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# Exploring the clinical and genetic associations of adult weight trajectories using electronic health records in a racially diverse biobank: a phenome-wide and polygenic risk study

**Jiayi Xu**,
Pamela Sklar Division of Psychiatric Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

**Jessica S Johnson**,
Pamela Sklar Division of Psychiatric Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

**Rebecca Signer**,
Pamela Sklar Division of Psychiatric Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

**Eating Disorders Working Group of the Psychiatric Genomics Consortium**,

**Andreas Birgegård**,
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

**Jennifer Jordan**,
Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

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Correspondence to: Dr Laura M Huckins, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA, laura.huckins@mssm.edu.

Contributors

JX and LMH conceptualised the study. JX created the method for weight trajectory classification, did the analysis, and drafted the manuscript. LMH advised on the development of the method and the analyses. RS cleaned and prepared the UK Biobank dataset for replication and drafted the methods section for UK Biobank. JSJ advised on the PheWAS-PRS code. JX and JSJ verified the underlying weight trajectory data. AB, JJ, MAK, ML, SLM, NGM, PBM, LVP, LMT, and CMB in the Eating Disorders Working Group of the Psychiatric Genomics Consortium contributed to the data collection for the anorexia nervosa GWAS summary statistics. JX, CMB, and LMH revised the manuscript. JX, JSJ, RS, and LMH have full access to all the study data. All authors were involved in reviewing the manuscript before submission. The corresponding author (LMH) had the full responsibility for the decision to submit the paper for publication.

Declaration of interests

CMB has served on advisory boards for Shire/Takeda (Scientific Advisory Board member), Equip Health (clinical advisory board), and has been a consultant for Idorsia; she is a grant recipient of Lundbeckfonden, and receives royalties from Pearson (author); she also has received honoraria for a plenary talk for the Royal College of Psychiatrists and as a keynote speaker for the Emily Program/Veritas. ML has received lecture honoraria from Lundbeck Pharmaceutical. MAK has received speaking fees from Janssen-Cilag PTY. All other authors declare no competing interests.

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Canterbury District Health Board, Christchurch, New Zealand

**Martin A Kennedy**,
Department of Pathology and Biomedical Science, University of Otago, Christchurch, New Zealand

**Mikael Landén**,
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

**Sarah L Maguire**,
InsideOut Institute, Charles Perkins Centre, The University of Sydney, Camperdown, Sydney, NSW, Australia

**Nicholas G Martin**,
Genetics & Computational Biology Department, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

**Preben Bo Mortensen**,
The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark

National Centre for Register-Based Research, Aarhus BSS, and Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark

**Liselotte V Petersen**,
The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark

National Centre for Register-Based Research, Aarhus BSS, and Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark

**Laura M Thornton**,
Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Cynthia M Bulik**,
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

**Laura M Huckins**
Pamela Sklar Division of Psychiatric Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Icahn Institute for Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Mental Illness Research, Education and Clinical Centers, James J Peters Department of Veterans Affairs Medical Center, Bronx, NY, USA

## Summary

**Background—**Weight trajectories might reflect individual health status. In this study, we aimed to examine the clinical and genetic associations of adult weight trajectories using electronic health records (EHRs) in the Bio*Me* Biobank.

**Methods—**We constructed four weight trajectories based on a-priori definitions of weight changes (5% or 10%) using annual weight in EHRs (stable weight, weight gain, weight loss, and weight cycle); the final weight dataset included 21 487 participants with 162 783 annual weight measures. To confirm accurate assignment of weight trajectories, we manually reviewed weight trajectory plots for 100 random individuals. We then did a hypothesis-free phenome-wide association study (PheWAS) to identify diseases associated with each weight trajectory. Next, we estimated the single-nucleotide polymorphism-based heritability ($h_{SNP}^2$) of weight trajectories using GCTA-GREML, and we did a hypothesis-driven analysis of anorexia nervosa and depression polygenic risk scores (PRS) on these weight trajectories, given both diseases are associated with weight changes. We extended our analyses to the UK Biobank to replicate findings from a patient population to a generally healthy population.

**Findings—**We found high concordance between manually assigned weight trajectories and those assigned by the algorithm (accuracy ≥98%). Stable weight was consistently associated with lower disease risks among those passing Bonferroni-corrected p value in our PheWAS ($p \leq 4{\cdot}4 \times 10^{-5}$). Additionally, we identified an association between depression and weight cycle (odds ratio [OR] 1·42, 95% CI 1·31–1·55, $p \leq 7{\cdot}7 \times 10^{-16}$). The adult weight trajectories were heritable (using 5% weight change as the cutoff: $h_{SNP}^2$ of 2·1%, 95% CI 0·9–3·3, for stable weight; 4·1%, 1·4–6·8, for weight gain; 5·5%, 2·8–8·2, for weight loss; and 4·7%, 2·3–7·1%, for weight cycle). Anorexia nervosa PRS was positively associated with weight loss trajectory among individuals without eating disorder diagnoses ($OR_{1SD}$ 1·16, 95% CI 1·07–1·26, per 1 SD higher PRS, p=0·011), and the association was not attenuated by obesity PRS. No association was found between depression PRS and weight trajectories after permutation tests. All main findings were replicated in the UK Biobank (p<0·05).

**Interpretation—**Our findings suggest the importance of considering weight from a longitudinal aspect for its association with health and highlight a crucial role of weight management during disease development and progression.

**Funding—**Klarman Family Foundation, US National Institute of Mental Health (NIMH).

## Introduction

Adult weight trajectories can be clinically important, potentially serving as indicators of underlying health.[1] Phenome-wide association studies (PheWAS) allow us to test associations between weight trajectory and health status in large-scale electronic health records (EHRs), which contain longitudinal data including frequent objective weight

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measurements taken as part of typical clinic visits. Previous weight-related PheWAS examined body-mass index (BMI)-related genetic scores,[2–5] genetic variants,[6,7] or average BMI values,[8] but they have not yet explored longitudinal weight trajectories. Therefore, in this study, we aimed to use the multiple weight measures in the Bio*Me* Biobank[9] to identify diseases associated with weight trajectories in a patient population. Gaining insights into the associations of weight trajectories with diseases could aid in monitoring disease progression and predicting prognosis.

Similarly, previous genetic studies have investigated the role of obesity genetic risk in weight gain,[10,11] but much less is known regarding the low end of the weight spectrum; that is, whether higher genetic risk for anorexia nervosa is associated with adult weight loss trajectory, even among individuals without any clinical diagnoses. Anorexia nervosa, characterised by extremely low bodyweight, has one of the highest mortality rates of all psychiatric disorders, with the exception of substance abuse.[12,13] Unlike anorexia nervosa, depression could be associated with either loss of appetite and substantial weight loss or increased appetite and weight gain.[14,15] Both anorexia nervosa and depression have a genetic basis.[16,17] The genome-wide single-nucleotide polymorphism-based heritability ($h_{SNP}^2$) was estimated to be about 15% for anorexia nervosa and 9% for depression, on a liability scale.[16–18] To our knowledge, only one previous study thus far has examined the association of the polygenic risk score (PRS) of anorexia nervosa with weight trajectory across childhood and young adulthood (ages 10–24 years), but they did not find an association between higher genetic risk for anorexia nervosa and weight loss trajectory.[19] Less is known about the association between the genetic risk for depression and weight trajectories.

In our study, by using the data in the Bio*Me* Biobank EHR, we aimed to investigate whether the PRS of anorexia nervosa and depression are associated with longitudinal weight changes among adults (aged 25–85 years) without a clinical diagnosis of an eating disorder or depression. Additionally, to assess if the effect of the genetic risk for anorexia nervosa on weight loss trajectory is independent of the BMI-related or obesity-related genetic risk, we aimed to examine the anorexia nervosa PRS association with weight trajectory, adjusted for obesity PRS.

## Methods

### Study population

Bio*Me* is a non-selective patient-based EHR-linked biorepository at Mount Sinai Medical Center (New York, NY, USA). It serves a diverse population (28% African, 37% Hispanic Latino, 30% European, and 5% other ancestry). Genotyping was done with use of the Illumina Global Screening Array (Illumina, San Diego, CA, USA; appendix p 4).[20,21] All patient data in this study are subject to the general patient consent covered by the Bio*Me* Biobank. Because only deidentified patient data were used, our study was not considered as human research under the US Department of Health and Human Services regulations and was thus exempt from the Mount Sinai ethics committee. Additionally, our study complies with the regulation by the Health Insurance Portability and Accountability Act for the privacy of patient health data.

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### Weight trajectory

Weight was measured at each physician visit as part of routine clinical practice. Annual weight was calculated as an average of weight measures in kg within a calendar year. All participants with three or more annual weight measures were included to construct the weight trajectory. We did extensive data cleaning (appendix pp 4–6), and the final weight dataset included 21 487 participants with 162 783 annual weight measures.

We created weight trajectories following two weight change thresholds: 5%[22] and 10%,[23] based on previous evidence for clinical relevance. We generated four types of weight trajectories: stable weight, weight gain, weight loss, and weight cycle (figure 1; detailed definitions in the appendix, pp 5–6). Briefly, we classified individuals with minimal weight change as having a stable weight (eg, cutoffs of less than 5% or 10% weight change), and individuals with weight change greater than each cutoff as weight gain, loss, or cycle depending on the direction of weight changes. Stable weight, weight gain, and weight loss are mutually exclusive, as are weight cycle and stable weight. However, weight cycle can accompany weight gain or loss (figure 1).

### Bio*Me* diagnoses

We converted 13 659 International Classification of Diseases (ICD) codes in the Bio*Me* EHR into 1135 phecodes (appendix pp 6–7), because ICD codes are used primarily for billing rather than for research purposes. Phecodes combine ICD codes into disease groupings (eg, the anorexia nervosa phecode, 305.21, includes F50.00 unspecified anorexia nervosa, F50.01 restricting type anorexia nervosa, and F50.02 binge eating or purging type anorexia nervosa).

### PheWAS, heritability, and genetic correlation of weight trajectories

We tested for associations between weight trajectories (exposure) and phecodes (outcome) using the R PheWAS package,[24] adjusting for genotype-confirmed sex and ancestry, age at baseline, age$^2$, BMI at baseline, smoking status (ever or never tobacco user), alcohol use status (yes or no), and number of doctor visits. We used a logistic regression model given the binary phecode outcomes. We adjusted for doctor visits as a proxy for overall wellness level of the individuals. Only phecodes with an effective size ($N_{eff}$) higher than 100 were included in the PheWAS. The equation to determine effect sample size is:

$$N_{eff} = \frac{4}{(1/N_{Cases}) + (1/N_{Controls})}$$

We established significance using a two-sided Bonferroni-corrected p value of $4{\cdot}4 \times 10^{-5}$, accounting for 1135 phecodes. For the PheWAS plots, phecodes are grouped into 17 different disease categories (listed in appendix p 33).

We estimated $h_{SNP}^2$ with GCTA-GREML using variants with minor allele frequency (MAF) higher than 0·0001 (appendix p 7).[25] To test the robustness of the heritability estimation, we also assessed the heritability using variants with MAF higher than 0·01. We estimated

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genetic correlations among four weight trajectories using bivariate GREML analysis,[26] adjusted for baseline BMI.

## PRS analysis

To construct the PRS, we calculated PRS for anorexia nervosa and depression in the Bio*Me* population using the most recent genome wide association study (GWAS) for each disorder (this version does not include 23andMe data).[16,18] We also calculated obesity PRS as a positive control for weight gain trajectory.[27] PRS were calculated for individuals without any ICD (tenth version) codes for eating disorder (ED, F50) and depression (F32, F33) to investigate the role of anorexia nervosa and depression genetics on weight change in individuals without clinical diagnoses. Details on PRS calculation and quality control are shown in the appendix (pp 8–9).

Because these base GWAS only included participants of European ancestry, our primary PRS analyses were done in participants of European ancestry in the Bio*Me* Biobank (n=4979). We did 10 000 permutations to reduce the type I error. Exploratory analyses were done in other ancestries (African and Hispanic Latino) to examine the external validity of any suggestive association of anorexia nervosa PRS with weight trajectories. Ancestry was genotype-confirmed (HapMap 3 was used as a reference to infer genetic ancestry of the individuals),[28] and the three ancestry groups (European, African, and Hispanic Latino) are mutually exclusive to each other.

We adjusted for age at baseline, age$^2$, BMI at baseline, sex, disease or health history that might influence weight (ie, cancer, chronic obstructive pulmonary disease, HIV, hypothyroidism, end-stage renal disease, bariatric surgery, and pregnancy; more details in the appendix, pp 9–10), and genotype-derived principal components 1–5. We adjusted for disease history to better estimate the effect of anorexia nervosa PRS on weight trajectory and the amount of variance that anorexia nervosa PRS could explain that is not influenced by disease status. Sensitivity analyses were done to adjust for smoking status and alcohol use status.

To examine the effect of PRS on weight trajectory in a low versus high genetic risk population, we did follow-up PRS analyses that examined the association of PRS deciles (exposure—eg, top *vs* bottom decile) with weight trajectories (outcome—eg, weight loss trajectory *vs* stable weight as the reference group); these were done in R using logistic regression (version 3.5.3). We tested sex modification of the association of PRS with weight trajectories for any significant findings from the main PRS analyses ($p_{empirical}<0{\cdot}05$). Further conditional analyses were done to assess the independence of anorexia nervosa PRS, depression PRS, and obesity PRS regarding their effects on weight trajectory. To compare the genetic and phenotypic associations of anorexia nervosa and depression with weight trajectories, we also tested the association of eating disorder (305.2) and depression (296.2) phecodes with weight trajectories in the European participants. We used the eating disorder phecode (305.2, n=9) rather than anorexia nervosa (305.21) because very few European individuals had an anorexia nervosa diagnosis record and all covariate information available in the Bio*Me* Biobank (n=1).

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### Replication in UK Biobank

We extended our main findings to the UK Biobank, which is a longitudinal population-based cohort with repeated weight measures in a subset of individuals (two to four weight measures per individual collected at assessment centre visits, n=59 561), to examine whether our findings are generalisable to a fairly healthy population.[29] Covariates included in the replication analysis of weight cycle trajectory and depression were sex, ethnicity, age at baseline, age$^2$, and BMI at baseline. Additional covariates included in the anorexia nervosa PRS analysis were genotype batches and genetic principal components 1–5. The meta-analysis of $h_{SNP}^2$ across Bio*Me* and the UK Biobank was done with the metafor package in R (version 3.5.3), using inverse-variance weighting and a fixed-effects model.

### Role of the funding source

The funding source had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

## Results

We created four weight trajectories: stable weight, weight gain, weight loss, and weight cycle (table 1, figure 1) for 20 550 Bio*Me* participants included in the PheWAS analyses. On average, Bio*Me* participants have a median of seven annual weight measures (IQR 5–10, range 3–18) across an 8 year span (IQR 5–10, range 2–21). The largest weight changes per year per individual ranged from −59 kg to +30 kg. Using a 5% weight change cutoff, we assessed the accuracy of weight trajectory classifications through manual review of 100 random individuals (appendix p 34) with similar weight trajectory distributions as in the overall samples (appendix p 35). Excellent sensitivity (≥97%), specificity (≥98%), and accuracy (≥98%) were achieved for weight trajectory classifications (appendix p 36).

With a 5% cutoff, all trajectories were heritable, with $h_{SNP}^2$ of 2·1% (95% CI 0·9–3·3) for stable weight, 4·1% (1·4–6·8) for weight gain, 5·5% (2·8–8·2) for weight loss, and 4·7% (2·3–7·1) for weight cycle ($p \leq 5{\cdot}5 \times 10^{-11}$; appendix pp 37–38). The heritability estimates were robust regardless of the choice of MAF (≥0·0001 or ≥0·01) and remained significant after adjusting for baseline BMI ($p \leq 2{\cdot}1 \times 10^{-6}$, appendix pp 37–38). Additionally, we replicated the heritability in the UK Biobank, in which most individuals had a stable weight trajectory (34 799 [58%] of 59 561 *vs* 3444 [17%] of 20 550 in Bio*Me*, appendix p 39). The participants in the UK Biobank have a median of two annual weight measures (IQR 2–2, range 2–4) across a 9 year span (IQR 6–10, range 2–14). We could not assess heritability of weight cycle trajectory accurately in the UK Biobank because most participants (48 908 [82%] of 59 561) had only two weight measures (appendix pp 37–38). Across the two biobanks, the meta-analysed $h_{SNP}^2$ was 2·7% (1·6–3·7) for stable weight, 5·0% (3·1–6·9) for weight gain, and 5·6% (3·7–7·5) for weight loss (appendix p 19).

Weight loss trajectory had a strong negative correlation with weight gain trajectory (phenotypic correlation, $r_{phenotype}$=−0·53; genetic correlation, $r_g$=−0·85), and a weaker negative correlation with stable weight ($r_{phenotype}$=−0·36, $r_g$=−0·23). Weight cycle was weakly correlated with weight loss and weight gain only on a genetic level ($r_{phenotype}$=0·05

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for weight loss, $r_{phenotype}$=−0·03 for weight gain; $r_g$ 0·22=for weight loss, $r_g$=−0·31 for weight gain; appendix pp 20–21).

We did a PheWAS for each weight trajectory at the 5% cutoff (presented here and in the appendix, pp 12–13, 40–51, 68–74, 87–91) and 10% cutoff (shown in appendix pp 14–15, 30, 52–67, 75–82, 87–91), as well as stratified by sex (shown in the appendix, pp 12–15, 27–29, 32, 92–115). Using the 5% cutoff, after Bonferroni correction, we identified 13 diseases positively associated with weight gain trajectory, 36 diseases with weight loss, and 143 diseases with weight cycle. We found a consistently negative relationship between diseases and maintaining stable weight (103 diseases, figure 2). For example, depression was negatively associated with stable weight trajectory (odds ratio [OR] 0·63, 95% CI 0·55–0·72, $p=7{\cdot}5 \times 10^{-12}$; appendix p 48).

The strongest positive associations for the weight gain trajectory were a cluster of obesity-related phecodes (OR 2·81, 2·50–3·16, $p \leq 6{\cdot}5 \times 10^{-41}$; figure 2, appendix p 40), whereas the top phecode positively associated with weight loss was protein-calorie malnutrition (4·30, 3·28–5·65, $p=6{\cdot}3 \times 10^{-26}$; figure 2, appendix p 41). No disease was simultaneously positively associated with weight gain and weight loss (appendix pp 22–23).

We identified 110 phecodes uniquely associated with weight cycle trajectory (ie, Bonferroni-corrected significant only for weight cycle, but not for weight gain or weight loss), including depression-related phecodes (OR 1·42, 1·31–1·55, $p \leq 7{\cdot}7 \times 10^{-16}$, appendix p 42). This was replicated in the UK Biobank (1·25, 0·96–1·62, p=0·092, with a 5% cutoff; 1·95, 1·17–3·24, p=0·010, with a 10% cutoff). Additionally, we did a sensitivity analysis using a stricter definition of weight cycle in the Bio*Me* (ie, only including individuals with five or more weight points and three inflection points to ensure there was a clear cyclical pattern; appendix p 83) and the result for depression remained.

Our sex-stratified PheWAS results suggest that some weight trajectory–phenotype associations could be sex-specific. For example, using a 5% weight change cutoff, we identified three sex-stratified positive associations with weight gain (eg, greater risk in female individuals with obstructive sleep apnoea than in male individuals), six with weight loss (eg, positive association with osteoporosis only in female individuals when using Bonferroni-corrected significance threshold), and ten with weight cycle (eg, positive association with vitamin B-complex deficiencies only in male individuals when using Bonferroni-corrected significance threshold; appendix pp 92–115).

Next, to investigate our hypothesis of whether individuals at a higher genetic risk of anorexia nervosa are also at a higher risk of weight loss, we examined the association of anorexia nervosa PRS with weight trajectories. First, as a positive control, we confirmed that obesity PRS was associated with a weight gain trajectory ($OR_{1SD}$ 1·14 per 1 SD higher PRS, 95% CI 1·04–1·24, $p_{empirical}$=0·042; appendix p 84) and that individuals in the top obesity PRS decile had increased likelihood of a weight gain trajectory compared with those in the bottom decile (top *vs* bottom OR 1·38, 0·95–2·01; figure 3).

Next, we found that anorexia nervosa PRS was positively associated with weight loss trajectory ($OR_{1SD}$ 1·16, 1·07–1·26, $p_{empirical}$=0·011, $R^2$=0·52%; appendix p 85) and

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negatively associated with stable weight trajectory ($OR_{1SD}$ 0·89, 0·83–0·95, $p_{empirical}$=0·027, $R^2$=0·29%). Individuals in the top decile of anorexia nervosa PRS (who did not have a clinical eating disorder diagnosis) were twice as likely to have a weight loss trajectory (top *vs* bottom OR 1·95, 1·36–2·82) and half as likely to have a stable weight trajectory (0·58, 0·43–0·79) compared with individuals in the bottom decile (figures 3, 4 and table 2). The association between anorexia nervosa PRS and weight loss had a consistent direction of effect whether using individuals with stable weight as controls (as previously) or all non-weight-loss individuals as controls (top *vs* bottom OR 1·42, 1·07–1·88). On average, anorexia nervosa PRS scores were highest in individuals with weight loss trajectories, followed by those with stable weight, and then those with weight gain (appendix p 24). We found no sex modification effect (p=0·58) and no effect difference in those who had a weight loss trajectory with or without weight cycle (p=0·22). We also observed consistent directions of effect among African (top *vs* bottom OR 1·90, 1·14–3·19) and Hispanic individuals (1·27, 0·82–1·98), although these estimates were not significant when PRS was modelled continuously ($p_{empirical}$=0·27 for African individuals and $p_{empirical}$=0·63 for Hispanic Latino individuals). To further corroborate our finding, we were able to replicate the association between anorexia nervosa PRS and weight loss in the UK Biobank ($OR_{1SD}$ 1·03, 1·00–1·05, p=0·024; top *vs* bottom OR 1·17, 1·06–1·30, $p=2{\cdot}9 \times 10^{-3}$, table 2).

We did additional sensitivity analyses to test the mediating effect of obesity PRS on the effect of anorexia nervosa PRS on weight loss trajectory. The association changed minimally in both biobanks (table 2), indicating little genetic overlap between anorexia nervosa PRS and obesity PRS regarding their effects on weight loss trajectory. This finding was supported by the minimal overlap between the number of single-nucleotide polymorphisms included for the anorexia nervosa and obesity PRS in Bio*Me* (<1% overlap, appendix p 25). The positive association between anorexia nervosa PRS and weight loss remained after further adjustment for smoking and alcohol use status (more sensitivity analyses presented in the appendix, p 17).

Finally, we did not observe any association of depression PRS with weight trajectories (ie, gain, loss, or cycle; $p_{empirical}$≥0·17, appendix pp 17–18, 86), nor did we observe a mediating effect of depression PRS on the association between anorexia nervosa PRS and weight loss (table 2).

## Discussion

Weight changes can be an important indicator of individual health status. However, the association of weight trajectories with the full disease spectrum, as well as their genetic causes, remains unclear. Our study defined and constructed four weight trajectories among adults and showed that a stable weight trajectory is associated with lower risk of diseases. These negative associations remained when restricted to individuals with at least seven annual weight measures (appendix pp 16, 87–91), suggesting a robust association of stable weight with lower risk of diseases that is unlikely to be influenced by misclassification of individuals with fewer weight measures as having stable weight (appendix pp 16, 87–91). Because our study concerned weight trajectory rather than absolute weight or BMI, we corrected for BMI at baseline. Our association between stable weight and lower risk

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of diseases, then, is striking; having a stable weight was associated with a lower risk of diseases, regardless of BMI. Future studies that adjust for more granular terms for baseline weight and BMI might be of interest (eg, central adiposity, muscle mass, and bone mass). It is important to keep in mind that our analysis is cross-sectional and it does not infer causality from maintaining a stable weight to being disease-free, and does not suggest that maintaining a stable weight at the extreme ends of the weight spectrum is health promoting (eg, severely underweight or severely obese), given most people with a stable weight in our study had BMIs ranging from 21·1 (tenth percentile) to 35·9 (90th percentile). By contrast, we found strong associations between weight cycling and depression in both the Bio*Me* and UK Biobank. Although we cannot infer causality, this association is in line with well established roles for appetite and weight change as vegetative signs of depression.

To our knowledge, no study to date has explored the genetic basis of adult weight trajectories. Here, we showed that weight trajectory is heritable, even when adjusting for baseline BMI (appendix pp 37–38); that is, weight change is itself heritable and genetically regulated, regardless of underlying bodyweight. Our results were robust to MAF cutoff. Additionally, we mostly replicated the heritability of weight trajectory in the UK Biobank, which is comprised of individuals with predominantly European ancestry (eg, $h_{SNP}^2$ of 5·5% for weight loss in Bio*Me*, and 5·7% in the UK Biobank), further suggesting that the heritability estimates of weight trajectory are less likely to be influenced by ancestry composition (eg, inflation due to population stratification). However, we were unable to replicate the heritability of weight cycle in the UK Biobank due to the small number of individuals with sufficient data to identify weight cycles (617 for the 5% cutoff and 108 for the 10% cutoff).

Given the role of weight loss in anorexia nervosa aetiopathology, we next sought to establish whether polygenic risk for anorexia nervosa regulates weight loss among adults, selecting a 5% weight change cutoff to maximise sample size. We found that higher anorexia nervosa PRS was associated with having a weight loss trajectory. To our knowledge, our study is the first to show that anorexia nervosa PRS is associated with weight change among adults without clinical diagnoses of eating disorders. Replication in the UK Biobank, the use of obesity PRS with weight gain trajectory as a positive control, the dose–response relationship observed across anorexia nervosa PRS deciles, the consistent effect direction across ancestry groups (European, African, and Hispanic Latino), and the reduction of false positive rate through permutation strongly support our finding of the association of a higher anorexia nervosa PRS with having a weight loss trajectory. Additionally, we showed in the UK Biobank that the association between anorexia nervosa PRS and weight loss was not mediated through obesity genetics. One previous study examining the effect of anorexia nervosa PRS on early weight trajectory (from birth to age 24 years)[19] found a negative (albeit non-significant) association between anorexia nervosa PRS and weight change (per 1 SD higher anorexia nervosa PRS, weight was lowered by 0·63% in female individuals and 0·44% in male individuals, $p \geq 0·13$). Future studies that examine the causal effects of anorexia nervosa and obesity on a given weight trajectory would be of interest, using tools such as multivariable Mendelian randomisation. We excluded individuals with eating disorders or depression in the PRS analysis, so the association between anorexia nervosa

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PRS and weight was less likely to be driven by the disease itself and more likely to be driven by genetics.

Our study has several limitations that are worth mentioning. First, we cannot distinguish unintentional from intentional weight loss from the weight data. Second, weight measures are taken on an ad-hoc basis, with no set timeframe, and measurement error can occur. However, one past study found a very high correlation (0·99)[30] between clinic-measured weight and researcher-measured weight. Additionally, we achieved a weight trajectory classification accuracy of 98% or higher (appendix p 36) through minimising misclassification by studying the overall weight trajectory using annual weight and by removing implausible weight outliers. Although we reduced error in weight through studying annual weight, we lost the granularity to model weight changes happening within a year. Third, our PheWAS analysis is cross-sectional and does not imply causality. Fourth, undiagnosed patients in the Bio*Me* Biobank might be included in our analysis. For example, an individual might not have an EHR record of anorexia nervosa if they had an anorexia nervosa-related visit at another healthcare facility or when they were adolescents (the youngest patient included in this study was aged 25 years). However, given the low prevalence of anorexia nervosa (approximately 1%)[31] and our exclusion of individuals with any eating disorder diagnosis, we expect the impact of diagnostic contamination to be minimal.[9] Fifth, our analysis relied on PRS derived from a European anorexia nervosa GWAS,[16] reducing predictive accuracy in individuals with African and Hispanic Latino ancestry. Future GWAS that include diverse populations are crucial to accurately estimate the heritability of weight trajectories and the effect of anorexia nervosa PRS across ancestries.

Our study also has notable strengths. First, we used hundreds of thousands of objectively measured weights, taken as part of the routine clinical practice in Bio*Me* EHR data, to construct weight trajectories, yielding significant power. The extensive weight measurements made it possible to construct weight trajectories in a sample size of 21 487 for the first time, with a median of seven weight measurements per patient (IQR 5–10) spanning 8 years (5–10). Next, we used the repeated weight measures collected at assessment centres in the UK Biobank for replication in a generally healthy population with a sample size of 59 561, with a median of two weight measures (2–2) per person spanning 9 years (6–10). Objective weight measures are less prone to subjective perception and self-sensitivity to weight than the self-reported weight changes in the UK Biobank. For example, among 4639 individuals who always self-reported weight gain, 2590 (56%) had a stable weight trajectory (weight change <5%), and among 22 446 who always self-reported stable weight, 2155 (10%) had a weight gain trajectory (measured weight gain ≥5%). Second, the associations of weight cycle across the disease spectrum have not yet been deeply studied. In our analysis, we identified 70 diseases associated with weight cycle under both 5% and 10% cutoffs. Third, to our knowledge, this is the first time that heritability of adult weight trajectory was assessed and replicated. Fourth, the replication in the UK Biobank strengthens the generalisability of our key findings from a patient population to a general population.

To summarise, maintaining a stable weight is an indicator of wellbeing, shown by its negative associations with various diseases, whereas fluctuating weight is associated with

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diseases such as depression. Additionally, adult weight trajectories are heritable and have genetic links with anorexia nervosa, such that adults with higher genetic risk of anorexia nervosa are more likely to lose weight. Future studies are necessary to identify shared and distinct genetic pathways of anorexia nervosa and obesity related to weight regulation.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Data sharing

The genotype and electronic health record datasets for the Bio*Me* participants in this study is not publicly available and will only be made available through appropriate collaboration or data sharing agreements. Data in the UK Biobank can be applied through the UK Biobank website (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). Full PheWAS summary statistics and codes for constructing the longitudinal weight trajectories in a biobank setting are available on GitHub (https://github.com/xuj18/BioMe_weight_project).

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## Research in context

### Evidence before this study

We used PubMed and medRxiv to search for phenome-wide association studies (PheWAS) on weight or body-mass index (BMI). For the weight PheWAS, we used the following search terms: "(phewas[tiab] OR phenome wide[tiab]) AND (weight[tiab] OR BMI[tiab] OR body mass index[tiab])" on PubMed, and "phewas weight", "phewas BMI", "phewas body mass index", "phenome weight", "phenome BMI", or "phenome body mass index" for abstract or title search on medRxiv (up to Feb 2, 2022) with no language restrictions. The literature search identified 63 studies in total. From title screening, 16 studies were further reviewed, and seven studies were ultimately included as relevant evidence of PheWAS on weight or BMI. These seven PheWAS included five studies in adult populations of European ancestry and two studies in children of European ancestry. The weight-related exposure variables used in these studies were genetic variants of the obesity-associated FTO gene, BMI-associated single-nucleotide polymorphisms (SNPs), BMI polygenic risk scores (PRS), BMI value, obesity PRS, and obesity status. Through using BMI or obesity-related exposures, these PheWAS identified comorbidities associated with obesity, including type 2 diabetes, sleep apnoea, hypertension, oedema, liver disease, asthma, bronchitis, earlier age of puberty, hypothyroidism, and nerve disorders in at least two of the PheWAS. The childhood PheWAS by Millard and colleagues found positive associations of BMI PRS with multiple biomarkers, including leptin, C-reactive protein, interleukin 6, triglyceride, and very low-density lipoprotein, and a negative association with high-density lipoprotein. The BMI PheWAS by Schlauch and colleagues in adults observed that hyperlipidaemia and gastroesophageal reflux disease were only significantly associated with BMI on a phenotypic level but not on a genetic level (eg, BMI or obesity SNPs), probably because of the small effect of genetic variants.

Regarding the effect of anorexia nervosa and depression genetic risk on weight trajectory, we searched PubMed with the search terms "anorexia nervosa[title] AND (weight[title] OR BMI[title] OR body mass index[title]) AND (genetic[tiab])" or "depression[title] AND (weight[title] OR BMI[title] OR body mass index[title]) AND (genetic[tiab])", and we searched abstracts or titles on medRxiv with the terms "anorexia polygenic weight" or "anorexia polygenic BMI" or "anorexia polygenic body mass index" or "depression polygenic weight" or "depression polygenic BMI" or "depression polygenic body mass index" (up to Feb 2, 2022) with no language restrictions. The literature search identified 59 studies in total, and 31 were further reviewed through title screening. No studies were identified that examined the effect of depression genetic risk on BMI or weight, and only two were included as relevant evidence of anorexia nervosa genetic risk on BMI. Of these two studies, the one by Leehr and colleagues was cross-sectional in a small adult sample (ages 18–59 years, n=380), and the other one by Abdulkadir and colleagues was longitudinal in children and young adults in the ALSPAC cohort (ages 10–24 years, n=8654). Both studies were balanced in male to female ratio (close to 1:1) and found that anorexia nervosa PRS was associated with lower BMI only in female individuals. Only

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the study by Abdulkadir and colleagues assessed weight trajectory, but it did not observe any significant results.

**Added value of this study**

In this study, we created a novel inflection-point based method to classify weight trajectory using extensive weight records in electronic health records, taken as part of routine clinical care, in a racially diverse hospital-based biobank (Mount Sinai Bio*Me* Biobank), with an accuracy of 98% or higher through our validation study (n=100). Through this novel approach, we were able to examine comorbidity associated with weight changes across the weight spectrum and across time. Additionally, this approach afforded us the opportunity to study weight cycle, which has been less commonly studied in previous literature compared with weight gain or weight loss.

We found that being in the stable weight trajectory was consistently associated with lower risk of diseases. Using 5% as the cutoff for clinically relevant weight change, we identified 143 diseases positively associated with weight cycle (eg, depression, anaemias, and renal failure), 13 diseases positively associated with weight gain trajectory (eg, obesity, obstructive sleep apnoea, and oedema), and 36 positively associated with weight loss (eg, protein-calorie malnutrition, gastrointestinal complications, and end-stage renal disease), after Bonferroni correction. Additionally, we did, to our knowledge, the first sex-stratified PheWAS related to weight trajectory and identified three sex-stratified positive associations with weight gain (eg, obstructive sleep apnoea in female individuals), six with weight loss (eg, osteoporosis in female individuals), and ten with weight cycle (eg, vitamin B-complex deficiencies in male individuals).

On a genetic level, our study answered the question of the influence of anorexia nervosa genetic risk on weight trajectory in the adult population (ages 25–85 years), in which we found that higher anorexia nervosa genetic risk was associated with weight loss trajectory, regardless of sex, in adults of European ancestry (male to female ratio was close to 1:1), and this effect was independent of the influence of obesity or BMI-related genetic variants on weight. Additionally, we observed this association between anorexia nervosa PRS and weight loss in both a patient population (Bio*Me* Biobank) and a general population (UK Biobank).

**Implications of all the available evidence**

PheWAS is an excellent tool for exploring comorbidities associated with weight trajectory across the weight spectrum. Our PheWAS findings identified diseases associated with particular weight trajectories (eg, depression and weight cycle), which might reflect characteristics of these diseases, including age of onset, progression pattern, severity, and chronicity (eg, the episodic nature of depression with the weight cycle pattern).

Our study also suggests that people of European ancestry who have high anorexia nervosa genetic risks are at greater risk of having a weight loss trajectory during adulthood. Similar direction of effect was observed in other ancestries, although not significant with permutation. Additionally, given the limited amount of variation in the outcome of interest (eg, weight loss) explained by the anorexia nervosa PRS, PRS might

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have to be jointly modelled with other risk factors to predict weight loss more accurately or to identify subgroups at risk of weight loss. Furthermore, given our finding that the effect of anorexia nervosa genetics on weight loss was minimally affected by obesity-related genetics, and the previously reported low genetic correlation of −0·22 between anorexia nervosa and obesity in the 2019 anorexia nervosa GWAS, these findings might indicate that anorexia nervosa-related and obesity-related weight changes might have unique genetic underpinnings. Future studies that include more diverse populations and assess the pathway-specific genetic risks of different weight trajectories will further our understanding of the genetic architecture of longitudinal weight trajectory.

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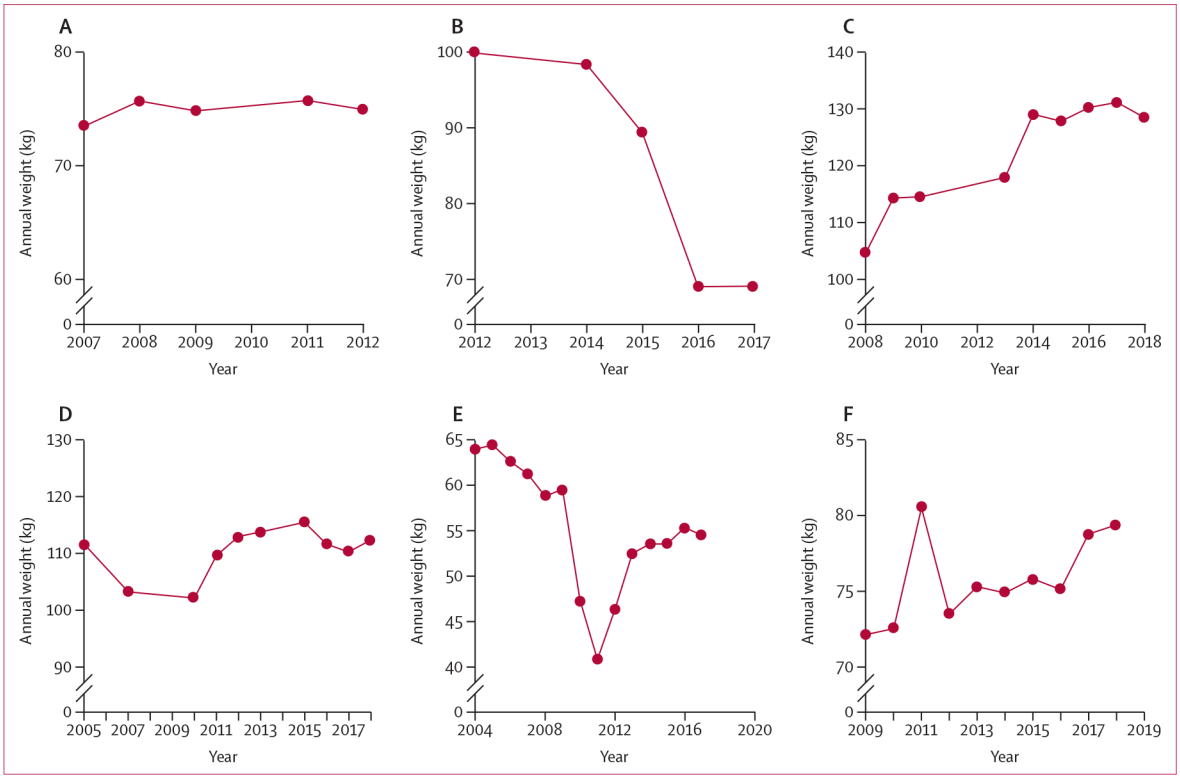


**Figure 1: Examples of different types of individual weight trajectories based on annual weight**

(A) Stable weight trajectory. (B) Weight loss trajectory. (C) Weight gain trajectory. (D) Weight cycle trajectory. (E) Weight cycle plus weight loss trajectory. (F) Weight cycle plus weight gain trajectory.

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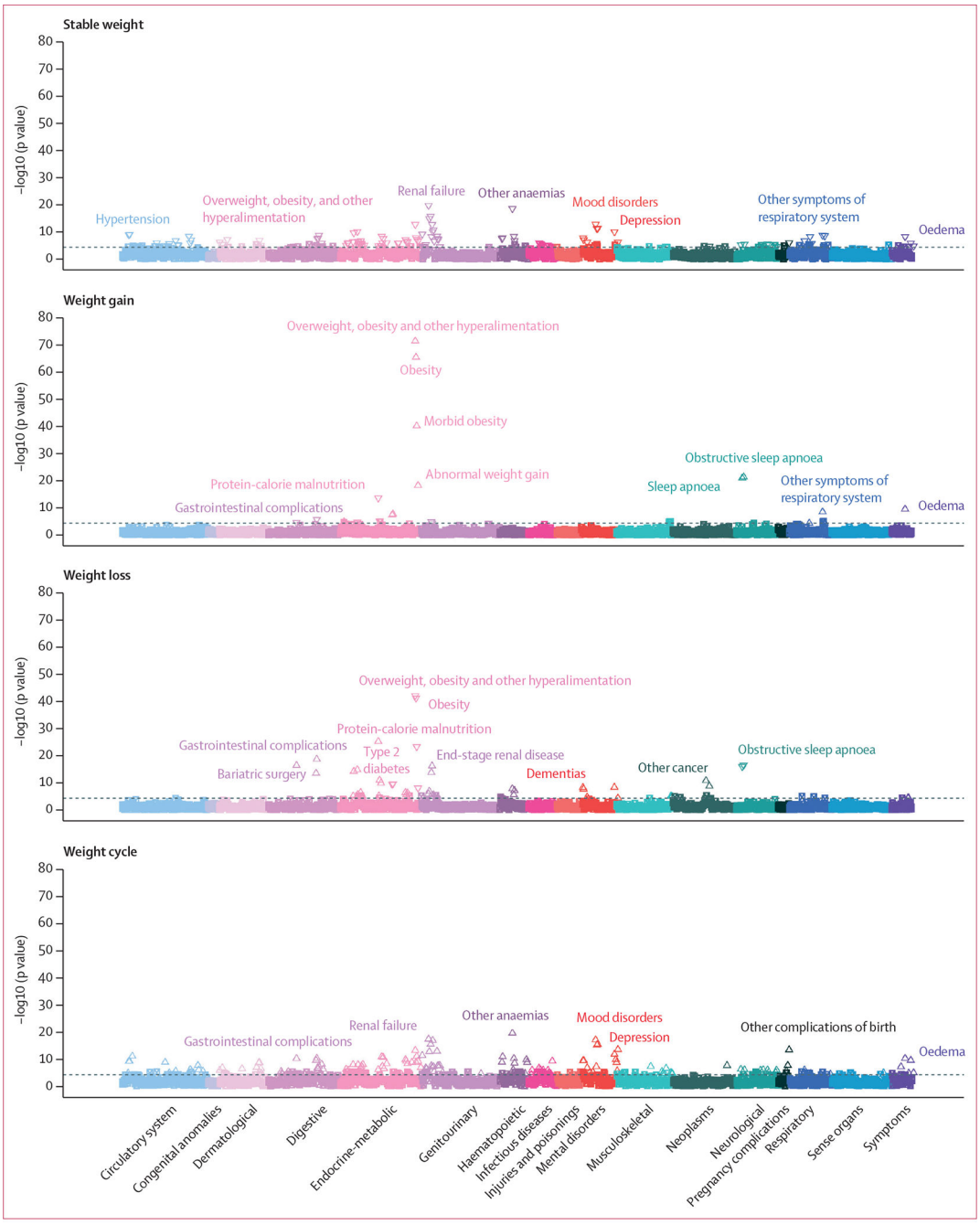


**Figure 2: Phenome-wide association plots of weight trajectories with the Bio*Me* Biobank phecodes with the 5% weight change cutoff**

Phecodes above the blue line passed the Bonferroni-corrected p value threshold ($p \leq 4{\cdot}4 \times 10^{-5}$). Phecodes are grouped into 17 different disease categories (appendix p 33). An upward triangle (Δ) denotes a positive association, whereas a downward triangle (∇) denotes a negative association. The top associations are annotated in each plot.

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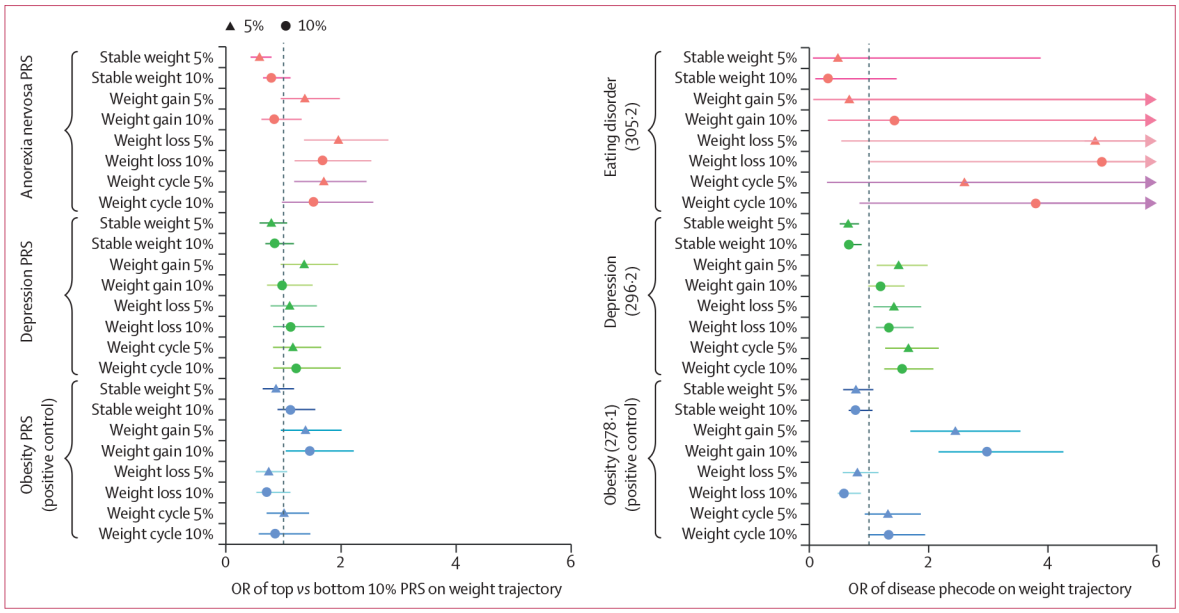


**Figure 3: Associations of anorexia nervosa and depression with weight trajectories in participants with European ancestry in the Bio*Me* Biobank**

The left panel shows the OR of individuals in the top versus bottom decile of PRS (anorexia nervosa, depression, and obesity class I) with different weight trajectories (defined by either 5% or 10% weight change cutoff). The right panel shows the association of anorexia nervosa and depression with different weight trajectories on a phenotypic level using phecodes as the exposure. Individuals with stable weight were used as controls for those with weight gain, weight loss, and weight cycle trajectories. Given the small sample size of individuals with diagnosed anorexia nervosa in the European ancestry samples (n=1), its parent phecode, eating disorder, was used for the phenotypic association (n=9). Obesity PRS and phecode were used as positive controls. OR=odds ratio. PRS=polygenic risk score.

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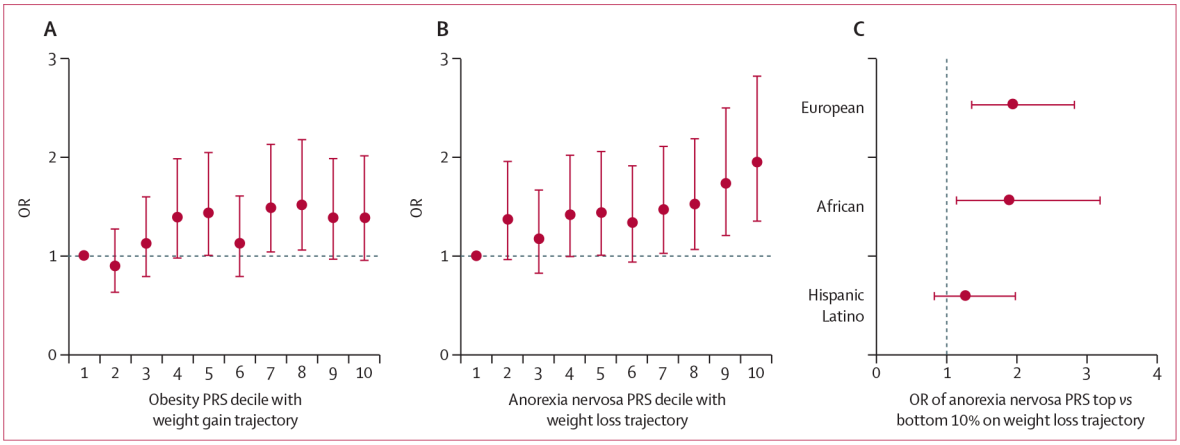


**Figure 4: Associations of PRS with weight trajectory by deciles and by ancestry**

(A) OR of each obesity PRS decile with weight gain trajectory, using the bottom decile as the reference group. (B) OR of each anorexia nervosa PRS decile with weight loss trajectory, using the bottom decile as the reference group. (C) OR of individuals in the top versus bottom decile of anorexia nervosa PRS with weight loss trajectory (defined by 5% cutoff) across different ancestry groups (European, African, or Hispanic Latino). OR=odds ratio. PRS=polygenic risk score.

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**Table 1:**

Characteristics of participants included in PheWAS and PRS analyses

| | Overall (PheWAS; n=20 550) | European ancestry (PRS; n=4904) | African ancestry (PRS; n=3799) | Hispanic Latino ancestry (PRS; n=3930) |
|---|---|---|---|---|
| Sex | | | | |
| Male | 7858 (38%) | 2286 (47%) | 1434 (38%) | 1487 (38%) |
| Female | 12 692 (62%) | 2618 (53%) | 2364 (62%) | 2443 (62%) |
| Age, years | | | | |
| 25–29 | 2210 (11%) | 500 (10%) | 395 (10%) | 491 (12%) |
| 30–39 | 3010 (15%) | 674 (14%) | 579 (15%) | 573 (15%) |
| 40–49 | 4454 (22%) | 864 (18%) | 956 (25%) | 786 (20%) |
| 50–59 | 5046 (25%) | 1140 (23%) | 954 (25%) | 909 (23%) |
| 60–69 | 3718 (18%) | 1029 (21%) | 610 (16%) | 715 (18%) |
| 70–79 | 1911 (9%) | 607 (12%) | 276 (7%) | 415 (11%) |
| 80–85 | 201 (1%) | 90 (2%) | 28 (1%) | 41 (1%) |
| BMI, kg/m$^2$ | | | | |
| <18·5 | 322 (2%) | 101 (2%) | 58 (2%) | 36 (1%) |
| 18·5 to <25 | 5832 (28%) | 2071 (42%) | 828 (22%) | 862 (22%) |
| 25 to <30 | 6676 (32%) | 1642 (33%) | 1136 (30%) | 1415 (36%) |
| 30 to <35 | 4138 (20%) | 693 (14%) | 840 (22%) | 951 (24%) |
| 35 to <40 | 1985 (10%) | 259 (5%) | 483 (13%) | 386 (10%) |
| ≥40 | 1597 (8%) | 138 (3%) | 453 (12%) | 280 (7%) |
| Number of doctor visits * | 50 (23–100) | 28 (15–56) | 50 (24–92) | 42 (20–85) |
| Alcohol use † | 10 239 (50%) | 3015 (61%) | 1709 (45%) | 1608 (41%) |
| Ever smoking ‡ | 10 452 (51%) | 2285 (47%) | 1995 (53%) | 1796 (46%) |
| Number of weight measures per person | 8 (5–10) | 7 (4–9) | 7 (5–10) | 7 (4–10) |
| Time span of weight measures, years | 8 (5–10) | 7 (5–9) | 8 (5–10) | 7 (5–10) |
| Weight trajectory (5% change) § | | | | |
| Stable weight | 3444 (17%) | 1200 (24%) | 584 (15%) | 722 (18%) |
| Weight gain | 6642 (32%) | 1526 (31%) | 1251 (33%) | 1296 (33%) |
| Weight loss | 7782 (38%) | 1616 (33%) | 1467 (39%) | 1470 (37%) |
| Weight cycle | 9472 (46%) | 1810 (37%) | 1773 (47%) | 1649 (42%) |
| Weight trajectory (10% change) ¶ | | | | |
| Stable weight | 10 242 (50%) | 3002 (61%) | 1824 (48%) | 2054 (52%) |
| Weight gain | 4069 (20%) | 827 (17%) | 781 (21%) | 784 (20%) |
| Weight loss | 5013 (24%) | 878 (18%) | 983 (26%) | 912 (23%) |
| Weight cycle | 3443 (17%) | 545 (11%) | 619 (16%) | 525 (13%) |

Data are n (%) or median (IQR). Overall includes participants of different ancestry groups, such as European (30%), African (28%), and Hispanic (37%), among others. This was the sample size used for the PheWAS analysis and thus some of the individuals might not have genetic data, whereas samples used in the PRS analysis all have genetic data.

BMI=body-mass index. PheWAS=phenome-wide association study. PRS=polygenic risk score.

[*] Total number of doctor visits in the electronic health records.

[†] A participant would be classified as an alcohol user if they had any record of being marked as “is an alcohol user” during the study; missing values for alcohol use in 330 European (7%), 96 African (3%), and 143 Hispanic participants (4%).

[‡] Applies to any type of tobacco products (eg, cigarette, pipe, cigar, snuff, and chew); for the main PRS analysis, this covariate was not included; missing values for smoking status in 113 European (2%), 32 African (1%), and 70 Hispanic participants (2%).

[§] Weight trajectory was defined with use of the 5% cutoff for weight change; stable weight is mutually exclusive from weight gain, weight loss, and weight cycle; however, weight cycle could accompany weight gain or weight loss, and thus the sum of each column can exceed 100% (ie, the weight loss category contains individuals with only weight loss as well as those who had weight loss plus weight cycle; the same is applied to weight gain).

[¶] Weight trajectory was defined with use of the 10% cutoff for weight change.

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**Table 2:**

The association of anorexia nervosa PRS with weight loss trajectory in the discovery cohort (Bio*Me* Biobank) and the replication cohort (UK Biobank)

| | Top *vs* bottom decile OR | p value |
|---|---|---|
| **Bio*Me* Biobank** | | |
| Original | 1·95 (1·36–2·82) | $3{\cdot}5 \times 10^{-4}$ |
| Conditioning on obesity PRS | 1·94 (1·35–2·81) | $4{\cdot}0 \times 10^{-4}$ |
| Conditioning on depression PRS | 1·92 (1·33–2·79) | $5{\cdot}0 \times 10^{-4}$ |
| Additional adjustment of smoking status and alcohol use | 1·79 (1·23–2·62) | $2{\cdot}6 \times 10^{-3}$ |
| **UK Biobank** | | |
| Replication | 1·17 (1·06–1·30) | $2{\cdot}9 \times 10^{-3}$ |
| Conditioning on obesity PRS | 1·17 (1·06–1·30) | $3{\cdot}0 \times 10^{-3}$ |

Data are OR (95% CI) unless otherwise specified. OR=odds ratio. PRS=polygenic risk score.