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# Association of bodyweight loss with changes in lipids, blood pressure, and fasting serum glucose following tirzepatide treatment in Japanese participants with type 2 diabetes: A post hoc analysis of the SURPASS J-mono trial

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## ABSTRACT

**Aims/Introduction:** In the SURPASS J-mono trial, tirzepatide demonstrated significant improvements in bodyweight and several metabolic parameters in Japanese participants with type 2 diabetes. This post hoc analysis evaluated the potential relationships between weight loss and metabolic improvements in SURPASS J-mono.

**Materials and Methods:** Metabolic parameter data from tirzepatide-treated participants were analyzed by weight loss subgroups and compared to dulaglutide 0.75 mg. Correlations between changes from baseline to week 52 in weight loss and each metabolic parameter were assessed; Pearson correlation coefficients were derived. Mediation analyses were conducted to evaluate weight loss-associated and -unassociated effects of tirzepatide vs dulaglutide 0.75 mg.

**Results:** This analysis included 548 participants (tirzepatide: $n = 411$, dulaglutide: $n = 137$). Weight loss subgroups showed greater improvement in metabolic parameters with greater bodyweight loss. Significant ($P < 0.05$) but weak correlations between changes in bodyweight and triglycerides ($r = 0.18$–$0.25$), high-density lipoprotein cholesterol ($r = -0.37$ to $-0.29$), and systolic blood pressure ($r = 0.19$–$0.41$) were observed across treatment groups; in diastolic blood pressure in the tirzepatide 5-mg ($r = 0.28$), pooled tirzepatide ($r = 0.20$), and dulaglutide 0.75-mg ($r = 0.23$) groups; and in fasting serum glucose in the dulaglutide 0.75-mg ($r = 0.18$) and pooled tirzepatide ($r = 0.13$) groups. Weight loss was associated with treatment differences between tirzepatide and dulaglutide 0.75 mg to varying degrees across metabolic parameters, with improvements in fasting serum glucose having the lowest association with weight loss (36.6%–43.5%).

**Conclusions:** In this post hoc analysis, non-glycemic and glycemic parameter improvements appeared differentially associated with weight loss, suggesting both weight loss-associated and -unassociated effects of tirzepatide.

## INTRODUCTION

Over the past two decades, the prevalence of obesity has progressively increased in Japan, paralleled by an increase in the prevalence of type 2 diabetes (T2D)[1]. Obesity, defined as body

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mass index (BMI) ≥25 kg/m$^2$ in Japan[2], is commonly associated with multiple metabolic abnormalities, including hypertension, insulin resistance, hyperglycemia, and dyslipidemia. Multiple metabolic abnormalities that occur together with visceral obesity are termed the 'metabolic syndrome,' which is associated with an increased risk for cardiovascular disease and other comorbidities[3]. The prevalence of metabolic syndrome is high (43.0%) among patients with T2D in Japan and further increased in Japanese people with both T2D and obesity (54.6% and 66.1% in people with BMI ≥25 to <30 and ≥ 30 kg/m$^2$, respectively)[4]. In patients with T2D, loss of ≥15% of bodyweight has been associated with clinically significant improvements in blood glucose levels and reduction in the rates of metabolic abnormalities and cardiovascular comorbidities[5].

Given the known beneficial cardiovascular and metabolic effects of weight loss for patients with T2D, obesity management is an integral component of T2D treatment strategies[5]. It is important to determine the effects of new T2D therapeutics on bodyweight[6], as those that contribute to weight loss as well as glycemic control may be anticipated to have added metabolic benefit. Furthermore, it is of interest to determine the weight loss-associated (WL-A) and weight loss-unassociated (WL-UA) effects of new T2D therapeutics to gain mechanistic insights into their actions, as agents with multiple beneficial actions on metabolism may be advantageous in treating T2D and its related comorbidities.

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor/glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of T2D in the United States, Europe, and Japan[7–9]. The phase 3 SURPASS J-mono study examined the efficacy and safety of once-weekly tirzepatide as monotherapy in Japanese adults with T2D[10]. In this study, tirzepatide 5, 10, and 15 mg demonstrated superior reductions in glycated hemoglobin (HbA1c), fasting serum glucose (FSG), and bodyweight compared to dulaglutide 0.75 mg over 52 weeks of treatment[10]. Mean bodyweight reductions were observed across tirzepatide treatment arms at week 52, representing loss of 7.8%, 11.0%, and 13.9% of bodyweight from baseline in the 5-, 10-, and 15-mg arms, respectively[10]. At week 52, tirzepatide 5, 10, and 15 mg also demonstrated clinically significant improvements in systolic blood pressure (SBP; −6.5 to −11.0 mmHg), diastolic blood pressure (DBP; −3.2 to −5.6 mmHg), and lipid levels[10], reducing the prevalence of abnormalities in these metabolic parameters[11].

The objective of the current study was to investigate the association between bodyweight loss and metabolic improvements in the SURPASS J-mono trial. Analysis of data from the trial was conducted to evaluate the association of weight loss with improvements in parameters that comprise the Japanese Definition and Criteria of Metabolic Syndrome[3], including triglycerides, high-density lipoprotein cholesterol (HDL-C), SBP, DBP, and FSG. It is anticipated that the results of this analysis may help predict treatment response in Japanese patients with T2D and obesity (BMI ≥ 25 kg/m$^2$) who have coexisting abnormalities in various metabolic parameters.

## MATERIALS AND METHODS

### Study design and participants

This post hoc analysis used data from SURPASS J-mono (ClinicalTrials.gov identifier: NCT03861052), a multicenter, randomized, double-blind, active-controlled, phase 3 trial which compared the efficacy and safety of tirzepatide 5, 10, and 15 mg to dulaglutide 0.75 mg in Japanese participants with T2D. The study design and eligibility criteria of the trial have been previously described[10]. In brief, the study enrolled Japanese adults with T2D (World Health Organization classification), who used diet and exercise alone to manage their T2D or were on oral antihyperglycemic medication (OAM) monotherapy except thiazolidinedione and willing to discontinue the OAM.

Participants were randomly assigned 1:1:1:1 to receive tirzepatide 5, 10, or 15 mg, or dulaglutide 0.75 mg, administered once weekly by subcutaneous injection. The study design included a 4-week (OAM-naïve) or 10-week (≥8-week OAM washout if discontinuing OAM) screening/lead-in period, a 52-week treatment period with dose escalation[10], and a 4-week safety follow-up period. The current analysis assessed the relationship between bodyweight loss and improvements in several metabolic parameters, including triglycerides, HDL-C, SBP, DBP, and FSG. To support the FSG analysis, the correlation between changes in bodyweight and in 2-h postprandial glucose from the 7-point self-monitored blood glucose (SMBG) profile was also examined.

The study protocol was approved by independent ethical review boards at each participating site (the protocol and list of ethical review boards are published[10]). The study was conducted in accordance with the Declaration of Helsinki in 1995 (as revised in Fortaleza, Brazil, October 2013) and the Council for International Organizations of Medical Sciences International Ethical Guidelines. Participants provided written informed consent prior to participating in the trial.

### Statistical analyses

Analyses were performed on the modified intent-to-treat population, which comprised all randomized participants who received one or more doses of the study drug. Of the modified intent-to-treat population, analyses included participants on treatment at the 52-week visit with ≥75% treatment compliance without rescue therapy and excluded participants with missing bodyweight at week 52.

Participants treated with tirzepatide were pooled and divided into subgroups based on achievement of weight loss target thresholds of <5%, ≥5% to <10%, ≥10% to <15%, and ≥15% of baseline bodyweight at week 52. For baseline characteristics, descriptive statistics were summarized by tirzepatide weight loss subgroups compared to dulaglutide 0.75 mg, shown as mean (standard deviation [SD]) or median (25th–75th percentile) for

continuous variables and frequency (percentage) for categorical variables.

Metabolic parameters were assessed from baseline to 52 weeks by weight-loss target achievement subgroups for tirzepatide compared to dulaglutide 0.75 mg. Least-squares mean (standard error) of each metabolic parameter over 52 weeks was calculated for each weight loss subgroup for tirzepatide and dulaglutide 0.75 mg using a mixed model for repeated measures linear regression model with treatment (tirzepatide groups only), visit, and treatment-by-visit interaction as fixed effects. Tirzepatide treatment groups were pooled within each weight loss subgroup. Correlations between changes from baseline in bodyweight and each parameter at 52 weeks were assessed by treatment group and pooled tirzepatide data, and Pearson correlation coefficients were derived. A $P$-value <0.05 was considered statistically significant.

Mediation analyses were conducted to evaluate WL-A and WL-UA effects of tirzepatide on metabolic parameters, with data presented as estimated treatment differences (ETDs) between 5, 10, and 15 mg, and pooled tirzepatide groups compared with dulaglutide 0.75 mg. The model for estimation of WL-A and WL-UA effects on each parameter included the interaction between treatment and weight change with the baseline measure for each parameter, use of lipid-lowering drugs (for triglycerides or HDL-C only), use of antihypertensive drugs (for SBP and DBP only), HbA1c (≤8.5% or >8.5%), baseline BMI (<25 or ≥25 kg/m$^2$), and washout of antidiabetic medication (yes or no) as covariates in the model. Bootstrap methods were used to estimate 95% confidence intervals (CIs) using 5,000 bootstrap samples. Only subjects with non-missing baseline and week 52 data for the response variable were included in the analyses.

Statistical analyses were performed using R Statistical Software, versions 4.1.2 and 4.3.2[12]. Mediation analyses were conducted using the Comprehensive R Archive Network regression-based causal mediation analysis with interaction and effect modification terms, version 1.0.1[13].

## RESULTS

### Baseline demographics and characteristics

In total, 548 participants were included in the analysis, of whom 411 were treated with tirzepatide and 137 were treated with dulaglutide 0.75 mg. The 5-mg arm had a higher proportion of participants who achieved <5% bodyweight loss at 52 weeks (58.3%) compared to the ≥5% to <10%, ≥10% to <15%, and ≥15% weight loss groups (30.6%, 28.1%, and 22.5%, respectively; Table 1). Conversely, ≥15% bodyweight loss at 52 weeks was achieved by more participants in the 15-mg arm (50.5%) compared to the <5%, ≥5% to <10%, and ≥10% to <15% groups (14.6%, 30.6%, and 33.7%, respectively). The 10-mg arm was more evenly represented across weight loss achievement subgroups (27.0%–38.9%; Table 1).

The majority of participants enrolled in SURPASS J-mono were men[10], ranging from 61.3% to 85.2% across tirzepatide weight loss subgroups and the dulaglutide 0.75 mg group (Table 1). No trends were observed among the tirzepatide subgroups and the dulaglutide group in baseline mean [SD] HbA1c (8.0% [0.9]–8.4% [0.9]), FSG (160.8 [29.2]–174.0 [37.7] mg/dL), SBP (129.9 [14.3]–131.6 [14.4] mmHg), DBP (81.4 [9.2]–84.5 [10.8] mmHg), triglycerides (162.7 [148.0]–190.4 [150.7] mg/dL), and HDL-C (50.6 [13.0]–52.4 [11.1–13.5] mg/dL; Table 1).

Trends were observed across tirzepatide weight loss subgroups in baseline bodyweight, BMI, and waist circumference, in which the highest mean values were observed in the <5% weight loss subgroup and the lowest in the ≥15% weight loss subgroup (mean [SD] baseline bodyweight: 84.0 [16.3] and 73.6 [10.8] kg in the <5% and ≥15% weight loss subgroups, respectively; Table 1).

At baseline, approximately one-third to one-half of participants used one or more antihypertensive medications (34.8%–52.8%) and one or more lipid-lowering (31.1%–46.3%) medications, with no trends observed across tirzepatide weight loss subgroups and the dulaglutide 0.75 mg group (Table 1).

### Parameter change over time by tirzepatide weight loss subgroup and dulaglutide 0.75 mg

bodyweight was progressively reduced over the 52-week treatment period in the tirzepatide ≥5% to <10%, ≥10% to <15%, and ≥15% weight loss subgroups, whereas bodyweight was relatively stable in the dulaglutide 0.75 mg and tirzepatide <5% groups (Figure 1). Improvements in metabolic parameters were observed across 52 weeks of treatment in the ≥5% to <10%, ≥10% to <15%, and ≥15% weight loss subgroups, with greater improvements observed with greater weight loss (Figure 1). FSG was reduced during the first 12 weeks of treatment across all weight loss subgroups, with the curves separating after this timepoint (Figure 1f). Lipid levels and blood pressure generally showed greater improvement with greater weight loss in tirzepatide subgroups, regardless of the use of lipid-lowering and antihypertensive medications at baseline (Figure S1).

### Association between weight loss and improvements in metabolic parameters

No trend was observed between baseline bodyweight and bodyweight loss at 52 weeks (Figure 2). At 52 weeks, significant correlations ($P < 0.05$) were observed in all treatment groups and in the pooled tirzepatide group between change in bodyweight and triglyceride levels ($r$ = 0.18–0.25), HDL-C levels ($r$ = −0.37 to −0.29), and SBP ($r$ = 0.19–0.41; Figure 2). In addition, DBP was significantly correlated to change in bodyweight in the tirzepatide 5-mg and dulaglutide 0.75-mg arms ($r$ = 0.28 and $r$ = 0.23, respectively) and in the pooled tirzepatide group ($r$ = 0.20). FSG was significantly correlated to change in bodyweight in the dulaglutide 0.75-mg arm ($r$ = 0.18) and in the pooled tirzepatide group ($r$ = 0.13), with similar findings observed for 2-h postprandial glucose (Figure S2). Significant correlations were observed between change in bodyweight at

**Table 1** | Demographics and baseline characteristics by bodyweight loss achievement at 52 weeks

| | Tirzepatide | | | | Dulaglutide 0.75 mg |
|---|---|---|---|---|---|
| | Weight loss <5% *N* = 103 | Weight loss 5 to <10% *N* = 108 | Weight loss 10 to <15% *N* = 89 | Weight loss ≥15% *N* = 111 | *N* = 137 |
| Treatment group, *n* (%) | | | | | |
| Tirzepatide 5 mg | 60 (58.3) | 33 (30.6) | 25 (28.1) | 25 (22.5) | NA |
| Tirzepatide 10 mg | 28 (27.2) | 42 (38.9) | 34 (38.2) | 30 (27.0) | NA |
| Tirzepatide 15 mg | 15 (14.6) | 33 (30.6) | 30 (33.7) | 56 (50.5) | NA |
| Age, years | 54.1 (10.4) | 54.7 (11.7) | 56.2 (9.9) | 57.3 (8.5) | 57.1 (10.1) |
| Sex, *n* (%) | | | | | |
| Women | 23 (22.3) | 16 (14.8) | 18 (20.2) | 43 (38.7) | 38 (27.7) |
| Men | 80 (77.7) | 92 (85.2) | 71 (79.8) | 68 (61.3) | 99 (72.3) |
| Diabetes duration, years | 5.7 (4.2) | 6.1 (5.6) | 6.4 (5.0) | 4.8 (4.6) | 6.2 (6.0) |
| HbA1c, % | 8.4 (0.9) | 8.3 (0.9) | 8.0 (0.9) | 8.2 (0.8) | 8.1 (0.9) |
| FSG, mg/dL | 174.0 (37.7) | 172.7 (38.6) | 165.9 (47.8) | 162.6 (37.2) | 160.8 (29.2) |
| Weight, kg | 84.0 (16.3) | 82.3 (17.7) | 78.9 (11.5) | 73.6 (10.8) | 76.3 (13.4) |
| BMI, kg/m$^2$ | 29.8 (5.5) | 28.8 (5.3) | 28.2 (4.4) | 27.4 (3.0) | 27.8 (3.7) |
| Waist circumference, cm | 100.0 (12.4) | 97.6 (11.6) | 96.3 (8.8) | 94.8 (7.6) | 94.8 (9.2) |
| SBP, mmHg | 131.0 (13.8) | 131.6 (14.4) | 130.3 (13.6) | 129.9 (14.3) | 130.5 (15.6) |
| DBP, mmHg | 84.5 (10.8) | 84.0 (9.6) | 82.9 (9.1) | 81.4 (9.2) | 82.7 (10.1) |
| eGFR (CKD-EPI), mL/min/1.73 m$^2$ | 80.4 (12.4) | 80.1 (13.0) | 77.2 (13.1) | 77.3 (10.1) | 78.0 (11.3) |
| HDL-C, mg/dL | 51.1 (12.7) | 50.6 (13.0) | 52.4 (11.1) | 52.2 (13.9) | 52.4 (13.5) |
| Median (IQR) | 48 (42, 57) | 47 (40, 62) | 52 (45, 59) | 51 (41, 62) | 49 (42, 61) |
| Triglycerides, mg/dL | 168.4 (108.0) | 189.8 (151.4) | 184.3 (244.4) | 190.4 (150.7) | 162.7 (148.0) |
| Median (IQR) | 139 (94, 188) | 137 (107, 215) | 137 (93, 199) | 140 (112, 207) | 132 (106, 176) |
| Anti-hypertensive drug use, *n* (%) 'yes' | 37 (36.0) | 57 (52.8) | 31 (34.8) | 51 (46.0) | 54 (39.4) |
| Lipid-lowering drug use, *n* (%) 'yes' | 32 (31.1) | 50 (46.3) | 36 (40.5) | 41 (37.0) | 48 (35.0) |

Data are presented as mean (SD) unless otherwise indicated. Data are from participants on treatment at the 52-week visit with ≥75% compliance without rescue therapy. BMI, body mass index; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FSG, fasting serum glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range, is shown as the 25th–75th percentile; *N*, total number of participants in each weight subcategory; *n*, number of participants per group; NA, not applicable; SBP, systolic blood pressure; SD, standard deviation.

week 24 and week 52 changes in HDL-C levels (all treatment groups, $r = -0.19$ to $-0.36$), SBP (tirzepatide 5 and 15 mg, $r = 0.29$ and 0.18, respectively), triglycerides (tirzepatide 10 mg, $r = 0.31$), and DBP (tirzepatide 5 mg, $r = 0.18$; Figure S3).

WL-A effects between tirzepatide and dulaglutide groups in changes in lipid parameters ranged from ETD (95% CI) −17.80 (−26.25, −10.20) to −43.3 (−61.27, −28.07) mg/dL for triglycerides and 2.71 (1.54, 4.14) to 5.33 (3.00, 8.15) mg/dL for HDL-C (Figure 3). For WL-UA effects between tirzepatide and dulaglutide 0.75-mg groups, ETD (95% CI) ranged from −2.62 (−26.82, 22.76) to −10.73 (−29.05, 6.88) mg/dL for triglycerides and −1.07 (−3.06, 0.96) to −2.47 (−5.10, 0.11) mg/dL for HDL-C; however, the 95% confidence intervals included 0 for all WL-UA ETDs. The differences between tirzepatide and dulaglutide groups in improved lipid levels were potentially mediated by weight loss (triglycerides, 61.4–95.9% [pooled tirzepatide: 79.1%]; HDL-C, 164.6–220.5% [pooled tirzepatide: 178.3%]; Figure 3).

For WL-A effects between tirzepatide and dulaglutide 0.75 mg groups on SBP, ETD (95% CI) was −3.87 (−7.26, −0.88) to −5.92 (−9.91, −2.08) mmHg across treatment comparisons (Figure 3). WL-UA effects contributed to a generally similar extent, as the ETD (95% CI) in mean change from baseline between the tirzepatide and dulaglutide groups ranged from −0.87 (−3.69, 2.02) to −4.75 (−9.25, −0.25) mmHg for SBP. Similar trends were observed for DBP (WL-A ETD −1.74 to −2.90 mmHg; WL-UA ETD −0.88 to −3.08 mmHg; Figure 3). WL-A improvements in SBP and DBP accounted for 45.2–87.1% (pooled tirzepatide: 67.9%) and 38.7–75.4% (pooled tirzepatide: 59.7%), respectively, of the differences between tirzepatide and dulaglutide 0.75 mg groups (Figure 3).

WL-A effects on FSG improvement were lower than WL-UA effects for all comparisons between tirzepatide and dulaglutide 0.75 mg: WL-A ETD (95% CI) −8.68 (−12.61, −5.51) to −13.23 (−17.11, −9.53) mg/dL vs WL-UA ETD (95% CI) −14.87 (−20.77, −8.55) to −18.81 (−24.76, −13.14) mg/dL.

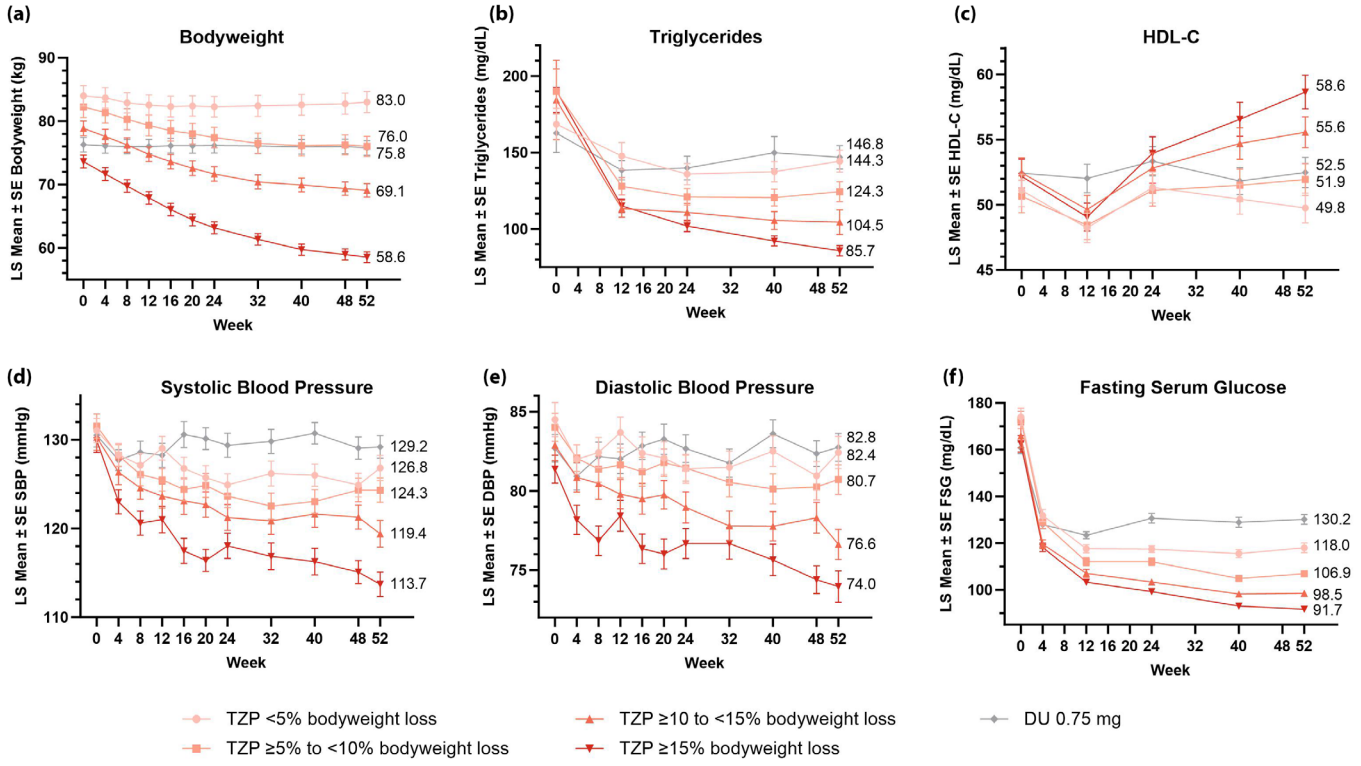


**Figure 1** | Time course of clinical characteristics from baseline to 52 weeks in SURPASS J-mono. Data are shown by tirzepatide weight loss achievement subgroups compared to dulaglutide 0.75 mg. LS mean (SE) was calculated for each metabolic parameter, including (a) bodyweight, (b) triglycerides, (c) HDL-C, (d) SBP, (e) DBP, and (f) FSG, at each visit over 52 weeks using a mixed model for repeated measures. DBP, diastolic blood pressure; DU, dulaglutide; FSG, fasting serum glucose; HDL-C, high-density lipoprotein cholesterol; LS, least squares; SBP, systolic blood pressure; SE, standard error; TZP, tirzepatide.

The estimated percentage improvement associated with weight loss was consistent across tirzepatide dose groups for FSG and smaller in magnitude than that observed for other metabolic parameters, accounting for 36.6% to 41.4% of the difference observed with tirzepatide treatment (pooled tirzepatide: 43.5%; Figure 3).

## DISCUSSION

In SURPASS J-mono, statistically significant weight loss was achieved following 52 weeks of tirzepatide treatment at 5, 10, and 15 mg in Japanese participants with T2D, which was accompanied by clinically meaningful improvements in several metabolic parameters[10]. The current analyses show that weight loss occurred regardless of baseline bodyweight and was directly correlated with improvements in blood lipid levels and blood pressure following 52 weeks of tirzepatide treatment. Weak correlations were also observed between weight loss and FSG and postprandial glucose levels in the pooled tirzepatide group. Similar trends were observed between weight loss at 24 weeks and improvements in blood pressure and lipid levels at 52 weeks, suggesting earlier benefits of bodyweight loss on these metabolic parameters. In the mediation analyses, weight loss was found to contribute in varying degrees to the treatment differences between tirzepatide and dulaglutide 0.75 mg across metabolic parameters, suggesting both WL-A and WL-UA mechanisms of tirzepatide action. Mediation analyses performed using percent change from baseline in bodyweight rather than absolute change confirm the current findings (Mimura et al, 2024, unpublished data).

No significant correlations were observed between baseline bodyweight and bodyweight loss in SURPASS J-mono. As East Asian populations develop T2D at a lower BMI than non-Asian populations[14], this lack of correlation may be due to the Japanese study participants having a lower mean bodyweight within a more limited range compared to non-Asian study populations. The correlations between changes in bodyweight and changes in lipid levels at week 52 are consistent with a large body of evidence supporting an association between weight loss and improvements in serum lipid levels[15]. Weight loss has been shown to counter diabetic dyslipidemia and, when accompanied by significant reduction in visceral adiposity, to improve lipid levels and other cardiometabolic parameters in patients with T2D or overweight/obesity[5,16–19]. The current analysis indicates that weight loss potentially

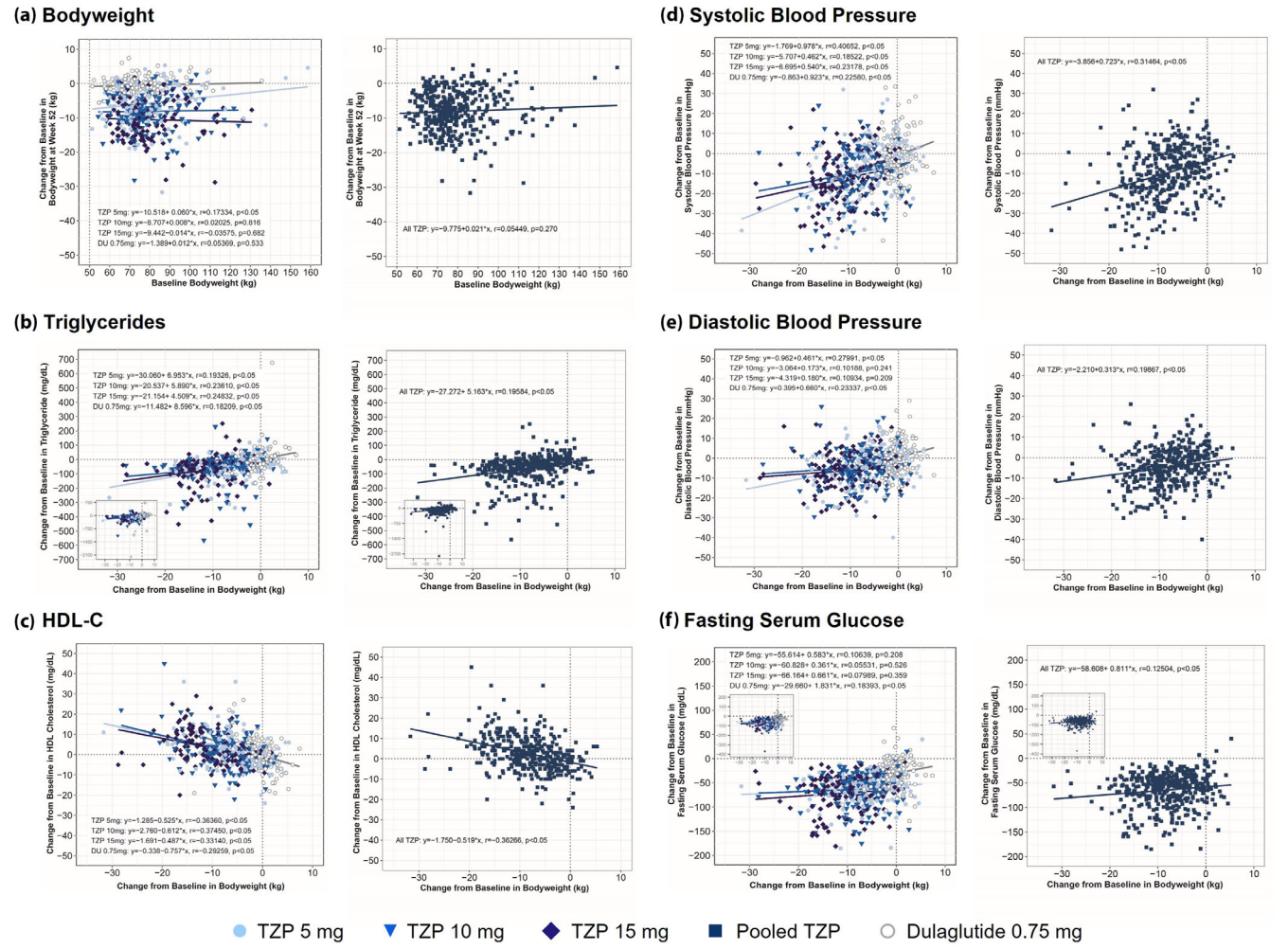


**Figure 2** | Scatterplots showing the correlations between change from baseline in bodyweight and individual metabolic parameters. Data shown in (a) are correlations in baseline bodyweight to change in bodyweight from baseline at 52 weeks. Correlations between changes from baseline to week 52 in weight loss and each parameter are shown for (b) triglycerides, (c) HDL-C, (d) systolic blood pressure, (e) diastolic blood pressure, and (f) fasting serum glucose. The *P*-values are from Pearson correlation and were considered statistically significant if <0.05. Inset graphs in (b) and (f) include all data points; main graphs are shown for readability. Equations, correlation coefficients, and *P*-values were derived using all data points. DU, dulaglutide; HDL-C, high-density lipoprotein cholesterol; *r*, Pearson correlation coefficient; TZP, tirzepatide.

mediated the treatment effect of tirzepatide on improvement in lipid levels in SURPASS J-mono, suggesting that in Japanese patients with T2D, weight loss following tirzepatide treatment may reverse changes in lipid metabolism that have become altered through obesity-related mechanisms, including increased insulin resistance[20]. However, a prior study found that weight loss only explained up to 4.4% of the variability in triglyceride levels following tirzepatide treatment, suggesting the possibility of additional WL-UA effects of tirzepatide on lipid metabolism[21].

In SURPASS J-mono, the effects of tirzepatide on SBP were associated relatively equally with WL-A and WL-UA mechanisms in Japanese patients with T2D, with DBP showing similar trends to SBP. In accordance with these findings, a post hoc analysis of the global SURPASS-1–5 trials found tirzepatide-induced improvements in SBP were potentially mediated through WL-A mechanisms, with a smaller contribution of WL-UA mechanisms[22]. The role of weight loss in the improvement in blood pressure is well established[23]. In T2D, overactivity of the renin-angiotensin-aldosterone system is strongly linked to the development of hypertension and related complications[24]. A 5% bodyweight loss has been shown to significantly reduce expression of the renin-angiotensin-aldosterone system in plasma and adipose tissue in postmenopausal women with obesity, which was accompanied by a 7-mmHg reduction in 24-h ambulatory SBP[25]. In terms of

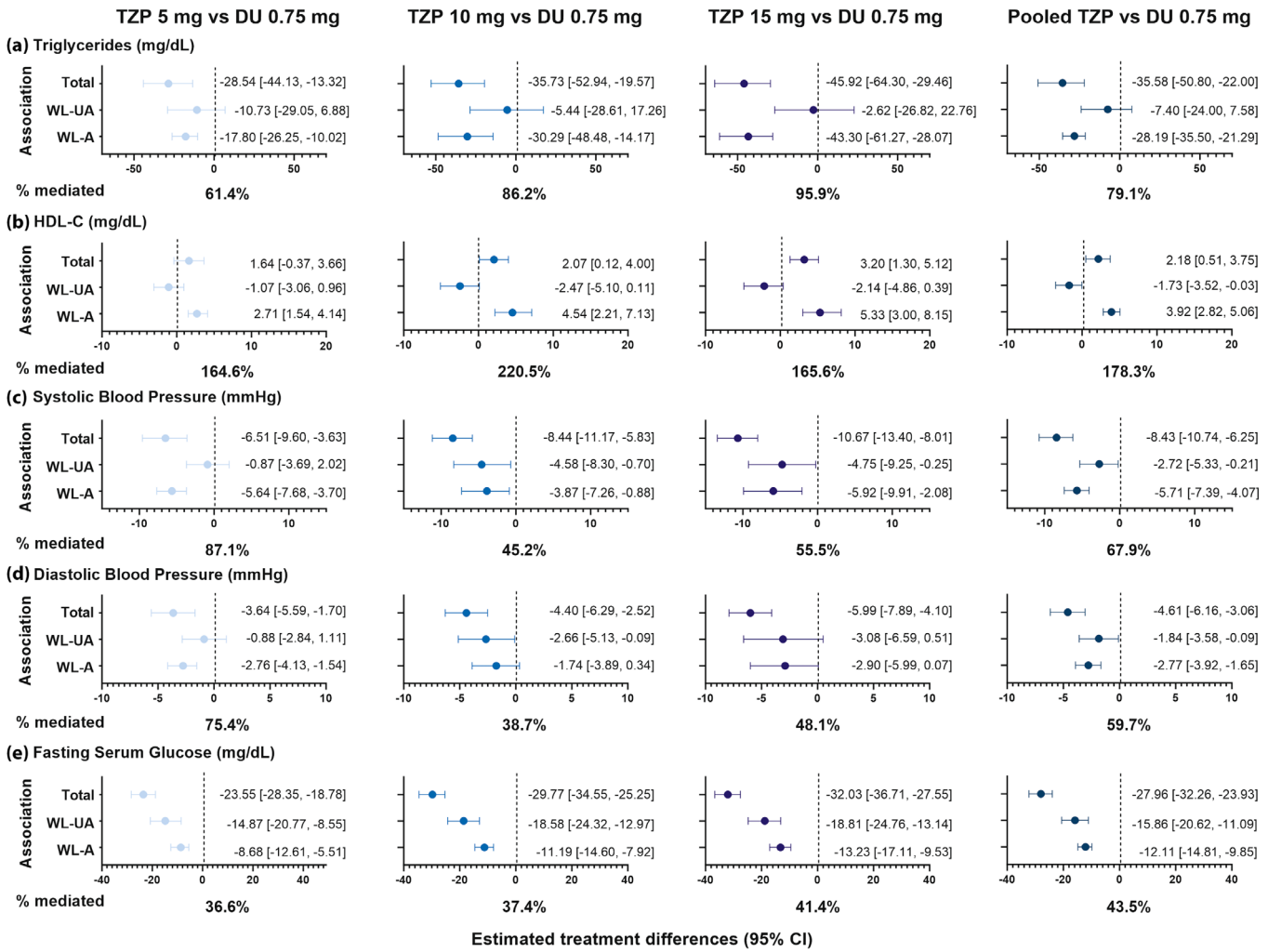


**Figure 3** | Mediation analyses for metabolic parameters using bodyweight loss as a mediator at Week 52. Data are shown for (a) triglycerides, (b) HDL-C, (c) systolic blood pressure, (d) diastolic blood pressure, and (e) fasting serum glucose. WL-A and WL-UA effects of tirzepatide were estimated using a model that included the interaction between treatment and weight change together with baseline parameters. For improvement in each metabolic parameter, WL-A, WL-UA, and total effects are shown as the estimated treatment difference between tirzepatide and dulaglutide 0.75 mg groups and are presented as bootstrap means (95% CI). Percent mediated indicates the improvement in each parameter potentially mediated by weight loss and is shown as a point estimate. Data pertain to participants on treatment at the 52-week visit with ≥75% compliance without rescue therapy. Only participants with non-missing data at baseline and 52 weeks were included in the analysis for each parameter. CI, confidence interval; DU, dulaglutide; HDL-C, high-density lipoprotein cholesterol; TZP, tirzepatide; WL-A, weight loss associated; WL-UA, weight loss unassociated.

WL-UA observations regarding tirzepatide and SBP, multiple potential mechanisms have been proposed[22], including natriuresis, vasodilation, and changes in autonomic nervous system activity[26–28]. Additionally, tirzepatide may have beneficial effects on the cardiovascular system, supported by data showing reduced biomarkers of inflammation and endothelial dysfunction in patients with T2D following 26 weeks of tirzepatide treatment[29].

In contrast to the other examined metabolic parameters, changes from baseline in bodyweight and FSG or postprandial SMBG at 52 weeks were not significantly correlated with each other in the tirzepatide dose groups and only weakly correlated in the pooled tirzepatide group. This might indicate that glycemic parameters had plateaued in all tirzepatide dose groups at 52 weeks. A plateau in glycemic parameters is consistent with evidence suggesting that tirzepatide and other incretin-based therapies may provide better glycemic control in Asian patients compared with non-Asian patients[30,31], possibly due to ethnic differences in beta-cell function and insulin sensitivity[31]. Additionally, as WL-A effects accounted for only 36.6–43.5% of the

observed association between tirzepatide treatment and the improvement in FSG, WL-UA mechanisms may contribute to tirzepatide-induced improvements in glycemic control. Prior studies have concluded that improvements in insulin sensitivity with tirzepatide treatment are not entirely WL-A effects[32], with improvements observed in HbA1c and FSG both in patients who did and did not lose substantial weight in the global SURPASS-1–5 trials[33,34]. It is important to note that the current time-course data indicate that WL-UA mechanisms predominate early during treatment, as all participants experienced similar rates of FSG reduction during the first 12 weeks of treatment, regardless of weight loss subgroup. However, after 12 weeks, subgroups with greater weight loss exhibited greater FSG reduction, suggesting WL-A mechanisms may contribute to enhanced FSG reduction at later time points. Several WL-A mechanisms for tirzepatide-mediated blood glucose level lowering have been proposed[34], including improved insulin sensitivity and beta-cell function[35] and changes in body composition such as the reductions in body fat mass, liver fat content, and volume of visceral adipose tissue[36,37]. Furthermore, weight loss was reported as one of the most influential factors for glycemic control in patients with T2D in a large Japanese administrative database study, which found that T2D remission at 1 year was significantly associated with higher BMI reduction, whereas relapse was associated with lower BMI reduction[38].

The mechanisms underlying WL-UA effects of tirzepatide are still unclear, with potential contributions from both GIP receptor (GIPR) and GLP-1 receptor (GLP-1R)-regulated processes. In an obese insulin-resistant mouse model, tirzepatide-induced insulin sensitization was associated with the induction of glucose, free fatty acids, and branched-chain amino acid oxidation in brown adipose tissue, with WL-UA insulin sensitization mediated by GIPR[39]. Additionally, in a mouse model of dyslipidemia-induced atherosclerosis, a long-acting acylated GIP analog reduced hyperlipidemia and atherogenesis independent of weight loss, supporting direct involvement of GIP agonism in the improvement in lipid levels[40]. However, GIPR-related mechanisms of tirzepatide action have not been well studied in humans[41]. Evidence for the existence of WL-UA, GLP-1R-dependent mechanisms for insulin sensitization in humans comes from a recent study by Mashayekhi *et al.*, (2024)[42], which found that the GLP-1R agonist liraglutide rapidly improved insulin sensitivity and decreased fasting and postprandial glucose levels prior to weight loss in individuals with obesity and prediabetes, effects that were reversed with a GLP-1R antagonist.

## LIMITATIONS

This analysis had limitations. The analyses were post hoc and exploratory in nature, and the methods used do not prove causality. Data on additional factors potentially affecting the analysis results, including visceral fat and lifestyle modifications such as exercise, and known biomarkers of lipid metabolism, inflammation, and endothelial dysfunction were not collected in SURPASS J-mono, precluding analyses of these factors herein. Consideration must also be given to potential ethnic differences, which may limit the generalizability of the results. Finally, relatively earlier-staged participants were enrolled in SURPASS J-mono, and it is unknown whether the findings apply to later-staged patients.

In SURPASS J-mono, tirzepatide-induced improvements in metabolic parameters were associated to different degrees with weight loss, suggesting that tirzepatide may improve metabolic parameters through multiple mechanisms. Weight loss was associated with improvement in lipids and blood pressure, with improvements in FSG having a weak association with weight loss. Although further study is necessary, the current data provide insights into the mechanisms of action of tirzepatide, supporting both potential WL-A and WL-UA effects of tirzepatide on metabolism, underlying the potentially beneficial actions of this drug on various metabolic abnormalities in patients with T2D. More mechanism of action data are needed to inform the development of future therapeutics to treat T2D and its associated metabolic comorbidities.

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## DISCLOSURE

Hirohito Sone is an editorial board member of the *Journal of Diabetes Investigation* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.
Approval of the research protocol: The study protocol was approved by independent ethical review boards at each participating site (protocol and ethical review boards have been published[10]). The study was conducted in accordance with the Declaration of Helsinki in 1995 (as revised in Fortaleza, Brazil, October 2013) and the Council for International Organizations of Medical Sciences International Ethical Guidelines.
Informed consent: All participants provided written informed consent prior to participating in the trial.
Registry and the registration no. of the study/trial: ClinicalTrials.gov, NCT03861052; March 1, 2019.
Animal studies: N/A.

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## SUPPORTING INFORMATION

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

**Figure S1.** Change from baseline in metabolic parameters by baseline concomitant medication use. Data are shown by tirzepatide weight loss achievement subgroups compared to dulaglutide 0.75 mg. LS means (SE) were calculated at 52 weeks using a mixed model for repeated measures, with baseline measure, treatment (tirzepatide groups only), visit, and treatment-by-visit interaction as fixed effects. Lipid data were log transformed. Percent change from baseline in (a) triglycerides and (b) HDL-C is shown by lipid-lowering drug use (yes/no). Change from baseline in (c) SBP and (d) DBP are shown by antihypertensive drug use (yes/no). Numbers in italics indicate the number of participants per subgroup. DBP, diastolic blood pressure; DU, dulaglutide; HDL-C, high-density lipoprotein cholesterol; LS, least squares; SBP, systolic blood pressure; SE, standard error; TZP, tirzepatide.

**Figure S2.** Scatterplots showing the correlations between change from baseline in bodyweight and postprandial SMBG levels at 52 weeks. Correlations were examined between mean changes from baseline to week 52 in weight loss and 2-h postprandial glucose levels. The *P*-values are from Pearson correlation and were considered statistically significant if <0.05. DU, dulaglutide; r, Pearson correlation coefficient; SMBG, self-monitored blood glucose; TZP, tirzepatide.

**Figure S3.** Scatterplots showing the correlations between changes in bodyweight at week 24 and metabolic parameters at week 52. Data shown in (a) are baseline bodyweight versus change in bodyweight from baseline at 24 weeks in bodyweight. Correlations between changes from baseline to week 24 in weight loss and each parameter are shown for (b) triglycerides, (c) HDL-C, (d) systolic blood pressure, (e) diastolic blood pressure, and (f) fasting serum glucose. The *P*-values are from Pearson correlation and were considered statistically significant if <0.05. The inset graph in (f) includes all data points; the main graph is shown for readability. Equations, correlation coefficients, and *P*-values were derived using all data points. DU, dulaglutide; HDL-C, high-density lipoprotein cholesterol; *r*, Pearson correlation coefficient; TZP, tirzepatide.