Mediation analysis of metabolic and inflammatory factors on the association between sleep apnoea and coronary heart disease in the large population–based cohort

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Research Article

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Abstract

Background

Previous research has linked a history of sleep apnoea with coronary heart disease (CHD). This study is aimed to assess the association between sleep apnoea and CHD and to explore the extent to which this association is mediated by metabolic factors and C–reactive protein (CRP).

Methods

In this large population–based cohort study based on the UK Biobank, 213,442 CHD–free (mean age: 55.00) adults were followed up for 15 years to detect incident CHD. Sleep apnoea and CHD were ascertained from self–report and hospital records. Metabolic factors were included hyperglycemia, hypertension, dyslipidemia, hypertriglyceridemia and hyperuricemia. Higher CRP concentration level was defined as a cut–off point of > 3.0 mg/L. Data were analyzed using Cox proportional hazards models and generalized structural equation model (GSEM).

Results

During follow–up (median: 11.74 years, interquartile range: 10.97 to 12.48 years), 9,278 participants developed incident CHD (4.3%). The multi–adjusted hazard ratio (HR) and 95% confidence interval (CI) of CHD related to sleep apnoea was 1.76 (1.44–2.15). In the mediation analysis, the strongest indirect association was for dyslipidemia, accounting for 20.8% of the association between sleep apnoea and CHD (β = 0.22, 95% CI = 0.16–0.28), followed by hypertriglyceridemia (12.3%) and hyperglycemia mediated (8.5%). The proportion of mediation increased to 29.1% when CRP was added to the metabolic mediators.

Conclusions

Sleep apnoea was associated with an increased risk of CHD. 20.8% and 12.3% of the association of sleep apnoea with CHD may be accounted respectively for by dyslipidemia and hypertriglyceridemia. CRP increased the magnitude of every metabolic factors–mediated association to 29.1%.

Background

Sleep apnoea has been a common disorder in which is characterised by repetitive reduction or cessation of airflow in the upper airway during sleep [1]. Moreover, sleep apnoea is now also an important public health issue that affects 3–7% of the middle–aged population (30–70 years) and 5–15% of the general population, becoming increasingly prevalent with age [2]. And the prevalence of sleep apnoea increases with age and is approximately twice as common in men as in women [3]. In particular, intermittent

hypoxia plays an essential role in the pathophysiology of apnoeas and hypopnoeas and its consequences [4, 5], it may result in cardiovascular comorbidities [6], and overall increased cardiovascular mortality, as well as metabolic dysfunction [4]. So far, several cohort studies have consistently shown that sleep apnoea is associated with the risk of total cardiovascular diseases (CVDs) [7, 8]. However, this positive association between sleep apnoea and coronary heart disease (CHD) was only surmised among a certain population (among US veterans) [9]. Therefore, studies of sleep apnoea in relation to specific types of cardiovascular endpoint events are scarce [10], there is still lacking a large–scale, general population–based cohort study examining this relationship using causal models [11].

Although it is equally plausible that sleep apnoea and metabolic diseases might have synergistic health risks, and both conditions are predictive of CHD morbidity, our understanding of the mediated mechanisms for such an association is still limited. Sleep apnoea events incorporate a range of stressors that activate mechanisms contributing to the initiation and progression of metabolic diseases, for instance, type 2 diabetes, dyslipidemia, fatty liver disease and so on [12, 13]. In addition, the hypoxaemic stress is further amplified by the subsequent reoxygenation (intermittent hypoxia), resulting in the generation of reactive oxygen species and inflammation [14–16]. Therefore, an extremely important unknown question for public health is the extent to which the adverse effect of sleep apnoea on CHD might be mitigated by targeting modifiable metabolic and inflammatory mediators. To address this concern, we need to better understand the role of metabolic and inflammatory factors in mediating the association of sleep apnoea with CHD. The extent to which this mediation differs by sex is critical given that the prevalence of hypertension, diabetes and other metabolic diseases [17]. In addition, previous researches on the association of sleep apnoea with cardiovascular risk is mainly based on men, most studies had few or no women [18]. Sex–specific mediating effects of metabolic and inflammatory factors are generally underexplored. There is an increasing serious issue given the increasing prevalence of metabolic and inflammatory diseases among women. So we aimed to investigate the extent to which the mediated effects of metabolic and inflammatory mediators differed by gender.

In this large general population–based prospective cohort study, we sought to: (1) examine the relationship between sleep apnoea and the risk of CHD; (2) explore whether and to what extent the association between sleep apnoea and CHD is mediated by metabolic factors and CRP among male and female, respectively.

Methods

Study design and participants

This was a large population–based cohort study of participants enrolled in the UK Biobank. Between April 2006 and December 2010, the UK Biobank recruited 502,507 adults aged 40–70 years from 23 centers across England, Scotland, and Wales who completed a touch–screen questionnaire and a face–to–face interview. The North West Multi–centre Ethics Committee granted ethical approval to UK Biobank, and all participants provided written informed consent. Finally, a total of 213,442 CHD–free adults aged 38–65

years at baseline were included. **Additional file 1: Fig. S1** showed that more detailed information on inclusion and exclusion.

Assessment of sleep apnoea

Information on sleep apnoea was ascertained using hospital inpatient records containing data on admissions and diagnoses obtained from the Hospital Episode Statistics for England, the Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales. Diagnoses were recorded using the International Classification of Diseases (version10; code ICD–10) coding system (ICD–10 codes: G473). And information on sleep apnoea also included the code recording a sleep apnoea diagnosis (UK Biobank field: 20002) using given codes (UK Biobank codes: 1123).

Assessment of premature coronary heart disease

Information on CHD diagnoses (ICD–10 codes: I20–25) was obtained from the Hospital Episode Statistics for England, the Scottish Morbidity Record data for Scotland, and the Patient Episode Database for Wales.

Assessment of mediators

Mediators in the current study included metabolic (hypertension, hyperglycemia, dyslipidemia, hypertriglyceridemia, and hyperuricemia) and inflammatory mediators (CRP). The detailed definition of mediators was illustrated in the **Additional file 1: Methods S1** [19, 20].

Covariates

Data on demographic characteristics (age, gender, ethnicity, education level, and the Townsend deprivation index), behavioral factors (smoking status, alcohol consumption, physical activity, diet pattern, and body mass index [BMI]) were obtained at study entry.

Statistical Analyses

Cox proportional hazards regression models were performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of sleep apnoea with CHD. The proportional hazard assumption was checked by tests based on Schoenfeld residuals, and the results indicated that the assumptions had not been violated.

Once the temporal association between sleep apnoea and CHD had been established, mediation models were constructed to examine whether the association between sleep apnoea and CHD were respectively mediated by metabolic factors and CRP (**Additional file 1: Methods S2**) [21–23].

We performed a series of sensitive analyses to assess the robustness of our findings as follows: (1) using the complete data set with multiple imputations; (2) excluding participants with incident coronary heart disease during the first 2 years of follow–up. (3) removing participants who had no any hospital inpatient records. All tests were two–sided, and statistical significance was considered $P < 0.05$. Statistical analyses were performed in Stata 16 and RStudio V.1.4.

Results

Characteristics of the study population

Among the 213,442 CHD–free participants (mean age: 55.00 ± 8.08 years; female: 55.8%), 892 (0.42%) were diagnosed as sleep apnoea at baseline. Compared with sleep apnoea–free participants, those with sleep apnoea were more likely to have previous or current smoking status, an unhealthy diet, higher BMI, and to be with metabolic diseases and higher CRP (> 3.0 mg/L), and to never do physical activity. (Table 1).

Table 1
Baseline characteristics of the study population by sleep apnoea.

Characteristics	Total (N = 213,422)	Sleep apnoea (%)	
		No (n = 212,550)	Yes (n = 892)
Age	55 ± 8.08	54.87 ± 8.09	56.20 ± 7.74
Townsend deprivation index	-2.36 ± 2.89	-1.60 ± 2.89	-1.26 ± 2.98
Gender			
Female	119,030 (55.8)	118,795 (55.9)	235 (26.3)
Male	94,412 (44.2)	93,755 (44.1)	657 (73.7)
Education			
College or University degree	82,277 (38.5)	81,939 (38.6)	338 (37.9)
Upper secondary	26,088 (12.2)	25,994 (12.2)	94 (10.5)
Lower secondary	57,978 (27.2)	57,739 (27.2)	239 (26.8)
Vocational	12,564 (5.9)	12,496 (5.9)	68 (7.6)
Other	34,535 (16.2)	34,382 (16.1)	153 (17.2)
Ethnicity			
White	194,981 (91.4)	194,171 (91.4)	810 (90.8)
Mixed background	7,496 (3.5)	7,469 (3.5)	27 (3.0)
Asian or Asian British	7,824 (3.7)	7,785 (3.7)	39 (4.4)
Black or black British	1,022 (0.5)	1,016 (0.5)	6 (0.7)
Chinese	576 (0.3)	576 (0.3)	0 (0.0)
Others	1,543 (0.7)	1,533 (0.7)	10 (1.1)
Smoking status			
Never	121,772 (57.1)	121,343 (57.1)	429 (48.1)
Previous or current	91,670 (42.9)	91,207 (42.9)	463 (51.9)
Alcohol consumption			
Moderate alcohol intake	134,534 (63.0)	133,939 (63.0)	595 (66.7)
Heavy alcohol intake	78,908 (37.0)	78,611 (37.0)	297 (33.3)
Physical activity			
Regular physical activity	193,107 (90.5)	192,349 (90.5)	758 (85.0)

Characteristics	Total (N = 213,422)	Sleep apnoea (%)	
		No (n = 212,550)	Yes (n = 892)
Never physical activity	20,335 (9.5)	20,201 (9.5)	134 (15.0)
Diet pattern			
Healthy diet	204,764 (95.9)	203,946 (96.0)	818 (91.7)
Unhealthy diet	8,678 (4.1)	8,604 (4.0)	74 (8.3)
Body mass index			
< 25 (Normal)	86,949 (40.7)	86,829 (40.9)	120 (13.5)
≥ 25 (Over weight)	126,493 (59.3)	125,721 (59.1)	772 (86.5)
Dyslipidemia			
No	178,835 (83.8)	178,244 (83.9)	591 (66.3)
Yes	34,607 (16.2)	34,306 (16.1)	301 (33.7)
Hypertension			
No	130,767 (61.3)	130,299 (61.3)	468 (52.5)
Yes	82,675 (38.7)	82,251 (38.7)	424 (47.5)

(continued).

Characteristics	Total (N=213,422)	Sleep apnoea (%)	
		No (n=212,550)	Yes (n=892)
Hyperglycemia			
No	204,505 (95.8)	203,695 (95.8)	810 (90.8)
Yes	8,937 (4.2)	8,855 (4.2)	82 (9.2)
Hypertriglyceridemia			
No	137,622 (64.5)	137,257 (64.6)	365 (40.9)
Yes	75,820 (35.5)	75,293 (35.4)	527 (59.1)
Hyperuricemia			
No	193,775 (90.8)	193,058 (90.8)	717 (80.4)
Yes	19,667 (9.2)	19,492 (9.2)	175 (19.6)
CRP			
≤ 3.0 mg/L	174,261 (81.6)	173,636 (81.7)	625 (70.1)
>3.0 mg/L	39,181 (18.4)	38,914 (18.3)	267 (29.9)
Abbreviation: CRP, C–reactive protein.			

Association between sleep apnoea and incident CHD

During the follow–up (median: 11.74 years, interquartile range: 10.97 to 12.48 years), 9,278 (4.3%) participants developed incident CHD. After full adjustment for potential confounders, compared with participants without sleep apnoea, people with sleep apnoea had an increased risk of CHD (HR = 1.76, 95% CI: 1.44–2.15). Among metabolic factors, participants with dyslipidemia had a higher incident risk of CHD (HR = 1.45, 95% CI: 1.38–1.53), but the association between hypertension and CHD seemed to slightly attenuate (HR = 1.15, 95% CI: 1.11–1.20). In addition, compared with the participants with CRP concentration level lower than 3.0 mg/L, the association between higher CRP concentration level (> 3.0 mg/L) and incident CHD was third only to the relationship between hypertriglyceridemia and incident CHD (HR = 1.33, 95% CI: 1.27–1.40) (Table 2).

Table 2
Adjusted hazard ratios (HRs) for the association of sleep apnoea, metabolic factors and C–reactive protein with coronary heart disease.

Exposures	Coronary heart disease			
	Events/Total	HR (95% CI)[a]	HR (95% CI)[b]	E Value[c]
Sleep apnoea				
No	9,181/212,550	1 (Ref.)	1 (Ref.)	NA
Yes	97/892	2.65 (2.17–3.23)	1.76 (1.44–2.15)	2.92
Hyperglycemia				
No	8,745/204,505	1 (Ref.)	1 (Ref.)	NA
Yes	533/8,937	1.42 (1.30–1.55)	1.22 (1.12–1.32)	1.74
Hypertension				
No	4,770/130,767	1 (Ref.)	1 (Ref.)	NA
Yes	4,508/82,675	1.52 (1.46–1.58)	1.15 (1.11–1.20)	1.57
Dyslipidemia				
No	7,253/178,835	1 (Ref.)	1 (Ref.)	NA
Yes	2,025/34,607	1.47 (1.40–1.54)	1.45 (1.38–1.53)	2.26
Hypertriglyceridemia				
No	4,580/137,622	1 (Ref.)	1 (Ref.)	NA
Yes	4,698/75,820	1.90 (1.82–1.98)	1.40 (1.34–1.46)	2.15
Hyperuricemia				
No	7,944/193,775	1 (Ref.)	1 (Ref.)	NA
Yes	1,334/19,667	1.69 (1.59–1.79)	1.26 (1.19–1.34)	1.83
CRP				
≤ 3.0 mg/L	6,942/174,261	1 (Ref.)	1 (Ref.)	NA
> 3.0 mg/L	2,336/39,181	1.54 (1.47–1.61)	1.33 (1.27–1.40)	1.99

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence intervals; IR, incident rate; CRP, C–reactive protein. [a] Unadjusted. [b] Adjusted for age, gender, education, ethnic, Townsend deprivation index, physical activity, diet pattern, smoking status, alcohol consumption and body mass index (BMI). [c] The E–value is the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome, conditional on the measured covariates, to explain away a treatment–outcome association.

By age subgroup, the participants with sleep apnoea compared with participants without sleep apnoea were significantly associated with a 60% increased risk of CHD (HR = 1.60, 95% CI: 1.04–2.46) for participants over 65 years old. By sex subgroup, the participants with sleep apnoea were significantly associated with a 143% increased risk of CHD (HR = 2.43, 95% CI: 1.55–3.82) for women. The association between sleep apnoea and the risk of CHD was not meaningfully differ in the age– and sex–stratified analysis.(Fig. 1)

The mediating role of metabolic factors and CRP between sleep apnoea and CHD

In the mediation analysis of metabolic factors, after controlling for a range of potential confounders, dyslipidemia mediated ≈ 20.8% of the association between sleep apnoea and CHD (β = 0.22, 95% CI: 0.16–0.28), following by hypertriglyceridemia (12.3%, β = 0.13, 95% CI: 0.08–0.17) and hyperglycemia (8.5%, β = 0.09, 95% CI: 0.01–0.16). However, hypertension was not mediated by the association between sleep apnoea and CHD. In the CRP–mediation analysis, higher CRP concentration level (> 3.0 mg/L) mediated ≈ 16.2% of this association (β = 0.12, 95% CI: 0.07–0.17). Notably, in the mediation analysis of metabolic mediators–CRP combination, CRP as an extra component of metabolic factors increased the magnitude of every metabolic mediators–mediated association to 29.1% (Fig. 2 and **Additional file 1: Table S1**).

We found the similar trends among the mediation analysis stratified by sex. Dyslipidemia was always the strongest mediation effect on the association between sleep apnoea and CHD (female, 17.0%; male, 21.7%). The combination of CRP and metabolic mediators mediated respectively 31.6% for female and 24.7 for male on this association.(**Additional file 1: Table S2, Table S3, Fig. S2** and **Fig. S3**)

Sensitive analysis

We found that the mediation effects of dyslipidemia, hypertriglyceridemia, and hyperuricemia were always stable. Hypertension mediated respectively ≈ 2.0% and 2.4% of the association between sleep apnoea and CHD (β = 0.02, 95% CI: 0.01–0.03; β = 0.02, 95% CI: 0.002–0.04) when we used completed data and restricted the analysis to participants having any hospital inpatient records, but this mediation effect was insignificantly statistical when we excluded participants with incident CHD during the first two years of follow–up, which was as same as the main analysis in our study.

Discussion

In this large population–based prospective cohort study, sleep apnoea was independently associated with an increased risk of developing CHD. Dyslipidemia was the strongest indirect association, CRP increased the magnitude of every metabolic factors–mediated association to 29.1%. The mediating effects of hyperglycemia and hypertension were not always stable.

Abundant literature states that sleep apnoea is an independent risk factor for cardiometabolic disturbances, such as atherosclerosis [24]. But the evaluation of CVDs risk in sleep apnoea patients has

generally been studied in men only, there is a dearth of evidence on women [25, 26]. Moreover, studies of sleep apnoea in relation to specific types of CVDs are scarce [27]. Our study contributes to ongoing research efforts to better understand the risk of CHD associated with sleep apnoea. We proved the potential indirect ways of metabolic and inflammatory factors on the association between sleep apnoea and CHD. In addition, we also identified the lipid factor as the key player in the association of sleep apnoea with CHD [28]. The underlying mechanisms explaining relationship may be involved including sustained sympathetic activation, intrathoracic pressure changes, and oxidative stress, disorders in coagulation factors, endothelial damage, platelet activation [8, 29–32]. Intermittent hypoxia (IH) has been shown to induce lipid abnormalities such as increased serum cholesterol and phospholipid levels, upregulation of triglycerides and phospholipids biosynthesis, and inhibition of triglycerides uptake in the liver in humans and animals. Hypoxia is also associated with lipoprotein lipase inhibition in adipose tissue, which leads to an increase in plasma chylomicrons and very low–density lipoprotein cholesterol, possibly favouring the progression of atherosclerosis [33, 34]. A recent study in sleep apnoea patients corroborates the previous results from rodents exposed to IH, showing a decreased lipolysis of triglyceride–rich lipoproteins in patients with severe sleep apnoea [35]. And the majority of observational studies support a link between sleep apnoea and dyslipidemia [36].

Previous experimental research among animals found that intermittent hypoxia in rodents reduces glucose uptake in oxidative muscles [37], increases β–cell proliferation and β–cell death; this latter phenomenon is attributed to oxidative stress. Another experimental research explored the elevated NADPH oxidase activity and the associated oxidative stress in rats' hearts seem to mediate the deleterious cardiovascular effects of intermittent hypoxia, in particular, the increased myocardial susceptibility to infarction [38, 39], which may explain part of the incident CHD mediated by hyperglycemia seen in patients with sleep apnoea. In addition to the metabolic defects traditionally implicated in metabolic syndrome, it is important to note that hyperuricemia is becoming another potential marker of the syndrome [40]. However, there are few clinical trials on how hyperuricemia mediated the relationship between sleep apnoea and CHD.

Inflammatory factor exacerbated the mediating role of metabolic factors in the sleep apnoea–CHD association. Increased inflammatory mediators might also play a role in the pathogenesis of CHD [11]. The role of sleep apnoea in triggering or exacerbating a widespread inflammatory response that may affect the whole vasculature and myocardium. The episodes of hypoxia that occur in sleep apnoea, although brief, have a cumulative effect as they happen many times a night often for years. The excitation of the sympathetic nervous system persists into the waking period and the repeated episodes of hypoxia elicit a widespread inflammatory response involving pro–inflammatory cytokines and growth factors [41]. Not only does inflamm–aging promote atherosclerosis perse but it also interacts with traditional CVDs risk factors (e.g. overweight/obesity, hypertension, and type 2 diabetes) to exacerbate their deleterious CVDs effects [42].

Although we detected that weaker mediation effects of hypertension were showed in the sensitivity analysis using completed data by multiple imputations and restricting the analysis to participants having

any hospital inpatient records, the result of the mediation effect of hypertension was still unstable. We deemed that it related to the weaker association between hypertension and CHD compared with dyslipidemia and other metabolic factors after full adjustment for potential confounders in our study. We also found that many studies have shown that the connection between sleep apnoea and hypertension is weak when covariates are accounted for [43–45], which may explain our results. But there are previous studies [46] which demonstrate a stronger association between hypertension with sleep apnoea only among males. And therefore, this should be verified in other large population–based cohort further.

Strength And Limitations

This study has several strengths, including its relatively large sample size, which allowed for sufficient statistical analysis from multiple races of population. To our best knowledge, this was the first study to investigate the association between sleep apnoea and CHD among the large general population–based cohort, and to examine the mediated effects of metabolic factors, CRP, and their combined mediation effect on this association.

Despite these strengths, this study also has limitations. Firstly, the incidence of sleep apnoea may be underestimated. Because the main source of data is hospitalized cases and self–report cases, potentially missing cases who only had their condition diagnosed as an outpatient. In addition, many people affected by sleep apnoea still remain undiagnosed. When restricting the analysis to participants having any hospital inpatient records, the association results were essentially unchanged. Also, we found that another study reported the incidence of sleep apnoea was about 0.7% after removing participants who developed sleep apnoea after baseline visit in UK Biobank [47]. Secondly, there is no doubt that obesity and many of the illnesses associated with obesity interfere with normal sleep [48]. Many of people were unable to determine the order in which obesity or central obesity and sleep apnoea occurred at the start of the study. And thus obesity was not defined as the mediator but a covariate. Future studies with more complete data are required to explore the mediation effect of obesity on the association between sleep apnoea and CHD. Third, a further limitation of this analysis is the lack of detailed information on treatment for sleep apnoea, such as with continuous positive airway pressure.

Conclusions

In the population–based cohort study, sleep apnoea was associated with incident CHD. Our study findings identified that the highest and second–highest proportion of the association between sleep apnoea and CHD were mediated by lipid factors, the involvement of CRP aggravated the mediating effect of metabolic mediators. Consequently, the risk of CHD may be potentially prevented by addressing the combined effects of metabolic factors and inflammation.

Abbreviations

CHD: coronary heart disease; CRP: C–reactive protein; CVD: cardiovascular disease; BMI: body mass index; HR: hazard ratio; CI: confidence interval; GSEM: generalized structural equation model; HI: intermittent hypoxia.

Declarations

Ethics approval and consent to participate

The North West Multi–centre Ethics Committee granted ethical approval to UK Biobank, and all participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflicts of interests.

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Authors' contributions

YGW was involved in study concept and design. YGW, JL and RRY had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JL and RRY did the statistical analysis and drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. YGW obtained funding for the study. YGW and RRY were involved in study supervision. All authors gave their final approval of the version to be published.

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Figures

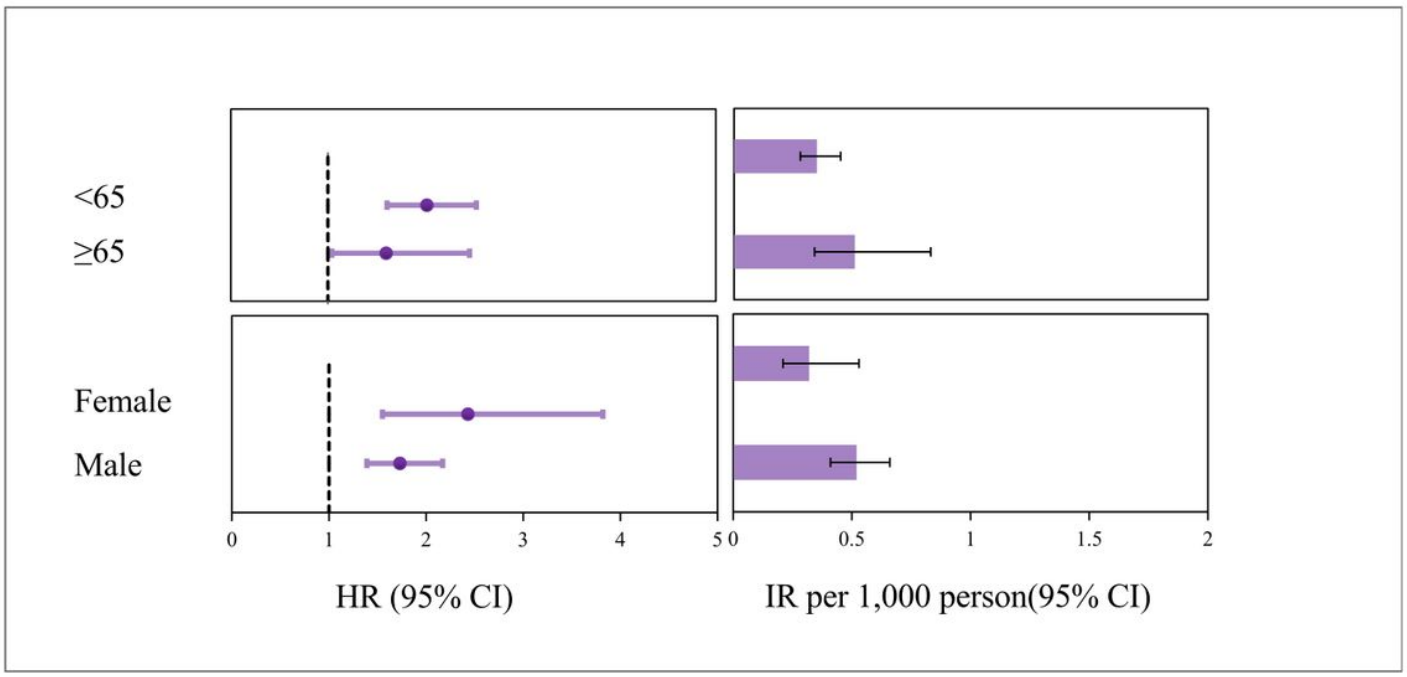

Figure 1

Association of sleep apnoea with incident coronary heart disease stratified by age and gender. Abbreviation: HR, hazard ratio; 95% CI, 95% confidence intervals; IR, incident rate. Adjusted for age, gender, education, ethnic, Townsend deprivation index, physical activity, diet pattern, smoking status, alcohol consumption and body mass index (BMI), if applicable.

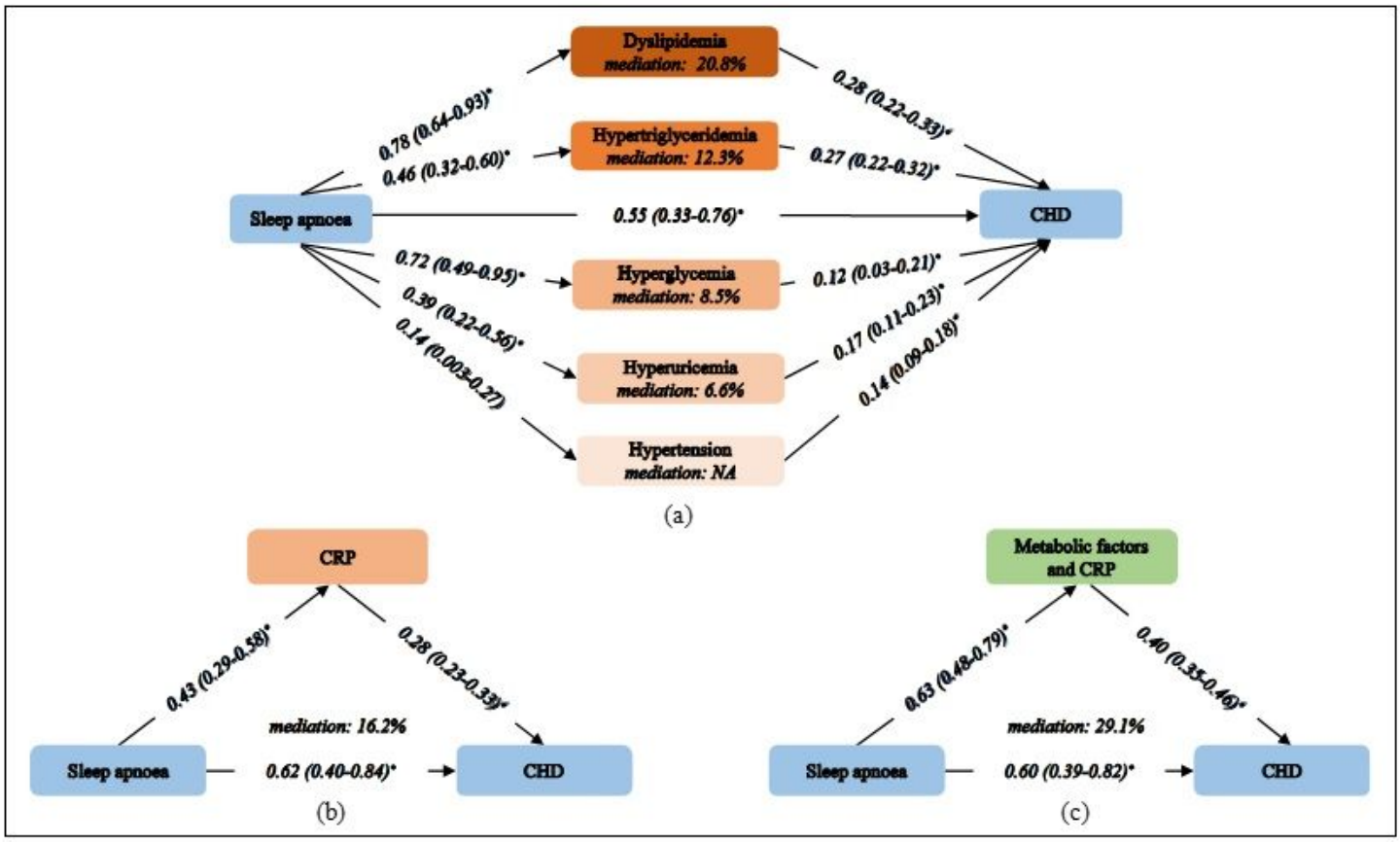

Figure 2

Mediating effects of metabolic factors and C–reactive protein on the association of sleep apnoea with coronary heart disease. Abbreviation: CRP, C–reactive protein; CHD, coronary heart disease. (a) the mediation effect of metabolic mediators; (b) the mediation effect of CRP; (C) the mediation effect of combination of metabolic mediators and CRP. Adjusted for age, gender, education, ethnic, Townsend deprivation index, physical activity, diet pattern, smoking status, alcohol consumption and body mass index (BMI). *$P < 0.05$

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