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Cough hypersensitivity in patients with obstructive sleep apnea hypopnea syndrome

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Abstract

Purpose The purpose of this study was to investigate cough hypersensitivity and its potential mechanisms in patients with obstructive sleep apnea hypopnea syndrome (OSAHS).

Methods Fifteen OSAHS patients, 12 simple snoring patients, and 15 healthy volunteers received cough sensitivity test and induced sputum cytology. Cough thresholds C2 and C5 (the minimum of capsaicin inducing ≥ 2 and ≥ 5 coughs, respectively), total cell count, cell differentials and the levels of bradykinin, histamine, prostaglandin E_2, substance P, calcitonin gene-related peptide, pepsin, and interleukin-2 in the induced sputum detected by enzyme-linked immunosorbent assay were compared. The linear correlation between lgC2 and lgC5 and apnea hypopnea index, cell differentials, and inflammatory mediators in the induced sputum was calculated in OSAHS patients.

Results OSAHS patients presented with a significant lower C2 and C5 ($P < 0.01$), increased lymphocyte but decreased macrophage and neutrophil proportions in the induced sputum ($P < 0.01$), and higher contents of substance P, calcitonin gene-related peptide and interleukin-2 ($P < 0.01$) but similar levels of bradykinin, pepsin, prostaglandin E_2, and histamine ($P > 0.05$) in the supernatant of induced sputum, when compared with simple snoring patients and healthy volunteers. However, theses variable were comparable between simple snoring patients and healthy volunteers ($P > 0.05$). Finally, lgC2 or lgC5 was negatively related to apnea hypopnea index, lymphocyte percentage, and the levels of substance P, calcitonin gene-related peptide or interleukin-2 in the sputum ($P < 0.01$). There was a positive linear correlation between lymphocyte percentage and interleukin-2 level in the induced sputum ($r = 0.63$, $P = 0.00$).

Conclusion OSAHS patients have a predisposition of cough hypersensitivity associated with airway inflammation.

Keywords Obstructive sleep apnea–hypopnea syndrome · Cough sensitivity · Airway inflammation · Induced sputum · Capsaicin

Introduction

Chronic cough is a common symptom in the patients who are referred to respiratory physicians and can be caused by a variety of causes such as cough variant asthma, upper airway cough syndrome, eosinophilic bronchitis, and gastroesophageal reflux [1]. Recently, obstructive sleep apnea hypopnea syndrome (OSAHS) has been recognized as a potential cause of chronic cough [2] and may trigger cough in 33–44% of the patients with OSAHS [3–5]. However, the underlying mechanisms remain unclear. Although the coexisting gastroesophageal reflux, rhinitis, and upper airway inflammation were proposed [2], the inherent association between chronic cough and OSAHS needs to be elucidated. Since the patients with chronic cough share an almost universal characteristics of the cough hypersensitivity (now known as cough hypersensitivity syndrome) [6, 7], we hypothesize that the patients with OSAHS may have an increased cough sensitivity and thus are susceptible to elicit an exaggerated cough response when expose to a variety of tussive stimuli. To verify the hypothesis and explore the underlying mechanisms, the cough sensitivity to capsaicin and airway inflammation were compared among the patients with OSAHS and simple snoring and healthy volunteers in the present study.

Cuiqin Shi and Siwei Liang contributed equally to this work.

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Subjects and methods

Subjects

Fifteen patients with OSAHS (OSAHS group) and 12 patients with simple snoring (snoring group) referred to sleep clinic in our department were consecutively recruited into the study. Besides, 15 healthy volunteers without snoring were enrolled from the staff and medical students in the hospital and designated as healthy group. No one in healthy group had known chronic respiratory, gastrointestinal or allergic disease, and coughed currently. OSAHS and simple snoring were diagnosed according to international classification of sleep disorder (third ed.) (ICSD-3, 2014). OSAHS patients were selected if the apnea-hypopnea index (AHI) was > 10.0, and patients with simple snoring or healthy volunteers were selected if AHI was < 5.0. The other inclusion criteria for OSAHS and simple snoring groups included the following: (1) subjects' age were between 18 and 65 years; (2) the repudiation of the medical histories of chronic rhinitis or sinusitis, chronic cough and gastroesophageal reflux disease, and the absence of fever, cough, expectoration, hemoptysis, dyspnea, nasal symptoms such as nasal obstruction, itching, runny nose or sneezing, or gastrointestinal symptoms including heartburn, regurgitation, belching and abdominal pain, and adventitious lung sounds on physical examination; (3) normal chest radiography; (4) $FEV_1 > 80\%$ of predicted and ratio of FEV_1/FVC > 70%; and (5) tolerable to cough sensitivity test to capsaicin and sputum induction. Exclusion criteria were as follows: (1) the current smokers or ex-smokers for <2 years; (2) respiratory tract infection within the preceding 8 weeks; and (3) women in pregnancy or lactation.

This study was approved by the Ethics Committee of Tongji Hospital [LL(H)-10-06-2], and informed consent was obtained from each subject before study.

Study procedure

After the general information was collected and chest X-ray and lung function testing were taken, a standard full-night polysomnography (PSG) test (Alice5, Respironics Inc., USA) was performed in all the subjects, which recorded multi-parameters including nasal and oral airflow, blood oxygen saturation, electroencephalogram, eye movement, mandibular electromyogram, chest wall and upper abdominal movement, body position, leg movement, and snoring for at least 7 h. When monitoring was finished, the lowest and average oxygen saturation at nighttime was recorded, and AHI was automatically calculated but manually corrected by a sleep physician (Dr. Wang). Before polysomnography test, the patients were respectively evaluated by Epworth Sleepiness Scale (ESS) [8] and gastroesophageal reflux disease questionnaire (GerdQ) [9] to grade their daytime sleepiness and classical reflux-related symptoms as described previously [10].

Cough sensitivity to capsaicin was detected according to the method described by Fujimura [11] with minor modifications [12] adapted to the ERS guidelines [13]. Briefly, the patient inhaled an aerosolized physiological saline, followed by progressively increasing double concentrations (0.49–1000 μmol/L) of the capsaicin solution (Wako Pure Chemical Ind., Japan), delivered through a PARI BOY N085 air-compressed nebulizer (PARI GmbH, German) at an output rate of 0.5 ml/min with a mass median diameter of the particles in 3.7 μm. Each concentration of solutions was inhaled by tidal mouth breathing for 15 s; the number of cough was counted within that time. Cough threshold was defined as the lowest concentration of capsaicin causing ≥ 2 (C2) or ≥ 5 coughs (C5) during 15 s inhalation period and used to reflect the cough sensitivity.

Sputum was induced and processed according to the method described previously [14]. Briefly, subjects were asked to inhale 4% saline through an ultrasonic nebulizer (YS9801, Yisheng Corp, Shanghai, China) for 20–30 min and expectorate sputum into a sterile pot put on ice each 5 min, after blowing their noses and rinsing their mouths. The procedure was repeated until the enough sputum (2–3 ml) was collected. The sputum with the minimum of salivary contamination was mixed with four times the sputum volume of 0.1% dithiothreitol and then incubated at 37 °C for 10 min. After filtered through a 48-μm gauze, the sputum mixture was centrifuged at 3000 r/min for 10 min. The cell-free supernatant was collected and stored at − 80 °C. The cell pellet was resuspended, smeared on glass slides, and the total cells were counted using a standard hemocytometer. The air-dried smears were fixed with 4% paraformaldehyde and stained with HE staining. The cells were differentiated through counting 400 nucleated cells according to the standard morphologic criteria.

The inflammatory mediators and pepsin in the supernatant were measured in duplicate by enzyme-linked immunosorbent assay (ELISA) according to manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). The lower limits of detection for histamine, interleukin (IL)-2, prostaglandin (PG) E_2, pepsin, bradykinin, substance P (SP), and calcitonin gene related peptide (CGRP) were 0.78 ng/ml, 15 pg/ml, 7.8 pg/ml, 19.5 pg/ml, 39 pg/ml, 19.5 ng/ml, and 7.8 pg/ml. The intra-assay and inter-assay variabilities of the measurement were 5 and 10%, respectively, across the range of measured concentrations. These inflammatory mediators were selected because IL-2 is a cytokine that regulates the proliferation and differentiation of lymphocytes [15] while histamine, PGE2, bradykinin, SP, and CGRP are tussive mediators and related to cough sensitivity [16]. Moreover, pepsin in the sputum is an emerging biomarker of pulmonary microaspiration as an indirect marker of proximal gastroesophageal reflux [17].

Statistical analysis

Data with normal distribution are expressed as mean ± standard deviation and those with skew distribution as median (interquartile range). Cough threshold C2 and C5 were log transformed to normalize the data and expressed as geometric mean ±standard deviation. Comparisons among three groups were conducted using one-way analysis of variance (ANOVA) followed by Newman–Keuls test (for normal distribution data) or Kruskal–Wallis test followed by Mann–Whitney *U* test (for skew distribution data) respectively. Correlation analyses were performed using Pearson correlation coefficients. SPSS 17.0 Software (SPSS Inc., Chicago, IL, USA) was used for statistical calculation. A *P* value of < 0.05 was accepted as significant.

Results

General characteristics and PSG findings

The general characteristics of subjects in each group are shown in Table 1. There were no significant differences in the age, gender distribution, GerdQ score, and lung function parameters among the three groups. AHI, BMI, ESS score, and neck circumference were significantly higher while the lowest and mean oxygen saturation were markedly lower in OSAHS group than in snoring and healthy groups. However, the differences of these variables were not significant between snoring group and healthy group.

Cough threshold to capsaicin

Cough threshold, expressed either as C2 and C5 or as IgC2 and IgC5, was significantly lower in OSAHS group than in snoring and healthy groups while that was comparable between snoring group and healthy group (Fig. 1).

Cell count and differentials in the induced sputum

The total cell count and proportion of eosinophils were comparable among the three groups. Moreover, the proportion of lymphocytes was significantly higher while those of macrophages and neutrophils were markedly lower in OSAHS group than in both snoring and healthy groups. However, these were not statistically different between snoring group and healthy group (Table 2).

Inflammatory mediators in the supernatant of induced sputum

The contents of CGRP, SP, and IL-2 were markedly higher in OSAHS group than in snoring and healthy groups while the levels of bradykinin, pepsin, PGE2, and histamine were not statistically different among the three groups. There were no significant differences in the inflammatory mediators between snoring group and healthy group (Table 3).

Relationships between cough threshold to capsaicin and the other parameters

In the patients with OSAHS, there were significantly negative linear correlations between lgC2 or lgC5 and AHI,

Table 1 General characteristics of subjects among the three groups

	OSAHS group	Snoring group	Healthy group
Number (male)	15 (12)	12 (10)	15 (11)
Age	44.46 ± 12.56	41.25 ± 11.33	41.33 ± 9.44
Body mass index (kg/m^2)	27.00 ± 2.21*	25.09 ± 1.40	24.65 ± 1.86
Neck circumference (cm)	40.53 ± 1.84*	39.25 ± 1.35	38.73 ± 1.33
GerdQ score	6 (0)	6 (0)	6 (0)
ESS score	9 (4.5)*	3.5 (2.5)	2 (3.0)
FVC/predicted value (%)	84.90 ± 6.63	84.25 ± 8.24	87.85 ± 9.83
FEV1/ predicted value (%)	83.89 ± 8.28	83.80 ± 7.47	86.80 ± 10.01
FEV1/FVC%	83.03 ± 7.11	84.08 ± 8.40	83.71 ± 9.74
AHI (times/h)	33.30 ± 21.68*	3.13 ± 0.77	2.07 ± 0.83
Lowest oxygen saturation (%)	68.87 ± 8.12*	83.41 ± 2.94	89.07 ± 1.39
Mean oxygen saturation (%)	85.58 ± 10.42*	90.74 ± 12.87	93.25 ± 9.27

OSAHS obstructive sleep apnea hypopnea syndrome, *GerdQ* gastroesophageal reflux disease questionnaire, *ESS* Epworth Sleepiness Scale, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 s, *AHI* apnea–hypopnea index

*$P < 0.05$ vs both snoring and healthy groups

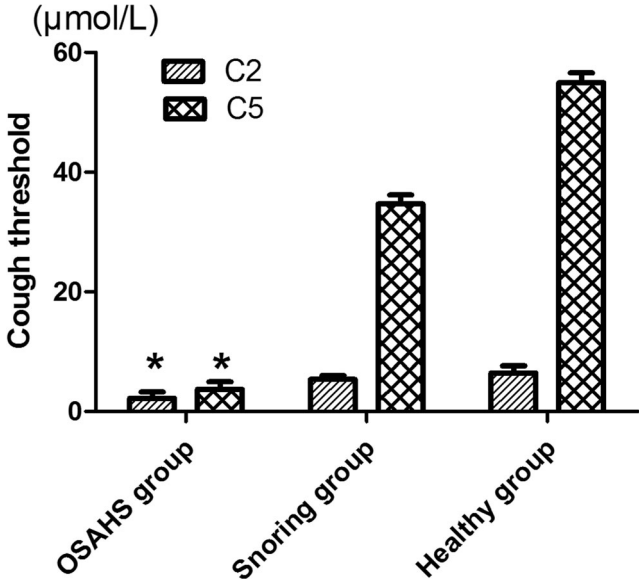

Fig. 1 Comparison of cough threshold to capsaicin among OSAHS group, snoring group, and the healthy group. (Data are presented as geometric mean ± standard deviation. *$P < 0.05$ vs both snoring and healthy groups; OSAHS, obstructive sleep apnea hypopnea syndrome; C2, the minimum concentration of inhaled capsaicin eliciting two cough; C5, the minimum concentration of inhaled capsaicin eliciting five cough)

lymphocyte percentage, and IL-2, SP, or CGRP in the induced sputum (Table 4). Furthermore, there was a positive linear correlation between lymphocyte percentage and IL-2 level in the induced sputum ($r = 0.63$, $P = 0.00$).

Discussion

The study has shown that cough sensitivity to capsaicin increased in OSAHS patients, as indicated by a decrease in cough threshold C2 and C5. In parallel, the increase of lymphocyte percentage in the induced sputum and the elevations of IL-2, SP, and CGRP in the supernatant of induced sputum were observed. Moreover, lgC2 and lgC5 in OSAHS patients are negatively related to AHI, lymphocyte percentage, and the levels of IL-2, SP, or CGRP in the induced sputum. These findings suggest that OSAHS patients have a predisposition of cough hypersensitivity and are susceptible to cough, and airway inflammation, especially neurogenic inflammation in the airway, may play an important role in the pathogenesis of cough hypersensitivity in these patients.

Table 2 Total cell count and cell differentials in the induced sputum

	OSAHS group	Snoring group	Healthy group
Total cells (× 10^6/ml)	3.77 ± 1.49	3.40 ± 1.18	3.03 ± 0.81
Lymphocytes (%)	39.80 ± 14.47*	14.92 ± 7.56	12.00 ± 7.44
Neutrophils (%)	4.25 ± 3.72*	13.88 ± 6.98	12.80 ± 6.81
Macrophages (%)	56.20 ± 13.60*	71.13 ± 5.51	75.19 ± 7.40
Eosinophils (%)	0(0.13)	0(0)	0(0)

OSAHS obstructive sleep apnea hypopnea syndrome

*$P < 0.05$ vs both snoring and healthy groups

Our results are opposite to a previous study that reported an impaired and decreased cough reflex sensitivity in female obese patients with OSAHS [18]. We have no definite explanation why this happened. However, the patients recruited may mean something for the different results between the two studies. In our study, the selected patients with OSAHS have a relatively normal BMI even though it is higher than those in the patients from the snoring and healthy groups. In contrast, the previous study selected a cohort of the female patients with mean BMI of 49.9 and mean AHI of 20.5, who are obviously more obese but have less severe OSAHS than the patients in the present study. It seems that the obesity may be a major risk factor for the impaired cough reflex sensitivity in the previous study, especially considering the patients recruited are all female [18]. Since women have a more sensitive cough reflex than men [11], the obesity may have a more negative impact on cough reflex sensitivity in women. We believe our results truly reflected the reality of cough reflex hypersensitivity in the patients with OSAHS. It is supported by a case report in which Faruqi et al. have shown a patient with chronic cough due to OSAHS who presented an initial heightened cough sensitivity to inhaled citric acid but subsequent recover to a normal level when cough resolved after treatment with CPAP for 1 year [19].

There is no understanding of the mechanisms underlying cough hypersensitivity in the patients with OSAHS. Twenty-four-hour esophageal pH monitoring has revealed the abnormal acid reflux events in OSAHS patients [20]. The study with a large cohort of patients has demonstrated the presence of nocturnal reflux symptoms in 10.2% of the patients with OSAHS, two times as much as that in healthy population [21]. In addition, the severity of reflux esophagitis was reported to be positively related to AHI in these patients [22]. Gastroesophageal reflux due to OSAHS may be caused by airway obstruction during sleep, which results in the increased intrathoracic and intraesophageal negative pressure, followed by the backflow of stomach contents into the esophagus. The lower esophageal sphincter relaxations during sleep also precipitate gastroesophageal reflux [23]. It is well known that gastroesophageal reflux increases cough sensitivity through activating the cough receptors in the airway mediated by microaspiration or esophageal-bronchial reflex [14]. However, in the present study, the GerdQ score and the level of pepsin in the sputum, reflecting classical reflux-associated symptoms and microaspiration, respectively, in OSAHS patients were comparable with those in snoring and healthy groups. Therefore, the excessive reflux cannot explain cough hypersensitivity in OSAHS patients.

Table 3 Inflammatory mediators and pepsin in the supernatant of induced sputum

	OSAHS group	Snoring group	Healthy group
Bradykinin (pg/ml)	171.22 ± 50.84	167.04 ± 45.24	152.56 ± 42.31
CGRP(pg/ml)	18.66 ± 2.22*,	15.31 ± 2.64	14.42 ± 3.30
Pepsin (ng/ml)	2.16 ± 0.82	1.87 ± 0.87	2.10 ± 0.77
PGE_2 (pg/ml)	20.69 ± 4.15	19.25 ± 6.22	17.89 ± 5.82
SP (pg/ml)	40.77 ± 6.38*,	36.12 ± 8.76	33.16 ± 7.21
Histamine (ng/ml)	2.26 ± 0.14	2.03 ± 0.30	2.21 ± 0.33
IL-2 (pg/ml)	59.98 ± 8.57*,	42.20 ± 9.12	36.58 ± 6.20

OSAHS obstructive sleep apnea hypopnea syndrome, *CGRP* calcitonin gene related peptide, *PG* prostaglandin, *SP* substance P, *IL* interleukin

*$P < 0.05$ vs both snoring and healthy groups

Postnasal drip is possibly involved in cough hypersensitivity in the patients with OSAHS. Rhinitis and sinusitis are the independent risk factors of OSAHS. Twenty-six percent of the patients with allergic rhinitis and 83% of the patients with non-allergic rhinitis had concomitant OSAHS [24]. On the contrary, 11% of the patients with OSAHS suffered from allergic rhinitis [25]. In case of rhinitis and sinusitis, the redundant secretions from the nose or paranasal sinuses may drip into the pharynx or lower airway and stimulate the local cough sensors, inducing cough or cough hypersensitivity [12]. However, our cohort of the patients with OSAHS had no history of rhinitis or sinusitis and no upper airway symptoms as indicated by the inclusion criteria of the study, which has minimized the possibility of postnasal drip. Therefore, we do not think that postnasal drip is a significant mechanism underlying cough hypersensitivity in the patients with OSAHS.

Both upper and lower airway inflammations are common pathologies of OSAHS. The recurrent opening and closing of the upper airway in OSAHS patients may cause mechanical damage to the mucosal epithelium, induce the local expression of chemokines and cytokines, and then initiate upper airway inflammation. Chronic intermittent hypoxia in OSAHS may lead to oxidative stress response similar to ischemia/reperfusion injury [26]. Moreover, the excitation of sympathetic nervous system, sleep fragmentation, and obesity is also involved in the systemic inflammation of OSAHS [27]. Thus, airway inflammation in OSAHS can be considered as a local manifestation of systemic inflammation [27]. The neutrophilia was observed in the nasal lavage fluid as well as in the induced sputum from the patients with OSAHS [28, 29]. In addition, the increased levels of inflammation markers such as nitric oxide, hydrogen peroxide, and leukotriene B4 have also been demonstrated in the exhaled condensates from the patients with OSAHS [30, 31]. Contrary to the previous studies [28, 29], we have observed an airway inflammation characterized by lymphocyte infiltration but not neutrophilia as shown by cytology in the induced sputum. There is evidence that the upper airway is mainly infiltrated by the activated CD4 and CD8+ lymphocytes in OSAHS patients, with CD4+ lymphocytes predominantly in the muscular layer and CD8+ lymphocytes predominantly in the mucosa [32]. Considering the chronic nature of OSAHS, the airway inflammation characterized by lymphocyte infiltration may represent the reality of this disease. The positive relationship between the levels of IL-2 and lymphocyte percentage in the induced sputum suggests that IL-2 plays an important role in the recruitment and infiltration of lymphocytes into the airway. However, the similar cell differentials in the induced sputum from snoring and healthy groups have revealed that snoring vibration itself is not associated with the airway inflammation in the patients with OSAHS.

Table 4 Correlation of lgC_2 and lgC_5 with AHI, proportion of lymphocytes in induced sputum, SP, CGRP and IL-2

	AHI	L(%)	IL-2	CGRP	SP
lgC_2	− 0.62*	− 0.52*	− 0.61*	− 0.40*	− 0.39*
lgC_5	− 0.77*	− 0.64*	− 0.76*	− 0.51*	− 0.56*

C2 the minimum concentration of inhaled capsaicin eliciting two cough, *C5* the minimum concentration of inhaled capsaicin eliciting five cough, *AHI* apnea–hypopnea index, *L* lymphocytes, *IL* interleukin, *CGRP* calcitonin gene related peptide, *SP* substance P

*$P < 0.05$

Cough sensitivity is closely related to airway inflammation. The vasodilation, plasma exudation, tissue edema, and infiltration of inflammatory cells are the typical pathological features of airway inflammation. The shedding of epithelial cells caused by the inflammatory injury directly exposes cough receptors to the airway lumen and makes them more susceptible to the various tussive stimuli. C afferent fibers, the cough receptors that are sensitive to chemical irritation of the airways, contain the transient receptor potential vanilloid 1 (TRPV1) on their ending surface, which can be activated/sensitized by heat, protons, and a range of inflammatory mediators such as bradykinin and tachykinin released during inflammatory processes in the airway [33]. TRPV1 activation induces Ca^{2+} influx into the nerve endings, inspiring action potential and nerve impulse [34], leading to the cough hypersensitivity. Several lines of evidence have confirmed that the major function of tachykinins such as SP and CGRP in the human airway is to modulate the cough reflex

[33]. Our results have shown that lgC2 and lgC5 were negatively related to the levels of SP and CGRP in the induced sputum, indicating that airway inflammation, especially airway neurogenic inflammation, precipitates the pathogenesis of cough hypersensitivity in the patients with OSAHS.

The recurrent upper airway obstruction itself may also be a risk factor for cough hypersensitivity. In the patients with OSAHS, the upper airway collapse brings the anterior and posterior walls of the airway together and the tongue dropping to the back of the mouth pressures hypopharynx, directly stimulating the local cough receptors and resulting in cough hypersensitivity. This was supported by our findings that lgC2 and lgC5 were negatively related to AHI in the patients with OSAHS. Since snoring alone does not mean the repetitive airway obstruction, the absence of cough hypersensitivity can be explained in patients with simple snoring.

In summary, OSAHS patients have cough hypersensitivity, which may reflect the elevated susceptibility to cough. Airway inflammation, especially the airway neurogenic inflammation and repeated airway obstruction, plays an important role in the pathogenesis of cough hypersensitivity in OSAHS patients. The concomitant gastroesophageal reflux and rhinitis are not the inherent underlying mechanisms even though they may contribute to the occurrence of cough in the patients with OSAHS.

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Compliance with ethical standards

This study was approved by the Ethics Committee of Tongji Hospital [LL(H)-10-06-2], and informed consent was obtained from each subject before study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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