Nocturnal intermittent hypoxia and C reactive protein among middle-aged community residents: a cross-sectional survey

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ABSTRACT

Background There are conflicting results for the association between obstructive sleep apnoea and raised C reactive protein (CRP) levels. A study was undertaken to investigate whether nocturnal intermittent hypoxia, a surrogate marker for obstructive sleep apnoea, was associated with CRP levels among a community-dwelling Japanese population.

Methods Among participants in the Circulatory Risk in Communities Study (CIRCS), 1422 male and 2466 female community residents aged 40—69 years were tested during sleep. No nocturnal intermittent hypoxia, mild nocturnal intermittent hypoxia and moderate to severe nocturnal intermittent hypoxia were defined using 3% oxygen desaturation index cut-off points at 5 and 15 events/h, respectively. High-sensitivity CRP levels were measured using a latex particle-enhanced immunonephelometric assay. Multivariate analysis was adjusted for age, sex, body mass index, smoking status, current alcohol intake, hypertension, hypercholesterolaemia, diabetes mellitus and menopausal status for women.

Results Multivariable-adjusted mean CRP levels among men were 0.70 mg/l (95% CI 0.65 to 0.75) for no nocturnal intermittent hypoxia, 0.82 mg/l (95% CI 0.74 to 0.89) for mild nocturnal intermittent hypoxia and 0.84 mg/l (95% CI 0.70 to 1.00) for moderate to severe nocturnal intermittent hypoxia (p for trend=0.03). The values for women were 0.59 mg/l (95% CI 0.57 to 0.62), 0.66 mg/l (95% CI 0.59 to 0.73) and 0.82 mg/l (95% CI 0.62 to 1.03), respectively (p for trend=0.008). Compared with no nocturnal intermittent hypoxia, the prevalence of a high CRP level (≥1.0 mg/l) was 1.4—1.7-fold higher for mild to severe nocturnal intermittent hypoxia in both sexes.

Conclusions Nocturnal intermittent hypoxia is associated with raised serum CRP levels among middle-aged Japanese subjects.

INTRODUCTION

Low-grade systemic inflammation is a new atherosclerotic risk marker for cardiovascular disease. C reactive protein (CRP) is one of the sensitive systemic inflammatory markers, and high CRP levels are associated with high mortality and morbidity due to cardiovascular disease.[1]

Obstructive sleep apnoea (OSA), one of the prevalent sleep disturbances, is characterised by repetitive upper airway collapse during sleep causing snoring, hypoxia and sleep fragmentation. This leads to enhanced sympathetic activity and increased oxidative stress.[2] Hypoxaemia and increased oxidative stress are important mechanisms related to enhanced systemic inflammation.[3 4] An association between OSA and systemic inflammatory markers (eg, interleukin 6 (IL-6) and CRP) has been reported in several hospital-based studies[5–7] and a population-based study,[8] while no association was found in other hospital-based studies[9 10] and a population-based study.[11] Interventional studies have also shown conflicting results on the improvement of systemic inflammatory markers.[12–14]

Because previous studies have shown conflicting results, we examined the association between nocturnal intermittent hypoxia, a surrogate marker for OSA, and high-sensitivity CRP (hs-CRP) among community-dwelling Japanese in the Circulatory Risk in Communities Study (CIRCS). Our a priori hypothesis was that the severity of nocturnal intermittent hypoxia was associated with raised hs-CRP levels independent of traditional atherosclerotic risk factors.

METHODS

Subjects

The CIRCS is a prospective cohort study launched in five communities across Japan since 1963 to examine risk factors for cardiovascular disease and is described in detail elsewhere.[15] Subjects aged 40—69 years participating in annual cardiovascular surveys between 2002 and 2005 were recruited to the present sleep study in three communities; Ikawa (a north-east rural community) in 2002—5, Kyowa (a central-east rural community) in 2002 and Yao (a suburban community) in 2003—5.[16] There were 355 men and 783 women from Yao, 395 men and 571 women from Ikawa, and 918 men and 1507 women from Kyowa. No subject had a history of OSA as diagnosed by a physician because OSA was unfamiliar to physicians until recently in Japan. We excluded those who had a history of heart disease (n=29) and stroke (n=51), those who had hs-CRP levels ≥10 mg/dl (n=64) and those who had missing data on hs-CRP (n=505). A total of 1422 men and 2466 women were enrolled in the present study. Physicians and trained staff explained the protocol in detail to each subject and obtained informed consent.

Assessment of nocturnal intermittent hypoxia

Nocturnal intermittent hypoxia was estimated by hourly occurrences of oxygen desaturation of ≥3% during sleep (3% oxygen desaturation index (ODI)). This was measured by a pulse oximeter (PULSOX-3Si, Minolta Co, Osaka, Japan) during a night's sleep in the participant's own home.[16] The sensor probe was fitted to the fourth or fifth finger with tape. The device stored the values of peripheral blood oxygen saturation by performing a moving average of the last 5 s and updated each second; this sampling time was short enough to avoid underestimation of oxygen desaturation.[17] Data were downloaded to a personal computer through an interface (PULSOX IF-3, Minolta) and analysed by proprietary software (DS-3 ver. 2.0a, Minolta). The program calculated the number of peripheral blood oxygen saturation (Spo_2) reductions ≥3%. A desaturation event was defined as one beginning with a saturation decrease of ≥3% at intervals of 8–120 s and terminating when the saturation rose within 20 s by the appropriate percentage above the lowest saturation recorded during that event. A sleep log was recorded by participants in the morning after pulse oximetry. The sleep log included three questions: (1) When did you fall asleep last night? (2) When did you wake up this morning? and (3) When and how long did you wake up to do anything (eg, going to the bathroom) during night? Because the measurement time estimated by pulse oximetry was often longer than the true total sleep time, we applied a sleep log to exclude the waking time from the analysis, which minimised potential overestimation of sleep time. The 3% ODI during the estimated sleep duration (>4 h) was computed for each subject and used for the analysis. The severity of nocturnal intermittent hypoxia was defined by 3% ODI levels at 5 and 15 events/h, corresponding to mild and moderate to severe nocturnal intermittent hypoxia, respectively.

The validity of pulse oximetry using synchronous overnight recording of both PULSOX-3Si and standard polysomnography (PSG) has previously been reported in 256 consecutive patients in a sleep-disordered breathing centre (mean body mass index (BMI) 26.8 kg/m^2). The sensitivity and specificity were 80% and 95%, respectively, for detecting an apnoea-hypopnoea index (AHI) of ≥5 by PSG using a cut-off threshold of 3% ODI=5.[18] The sensitivity of 3% ODI of ≥5 to screen for AHI of ≥5 was 68% for those with a BMI of ≤27.0 kg/m^2 and 94% for those with a BMI of >27.0 kg/m^2. To examine the reproducibility of pulse oximetry, measurements were conducted during two overnight periods among 61 men in the present study. The median values for 3% ODI were 5.4 on the first night and 4.8 on the second night (p=0.95, Wilcoxon signed-rank test). Spearman rank correlation coefficient was 0.81 (p<0.001).

Measurement of hs-CRP and confounding variables

Venous blood was drawn from seated participants into plain silicon-coated glass tubes and serum was separated within 30 min. Fasting was not required. The serum sample was transported on dry ice to the Osaka Medical Center for Health Science and Promotion and stored at −70°C until assayed. hs-CRP levels were measured using latex particle-enhanced immunonephelometric assay (Dade Behring Inc, Illinois, USA) which was standardised by a CRP survey program provided by the Center for Disease Control and Prevention (CDC).[19] For results under the measurement limit of hs-CRP (<0.154 mg/l), we used a value of 0.154 mg/l. Serum total cholesterol and glucose were determined using enzymatic methods for total cholesterol and the hexokinase method for glucose by an automatic analyser (AU2700, Olympus Co, Tokyo, Japan) at the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network.[20]

We measured several potential confounders that might also be associated with the incidence of OSA.[21] BMI was calculated as the weight (kg) in light clothing divided by the square of height (m) in stocking feet. Arterial systolic and diastolic blood pressure (SBP and DBP) were measured by physicians using a standard mercury sphygmomanometer on the right arm of a subject while quietly seated and after at least 5 min of rest. Trained nurses interviewed the participants for assessing drinking and smoking habits, the frequency of snoring, apnoea and excessive daytime sleepiness, use of antihypertensive medication, lipid-lowering medication and antidiabetic medication, and menopausal status for women. Typical weekly alcohol intake was converted into grams of ethanol per day. People who smoked ≥1 cigarette/day were defined as current smokers and those who had stopped smoking in the past were defined as former smokers. Hypertension was defined as either SBP ≥140 mm Hg, DBP ≥90 mm Hg or use of antihypertensive medication. Hypercholesterolaemia was defined as total cholesterol ≥220 mg/dl or use of lipid-lowering medication. Diabetes mellitus was defined as either fasting serum glucose ≥126 mg/dl, non-fasting serum glucose ≥200 mg/dl or use of antidiabetic medication. We defined persons who reported snoring 'often' as having habitual snoring, those who reported having apnoea 'sometimes' or 'often' as having apnoea, and those who reported having excessive sleepiness during daytime 'often' as having excessive daytime sleepiness.

Statistical analysis

Because of a skewed distribution, we transformed (hs-CRP+1) values using natural logarithms and, after the statistical analysis, log (hs-CRP+1) was transformed back to the original scale. Age-adjusted mean values and prevalence of cardiovascular risk factors were tested by analysis of covariance (ANCOVA) according to the 3% ODI category. Age- and multivariable-adjusted mean values (95% CI) for hs-CRP and ORs for the prevalence of high hs-CRP (≥1.0 mg/l) were evaluated by ANCOVA and a multiple logistic regression model according to 3% ODI, respectively. A linear trend was examined by a regression model for adjusted mean values and by a multiple logistic regression model for adjusted ORs using the median values of 3% ODI as representative values of the 3% ODI categories. The interactions of 3% ODI with sex, BMI and smoking status were tested using cross-product terms for these variables in the regression model. We included age (years), sex, BMI (kg/m^2), smoking status (never, former and current smoker), current alcohol intake (g/day), community and menopausal status (pre- and post-menopause) for women into the multivariable model 1, and further adjustment for hypertension (yes and no), hypercholesterolaemia (yes and no) and diabetes mellitus (yes and no) into the multivariate model 2 as potential confounders. Analyses used SAS statistical package Version 9.13 (SAS Institute Inc). All statistical tests were two-tailed and p<0.05 was regarded as statistically significant.

RESULTS

Mean values for age and BMI and the prevalence of hypertension were progressively higher with higher 3% ODI categories for both sexes (table 1). Mean alcohol intake was higher and the proportion of current smokers tended to be lower in higher 3% ODI categories only among men.

Table 2 shows the age-, sex- and multivariable-adjusted mean values (95% CI) for hs-CRP levels according to 3% ODI category.

Table 1 Age-adjusted means (±standard errors) and prevalence of risk factors according to 3% ODI levels

	Men				Women			
	3% ODI				3% ODI			
	0–<5	5–<15	≥15	p for trend	0–<5	5–<15	≥15	p for trend
No.	879	428	115		2033	385	48	
Age (years)	57.8 (0.3)	58.4 (0.4)	59.8 (0.7)	0.006	56.0 (0.2)	60.1 (0.4)	60.8 (1.1)	<0.001
BMI (kg/m^2)	23.2 (0.1)	25.0 (0.1)	26.6 (0.3)	<0.001	22.9 (0.1)	25.0 (0.2)	26.9 (0.4)	<0.001
Current alcohol intake (g/day)	22.4 (0.8)	24.8 (1.1)	28.3 (2.2)	0.006	1.7 (0.2)	2.0 (0.4)	2.8 (1.0)	0.22
Current smokers (%)	45	41	35	0.03	5	4	3	0.38
Postmenopause (%)	–	–	–		76	76	77	0.54
Hypertension (%)	40	50	58	<0.001	29	40	59	<0.001
Hypercholesterolaemia (%)	16	23	26	0.001	33	34	27	0.57
Diabetes mellitus (%)	9	8	14	0.20	4	6	3	0.40
Habitual snoring (%)	19	34	56	<0.001	7	19	34	<0.001
Apnoea (%)	11	25	37	<0.001	3	6	15	<0.001
Excessive daytime sleepiness (%)	6	8	5	0.90	3	4	6	0.21
Median 3% ODI (events/h)	2.0	7.7	19.8	–	1.3	7.1	20.0	
Median Spo_2 (%)	96	96	96	–	97	96	95	
Median lowest Spo_2 (%)	88	84	78	–	90	84	78	

BMI, body mass index; ODI, oxygen desaturation index; Spo_2, oxygen saturation.

Age- and sex-adjusted mean values for hs-CRP were progressively higher with increased 3% ODI for both sexes, non-overweight and overweight persons (BMI <25 kg/m^2 and ≥25 kg/m^2) and non-current and current smokers. A weaker association among current smokers was primarily due to confounding by BMI. After adjusting for potential confounding factors, these associations were weakened somewhat, but remained statistically significant, except among current smokers. The interactions of nocturnal intermittent hypoxia with sex, BMI and current smoking status were not statistically significant (p for interaction=0.50 for sex, 0.51 for BMI and 0.18 for current smoking; results not shown).

Compared with 3% ODI of <5, the prevalence of high CRP levels (≥1.0 mg/l) was 1.4-fold higher in the 3% ODI 5–<15 category and 1.7-fold higher in the 3% ODI ≥15 category (table 3). The trend for the prevalence of high CRP levels was statistically significant, except among current smokers.

DISCUSSION

This study shows a direct association between nocturnal intermittent hypoxia (evaluated by 3% ODI) and hs-CRP levels in men and women that is independent of atherosclerotic risk factors. Several hospital-based studies have shown that CRP levels were higher in patients with OSA than in controls,[5–7] and a recent small population-based study of elderly people has shown that 3% ODI was associated with raised CRP levels.[8] Interventional studies showed that continuous positive airway pressure therapy decreased serum CRP levels among patients with OSA.[12 13] Our population-based study extended the evidence for an association between nocturnal intermittent hypoxia and hs-CRP levels in middle-aged men and women.

In contrast, in the Wisconsin Sleep Cohort Study, OSA was found to be significantly associated with CRP in crude analysis, but there was no association after adjustment for atherosclerotic risk factors.[10] The discrepancy of the results between this population-based study and our study may be due to differences in subject characteristics and the methodology used to assess OSA. First, obesity is a strong confounder for the association between OSA and CRP. Overall, our study population had a lower BMI than did Western studies (median (IQR) 23.4 (21.4–25.4) vs 29.1 (25.9–33.4)).[10] The effect of OSA on CRP levels may be masked by the influence of body habitus in the Wisconsin Sleep Cohort Study. However, our study did not find an interaction between 3% ODI and BMI. Second, the Wisconsin Sleep Cohort Study estimated the AHI using full PSG whereas we measured 3% ODI by pulse oximetry. The AHI may dilute the effects of nocturnal intermittent hypoxia on CRP levels as this index reflects complete or partial cessation of airflow without regard to the presence or absence of oxygen desaturation.[8]

The mechanisms underlying the effect of nocturnal intermittent hypoxia on raised CRP levels may be related to hypoxia and oxidative stress due to repetitive hypoxia and reoxygenation.[22] First, in vitro, hypoxia induces IL-6 synthesis in cardiac myocytes[23] and endothelial cells.[24] Hypoxic exposure at high altitudes increases IL-6 and CRP levels in healthy persons.[5] IL-6 is principally involved with the initiation of the hepatic acute phase response.[25] Second, oxidative stress activates transcription nuclear factor-kappa B (NF-κB)[26] which upregulates proinflammatory gene expressions and the transcription of proinflammatory cytokines in vitro.[27] Previous in vivo studies also showed that oxidative stress was associated with raised IL-6 levels in diabetic pigs[28] and raised CRP levels in healthy adult humans.[4]

There are several strengths and limitations of the present study. The strengths are the large sample size and a community-based study for populations with a lower BMI. Thus, we were able to minimise the confounding effect of being overweight.

One limitation was that we only measured the oxygen desaturation during sleep by pulse oximetry to evaluate nocturnal intermittent hypoxia. The sensitivity of 3% ODI ≥5 to screen for AHI ≥5 and 3% ODI ≥15 to screen for AHI ≥20 was 68% and 76% in those with BMI ≤27.0 kg/m^2 and 94% and 93% in those with BMI >27.0 kg/m^2.[18] Because our study population had a low BMI (mean 23.4 kg/m^2), pulse oximetry is not comparable to gold standard PSG, provides no information about sleep stage or body position, and could underestimate the degree of OSA. A second limitation was that a history of chronic lung disease was not available in the present study. Chronic obstructive pulmonary disease and asthma cause hypoxia, and pulse oximetry cannot distinguish nocturnal intermittent hypoxia caused by OSA from that caused by lung diseases. However, according to the 2005 Japan National Patient Survey, the consultation rate of these lung diseases was only 0.1%

Table 2 Multivariable-adjusted* means (95% CI) for hs-CRP levels according to 3% ODI levels

	3% ODI			
	0–<5	5–<15	≥15	p for trend
Men				
No. at risk	879	428	115	
Age-adjusted means	0.66 (0.62 to 0.71)	0.87 (0.79 to 0.95)	0.97 (0.82 to 1.14)	<0.001
Multivariable model 1	0.70 (0.65 to 0.75)	0.82 (0.74 to 0.90)	0.85 (0.70 to 1.01)	0.02
Multivariable model 2	0.70 (0.65 to 0.75)	0.82 (0.74 to 0.89)	0.84 (0.70 to 1.00)	0.03
Women				
No. at risk	2033	385	48	
Age-adjusted means	0.57 (0.54 to 0.60)	0.75 (0.68 to 0.83)	1.05 (0.82 to 1.30)	<0.001
Multivariable model 1	0.59 (0.56 to 0.62)	0.66 (0.60 to 0.73)	0.82 (0.62 to 1.03)	0.005
Multivariable model 2	0.59 (0.57 to 0.62)	0.66 (0.59 to 0.73)	0.81 (0.62 to 1.03)	0.008
Non-overweight				
No. at risk	2284	417	59	
Age, sex-adjusted means	0.55 (0.53 to 0.58)	0.65 (0.59 to 0.71)	0.76 (0.59 to 0.95)	<0.001
Multivariable model 1	0.56 (0.53 to 0.58)	0.63 (0.56 to 0.69)	0.69 (0.53 to 0.87)	0.02
Multivariable model 2	0.56 (0.53 to 0.58)	0.63 (0.56 to 0.69)	0.68 (0.52 to 0.86)	0.02
Overweight				
No. at risk	627	396	104	
Age, sex-adjusted means	0.80 (0.74 to 0.87)	0.99 (0.90 to 1.08)	1.11 (0.93 to 1.31)	<0.001
Multivariable model 1	0.83 (0.76 to 0.89)	0.97 (0.88 to 1.06)	1.03 (0.85 to 1.22)	0.02
Multivariable model 2	0.83 (0.76 to 0.90)	0.96 (0.87 to 1.05)	1.03 (0.85 to 1.22)	0.02
Non-current smoker				
No. at risk	2419	624	123	
Age, sex-adjusted means	0.58 (0.55 to 0.60)	0.80 (0.74 to 0.86)	0.98 (0.84 to 1.13)	<0.001
Multivariable model 1	0.60 (0.58 to 0.63)	0.72 (0.66 to 0.78)	0.79 (0.66 to 0.93)	<0.001
Multivariable model 2	0.60 (0.58 to 0.63)	0.72 (0.66 to 0.77)	0.78 (0.66 to 0.92)	<0.001
Current smoker				
No. at risk	489	188	40	
Age, sex-adjusted means	0.73 (0.66 to 0.80)	0.85 (0.73 to 0.97)	0.95 (0.69 to 1.25)	0.04
Multivariable model 1	0.76 (0.69 to 0.83)	0.78 (0.67 to 0.90)	0.82 (0.58 to 1.10)	0.63
Multivariable model 2	0.77 (0.70 to 0.84)	0.77 (0.66 to 0.89)	0.79 (0.55 to 1.06)	0.92

*Model 1 adjusted for age (year), sex, body mass index (kg/m^2), current alcohol intake (g/day), smoking status (never, former and current smoker), menopausal status (pre- and post-menopause) and community. Model 2 adjusted for the covariates included in model 1 and hypertension (yes and no), hypercholesterolaemia (yes and no) and diabetes mellitus (yes and no).
hs-CRP, high-sensitivity C reactive protein; ODI, oxygen desaturation index.

among persons aged 40–69 years.[29] Therefore, any contamination by lung diseases may be minimal. A third limitation was that we used BMI as a variable for body habitus. Waist circumference was shown to be more strongly associated with CRP than BMI.[30] However, because the correlation of waist circumference with BMI is very high, the use of BMI as a confounding variable may be adequate.[31] The final limitation was the use of a single measurement for serum CRP. Because of regression dilution, the real association would be stronger.

In conclusion, nocturnal intermittent hypoxia was associated with raised hs-CRP levels in a middle-aged Japanese population which was independent of atherosclerotic risk factors.

Table 3 Multivariable-adjusted* ORs (95% CI) for high CRP (≥1.0 mg/l) according to 3% ODI levels

	3% ODI			
	0–<5	5–<15	≥15	p for trend
Men	1	1.4 (1.0 to 1.8)	1.6 (1.0 to 2.5)	0.01
Women	1	1.4 (1.0 to 1.8)	1.7 (0.9 to 3.1)	0.01
Non-overweight	1	1.3 (1.0 to 1.7)	1.5 (0.8 to 2.6)	0.04
Overweight	1	1.5 (1.1 to 2.0)	1.7 (1.1 to 2.8)	0.009
Non-current smoker	1	1.4 (1.2 to 1.8)	1.7 (1.1 to 2.6)	<0.001
Current smoker	1	1.2 (0.8 to 1.8)	1.2 (0.6 to 2.4)	0.46

*Adjusted for age (year), sex, body mass index (kg/m^2), current alcohol intake (g/day), smoking status (never, former and current smoker), menopausal status (pre- and post-menopause), hypertension (yes and no), hypercholesterolaemia (yes and no), diabetes mellitus (yes and no) and community.
CRP, C reactive protein; ODI, oxygen desaturation index.

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