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Distinct severity stages of obstructive sleep apnoea are correlated with unique dyslipidaemia: large-scale observational study

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ABSTRACT

Background Dyslipidaemia is an intermediary exacerbation factor for various diseases but the impact of obstructive sleep apnoea (OSA) on dyslipidaemia remains unclear.

Methods A total of 3582 subjects with suspected OSA consecutively admitted to our hospital sleep centre were screened and 2983 (2422 with OSA) were included in the Shanghai Sleep Health Study. OSA severity was quantified using the apnoea–hypopnea index (AHI), the oxygen desaturation index and the arousal index. Biochemical indicators and anthropometric data were also collected. The relationship between OSA severity and the risk of dyslipidaemia was evaluated via ordinal logistic regression, restricted cubic spline (RCS) analysis and multivariate linear regressions.

Results The RCS mapped a nonlinear dose–effect relationship between the risk of dyslipidaemia and OSA severity, and yielded knots of the AHI (9.4, 28.2, 54.4 and 80.2). After integrating the clinical definition and RCS-selected knots, all subjects were regrouped into four AHI severity stages. Following segmented multivariate linear modelling of each stage, distinguishable sets of OSA risk factors were quantified: low-density lipoprotein cholesterol (LDL-C), apolipoprotein E and high-density lipoprotein cholesterol (HDL-C); body mass index and/or waist to hip ratio; and HDL-C, LDL-C and triglycerides were specifically associated with stage I, stages II and III, and stages II–IV with different OSA indices.

Conclusions Our study revealed the multistage and non-monotonic relationships between OSA and dyslipidaemia and quantified the relationships between OSA severity indexes and distinct risk factors for specific OSA severity stages. Our study suggests that a new interpretive and predictive strategy for dynamic assessment of the risk progression over the clinical course of OSA should be adopted.

Key messages

What is the key question?

- Dyslipidaemia is an intermediary exacerbation factor for various diseases and the impact of obstructive sleep apnoea (OSA) on dyslipidaemia remains unclear. Has research progress been hindered by linear and monotonic research strategies?

What is the bottom line?

- Distinguishable sets of risk factors (including serum lipids) associated with different OSA severity stages independently.

Why read on?

- Our study first revealed the multistage and non-monotonic relationships between OSA and dyslipidaemia and quantified the relationships between OSA severity indexes and distinct risk factors for specific OSA severity stages.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a highly prevalent sleep disorder that affects 4% of adults.[1] The main clinical manifestations of OSA are intermittent hypoxia, hypoxaemia, sleep fragmentation and excessive daytime sleepiness. The clinical consequences of OSA are contingent on its severity, the individual patient's susceptibility, and intricate associations between OSA and various comorbidities.[2 3] Many neural, hormonal, thrombotic and metabolic pathways are malfunctional in patients with OSA, and most of those abnormalities are known to promote cardiovascular disease (CVD).[4 5] Therefore, OSA has been considered a causative factor for CVD. This idea has gained support through the results of many cross-sectional, prospective and multicentre cohort studies.[5–10] To explore the potential links between OSA and CVD, the role of metabolic disorders[11 12] (including dyslipidaemia[13]) has drawn special attention, since it promotes CVD and always coexists with OSA.[4 14]

Many studies have attempted to address the relationship between OSA and dyslipidaemia but produced rather conflicting results (see reviews by Drager[13 15] and Adedayo[16]). The reason underlying such conflicts is likely multifaceted, for example, the small sample sizes or inadequate adjustment for confounding covariates such as obesity, abdominal obesity, insulin resistance (IR) and excessive daytime sleepiness in previous studies.[12 17–20] More importantly, there is an oversimplified

assumption that dyslipidaemia is linearly related to OSA. The real relationship may be much more complex. In fact, the study of Shahar *et al*[7] on the dose–effect relationship between the risk of CVD and OSA severity raised the possibility that a nonlinear relationship existed between the disorder in blood lipid homeostasis and OSA development.

Human diseases, especially chronic ones, are developed in a very complex manner, and the process of pathological development is influenced by many confounding factors and their interactions.[21] When many risk factors are engaged, the causal relation for a complex disease is unlikely accounted for by a simple linear model. However, for research simplicity, a majority of studies aiming to explore a causal/correlation role of a factor in any given chronic disease often fit the data into a linear or log-linear model. These approaches might be justified for segmental description of a chronic disease or an acute disease itself, but is clearly deficient for studying the overall OSA–dyslipidaemia relationship seen across a long period of years. It is therefore highly desirable to develop a new analysis strategy that is solely based on raw data independent of any monotonic model assumption.

To explore if there is a nonlinear and even non-monotonic relationship between dyslipidaemia and OSA severity, we established a novel model adaptive strategy via mixed and multilevel statistical analyses to evaluate our data in a large sample across the whole range of OSA severity. Remarkably, our results reveal a nonlinear multistage relationship between the risk of dyslipidaemia and the severity of OSA, and establish a new set of quantitative indices that can be readily used both in clinical research on and management of dyslipidaemia in patients with OSA. The detailed clinical implications of our findings are herein discussed.

METHODS

Patients and study design

The data reported in the present paper are from the Shanghai Sleep Health Study (SSHS) cohort, in which we consecutively recruited 3582 unrelated patients from January 2007 to July 2013 who were suspected to have OSA. All patients were hospitalised and observed in the Sleep Center of the 6th Affiliated Hospital of Shanghai Jiao Tong University. The sample comprised mainly residents of cities in southern China. Every participant was asked to complete a questionnaire regarding his or her history of illnesses. The exclusion criteria were (1) a history of continuous positive airway pressure (CPAP) treatment or upper airway surgery, (2) the use of nocturnal oxygen or oral appliances, (3) the use of lipid-lowering drugs, (4) unstable cardiopulmonary disease such as congestive heart failure or intrinsic pulmonary disease, (5) a drug dependency, (6) severe psychiatric disturbances, chronic kidney disease, or pregnancy, (7) alcoholism (for definition, see online supplementary materials), (8) systemic steroid treatment or hormone-replacement therapy, (9) sleep disorders other than OSA (such as upper airway resistance syndrome, restless leg syndrome or narcolepsy), and (10) unavailable clinical data (figure 1). Informed consent was obtained in writing according to the guidance of the National Ethics Regulation Committee of China. This study was approved by the Institutional Ethics Committee of the 6th Affiliated Hospital of Shanghai Jiao Tong University.

Please see the online supplementary materials and data for details regarding the following items: anthropometric measurements, the Epworth Sleepiness Scale (ESS) questionnaire, the definitions of polysomnography and sleep events, laboratory biochemical measurements, the definition and assignment of all variables (see online supplementary tables S1 and S2).

Statistical analysis

Normally distributed data are presented as means±SDs, skewed data are presented as medians with IQRs, and categorical data are presented as percentages. Differences in baseline characteristics among the four groups were examined using the Kruskal–Wallis H test, one-way analysis of variance (ANOVA), or the χ^2 test according to the distribution characteristics of the data.

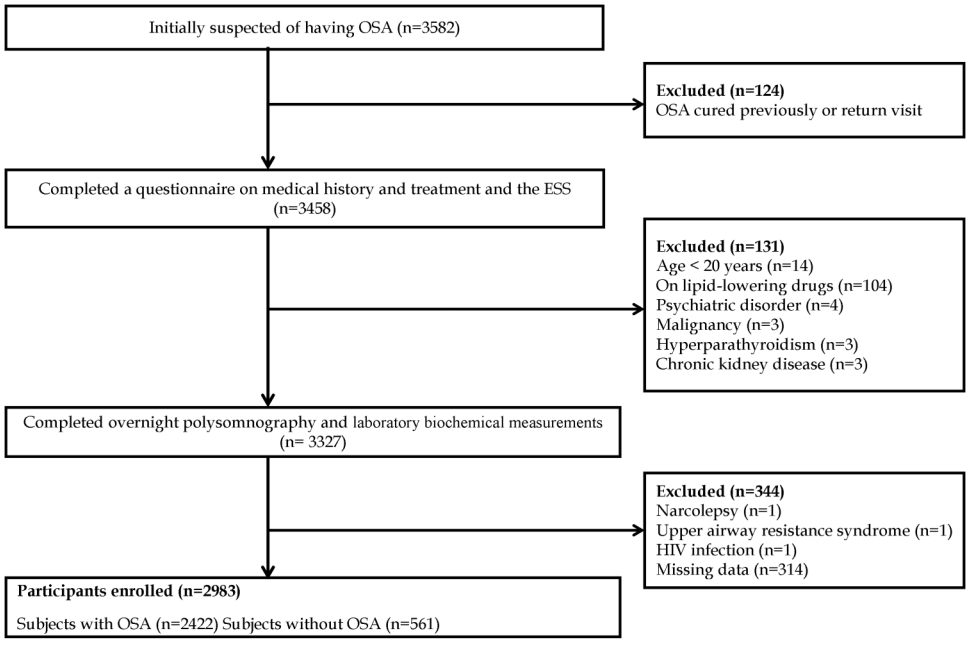

Figure 1 Enrolment flow chart for the study population. The Shanghai Sleep Health Study cohort included 3582 unrelated patients suspected to have obstructive sleep apnoea (OSA) who were consecutively recruited after being admitted to the hospital sleep centre from January 2007 to July 2013. In total, 2983 patients met the inclusion criteria and were enrolled in this study. ESA, Epworth Sleepiness Scale.

To determine whether dyslipidaemia is independently related to OSA severity, ordinal multivariate logistic regression analysis was performed in which the apnoea–hypopnea index (AHI) was ordered into four categories of OSA severity using current standards (<5.0, 5.0–14.9, 15.0–29.9 and ≥30.0). Ordinal multivariate logistic regression was used to model the associations between OSA indices and dyslipidaemia. The ordinal model specifies a log-linear relation for the odds of being in one category (eg, mild OSA (5.0≤AHI<15.0)) compared with being in a lower category (eg, normal (AHI<5.0)), and assumes proportional odds for any dichotomy in the four levels of OSA status. The following variables were included in the analysis: five lipid components (total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and apolipoprotein E (ApoE)) and the covariates age, glucose level, IR index, body mass index (BMI), waist to hip ratio (WHR), ESS score, sex, hypertension and smoking status. The assumption of proportional odds was verified by parallel line testing.

The association between OSA severity and the probability of dyslipidaemia for each lipid component (TC, TG, LDL-C, HDL-C, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB) and ApoE) was quantitatively assessed using restricted cubic spline (RCS) modelling after adjustment against major covariates including age, sex, BMI, WHR and IR.[7 22] Knots for the AHI, oxygen desaturation index (ODI) and arousal index (ArI) were

Table 1 Characteristics of the groups classified according to OSA severity using current clinical definitions

Variables	Non-OSA (AHI<5) (N=561)	Mild OSA (5≤AHI<15) (N=505)	Moderate (15<AHI≤30) (N=478)	Severe OSA (AHI≥30) (N=1439)	p Value
Demographics					
Age (years)	39 (30–49)	42 (34–52)	44 (35–54)	42 (35–53)	<0.001§
Female, N (%)	226 (40.3)	115 (22.8)	95 (19.9)	134 (9.3)	<0.001§
Body mass index (kg/m^2)	23.7 (21.7–25.7)	25.4±3.2	26.0 (24.2–28.1)	27.7 (25.6–30.0)	<0.001*
Neck circumference (cm)	36.0 (34.0–38.5)	38.0 (36.0–40.0)	39.0 (37.0–41.0)	40.0 (38.5–42.0)	<0.001*
Waist circumference (cm)	86.0 (79.0–92.0)	91.0 (86.0–96.8)	94.0 (89.0–99.0)	98.0 (993.0–104.0)	<0.001*
Hip circumference (cm)	96.0 (81.0–100.0)	98.0 (94.0–102.0)	100.0 (96.0–104.0)	102.0 (98.0–106.3)	<0.001*
Waist/hip circumference ratio	0.90 (0.85–0.94)	0.93±0.05	0.94±0.05	0.96 (0.93–1.00)	<0.001*
Biochemistry assays					
Glucose (mmol/L)	4.97 (4.62–5.30)	5.13 (4.81–5.55)	5.25 (4.95–5.68)	5.39 (5.01–5.95)	<0.001*
Insulin (μU/mL)	7.17 (4.88–9.96)	8.93 (5.94–13.68)	10.95 (7.30–15.51)	13.01 (8.61–19.01)	<0.001*
Insulin resistance index	0.42±0.60	0.72±0.68	0.92±0.63	1.13±0.64	<0.001#
TC (mmol/L)	4.37 (3.80–5.06)	4.64 (4.13–5.28)	4.76 (4.23–5.42)	4.87 (4.29–5.43)	<0.001*
TG (mmol/L)	1.10 (0.73–1.61)	1.40 (0.96–1.99)	1.60 (1.18–2.38)	1.76 (1.28–2.57)	<0.001*
HDL-C (mmol/L)	1.12 (1.97–1.33)	1.10 (0.95–1.29)	1.04 (0.91–1.21)	1.02 (0.90–1.16)	<0.001*
LDL-C (mmol/L)	2.67 (2.16–3.21)	2.99 (2.46–3.54)	3.04 (2.53–3.61)	3.16 (2.64–3.69)	<0.001*
apoA-I (g/L)	1.08 (0.96–1.24)	1.08 (0.96–1.21)	1.04 (0.94–1.17)	1.03 (0.93–1.15)	<0.001*
apoB (g/L)	0.73 (0.63–0.86)	0.82 (0.71–0.94)	0.83 (0.73–0.96)	0.86 (0.76–0.97)	<0.001*
apoE (mg/dL)	3.83 (3.15–4.84)	4.09 (3.40–5.10)	4.38 (3.59–5.33)	4.48 (3.63–5.60)	<0.001*
Lp (a) (mg/L)	8.50 (4.45–17.1)	8.60 (4.82–15.30)	7.80 (4.20–14.73)	7.80 (4.10–15.60)	0.14
Dyslipidaemia					
HyperTC, N (%)	124 (22.1)	148 (29.3)	150 (31.4)	531 (36.9)	<0.001
HyperTG, N (%)	124 (22.1)	179 (35.4)	222 (46.4)	771 (53.6)	<0.001
HypoHDL-C, N (%)	208 (37.1)	204 (40.4)	232 (48.5)	774 (53.8)	<0.001
HyperLDL-C, N (%)	108 (19.3)	163 (32.3)	158 (33.1)	575 (40.0)	<0.001
HyperapoA-I, N (%)	378 (67.4)	364 (72.1)	377 (78.9)	1190 (82.7)	<0.001
HyperapoB, N (%)	14 (2.5)	28 (5.5)	30 (6.3)	119 (8.3)	<0.001
HyperapoE, N (%)	223 (39.8)	200 (39.6)	201 (42.1)	666 (46.3)	0.011
Sleep apnoea					
Apnoea–hypopnea index	1.3 (0.4–2.8)	9.2 (6.9–11.7)	21.7 (18.5–25.8)	57.7 (44.6–70.4)	<0.001*
Mean SaO_2	97.0 (95.8–97.9)	95.7 (94.3–96.9)	95.0 (93.7–96.0)	92.7 (90.0–94.0)	<0.001*
Minimum SaO_2	93.0 (90.0–96.0)	87.0 (82.7–90.0)	82.0 (76.9–86.0)	71.0 (63.0–79.0)	<0.001*
Oxygen desaturation index	1.4 (0.5–3.4)	9.6 (6.7–13.8)	23.8 (17.5–31.2)	58.1 (44.6–71.9)	<0.001*
Arousal index	12.1 (6.6–20.5)	18.5 (9.2–29.0)	23.4 (10.1–33.5)	37.0 (16.5–57.5)	<0.001*
Medical history					
ESS	4 (0–8)	7 (3–10)	8 (4–11)	11 (6–15)	<0.001§
Non-smoker, N (%)	441 (78.6)	320 (63.4)	290 (60.7)	773 (53.7)	<0.001§
Non-drinker, N (%)	460 (82.0)	399 (79.0)	370 (77.4)	1040 (72.3)	<0.001§
Presence of hypertension, N (%)	61 (10.9)	114 (22.6)	142 (29.7)	557 (38.7)	<0.001§
Presence of diabetes, N (%)	28 (5.0)	54 (10.7)	64 (13.4)	313 (21.8)	<0.001§

The data are presented as means±SD; skewed data are presented as the median (IQR), and categorical data as the number (percentage). Differences in the baseline characteristics among the four groups were examined using a Kruskal–Wallis H test (*), one-way analysis of variance (ANOVA) (#) or χ^2 tests (§) according to the characteristics of the data distribution.
AHI, apnoea–hypopnea index; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; apoE, apolipoprotein E; Lp(a), lipoprotein(a); SaO_2, oxygen saturation; TC, total cholesterol.

identified in the RCS analysis using MATLAB 8.0 and the R software package (http://www.r-project.org/), and the knots of the AHI were referenced for subsequent analyses.

Segmented multivariate linear regression analyses were respectively performed against the lipid indices and all variables (age, sex, BMI, WHR, glucose level, IR, hypertension and smoking status) to verify potential interactions among these independent risk factors and OSA severity. After integrating the clinical definition of OSA severity and the OSA knots generated in our RCS analysis, the patients were regrouped according to the AHI into a new set of four severity stages, in which multiple stepwise regressions were performed using the AHI, ODI and ArI as dependent variables, respectively, against the independent risk factors listed above. Before further statistical analysis, collinearity diagnostics were performed to eliminate any possible multicollinearity among variables. Statistical analyses were performed using SPSS V.17.0.0 (SPSS, Chicago, Illinois, USA). p Values of <0.05 were considered to reflect statistical significance.

RESULTS

Patients' baseline characteristics

Of the 3582 patients initially recruited, 599 met the exclusion criteria (figure 1). The remaining 2983 patients were categorised into the following four groups of OSA severity according to current standards: no OSA (AHI<5, n=561), mild OSA (5≤AHI<15, n=505), moderate OSA (15≤AHI<30, n=478) and severe OSA (AHI≥30, n=1439). Table 1 summarises the baseline characteristics of all variables in each group. Consistent with previous reports, the percentages of female patients, non-smokers and non-drinkers, serum HDL-C and ApoA-I concentrations, and mean oxygen saturation (SaO_2) and minimum SaO_2 were negatively correlated with the AHI. However, BMI, neck circumference, waist circumference, hip circumference, WHR; serum concentrations of glucose, insulin, TC, TG, LDL-C, ApoB, and ApoE; IR; ESS score; the percentages of patients with dyslipidaemia, hypertension, and diabetes were positively correlated with the AHI. All changes were statistically significant (univariate analysis) with the exception of lipoprotein (a).

Multivariate ordinal logistic analysis and dyslipidaemia stratification analysis

Multivariate ordinal logistic analysis was performed to examine the association between the AHI and lipid levels and thus determine whether and how OSA is associated with dyslipidaemia. Results were generated using the Logit link function, but none passed the parallel line test ($p<0.05$) (see online supplementary table S2). This result suggests that the ordinal linear model was not valid. This unsuitability of the ordinal log-linear model indicated that inadequate stratification of OSA might have concealed the actual correlations. Given the wide range of severity of OSA (AHIs (30–114)) and the fact that our sample was skewed toward high AHI values (1439 patients in the high-severity group), we engaged in further stratification to describe our data more clearly.

To explore this problem, we divided the patients in the OSA group of AHI>30 into quartiles corresponding to an AHI of 44.6, 57.7 and 70.4, yielding a seven-group stratification. The distribution patterns for the proportion of patients with dyslipidaemia shown under the two stratifications are compared in figure 2A and 2B (for the definitions of the variables, please see online supplementary table S1). When a traditional four-group stratification was used, a linear increase in the proportion of patients with dyslipidaemia was seen with an increasing AHI for every lipid component (figure 2A and table 1). However, under the seven-group stratification, the functions were not linear or monotonic (figure 2B): for some lipid components, the proportion of patients with dyslipidaemia decreased dramatically at very high AHI values. Obviously, conventional log-linear or linear models cannot reveal nonlinear or non-monotonic relationships between dyslipidaemia and OSA severity.

Nonlinear model RCS analysis

To delineate the dose–effect relationship between the risk of dyslipidaemia and OSA severity, the serum concentration of each lipid component was first defined as either normal or abnormal according to the diagnostic criteria (see online supplementary table S1). This information was then used in RCS analysis to establish the functions between the log odds of dyslipidaemia (figure 3, left y-axis) for each lipid component and the AHI, ODI and ArI, respectively, under adjustments for five covariates (age, sex, BMI, WHR and IR), independently and in combination. The results are shown in figure 3 (TC, TG, LDL-C and HDL-C) and online supplementary figure S1 (ApoA-I, ApoB and ApoE), in which each panel exhibits one lipid against one OSA index. For simplicity, only the 95% CI is shown for the unadjusted data (dashed lines). The dyslipidaemia risk curve of each lipid varied slightly across the adjustments

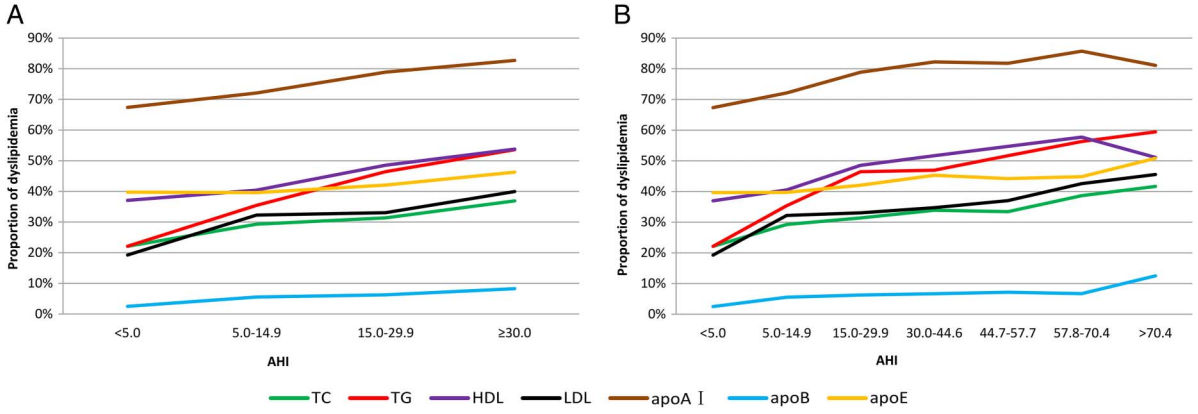

Figure 2 Distribution pattern of dyslipidaemia. The proportion of dyslipidaemia according to total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein E (apoE), apoA-I and apoB in each group is shown. (A) Current four clinical categories. (B) The severe obstructive sleep apnea group (apnoea–hypopnea index (AHI) ≥30) was further divided equally according to quartile.

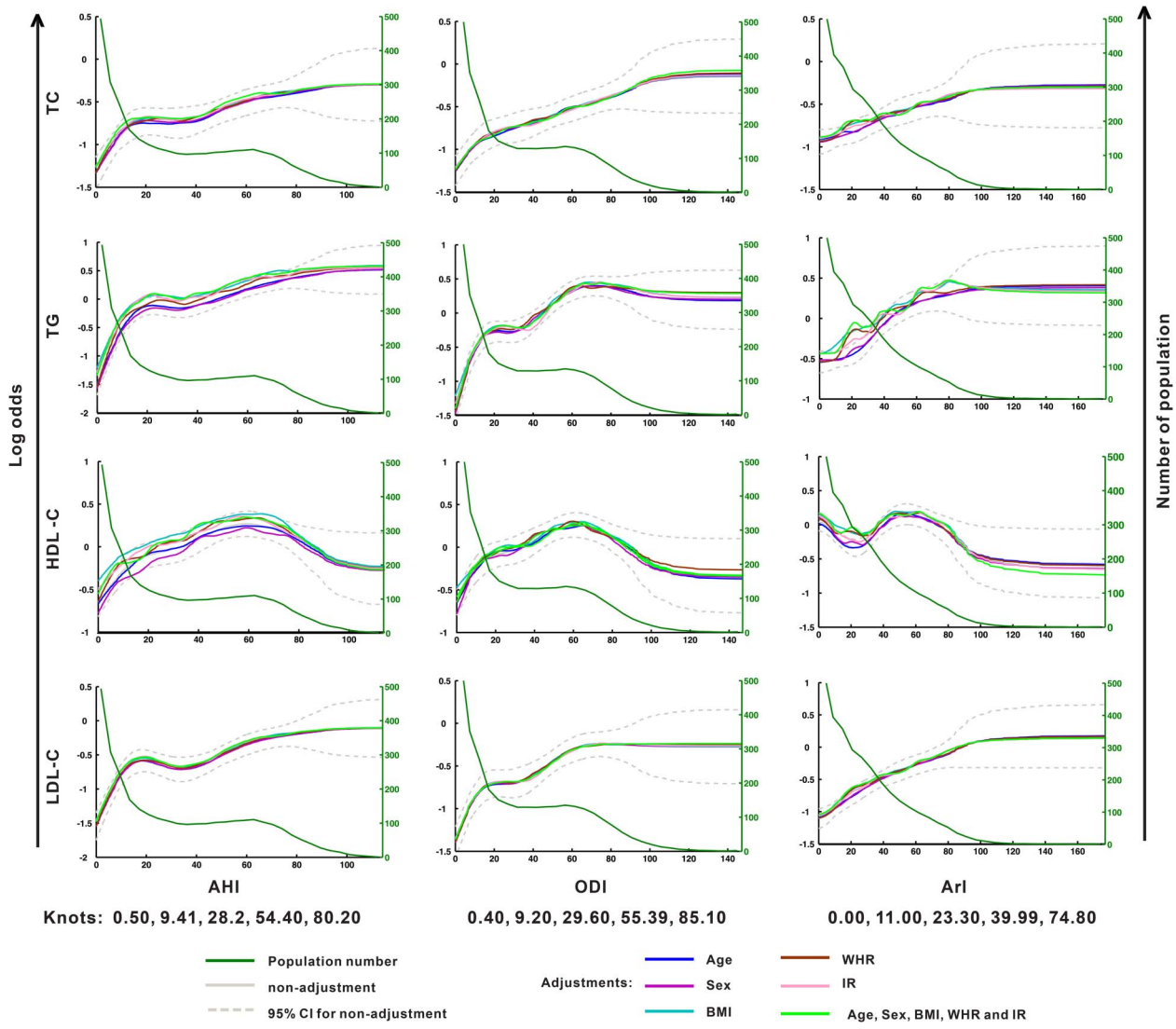

Figure 3 Restricted cubic spline regression of the multistage correlation patterns between dyslipidaemia and the severity of obstructive sleep apnoea (OSA) (showing total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) data). The left y-axis represents the log odds of dyslipidaemia for each serum lipid level. The right y-axis represents the number of patients. The x-axis represents the continuous values of the apnoea–hypopnea index (AHI), oxygen desaturation index (ODI) or arousal index (ArI). The population number for each OSA severity measure unit is indicated by the green line. BMI, body mass index; IR, insulin resistance; WHR, waist to hip ratio.

against the different covariates, suggesting that the stability and robustness of RCS modelling were ensured by the large sample size.

Notably, the risk of any lipid factor did not increase linearly with OSA severity. The presence of plateaus in many curves provided evidence of this nonlinearity and non-monotonicity. For example, the change in the risk of LDL-C disorders against the AHI and ODI exhibited a rapid rise during the mild stage of OSA (AHI<10), followed by a 'plateau' throughout the moderate to severe stages and then a tardily rising period associated with further increase in OSA severity. Such a plateau was seen in many panels in which the OSA severity was quantified by the AHI and ODI (figure 3). Further evidence of this nonlinearity was the non-monotonic feature of many curves: the lipid risk did not always grow with increasing OSA severity, but sometimes decreased with greater OSA severity (see figure 3 and online supplementary figure S1, see the HDL-C and ApoA-I data). Interestingly, a similarity was observed between the AHI curves and ODI curves for every lipid factor investigated; no such similarity was seen between AHI/ODI and ArI.

For further analysis, knots for the AHI, ODI and ArI were calculated from the curves in figure 3 using the MATLAB and R software (AHI: 0.4, 9.2, 29.6, 55.4 and 85.1; ODI: 0.5, 9.4, 28.2, 54.4 and 80.2; ArI: 0.0, 11.0, 23.3, 39.9 and 74.8).

Segmented stepwise multivariate linear regression

To explore independent associations between dyslipidaemia and OSA severity after multistage patterning, a segmented multivariate linear regression analysis was used to identify risk factors. Because the current clinical categorisation standard for OSA severity is mainly based upon the AHI, we used this index for regression. However, based upon the AHI knots generated by RCS analysis, we regrouped the patients into a new set of four-stage groups: AHI<10, 10≤AHI<30, 30≤AHI<55 and AHI ≥55 (see online supplementary table S3 for the baseline data of the new groups). In each stage, we performed multivariate

linear regressions between each of the three indices of OSA severity and the risk factors of dyslipidaemia with selected lipid components (LDL-C, HDL-C, TG and ApoE), and the covariates of dyslipidaemia (such as BMI, WHR, etc) based upon the multicollinearity analysis. Surprisingly, the risk factors for dyslipidaemia and the covariates were differentially associated with three OSA severity indices (the AHI, ODI and ArI) across different OSA stages. These results are shown in 4×3 models (four stages and three indices of OSA severity) (tables 2–4).

When OSA severity was indexed by AHI, BMI and/or WHR (the indicators of obesity or central obesity) were always independent risk factors across all four stages. Notably, in stages II and III, BMI (β=0.163, p=0.029) and WHR (β=16.671, p=0.002), but not other factors were risk factors associated with the AHI. However, age, sex, IR, ESS score and hypertension were risk factors only in stages I and IV, and the serum glucose level was an associated factor only in stage IV. LDL-C (β=0.331, p=0.009) was the only lipid component that was an independent risk factor in stage I (table 2).

When OSA severity was indexed by ODI, ApoE was the only lipid component that was an independent risk factor only in stage I (β=−0.453, p=0.016). IR and BMI remained as independent risk factors in all four stages, and were dominant risk factors in stages II and III. Sex was an independent risk factor in stages II and IV. No lipid component appeared to be a risk factor in stages II and III (table 3).

Only when the OSA severity was indexed by the sleep fragmentation index-ArI, serum lipids appear as actively independent risk factors. In fact, HDL-C remained an independent risk factor, with only slight changes in the regression coefficients for all stages, whereas ApoE, LDL-C and TG remained as risk factors in stages II–IV (table 4).

DISCUSSION

In the present study, we mapped a nonlinear, multistage relationship between the severity of OSA and the risk of dyslipidaemia. Complicated changes in the risk of dyslipidaemia were revealed in association with distinct stages of OSA severity. Such complexity was evident in the quantitative relationships between OSA severity revealed by different indices and specific lipid-related risk factors for each index.

The first important finding of this study is the clear multistage and non-monotonic relationship between dyslipidaemia and OSA severity. Our data showed that the risk of lipid disorders did not linearly increase with OSA exacerbation, but rather plateaued, and even non-monotonic patterns were evident at certain OSA stages. A plateau in the relationship between CVD and OSA was revealed in the Sleep Heart Health Study by Shahar *et al*,[7] which focused on patients with a moderately elevated AHI. However, the plateau was attributed to the inherent limitations of the portable device used for AHI testing, rather than to a real trend in the relationship.[7] As laboratory-standard polysomnography was used in the present study, we believe that the complex curves and the plateau reflect the genuine presence of a multistage nonlinear dose–effect correlation between the risk of dyslipidaemia and OSA severity.

The mechanisms underlying the plateau are unclear, but are likely associated with protective adaptations evident in many aspects of system homeostasis. For example, during highland anoxia, protective adaptation reduces the incidence of myocardial infarction.[23] Additionally, ischaemic preconditioning[24] exerts a cardio-protective benefit if applied within the appropriate paradigm. As in sleep apnoea, intermittent hypoxia may have either beneficial or detrimental effects according to the severity and duration of exposure.[3] Therefore, the plateau with lipid metabolism is likely to be the result of an adaptation that may cause remodelling of lipid homeostasis in patients with chronic intermittent hypoxia and long-term sleep fragmentation in OSA.

The second important finding is that the OSA indices are differentially associated with different risk factors in different stages of OSA. Because obesity is closely related to both dyslipidaemia and CVD, the BMI and WHR have been traditionally considered as important confounding factors for OSA. However, previous reports have shown different and even conflicting outcomes. For example, in a large community-based sample[25] and a clinical sample of older patients,[26] OSA quantified by the AHI was reported to be positively correlated with the lipid abnormalities but was independent of BMI. However, in a study by Sharma *et al*[18] OSA was associated with obesity (BMI), but not lipid levels. We found that, in both stages I and IV, lipid factors were associated with OSA severity as indicated by the AHI; in stages II and III, however, only BMI and WHR were independently associated. Previous studies might have been

Table 2 Segmented multivariate stepwise regression analysis (dependent variable—apnoea-hypopnea index (AHI))

	Stage I: AHI<10(N=848)			Stage II: 10≤AHI<30(N=695)			Stage III: 30≤AHI<55(N=633)			Stage IV: AHI ≥55(N=807)		
Variables	β	95% CI	p Value	β	95% CI	p Value	β	95% CI	p Value	β	95% CI	p Value
Age	0.025	0.007 to 0.043	0.007	–	–	–	–	–	–	−0.247	−0.324 to −0.169	<0.001
Sex	−0.636	−1.122 to −0.015	0.010	–	–	–	–	–	–	7.267	4.345 to 10.190	<0.001
BMI	–	–	–	0.163	0.017 to 0.308	0.029	–	–	–	0.370	0.135 to 0.605	0.002
WHR	6.601	3.140 to 10.061	<0.001	–	–	–	16.671	6.08 to 27.26	0.002	19.834	3.309 to 36.360	0.019
Glucose	–	–	–	–	–	–	–	–	–	1.198	0.412 to 1.984	0.003
IR	0.720	0.386 to 1.054	<0.001	–	–	–	–	–	–	2.793	1.299 to 4.287	<0.001
ESS	0.065	0.026 to 0.105	0.001	–	–	–	–	–	–	0.178	0.048 to 0.307	0.007
Presence of hypertension	0.695	0.096 to 1.295	0.023	–	–	–	–	–	–	2.325	0.723 to 3.927	0.005
Smoking status	0.571	0.096 to 1.047	0.018	–	–	–	–	–	–	−2.830	−4.371 to −1.288	<0.001
LDL-C	0.331	0.083 to 0.579	0.009	–	–	–	–	–	–	–	–	–

Subjects were divided into four groups. In each segmented multiple stepwise regression model, AHI, was the dependent variable, and age, sex, BMI, WHR, blood glucose, IR, hypertension, ESS, and serum lipids profile were the independent variables. Variables were entered or removed from the model depending on the significance of the F-value.
–, covariant was not a risk factor in the corresponding models; AHI, apnoea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale score; IR, insulin resistance index; LDL-C, low-density lipoprotein cholesterol; WHR, waist circumference/hip circumference ratio; β, regression coefficient.

Table 3 Segmented multivariate stepwise regression analysis (dependent variable: oxygen desaturation index (ODI))

	Stage I: AHI<10 (N=848)			Stage II: 10≤AHI<30 (N=695)			Stage III: 30≤AHI<55 (N=633)			Stage IV: AHI≥55 (N=807)		
Variables	**β**	**95% CI**	**p Value**	**β**	**95% CI**	**p Value**	**β**	**95% CI**	**p Value**	**β**	**95% CI**	**p Value**
Age	0.068	0.025 to 0.110	0.002	–	–	–	–	–	–	−0.268	−0.39 to −0.146	<0.001
Sex	–	–	–	3.621	1.399 to 5.843	0.001	–	–	–	11.290	6.556 to 16.024	<0.001
BMI	0.337	0.169 to 0.506	<0.001	1.047	0.724 to 1.369	<0.001	1.165	0.744 to 1.586	<0.001	0.481	0.101 to 0.861	0.013
IR	1.482	0.587 to 2.377	0.001	2.409	0.890 to 3.929	0.002	3.157	0.909 to 5.404	0.006	6.239	3.965 to 8.514	<0.001
ApoE	−0.453	−0.821 to 0.900	0.016	–	–	–	–	–	–	–	–	–

Subjects were divided into four groups. In each segmented multiple stepwise regression model, ODI was the dependent variable, and age, sex, BMI, WHR, blood glucose, IR, hypertension, ESS and serum lipids profile were the independent variables. Variables were entered or removed from the model depending on the significance of the F value.
–, means covariant was not a risk factor in corresponding models; AHI, apnoea–hypopnea index; apoE, apolipoprotein E; BMI, body mass index; ESS, Epworth Sleepiness Scale; IR, insulin resistance index; WHR, waist to hip ratio; β, regression coefficient.

biased toward different stages of OSA because of small sample size. Therefore, earlier results might have revealed only one phase of the correlation pattern between dyslipidaemia and OSA, creating conflicting conclusions. Our findings may help us to comprehend the uncertainties of previous reports, but also provide a new framework for comprehensive clinical investigation and treatment of relationships between dyslipidaemia and OSA severity.

In this work, we have demonstrated that OSA severity indices are associated with different lipid risk factors (tables 2–4). A large number of previous studies used only the AHI[25 27 28] or ODI[29] to quantify the severity of OSA. Our study was the first to simultaneously use three indices, including the ArI. The AHI, ODI or ArI alone may not comprehensively or accurately indicate the severity of breathing and sleeping disorders or their impacts on lipid metabolism.[5 20 30] Specifically, the ArI was strongly associated with the risks of multiple lipid components. This interesting finding suggests that sleep fragmentation as quantified by the ArI is an important parameter when studying the relationship between OSA and dyslipidaemia, especially moderate and severe OSA. However, the results also suggest that further investigations are required to explore the implications of different indices.

Our data indicate that the risk of HDL-C disorders decreased with OSA severity at an AHI of ≥55. This is an intriguing finding that necessitates further investigation because an increasing HDL-C level is currently used as a major protective index of serum lipids in patients with CVD.[31] Therefore, whether an increasing HDL-C level contributes to a lowered risk of CVD in patients awaits further evaluation.[32 33]

Our study was based on an unusually large sample size in terms of OSA severity (1439 cases), which ensured the accuracy of the data for the population with 30≤AHI≤80. However, among the 1439 patients, only 153 (10.6%,) had an AHI≥80. Thus, as shown in figure 3, the 95% CI for this population was very broad.

The identification of a non-linear and non-monotonic pattern between the risk of dyslipidaemia and the severity of OSA, as revealed in our study, has several important clinical implications. The unique strategy used in this study allowed us to unravel the complex nature of the interactions of multiple risk factors. This would have been impossible with a simple linear model. Our results go far in explaining the discrepancies in interventional and prospective studies[34–37] as well as in observational studies[18]. This is best exampled by our findings regarding patients in stage I (figure 3), in whom dyslipidaemia increased with OSA exacerbation; in these patients, CPAP treatment might reduce dyslipidaemia significantly. By contrast, in plateau stage II disease, dyslipidaemia development was not associated with OSA exacerbation such that these patients are unlikely to respond to CPAP. Taken together, our results suggest that mixed and multilevel statistical models can be used to evaluate and quantify the complicated relationship between OSA and other chronic diseases.

Table 4 Segmented multivariate stepwise regression analysis (dependent variable: arousal index (ArI))

	Stage I: AHI<10 (N=848)			Stage II: 10<AHI<30 (N=695)			Stage III: 30<AHI<55 (N=633)			Stage IV: AHI>55 (N=807)		
Variables	**β**	**95% CI**	**p Value**	**β**	**95% CI**	**p Value**	**β**	**95% CI**	**p Value**	**β**	**95% CI**	**p Value**
Sex	−4.200	−6.539 to −1.861	<0.001	−5.076	−8.815 to −1.337	0.008	–	–	–	−8.377	−15.873 to −0.881	0.029
BMI	–	–	–	–	–	–	–	–	–	−0.804	−1.401 to −0.206	0.008
IR	3.424	1.630 to 5.218	<0.001	–	–	–	–	–	–	9.103	5.511 to 12.694	<0.001
ESS	–	–	–	–	–	–	–	–	–	0.629	0.286 to 0.971	<0.001
ApoE	–	–	–	−2.037	−3.403 to −0.671	0.004	−3.044	−4.987 to −1.10	0.002	−3.203	−5.131 to −1.274	0.001
HDL-C	5.163	0.940 to 9.386	0.017	11.786	4.992 to 18.580	0.001	13.484	3.678 to 23.289	0.007	10.211	0.149 to 20.274	0.047
LDL-C	–	–	–	3.220	1.472 to 4.968	<0.001	4.238	1.778 to 6.699	0.001	3.742	1.134 to 6.351	0.005
TG	–	–	–	4.039	2.039 to 6.040	<0.001	5.461	2.967 to 7.955	<0.001	5.360	2.678 to 8.041	<0.001
Smoking status	–	–	–	–	–	–	–	–	–	−6.316	−10.386 to −2.247	0.002

Subjects were divided into four groups. In each segmented multiple stepwise regression model, arousal index was the dependent variable, and age, sex, BMI, WHR, blood glucose, IR, hypertension, ESS and serum lipids profile were the independent variables. Variables were entered or removed from the model depending on the significance of the F-value.
–, means covariant was not a risk factor in corresponding models; AHI, apnoea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale score; HDL-C, high-density lipoprotein cholesterol; IR, insulin resistance index; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; WHR, waist to hip ratio; β, regression coefficient.

Although it was based on clinical samples analysed using a cross-sectional approach, this observational study was of high quality and was optimised by large-scale sampling, strict data acquisition and innovative analytical approaches (including hierarchical modelling, determination of dose–effect relationships, and adequate control of potential confounders), in line with the guidelines for evidence-based medicine.[38] In addition, our study was large scale and used data collected by laboratory-based polysomnography, including patients with a wide range of AHIs. This strategy of sample collection reduced the risk of selection bias and met our goal of exploring the relationship between dyslipidaemia and OSA severity. Although a causal role of a factor to a disease is to be revealed by an interventional or a prospective study, it is not readily feasible for OSA and dyslipidaemia, such as ethical issue.[39] To avoid bias, study of the OSA–dyslipidaemia relationship must follow the subjects from the very beginning of OSA for a long period to cover the multiple stages of OSA development. Additional large-scale, well designed randomised controlled trials featuring good adherence to therapy and long-term follow-up are required.[40]

In our study, as in most other studies, there were numerous confounding factors that were difficult to overcome. For example, alcohol consumption is well known to influence lipid metabolism. Although we excluded alcoholism, the lack of a covariate of alcohol consumption was a deficiency of our study.

Conclusions

A multi-stage relationship exists between OSA severity and dyslipidaemia, and the definition of unique risk factors for each stage lays a solid foundation for better understanding of OSA relative to CVD and other comorbidities.

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Supplementary Material and Data

1. Materials and methods

1.1 Alcoholism definition

Alcoholism refers to both alcohol abuse and alcohol dependence. Consistent with the definition provided by the National Institute on Alcohol Abuse and Alcoholism, in this study alcoholism in men was defined as alcohol consumption exceeding 14 standard drinks per week, or 4 drinks per day; alcoholism in women was defined as > 7 standard drinks per week or 3 drinks per day. A standard drink was defined as one 12-ounce bottle of beer, one 5-ounce glass of wine, or 1.5 ounces of distilled spirits (http://pubs.niaaa.nih.gov/publications/aa68/aa68.htm; http://pubs.niaaa.nih.gov/publications/arh27-1/5-17.htm).

1.2 Anthropometric measurements, Epworth Sleepiness Scale (ESS) questionnaire, and definition of hypertension

Body habitus was measured using standard anthropometric methods, with the participants dressed in lightweight clothing and with bare feet. Waist circumference (WC) was measured midway between the lower costal margin and iliac crest, and hip circumference (HC) was measured as the maximum girth at the greater trochanters. Neck circumference (NC) was measured in the standing patient at the level of the cricothyroid membrane. The data were recorded as the mean of two independent measurements. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

The ESS is a self-administered questionnaire that subjectively assesses an

individual's daytime sleepiness level in eight different situations. The ESS used in this study was translated from the original version and has been validated by. Respondents are asked to respond to each of the eight questions using a four-point scale (0–3). The scores are then summed to yield an overall score of 0–24 [1].

Waking blood pressure was measured at approximately 8:00 AM using a mercury sphygmomanometer, with the patient in a seated position after a 5-min rest, as recommended by the American Society of Hypertension guidelines. Two measurements were taken at 1-min intervals. Hypertension was defined as a systolic blood pressure of > 140 mmHg or a diastolic blood pressure of > 90 mmHg. A history of hypertension and current antihypertensive drug treatment were considered to be additional indicators of hypertension.

1.3 Polysomnography and definition of sleep events

Respiratory events were scored using a laboratory-based polysomnographic device (Alice 4 or 5; Respironics, Pittsburgh, PA, USA) according to the American Academy of Sleep Medicine criteria [2]. Apnea was defined as a complete cessation of airflow lasting ≥ 10 s, and hypopnea as either a ≥ 50% reduction in airflow for ≥ 10 s or a < 50% reduction in airflow that was discernible and accompanied by either a ≥ 4% decrease in oxyhemoglobin saturation or an arousal. The AHI was determined based on the number of apnea and hypopnea events per hour during sleep. The total oxygen desaturation index (ODI) was defined as the total number of episodes of ≥ 4% oxyhemoglobin desaturation per total sleep time in hours.

An arousal was identified as an abrupt shift in the electroencephalogram frequency that lasted ≥ 3 s. During rapid eye movement sleep, a concurrent increase in the electromyogram amplitude was required to label an event as an arousal. The arousal index (ArI) was defined as the average number of arousals per hour of sleep.

1.4 Laboratory biochemical measurements

For each patient, a fasting blood sample was drawn from the antecubital vein the morning after polysomnographic monitoring. Serum lipid and fasting serum glucose levels were measured in the hospital laboratory using an autoanalyzer (H-7600; Hitachi, Tokyo, Japan). Serum lipids included total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB), apolipoprotein E (ApoE), and lipoprotein (a) (Lp(a)). An immunoradiological method was used to measure the fasting serum insulin level. IR was estimated using the previously described homeostasis model assessment method [3]: fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L) / 22.5. Diabetes was defined as a fasting plasma glucose concentration of ≥ 7.0 mmol/L or the known use of antidiabetic medication before the measurement. Dyslipidaemia with respect to TC, TG, HDL-C, and LDL-C was defined as a serum level of ≥ 5.17, ≥ 1.70, < 1.03, and ≥ 3.33 mmol/L, respectively, according to the diagnostic criteria of the US National Cholesterol Education Program Adult Treatment Panel III [4]. Dyslipidaemia of ApoA, ApoB, and ApoE was defined as a serum level of < 1.20, > 1.10, and > 0.05 or < 0.03 g/L,

respectively, according to the diagnostic criteria of the Joint Committee for Developing Chinese Guidelines on the Prevention and Treatment of dyslipidaemia in Adults[5].

1.5 Statistical analysis

1.5.1 Multivariate ordinal logistic regression analyses

Multivariate analyses were performed using ordinal logistic regression under a proportional odds model, in which AHI was grouped in four ordered categories (see Table 1). This approach simultaneously modeled three cumulative logits, corresponding to the use of binary cut points at 5, 15, and 30 and expressed as log {Pr(AHI≥5)/Pr(AHI<5)}, log{Pr(AHI≥15)/Pr(AHI<15)}, and log{Pr(AHI) ≥30/Pr(AHI<30)}, respectively. Under this proportional odds model, one parameter is estimated for each predictor in the model. The parameter represents the effect of a 1-unit increase in the predictor variable on the logit (log odds), which is assumed to be the same for all three logits. A test of parallel lines was used to verify whether the location parameters (slope coefficients) differed across response categories (sTable 3).

1.5.2 RCS analysis

We performed RCS analysis using two steps:

1) The R software package (http://www.r-project.org/) within R for Windows (ver. 3.02) was used to obtain the knots: The restricted cubic splines analysis was performed using the R package Hmisc. The knots were equally spaced between

the splines on the quantile scale using the default setting (typically 5). The functional form of the relation between each variable and the outcome was visually evaluated using the function rcspline.plot, from the Hmisc library. This graphically shows the relation between the continuous confounder and the log(odds) of the outcome.

An example of our R code is as follows:

```
Library (Hmisc)
load (data)
rcspline.plot(ODI,LDL2,showknots=TRUE,plotcl=TRUE,statloc=11,adj=BMI,smooth=T)
```

AHI, ODI and ArI were modeled separately.

2) MATLAB 8.0 software was used to map the RCS curves:

The spline functions of the regression model were as follows:

$$\text{Log}(p/(1-p))=\beta_0 + \beta_1 x_1 + \sum_{i=1}^{k-2} \beta_{1i} S_i(x_1) + \sum_{i=2}^{p} \beta_i x_i \quad (1)$$

The main effect in Eq. (1) is x1; xi is used to correct the model. The main effect, which is $S_i(x_1)$ in Eq. (1), was expanded using RCS as follows:

Several low-order polynomials defined in the subset of the variable domain were used to replace the function, defined in the whole domain. This accounts for the use of splines, the points of which are used to divide the variable domain into so-called knots. For k knots, as in Eq. (1), the number of knots of low-order functions is k−2.

For RCS, a third-order polynomial was used.

Equation (2) is the RCS function:

$$S_i(x_1) = (x_1 - t_i)_+^3 - \frac{t_k - t_i}{t_k - t_{k-1}}(x_1 - t_{k-1})_+^3 + \frac{t_{k-1} - t_i}{t_k - t_{k-1}}(x_1 - t_k)_+^3 \quad (2)$$

$$(x_1 - t_i)_+^3 = \begin{cases} (x_1 - t_i)^3 & if \ x_1 \geq t_i \\ 0 & otherwise \end{cases}$$

1.5.3 Segmented multivariate linear regression analyses

A segmented multivariate linear regression analysis was used to identify risk factors [6]. Because the current clinical categorization standard for OSA severity is mainly based upon the AHI, this index was used for the regression. However, based upon the AHI knots generated by the RCS analysis, the patients were regrouped into four stage-specific groups: AHI <10, 10 ≤ AHI < 30, 30 ≤ AHI < 55, and AHI ≥ 55 (see Supplementary Table 4 for the baseline data of these new groups). Each stage was subjected to multivariate linear regressions between each of the three indices of OSA severity and the risk factors of dyslipidaemia in selected lipid components (LDL-C, HDL-C, TG, and ApoE), and the covariates of dyslipidaemia (BMI, WHR, etc.) based upon the multicollinearity analysis.

The two steps of the collinearity analyses were: (1) a preliminary analysis using a Pearson correlation and (2) collinearity diagnostics to determine the selected covariates in the multivariate linear regression analyses. For detail, please see Supplementary Tables 5-7.

2. Results

2.1 Distribution characteristics of dyslipidaemia in groups categorized by the new OSA severity knots

The study population was regrouped using the new OSA severity knots to verify both the clinical significance of our findings and the multistage dose–effect relationship between OSA severity and dyslipidaemia. The numbers of patients in the four stages were 848, 695, 633, and 807, respectively. The baselines of the patients grouped according to the new knots are shown in sTable 4. Although the ratio of dyslipidaemia generally increased with the severity of OSA, the ratios of TC, TG, LDL-C, and ApoE disorders did not significantly differ between stage II and stage III, and the ratio of HDL-C disorders did not significantly differ between stages III and IV (sTable 4). These results further accentuated the increasing and plateau phases in the comprehensive correlation patterns between dyslipidaemia and the severity of OSA.

3. Supplementary References

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4. **Supplementary Figure legends**

sFigure 1. Restricted cubic spline regression of the multistage correlation patterns between dyslipidaemia and the severity of OSA (data for ApoA-I, ApoB and ApoE are shown).

The left *y*-axis shows the log odds of dyslipidaemia for each serum lipid level, and the right *y*-axis represents the number of patients. The x-axis shows the continuous values for the AHI, ODI, or ArI. The population number for each OSA severity-measure unit is indicated by the green line.

5. sTable (1-7)

sTable 1 The definition and assignment of the variables

Parameters	Definition and assignment
Sex	Female = 1, Male = 0
Diabetes	Subjects with diabetes = 1, subjects without diabetes = 0
Hypertension	Subjects with hepertension = 1, subjects without hepertension = 0
Smoking status	Smoking = 1, never smoking = 0
Drinking status	Drinking = 1, never drinking = 0
TC	≥5.17mmol/L = 1; normal = 0
TG	≥ 1.7 mmol/L = 1; normal = 0
HDL-C	HDL-C<1.03 mmol/L = 1; HDL-C ≥1.03mmol/L = 0
LDL-C	LDL-C≥ 3.33mmol/L = 1; LDL-C < 3.33mmol/L = 0
ApoA-I	ApoA-I <1.2 g/L = 1; ApoA-I≥1.2g/L = 0
ApoB	ApoB >1.1g/L = 1; ApoB ≤1.1g/L = 0
ApoE	ApoE >0.05g/L or < 0.03g/L = 1; 0.03g/L< ApoE >0.05g/L= 0

sTable 2. Abbreviations list.

Parameters and terminology	Abbreviations
body mass index	BMI
neck circumference	NC
waist circumference	WC
hip circumference	HC
waist circumference/hip circumference ratio	WHR
insulin resistance index	IR
total cholesterol	TC
triglyceride	TG
high density lipoprotein cholesterol	HDL-C
low density lipoprotein cholesterol	LDL-C
apolipoprotein A-I	ApoA-I
apolipoprotein B	ApoB
apolipoprotein E	ApoE
lipoprotein(a)	Lp(a)
obstructive sleep apnea	OSA
apnea-hypopnea index	AHI
polysomnography	PSG
percentage of time with SaO2<90%	CT90
arterial oxygen saturation	SaO2
arousal index	ArI
oxygen desaturation index	ODI
Epworth sleepiness score	ESS
continuous positive airway pressure	CPAP
cardiovascular disease	CVD
restricted cubic spline	RCS
95%confidence interval	95% CI
odds ratio	OR

sTable 3. Ordinal multivariate logistic regression analyses .

		Estimate	95% CI		P value
			Lower Bound	Upper Bound	
Threshold	[AHI4 = 0]	8.839	7.253	10.424	<0.001
	[AHI4 = 1]	10.090	8.494	11.686	<0.001
	[AHI4 = 2]	11.012	9.408	12.617	<0.001
Location	Age	0.021	0.014	0.029	<0.001
	Glucose	0.037	-0.059	0.134	0.448
	insulin resistance inde	0.455	0.299	0.610	<0.001
	TG	0.097	-0.016	0.209	0.093
	LDL-C	0.263	0.161	0.364	<0.001
	HDL-C	-0.113	-0.479	0.254	0.546
	ApoE	-0.033	-0.111	0.045	0.408
	BMI	0.125	0.096	0.154	<0.001
	WHR	4.449	2.820	6.079	<0.001
	ESS	0.098	0.083	0.113	<0.001
	[Sex=0]	0.828	0.601	1.055	<0.001
	[Sex=1]	0[a]	.	.	
	[Hypertension=0]	-0.416	-0.603	-0.229	<0.001
	[Hypertension=1]	0[a]	.	.	.
	[Smoke=0]	-0.195	-0.365	-0.025	0.024
	[Smoke=1]	0[a]	.	.	.

Multivariate analyses were performed using ordinal logistic regression under a proportional odds model, for which AHI was grouped in 4 ordered categories (please see table 1).Test of parallel lines for Logit link functions, displayed significance(P<0.01). Only showed Logit link functions.

Abbreviations: WHR, waist circumference/hip circumference ratio; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; apoE, apolipoprotein E; AHI, apnea-hypopnea index; ESS, Epworth sleepiness score.

sTable 4. The characteristics of parameters in groups classified by new knots for OSA severity.

Variable	Stage I: AHI < 10 (N = 848)	Stage II: 10 < AHI < 30 (N=695)	Stage III: 30 < AHI < 55 (N=633)	Stage IV: AHI > 55 (N=807)	*P* value
Demographics					
Age (yrs)	40(31-49)	43 (35-54)	44 (35.5-55)	42 (35-51)	<0.001
Female, N (%)	297 (52.1)	139 (24.4)	65 (11.4)	69 (12.1)	<0.001
BMI (kg/m^2)	24.0(22.1-26.1)	25.9(24.2-28.0)	26.7(24.8-28.7)	28.4(26.4-30.9)	<0.001
WHR	0.90(0.87-0.95)	0.94(0.91-0.97)	0.96(0.93-0.99)	0.97(0.94-1.00)	<0.001
Biochemistry assays					
Glucose (mmol/L)	5.01(4.68-5.33)	5.23 (4.89-5.67)	5.32 (4.93-5.77)	5.46 (5.06-6.11)	<0.001
insulin resistance index	0.51(0.09-0.91)	0.91(0.46-1.27)	0.97(0.55-1.42)	1.28(0.85-1.68)	<0.001
TC (mmol/L)	4.49(3.88-5.13)	4.74 (4.22-5.4)	4.83 (4.22-5.38)	4.88 (4.32-5.49)	<0.001
TG (mmol/L)	1.16(0.78-1.7)	1.58 (1.12-2.32)	1.68(1.23-2.41)	1.83 (1.33-2.68)	<0.001
HDL-C (mmol/L)	1.12 (0.97-1.33)	1.05 (0.91-1.22)	1.02 (0.91-1.17)	1.02 (0.89-1.16)	<0.001
LDL-C (mmol/L)	2.75 (2.27-3.32)	3.02 (2.53-3.6)	3.08 (2.59-3.59)	3.22 (2.7-3.77)	<0.001
apoE (mg/dL)	3.86 (3.23-4.86)	4.35 (3.56-5.31)	4.36 (3.55-5.49)	4.56 (3.73-5.68)	<0.001
Dyslipidemia					
HyperTC, N (%)	204 (24.1)	218 (31.4)*	217 (34.3)*	314 (38.9)	<0.001
HyperTG, N (%)	213 (25.1)	311 (44.7)*	313 (49.4)*	459 (56.9)	<0.001
HypoHDL-C, N (%)	317 (37.4)	327 (47.1)	336 (53.1)*	438 (54.3)*	<0.001
HyperLDL-C, N (%)	195 (23.0)	234 (33.7)*	227 (35.9)*	348 (43.1)	<0.001
HyperapoE, N (%)	328 (38.7)	296 (42.6)*	291 (46.0)*	375 (46.5)	0.005
Sleep apnea					
AHI	2.9(0.8-6.2)	18.7 (13.8-23.9)	43.0 (36.65-48.85)	68.6 (61.8-77.2)	<0.001
CT90	0 (0-0.3)	1.7(0.4- 4.8)	9.02 (3.1-19.3)	30.9(13.48-47.97)	<0.001
Minimum SaO_2	91.0 (88.0-95.0)	83.0 (78.0-88.0)	76.0 (68.0-82.0)	68.0 (60.0-74.0)	<0.001
ODI	3.1 (0.9-6.9)	19.9 (13.6-27.6)	44.6 (35.8-52.25)	68.6 (59.5-79.1)	<0.001
Arousal index	13.95 (7-22.6)	22.2 (10.1-32.5)	27.1 (9.9-41.3)	48.2 (24.1-66.7)	<0.001
Medical history					
ESS	5 (1-9)	8 (4-11)	9 (6-13)	12 (8-16)	<0.001
Non-smoker, N (%)	618 (72.9)	432 (62.2)	341 (53.9)	433 (53.7)	<0.001
Non-drinker, N (%)	686 (80.9)	543 (78.1)	459 (72.5)	581 (72.0)	<0.001
Presence of hypertension, N (%)	111 (13.1)	205 (29.5)	219 (34.6)	339 (42.0)	<0.001
Presence of diabetes, N (%)	51 (6.0)	95 (13.7)	109 (17.2)	204 (25.3)	<0.001

Distributed data are presented as the means means ± standard deviation (SD); skewed data are presented as the median (interquartile range); and categorical data are presented as the number (percentage). * $\chi 2$ tests for two groups, P>0.05.

Abbreviations: BMI, Body mass index; WHR, waist circumference/hip circumference ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; apoE, apolipoprotein E; Lp(a), Lipoprotein(a); AHI, apnea-hypopnea index; CT90, percentage of time with SaO2<90%; SaO2, oxygen saturation; ODI, oxygen desaturation index; ESS, Epworth sleepiness score.

Differences of baseline characteristics among four groups were examined by using Kruskal-Wallis H test, one-way ANOVA, $\chi 2$ tests according to the characteristics of data distribution.

The population was categorized by new knots for OSA severity.

sTable 5. The result of Pearson correlation.

		age	sex	Glu-0	TC	TG	HDL	LDL	APOA-1	APOB	APOE	insulin-0	BMI	waist/hip	IR
age	Pearson Correlation	1	.180**	.161**	.099**	.010	.085**	.050**	.166**	.082**	.033	-.064**	.006	.105**	-.022
	Sig. (2-tailed)		.000	.000	.000	.579	.000	.006	.000	.000	.075	.001	.748	.000	.238
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
sex	Pearson Correlation	.180**	1	-.064**	-.022	-.171**	.292**	-.075**	.263**	-.111**	.003	-.114**	-.192**	-.349**	-.133**
	Sig. (2-tailed)	.000		.000	.230	.000	.000	.000	.000	.000	.851	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
Glu-0	Pearson Correlation	.161**	-.064**	1	.173**	.231**	-.080**	.141**	.008	.203**	.182**	.278**	.273**	.243**	.499**
	Sig. (2-tailed)	.000	.000		.000	.000	.000	.000	.656	.000	.000	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
TC	Pearson Correlation	.099**	-.022	.173**	1	.317**	.268**	.839**	.311**	.847**	.494**	.132**	.143**	.167**	.184**
	Sig. (2-tailed)	.000	.230	.000		.000	.000	.000	.000	.000	.000	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
TG	Pearson Correlation	.010	-.171**	.231**	.317**	1	-.349**	.011	-.116**	.288**	.744**	.283**	.256**	.288**	.345**
	Sig. (2-tailed)	.579	.000	.000	.000		.000	.538	.000	.000	.000	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
HDL	Pearson Correlation	.085**	.292**	-.080**	.268**	-.349**	1	.207**	.764**	.009	-.061**	-.198**	-.241**	-.266**	-.247**
	Sig. (2-tailed)	.000	.000	.000	.000	.000		.000	.000	.623	.001	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
LDL	Pearson Correlation	.050**	-.075**	.141**	.839**	.011	.207**	1	.156**	.815**	.160**	.128**	.145**	.154**	.176**
	Sig. (2-tailed)	.006	.000	.000	.000	.538	.000		.000	.000	.000	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
APOA-1	Pearson Correlation	.166**	.263**	.008	.311**	-.116**	.764**	.156**	1	.093**	.136**	-.091**	-.140**	-.142**	-.113**
	Sig. (2-tailed)	.000	.000	.656	.000	.000	.000	.000		.000	.000	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
APOB	Pearson Correlation	.082**	-.111**	.203**	.847**	.288**	.009	.815**	.093**	1	.388**	.185**	.223**	.248**	.250**
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.623	.000	.000		.000	.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
APOE	Pearson Correlation	.033	.003	.182**	.494**	.744**	-.061**	.160**	.136**	.388**	1	.245**	.190**	.191**	.285**
	Sig. (2-tailed)	.075	.851	.000	.000	.000	.001	.000	.000	.000		.000	.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
insulin-0	Pearson Correlation	-.064**	-.114**	.278**	.132**	.283**	-.198**	.128**	-.091**	.185**	.245**	1	.497**	.329**	.893**
	Sig. (2-tailed)	.001	.000	.000	.000	.000	.000	.000	.000	.000	.000		.000	.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
BMI	Pearson Correlation	.006	-.192**	.273**	.143**	.256**	-.241**	.145**	-.140**	.223**	.190**	.497**	1	.541**	.539**
	Sig. (2-tailed)	.748	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000		.000	.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
waist/hip	Pearson Correlation	.105**	-.349**	.243**	.167**	.288**	-.266**	.154**	-.142**	.248**	.191**	.329**	.541**	1	.395**
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000		.000
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983
IR	Pearson Correlation	-.022	-.133**	.499**	.184**	.345**	-.247**	.176**	-.113**	.250**	.285**	.893**	.539**	.395**	1
	Sig. (2-tailed)	.238	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	.000	
	N	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983	2983

**. Correlation is significant at the 0.01 level (2-tailed).

sTable 6. Result of Collinearity Diagnostics

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	-86.797	7.957		-10.908	.000		
	age	.109	.037	.047	2.917	.004	.867	1.154
	sex	-6.672	1.195	-.096	-5.585	.000	.759	1.318
	Glu-0	.737	.531	.027	1.387	.166	.580	1.723
	TC	-6.493	1.326	-.227	-4.896	.000	.104	9.629
	TG	1.540	.620	.068	2.485	.013	.298	3.361
	HDL	9.850	3.115	.090	3.162	.002	.277	3.615
	LDL	5.324	1.243	.165	4.282	.000	.151	6.634
	APOA-1	-6.395	3.577	-.045	-1.788	.074	.358	2.791
	APOB	14.791	5.377	.094	2.751	.006	.192	5.213
	APOE	.753	.453	.044	1.663	.096	.320	3.122
	insulin-0	.099	.128	.029	.773	.439	.163	6.143
	BMI	1.559	.144	.217	10.861	.000	.561	1.782
	waist/hip	51.655	8.509	.118	6.070	.000	.588	1.700
	ESS	1.139	.076	.244	15.067	.000	.855	1.170
	IR	4.490	1.686	.114	2.662	.008	.122	8.191

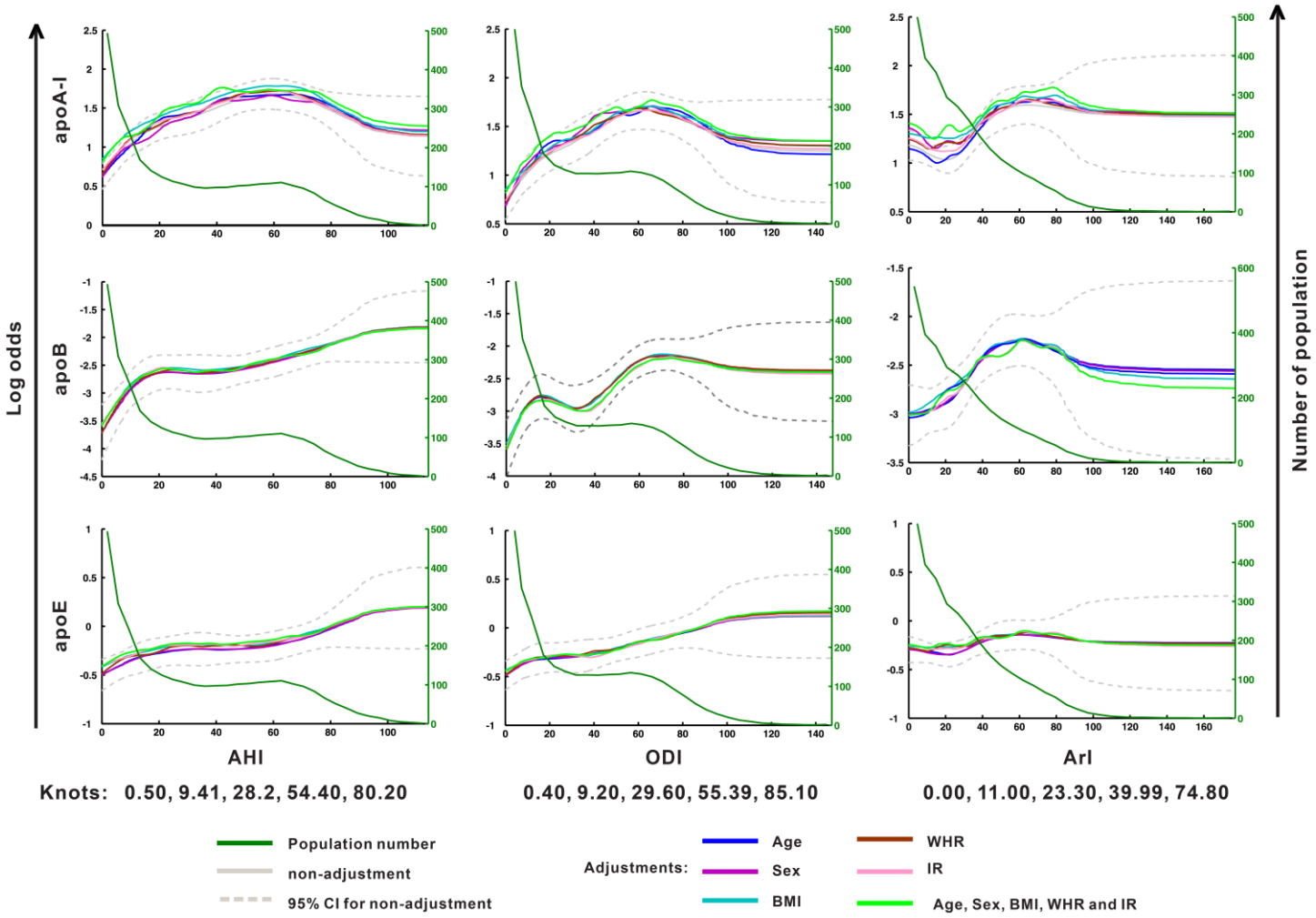
a. Dependent Variable: AHI/Total

sTable 7. Result of Collinearity Diagnostics

Model	Dimension	Eigenvalue	Condition Index	Variance Proportions														
				(Constant)	age	sex	Glu-0	TC	TG	HDL	LDL	APOA-1	APOB	APOE	insulin-0	BMI	waist/hip	ESS	IR
1	1	13.742	1.000	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00
	2	.923	3.858	.00	.00	.51	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.00	.01	.00
	3	.494	5.272	.00	.00	.23	.00	.00	.00	.00	.00	.00	.00	.00	.02	.00	.00	.00	.03
	4	.284	6.959	.00	.00	.00	.00	.00	.17	.00	.00	.00	.00	.02	.00	.00	.00	.23	.00
	5	.258	7.294	.00	.00	.06	.00	.00	.04	.00	.00	.00	.00	.00	.01	.00	.00	.70	.01
	6	.089	12.450	.00	.16	.02	.01	.01	.00	.00	.04	.00	.01	.01	.00	.00	.00	.00	.00
	7	.062	14.885	.00	.30	.01	.01	.00	.00	.05	.01	.02	.01	.04	.06	.00	.00	.01	.03
	8	.043	17.908	.00	.37	.02	.13	.00	.00	.00	.00	.00	.00	.01	.27	.01	.00	.01	.13
	9	.037	19.228	.01	.11	.08	.00	.00	.05	.04	.00	.02	.00	.13	.12	.05	.01	.01	.17
	10	.028	22.136	.00	.00	.00	.00	.00	.61	.06	.01	.02	.00	.66	.00	.02	.00	.00	.00
	11	.015	30.768	.00	.00	.00	.67	.00	.00	.00	.00	.02	.00	.00	.43	.16	.00	.00	.41
	12	.009	39.905	.00	.02	.00	.01	.00	.03	.29	.13	.45	.24	.03	.00	.10	.00	.01	.01
	13	.007	44.998	.08	.00	.00	.14	.00	.00	.11	.02	.23	.02	.00	.05	.52	.06	.00	.16
	14	.006	49.066	.02	.00	.00	.01	.00	.00	.33	.41	.23	.48	.02	.00	.11	.03	.00	.00
	15	.003	66.781	.00	.00	.00	.00	.99	.09	.10	.37	.01	.23	.09	.00	.00	.00	.00	.00
	16	.001	97.231	.88	.02	.07	.02	.00	.00	.02	.00	.00	.00	.00	.02	.03	.89	.01	.04

a. Dependent Variable: AHI/Total

6. sFigure 1.


Log odds
apoA-I
apoB
apoE
Number of population
AHI
ODI
ArI
Knots: 0.50, 9.41, 28.2, 54.40, 80.20
0.40, 9.20, 29.60, 55.39, 85.10
0.00, 11.00, 23.30, 39.99, 74.80
Population number
non-adjustment
95% CI for non-adjustment
Adjustments:
Age
Sex
BMI
WHR
IR
Age, Sex, BMI, WHR and IR