Supplementary Table 1. Effect of Small Doses (5g, 10g) of Fructose on Secondary and Exploratory Outcome Measures

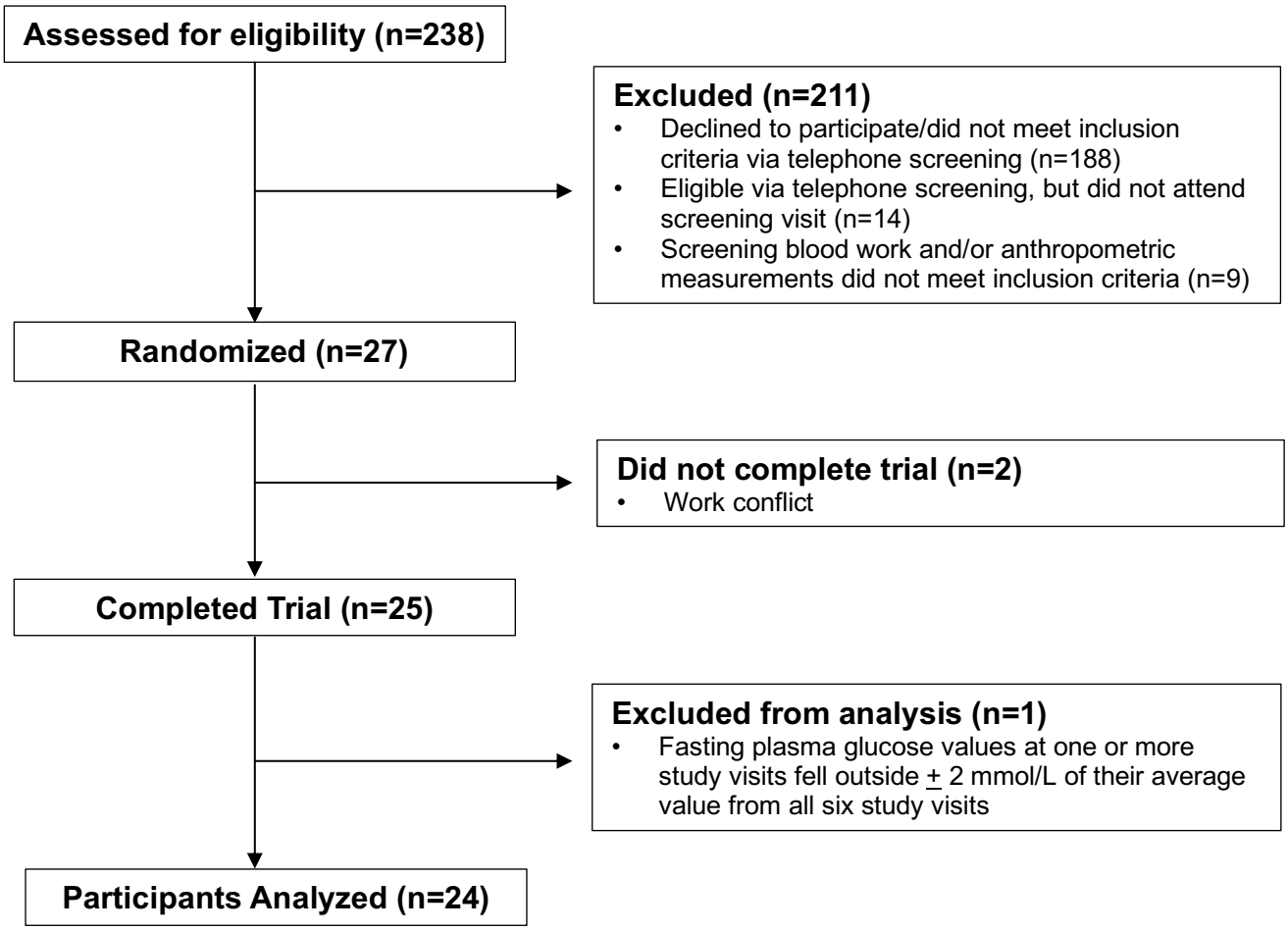
Outcome Measures	75g-OGTT 0g fructose (control)	75g-OGTT + 5g fructose	75g-OGTT + 10g fructose	5g vs. control, contrast (SE)	10g vs. control, contrast (SE)	5g vs. control, p-value†	10g vs. control, p-value†
Secondary							
Absolute C_{max} PG (mmol/L)	17.5 ± 0.6	17.3 ± 0.7	17.4 ± 0.7	-0.2 (0.4)	-0.1 (0.4)	0.651	0.747
T_{max} PG (mins)	88.8 ± 4.0	91.3 ± 3.8	90.0 ± 4.8	2.5 (3.1)	1.3 (3.1)	0.424	0.689
Incremental PG (mmol/L)	6.0 ± 0.3	5.9 ± 0.3	5.9 ± 0.3	0.0 (0.2)	-0.1 (0.2)	0.887	0.773
iAUC PI (pmol·min/L)	38405 ± 6917	39963 ± 7285	39345 ± 6353	1557.7 (1921.8)	940.2 (1921.8)	0.542	0.195
Absolute C_{max} PI (pmol/L)	649.0 ± 126.2	655.2 ± 117.7	624.9 ± 95.5	6.2 (41.6)	-24.1 (41.6)	0.602	0.484
T_{max} PI (mins)	93.8 ± 5.3	88.8 ± 5.8	91.3 ± 5.6	-5.0 (5.2)	-2.5 (5.2)	0.332	0.628
Incremental PI (pmol/L)	302.1 ± 57.1	312.4 ± 58.6	307.4 ± 50.6	10.3 (16.2)	5.3 (16.2)	0.519	0.182
$\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$*	50.1 ± 8.5	40.9 ± 6.2	44.4 ± 6.5	-9.2 (3.6)	-5.7 (3.6)	0.060	0.750
Matsuda ISI_{OGTT}	2.9 ± 0.4	2.8 ± 0.4	2.8 ± 0.5	-0.1 (0.2)	-0.1 (0.2)	0.278	0.294
Exploratory							
Total AUC PG (mmol·min/L)	1694.1 ± 57.8	1692.9 ± 63.5	1667.1 ± 62.6	-1.1 (28.9)	-27.0 (28.9)	0.968	0.350
Incremental C_{max} PG (mmol/L)	9.8 ± 0.5	9.7 ± 0.5	9.9 ± 0.6	-0.1 (0.3)	0.0 (0.3)	0.699	0.931
Absolute mean PG (mmol/L)	13.6 ± 0.5	13.6 ± 0.5	13.4 ± 0.5	-0.1 (0.2)	-0.2 (0.2)	0.807	0.364
Total AUC PI (pmol·min/L)	47934 ± 7537	49883 ± 8112	49115 ± 7046	1948.9 (2027.6)	1181.4 (2027.6)	0.379	0.113
Incremental C_{max} PI (pmol/L)	569.6 ± 122.9	572.5 ± 112.3	543.5 ± 90.7	3.0 (41.4)	-26.1 (41.4)	0.711	0.549
Absolute mean PI (pmol/L)	381.5 ± 61.9	395.1 ± 65.2	388.8 ± 56.2	13.6 (17.0)	7.3 (17.0)	0.376	0.113
ISSI-2	188.9 ± 25.3	182.8 ± 20.4	194.6 ± 24.6	-6.1 (12.0)	5.7 (12.0)	0.895	0.447

Data reported as mean ± SEM. Mean ± SEM and p-values are reported for n=24. *For $\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$, descriptive statistics are reported for n=23 due to one participant visit value being negative which generated a missing value when log-transformed. A linear mixed effect model was used to assess the differences in all outcome measures with unstructured covariance for repeated measures within subjects. P-values <0.0125 are significant. †P-values for iAUC and total AUC PI, absolute and incremental C_{max} PI, absolute and incremental mean PI, $\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$, Matsuda ISI_{OGTT} and ISSI-2 correspond to log-transformed data due to non-normal distributions of residuals. PG, plasma glucose; PI, plasma insulin; iAUC, incremental area under the curve; C_{max}, maximum concentration; T_{max}, time of maximum concentration; $\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$, early insulin secretion index; Matsuda ISI_{OGTT}, Matsuda whole body insulin sensitivity index; AUC, area under the curve; ISSI-2, insulin secretion-sensitivity index-2.

Supplementary Table 2: Effect of Small Doses (5g, 10g) of Allulose on Secondary and Exploratory Outcome Measures

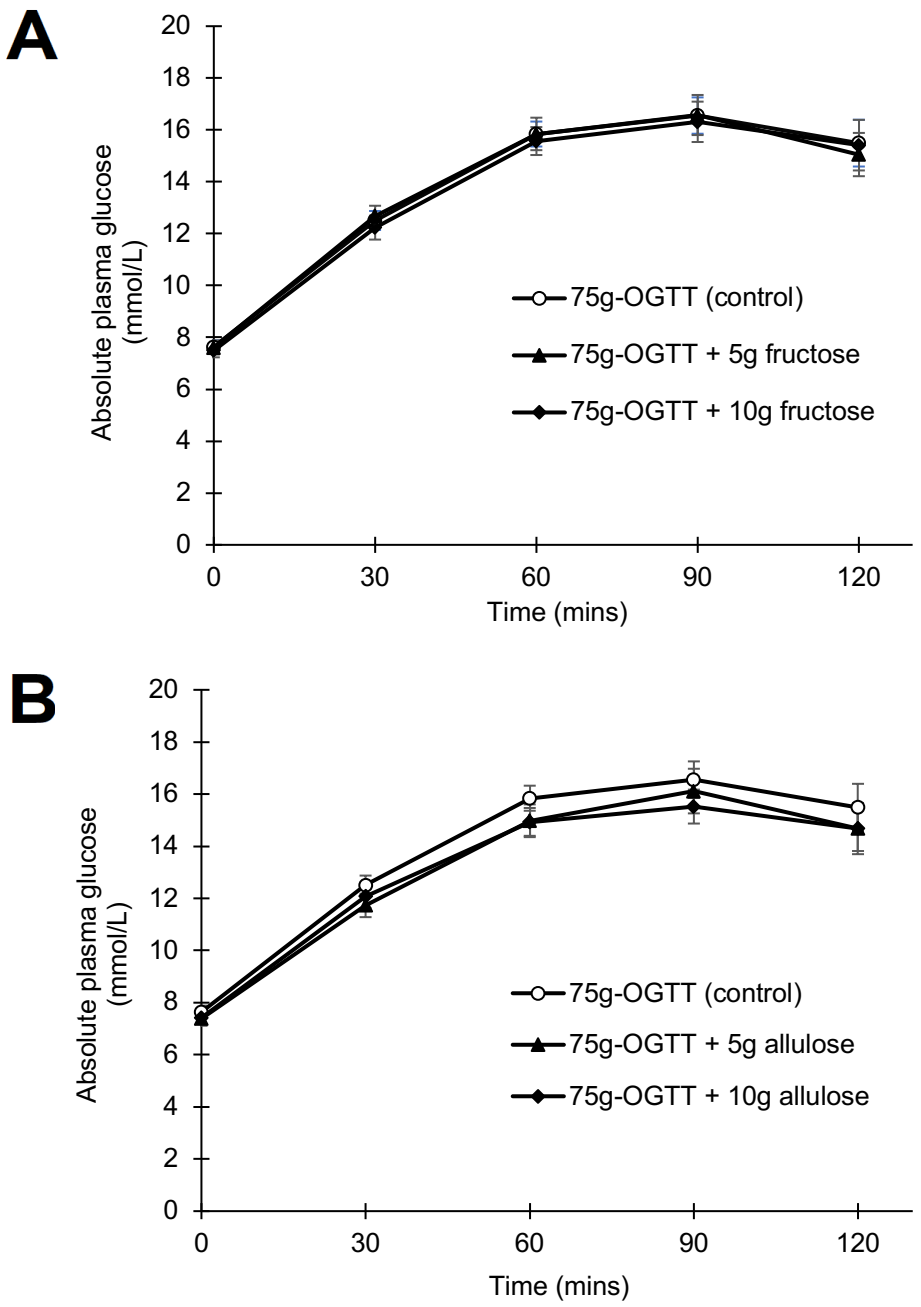
Outcome Measures	75g-OGTT + 0g allulose (control)	75g-OGTT + 5g allulose	75g-OGTT + 10g allulose	5g vs. control, contrast (SE)	10g vs. control, contrast (SE)	5g vs. control, p-value†	10g vs. control, p-value†
Secondary							
Absolute C_{max} PG (mmol/L)	17.5 ± 0.6	16.9 ± 0.8	16.1 ± 0.7	-0.6 (0.3)	-1.3 (0.3)	0.062	<0.001*
T_{max} PG (mins)	88.8 ± 4.0	91.3 ± 4.9	87.5 ± 6.5	2.5 (4.6)	-1.3 (4.6)	0.586	0.785
Incremental PG (mmol/L)	6.0 ± 0.3	5.6 ± 0.4	5.5 ± 0.3	-0.4 (0.2)	-0.5 (0.2)	0.041	0.013
iAUC PI (pmol·min/L)	38405 ± 6917	38054 ± 6599	34065 ± 5292	-350.9 (2256.7)	-4340.2 (2256.7)	0.962	0.151
Absolute C_{max} PI (pmol/L)	649.0 ± 126.2	595.1 ± 96.4	531.6 ± 77.3	-53.9 (45.7)	-117.4 (45.7)	0.269	0.015
T_{max} PI (mins)	93.8 ± 5.3	92.5 ± 4.7	88.8 ± 6.4	-1.3 (4.8)	-5.0 (4.8)	0.796	0.301
Incremental PI (pmol/L)	302.1 ± 57.1	295.6 ± 51.8	268.2 ± 42.6	-6.5 (17.2)	-33.8 (17.2)	0.924	0.194
$\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$	49.3 ± 8.2	47.5 ± 7.5	43.7 ± 6.3	-1.8 (5.0)	-5.6 (5.0)	0.897	0.685
Matsuda ISI_{OGTT}	2.9 ± 0.4	3.1 ± 0.6	3.2 ± 0.6	0.2 (0.2)	0.3 (0.2)	0.562	0.063
Exploratory							
Total AUC PG (mmol·min/L)	1694.1 ± 57.8	1615.7 ± 67.6	1607.7 ± 59.3	-78.4 (26.7)	-86.4 (26.7)	0.003*	0.001*
Incremental C_{max} PG (mmol/L)	9.8 ± 0.5	9.5 ± 0.6	8.7 ± 0.5	-0.3 (0.3)	-1.1 (0.3)	0.287	<0.001*
Absolute mean PG (mmol/L)	13.6 ± 0.5	13.0 ± 0.6	12.9 ± 0.5	-0.6 (0.2)	-0.7 (0.2)	0.002*	0.001*
Total AUC PI (pmol·min/L)	47934 ± 7537	47727 ± 7213	42957 ± 5739	-206.7 (2349.9)	-4976.4 (2349.9)	0.997	0.063
Incremental C_{max} PI (pmol/L)	569.6 ± 122.9	514.5 ± 92.4	457.5 ± 74.6	-55.1 (46.2)	-112.1 (46.2)	0.271	0.037
Absolute mean PI (pmol/L)	381.5 ± 61.9	376.2 ± 56.7	342.3 ± 46.2	-5.3 (18.2)	-39.1 (18.2)	0.949	0.073
ISSI-2	188.9 ± 25.3	206.4 ± 26.1	200.9 ± 24.8	17.5 (10.9)	12.0 (10.9)	0.062	0.091

Data reported as mean ± SEM. Mean ± SEM and p-values are reported for n=24. A linear mixed effect model was used to assess the differences in all outcome measures with unstructured covariance for repeated measures within subjects. *P-values <0.0125 are significant. †P-values for iAUC and total AUC PI, absolute and incremental C_{max} PI, absolute and incremental mean PI, $\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$, Matsuda ISI_{OGTT} and ISSI-2 correspond to log-transformed data due to non-normal distributions of residuals. PG, plasma glucose; PI, plasma insulin; iAUC, incremental area under the curve; C_{max}, maximum concentration; T_{max}, time of maximum concentration; $\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$, early insulin secretion index; Matsuda ISI_{OGTT}, Matsuda whole body insulin sensitivity index; AUC, area under the curve; ISSI-2, insulin secretion-sensitivity index-2; MD, mean difference; SE, standard error.

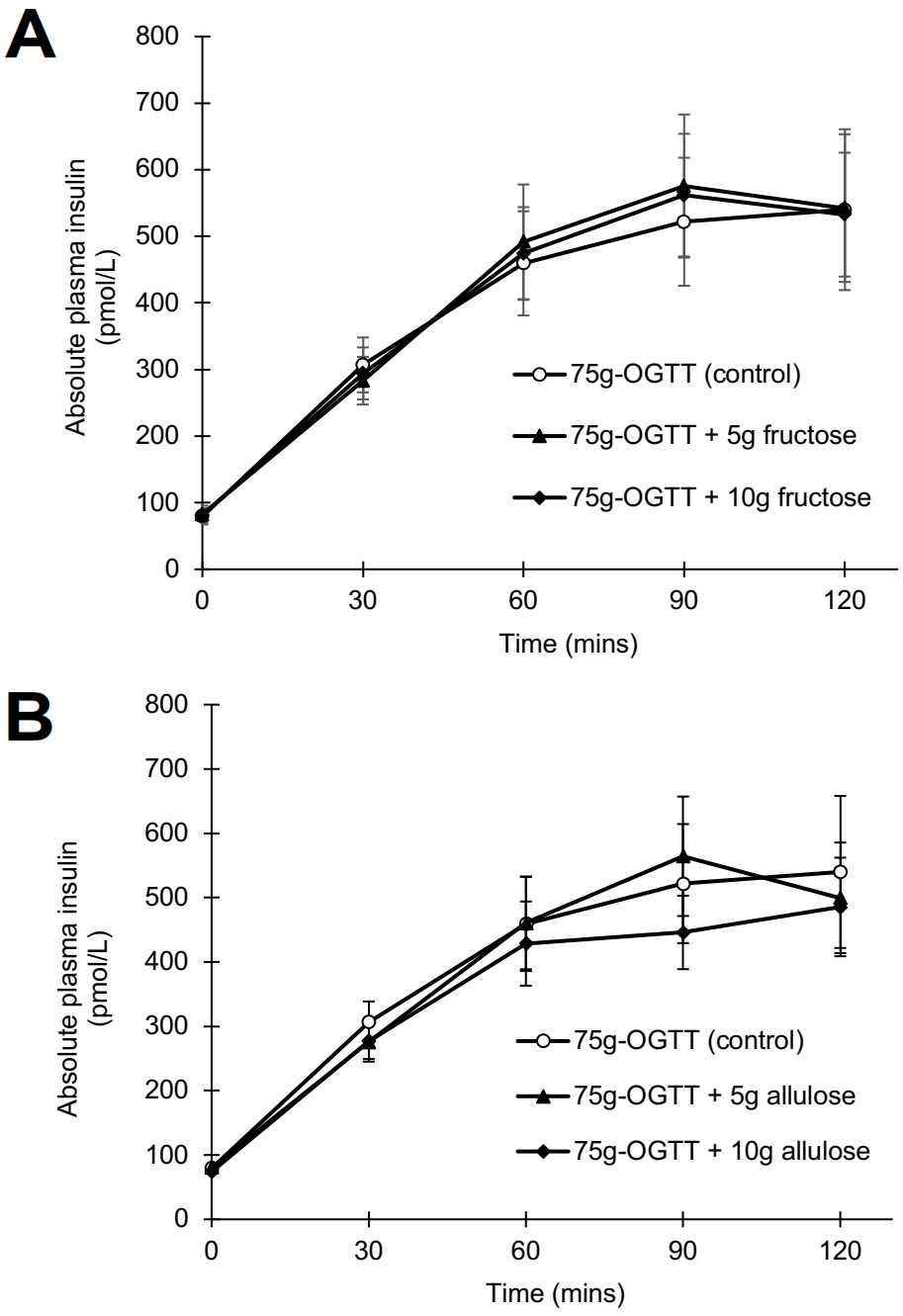


Recruitment period: November 2015 – July 2016
First participant to start trial: 8-March-2016
Last participant to finish trial: 18-August-2016

Supplemental Figure 1. CONSORT Flow of Participants Diagram

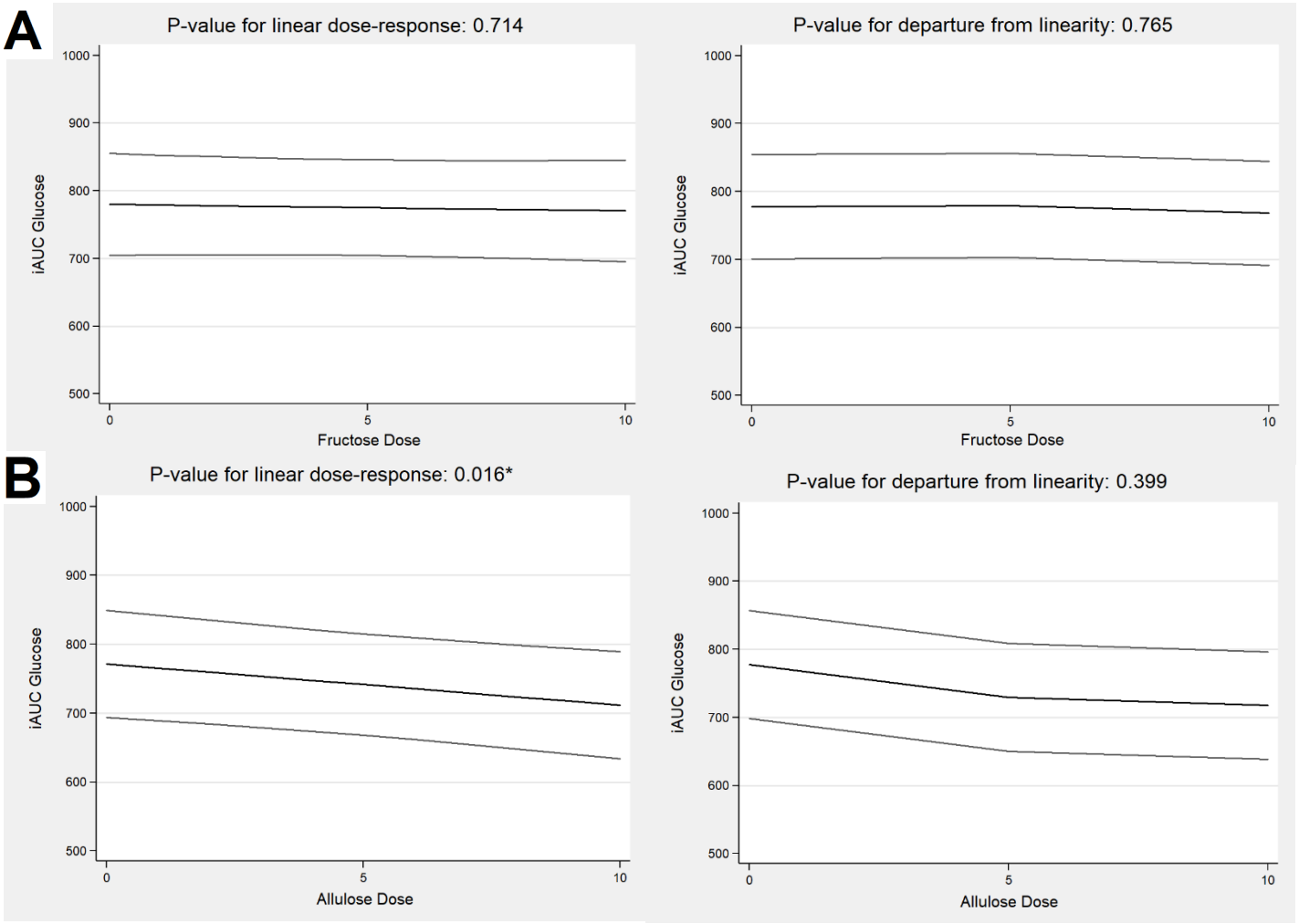


Supplementary Figure 2. A) Effect of small doses of fructose on absolute plasma glucose following consumption of 75g-OGTT + 0g fructose (control), 75g-OGTT + 5g fructose and 75g-OGTT + 10g fructose in 24 participants with type 2 diabetes. Mean fasting glucose concentrations were similar prior to consumption of 75g-OGTT (control), 75g-OGTT + 5g fructose and 75g-OGTT + 10g fructose at 7.64±0.25, 7.61±0.27 and 7.49±0.26 mmol/L, respectively ($p>0.05$, linear mixed-effects models). **B)** Effect of small doses of allulose on absolute plasma glucose following consumption of 75g-OGTT + 0g allulose (control), 75g-OGTT + 5g allulose and 75g-OGTT + 10g allulose in 24 participants with type 2 diabetes. Mean fasting glucose concentrations were similar prior to consumption of 75g-OGTT (control), 75g-OGTT + 5g allulose and 75g-OGTT + 10g allulose at 7.64±0.25, 7.39±0.27 and 7.42±0.29 mmol/L, respectively ($p>0.05$, linear mixed-effects models). *represents a statistically significant difference ($p<0.05$, linear mixed-effects models) compared with control (0g). Data reported as mean ± SEM.

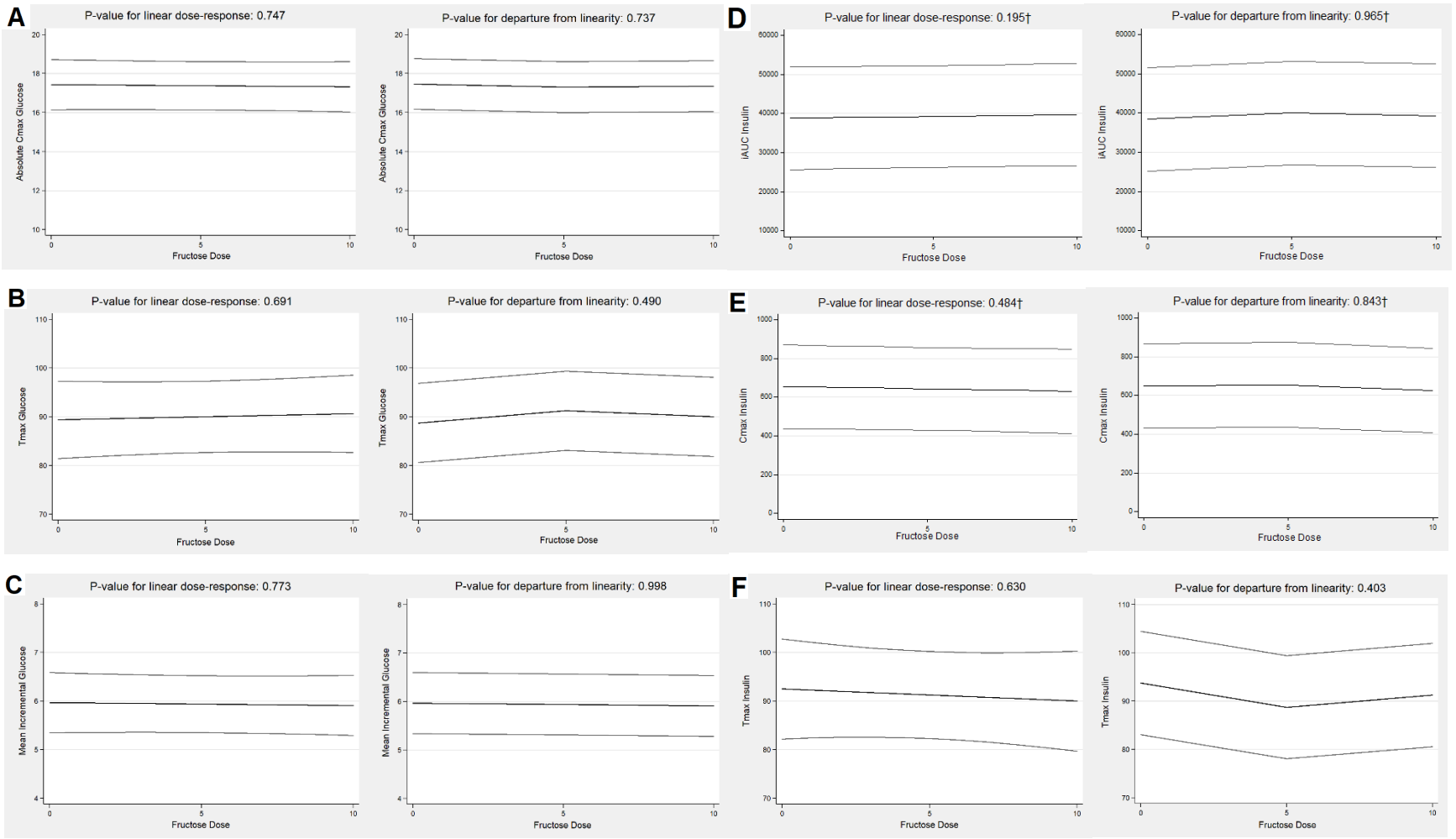


Supplementary Figure 3. A) Effect of small doses of fructose on absolute plasma insulin following consumption of 75g-OGTT+ 0g fructose (control), 75g-OGTT + 5g fructose and 75g-OGTT + 10g fructose in 24 participants with type 2 diabetes. Mean fasting insulin concentrations were similar prior to consumption of 75g-OGTT + 0g fructose (control), 75g-OGTT + 5g fructose and 75g-OGTT + 10g fructose at 79.4±12.1, 82.7±12.9 and 81.4±10.0 pmol/L, respectively ($p>0.05$, linear mixed-effects models). **B)** Effect of small doses of allulose on absolute plasma insulin following consumption of 75g-OGTT + 0g allulose (control), 75g-OGTT + 5g allulose and 75g-OGTT + 10g allulose in 24 participants with type 2 diabetes. Mean fasting insulin concentrations were similar prior to consumption of 75g-OGTT + 0g allulose (control), 75g-OGTT + 5g allulose and 75g-OGTT + 10g allulose at 79.4±12.1, 80.6±11.9 and 74.1±8.7, respectively ($p>0.05$, linear mixed-effects models). *represents a statistically

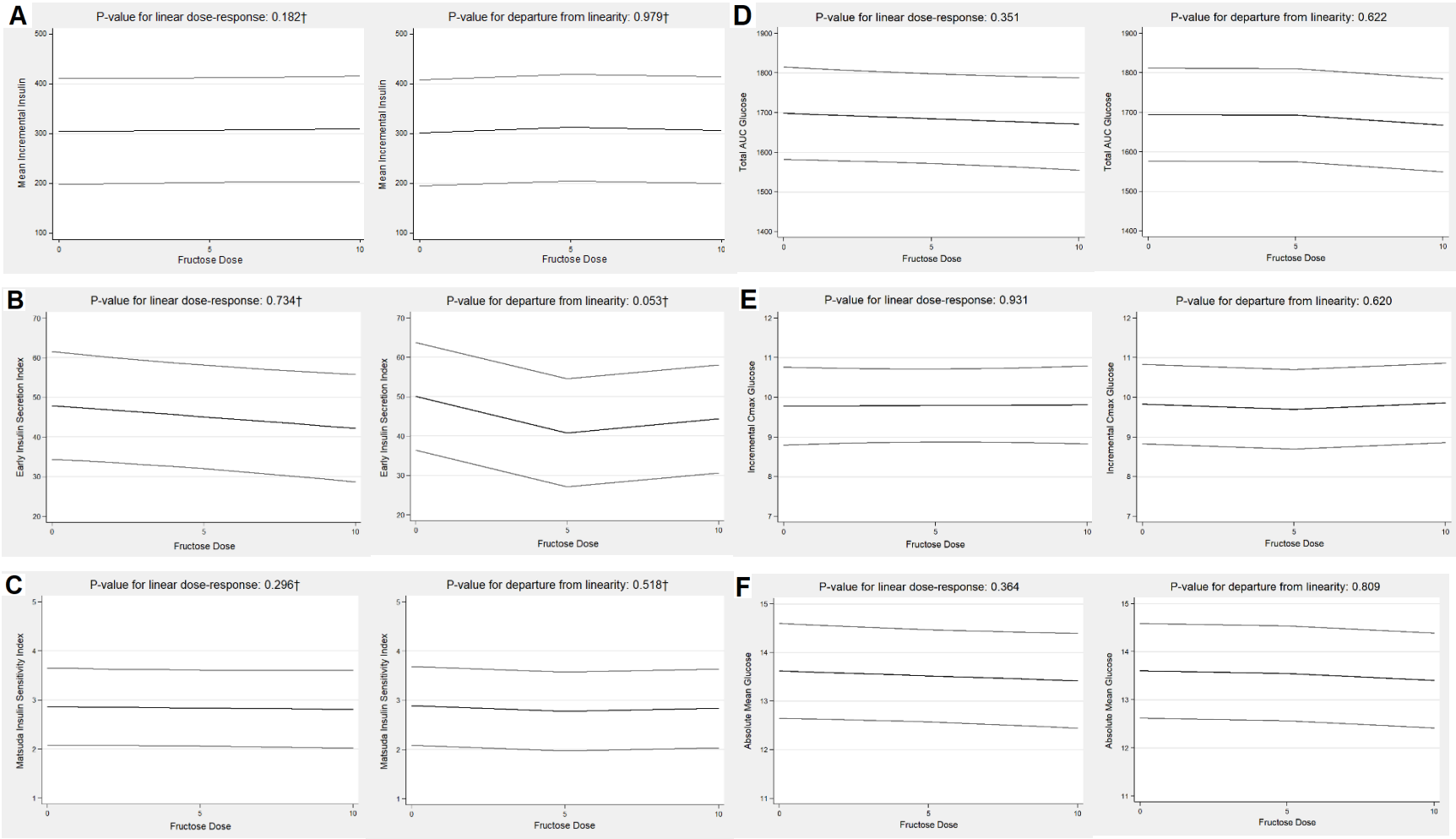
significant difference ($p<0.0125$, linear mixed-effects models) compared with control (0g). p-values correspond to log-transformed data due to non-normal distribution of residuals. Data reported as mean $\pm$ SEM.



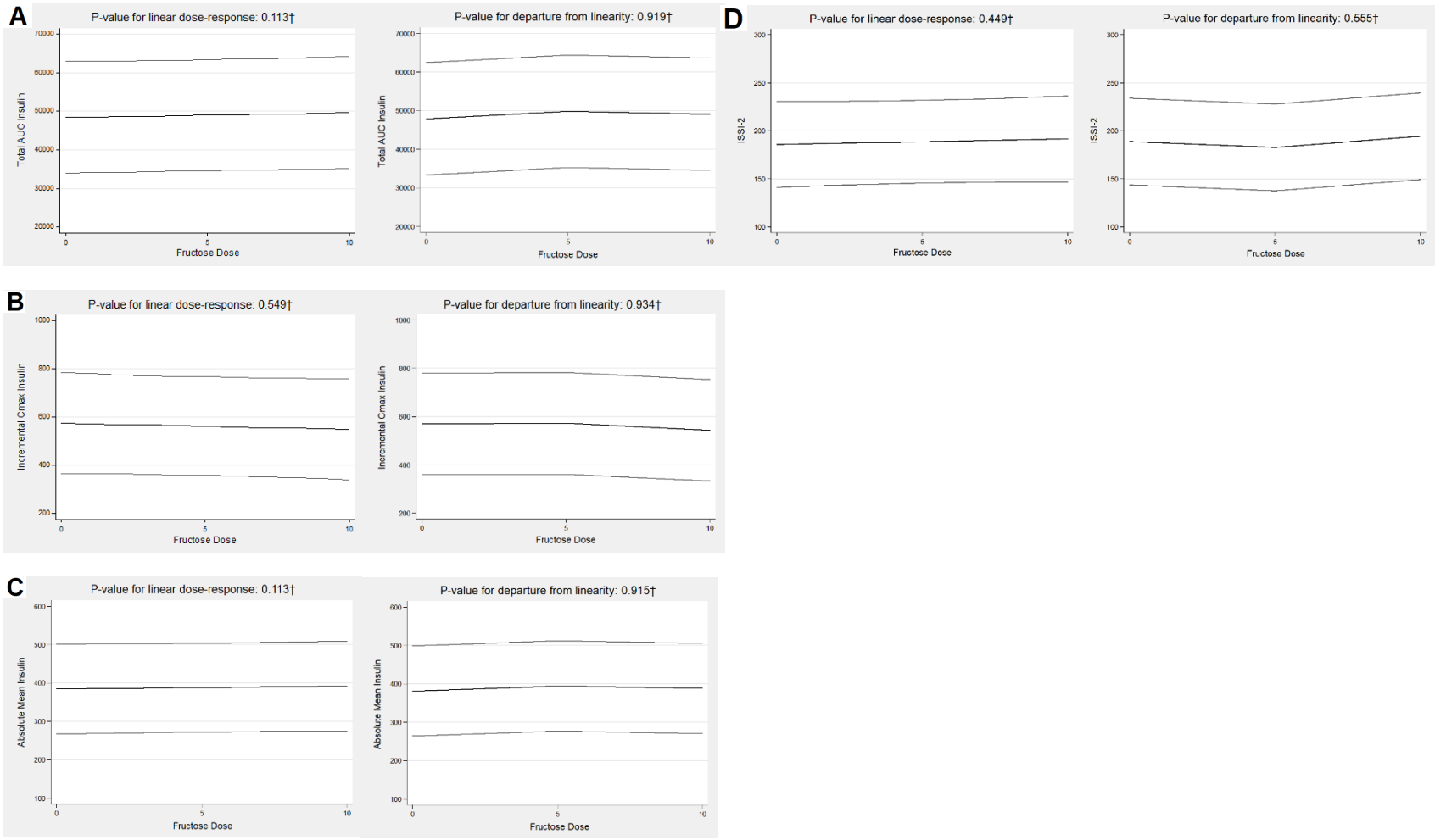
Supplemental Figure 4. A) Linear (left) and non-linear dose-response (right) analysis of the effect of small doses of fructose on plasma glucose iAUC. **B)** Linear (left) and non-linear (right) dose-response analysis of the effect of small doses of allulose on plasma glucose iAUC. In the linear dose-response graphs, the middle black line represents the predicted linear trend, while the two grey lines represent the 95% CIs. In the non-linear dose-response graphs, the middle black line represents the mean, while the two grey lines represent the 95% CIs. *P<0.05 indicates a significant dose-response relationship.



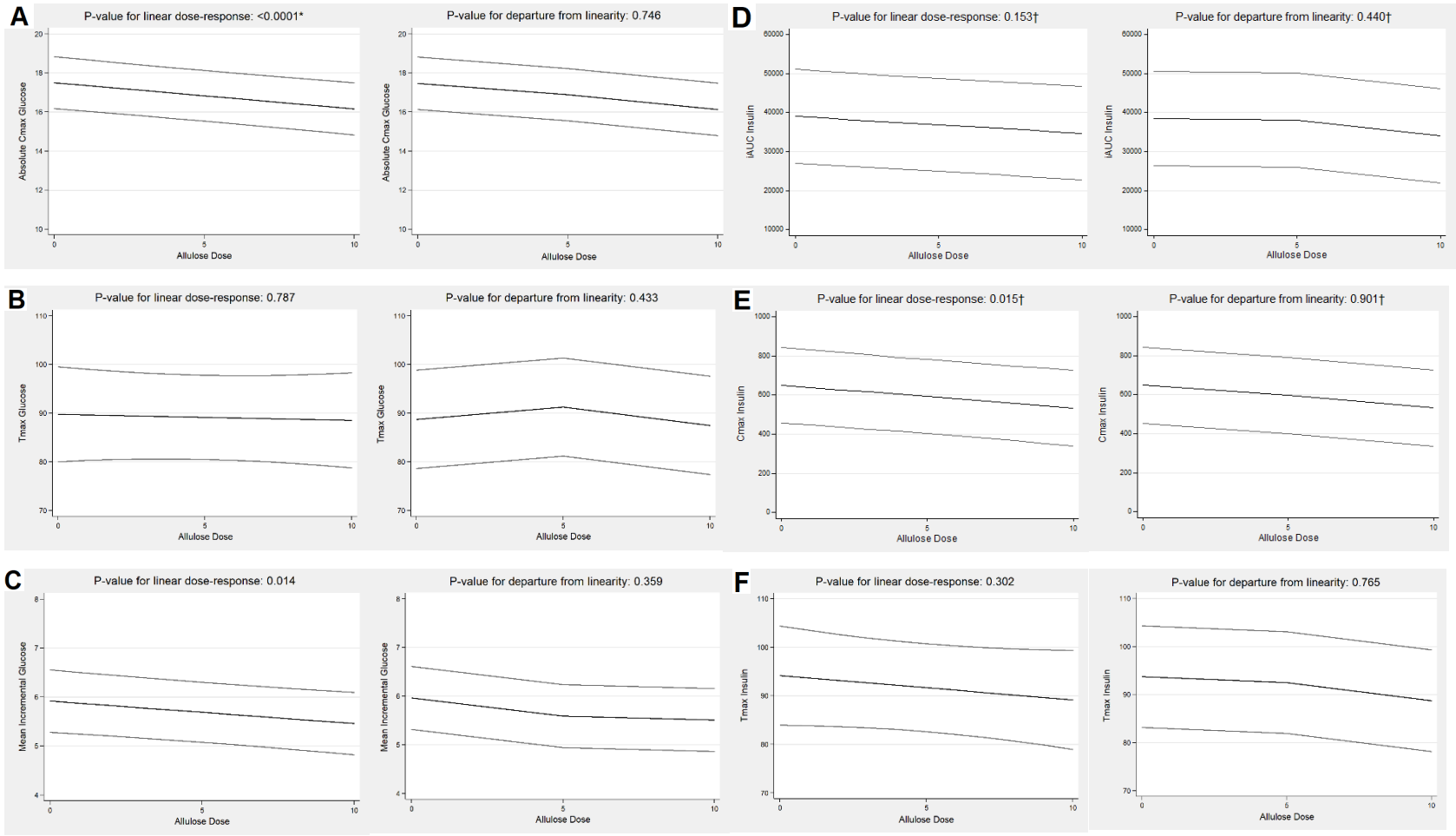
Supplementary Figure 5. Linear (left) and non-linear (right) dose-response analysis of the effect of small doses of fructose on absolute C_{max} glucose (A), T_{max} glucose (B), mean incremental glucose (C), insulin iAUC (D), absolute C_{max} insulin (E) and T_{max} insulin (F). In the linear dose-response graphs, the middle black line represents the predicted linear trend, while the two grey lines represent the 95% CIs. In the non-linear dose-response graphs, the middle black line represents the mean, while the two grey lines represent the 95% CIs. *P<0.0125 indicates a significant dose-response relationship. †p-values correspond to log-transformed data due to non-normal distribution of residuals.



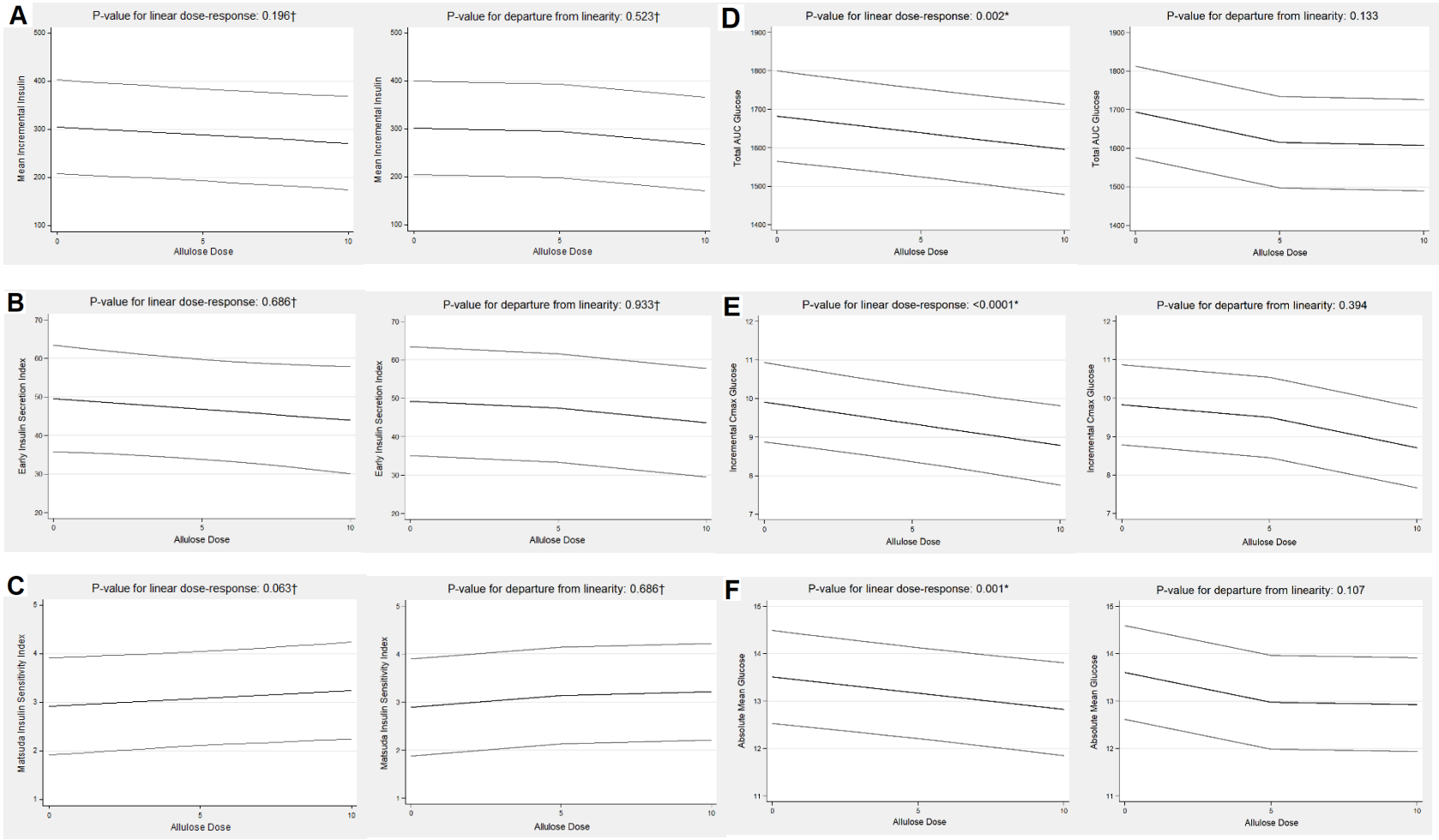
Supplementary Figure 6. Linear (left) and non-linear (right) dose-response analysis of the effect of small doses of fructose on mean incremental insulin (A), Early Insulin Secretion Index ($\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$) (B), Matsuda Insulin Sensitivity Index$_{OGTT}$ (C), total AUC glucose (D), incremental C_{max} glucose (E) and absolute mean glucose (F). For $\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$, figures were generated using data from 23 participants due to one participant visit value being negative which generated a missing value when log-transformed. In the linear dose-response graphs, the middle black line represents the predicted linear trend, while the two grey lines represent the 95% CIs. In the non-linear dose-response graphs, the middle black line represents the mean, while the two grey lines represent the 95% CIs. *P<0.0125 indicates a significant dose-response relationship. †p-values correspond to log-transformed data due to non-normal distribution of residuals.



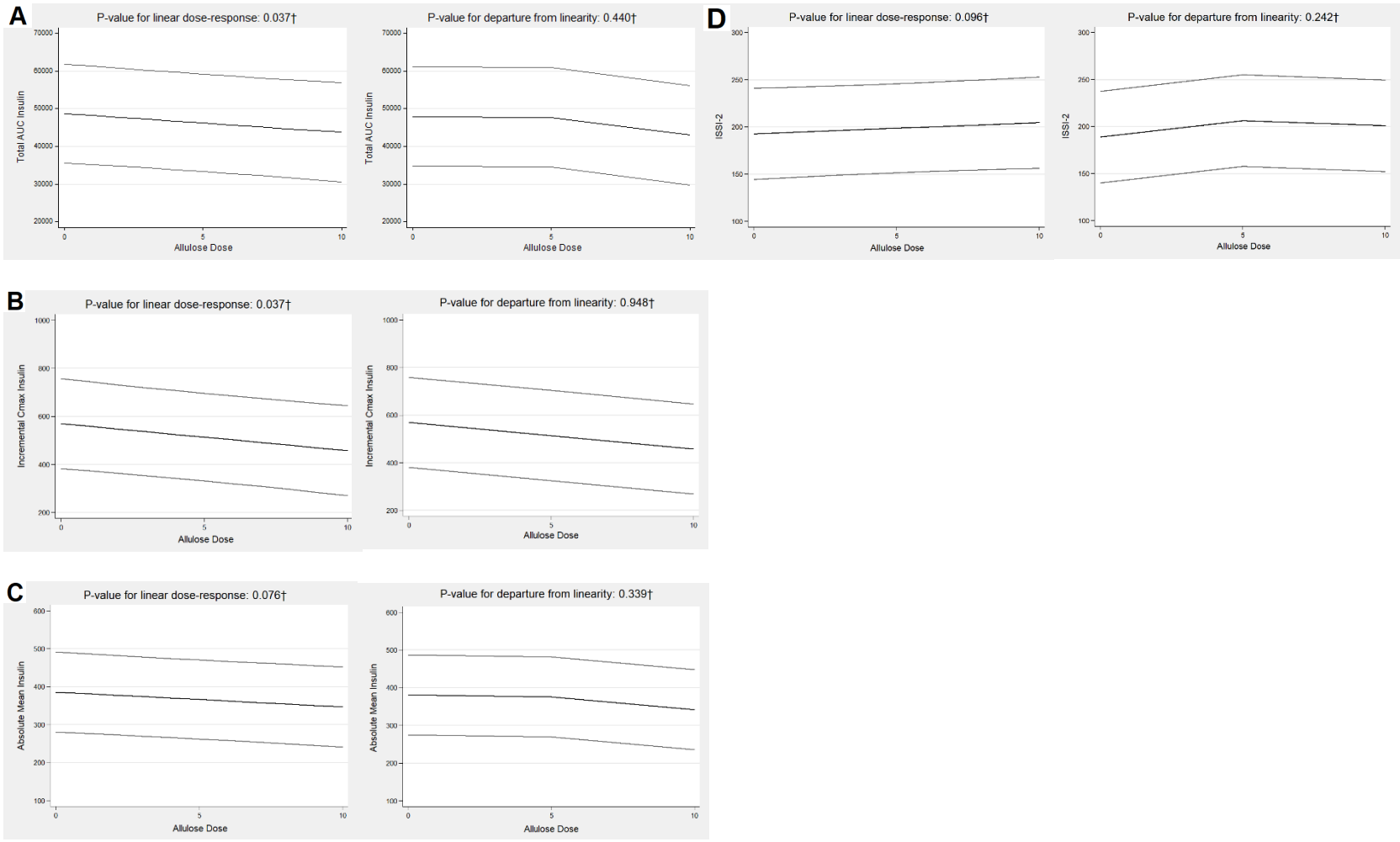
Supplementary Figure 7. Linear (left) and non-linear (right) dose-response analysis of the effect of small doses of fructose on total AUC insulin (A), incremental C_{max} insulin (B), absolute mean insulin (C) and Insulin Secretion-Sensitivity Index-2 (ISSI-2) (D). In the linear dose-response graphs, the middle black line represents the predicted linear trend, while the two grey lines represent the 95% CIs. In the non-linear dose-response graphs, the middle black line represents the mean, while the two grey lines represent the 95% CIs. *P<0.0125 indicates a significant dose-response relationship. †p-values correspond to log-transformed data due to non-normal distribution of residuals.



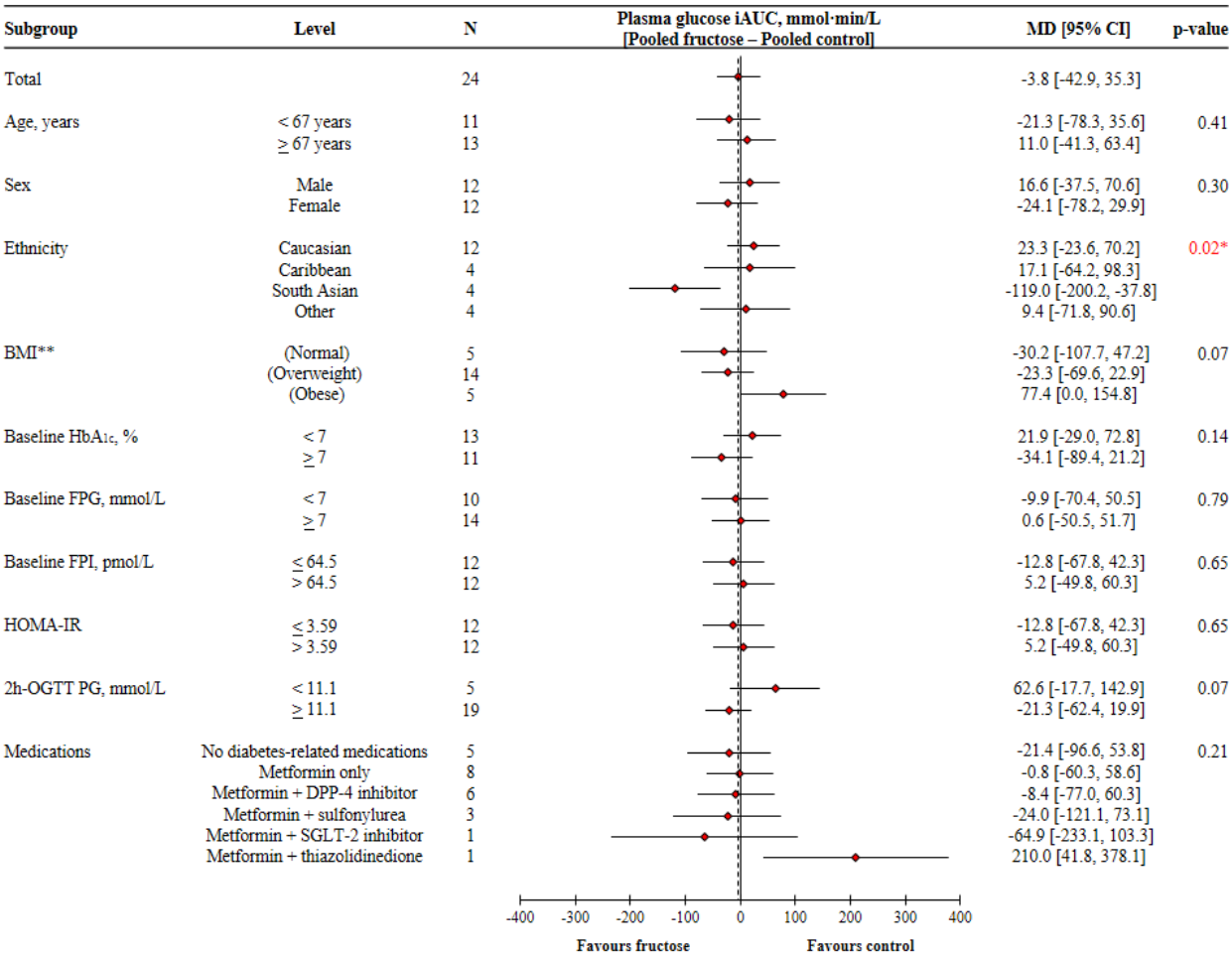
Supplementary Figure 8. Linear (left) and non-linear (right) dose-response analysis of the effect of small doses of allulose on absolute C_{max} glucose (A), T_{max} glucose (B), mean incremental glucose (C), insulin iAUC (D), absolute C_{max} insulin (E) and T_{max} insulin (F). In the linear dose-response graphs, the middle black line represents the predicted linear trend, while the two grey lines represent the 95% CIs. In the non-linear dose-response graphs, the middle black line represents the mean, while the two grey lines represent the 95% CIs. *P<0.0125 indicates a significant dose-response relationship. †p-values correspond to log-transformed data due to non-normal distribution of residuals.



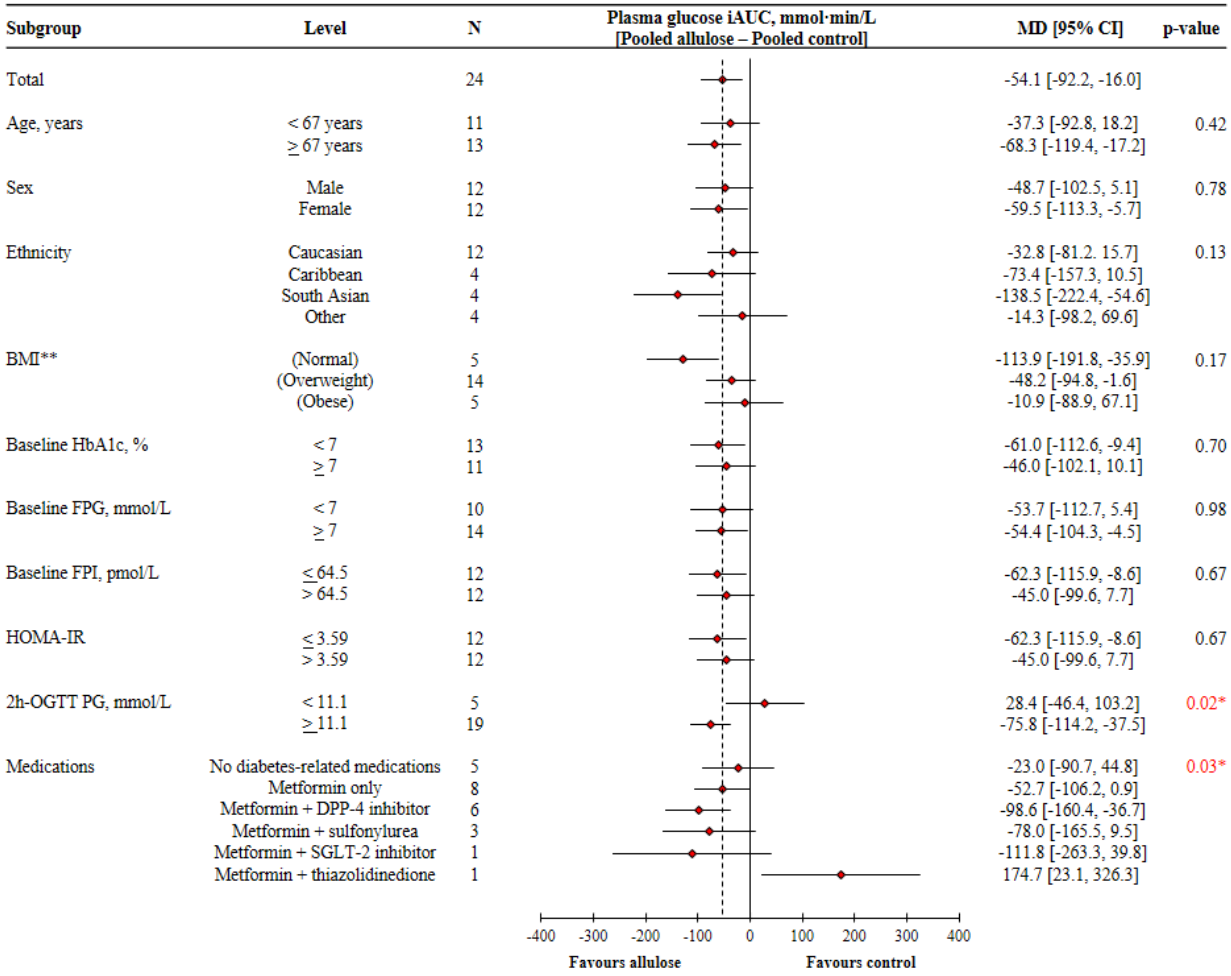
Supplementary Figure 9. Linear (left) and non-linear (right) dose-response analysis of the effect of small doses of allulose on mean incremental insulin (A), Early Insulin Secretion Index ($\Delta PI_{30\text{-}0}/\Delta PG_{30\text{-}0}$) (B), Matsuda Insulin Sensitivity Index$_{OGTT}$ (C), total AUC glucose (D), incremental C_{max} glucose (E) and absolute mean glucose (F). In the linear dose-response graphs, the middle black line represents the predicted linear trend, while the two grey lines represent the 95% CIs. In the non-linear dose-response graphs, the middle black line represents the mean, while the two grey lines represent the 95% CIs. *P<0.0125 indicates a significant dose-response relationship. †p-values correspond to log-transformed data due to non-normal distribution of residuals.



Supplementary Figure 10. Linear (left) and non-linear (right) dose-response analysis of the effect of small doses of allulose on total AUC insulin (A), incremental C_{max} insulin (B), absolute mean insulin (C) and Insulin Secretion-Sensitivity Index-2 (ISSI-2) (D). In the linear dose-response graphs, the middle black line represents the predicted linear trend, while the two grey lines represent the 95% CIs. In the non-linear dose-response graphs, the middle black line represents the mean, while the two grey lines represent the 95% CIs. *P<0.0125 indicates a significant dose-response relationship. †p-values correspond to log-transformed data due to non-normal distribution of residuals.



Supplementary Figure 11. Subgroup analysis of the effect of pooled doses of fructose on plasma glucose incremental area under the curve (iAUC) compared with control. For each subgroup, the diamonds represent the effect size and the solid lines represent the 95% CI. The dashed line represents the overall effect size. Linear mixed-effects models with interactions terms were used to identify significant effect modifiers. *P<0.05 was considered significant (red). **BMI categories were assessed using ethnic specific cut-offs for normal weight, overweight, and obesity: 18.5-22.9 kg/m^2, 23-27.5 kg/m^2 and >27.5 kg/m^2 respectively for Asian individuals, and 18.5-24.9 kg/m^2, 25-29.9 kg/m^2, and ≥30kg/m^2 respectively for other individuals (Reference: Hsu et al., *Diabetes Care*; 38 (1): pgs. 150-158). FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostatic model assessment-insulin resistance; 2h-OGTT PG, 2-hour oral glucose tolerance test plasma glucose



Supplementary Figure 12. Subgroup analysis of the effect of pooled doses of allulose on plasma glucose incremental area under the curve (iAUC) compared with control. For each subgroup, the diamonds represent the effect size and the solid lines represent the 95% CI. The dashed line represents the overall effect size. Linear mixed-effects models with interactions terms were used to identify significant effect modifiers. *P<0.05 was considered significant (red). **BMI categories were assessed using ethnic specific cut-offs for normal weight, overweight, and obesity: 18.5-22.9 kg/m^2, 23-27.5 kg/m^2 and >27.5 kg/m^2 respectively for Asian individuals, and 18.5-24.9 kg/m^2, 25-29.9 kg/m^2, and ≥30kg/m^2 respectively for other individuals (Reference: Hsu et al., *Diabetes Care*; 38 (1): pgs. 150-158). FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostatic model assessment-insulin resistance; 2h-OGTT PG, 2-hour oral glucose tolerance test plasma glucose