

SUPPLEMENTARY DATA

Supplementary Figure 1. Consort diagram of the study design and number of participants within each group

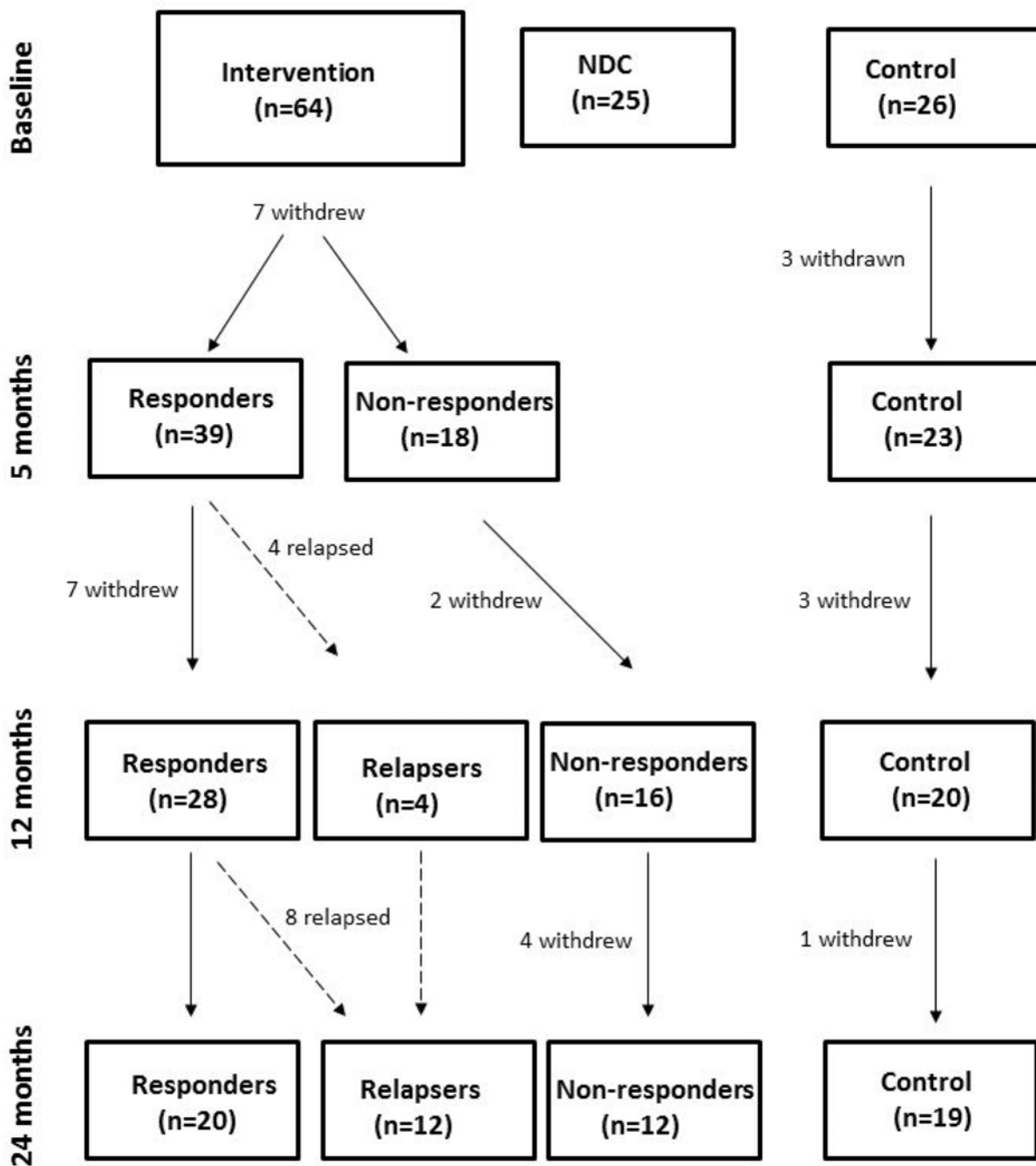
At baseline, there were 64 participants within the intervention group. By the end of weight loss stage, there were 7 people who left the study for personal reasons (moving out of area and change in circumstances, most commonly lack of time to due to work pressures or family commitments).

At 12 months, 7 other people had left the study, and thereby the remained people within the intervention group was 48 participants (28 Responders, 16 Non-Responders, and 4 who reverted to diabetes). By 24 months, an additional 3 people had left the study, all for personal reasons, a further one did not provide blood, and 8 had relapsed into diabetes.

Of those randomized to the Control group, at 5 months, 1 subject withdrew for personal reasons and 2 had lost more than 5kg in weight. There were 3 subjects who withdrew at 12 months and one by 24 months.

The Non-Diabetic Controls (NDC) were studied at one single occasion.

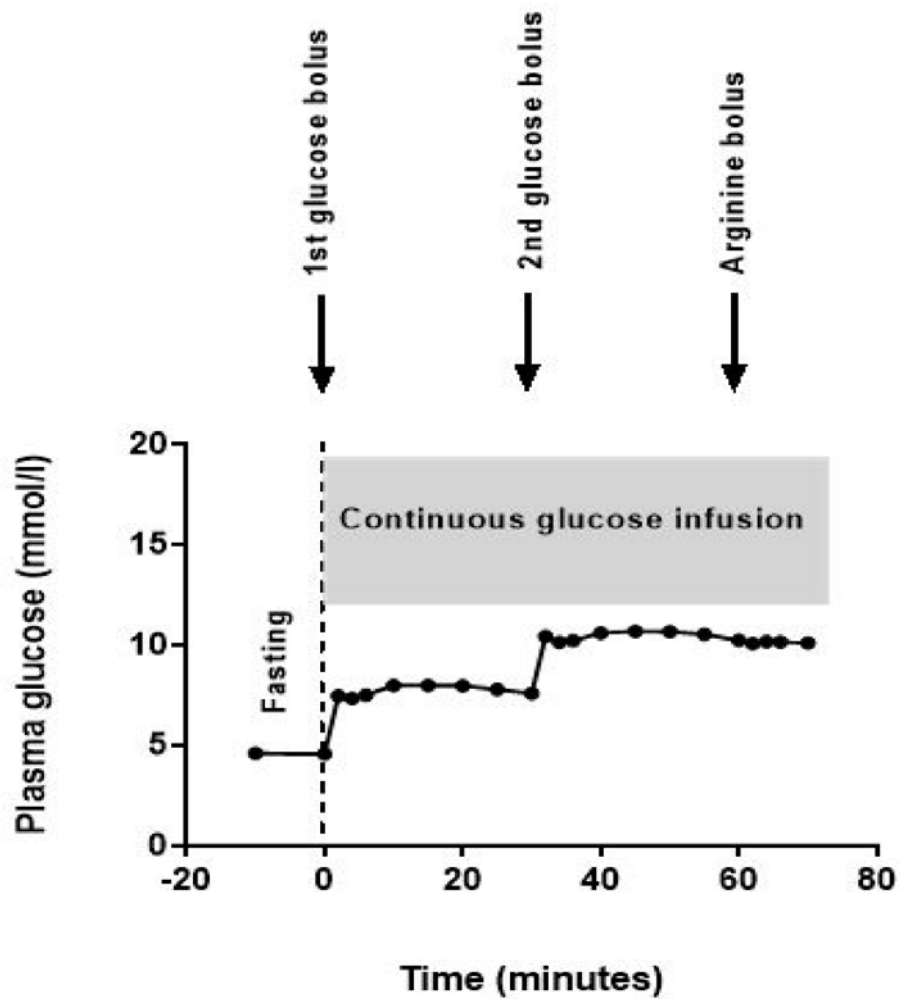
SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Figure 2. Schematic of the Stepped Insulin Secretion test with Arginine (SISTA) protocol

After an overnight fast a bolus of 20% Glucose was given at times 0 to induce first phase insulin response. The bolus was followed by 20% Glucose infusion to clamp plasma glucose, achieving a square wave step increase in plasma glucose level: +2.8 mmol/l. This was repeated at 30 minutes and plasma glucose was clamped at +5.6 mmol/l above fasting level for the rest of the test. At 60 minutes a bolus of 5 g of Arginine was given intravenously to elicit a maximal insulin response under the condition of the test.



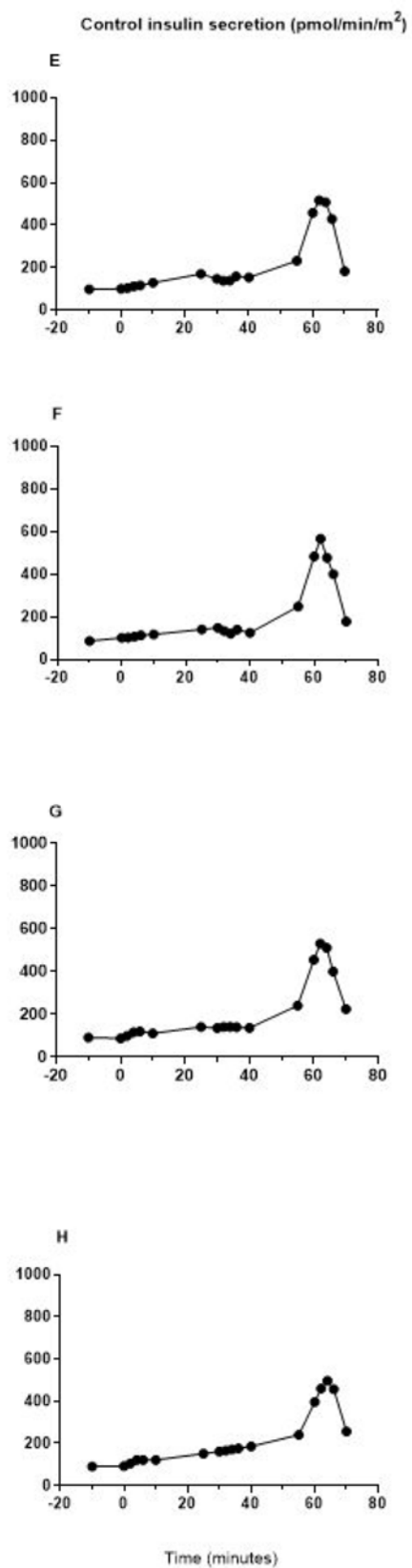
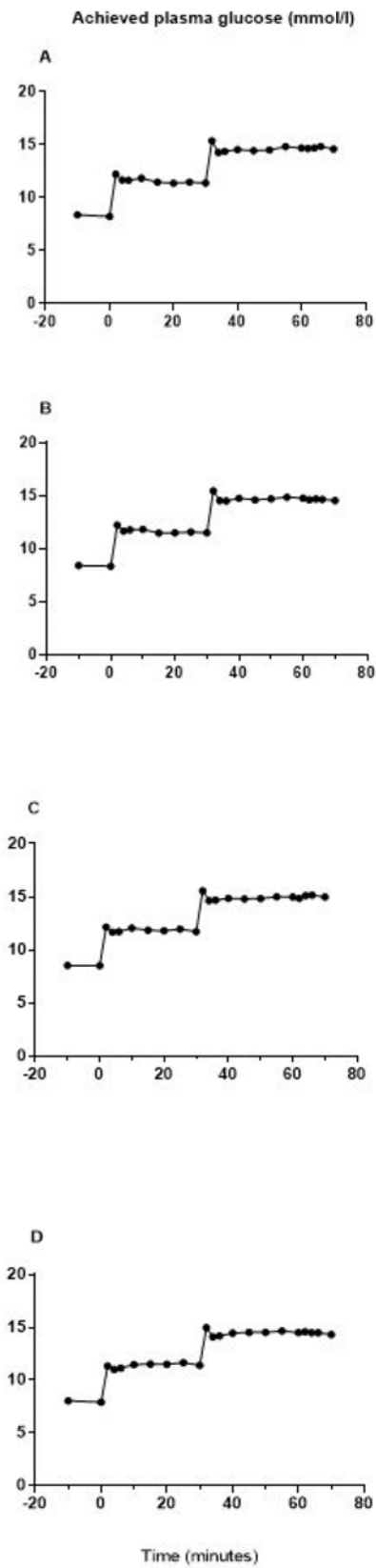
SUPPLEMENTARY DATA

Supplementary Figure 3. Stepped insulin secretion test with Arginine in DiRECT Tyneside Control subjects.

A, B, C, D: mean plasma glucose during SISTA in Control subjects at baseline, 5 months, 12 months, and 24 months respectively.

E, F, G, H: median insulin secretion rates (ISR) in Control subjects at baseline, 5 months, 12 months, and 24 months respectively.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Glucose bolus calculations

Desired glucose increment = 2.8 mmol/L

$$\approx 2.8 \times 18 \text{ (mg/dL)}$$

$$\approx 2.8 \times 18 / 100 \text{ (mg/mL)}$$

Volume to be incremented (ie. The glucose pool) was assumed to be 150ml per kg

$$\text{Volume to be incremented (mL)} = 150\text{mL/kg} \times \text{body weight (kg)}$$

Glucose required (mg) = desired glucose increment (mg/mL) x volume to be incremented (ml) = $2.8 \times 18 / 100 \text{ mg/ml} \times 150\text{ml/kg} \times \text{body weight(kg)}$

20% dextrose = 200g/L of glucose = 200mg/mL

$$\begin{aligned} \text{Amount of dextrose required (mL)} &= \text{glucose required (mg)} / \text{Dextrose strength (mg/mL)} = (2.8 \times 18 / \\ &100 \text{ mg/mL} \times 150\text{mL/kg} \times \text{body weight}) / 200\text{mg/mL} \\ &= 0.378 \times \text{bodyweight (kg)} \end{aligned}$$

Glucose Infusion rates

20% dextrose strength = 200g/L of glucose = 200mg/mL

Infusion rate (ml/min) = infusion rate (ml/hr) / 60 (min/hr)

Glucose infusion rate (mg/kg/min) = infusion strength (mg/mL) x infusion rate (ml/min) / body weight (kg)

Therefore, 1mg/kg/min infusion rate will be:

$$1\text{mg/kg/min} = 200 \text{ (mg/mL)} \times \text{infusion rate (ml/min)} / \text{body weight (kg)}$$

$$\begin{aligned} \text{infusion rate (ml/min)} &= 1\text{mg/kg/min} \times \text{body weight (kg)} / 200 \text{ (mg/mL)} \\ &= \text{bodyweight} / 200 \end{aligned}$$

$$\begin{aligned} \text{infusion rate (ml/hr)} &= \text{infusion rate (ml/min)} \times 60 \\ &= \text{bodyweight} \times 60 / 200 \\ &= \text{bodyweight} \times 0.3 \end{aligned}$$