**Supplementary Appendix**

**The effects of empagliflozin, dietary energy restriction, or both on appetite-regulatory gut peptides in individuals with type 2 diabetes and overweight or obesity: the SEESAW randomised, double-blind, placebo-controlled trial**

Jack A Sargeant PhD1,2,\*, James A King PhD2,3,\*, Thomas Yates PhD1,2, Emma L Redman PhD1,2,4, Danielle H Bodicoat PhD5, Sudesna Chatterjee MD6, Charlotte L Edwardson PhD1,2, Laura J Gray PhD7, Benoit Poulin PhD1,2, Ghazala Waheed MSc1,2, Helen L Waller PhD1,2, David R Webb PhD1,2,4, Scott A Willis PhD2,3, John P H Wilding DM8, Kamlesh Khunti PhD1,4,9, David J Stensel PhD2,3, Melanie J Davies MD1,2,4

\*joint first authors

1 Diabetes Research Centre, University of Leicester, Leicester, UK

2 National Institute for Health Research (NIHR) Leicester Biomedical Research Centre, Leicester, UK

3 School of Sport, Exercise and Health Sciences, Loughborough University, Leicestershire, UK

4 Leicester Diabetes Centre, University Hospitals of Leicester NHS Trust, Leicester, UK

5 Simplified Data, Leicester, UK

6 Milton Keynes University Hospital, Milton Keynes, UK

7 Department of Health Sciences, University of Leicester, Leicester, UK

8 Department of Cardiovascular and Metabolic Medicine, University of Liverpool, Liverpool, UK

9 NIHR Applied Research Collaboration East Midlands, Leicester, UK

**Short running title:** Empagliflozin, energy-restriction and appetite-regulatory peptides

**Corresponding author:** Dr Jack A Sargeant, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, LE5 4PW, UK; jack.sargeant@leicester.ac.uk.

**Supplemental Tables:** 5

**Supplemental Figures:** 2

**Clinical trials registration:** NCT02798744, www.ClinicalTrials.gov; 2015-001594-40, www.EudraCT.ema.europa.eu; ISRCTN82062639, www.ISRCTN.org.

**Supplementary methods**

*Full list of participant eligibility criteria*

Inclusion

* Men or postmenopausal women (≥2 years since last menstrual period if <50 years of age, or ≥1 year since last menstrual period if >50 years of age)
* Aged 30 to 75 years inclusive
* Diagnosed type 2 diabetes, managed through diet and lifestyle advice with or without metformin monotherapy (stable for at least the preceding 3 months)
* HbA1c 6.0 to 10.0% (42 to 86mmol/mol) inclusive
* Weight-stable BMI ≥25kg/m2 (<5% change in body weight in the preceding 3 months)

Exclusion

* Currently taking any pharmacological glucose-lowering therapy other than metformin
* Unstable diabetes, including HbA1c >10% (>86mmol/mol) or recent hospital admission with diabetic emergency in preceding 3 months
* Other forms of diabetes, including type 1 diabetes and latent autoimmune diabetes in adults (LADA)
* Currently taking loop diuretics
* Moderate or severe renal impairment (eGFR <60ml/min/1.73m2)
* History of chronic pancreatitis
* History of excessive alcohol consumption, that in the opinion of the investigator or any sub-investigators would preclude safe participation, or would make implementation of the protocol or interpretation of the study results difficult.
* Familial glucosuria
* Evidence of conditions that lead to restricted food intake or severe dehydration
* Currently undertaking a severely calorie restricted diet (i.e., ≤800 kcal/day)
* History of recurrent balanitis, vaginal or urinary tract infections
* Hypersensitivity to empagliflozin therapy or any of the excipients
* Active malignancy
* Serious illness with a life-expectancy <1 year
* Any other contraindication to trial interventions or procedures
* Shift workers with rotating night/day shift patterns
* Participation in another study of an investigational medicinal product in the preceding 3 months
* Unable or unwilling to provide informed, written consent

*Further details of trial design*

Blinding, masking, dispensing and accountability

Participants and trial personnel were masked to treatment allocation (empagliflozin and placebo) throughout the trial. Empagliflozin and placebo were prepared in visually identical tablets by Boehringer Ingelheim and provided in sealed packs to a third-party company that was responsible for blinding, packaging and labelling. Each were then dispensed at baseline (randomisation), and two and 12 weeks after randomisation. Unused tablets were returned to the research team at each experimental visit, counted and recorded.

Standardisation procedures before experimental visits

Participants were instructed to refrain from alcohol, caffeine and structured physical activity for 48 hours before Visits 1 to 5, and to standardise their dietary intake on the day before each visit. The latter included recording all food and energy-containing beverages consumed on the day prior to Visit 1 and replicating these before Visits 2 to 5. To support compliance, participants completed a food and drink diary for at least 4 days before each visit, which was checked by a member of the research team. Participants were also provided with a standardised evening meal (based on their estimated daily energy requirements),1 which they consumed ≥10 hours before attending the laboratory, refraining from all food and energy-containing beverages after consumption of this meal (water was permitted *ad libitum*).

Concomitant medication and other medical treatments

Concomitant medication and other medical treatments were reviewed at screening and each follow-up visit to ensure that participants remained within eligibility criteria and, in the opinion of the investigators, any changes would not influence trial outcomes. No changes occurred throughout the trial which resulted in any participant being withdrawn.

*Further details of trial assessments*

Anthropometry and indirect calorimetry

All anthropometric assessments were performed using standardised protocols by trained members of the research team, and with participants removing shoes, socks and any heavy items of clothing. Body mass and total body fat percentage were measured to the nearest 0.1kg and 0.1%, respectively, the latter using bioelectrical impedance analysis (TBE611, Tanita, West Drayton, UK). Waist and hip circumferences were measured (each to the nearest 0.5cm) at the midpoint between the lower costal margin and iliac crest, and the maximum extension of the buttocks, respectively. Resting energy expenditure was assessed using indirect calorimetry (GEM open-circuit ventilated hood system, GEM Nutrition Ltd., Cheshire, UK), with participants laying supine for approximately 45 minutes under a rigid, transparent ‘hood’. Mean oxygen consumption (*V̇*O2), carbon dioxide production (*V̇*CO2), respiratory exchange ratio (RER; *V̇*O2 divided by *V̇*CO2) and energy expenditure were calculated after exclusion of data from the first 10 and final 5 minutes. Seated, resting blood pressure and heart rate were measured using an automated sphygmomanometer, calculating the mean of two consecutive measurements after participants had been sitting quietly for ≥5 minutes and a familiarisation measurement had been conducted.

Biochemical assessments

Clinical biomarkers were transported on the day of collection to the pathology laboratories of University Hospitals of Leicester NHS Trust and measured using standardised quality-controlled assays. Plasma glucose was assessed in all blood samples collected during the MMTT (i.e. fasting and postprandial), whilst HbA1c, total cholesterol, HDL, LDL (estimated), C-reactive protein (CRP), alkaline phosphatase (ALP), alanine aminotransferase (ALT), bilirubin, albumin, and eGFR were assessed in the fasting sample only. Samples for fasting plasma non-esterified fatty acids (NEFA) were transported and analysed in a similar manner by the pathology laboratories of Nottingham University Hospitals NHS Trust. Remaining samples were spun immediately after collection in a refrigerated centrifuge (4ºC) for 10 minutes at 1500*g*, before plasma/serum were isolated and stored at -80ºC for future batch analysis. Total PYY, total GLP-1 (both Millipore, Hertfordshire, UK), acylated ghrelin (Bertin Technologies, Montigny le Bretonneux, France) and leptin (R&D Systems, Oxford, UK) were measured via ELISA. Insulin, glucagon, and C-peptide were measured via multiplex assay (Milliplex human metabolic hormone bead panel; Millipore, Hertfordshire, UK). The mean intraplate co-efficient of variation of total PYY, total GLP-1, acylated ghrelin, leptin, insulin, glucagon and C-peptide analyses were 2⋅7%, 4⋅4%, 6⋅5%, 3⋅9%, 13⋅4%, 3⋅4%, and 10⋅7%, respectively.

Habitual physical activity

Participants were instructed to wear the GT3X+BT accelerometer on the right hip during waking hours only for 7 days after Visits 0, 3, 4 and 5. Participants were asked to record any periods of removal, the times they got into or out of bed, and estimated sleeping and waking times using a log provided by the research team. Data were processed using KineSoft version 3.3.76 (Loughborough University, UK), with Freedson intensity cutpoints applied to the re-integrated 60-second epoch data to determine intensity of physical activity. A valid day was defined as having ≥10 hours of wear data, with ≥3 valid days of data required at a given timepoint to be included in analyses at that timepoint.

Habitual daily energy intake

Daily energy intake was measured at baseline and 24 weeks using the self-reported food dairies completed prior to Visits 0 and 5 (see *“Further details of standardisation procedures before each visit”* above). Data were entered into a specialist dietary analysis online tool (Nutritics; <https://www.nutritics.com>) by a member of the research team, and checked by a second for accuracy. Mean daily energy intake was calculated from the first 3 days of data. Day 4 was excluded because food intake was standardised on this day in preparation for experimental visits.

*Further details of data analyses*

Procedures to account for missing data during the 3-hours mixed meal tolerance test

Where data from one to three samples within a MMTT were missing (out of seven; most commonly due to cannula patency), these missing data were imputed using a linear regression model developed previously for postprandial responses,2 with randomisation group, ethnicity, age, BMI and fasting value (unless fasting value was itself being predicted) as predictors. If data from ≥4 timepoints were missing, AUC was not calculated, and this assessment was classified as missing.

Statistical analysis

Statistical analyses were conducted according to a pre-specified statistical analysis plan except that analyses of self-reported daily energy intake were also performed, and those of urinary glucose excretion were omitted due to missing data. Adjustment for age and BMI in all models were categorised as per randomisation. A normal distribution with an identity link provided a robust model fit for the primary analysis, which was not improved by selecting alternative model criteria, and was thus used for analyses of all outcomes.

For the intention-to-treat (ITT) analysis of the primary outcome (change in postprandial total PYY from baseline to 24 weeks), multiple imputation was employed using chained equations to impute missing data for total PYY, with treatment group, baseline value, age and BMI as predictors. Parameter estimates were combined from 100 imputations using Rubin’s rule.3

For the per protocol analysis, data were included only from participants who met the following criteria:

1. Evidence of ≥80% adherence to prescribed empagliflozin or placebo therapy,
2. Evidence of meeting individual daily energy intake targets (placebo-plus-diet and empagliflozin-plus-diet groups only),
3. Absence of any logged protocol deviation that, in the opinion of the investigators, may affect the primary outcome.

**Supplementary Tables**

**Table S1 – Participant characteristics at baseline in the combined population**

|  |  |
| --- | --- |
| Sex (Male / Female) | 44 (64.7) / 24 (35.3) |
| Ethnicity (White European / South Asian / Other) | 49 (72.1) / 13 (19.1) / 6 (8.8) |
| Age (years) | 63 (57.3 – 69.0) |
| Duration of diabetes (years) | 6.0 (4.0 – 10.0) |
| Diabetes management ( Lifestyle advice only / Lifestyle advice plus metformin monotherapy) | 12 (17.7) / 56 (82.4) |
| **Glycaemic control** |  |
| HbA1c (%) [mmol/mol] | 6.9 (6.5 – 7.1) [52 (48 – 55)] |
| Fasting plasma glucose (mmol/L) | 6.7 (5.9 – 7.5) |
| Fasting plasma insulin (mU/L) | 13.7 (9.6 – 21.5) |
| Fasting plasma glucagon (pg/mL) | 53 (39 – 87) |
| Fasting plasma C-peptide (pg/mL) | 1667 (1297 – 2062) |
| **Anthropometry and body composition** |  |
| Body weight (kg) | 91.4 (78.5 – 107.1) |
| BMI (kg/m2) | 31.8 (29.2 – 35.0) |
| Body fat percentage (%) | 34.0 (29.0 – 39.0) |
| Total fat mass (kg) | 34.7 (29.0 – 40.8) |
| Total lean body mass (kg) | 55.0 (44.6 – 61.9) |
| Total bone mass (kg) | 2.96 (2.38 – 3.36) |
| Total bone mineral density (g/cm2) | 1.23 (1.13 – 1.33) |
| Waist circumference (cm) | 110.0 (101.5 – 118.0) |
| Hip circumference (cm) | 119.5 (103.8 – 118.0) |
| **Energy balance and habitual physical activity** |  |
| Daily energy intake (kcal/day) | 1625 (1335 – 1889) |
| Resting energy expenditure (kcal/day) | 1473 (1252 – 1674) |
| Steps (number per day) | 4965 (3867 – 7729) |
| Sedentary time (min/day) | 582 (529 – 656) |
| Light-intensity physical activity (min/day) | 269 (221 – 328) |
| Moderate-to-vigorous-intensity physical activity (min/day) | 18 (9 – 32) |
| **Renal and liver function** |  |
| eGFR (mL/min per 1.73m2) | 90 (86 – 90) |
| Albumin (g/L) | 45 (44 – 47) |
| Alkaline phosphatase (U/L) | 80 (66 – 91) |
| Alanine transaminase (U/L) | 28 (20 – 42) |
| Total bilirubin (µmol/L) | 9 (7 – 10) |
| **Blood pressure, lipids and other cardiometabolic risk factors** |  |
| Total cholesterol (mmol/L) | 3.8 (3.3 – 4.6) |
| HDL (mmol/L) | 1.2 (1.0 – 1.4) |
| LDL (mmol/L) | 1.8 (1.5 – 2.4) |
| Triglycerides (mmol/L) | 1.67 (1.29 – 2.13) |
| Non-esterified fatty acids (mmol/L) | 0.47 (0.36 – 0.65) |
| Systolic blood pressure (mmHg) | 124 (113 – 136) |
| Diastolic blood pressure (mmHg) | 74 (69 – 80) |
| Resting heart rate (beats/min) | 73 (64 – 82) |
| Smoking status (Never smoked / Ex-smoker / Current Smoker) | 30 (44.1) / 32 (47.1) / 6 (8.8) |
| C-reactive protein (mg/L) | 5.0 (5.0 – 5.0) |
| **Appetite-regulatory peptides and three-factor eating questionnaire dimensions** |  |
| Fasting total PYY (pg/mL) | 78 (59 – 107) |
| Postprandial total PYY (pg/mL)\* | 133 (101 – 173) |
| Fasting acylated ghrelin (pg/mL) | 48 (29 – 89) |
| Postprandial acylated ghrelin (pg/mL)\* | 25 (16 – 50) |
| Fasting total GLP-1 (pmol/L) | 31 (23 – 41) |
| Postprandial total GLP-1 (pmol/L)\* | 44 (35 – 53) |
| Fasting leptin (ng/mL) | 15.3 (8.9 – 28.4) |
| Cognitive dietary restraint (AU) | 27 (22 – 30) |
| Disinhibition (AU) | 12 (8 – 15) |
| Hunger (AU) | 11 (9 – 13) |

Continuous and categorical data presented as median (interquartile range) and frequency (%), respectively. \*calculated as time-averaged area under the concentration-time curve during the standardised 3-hour mixed meal tolerance test. Abbreviations: AU, arbitrary units; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; PYY, peptide YY.

**Table S2 – Appetite-regulatory peptides, subjective appetite perceptions and three-factor eating questionnaire dimensions: within-group change from baseline in each group, and differences between experimental groups (placebo-plus-diet, empagliflozin-only, and empagliflozin-plus-diet) and placebo-only at 2, 6, 12 and 24 weeks and across follow-up collectively.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ***Within-group change from baseline*** | | | | | | | |  | ***Between-group difference versus PLA*** | | | | | |
|  |  | **Placebo only** | | **Placebo + Diet** | | **Empagliflozin only** | | **Empagliflozin + Diet** | |  | **Placebo + Diet** | | **Empagliflozin only** | | **Empagliflozin + Diet** | |
|  |  | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] |  | *β*-coefficient [95% CI] | *p*-value | *β*-coefficient [95% CI] | *p*-value | *β*-coefficient [95% CI] | *p*-value |
| Postprandial total PYY (pg/mL)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | 0.4  [-18.2 to 19.0] | 14 | 2.3  [-21.0 to 25.5] | 15 | 9.2  [-7.9 to 26.4] | 17 | 6.9  [-6.4 to 20.3] |  | 7.6  [-15.0 to 30.1] | 0.511 | 9.3  [-12.7 to 31.3] | 0.406 | 4.0  [-17.3 to 25.4] | 0.711 |
| *6 weeks* |  | 16 | 6.7  [-7.9 to 21.3] | 13 | -5.6  [-26.5 to 15.3] | 16 | 13.1  [-0.7 to 26.9] | 16 | 12.1  [-2.3 to 26.5] |  | -7.0  [-28.2 to 14.3] | 0.521 | 6.9  [-13.0 to 26.8] | 0.498 | 3.4  [-16.6 to 23.5] | 0.738 |
| *12 weeks* |  | 16 | -7.4  [-23.0 to 8.2] | 14 | -7.9  [-24.7 to 8.8] | 15 | 27.0  [5.0 to 49.1] | 16 | 8.2  [-5.5 to 21.8] |  | 3.5  [-20.0 to 26.9] | 0.772 | 34.3  [11.4 to 57.3] | **0.003** | 15.6  [-7.0 to 38.2] | 0.177 |
| *24 weeks* |  | 15 | 4.4  [-5.4 to 14.2] | 14 | -7.8  [-24.8 to 9.1] | 15 | 16.3  [-2.5 to 35.2] | 17 | 6.8  [-5.2 to 18.8] |  | -8.6  [-28.6 to 11.4] | 0.400 | 13.4  [-6.1 to 33.0] | 0.179 | 1.0  [-18.0 to 19.9] | 0.920 |
| *Across follow-up collectively* | | | | | | | | | |  | -1.0  [-16.2 to 14.1] | 0.895 | 17.0  [2.4 to 31.6] | 0.023 | 6.4  [-8.0 to 20.8] | 0.381 |
| Postprandial acylated ghrelin (pg/mL)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -2.0  [-13.6 to 9.6] | 14 | 42.6  [-27.9 to 113.1] | 14 | -0.4  [-6.5 to 5.8] | 17 | -0.7  [-16.7 to 15.2] |  | 42.9  [2.6 to 83.1] | 0.037 | -3.3  [-43.4 to 36.9] | 0.874 | -10.7  [-49.1 to 27.8] | 0.586 |
| *6 weeks* |  | 16 | -6.6  [-18.7 to 5.5] | 13 | 55.9  [-41.1 to 152.9] | 16 | -0.6  [-5.4 to 4.3] | 16 | -2.8  [-21.0 to 15.4] |  | 61.2  [9.7 to 112.8] | 0.020 | -1.1  [-49.7 to 47.5] | 0.965 | -7.1  [-55.9 to 41.7] | 0.775 |
| *12 weeks* |  | 16 | 3.0  [-5.0 to 11.0] | 14 | 38.1  [-26.4 to 102.7] | 15 | 16.3  [-0.1 to 32.7] | 16 | 8.8  [-5.9 to 23.4] |  | 32.5  [0.2 to 64.9] | 0.049 | 3.9  [-27.9 to 35.7] | 0.810 | -9.9  [-41.4 to 21.6] | 0.538 |
| *24 weeks* |  | 15 | 13.7  [2.0 to 25.4] | 14 | 17.7  [-7.1 to 42.6] | 15 | 1.0  [-9.6 to 11.6] | 17 | 4.3  [-9.3 to 18.0] |  | 3.2  [-17.7 to 24.1] | 0.765 | -13.8  [-34.3 to 6.7] | 0.187 | -13.5  [-33.5 to 6.5] | 0.185 |
| *Across follow-up collectively* | | | | | | | | | |  | 34.2  [2.2 to 66.3] | 0.036 | -3.0  [-34.0 to 27.9] | 0.849 | -10.4  [-41.1 to 20.2] | 0.504 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Postprandial total GLP-1 (pmol/L)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -1.5  [-5.4 to 2.4] | 14 | 1.3  [-3.0 to 5.6] | 15 | 3.9  [-0.6 to 8.4] | 17 | 5.2  [0.8 to 9.5] |  | 3.4  [-2.7 to 9.4] | 0.280 | 6.0  [0.0 to 12.0] | 0.049 | 6.5  [0.7 to 12.3] | 0.028 |
| *6 weeks* |  | 16 | -1.2  [-4.9 to 2.5] | 13 | -1.4  [-5.1 to 2.3] | 16 | 3.0  [-0.5 to 6.5] | 16 | 1.7  [-1.9 to 5.3] |  | 0.3  [-5.1 to 5.7] | 0.922 | 4.3  [-0.7 to 9.4] | 0.093 | 2.9  [-2.1 to 8.0] | 0.257 |
| *12 weeks* |  | 16 | -1.4  [-5.2 to 2.5] | 14 | -2.3  [-7.1 to 2.6] | 15 | 5.7  [-1.2 to 12.6] | 16 | 3.8  [-1.6 to 9.1] |  | -0.1  [-7.6 to 7.4] | 0.976 | 7.2  [-0.1 to 14.6] | 0.055 | 5.1  [-2.1 to 12.4] | 0.163 |
| *24 weeks* |  | 15 | -0.3  [-4.6 to 4.0] | 14 | 0.8  [-3.4 to 4.9] | 15 | 2.6  [-1.2 to 6.4] | 17 | 0.7  [-2.6 to 4.1] |  | 1.2  [-4.1 to 6.6] | 0.657 | 3.1  [-2.2 to 8.3] | 0.250 | 0.3  [-4.8 to 5.5] | 0.896 |
| *Across follow-up collectively* | | | | | | | | | |  | 1.2  [-3.4 to 5.9] | 0.598 | 5.5  [1.0 to 10.0] | **0.016** | 3.8  [-0.6 to 8.2] | 0.091 |
| Fasting plasma leptin (ng/mL) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -0.9  [-2.9 to 1.0] | 14 | -0.2  [-2.0 to 1.7] | 15 | 0.2  [-3.2 to 3.5] | 17 | -2.2  [-3.5 to -1.0] |  | 0.0  [-3.0 to 2.9] | 0.991 | 1.6  [-1.3 to 4.5] | 0.283 | -1.2  [-4.0 to 1.6] | 0.389 |
| *6 weeks* |  | 16 | -0.3  [-2.2 to 1.5] | 13 | -0.6  [-2.3 to 1.1] | 16 | -0.6  [-3.3 to 2.1] | 16 | -3.0  [-5.6 to -0.4] |  | -0.8  [-4.1 to 2.5] | 0.637 | 0.1  [-3.0 to 3.3] | 0.939 | -2.8  [-5.9 to 0.4] | 0.082 |
| *12 weeks* |  | 16 | 0.2  [-2.7 to 3.1] | 14 | -1.2  [-3.2 to 0.9] | 15 | 0.2  [-3.1 to 3.5] | 16 | -4.1  [-8.1 to -0.1] |  | -2.3  [-6.8 to 2.2] | 0.320 | 0.6  [-3.8 to 5.0] | 0.775 | -4.1  [-8.4 to 0.2] | 0.061 |
| *24 weeks* |  | 15 | -1.2  [-4.1 to 1.8] | 14 | -0.8  [-2.8 to 1.2] | 15 | -1.6  [-6.6 to 3.3] | 17 | -6.2  [-9.6 to -2.9] |  | -1.2  [-5.5 to 3.1] | 0.588 | 0.6  [-3.6 to 4.9] | 0.774 | -4.8  [-8.9 to -0.7] | 0.022 |
| *Across follow-up collectively* | | | | | | | | | |  | -1.1  [-3.9 to 1.6] | 0.424 | 0.8  [-1.8 to 3.5] | 0.541 | -3.3  [-5.9 to -0.7] | **0.014** |
| Fasting plasma leptin to body weight ratio (ng/mL per kg) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -0.011  [-0.030 to 0.009] | 14 | -0.002  [-0.021 to 0.016] | 15 | 0.007  [-0.033 to 0.046] | 17 | -0.021  [-0.033 to -0.009] |  | 0.003  [-0.031 to 0.036] | 0.884 | 0.023  [-0.010 to 0.057] | 0.167 | -0.008  [-0.040 to 0.024] | 0.613 |
| *6 weeks* |  | 16 | -0.004  [-0.022 to 0.013] | 13 | -0.008  [-0.028 to 0.011] | 16 | -0.004  [-0.036 to 0.028] | 16 | -0.028  [-0.057 to 0.002] |  | -0.009  [-0.046 to 0.028] | 0.636 | 0.008  [-0.028 to 0.043] | 0.677 | -0.024  [-0.059 to 0.011] | 0.185 |
| *12 weeks* |  | 16 | 0.000  [-0.028 to 0.028] | 14 | -0.011  [-0.035 to 0.012] | 15 | 0.013  [-0.028 to 0.054] | 16 | -0.042  [-0.087 to 0.002] |  | -0.020  [-0.071 to 0.030] | 0.426 | 0.025  [-0.025 to 0.074] | 0.330 | -0.038  [-0.086 to 0.010] | 0.120 |
| *24 weeks* |  | 15 | -0.013  [-0.047 to 0.020] | 14 | -0.003  [-0.020 to 0.014] | 15 | -0.011  [-0.070 to 0.048] | 17 | -0.060  [-0.096 to -0.024] |  | -0.002  [-0.053 to 0.049] | 0.945 | 0.021  [-0.029 to 0.072] | 0.411 | -0.039  [-0.087 to 0.010] | 0.118 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.008  [-0.038 to 0.023] | 0.624 | 0.020  [-0.009 to 0.050] | 0.181 | -0.028  [-0.057 to 0.001] | 0.058 |
| VAS – Postprandial hunger (mm)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -1.3  [-7.4 to 4.9] | 15 | 2.7  [-4.1 to 9.5] | 15 | 0.4  [-11.1 to 11.9] | 17 | 0.3  [-7.1 to 7.7] |  | 0.6  [-9.4 to 10.6] | 0.912 | 5.5  [-4.5 to 15.5] | 0.279 | 1.6  [-8.0 to 11.2] | 0.747 |
| *6 weeks* |  | 17 | 2.7  [-5.2 to 10.6] | 13 | 2.2  [-5.0 to 9.5] | 16 | -0.1  [-12.5 to 12.3] | 16 | 2.0  [-7.1 to 11.1] |  | -3.3  [-16.3 to 9.7] | 0.621 | 0.1  [-12.2 to 12.3] | 0.991 | -0.5  [-12.7 to 11.6] | 0.932 |
| *12 weeks* |  | 17 | -1.7  [-10.2 to 6.9] | 14 | 9.8  [-1.2 to 20.9] | 15 | -5.5  [-17.4 to 6.3] | 16 | 3.8  [-6.0 to 13.5] |  | 8.4  [-4.9 to 21.6] | 0.215 | -0.7  [-13.6 to 12.2] | 0.910 | 4.9  [-7.6 to 17.5] | 0.441 |
| *24 weeks* |  | 16 | 3.3  [-4.5 to 11.0] | 14 | 3.0  [-7.2 to 13.3] | 14 | 8.8  [2.6 to 14.9] | 17 | 6.5  [-1.7 to 14.6] |  | -2.6  [-13.4 to 8.2] | 0.634 | 7.5  [-3.2 to 18.3] | 0.171 | 3.6  [-6.6 to 13.8] | 0.488 |
| *Across follow-up collectively* | | | | | | | | | |  | 0.3  [-8.9 to 9.6] | 0.942 | 2.4  [-6.6 to 11.5] | 0.596 | 2.5  [-6.3 to 11.3] | 0.574 |
| VAS – Postprandial fullness (mm)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | 1.1  [-10.7 to 12.8] | 15 | -2.1  [-9.4 to 5.2] | 16 | 7.6  [-3.9 to 19.2] | 17 | -0.5  [-8.4 to 7.5] |  | 1.9  [-11.6 to 15.4] | 0.782 | 5.9  [-7.0 to 18.8] | 0.371 | 0.3  [-12.4 to 13.1] | 0.958 |
| *6 weeks* |  | 17 | 1.3  [-9.1 to 11.6] | 13 | 0.5  [-10.2 to 11.1] | 17 | 10.5  [-1.2 to 22.3] | 16 | 0.6  [-8.4 to 9.6] |  | 3.9  [-10.5 to 18.3] | 0.597 | 9.4  [-3.8 to 22.6] | 0.165 | 1.0  [-12.4 to 14.5] | 0.883 |
| *12 weeks* |  | 17 | 5.5  [-7.2 to 18.1] | 14 | -1.3  [-11.6 to 9.0] | 16 | 6.9  [-6.9 to 20.8] | 16 | -2.2  [-14.3 to 9.9] |  | -0.9  [-17.2 to 15.5] | 0.915 | 1.3  [-14.3 to 16.8] | 0.874 | -4.6  [-20.2 to 11.0] | 0.565 |
| *24 weeks* |  | 16 | 1.6  [-9.5 to 12.7] | 14 | 1.3  [-9.2 to 11.9] | 15 | -0.3  [-6.5 to 5.9] | 17 | -3.3  [-12.3 to 5.8] |  | 3.9  [-8.4 to 16.3] | 0.534 | -1.2  [-13.1 to 10.8] | 0.850 | -3.5  [-15.1 to 8.1] | 0.556 |
| *Across follow-up collectively* | | | | | | | | | |  | 3.4  [-8.3 to 15.2] | 0.567 | 5.4  [-5.7 to 16.5] | 0.337 | -1.4  [-12.5 to 9.7] | 0.807 |
| VAS – Postprandial satisfaction (mm)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -3.1  [-11.8 to 5.5] | 15 | 0.7  [-5.8 to 7.2] | 16 | 10.6  [-0.6 to 21.8] | 17 | -3.5  [-12.0 to 5.0] |  | 6.5  [-5.8 to 18.7] | 0.302 | 11.0  [-1.0 to 23.0] | 0.071 | 0.1  [-11.6 to 11.9] | 0.986 |
| *6 weeks* |  | 17 | -1.0  [-10.0 to 8.0] | 13 | -0.3  [-10.5 to 9.9] | 17 | 13.5  [1.8 to 25.2] | 16 | -4.4  [-14.9 to 6.1] |  | 4.1  [-10.5 to 18.8] | 0.582 | 12.3  [-1.2 to 25.9] | 0.075 | -2.4  [-16.1 to 11.3] | 0.730 |
| *12 weeks* |  | 17 | 2.5  [-7.3 to 12.2] | 14 | 1.1  [-9.7 to 11.9] | 16 | 17.5  [5.2 to 29.8] | 16 | -1.8  [-12.5 to 8.8] |  | 2.0  [-12.5 to 16.6] | 0.784 | 11.6  [-2.4 to 25.6] | 0.105 | -2.5  [-16.4 to 11.4] | 0.724 |
| *24 weeks* |  | 16 | 0.4  [-8.3 to 9.1] | 14 | 3.3  [-7.1 to 13.7] | 15 | 3.4  [-3.5 to 10.4] | 17 | -5.8  [-16.2 to 4.6] |  | 5.4  [-7.2 to 17.9] | 0.401 | 1.3  [-11.0 to 13.6] | 0.833 | -5.7  [-17.6 to 6.1] | 0.344 |
| *Across follow-up collectively* | | | | | | | | | |  | 5.4  [-6.1 to 17.0] | 0.357 | 10.4  [-0.6 to 21.5] | 0.065 | -2.6  [-13.6 to 8.4] | 0.643 |
| VAS – Postprandial prospective food consumption (mm)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -1.9  [-7.2 to 3.4] | 15 | 1.5  [-4.7 to 7.7] | 16 | -8.3  [-21.6 to 5.0] | 17 | 0.2  [-6.7 to 7.2] |  | -1.9  [-13.3 to 9.6] | 0.748 | -2.8  [-13.8 to 8.3] | 0.624 | 0.4  [-10.4 to 11.1] | 0.947 |
| *6 weeks* |  | 17 | -1.3  [-13.6 to 11.0] | 13 | 7.2  [-1.8 to 16.1] | 17 | -6.6  [-19.8 to 6.6] | 16 | -0.9  [-9.1 to 7.4] |  | 1.0  [-14.2 to 16.2] | 0.896 | -2.8  [-16.5 to 10.8] | 0.684 | -2.6  [-16.6 to 11.3] | 0.712 |
| *12 weeks* |  | 17 | -9.7  [-19.3 to -0.1] | 14 | 5.3  [-3.6 to 14.3] | 16 | -10.9  [-24.2 to 2.3] | 16 | 2.7  [-8.3 to 13.7] |  | 9.2  [-5.4 to 23.9] | 0.217 | 0.9  [-12.8 to 14.6] | 0.894 | 9.4  [-4.4 to 23.2] | 0.183 |
| *24 weeks* |  | 16 | -1.9  [-8.9 to 5.2] | 14 | 1.6  [-7.2 to 10.4] | 15 | 0.4  [-7.0 to 7.8] | 17 | 2.9  [-4.6 to 10.4] |  | -0.5  [-11.3 to 10.2] | 0.922 | 3.0  [-7.3 to 13.3] | 0.564 | 3.1  [-6.9 to 13.1] | 0.539 |
| *Across follow-up collectively* | | | | | | | | | |  | 1.6  [-8.8 to 12.0] | 0.765 | -0.9  [-10.5 to 8.8] | 0.863 | 2.7  [-7.0 to 12.4] | 0.588 |
| TFEQ - Cognitive dietary restraint (AU) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.5  [-2.7 to 1.7] | 15 | 2.2  [0.5 to 3.9] | 17 | 0.0  [-2.1 to 2.1] | 17 | 2.2  [-0.2 to 4.6] |  | 2.8  [-0.2 to 5.7] | 0.066 | 0.9  [-2.0 to 3.7] | 0.546 | 3.1  [0.2 to 6.0] | 0.034 |
| *6 weeks* |  | 17 | -0.1  [-2.1 to 2.0] | 14 | 3.1  [1.3 to 5.0] | 17 | -0.3  [-2.1 to 1.5] | 16 | 2.6  [-0.3 to 5.5] |  | 3.1  [-0.1 to 6.3] | 0.057 | -0.1  [-3.1 to 3.0] | 0.970 | 2.8  [-0.4 to 5.9] | 0.083 |
| *12 weeks* |  | 17 | -0.8  [-2.8 to 1.3] | 14 | 4.8  [3.1 to 6.4] | 17 | 0.5  [-1.1 to 2.1] | 17 | 3.5  [1.0 to 5.9] |  | 5.5  [2.6 to 8.4] | **<0.001** | 1.5  [-1.3 to 4.3] | 0.282 | 4.5  [1.7 to 7.2] | **0.002** |
| *24 weeks* |  | 16 | 0.2  [-2.5 to 2.9] | 14 | 3.1  [1.8 to 4.5] | 16 | 1.3  [-0.2 to 2.8] | 17 | 4.5  [2.3 to 6.7] |  | 2.9  [-0.1 to 5.9] | 0.056 | 1.4  [-1.5 to 4.3] | 0.349 | 4.6  [1.7 to 7.5] | **0.002** |
| *Across follow-up collectively* | | | | | | | | | |  | 3.6  [1.2 to 6.0] | **0.003** | 0.9  [-1.4 to 3.3] | 0.430 | 3.7  [1.4 to 6.1] | **0.002** |
| TFEQ - Disinhibition (AU) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.7  [-1.8 to 0.4] | 15 | -1.0  [-2.1 to 0.1] | 17 | -0.5  [-2.0 to 0.9] | 17 | -0.4  [-1.4 to 0.7] |  | 0.0  [-1.7 to 1.6] | 0.976 | 0.3  [-1.2 to 1.9] | 0.668 | 0.4  [-1.1 to 2.0] | 0.577 |
| *6 weeks* |  | 17 | 0.2  [-1.0 to 1.4] | 14 | -0.5  [-2.0 to 1.0] | 17 | -1.1  [-2.2 to 0.1] | 16 | -0.8  [-1.9 to 0.4] |  | -0.3  [-1.9 to 1.3] | 0.715 | -1.0  [-2.6 to 0.5] | 0.181 | -0.9  [-2.4 to 0.6] | 0.259 |
| *12 weeks* |  | 17 | -0.2  [-1.2 to 0.9] | 14 | -1.4  [-3.1 to 0.3] | 16 | -1.1  [-2.2 to 0.1] | 17 | -0.9  [-2.5 to 0.6] |  | -1.1  [-2.9 to 0.7] | 0.236 | -0.7  [-2.5 to 1.0] | 0.407 | -0.7  [-2.4 to 1.0] | 0.408 |
| *24 weeks* |  | 16 | -0.6  [-1.9 to 0.8] | 14 | -0.6  [-2.0 to 0.8] | 16 | -0.2  [-1.3 to 0.9] | 17 | 0.1  [-1.5 to 1.6] |  | -0.1  [-2.0 to 1.8] | 0.931 | 0.4  [-1.4 to 2.2] | 0.679 | 0.6  [-1.1 to 2.4] | 0.475 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.4  [-1.8 to 1.0] | 0.580 | -0.3  [-1.6 to 1.0] | 0.663 | -0.2  [-1.5 to 1.1] | 0.797 |
| TFEQ - Hunger (AU) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 0.9  [0.0 to 1.9] | 15 | 1.0  [0.0 to 2.0] | 17 | -0.5  [-2.1 to 1.1] | 17 | -0.6  [-1.6 to 0.5] |  | 0.5  [-1.2 to 2.2] | 0.579 | -1.0  [-2.7 to 0.7] | 0.268 | -1.3  [-2.9 to 0.4] | 0.125 |
| *6 weeks* |  | 17 | -0.2  [-1.2 to 0.8] | 14 | -0.1  [-1.3 to 1.2] | 17 | -0.4  [-2.0 to 1.1] | 16 | -0.3  [-1.4 to 0.8] |  | 0.9  [-0.8 to 2.7] | 0.291 | 0.6  [-1.1 to 2.2] | 0.499 | 0.3  [-1.4 to 1.9] | 0.761 |
| *12 weeks* |  | 17 | 0.9  [0.0 to 1.9] | 14 | -0.8  [-2.0 to 0.4] | 16 | -0.8  [-1.8 to 0.2] | 17 | 0.1  [-0.9 to 1.1] |  | -1.4  [-2.9 to 0.1] | 0.064 | -1.4  [-2.9 to 0.1] | 0.060 | -0.6  [-2.0 to 0.8] | 0.371 |
| *24 weeks* |  | 16 | 0.4  [-0.7 to 1.5] | 14 | 0.0  [-1.2 to 1.2] | 16 | 0.9  [-0.1 to 2.0] | 17 | -0.5  [-1.7 to 0.8] |  | -0.2  [-1.9 to 1.5] | 0.825 | 0.8  [-0.9 to 2.4] | 0.367 | -0.7  [-2.3 to 0.8] | 0.364 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.1  [-1.3 to 1.2] | 0.923 | -0.2  [-1.5 to 1.0] | 0.707 | -0.6  [-1.8 to 0.6] | 0.301 |

All analyses at each timepoint were conducted using a complete case approach, with generalised linear models adjusted for age, BMI (both categorized as per randomisation) and baseline value of the outcome. Analyses across follow-up collectively used generalised estimating equations, adjusted in the same way as generalised linear models, with a normal distribution and exchangeable correlation matrix; *p*-values in bold are statistically significant (assessments of statistical significance for between-group comparison used the Holm sequential Bonferroni procedure to account for multiple comparisons); \*calculated as time-averaged area under the concentration-time curve during the standardised 3-hour mixed meal tolerance test. Abbreviations: AU, arbitrary units; GLP-1, glucagon-like peptide-1; PYY, peptide YY; TFEQ, three-factor eating questionnaire; VAS, visual analogue scale.

**Table S3 – Anthropometry, body composition, energy intake, resting energy expenditure and habitual physical activity: within-group change from baseline in each group, and differences between experimental groups (placebo-plus-diet, empagliflozin-only, and empagliflozin-plus-diet) and placebo-only at 2, 6, 12 and 24 weeks and across follow-up collectively.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ***Within-group change from baseline*** | | | | | | | |  | ***Between-group difference versus PLA*** | | | | | |
|  |  | **Placebo only** | | **Placebo + Diet** | | **Empagliflozin only** | | **Empagliflozin + Diet** | |  | **Placebo + Diet** | | **Empagliflozin only** | | **Empagliflozin + Diet** | |
|  |  | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] |  | *β*-coefficient [95% CI] | *p*-value | *β*-coefficient [95% CI] | *p*-value | *β*-coefficient [95% CI] | *p*-value |
| Body weight (kg) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.16  [-0.55 to 0.23] | 15 | -0.67  [-1.31 to -0.03] | 17 | -0.80  [-1.36 to -0.24] | 17 | -1.59  [-1.96 to -1.23] |  | -0.53  [-1.24 to 0.17] | 0.135 | -0.75  [-1.44 to -0.07] | 0.031 | -1.51  [-2.19 to -0.83] | **<0.001** |
| *6 weeks* |  | 17 | -0.04  [-0.67 to 0.59] | 14 | -1.18  [-2.22 to -0.14] | 17 | -1.26  [-1.95 to -0.56] | 16 | -3.23  [-4.12 to -2.33] |  | -1.19  [-2.34 to -0.04] | **0.042** | -1.44  [-2.54 to -0.34] | **0.011** | -3.28  [-4.39 to -2.17] | **<0.001** |
| *12 weeks* |  | 17 | -0.07  [-0.88 to 0.74] | 14 | -1.45  [-3.31 to 0.41] | 16 | -1.82  [-2.68 to -0.96] | 17 | -4.39  [-5.75 to -3.04] |  | -1.36  [-3.07 to 0.36] | 0.121 | -2.24  [-3.92 to -0.56] | **0.009** | -4.60  [-6.23 to -2.96] | **<0.001** |
| *24 weeks* |  | 16 | -0.44  [-1.39 to 0.50] | 14 | -1.91  [-4.40 to 0.59] | 16 | -2.22  [-3.34 to -1.11] | 17 | -5.74  [-7.39 to -4.08] |  | -1.52  [-3.79 to 0.76] | 0.191 | -2.23  [-4.45 to -0.01] | 0.049 | -5.62  [-7.79 to -3.44] | **<0.001** |
| *Across follow-up collectively* | | | | | | | | | |  | -1.18  [-2.36 to 0.00] | 0.051 | -1.65  [-2.80 to -0.50] | **0.005** | -3.78  [-4.92 to -2.64] | **<0.001** |
| Body fat percentage (%) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 0.1  [-0.7 to 1.0] | 14 | -0.4  [-1.5 to 0.6] | 17 | -0.2  [-1.0 to 0.5] | 17 | 0.9  [0.0 to 1.8] |  | -0.5  [-1.8 to 0.8] | 0.461 | -0.3  [-1.6 to 0.9] | 0.592 | 0.8  [-0.4 to 2.0] | 0.208 |
| *6 weeks* |  | 17 | 0.4  [-0.7 to 1.5] | 13 | -0.8  [-2.0 to 0.4] | 17 | -0.1  [-1.1 to 0.9] | 16 | 0.3  [-0.5 to 1.0] |  | -1.1  [-2.6 to 0.5] | 0.173 | -0.5  [-1.9 to 0.9] | 0.497 | -0.1  [-1.5 to 1.4] | 0.925 |
| *12 weeks* |  | 17 | 0.5  [-0.8 to 1.7] | 13 | -1.5  [-2.8 to -0.3] | 16 | -1.1  [-2.3 to 0.1] | 17 | -0.9  [-1.7 to -0.2] |  | -2.0  [-3.7 to -0.3] | 0.020 | -1.5  [-3.1 to 0.1] | 0.059 | -1.4  [-3.0 to 0.1] | 0.075 |
| *24 weeks* |  | 16 | 0.6  [-0.9 to 2.0] | 13 | -1.2  [-2.9 to 0.6] | 15 | -0.4  [-1.7 to 0.9] | 17 | -2.4  [-4.3 to -0.4] |  | -1.7  [-4.1 to 0.7] | 0.168 | -0.6  [-2.9 to 1.8] | 0.631 | -2.9  [-5.1 to -0.7] | **0.011** |
| *Across follow-up collectively* | | | | | | | | | |  | -1.3  [-2.6 to 0.0] | 0.055 | -0.8  [-2.0 to 0.5] | 0.222 | -0.9  [-2.1 to 0.3] | 0.142 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Total fat mass (kg) | | | | | | | | | | | | | | | | |
| *24 weeks* |  | 16 | -0.63  [-1.40 to 0.13] | 14 | -2.37  [-4.27 to -0.47] | 16 | -1.26  [-2.15 to -0.37] | 17 | -4.38  [-5.96 to -2.80] |  | -1.94  [-3.72 to -0.16] | 0.033 | -0.98  [-2.71 to 0.74] | 0.264 | -4.06  [-5.76 to -2.36] | **<0.001** |
| Total lean body mass (kg) | | | | | | | | | | | | | | | | |
| *24 weeks* |  | 16 | 0.48  [-0.02 to 0.98] | 14 | 0.81  [0.06 to 1.56] | 16 | -0.83  [-1.44 to -0.22] | 17 | -1.05  [-1.51 to -0.60] |  | 0.34  [-0.50 to 1.18] | 0.428 | -1.41  [-2.23 to -0.60] | **0.001** | -1.60  [-2.40 to -0.80] | **<0.001** |
| Total bone mass (kg) | | | | | | | | | | | | | | | | |
| *24 weeks* |  | 16 | 0.00  [-0.02 to 0.02] | 14 | -0.01  [-0.04 to 0.01] | 16 | 0.02  [-0.01 to 0.04] | 17 | -0.01  [-0.04 to 0.01] |  | -0.01  [-0.05 to 0.02] | 0.375 | 0.02  [-0.02 to 0.05] | 0.306 | -0.01  [-0.04 to 0.02] | 0.418 |
| Total bone mineral density (g/cm2) | | | | | | | | | | | | | | | | |
| *24 weeks* |  | 16 | 0.00  [-0.01 to 0.02] | 14 | 0.01  [-0.01 to 0.02] | 16 | -0.01  [-0.02 to 0.00] | 17 | 0.01  [0.00 to 0.02] |  | 0.01  [-0.01 to 0.03] | 0.479 | -0.01  [-0.03 to 0.00] | 0.146 | 0.01  [-0.01 to 0.03] | 0.358 |
| Waist circumference (cm) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 0.9  [-1.1 to 2.9] | 15 | -0.7  [-1.7 to 0.3] | 17 | -1.4  [-3.6 to 0.8] | 17 | -1.5  [-3.0 to 0.1] |  | -1.7  [-4.2 to 0.9] | 0.203 | -2.4  [-4.8 to 0.1] | 0.060 | -2.7  [-5.2 to -0.2] | 0.034 |
| *6 weeks* |  | 17 | 0.0  [-1.7 to 1.7] | 14 | -0.6  [-2.1 to 1.0] | 17 | -2.4  [-5.0 to 0.1] | 16 | -1.7  [-3.0 to -0.4] |  | -0.6  [-3.4 to 2.1] | 0.655 | -2.5  [-5.1 to 0.1] | 0.063 | -1.8  [-4.5 to 0.9] | 0.193 |
| *12 weeks* |  | 17 | -0.1  [-2.0 to 1.8] | 14 | -1.6  [-3.7 to 0.5] | 16 | -2.4  [-5.4 to 0.6] | 17 | -2.7  [-4.4 to -1.0] |  | -1.6  [-4.8 to 1.7] | 0.348 | -2.5  [-5.6 to 0.6] | 0.120 | -2.9  [-6.0 to 0.2] | 0.066 |
| *24 weeks* |  | 16 | 0.5  [-1.6 to 2.7] | 14 | -1.9  [-4.4 to 0.5] | 16 | -3.2  [-5.5 to -0.8] | 17 | -3.9  [-5.8 to -2.1] |  | -2.4  [-5.6 to 0.8] | 0.146 | -3.8  [-6.9 to -0.7] | **0.016** | -4.8  [-7.8 to -1.7] | **0.002** |
| *Across follow-up collectively* | | | | | | | | | |  | -1.5  [-3.9 to 0.9] | 0.231 | -2.8  [-5.1 to -0.5] | **0.018** | -3.0  [-5.3 to -0.6] | **0.012** |
| Hip circumference (cm) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 0.5  [-1.0 to 2.0] | 15 | -1.5  [-4.5 to 1.6] | 17 | 0.8  [-2.3 to 3.9] | 17 | -0.1  [-0.8 to 0.7] |  | -2.0  [-5.3 to 1.3] | 0.227 | 0.1  [-3.0 to 3.3] | 0.928 | -0.5  [-3.7 to 2.7] | 0.742 |
| *6 weeks* |  | 15 | 0.6  [-0.6 to 1.8] | 14 | -0.5  [-2.2 to 1.3] | 17 | -0.1  [-3.2 to 3.1] | 16 | -1.7  [-3.3 to 0.0] |  | -1.1  [-4.0 to 1.8] | 0.465 | -1.0  [-3.8 to 1.8] | 0.486 | -2.1  [-5.0 to 0.7] | 0.141 |
| *12 weeks* |  | 17 | 1.4  [-0.3 to 3.0] | 14 | -1.1  [-2.9 to 0.8] | 16 | -1.4  [-4.8 to 2.1] | 17 | -2.3  [-3.6 to -1.0] |  | -2.4  [-5.3 to 0.4] | 0.097 | -3.2  [-5.9 to -0.4] | **0.023** | -3.6  [-6.3 to -0.9] | **0.010** |
| *24 weeks* |  | 16 | 0.8  [-0.8 to 2.3] | 14 | -2.2  [-4.6 to 0.2] | 16 | -1.7  [-4.4 to 1.1] | 17 | -4.1  [-5.8 to -2.4] |  | -3.2  [-5.9 to -0.4] | **0.025** | -2.7  [-5.3 to 0.0] | **0.050** | -4.9  [-7.5 to -2.2] | **<0.001** |
| *Across follow-up collectively* | | | | | | | | | |  | -2.0  [-4.4 to 0.4] | 0.100 | -1.5  [-3.9 to 0.8] | 0.191 | -2.7  [-5.0 to -0.4] | 0.022 |
| Daily energy intake (kcal/day) | | | | | | | | | | | | | | | | |
| *24 weeks* |  | 14 | -308 [-570 to -45] | 15 | -8 [-221 to 205] | 14 | -46 [-310 to 218] | 13 | -11 [-167 to 145] |  | 226 [-82 to 535] | 0.151 | 252 [-56 to 560] | 0.109 | 210 [-112 to 532] | 0.202 |
| Resting energy expenditure (kcal/day) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | 28  [-127 to 184] | 15 | -6  [-173 to 161] | 17 | -8  [-140 to 124] | 17 | 0  [-99 to 98] |  | -13  [-204 to 178] | 0.892 | -45  [-229 to 139] | 0.633 | -45  [-229 to 139] | 0.633 |
| *6 weeks* |  | 16 | 111  [-94 to 317] | 14 | 16  [-66 to 98] | 16 | 18  [-68 to 104] | 16 | 1  [-88 to 89] |  | -71  [-256 to 115] | 0.456 | -106  [-284 to 73] | 0.246 | -110  [-288 to 68] | 0.228 |
| *12 weeks* |  | 16 | 37  [-103 to 176] | 14 | -63  [-153 to 27] | 17 | -2  [-68 to 63] | 17 | -42  [-153 to 69] |  | -85  [-238 to 67] | 0.271 | -43  [-187 to 100] | 0.553 | -88  [-232 to 55] | 0.229 |
| *24 weeks* |  | 15 | 140  [-46 to 326] | 13 | 44  [-62 to 150] | 16 | 16  [-75 to 107] | 17 | -64  [-163 to 34] |  | -80  [-261 to 101] | 0.387 | -129  [-297 to 40] | 0.134 | -212  [-378 to -45] | **0.013** |
| *Across follow-up collectively* | | | | | | | | | |  | -62  [-176 to 52] | 0.286 | -75  [-185 to 34] | 0.176 | -114  [-224 to -5] | 0.040 |
| Steps (number/day) | | | | | | | | | | | | | | | | |
| *6 weeks* |  | 17 | 1036  [165 to 1908] | 10 | 652  [49 to 1255] | 16 | -550  [-1361 to 261] | 15 | 562  [-382 to 1507] |  | -318  [-1607 to 971] | 0.628 | -1411  [-2580 to -241] | 0.018 | -437  [-1580 to 707] | 0.454 |
| *12 weeks* |  | 17 | 201  [-502 to 905] | 13 | 1085  [291 to 1880] | 16 | 14  [-960 to 988] | 16 | 302  [-650 to 1253] |  | 507  [-532 to 1546] | 0.339 | -167  [-1144 to 810] | 0.737 | 50  [-922 to 1023] | 0.919 |
| *24 weeks* |  | 16 | 303  [-765 to 1371] | 13 | 1005  [610 to 1400] | 15 | -633  [-1403 to 138] | 14 | 775  [-424 to 1975] |  | 604  [-698 to 1906] | 0.363 | -800  [-2047 to 447] | 0.209 | 574  [-695 to 1843] | 0.375 |
| *Across follow-up collectively* | | | | | | | | | |  | 238  [-595 to 1071] | 0.575 | -818  [-1593 to -44] | 0.038 | 98  [-679 to 875] | 0.804 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sedentary time (min/day) | | | | | | | | | | | | | | | | |
| *6 weeks* |  | 17 | -24  [-48 to 0] | 10 | 5  [-37 to 47] | 16 | -36  [-67 to -5] | 15 | -8  [-46 to 29] |  | 25  [-20 to 71] | 0.275 | 6  [-35 to 47] | 0.769 | 15  [-25 to 55] | 0.470 |
| *12 weeks* |  | 17 | -20  [-41 to 2] | 13 | -12  [-48 to 25] | 16 | -19  [-51 to 12] | 16 | -13  [-43 to 16] |  | 0  [-40 to 40] | 0.990 | -13  [-51 to 25] | 0.495 | 0  [-38 to 37] | 0.991 |
| *24 weeks* |  | 16 | -9  [-52 to 34] | 13 | -16  [-42 to 10] | 15 | 9  [-46 to 65] | 14 | -8  [-38 to 21] |  | -23  [-65 to 19] | 0.283 | 1  [-40 to 41] | 0.974 | -18  [-59 to 23] | 0.395 |
| *Across follow-up collectively* | | | | | | | | | |  | -1  [-33 to 31] | 0.950 | -1  [-31 to 29] | 0.966 | -3  [-33 to 27] | 0.828 |
| Light-intensity physical activity (min/day) | | | | | | | | | | | | | | | | |
| *6 weeks* |  | 17 | 13  [-11 to 36] | 10 | -9  [-40 to 22] | 16 | -7  [-40 to 25] | 15 | -7  [-34 to 19] |  | -29  [-70 to 11] | 0.157 | 2  [-35 to 39] | 0.916 | -17  [-52 to 19] | 0.367 |
| *12 weeks* |  | 17 | -2  [-26 to 22] | 13 | 19  [-19 to 57] | 16 | 17  [-17 to 51] | 16 | 8  [-22 to 38] |  | -4  [-40 to 33] | 0.851 | 12  [-22 to 47] | 0.484 | 1  [-33 to 36] | 0.948 |
| *24 weeks* |  | 16 | -2  [-31 to 26] | 13 | 24  [3 to 45] | 15 | -12  [-38 to 14] | 14 | 6  [-18 to 29] |  | 20  [-15 to 56] | 0.261 | -2  [-36 to 32] | 0.909 | 10  [-24 to 45] | 0.558 |
| *Across follow-up collectively* | | | | | | | | | |  | -1  [-30 to 27] | 0.919 | 3  [-23 to 29] | 0.825 | 0  [-26 to 26] | 0.992 |
| Moderate- to-vigorous-intensity physical activity (min/day) | | | | | | | | | | | | | | | | |
| *6 weeks* |  | 17 | 4  [-3 to 11] | 10 | 6  [-2 to 14] | 16 | -1  [-6 to 3] | 15 | 7  [-8 to 22] |  | 3  [-10 to 16] | 0.644 | -9  [-21 to 3] | 0.143 | 2  [-9 to 14] | 0.680 |
| *12 weeks* |  | 17 | 0  [-9 to 9] | 13 | 6  [-1 to 12] | 16 | 2  [-6 to 9] | 16 | 0  [-10 to 11] |  | 3  [-8 to 15] | 0.558 | 0  [-11 to 10] | 0.944 | -1  [-11 to 10] | 0.905 |
| *24 weeks* |  | 16 | -2  [-13 to 10] | 13 | 2  [-3 to 8] | 15 | 0  [-4 to 4] | 14 | 5  [-8 to 18] |  | 3  [-9 to 15] | 0.586 | -1  [-13 to 11] | 0.863 | 7  [-5 to 19] | 0.249 |
| *Across follow-up collectively* | | | | | | | | | |  | 2  [-7 to 11] | 0.624 | -4  [-12 to 5] | 0.401 | 3  [-5 to 12] | 0.457 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| IPAQ – Sitting time (min/day) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -60  [-155 to 35] | 15 | -15  [-79 to 48] | 17 | -58  [-175 to 60] | 17 | -18  [-59 to 23] |  | 24  [-81 to 128] | 0.657 | -11  [-112 to 90] | 0.826 | 14  [-87 to 116] | 0.785 |
| *6 weeks* |  | 17 | -22  [-114 to 70] | 14 | -37  [-135 to 61] | 17 | -85  [-181 to 11] | 16 | -23  [-88 to 43] |  | -48  [-143 to 47] | 0.323 | -80  [-170 to 10] | 0.080 | -37  [-129 to 54] | 0.427 |
| *12 weeks* |  | 17 | -72  [-145 to 1] | 13 | -54  [-140 to 32] | 16 | -61  [-177 to 55] | 17 | -26  [-58 to 7] |  | 16  [-80 to 112] | 0.746 | -10  [-101 to 80] | 0.828 | 15  [-75 to 104] | 0.749 |
| *24 weeks* |  | 16 | -78  [-164 to 9] | 14 | 8  [-86 to 101] | 16 | 9  [-107 to 125] | 17 | -49  [-101 to 3] |  | 76  [-33 to 186] | 0.172 | 74  [-32 to 180] | 0.170 | 2  [-102 to 107] | 0.969 |
| *Across follow-up collectively* | | | | | | | | | |  | 13  [-65 to 90] | 0.748 | -7  [-82 to 67] | 0.851 | -2  [-77 to 72] | 0.948 |
| IPAQ – Walking (MET-min/week) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 107  [-573 to 787] | 15 | 454  [-438 to 1346] | 17 | -271  [-1342 to 801] | 17 | 63  [-784 to 910] |  | 365  [-681 to 1410] | 0.494 | 19  [-1002 to 1040] | 0.971 | 132  [-880 to 1143] | 0.798 |
| *6 weeks* |  | 17 | -199  [-881 to 483] | 15 | -52  [-387 to 284] | 17 | 376  [-840 to 1591] | 17 | 118  [-490 to 727] |  | 126  [-972 to 1224] | 0.822 | 773  [-299 to 1845] | 0.158 | 384  [-678 to 1446] | 0.478 |
| *12 weeks* |  | 17 | -156  [-775 to 462] | 14 | 372  [-417 to 1162] | 17 | -626  [-1822 to 570] | 17 | -439  [-1047 to 170] |  | 511  [-562 to 1583] | 0.351 | -97  [-1123 to 930] | 0.854 | -142  [-1158 to 875] | 0.785 |
| *24 weeks* |  | 16 | -24  [-880 to 832] | 14 | 161  [-555 to 878] | 16 | -111  [-1444 to 1222] | 17 | -216  [-1792 to 1359] |  | 223  [-1207 to 1652] | 0.760 | 221  [-1161 to 1602] | 0.754 | -5  [-1362 to 1352] | 0.994 |
| *Across follow-up collectively* | | | | | | | | | |  | 291  [-502 to 1084] | 0.472 | 242  [-529 to 1013] | 0.538 | 97  [-666 to 860] | 0.803 |
| IPAQ – Moderate-intensity activity (MET-min/week) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -524  [-1191 to 143] | 15 | -14  [-999 to 970] | 17 | -154  [-1849 to 1542] | 17 | -104  [-1037 to 829] |  | 588  [-811 to 1986] | 0.410 | 795  [-564 to 2154] | 0.251 | 691  [-663 to 2045] | 0.317 |
| *6 weeks* |  | 17 | 211  [-1025 to 1447] | 15 | -99  [-1260 to 1063] | 17 | -70  [-1927 to 1787] | 17 | -464  [-1768 to 839] |  | -319  [-2080 to 1442] | 0.722 | 233  [-1478 to 1945] | 0.789 | -409  [-2115 to 1297] | 0.639 |
| *12 weeks* |  | 17 | -84  [-667 to 500] | 14 | 258  [-874 to 1390] | 17 | -385  [-1890 to 1121] | 17 | -316  [-1546 to 913] |  | 485  [-909 to 1878] | 0.495 | 152  [-1175 to 1479] | 0.822 | 53  [-1269 to 1375] | 0.937 |
| *24 weeks* |  | 16 | -266  [-1401 to 869] | 14 | 845  [-1378 to 3068] | 16 | -106  [-2157 to 1945] | 17 | 646  [-339 to 1632] |  | 1189  [-1009 to 3387] | 0.289 | 618  [-1513 to 2749] | 0.570 | 1156  [-934 to 3246] | 0.278 |
| *Across follow-up collectively* | | | | | | | | | |  | 459  [-763 to 1681] | 0.462 | 465  [-719 to 1650] | 0.441 | 382  [-797 to 1562] | 0.525 |
| IPAQ – Vigorous-intensity activity (MET-min/week) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -226  [-785 to 334] | 15 | 448  [-1051 to 1947] | 17 | 148  [-104 to 400] | 17 | 7  [-273 to 287] |  | 697  [-345 to 1738] | 0.190 | 178  [-835 to 1190] | 0.731 | 450  [-565 to 1465] | 0.385 |
| *6 weeks* |  | 17 | 226  [-77 to 529] | 15 | -75  [-822 to 673] | 17 | 367  [-243 to 977] | 17 | 56  [-738 to 851] |  | -304  [-1085 to 478] | 0.446 | -82  [-842 to 677] | 0.831 | 66  [-695 to 827] | 0.865 |
| *12 weeks* |  | 17 | -212  [-513 to 90] | 14 | -189  [-1200 to 823] | 17 | -12  [-99 to 76] | 17 | -506  [-1728 to 716] |  | 89  [-857 to 1036] | 0.853 | -77  [-979 to 824] | 0.867 | 51  [-853 to 955] | 0.912 |
| *24 weeks* |  | 16 | -293  [-953 to 368] | 14 | 57  [-790 to 904] | 16 | 373  [-20 to 765] | 17 | -231  [-1223 to 762] |  | 359  [-476 to 1194] | 0.399 | 347  [-463 to 1157] | 0.401 | 388  [-410 to 1186] | 0.340 |
| *Across follow-up collectively* | | | | | | | | | |  | 191  [-396 to 777] | 0.524 | 85  [-483 to 653] | 0.769 | 242  [-327 to 810] | 0.405 |
| IPAQ – Total activity (MET-min/week) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -643  [-1373 to 86] | 15 | 888  [-1654 to 3430] | 17 | -276  [-2087 to 1534] | 17 | -34  [-1694 to 1626] |  | 1658  [-610 to 3925] | 0.152 | 681  [-1513 to 2876] | 0.543 | 1115  [-1087 to 3318] | 0.321 |
| *6 weeks* |  | 17 | 238  [-1421 to 1896] | 15 | -225  [-1982 to 1532] | 17 | 672  [-1641 to 2986] | 17 | -290  [-2460 to 1881] |  | -537  [-3246 to 2173] | 0.698 | 760  [-1862 to 3382] | 0.570 | -119  [-2750 to 2513] | 0.930 |
| *12 weeks* |  | 17 | -452  [-1517 to 614] | 14 | 442  [-1784 to 2668] | 17 | -1023  [-2766 to 721] | 17 | -1261  [-3922 to 1400] |  | 1072  [-1236 to 3380] | 0.363 | -96  [-2286 to 2093] | 0.931 | -67  [-2265 to 2130] | 0.952 |
| *24 weeks* |  | 16 | -582  [-2325 to 1160] | 14 | 1064  [-2060 to 4187] | 16 | 155  [-2124 to 2435] | 17 | 199  [-2925 to 3324] |  | 1812  [-1549 to 5172] | 0.291 | 1051  [-2188 to 4290] | 0.525 | 1453  [-1748 to 4655] | 0.374 |
| *Across follow-up collectively* | | | | | | | | | |  | 924  [-969 to 2817] | 0.339 | 610  [-1216 to 2437] | 0.513 | 609  [-1222 to 2440] | 0.514 |

All analyses at each timepoint were conducted using a complete case approach, with generalised linear models adjusted for age, BMI (both categorised as per randomisation) and baseline value of the outcome. Analyses across follow-up collectively used generalised estimating equations, adjusted in the same way as generalised linear models, with a normal distribution and exchangeable correlation matrix; *p*-values in bold are statistically significant (assessments of statistical significance for between-group comparison used the Holm sequential Bonferroni procedure to account for multiple comparisons). Abbreviation: IPAQ, international physical activity questionnaire.

**Table S4 – Glycaemic control, renal and hepatic function, blood pressure, lipids and systemic inflammation: within-group change from baseline in each group, and differences between experimental groups (placebo-plus-diet, empagliflozin-only, and empagliflozin-plus-diet) and placebo-only at 2, 6, 12 and 24 weeks and across follow-up collectively.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | ***Within-group change from baseline*** | | | | | | | |  | ***Between-group difference versus PLA*** | | | | | |
|  |  | **Placebo only** | | **Placebo + Diet** | | **Empagliflozin only** | | **Empagliflozin + Diet** | |  | **Placebo + Diet** | | **Empagliflozin only** | | **Empagliflozin + Diet** | |
|  |  | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] | N | *β*-coefficient [95% CI] |  | *β*-coefficient [95% CI] | *p*-value | *β*-coefficient [95% CI] | *p*-value | *β*-coefficient [95% CI] | *p*-value |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| HbA1c (mmol/mol) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.8  [-1.5 to 0.0] | 13 | -2.2  [-3.1 to -1.2] | 14 | -1.2  [-2.4 to 0.0] | 17 | -1.6  [-2.4 to -0.9] |  | -1.6  [-2.7 to -0.4] | **0.007** | -0.7  [-1.8 to 0.4] | 0.206 | -1.2  [-2.3 to -0.1] | 0.026 |
| *6 weeks* |  | 16 | -2.0  [-3.8 to -0.2] | 13 | -4.3  [-6.1 to -2.5] | 15 | -4.4  [-6.4 to -2.4] | 14 | -5.4  [-7.0 to -3.8] |  | -2.7  [-4.9 to -0.5] | **0.016** | -2.7  [-4.8 to -0.5] | **0.014** | -3.8  [-5.9 to -1.6] | **0.001** |
| *12 weeks* |  | 16 | -1.6  [-3.9 to 0.8] | 14 | -1.9  [-5.3 to 1.6] | 16 | -5.8  [-8.9 to -2.6] | 17 | -5.4  [-7.5 to -3.4] |  | -1.1  [-4.6 to 2.4] | 0.533 | -4.7  [-8.1 to -1.4] | **0.006** | -4.8  [-8.1 to -1.5] | **0.005** |
| *24 weeks* |  | 16 | 0.0  [-2.8 to 2.8] | 14 | -0.5  [-5.2 to 4.2] | 16 | -3.5  [-6.2 to -0.8] | 17 | -3.9  [-5.5 to -2.3] |  | -1.4  [-5.5 to 2.7] | 0.512 | -4.4  [-8.3 to -0.4] | 0.032 | -4.8  [-8.7 to -0.9] | **0.016** |
| *Across follow-up collectively* | | | | | | | | | |  | -1.6  [-4.0 to 0.7] | 0.170 | -3.2  [-5.5 to -1.0] | **0.005** | -3.7  [-5.9 to -1.4] | **0.001** |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| HbA1c (%)† | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.08  [-0.14 to -0.01] | 13 | -0.17  [-0.27 to -0.06] | 14 | -0.11  [-0.22 to -0.01] | 17 | -0.14  [-0.20 to -0.07] |  | -0.11  [-0.21 to -0.01] | - | -0.06  [-0.16 to 0.04] | - | -0.09  [-0.19 to 0.00] | - |
| *6 weeks* |  | 16 | -0.19  [-0.34 to -0.03] | 13 | -0.39  [-0.56 to -0.23] | 15 | -0.42  [-0.59 to -0.25] | 14 | -0.46  [-0.60 to -0.31] |  | -0.25  [-0.44 to -0.05] | - | -0.26  [-0.45 to -0.07] | - | -0.31  [-0.51 to -0.12] | - |
| *12 weeks* |  | 16 | -0.13  [-0.35 to 0.09] | 14 | -0.15  [-0.48 to 0.18] | 16 | -0.54  [-0.82 to -0.26] | 17 | -0.49  [-0.67 to -0.30] |  | -0.10  [-0.43 to 0.23] | - | -0.46  [-0.77 to -0.14] | - | -0.45  [-0.77 to -0.14] | - |
| *24 weeks* |  | 16 | -0.02  [-0.28 to 0.24] | 14 | -0.03  [-0.46 to 0.40] | 16 | -0.33  [-0.57 to -0.08] | 17 | -0.35  [-0.50 to -0.20] |  | -0.09  [-0.47 to 0.28] | - | -0.38  [-0.74 to -0.02] | - | -0.42  [-0.78 to -0.06] | - |
| *Across follow-up collectively* | | | | | | | | | |  | -0.13  [-0.35 to 0.08] | - | -0.30  [-0.50 to -0.09] | - | -0.32  [-0.53 to -0.12] | - |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Fasting plasma glucose (mmol/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.34  [-0.66 to -0.02] | 14 | -0.34  [-0.65 to -0.03] | 16 | -0.52  [-0.81 to -0.23] | 16 | -0.85  [-1.20 to -0.50] |  | -0.13  [-0.53 to 0.26] | 0.503 | -0.44  [-0.83 to -0.05] | 0.026 | -0.73  [-1.12 to -0.35] | **<0.001** |
| *6 weeks* |  | 17 | -0.39  [-0.78 to 0.00] | 12 | -0.43  [-0.93 to 0.06] | 17 | -0.83  [-1.20 to -0.46] | 15 | -1.15  [-1.58 to -0.73] |  | -0.25  [-0.73 to 0.23] | 0.305 | -0.77  [-1.22 to -0.32] | **0.001** | -1.05  [-1.51 to -0.59] | **<0.001** |
| *12 weeks* |  | 17 | -0.31  [-0.80 to 0.18] | 13 | -0.01  [-0.88 to 0.86] | 15 | -0.71  [-1.11 to -0.31] | 16 | -1.19  [-1.62 to -0.76] |  | -0.03  [-0.61 to 0.55] | 0.923 | -0.99  [-1.57 to -0.42] | **0.001** | -1.25  [-1.80 to -0.69] | **<0.001** |
| *24 weeks* |  | 16 | -0.31  [-0.87 to 0.25] | 13 | -0.11  [-0.84 to 0.63] | 16 | -0.78  [-1.00 to -0.55] | 17 | -1.22  [-1.57 to -0.87] |  | -0.05  [-0.63 to 0.53] | 0.872 | -0.88  [-1.44 to -0.31] | **0.002** | -1.23  [-1.78 to -0.69] | **<0.001** |
| *Across follow-up collectively* | | | | | | | | | |  | -0.10  [-0.47 to 0.26] | 0.577 | -0.79  [-1.15 to -0.44] | **<0.001** | -1.09  [-1.44 to -0.74] | **<0.001** |
| Postprandial plasma glucose (mmol/L)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.11  [-0.67 to 0.45] | 15 | -0.55  [-1.23 to 0.13] | 16 | -1.28  [-2.26 to -0.31] | 17 | -1.24  [-2.25 to -0.22] |  | -0.61  [-1.54 to 0.33] | 0.201 | -1.03  [-1.95 to -0.12] | 0.027 | -1.15  [-2.05 to -0.25] | **0.013** |
| *6 weeks* |  | 17 | -0.09  [-0.87 to 0.69] | 13 | -0.06  [-0.96 to 0.84] | 17 | -1.31  [-2.14 to -0.49] | 15 | -1.67  [-2.63 to -0.72] |  | -0.12  [-1.08 to 0.84] | 0.809 | -1.15  [-2.03 to -0.26] | **0.011** | -1.54  [-2.46 to -0.62] | **0.001** |
| *12 weeks* |  | 17 | 0.37  [-0.33 to 1.08] | 14 | 0.40  [-0.85 to 1.65] | 16 | -1.67  [-2.56 to -0.79] | 16 | -1.70  [-2.59 to -0.80] |  | -0.14  [-1.18 to 0.89] | 0.786 | -1.94  [-2.94 to -0.95] | **<0.001** | -2.15  [-3.15 to -1.15] | **<0.001** |
| *24 weeks* |  | 15 | 0.07  [-0.67 to 0.81] | 14 | 0.27  [-1.00 to 1.54] | 15 | -1.20  [-1.97 to -0.43] | 17 | -1.60  [-2.37 to -0.84] |  | 0.06  [-1.12 to 1.24] | 0.919 | -1.24  [-2.40 to -0.08] | 0.036 | -1.66  [-2.78 to -0.53] | **0.004** |
| *Across follow-up collectively* | | | | | | | | | |  | -0.24  [-0.95 to 0.46] | 0.499 | -1.37  [-2.05 to -0.69] | **<0.001** | -1.64  [-2.32 to -0.96] | **<0.001** |
| Fasting plasma insulin (mU/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -0.5  [-3.1 to 2.1] | 13 | -2.3  [-5.1 to 0.6] | 15 | -3.8  [-6.0 to -1.6] | 17 | -1.8  [-4.1 to 0.6] |  | -2.0  [-5.4 to 1.4] | 0.245 | -3.1  [-6.3 to 0.2] | 0.065 | -2.3  [-5.6 to 0.9] | 0.158 |
| *6 weeks* |  | 16 | -2.2  [-4.3 to -0.1] | 12 | -3.1  [-5.9 to -0.4] | 16 | -5.2  [-8.4 to -2.1] | 16 | -3.1  [-4.8 to -1.4] |  | -1.4  [-4.2 to 1.3] | 0.309 | -3.1  [-5.6 to -0.5] | 0.018 | -2.7  [-5.3 to -0.1] | 0.040 |
| *12 weeks* |  | 16 | -4.4  [-7.9 to -0.8] | 13 | 0.3  [-4.9 to 5.5] | 15 | -4.8  [-7.1 to -2.4] | 16 | -1.9  [-6.7 to 2.9] |  | 3.7  [-1.1 to 8.5] | 0.130 | -0.4  [-5.0 to 4.2] | 0.865 | -0.8  [-5.4 to 3.9] | 0.749 |
| *24 weeks* |  | 15 | -1.3  [-5.3 to 2.7] | 14 | -1.7  [-6.3 to 2.8] | 15 | -5.5  [-8.7 to -2.3] | 17 | -3.6  [-5.7 to -1.5] |  | -1.2  [-5.7 to 3.3] | 0.613 | -4.4  [-8.7 to 0.0] | 0.048 | -4.3  [-8.6 to 0.0] | 0.048 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.2  [-2.6 to 2.2] | 0.866 | -2.7  [-4.9 to -0.4] | 0.020 | -2.5  [-4.8 to -0.3] | 0.028 |
| Postprandial plasma insulin (mU/L)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | 3.0  [-7.2 to 13.3] | 14 | -8.6  [-22.5 to 5.4] | 15 | -24.1  [-51.1 to 2.8] | 17 | -4.4  [-20.0 to 11.2] |  | -11.2  [-31.6 to 9.2] | 0.282 | -14.0  [-34.6 to 6.5] | 0.181 | -7.3  [-26.6 to 12.1] | 0.462 |
| *6 weeks* |  | 16 | 7.9  [-5.5 to 21.4] | 13 | -0.2  [-16.7 to 16.4] | 16 | -15.0  [-26.3 to -3.6] | 16 | -3.1  [-19.0 to 12.7] |  | -8.3  [-29.4 to 12.8] | 0.439 | -19.9  [-40.2 to 0.4] | 0.055 | -11.0  [-30.8 to 8.9] | 0.279 |
| *12 weeks* |  | 16 | 6.5  [-6.2 to 19.2] | 14 | -8.4  [-24.0 to 7.2] | 15 | -28.7  [-56.2 to -1.2] | 16 | -6.4  [-15.1 to 2.2] |  | -12.2  [-33.3 to 8.9] | 0.256 | -25.2  [-46.2 to -4.1] | 0.019 | -14.3  [-34.6 to 6.1] | 0.169 |
| *24 weeks* |  | 15 | 10.8  [-1.8 to 23.4] | 14 | -17.2  [-31.6 to -2.8] | 15 | -34.2  [-60.1 to -8.2] | 17 | -10.3  [-19.9 to -0.7] |  | -26.8  [-45.7 to -7.9] | **0.006** | -32.3  [-51.4 to -13.3] | **0.001** | -20.9  [-38.9 to -2.9] | **0.023** |
| *Across follow-up collectively* | | | | | | | | | |  | -14.6  [-28.8 to -0.4] | 0.044 | -22.4  [-36.5 to -8.4] | **0.002** | -13.4  [-26.9 to 0.1] | 0.052 |
| Postprandial plasma glucagon (pg/mL)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -3.0  [-9.2 to 3.2] | 14 | -5.5  [-20.8 to 9.7] | 15 | 1.6  [-9.4 to 12.6] | 17 | 10.6  [-4.0 to 25.2] |  | -1.8  [-18.3 to 14.6] | 0.827 | 5.8  [-10.4 to 21.9] | 0.483 | 13.3  [-2.4 to 28.9] | 0.096 |
| *6 weeks* |  | 16 | 3.0  [-4.7 to 10.8] | 13 | -19.6  [-48.3 to 9.2] | 16 | -0.8  [-12.7 to 11.2] | 16 | 5.5  [-6.7 to 17.7] |  | -19.2  [-37.3 to -1.0] | 0.038 | -2.2  [-19.3 to 14.8] | 0.798 | 2.1  [-14.9 to 19.2] | 0.807 |
| *12 weeks* |  | 16 | 0.5  [-9.3 to 10.3] | 14 | -13.2  [-32.1 to 5.8] | 15 | 4.4  [-7.7 to 16.5] | 16 | 3.4  [-8.2 to 15.0] |  | -10.2  [-25.0 to 4.7] | 0.180 | 5.4  [-9.2 to 19.9] | 0.470 | 4.0  [-10.3 to 18.2] | 0.588 |
| *24 weeks* |  | 15 | 3.8  [-8.1 to 15.7] | 14 | -2.4  [-12.0 to 7.2] | 15 | -1.2  [-14.1 to 11.7] | 17 | -2.1  [-9.7 to 5.4] |  | -5.5  [-20.1 to 9.1] | 0.461 | -4.6  [-18.9 to 9.7] | 0.530 | -6.5  [-20.4 to 7.5] | 0.363 |
| *Across follow-up collectively* | | | | | | | | | |  | -8.9  [-20.5 to 2.7] | 0.133 | 1.3  [-9.9 to 12.5] | 0.818 | 2.9  [-8.1 to 13.9] | 0.610 |
| Postprandial plasma C-peptide (pg/mL)\* | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -197  [-469 to 74] | 14 | -484  [-1043 to 76] | 15 | -523  [-1537 to 491] | 17 | 156  [-476 to 788] |  | -155  [-923 to 613] | 0.692 | -39  [-795 to 717] | 0.919 | 187  [-542 to 915] | 0.616 |
| *6 weeks* |  | 16 | -100  [-483 to 283] | 13 | -974  [-1571 to -377] | 16 | -160  [-609 to 288] | 16 | 300  [-104 to 704] |  | -818  [-1410 to -227] | **0.007** | 77  [-482 to 637] | 0.786 | 303  [-254 to 860] | 0.286 |
| *12 weeks* |  | 16 | -205  [-619 to 209] | 14 | -984  [-1554 to -415] | 15 | -629  [-1849 to 590] | 16 | 121  [-184 to 426] |  | -521  [-1174 to 133] | 0.118 | -103  [-745 to 539] | 0.752 | 89  [-541 to 719] | 0.782 |
| *24 weeks* |  | 15 | -107  [-431 to 217] | 14 | -738  [-1266 to -209] | 15 | -832  [-1834 to 170] | 17 | 235  [-147 to 616] |  | -474  [-1141 to 193] | 0.164 | -387  [-1046 to 272] | 0.250 | 205  [-428 to 839] | 0.525 |
| *Across follow-up collectively* | | | | | | | | | |  | -489  [-999 to 21] | 0.060 | -83  [-577 to 412] | 0.744 | 192  [-292 to 676] | 0.437 |
| eGFR (mL/min per 1.73m2) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -1  [-3 to 2] | 15 | 0  [-3 to 2] | 17 | -3  [-7 to 1] | 17 | -2  [-4 to 1] |  | -1  [-5 to 3] | 0.738 | -2  [-6 to 2] | 0.377 | -1  [-4 to 3] | 0.751 |
| *6 weeks* |  | 17 | 0  [-2 to 1] | 14 | 0  [-2 to 2] | 16 | -3  [-6 to 0] | 15 | -1  [-4 to 3] |  | 0  [-4 to 3] | 0.904 | -2  [-5 to 2] | 0.330 | 0  [-3 to 3] | 0.983 |
| *12 weeks* |  | 17 | 0  [-2 to 2] | 14 | 1  [-1 to 2] | 16 | -3  [-5 to 0] | 17 | 0  [-2 to 2] |  | 0  [-3 to 3] | 0.975 | -2  [-6 to 1] | 0.131 | 0  [-3 to 3] | 0.954 |
| *24 weeks* |  | 16 | 0  [-1 to 2] | 14 | 2  [0 to 3] | 16 | -4  [-8 to 0] | 17 | -1  [-4 to 1] |  | 1  [-3 to 4] | 0.760 | -4  [-7 to 0] | 0.030 | -1  [-5 to 2] | 0.437 |
| *Across follow-up collectively* | | | | | | | | | |  | 0  [-3 to 2] | 0.904 | -2  [-5 to 0] | 0.062 | 0  [-3 to 2] | 0.706 |
| Alanine transaminase (U/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 0  [-2 to 2] | 15 | 1  [-5 to 6] | 17 | 4  [-3 to 12] | 17 | -1  [-3 to 2] |  | 1  [-6 to 8] | 0.843 | 4  [-3 to 11] | 0.271 | 0  [-7 to 7] | 0.975 |
| *6 weeks* |  | 17 | -1  [-5 to 4] | 14 | -2  [-6 to 2] | 16 | -1  [-7 to 6] | 15 | -3  [-6 to 1] |  | 0  [-7 to 6] | 0.902 | 0  [-6 to 7] | 0.883 | -2  [-8 to 5] | 0.619 |
| *12 weeks* |  | 17 | -1  [-3 to 2] | 14 | -6  [-12 to 0] | 16 | -6  [-14 to 3] | 16 | -3  [-8 to 3] |  | -4  [-11 to 4] | 0.331 | -3  [-11 to 4] | 0.361 | -2  [-9 to 5] | 0.592 |
| *24 weeks* |  | 16 | 0  [-5 to 4] | 14 | -6  [-13 to 0] | 16 | -7  [-14 to 1] | 17 | -4  [-9 to 1] |  | -3  [-11 to 4] | 0.343 | -4  [-11 to 3] | 0.316 | -4  [-11 to 3] | 0.257 |
| *Across follow-up collectively* | | | | | | | | | |  | -2  [-8 to 4] | 0.590 | -1  [-6 to 5] | 0.822 | -2  [-8 to 4] | 0.533 |
| Systolic blood pressure (mmHg) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -2  [-8 to 4] | 15 | 0  [-5 to 6] | 17 | -4  [-9 to 0] | 17 | -3  [-7 to 1] |  | 4  [-2 to 10] | 0.234 | -1  [-7 to 5] | 0.680 | -1  [-7 to 5] | 0.672 |
| *6 weeks* |  | 17 | -1  [-6 to 4] | 14 | 1  [-6 to 7] | 17 | -6  [-11 to -2] | 16 | -3  [-8 to 2] |  | 3  [-3 to 9] | 0.321 | -4  [-10 to 2] | 0.159 | -2  [-8 to 4] | 0.518 |
| *12 weeks* |  | 17 | -1  [-6 to 4] | 14 | 2  [-4 to 7] | 16 | -7  [-13 to -1] | 17 | -2  [-8 to 3] |  | 5  [-2 to 13] | 0.168 | -4  [-11 to 3] | 0.229 | -2  [-9 to 5] | 0.636 |
| *24 weeks* |  | 16 | -1  [-5 to 3] | 14 | 3  [-2 to 7] | 16 | -8  [-12 to -4] | 17 | -6  [-9 to -3] |  | 5  [0 to 10] | 0.059 | -7  [-12 to -2] | **0.009** | -5  [-10 to 0] | 0.044 |
| *Across follow-up collectively* | | | | | | | | | |  | 5  [1 to 8] | 0.022 | -4  [-8 to 0] | 0.029 | -3  [-6 to 1] | 0.181 |
| Diastolic blood pressure (mmHg) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -1  [-4 to 3] | 15 | 0  [-5 to 4] | 17 | -2  [-5 to 1] | 17 | 0  [-3 to 2] |  | 1  [-4 to 6] | 0.701 | -1  [-6 to 4] | 0.720 | 0  [-5 to 5] | 0.964 |
| *6 weeks* |  | 17 | 0  [-3 to 3] | 14 | 0  [-5 to 5] | 17 | -4  [-7 to -1] | 16 | 1  [-3 to 5] |  | 0  [-5 to 5] | 0.961 | -4  [-8 to 1] | 0.155 | 1  [-4 to 6] | 0.741 |
| *12 weeks* |  | 17 | -1  [-5 to 3] | 14 | -1  [-5 to 3] | 16 | -4  [-7 to 0] | 17 | 0  [-4 to 3] |  | 1  [-5 to 6] | 0.832 | -3  [-8 to 2] | 0.256 | 0  [-5 to 5] | 0.997 |
| *24 weeks* |  | 16 | 0  [-3 to 3] | 14 | 2  [-1 to 6] | 16 | -4  [-7 to -1] | 17 | -1  [-4 to 3] |  | 2  [-2 to 7] | 0.267 | -4  [-8 to 0] | 0.048 | -1  [-5 to 3] | 0.621 |
| *Across follow-up collectively* | | | | | | | | | |  | 1  [-2 to 4] | 0.506 | -3  [-6 to 0] | 0.070 | 0  [-3 to 3] | 0.960 |
| Resting heart rate (beats/min) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 0  [-5 to 6] | 15 | -4  [-7 to -1] | 17 | 0  [-4 to 4] | 17 | -4  [-8 to 0] |  | -4  [-9 to 2] | 0.196 | 1  [-4 to 7] | 0.614 | -3  [-8 to 3] | 0.332 |
| *6 weeks* |  | 17 | -3  [-6 to 0] | 14 | -4  [-8 to 1] | 17 | 0  [-5 to 5] | 16 | -6  [-9 to -3] |  | 1  [-5 to 6] | 0.846 | 4  [-1 to 9] | 0.081 | -1  [-6 to 4] | 0.574 |
| *12 weeks* |  | 17 | -1  [-4 to 2] | 14 | -3  [-7 to 1] | 16 | -3  [-7 to 2] | 17 | -4  [-8 to 0] |  | -1  [-6 to 4] | 0.709 | -1  [-6 to 4] | 0.784 | -2  [-7 to 3] | 0.429 |
| *24 weeks* |  | 16 | -6  [-9 to -2] | 14 | -2  [-6 to 2] | 16 | -1  [-6 to 4] | 17 | -2  [-7 to 3] |  | 5  [-2 to 11] | 0.155 | 5  [-1 to 12] | 0.077 | 5  [-1 to 11] | 0.075 |
| *Across follow-up collectively* | | | | | | | | | |  | 0  [-4 to 4] | 0.923 | 3  [-1 to 6] | 0.150 | 0  [-4 to 4] | 0.997 |
| Total cholesterol (mmol/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.1  [-0.2 to 0.1] | 15 | -0.2  [-0.4 to 0.0] | 16 | 0.0  [-0.2 to 0.2] | 17 | -0.2  [-0.4 to 0.0] |  | -0.1  [-0.4 to 0.2] | 0.422 | 0.1  [-0.2 to 0.4] | 0.397 | -0.1  [-0.4 to 0.1] | 0.320 |
| *6 weeks* |  | 17 | -0.2  [-0.4 to 0.1] | 14 | 0.1  [-0.4 to 0.7] | 16 | -0.1  [-0.2 to 0.1] | 15 | -0.3  [-0.6 to 0.0] |  | 0.3  [-0.2 to 0.7] | 0.238 | 0.1  [-0.4 to 0.6] | 0.663 | -0.2  [-0.6 to 0.3] | 0.499 |
| *12 weeks* |  | 17 | 0.1  [-0.1 to 0.2] | 14 | -0.2  [-0.6 to 0.2] | 16 | -0.1  [-0.2 to 0.1] | 16 | -0.2  [-0.4 to 0.0] |  | -0.3  [-0.7 to 0.1] | 0.116 | -0.2  [-0.5 to 0.2] | 0.358 | -0.3  [-0.6 to 0.1] | 0.124 |
| *24 weeks* |  | 16 | 0.0  [-0.2 to 0.2] | 14 | -0.3  [-0.8 to 0.1] | 16 | -0.2  [-0.5 to 0.0] | 17 | -0.2  [-0.5 to 0.0] |  | -0.3  [-0.7 to 0.1] | 0.164 | -0.2  [-0.5 to 0.2] | 0.423 | -0.2  [-0.5 to 0.2] | 0.398 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.1  [-0.4 to 0.2] | 0.436 | 0.0  [-0.3 to 0.2] | 0.840 | -0.2  [-0.4 to 0.1] | 0.161 |
| HDL (mmol/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | 0.0  [0.0 to 0.1] | 15 | 0.0  [0.0 to 0.1] | 16 | 0.0  [-0.1 to 0.1] | 17 | 0.0  [0.0 to 0.1] |  | 0.0  [-0.1 to 0.1] | 0.911 | 0.0  [-0.1 to 0.1] | 0.725 | 0.0  [-0.1 to 0.1] | 0.849 |
| *6 weeks* |  | 17 | 0.0  [-0.1 to 0.0] | 14 | 0.1  [0.0 to 0.2] | 16 | 0.0  [-0.1 to 0.1] | 15 | 0.0  [-0.1 to 0.1] |  | 0.1  [0.0 to 0.2] | 0.040 | 0.0  [-0.1 to 0.1] | 0.578 | 0.0  [-0.1 to 0.1] | 0.458 |
| *12 weeks* |  | 17 | 0.0  [0.0 to 0.1] | 14 | 0.0  [0.0 to 0.1] | 16 | 0.0  [-0.1 to 0.1] | 16 | 0.0  [-0.1 to 0.1] |  | 0.0  [-0.1 to 0.1] | 0.875 | 0.0  [-0.1 to 0.1] | 0.691 | 0.0  [-0.1 to 0.1] | 0.830 |
| *24 weeks* |  | 16 | 0.0  [-0.1 to 0.1] | 14 | 0.0  [-0.1 to 0.1] | 16 | 0.0  [0.0 to 0.1] | 17 | 0.1  [0.0 to 0.2] |  | 0.0  [-0.1 to 0.1] | 0.531 | 0.0  [-0.1 to 0.1] | 0.622 | 0.1  [0.0 to 0.2] | 0.058 |
| *Across follow-up collectively* | | | | | | | | | |  | 0.0  [0.0 to 0.1] | 0.320 | 0.0  [-0.1 to 0.1] | 0.714 | 0.0  [0.0 to 0.1] | 0.321 |
| LDL (mmol/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 17 | -0.1  [-0.2 to 0.0] | 15 | -0.2  [-0.4 to -0.1] | 16 | 0.0  [-0.1 to 0.2] | 16 | -0.2  [-0.4 to 0.1] |  | -0.1  [-0.4 to 0.1] | 0.193 | 0.1  [-0.1 to 0.3] | 0.267 | -0.1  [-0.3 to 0.1] | 0.193 |
| *6 weeks* |  | 17 | 0.0  [-0.1 to 0.1] | 14 | -0.1  [-0.3 to 0.1] | 16 | 0.0  [-0.2 to 0.1] | 14 | -0.3  [-0.5 to 0.0] |  | -0.1  [-0.4 to 0.2] | 0.589 | 0.0  [-0.3 to 0.2] | 0.854 | -0.3  [-0.5 to 0.0] | 0.075 |
| *12 weeks* |  | 17 | 0.0  [-0.1 to 0.1] | 14 | -0.1  [-0.5 to 0.2] | 16 | 0.0  [-0.2 to 0.1] | 15 | -0.1  [-0.3 to 0.1] |  | -0.1  [-0.4 to 0.2] | 0.482 | 0.0  [-0.3 to 0.2] | 0.768 | -0.1  [-0.4 to 0.2] | 0.642 |
| *24 weeks* |  | 15 | 0.0  [-0.2 to 0.1] | 14 | -0.3  [-0.6 to 0.1] | 16 | -0.1  [-0.3 to 0.0] | 16 | -0.3  [-0.5 to -0.1] |  | -0.2  [-0.5 to 0.1] | 0.241 | -0.1  [-0.4 to 0.2] | 0.598 | -0.2  [-0.5 to 0.1] | 0.244 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.1  [-0.3 to 0.1] | 0.179 | 0.0  [-0.2 to 0.2] | 0.936 | -0.2  [-0.3 to 0.0] | 0.087 |
| Non-esterified fatty acids (mmol/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 15 | -0.04  [-0.12 to 0.04] | 14 | -0.08  [-0.18 to 0.02] | 15 | 0.04  [-0.07 to 0.14] | 16 | 0.03  [-0.08 to 0.14] |  | -0.01  [-0.13 to 0.12] | 0.910 | 0.06  [-0.06 to 0.18] | 0.310 | 0.13  [0.01 to 0.25] | 0.034 |
| *6 weeks* |  | 15 | 0.01  [-0.05 to 0.07] | 11 | -0.20  [-0.34 to -0.05] | 15 | 0.06  [-0.06 to 0.17] | 16 | 0.03  [-0.10 to 0.16] |  | -0.16  [-0.31 to -0.01] | 0.038 | 0.03  [-0.11 to 0.16] | 0.690 | 0.09  [-0.04 to 0.23] | 0.174 |
| *12 weeks* |  | 14 | -0.04  [-0.14 to 0.06] | 11 | -0.06  [-0.31 to 0.19] | 15 | 0.03  [-0.12 to 0.18] | 17 | -0.07  [-0.18 to 0.03] |  | 0.03  [-0.17 to 0.22] | 0.799 | 0.07  [-0.11 to 0.25] | 0.446 | 0.05  [-0.13 to 0.23] | 0.571 |
| *24 weeks* |  | 14 | -0.05  [-0.17 to 0.06] | 12 | -0.14  [-0.32 to 0.03] | 14 | -0.02  [-0.12 to 0.09] | 17 | -0.02  [-0.17 to 0.13] |  | -0.01  [-0.17 to 0.15] | 0.938 | 0.05  [-0.10 to 0.20] | 0.526 | 0.13  [-0.01 to 0.28] | 0.075 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.04  [-0.14 to 0.06] | 0.468 | 0.05  [-0.05 to 0.14] | 0.308 | 0.09  [0.00 to 0.19] | 0.050 |
| Fasting plasma C-reactive protein (mg/L) | | | | | | | | | | | | | | | | |
| *2 weeks* |  | 16 | -0.8  [-2.6 to 1.0] | 14 | -0.1  [-0.2 to 0.1] | 16 | -0.3  [-0.7 to 0.1] | 17 | 2.5  [-2.9 to 7.8] |  | -0.4  [-4.9 to 4.2] | 0.876 | -0.5  [-4.9 to 3.9] | 0.826 | 2.3  [-2.1 to 6.6] | 0.302 |
| *6 weeks* |  | 16 | -0.4  [-2.5 to 1.6] | 13 | -0.1  [-0.2 to 0.1] | 16 | 2.4  [-3.0 to 7.7] | 15 | -0.3  [-0.8 to 0.3] |  | -0.8  [-5.4 to 3.8] | 0.724 | 1.9  [-2.4 to 6.2] | 0.395 | -0.9  [-5.2 to 3.5] | 0.698 |
| *12 weeks* |  | 16 | -1.3  [-3.0 to 0.5] | 13 | 0.0  [0.0 to 0.0] | 15 | -0.3  [-0.8 to 0.1] | 16 | 0.0  [0.0 to 0.0] |  | -0.2  [-0.7 to 0.4] | 0.542 | -0.3  [-0.7 to 0.2] | 0.321 | -0.2  [-0.7 to 0.3] | 0.370 |
| *24 weeks* |  | 15 | -1.0  [-2.9 to 0.9] | 13 | -0.1  [-0.2 to 0.1] | 16 | 0.3  [-0.4 to 1.0] | 17 | 2.8  [-1.7 to 7.3] |  | -0.4  [-4.4 to 3.6] | 0.854 | 0.3  [-3.4 to 4.1] | 0.858 | 2.7  [-1.1 to 6.4] | 0.164 |
| *Across follow-up collectively* | | | | | | | | | |  | -0.4  [-2.4 to 1.5] | 0.659 | 0.4  [-1.4 to 2.2] | 0.666 | 1.0  [-0.8 to 2.9] | 0.263 |

All analyses at each timepoint were conducted using a complete case approach, with generalised linear models adjusted for age, BMI (both categorised as per randomisation) and baseline value of the outcome. Analyses across follow-up collectively used generalised estimating equations, adjusted in the same way as generalised linear models, with a normal distribution and exchangeable correlation matrix; *p*-values in bold are statistically significant (assessments of statistical significance for between-group comparison used the Holm sequential Bonferroni procedure to account for multiple comparisons); \*calculated as time-averaged area under the concentration-time curve during the standardised 3-hour mixed meal tolerance test. †statistical analyses of HbA1c were performed on data in mmol/mol only. Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

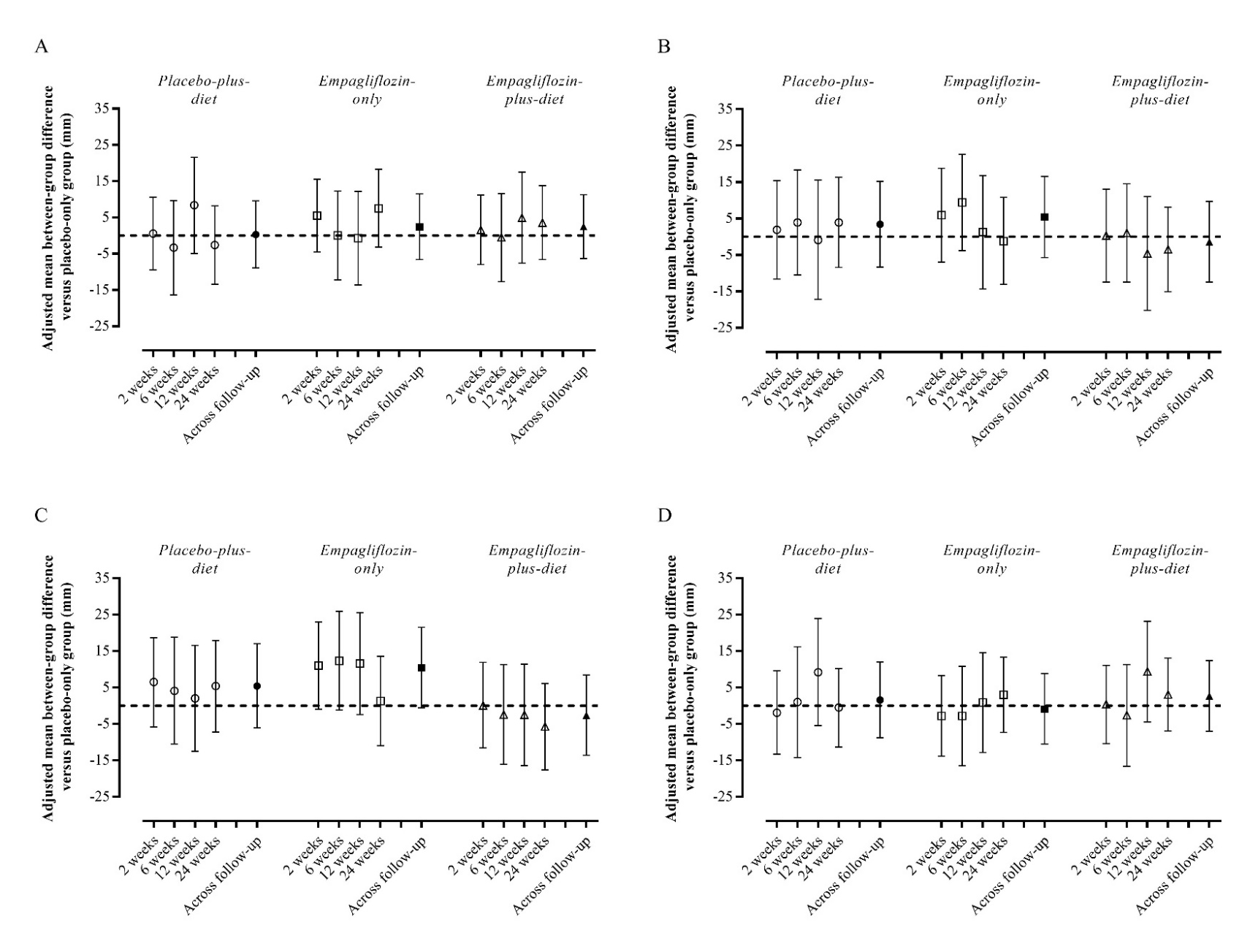
**Table S5 – Adverse and serious adverse events**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Placebo-only** | **Placebo-plus-diet** | **Empagliflozin-only** | **Empagliflozin-plus-diet** |
| *All adverse events* |  |  |  |  |
| Number of adverse events (proportion of all adverse events) | 17 (23%) | 18 (25%) | 18 (25%) | 20 (27%) |
| Participants with ≥1 adverse event (proportion of group) | 8 (47%) | 8 (47%) | 6 (35%) | 7 (41%) |
| *Serious adverse events* |  |  |  |  |
| Number of serious adverse events (proportion of all serious adverse events) | 1 (50%)\* | 1 (50%)\* | 0 | 0 |
| Participants with ≥1 serious adverse event (proportion of group) | 1 (6%) | 1 (6%) | 0 | 0 |
| Number of fatal events | 0 | 0 | 0 | 0 |
| *Adverse events of specific clinical interest (number of unique participants affected)* |  |  |  |  |
| Hypoglycaemia - mild | 0 | 0 | 1 (1) | 0 |
| Hypoglycaemia – moderate or greater | 0 | 0 | 0 | 0 |
| Urinary tract infections (including dysuria) | 1 (1) | 0 | 1 (1) | 1 (1) |
| Mycotic genital infections | 0 | 0 | 0 | 0 |
| Postural hypotension (including dizziness or presyncope) | 1 (1) | 2 (1) | 2 (2) | 2 (2) |
| Dehydration (including thirst) | 0 | 0 | 0 | 1 (1) |
| Decreased renal function | 0 | 0 | 0 | 0 |
| Decreased hepatic function | 0 | 0 | 0 | 0 |
| Diabetic ketoacidosis | 0 | 0 | 0 | 0 |
| Lower limb amputation | 0 | 0 | 0 | 0 |
| *Adverse events with >10% frequency of all events in any group (number of unique participants affected)* |  |  |  |  |
| Alopecia | 0 | 0 | 0 | 2 (1) |
| Diarrhoea | 1 (1) | 3 (3) | 0 | 0 |
| Influenza | 2 (2) | 0 | 2 (2) | 0 |
| Presyncope | 0 | 2 (1) | 1 (1) | 1 (1) |
| Upper respiratory tract infection | 1 (1) | 0 | 3 (3) | 3 (2) |

\*Both serious adverse events (one occurrence of pyrexia requiring hospitalisation in the placebo only group, and one occurrence of exacerbation of asthma in the placebo + diet group) were deemed unrelated to the intervention or trial procedures. The participant reporting pyrexia voluntarily withdrew from the trial, citing lack of interest following this adverse even

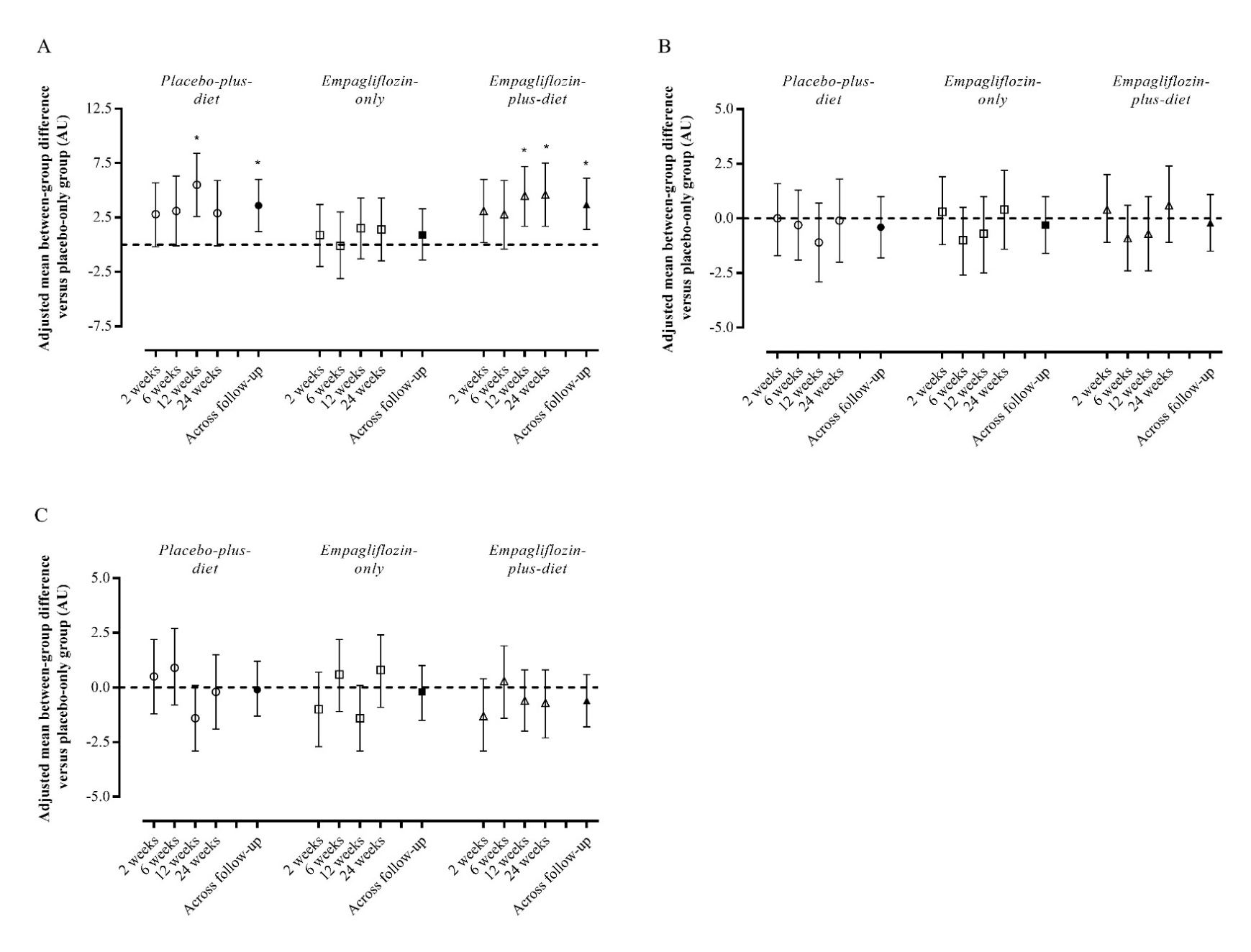
**Supplementary Figures**

**Figure S1 – Difference between experimental groups and placebo-only at each timepoint (open symbols) and across follow-up (filled symbols) in VAS-derived postprandial appetite perceptions: (A) hunger, (B) fullness, (C) satisfaction, and (D) prospective food consumption.**

****

Data are presented as adjusted mean difference (experimental group minus placebo-only) with 95% CI. Postprandial responses were assessed as time-averaged area under the concentration-time curve during the standardised 3-hour mixed meal tolerance test. All analyses were adjusted for age, BMI (both categorised as per randomisation) and baseline value of the outcome. GEE analyses across follow-up can be inferred as the summary intervention effect. Abbreviations: GEE, generalised estimating equations.

**Figure S2 – Difference between experimental groups and placebo-only at each timepoint (open symbols) and across follow-up (filled symbols) in three-factor eating questionnaire domains: (A) cognitive dietary restraint, (B) disinhibition, and (C) hunger.**

****

Data are presented as adjusted mean difference (experimental group minus placebo-only) with 95% CI. All analyses were adjusted for age, BMI (both categorised as per randomisation) and baseline value of the outcome \* Denotes comparison with placebo-only group was statistically significant after application of Holm’s sequential Bonferroni procedure to account for multiple comparisons. GEE analyses across follow-up can be inferred as the summary intervention effect. Abbreviations: GEE, generalised estimating equations.

**Supplemental References**

1. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241–247.
2. Henson J, Davies MJ, Bodicoat DH, Edwardson CL, Gill JMR, Stensel DJ, et al. Breaking up prolonged sitting with standing or walking attenuates the postprandial metabolic response in postmenopausal women: a randomized acute study. Diabetes Care. 2016;39(1):130-138.
3. Rubin D. Inference and missing data. Biometrika 1976;63(3):581-592.