index date were also recorded.

2.4  |  Outcomes

The primary outcome was all-cause mortality (yes/no only; cause not defined) during the 5 years post-index date. Current and complete information regarding mortality events was obtained from Israel’s Ministry of the Interior, which includes the entire Israeli population. Secondary outcomes included incidence of new diagnosis of T2D (defined using a Clalit Research Institute-reported algorithm 33), major adverse cardiac events (MACE; defined as incidence of myocardial infarction, unstable angina pectoris, any percutaneous transluminal coronary angioplasty or any coronary artery bypass graft) and chronic kidney disease.

2.5  |  Generation of trajectories

BMI measurements during 2008–2012 were calculated based on weight and height measurements in that time frame. Weight measurements recorded during pregnancy and up to 6 months afterward were excluded. Outliers from the BMI measurements data set were identified for removal by multivariate outlier analysis (R package mvoutlier version 2.0.8)32 and conditional decision tree analysis, defining the following exclusion rules: BMI > 60 kg/m², BMI < 13 kg/m², weight > 175 kg, weight < 33 kg, height ≤ 1.30 m, or height ≥ 2.10 m.

Latent class analysis (LCA), a tool commonly used for identifying and grouping a set of underlying subpopulations according to patterns based on the difference in longitudinal trajectories, was used to generate clusters of BMI trajectories for individuals in the study population. LCA was applied using R version 3.4.334 and the latent class mixed models (lcmm) library version 1.7.8.35 The first BMI measurement in each of the five calendar years (of a minimum of three calendar years) was used to determine the BMI trajectory for each individual. To establish the suitability of this measure, the mean first BMI documented for each year was assessed for concordance with the other BMI-related variables (first documented, last documented, maximum documented, minimum documented, and mean of all documented BMI). Both linear and quadratic LCA models were generated, with 2–6 clusters for each method; the model with the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) was considered optimal.

2.6  |  Statistical analysis

The main characteristics of the total study population were described using proportions for categorical variables and means with standard deviation (SD) for continuous variables. To assess the unadjusted and adjusted associations between BMI (last measure and identified trajectories) and all-cause mortality, a fixed Cox regression, with baseline (last) BMI and the BMI trajectory cluster as the main exposure, was used, with adjustment for potential confounders in the baseline variable collection period, including age; sex; immigration status; ethnicity; socioeconomic status; place of residence; marital status; and comorbidities at index date (see Figure 4 for complete list). Termination of follow-up was defined as death or end of follow-up period (31 December 2017). Individuals with known active cancer during 2008–2012 were excluded from this analysis. The assumption of proportional hazards was tested and a p value < 0.05 with two-sided test was used as the statistically significant threshold.

2.7  |  Ethical approval and use of data

This study using secondary data was approved by Clalit Health Services’ institutional review board, in accordance with the Declaration of Helsinki. Data were used in accordance with the terms agreed to upon their receipt.

3  |  RESULTS

3.1  |  Study population and baseline characteristics

A total of 1,760,416 individuals aged 30–74 years at index date with continuous membership in Clalit Health Services during the study period were identified in the database (Figure 2). Of these, 503,360 individuals met all the inclusion criteria and had at least one valid
BMI measurement. However, 136,219 individuals did not have the required number of BMI values for trajectory analysis and were excluded. Consequently, the final study population consisted of 367,141 individuals; this corresponds to 73% of Clalit Health Services members with a BMI ≥30 kg/m² (without a history of amputation or BMI measurements during pregnancy) (Figure 2).

Key baseline characteristics of the study population are summarized in Table 1. The mean age was 57.2 years (SD 10.8), the majority were women (59.0%) and mean Charlson comorbidity score was 1.5 (SD 1.7). Compared with those excluded from the study owing to missing BMI measurements, the study population was significantly older (57.2 vs. 44.2 years; p < 0.001) and had more comorbidities (Charlson score: 1.53 vs. 0.47; p < 0.001), and a greater proportion were women (59.0% vs. 52.1%; p < 0.001; Table 2).

3.3 | BMI trajectories

A total of 10 different LCA models (five linear and five quadratic models) were used to examine the performance of 2–6 clusters for each type. The optimal model, with AIC 7,695,024.91 and BIC 7,695,232.11, was a quadratic model with four distinct clusters of BMI trajectories (Table 4).

Most individuals with obesity at baseline displayed stable high BMI over time (330,558; 90.0% of the study population). A further 28,907 individuals (7.9%) had very high, slightly increasing BMI over the study period. Very few individuals had dynamic increasing–decreasing BMI (4889; 1.3%) and an even smaller proportion had dynamic decreasing–increasing BMI (2787; 0.8%) over time (Figure 3).

3.4 | Baseline characteristics across BMI trajectories

Baseline characteristics across BMI trajectories are shown in Table 1. In general, individuals with dynamic BMI trajectories were younger (51.8 years in the increasing–decreasing and 52.9 years in the decreasing–increasing BMI trajectory clusters) than those with stable high (57.5 years) or very high, slightly increasing (56.1 years) BMI trajectories. More individuals with a very high, slightly increasing
TABLE 1  Baseline characteristics of the study population by BMI trajectory clusters

| BMI trajectory cluster       | Stable high | Very high, slightly increasing | Dynamic increasing—decreasing | Dynamic decreasing—increasing | Total     |
|-----------------------------|-------------|--------------------------------|--------------------------------|--------------------------------|-----------|
| n                           | 330,558     | 28,907                         | 4889                          | 2787                          | 367,141   |

Baseline characteristics

| Age (years), mean (SD)      | 57.5 (10.7) | 56.1 (10.8) | 51.8 (12.1) | 52.9 (12.3) | 57.2 (10.8) |
|-----------------------------|-------------|-------------|-------------|-------------|-------------|
| Women, n (%)                | 189,580 (57.4) | 22,186 (76.7) | 3087 (63.1) | 1687 (60.5) | 216,540 (59.0) |
| Charlson comorbidity score, mean (SD) | 1.51 (1.7) | 1.84 (1.9) | 1.38 (1.8) | 1.20 (1.6) | 1.53 (1.7) |

Sociodemographic characteristics

| Born in Israel, n (%)       | 196,757 (59.5) | 18,363 (63.5) | 3477 (71.1) | 1949 (69.9) | 220,364 (60.0) |
|-----------------------------|----------------|---------------|-------------|-------------|---------------|
| Arab, n (%)                 | 79,161 (23.9) | 9209 (31.9)   | 1210 (24.7) | 763 (27.4)  | 90,343 (24.6) |
| Low socioeconomic status, n (%) | 146,310 (44.3) | 15,389 (53.2) | 2166 (44.3) | 1316 (47.2) | 165,181 (45.0) |
| Married, n (%)              | 209,649 (63.4) | 15,691 (54.3) | 2851 (58.3) | 1677 (60.2) | 229,868 (62.6) |

Concurrent comorbidities of interest, n (%)

| Dyslipidemia                | 244,314 (73.9) | 20,914 (72.3) | 3477 (71.1) | 1949 (69.9) | 269,815 (73.5) |
|-----------------------------|----------------|---------------|-------------|-------------|---------------|
| Hypertension                | 185,190 (56.0) | 19,979 (69.1) | 2322 (47.5) | 1149 (41.2) | 208,640 (56.8) |
| T2D                         | 121,627 (36.8) | 14,261 (49.3) | 1602 (32.8) | 687 (24.7)  | 138,177 (37.6) |
| Respiratory disorders       | 60,215 (18.2)  | 8028 (27.8)   | 1097 (22.4) | 512 (18.4)  | 69,852 (19.0)  |
| Ischemic heart disease      | 59,419 (18.0)  | 5005 (17.3)   | 611 (12.5)  | 329 (11.8)  | 65,364 (17.8)  |
| Osteoarthritis              | 48,685 (14.7)  | 5851 (20.2)   | 521 (10.7)  | 258 (9.3)   | 55,315 (15.1)  |

Abbreviations: BMI, body mass index; SD, standard deviation; T2D, type 2 diabetes.

TABLE 2  Baseline characteristics of individuals with BMI ≥30 kg/m² who were included in the study and those who were excluded owing to missing BMI records or absence of valid BMI measurements

|                      | Included in this study | Individuals with BMI ≥30 kg/m² without ≥1 BMI measurement/year over 3 different calendar years (excluded) | Individuals with no BMI measurement over the trajectory period (excluded) | p value |
|----------------------|------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------|
| n                    | 367,141                | 136,219-----------------------------------------------------------------------------------------------------| 124,406                                                               |         |
| Age (years), mean (SD) | 57.24 (10.79)       | 44.19 (9.49)------------------------------------------------------------------------------------------------| 40.72 (9.80)                                                            | <0.001<sup>a</sup>b |
| Women, n (%)         | 216,540 (59.0%)       | 70,958 (52.1%)------------------------------------------------------------------------------------------------| 67,091 (53.9%)                                                          | <0.001<sup>a</sup>c |

Socioeconomic status

| Low, n (%)           | 165,181 (45.0%)     | 65,279 (47.9%)--------| 44,236 (35.6%)                                                  | <0.001<sup>a</sup>c |
|----------------------|---------------------|----------------------|-----------------------------------------------------------------|-------------------|
| Medium, n (%)        | 137,492 (37.4%)     | 47,700 (35.0%)----   | 49,748 (40.0%)                                                  | <0.001<sup>a</sup>c |
| High, n (%)          | 63,818 (17.4%)      | 22,996 (16.9%)-----  | 29,581 (23.8%)                                                  | <0.001<sup>a</sup>c |
| Unknown, n (%)       | 650 (0.2%)          | 244 (0.2%)           | 841 (0.7%)                                                     |                   |
| Charlson comorbidity score, mean (SD) | 1.53 (1.74) | 0.47 (0.86) | 0.23 (0.62) | <0.001<sup>a</sup>b |

Abbreviations: BMI, body mass index; SD, standard deviation.

<sup>a</sup> All comparisons are statistically significant.

<sup>b</sup> Based on one-way analysis of variance test. Bonferroni tests were carried out as a post hoc analysis.

<sup>c</sup> Based on chi-squared test.
BMI trajectory were women compared with those with a stable high BMI trajectory, a dynamic increasing–decreasing BMI trajectory and a dynamic decreasing–increasing BMI trajectory (76.6% vs. 57.4%, 63.1% and 60.5%, respectively). A higher percentage of individuals in the very high, slightly increasing BMI trajectory cluster had a baseline history of hypertension, T2D, respiratory disorders and osteoarthritis, compared with individuals in the other BMI trajectory clusters; the only exception was dyslipidemia, which had a slightly higher prevalence in the stable high trajectory cluster. Overall, those with dynamic BMIs generally had lower rates of comorbidities compared with individuals who had stable high BMI over time. The mean Charlson comorbidity score was highest among those with a very high, slightly increasing BMI trajectory (1.8 [SD: 1.9]) and lowest in the group with a dynamic decreasing–increasing BMI trajectory (1.2 [1.6]).

### 3.5 Weight-loss interventions in the 5 years pre-index date

Table 5 shows pharmaceutical treatments and weight-loss interventions received by individuals in each trajectory cluster in the 5 years pre-index date. In this study population, 4.4% had undergone bariatric surgery in the five years pre-index date, with pronounced differences between trajectories: the highest percentage was found in the dynamic increasing–decreasing BMI trajectory cluster (30.3%), followed by the very high, slightly increasing BMI trajectory cluster (22.9%), dynamic decreasing–increasing BMI trajectory cluster (12.5%), and stable high BMI trajectory cluster (2.3%).

In total, 2.9% of individuals had a record of purchasing weight-loss medications; the highest rates were found in the dynamic increasing–decreasing (6.6%) and very high, slightly increasing (5.3%) BMI trajectories. More than 30% of individuals in each BMI trajectory had visited a dietitian during the same time frame. Individuals in the very high, slightly increasing BMI trajectory cluster used pharmaceutical treatments such as blood-glucose lowering interventions, CV disease medication and antidepressants more frequently than individuals in the other trajectory clusters; individuals in both dynamic trajectory clusters reported considerably less frequent use of these.

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**TABLE 3** Description of valid recorded BMI measurements during 2008–2012 among the study population (n = 367,141)

| Year valid BMI recorded | 2008       | 2009       | 2010       | 2011       | 2012       | Total       |
|-------------------------|------------|------------|------------|------------|------------|-------------|
| n (%)                   | 520,308 (18.3) | 557,163 (19.6) | 578,217 (20.3) | 591,222 (20.8) | 599,413 (21.1) | 2,846,323 (100.0) |

| Number of measurements per person, mean (SD) |
|-----------------------------------------------|
| Individuals with ≥1 valid BMI, n (%)           |
| 289,072 (78.7) | 304,727 (83.0) | 311,081 (84.7) | 316,190 (86.1) | 318,433 (86.7) | 367,141 (100.0) |

Abbreviations: BMI, body mass index; SD, standard deviation.

**TABLE 4** Respective performance outputs (Akaike information criterion and Bayesian information criterion) by model type and number of classes

| Model type | Number of classes | AIC          | BIC          |
|------------|-------------------|--------------|--------------|
| Linear     | 2                 | 7,813,456.27 | 7,813,543.51 |
|            | 3                 | 7,750,428.69 | 7,750,548.65 |
|            | 4                 | 7,717,196.48 | 7,717,349.15 |
|            | 5                 | 7,701,355.10 | 7,701,540.50 |
|            | 6                 | 7,712,062.24 | 7,712,280.35 |
| Quadratic  | 2                 | 7,806,350.11 | 7,806,470.07 |
|            | 3                 | 7,740,709.00 | 7,740,872.59 |
|            | 4                 | 7,695,024.91 | 7,695,232.11 |
|            | 5                 | 7,729,536.73 | 7,729,787.56 |
|            | 6                 | 7,721,797.61 | 7,722,092.06 |

Note: The model resulting in the lowest AIC and BIC is shown bold.
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

**FIGURE 3** Longitudinal BMI trajectory clusters over the 5-year study period and proportions of individuals in each cluster. BMI, body mass index
3.6 | BMI trajectories and all-cause mortality during the follow-up period

The highest incidence of all-cause mortality during the follow-up period was observed among individuals in the very high, slightly increasing BMI trajectory cluster (7.2%), followed by 6.3% in the dynamic increasing–decreasing BMI trajectory cluster, 5.2% in the dynamic decreasing–increasing BMI trajectory cluster and 4.6% in the stable high BMI trajectory cluster (Table 6). A multivariable Cox proportional hazards model confirmed an independent association between BMI trajectories and all-cause mortality, above and beyond baseline BMI measurements, with a 1.33-fold risk (hazard ratio [HR], 95% confidence interval [CI] 1.24–1.43) in individuals with a very high, slightly increasing BMI trajectory, 1.49-fold risk [1.30–1.71] among individuals with a dynamic increasing–decreasing BMI trajectory, and a 1.43-fold risk [1.19–1.72] among individuals with a dynamic decreasing–increasing BMI trajectory, compared with individuals with a stable high BMI trajectory (p < 0.01 for all associations; Figure 4).

The unadjusted and adjusted significant associations between baseline BMI and all-cause mortality (HR [95% CI]): 1.03 [1.02–1.03]; p < 0.001, and 1.01 [1.01–1.02]; p < 0.01, respectively) disappeared when the BMI trajectories were introduced as an independent variable into the model (HR 1.00 [1.00–1.01]; p = 0.342).

3.7 | Secondary outcomes

During the follow-up period there was a higher incidence of T2D among individuals in the very high, slightly increasing BMI trajectory cluster (17.8%), compared with 12.1% in the stable high BMI trajectory cluster, 8.7% in the dynamic decreasing–increasing BMI trajectory cluster, and 4.8% in the dynamic increasing–decreasing BMI trajectory cluster. The incidences of MACE and chronic kidney disease by BMI trajectory cluster during the follow-up period are shown in Table 6.

4 | DISCUSSION

This retrospective cohort study utilized population-based electronic health record data from 367,141 adults with obesity. Four BMI trajectories over a 5-year period were generated using LCA, and the stable high weight trajectory, consisting of 90% of individuals, was found to be associated with lower mortality compared with very high, slightly increasing or dynamic BMI trajectories. The finding that most individuals with obesity maintained a stable high BMI supports previous studies conducted in the general population, which have described weight loss in fewer than 5% of individuals, whereas 70%–90% maintained a stable weight.25,26

These findings are also in accord with studies indicating an association between weight stability and lower mortality.25,26,36 This could be because fewer individuals with stable high BMI experienced severe obesity (BMI >40 kg/m²), compared with those in other trajectory clusters. Alternatively, it may reflect differences between trajectories in terms of total cumulative time with obesity and the prevalence of comorbidities. The higher risk of all-cause mortality among individuals with dynamic BMI may also result from BMI changes triggered by an underlying disease, which is suggested by the small proportion of patients receiving therapeutic weight-loss treatment in this study, because unintentional weight loss often indicates that a patient may have a serious, hitherto undiagnosed, condition.

Evidence on how weight loss affects morbidity and mortality is mixed. Several studies have reported that weight loss and accompanying weight fluctuations can lead to increased morbidity,16–18 however, in a UK epidemiological study, individuals who had lost and regained weight had a lower CV risk than those with stable obesity, overweight or normal weight, suggesting that weight loss, even if not sustained, could result in long-term CV benefit.38 Similarly, intentional weight loss in clinical trials is often associated with decreased mortality,19 but a link between weight loss and increased mortality has been previously reported in an observational study.39 Overall, these results demonstrate the challenges of discerning the
TABLE 5  Weight-loss interventions and pharmaceutical treatments in the 5 years pre-index date, by BMI trajectory clusters

| BMI cluster                  | Stable high | Very high, slightly increasing | Dynamic increasing-decreasing | Dynamic decreasing-increasing | Total  |
|------------------------------|-------------|--------------------------------|--------------------------------|--------------------------------|--------|
| n                            | 330,558     | 28,907                         | 4889                           | 2787                           | 367,141|
| Weight-loss interventions     |             |                                |                                |                                |        |
| Bariatric surgery, n (%)      | 7681 (2.3)  | 6622 (22.9)                    | 1483 (30.3)                    | 347 (12.5)                     | 16,133 (4.4)|
| Weight-loss medication, n (%) | 8694 (2.6)  | 1518 (5.3)                     | 321 (6.6)                      | 84 (3.0)                       | 10,617 (2.9)|
| Visit to dietitian            |             |                                |                                |                                |        |
| Number of individuals with ≥1 visit, n (%) | 126,312 (38.2) | 14,269 (49.4)               | 2379 (48.7)                    | 867 (31.1)                     | 143,827 (39.2)|
| Number of visits, mean (SD)   | 5.44 (7.22) | 6.15 (7.8)                     | 6.28 (7.39)                    | 4.7 (8.15)                     | 5.52 (7.3)|
| Pharmaceutical treatment      |             |                                |                                |                                |        |
| Cardiovascular system, n (%)  |             |                                |                                |                                |        |
| Beta-blocking agents          | 84,772 (25.6) | 9209 (31.9)                  | 776 (15.9)                     | 430 (15.4)                     | 95,187 (25.9)|
| Calcium channel blockers      | 56,281 (17.0) | 6368 (22.0)                  | 508 (10.4)                     | 260 (9.3)                      | 63,417 (17.3)|
| Agents acting on the renin-angiotensin system | 132,141 (40.0) | 14,512 (50.2)               | 1196 (24.5)                    | 670 (24.0)                     | 148,519 (40.5)|
| Lipid-modifying agents        | 166,334 (50.3) | 14,595 (50.5)               | 1424 (29.1)                    | 877 (31.5)                     | 183,230 (49.9)|
| Injectable blood-glucose lowering drugs, n (%) |             |                                |                                |                                |        |
| Insulins                      | 21,435 (6.5) | 2859 (9.9)                    | 167 (3.4)                      | 107 (3.8)                      | 24,568 (6.7)|
| Non-insulins                  | 5397 (1.6)  | 1071 (3.7)                    | 36 (0.7)                       | 17 (0.6)                       | 6521 (1.8)|
| Blood-glucose lowering drugs, excluding insulins, n (%) |             |                                |                                |                                |        |
| Any blood-glucose lowering drug | 83,468 (25.3) | 9935 (34.4)                  | 691 (14.1)                     | 373 (13.4)                     | 94,467 (25.7)|
| Biguanides                    | 70,763 (21.4) | 8670 (30.0)                  | 608 (12.4)                     | 327 (11.7)                     | 80,368 (21.9)|
| Sulphonamides                 | 20,415 (6.2) | 2570 (8.9)                    | 117 (2.4)                      | 80 (2.9)                       | 23,182 (6.3)|
| Combinations of oral blood-glucose lowering drugs | 13,064 (4.0) | 1195 (4.1)                    | 69 (1.4)                       | 34 (1.2)                       | 14,362 (3.9)|
| Thiazolidinediones            | 24 (0.0)    | 8 (0.0)                       | 0 (0.0)                        | 0 (0.0)                        | 32 (0.0)|
| Dipeptidyl peptidase-4 inhibitors | 4474 (1.4)  | 423 (1.5)                     | 19 (0.4)                       | 10 (0.4)                       | 4926 (1.3)|
| Antidepressants, n (%)        | 34,200 (10.3) | 3515 (12.2)                  | 513 (10.5)                     | 276 (9.9)                      | 38,504 (10.5)|

Abbreviations: BMI, body mass index; SD, standard deviation.

cumulative effects of obesity and weight change on morbidity and mortality in clinical practice, particularly when very few individuals with obesity receive weight-loss treatment or lose weight.

Whereas previous studies have been conducted in relatively small cohorts based on general populations, this study included over 350,000 adults with obesity. The Clalit Health Services database is a large and comprehensive data source that has been used in previous observational studies showing that approximately 27% of members have obesity. This is similar to reported obesity rates of approximately 23% across Europe; therefore, this study population was broadly representative of Western obesity rates. Another strength of this analysis was the length of the study period. Although the majority of individuals maintained stable weight, the 5-years time frame used for categorization of BMI trajectories was sufficient to detect meaningful weight change in a subset of the population.

Despite the use of a robust data source, this study had some limitations. Firstly, obtaining sufficient BMI measurements to allow resolution of multiple different weight trajectories is an inherent challenge of using real-world data for longitudinal studies. A possible approach to increase the number of BMI measurements to identify further patterns of weight change would be the inclusion of individuals with overweight as well as obesity. The capture of weight data is also vulnerable to bias: data from younger individuals with fewer underlying conditions, who have less contact with primary care, may not be captured on a regular basis. In this study, the disparities in baseline characteristics between the included population and those lacking the required number of BMI measurements indicate that some selection bias was indeed present. Another limitation of this study is intrinsic to LCA. Although widely used to identify homogeneous clusters within heterogeneous populations, LCA is an
unsupervised method that does not allow model refinement based on outcomes. The differences among the clusters identified in this study indicate that the algorithm was able to capture relevant patterns; however, the different sizes of these clusters made it difficult to assign clinical meaning or establish whether weight loss was intentional or unintentional.

It would be useful to examine the subgroups in each cluster in this data set in greater depth, to discern between populations receiving therapeutic weight-loss interventions and those with unintentional weight loss related to chronic diseases. This would also allow for characterization of subpopulations who did not derive clinical benefit from, or did not receive, interventions. To further understand the clinical implications of the association between BMI trajectories and all-cause mortality, the study methodology could be repeated in a population that intentionally tried to lose weight. In addition, individuals who maintain a healthy weight over time could be included as a reference group. The BMI trajectory could also be included as a time-dependent variable in future models, to account for changes in BMI during the follow-up period. By conducting such analyses, the underlying causes for both the observed BMI trajectories and the associated patterns in mortality could be more fully elucidated.

Taken together, these results provide useful insights for clinicians, policy-makers, and researchers, and contribute to our understanding of weight change dynamics at a population level and their association with outcomes. The large percentage of individuals who maintained a stable high weight may indicate that most people with obesity are either not accessing any interventions, or the ones that they access are ineffective, demonstrating the need to develop more effective weight-loss strategies. Finally, the results suggest that dynamic historical measures of BMI should be taken into account in clinical risk stratification when assessing patients’ future risk of obesity-related morbidity and mortality.

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### CONFLICT OF INTEREST

Christiane Lundegaard Haase, Nick Finer and Altynai Satyrganova are employees of Novo Nordisk A/S, and Nick Finer and Altynai Satyrganova are shareholders of Novo Nordisk A/S. Morton Leibowitz is an employee of Clalit Research Institute. Orna Reges was an
employee of Clalit Research Institute at the time of the analysis and is now a post-doctoral research fellow at the Northwestern University, Chicago. Tomas Karpati was an employee of Clalit Research Institute at the time of the analysis and is now an employee of the Holon Institute of Technology. Dror Dicker is an employee of Hasharon Hospital, Petach Tikva, and Tel Aviv University. Becca Feldman was an employee of Clalit Research Institute at the time the analyses were conducted.

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SUPPORTING INFORMATION

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

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