Continuous Positive Airway Pressure Treatment, Glycemia, and Diabetes Risk in Obstructive Sleep Apnea and Comorbid Cardiovascular Disease

Diabetes Care 2020;43:1859–1867 | https://doi.org/10.2337/dc19-2006

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OBJECTIVE

Despite evidence of a relationship among obstructive sleep apnea (OSA), metabolic dysregulation, and diabetes, it is uncertain whether OSA treatment can improve metabolic parameters. We sought to determine effects of long-term continuous positive airway pressure (CPAP) treatment on glycemic control and diabetes risk in patients with cardiovascular disease (CVD) and OSA.

RESEARCH DESIGN AND METHODS

Blood, medical history, and personal data were collected in a substudy of 888 participants in the Sleep Apnea cardioVascular Endpoints (SAVE) trial in which patients with OSA and stable CVD were randomized to receive CPAP plus usual care, or usual care alone. Serum glucose and glycated hemoglobin A_{1c} (HbA_{1c}) were measured at baseline, 6 months, and 2 and 4 years and incident diabetes diagnoses recorded.

RESULTS

Median follow-up was 4.3 years. In those with preexisting diabetes ($n = 274$), there was no significant difference between the CPAP and usual care groups in serum glucose, HbA_{1c}, or antidiabetic medications during follow-up. There were also no significant between-group differences in participants with prediabetes ($n = 452$) or new diagnoses of diabetes. Interaction testing suggested that women with diabetes did poorly in the usual care group, while their counterparts on CPAP therapy remained stable.

CONCLUSIONS

Among patients with established CVD and OSA, we found no evidence that CPAP therapy over several years affects glycemic control in those with diabetes or prediabetes or diabetes risk over standard-of-care treatment. The potential differential effect according to sex deserves further investigation.

Obstructive sleep apnea (OSA) is characterized by repeated episodes of upper-airway collapse during sleep that causes intermittent hypoxemia, sleep fragmentation, and daytime sleepiness. The standard therapy for OSA is continuous positive airway pressure (CPAP) to prevent airway obstruction (1).

OSA is common in the population and strongly associated with obesity (2). Prospective cohort studies have found associations between moderate to severe OSA and

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incident type 2 diabetes (3–5), and this association may be bidirectional (6–8). However, there is uncertainty regarding the efficacy of long-term treatment of OSA in the prevention of diabetes. A recent retrospective long-term clinical cohort study (median follow-up 7.3 years) reported that moderate to severe OSA is associated with an increased risk of incident diabetes and that this was substantially reduced by regular CPAP use (9). Long-term randomized controlled trials investigating the effect of CPAP treatment on incident diabetes in OSA are lacking.

A 2-week study of intensive, supervised CPAP treatment in individuals with prediabetes showed improvements in glucose response and insulin sensitivity (10), while a similar trial in individuals with diabetes suggested improvements in 24-h glucose, without significant change in insulin levels (11). Conversely, a study of acute treatment withdrawal in patients with OSA habituated to CPAP showed increased nocturnal glucose (12).

Assessments of medium-term CPAP treatment interventions between 2 and 6 months duration show mixed results: Some trials showed improvements in markers of glycemic control (13,14), while others showed no significant changes (15–21), with a meta-analysis suggesting overall neutral outcomes in participants with diabetes (22).

The Sleep Apnea and cardioVascular Endpoints (SAVE) study was an international, multicenter, randomized controlled trial designed to determine whether CPAP reduced the risk of secondary major cardiovascular disease (CVD) events in participants with coexisting coronary artery and/or cerebrovascular disease and moderate to severe OSA who were followed for several years (23). At participating sites in four of the seven countries, individuals enrolled in SAVE were invited to join a preplanned substudy to investigate the impact of CPAP treatment on several blood biomarkers of CVD risk. Here, we report the findings on glycemic control, as assessed by fasting serum glucose and glycated hemoglobin A_{1c} (HbA_{1c}), for the substudy population as whole and according to diabetes status at enrollment. We further assessed whether CPAP influenced new diagnoses of diabetes during the trial. Because the level of CPAP adherence may be an important determinant of whether glycemic control is improved, we also conducted an analysis to examine how average long-term CPAP adherence level affected the results.

RESEARCH DESIGN AND METHODS

The SAVE study was an international, randomized, open, blinded outcome–assessed clinical trial for which the details have been previously reported (23). Participants recruited were aged 45–75 years with moderate to severe OSA defined as an oxygen desaturation index (ODI) of $\geq$12 (i.e., $\geq$12 events of $\geq$4% oxygen desaturation per hour during home overnight screening [ApneaLink; ResMed]) but without severe daytime sleepiness (Epworth Sleepiness Scale [ESS] $<$15) and a prior diagnosis of coronary or cerebrovascular disease according to standard definitions. Very severe nocturnal hypoxemia (oxygen saturation $\leq$80% for $>$10% of the monitoring time) or a predominantly Cheyne-Stokes respiration pattern in screening resulted in exclusion. Potential participants underwent a 1-week trial of subtherapeutic sham CPAP; individuals who recorded a daily average sham CPAP usage of $<$3 h were considered unlikely to tolerate CPAP treatment or adhere to procedures and were excluded. Eligible patients were then randomized to CPAP plus their usual CVD care (CPAP group) or to usual care alone (usual care group). Recruitment was undertaken between December 2008 and November 2013, with 51 sites in four countries enrolling participants for this substudy. The SAVE trial was conducted in accordance with the principles of the amended Declaration of Helsinki and Good Clinical Practice. Local institutional review boards or independent ethics committees at recruiting sites approved the protocol, and all participants provided written informed consent to both the main trial and the substudy.

Blood samples for the substudy were collected after overnight fast at baseline, 6 months, 24 months, and 48 months at sites in Australia, Brazil, China, and New Zealand. Serum was isolated, and glucose and HbA_{1c} were measured locally at each site in accordance with local clinical practice and laboratory standards. Results were reported in a central standardized database and collated with medical history, behavioral, and anthropometric data collected as part of the main SAVE protocol. Concomitant medication information was prospectively collected by trial staff or investigators as part of the structured interview at baseline and every in-clinic follow-up time point (1 month, 3 months, 6 months, 12 months, 24 months, and annually thereafter). This schedule was the same for all participants in both treatment arms. CPAP use in those individuals allocated to receive the intervention was also recorded at each scheduled follow-up appointment.

Participants were included in these analyses if they provided a baseline blood sample within 14 days prior to or up to 7 days after their trial protocol randomization date. For inclusion in the designated 6-month, 24-month, and 48-month follow-up time point analyses, appointments were included if they fell within $\pm$30, 60, or 90 days of the respective scheduled follow-up appointment, calculated from the date of randomization. Blood samples corresponding to these follow-up time points were included if they were taken within $\pm$30 days of the appointment at 6 months and 24 months or $\pm$60 days for 48-month appointments.

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Received 8 October 2019 and accepted 15 March 2020

Clinical trial reg. nos. NCT00738179, clinicaltrials.gov, and ACTRN12608000409370, www.anzctr.org.au

This article contains supplementary material online at https://doi.org/10.2337/dc20-1234/suppl.11996421.

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See accompanying articles, pp. 1681 and 1868.

Any blood samples taken when a participant was noted to have been in a nonfasted state were excluded. Baseline diabetes status was categorized on the basis of the recorded known diagnosis of diabetes reported at enrollment; participants who did not have a previous diabetes diagnosis but who met the published criteria for prediabetes (as defined by fasting serum glucose ≥5.6 mmol/L or HbA_{1c} ≥5.7%) (24) were classified accordingly. New diagnoses of diabetes during the follow-up period were defined by confirmation of any of the following: fasting plasma glucose ≥7.0 mmol/L, HbA_{1c} ≥6.5%, 2-h 75-g oral glucose tolerance test of ≥11.1 mmol/L, or initiation of antidiabetic medication. Blood test results obtained as part of this trial could act as the trigger for a new diagnosis; such results were flagged back to trial sites for reporting as adverse events and adjudication according to the trial protocol.

Primary analyses were based on the randomized treatment group allocation of each participant in the main SAVE trial. Continuous variables were compared between groups by *t* test if distribution approximated normal. For nonnormal distributions, Mann-Whitney *U* tests were used. Categorical variables were compared between treatment groups by χ^2 or Fisher exact test. Linear mixed models were used to compare serum glucose and HbA_{1c} concentrations between treatment groups, stratified according to reported diabetes status at baseline, adjusted only for the corresponding value of glucose or HbA_{1c} at baseline. We assessed the potential importance of participant weight as a time-varying covariate and of baseline ESS, ODI, sex, and race/ethnicity by addition of an interaction term with treatment allocation to the previous linear mixed model. Kaplan-Meier and Cox regression survival analyses were used to assess new diagnoses of diabetes in those participants who did not have a preexisting diagnosis of diabetes at baseline. We also conducted a further examination of the potential role of CPAP adherence as a continuous metric (average hours/night) in those allocated to receive the treatment using a linear mixed model; changes in glucose and HbA_{1c} from baseline to end of study were also assessed in relation to CPAP adherence using linear regression.

Because the length of follow-up varied among participants as a result of the extended period of recruitment, many individuals did not reach 48 months, and thus there was a high percentage of data missing at this time point. To address this, we conducted a sensitivity analysis for glucose and for HbA_{1c} in which data from baseline and 6 and 24 months were included only from participants who had a valid blood collection at all three of these time points; linear mixed models were used to assess differences according to treatment allocation adjusted for the baseline value of the variable of interest.

All analyses were carried out using IBM SPSS version 25 statistical software. $P < 0.05$ was considered significant.

RESULTS

Of the 2,687 participants included in the SAVE trial, 965 consented to the blood biomarker substudy. This subpopulation was representative of participants of the SAVE trial (23), being predominantly male, overweight or obese, and middle aged or older with a history of cardiac or cerebrovascular disease and moderate to severe OSA. Supplementary Fig. 1 shows the substudy design and numbers of included participants and samples. Of the consenting individuals, 888 (92.0%) had at least one blood sample collected that met acceptable time windows for inclusion in this analysis; their characteristics are outlined in Supplementary Table 1. Baseline features of the 77 participants who consented to participate but did not provide usable blood samples are shown for comparison in Supplementary Table 1. Of the participants with samples included in analyses, almost one-third had a preexisting diagnosis of diabetes at baseline, while a further one-half met the criteria for prediabetes. The median period of follow-up of the 888 participants with blood included for analysis was 4.3 years (range 16 days to 6.9 years). Because of the extended period of recruitment for SAVE, with an intended minimum follow-up duration of 2 years, not all participants had the opportunity to reach the 48-month time point; 336 samples were included for analysis at 48 months (34.8% of 965 consenting participants). Mean CPAP usage for the duration of the trial in those allocated to receive the intervention was 3.5 ± 2.3 h/night.

There were also no between-group differences in anthropometric indices in the current study population either at baseline (Table 1) or during follow-up (weight shown in Supplementary Fig. 2). As a key potential confounder of analyses of metabolic health, we also assessed weight change in these substudy participants. In general, most participants' weight stayed relatively stable over the duration of the study, with no differences between treatment groups at baseline or end of study and no difference between groups in the individual change from baseline (Supplementary Fig. 2).

Glycemic Control in All Participants

Observed mean serum glucose and HbA_{1c} concentrations for the whole participant group were not different between the CPAP and usual care groups at any time point (Supplementary Fig. 3).

Glycemic Control and Antidiabetic Medication Use in Participants With Known Diabetes

More than one-quarter of participants had a known diagnosis of diabetes at enrollment (146 CPAP, 128 usual care). Baseline features of this group are shown in Table 1. Serum glucose concentration during follow-up was not significantly affected by CPAP treatment allocation, nor was HbA_{1c} (Table 2). Estimated mean baseline-adjusted fasting glucose was 7.68 mmol/L (95% CI 7.43, 7.93) for the CPAP group and 7.71 mmol/L (7.46, 7.96) for the usual care group ($P = 0.864$). Estimated mean baseline-adjusted HbA_{1c} was 7.33% (7.22, 7.43) for the CPAP group compared with 7.26% (7.15, 7.37) for those allocated to usual care ($P = 0.419$). Inclusion of participant weight as a time-varying covariate slightly improved the overall model fit for both glucose and HbA_{1c} but made no appreciable difference to the estimated effect of treatment allocation (data not shown). Interaction testing did not reveal any differences in the apparent effect of CPAP allocation according to ethnicity (treatment × ethnicity interaction term for glucose *F* 0.502 [$P_{interaction} = 0.606$] and for HbA_{1c} *F* 0.140 [$P_{interaction} = 0.869$]) (Supplementary Fig. 4*A*). There were also no sex differences in HbA_{1c} by treatment group (*F* 2.950, $P_{interaction} = 0.086$) (Supplementary Fig. 4*B*). However, there was evidence of a differential effect of CPAP treatment in follow-up serum glucose measurements by sex (*F* 7.070, $P_{interaction} = 0.008$; estimate in females allocated to CPAP −1.037 mmol/L [95% CI −1.802, −0.271]) (Supplementary Fig. 4*B*).

Table 1—Baseline characteristics of included participants according to treatment allocation and preexisting diabetes diagnosis or criteria for prediabetes

	Known diabetes (n = 274, 30.8%)		Prediabetes (n = 452, 50.9%)		Neither diabetes nor prediabetes (n = 162, 18.2%)		Total (N = 888)	
	Usual care (n = 128)	CPAP (n = 146)	Usual care (n = 230)	CPAP (n = 222)	Usual care (n = 78)	CPAP (n = 84)	Usual care (n = 436)	CPAP (n = 452)
Age at randomization (years)	61.94 ± 7.37	61.85 ± 7.36	61.18 ± 8.1	62.61 ± 7.45	61.11 ± 7.88	59.91 ± 7.72	61.39 ± 7.84	61.87 ± 7.52
BMI (kg/m^2)	30.4 ± 4.4	30.9 ± 5.6	29.2 ± 4.2	29.1 ± 4.6	28.0 ± 4.0	29.4 ± 5.8	29.3 ± 4.3	29.8 ± 5.2
Waist-to-hip ratio	0.97 ± 0.07	0.98 ± 0.07	0.96 ± 0.07	0.96 ± 0.07	0.95 ± 0.07	0.96 ± 0.08	0.96 ± 0.07	0.97 ± 0.07
SBP (mmHg)	132 ± 19	135 ± 18	131 ± 15	133 ± 17	136 ± 19	130 ± 14	132 ± 17	133 ± 17
DBP (mmHg)	78 ± 11	80 ± 10	80 ± 10	81 ± 11	84 ± 13	81 ± 9	80 ± 11	81 ± 10
AHI (events/h)	25 ± 13	27 ± 14	29 ± 17	28 ± 15	29 ± 18	30 ± 16	28 ± 16	28 ± 15
ODI (4% events/h)	27 ± 13	27 ± 13	29 ± 16	27 ± 14	27 ± 13	29 ± 16	28 ± 14	27 ± 14
Time <90% SpO_2 (%)	17.99 ± 21.31	15.54 ± 19.11	16.07 ± 15.62	18.09 ± 19.64	16.89 ± 20.02	16.96 ± 16.4	16.78 ± 18.25	17.06 ± 18.9
ESS	9 ± 4	8 ± 4	8 ± 4	8 ± 4	7 ± 4	8 ± 4	8 ± 4	8 ± 4
Male sex	103 (80.5)	112 (76.7)	196 (85.2)	190 (85.6)	65 (83.3)	71 (84.5)	364 (83.5)	373 (82.5)
Country								
Australia	27 (21.1)	25 (17.1)	46 (20)	44 (19.8)	16 (20.5)	15 (17.9)	89 (20.4)	84 (18.6)
Brazil	42 (32.8)	47 (32.2)	39 (17)	35 (15.8)	10 (12.8)	9 (10.7)	91 (20.9)	91 (20.1)
China	54 (42.2)	67 (45.9)	117 (50.9)	120 (54.1)	44 (56.4)	46 (54.8)	215 (49.3)	233 (51.5)
New Zealand	5 (3.9)	7 (4.8)	28 (12.2)	23 (10.4)	8 (10.3)	14 (16.7)	41 (9.4)	44 (9.7)
Race/ethnicity								
Caucasian/European	49 (38.3)	53 (36.3)	83 (36.1)	85 (38.3)	25 (32.1)	28 (33.3)	157 (36)	166 (36.7)
Asian	58 (45.3)	69 (47.3)	118 (51.3)	120 (54.1)	46 (59)	48 (57.1)	222 (50.9)	237 (52.4)
Other	21 (16.4)	24 (16.4)	29 (12.6)	17 (7.7)	7 (9)	8 (9.5)	57 (13.1)	49 (10.8)
CVD history								
Cardiac only	85 (66.4)	101 (69.2)	151 (65.7)	151 (68)	46 (59)	50 (59.5)	282 (64.7)	302 (66.8)
Cerebrovascular only	35 (27.3)	39 (26.7)	67 (29.1)	64 (28.8)	27 (34.6)	31 (36.9)	129 (29.6)	134 (29.6)
Both	8 (6.3)	6 (4.1)	12 (5.2)	7 (3.2)	5 (6.4)	3 (3.6)	25 (5.7)	16 (3.5)
Smoking status								
Never	48 (37.5)	50 (34.2)	89 (38.7)	83 (37.4)	38 (48.7)	34 (40.5)	175 (40.1)	167 (36.9)
Past	70 (54.7)	81 (55.5)	105 (45.7)	102 (45.9)	32 (41)	33 (39.3)	207 (47.5)	216 (47.8)
Current	10 (7.8)	15 (10.3)	36 (15.7)	37 (16.7)	8 (10.3)	17 (20.2)	54 (12.4)	69 (15.3)
Insulin	40 (31.3)	24 (16.4)	—	—	—	—	40 (9.2)	24 (5.3)
Oral antidiabetic medication	98 (76.6)	110 (75.3)	—	—	—	—	98 (22.5)	110 (24.3)
Fasting glucose at baseline (mmol/L)	7.75 ± 3.01	7.34 ± 2.22	5.65 ± 1.00	5.61 ± 0.83	4.89 ± 0.58	4.98 ± 0.43	6.18 ± 2.11	6.11 ± 1.71
Fasting HbA_{1c} at baseline (%)	7.40 ± 1.46	7.21 ± 1.33	6.04 ± 0.64	6.02 ± 0.56	5.34 ± 0.35	5.36 ± 0.32	6.36 ± 1.19	6.34 ± 1.10

Data are mean ± SD or n (%). AHI, apnea-hypopnea index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SpO_2, overnight oxygen saturation measured by pulse oximeter (ApneaLink).

As shown in Supplementary Table 2, most individuals with a known diagnosis of diabetes at baseline were taking prescribed oral antidiabetic medication, with a smaller subset using insulin. The proportion using insulin at baseline was higher in the usual care group (Supplementary Table 2). There was no difference between treatment arms in the number of participants who started taking oral antidiabetic medications or insulin during the course of the study. Only a small number of participants reported any change in dose of oral antidiabetic medications during the trial, and the ratio of reported dose to defined daily dose of oral antidiabetic drugs was not statistically different between treatment groups at baseline or end of study (data not shown). Consistent with the difference observed at baseline, the number of participants using insulin at the end of study was higher in the usual care than CPAP group (Supplementary Table 2). No participants in either arm reported cessation of insulin treatment during the study.

However, because use of exogenous insulin could be expected to exert a profound effect on the metabolic responses of study participants, we repeated our analysis of glucose and HbA_{1c} measurements excluding participants who reported baseline insulin use. Restricted to participants not reliant on insulin, treatment allocation remained nonsignificant for serum glucose (estimated mean difference CPAP vs. usual care 0.24 mmol/L [95% CI −0.07, 0.546], P = 0.126), but became significant for HbA_{1c}, with higher measurements in the CPAP group during follow-up (estimated mean difference 0.18% [0.03, 0.33], P = 0.021). Because of low participant numbers, we were unable to draw conclusions about the effect of CPAP in the participant subgroup who reported using exogenous insulin.

Table 2—Fasting serum glucose and HbA_{1c} according to treatment allocation and diabetes status at baseline

	Usual care		CPAP		Adjusted mean difference	*P* value	
	Mean (95% CI)	*n*	Mean (95% CI)	*n*	CPAP – usual care (95% CI)	Treatment allocation	Treatment × visit
Known diabetes at baseline							
Glucose (mmol/L)							
Baseline	7.60 (7.21, 7.98)	122	7.49 (7.13, 7.86)	135			
6 months	7.25 (6.82, 7.68)	96	7.52 (7.11, 7.93)	108	−0.031	0.864	0.466
24 months	8.00 (7.55, 8.45)	88	8.24 (7.81, 8.67)	97	(−0.386, 0.324)		
48 months	7.98 (7.30, 8.67)	38	7.45 (6.73, 8.17)	35			
HbA_{1c} (%)							
Baseline	7.30 (7.13, 7.47)	122	7.27 (7.11, 7.43)	135			
6 months	7.08 (6.89, 7.27)	96	7.25 (7.08, 7.43)	107	0.063	0.419	0.719
24 months	7.31 (7.12, 7.51)	88	7.40 (7.21, 7.59)	96	(−0.091, 0.217)		
48 months	7.36 (7.05, 7.66)	37	7.38 (7.08, 7.68)	37			
Prediabetes at baseline							
Glucose (mmol/L)							
Baseline	5.65 (5.50, 5.80)	230	5.64 (5.49, 5.79)	220			
6 months	5.85 (5.68, 6.01)	181	5.59 (5.43, 5.75)	190	−0.071	0.277	0.377
24 months	5.74 (5.57, 5.92)	157	5.75 (5.57, 5.93)	156	(−0.200, 0.057)		
48 months	5.91 (5.66, 6.15)	86	5.88 (5.66, 6.10)	99			
HbA_{1c} (%)							
Baseline	6.04 (5.97, 6.11)	230	6.03 (5.96, 6.10)	220			
6 months	6.09 (6.01, 6.17)	179	6.00 (5.92, 6.07)	187	−0.049	0.124	0.258
24 months	6.02 (5.94, 6.11)	157	6.06 (5.97, 6.14)	155	(−0.111, 0.013)		
48 months	6.15 (6.03, 6.26)	82	6.02 (5.91, 6.13)	95			
No diabetes or prediabetes							
Glucose (mmol/L)							
Baseline	4.91 (4.78, 5.05)	55	4.95 (4.81, 5.09)	51			
6 months	5.25 (5.10, 5.40)	43	5.29 (5.13, 5.44)	41	−0.142	0.028	0.025
24 months	5.40 (5.23, 5.57)	35	5.03 (4.86, 5.20)	35	(−0.269, −0.016)		
48 months	5.52 (5.27, 5.77)	16	5.24 (5.02, 5.46)	21			
HbA_{1c} (%)							
Baseline	5.34 (5.26, 5.42)	52	5.36 (5.27, 5.44)	47			
6 months	5.56 (5.47, 5.66)	41	5.47 (5.38, 5.56)	40	0.015	0.704	0.339
24 months	5.48 (5.38, 5.58)	33	5.50 (5.40, 5.61)	31	(−0.062, 0.092)		
48 months	5.44 (5.29, 5.59)	16	5.55 (5.41, 5.69)	18			

Data are estimated marginal means, corresponding CIs, and significance from linear mixed models.

Glycemic Control in Participants Meeting Criteria for Prediabetes at Baseline

Most participants enrolled in this substudy had no known prior diagnosis of diabetes; however, many of these individuals did meet the criteria for prediabetes (222 CPAP, 230 usual care). Baseline features of these individuals are shown in Table 1. As shown in Table 2, serum glucose concentration during follow-up was not significantly different between the CPAP and usual care groups, nor was HbA_{1c}. Estimated mean baseline-adjusted fasting glucose was 5.71 mmol/L (95% CI 5.62, 5.80) for the CPAP group and 5.79 mmol/L (5.69, 5.88) for the usual care group ($P = 0.277$). Estimated mean baseline-adjusted HbA_{1c} was 6.03% (5.98, 6.07) for the CPAP group compared with 6.07% (6.03, 6.12) for those allocated to usual care ($P = 0.124$). Adjustment for weight as a time-varying covariate slightly improved the overall model fit for both glucose and HbA_{1c} but made no appreciable difference to the estimated effect of treatment allocation (data not shown). Interaction testing did not reveal any differences in the efficacy of CPAP according to ethnicity (treatment × ethnicity interaction term for glucose F 0.571 [$P_{interaction} = 0.565$] and for HbA_{1c} F 2.903 [$P_{interaction} = 0.055$]) (Supplementary Fig. 4*A*) or sex (treatment × sex interaction term glucose F 3.852 [$P_{interaction} = 0.050$] and for HbA_{1c} F 2.995 [$P_{interaction} = 0.084$]) (Supplementary Fig. 4*B*).

Glycemic Control in Participants With Neither Diabetes Nor Prediabetes at Baseline

Only 18% of participants had neither diabetes nor prediabetes at baseline (84 CPAP, 78 usual care). Baseline features of these individuals are shown in Table 1. As shown in Table 2, serum glucose concentration during follow-up was different between the CPAP and usual care groups. Estimated mean baseline-adjusted fasting glucose was 5.13 mmol/L (95% CI 5.04, 5.21) for the CPAP group and 5.27 mmol/L (5.18, 5.36) for the usual care group ($P = 0.028$). Estimated mean baseline-adjusted HbA_{1c} was 5.47% (5.42, 5.52) for the CPAP group compared with 5.45% (5.40, 5.51) for those allocated to usual care ($P = 0.704$). Adjustment for weight as a time-varying covariate resulted in deterioration of the overall model fit for both glucose and HbA_{1c}, but the alterations in estimated effects of treatment allocation were negligible (data not shown). Interaction testing did not reveal any differences in the apparent effectiveness of CPAP according to ethnicity (treatment × ethnicity interaction term for glucose F 1.039 [$P_{interaction} = 0.355$] and for HbA_{1c} F 0.321 [$P_{interaction} = 0.726$]) (Supplementary Fig. 4*A*) or sex (treatment × sex interaction term glucose F 0.024 [$P_{interaction} = 0.876$] and for HbA_{1c} F 0.185 [$P_{interaction} = 0.668$]) (Supplementary Fig. 4*B*).

Sensitivity Analysis: Individuals With Blood Collected at All Three Time Points to 24 Months

Assessment of only participants who had blood collected at baseline and 6 and 24 months, but excluding the 48-month time point at which there were more missing data, also revealed no differences between the CPAP and usual care groups in follow-up serum glucose and HbA_{1c} concentrations, either in participants with known diabetes or in those with prediabetes, adjusted for each participant's baseline measurement (Supplementary Table 3). In participants with neither diabetes nor prediabetes, there was no difference in HbA_{1c}, but a difference between treatment arms in fasting glucose was apparent (Supplementary Table 3), particularly at 24 months.

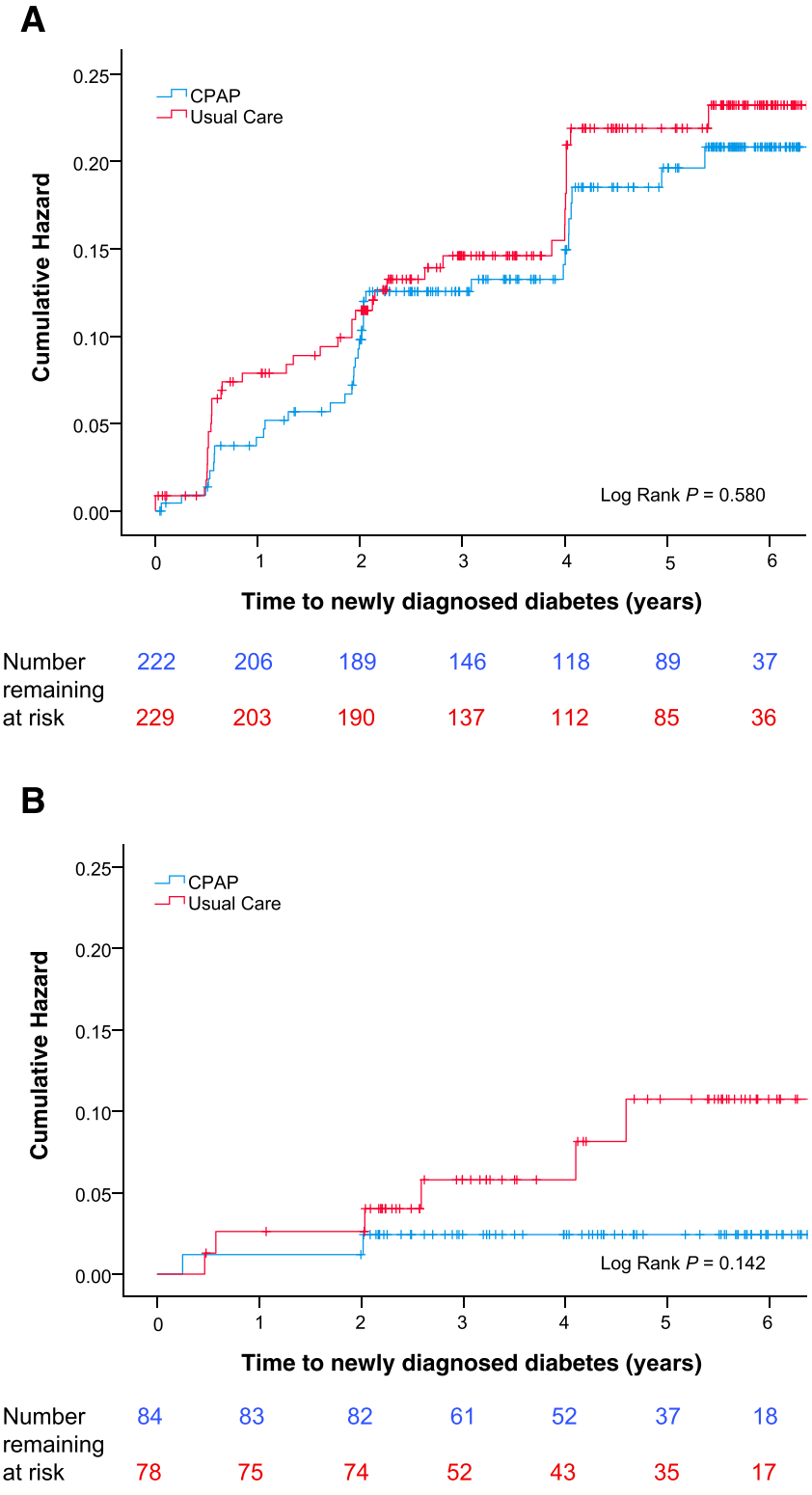

Figure 1—CPAP and new diagnoses of diabetes. Hazard function for new diagnoses of diabetes during follow-up in participants with prediabetes at baseline (*A*) and those who had neither diabetes nor prediabetes at baseline (*B*). Log-rank significance is indicated.

New Diagnoses of Diabetes in Participants With Prediabetes at Baseline

There was no significant difference between treatment groups in new diagnoses of diabetes during the study follow-up among participants who met the criteria for prediabetes at baseline (34 of 222 CPAP, 38 of 230 usual care, hazard ratio 0.878 [95% CI 0.553, 1.394], $P = 0.580$) or in participants with neither diabetes nor prediabetes at baseline. However, the number of new diagnoses in those individuals without prediabetes at baseline was small (2 of 84 CPAP, 6 of 78 usual care; 0.301 [0.061, 1.492], $P = 0.142$) (Fig. 1).

Secondary Analysis: The Role of CPAP Adherence

In participants allocated to receive the CPAP intervention, CPAP adherence in average hours per night for the duration of the trial showed no relationship with glucose (effect estimate −0.008 [95% CI −0.043, 0.027], $P = 0.651$) or HbA_{1c} concentrations (−0.050 [−0.027, 0.013], $P = 0.578$). This observation, with adherence explaining <4% of observed variance in the change in glucose or HbA_{1c} values from baseline to end of study (Fig. 2), was similar regardless of participants' baseline diabetes or prediabetes status.

Secondary Analysis: OSA Severity and Daytime Sleepiness

To test whether baseline severity of OSA, as measured by ODI or ESS, affected the glycemic response to CPAP therapy, we assessed the addition of these variables to linear mixed models for glucose and HbA_{1c}, and their potential interaction with treatment allocation. Estimated effects calculated by these methods were very small, and most did not reach statistical significance (Supplementary Table 4).

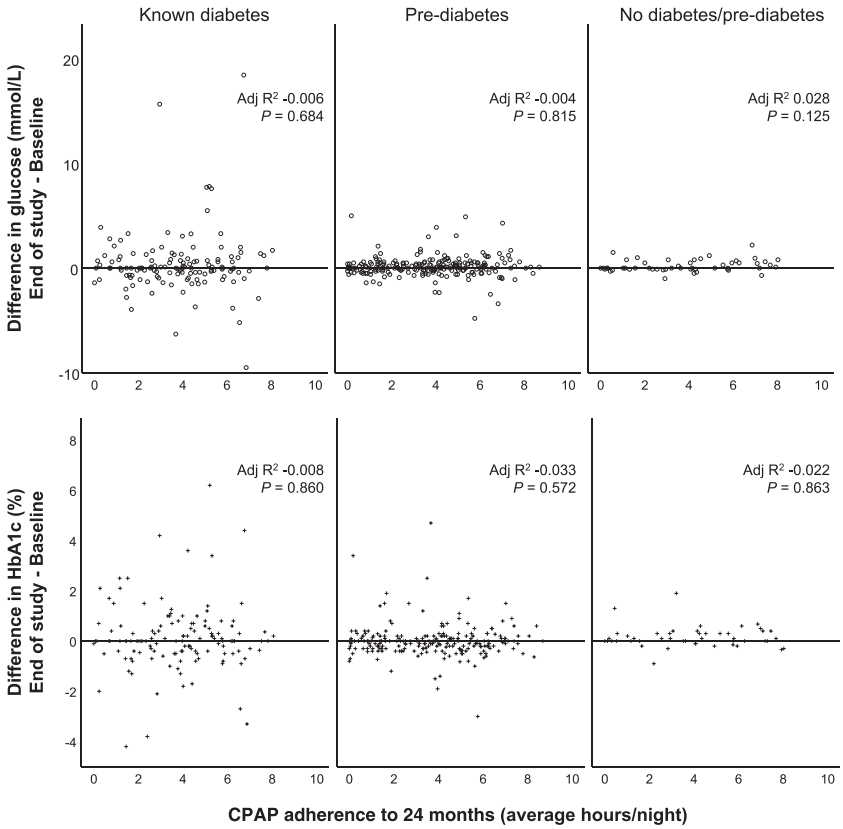

Figure 2—Glycemic control and treatment adherence in participants allocated to receive CPAP. Change in serum glucose and HbA_{1c} (final – baseline) compared with mean CPAP adherence over 2 years, according to diabetes status at baseline. Zero value on the *y*-axis indicates no change. Only participants randomized to receive CPAP treatment are shown. Adjusted (Adj) R^2 from regression and corresponding *P* values from ANOVA.

CONCLUSIONS

In this substudy of almost 900 SAVE study participants with OSA and CVD, CPAP treatment of OSA for ~4 years did not improve glycemic control either for the study population as a whole or in the subgroups with preexisting diabetes or prediabetes. CPAP treatment did not prevent the onset of diabetes in participants with prediabetes at enrollment, and consistent with previously reported shorter studies (25), it did not reduce prescriptions or the dose of antidiabetic medication among participants who were diagnosed with diabetes before enrollment. While previous studies have reported potential beneficial metabolic effects with very-short-term high adherence to CPAP therapy (10,11,26), our results during long-term follow-up showed no evidence that CPAP conferred a beneficial effect on metabolic biomarkers, even in those with high adherence to the treatment, in patients either with diabetes or prediabetes or without diabetes, and indeed, even suggested a deterioration in HbA_{1c} in participants with diabetes but who were not using exogenous insulin. A small decrease in fasting glucose was found in CPAP-treated participants with neither prediabetes nor diabetes at baseline. However, both baseline and follow-up glucose values were within the normal range, and the treatment effect (−0.1 mmol/L) was below levels considered clinically significant (27) and not supported by any concomitant change in HbA_{1c} (28). Despite expectations that individuals with more severe disease would be more likely to benefit from therapy, we did not find any convincing evidence of a differential effect in those with more severe OSA as measured either by baseline ODI or by symptomatic daytime sleepiness measured by the ESS. However, a sex × CPAP interaction was found for fasting glucose in participants with preexisting diabetes, suggesting that women with OSA and diabetes might respond more favorably to CPAP in terms of glycemic control. Inspection of group data suggests that women with diabetes assigned to CPAP remained stable, while those allocated to usual care showed a deterioration in glycemic control during follow-up.

Our findings extend over a much longer time frame and are in agreement with the results of a recent meta-analysis of prior randomized controlled trials of CPAP treatment of OSA in which follow-up ranged from 2 to 6 months (29). As with our study, the meta-analysis found no effect of OSA treatment with CPAP on fasting glucose or HbA_{1c} in either prediabetes or diabetes groups. Our results are also consistent with a previous study of CPAP and lifestyle interventions in an obese diabetes population, which showed that benefits in glycemic control were largely attributable to improvements in weight rather than to reduction in OSA severity with CPAP treatment (30). Analysis in SAVE (31), and in this substudy, indicates that most participants' weights remained quite stable over the duration of the trial and is therefore unlikely to have confounded our assessments here.

It appears that high levels of CPAP treatment (>7 h/night) can improve glycemic control acutely over 1–2 weeks (10,11). The fact that similar improvements have not been found in this and other clinical trials could be because such beneficial effects are short-lived or because the reduction in exposure to OSA is limited by patients' incomplete long-term adherence to the treatment, notwithstanding the absence of any obvious CPAP dose effect in the current study.

Risk of Incident Diabetes in Participants Who Were Not Reported as Having Diabetes at Baseline

OSA is associated with elevated risk of incident type 2 diabetes (3–7,32), and observational data suggest that regular CPAP treatment may reduce the risk (9,26). However, until now, randomized studies addressing this question have been lacking. We previously reported no difference between the CPAP and usual care groups in incident diabetes when reported as an adverse event in the entire SAVE trial population (23). The results of this substudy of participants who had blood collected at regular intervals extend that finding. How can these results be reconciled with previous longitudinal cohort study findings? Possible explanations include *1*) that observational

studies have overestimated the metabolic risk associated with OSA because of residual confounding from other diabetogenic factors (e.g., visceral obesity, sedentary behavior); *2*) that the participant population recruited to SAVE had strong, long-established physiological and behavioral contributors to metabolic risk, making it difficult to detect a relatively small contribution from OSA, perhaps compounded by incomplete participant adherence to CPAP; and *3*) that previous nonrandomized observational studies showing benefits with CPAP therapy were confounded by unmeasured effects, such as healthy user bias with increased compliance with other health interventions (e.g., medications, lifestyle advice).

Study Strengths and Limitations

The main strengths of this study were the inclusion of a large number of well-characterized participants in a multicenter, multinational, randomized study with relatively long-term follow-up. Furthermore, diabetes incidence was a prespecified end point, and medication information was systematically recorded at each scheduled follow-up appointment. However, we acknowledge the following limitations. SAVE was not primarily designed to explore metabolic outcomes, and dietary habits and physical activity were not monitored quantitatively in this study, raising the potential for other unknown confounding effects. Because of the study design, this was a potential systematic bias for both groups. Education and encouragement to follow healthy dietary and exercise habits were available to all participants during the follow-up period. Likewise, we are unable to comment on insulin resistance or postprandial glucose handling because these were not measured directly. This may be an informative angle for future investigation because the potential benefits of intervention may vary in individuals with prediabetes defined by either impaired fasting glucose or insulin sensitivity. Others have suggested that individuals who have had diabetes for a long time are likely to have β-cell defects and, thus, may have irreversible metabolic regulatory impairment (33). We are unable to address this directly but note that only a small proportion of these participants were reliant on exogenous insulin, thus limiting the conclusions that we can draw. Conversely, however, when restricted to participants with preexisting diabetes but not using insulin, our data indicate a slight deterioration in HbA_{1c} in CPAP users but no change in fasting glucose levels.

We must also acknowledge the statistical limitations of our analysis. While SAVE is by far the largest and longest running randomized trial of CPAP treatment for OSA and CVD risk, the number of participants is still small compared with many diabetes prevention trials, and we lacked statistical power to definitively address metabolic outcomes, especially in subgroup analyses with even fewer participants. However, calculations show that a sample of 200 participants with diabetes and 400 with prediabetes would have been sufficient to detect effect sizes of 0.199 and 0.140, corresponding to reductions in HbA_{1c} as small as 0.3% and 0.1%, respectively. Because the recruitment criteria of the SAVE trial excluded individuals with very severe OSA (23), some caution should be applied in extrapolating these results to the general sleep clinic population. Curiously, participants with neither diabetes nor prediabetes at baseline were slightly underrepresented in this analysis compared with the composition of the whole SAVE trial. We consider this unlikely to have substantially altered our conclusions. It seems plausible that individuals with known diabetes were both more interested in this substudy topic and were likely to comply with the requirement for repeated fasting blood collections. Finally, we did see evidence of a differential effect according to sex in glucose levels, and while SAVE, and indeed most analyses of sleep apnea populations, comprised mainly men, this observation suggests a need for further targeted investigation in women.

In summary, long-term CPAP in addition to usual care in patients with CVD and OSA was not associated with improved glycemic control in those with diabetes, or prevention of new diabetes diagnoses, compared with usual care alone. Management of traditional cardiometabolic risk factors remains of key importance in this high-risk patient group, many of whom have diabetes or prediabetes. While this study does not indicate a beneficial effect of long-term CPAP on metabolic parameters in such participants in general, reported improvements in mood and health-related quality of life in CPAP users (23,34) suggest that management of OSA as part of a holistic approach in individuals with comorbidities is likely to provide broader health benefits.

Acknowledgments. A full list of the sites and investigators involved in the substudy of the SAVE trial is provided in the Supplementary Material. The authors thank the participants and their families who made this work possible.

Funding and Duality of Interest. The SAVE trial was funded by National Health and Medical Research Council (NHMRC) of Australia project grants 1006501 and 1060078 as well as by the Respironics Sleep and Respiratory Research Foundation and Philips Respironics. Supplementary trial funding was provided by Fisher & Paykel Healthcare and the Australasian Sleep Trials Network (enabling grant 343020 from the NHMRC). In-kind donations were provided by Philips Respironics for CPAP equipment and by ResMed for sleep apnea diagnostic devices. L.R.B. reports grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (numbers 401569/2016-0 and 309336/2017-1). M.H. is a shareholder of CanSleep, a company that provides diagnostic testing and therapy for patients with sleep disorders. N.M. reports funding support from ResMed for other research projects and travel expenses to present results from those projects at an international conference and research funding support/grants from Oventus (Brisbane, Queensland, Australia), Nyxoah (Mont-Saint-Guibert, Belgium), and Zelda Therapeutics (Perth, Western Australia, Australia). R.D.M. reports grants and nonfinancial support from Philips Respironics, nonfinancial support from ResMed, grants from NHMRC of Australia, and grants from Fisher & Paykel, during the conduct of the study; nonfinancial support from Air Liquide; and speaker's fees from ResMed. L.F.D. reports receiving research study equipment from Philips Respironics. No other potential conflicts of interest relevant to this article were reported.

Funding agencies played no role in conduct of the trial, data analysis, drafting of the manuscript, or the decision to submit for publication.

Author Contributions. K.A.L., R.F., and R.M. contributed to the data collation and analysis. K.A.L., R.D.M., and L.F.D. contributed to the writing of the manuscript. K.A.L., C.S.A., R.D.M., and L.F.D. contributed to data interpretation. E.H., R.F., L.R.B., C.C.G.C., R.C., M.H., Z.L., G.L.-F., Y.L., N.M., S.M., H.S.Y., X.Z., L.J.P., C.S.A., R.D.M., and L.F.D. contributed to the data and sample collections. E.H., C.S.A., and R.D.M. contributed to the study design. All authors contributed to the drafting of the manuscript and approval for submission. K.A.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at Sleep DownUnder 2019, Sydney, New South Wales, Australia, 16–19 October 2019.

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