# Electronic Supplementary Material

**ESM Table 1** Composition of the CD and CRHP diets (standardised to a 10,000 kJ/day or 2390 kcal/day energy intake) and weekly energy provision

| Diet composition (7-day menu) | CD diet | CRHP diet |
|---|---|---|
| Total carbohydrate, E% | 50.0 (±0.2)* | 30.0 (±0.2)* |
| Simple carbohydrate, E% | 11.4 (±2.7)§ | 6.1 (±2.8)§ |
| Fibre, g | 48 (±4)‡ | 36 (±6)‡ |
| Total protein, E% | 17.0 (±0.2)* | 30.0 (±0.1)* |
| Dairy protein, E% | 3.0 (±1.0)* | 10.7 (±1.8)* |
| Animal protein, E% | 8.9 (±0.7)* | 23.0 (±1.0)* |
| Total fat, E% | 33.0 (±0.1)* | 40.0 (±0.2)* |
| Saturated fatty acid, E% | 9.9 (±1.8)* | 11.5 (±3.0)* |
| Monounsaturated fatty acid, E% | 13.1 (±0.7)† | 18.2 (±3.1)† |
| Polyunsaturated fatty acid, E% | 6.5 (±1.2)* | 7.0 (±1.2)† |
| Omega-3 fatty acid, E% | 0.8 (±0.3)§ | 0.9 (±0.5)§ |
| Trans fat, g | 0.9 (±0.5)§ | 0.7 (±0.5)§ |
| Cholesterol, mg | 375 (±84)§ | 438 (±198)§ |
| Calcium, mg | 878 (±205)§ | 1605 (±512)§ |
| Sodium, mg | 2222 (±812)§ | 2169 (±707)§ |
| Potassium, mg | 3135 (±512)§ | 3165 (±630)§ |

| Energy provision | CD diet | CRHP diet |
|---|---|---|
| Estimated baseline daily TEE, kJ | 10,881 (±2644) | 11,100 (±1523) |
| Provided daily energy, kJ | | |
| Week 1 | 7784 (±1644) | 7993 (±1436) |
| Week 2 | 7367 (±1588) | 7452 (±1151) |
| Week 3 | 6830 (±1677) | 6963 (±1443) |
| Week 4 | 6424 (±1550) | 6618 (±1504) |
| Week 5 | 6235 (±1517) | 6324 (±1373) |
| Week 6 | 8553 (±2219) | 8610 (±1854) |

Data are presented as mean (±SD) and were generated using Dankost Pro software. Some dietary data have suboptimal validity, defined as percentage of registered food items specifying this dietary component, weighted relatively to their energy contribution: * ≥95-100; † ≥85-95; ‡ ≥70-85; § ≥45-70. Energy per cent (E%) is calculated using the assumption of 17, 17, and 37 kJ per gram of carbohydrate, protein and fat, respectively. To convert from kJ to kcal; 1 kJ = 0.239 kcal. CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein; TEE, total energy expenditure

**ESM Table 2** List of ingredients of a daily menu of the CD and CRHP diets (standardised to a 10,000 kJ/day or 2390 kcal/day energy intake)

| Breakfast, day 1 | CD diet | CRHP diet | Dinner, day 1 | CD diet | CRHP diet |
|---|---|---|---|---|---|
| Energy, kJ | 2500 | 2500 | Energy, kJ | 3000 | 3000 |
| Ingredients, g | | | Ingredients, g | | |
| Bread | 98 | 50 | Plaice fillet | 140 | - |
| Ryebread | 50 | - | Butter | 7 | - |
| Ham | 45 | 28 | Carrot | 100 | - |
| Butter | 8 | - | Remoulade | 48 | - |
| Brie cheese | 25 | - | Apple | 100 | - |
| Raspberry jam | 19 | - | Raisins | 14 | - |
| Skyr[a] with vanilla and topping | - | 170 | Potato | 295 | - |
| | | | Lemon juice | 3 | - |
| Cheese | - | 60 | Rapeseed oil | 5 | 3 |
| Tomato | - | 30 | Green beans | - | 50 |
| Mayonnaise | - | 11 | Wheat kernels | - | 50 |
| **Lunch, day 1** | | | Minced beef | - | 150 |
| Energy, kJ | 3000 | 3000 | Egg white | - | 80 |
| Ingredients, g | | | Oatmeal | - | 13 |
| Bread | 50 | - | Onion | - | 25 |
| Ryebread | 140 | 88 | Garlic | - | 1 |
| Lunch meat, beef | 20 | - | Tomato puree | - | 36 |
| Liver pâté | 40 | - | Whipping cream | - | 15 |
| Tomato | 80 | 100 | Cheese | - | 15 |
| Cucumber | 80 | - | **Snacks, day 1 (separated and consumed in two)** | | |
| Ham salad | 57 | - | Energy, kJ | 1500 | 1500 |
| Smoked salmon | - | 60 | Ingredients, g | | |
| Shrimps | - | 80 | Crispbread | 40 | - |
| Egg | - | 90 | Cream cheese | 40 | - |
| Pesto | - | 17 | Pear | 140 | - |
| Milk | - | 245 | Almond | 6 | 39 |
| Mayonnaise | - | 10 | Skyr[a] drink | - | 266 |

**ESM Table 2** *(continued)*

| Breakfast, day 2 | CD diet | CRHP diet | Dinner, day 2 | CD diet | CRHP diet |
|---|---|---|---|---|---|
| Energy, kJ | 2500 | 2500 | Energy, kJ | 3000 | 3000 |
| Ingredients, g | | | Ingredients, g | | |
| Bread | 100 | - | Salmon | 72 | - |
| Ryebread | 54 | - | Pasta | 100 | - |
| Cheese | 20 | - | Green beans | 120 | - |
| Egg | 60 | - | Juice | 24 | - |
| Chocolate, dark | 8 | - | Pesto | 31 | - |
| Mayonnaise | 5 | - | Cinnamon snail | 35 | - |
| Skyr[a] | - | 210 | Cod fillet | - | 130 |
| Blueberries | - | 100 | Ham | - | 27 |
| Crispbread | - | 33 | Potato | - | 100 |
| Butter | - | 8 | Carrot | - | 100 |
| Ham | - | 40 | Corn | - | 40 |
| Almonds | - | 16 | Cauliflower | - | 100 |
| Cucumber | - | 50 | Rapeseed oil | - | 8 |
| Sesame seeds | - | 18 | Olive oil | - | 8 |
| **Lunch, day 2** | | | Milk | - | 240 |
| Energy, kJ | 3000 | 3000 | Almond | - | 20 |
| Ingredients, g | | | Garlic | - | 4 |
| Ryebread | 130 | - | **Snacks, day 2 (separated and consumed in two)** | | |
| Meatballs | 128 | - | Energy, kJ | 1500 | 1500 |
| Carrot | 100 | - | Ingredients, g | | |
| Apple | 100 | 50 | Crispbread | 40 | - |
| Pickle | 35 | - | Cheese | 20 | - |
| Almonds | 10 | - | Apple | 140 | - |
| Pita bread | - | 65 | Almond | 12 | - |
| Chicken | - | 116 | White beans | - | 42 |
| Tomato | - | 40 | Cream cheese | - | 14 |
| White cabbage | - | 40 | Cottage cheese | - | 40 |
| Mozzarella | - | 45 | Cucumber | - | 100 |
| Milk | - | 250 | Cheese | - | 35 |
| Mayonnaise | - | 21 | Lemon juice | - | 4 |
| Parsley | - | 2 | Garlic | - | 2 |

[a] Icelandic yogurt that is rich in protein and poor in sugar

CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein

**ESM Table 3**  Weight loss algorithm during first the 5 weeks of intervention exemplified for a male of 110 kg, 180 cm and 65 years

**1. Energy requirements by the Mifflin St-Jeor equation**

| | | |
|---|---|---|
| 1a. REE = 9.99 x weight + 6.25 x height - 4.92 x age + 166 x sex [1 for males, 0 for females] – 161) | 7992 kJ | 1909 kcal |
| 1b. TEE = REE x PAL = 7992 kJ x 1.6 | 12,787 kJ | 3054 kcal |

**2. Estimated energy intake**

| | | |
|---|---|---|
| 2a. Weight loss target = 6% x baseline body weight = 0.06 x 110 kg | 6.6 kg | |
| 2b. Total energy equivalent = weight loss target x energy density of weight lost = 6.6 kg x 27,000 kJ/kg[a] (6453 kcal/kg) | 178,200 kJ | 42,562 kcal |
| 2c. Daily energy intake (week 1) = TEE - (total energy equivalent / duration) x 80% = 12,787 kJ - (178,200 kJ / 35 days) x 0.80 | 8714 kJ | 2081 kcal |
| (week 2) = TEE - (total energy equivalent / duration) x 80% = 12,787 kJ - (178,200 kJ / 35 days) x 0.80 | 8714 kJ | 2081 kcal |
| (week 3) = TEE - (total energy equivalent / duration) x 110% = 12,787 kJ - (178,200 kJ / 35 days) x 1.1 | 7187 kJ | 1717 kcal |
| (week 4) = TEE - (total energy equivalent / duration) x 110% = 12,787 kJ - (178,200 kJ / 35 days) x 1.1 | 7187 kJ | 1717 kcal |
| (week 5) = TEE - (total energy equivalent / duration) x 120% = 12,787 kJ - (178,200 kJ / 35 days) x 1.2 | 6678 kJ | 1595 kcal |

**3. Weight loss evaluation twice weekly**

3a. Body weight measurements and comparison with targeted value

3b. Adjustment of energy intake by reduction/increase in portion sizes or omission/introduction of snack meals

[a] Energy density reflecting lost body weight to be a mixture of adipose tissue (~75%) and lean mass (~25%) [1]

REE, resting energy expenditure; TEE, total energy expenditure; PAL, physical activity level

**ESM Table 4** List of prespecified outcomes. All outcomes are evaluated following 6 weeks of a hypo-energetic CRHP diet compared with a hypo-energetic CD diet. Complete list is available on ClinicalTrials.gov Identifier: NCT03814694

| **Primary outcome** | **Presented in this paper** |
| --- | --- |
| - Change in HbA$_{1c}$ | X |

**Secondary outcomes**

| | |
| --- | --- |
| - Change in hepatic fat content assessed by MR spectroscopy | X |
| - Change in fasting plasma triacylglycerol | X |

**Exploratory outcomes**

| | |
| --- | --- |
| - Change in fat content subcutaneously, viscerally and ectopically in pancreas and skeletal muscle assessed by MR imaging and spectroscopy | X |
| - Change in lean body mass and fat mass assessed by DXA | X |
| - Change in diurnal blood pressure assessed by intermittent 24-hour ambulatory BP monitor | |
| - Change in heart rate variability assessed by 48-hour Holter-monitoring | |
| - Change in diurnal glycemia and glycemic variability assessed by 7-day continuous glucose monitoring | X |
| - Change in insulin sensitivity assessed by the Composite Index following an OGTT | |
| - Change in beta-cell function assessed by the Insulinogenic Index and Disposition Index following an OGTT | |
| - Change in Homeostasis Model Assessment of insulin resistance | X |
| - Change in Homeostasis Model Assessment of beta-cell function | |
| - Change in lipid profile including lipoprotein subfractions | |
| - Change in fasting glucose, insulin, C-peptide and NEFA | X |
| - Change in glucose, insulin, C-peptide, NEFA and triacylglycerol following an OGTT | |
| - Change in glucagon, GLP-1, GIP, PYY, ghrelin, CCK, gastrin, GH and IGFBP-1 following an OGTT | |
| - Change in IGF-1, leptin and adiponectin | |
| - Change in TNF-α, IL-6 and hsCRP | |
| - Change in eGFR and diurnal excretion of albumin | X |
| - Change in urinary excretion of urea | X |
| - Change in urinary excretion of glucose | |
| - Change in urinary oxidative DNA and RNA modifications | |
| - Change in health-related quality of life assessed by the 36-item Short-Form health survey | |

CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein; MR, magnetic resonance; DXA, dual-energy X-ray absorptiometry; BP, blood pressure; OGTT, oral glucose tolerance test; NEFA, non-esterified fatty acids; GLP-1, glucagon-like-peptide-1; GIP, glucose-dependent insulinotropic polypeptide; PYY, peptide YY; CCK, cholecystokinin; GH, growth hormone; IGFBP-1, insulin-like growth factor-binding protein 1; IGF-1, insulin-like growth factor-1; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; hsCRP, high-sensitive C-reactive protein; eGFR, estimated glomerular filtration rate

**ESM Table 5** Between-diet differences of a CD and a CRHP diet in individuals with type 2 diabetes and overweight or obesity

| Variable | Model 1[a] | | | Model 2[b] | | |
|---|---|---|---|---|---|---|
| | Difference | $p$ value | RSE | Difference | $p$ value | RSE |
| **Anthropometry** | | | | | | |
| Body weight, kg | 0.1 (-0.6, 0.7) | 0.83 | 19.4 | 0.0 (-0.6, 0.7) | 0.92 | 7.7 |
| Body mass index, kg/m$^2$ | -0.0 (-0.2, 0.2) | 0.94 | 4.7 | -0.0 (-0.2, 0.2) | 0.94 | 4.9 |
| Waist circumference, mm | -0.1 (-12.4, 12.2) | 0.99 | 108 | -0.3 (-12.5, 11.8) | 0.96 | 47 |
| **Body composition** | | | | | | |
| Fat free mass, kg | 0.5 (-0.2, 1.1) | 0.18 | 11.8 | 0.3 (-0.4, 1.0) | 0.40 | 6.0 |
| Fat mass, kg | -0.4 (-1.1, 0.3) | 0.24 | 11.0 | -0.4 (-1.2, 0.3) | 0.25 | 4.3 |
| Body fat fraction, % | -0.5 (-1.0, 0.1) | 0.10 | 5.9 | -0.5 (-1.1, 0.1) | 0.092 | 3.3 |
| **Fat distribution** | | | | | | |
| Hepatic fat fraction, % | -26 (-45, 0)[c] | 0.051 | 1.12 | -25 (-45, 1)[c] | 0.058 | 1.08 |
| Pancreatic fat fraction, % | 33 (7, 65)[c] | 0.010 | 0.79 | 32 (6, 64)[c] | 0.013 | 0.75 |
| Muscle fat fraction, % | 15 (-12, 49)[c] | 0.31 | 0.66 | 13 (-13, 48)[c] | 0.35 | 0.66 |
| VAT, cm$^3$ | 0.9 (-15.1, 17.0) | 0.91 | 100 | -0.2 (-16.1, 15.7) | 0.98 | 76 |
| SAT, cm$^3$ | -5.6 (-19.4, 8.2) | 0.42 | 120 | -7.5 (-21.0, 6.0) | 0.27 | 58 |
| **Glucose metabolism** | | | | | | |
| HbA$_{1c}$, mmol/mol | -1.9 (-3.5, -0.3) | 0.018 | 8.1 | -1.9 (-3.6, -0.3) | 0.021 | 7.6 |
| Fasting glucose, mmol/l | -2 (-8, 5)[c] | 0.64 | 0.20 | -1 (-8, 6)[c] | 0.68 | 0.20 |
| Fasting insulin, pmol/l | -1 (-16, 17)[c] | 0.92 | 0.45 | -1 (-16, 17)[c] | 0.87 | 0.40 |
| Fasting C-peptide, pmol/l | 3 (-6, 14)[c] | 0.50 | 0.32 | 3 (-6, 14)[c] | 0.48 | 0.27 |
| HOMA2-IR | -1 (-18, 18)[c] | 0.89 | 0.42 | -2 (-18, 17)[c] | 0.83 | 0.39 |
| **CGM** | | | | | | |
| Diurnal mean glucose, mmol/l | -0.8 (-1.2, -0.4) | <0.001 | 1.91 | -0.7 (-1.1, -0.3) | <0.001 | 1.89 |
| Coefficient of variation, % | -4.1 (-5.9, -2.2) | <0.001 | 4.3 | -4.2 (-5.9, -2.5) | <0.001 | 4.2 |
| TIR (3.9-10 mmol/l), % | -5.8 (-12.4, 0.7) | 0.082 | 21.6 | -5.1 (-11.8, 1.7) | 0.14 | 21.1 |
| TAR (>10 mmol/l), % | -3.5 (-6.4, -0.6) | 0.019 | 21.8 | -3.2 (-6.2, -0.2) | 0.035 | 22.0 |
| TBR (<3.9 mmol/l), % | 8.1 (2.4, 13.9) | <0.01 | 1.70 | 8.0 (2.3, 13.8) | <0.01 | 1.69 |
| **Fasting lipid profile** | | | | | | |
| Triacylglycerol, mmol/l | -18 (-29, -6)[c] | <0.01 | 0.45 | -17 (-28, -5)[c] | <0.01 | 0.44 |
| NEFA, mmol/l | -1 (-11, 10)[c] | 0.81 | 0.31 | -1 (-11, 11)[c] | 0.80 | 0.31 |
| Total cholesterol, mmol/l | -0.2 (-0.4, 0.1) | 0.23 | 0.95 | -0.1 (-0.4, 0.1) | 0.33 | 0.93 |
| LDL cholesterol, mmol/l | 0.0 (-0.2, 0.2) | 0.98 | 0.78 | 0.0 (-0.2, 0.2) | 0.87 | 0.74 |
| HDL cholesterol, mmol/l | 0.02 (-0.03, 0.08) | 0.41 | 0.28 | 0.03 (-0.02, 0.09) | 0.25 | 0.27 |
| Non-HDL cholesterol, mmol/l | -0.2 (-0.4, 0.1) | 0.16 | 0.93 | -0.2 (-0.4, 0.1) | 0.23 | 0.91 |
| ApoB, g/l | -0.04 (-0.10, 0.02) | 0.17 | 0.23 | -0.03 (-0.09, 0.03) | 0.27 | 0.23 |
| ApoA-1, g/l | -0.01 (-0.07, 0.04) | 0.64 | 0.23 | -0.00 (-0.06, 0.06) | 0.99 | 0.21 |
| ApoB/ApoA-1 | -4 (-11, 5)[c] | 0.38 | 0.30 | -3 (-11, 5)[c] | 0.43 | 0.29 |

**ESM Table 5** *(continued)*

| Variable | Model 1[a] | | | Model 2[b] | | |
|---|---|---|---|---|---|---|
| | Difference | *p* value | RSE | Difference | *p* value | RSE |
| Renal function | | | | | | |
| eGFR, ml min$^{-1}$ 1.73 m$^{-2}$ | 5.3 (-2.9, 13.5) | 0.21 | 17.7 | 5.3 (-2.8, 13.4) | 0.20 | 13.7 |
| Albumin, mg 24 h$^{-1}$ | 28 (-4, 69)[c] | 0.090 | 1.20 | 26 (-5, 66)[c] | 0.11 | 1.21 |
| Albumin/creatinine, mg/g | 19 (-10, 58)[c] | 0.23 | 1.18 | 19 (-10, 58)[c] | 0.21 | 1.19 |
| Compliance | | | | | | |
| Urea excretion, mmol 24 h$^{-1}$ | 184 (140, 229) | <0.001 | 123 | 185 (143, 227) | <0.001 | 107 |
| Physical activity, MET min wk$^{-1}$ | 0 (-27, 37)[c] | 0.99 | 0.94 | 0 (-28, 41)[c] | 0.98 | 0.92 |

Differences are estimated marginal means (95% CI), presented as absolute or relative between-diet differences (CRHP vs CD) for normally distributed or log-transformed data, respectively

[a] Constrained linear mixed model with inherent baseline adjustment

[b] Constrained linear mixed model with inherent baseline adjustment, further adjusting for differences in sex, age, BMI, diabetes duration and therapy with metformin and DPP-4 inhibitors

[c] Relative difference (%)

CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein, RSE, residual standard error; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; CGM, continuous glucose monitoring; TIR, time-in-range; TAR, time-above-range; TBR, time-below-range; apo, apolipoprotein

**ESM Table 6** Measures of renal function, urea excretion, and physical activity before and after matched weight loss by a CD or a CRHP diet in individuals with type 2 diabetes and overweight or obesity

| Variable | CD diet | | | CRHP diet | | | Between diets | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Treatment effect | $n$ | Baseline | Treatment effect | $n$ | Difference | $p$ value |
| Renal function | | | | | | | | |
| eGFR, ml min$^{-1}$ 1.73 m$^{-2}$ | 78.1 (±17.1) | -1.2 (±6.3) | 33 | 80.3 (±18.2) | 3.6 (±23.7) | 34 | 5.3 (-2.9, 13.5) | 0.21 |
| Albumin, mg 24 h$^{-1}$ | 10.3 (4.0, 15.6) | -2.5 (-8.3, 0.1)[‡] | 33 | 9.8 (4.4, 14.1) | -1.6 (-5.1, 0.4) | 34 | 28 (-4, 69)[a] | 0.090 |
| Albumin/creatinine, mg/g | 6.3 (3.0, 12.1) | -1.1 (-5.6, 0.7)[†] | 33 | 6.1 (3.2, 10.6) | -0.9 (-3.7, 0.2) | 34 | 19 (-10, 58)[a] | 0.23 |
| Compliance | | | | | | | | |
| Urea excretion, mmol 24 h$^{-1}$ | 417 (±127) | -121 (±92)[‡] | 33 | 444 (±120) | 53 (±115)[‡] | 34 | 184 (140, 229) | <0.001 |
| Physical activity[b], MET min wk$^{-1}$ | 5246 (3278, 6969) | 240 (-1438, 1089) | 23 | 3090 (1670, 7102) | 382 (-1279, 1440) | 30 | 0 (-27, 37)[a] | 0.99 |

Data at baseline and changes from baseline are presented as means±SD or medians (25th, 75th percentiles); between-diet differences are estimated marginal means (95% CI), presented as absolute or relative differences (CRHP vs CD) for normally distributed or log-transformed data, respectively, and derived from constrained linear mixed models with inherent baseline adjustment using all available data
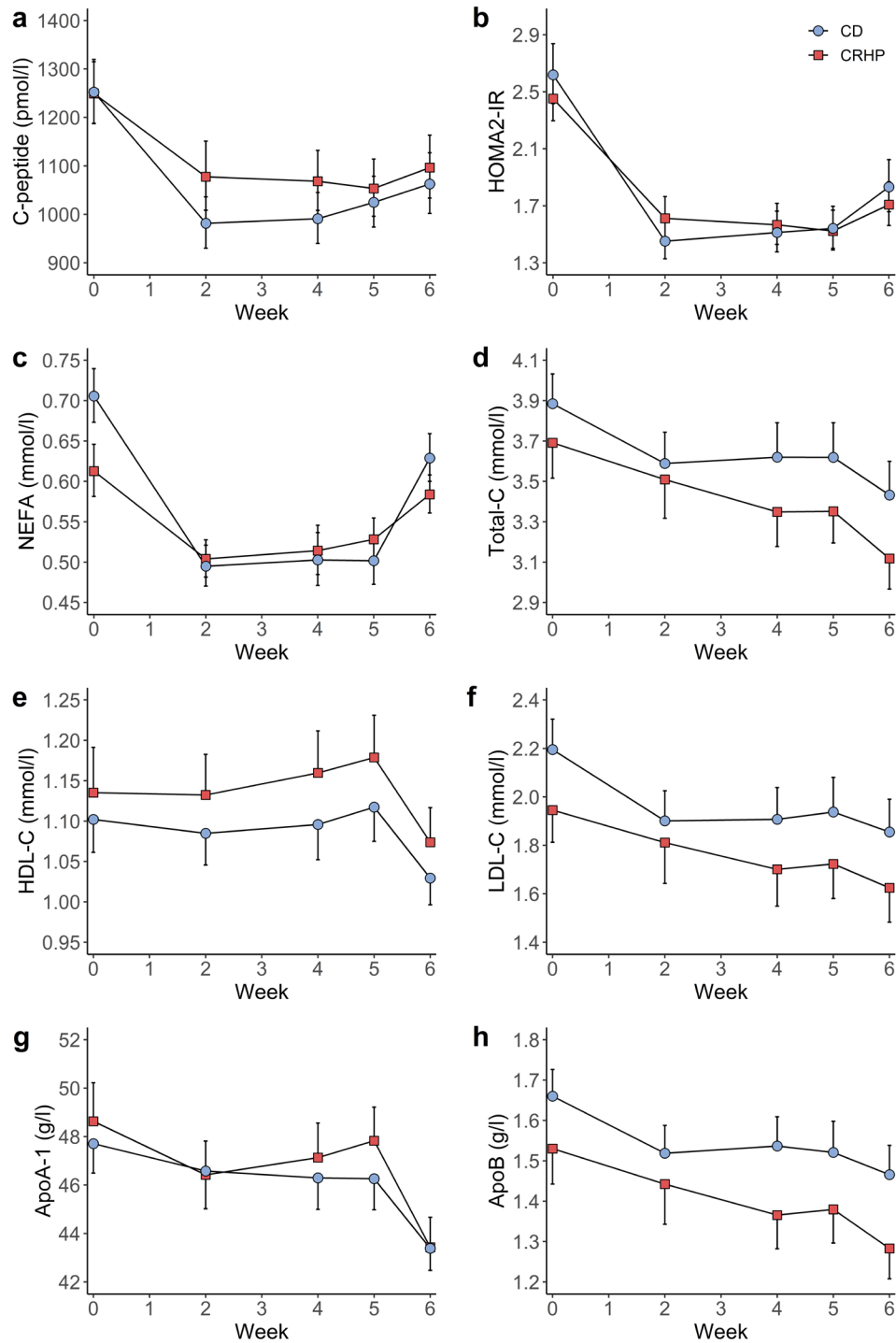
[a] Relative difference (%)

[b] Missing data were observed for physical activity due to inadequately or erroneously answered questionnaires

[†]p<0.01 and [‡]p<0.001 vs baseline

CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein; eGFR, estimated glomerular filtration rate

**ESM Fig. 1**



**ESM Fig. 1** Fasting measures of serum C-peptide ($p = 0.50$) (**a**), HOMA2-IR ($p = 0.89$) (**b**), serum NEFA ($p = 0.81$) (**c**), serum total ($p = 0.23$), HDL ($p = 0.40$), and LDL ($p = 0.98$) cholesterol (**d-f**), and apolipoprotein (apo) A-1 ($p = 0.64$) and B ($p = 0.17$) (**g-h**) during 6 weeks of a carbohydrate-reduced high-protein (CRHP) or conventional diabetes (CD) diet. Data are presented as mean with SEM error bars, including back-transformed data in (**a-c**) following log-transformation. Changes from baseline to week 6 were evaluated between diets, and $p$-values for these differences are included

**References**

[1]     Hall KD (2008) What is the required energy deficit per unit weight loss? Int J Obes (Lond) 32(3): 573-576. 10.1038/sj.ijo.0803720