Online Data Supplements

Cardiovascular outcomes in obstructive sleep apnoea and implications of clinical phenotyping on effect of continuous positive airway pressure treatment

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Xu P-H, *et al. Thorax* 2022; 78:76–84. doi: 10.1136/thoraxjnl-2021-217714

Materials and Methods

CPAP treatment

Per clinical indication criteria, continuous positive airway pressure (CPAP) therapy was recommended for treatment of moderate to severe obstructive sleep apnoea (OSA) or mild OSA with symptoms or other significant risks [E1]. Patients were followed up at the specialist sleep clinics, usually at 3 and 6 months after CPAP titration, and yearly thereafter, at which both objective (machine-reported) and subjective (self-reported) compliance were assessed.

Variables

Available variables were derived from the cohort database for the research purpose: 1) Demographics — age and gender; 2) Anthropometric parameters — body mass index (BMI), neck/waist/hip circumferences and body weight change; 3) Epworth sleepiness scale (ESS) scores; 4) Medical history — prior hypertension, prior diabetes, prior hyperlipidaemia, prior cardiovascular disease (CVD),family history of CVD, statin use and beta blocker use; 5) Baseline blood samples — fasting glucose, total cholesterol, triglycerides; 6) Lifestyle behaviour — cigarette smoking, alcohol use, physical activity and educational level; 7) Polysomnographic parameters — apnoea-hypopnoea index (AHI), apnoea-hypopnoea index during rapid eye movement sleep (REM-AHI), total sleep time (TST), sleep time with oxygen saturation below 90% (TST90), oxygen desaturation index (ODI), minimum oxygen saturation (SpO_2), mean SpO_2, nocturnal and wake mean heart rate (MHR), mean apnoea-hypopnoea duration (AHD) and arousal index; 8) CPAP compliance.

Statistical analysis

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Distribution of covariates and sleep measures were summarized by outcome status. The association between AHI and TST90 was explored with scatter plot with marginal histograms. Mid-*P* test [E1] was used to calculate the 95%CI of incidence rate.

A series of Kaplan-Meier plots and Cox regression models were constructed to assess the association between OSA and major adverse cardiovascular events (MACEs) in entire dataset and untreated subgroup. To avoid arbitrary cut-off, PSG parameters were modelled as continuous variables, comparing by 75^{th} vs. 25^{th} percentiles. Covariates were chosen *a priori*. Models were estimated with and without adjusting for these covariates. As a secondary endpoint, we analysed the association with incidence of non-fatal MACEs as well.

To investigate the effect of CPAP therapy on MACEs, Cox regression on CPAP compliance, with and without adjustment of potential confounders, was conducted. We further proposed a two-stage least absolute shrinkage and selection operator (LASSO)-latent class analysis (LCA) algorithm. LASSO regression was used to determine the optimal features for this OSA cohort, which removed redundant and irrelevant features to provide important feature information by penalizing some regression coefficients to zero [E2]. Twenty-four variables had been entered into this selection process in the first stage, including age, gender, BMI, neck circumference, waist circumference, body weight change, ESS, TST, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia, prior diabetes and PSG parameters (AHI, ODI, TST90, heart rate, REM-AHI, MinSpO_2, MeanSpO_2, Mean AHD and arousal index). The indicators in cluster analysis were finally selected by the overall consideration. LCA models based

on selected features was constructed in the second stage to uncover the hidden clusters with different treatment response [E3]. The “depmixS4” package in R was used to run the data-driven LCA cluster analyses from two to five clusters, and the number of clusters was chosen based on Bayesian Information Criteria and law of parsimony [E4]. In each identified subgroup, Cox models were refitted with additional adjustment for CPAP compliance.

Multiple imputation was conducted to handle missing data. For a unified presentation of the results, the findings were shown by a single imputed dataset. Analyses in other multiple datasets or complete-data analysis were conducted. Results from Cox-regression were presented as hazard ratio (HR) with 95% confidence interval (CI). *P* values were determined using 2-tailed tests and significance level was set at 0.05. All statistical analyses were conducted using R statistical software, version 3.4.3 (https://www.r-project.org).

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Table E1. Associations of polysomnographic parameters and incident non-fatal MACEs

PSG parameters	Univariate Model		Multivariable Model*	
	HR (95%CI)		HR (95%CI)	
Total dataset (n=1860)				
AHI (46.9 vs 8.0)	**1.24**	**(1.05-1.47)**	0.97	(0.78-1.21)
REM-AHI (54.4 vs 11.1)	1.17	(0.96-1.43)	1.02	(0.80-1.32)
3% ODI (41.3 vs 4.9)	**1.25**	**(1.08-1.46)**	1.03	(0.84-1.26)
Mean AHD (26.8 vs 18.9)	1.04	(0.90-1.21)	0.99	(0.84-1.16)
TST90† (36.4 vs 0.7)	**1.11**	**(1.05-1.16)**	**1.43**	**(1.11-1.85)**
Mean SpO_2 (96.0 vs 93.7)	0.89	(0.82-0.96)	0.97	(0.87-1.07)
Min SpO_2 (87.0 vs 71.0)	0.84	(0.74-0.96)	0.96	(0.83-1.12)
Arousal index (30.9 vs 11.8)	**1.18**	**(1.05-1.33)**	1.04	(0.90-1.19)
Nocturnal MHR (70.2 vs 58.5)	**1.20**	**(1.04-1.39)**	**1.25**	**(1.08-1.45)**
Wake MHR (75.7 vs 63.1)	**1.22**	**(1.05-1.41)**	**1.27**	**(1.09-1.48)**
Untreated subset (n=1567)				
AHI (39.4 vs 6.3)	**1.31**	**(1.12-1.53)**	1.01	(0.82-1.25)
REM-AHI (51.0 vs 8.9)	**1.25**	**(1.01-1.54)**	1.06	(0.81-1.38)
3% ODI (34.0 vs 3.8)	**1.29**	**(1.12-1.48)**	1.06	(0.87-1.28)
Mean AHD (26.5 vs 18.7)	1.00	(0.85-1.17)	0.95	(0.79-1.15)
TST90† (25.4 vs 0.3)	**1.09**	**(1.05-1.13)**	**1.47**	**(1.15-1.88)**
Mean SpO_2 (96.2 vs 9.0)	0.88	(0.81-0.95)	0.97	(0.87-1.08)
Min SpO_2 (88.0 vs 74.0)	0.81	(0.72-0.92)	0.93	(0.81-1.08)
Arousal index (27.4 vs 11.0)	**1.23**	**(1.11-1.37)**	1.09	(0.95-1.24)
Nocturnal MHR (70.0 vs 58.6)	**1.28**	**(1.11-1.49)**	**1.31**	**(1.12-1.53)**
Wake MHR (75.7 vs 63.0)	**1.32**	**(1.13-1.53)**	**1.35**	**(1.16-1.59)**

These parameters were modelled separately. The PSG variables are compared by 75^{th} vs. 25^{th} percentiles.

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*Multivariable models adjusted for age, gender, body mass index, neck circumference, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.
†TST90 with non-linearity was transformed using restricted cubic spline transformation with 3 knots at default 0.1, 0.5 and 0.9 quantiles.
Definition of abbreviations: AHD, apnoea-hypopnoea duration; AHI, apnoea-hypopnoea index; BMI, body mass index; PSG, polysomnography; HR, hazard ratio; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnoea index during rapid eye movement sleep; SpO_2, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

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Table E2. Multivariate regression analyses: associations of polysomnographic parameters and incident MACEs (n=1860)

PSG parameters	Cox survival model*		Competing risk survival model*	
	HR (95% CI)		HR (95% CI)	
Total dataset (n=1860)				
AHI (46.9 vs 8.0)	0.95	(0.76-1.17)	0.94	(0.76-1.18)
REM-AHI (54.4 vs 11.1)	1.03	(0.80-1.31)	1.04	(0.80-1.36)
3% ODI (41.3 vs 4.9)	1.00	(0.82-1.22)	0.99	(0.80-1.22)
Mean AHD (26.8 vs 18.9)	0.96	(0.82-1.13)	0.99	(0.84-1.16)
TST90† (36.4 vs 0.7)	**1.41**	**(1.10-1.81)**	**1.37**	**(1.07-1.43)**
Mean SpO_2 (96.0 vs 93.7)	0.99	(0.89-1.10)	0.99	(0.89-1.10)
Min SpO_2 (87.0 vs 71.0)	0.99	(0.85-1.15)	1.00	(0.86-1.16)
Arousal index (30.9 vs 11.8)	1.03	(0.90-1.17)	1.04	(0.91-1.19)
Nocturnal MHR (70.2 vs 58.5)	**1.27**	**(1.10-1.46)**	**1.21**	**(1.03-1.42)**
Wake MHR (75.7 vs 63.1)	**1.30**	**(1.12-1.50)**	**1.26**	**(1.08-1.48)**
Untreated subset (n=1567)				
AHI (39.4 vs 6.3)	0.99	(0.81-1.22)	0.99	(0.80-1.23)
REM-AHI (51.0 vs 8.9)	1.06	(0.82-1.38)	1.08	(0.81-1.43)
3% ODI (34.0 vs 3.8)	1.03	(0.86-1.24)	1.02	(0.84-1.25)
Mean AHD (26.5 vs 18.7)	0.93	(0.78-1.11)	0.95	(0.79-1.13)
TST90† (25.4 vs 0.3)	**1.46**	**(1.14-1.86)**	**1.35**	**(1.10-1.42)**
Mean SpO_2 (96.2 vs 9.0)	0.99	(0.89-1.11)	1.00	(0.89-1.12)
Min SpO_2 (88.0 vs 74.0)	0.96	(0.83-1.10)	0.97	(0.84-1.12)
Arousal index (27.4 vs 11.0)	1.08	(0.95-1.22)	1.09	(0.95-1.24)
Nocturnal MHR (70.0 vs 58.6)	**1.33**	**(1.15-1.54)**	**1.29**	**(1.09-1.53)**
Wake MHR (75.7 vs 63.0)	**1.38**	**(1.19-1.61)**	**1.35**	**(1.14-1.60)**

These parameters were modelled separately. The PSG variables are compared by 75th vs. 25th percentiles.

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*Models adjusted for age, gender, body mass index, neck circumference, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.

†TST90 with non-linearity was transformed using restricted cubic spline transformation with 3 knots at default 0.1, 0.5 and 0.9 quantiles.

Definition of abbreviations: AHD, apnoea-hypopnea duration; AHI, apnoea-hypopnea index; BMI, body mass index; PSG, polysomnography; HR, hazard ratio; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnea index during rapid eye movement sleep; SpO_2, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

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Table E3. Associations of polysomnographic parameters and incident MACEs in patients with BMI <25kg/m² (n=624)

PSG parameters	Univariate Model		Multivariable Model*	
	HR (95%CI)		HR (95%CI)	
AHI (26.8 vs 3.6)	**1.35**	**(1.05-1.73)**	0.96	(0.72-1.29)
REM-AHI (34.2 vs 4.07)	1.32	(0.97-1.79)	0.96	(0.69-1.36)
3% ODI (17.7 vs 1.6)	**1.26**	**(1.07-1.50)**	0.98	(0.81-1.19)
Mean AHD (28.4 vs 19.9)	0.91	(0.69-1.20)	0.85	(0.61-1.17)
TST90 (8.62 vs 0.0)	**1.07**	**(1.04-1.10)**	**1.03**	**(1.00-1.07)**
Mean SpO_2 (97.0 vs 95.0)	0.70	(0.55-0.89)	0.96	(0.73-1.26)
Min SpO_2 (91.0 vs 79.0)	0.87	(0.69-1.10)	1.14	(0.84-1.55)
Arousal index (30.9 vs 11.8)	**1.18**	**(1.05-1.33)**	1.04	(0.90-1.19)
Nocturnal MHR (68.1 vs 57.6)	1.21	(0.95-1.55)	1.24	(0.97-1.57)
Wake MHR (73.6 vs 62.6)	**1.38**	**(1.09-1.75)**	**1.34**	**(1.06-1.69)**

These parameters were modelled separately. The PSG variables are compared by 75th vs. 25th percentiles.

*Multivariable models adjusted for age, gender, body mass index, neck circumference, waist circumference, body weight change, Epworth sleepiness scale, total sleep time, cigarette smoking, alcohol use, physical activity, prior hypertension, prior cardiovascular disease, prior hyperlipidaemia and prior diabetes.

Definition of abbreviations: AHD, apnoea-hypopnoea duration; AHI, apnoea-hypopnoea index; BMI, body mass index; PSG, polysomnography; HR, hazard ratio; MACEs, major adverse cardiovascular events; MHR, mean heart rate; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnoea index during rapid eye movement sleep; SpO_2, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

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Table E4. Characteristics of CPAP-treated and untreated patients with moderate-severe OSA (n=1108)

Variables	Moderate-severe OSA (AHI≥15/hr)		*p* for difference
	CPAP Untreated (n=843, 76%)	CPAP Treated (n=265, 24%)	
Demographics			
Male, n (%)	617 (73.2%)	210 (79.2%)	0.058
Age, year	53.8 (12.5)	52.9 (11.2)	0.305
Symptom and measures			
BMI, kg/m^2	29.3 (5.6)	29.1 (4.8)	0.566
Neck circumference, cm	39.7 (4.1)	39.9 (3.6)	0.564
Waist circumference, cm	97.1 (12.6)	97.2 (11.2)	0.903
Hip circumference, cm	101.7 (10.4)	101.7 (8.7)	0.945
Epworth sleepiness scale	8.7 (5.4)	9.4 (5.4)	0.060
Polysomnogram			
TST, min	417.5 (367.0-457.5)	424.5 (382.0-459.5)	0.047
AHI, /hr	37.2 (24.6-60.0)	50.4 (35.6-66.7)	<0.001
REM-AHI, /hr	48.5 (29.2-63.4)	52.1 (41.5-65.8)	<0.001
3% ODI, /hr	30.4 (18.0-55.1)	44.8 (27.3-65.2)	<0.001
Mean SpO_2, %	94.3 (92.9-95.7)	93.7 (92.0-94.9)	<0.001
Min SpO_2, %	76.0 (66.0-82.0)	72.0 (60.0-79.0)	<0.001
TST90, min	20.2 (5.8-58.2)	40.9 (12.2-112.7)	<0.001
Arousal Index, /hr	25.1 (15.6-39.0)	32.3 (21.6-49.4)	<0.001
Mean AHD, sec	22.1 (18.8-26.0)	23.4 (20.3-27.9)	<0.001
Nocturnal MHR, /min	65.2 (59.1-71.5)	65.2 (58.4-71.1)	0.664
Wake MHR, /min	70.2 (63.3-76.8)	70.1 (63.3-77.3)	0.848
History			
Prior hypertension, n (%)	610 (72.4%)	179 (67.5%)	0.152
Prior diabetes, n (%)	290 (34.4%)	59 (22.3%)	<0.001
Fasting glucose, mmol/L	5.5(5.0-6.6)	5.6(5.0-6.2)	0.439
Prior hyperlipidaemia, n (%)	314 (37.2%)	96 (36.2%)	0.820
Total cholesterol, mmol/L	4.9(4.2-5.6)	4.9(4.2-5.4)	0.864
Triglycerides, mmol/L	1.7(1.2-2.3)	1.7(1.2-2.3)	0.983
Prior CVDs, n (%)	130 (15.4%)	38 (14.3%)	0.741
Statin use, n (%)	232 (27.5%)	71 (26.8%)	0.878
Beta blocker use, n (%)	234 (27.8%)	70 (26.4%)	0.728
Family history of CVD, n (%)	198 (23.5%)	78 (29.4%)	0.061
Cigarette smoking, n (%)			0.235
No	527(62.5%)	181(68.3%)	
Former	134(15.9%)	34(12.8%)	
Current	180(21.4%)	50(18.9%)	
Alcohol use, n (%)			0.690
No	614(72.8%)	188(70.9%)	

Former	161(19.1%)	57(21.5%)	
Current	64(7.6%)	19(7.2%)	
Physical activity, n (%)			0.323
Low	553(65.6%)	165(62.3%)	
Medium	235(27.9%)	84(31.7%)	
High	48(5.7%)	11(4.2%)	
Education level, n (%)			0.011
Primary or below	247 (29.3%)	60 (22.6 %)	
Secondary	379 (45.0%)	113 (42.6%)	
Tertiary	216 (25.6%)	91 (34.3%)	
Body weight change*, kg	1.0 (7.0)	1.9 (6.4)	0.059
Follow-up time, months	97.4 (67.4-118.4)	97.6 (71.3-123.4)	0.251
Incident MACEs, n (%)	146 (17.3%)	38 (14.3%)	0.297

*Body weight change was defined as body weight at endpoint or censoring minus baseline body weight.

Data are given as mean (SD), median (IQR) or n (%). Numbers may not add to total because of missing values.

Definition of abbreviations: AHD, apnoea-hypopnoea duration; AHI, apnoea-hypopnoea index; BMI, body mass index; CVDs, cardiovascular diseases; PSG, polysomnography; MACEs, major adverse cardiovascular events; ODI, oxygen desaturation index; MHR, mean heart rate; OSA, obstructive sleep apnoea; REM-AHI, apnoea-hypopnoea index during rapid eye movement sleep; SpO_2, peripheral capillary oxygen saturation; TST, total sleep time; TST90, sleep time with oxygen saturation below 90%.

Table E5. Landmark analysis: the effect of CPAP on MACEs in moderate-severe OSA patients by clusters

	Cluster 1		Cluster 2		Cluster 3		Cluster 4	
Subset of follow-up more than 0 days (n=1108)								
No. of subjects	333		265		271		239	
Incident MACEs, n (%)	57 (17.1%)		38 (14.3%)		46 (17.0%)		43 (18.0%)	
Unadjusted HR	**0.49**	**(0.25 - 0.95)**	0.85	(0.33 - 2.19)	0.94	(0.45 - 1.95)	1.18	(0.62 - 2.27)
Partially adjusted HR*	**0.44**	**(0.22 - 0.85)**	0.85	(0.33 - 2.19)	0.85	(0.41 - 1.77)	1.57	(0.79 - 3.13)
Fully adjusted HR†	**0.45**	**(0.23 - 0.90)**	0.79	(0.30 - 2.12)	0.68	(0.31 - 1.45)	1.40	(0.67 - 2.91)
Subset of follow-up more than 180 days (n=1098)								
No. of subjects	330		263		269		236	
Incident MACEs, n (%)	54 (16.4%)		36 (13.7%)		44 (16.4%)		41 (17.4%)	
Unadjusted HR	**0.46**	**(0.23 - 0.92)**	0.86	(0.34 - 2.23)	0.99	(0.48 - 2.06)	1.14	(0.58 - 2.23)
Partially adjusted HR*	**0.41**	**(0.21 - 0.83)**	0.90	(0.35 - 2.33)	0.90	(0.43 - 1.89)	1.48	(0.73 - 3.01)
Fully adjusted HR†	**0.42**	**(0.21 - 0.86)**	0.84	(0.31 - 2.26)	0.74	(0.34 - 1.60)	1.27	(0.59 - 2.72)
Subset of follow-up more than 365 days (n=1084)								
No. of subjects	324		260		276		233	
Incident MACEs, n (%)	50 (15.4%)		33 (12.7%)		43 (15.6%)		39 (16.7%)	
Unadjusted HR	0.51	(0.25 - 1.01)	0.74	(0.26 - 2.11)	1.02	(0.49 - 2.13)	1.23	(0.62 - 2.42)
Partially adjusted HR*	**0.46**	**(0.23 - 0.92)**	0.75	(0.26 - 2.13)	0.93	(0.44 - 1.94)	1.65	(0.80 - 3.38)
Fully adjusted HR†	**0.47**	**(0.23 - 0.95)**	0.75	(0.25 - 2.24)	0.75	(0.35 - 1.63)	1.47	(0.67 - 3.22)

* Adjusted for age, gender and body mass index.

† Adjusted for age, gender, body mass index, waist circumference, neck circumference, AHI, TST90 and mean heart rate.

Definition of abbreviations: CPAP, continuous positive airway pressure; HR, hazard ratio; MACEs, major adverse cardiovascular events; OSA, obstructive sleep apnoea.

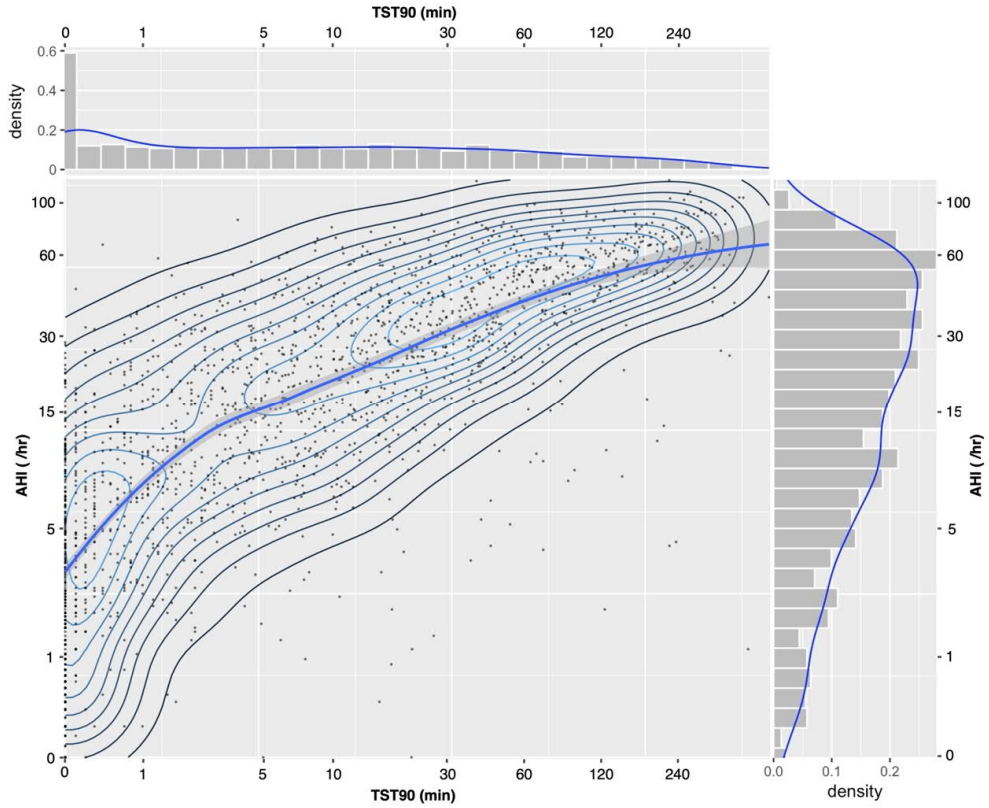

Figure E1. Scatter plot with marginal histograms of AHI and TST90

The contour reflects their distribution and the smoothing curve with 95%CI indicates their association. The log-transformation was used as $\log_2$(TST90+1) and $\log_2$(AHI+1), 1 was added in the arguments to allow for analysis of many zero values. Two OSA measures are mildly correlated, and variability is high. A short duration of TST90 near zero is frequently observed in combination with a wide range of AHI values. AHI, apnoea-hypopnoea index; TST90, sleep time with oxygen saturation below 90%.

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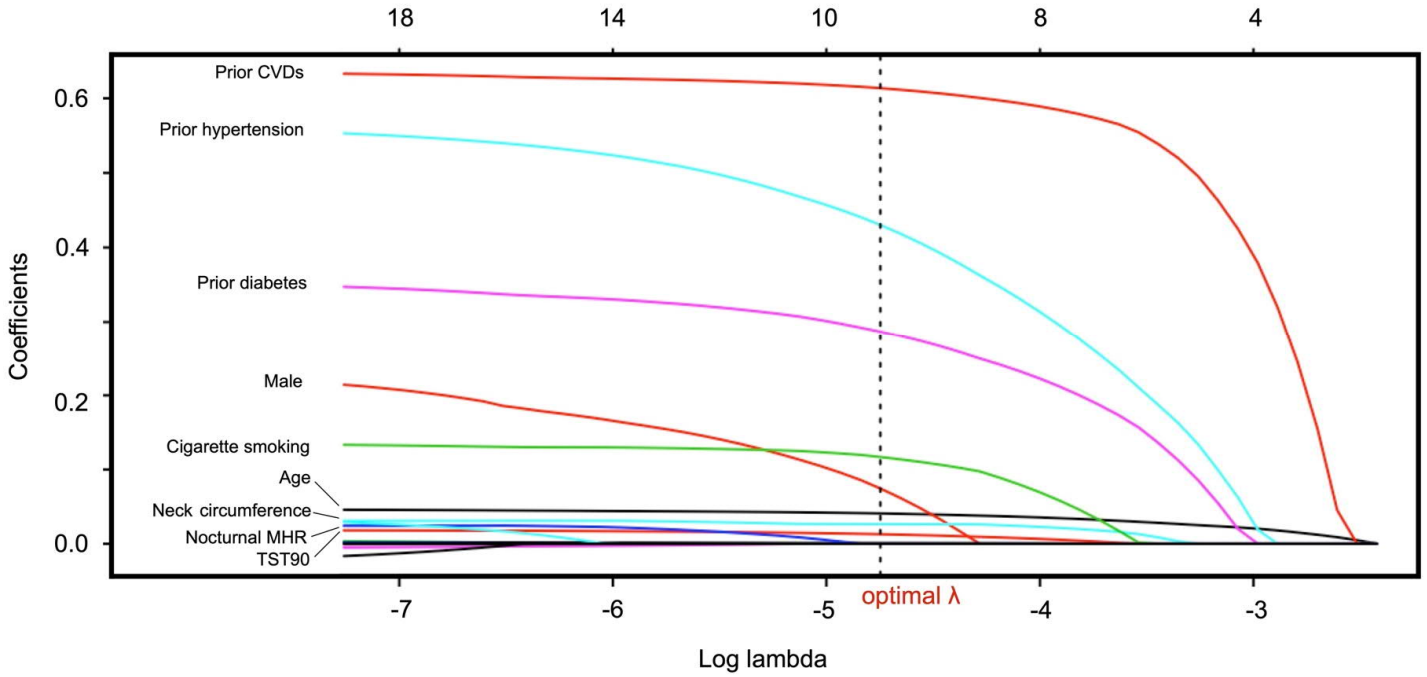

Figure E2. Coefficient progression of the LASSO regression model (n=1860)

Tuning log(lambda) sequence in the LASSO model used 10-fold cross-validation via minimum MSE (dotted vertical line). The most distinguishing indicators were determined according to the minimum MSE criteria, where optimal lambda resulted in 9 non-zero coefficients. Together with *a priori* selection of AHI, BMI and waist circumference, we finalized 12 indicators for further cluster profile identification. AHI, apnoea-hypopnoea index; BMI, body mass index; CVDs, cardiovascular diseases; LASSO, least absolute shrinkage and selection operator; MHR, mean heart rate; MSE, mean squared error; TST90, sleep time with oxygen saturation below 90%.

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