1.0 RESULTS

1.1 Participant flow and baseline characteristics

Between 1st April 2017 (first patient first visit) and 9th July 2019 (last patient last visit), 190 participants with T2D were screened for eligibility. 68 participants were enrolled and randomly assigned to a treatment group. All participants received at least one dose of study medication. 64 participants completed the study, of which primary outcome data were available at Week 24 for 61 participants. The flow of participants through the study is outlined in Figure 2.

As outlined in Tables 1 and 2, the median age of the combined study population was 63 years and they had been diagnosed with T2DM for a median duration of 6 years. A total of 65.7% were male and 35.3% were female, 72% were of white European ethnicity and 94% were above 50 years of age. 82.4% of patients were prescribed metformin monotherapy at baseline. Furthermore, the median body weight was 91kg and the median BMI was 31.8kg·m^{-2}. The median HbA1c value was 6.8% with a median systolic and diastolic blood pressure of 127mmHg and 78mmHg, respectively.

Figure 1: Study Consort Diagram

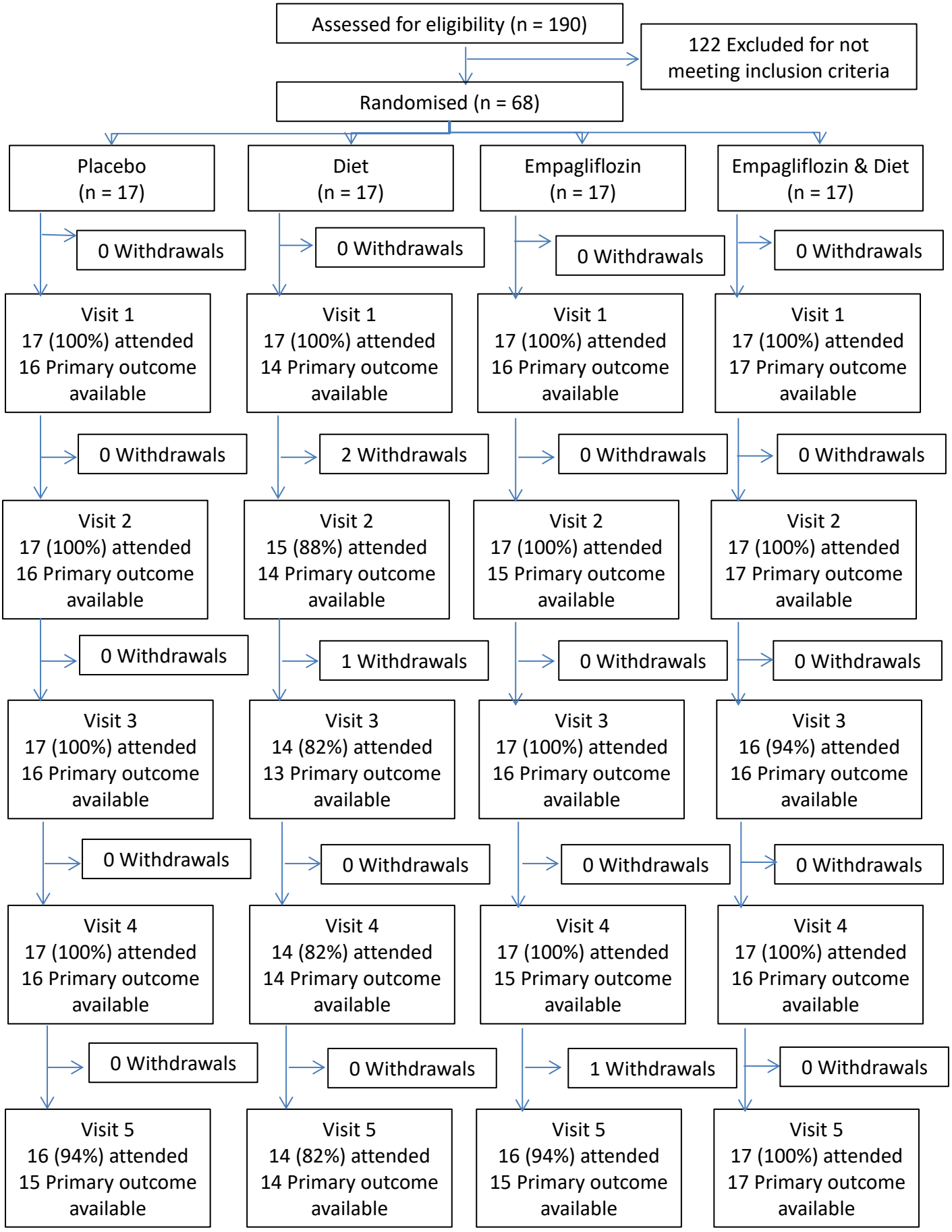

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Table 1: Summary of Baseline characteristics (continuous variables) – Data presented as median (IQR)

	Placebo (n=17)	Diet (n=17)	Empagliflozin (n=17)	Empagliflozin & Diet (n=17)	All (n = 68)
Age (years)	63 (56 – 69)	63 (60 – 69)	61 (57 – 68)	65 (55 – 69)	63 (57.3 – 69.0)
Duration of Diabetes (years)	7.0 (6.5 – 8.0)	4.0 (3.0 – 8.5)	6.0 (2.5 – 11.0)	6.5 (4.3 – 12.3)	6 (4 – 10)
Systolic Blood Pressure (mmHg)	125 (116 – 139)	136 (118 – 140)	134 (122 – 144)	121 (119 – 135)	127 (118 – 139)
Diastolic Blood Pressure (mmHg)	76 (69 – 81)	81 (76 – 87)	79 (74 – 86)	75 (70 – 83)	78 (72 – 83)
Heart Rate	72 (59 – 74)	69 (64 – 78)	68 (61 – 76)	67 (62 – 76)	68 (61 – 107)
Weight (kg)	98.5 (88.0 – 108.1)	96.7 (77.8 – 110.4)	89.8 (74.5 – 96.3)	90.0 (77.3 – 104.1)	91.0 (77.6 – 107.2)
Body Mass Index (kg/m^2)	32.8 (30.0 – 36.2)	31.9 (28.4 – 36.8)	31.4 (29.6 – 34.9)	31.2 (28.8 – 34.3)	31.8 (29.2 – 35.0)
Hip Circumference (cm)	113.0 (107.0 – 118.3)	111.3 (100.8 – 118.1)	111.2 (107.4 – 118.4)	109.5 (102.4 – 121.7)	111.5 (105.0 – 119.6)
Waist Circumference (cm)	112.0 (102.8 – 117.5)	114.5 (103.5 – 119.7)	107.0 (101.6 – 116.5)	107.2 (95.5 – 119.3)	110.9 (101.3 – 119.0)
Sodium (mmol/L)	140 (139 – 141)	140 (139 – 142)	141 (139 – 142)	140 (139 – 140)	140 (139 – 141)
Potassium (mmol/L)	4.4 (4.0 – 4.4)	4.2 (3.9 – 4.4)	4.4 (4.2 – 4.6)	4.3 (4.1 – 4.6)	4.3 (4.1 – 4.5)
Urea (mmol/L)	6.0 (5.5 – 6.7)	5.8 (4.8 – 6.2)	5.8 (4.9 – 7.0)	5.7 (5.0 – 7.4)	5.8 (5.1 – 7.0)
Creatinine (umol/L)	70 (64 – 82)	75 (64 – 91)	70 (63 – 82)	66 (63 – 79)	70.5 (63.8 – 82.0)
eGFR	90 (83 – 90)	87 (77 – 90)	89 (81 – 90)	90 (85 – 90)	89 (82 – 90)
Albumin (g/L)	46 (43 – 48)	45 (44 – 48)	46 (44 – 47)	46 (44 – 47)	45 (44 – 47)
Alkaline Phosphatase (iu/L)	82 (75 – 94)	66 (58 – 83)	76 (65 – 92)	85 (74 – 106)	80 (66 – 91)
Alanine Transaminase (iu/L)	26 (19 – 34)	26 (20 – 37)	28 (16 – 48)	24 (22 – 28)	25.5 (21.3 – 36.5)
Bilirubin	9 (8 – 10)	10 (7 – 13)	10 (8 – 10)	7 (6 – 10)	9 (7 – 10)
Total Cholesterol (mmol/L)	3.7 (3.2 – 4.4)	4.4 (3.8 – 5.1)	4.3 (3.8 – 5.2)	4.1 (2.9 – 5.0)	4.1 (3.3 – 4.8)
Triglycerides (mmol/L)	1.76 (1.34 – 2.54)	1.77 (1.16 – 2.21)	1.70 (0.95 – 2.39)	1.43 (1.26 – 1.79)	1.67 (1.29 – 2.13)
HDL Cholesterol (mmol/L)	1.1 (0.9 – 1.3)	1.3 (1.1 – 1.6)	1.4 (1.3 – 1.5)	1.1 (0.8 – 1.4)	1.2 (1.0 – 1.5)
Total cholesterol:HDL ratio	3.4 (2.4 – 4.0)	3.2 (2.8 – 3.9)	3.1 (2.5 – 3.6)	3.5 (2.7 – 3.9)	3.4 (2.7 – 3.9)
LDL Cholesterol (calculated)	1.9 (1.3 – 2.2)	2.2 (1.4 – 3.0)	1.9 (1.6 – 2.7)	2.1 (1.5 – 2.7)	2 (1.5 – 2.5)
HbA1c (%)	7.1 (6.7 – 7.5)	6.8 (6.6 – 7.4)	6.8 (6.5 – 7.2)	6.7 (6.7 – 7.0)	6.8 (6.6 – 7.2)
HbA1c (mmol/mol)	54 (50 – 58)	51 (48 – 57)	51 (48 – 55)	50 (50 – 53)	51 (48 – 55)

Table 2: Summary of Baseline characteristics (categorical variables) – Data presented as absolute frequency (count) and within-group percentage

		Placebo (n=17)		Diet (n=17)		Empagliflozin (n=17)		Empagliflozin & Diet (n=17)		All (n = 68)	
Variable	**Categories**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
BMI Group (kg/m^2)	25.0 - 29.9	4	23.5	5	29.4	4	23.5	5	29.4	18	26.5
	≥30.0	13	76.5	12	70.6	13	76.5	12	70.6	50	73.5
Age Group (years)	>50	16	94.1	16	94.1	16	94.1	16	94.1	64	94.1
	≤50	1	5.9	1	5.9	1	5.9	1	5.9	4	5.9
Sex	Male	13	76.5	13	76.5	8	47.1	10	58.8	44	64.7
	Female	4	23.5	4	23.5	9	52.9	7	41.2	24	35.3
Ethnicity	White	12	70.6	13	76.5	12	70.6	12	70.6	49	72.1
	South Asian	3	17.7	3	17.7	3	17.7	4	23.5	13	19.1
	Other	2	11.8	1	5.9	2	11.8	1	5.9	6	8.8
Smoking Status	Never Smoker	5	29.4	8	47.1	7	41.2	10	58.8	30	44.1
	Ex-Smoker	9	52.9	9	52.9	9	52.9	5	29.4	32	47.1
	Current Smoker	3	17.7	0	0	1	5.9	2	11.8	6	8.8
Alcohol Drinking Status	Never Drinker	2	11.8	3	17.7	5	29.4	4	23.5	14	20.6
	Ex-Drinker	1	5.9	1	5.9	1	5.9	0	0	3	4.4
	Current Drinker	14	82.4	13	76.5	11	64.7	13	76.5	51	75.0
Concomitant Medication - Metformin	Yes	16	94.1	13	76.5	15	88.2	12	70.6	56	82.4
	No	1	5.9	4	23.5	2	11.8	5	29.4	12	17.7

1.2 Study outcomes

1.2.1 Appetite hormones (including the primary outcome - PYY)

The effects of study treatments compared with placebo on the primary outcome (PYY) and additional appetite-related hormones can be seen in Table 3 and Figure 3. Supplementary Table 1 shows the overall average response across follow-up. Compared with placebo, PYY AUC was no different in any experimental group at 24 weeks. PYY AUC was higher in the empagliflozin group at 12 weeks (P = 0.003) but unchanged at all other time-points, and in all other study groups (Figure 3). No other differences at any follow-up were observed for any other appetite hormone (including leptin).

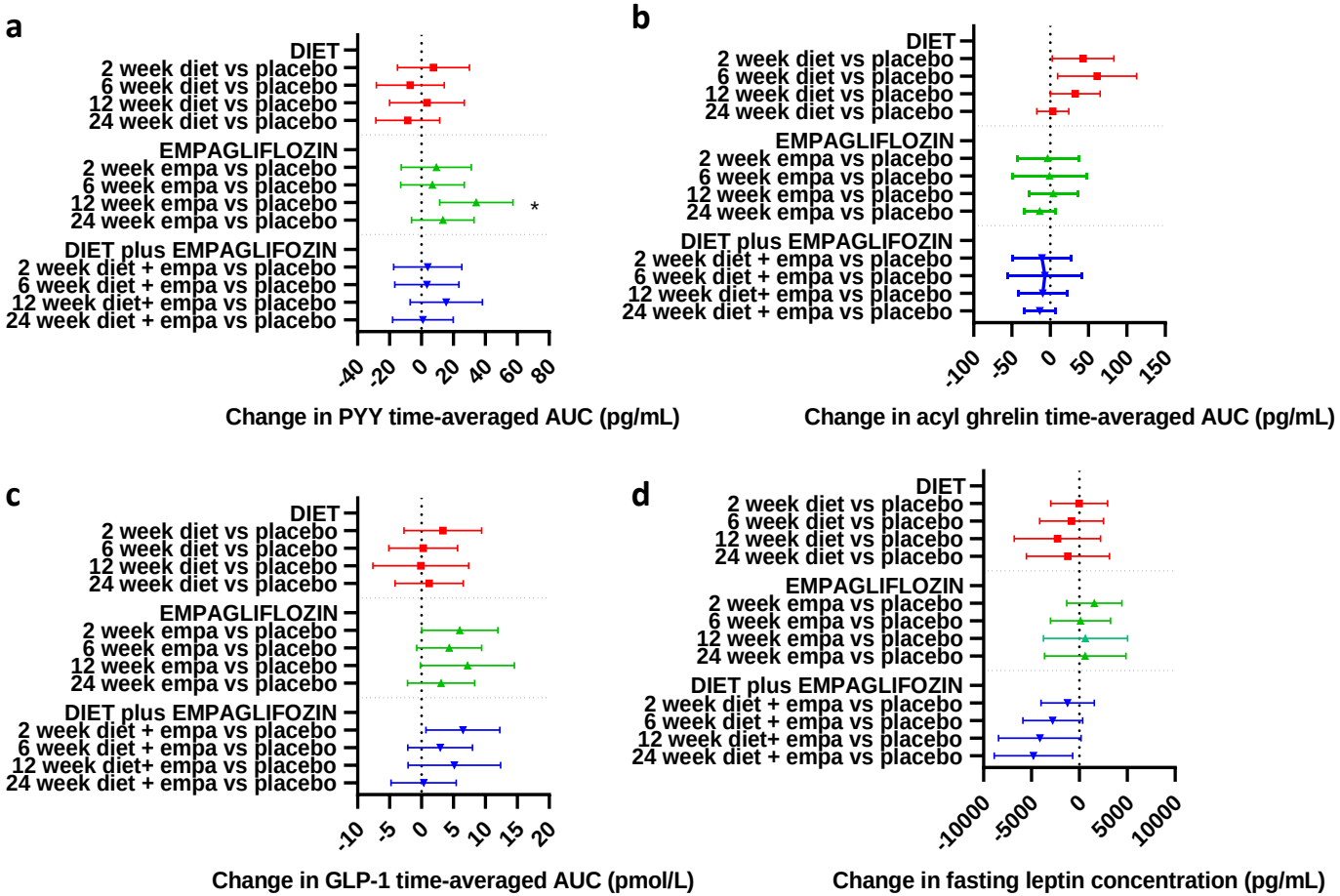
As an overall average response, circulating GLP-1 was higher over the course of the study in the empagliflozin group compared with placebo (P = 0.016) (Supplementary Table 1).

Table 3: Appetite-related hormone responses to study treatments (vs. placebo) over 24 weeks

				Treatment Effect Compared With Placebo											
				Diet				Empagliflozin				Empagliflozin & Diet			
Outcome	Visit	N Outliers	N Participants	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value
PYY AUC	2	0	62	7.56	-14.97	30.09	0.511	9.33	-12.67	31.32	0.406	4.04	-17.35	25.42	0.711
PYY AUC	3	0	61	-6.95	-28.17	14.27	0.521	6.89	-13.02	26.80	0.498	3.43	-16.65	23.51	0.738
PYY AUC	4	0	61	3.47	-20.00	26.94	0.772	**34.33**	**11.38**	**57.29**	**0.003**	15.58	-7.04	38.19	0.177
PYY AUC	5	0	61	-8.59	-28.58	11.40	0.400	13.42	-6.13	32.97	0.179	0.97	-18.01	19.95	0.920
Ghrelin AUC	2	1	61	42.88	2.65	83.12	0.037	-3.25	-43.40	36.89	0.874	-10.68	-49.12	27.75	0.586
Ghrelin AUC	3	1	61	61.23	9.67	112.79	0.020	-1.08	-49.68	47.52	0.965	-7.12	-55.92	41.69	0.775
Ghrelin AUC	4	1	61	32.54	0.16	64.92	0.049	3.90	-27.88	35.67	0.810	-9.89	-41.35	21.58	0.538
Ghrelin AUC	5	1	61	3.19	-17.69	24.06	0.765	-13.79	-34.26	6.68	0.187	-13.50	-33.47	6.47	0.185
GLP-1 AUC	2	0	62	3.35	-2.73	9.43	0.280	6.01	0.03	11.99	0.049	6.50	0.72	12.28	0.028
GLP-1 AUC	3	0	61	0.27	-5.12	5.66	0.922	4.35	-0.73	9.42	0.093	2.93	-2.14	8.01	0.257
GLP-1 AUC	4	0	61	-0.12	-7.61	7.38	0.976	7.21	-0.15	14.57	0.055	5.14	-2.09	12.38	0.163
GLP-1 AUC	5	0	61	1.21	-4.14	6.56	0.657	3.08	-2.17	8.32	0.250	0.34	-4.77	5.45	0.896
Leptin (pg/mL)	2	0	62	-17.18	-2977.23	2942.86	0.991	1577.94	-1303.73	4459.60	0.283	-1222.28	-4005.32	1560.77	0.389
Leptin (pg/mL)	3	0	61	-805.79	-4147.65	2536.08	0.637	121.39	-3013.10	3255.88	0.939	-2773.15	-5897.68	351.38	0.082
Leptin (pg/mL)	4	0	61	-2287.38	-6795.94	2221.19	0.320	640.01	-3756.48	5036.49	0.775	-4114.86	-8421.63	191.91	0.061
Leptin (pg/mL)	5	0	61	-1197.86	-5532.78	3137.07	0.588	619.78	-3620.19	4859.75	0.774	-4779.98	-8875.36	-684.61	0.022

Data adjusted for baseline (visit 1), age and group. AUC = time averaged area under the curve (meal-tolerance test response). Highlighted cells = statistically significant

Figure 3: Change in circulating (a) PYY, (b) acyl ghrelin, (c) GLP-1, and (d) leptin (3 h AUC meal-tolerance test) across study visits and treatment groups. Data are mean difference (95% CI); adjusted for baseline values, age and BMI. * = significantly different to placebo after Holm Bonferroni correction.

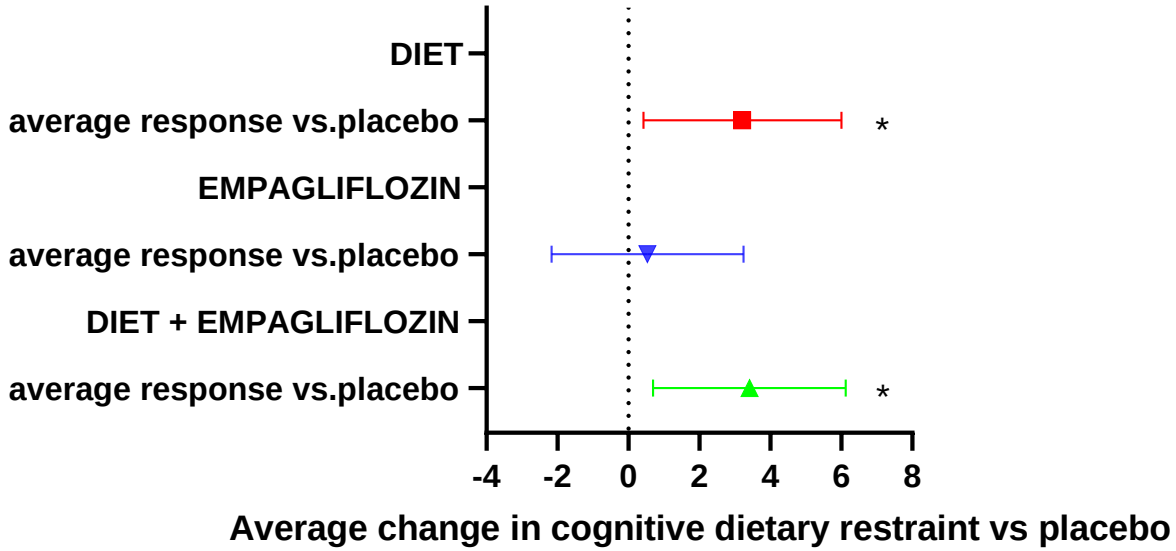


1.2.2 Appetite perceptions and eating traits

The effects of study treatments compared with placebo on appetite perceptions (3 h mixed meal-tolerance test responses) and eating traits at each visit can be seen in Table 4. Overall responses across visits are presented in supplementary Table 1. Study treatments had no effects on subjective perceptions of hunger, fullness, satisfaction or prospective food consumption.

Compared with placebo, dietary cognitive restraint was increased at 12 weeks in the diet study group (6.0 au [1.6, 10.4]; P = 0.007); and 12 (5.1 au [0.9, 9.3]; P = 0.018) and 24 weeks (4.6 au [1.7, 7.5]; P = 0.002) in the diet plus empagliflozin group. Across visit dietary cognitive restraint was elevated in the diet (3.2 au [0.4, 6.0]; P = 0.024) and diet plus empagliflozin (3.4 au [0.7, 6.1]; P = 0.014) study groups, compared with placebo (Figure 4).

Figure 4: Overall change in dietary cognitive restraint across treatment groups versus placebo.



Data are mean difference (95% CI); adjusted for baseline values, age and BMI. * = statistically significant after Holm Bonferroni correction.

Table 4: Perceived appetite and eating trait responses to study treatments (vs. placebo) over 24 weeks

				Treatment Effect Compared With Placebo											
				Diet				Empagliflozin				Empagliflozin & Diet			
Outcome	Visit	Outliers	*n*	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value
Hunger AUC	2	0	63	0.40	-9.46	10.26	0.937	5.60	-4.27	15.47	0.266	1.56	-7.86	10.99	0.745
Hunger AUC	3	0	63	-5.17	-17.74	7.39	0.420	-0.01	-12.07	12.06	0.999	-0.67	-12.63	11.30	0.913
Hunger AUC	4	0	63	8.25	-5.08	21.57	0.225	-0.85	-13.87	12.17	0.898	1.67	-10.81	14.15	0.793
Hunger AUC	5	0	61	-2.50	-13.12	8.13	0.645	6.96	-3.67	17.58	0.199	3.49	-6.53	13.51	0.495
Fullness AUC	2	0	64	2.04	-11.52	15.59	0.769	6.12	-6.88	19.13	0.356	0.23	-12.65	13.11	0.972
Fullness AUC	3	0	64	-2.41	-18.41	13.59	0.768	9.64	-5.26	24.55	0.205	1.15	-14.03	16.33	0.882
Fullness AUC	4	0	64	-1.05	-17.91	15.81	0.903	0.30	-15.73	16.33	0.971	-8.51	-24.33	7.32	0.292
Fullness AUC	5	0	62	4.58	-8.09	17.24	0.479	-1.11	-13.40	11.19	0.860	-3.12	-15.05	8.80	0.608
Satisfaction AUC	2	0	64	6.46	-5.90	18.82	0.306	10.97	-1.12	23.07	0.075	0.10	-11.75	11.96	0.986
Satisfaction AUC	3	0	64	-2.39	-18.56	13.79	0.772	11.70	-3.54	26.93	0.132	-2.44	-17.86	12.99	0.757
Satisfaction AUC	4	0	64	2.13	-13.54	17.80	0.790	11.54	-3.56	26.64	0.134	-6.53	-21.31	8.25	0.387
Satisfaction AUC	5	0	62	5.93	-7.00	18.86	0.369	0.79	-11.89	13.46	0.903	-5.45	-17.69	6.79	0.383
PFC AUC	2	0	64	-1.88	-13.23	9.47	0.745	-2.86	-13.78	8.06	0.607	0.34	-10.34	11.02	0.950
PFC AUC	3	0	64	-0.85	-15.82	14.11	0.911	-2.89	-16.60	10.82	0.679	-2.44	-16.41	11.53	0.732
PFC AUC	4	0	64	9.29	-5.62	24.21	0.222	0.68	-13.28	14.63	0.924	6.32	-7.45	20.10	0.368
PFC AUC	5	0	62	-0.16	-10.66	10.34	0.976	2.30	-7.71	12.31	0.652	3.25	-6.49	12.99	0.513
TFEQ Restraint	2	0	66	2.75	-0.19	5.69	0.066	0.88	-1.97	3.73	0.546	3.11	0.24	5.99	0.034
TFEQ Restraint	3	0	66	1.23	-3.91	6.36	0.640	0.18	-4.80	5.16	0.945	0.80	-4.23	5.83	0.755
TFEQ Restraint	4	0	65	**5.97**	**1.60**	**10.35**	**0.007**	-0.38	-4.53	3.78	0.859	**5.06**	**0.86**	**9.26**	**0.018**
TFEQ Restraint	5	0	63	2.94	-0.07	5.95	0.056	1.39	-1.52	4.31	0.349	**4.62**	**1.73**	**7.51**	**0.002**
TFEQ - Disinhibition	2	0	66	-0.03	-1.69	1.64	0.976	0.35	-1.25	1.95	0.668	0.45	-1.12	2.02	0.577
TFEQ - Disinhibition	3	0	66	-0.83	-2.93	1.27	0.440	-1.03	-3.05	0.99	0.318	-1.72	-3.71	0.26	0.089
TFEQ - Disinhibition	4	0	65	-1.10	-2.92	0.72	0.235	-1.06	-2.77	0.66	0.228	-0.69	-2.38	0.99	0.420
TFEQ - Disinhibition	5	0	63	-0.08	-2.00	1.83	0.931	0.39	-1.45	2.22	0.679	0.65	-1.13	2.43	0.475
TFEQ - Hunger	2	0	66	0.49	-1.24	2.22	0.579	-0.96	-2.67	0.74	0.268	-1.29	-2.93	0.36	0.125
TFEQ - Hunger	3	0	66	0.22	-1.86	2.31	0.835	0.46	-1.59	2.52	0.657	-0.50	-2.48	1.48	0.621
TFEQ - Hunger	4	0	65	-1.39	-3.06	0.28	0.103	**-1.99**	**-3.61**	**-0.38**	**0.016**	-0.63	-2.19	0.93	0.429
TFEQ - Hunger	5	0	63	-0.19	-1.88	1.49	0.825	0.76	-0.89	2.42	0.367	-0.73	-2.31	0.85	0.364

Data analysed by GLM with models adjusted for baseline (visit 1), age and group. PFC = prospective food consumption; TFEQ = Three-Factor Eating Questionnaire; AUC = 3 h Area Under the Curve (meal-tolerance test response). Highlighted cells = statistically significant

1.2.3 Anthropometric variables and resting metabolic rate

The effects of study treatments compared with placebo on anthropometric variables and resting metabolic rate at each visit are presented in Table 5 and Figure 5; with overall average response across visits presented in Supplementary Table 1. Body weight declined across the course of the trial in all study groups, with the diet plus empagliflozin group lower than placebo at 24 weeks (-5.6 kg [-7.7, -3.4]; P = <0.001). Across all visits , the reduction in body weight was also lower in the diet plus empagliflozin study group vs placebo (-3.78 kg [-5.4,-2.2]; P < 0.001).

At 24 weeks, fat mass (determined by DEXA) was nominally lower in all treatment groups, with significant differences observed in the diet and empagliflozin group versus placebo only (-4.1 kg [-5.8,-2.4]; P <0.001). Lean mass (determined by DEXA) was different between study groups at 24 weeks (P < 0.001); being lower than placebo at 24 weeks in the empagliflozin (-1.4 kg [-2.2,-0.6]; P = 0.001) and diet plus empagliflozin groups (-1.6 kg [-2.4,-0.8]; P < 0.001).

Waist circumference was reduced at all timepoints across each group, with differences versus placebo at 24 weeks seen in the empagliflozin (-3.8 cm [-6.9,-0.7]; P = 0.016) and diet plus empagliflozin groups (-4.8 cm [-7.9,-1.7]; P = 0.002). Overall, across follow-up waist circumference was reduced in the empagliflozin (-2.8 cm [-5.1,-0.5]; P = 0.018) and diet plus empagliflozin (-3.0 cm [-5.3,-0.6]; P = 0.012) groups compared with placebo.

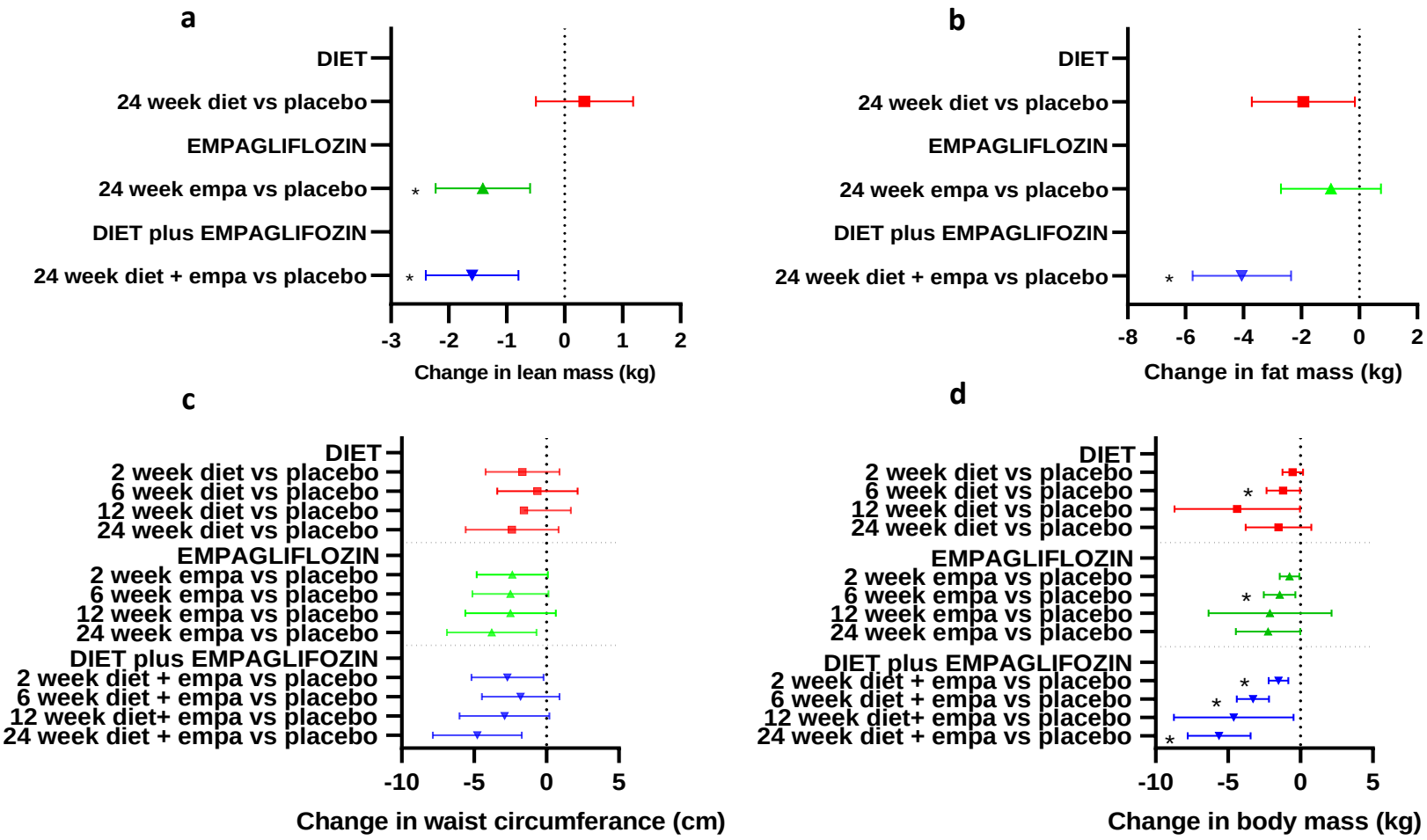
Although there were clear trends for resting metabolic rate to decline across the study in all groups, no statistically significant differences were identified.

Table 5: Anthropometric and metabolic rate responses to study treatments (vs. placebo) over 24 weeks

				Treatment Effect Compared With Placebo											
				Diet				Empagliflozin				Empagliflozin & Diet			
Outcome	Visit	N Outliers	N Participants	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value
Weight (kg)	2	0	66	-0.53	-1.24	0.17	0.135	-0.75	-1.44	-0.07	0.031	**-1.51**	**-2.19**	**-0.83**	**<0.001**
Weight (kg)	3	0	64	**-1.19**	**-2.34**	**-0.04**	**0.042**	**-1.44**	**-2.54**	**-0.34**	**0.011**	**-3.28**	**-4.39**	**-2.17**	**<0.001**
Weight (kg)	4	0	64	-4.37	-8.70	-0.04	0.048	-2.10	-6.34	2.14	0.333	-4.61	-8.74	-0.48	0.029
Weight (kg)	5	0	63	-1.52	-3.79	0.76	0.191	-2.23	-4.45	-0.01	0.049	**-5.62**	**-7.79**	**-3.44**	**<0.001**
Body fat % (BIA)	2	0	65	-0.49	-1.79	0.81	0.461	-0.34	-1.58	0.90	0.592	0.79	-0.44	2.03	0.208
Body fat % (BIA)	3	0	63	-1.06	-2.59	0.47	0.173	-0.49	-1.92	0.93	0.497	-0.07	-1.51	1.37	0.925
Body fat % (BIA)	4	0	63	-2.00	-3.68	-0.32	0.020	-1.54	-3.13	0.06	0.059	-1.41	-2.97	0.14	0.075
Body fat % (BIA)	5	0	61	-1.69	-4.10	0.72	0.168	-0.57	-2.92	1.77	0.631	**-2.90**	**-5.13**	**-0.66**	**0.011**
DEXA - Fat Mass	5	0	63	-1.94	-3.72	-0.16	0.033	-0.98	-2.71	0.74	0.264	**-4.06**	**-5.76**	**-2.36**	**<0.001**
DEXA - Bone Mass	5	0	63	-0.01	-0.05	0.02	0.375	0.02	-0.02	0.05	0.306	-0.01	-0.04	0.02	0.418
DEXA - Bone Density	5	0	63	0.01	-0.01	0.03	0.479	-0.01	-0.03	0.00	0.146	0.01	-0.01	0.03	0.358
DEXA - Lean Mass	5	0	63	0.34	-0.50	1.18	0.428	**-1.41**	**-2.23**	**-0.60**	**0.001**	**-1.60**	**-2.40**	**-0.80**	**<0.001**
Waist Ciirc (cm)	2	0	66	-1.66	-4.21	0.89	0.203	-2.36	-4.83	0.10	0.060	-2.70	-5.19	-0.21	0.034
Waist Ciirc (cm)	3	0	64	-0.63	-3.40	2.14	0.655	-2.49	-5.11	0.14	0.063	-1.78	-4.46	0.90	0.193
Waist Ciirc (cm)	4	0	64	-1.55	-4.79	1.69	0.348	-2.48	-5.60	0.64	0.120	-2.90	-6.00	0.20	0.066
Waist Ciirc (cm)	5	0	63	-2.38	-5.59	0.83	0.146	**-3.78**	**-6.87**	**-0.69**	**0.016**	**-4.78**	**-7.85**	**-1.71**	**0.002**
Hip Circ (cm)	2	0	66	-2.03	-5.33	1.26	0.227	0.15	-3.04	3.33	0.928	-0.54	-3.72	2.65	0.742
Hip Circ (cm)	3	0	62	-1.10	-4.05	1.85	0.465	-1.00	-3.80	1.80	0.486	-2.14	-4.98	0.71	0.141
Hip Circ (cm)	4	0	64	-2.42	-5.27	0.44	0.097	-3.19	-5.94	-0.44	0.023	-3.56	-6.27	-0.86	**0.010**
Hip Circ (cm)	5	0	63	**-3.17**	**-5.95**	**-0.40**	**0.025**	**-2.67**	**-5.35**	**0.00**	**0.050**	**-4.86**	**-7.49**	**-2.23**	**<0.001**
RMR (kcal/d)	2	0	65	-5.23	-199.79	189.33	0.958	-47.53	-235.22	140.15	0.620	-15.07	-203.60	173.46	0.875
RMR (kcal/d)	3	0	62	-62.24	-317.62	193.15	0.633	-108.70	-353.86	136.47	0.385	-250.71	-495.64	-5.79	0.045
RMR (kcal/d)	4	0	64	-72.54	-228.17	83.09	0.361	-46.55	-193.31	100.21	0.534	-51.63	-199.06	95.81	0.493
RMR (kcal/d)	5	0	61	-58.87	-249.44	131.71	0.545	-133.22	-311.28	44.84	0.143	-176.03	-351.85	-0.21	0.050

Data analysed by GLM with models adjusted for baseline (visit 1), age and group. RMR = resting metabolic rate. Highlighted cells = statistically significant

Figure 5: Change in (a) lean mass, (b) fat mass, (c) waist circumference and (d) body mass across study visits versus placebo.



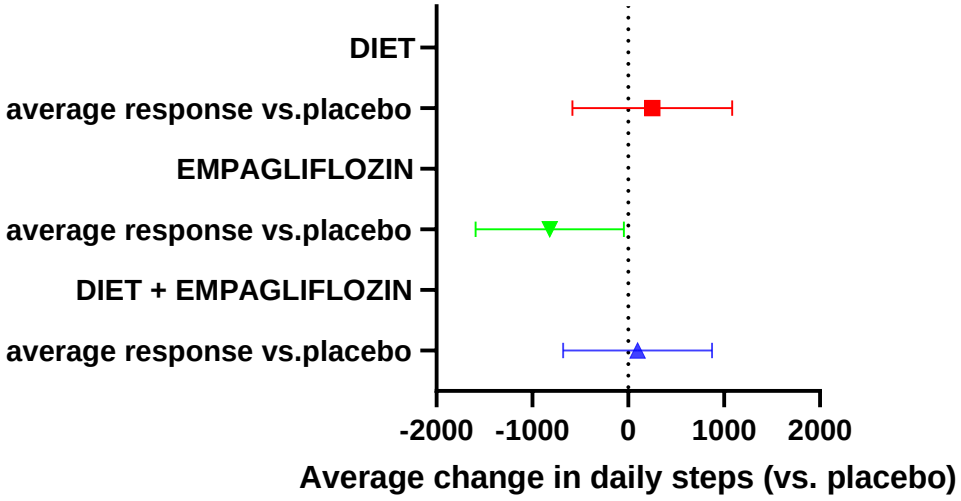
Data are mean difference (95% CI); adjusted for baseline values, age and BMI. * = significantly different after Holm Bonferroni correction.

1.2.4 Objectively measured physical activity and sedentary time

The effects of study treatments compared with placebo on average daily steps and time spent undertaking sedentary, light and moderate-to-vigorous activities for each visit is shown in Table 6 with the overall average response across visits shown in Supplementary Table 1.

None of the intervention groups were different to placebo at any visit. However, average daily steps were different between study groups for the overall average response across visits (P = 0.046). Empirically, compared with placebo, steps declined in the empagliflozin group yet increased in the diet and diet plus empagliflozin groups; however these responses were not statistically significant (Figure 6).

Figure 6: Overall change in average daily steps across treatment groups versus placebo.



Data are mean difference (95% CI); adjusted for baseline values, age and BMI. A statistically significant difference in response between groups was identified (P = 0.046).

Table 6: Objectively measured physical activity responses to study treatments (vs. placebo) over 24 weeks

				Treatment Effect Compared With Placebo											
				Diet				Empagliflozin				Empagliflozin & Diet			
Outcome	Visit	N Outliers	*n*	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value
Steps per day	3	0	58	-318.39	-1607.36	970.59	0.628	-1410.77	-2580.31	-241.24	0.018	-436.70	-1580.43	707.03	0.454
Steps per day	4	0	62	507.19	-531.65	1546.02	0.339	-167.28	-1144.49	809.94	0.737	50.16	-922.41	1022.73	0.919
Steps per day	5	0	58	604.13	-697.64	1905.90	0.363	-799.96	-2046.99	447.07	0.209	573.91	-694.97	1842.79	0.375
Sedentary minutes per day	3	0	58	25.35	-20.19	70.89	0.275	6.20	-35.09	47.48	0.769	14.80	-25.37	54.98	0.470
Sedentary minutes per day	4	0	62	-0.26	-40.29	39.77	0.990	-13.12	-50.76	24.52	0.495	-0.22	-37.64	37.20	0.991
Sedentary minutes per day	5	1	58	-23.15	-65.38	19.08	0.283	0.67	-39.70	41.04	0.974	-17.81	-58.86	23.24	0.395
Light activity minutes per day	3	0	58	-29.43	-70.20	11.34	0.157	1.99	-35.16	39.13	0.916	-16.53	-52.46	19.39	0.367
Light activity minutes per day	4	0	62	-3.54	-40.49	33.41	0.851	12.47	-22.41	47.35	0.484	1.15	-33.40	35.70	0.948
Light activity minutes per day	5	0	58	20.43	-15.19	56.06	0.261	-1.99	-36.17	32.18	0.909	10.34	-24.30	44.98	0.558
MVPA minutes per day	3	1	58	3.04	-9.87	15.95	0.644	-8.85	-20.70	3.01	0.143	2.40	-9.03	13.84	0.680
MVPA minutes per day	4	0	62	3.38	-7.92	14.68	0.558	-0.38	-11.01	10.24	0.944	-0.64	-11.20	9.91	0.905
MVPA minutes per day	5	0	58	3.34	-8.68	15.36	0.586	-1.03	-12.67	10.61	0.863	6.89	-4.81	18.58	0.249

Data analysed by GLM with models adjusted for baseline (visit 1), age and group. MVPA – moderate-to-vigorous physical activity.

1.2.5 Glycaemic control

The effects of study treatments on gluco-regulatory variables are shown in Table 7 and Figure 7; with overall average response across visits presented in supplementary Table 1.

Compared with placebo, HbA1c was empirically lower at all assessment points in each trial group, with significant differences identified at 6 weeks in the diet (-0.25% [-0.44,-0.05]; P = 0.015), empagliflozin (-0.26 [-0.45,-0.07]; P = 0.008) and diet plus empagliflozin (-0.31 [-0.51,-0.12]; P =0.002) groups. Additional differences versus placebo were identified at 12 weeks in the empagliflozin (-0.47 [-0.82,-0.12]; P = 0.009) and diet plus empagliflozin (-0.49 [-0.84,-0.14]; P = 0.006) groups. When comparing overall average responses, statistically significant differences versus placebo were apparent in the empagliflozin (-0.30% [-0.50,-0.10]; P = 0.003) and diet plus empagliflozin (-0.33% [-0.53,-0.13]; P = 0.001) groups.

Compared with placebo, fasting glucose concentrations were significantly reduced at all time points in the diet plus empagliflozin group (-0.73 to -1.23 mmol/L; P ≤ 0.001) and from 6 weeks onwards in the empagliflozin group (-0.77 to -0.99 mmol/L; P ≤ 0.002). Differences across visits were not significant in the diet group. When comparing overall average responses versus placebo, differences were identified in the empagliflozin (-0.79 mM [-1.15,-0.44]; P < 0.001) and diet plus empagliflozin (-1.09 mM [-1.44,-0.74]; P< 0.001) groups.

Across study timepoints, no statistically significant differences in fasting insulin concentrations were identified. However, the overall average response in the empagliflozin (-2.68 mU [-4.93,-0.43]; P = 0.002) and diet plus empagliflozin (-2.54 mU [-4.81,-0.28]; P = 0.028) groups were significantly different versus placebo.

Across study timepoints, glucose responses (AUC) to the mixed meal tolerance test were different to placebo at all follow-up visits in the diet and empagliflozin group (-1.15 to -2.15 mmol/L/3h; P ≤ 0.013). In the empagliflozin group, values differed to placebo at 6 and 12 weeks (-1.15 to -1.94 mmol/L/3 h; P ≤ 0.001). Overall average responses were different to placebo in the empagliflozin (-1.37 mM/3h [-2.05,-0.69]; P < 0.001) and diet plus empagliflozin (-1.64 mM/3h [-2.32,-0.96]; P < 0.001) groups.

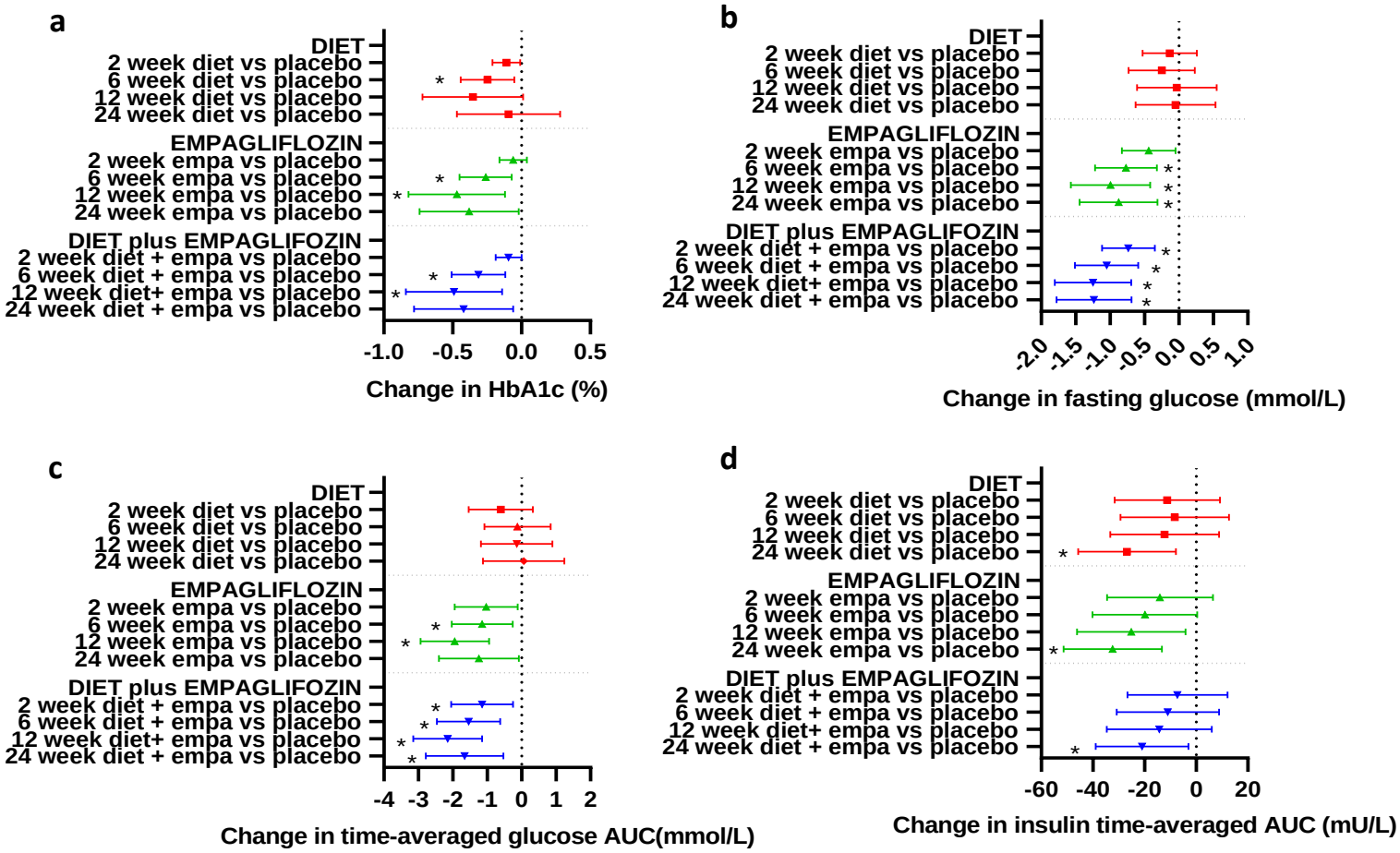
For the insulin response to the mixed meal tolerance test, differences versus placebo were found at 24 weeks in all study groups: diet; -26.78 mU/3h [-45.69,-7.87]: P = 0.006); empagliflozin (-32.35 mU/3h [-51.39,-13.30]: P = 0.001); diet plus empagliflozin (-20.92 mU/3h [-38.90,-2.94]; P = 0.023). Overall, average responses were different to placebo in the empagliflozin group (-22.45 mU/3h [-36.48,-8.24]; P = 0.002).

Table 7: Gluco-regulatory responses to study treatments (vs. placebo) over 24 weeks

				Treatment Effect Compared With Placebo											
				Diet				Empagliflozin				Empagliflozin & Diet			
Outcome	Visit	N Outliers	*n*	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value
Insulin AUC	2	0	62	-11.22	-31.63	9.20	0.282	-14.03	-34.57	6.51	0.181	-7.26	-26.63	12.10	0.462
Insulin AUC	3	0	61	-8.31	-29.37	12.75	0.439	-19.86	-40.16	0.45	0.055	-10.97	-30.82	8.88	0.279
Insulin AUC	4	0	61	-12.23	-33.33	8.87	0.256	-25.18	-46.21	-4.14	0.019	-14.26	-34.59	6.06	0.169
Insulin AUC	5	0	61	**-26.78**	**-45.69**	**-7.87**	**0.006**	**-32.35**	**-51.39**	**-13.30**	**0.001**	**-20.92**	**-38.90**	**-2.94**	0.023
Glucose AUC	2	0	65	-0.61	-1.54	0.33	0.201	-1.03	-1.95	-0.12	0.027	**-1.15**	**-2.05**	**-0.25**	0.013
Glucose AUC	3	0	62	-0.12	-1.08	0.84	0.809	**-1.15**	**-2.03**	**-0.26**	**0.011**	**-1.54**	**-2.46**	**-0.62**	0.001
Glucose AUC	4	0	63	-0.14	-1.18	0.89	0.786	**-1.94**	**-2.94**	**-0.95**	**<0.001**	**-2.15**	**-3.15**	**-1.15**	<0.001
Glucose AUC	5	0	61	0.06	-1.12	1.24	0.919	-1.24	-2.40	-0.08	0.036	**-1.66**	**-2.78**	**-0.53**	0.004
Glucagon AUC	2	0	62	-1.84	-18.33	14.65	0.827	5.77	-10.37	21.91	0.483	13.26	-2.37	28.88	0.096
Glucagon AUC	3	0	61	-19.18	-37.32	-1.04	0.038	-2.22	-19.26	14.81	0.798	2.12	-14.93	19.17	0.807
Glucagon AUC	4	0	61	-10.16	-25.01	4.69	0.180	5.36	-9.17	19.89	0.470	3.95	-10.34	18.24	0.588
Glucagon AUC	5	0	61	-5.50	-20.14	9.14	0.461	-4.59	-18.93	9.75	0.530	-6.46	-20.38	7.46	0.363
C Peptide AUC	2	1	62	-155.09	-922.99	612.81	0.692	-39.29	-795.46	716.87	0.919	186.67	-542.02	915.36	0.616
C Peptide AUC	3	1	61	**-818.46**	**-1410.36**	**-226.56**	**0.007**	77.47	-482.08	637.03	0.786	303.02	-253.86	859.90	0.286
C Peptide AUC	4	0	61	-520.65	-1174.02	132.73	0.118	-103.33	-745.20	538.55	0.752	89.10	-541.02	719.23	0.782
C Peptide AUC	5	0	61	-473.79	-1140.95	193.36	0.164	-386.80	-1045.88	272.29	0.250	205.34	-427.99	838.66	0.525
FPG (mmol/L)	2	0	63	-0.13	-0.53	0.26	0.503	-0.44	-0.83	-0.05	0.026	**-0.73**	**-1.12**	**-0.35**	<0.001
FPG (mmol/L)	3	0	61	-0.25	-0.73	0.23	0.305	**-0.77**	**-1.22**	**-0.32**	**0.001**	**-1.05**	**-1.51**	**-0.59**	<0.001
FPG (mmol/L)	4	0	61	-0.03	-0.61	0.55	0.923	**-0.99**	**-1.57**	**-0.42**	**0.001**	**-1.25**	**-1.80**	**-0.69**	<0.001
FPG (mmol/L)	5	0	62	-0.05	-0.63	0.53	0.872	**-0.88**	**-1.44**	**-0.31**	**0.002**	**-1.23**	**-1.78**	**-0.69**	<0.001
HbA1c (%)	2	0	61	-0.11	-0.21	-0.01	0.034	-0.06	-0.16	0.04	0.221	-0.09	-0.19	0.00	0.058
HbA1c (%)	3	0	58	**-0.25**	**-0.44**	**-0.05**	**0.015**	**-0.26**	**-0.45**	**-0.07**	**0.008**	**-0.31**	**-0.51**	**-0.12**	0.002
HbA1c (%)	4	0	63	-0.35	-0.72	0.01	0.060	**-0.47**	**-0.82**	**-0.12**	**0.009**	**-0.49**	**-0.84**	**-0.14**	0.006
HbA1c (%)	5	0	63	-0.09	-0.47	0.28	0.626	-0.38	-0.74	-0.02	0.041	-0.42	-0.78	-0.06	0.021

Data analysed by GLM with models adjusted for baseline (visit 1), age and group. AUC – area under the curve (responses to a 3 h mixed-meal tolerance test

Figure 7: Change in (a) HbA1c, (b) fasting glucose, (c) glucose AUC, and (d) insulin AUC across study visits and treatment groups.



Data are mean difference (95% CI); adjusted for baseline values, age and BMI. * = significantly different to placebo after Holm Bonferroni correction.

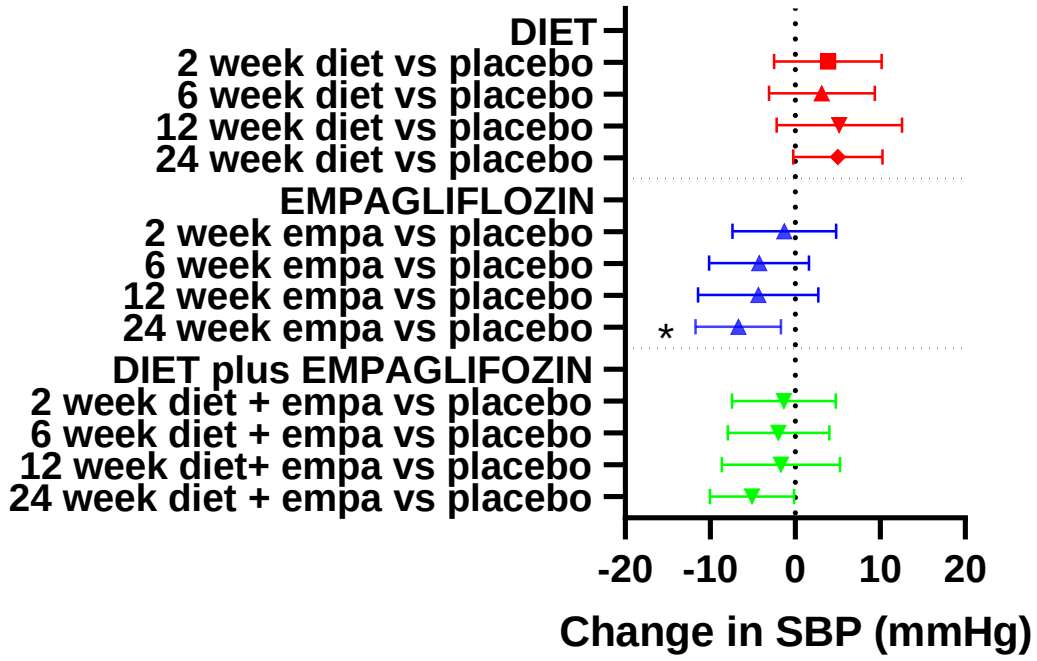
1.2.6 Metabolic health biomarker responses

The effects of study treatments on metabolic biomarkers and blood pressure across study timepoints are shown in Table 8. Overall average response across follow-up are presented in supplementary Table1.

At 24 weeks, SBP was significantly different versus placebo in the empagliflozin group (-6.7 mmHg [-11.7,-1.7]; P = 0.009)(Figure 8). For DBP, no individual treatment effects (versus placebo) were seen.

When examining responses across visits, or average response, no statistically significant differences were identified for free-fatty acids, C-reactive protein, cholesterol (total, HDL, LDL), ALT or eGFR.

Figure 8: Change in SBP across study visits and treatment groups versus placebo.



Data are mean difference (95% CI); adjusted for baseline values, age and BMI. * = significantly different to placebo after Holm Bonferroni correction.

Table 8: Metabolic health biomarker responses to study treatments (vs. placebo) over 24 weeks

				Treatment Effect Compared With Placebo											
				Diet				Empagliflozin				Empagliflozin & Diet			
Outcome	Visit	N Outliers	N Participants	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value
C - Reactive Protein	2	1	63	-0.36	-4.93	4.21	0.876	-0.49	-4.85	3.88	0.826	2.29	-2.05	6.62	0.302
C - Reactive Protein	3	1	60	-0.83	-5.41	3.76	0.724	1.86	-2.43	6.16	0.395	-0.87	-5.25	3.51	0.698
C - Reactive Protein	4	1	60	4.50	-1.34	10.34	0.131	-0.23	-5.78	5.31	0.934	-0.04	-5.61	5.54	0.990
C - Reactive Protein	5	1	61	-0.38	-4.40	3.65	0.854	0.35	-3.44	4.13	0.858	2.67	-1.09	6.43	0.164
Total Cholesterol (mmol/L)	2	0	65	-0.11	-0.39	0.16	0.422	0.12	-0.15	0.39	0.397	-0.14	-0.40	0.13	0.320
Total Cholesterol (mmol/L)	3	0	62	0.28	-0.19	0.75	0.238	0.10	-0.35	0.55	0.663	-0.16	-0.62	0.30	0.499
Total Cholesterol (mmol/L)	4	0	63	-0.29	-0.65	0.07	0.116	-0.16	-0.51	0.19	0.358	-0.28	-0.63	0.08	0.124
Total Cholesterol (mmol/L)	5	0	63	-0.28	-0.68	0.12	0.164	-0.16	-0.54	0.23	0.423	-0.16	-0.54	0.22	0.398
HDL Cholesterol (mmol/L)	2	0	65	0.06	-0.11	0.24	0.484	0.01	-0.18	0.19	0.941	0.07	-0.11	0.24	0.453
HDL Cholesterol (mmol/L)	3	0	62	0.15	-0.01	0.30	0.068	0.05	-0.11	0.22	0.532	0.07	-0.09	0.22	0.381
HDL Cholesterol (mmol/L)	4	0	63	0.01	-0.09	0.11	0.875	0.02	-0.08	0.12	0.691	-0.01	-0.11	0.09	0.830
HDL Cholesterol (mmol/L)	5	0	63	0.09	-0.08	0.25	0.314	0.05	-0.12	0.22	0.571	0.15	-0.01	0.31	0.069
LDL Cholesterol (mmol/L)	2	1	64	-0.09	-0.60	0.42	0.734	0.14	-0.37	0.64	0.595	0.28	-0.23	0.79	0.274
LDL Cholesterol (mmol/L)	3	0	61	-0.08	-0.35	0.20	0.589	-0.02	-0.29	0.24	0.854	-0.25	-0.53	0.03	0.075
LDL Cholesterol (mmol/L)	4	1	62	-0.10	-0.39	0.19	0.482	-0.04	-0.32	0.24	0.768	-0.07	-0.35	0.22	0.642
LDL Cholesterol (mmol/L)	5	0	61	-0.18	-0.49	0.12	0.241	-0.08	-0.37	0.21	0.598	-0.18	-0.47	0.12	0.244
Fatty Free Acid	2	1	29	0.02	-0.13	0.17	0.766	0.01	-0.14	0.17	0.859	0.12	-0.04	0.28	0.145
Fatty Free Acid	3	0	27	-0.20	-0.43	0.03	0.083	0.06	-0.14	0.27	0.529	0.06	-0.17	0.28	0.612
Fatty Free Acid	4	0	25	-0.13	-0.37	0.11	0.300	-0.11	-0.33	0.11	0.319	-0.08	-0.33	0.16	0.519
Fatty Free Acid	5	0	20	-0.04	-0.29	0.21	0.732	-0.11	-0.38	0.16	0.430	0.15	-0.18	0.48	0.368
eGFR	2	0	66	-0.68	-4.69	3.32	0.738	-1.74	-5.61	2.12	0.377	-0.62	-4.48	3.23	0.751
eGFR	3	0	62	-0.21	-3.69	3.26	0.904	-1.67	-5.03	1.69	0.330	-0.04	-3.43	3.36	0.983
eGFR	4	1	64	4.62	-4.09	13.34	0.298	3.23	-5.11	11.56	0.448	5.23	-2.95	13.41	0.210
eGFR	5	0	63	0.55	-2.96	4.06	0.760	-3.76	-7.16	-0.37	0.030	-1.31	-4.63	2.00	0.437
Alanine Transaminase (iu/L)	2	0	65	-4.03	-10.17	2.11	0.198	2.91	-3.13	8.94	0.345	-0.49	-6.38	5.41	0.872
Alanine Transaminase (iu/L)	3	0	61	0.02	-4.80	4.84	0.994	-1.74	-6.45	2.98	0.470	-1.58	-6.26	3.10	0.509

Alanine Transaminase (iu/L)	4	0	62	-2.97	-8.64	2.71	0.306	-5.84	-11.38	-0.30	0.039	-2.02	-7.42	3.38	0.464
Alanine Transaminase (iu/L)	5	1	63	-3.48	-10.66	3.71	0.343	-3.56	-10.52	3.40	0.316	-3.91	-10.66	2.85	0.257
SBP (mmHg)	2	0	66	3.85	-2.49	10.19	0.234	-1.29	-7.39	4.82	0.680	-1.32	-7.42	4.79	0.672
SBP (mmHg)	3	0	64	3.14	-3.07	9.36	0.321	-4.23	-10.11	1.65	0.159	-1.97	-7.94	4.00	0.518
SBP (mmHg)	4	0	64	5.20	-2.19	12.58	0.168	-4.34	-11.40	2.73	0.229	-1.68	-8.63	5.27	0.636
SBP (mmHg)	5	0	63	5.04	-0.20	10.29	0.059	**-6.70**	**-11.71**	**-1.68**	**0.009**	-5.07	-10.01	-0.13	0.044
DBP (mmHg)	2	0	66	0.96	-3.92	5.83	0.701	-0.86	-5.57	3.85	0.720	0.11	-4.61	4.83	0.964
DBP (mmHg)	3	0	64	0.13	-5.05	5.31	0.961	-3.57	-8.48	1.35	0.155	0.84	-4.16	5.85	0.741
DBP (mmHg)	4	0	64	0.56	-4.62	5.74	0.832	-2.89	-7.86	2.09	0.256	0.01	-4.89	4.91	0.997
DBP (mmHg)	5	0	63	2.50	-1.91	6.90	0.267	-4.26	-8.49	-0.03	0.048	-1.06	-5.25	3.13	0.621
Heart Rate (bpm)	2	0	66	-3.55	-8.93	1.83	0.196	1.35	-3.88	6.57	0.614	-2.59	-7.84	2.65	0.332
Heart Rate (bpm)	3	0	64	0.51	-4.59	5.60	0.846	4.32	-0.54	9.18	0.081	-1.42	-6.38	3.54	0.574
Heart Rate (bpm)	4	0	64	-1.01	-6.30	4.29	0.709	-0.72	-5.86	4.42	0.784	-2.04	-7.09	3.01	0.429
Heart Rate (bpm)	5	0	63	4.55	-1.71	10.81	0.155	5.46	-0.58	11.50	0.077	5.45	-0.55	11.44	0.075

Data analysed by GLM with models adjusted for baseline (visit 1), age and group. Highlighted cells = statistically significant effect

1.0 ADVERSE EVENTS

Safety data are summarised in **Tables 9 and 10,** with a list of non-serious adverse events (split by treatment group) presented in **Table 11,** and a list of serious adverse events (split by treatment group) in **Table 12**. A full line listing of adverse events is presented in **Supplemental Table 2.**

A total of seventy one non-serious adverse events (AEs) were reported across all treatment groups. The most common adverse events were diarrhoea, upper respiratory tract infection, influenza and vasovagal reaction.

A total of fourteen AEs were considered by the investigator to be possibly, probably or definitely related to the IMP/placebo at the time of assessment. Ten AEs were deemed possibly related to the IMP/placebo, namely:

- ankle oedema (one participant),
- constipation (one participant),
- dizziness upon standing (one participant),
- dry skin (one participant),
- haematuria (one participant),
- haemorrhoids (one participant),
- hypoglycaemia (one participant),
- micturition burning (one participant),
- sweating (one participant),
- vision abnormal NOS (one participant)

Two AEs were deemed probably related to the IMP/placebo, namely:

- cystitis (one participant)
- thirst (one participant).

Two AEs were deemed definitely related to the IMP/placebo, namely:

- increased micturition and micturition urgency (one participant).

Four AEs were documented as expected in line with the reference safety information for the IMP, namely:

- cystitis (one participant)
- micturition burning (one participant)
- increased micturition and micturition urgency (one participant).

One AE was deemed possibly related to the diet, namely:

- diarrhoea (one participant).

The non-serious AEs were reported equally by each treatment group. **Tables 11 and 12** present unblinded trial data.

A total of two serious adverse events (SAEs) were reported; one each in the placebo and diet treatment groups. Both were deemed unrelated to the intervention; however one (pyrexia of unknown origin) did lead to withdrawal from the study.

In summary, there were no SAEs in patients receiving empagliflozin +/- diet. The pattern of AEs raises no additional concerns to the known safety profile of the diet intervention, empagliflozin treatment or when administered in combination.

Table 9: Number of adverse events experienced by patients during the course of the study, overall and by treatment group

		Treatment group			
	Overall	Placebo	Placebo & Diet	Empagliflozin	Empagliflozin & Diet
	N = 68	N = 17	N = 17	N = 17	N = 17
Adverse events					
Yes	29 (42.6%)	8 (47.1%)	8 (47.1%)	6 (35.3%)	7 (41.2%)
No	39 (57.3%)	9 (52.9%)	9 (52.9%)	11 (64.7%)	10 (58.8%)
Number of adverse events					
1	6 (20.7%)	2 (25%)	2 (25%)	0 (0.0%)	2 (28.6%)
2	12 (41.4%)	3 (37.5%)	5 (62.5%)	3 (50%)	1 (14.3%)
3	6 (20.7%)	3 (37.5%)	0 (0.0%)	1 (16.7%)	2 (28.6%)
4	2 (6.9%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (14.3%)
5	2 (6.9%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (14.3%)
6	1 (3.4%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)

Table 10: Number of serious adverse events experienced by patients during the course of the study, overall and by treatment group

		Treatment group			
	Overall	Placebo	Placebo & diet	Empagliflozin	Empagliflozin & Diet
	N = 68	N = 17	N = 17	N = 17	N = 17
Serious adverse events					
Yes	2 (2.9%)	1 (5.9%)	1 (5.9%)	0 (0%)	0 (0%)
No	66 (97.1%)	16 (94.1%)	16 (94.1%)	17 (100%)	17 (100%)
Number of serious adverse events					
1	2 (100%)	1 (100%)	1 (100%)	0 (0.0%)	0 (0.0%)

Table 11: A full list of non-serious adverse events experienced by participants during the study, split by treatment group, and presented as SOC type.

System Organ Class	MedDRA preferred term	Placebo	Placebo & Diet	Empagliflozin	Empagliflozin & Diet	Total
Blood and lymphatic system disorders	Normocytic anaemia		1			1
Ear and labyrinth disorders	Vertigo Positional				1	1
Eye Disorders	Eyes swelling***				1	1
	lacrimation increased***				1	1
	Visual impairment			1		1
Gastrointestinal Disorders	Abdominal pain (localised)	1				1
	Diarrhoea	1	3 (3)			4
	Constipation		1			1
	Haemorrhoids		1			1
	Toothache	1				1
General Disorders and administration site conditions	Oedema peripheral	1				1
	Thirst				1	1
Infections and infestations	Cellulitis	1				1
	Cystitis				1	1
	Influenza	2 (2)		2 (2)		4
	Upper Respiratory Tract Infection	1		3(3)	3(2)	7
	Viral infection NOS			1		1
	Fibula Fracture			1		1
	Fall		1			1
	Fall (mechanical)	1				1
	Head Injury			1		1
	Muscle strain				1	1

	Splinter		1			1
	Thermal burn				1	1
Investigations	Haemoglobin decreased	1				1
Metabolism and Nutrition	Decreased appetite		1			1
	Gout			1		1
	Hypoglycaemia			1		1
	Iron deficiency				1	1
Musculoskeletal and connective tissue disease disorders	Arthralgia			1		1
	Joint swelling*				1	1
	Musculoskeletal pain	1				1
	Plantar fasciitis*				1	1
Nervous System Disorders	Dizziness	1				1
	Dizziness postural			1		1
	Headache			1		1
	Hypoaesthesia				1	1
	Paraesthesia		1			1
	Presyncope		2 (1)	1	1	4
Psychiatric Disorders	Insomnia		1			1
	Depressed mood		1			1
	Depression		1			1
Renal and urinary disorders	Haematuria		1			1
	Pollakiuria**			1		1
	Dysuria			1		1
	Micturition Urgency**			1		1
	Urinary tract infection	1				1
Respiratory, thoracic	Productive cough	1				1

and mediastinal disorders	Oropharyngeal pain	1				1
Skin and subcutaneous tissue disorders	Alopecia				2	2
	Dry skin				1	1
	Hyperhidrosis				1	1
	Rash	1			1	2
Vascular Disorders	Hypertension		1			1
Total		**16**	**17**	**18**	**20**	**71**

Data presented as frequency and (number of unique individuals within each treatment group).

*Both adverse events were reported by the same patient throughout the duration of the study. **Both adverse events were reported by the same patient on the same date). *** Both adverse events were reported by the same patient on the same date. The adverse events have different preferred terms in MedDRA which is the reason they are presented separately.

Table 12: A list of serious adverse events experienced by participants during the study, split by treatment group, and presented as SOC type.

System Organ Class	Adverse Event Description	Placebo	Placebo & Diet	Empagliflozin	Empagliflozin & Diet	Total
General disorders and administration site conditions	Pyrexia *	1				1
Respiratory, thoracic and mediastinal disorders	Exacerbation of Asthma		1			1

Data presented as frequency of serious adverse events

*pParticipant reported two hospital admissions for the investigation and treatment of pyrexia. Minimal information provided to the study team. Study clinician deemed the SAE to be unrelated to the intervention. Participant requested to be withdrawn from the study.

Supplementary Table 1: Study outcomes analysed using generalised estimating equations to assess overall treatment effect across all study visits

		Treatment Effect Compared With Placebo												
		Diet				Empagliflozin				Empagliflozin & Diet				
Outcome	N	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Coefficient	Lower CI	Upper CI	P-value	Overall p-value
PYY AUC	245	-1.02	-16.19	14.15	0.895	16.97	2.36	31.58	0.023	6.44	-7.98	20.85	0.381	0.067
Ghrelin AUC	244	34.24	2.18	66.30	0.036	-3.00	-33.95	27.94	0.849	-10.43	-41.07	20.20	0.504	**0.034**
GLP-1 AUC	245	1.25	-3.39	5.89	0.598	**5.52**	**1.04**	**10.01**	**0.016**	3.81	-0.61	8.22	0.091	0.070
RMR (kcal)	252	-49.69	-173.94	74.56	0.433	-79.84	-198.70	39.01	0.188	-119.60	-238.61	-0.59	0.049	0.250
Insulin AUC	245	-14.58	-28.77	-0.39	0.044	**-22.45**	**-36.48**	**-8.42**	**0.002**	-13.38	-26.85	0.10	0.052	**0.017**
Glucose AUC	251	-0.24	-0.95	0.46	0.499	**-1.37**	**-2.05**	**-0.69**	**<0.001**	**-1.64**	**-2.32**	**-0.96**	**<0.001**	**<0.001**
Glucagon AUC	245	-8.90	-20.50	2.70	0.133	1.31	-9.87	12.49	0.818	2.86	-8.14	13.86	0.610	0.196
C Peptide AUC	245	-488.74	-998.74	21.25	0.060	-82.59	-577.44	412.26	0.744	192.07	-292.20	676.33	0.437	0.065
Leptin (pg/mL)	245	-1129.60	-3896.22	1637.03	0.424	828.77	-1828.55	3486.09	0.541	-3279.38	-5883.61	-675.15	0.014	**0.013**
HbA1c (%)	245	-0.19	-0.40	0.02	0.074	**-0.30**	**-0.50**	**-0.10**	**0.003**	**-0.33**	**-0.53**	**-0.13**	**0.001**	**0.006**
C - Reactive Protein (mg/L)	244	0.70	-1.66	3.07	0.561	0.40	-1.83	2.64	0.723	1.07	-1.18	3.31	0.351	0.819
Fasting Glucose (mmol/L)	247	-0.10	-0.47	0.26	0.577	**-0.79**	**-1.15**	**-0.44**	**<0.001**	**-1.09**	**-1.44**	**-0.74**	**<0.001**	**<0.001**
Fasting Insulin (mU)	241	-0.20	-2.58	2.17	0.866	**-2.68**	**-4.93**	**-0.43**	**0.020**	**-2.54**	**-4.81**	**-0.28**	**0.028**	**0.026**
Total Cholesterol (mmol/L)	253	-0.10	-0.37	0.16	0.436	-0.03	-0.28	0.23	0.840	-0.18	-0.44	0.07	0.161	0.493
HDL Cholesterol (mmol/L)	253	0.08	-0.04	0.21	0.200	0.03	-0.10	0.16	0.606	0.08	-0.04	0.20	0.198	0.496
LDL Cholesterol (mmol/L)	248	-0.11	-0.32	0.10	0.284	0.00	-0.20	0.20	0.987	-0.05	-0.26	0.15	0.612	0.682
Fatty Free Acid (mmol/L)	101	-0.08	-0.20	0.04	0.182	-0.02	-0.14	0.09	0.706	0.04	-0.08	0.17	0.501	0.167
eGFR	255	1.05	-2.10	4.21	0.513	-0.97	-4.01	2.06	0.529	0.85	-2.17	3.86	0.582	0.572
Alanine Transaminase (iu/L)	251	-2.68	-6.61	1.25	0.181	-1.73	-5.57	2.11	0.377	-1.94	-5.70	1.82	0.311	0.575
Steps per day	178	238.10	-595.19	1071.38	0.575	-818.23	-1592.84	-43.62	0.038	98.23	-679.01	875.47	0.804	**0.046**
Sedentary (min/d)	178	-1.02	-33.35	31.31	0.950	-0.65	-30.72	29.43	0.966	-3.32	-33.35	26.70	0.828	0.997
Light activity (min/d)	178	-1.46	-29.67	26.74	0.919	2.96	-23.36	29.28	0.825	0.13	-26.07	26.33	0.992	0.992
MVPA (min/d)	178	2.28	-6.83	11.39	0.624	-3.66	-12.19	4.88	0.401	3.22	-5.26	11.69	0.457	0.426
TFEQ - Cognitive Restraint	260	**3.21**	**0.42**	**6.00**	**0.024**	0.54	-2.17	3.24	0.698	**3.41**	**0.69**	**6.13**	**0.014**	**0.022**
TFEQ - Disinhibition	260	-0.51	-1.96	0.94	0.491	-0.39	-1.78	0.99	0.578	-0.35	-1.71	1.02	0.616	0.908
TFEQ - Hunger	260	-0.24	-1.54	1.05	0.712	-0.46	-1.73	0.81	0.477	-0.80	-2.03	0.43	0.203	0.626

Hunger AUC	250	-0.12	-9.23	9.00	0.980	2.30	-6.61	11.21	0.613	1.70	-6.98	10.37	0.701	0.939
Fullness AUC	254	0.84	-11.04	12.72	0.890	5.20	-6.08	16.48	0.366	-2.14	-13.43	9.15	0.710	0.633
Satisfaction AUC	254	2.76	-9.17	14.69	0.650	9.90	-1.57	21.37	0.091	-3.33	-14.74	8.08	0.567	0.138
PFC AUC	254	1.19	-9.05	11.43	0.820	-1.08	-10.64	8.48	0.825	2.13	-7.45	11.71	0.663	0.929
Weight (kg)	257	-1.89	-3.55	-0.23	0.026	-1.63	-3.25	-0.02	0.048	**-3.78**	**-5.39**	**-2.18**	**<0.001**	**<0.001**
Body fat %	252	-1.27	-2.56	0.03	0.055	-0.77	-2.00	0.46	0.222	-0.91	-2.13	0.31	0.142	0.250
Waist Circumference (cm)	257	-1.47	-3.86	0.93	0.231	**-2.79**	**-5.10**	**-0.48**	**0.018**	**-2.98**	**-5.31**	**-0.64**	**0.012**	**0.044**
Hip Circumference (cm)	255	-2.02	-4.43	0.39	0.100	-1.55	-3.87	0.77	0.191	-2.71	-5.03	-0.39	0.022	0.131
SBP (mmHg)	257	4.50	0.64	8.37	0.022	-4.11	-7.82	-0.41	0.029	-2.52	-6.21	1.17	0.181	**<0.001**
DBP (mmHg)	257	1.08	-2.10	4.26	0.506	-2.83	-5.88	0.23	0.070	-0.08	-3.14	2.98	0.960	0.088
Heart Rate (bpm)	257	0.19	-3.57	3.94	0.923	2.67	-0.96	6.30	0.150	-0.01	-3.65	3.63	0.997	0.394

Green highlights indicate statistical significance with Holm's sequential Bonferroni procedures applied to individual treatment (vs placebo) post-hoc effects. AUC indicates time-averaged responses over a 3 h meal-tolerance test.

Supplementary Table 2: Details of each adverse event experienced, including frequency of event, outcome, current treatment, severity and relation to the IMP/Placebo

Trial ID	MedDRA Preferred Term (PT)	Treatment Group	Frequency	Outcome	Treatment	Severity	IMP Action	Related to IMP/Placebo	Related to diet	Serious	Expected
018	Haemoglobin decreased	Placebo	Continuous	Continuing	None	Mild	None	Unlikely	Not related	No	No
018	Oedema peripheral	Placebo	Intermittent	Continuing	None	Mild	None	Possible	Not related	No	No
018	Dizziness	Placebo	Intermittent	Continuing	None	Mild	None	Unlikely	Not related	No	No
026	Dry skin	Empagliflozin and diet	Continuous	Resolved	Conc. Medication	Mild	None	Possible	Not related	No	No
026	Plantar fasciitis	Empagliflozin and diet	Intermittent	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
026	Joint swelling	Empagliflozin and diet	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
027	Upper respiratory tract infection	Empagliflozin and diet	Single	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
027	Upper respiratory tract infection	Empagliflozin and diet	Single	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
027	Alopecia	Empagliflozin and diet	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Unlikely	No	No

027	Iron Deficiency	Empagliflozin and diet	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
027	Alopecia	Empagliflozin and diet	Single	Resolved	None	Mild	None	Not related	Not related	No	No
028	Diarrhoea	Placebo and diet	Single	Resolved	None	Severe	Study interrupted	Unlikely	Possible	No	No
028	Musculoskeletal pain	Placebo and diet	Single	Continuing	None	Moderate	None	Not related	Not related	No	No
029	Constipation	Placebo and diet	Single	Resolved	Conc. Medication	Moderate	None	Possible	Not related	No	Yes
029	Haemorrhoids	Placebo and diet	Single	Resolved	Conc. Medication	Mild	None	Possible	Not related	No	No
031	Arthralgia	Empagliflozin	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
031	Upper respiratory tract infection	Empagliflozin	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
032	Dizziness postural	Empagliflozin	Intermittent	Resolved	None	Mild	None	Possible	Not related	No	No
032	Influenza	Empagliflozin	Single	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No
032	Hypoglycaemia	Empagliflozin	Intermittent	Resolved	None	Mild	None	Possible	Not related	No	No

034	Diarrhoea	Placebo and diet	Continuous	Resolved	None	Mild	None	Unlikely	Not related	No	No
034	Normocytic anaemia	Placebo and diet	Single	Continuing	None	Mild	None	Not related	Unlikely	No	No
036	Haematuria	Placebo and diet	Continuous	Continuing	None	Mild	None	Possible	Not related	No	No
036	Depression	Placebo and diet	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
036	Decreased appetite	Placebo and diet	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
036	Insomnia	Placebo and diet	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
036	Exacerbation of asthma	Placebo and diet	Continuous	Resolved	Conc. Medication	Severe	None	Not related	Not related	Yes	No
036	Paraesthesia	Placebo and diet	Continuous	Continuing	None	Mild	None	Unlikely	Not related	No	No
038	Fall	Placebo	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
038	Diarrhoea	Placebo	Single	Resolved	None	Mild	None	Unlikely	Possible	No	No
038	Cellulitis	Placebo	Single	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No
039	Cystitis	Empagliflozin and diet	Single	Resolved	Conc. Medication	Mild	None	Probable	Not related	No	Yes

044	Thermal burn	Empagliflozin and diet	Single	Continuing	Non-drug therapy	Mild	None	Not related	Not related	No	No
044	Presyncope	Empagliflozin and diet	Single	Resolved	None	Moderate	None	Not related	Not related	No	No
044	Muscle strain	Empagliflozin and diet	Continuous	Resolved	Conc. Medication	Moderate	None	Not related	Not related	No	No
048	Gout	Empagliflozin	Single	Resolved	Conc. Medication	Mild	None	Unlikely	Not related	No	No
048	Dysuria	Empagliflozin	Intermittent	Continuing	None	Mild	None	Possible	Not related	No	Yes
049	Rash	Placebo	Continuous	Continuing	Conc. Medication	Mild	None	-7	-7	-7	-7
050	Vertigo Positional	Empagliflozin and diet	Single	Resolved	None	Mild	None	Not related	Not related	No	No
050	Thirst	Empagliflozin and diet	Continuous	Continuing	None	Mild	None	Probable	Not related	No	No
050	Hyperhidrosis	Empagliflozin and diet	Intermittent	Continuing	None	Mild	None	Possible	Not related	No	No
050	Hypoaesthesia	Empagliflozin and diet	Continuous	Continuing	None	Mild	None	Unlikely	Not related	No	No
053	Upper respiratory tract infection	Placebo	Single	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No

053	Abdominal pain	Placebo	Single	Resolved	Non-drug therapy	Moderate	None	Not related	Not related	No	No
053	Urinary tract infection	Placebo	Single	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No
054	Presyncope	Placebo and diet	Single	Resolved	None	Moderate	None	Not related	Not related	No	No
054	Presyncope	Placebo and diet	Single	Resolved	None	Mild	None	Not related	Not related	No	No
055	Influenza	Placebo	Single	Resolved	None	Severe	None	Not related	Not related	No	No
057	Oropharyngeal pain	Placebo	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
057	Toothache	Placebo	Intermittent	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No
058	Eye Swelling	Empagliflozin and diet	Single	Resolved	None	Mild	None	Unlikely	Not related	No	No
058	Lacrimation increased	Empagliflozin and diet	Single	Resolved	None	Mild	None	Unlikely	Not related	No	No
058	Rash	Empagliflozin and diet	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
063	Splinter	Placebo and diet	Single	Resolved	None	Mild	None	Not related	Not related	No	No
064	Influenza	Empagliflozin	Single	Resolved	None	Mild	None	Not related	Not	No	No

									related		
064	Visual impairment	Empagliflozin	Single	Continuing	None	Mild	None	Possible	Not related	No	No
064	Pollakiuria	Empagliflozin	Continuous	Continuing	None	Moderate	None	Definite	Not related	No	Yes
064	Micturition urgency	Empagliflozin	Continuous	Continuing	None	Moderate	None	Definite	Not related	No	Yes
064	Fibula fracture	Empagliflozin	Single	Continuing	Conc. Medication	Moderate	None	Not related	Not related	No	No
065	Head injury	Empagliflozin	Single	Resolved-sequelae	None	Mild	None	Not related	Not related	No	No
065	Presyncope	Empagliflozin	Single	Resolved	None	Moderate	None	Not related	Not related	No	No
065	Headache	Empagliflozin	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
065	Influenza	Empagliflozin	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
067	Influenza	Placebo	Continuous	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No
067	Productive Cough	Placebo	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
068	Viral infection NOS	Empagliflozin	Single	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No

068	Upper respiratory tract infect	Empagliflozin	Single	Resolved	Conc. Medication	Mild	None	Not related	Not related	No	No
071	Diarrhoea	Placebo and diet	Single	Resolved	Conc. Medication	Severe	None	Unlikely	Not related	No	No
071	Depressed mood	Placebo and diet	Continuous	Continuing	None	Mild	None	Not related	Not related	No	No
075	Musculoskeletal pain	Placebo	Continuous	Continuing	Conc. Medication	Moderate	None	Not related	Not related	No	No
075	Pyrexia	Placebo	Single	Resolved	Non-drug therapy	Severe	Study discontinued	Not related	Not related	Yes	No
076	Hypertension	Placebo and diet	Continuous	Continuing	Conc. Medication	Mild	None	Not related	Not related	No	No
079	Upper respiratory tract infection	Empagliflozin and diet	Single	Resolved	None	Mild	None	Not related	Not related	No	No