Weight Fluctuation and Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

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Abstract

The association between body weight fluctuation and the risk of cardiovascular disease (CVD) has been investigated previously with mixed findings. However, there has been no extensive study which systematically evaluates the current evidence. Furthermore, the impact of ethnicity and type 2 diabetes on this phenomena has not yet been investigated. Therefore, the aim of this study was to comprehensively evaluate the effect of weight fluctuation on risk of CVD (any cardiovascular (CV) event, composite CV outcome, CV death, Stroke, Myocardial Infarction) and the influence of ethnicity and type 2 diabetes status on the observed association. A systematic review and meta-analysis was performed according to the meta-analyses of observational studies in epidemiology (MOOSE) guidelines. The electronic databases PubMed, Web of Science, and the Cochrane Library were searched for studies that investigated the relationship between body weight or BMI fluctuation and CV diseases using Medical Subject Headings (MeSH) terms and keywords. The relative risks (RRs) for the outcomes were collected from studies, pooled, and analysed using a random-effects model to estimate the overall relative risk. Of 5645 articles screened, 23 studies with a total population of 15,382,537 fulfilled the prespecified criteria and were included. Individuals in the highest strata of body weight fluctuation were found to have significantly increased risk of any CV events (RR = 1.27; 95% Confidence Interval (CI) 1.17–1.38; P < 0.0001), cardiovascular death (RR = 1.24; 95% CI 1.02–1.46), myocardial infarction (RR = 1.32; 95% CI 1.09–1.59; P = 0.0037), stroke (RR = 1.21; 95% CI 1.19–1.24; P < 0.0001), and compound CVD outcomes (RR = 1.36; 95% CI 1.08–1.73; P = 0.01). Similar RRs were observed regarding BMI fluctuation and per unit standard deviation (SD) increase in body weight fluctuation. Comparable effects were seen in people with and without diabetes, in White Europeans and Asians. In conclusion, body weight variability is associated with increased risk of CV diseases regardless of ethnicity or diabetes status. Future research is needed to prove a causative link between weight cycling and CVD risk, as appropriate interventions to maintain stable weight could positively influence CVD.

Introduction

Obesity is the strongest risk factor for both T2D and CVD (1). Adolescents with a BMI over 30 at 18 years of age have a greater than 50% risk of developing T2D during their life (1). Furthermore, the lifetime risk of incident CVD has been shown to be higher in overweight and obese adults, with hazard ratios of 1.67 (95% CI 1.55–1.79) and 1.85 (95% CI 1.72–1.99) for obese mean and women, respectively (2). As T2D independently increases the risk of CVD (3), the combination of obesity and T2D can be considered particularly adverse.

Due to the large contribution that obesity has to both T2D and CVD, weight loss is commonly recommended as a lifestyle intervention. However, weight loss is frequently followed by weight gain leading to patterns of weight cycling. Whether such fluctuations in body weight are associated with worse CV prognosis is controversial. While there are multiple studies that reported an association between weight fluctuation and CVD (4–6), others failed to corroborate these findings (5, 7, 8). Currently, there has been no extensive study which systematically evaluates available evidence. In addition, the impact of
ethnicity and T2D has not been investigated yet. Therefore, the aim of this study is to comprehensively evaluate the effect of weight fluctuation on risk of CVD and, the influence of ethnicity and T2D status on any observed association.

Methods

Before data collection was instigated, the purpose and preliminary protocol of this meta-analysis was registered with the PROSPERO International prospective register of systematic reviews (registration number CRD42021284787). This systematic review and meta-analysis assessing the association between body weight fluctuation and cardiovascular (CV) events was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines (9).

Search Strategy and Study Selection

In this systematic review and meta-analysis, we searched PubMed, Web of Science, and the Cochrane Library for studies that investigate association between weight/BMI fluctuation and CV disease up to 26th of October 2021. For key terms and the search methods used see Appendix 1, Additional File 1. Studies that fulfilled the inclusion criteria were included. If full studies were not available electronically online, the primary authors were contacted via email to request a copy. For a description of the emails, see Appendix 2, Additional File 1. No response was received from contacted authors.

Our analysis included any study that investigated the association between weight cycling and the risk of subsequent cardiovascular events in individuals aged ≥ 18 years. Studies must have had at least 500 participants and a minimum follow-up period of 1 year. Included studies must have published relative risk (RR) estimates such as risk ratios, rate ratios, odds ratios, or hazard ratios with associated 95% confidence intervals (CIs) for events. Any definition and measurement of weight fluctuation (i.e. variability independent of the mean (VIM), coefficient of variation (CoV), average successive variability (ASV), standard deviation (SD), and root mean squared error of residual variation (RMSE) was considered. Weight fluctuation was recorded either as a continuous or categorical variable. The effects of weight fluctuation were reported as either the estimated RR of cardiovascular event per unit increase in SD of fluctuation or by splitting the study population into strata of fluctuation and then using the least fluctuating or stable group as a reference. For descriptions of the definitions and measurements of weight fluctuation used by the studies included in this analysis, see Table S1, Additional File 1. The primary outcome was the development of any new cardiovascular event. Secondary outcomes were cardiovascular death, MI, stroke, and the most composite CVD outcomes recorded by studies. Studies not published in English were not included.

Data Extraction

From the studies that met all eligibility criteria, data concerning the name of the primary author, the year of publication, total and strata sample sizes, description of study population, whether the study investigated BMI or weight fluctuation, definition and calculation of fluctuation, definition of CV outcome,
number of events, the RRs of the most adjusted model and associated 95% CIs, and the covariates included in the model were extracted.

Outcomes recorded were categorised based on how they were defined in their original studies. Any recorded MI, cardiovascular death, or stroke events that were defined as such by their original papers were grouped by these definitions in the secondary analyses. This method had three notable exceptions, where one report of ischaemic heart disease deaths (10), one report of cerebrovascular deaths (10), and two reports of coronary heart disease deaths (11), have been included in the cardiovascular death analysis. Similarly, two separate studies recorded RRs for CVD, and these reports have been treated as a compound outcomes and thus included in the most composite CVD outcome analysis (5, 12).

**Statistical Methods**

Summary RR statistics from the individual studies included were pooled based on whether the study they were taken from had investigated fluctuations in body weight or BMI. The standard error (SE) of each collected RR was calculated from respective 95% CIs using the formula

\[ SE = \frac{\text{upperCIlimit} - \text{lowerCIlimit}}{3.92} \]

These estimates were combined using random effects model separately for weight and BMI fluctuations. First, we compared the RR of CV outcomes for the most fluctuating group versus the least fluctuating group (4–8, 10–25). Then RRs per +1 SD increase of the unit of weight fluctuation (4, 6, 14, 19, 26, 27). This second analysis was not performed for BMI fluctuation as there are no studies that report recording CV risks per +1 SD of BMI fluctuation. Lissner et al. produced estimated RRs that were only available stratified by sex, and as such the male and female RRs were treated as separate reports (11). Nam et al. took BMI and body weight measurements for all participants and treated these 2 sets of data as 2 separate reports, and we have used these reports separately in the respective BMI/body weight fluctuation analyses (20). When a study recorded RR estimates for 2 or more separate single CVD events (e.g. MI, Stroke, etc.), these were also treated as separate reports. When a study reported multiple compound outcomes, only the most composite outcome (i.e. the composite outcome containing the greatest number of different cardiovascular outcomes) was collected. For each report gathered, only the RR estimates from the most adjusted models available were included in the final analyses. Meta-analysis was performed using the ‘metafor’ package in R (version 4.1.1) (28).

Weight cycling was defined and measured in studies via 2 different measures: categorical and continuous. Continuous definitions included CoV (11, 13, 20), ASV (4, 6, 12, 14, 25, 27), RMSE (10, 26), SD (15), and VIM (16–19, 21). Categorical definitions included a BMI loss of ≥ 2 followed by a gain of ≥ 2 or vice-versa (5), a weight loss of at least 10 lbs (4.5 kg) at least 3 times (22), a BMI loss of ≥ 4% from baseline to midpoint follow-up and then a BMI gain of ≥ 4% from midpoint follow-up to last visit or vice-versa (7), a sum of deviations > 5.04 for those with < 3.0 unit difference from their initial to final BMI (23), being in the top quintile of VIM-defined body-weight fluctuation (8), and experiencing a loss then a gain in body weight or vice versa (24).

**Quality assessment**
The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (NOS) was used for assessing the quality and bias of the studies included in the final analyses (29). For the results of this analysis, see Table S3, Additional File 1. Heterogeneity between studies was estimated for the primary and secondary outcome analyses using the \( I^2 \) statistic, Egger’s regression test, and funnel plot. If heterogeneity was observed, the Duval and Tweedie trim-and-fill method was used to adjust for publication bias (30).

**Sensitivity analysis**

Sensitivity analyses was performed to investigate the effect of ethnicity, diabetes status and metric of fluctuation (e.g. CoV, ASV, etc.). This was only performed on summary RRs collected from studies that investigated body weight fluctuations due to lack of data regarding BMI fluctuation). Sensitivity analysis by ethnicity was done in White Europeans and Asians as there are not enough studies for the analysis of any other ethnic groups.

**Results**

**Study Selection**

Of the 5645 articles screened for eligibility, 23 studies with 15,382,537 individuals were included in the final meta-analyses (4–8, 10–27) (Fig. 1). From these 23 studies, 21 studies were for cardiovascular events (4–8, 10–21, 23, 24, 26, 27), 11 for cardiovascular death (4, 5, 7, 10–12, 14, 20, 23, 24, 26), 8 for MI events (4, 6, 13–17, 21), 7 for any stroke event (5, 6, 14–17, 21), and 9 for composite CVD outcomes (4–6, 8, 11, 12, 14, 22, 27). Of these 23 studies, 17 investigated body weight fluctuation (4–6, 11, 13–22, 25–27), whilst 7 investigated BMI fluctuation (7, 8, 10, 12, 20, 23, 24). Despite meeting inclusion criteria, estimated RRs from the 2019 study by Oh et al. were not included in the final analyses due to only recording estimated RRs per +1 increase in average successive variability (ASV), and as such not compatible with our analysis (31).

**Study Characteristics**

The recorded average (mean or median) age of the participants within studies ranged from 35 years to 72 years. The average weight of participants ranged from 63.5 kg to 92.5 kg. The average BMI of participants ranged from 22.1 kg/m\(^2\) to 33.2 kg/m\(^2\). Almost every study included in this analysis had >50% male participation, except for 3 (8, 11, 22). Of the included studies, 12 had >50% White participants (4, 6, 8, 11, 13–15, 22–24, 26, 27), and 11 had >50% East Asian participants (5, 7, 10, 12, 16–21, 25). The participants of 6 of the studies had been previously diagnosed with T2D (13–15, 18, 21, 27), whilst 1 more provided separate statistics for the participants within the study who had been previously diagnosed with T2D (12). The average follow up time for the included studies ranged from 3.7 years to 32 years (See Table S2, Additional File 1). Of the 23 studies, 16 were judged as having a high quality (≥7) based on the Newcastle-Ottawa scale (See Table S3, Additional File 1). Sponholtz et al. separated their participant population based upon whether they were obese, and as such generated 2 reports per
cardiovascular outcome. Similarly, Wannamethee et al. stratified their population based upon whether their participants initially lost or gained weight (24), Lissner et al. stratified their population by gender (11), and Youk et al. stratified by diabetes status (12), and as such each of these studies produced 2 reports per cardiovascular outcome. In total, 58 reports regarding cardiovascular outcomes were collected from the 23 studies. Of these 58 reports, 47 reported on a singular (i.e. non-compound) recorded CV event, and 11 reported composite CVD outcomes. Of the 47 reports of singular CV events, 17 reports were for CV death, 8 for MI, and 7 for stroke.

**Body weight and BMI fluctuations were associated with increased risk of any cardiovascular event**

A total of 21 studies (15 for body weight and 6 for BMI) consisting of 15,141,102 individuals investigated the association between weight/BMI fluctuations and any CV outcomes. Compared to the least fluctuating group, the summary RR for any CV outcomes for people in the most fluctuating group of body weight was 1.27 (95% CI 1.17–1.38; P < 0.0001; I² = 97.28%; P < 0.0001 for heterogeneity; Fig. 2). A similar summary RR of 1.39 (95% CI 1.17–1.64; P < 0.0001; I² = 76.39%; P < 0.0001 for heterogeneity; See Figure S2a, Additional File 1) was found when the fluctuation was defined using BMI. The summary RR estimate for the association between per + 1 SD increase in unit of body weight fluctuation and any cardiovascular event was 1.16 (95% CI 1.06–1.26; P < 0.0001; I² = 94.70%; P = 0.0013 for heterogeneity; See Figure S1a, Additional File 1).

**Body weight and BMI fluctuations were associated with increased risk of cardiovascular death**

A total of 11 studies (5 for body weight fluctuations and 6 for BMI fluctuations) consisting of 633,592 participants investigated the association between weight/BMI fluctuations and risk of CV death. Compared to the least fluctuating group, the summary RR for CV deaths for the most fluctuating group of body weight and BMI was 1.29 (95% CI 1.03–1.60; P < 0.0001; I² = 55.16%; P = 0.062 for heterogeneity; Fig. 3) and 1.27 (95% CI 1.09–1.49; P = 0.0027; I² = 68.51%; P = 0.002 for heterogeneity; See Figure S2b, Additional File 1), respectively. The summary RR for CV Deaths per + 1 SD increase in body weight fluctuation was 1.11 (95% CI 1.02–1.21; P = 0.0132; I² = 49.66%; P for heterogeneity = 0.1359; See Figure S1b, Additional File 1).

**Body weight fluctuation was associated with increased risk of myocardial infarction**

There were eight studies with a total population of 5,742,933 that investigated the association between body weight fluctuation and MI. The summary RR for MI associated with being in the most fluctuating strata of body weight compared to the least fluctuating strata was 1.32 (95% CI 1.09–1.59; P = 0.0037; I² = 97.14%; P for heterogeneity < 0.0001; Fig. 3), and the summary RR per + 1 SD increase in body weight
fluctuation was 1.14 (95% CI 0.92–1.42; \( P = 0.2234 \); \( \text{I}^2 = 82.32\% \); \( P \) for heterogeneity = 0.0174; See Figure S1b, Additional File 1). No study that investigated BMI fluctuation reported RR for MI.

**Body weight fluctuation was associated with increased risk of stroke**

There were 7 studies consisting of 5,779,027 subjects that investigated the association between body weight fluctuation and risk of stroke. The summary RR for stroke associated with being in the most fluctuating strata of body weight compared to the least fluctuating strata was 1.21 (95% CI 1.19–1.24; \( P < 0.0001 \); Fig. 3). Significant heterogeneity was detected in this analysis (\( \text{I}^2 = 0.06\% \); \( P \) for heterogeneity = 0.0073). No study that investigated BMI fluctuation recorded RR estimates for stroke outcomes. Similarly, it was not possible to perform a meta-analysis on the risk of stroke per +1 SD increase in body weight fluctuation, as there is only 1 study that reported RR for stroke (6).

**Body weight fluctuation and risk of composite cardiovascular outcomes**

Eight studies consisting of 339,566 participants reported association between body weight fluctuation and composite CV outcomes. The RR for composite CVD outcomes associated with being in the most fluctuating body weight group compared to the least fluctuating was 1.36 (95% CI 1.08–1.73; \( P = 0.01 \); \( \text{I}^2 = 92.41\% \); \( P \) for heterogeneity < 0.0001; Fig. 3), and the RR of composite CVD outcomes associated per +1 SD increase in body weight fluctuation was 1.14 (95% CI 1.04–1.25; \( P = 0.0047 \); \( \text{I}^2 = 91.77\% \); \( P \) for heterogeneity < 0.0001; See Figure S1b, Additional File 1). There was only one study that investigated the association between BMI fluctuation and composite CV outcome (8) and thus a meta-analysis is not performed.

_The association between weight fluctuation and CV outcomes was not modified by ethnicity or diabetes status_

Given ethnicity and diabetes status are known risk factors for CV outcomes (32, 33), we performed subgroup analyses stratified by ethnicity and diabetes status. Due to a lack of data on other ethnicities, this analysis was performed in White Europeans and East Asians. We observed that both ethnicity and diabetic status generally had no significant effect on the observed association between body weight fluctuation and CV events (See Figures S3 and S4, Additional File 1). Compared to the group with the least fluctuation, a significantly higher risk of any CV event was observed in the group with the highest degree of body weight fluctuation in both the White (RR = 1.42; 95% CI 1.25–1.62; \( P < 0.0001 \); See Figure S3a, Additional File 1) and East Asian populations (RR = 1.16; 95% CI 1.12–1.19; \( P < 0.0001 \);

See Figure S3b, Additional File 1). The RR for CV death was not statistically significant in either the Whites (RR = 1.33; 95% CI 0.97–1.83; \( P = 0.0741 \); See Figure S3c, Additional File 1) or the East Asians (RR = 1.22; 95% CI 0.90–1.66; \( P = 0.2022 \); See Figure S3d, Additional File 1). The RR of composite CVD
outcome in East Asians was also not significant (RR = 1.11; 95% CI 0.81–1.52; P = 0.5154; See Figure S3d, Additional File 1). This could most likely be due to a lack of power after stratification.

Similar results were obtained after stratifying by diabetes status. The RR for any CV event in the most fluctuating group compared to the least fluctuating group with diabetes was 1.25 (95% CI 1.13–1.38; P < 0.0001; $I^2 = 98.03\%$; P for heterogeneity < 0.0001) and in non-diabetics it was 1.29 (95% CI 1.14–1.46; P < 0.0001; $I^2 = 98.03\%$; P for heterogeneity < 0.0001). No differential association by diabetes status was also observed between weight fluctuation and MI, however the association between weight fluctuation and stroke was observed to be insignificant in the non-diabetic population (RR = 1.31; 95% CI 0.99–1.72; P = 0.0566; $I^2 = 98.35\%$; P for heterogeneity = 0.0029) (See Figures S4c and S4d, Additional File 1). Only one of the papers included in this analysis investigated cardiovascular death or composite cardiovascular outcomes in individuals with type II diabetes (14), and as such these outcomes were not suitable for subgroup meta-analysis. Therefore, the effect of diabetes status on the risk of these outcomes cannot be analysed.

**Sensitivity analyses**

Given different studies capture weight fluctuation using different metrics (i.e. ASV, SD, CoV, VIM, RMSE), we performed sensitivity analysis after stratification by exposure definition. Overall, exposure definition had little impact on the results, with a few notable exceptions (See Figures S5a-i, Additional File 1). When ASV was used, the summary RRs associated with the top fluctuating strata of body weight (compared to the least fluctuating) for both MI and stroke were significantly higher, with the RR for MI 1.97 (95% CI 1.60–2.44; P < 0.0001; See Figure S5b, Additional File 1) and stroke 2.17 (95% CI 1.57–3.00; P < 0.0001; See Figure S5b, Additional File 1). However, when ASV was used as a measure of fluctuation in the per + 1 SD increase in body weight variability analysis, the summary RR for MI became insignificant (See Figure S5i, Additional File 1). Similarly, when ASV was used as a measure of fluctuation, the summary RR for CV death became insignificant (See Figures S5b and S5i, Additional File 1). These changes are most likely explained by a lack of power in these sub-analyses. Of note however is the general trend of decreased heterogeneity of results observed after stratifying by metric of effect.

**Heterogeneity and Bias Analysis**

As heterogeneity was significant in the analysis of the RRs of the primary and secondary outcomes associated with being in the top strata of body weight fluctuation, it was important to investigate whether this heterogeneity was due to publication bias. As such, Egger’s regression test and funnel plots were created for these analyses. Egger’s regression found no funnel plot asymmetry for the CV event (z = 1.7567; P = 0.079; See Figure S6a, Additional File 1), CV death (z = -1.0027; P = 0.316; See Figure S6b, Additional File 1), MI (z = 1.1849; P = 0.236; See Figure S6c, Additional File 1), or the most composite CVD outcomes (z = -1.7294; P = 0.0837; See Figure S6e, Additional File 1) analyses, however, significant asymmetry was found for the analysis of stroke (z = 2.9287; P = 0.0034; See Figure S6d, Additional File 1). As such, the Duval and Tweedie trim-and-fill method was employed in order to estimate the effect that hypothetical missing publications would have on the summary RR estimate. This analysis found no
significant change in the estimated summary RR of any cardiovascular event associated with degree of body weight fluctuation (RR = 1.21; 95% CI 1.19–1.24; P < 0.0001; See Figure S6f, Additional File 1).

To assess the effect that low quality papers had on the results, the 7 studies that scored < 7 using NOS were removed and then the primary and secondary outcomes were analysed a second time. No significant change was observed in the estimated RRs for analyses after the removal of low-quality studies (See Figure S7, Additional File 1).

**Discussion**

In this systematic review and meta-analysis of 23 studies involving over 15,000,000 participants, body weight fluctuation was associated with significantly increased risk of cardiovascular morbidity and mortality. This risk remains present regardless of ethnicity or diabetic status.

A previous meta-analysis performed by Zou et al. (34) also observed a similar significantly increased risk of CVD deaths (RR = 1.36; 95% CI 1.22–1.52; P < 0.0001) and CVD events (RR = 1.49; 95% CI 1.26–1.76; P < 0.0001) associated with body-weight fluctuations, however no analysis on the risk of other cardiovascular outcomes or the effect of ethnicity or diabetes status on CV risk was performed. Our meta-analysis further builds upon this previous study by analysing the summative risk of cardiovascular outcomes associated with a +1 SD increase in body weight variability. Our analysis also includes 16 studies published since 2018 that were not present in this previous meta-analysis, providing an additional 14,945,638 participants in total (4, 5, 8, 10, 12, 15–22, 25, 27).

The results between sub-groups of ethnicities are remarkably consistent. However, this study has only White Europeans and East Asians and as such data on different ethnicities is required. A recent study of individuals living with T2D in Scotland found that ethnically Pakistani individuals had a significantly higher risk of CVD than their White counterparts (35). A similar study found that South Asians with T2D had a higher risk of experiencing MI than Caucasians (36). The American Heart Association has reported that African Americans have the highest risk of CVD relative to other ethnic populations, with ~ 47% of African American individuals over the age of 20 suffering from at least one form of CVD (37). Future studies investigating weight fluctuation and associated CV risk should focus these at-risk populations in order to address this gap in the data and investigate whether this observed risk is robust in these ethnicities.

Obesity is a major risk factor for type 2 diabetes, cardiovascular disease, and death (38–40). Therefore, weight loss is recommended, and it has been shown to produce significant improvements in cardio-metabolic health (41). However, maintaining the lost weight is challenging and this is usually followed by progressive regain (42). The effect of weight cycling to health is controversial. Our meta-analysis showed that body weight fluctuation was associated with a significant increase in the risk of any cardiovascular events and MI independent of diabetes status and ethnicity. It also found that weight fluctuation is significantly associated with increased risk of stroke in individuals with diabetes. This could have implications specific to the treatment plans of individuals who are at increased risk of CV events. In
addition, this adds to the growing body of evidence that treatment plans promoting weight loss may need to consider weight cycling too. However, as observational data was used in this analysis, causality cannot be established between weight fluctuation and CVD. The use of genomic techniques such as mendelian randomisation may be useful in establishing future causality.

The biological mechanism by which body weight fluctuation may increase the risk of CVD is uncertain. Some have suggested that this fluctuation may increase oxidative stress and generate a low-level inflammation which (43), as the link between inflammation and certain CV diseases such as atherosclerosis is well established (44), this could increase the risk of CVD. Others have suggested an epigenetic link, as weight cycling has been shown cause the up regulation of genes associated with clotting and cardiomyopathy (45). However, the exact mechanism for how weight fluctuation may lead to CVD is still unclear. Investigating the biological mechanism and identifying biomarkers of weight fluctuation could be crucial in identifying those individuals most at risk of CVD.

Weight fluctuation itself may not cause CV disease per se, rather it could be a consequence of pre-existing illnesses that have worse prognoses. People with diabetes are previously shown to experience greater weight fluctuation than people without diabetes (46). In addition, weight change has been shown to vary by race/ethnicity (47). However, sensitivity analysis by diabetes status and ethnicity yielded largely similar results.

**Limitations**

This study had several limitations. The studies included in this analysis used various definitions and metrics to capture weight fluctuation, which make comparison between studies difficult. However, subgroup analysis has found that the association between weight fluctuation and CVD remains significant regardless of the metric used. This meta-analysis was also performed on observational data, and as such a causative link between weight fluctuation and CVD cannot be made. This study also did not consider whether weight loss was intentional or unintentional, which may add confounding variables as some unintentional weight fluctuation in participants may be caused by an underlying pathology that may simultaneously negatively affect the participants cardiovascular health. Similarly, interventions or co-morbidities (other than T2D) were not accounted or adjusted for.

**Conclusions**

This systematic review and meta-analysis has found that body weight fluctuation is associated with an increased risk of cardiovascular events, cardiovascular death, myocardial infarction, stroke, and compound CVD outcomes independent of diabetes status and ethnicity. More research is needed to prove causation and investigate the mechanisms responsible for this effect.

**Abbreviations**

ASV - Average Successive Variation
Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: All data analysed during this study can be found in the included published articles. The datasets generated during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that no competing interests exist.

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Authors’ contributions: R. M. and A. D. conceived the original hypothesis and planned the framework of the presented analysis. R. M. and A. D. performed the screening process. R. M. extracted the data from included papers and performed the computational analyses under the supervision of A. D. The results
presented were discussed with E. P. and M. S., and all authors contributed to the final manuscript. R. M. and A. D. assume full responsibility for the contents of this article.

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Authors' Information: Not Applicable.

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**Figures**

**Figure 1**

A flow chart of the study selection process.

**Figure 2**

A forest plot showing the summative risk of any cardiovascular event associated with being in the most fluctuating body weight group compared to the least fluctuating. The number of participants in the most fluctuating group are shown in the column “Group Size”. RR = 1.27; 95% CI 1.17 – 1.38; P < 0.0001; Significant Heterogeneity (I² = 97.28%; P < 0.0001).

**Figure 3**

A compound forest plot showing the summative risk of the secondary outcomes associated with being in the most fluctuating body weight group compared to the least fluctuating. The subheadings “Stroke”, “Myocardial Infarction”, “Cardiovascular Death”, and “Composite Outcomes” are followed by the reports included in the respective sub-analysis. The number of participants in the most fluctuating group are
shown in the column “Group Size”. CV Death RR = 1.29 (95% CI 1.03 – 1.60; P = 0.0233; I² = 55.16%; P for heterogeneity = 0.062). MI RR = 1.32 (95% CI 1.09 – 1.59; P = 0.0037; I² = 97.14%; P for heterogeneity < 0.0001). Stroke RR = 1.21 (95% CI 1.19 – 1.24; P < 0.0001; I² = 0.06%; P for heterogeneity = 0.0073). Most composite CV outcome RR = 1.36 (95% CI 1.08 – 1.73; P = 0.01; I² = 92.41%; P for heterogeneity < 0.0001).

**Supplementary Files**

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- AdditionalFile1.docx