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Morning levels of fibrinogen in children with sleep-disordered breathing

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ABSTRACT: Elevated fibrinogen level is a predictor of cardiovascular disease in adults, and it is associated with sleep-disordered breathing. Levels of fibrinogen in adults are affected by other co-existing cardiovascular risk factors, which are not usually present in children.

To investigate the association between fibrinogen and sleep-disordered breathing, a case-control study was carried out in children with and without habitual snoring. All snoring children underwent polysomnography.

Morning fibrinogen values in 30 children with snoring and an apnoea-hypopnoea index (AHI) $\geqslant$5 episodes·h^{-1} (median (interquartile range) 318 mg·dL^{-1} (290–374)) were similar to values in 61 children with snoring and an AHI <5 episodes·h^{-1} (307 (269–346)). Both groups had higher fibrinogen values than those in 23 controls without snoring (271 mg·dL^{-1} (244–294)). There was no correlation between fibrinogen values and AHI, respiratory movement/arousal index or haemoglobin desaturation index.

In conclusion, fibrinogen values are higher in children with snoring than in controls, but there is no association between these values and polysomnography indices.

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Several investigators have identified important correlations between obstructive sleep apnoea-hypopnoea and cardiovascular disease in adults. Obstructive sleep apnoea-hypopnoea is associated with systemic hypertension, coronary artery disease, congestive heart failure and stroke [1–3]. These associations have been reported even for subjects with mild elevations of apnoea-hypopnoea index (AHI; 1–10 episodes·h^{-1}) [3].

Elevated fibrinogen level is a predictor of cardiovascular events in adults [4–6]. In an effort to identify pathophysiological links between obstructive sleep apnoea-hypopnoea and cardiovascular disease, the association between sleep-disordered breathing and fibrinogen values has been investigated [7–9]. However, these values are affected by other known risk factors for cardiovascular disease, such as obesity, hyperlipidaemia, hypertension, diabetes mellitus and cigarette smoking [5, 6]. Therefore, reported increased levels of fibrinogen in adults with obstructive sleep apnoea-hypopnoea may simply reflect the effect of other co-existing risk factors for cardiovascular events and not the result of sleep-disordered breathing.

Some studies have suggested that obstructive sleep-disordered breathing may affect the cardiovascular system of children similarly to adults [10–12]. Children do not usually have risk factors for cardiovascular disease, and, for this reason, they are an appropriate population to study the relationship between obstructive sleep apnoea-hypopnoea and fibrinogen. The aim of the present investigation was to compare morning values of fibrinogen in children with and without habitual snoring. The hypothesis was that children with sleep-disordered breathing have higher levels of fibrinogen than controls without snoring, and that these levels are correlated with severity of disturbance in respiration.

Patients and methods

Study design

A case-control study was carried out of all children who were referred to the Paediatric Sleep Disorders Laboratory, Larissa University Hospital, Larissa, Greece, between March 2001 and February 2003 and who met the following inclusion criteria: 1) snoring present for >3 nights·week^{-1}; and 2) persistence of snoring for $\geqslant$6 months (habitual snoring). Healthy children without a history of sleep-disordered breathing symptoms (snoring, witnessed apnoeas, difficulty breathing while asleep) who presented to the General Paediatrics clinic for well-child visits during the study period and had blood drawn for routine measurement of haematocrit were also recruited as controls. Exclusion criteria both for children with snoring and controls were the following: 1) symptoms or signs of acute or chronic inflammation; 2) use of corticosteroids or antibiotics for the 4 weeks preceding recruitment in the study; 3) history of cardiovascular disease; 4) a diagnosis of diabetes mellitus; and 5) history of neuromuscular or genetic disorders.

The study protocol was approved by the University of Thessaly Ethics Committee. Informed consent was obtained

from the parents of all participants. Parents of subjects with snoring and controls were interviewed by one of the investigators and a questionnaire was answered (see Appendix). The questions inquired about symptoms of sleep-disordered breathing present for the previous 6 months and about past medical and family history.

Children with snoring and controls underwent a physical examination. Weight and height were measured, while blood pressure was determined as recommended by the Working Group of the National High Blood Pressure Education Program [13]. Tonsillar size was graded from 0–4+ as described by others; tonsillar hypertrophy was defined as tonsillar size $\geqslant$2+ [14, 15]. All children with symptoms of sleep-disordered breathing had lateral neck radiographs taken, and the adenoidal/nasopharyngeal diameter ratio was measured by a radiologist. Adenoidal hypertrophy was defined as an adenoidal/nasopharyngeal diameter ratio >0.5 [14, 16, 17].

Polysomnography and fibrinogen measurements

Polysomnograms were performed overnight in the Paediatric Sleep Disorders Laboratory for all children with habitual snoring under the supervision of a trained technician. Controls without snoring did not undergo polysomnography because this was not acceptable to their parents. The Alice-4 computerised system (Healthdyne, Marietta, GA, USA) was used to record the following parameters: electroencephalogram (electrodes at positions C3/A2, C4/A1 and O1/A2); right and left oculogram; submental and tibial electromyogram; electrocardiogram; thoracic and abdominal wall motion (piezoelectric transducers); oronasal airflow (3-pronged thermistor); and oxygen saturation of haemoglobin (oximetry). Bedtime and waking time were determined by each child′s routine, and polysomnography was terminated upon final awakening.

Arousals, sleep stages and architecture were assessed as recommended by the American Sleep Disorders Association [18, 19]. Total sleep time was determined based on both electroencephalography and the laboratory technician′s notes. Obstructive sleep apnoea was defined as the presence of chest/abdominal wall motion in the absence of airflow for at least two missed breaths in duration [20, 21]. Hypopnoea was defined as: 1) a reduction in the airflow signal amplitude of $\geqslant$50% compared with baseline; 2) in the presence of chest/abdominal wall motion; and 3) associated with oxygen desaturation of haemoglobin $\geqslant$4% compared with baseline or an arousal. AHI was the number of hypopnoeas, obstructive and mixed apnoeas (apnoeas with both central and obstructive components) per hour of sleep. Frequency of movement/arousals terminating apnoeas and hypopnoeas determined the respiratory movement/arousal index [22]. The number of episodes per hour of oxygen desaturation of haemoglobin $\geqslant$4% compared with baseline determined the oxygen desaturation of haemoglobin index. The arterial oxygen saturation (Sa,O_2) nadir and the percentage of total sleep time, during which Sa,O_2 was <95%, were also determined.

Venous blood was collected between 08:00–10:00 h from subjects with snoring and from controls. For children with habitual snoring, the collection was made in the morning following completion of polysomnography. Plasma fibrinogen was measured using a commercially available assay that was based on an excess of thrombin converting fibrinogen to fibrin (IL Coagulation Systems, Lexington, MA, USA). Serum triglycerides and total cholesterol levels were also determined.

Data analysis

Three groups of subjects were studied as follows: 1) healthy controls without snoring; 2) children with habitual snoring and AHI <5 episodes·h^{-1}; and 3) children with habitual snoring and AHI $\geqslant$5 episodes·h^{-1}. An AHI $\geqslant$5 episodes·h^{-1} has been used to distinguish primary snoring from obstructive sleep apnoea-hypopnoea [23–25].

The expected difference in mean fibrinogen levels between habitually snoring children and healthy controls was ~50 mg·dL^{-1}; the expected standard deviation for fibrinogen values in each group was also 50 mg·dL^{-1} [9, 26]. In order to have 90% power of detecting such a difference, with a significance level of 0.05, it was necessary to recruit $\geqslant$20 subjects in each group.

For continuous characteristics and the outcome (fibrinogen values), the three groups were initially compared using the Kruskal-Wallis test, and, then, the Mann-Whitney U-test with Bonferroni′s correction was applied to detect differences between pairs of groups. Blood pressure differences between the three groups were assessed using one-way ANOVA. For categorical characteristics, the three groups were compared using the Chi-squared test (Yate′s correction).

The Centers for Disease Control and Prevention 2000 Growth Charts were taken into account to calculate z-scores for body mass index (BMI), with adjustment for sex and age [27]. Blood pressure normative data from the Report of the National High Blood Pressure Education Program Working Group was used [13]. To control for the effect of subjects′ sex, age and height on blood pressure, the difference between the measured value and the respective 95th percentile value (adjusted for sex, age and height) was divided by the 95th percentile value. This quotient was defined as the blood pressure index [12, 13].

Spearman′s correlation was used to study the association between fibrinogen values of all children with snoring and indices of severity of sleep-disordered breathing. Controls were not included in the correlation analysis because they did not undergo polysomnography. The significance of interactions between study group and age ($\leqslant$5 yrs old, >5 yrs old), sex, and passive smoking in fibrinogen levels was tested by fitting a linear model. The model included all main effects (group, age, sex, passive smoking) and all possible two-way interactions.

Results

Patient characteristics and polysomnography results

A total of 101 children were referred to the Sleep Disorders Laboratory over the 2-yr study period. In total, 91 children with habitual snoring were recruited along with 23 healthy controls without snoring. Ten out of 101 habitually snoring children who were referred for polysomnography were excluded: eight subjects because of symptoms and signs of upper respiratory tract infection and two because of recent treatment with systemic corticosteroids for asthma exacerbation.

There were 61 children with snoring and AHI <5 episodes·h^{-1}, and 30 children with snoring and AHI $\geqslant$5 episodes·h^{-1}. Distribution of symptoms of sleep-disordered breathing, tonsillar and adenoidal size, and polysomnography indices in the three study groups are shown in table 1. Tonsillar hypertrophy was noted in 88 out of 91 (97%) subjects with snoring, but not in the controls. A total of 90 out of 91 (99%) children with snoring had adenoidal hypertrophy (adenoidal/nasopharyngeal diameter ratio >0.5). Mouth-breathing during day or night was reported in 84 out of 91 (92%) subjects with

Table 1. – Summary statistics for symptoms of sleep-disordered breathing, tonsillar and adenoidal size, and polysomnography indices in the three study groups

	Controls	Snoring and AHI <5 episodes·h^{-1}	Snoring and AHI ⩾5 episodes·h^{-1}
Subjects n	23	61	30
Snoring >3 nights·week^{-1}	0 (0)	61 (100)	30 (100)
Apnoea >3 nights·week^{-1}	0 (0)	15 (25)	18 (60)
Difficulty breathing >3 nights·week^{-1}	0 (0)	22 (36)	21 (70)
Mouth-breathing during day or night	0 (0)	56 (92)	28 (93)
Tonsillar size			
0	9	1	0
1	14	2	0
2	0	19	7
3	0	34	19
4	0	5	4
Adenoidal/nasopharyngeal diameter ratio		0.68±0.1	0.74±0.1
Apnoea index episodes·h^{-1}		0.5 (0.3–1.3)	2.7 (1.8–4.6)
AHI episodes·h^{-1}		1.8 (1–3.3)	8.5 (6.4–14.4)
Respiratory movement/arousal index episodes·h^{-1}		0.8 (0.4–1.4)	3.5 (2.7–4.6)
Oxygen desaturation of haemoglobin[#] index episodes·h^{-1}		1.8 (0.9–2.8)	8.2 (6.4–13.2)
Sa,O_2 nadir %		90 (88–92)	85 (81–88)
% sleep time with Sa,O_2 <95%		0.5 (0.2–0.8)	3.9 (2.3–5.2)

Data are presented as n, n (%), mean±SD and median (interquartile range). AHI: apnoea-hypopnoea index; Sa,O_2: arterial oxygen saturation. [#]: ⩾4%.

sleep-disordered breathing, but not in any of the 23 controls. When children exposed to cigarette smoke were compared with those who were not exposed, there were equal proportions of subjects with mouth-breathing (80.3% *versus* 79.2%; p>0.05).

The three study groups did not show statistically significant differences in most characteristics that may be confounded with fibrinogen levels (table 2). There were differences between the three groups regarding age (p=0.003). Children with snoring and AHI ⩾5 episodes·h^{-1} were younger than subjects with snoring and AHI <5 episodes·h^{-1} (p<0.0001). Median (interquartile range) z-scores for BMI were: 1.04 (0–1.28), 1.04 (0–1.65) and 1.15 (0.27–1.48) in controls, children with AHI <5 episodes·h^{-1} and children with AHI ⩾5 episodes·h^{-1}, respectively (p>0.05).

Mean systolic and diastolic blood pressures were not different among the three study groups (p>0.05; table 2). Mean±SD systolic blood pressure indices were: -0.14±0.08 (controls), -0.12±0.14 (AHI <5 episodes·h^{-1}), and -0.08±0.07 (AHI ⩾5 episodes·h^{-1}). Mean±SD diastolic blood pressure indices were: -0.16±0.08 (controls), -0.09±0.13 (AHI <5 episodes·h^{-1}), and -0.04±0.14 (AHI ⩾5 episodes·h^{-1}). There was a statistically significant difference only in mean diastolic blood pressure indices between children with AHI ⩾5 episodes·h^{-1} and controls (p=0.02).

Fibrinogen values

When all three groups were compared regarding fibrinogen values, there was a significant difference (p=0.002). Fibrinogen values in children with AHI ⩾5 episodes·h^{-1} were similar to those with AHI <5 episodes·h^{-1} (median (range) fibrinogen 318 mg·dL^{-1} (168–593) *versus* 307 mg·dL^{-1} (177–452), respectively; p>0.05). However, children with AHI ⩾5 episodes·h^{-1} and children with AHI <5 episodes·h^{-1} had higher values compared with healthy controls (271 mg·dL^{-1} (210–368); p=0.003 for children with AHI ⩾5 episodes·h^{-1} *versus* controls; p=0.006 for subjects with AHI <5 episodes·h^{-1} *versus* controls; fig. 1). Mean±SD fibrinogen values were: 335±87, 314±60 and 273±40 in snoring children with AHI

Table 2. – Summary statistics and significance of comparisons between study groups regarding fibrinogen values and factors that may be confounded with fibrinogen values

	Controls	Snoring and AHI <5 episodes·h^{-1}	Snoring and AHI ⩾5 episodes·h^{-1}
Subjects n	23	61	30
Age[#] yrs	6.5 (3–10)	7 (4–9)	4.5 (3–6)
Females	7 (30)	20 (33)	13 (43)
BMI kg·m^{-2}	17 (16.1–17.8)	17.4 (16.3–19)	18 (15.7–18.6)
Systolic blood pressure mmHg	103±11.2	104±9.6	102±8.2
Diastolic blood pressure mmHg	64±5.8	68±8.9	69±9.6
Season of blood sample collection			
February–May	6 (26)	21 (34)	10 (33)
June–September	9 (39)	22 (36)	12 (40)
October–January	8 (35)	18 (30)	8 (27)
Passive smoking	10 (43)	32 (52)	19 (63)
Triglycerides mg·dL^{-1}	71 (59–96)	59 (48–70)	52 (49–71)
Total cholesterol mg·dL^{-1}	169 (155–186)	167 (148–192)	153 (103–196)
Fibrinogen[¶] mg·dL^{-1}	271 (244–294)	307 (269–346)	318 (290–374)

Data are presented as n, median (interquartile range), n (%) and mean±SD. AHI: apnoea-hypopnoea index; BMI: body mass index. [#]: p<0.05 for comparison between snoring children with AHI <5 episodes·h^{-1} and those with AHI ⩾5 episodes·h^{-1}; [¶]: p<0.05 for comparisons between controls and snoring children with AHI <5 episodes·h^{-1} and between controls and snoring children with AHI ⩾5 episodes·h^{-1}.

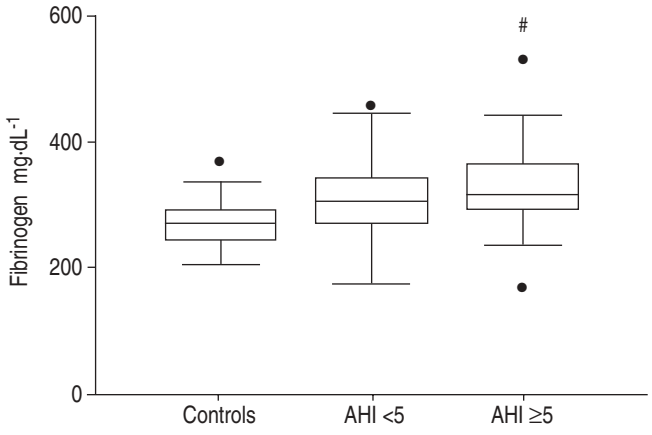

Fig. 1. – Fibrinogen levels in children without snoring (controls), with habitual snoring and apnoea-hypopnoea index (AHI) <5 episodes·h^{-1}, and with habitual snoring and apnoea-hypopnoea index ⩾5 episodes·h^{-1}. Horizontal bars are medians ($p<0.05$ for controls *versus* snoring children with AHI <5 episodes·h^{-1} and for controls *versus* snoring children with AHI ⩾5 episodes·h^{-1}). ●: outliers; #: extreme value.

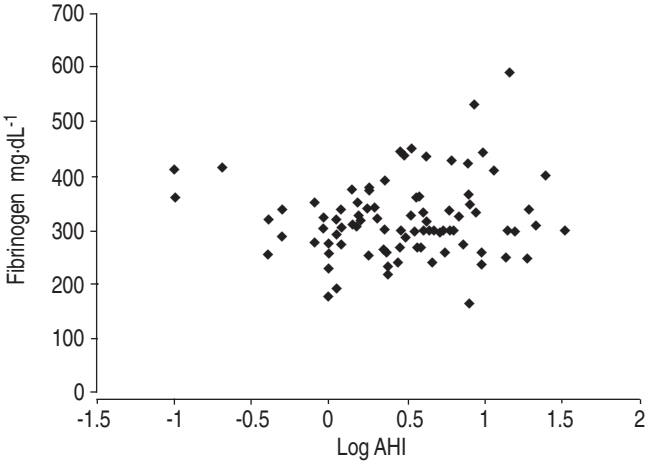

Fig. 2. – Fibrinogen values (mg·dL^{-1}) *versus* log apnoea-hypopnoea index (AHI) in 91 children with habitual snoring.

⩾5 episodes·h^{-1}, snoring children with AHI <5 episodes·h^{-1} and controls, respectively.

In the group of children with AHI ⩾5 episodes·h^{-1}, there were two subjects with fibrinogen levels in the 500–600 mg·dL^{-1} range. The first child was a 7-yr-old female with a BMI of 16.6 kg·m^{-2} (75th percentile for sex and age) and fibrinogen value of 530 mg·dL^{-1}. The second child was a 3-yr-old male with a BMI of 14.5 kg·m^{-2} (10th percentile for sex and age) and fibrinogen value of 593 mg·dL^{-1}. None of the two children had a personal history of passive smoking or family history of sleep-disordered breathing. When the two subjects with very high fibrinogen values were excluded, there was still a significant difference regarding fibrinogen between the three groups ($p=0.003$). Specifically, the two groups of children with snoring had similar values ($p>0.05$), whereas both groups had higher fibrinogen values compared with controls ($p=0.009$ for children with an AHI ⩾5 episodes·h^{-1} *versus* controls; $p=0.006$ for children with an AHI <5 episodes·h^{-1} *versus* controls).

Correlation between fibrinogen levels and indices of severity of sleep-disordered breathing was assessed only for children with snoring, since controls did not undergo polysomnography. There were no significant correlations between fibrinogen levels and AHI ($r=0.13$, $p>0.05$; fig. 2), respiratory movement/arousal index ($r=0.09$, $p>0.05$), oxygen desaturation of haemoglobin index ($r=0.11$, $p>0.05$) or % sleep time with Sa,O_2 <95% ($r=0.07$, $p>0.05$). There were no significant interactions between study group (*i.e.* controls, subjects with snoring and AHI <5 episodes·h^{-1}, subjects with snoring and AHI ⩾5 episodes·h^{-1}) and age ($p=0.46$), study group and sex ($p=0.68$), or study group and passive smoking ($p=0.58$) in fibrinogen levels.

Discussion

Studies in adults with obstructive sleep apnoea-hypopnoea have detected elevated fibrinogen levels that are associated with severity of sleep-disordered breathing [7–9, 26]. Elevated fibrinogen is a predictor of cardiovascular disease [5, 6], and the association of sleep-disordered breathing with fibrinogen levels has been suggested as one of the pathophysiological links for the reported correlation between obstructive sleep apnoea-hypopnoea and cardiovascular disease [3]. Nevertheless, fibrinogen levels in adults are affected by other co-existing cardiovascular risk factors [5, 6, 28].

Children do not usually have risk factors for cardiovascular disease. To the current authors' knowledge, this is the first study investigating the relationship between fibrinogen and mild-to-moderate sleep-disordered breathing in children. Statistically significant differences in the levels of fibrinogen between habitual snorers and healthy controls without snoring were identified. Fibrinogen values did not show any association with indices of sleep-disordered breathing severity (*i.e.* AHI, respiratory movement/arousal index, oxygen desaturation of haemoglobin index and % sleep time with Sa,O_2 <95%).

Fibrinogen was measured in three groups of children: healthy controls without symptoms of obstructive sleep-disordered breathing, habitual snorers with AHI <5 episodes·h^{-1} and habitual snorers with AHI ⩾5 episodes·h^{-1}. Almost all children with snoring had adenotonsillar hypertrophy. Obstructive sleep-disordered breathing in children includes a spectrum of abnormalities, ranging from primary snoring to upper airway resistance syndrome to obstructive sleep apnoea-hypopnoea, depending on the severity of increase in upper airway resistance during sleep [29]. While children with AHI ⩾5 episodes·h^{-1} usually require adenotonsillectomy [24, 25], even subjects with a lower index may have neurocognitive and behavioural abnormalities associated with sleep-disordered breathing [30]. Conceivably, minimal abnormalities in polysomnography could be accompanied by an elevation of fibrinogen levels.

In adults with obstructive sleep apnoea-hypopnoea (AHI >20 episodes·h^{-1}) and history of ischaemic stroke, mean values of fibrinogen were ~50–80 mg·dL^{-1} higher than in controls (AHI <5 episodes·h^{-1}) [9]. In a second report, including adults with and without obstructive sleep apnoea-hypopnoea, a similar difference in fibrinogen levels was detected [26]. Mean fibrinogen values in the current investigation were 62 mg·dL^{-1} higher in children with snoring and AHI ⩾5 episodes·h^{-1}, and 41 mg·dL^{-1} higher in children with snoring and AHI <5 episodes·h^{-1}, compared with controls without snoring.

In adults with stroke and obstructive sleep apnoea-hypopnoea, modest but significant correlations have been found between fibrinogen levels and respiratory disturbance index ($r=0.32$) or minimum Sa,O_2 ($r=-0.26$) [9]. Such associations were not detected in the present investigation, and this may be due to the fact that there were not enough subjects

with severe sleep-disordered breathing, as most children had AHI <20 episodes·h^{-1}. Alternatively, the absence of correlation between levels of fibrinogen and parameters of severity of sleep-disordered breathing could indicate inherent limitations of the currently used polysomnography indices to accurately describe the disturbance of respiration during sleep. Furthermore, the lack of correlation between severity of sleep-disordered breathing and several different procoagulant factors is the rule, rather than the exception, in adult studies. In a recent comprehensive review of the topic, it was noted that only two out of nine relative studies identified significant associations between haemostasis factors and indices of severity of obstructive sleep apnoea, although there were differences regarding levels of these factors between snorers and controls [31].

Fibrinogen was measured with a method based on an excess of thrombin converting fibrinogen to fibrin. The normal fibrinogen range in the Larissa University Hospital laboratories is 150–400 mg·dL^{-1}. In the current healthy controls without snoring (median age 6.5 yrs, interquartile range 3–10 yrs), the mean value was 273 mg·dL^{-1} with a corresponding 95% confidence interval (CI) of 256–290 mg·dL^{-1}. These values were similar to those reported for healthy children in other reports. GLOWINSKA *et al.* [32] calculated a mean value of 253 mg·dL^{-1} (95% CI 243–263), using an immunoenzymatic method in subjects with mean±SD age of 14.1±2.9 yrs; COOK *et al.* [33] reported a value of 245 mg·dL^{-1} (95% CI 239–251) for 10–11-yr-old males and 259 mg·dL^{-1} (95% CI 253–265) for 10–11-yr-old females, using a method based on the measurement of thrombin-clottable fibrinogen concentration.

In adults with obstructive sleep-disordered breathing, several different markers of hypercoagulability have been studied, such as fibrinogen, factor VII, von Willebrand factor, type-I plasminogen activator inhibitor, thrombin-antithrombin III complex, d-dimer and platelet activity [31]. In this study, fibrinogen was chosen as a hypercoagulability marker because it is measured by a low-cost test that is easily performed in the routine clinical laboratory. Since fibrinogen is elevated in the presence of acute or chronic inflammatory processes, subjects with any symptoms of inflammation were excluded from the present study [34]. Blood samples were drawn in the morning, since adults with obstructive sleep apnoea-hypopnoea (but not healthy controls) have higher fibrinogen levels in the morning compared with levels in the evening [7].

Polysomnography was not performed to rule out occult sleep-disordered breathing in subjects of the control group, as this was not acceptable by their parents. Nevertheless, none of these children had any history of snoring, witnessed apnoeas or difficulty breathing whilst asleep. One of the limitations of the present study is the use of thermistors to detect decreases in airflow due to hypoventilation. Measurement of end-tidal CO_2 is a more sensitive method to identify hypoventilation, but capnometers are not available in the current authors' Sleep Disorders Laboratory.

The mechanism responsible for higher fibrinogen values in subjects with obstructive sleep apnoea-hypopnoea compared with controls is unclear [35]. It has been proposed that the previous finding is due to haemoconcentration [7]. Adults with obstructive sleep apnoea-hypopnoea have increased salt and water excretion *via* the kidneys, which can be reversed by treatment with nasal continuous positive airway pressure [36]. In addition, fibrinogen levels in adults are positively and significantly related to hypertension, glucose intolerance, high serum cholesterol and cigarette smoking [5, 6, 28]. Thus, the reported elevated fibrinogen levels in adult studies could also reflect the effect of other co-existing cardiovascular risk factors.

In children and young adults, female sex, BMI and season of the year that blood samples were collected are factors known to affect fibrinogen values, whereas no association with age has been described [32, 33, 37]. Fibrinogen is increased among smoking males and females [38], and, therefore, a correlation between fibrinogen and passive smoking may exist in children. In the present paediatric investigation, no differences in the distribution of most parameters that may influence fibrinogen values were identified among the three study groups (table 2). Proportions of subjects who had blood drawn for fibrinogen measurement during a certain period of the year were similar among the three study groups (table 2). In addition, no significant interactions were found between study group and age, study group and sex, and study group and passive smoking in fibrinogen levels, using a linear model.

Passive smoking could increase fibrinogen levels by inducing nasal mucosa inflammation. Nasal mucosa inflammation would be clinically apparent as rhinorrhoea, nasal obstruction and associated mouth-breathing. This possibility is unlikely for the following reasons: 1) during recruitment, rhinorrhoea was considered to be a sign of acute inflammation, one of the exclusion criteria for participation in the study; 2) there were equal proportions of subjects with mouth-breathing among those with and without history of passive smoking; and 3) the majority of children with sleep-disordered breathing had history of snoring and mouth-breathing most likely caused by adenoidal hypertrophy (adenoidal hypertrophy was documented in almost all subjects with snoring by lateral neck radiographs).

Elevated fibrinogen in adults is an independent risk factor for myocardial infarction and stroke [5, 6]. Even in the presence of other powerful cardiovascular risk factors like obesity, older age, hypertension or glucose intolerance, a fibrinogen value near the upper limit of normal has been associated with increased frequency of cardiovascular disease [5]. Similarly, adults with obstructive sleep apnoea-hypopnoea are at an increased risk for systemic hypertension, coronary artery disease, congestive heart failure and stroke [1–3].

Recent data indicate that obstructive sleep-disordered breathing is associated with increases of the following: 1) production of reactive oxygen species in monocyte and granulocyte subpopulations as a result of repeated episodes of hypoxia/reoxygenation; 2) expression of adhesion molecules on monocytes; 3) levels of circulating soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1 and L-selectin; and 4) adherence of monocytes to endothelial cells in culture [39–42]. The reported increased production of reactive oxygen species, expression of adhesion molecules and adherence of monocytes to human endothelial cells may potentially promote vascular inflammation and atherosclerosis [43–45]. Higher values of C-reactive protein predict increased risks of coronary heart disease [46], and patients with obstructive sleep apnoea-hypopnoea have greater levels of C-reactive protein than controls [47, 48]. Finally, fibrinogen is an acute-phase reactant and elevated values in adults with obstructive sleep-disordered breathing could reflect vascular inflammation [9].

A number of older case reports and some recent studies have focused on the cardiovascular complications of sleep-disordered breathing in childhood. Children with severe obstructive sleep apnoea-hypopnoea can develop cor pulmonale, probably secondary to recurrent hypoxia and hypercapnia during sleep [49, 50]. Echocardiography and radionuclide ventriculography have revealed decreased right ventricular ejection fraction that improved post-adenotonsillectomy [51, 52], whereas obstructive sleep apnoea has been associated with cardiac remodelling and hypertrophy involving both the right and left ventricle [53]. It is speculated that increased levels of fibrinogen in children with sleep-disordered breathing

may be associated with early vascular inflammation. In a recently published study [54], higher C-reactive protein values, an index of inflammation and predictor of cardiovascular morbidity, were reported in children with sleep-disordered breathing compared with controls.

Habitually snoring subjects of the present report with an AHI $\geqslant 5$ episodes·h^{-1} had higher mean diastolic blood pressure index than controls. Older studies have demonstrated that children with obstructive sleep apnoea have higher diastolic blood pressures than subjects with primary snoring [10], and those with primary snoring have higher daytime systolic and diastolic blood pressures compared with healthy controls without snoring [11]. A recent investigation detected increased blood pressure variability and decreased nocturnal blood pressure dipping in children with obstructive sleep apnoea [12].

In conclusion, habitually snoring children had higher fibrinogen levels than controls without snoring, but no association was identified between these levels and indices of severity of sleep-disordered breathing. An effort was made to take into account parameters that are known to increase fibrinogen levels, but further studies are necessary to reproduce the current findings and identify the exact mechanism that is responsible for increased fibrinogen in children with obstructive sleep apnoea-hypopnoea. Long-term elevation of fibrinogen in snoring children, especially among those who are not treated, may potentially be related with increased cardiovascular morbidity.

Appendix: Questionnaire used for clinical evaluation of snoring children and nonsnoring controls

Name (Last, First)
Telephone number

Demographics

1. Date today
   Day/month/year
2. Date of birth
   Day/month/year
3. Gender
   Male/female

Present and past medical history

4. Does your child′s cough with colds persist for more than 10 days?
   Yes/no/do not know
5. Has the paediatrician ever diagnosed your child with wheezing, bronchitis or bronchial asthma?
   Yes/no/do not know
6. Has your child ever used an albuterol inhaler?
   Yes/no/do not know
7. Have you seen your child struggling to breathe while asleep?
   Never
   Only with colds
   Less frequently than once a week
   One to three nights a week
   More frequently than three nights a week
   Do not know
8. Has this symptom (struggling to breathe while asleep) been present at least over the last six months?
   Yes/no/do not know
9. Does your child snore during night sleep?
   Never
   Only with colds
   Less frequently than once a week
   One to three nights a week
   More frequently than three nights a week
   Do not know
10. Has this symptom (snoring during night sleep) been present at least over the last six months?
   Yes/no/do not know
11. Have you seen your child stop breathing during sleep?
   Never
   Only with colds
   Less frequently than once a week
   One to three nights a week
   More frequently than three nights a week
   Do not know
12. Has this symptom (stop breathing during sleep) been present at least over the last six months?
   Yes/no/do not know
13. Does your child have restless sleep?
   Never
   Only with colds
   Less frequently than once a week
   One to three nights a week
   More frequently than three nights a week
   Do not know
14. Has this symptom (restless sleep) been present at least over the last six months?
   Yes/no/do not know
15. Has the teacher informed you that your child has a problem with excessive daytime sleepiness (falling asleep at school at least once a week)?
   Yes/no/do not know
16. Is your child a nighttime mouth-breather?
   Never
   Only with colds
   Less frequently than once a week
   One to three nights a week
   More frequently than three nights a week
   Do not know
17. Has this symptom (nighttime mouth-breathing) been present at least over the last six months?
   Yes/no/do not know
18. Is your child a daytime mouth-breather?
   Never
   Only with colds
   Less frequently than once a week
   One to three days a week
   More frequently than three days a week
   Do not know
19. Has this symptom (daytime mouth-breathing) been present at least over the last six months?
   Yes/no/do not know
20. Has your child had a congested nose for more than 3 months over the past year?
   Yes/no/do not know
21. Has the paediatrician ever diagnosed your child with chronic rhinitis?
   Yes/no/do not know
22. Has the paediatrician ever diagnosed your child with large adenoids?
   Yes/no/do not know
23. Has the paediatrician ever diagnosed your child with large tonsils?
   Yes/no/do not know
24. Has your child had an adenoidectomy?
   Yes/no/do not know
25. Has your child had a tonsillectomy?
   Yes/no/do not know
26. Has your child been diagnosed with diabetes mellitus?

Yes/no/do not know
27. Has your child had any other health problems?
Yes/no
If yes, please specify:

Family history

28. Does somebody in the family snore?
Yes/no/do not know
If yes, please specify:
Paternal grandfather/paternal grandmother/maternal grandfather/maternal grandmother/father/mother/siblings
29. Has anybody in the family had an adenoidectomy?
Yes/no/do not know
If yes, please specify:
Paternal grandfather/paternal grandmother/maternal grandfather/maternal grandmother/father/mother/siblings
30. Has anybody in the family been diagnosed with bronchial asthma?
Yes/no/do not know
If yes, please specify:
Paternal grandfather/paternal grandmother/maternal grandfather/maternal grandmother/father/mother/siblings
31. Has anybody in the family been diagnosed with chronic rhinitis?
Yes/no/do not know
If yes, please specify:
Paternal grandfather/paternal grandmother/maternal grandfather/maternal grandmother/father/mother/siblings
32. Does anybody smoke in the house where the child lives?
Yes/no

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