Sleep Apnea Indices Associated with Markers of Inflammation and Cardiovascular Disease: A Proteomic Study in the MUSTACHE Cohort

To the Editor:

There is an increasing awareness that the apnea–hypopnea index (AHI) does not sufficiently reflect the cardiovascular stress caused by obstructive sleep apnea (OSA) and that indices of hypoxic burden might better predict the risks (1). The cardiovascular effects from OSA might also differ by sleep stage, with a stronger risk by the rapid eye movement (REM) sleep–specific AHI (REM-AHI) (2–5).

Altered levels of protein biomarkers might be the first sign of cardiometabolic disease. To date, only a limited number of studies have used proteomic panels, enabling the analysis of multiple proteins from one small sample to explore the associations between different OSA indices and markers of inflammation and cardiometabolic disease (5, 6). In the Sleep and Health in Women (SHE) cohort, which analyzed two proteomic assays including 184 proteins and adjusted for potential confounders, women with severe REM-OSA displayed decreased levels of Sirt2 and latency-associated peptide–transforming growth factor-β_1 (LAP-TGF-β_1), both involved in antiinflammatory processes, and also lower levels of Axin1, a protein known to facilitate TGF-β signaling. In the SHE cohort, no significant proteomic associations were found for the AHI and the oxygen desaturation index (ODI) after adjustment for age and body mass index (BMI) (5).

Here, we aimed to investigate the associations between different OSA indices and protein expression in men and to study whether REM-OSA is associated with Sirt2, LAP-TGF-β_1, and Axin1, not only in women (5) but also in men.

Methods

The "Men in Uppsala; a Study of sleep, Apnoea and Cardiometabolic Health," or MUSTACHE, study was created as an age- and BMI-matched male cohort ($n = 400$) to the preexisting female population–based SHE cohort (7). The men were investigated using whole-night ambulatory polysomnography (EMBLA; Flaga); sleep was scored manually by the same investigator and with identical scoring criteria as in the SHE cohort (5, 7). The AHI, ODI, defined as the mean number of desaturations of ⩾ 3% per hour of sleep, and REM-AHI was calculated as previously described (5). As an index of the hypoxic burden, the severity adjusted AHI (AAHI)—which adjusted AHI for the severity of the obstructive events (duration and desaturation area)—was calculated using a RemLogic plug-in (1, 8). In these calculations, the hypopnea definition was a ⩾30% flow reduction for ⩾10 seconds with ⩾4% desaturation, according to the predefined algorithm. Data from the RemLogic plug-in were available in a subset of participants ($n = 255$).

On the morning after the polysomnography, fasting blood samples were drawn. The Olink Target 96 Inflammation and Target 96 Cardiovascular II panels, each measuring 92 proteins, were analyzed at the Olink Analysis Service (Olink Proteomics) using proximity extension assay technology (9, 10).

Associations between OSA-indices (AHI, ODI, REM-AHI) and protein levels were assessed in regression models adjusted for age, BMI, plate, and storage time, with the OSA-indices discretized, comparing men who had severe OSA (AHI, ODI, or REM-AHI ⩾30) with men who had no or mild OSA (AHI, ODI, or REM-AHI <15). The *P* values were adjusted for multiple testing using the Benjamini–Hochberg method for controlling the false discovery rate (11), which was set at 10% (5).

Proteins with 20–90% of the values below the limit of detection (LOD) were discretized as detectable or undetectable. For all proteins with less than 20% of the values below the LOD, the values below the LOD were replaced with the LOD. The AAHI was not available for all participants and was, therefore, not included in the main analysis. Nonetheless, for proteins with significant associations with any of the OSA indices in the main analyses, associations also with the AAHI were explored.

All participants gave their written informed consent, and the Uppsala University Ethics Committee approved the study protocol (2016/029).

Results

Characteristics of the study population are given in Table 1. In adjusted models using men with no or mild OSA as the reference group, an AHI ⩾30 was associated with one protein, and an ODI ⩾30 with eight proteins, whereas no significant associations between a REM-AHI ⩾30 and protein levels were found (Table 2).

Of the four different OSA indices, the AAHI had the highest coefficients for six of the eight proteins altered in severe OSA (Table 3). Three proteins were significantly associated with the AAHI. Only 15 men in the subsample had an AAHI ⩾30, and there was an association between an AAHI ⩾30 and one protein after adjustment (CD244 coefficient, 0.39; 95% confidence interval, 0.20–0.59; $P = 0.0001$; adjusted $P = 0.02$).

There were no significant associations between the REM-AHI and any of the three prehypothesized proteins Sirt2, LAP-TGF-β_1, and Axin1.

Discussion

In this male cohort, the ODI, but not the AHI or REM-AHI, was associated with several inflammatory and cardiovascular markers. The value of indices that reflect the hypoxic burden was further implied by the associations between AAHI and protein levels.

An ODI ⩾30 was associated with increased levels of eight proteins. Comparable data in men are lacking for six of these proteins involved in neuroinflammation (neurotrophin-3) (12); angiogenesis (hepatocyte growth factor; HGF) (13); iron homeostasis (bone morphogenetic protein 6; BMP6) (14); and immunoregulation, inflammation, and cancer (CD244, LIF-R, and PD-L2) (15–17). In the all-female SHE cohort, an ODI ⩾30 was not associated with any of these proteins (5). Men with an ODI ⩾30 also had higher levels of

Supported by the Swedish Heart Lung Foundation (Grant no. 20190218), Vetenskapsrådet (Grant no. 2020-02192), the Bror Hjerpstedts Foundation, and the Uppsala County Association against Heart and Lung Diseases.

Table 1. Participant characteristics

Characteristic	All	AHI <15	AHI ⩾30	ODI <15	ODI ⩾30	REM-AHI <15	REM-AHI ⩾30
Participants, *n*	394	286	44	279	46	249	76
Age, yr, mean (SD)	59.8 (11.2)	57.7 (11.3)	66.8 (9.6)	57.6 (11.4)	66.1 (9.3)	57.3 (11.8)	64.7 (9.2)
Body mass index, kg/m^2, mean (SD)	26.3 (4.4)	25.4 (3.9)	29.4 (5.2)	25.2 (3.9)	30.0 (5.0)	25.1 (3.7)	28.7 (4.8)
Smoking status, *n* (%)							
Never	244 (62.2)	183 (64.2)	31 (70.5)	181 (65.1)	31 (67.4)	164 (66.1)	40 (52.6)
Former	135 (34.4)	92 (32.3)	13 (29.5)	87 (31.3)	15 (32.6)	76 (30.6)	33 (43.4)
Current	13 (3.3)	10 (3.5)	0 (0.0)	10 (3.6)	0 (0.0)	8 (3.2)	3 (3.9)
Diabetes mellitus, *n* (%)	19 (4.9)	10 (3.6)	5 (11.6)	9 (3.3)	7 (15.6)	9 (3.7)	8 (10.5)
Systolic BP, mm Hg, mean (SD)	131.2 (13.8)	129.6 (13.0)	136.0 (14.1)	130.0 (13.5)	137.2 (14.8)	130.1 (13.3)	136.7 (14.9)
Diastolic BP, mm Hg, mean (SD)	79.1 (7.9)	78.7 (7.1)	80.8 (8.9)	78.6 (7.1)	81.1 (8.8)	78.5 (7.1)	82.1 (9.1)
ESS, points, mean (SD)	6.9 (4.0)	6.6 (3.8)	7.6 (3.9)	6.6 (3.8)	7.9 (4.1)	6.7 (3.9)	8.2 (4.2)
TST, min, mean (SD)	377.7 (65.7)	382.6 (64.1)	361.5 (66.7)	381.7 (64.0)	353.2 (68.1)	383.7 (61.9)	365.3 (67.0)
AHI, events/h, median (IQR)*	5.8 (1.6–16.1)	3.3 (1.0–7.3)	40.0 (34.8–54.8)	3.2 (0.9–6.6)	37.6 (31.1–54.5)	2.6 (0.8–5.8)	27.9 (17.6–45.6)
ODI, events/h, median (IQR)*	7.0 (2.0–18.5)	4.0 (1.3–8.3)	39.8 (31.4–55.7)	3.9 (1.2–7.8)	37.4 (32.6–54.9)	3.2 (1.2–7.5)	27.6 (19.8–39.5)
REM-AHI, events/h, median (IQR)*	7.7 (1.5–23.2)	3.8 (0.9–10.8)	45.4 (33.9–53.9)	3.5 (0.8–10.2)	42.9 (33.2–52.8)	2.7 (0.7–6.6)	42.0 (35.1–50.3)
Mean saturation, %, mean (SD)	93.8 (1.6)	94.1 (1.4)	92.7 (1.6)	94.2 (1.3)	92.3 (1.4)	94.2 (1.3)	92.7 (1.6)
Lowest saturation, %, mean (SD)	85.1 (5.9)	86.9 (4.6)	79.3 (6.4)	87.2 (4.3)	77.8 (6.2)	87.4 (4.3)	79.0 (6.6)
% of TST with saturation <90%, median (IQR)*	0.5 (0.0–3.8)	0.1 (0.0–1.5)	9.6 (2.2–21.0)	0.1 (0.0–1.2)	13.2 (6.0–21.7)	0.1 (0.0–1.3)	6.4 (2.3–17.9)
% of TST with REM sleep, mean (SD)	18.6 (5.8)	19.4 (5.4)	16.2 (6.9)	19.4 (5.5)	16.2 (5.6)	19.5 (5.4)	16.1 (5.7)

Definition of abbreviations: AHI = apnoea–hypopnea index; BP = blood pressure; ESS = Epworth Sleepiness Scale; IQR = interquartile range; ODI = oxygen desaturation index; REM = rapid eye movement; REM-AHI = REM sleep–specific AHI; TST = total sleep time.

Data are presented as mean (SD) for normally distributed data, as median (IQR) for not normally distributed data (indicated with an asterisk), or as *n* (%). AHI was defined as the mean number of apneas and hypopneas per hour of sleep. An apnoea was defined as the complete cessation of nasal and oral airflow lasting 10 seconds or more. A hypopnea was defined as a reduction ⩾50% for ⩾10 seconds compared with baseline, in combination with a desaturation of ⩾3% or an arousal. ODI was defined as the mean number of desaturations of ⩾3% per hour of sleep. REM-AHI was defined as the number of apneas and hypopneas during REM sleep divided by the hours spent in REM sleep.

*Data were not normally distributed.

Table 2. Top 10 associations for sleep apnea indices with plasma proteins

OSA Index and Protein	Coefficient	95% CI	*P* Value	Adj. *P* Value
AHI ⩾30				
Neurotrophin-3	**0.26**	**0.12, 0.39**	**0.0002**	**0.041**
CD244	0.20	0.07, 0.33	0.0025	0.212
Neurturin	1.38	0.41, 2.35	0.0055	0.212
CDCP1	0.23	0.07, 0.39	0.0060	0.212
BMP6	0.16	0.05, 0.27	0.0060	0.212
FLT3L	0.18	0.04, 0.31	0.0090	0.262
FGF23	0.99	0.23, 1.76	0.0111	0.266
MARCO	0.09	0.02, 0.17	0.0121	0.266
HGF	0.14	0.03, 0.26	0.0158	0.270
Prostasin	0.14	0.02, 0.25	0.0188	0.270
ODI ⩾30				
CD244	**0.22**	**0.09, 0.35**	**0.0009**	**0.083**
LIF-R	**0.15**	**0.06, 0.24**	**0.0011**	**0.083**
Neurotrophin-3	**0.22**	**0.08, 0.35**	**0.0017**	**0.083**
PD-L2	**0.19**	**0.07, 0.31**	**0.0021**	**0.083**
BMP6	**0.17**	**0.06, 0.28**	**0.0031**	**0.083**
HGF	**0.18**	**0.06, 0.29**	**0.0032**	**0.083**
IFN-γ	**0.51**	**0.17, 0.85**	**0.0033**	**0.083**
ACE2	**0.22**	**0.07, 0.38**	**0.0044**	**0.096**
VSIG2	0.20	0.06, 0.35	0.0060	0.116
TNF	0.27	0.08, 0.46	0.0067	0.117
REM-AHI ⩾30				
CD244	0.14	0.03, 0.24	0.0101	0.948
HAOX1	0.45	0.08, 0.82	0.0176	0.948
IL-18	0.17	0.02, 0.32	0.0301	0.948
IL-4	−1.24	−2.41, −0.08	0.0362	0.948
FLT3L	0.11	0.003, 0.22	0.0424	0.948
PTX3	−0.11	−0.23, −0.003	0.0436	0.948
OPG	0.09	0.001, 0.18	0.0479	0.948
Neurotrophin-3	0.11	−0.004, 0.22	0.0584	0.948
IL-18	0.14	−0.006, 0.30	0.0605	0.948
IL-22RA1	0.70	−0.04, 1.44	0.0640	0.948

Definition of abbreviations: ACE2 = angiotensin-converting enzyme 2; AHI = apnea–hypopnea index; Adj. = adjusted; BMP6 = bone morphogenetic protein 6; CD244 = natural killer cell receptor 2B4; CI = confidence interval; HGF = hepatocyte growth factor; IFN-γ = interferon gamma; IL = interleukin; LIF-R = leukemia inhibitory factor receptor; ODI = oxygen desaturation index; OPG = osteoprotegerin; OSA = obstructive sleep apnea; PD-L2 = programmed cell death 1 ligand 2; REM = rapid eye movement; REM-AHI = REM sleep–specific AHI; TNF = tumor necrosis factor.

Results from regression models adjusted for age, body mass index, plate, and storage time, comparing men with severe OSA (AHI, ODI, and REM-AHI ⩾30) with men who had no or mild OSA (AHI, ODI, and REM-AHI <15). *P* values were adjusted for multiple testing using the Benjamini–Hochberg method for controlling the false discovery rate, setting the false discovery rate at the 10% level (indicated in bold type).

interferon gamma (IFN-γ) and angiotensin-converting enzyme 2 (ACE2). IFN-γ is an important antiviral and immunoregulatory cytokine. The results from previous studies on OSA and IFN-γ levels are somewhat conflicting, possibly because of differences in the OSA indeces assessed in the studies, in the study populations, and in comorbid conditions (18, 19). ACE2, a regulator in the renin-angiotensin-aldosterone system, is a promising new biomarker for cardiovascular risk as well as the receptor protein for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus (20, 21). Previous studies on ACE2 levels in OSA are lacking, apart from our previous proteomic study in women, where there was a borderline association between an ODI ⩾30 and increased ACE2 levels in adjusted models ($P = 0.07$) (5). The results are also in accordance with studies reporting altered levels of other components of the renin-angiotensin-aldosterone system in OSA (22) and with experimental cell studies showing that hypoxia can increase ACE2 expression (20).

The AAHI was associated with altered levels of the proteins CD244, BMP6, and HGF, and the associations were stronger for the AAHI than for the other OSA indices. Higher levels of HGF is associated with cardiovascular disease progression and mortality, and elevated levels of BMP6 have been reported in severe heart failure (13, 23, 24). Although associations between the hypoxic burden and levels of these proteins have not been investigated before, an experimental study reported increased HGF levels in response to hypoxia in men (25). Furthermore, several recent studies have reported associations between the hypoxic burden and cardiovascular outcomes (1, 8, 26, 27).

In contrast to the previous study in women (5), we could not show a REM-AHI having a significant impact on protein levels in the present study. This might suggest a sex difference where the ODI is more important in men, whereas the REM-AHI is more important in women. Men have a greater proportion of apneas, and the hypopneas are associated with more severe desaturations, but men have a lesser proportion of their OSA in REM sleep (28, 29). The results are consistent with the finding that the REM-OSA is associated with atherosclerosis in women but not in men (7). A sex-specific

Table 3. Associations between sleep apnea indices as continuous variables and protein levels

Protein	AHI			ODI			REM-AHI			AAHI		
	Coefficient (95% CI)	*P* Value	Adj. *P* Value	Coefficient (95% CI)	*P* Value	Adj. *P* Value	Coefficient (95% CI)	*P* Value	Adj. *P* Value	Coefficient (95% CI)	*P* Value	Adj. *P* Value
CD244*	0.0048 (0.0019, 0.0077)	0.0012	0.105	**0.0051 (0.002, 0.008)**	**0.0006**	**0.096**	0.0030 (0.0004, 0.0056)	0.0252	0.726	**0.0095 (0.0043, 0.0147)**	**0.0004**	**0.023**
LIF-R	0.0017 (−0.0004, 0.0037)	0.1048	0.417	0.0019 (−0.0002, 0.0039)	0.0701	0.245	0.0008 (−0.0010, 0.0026)	0.3733	0.984	0.0028 (−0.0010, 0.0066)	0.1440	0.427
Neurotrophin-3†	**0.0058 (0.0027, 0.0088)**	**0.0002**	**0.041**	**0.0052 (0.0021, 0.0082)**	**0.0011**	**0.096**	0.0007 (−0.0021, 0.0035)	0.6084	0.984	0.0081 (0.0022, 0.0140)	0.0071	0.125
PD-L2	0.0015 (−0.0012, 0.0042)	0.2791	0.574	0.0019 (−0.0008, 0.0047)	0.1710	0.361	0.0003 (−0.0021, 0.0028)	0.7964	0.984	0.0031 (−0.0022, 0.0084)	0.2484	0.517
BMP6	0.0033 (0.0008, 0.0058)	0.0103	0.298	0.0038 (0.0013, 0.0063)	0.0030	0.106	0.0010 (−0.0013, 0.0032)	0.4033	0.984	**0.0074 (0.0027, 0.0120)**	**0.0019**	**0.054**
HGF	0.0034 (0.0007, 0.0061)	0.0131	0.298	0.0043 (0.0016, 0.0070)	0.0017	0.101	0.0018 (−0.0006, 0.0042)	0.1481	0.984	**0.0084 (0.0036, 0.0132)**	**0.0007**	**0.032**
IFN-γ	0.0083 (0.0005, 0.0160)	0.0364	0.298	0.0074 (−0.0004, 0.0152)	0.0619	0.241	0.0022 (−0.0048, 0.0092)	0.5437	0.984	0.0047 (−0.0095, 0.0190)	0.5138	0.695
ACE2	0.0038 (0.0001, 0.0075)	0.0458	0.298	0.0046 (0.0009, 0.0083)	0.0153	0.149	0.0020 (−0.0014, 0.0053)	0.2481	0.984	−0.0007 (−0.0071, 0.0056)	0.8260	0.892

Definition of abbreviations: AAHI = severity adjusted apnea–hypopnea index; ACE2 = angiotensin-converting enzyme 2; Adj. = adjusted; AHI = apnea–hypopnea index; BMP6 = bone morphogenetic protein 6; CD244 = natural killer cell receptor 2B4; HGF = hepatocyte growth factor; IFN-γ = interferon gamma; LIF-R = leukemia inhibitory factor receptor; ODI = oxygen desaturation index; PD-L2 = programmed cell death 1 ligand 2; REM-AHI = REM sleep–specific AHI.
Associations are between sleep apnea indices as continuous variables and protein levels for the proteins associated with an ODI ⩾30 (Table 2). Results from regression models adjusted for age, body mass index, and plate, and storage time. *P* values were adjusted for multiple testing using the Benjamini–Hochberg method for controlling the false discovery rate, setting the false discovery rate at the 10% level (indicated in bold type).
*Also associated with an AAHI ⩾30.
†Also associated with an AHI ⩾30.

differential response to continuous positive airway pressure therapy on cardiovascular biomarkers has also been reported (30).

The cross-sectional design—making conclusions on causality impossible—the limited sample size, and lack of information on ethnicity are important limitations. There is, therefore, a need for further studies, including with sex and with ethnic diversity, to confirm the associations, as well as the sex differences in the associations, between OSA indices and biomarkers. Another limitation is that the AAHI was only available in a subsample of participants, resulting in reduced power to detect any true associations and limiting the possibility to compare the performance of an AAHI ⩾30 with that of the other indices. Despite this, significant associations between the AAHI and several proteins were seen, supporting the growing evidence for the hypoxic burden as a promising OSA metric.

In conclusion, in men, OSA indices reflecting intermittent hypoxia and the hypoxic burden, the ODI and AAHI, were associated with elevated levels of several inflammatory proteins. As in our previous study in women, AHI showed few associations with plasma protein levels. In contrast to the findings in women, no association between REM-OSA and altered protein levels was identified in men. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Mirjam Ljunggren, M.D., Ph.D.*
Xingwu Zhou, Ph.D.
Jenny Theorell-Haglöw, Ph.D.
Christer Janson, M.D., Ph.D
Uppsala University
Uppsala, Sweden

Karl A. Franklin, M.D., Ph.D
Umeå University
Umeå, Sweden

Össur Emilsson, M.D., Ph.D
Eva Lindberg, M.D., Ph.D
Uppsala University
Uppsala, Sweden

ORCID IDs: 0000-0002-8486-6746 (M.L.); 0000-0002-9831-9102 (X.Z.); 0000-0003-2819-2799 (J.T.-H.); 0000-0001-5093-6980 (C.J.); 0000-0002-8552-4510 (E.L.).

*Corresponding author (e-mail: mirjam.ljunggren@medsci.uu.se).

References

1 Muraja-Murro A, Kulkas A, Hiltunen M, Kupari S, Hukkanen T, Tiihonen P, *et al.* Adjustment of apnea-hypopnea index with severity of obstruction events enhances detection of sleep apnea patients with the highest risk of severe health consequences. *Sleep Breath* 2014;18: 641–647.
2 Mokhlesi B, Finn LA, Hagen EW, Young T, Hla KM, Van Cauter E, *et al.* Obstructive sleep apnea during REM sleep and hypertension. Results of the Wisconsin Sleep Cohort. *Am J Respir Crit Care Med* 2014;190: 1158–1167.
3 Chen YL, Su MC, Liu WH, Wang CC, Lin MC, Chen MC. Influence and predicting variables of obstructive sleep apnea on cardiac function and remodeling in patients without congestive heart failure. *J Clin Sleep Med* 2014;10:57–64.
4 Appleton SL, Vakulin A, Martin SA, Lang CJ, Wittert GA, Taylor AW, *et al.* Hypertension is associated with undiagnosed OSA during rapid eye movement sleep. *Chest* 2016;150:495–505.

5 Ljunggren M, Theorell-Haglöw J, Freyhult E, Sahlin C, Franklin KA, Malinovschi A, *et al.* Association between proteomics and obstructive sleep apnea phenotypes in a community-based cohort of women. *J Sleep Res* 2020;29:e13041.
6 Ambati A, Ju YE, Lin L, Olesen AN, Koch H, Hedou JJ, *et al.* Proteomic biomarkers of sleep apnea. *Sleep (Basel)* 2020;43:zsaa086.
7 Ljunggren M, Naessén T, Theorell-Haglöw J, Franklin KA, Lindberg E. Rapid eye movement sleep apnea and carotid intima thickness in men and women: a SHE-MUSTACHE cohort study. *J Sleep Res* 2022;31: e13599.
8 Leppänen T, Särkkä M, Kulkas A, Muraja-Murro A, Kupari S, Anttonen M, *et al.* RemLogic plug-in enables clinical application of apnea-hypopnea index adjusted for severity of individual obstruction events. *J Med Eng Technol* 2016;40:119–126.
9 Assarsson E, Lundberg M, Holmquist G, Björkesten J, Thorsen SB, Ekman D, *et al.* Homogenous 96-plex PEA immunoassay exhibiting high sensitivity, specificity, and excellent scalability. *PLoS One* 2014;9: e95192.
10 Lundberg M, Eriksson A, Tran B, Assarsson E, Fredriksson S. Homogeneous antibody-based proximity extension assays provide sensitive and specific detection of low-abundant proteins in human blood. *Nucleic Acids Res* 2011;39:e102.
11 Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* 1995;57: 289–300.
12 Tseng PT, Chen YW, Tu KY, Wang HY, Chung W, Wu CK, *et al.* State-dependent increase in the levels of neurotrophin-3 and neurotrophin-4/5 in patients with bipolar disorder: a meta-analysis. *J Psychiatr Res* 2016;79:86–92.
13 Rychli K, Richter B, Hohensinner PJ, Kariem Mahdy A, Neuhold S, Zorn G, *et al.* Hepatocyte growth factor is a strong predictor of mortality in patients with advanced heart failure. *Heart* 2011;97:1158–1163.
14 García Muro AM, García Ruvalcaba A, Rizo de la Torre LDC, Sánchez López JY. Role of the BMP6 protein in breast cancer and other types of cancer. *Growth Factors* 2021;39:1–13.
15 Sun L, Gang X, Li Z, Zhao X, Zhou T, Zhang S, *et al.* Advances in understanding the roles of CD244 (SLAMF4) in immune regulation and associated diseases. *Front Immunol* 2021;12:648182.
16 Halder S, Parte S, Kshirsagar P, Muniyan S, Nair HB, Batra SK, *et al.* The Pleiotropic role, functions and targeted therapies of LIF/LIFR axis in cancer: old spectacles with new insights. *Biochim Biophys Acta Rev Cancer* 2022;1877:188737.
17 Wang Y, Du J, Gao Z, Sun H, Mei M, Wang Y, *et al.* Evolving landscape of PD-L2: bring new light to checkpoint immunotherapy. *Br J Cancer* 2023;128:1196–1207.
18 Tam CS, Wong M, McBain R, Bailey S, Waters KA. Inflammatory measures in children with obstructive sleep apnoea. *J Paediatr Child Health* 2006;42:277–282.
19 Al Lawati N, Mulgrew A, Cheema R, van Eeden S, Butt A, Fleetham J, *et al.* Pro-atherogenic cytokine profile of patients with suspected obstructive sleep apnea. *Sleep Breath* 2009;13:391–395.
20 Beacon TH, Delcuve GP, Davie JR. Epigenetic regulation of ACE2, the receptor of the SARS-CoV-2 virus. *Genome* 2021;64: 386–399.
21 Narula S, Yusuf S, Chong M, Ramasundarahettige C, Rangarajan S, Bangdiwala SI, *et al.* Plasma ACE2 and risk of death or cardiometabolic diseases: a case-cohort analysis. *Lancet* 2020;396: 968–976.
22 Jin ZN, Wei YX. Meta-analysis of effects of obstructive sleep apnea on the renin-angiotensin-aldosterone system. *J Geriatr Cardiol* 2016;13: 333–343.
23 Wallentin L, Eriksson N, Olszowka M, Grammer TB, Hagström E, Held C, *et al.* Plasma proteins associated with cardiovascular death in patients with chronic coronary heart disease: a retrospective study. *PLoS Med* 2021;18:e1003513.
24 Banach J, Gilewski W, Słomka A, Buszko K, Błażejewski J, Karasek D, *et al.* Bone morphogenetic protein 6-a possible new player in pathophysiology of heart failure. *Clin Exp Pharmacol Physiol* 2016;43: 1247–1250.
25 Ciulla MM, Cortiana M, Silvestris I, Matteucci E, Ridolfi E, Giofrè F, *et al.* Effects of simulated altitude (normobaric hypoxia) on cardiorespiratory parameters and circulating endothelial precursors in healthy subjects. *Respir Res* 2007;8:58.
26 Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, *et al.* The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019;40: 1149–1157.
27 Trzepizur W, Blanchard M, Ganem T, Balusson F, Feuilloy M, Girault JM, *et al.* Sleep apnea-specific hypoxic burden, symptom subtypes, and risk of cardiovascular events and all-cause mortality. *Am J Respir Crit Care Med* 2022;205:108–117.
28 O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;161:1465–1472.
29 Won CHJ, Reid M, Sofer T, Azarbarzin A, Purcell S, White D, *et al.* Sex differences in obstructive sleep apnea phenotypes, the multi-ethnic study of atherosclerosis. *Sleep (Basel)* 2020;43:zsz274.
30 May AM, Wang L, Strohl KP, Walia H, Hazen SL, Mehra R. Sex-specific differential responses of circulating biomarkers in obstructive sleep apnea treatment. A *post hoc* analysis of a randomized controlled trial. *Ann Am Thorac Soc* 2020;17:605–613.