Sleep Apnea and cardioVascular Endpoints randomised controlled trial (SAVE)
Consent to Substudy: 965 participants

491 randomised to receive Usual Care	495 randomised to receive CPAP

Attended baseline appointment but blood not taken: 43
Blood taken more than 14 days before randomisation or more than 7 days after randomisation: 93
Blood taken in time window but not fasting: 11

Fasting blood sample collected/analysed at baseline (BL): 818 (84.8% of 965)	
409 Usual Care	409 CPAP

Withdrew/ceased substudy or main trial <180 days: 28
Died <180 days: 3
Attended 6 month appointment but blood not taken: 100
Appointment more than ± 30 days from schedule or blood taken more than ± 30 days from appointment: 57
Blood taken in time window but not fasting: 7
Missed appointment/other missing data: 46

Fasting blood sample collected/analysed at 6 months: 724 (75.0% of 965)	
348 Usual Care	376 CPAP

Withdrew/ceased substudy or trial <730 days: 56
Died <730 days: 11
Attended 24 month appointment but blood not taken: 163
Appointment more than ± 60 days from schedule or blood taken more than ± 30 days from appointment: 43
Blood taken in time window but not fasting: 3
Missed appointment/other missing data: 65

Fasting blood sample collected/analysed at 24 months: 624 (64.7% of 965)	
301 Usual Care	323 CPAP

Reached trial conclusion/withdrew <1460 days: 414
Died <1460 days: 24
Attended 48 month appointment but blood not taken: 96
Appointment more than ± 90 days from schedule or blood taken more than ± 60 days from appointment: 51
Blood taken in time window but not fasting: 10
Missed appointment/other missing data: 34

Fasting blood sample collected/analysed at 48 months: 336 (34.8% of 965)	
157 Usual Care	179 CPAP

Fasting blood sample collected/analysed at any timepoint: 888 (92.0% of 965)	
436 Usual Care	452 CPAP

Figure S1:
Flowchart depicting participant and sample numbers in this substudy, with reasons for exclusion and missing data where available.

Table S1: Characteristics of 965 participants who consented to both main trial and substudy, were randomised in the main trial, but did/did not have blood included in analysis.

		No eligible blood in substudy (n = 77)		Blood included in substudy (n = 888)	
		Count	Column N %	Count	Column N %
Gender	Female	16	20.8%	151	17.0%
	Male	61	79.2%	737	83.0%
Country	Australia	8	10.4%	173	19.5%
	Brazil	2	2.6%	182	20.5%
	China	60	77.9%	448	50.5%
	New Zealand	6	7.8%	85	9.6%
	Spain	1	1.3%	0	0.0%
Age group at randomization	>60 years	38	49.4%	529	59.6%
	≤60 years	39	50.6%	359	40.4%
OSA severity (ODI category from baseline ApneaLink)	12-20	24	31.2%	361	40.7%
	>20-30	18	23.4%	235	26.5%
	>30	35	45.5%	292	32.9%
Daytime sleepiness (ESS at baseline)	0-10	59	76.6%	636	71.6%
	11-15	18	23.4%	252	28.4%
Obesity (BMI at baseline, kg/m^2)	≥30	15	20.0%	350	39.5%
	<30	60	80.0%	537	60.5%
Cardiovascular disease history at baseline	Cardiac only	36	46.8%	584	65.8%
	Cerebrovascular only	41	53.2%	263	29.6%
	Both	0	0.0%	41	4.6%
Diabetes at baseline		12	16.0%	274	30.9%

OSA = obstructive sleep apnoea; ODI = oxygen desaturation index, events/hour; ESS = Epworth Sleepiness Scale score; BMI = body mass index.
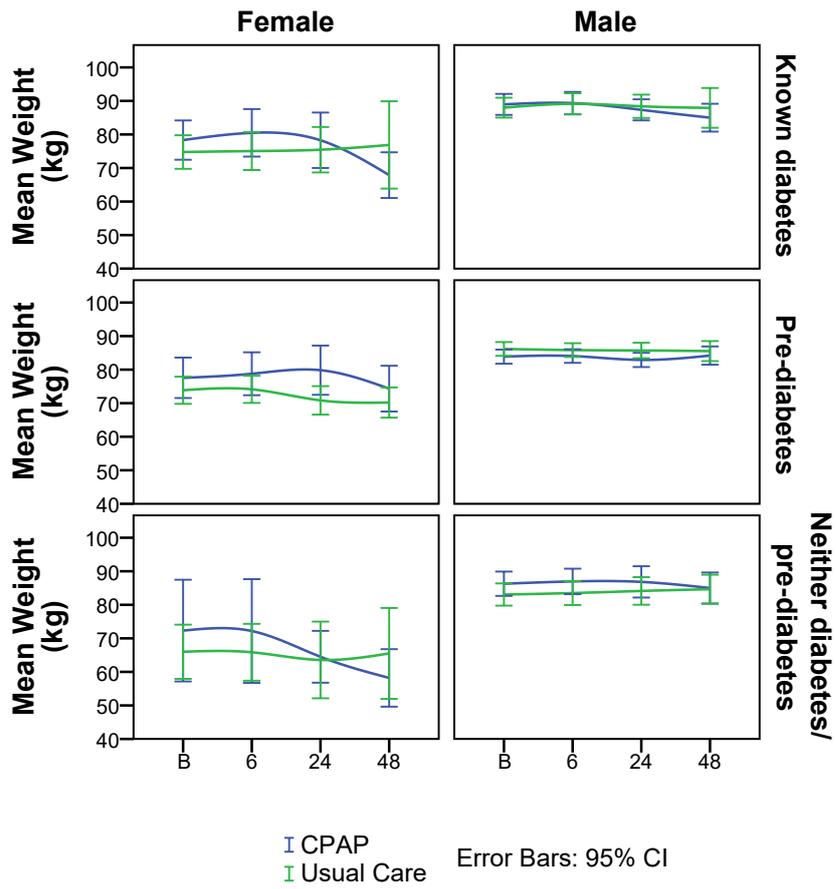
Figure S2:
Weight (kg) in CPAP (blue) and Usual Care (green) treatment groups. Observed mean and 95% CI from all available observations.
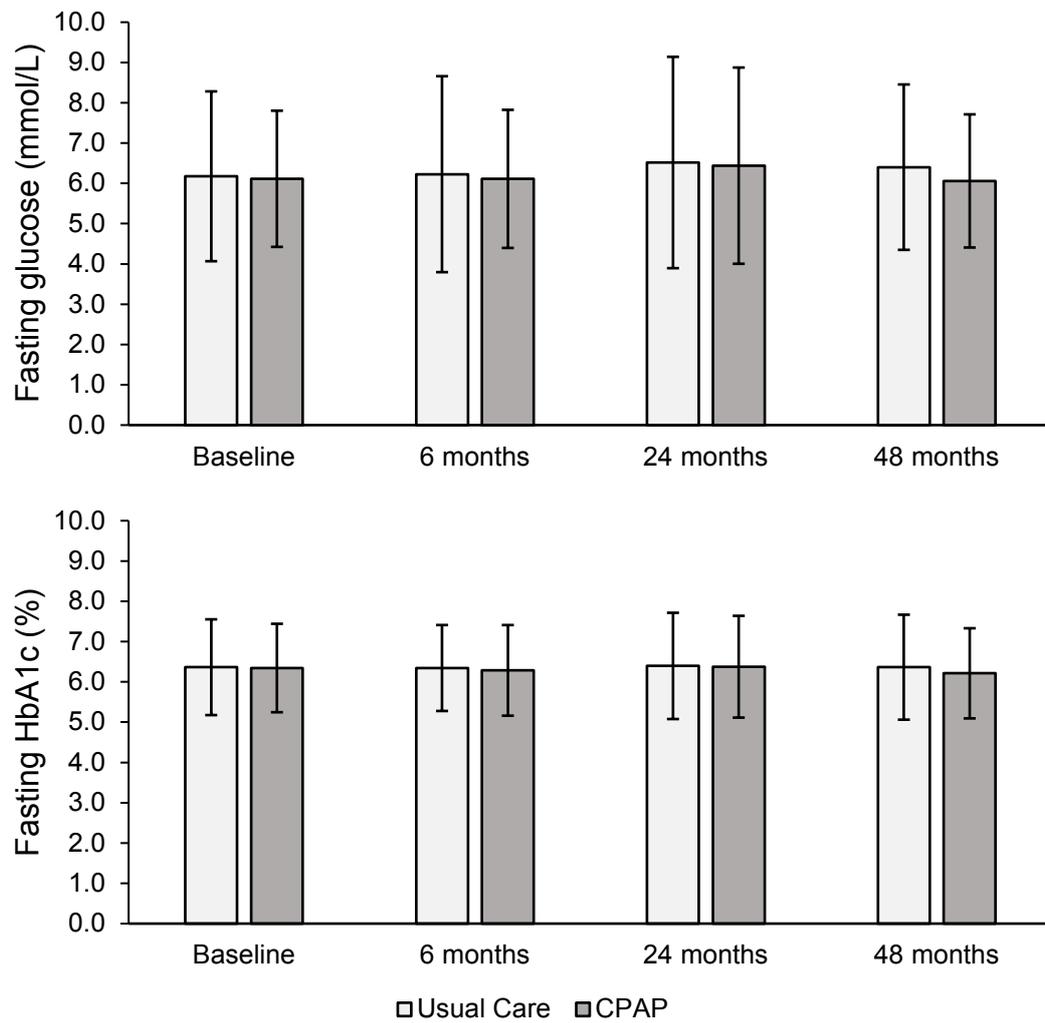
Figure S3:
Fasting serum glucose and HbA1c in CPAP (dark grey) and Usual Care (light grey) treatment groups. Observed mean and standard deviation from all available observations.
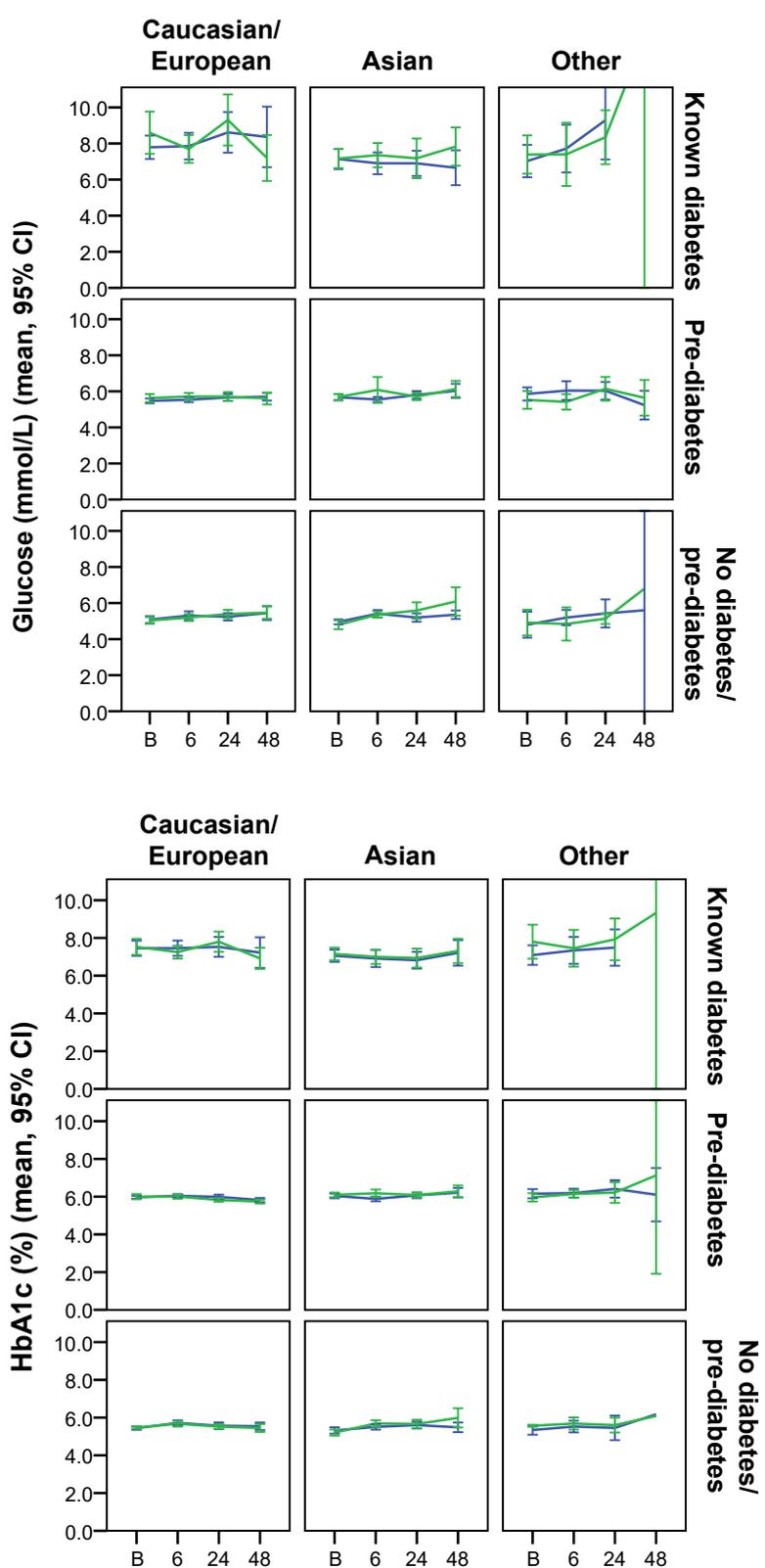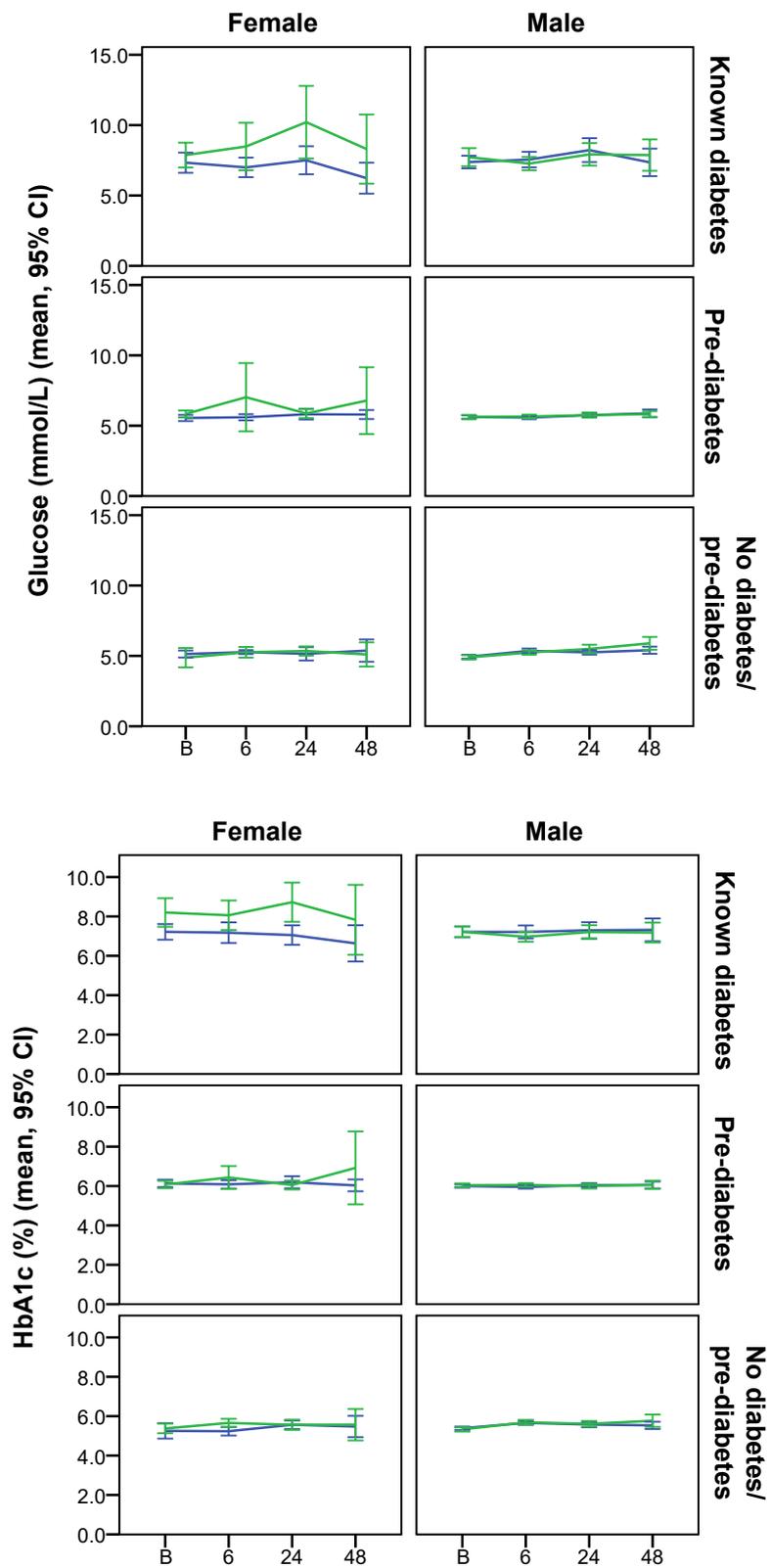
Figure S4a:

Fasting serum glucose and HbA1c in CPAP (blue) and Usual Care (green) treatment groups according to baseline diabetes status and self-reported race/ethnicity.

Estimated marginal means and 95% confidence intervals from linear mixed models. Due to small numbers of participants remaining, the error bars in the "Other" race/ethnicity group at 48 months are very large, extending beyond the scale of the figure, and for simplicity have been omitted from the plot showing HbA1c. X axis represents the timecourse of analysis, B = baseline, 6, 24 and 48 months.

Female **Male**

Glucose (mmol/L) (mean, 95% CI)

Known diabetes

Pre-diabetes

No diabetes/ pre-diabetes

15.0
10.0
5.0
0.0

B 6 24 48

Female **Male**

HbA1c (%) (mean, 95% CI)

Known diabetes

Pre-diabetes

No diabetes/ pre-diabetes

10.0
8.0
6.0
4.0
2.0
0.0

B 6 24 48

Figure S4b:
Fasting serum glucose and HbA1c in CPAP (blue) and Usual Care (green) treatment groups according to baseline diabetes status and sex. Estimated marginal means and 95% confidence intervals from linear mixed models. X axis represents the timecourse of analysis, B = baseline, 6, 24 and 48 months.

Supplementary Table S2: Medications

		Usual Care	CPAP	
		Count (%)	Count (%)	*P*-value*
Insulin	Baseline	40 (31.3%)	24 (16.4%)	0.004
	Started during study	6 (4.7%)	10 (6.8%)	0.446
	End of study	44 (34.4%)	34 (23.3%)	0.042
Oral anti-diabetic medications	Baseline	98 (76.6%)	110 (75.3%)	0.814
	Started during study	9 (7.0%)	10 (6.8%)	0.953
	End of study	103 (80.5%)	117 (80.1%)	0.945
		Mean ± SD	Mean ± SD	
Oral anti-diabetic medications: change in DDD		-58 ± 558	-16 ± 352	0.944

*Between group comparisons of count values by Pearson Chi Square test. Between group comparison of change in daily dose by Mann Whitney U test.

DDD = defined daily dose

Supplementary Table S3a: Fasting serum glucose according to treatment allocation. Only participants who had fasting blood collected at all three time points: baseline, 6 and 24 months.

Known diabetes at baseline	Usual Care			CPAP			Adjusted mean difference CPAP – Usual Care (95% CI)	*P*-value	
	Mean	95% CI	n	Mean	95% CI	n		Treatment allocation	Treatment * visit
Baseline	7.66	(7.21, 8.12)	78	7.52	(7.08, 7.95)	87			
6 months	7.29	(6.83, 7.74)	78	7.56	(7.12, 7.99)	87	0.113 (-0.253, 0.479)	0.544	0.606
24 months	7.86	(7.40, 8.31)	78	8.07	(7.64, 8.51)	86			

Pre-diabetes at baseline	Usual Care		CPAP				*P*-value	
	Mean (95% CI)	n	Mean (95% CI)	n			Treatment allocation	Treatment * visit
Baseline	5.72 (5.51, 5.93)	138	5.72 (5.51, 5.91)	145				
6 months	5.87 (5.66, 6.08)	138	5.65 (5.44, 5.85)	145	-0.085 (-0.252, 0.082)		0.318	0.506
24 months	5.79 (5.58, 5.99)	137	5.77 (5.57, 5.97)	143				

Neither diabetes nor pre-diabetes at baseline	Usual Care		CPAP				*P*-value	
	Mean (95% CI)	n	Mean (95% CI)	n			Treatment allocation	Treatment * visit
Baseline	4.91 (4.73, 5.10)	31	4.95 (4.76, 5.13)	33				
6 months	5.24 (5.05, 5.43)	30	5.23 (5.05, 5.41)	33	-0.128 (-0.281, 0.024)		0.098	0.042
24 months	5.45 (5.26, 5.64)	30	5.05 (4.86, 5.23)	33				

Stratified by diabetes/pre-diabetes status at baseline and adjusted for baseline measure of variable of interest (estimated marginal means, confidence intervals and significance from linear mixed models).

Supplementary Table S3b: Fasting serum HbA$_{1c}$ according to treatment allocation. Only participants who had fasting blood collected at all three time points: baseline, 6 and 24 months.

Known diabetes at baseline	Usual Care			CPAP			Adjusted mean difference CPAP – Usual Care (95% CI)	*P*-value	
	Mean	95% CI	n	Mean	95% CI	n		Treatment allocation	Treatment * visit
Baseline	7.30	(7.10, 7.49)	78	7.26	(7.08, 7.44)	87			
6 months	7.07	(6.88, 7.27)	78	7.21	(7.03, 7.39)	87	0.042 (-0.114, 0.197)	0.601	0.663
24 months	7.28	(7.09, 7.48)	78	7.31	(7.13, 7.50)	86			

Pre-diabetes at baseline	Usual Care		CPAP			*P*-value	
	Mean (95% CI)	n	Mean (95% CI)	n		Treatment allocation	Treatment * visit
Baseline	6.02 (5.93, 6.10)	138	6.02 (5.94, 6.10)	144			
6 months	6.07 (5.98, 6.15)	137	5.99 (5.91, 6.07)	141	-0.020 (-0.087, 0.046)	0.549	0.497
24 months	6.02 (5.94, 6.10)	138	6.03 (5.95, 6.11)	143			

Neither diabetes nor pre-diabetes at baseline	Usual Care		CPAP			*P*-value	
	Mean (95% CI)	n	Mean (95% CI)	n		Treatment allocation	Treatment * visit
Baseline	5.34 (5.23, 5.45)	29	5.36 (5.25, 5.47)	32			
6 months	5.57 (5.45, 5.68)	29	5.48 (5.37, 5.58)	32	-0.005 (-0.094, 0.084)	0.911	0.406
24 months	5.45 (5.34, 5.56)	29	5.50 (5.40, 5.61)	31			

Stratified by diabetes status at baseline and adjusted for baseline measure of variable of interest (estimated marginal means and significance from linear mixed models).

Supplementary Table S4: Assessment of differential effect of CPAP intervention according to baseline OSA disease severity, measured either by ODI or ESS.

Dependent variable:	Base model* plus:	Known diabetes at baseline				Pre-diabetes at baseline				Neither diabetes nor pre-diabetes at baseline			
		Estimate of fixed effect	95% CI		P	Estimate of fixed effect	95% CI		P	Estimate of fixed effect	95% CI		P
Glucose	ODI	0.0071	-0.0109	0.0251	0.440	0.0083	0.0026	0.0141	0.004	0.0006	-0.0063	0.0075	0.866
	Treatment*ODI	-0.0110	-0.0361	0.0141	0.391	-0.0062	-0.0146	0.0022	0.145	0.0017	-0.0075	0.0108	0.722
	ESS	-0.0105	-0.0712	0.0501	0.733	0.0085	-0.0142	0.0313	0.462	0.0062	-0.0161	0.0285	0.585
	Treatment*ESS	0.0596	-0.0242	0.1433	0.163	-0.0140	-0.0473	0.0194	0.412	-0.0112	-0.0431	0.0208	0.492
HbA1c	ODI	0.0022	-0.0057	0.0100	0.589	0.0015	-0.0012	0.0042	0.275	0.0001	-0.0042	0.0043	0.970
	Treatment*ODI	-0.0053	-0.0162	0.0056	0.342	-0.0003	-0.0044	0.0037	0.879	0.0038	-0.0017	0.0093	0.174
	ESS	-0.0141	-0.0402	0.0120	0.288	0.0011	-0.0098	0.0120	0.843	-0.0009	-0.0143	0.0124	0.889
	Treatment*ESS	0.0405	0.0046	0.0765	0.027	0.0095	-0.0066	0.0256	0.248	-0.0092	-0.0285	0.0102	0.353

*Base model includes: intercept, treatment allocation (CPAP or Usual Care), timepoint, baseline value of glucose or HbA1c respectively, and the interaction term treatment*timepoint.