
Table S1: MMACE and MMADE events prespecified for analysis in the DiRECT 5-year SAP

Moderate/Major Adverse Cardiovascular Events (MMACE):

Incident (new or recurrent) cases of:
Death attributed to cardiovascular disease
Non-fatal myocardial infarction,
Percutaneous coronary intervention (PCI),
Coronary artery bypass grafting/revascularisation

Heart failure, -
New onset of heart failure
worsening heart failure (ie requiring increased regular medication)
unplanned hospitalization
urgent visit resulting in intravenous therapy for heart failure"

Angina: new onset
Unstable angina (frequent, requiring increased regular medication)

Hospitalization for new or pre-existing cardiovascular-related illness, (including peripheral vascular disease/ foot ulcers)
New proven PVD
Lower limb amputation

TIA /stroke

Moderate/Major Adverse Diabetes Events (MMADE):

All the above MMACE events, plus new onset of:
Severe hypoglycaemia (requiring third-party assistance or hospitalisation)
Ketoacidosis
New proliferative retinopathy
Laser treatment
New diabetic renal deterioration:
EGFR decline of >40% from baseline figure
New onset macroalbuminuria
Renal replacement (dialysis or transplant)
New foot ulcer or infection
Hospitalisation for existing foot ulcers or infections

Any hospitalisation primarily for diabetes (decompensation, initiation of new treatment, investigation or treatment of complications).

Table S2: Other medications (non-glucose-lowering and non-antihypertensive), use of weight-loss-inducing medications, use of insulin, and use of statins over time. Intervention vs. Control, and within Intervention, Extension vs. No-Extension. Summaries are mean (SD) and N(%). 'Est' is the estimated mean difference or odds ratio. 'CI' indicates 95% confidence interval. Estimate and CI not shown for binary measures with zero events in one group. p-values and CIs for mean differences derived from bootstrapping with 10,000 replicated datasets.

		Control vs. Intervention					Intervention: Non-Extension vs. Extension				
		Control		Intervention		Est (CI), p-value	Non-Extension		Extension		Est (CI), p-value
		N	Summary	N	Summary		N	Summary	N	Summary	
Number of Other Medications	Baseline	149	3.6 (3.4)	149	3.5 (3.0)	-0.1 (-0.8, 0.6), p=0.79	54	4.0 (3.6)	95	3.2 (2.6)	-0.9 (-2.0, 0.2), p=0.12
	Year 1	148	4.2 (3.7)	148	4.0 (3.9)	-0.2 (-1.1, 0.7), p=0.64	53	4.9 (4.6)	95	3.4 (3.4)	-1.5 (-2.9, -0.1), p=0.029
	Year 2	143	4.6 (4.0)	129	4.0 (3.7)	-0.6 (-1.5, 0.3), p=0.22	34	5.2 (4.8)	95	3.6 (3.2)	-1.6 (-3.4, 0.0), p=0.056
	Year 3	132	5.0 (4.2)	141	4.2 (4.2)	-0.8 (-1.8, 0.2), p=0.13	47	5.3 (5.1)	94	3.7 (3.6)	-1.6 (-3.2, 0.0), p=0.047
	Year 4	127	5.3 (4.6)	139	4.4 (4.4)	-0.9 (-2.0, 0.2), p=0.12	46	5.4 (5.4)	93	3.9 (3.7)	-1.5 (-3.3, 0.2), p=0.081
	Year 5	121	5.3 (4.3)	136	4.7 (4.5)	-0.5 (-1.6, 0.5), p=0.30	43	5.7 (5.5)	93	4.3 (4.0)	-1.4 (-3.3, 0.4), p=0.12
Use of Weight Loss-Inducing Medications	Year 1	148	2 (1%)	148	9 (6%)	4.7 (1.0, 45.5), p=0.061	53	0 (0%)	95	9 (9%)	- (-, -), p=0.027
	Year 2	143	2 (1%)	129	7 (5%)	4.0 (0.7, 40.4), p=0.090	34	3 (9%)	95	4 (4%)	0.5 (0.1, 3.3), p=0.38
	Year 3	132	3 (2%)	141	4 (3%)	1.3 (0.2, 8.7), p=1.00	47	1 (2%)	94	3 (3%)	1.5 (0.1, 81.3), p=1.00
	Year 4	127	5 (4%)	139	4 (3%)	0.7 (0.1, 3.4), p=0.74	46	2 (4%)	93	2 (2%)	0.5 (0.0, 6.9), p=0.60
	Year 5	121	4 (3%)	136	3 (2%)	0.7 (0.1, 4.0), p=0.71	43	2 (5%)	93	1 (1%)	0.2 (0.0, 4.4), p=0.23
Use of Insulin	Year 1	148	3 (2%)	148	3 (2%)	1.0 (0.1, 7.6), p=1.00	53	2 (4%)	95	1 (1%)	0.3 (0.0, 5.4), p=0.29
	Year 2	143	3 (2%)	129	1 (1%)	0.4 (0.0, 4.6), p=0.62	34	0 (0%)	95	1 (1%)	- (-, -), p=1.00
	Year 3	132	6 (5%)	141	1 (1%)	0.2 (0.0, 1.3), p=0.059	47	0 (0%)	94	1 (1%)	- (-, -), p=1.00
	Year 4	127	6 (5%)	139	4 (3%)	0.6 (0.1, 2.6), p=0.53	46	2 (4%)	93	2 (2%)	0.5 (0.0, 6.9), p=0.60
	Year 5	121	6 (5%)	136	4 (3%)	0.6 (0.1, 2.5), p=0.52	43	2 (5%)	93	2 (2%)	0.5 (0.0, 6.5), p=0.59
Use of Statins	Year 1	148	100 (68%)	148	78 (53%)	0.5 (0.3, 0.9), p=0.013	53	30 (57%)	95	48 (51%)	0.8 (0.4, 1.6), p=0.50
	Year 2	143	99 (69%)	129	73 (57%)	0.6 (0.3, 1.0), p=0.033	34	20 (59%)	95	53 (56%)	0.9 (0.4, 2.1), p=0.84
	Year 3	132	95 (72%)	141	75 (53%)	0.4 (0.3, 0.8), p=0.0017	47	25 (53%)	94	50 (53%)	1.0 (0.5, 2.1), p=1.00
	Year 4	127	95 (75%)	139	78 (56%)	0.4 (0.2, 0.7), p=0.0019	46	25 (54%)	93	53 (57%)	1.1 (0.5, 2.4), p=0.86
	Year 5	121	92 (76%)	136	84 (62%)	0.5 (0.3, 0.9), p=0.016	43	27 (63%)	93	57 (61%)	0.9 (0.4, 2.1), p=1.00

Table S3: Data collected only in the DiRECT Extension group. Summaries are mean (SD) at each follow-up, and mean changes from baseline, with 95% confidence intervals (CI) and p-values derived using bootstrapping with 10,000 replicated datasets.

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
SBP (mmHg)							
Annual Follow-Up	N	95	95	94	79	73	73
	Mean (SD)	134.1 (17.8)	132.5 (16.7)	129.9 (13.9)	135.3 (14.0)	135.2 (14.6)	134.7 (11.9)
Change from Baseline	Mean (95% CI)	-	-1.6 (-5.2, 2.0)	-3.9 (-7.7, -0.3)	1.5 (-2.3, 5.2)	0.6 (-3.2, 4.4)	1.9 (-2.4, 5.7)
	p-value	-	p=0.38	p=0.034	p=0.43	p=0.73	p=0.37
DBP (mmHg)							
Annual Follow-Up	N	95	95	94	79	73	73
	Mean (SD)	83.7 (9.5)	83.1 (9.8)	81.0 (8.4)	82.8 (9.0)	82.2 (8.9)	82.5 (9.9)
Change from Baseline	Mean (95% CI)	-	-0.6 (-2.6, 1.4)	-2.6 (-4.5, -0.8)	-1.1 (-3.3, 1.2)	-1.3 (-3.2, 0.6)	-1.2 (-3.4, 1.0)
	p-value	-	p=0.55	p=0.0038	p=0.34	p=0.18	p=0.30
EQ-5D Health Utility							
Annual Follow-Up	N	95	93	93	78	73	74
	Mean (SD)	0.818 (0.266)	0.818 (0.260)	0.844 (0.244)	0.805 (0.263)	0.795 (0.240)	0.800 (0.229)
Change from Baseline	Mean (95% CI)	-	0.000 (-0.040, 0.041)	0.025 (-0.013, 0.063)	-0.027 (-0.076, 0.020)	-0.031 (-0.074, 0.013)	-0.015 (-0.068, 0.039)
	p-value	-	p=0.99	p=0.19	p=0.26	p=0.17	p=0.59
EQ-5D VAS							
Annual Follow-Up	N	95	93	93	78	73	74
	Mean (SD)	67.0 (17.5)	77.3 (15.4)	77.7 (15.8)	76.3 (14.9)	74.5 (18.0)	76.9 (16.0)
Change from Baseline	Mean (95% CI)	-	10.2 (6.1, 14.3)	10.5 (6.7, 14.4)	8.9 (4.9, 12.6)	6.7 (2.7, 10.2)	8.9 (4.4, 13.5)
	p-value	-	p<0.0001	p<0.0001	p=0.0002	p=0.0014	p=0.0002
Glucose (mmol/l)							
Annual Follow-Up	N	93	94	89	80	72	72
	Mean (SD)	8.63 (2.78)	6.82 (1.89)	6.86 (1.96)	7.55 (2.66)	8.16 (2.60)	8.60 (2.91)
Change from Baseline	Mean (95% CI)	-	-1.81 (-2.40, -1.22)	-1.78 (-2.41, -1.16)	-0.88 (-1.67, -0.09)	-0.26 (-0.97, 0.38)	0.28 (-0.41, 0.98)
	p-value	-	p<0.0001	p<0.0001	p=0.029	p=0.45	p=0.44
Insulin (µU/l)							
Annual Follow-Up	N	93	95	88	80	72	72
	Mean (SD)	24.29 (15.63)	13.89 (8.64)	14.49 (10.07)	17.68 (13.55)	19.93 (14.41)	18.61 (12.54)

Table S3: Data collected only in the DiRECT Extension group. Summaries are mean (SD) at each follow-up, and mean changes from baseline, with 95% confidence intervals (CI) and p-values derived using bootstrapping with 10,000 replicated datasets.

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Change from Baseline	Mean (95% CI) p-value	-	-10.29 (-13.21, -7.61) p<0.0001	-9.67 (-12.62, -7.04) p<0.0001	-6.35 (-9.70, -3.37) p<0.0001	-5.09 (-8.72, -1.71) p=0.0038	-3.99 (-6.68, -1.27) p=0.0022
C-rP (mg/l)							
Annual Follow-Up	N Mean (SD)	92 3.05 (2.81)	95 1.66 (1.67)	89 2.16 (2.29)	79 3.39 (5.08)	72 4.15 (10.94)	71 3.14 (3.50)
Change from Baseline	Mean (95% CI) p-value	-	-1.36 (-1.79, -0.94) p<0.0001	-0.94 (-1.40, -0.47) p=0.0008	0.55 (-0.41, 1.77) p=0.32	1.21 (-0.46, 4.07) p=0.44	0.37 (-0.33, 1.16) p=0.32
Gamma GT (U/l)							
Annual Follow-Up	N Mean (SD)	92 48 (53)	95 29 (20)	89 30 (20)	79 39 (43)	72 39 (42)	71 37 (33)
Change from Baseline	Mean (95% CI) p-value	-	-19 (-27, -12) p<0.0001	-19 (-28, -12) p<0.0001	-10 (-18, 0) p=0.046	-12 (-18, -6) p<0.0001	-13 (-22, -6) p<0.0001
Urea (mmol/l)							
Annual Follow-Up	N Mean (SD)	92 5.0 (1.3)	95 4.9 (1.3)	89 5.0 (1.2)	79 5.1 (1.3)	72 5.2 (1.4)	71 5.2 (1.4)
Change from Baseline	Mean (95% CI) p-value	-	-0.1 (-0.4, 0.1) p=0.38	0.0 (-0.3, 0.2) p=0.78	0.0 (-0.4, 0.3) p=0.77	0.1 (-0.3, 0.5) p=0.59	0.1 (-0.3, 0.4) p=0.66
Creatinine (µmol/l)							
Annual Follow-Up	N Mean (SD)	92 67 (14)	95 70 (15)	89 72 (13)	79 72 (16)	72 72 (15)	71 73 (17)
Change from Baseline	Mean (95% CI) p-value	-	2 (1, 4) p=0.0008	4 (2, 6) p<0.0001	3 (1, 5) p=0.0072	3 (0, 6) p=0.030	4 (2, 7) p=0.0008
ALT (U/l)							
Annual Follow-Up	N Mean (SD)	92 32.7 (17.5)	95 20.3 (9.2)	89 26.6 (10.8)	79 29.9 (25.3)	72 32.9 (30.2)	71 29.1 (14.5)
Change from Baseline	Mean (95% CI) p-value	-	-12.3 (-15.8, -9.0) p<0.0001	-6.7 (-10.4, -3.1) p=0.0004	-3.1 (-8.4, 4.2) p=0.34	-0.8 (-6.3, 6.0) p=0.77	-3.5 (-6.9, -0.1) p=0.045
AST (U/l)							

Table S3: Data collected only in the DiRECT Extension group. Summaries are mean (SD) at each follow-up, and mean changes from baseline, with 95% confidence intervals (CI) and p-values derived using bootstrapping with 10,000 replicated datasets.

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Annual Follow-Up	N	92	95	89	79	72	71
	Mean (SD)	23.6 (11.9)	19.1 (6.4)	21.1 (5.7)	24.2 (9.5)	26.4 (19.2)	23.9 (11.7)
Change from Baseline	Mean (95% CI)	-	-4.5 (-6.8, -2.5)	-2.8 (-5.3, -0.5)	0.3 (-2.5, 3.0)	1.5 (-2.6, 6.1)	-0.2 (-2.9, 2.3)
	p-value	-	p<0.0001	p=0.018	p=0.84	p=0.53	p=0.85
Magnesium (mmol/l)							
Annual Follow-Up	N	92	95	89	79	72	71
	Mean (SD)	0.78 (0.09)	0.84 (0.12)	0.79 (0.07)	0.77 (0.12)	0.77 (0.11)	0.75 (0.12)
Change from Baseline	Mean (95% CI)	-	0.07 (0.04, 0.09)	0.01 (-0.01, 0.03)	0.00 (-0.03, 0.02)	0.00 (-0.03, 0.02)	-0.02 (-0.05, 0.00)
	p-value	-	p<0.0001	p=0.48	p=0.94	p=0.89	p=0.085
Cholesterol (mmol/l)							
Annual Follow-Up	N	92	95	89	79	72	71
	Mean (SD)	4.22 (1.05)	4.49 (1.29)	4.67 (1.24)	4.75 (1.34)	4.58 (1.12)	4.66 (1.32)
Change from Baseline	Mean (95% CI)	-	0.27 (0.00, 0.53)	0.45 (0.20, 0.70)	0.54 (0.28, 0.81)	0.43 (0.12, 0.73)	0.48 (0.15, 0.82)
	p-value	-	p=0.046	p=0.0012	p<0.0001	p=0.0060	p=0.0036
HDL Cholesterol (mmol/l)							
Annual Follow-Up	N	92	95	89	79	72	71
	Mean (SD)	1.10 (0.23)	1.26 (0.33)	1.35 (0.36)	1.21 (0.34)	1.16 (0.31)	1.17 (0.29)
Change from Baseline	Mean (95% CI)	-	0.17 (0.12, 0.21)	0.24 (0.19, 0.30)	0.11 (0.06, 0.17)	0.08 (0.01, 0.14)	0.09 (0.03, 0.14)
	p-value	-	p<0.0001	p<0.0001	p<0.0001	p=0.026	p=0.0022
Triglycerides (mmol/l)							
Annual Follow-Up	N	92	95	89	79	72	71
	Mean (SD)	1.94 (1.30)	1.51 (1.15)	1.43 (0.68)	1.68 (0.83)	1.67 (0.83)	1.86 (1.23)
Change from Baseline	Mean (95% CI)	-	-0.41 (-0.69, -0.18)	-0.51 (-0.77, -0.29)	-0.20 (-0.40, -0.03)	-0.22 (-0.41, -0.03)	-0.03 (-0.19, 0.14)
	p-value	-	p<0.0001	p<0.0001	p=0.024	p=0.023	p=0.76
Sodium (mmol/l)							
Annual Follow-Up	N	89	89	88	72	72	69
	Mean (SD)	136 (4)	137 (5)	139 (4)	141 (4)	141 (3)	142 (3)
Change from Baseline	Mean (95% CI)	-	1 (0, 2)	3 (2, 4)	5 (3, 6)	5 (4, 6)	6 (5, 8)
	p-value	-	p=0.067	p<0.0001	p<0.0001	p<0.0001	p<0.0001

Table S3: Data collected only in the DiRECT Extension group. Summaries are mean (SD) at each follow-up, and mean changes from baseline, with 95% confidence intervals (CI) and p-values derived using bootstrapping with 10,000 replicated datasets.

		Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Potassium (mmol/l)							
Annual Follow-Up	N	87	95	86	77	70	68
	Mean (SD)	4.36 (0.50)	4.39 (0.52)	4.48 (0.49)	4.46 (0.40)	4.47 (0.50)	4.64 (0.48)
Change from Baseline	Mean (95% CI) p-value	-	0.01 (-0.11, 0.14) p=0.94	0.11 (-0.02, 0.24) p=0.091	0.04 (-0.09, 0.18) p=0.56	0.03 (-0.15, 0.20) p=0.69	0.24 (0.10, 0.38) p=0.0012
Chloride (mmol/l)							
Annual Follow-Up	N	92	95	89	79	72	71
	Mean (SD)	96.5 (4.4)	96.8 (5.2)	101.3 (3.4)	101.3 (6.5)	101.0 (8.1)	103.0 (7.0)
Change from Baseline	Mean (95% CI) p-value	-	0.2 (-1.1, 1.5) p=0.80	4.5 (3.5, 5.7) p<0.0001	4.6 (2.7, 6.3) p<0.0001	4.3 (1.8, 6.6) p=0.0016	6.5 (4.3, 8.5) p<0.0001

Table S4.1: Sensitivity analysis: Percentage of follow-up times with weight loss >5% from baseline, with HbA1c <48 mmol/mol, off all glucose-lowering medications, or in a state of remission, assuming these conditions were not met at follow-up times with missing data. 'Est' is the estimated mean difference. 'CI' indicates 95% confidence interval. p-values and CIs from bootstrapping with 10,000 replicated datasets.

		Control vs. Intervention			Non-Extension vs. Extension		
		Control	Intervention	Est (CI), p-value	Non-Extension	Extension	Est (CI), p-value
N		149	149		54	95	
Weight loss >5%	N	149	143	29 (22, 36), p<0.0001	48	95	35 (26, 44), p<0.0001
	Mean (SD)	23% (26%)	52% (34%)		29% (25%)	64% (32%)	
	Median	20%	40%		20%	60%	
	(IQR)	(0%, 40%)	(20%, 80%)		(20%, 45%)	(40%, 100%)	
HbA1c <48mmol/mol	N	149	144	13 (7, 19), p<0.0001	49	95	23 (15, 31), p<0.0001
	Mean (SD)	13% (23%)	25% (29%)		10% (18%)	33% (30%)	
	Median	0%	20%		0%	20%	
	(IQR)	(0%, 20%)	(0%, 40%)		(0%, 20%)	(0%, 50%)	
Off all glucose-lowering medication	N	149	148	34 (26, 41), p<0.0001	53	95	39 (28, 50), p<0.0001
	Mean (SD)	14% (29%)	47% (39%)		22% (29%)	61% (37%)	
	Median	0%	40%		20%	60%	
	(IQR)	(0%, 0%)	(0%, 85%)		(0%, 20%)	(30%, 100%)	
In remission	N	149	144	20 (15, 25), p<0.0001	49	95	25 (18, 33), p<0.0001
	Mean (SD)	3% (12%)	23% (29%)		7% (14%)	32% (31%)	
	Median	0%	20%		0%	20%	
	(IQR)	(0%, 0%)	(0%, 40%)		(0%, 0%)	(0%, 40%)	

Table S4.2: Percentage of follow-up time between year 3 and year 5 with weight loss >5% from baseline, with HbA1c <48 mmol/mol, off all glucose-lowering medications, or in a state of remission, based on available follow-up time for each participant. 'Est' is the estimated mean difference. 'CI' indicates 95% confidence interval. p-values and CIs from bootstrapping with 10,000 replicated datasets.

		Control vs. Intervention			Non-Extension vs. Extension		
		Control	Intervention	Est (CI), p-value	Non-Extension	Extension	Est (CI), p-value
N		149	149		54	95	
Weight loss >5%	N	124	134	8 (-2, 19), p=0.11	43	91	13 (-3, 28), p=0.10
	Mean (SD)	45% (43%)	54% (43%)		45% (42%)	58% (43%)	
	Median	50%	58%		50%	67%	
	(IQR)	(0%, 100%)	(0%, 100%)		(0%, 100%)	(0%, 100%)	
HbA1c <48mmol/mol	N	127	138	3 (-5, 10), p=0.50	45	93	6 (-6, 16), p=0.30
	Mean (SD)	14% (28%)	16% (32%)		13% (31%)	18% (32%)	
	Median	0%	0%		0%	0%	
	(IQR)	(0%, 0%)	(0%, 33%)		(0%, 0%)	(0%, 33%)	
Off all glucose-lowering medication	N	132	141	26 (17, 35), p<0.0001	47	94	30 (16, 44), p=0.0002
	Mean (SD)	14% (32%)	39% (44%)		19% (37%)	50% (44%)	
	Median	0%	33%		0%	33%	
	(IQR)	(0%, 0%)	(0%, 100%)		(0%, 0%)	(0%, 100%)	
In remission	N	127	138	9 (4, 15), p=0.0006	45	93	12 (3, 21), p=0.013
	Mean (SD)	3% (15%)	13% (30%)		4% (21%)	16% (32%)	
	Median	0%	0%		0%	0%	
	(IQR)	(0%, 0%)	(0%, 0%)		(0%, 0%)	(0%, 33%)	

Table S5: HbA1c and glucose-lowering medications over time. Intervention vs. Control, and within Intervention, Extension vs. No-Extension. Summaries are N (%). 'Est' is the estimated odds ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Fisher's Exact tests. Where no events observed in one group, only p-value reported.

		Control vs. Intervention					Intervention: Non-Extension vs. Extension				
		Control		Intervention		Est (CI), p-value	Non-Extension		Extension		Est (CI), p-value
		N	Summary	N	Summary		N	Summary	N	Summary	
HbA1c <48mmol/mol and Off Glucose-Lowering Medications (In remission)	Year 1	148	6 (4%)	138	68 (49%)	22.7 (9.3, 67.4), p<0.0001	43	9 (21%)	95	59 (62%)	6.1 (2.5, 16.2), p<0.0001
	Year 2	142	5 (4%)	129	52 (40%)	18.3 (7.0, 61.2), p<0.0001	34	4 (12%)	95	48 (51%)	7.6 (2.4, 31.8), p=0.0001
	Year 3	115	5 (4%)	126	25 (20%)	5.4 (1.9, 18.8), p=0.0003	37	2 (5%)	89	23 (26%)	6.0 (1.4, 55.7), p=0.0073
	Year 4	100	1 (1%)	119	9 (8%)	8.0 (1.1, 358.0), p=0.023	32	0 (0%)	87	9 (10%)	- (-, -), p=0.11
	Year 5	93	5 (5%)	118	12 (10%)	2.0 (0.6, 7.5), p=0.31	33	1 (3%)	85	11 (13%)	4.7 (0.6, 210.9), p=0.17
HbA1c <48mmol/mol and Taking Glucose-Lowering Medications	Year 1	148	17 (11%)	138	3 (2%)	0.2 (0.0, 0.6), p=0.0021	43	1 (2%)	95	2 (2%)	0.9 (0.0, 54.5), p=1.00
	Year 2	142	21 (15%)	129	0 (0%)	- (-, -), p<0.0001	34	0 (0%)	95	0 (0%)	- (-, -), p=1.00
	Year 3	115	15 (13%)	126	6 (5%)	0.3 (0.1, 1.0), p=0.037	37	4 (11%)	89	2 (2%)	0.2 (0.0, 1.4), p=0.061
	Year 4	100	12 (12%)	119	5 (4%)	0.3 (0.1, 1.0), p=0.042	32	3 (9%)	87	2 (2%)	0.2 (0.0, 2.1), p=0.12
	Year 5	93	7 (8%)	118	2 (2%)	0.2 (0.0, 1.2), p=0.045	33	1 (3%)	85	1 (1%)	0.4 (0.0, 30.8), p=0.48
HbA1c ≥48mmol/mol and Off Glucose-Lowering Medications	Year 1	148	21 (14%)	138	35 (25%)	2.0 (1.1, 3.9), p=0.025	43	11 (26%)	95	24 (25%)	1.0 (0.4, 2.5), p=1.00
	Year 2	142	18 (13%)	129	26 (20%)	1.7 (0.9, 3.6), p=0.10	34	4 (12%)	95	22 (23%)	2.2 (0.7, 9.7), p=0.21
	Year 3	115	11 (10%)	126	37 (29%)	3.9 (1.8, 9.0), p=0.0002	37	5 (14%)	89	32 (36%)	3.6 (1.2, 12.9), p=0.017
	Year 4	100	9 (9%)	119	29 (24%)	3.2 (1.4, 8.2), p=0.0038	32	1 (3%)	87	28 (32%)	14.5 (2.2, 618.9), p=0.0006
	Year 5	93	7 (8%)	118	25 (21%)	3.3 (1.3, 9.5), p=0.0066	33	1 (3%)	85	24 (28%)	12.4 (1.8, 532.3), p=0.0020
HbA1c ≥48mmol/mol and Taking Glucose-Lowering Medications	Year 1	148	104 (70%)	138	32 (23%)	0.1 (0.1, 0.2), p<0.0001	43	22 (51%)	95	10 (11%)	0.1 (0.0, 0.3), p<0.0001
	Year 2	142	98 (69%)	129	51 (40%)	0.3 (0.2, 0.5), p<0.0001	34	26 (76%)	95	25 (26%)	0.1 (0.0, 0.3), p<0.0001
	Year 3	115	84 (73%)	126	58 (46%)	0.3 (0.2, 0.6), p<0.0001	37	26 (70%)	89	32 (36%)	0.2 (0.1, 0.6), p=0.0007
	Year 4	100	78 (78%)	119	76 (64%)	0.5 (0.3, 0.9), p=0.026	32	28 (88%)	87	48 (55%)	0.2 (0.0, 0.6), p=0.0011
	Year 5	93	74 (80%)	118	79 (67%)	0.5 (0.3, 1.0), p=0.045	33	30 (91%)	85	49 (58%)	0.1 (0.0, 0.5), p=0.0004

Table S6: Intervention Patients Key study outcomes by site: Scotland and Tyneside

	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Scotland						
N with data	83	76	71	64	63	61
Mean (SD) Weight (kg)	100.8 (16.3)	90.8 (17.0)	92.7 (16.8)	95.1 (17.5)	94.8 (16.2)	93.7 (15.4)
Mean (SD) Weight Change (kg) from Baseline	-	-9.7 (7.4)	-7.8 (6.5)	-6.7 (5.4)	-5.5 (5.5)	-6.6 (5.4)
N with data	-	76	71	69	64	64
N (%) in remission	-	34 (44.7%)	26 (36.6%)	15 (21.7%)	4 (6.2%)	7 (10.9%)
Tyneside						
N with data	66	61	58	56	51	55
Mean (SD) Weight (kg)	101.3 (17.5)	90.0 (15.8)	93.8 (17.8)	95.0 (16.0)	92.0 (13.0)	95.5 (17.5)
Mean (SD) Weight Change (kg) from Baseline	-	-10.4 (8.7)	-7.4 (6.5)	-6.0 (7.5)	-5.2 (6.2)	-4.6 (6.1)
N with data	-	62	58	57	55	54
N (%) in remission	-	34 (54.8%)	26 (44.8%)	10 (17.5%)	5 (9.1%)	5 (9.3%)

Table S7: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during each year of follow up, split by randomised group (Intervention vs. Control) and, within the Intervention group, by Extension or Non-extension subgroups. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

		Control vs. Intervention							Intervention: Non-Extension vs. Extension						
		Control			Intervention			Est (CI), p-value	Non-Extension			Extension			Est (CI), p-value
		N	Events	Rate (/100py)	N	Events	Rate (/100py)		N	Events	Rate (/100py)	N	Events	Rate (/100py)	
SAE	Y1	149	3	2.0	148	6	4.1	2.0 (0.4, 9.1), p=0.36 ^{NB}	53	0	0.0	95	6	6.3	- (-, -), p=0.16 ^F
	Y2	146	23	15.8	144	7	4.9	0.3 (0.1, 0.9), p=0.024 ^{NB}	49	3	6.1	95	4	4.2	0.7 (0.1, 5.3), p=0.72 ^{NB}
	Y3	132	11	8.3	141	6	4.3	0.5 (0.2, 1.7), p=0.28 ^{NB}	47	2	4.3	94	4	4.3	1.0 (0.2, 5.5), p=1.00 ^P
	Y4	127	11	8.7	139	8	5.8	0.7 (0.2, 1.9), p=0.44 ^{NB}	46	5	10.9	93	3	3.2	0.3 (0.1, 1.2), p=0.096 ^P
	Y5	121	21	17.4	136	7	5.1	0.3 (0.1, 0.8), p=0.014 ^{NB}	43	2	4.7	93	5	5.4	1.2 (0.2, 6.0), p=0.86 ^P
MMACE	Y1	149	1	0.7	148	3	2.0	3.0 (0.3, 29.0), p=0.34 ^P	53	0	0.0	95	3	3.2	- (-, -), p=0.55 ^F
	Y2	146	7	4.8	144	5	3.5	0.7 (0.2, 2.3), p=0.58 ^P	49	2	4.1	95	3	3.2	0.8 (0.1, 4.6), p=0.78 ^P
	Y3	132	5	3.8	141	6	4.3	1.1 (0.3, 4.6), p=0.87 ^{NB}	47	3	6.4	94	3	3.2	0.5 (0.1, 3.3), p=0.47 ^{NB}
	Y4	127	3	2.4	139	5	3.6	1.5 (0.3, 7.5), p=0.60 ^{NB}	46	1	2.2	93	4	4.3	2.0 (0.2, 24.8), p=0.60 ^{NB}
	Y5	121	5	4.1	136	5	3.7	0.9 (0.3, 3.1), p=0.85 ^P	43	1	2.3	93	4	4.3	1.8 (0.2, 16.5), p=0.58 ^P
MADE	Y1	149	14	9.4	148	16	10.8	1.2 (0.5, 2.5), p=0.73 ^{NB}	53	6	11.3	95	10	10.5	0.9 (0.3, 3.1), p=0.90 ^{NB}
	Y2	146	25	17.1	144	21	14.6	0.9 (0.5, 1.5), p=0.59 ^P	49	11	22.4	95	10	10.5	0.5 (0.2, 1.1), p=0.083 ^P
	Y3	132	24	18.2	141	16	11.3	0.6 (0.3, 1.3), p=0.19 ^{NB}	47	8	17.0	94	8	8.5	0.5 (0.2, 1.6), p=0.23 ^{NB}
	Y4	127	19	15.0	139	26	18.7	1.3 (0.7, 2.3), p=0.46 ^P	46	7	15.2	93	19	20.4	1.3 (0.5, 3.5), p=0.55 ^{NB}
	Y5	121	16	13.2	136	22	16.2	1.2 (0.6, 2.3), p=0.54 ^P	43	6	14.0	93	16	17.2	1.2 (0.5, 3.2), p=0.66 ^P

Table S8: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetes Events (MADE) during follow up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. 'py' = 'person-years'

		Control vs. Intervention			Non-Extension vs. Extension		
		Control	Intervention	Est (CI), p-value	Non-Extension	Extension	Est (CI), p-value
	N	149	149		54	95	
SAE	N Patients	149	148		53	95	
	N Events	69	34	0.5 (0.3, 0.8), p=0.0080 ^{NB}	12	22	0.9 (0.4, 2.2), p=0.89 ^{NB}
	Event Rate (/100py)	10.2	4.8		5.0	4.7	
MMACE	N Patients	149	148		53	95	
	N Events	21	24	1.1 (0.6, 2.1), p=0.80 ^{NB}	7	17	1.2 (0.5, 3.0), p=0.65 ^P
	Event Rate (/100py)	3.1	3.4		2.9	3.6	
MADE	N Patients	149	148		53	95	
	N Events	98	101	1.0 (0.7, 1.3), p=0.89 ^{NB}	38	63	0.8 (0.5, 1.3), p=0.47 ^{NB}
	Event Rate (/100py)	14.5	14.3		16.0	13.4	

Table S9: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetes Events (MADE) after the first annual follow up, in relation to achievement of treatment goals at year 1. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F'). 'py' = 'person-years'.

		Control			Intervention		
		Weight Loss at 1 Year		Est (CI), p-value	Weight Loss at 1 Year		Est (CI), p-value
		≤10kg	>5%		≤10kg	>5%	
N Patients		127	18		33	103	
SAE	N Events	59	7	0.8 (0.2, 2.9), p=0.78 ^{NB}	7	18	0.8 (0.3, 2.3), p=0.65 ^{NB}
	Event Rate (/100py)	12.9	11.1		5.7	4.4	
MMACE	N Events	15	5	2.4 (0.9, 6.7), p=0.086 ^P	4	16	1.2 (0.4, 3.6), p=0.74 ^P
	Event Rate (/100py)	3.3	7.9		3.3	3.9	
MADE	N Events	74	10	1.0 (0.5, 1.9), p=0.96 ^P	28	52	0.6 (0.3, 0.9), p=0.031 ^{NB}
	Event Rate (/100py)	16.1	15.9		23.0	12.8	

		Control			Intervention		
		HbA1c <48mmol/mol at 1 Year		Est (CI), p-value	HbA1c <48mmol/mol at 1 Year		Est (CI), p-value
		No	Yes		No	Yes	
N Patients		122	23		67	70	
SAE	N Events	59	7	0.6 (0.2, 1.8), p=0.34 ^{NB}	16	11	0.7 (0.3, 1.7), p=0.37 ^{NB}
	Event Rate (/100py)	13.7	7.8		6.2	4.0	
MMACE	N Events	16	4	1.2 (0.4, 3.6), p=0.74 ^P	13	8	0.6 (0.2, 1.4), p=0.23 ^P
	Event Rate (/100py)	3.7	4.4		5.0	2.9	
MADE	N Events	70	14	1.0 (0.5, 1.7), p=0.89 ^P	51	30	0.6 (0.3, 0.9), p=0.022 ^{NB}
	Event Rate (/100py)	16.2	15.6		19.6	11.0	

		Control			Intervention		
		Glucose-Lowering Medications at 1 Year		Est (CI), p-value	Glucose-Lowering Medications at 1 Year		Est (CI), p-value
		Any	None		Any	None	
N Patients		119	26		38	106	
SAE	N Events	61	5	0.4 (0.1, 1.4), p=0.16 ^{NB}	8	20	0.9 (0.3, 2.4), p=0.80 ^{NB}
	Event Rate (/100py)	14.1	5.6		5.5	4.8	

Table S9: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetes Events (MADE) after the first annual follow up, in relation to achievement of treatment goals at year 1. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F'). 'py' = 'person-years'.

MMACE	N Events	16	4	1.2 (0.4, 3.6), p=0.74 ^P	6	15	0.9 (0.3, 2.3), p=0.78 ^P
	Event Rate (/100py)	3.7	4.4		4.1	3.6	
MADE	N Events	76	8	0.5 (0.2, 1.0), p=0.066 ^P	29	56	0.7 (0.4, 1.1), p=0.13 ^{NB}
	Event Rate (/100py)	17.6	8.9		20.0	13.5	
		Control			Intervention		
		Antihypertensive Medications at 1 Year		Est (CI), p-value	Antihypertensive Medications at 1 Year		Est (CI), p-value
		Any	None		Any	None	
N Patients		88	57		47	97	
SAE	N Events	57	9	0.3 (0.1, 0.6), p=0.0026 ^{NB}	9	19	1.0 (0.4, 2.6), p=0.97 ^{NB}
	Event Rate (/100py)	18.0	4.4		4.9	5.0	
MMACE	N Events	18	2	0.2 (0.0, 0.7), p=0.018 ^P	8	13	0.8 (0.3, 1.9), p=0.59 ^P
	Event Rate (/100py)	5.7	1.0		4.4	3.4	
MADE	N Events	59	25	0.7 (0.4, 1.0), p=0.076 ^P	32	53	0.8 (0.5, 1.3), p=0.37 ^{NB}
	Event Rate (/100py)	18.6	12.2		17.6	14.0	
		Control			Intervention		
		In Remission at 1 Year		Est (CI), p-value	In Remission at 1 Year		Est (CI), p-value
		No	Yes		No	Yes	
N Patients		139	6		70	67	
SAE	N Events	66	0	- (-, -), p=0.34 ^F	17	10	0.6 (0.2, 1.6), p=0.31 ^{NB}
	Event Rate (/100py)	13.2	0.0		6.2	3.8	
MMACE	N Events	20	0	- (-, -), p=1.00 ^F	13	8	0.6 (0.3, 1.5), p=0.32 ^P
	Event Rate (/100py)	4.0	0.0		4.8	3.1	
MADE	N Events	84	0	- (-, -), p=0.038 ^F	52	29	0.6 (0.4, 1.0), p=0.034 ^{NB}
	Event Rate (/100py)	16.8	0.0		19.1	11.1	

Table S10: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during each year of follow up, split by weight loss from baseline at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

		Control, by Weight Loss at T1								Intervention, by Weight Loss at T1								
		≤5%			>5%			Est (CI), p-value	≤5%			>5%			Est (CI), p-value			
T1	T2	N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)		N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)				
SAE	Y1	Y2	127	19	15.0	18	4	22.2	1.5 (0.3, 6.8), p=0.61 ^{NB}		33	1	3.0	103	4	3.9	1.3 (0.1, 17.5), p=0.85 ^{NB}	
	Y2	Y3	94	7	7.4	35	4	11.4	1.5 (0.2, 10.1), p=0.66 ^{NB}		47	1	2.1	79	4	5.1	2.4 (0.3, 21.3), p=0.44 ^P	
	Y3	Y4	63	3	4.8	47	6	12.8	2.7 (0.5, 13.6), p=0.23 ^{NB}		55	4	7.3	63	3	4.8	0.7 (0.1, 2.9), p=0.58 ^P	
	Y4	Y5	47	3	6.4	36	6	16.7	2.6 (0.7, 10.4), p=0.17 ^P		50	2	4.0	62	2	3.2	0.8 (0.1, 5.7), p=0.83 ^P	
MMACE	Y1	Y2	127	5	3.9	18	2	11.1	2.8 (0.5, 14.5), p=0.21 ^P		33	1	3.0	103	3	2.9	1.0 (0.1, 9.2), p=0.97 ^P	
	Y2	Y3	94	4	4.3	35	1	2.9	0.7 (0.1, 8.9), p=0.76 ^{NB}		47	2	4.3	79	3	3.8	0.9 (0.1, 8.0), p=0.92 ^{NB}	
	Y3	Y4	63	1	1.6	47	2	4.3	2.7 (0.2, 29.6), p=0.42 ^P		55	3	5.5	63	2	3.2	0.6 (0.1, 5.0), p=0.62 ^{NB}	
	Y4	Y5	47	1	2.1	36	0	0.0	- (-, -), p=1.00 ^F		50	4	8.0	62	1	1.6	0.2 (0.0, 1.8), p=0.15 ^P	
MADE	Y1	Y2	127	22	17.3	18	3	16.7	1.0 (0.3, 3.2), p=0.95 ^P		33	4	12.1	103	15	14.6	1.2 (0.4, 3.6), p=0.74 ^P	
	Y2	Y3	94	15	16.0	35	9	25.7	1.6 (0.6, 4.1), p=0.32 ^{NB}		47	6	12.8	79	7	8.9	0.7 (0.2, 2.1), p=0.51 ^P	
	Y3	Y4	63	8	12.7	47	8	17.0	1.3 (0.5, 3.6), p=0.56 ^P		55	12	21.8	63	12	19.0	0.9 (0.4, 2.2), p=0.77 ^{NB}	
	Y4	Y5	47	3	6.4	36	4	11.1	1.7 (0.4, 7.8), p=0.47 ^P		50	12	24.0	62	5	8.1	0.3 (0.1, 1.0), p=0.040 ^P	

Table S11: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during or after each year of follow up, split by weight loss from baseline at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

	T1	Control, by Weight Loss at T1							Intervention, by Weight Loss at T1						
		≤5%			>5%			Est (CI), p-value	≤5%			>5%			Est (CI), p-value
		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)	
SAE	Y1	127	59	12.9	18	7	11.1	0.8 (0.2, 2.9), p=0.78 ^{NB}	33	7	5.7	103	18	4.4	0.8 (0.3, 2.3), p=0.65 ^{NB}
	Y2	94	22	8.2	35	20	19.4	2.4 (0.8, 7.0), p=0.098 ^{NB}	47	6	4.3	79	13	5.6	1.3 (0.4, 3.9), p=0.66 ^{NB}
	Y3	63	10	8.0	47	18	20.0	2.6 (0.9, 7.7), p=0.090 ^{NB}	55	5	4.5	63	7	5.6	1.2 (0.4, 3.9), p=0.72 ^P
	Y4	47	3	6.4	36	6	16.7	2.6 (0.7, 10.4), p=0.17 ^P	50	2	4.0	62	2	3.2	0.8 (0.1, 5.7), p=0.83 ^P
MMACE	Y1	127	15	3.3	18	5	7.9	2.4 (0.9, 6.7), p=0.086 ^P	33	4	3.3	103	16	3.9	1.2 (0.4, 3.6), p=0.74 ^P
	Y2	94	10	3.7	35	3	2.9	0.8 (0.2, 2.8), p=0.71 ^P	47	6	4.3	79	8	3.4	0.8 (0.3, 2.3), p=0.67 ^P
	Y3	63	4	3.2	47	3	3.3	1.0 (0.2, 4.7), p=0.96 ^P	55	6	5.5	63	3	2.4	0.4 (0.1, 1.8), p=0.25 ^P
	Y4	47	1	2.1	36	0	0.0	- (-, -), p=1.00 ^F	50	4	8.0	62	1	1.6	0.2 (0.0, 1.8), p=0.15 ^P
MADE	Y1	127	74	16.1	18	10	15.9	1.0 (0.5, 1.9), p=0.96 ^P	33	28	23.0	103	52	12.8	0.6 (0.3, 0.9), p=0.031 ^{NB}
	Y2	94	42	15.7	35	17	16.5	1.0 (0.5, 2.0), p=0.89 ^{NB}	47	28	20.1	79	29	12.4	0.6 (0.4, 1.0), p=0.067 ^P
	Y3	63	16	12.8	47	15	16.7	1.3 (0.6, 2.6), p=0.46 ^P	55	25	22.7	63	16	12.8	0.6 (0.3, 1.1), p=0.073 ^P
	Y4	47	3	6.4	36	4	11.1	1.7 (0.4, 7.8), p=0.47 ^P	50	12	24.0	62	5	8.1	0.3 (0.1, 1.0), p=0.040 ^P

Table S12: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during each year of follow up, split by HbA1c at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

	T1	T2	Control, by HbA1c at T1							Intervention, by HbA1c at T1						
			≥48mmol/mol			<48mmol/mol			Est (CI), p-value	≥48mmol/mol			<48mmol/mol			Est (CI), p-value
			N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)		N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)	
SAE	Y1	Y2	122	22	18.0	23	1	4.3	0.2 (0.0, 2.2), p=0.21 ^{NB} - (-, -), p=0.35 ^F 1.7 (0.4, 8.6), p=0.49 ^{NB} 0.4 (0.0, 4.1), p=0.44 ^{NB}	67	3	4.5	70	4	5.7	1.3 (0.2, 9.5), p=0.81 ^{NB} 1.0 (0.2, 5.9), p=0.98 ^P - (-, -), p=0.19 ^F - (-, -), p=1.00 ^F
	Y2	Y3	105	11	10.5	24	0	0.0		75	3	4.0	51	2	3.9	
	Y3	Y4	93	8	8.6	20	3	15.0		94	8	8.5	30	0	0.0	
	Y4	Y5	85	18	21.2	12	1	8.3		104	6	5.8	14	0	0.0	
MMACE	Y1	Y2	122	6	4.9	23	1	4.3	0.9 (0.1, 7.3), p=0.91 ^P - (-, -), p=1.00 ^F - (-, -), p=1.00 ^F 7.1 (0.4, 113.2), p=0.17 ^P	67	2	3.0	70	3	4.3	1.4 (0.2, 8.6), p=0.69 ^P 0.4 (0.0, 4.4), p=0.43 ^{NB} 0.8 (0.1, 10.7), p=0.85 ^{NB} - (-, -), p=1.00 ^F
	Y2	Y3	105	5	4.8	24	0	0.0		75	4	5.3	51	1	2.0	
	Y3	Y4	93	3	3.2	20	0	0.0		94	4	4.3	30	1	3.3	
	Y4	Y5	85	1	1.2	12	1	8.3		104	5	4.8	14	0	0.0	
MADE	Y1	Y2	122	20	16.4	23	5	21.7	1.3 (0.5, 3.5), p=0.57 ^P 0.4 (0.1, 1.8), p=0.24 ^{NB} 0.3 (0.0, 2.2), p=0.23 ^P 2.7 (0.7, 10.0), p=0.15 ^P	67	12	17.9	70	8	11.4	0.6 (0.3, 1.6), p=0.32 ^P 0.3 (0.1, 1.2), p=0.086 ^P 0.4 (0.1, 1.4), p=0.17 ^P 1.2 (0.4, 4.2), p=0.73 ^P
	Y2	Y3	105	22	21.0	24	2	8.3		75	11	14.7	51	2	3.9	
	Y3	Y4	93	16	17.2	20	1	5.0		94	22	23.4	30	3	10.0	
	Y4	Y5	85	8	9.4	12	3	25.0		104	18	17.3	14	3	21.4	

Table S13: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during or after each year of follow up, split by HbA1c at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

	T1	Control, by HbA1c at T1							Intervention, by HbA1c at T1						
		≥48mmol/mol			<48mmol/mol			Est (CI), p-value	≥48mmol/mol			<48mmol/mol			Est (CI), p-value
		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)	
SAE	Y1	122	59	13.7	23	7	7.8	0.6 (0.2, 1.8), p=0.34 ^{NB}	67	16	6.2	70	11	4.0	0.7 (0.3, 1.7), p=0.37 ^{NB}
	Y2	105	35	11.6	24	7	10.1	0.9 (0.3, 3.5), p=0.92 ^{NB}	75	15	6.7	51	4	2.7	0.4 (0.1, 1.3), p=0.14 ^{NB}
	Y3	93	24	13.2	20	8	20.5	1.7 (0.5, 5.8), p=0.38 ^{NB}	94	12	6.5	30	1	1.7	0.3 (0.0, 2.0), p=0.19 ^P
	Y4	85	18	21.2	12	1	8.3	0.4 (0.0, 4.1), p=0.44 ^{NB}	104	6	5.8	14	0	0.0	- (-, -), p=1.00 ^F
MMACE	Y1	122	16	3.7	23	4	4.4	1.2 (0.4, 3.6), p=0.74 ^P	67	13	5.0	70	8	2.9	0.6 (0.2, 1.4), p=0.23 ^P
	Y2	105	9	3.0	24	4	5.8	1.9 (0.6, 6.3), p=0.27 ^P	75	9	4.0	51	5	3.4	0.8 (0.3, 2.5), p=0.75 ^P
	Y3	93	6	3.3	20	2	5.1	1.6 (0.3, 7.7), p=0.59 ^P	94	7	3.8	30	2	3.3	0.9 (0.2, 4.3), p=0.88 ^P
	Y4	85	1	1.2	12	1	8.3	7.1 (0.4, 113.2), p=0.17 ^P	104	5	4.8	14	0	0.0	- (-, -), p=1.00 ^F
MADE	Y1	122	70	16.2	23	14	15.6	1.0 (0.5, 1.7), p=0.89 ^P	67	51	19.6	70	30	11.0	0.6 (0.3, 0.9), p=0.022 ^{NB}
	Y2	105	48	15.9	24	11	15.9	1.0 (0.5, 2.1), p=0.99 ^{NB}	75	38	17.0	51	19	12.8	0.8 (0.4, 1.3), p=0.31 ^P
	Y3	93	29	15.9	20	4	10.3	0.6 (0.2, 1.8), p=0.41 ^P	94	37	19.9	30	5	8.3	0.4 (0.2, 1.1), p=0.068 ^P
	Y4	85	8	9.4	12	3	25.0	2.7 (0.7, 10.0), p=0.15 ^P	104	18	17.3	14	3	21.4	1.2 (0.4, 4.2), p=0.73 ^P

Table S14: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during each year of follow up, split by use of glucose-lowering medication at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

	T1	T2	Control, by use of glucose-lowering medication at T1							Intervention, by use of glucose-lowering medication at T1								
			Yes			No			Est (CI), p-value	Yes			No			Est (CI), p-value		
			N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)		N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)			
SAE	Y1	Y2	119	21	17.6	26	2	7.7	0.4 (0.1, 2.4), p=0.34 ^{NB}	38	0	0.0	106	7	6.6	-	(-, -), p=0.33 ^F	
	Y2	Y3	109	10	9.2	21	1	4.8		49	3	6.1	77	2	2.6			0.4 (0.1, 2.5), p=0.35 ^P
	Y3	Y4	109	8	7.3	18	3	16.7		72	8	11.1	67	0	0.0			- (-, -), p=0.014 ^F
	Y4	Y5	106	20	18.9	15	1	6.7		87	4	4.6	49	3	6.1			1.3 (0.3, 5.9), p=0.71 ^P
MMACE	Y1	Y2	119	6	5.0	26	1	3.8	0.8 (0.1, 6.3), p=0.80 ^P	38	0	0.0	106	5	4.7	-	(-, -), p=0.33 ^F	
	Y2	Y3	109	3	2.8	21	2	9.5		49	4	8.2	77	1	1.3			0.2 (0.0, 1.7), p=0.13 ^{NB}
	Y3	Y4	109	3	2.8	18	0	0.0		72	4	5.6	67	1	1.5			0.3 (0.0, 3.1), p=0.29 ^{NB}
	Y4	Y5	106	4	3.8	15	1	6.7		87	2	2.3	49	3	6.1			2.7 (0.4, 15.9), p=0.28 ^P
MADE	Y1	Y2	119	22	18.5	26	3	11.5	0.6 (0.2, 2.1), p=0.44 ^P	38	8	21.1	106	13	12.3	0.6 (0.2, 1.4), p=0.23 ^P		
	Y2	Y3	109	22	20.2	21	2	9.5		49	10	20.4	77	3	3.9		0.2 (0.1, 0.7), p=0.012 ^P	
	Y3	Y4	109	15	13.8	18	4	22.2		72	17	23.6	67	9	13.4		0.6 (0.2, 1.4), p=0.21 ^{NB}	
	Y4	Y5	106	13	12.3	15	3	20.0		87	16	18.4	49	6	12.2		0.7 (0.3, 1.7), p=0.40 ^P	

Table S15: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during or after each year of follow up, split by use of glucose-lowering medication at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models.

	T1	Control, by use of glucose-lowering medication at T1							Intervention, by use of glucose-lowering medication at T1						
		Yes			No			Est (CI), p-value	Yes			No			Est (CI), p-value
		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)	
SAE	Y1	119	61	14.1	26	5	5.6	0.4 (0.1, 1.4), p=0.16 ^{NB}	38	8	5.5	106	20	4.8	0.9 (0.3, 2.4), p=0.80 ^{NB}
	Y2	109	38	12.1	21	5	8.2	0.7 (0.2, 2.7), p=0.57 ^{NB}	49	11	7.5	77	8	3.5	0.5 (0.2, 1.3), p=0.15 ^{NB}
	Y3	109	25	11.8	18	7	19.4	1.6 (0.4, 6.2), p=0.48 ^{NB}	72	10	7.0	67	5	3.8	0.5 (0.2, 1.6), p=0.25 ^P
	Y4	106	20	18.9	15	1	6.7	0.4 (0.0, 3.4), p=0.37 ^{NB}	87	4	4.6	49	3	6.1	1.3 (0.3, 5.9), p=0.71 ^P
MMACE	Y1	119	16	3.7	26	4	4.4	1.2 (0.4, 3.6), p=0.74 ^P	38	6	4.1	106	15	3.6	0.9 (0.3, 2.3), p=0.78 ^P
	Y2	109	11	3.5	21	2	3.3	0.9 (0.2, 4.2), p=0.93 ^P	49	8	5.5	77	6	2.6	0.5 (0.2, 1.4), p=0.18 ^P
	Y3	109	7	3.3	18	1	2.8	0.8 (0.1, 6.8), p=0.87 ^P	72	5	3.5	67	5	3.8	1.1 (0.3, 3.7), p=0.92 ^P
	Y4	106	4	3.8	15	1	6.7	1.8 (0.1, 30.3), p=0.69 ^{NB}	87	2	2.3	49	3	6.1	2.7 (0.4, 15.9), p=0.28 ^P
MADE	Y1	119	76	17.6	26	8	8.9	0.5 (0.2, 1.0), p=0.066 ^P	38	29	20.0	106	56	13.5	0.7 (0.4, 1.1), p=0.13 ^{NB}
	Y2	109	54	17.3	21	5	8.2	0.5 (0.2, 1.3), p=0.14 ^{NB}	49	28	19.2	77	29	12.8	0.7 (0.4, 1.1), p=0.13 ^P
	Y3	109	27	12.7	18	8	22.2	1.7 (0.8, 3.8), p=0.17 ^P	72	26	18.3	67	22	16.5	0.9 (0.5, 1.6), p=0.73 ^P
	Y4	106	13	12.3	15	3	20.0	1.6 (0.4, 7.3), p=0.52 ^{NB}	87	16	18.4	49	6	12.2	0.7 (0.3, 1.7), p=0.40 ^P

Table S16: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during each year of follow up, split by use of antihypertensive medication at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

	T1	T2	Control, by use of antihypertensive medication at T1							Intervention, by use of antihypertensive medication at T1						
			Yes			No			Est (CI), p-value	Yes			No			Est (CI), p-value
			N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)		N	Events (T1-T2)	Rate (/100py)	N	Events (T1-T2)	Rate (/100py)	
SAE	Y1	Y2	88	20	22.7	57	3	5.3	0.2 (0.1, 0.9), p=0.036 ^{NB} - (-, -), p=0.043 ^F 0.4 (0.1, 1.9), p=0.24 ^{NB} 0.3 (0.1, 1.3), p=0.11 ^{NB}	47	3	6.4	97	4	4.1	0.6 (0.1, 5.0), p=0.68 ^{NB} 3.5 (0.4, 31.5), p=0.26 ^P 2.7 (0.5, 13.4), p=0.22 ^P 0.4 (0.1, 2.1), p=0.29 ^P
	Y2	Y3	80	11	13.8	50	0	0.0		59	1	1.7	67	4	6.0	
	Y3	Y4	79	9	11.4	48	2	4.2		66	2	3.0	73	6	8.2	
	Y4	Y5	79	18	22.8	42	3	7.1		69	5	7.2	67	2	3.0	
MMACE	Y1	Y2	88	6	6.8	57	1	1.8	0.3 (0.0, 2.1), p=0.21 ^P - (-, -), p=0.30 ^F 0.8 (0.1, 9.1), p=0.87 ^P - (-, -), p=0.30 ^F	47	1	2.1	97	4	4.1	1.9 (0.2, 17.3), p=0.55 ^P 1.3 (0.2, 11.5), p=0.80 ^{NB} 1.4 (0.2, 11.8), p=0.78 ^{NB} - (-, -), p=0.058 ^F
	Y2	Y3	80	5	6.2	50	0	0.0		59	2	3.4	67	3	4.5	
	Y3	Y4	79	2	2.5	48	1	2.1		66	2	3.0	73	3	4.1	
	Y4	Y5	79	5	6.3	42	0	0.0		69	5	7.2	67	0	0.0	
MADE	Y1	Y2	88	16	18.2	57	9	15.8	0.9 (0.4, 2.0), p=0.73 ^P 0.8 (0.3, 2.1), p=0.64 ^{NB} 0.4 (0.1, 1.3), p=0.14 ^P 0.4 (0.1, 1.7), p=0.23 ^{NB}	47	11	23.4	97	10	10.3	0.4 (0.2, 1.0), p=0.061 ^P 1.4 (0.5, 4.3), p=0.55 ^P 1.1 (0.4, 2.5), p=0.90 ^{NB} 0.7 (0.3, 1.7), p=0.44 ^P
	Y2	Y3	80	16	20.0	50	8	16.0		59	5	8.5	67	8	11.9	
	Y3	Y4	79	15	19.0	48	4	8.3		66	12	18.2	73	14	19.2	
	Y4	Y5	79	13	16.5	42	3	7.1		69	13	18.8	67	9	13.4	

Table S17: Incidence of Serious Adverse Events (SAE), Moderate/Major Adverse Cardiovascular Events (MMACE), and Major Adverse Diabetic Events (MADE) during or after each year of follow up, split by use of antihypertensive medication at the start of each year of follow-up. 'Est' is the estimated incidence rate ratio. 'CI' indicates 95% confidence interval. p-values and CIs from Wald tests of incidence rate ratios using Negative Binomial ('NB') or Poisson ('P') regression models. Where no events observed in one group, p-value reported from Fisher's Exact test ('F').

	T1	Control, by use of antihypertensive medication at T1							Intervention, by use of antihypertensive medication at T1							
		Yes			No			Est (CI), p-value	Yes			No			Est (CI), p-value	
		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)		N	Events (After T1)	Rate (/100py)	N	Events (After T1)	Rate (/100py)		
SAE	Y1	88	57	18.0	57	9	4.4	0.3 (0.1, 0.6), p=0.0026 ^{NB}	47	9	4.9	97	19	5.0	1.0 (0.4, 2.6), p=0.97 ^{NB}	
	Y2	80	37	16.3	50	6	4.1		59	7	4.0	67	12	6.0		1.5 (0.5, 4.3), p=0.47 ^{NB}
	Y3	79	26	17.0	48	6	6.3		66	7	5.3	73	8	5.6		1.0 (0.4, 2.9), p=0.94 ^P
	Y4	79	18	22.8	42	3	7.1		69	5	7.2	67	2	3.0		0.4 (0.1, 2.1), p=0.29 ^P
MMACE	Y1	88	18	5.7	57	2	1.0	0.2 (0.0, 0.7), p=0.018 ^P	47	8	4.4	97	13	3.4	0.8 (0.3, 1.9), p=0.59 ^P	
	Y2	80	12	5.3	50	1	0.7		59	7	4.0	67	7	3.5		0.9 (0.3, 2.5), p=0.79 ^P
	Y3	79	7	4.6	48	1	1.1		66	6	4.6	73	4	2.8		0.6 (0.2, 2.1), p=0.44 ^P
	Y4	79	5	6.3	42	0	0.0		69	5	7.2	67	0	0.0		- (-, -), p=0.058 ^F
MADE	Y1	88	59	18.6	57	25	12.2	0.7 (0.4, 1.0), p=0.076 ^P	47	32	17.6	97	53	14.0	0.8 (0.5, 1.3), p=0.37 ^{NB}	
	Y2	80	43	18.9	50	16	10.9		59	24	13.9	67	33	16.5		1.2 (0.7, 2.0), p=0.52 ^P
	Y3	79	28	18.3	48	7	7.4		66	22	16.8	73	26	18.1		1.1 (0.6, 1.9), p=0.80 ^P
	Y4	79	13	16.5	42	3	7.1		69	13	18.8	67	9	13.4		0.7 (0.3, 1.7), p=0.44 ^P

Figure S1. Flow Diagram: DiRECT 2-year cluster-randomised controlled trial, followed by 3 years DiRECT-Extension study

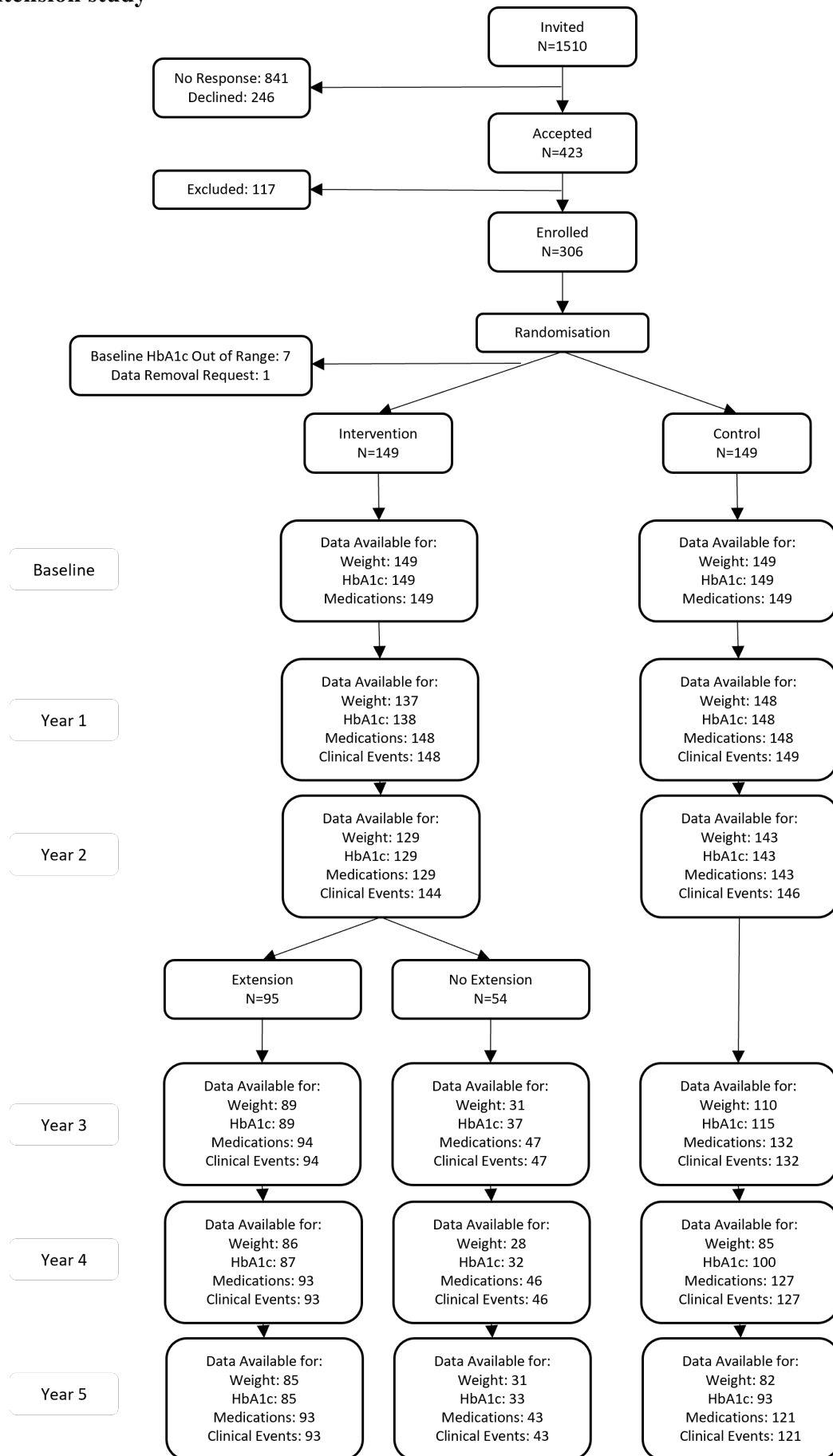


Figure S2: Mean (a) Weight (kg) and (b) HbA1c (mmol/mol) each year, with 95% confidence intervals

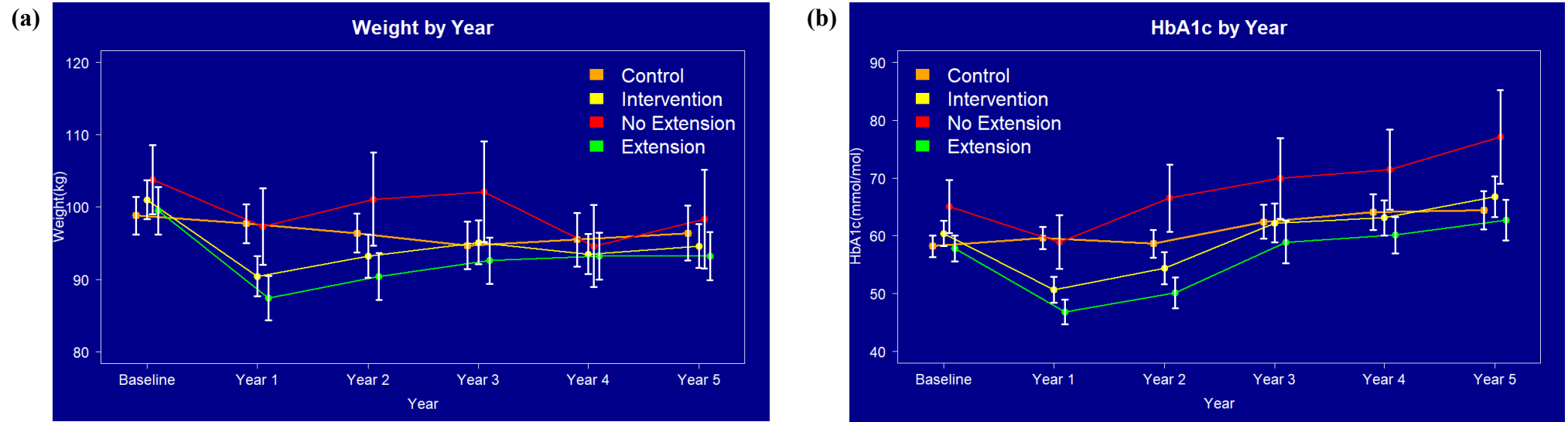


Figure S3: Pearson correlation of Year 1 Weight Loss with HbA1c, with linear regression line and 95% confidence band. Adequacy of model fit assessed by visual inspection of residual distribution and assessment of quadratic association.

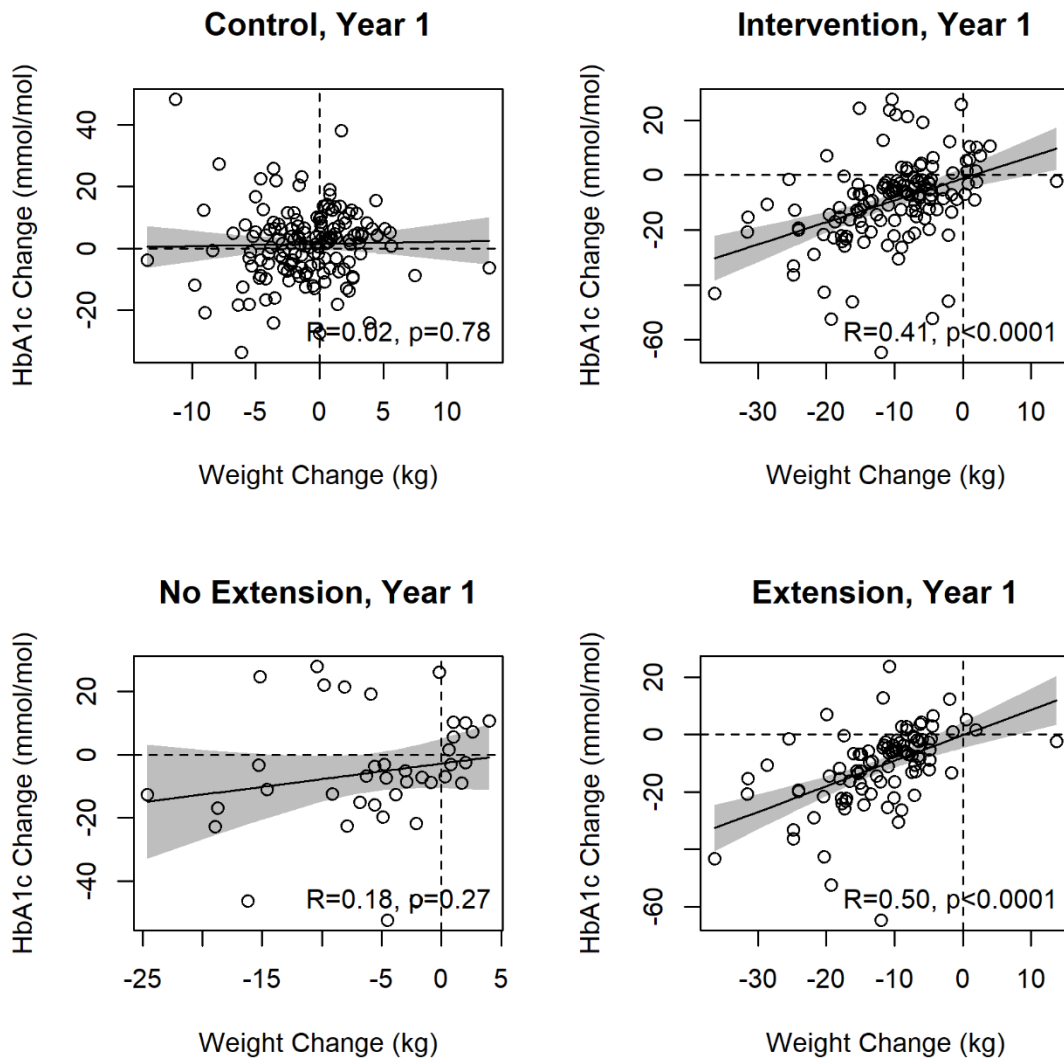


Figure S4: Pearson correlation of Year 2 Weight Loss with HbA1c, with linear regression line and 95% confidence band. Adequacy of model fit assessed by visual inspection of residual distribution and assessment of quadratic association.

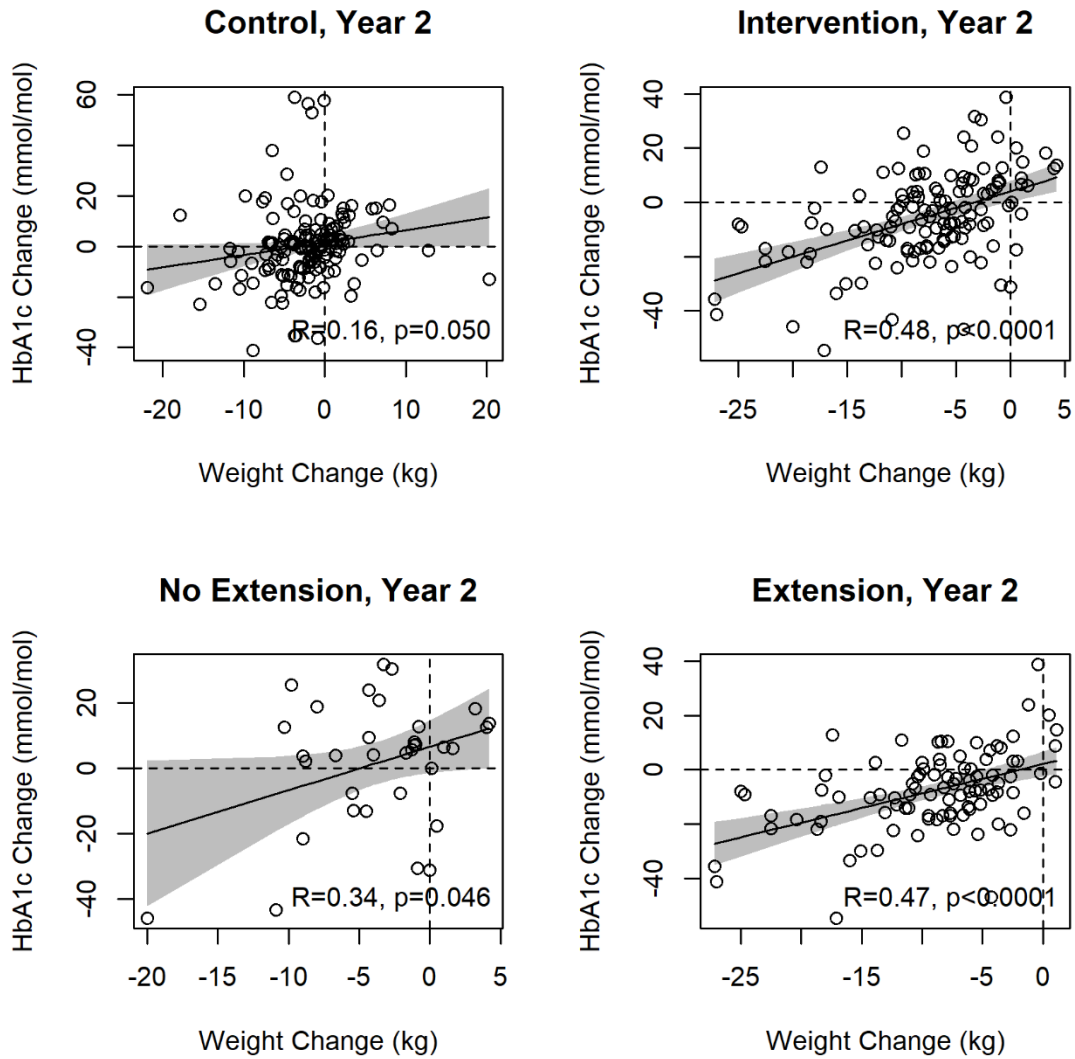


Figure S5: Pearson correlation of Year 3 Weight Loss with HbA1c, with linear regression line and 95% confidence band. Adequacy of model fit assessed by visual inspection of residual distribution and assessment of quadratic association.

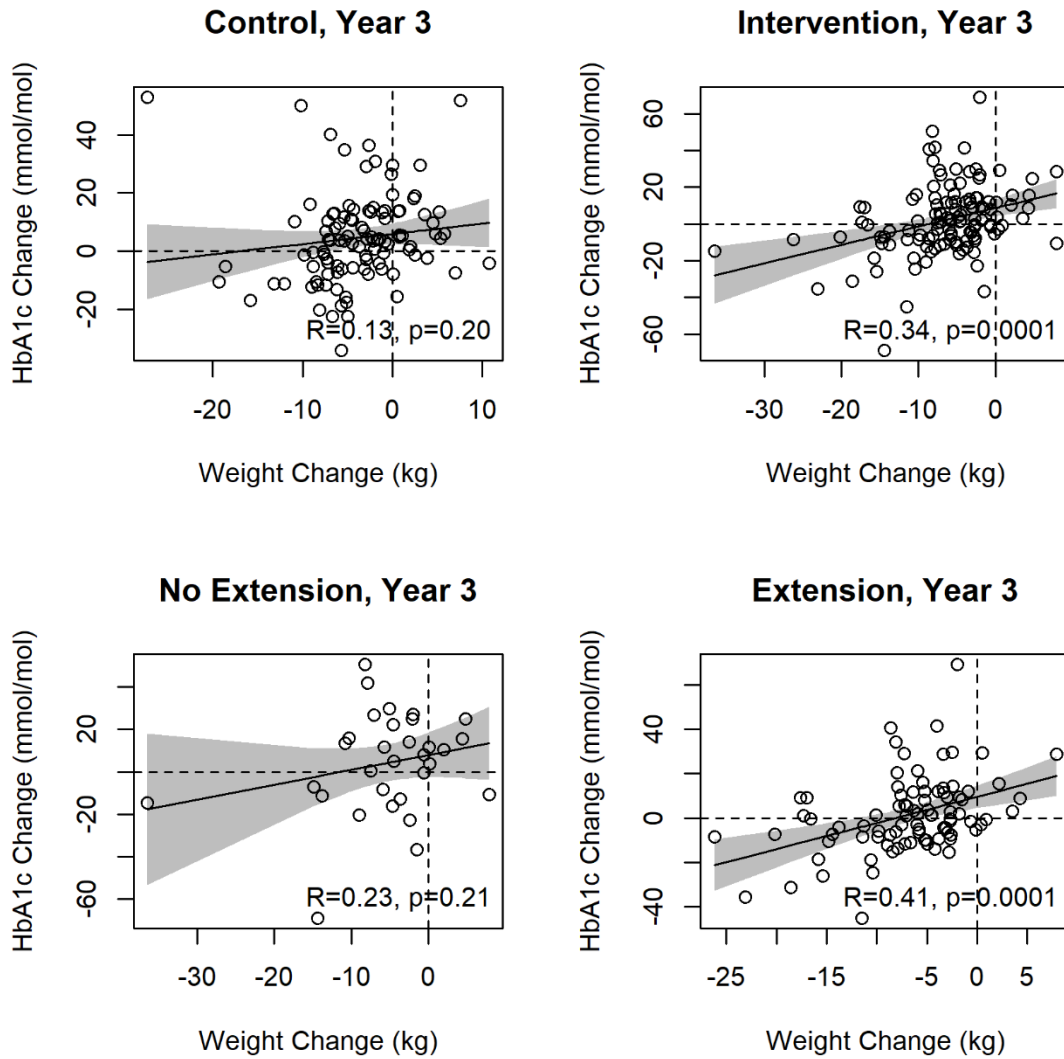


Figure S6: Pearson correlation of Year 4 Weight Loss with HbA1c, with linear regression line and 95% confidence band. Adequacy of model fit assessed by visual inspection of residual distribution and assessment of quadratic association.

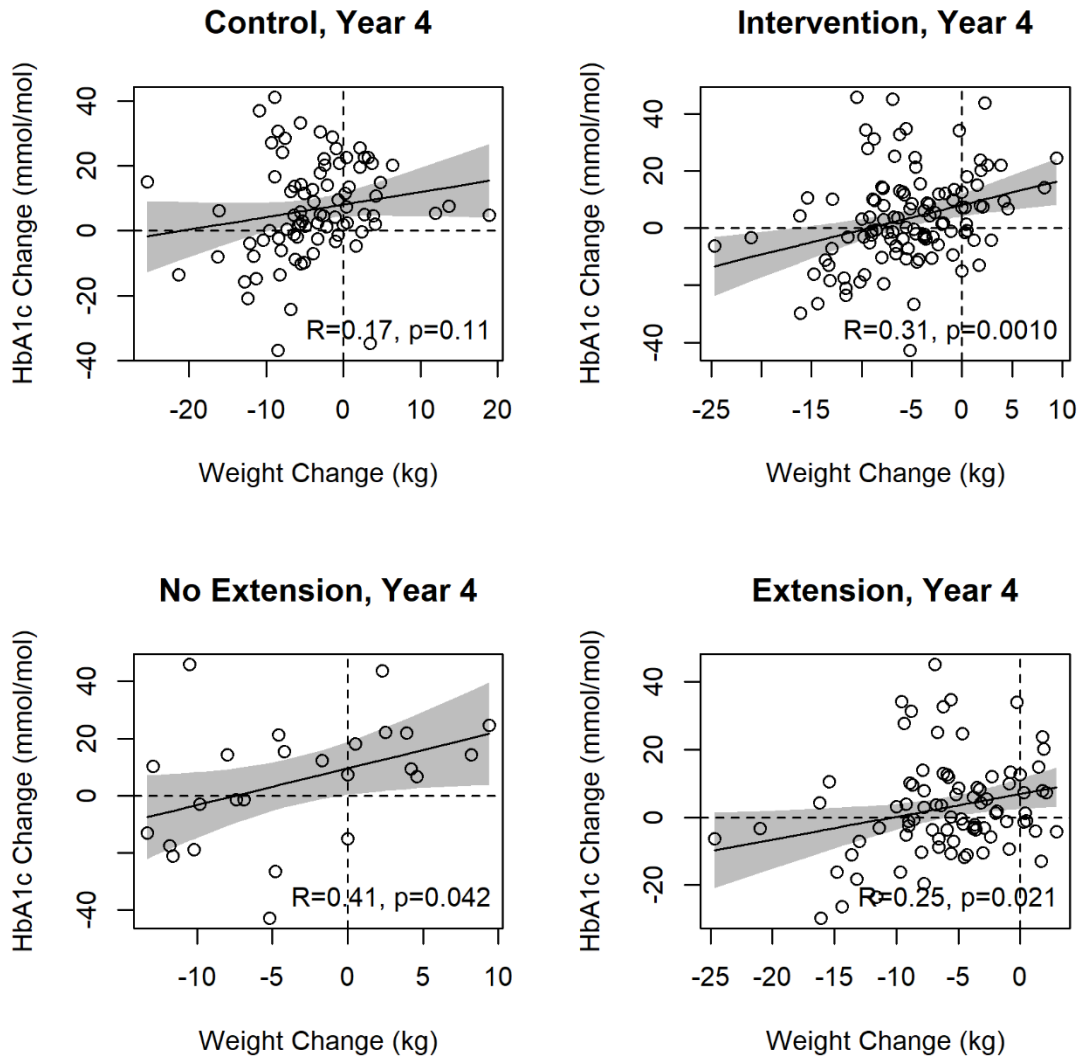
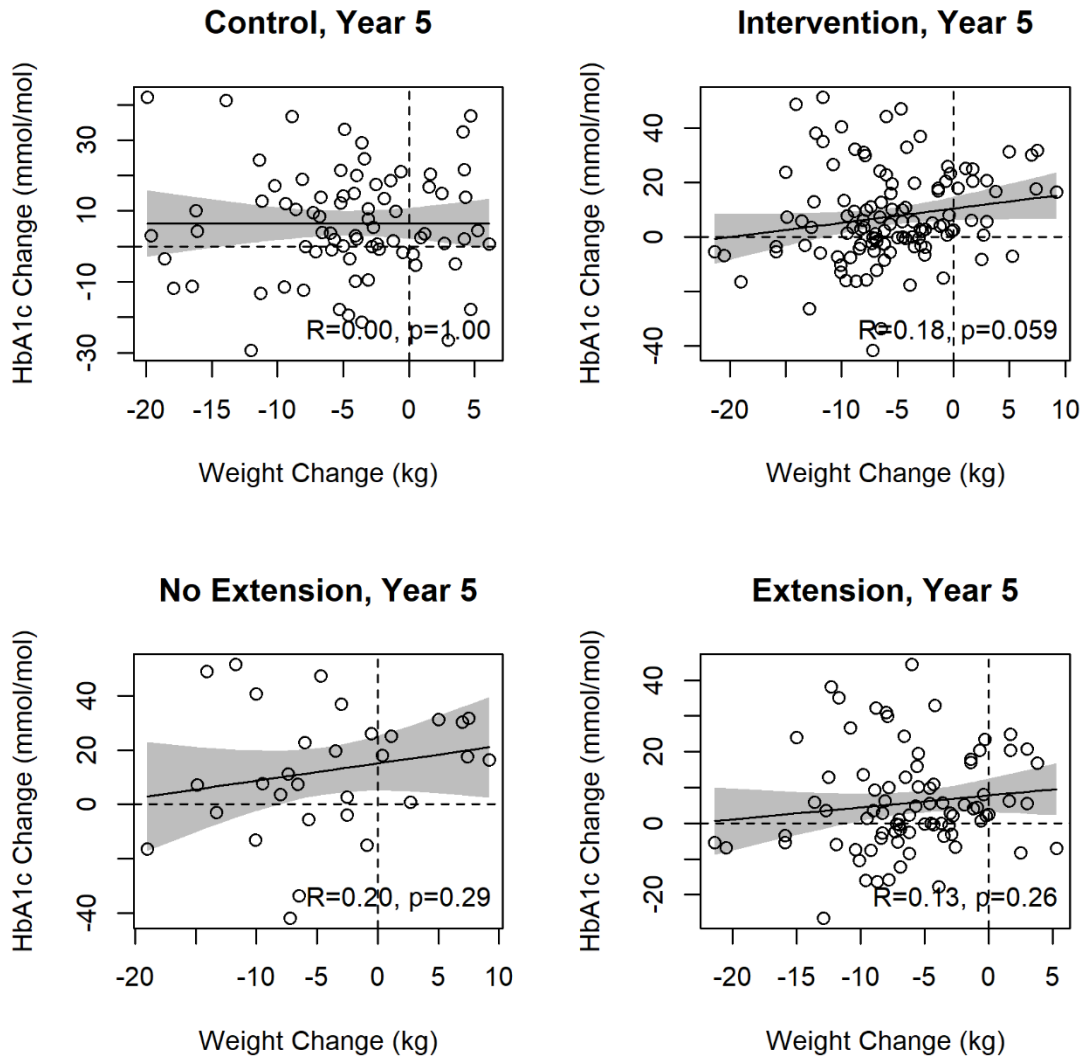


Figure S7: Pearson correlation of Year 5 Weight Loss with HbA1c, with linear regression line and 95% confidence band. Adequacy of model fit assessed by visual inspection of residual distribution and assessment of quadratic association.





 University
of Glasgow
School of Medicine,
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Dear (participant),

Diabetes Remission Clinical Trial (DiRECT)

Now that the first 2 years of DiRECT has been completed, and we have the main results, we want to thank you for your help as a participant. Without your help the study could not have been done. Our thanks is on behalf of the entire research team, and also of the huge numbers of people who develop type 2 diabetes, now and in the future, who can benefit from the results.

You may have heard about some of the results of DiRECT from the news or other media. Very briefly, the main results, which you helped us to show, are these:

1. Most people with type 2 diabetes can put the disease into remission, where it can do no harm, if they lose enough weight.
2. The amount of weight loss needed for diabetes remission varies between people, but almost 9/10 are free of type 2 diabetes if they lose 15kg (about 2 1/2 stone).
3. Diabetes will come back if there is weight regain, and likely then to do harm. Maintaining substantial weight loss is the main key to protect future health.
4. People who lost more weight and managed to achieve remission had fewer diabetes-related medical problems in the second year of DiRECT (fewer heart problems and fewer cancers).
5. There are a very few overweight people for whom substantial weight loss does not greatly improve their diabetes. They still benefit from weight loss in other ways.

Do share these results with your family and friends. You can find more details of results on our website www.directclinicaltrial.org.uk and on www.diabetes.org.uk. More information is available on what happens in the body during remission, and simple diet programmes on go.ncl.ac.uk/diabetes-reversal and <https://www.directclinicaltrial.org.uk/Resources.html>

Many of the original participants in DiRECT are continuing to help with the DiRECT extension, funded by the charity Diabetes UK for 5 years. This will help us find the best ways to maintain the necessary weight loss for long term diabetes remission.

Thank you again for helping make the DiRECT study a success. Hailed as a 'landmark study' in the UK and worldwide, the results of DiRECT have made remission a key aim of treatment for people who develop type 2 diabetes.

Yours sincerely

Professors Mike Lean (Glasgow) and Roy Taylor (Newcastle)

Dietetic team: Wilma Leslie, Naomi Brosnahan, Louise McCombie, George Thom, Alison Barnes

<p>Intervention intensity</p>	<p>3-monthly appointments for 15-30 minutes, in-person at GP practice or remotely by telephone/text/email. A total of 12 appointments were offered between 3-5 years.</p> <p>Rescue plans entailed an additional 2-4 visits.</p> <p>At each appointment: Weight Loss Maintenance Progress Review (including discussion on Rescue Plan if appropriate)</p> <ul style="list-style-type: none"> o Changes and Barriers o Goal Setting
<p>Monitoring measurements (Weight, Blood Glucose, +/- Blood Pressure)</p> <p>Covid-19</p>	<p>Participants were advised to self-monitor body weight on a weekly basis.</p> <p>Weight, blood glucose and blood pressure were measured by the health care professional (nurse or dietitian) at each 3-monthly visit.</p> <p>From end March 2020 and until permissions were received to resume follow up in person (or if participants were unable or unwilling to attend in person), participants were managed as follows:</p> <p>Remote support (described in the main text) involved participants self-monitoring body weight on a weekly/monthly basis, and reporting results to the study research dietitian. If weight regained >5kg over 3m, guidance was given to have BP and blood glucose/ HbA1c checked and Rescue Plan was discussed.</p>