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EXERCISE

Bronchial provocation testing does not detect exercise-induced laryngeal obstruction

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ABSTRACT

Introduction: Exercise-induced laryngeal obstruction (EILO) is a key differential diagnosis for asthma in the presence of exertional respiratory symptoms. Continuous laryngoscopy during exercise (CLE), the current gold standard diagnostic test for EILO, has practical limitations. We aimed to establish if inspiratory flow data obtained during standard bronchoprovocation testing, to establish the presence of extra-thoracic hyper-responsiveness, may prove diagnostic for EILO and thus preclude requirement for CLE testing. **Methods:** We consecutively evaluated 37 adult subjects with exertional dyspnea and possible asthma referred over 6 months. All subjects received comprehensive assessment including a detailed clinical evaluation; pulmonary function testing, indirect and direct bronchial provocation testing, and CLE testing. **Results:** Out of 37 subjects, moderate or severe EILO was diagnosed in 8 subjects (22%, all female) while 5 (14%) had both asthma and EILO. There was no correlation between degree of EILO during CLE and mean decrease in forced inspiratory flow (%FIF₅₀) obtained during neither the Methacholine ($r = -0.15$; $p = 0.38$) nor Mannitol ($r = 0.04$; $p = 0.84$) provocation tests. **Conclusion:** Inspiratory flow parameters obtained during bronchoprovocation tests did not reliably detect EILO. It remains that CLE is an important and key investigation modality in establishing a secure diagnosis of EILO.

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Introduction

Dyspnea and wheeze precipitated by physical exertion are common symptoms in individuals with airways disease [1]. These symptoms however, may also arise from a transient obstruction that occurs at the level of the larynx; a phenomenon termed exercise-induced laryngeal obstruction (EILO) [2,3]. The latter typically arises from adduction of the supraglottic or arytenoid mucosa or vocal cords acting to reduce the glottic aperture and create air-flow turbulence. Exercise is known to be one of many triggers of transient glottic obstruction, also termed Vocal Cord Dysfunction (VCD) [4]. In contrast, supraglottic collapse has of yet been described as phenomenon occurring on exertion and although the glottic and supraglottic conditions can co-exist, no clear relationship between them has been established. In the context of EILO, both components should be evaluated [5].

It can be difficult to differentiate EILO from exercise-induced bronchoconstriction (EIB) by clinical assessment or a questionnaire based approach [6]. Thus, objective testing is strongly recommended to ensure secure diagnosis [7]. Considering a prevalence in unselected

populations of 6%–8% [8,9] and as high as 35% in our previous study of a selected population of athletes [6], EILO is an important differential diagnosis to consider in the asthma clinic; not only in athletes but also in any subject presenting with otherwise unexplained exertional dyspnea [1].

The continuous laryngoscopy during exercise (CLE) test [5] is currently advocated as the gold-standard means for diagnosing EILO. The CLE test is generally well tolerated [10] and reproducible but has several limitations. Specifically, it is invasive and requires staff with specialized expertise and training, laryngoscopy equipment with provision for sterilization and a specialist exercise laboratory. There are currently few centres worldwide with facilities and the capacity to perform CLE testing and thus more accessible and pragmatic methods to diagnose EILO are desirable.

Recent work suggests that EILO cannot be accurately detected from baseline or post-exercise lung function measurement [11]. However, previous investigators have reported the validity of changes in inspiratory flow loop parameters (e.g., forced inspiratory flow at 50% of inspired volume, FIF₅₀) during

bronchoprovocation testing, to detect extra-thoracic or laryngeal hyper-responsiveness [12,13]. Indeed, changes in inspiratory flow parameters following bronchoprovocation have been used to diagnose and assess therapeutic response to laryngeal closure occurring at the glottic-level [14]. However, laryngeal hyperreactivity is also seen in healthy individuals as well as individuals with asthma, but without known EILO or VCD [15].

The role of this type of diagnostic approach has not, however, been investigated in a condition typified by laryngeal obstruction occurring at the supra-glottic level, i.e., as is classically seen in EILO. We hypothesized that the mechanisms suspected to cause glottic closure on exertion (i.e., laryngeal hypersensitivity mediating an altered reflex response [16]) would also detect supraglottic laryngeal obstruction, thereby explaining the discordant findings when using bronchoprovocation testing to investigate laryngeal closure.

The aim of this study was to undertake a prospective study to determine if inspiratory flow parameters, obtained during bronchoprovocation testing could reliably predict the presence of EILO in a cohort of patients with suspected asthma, thereby providing a simple diagnostic tool for asthma clinics by the means of a widely employed and accessible methodology.

Materials and methods

Study design

We prospectively included subjects (aged 15 to 45 years) referred for investigation of asthma or suspected asthma to the outpatient clinic at Bispebjerg University Hospital in Copenhagen, Denmark over a period of 6 months (April to October 2012). We included all subjects complaining of exercise related symptoms regardless of their level of physical activity. Subjects referred with suspicion of EILO or VCD were excluded, as were subjects with a significant smoking history (>10 pack-years).

All subjects received a 4-day comprehensive diagnostic work-up, consisting of a detailed clinical assessment, skin prick testing, pulmonary function with direct and indirect bronchoprovocation challenge, and a CLE test.

Asthma was diagnosed on the basis of the presence of consistent symptoms *and* a positive bronchoprovocation test (BPT) to either Methacholine or Mannitol in those with a baseline FEV₁ of >70% of expected. In those with no BPT (i.e., if baseline FEV₁ of ≤70%), asthma was diagnosed on the basis of a specialist evaluation taking into account symptoms, bronchodilator reversibility, peak flow variation (>20%), and asthma history.

The study was approved by the Danish Ethics Committee (H-3-2011-138) and all subjects provided written informed consent.

Study procedures

Clinical review and baseline measures

All subjects provided detailed information on respiratory symptoms during exercise, and their current level of physical exercise. Furthermore, subjects completed the Asthma Control Questionnaire (ACQ) [17], Asthma Quality-Of-Life Questionnaire (Mini-AQLQ) [17] and the Nijmegen questionnaire [18].

Age, sex, height and weight were recorded and Body Mass Index (BMI, kg/m²) was calculated. Atopic status was determined by skin prick test to a panel of common aeroallergens (Soluprick, ALK, Horsholm) [19].

Pulmonary function

Pulmonary function and bronchodilator reversibility testing

Lung function and bronchodilator reversibility testing was measured using maximum expiratory flow volume in accordance with guideline recommendations [20].

Bronchoprovocation tests

Subjects withheld any asthma medications in line with recommendations [21] prior to BPT. Standard BPTs were employed but adapted in line with Bucca et al. [12,22], i.e., subjects performed a full forced expiration immediately followed by a full forced inspiration. This manoeuvre was repeated twice at each step with the best FEV₁ taken as the reference result. The FIF₅₀ was calculated from the FVC of this reference result. The change in FIF₅₀ was calculated as the percentage change between the baseline FIF₅₀ and the FIF₅₀ at the last measurement performed in the test. Extrathoracic airway hyper-responsiveness (EAHR) was defined as a decrease in FIF₅₀ of 25% or more from baseline to last measurement [12,22]. Bronchoprovocation was only performed in those with an FEV₁ > 70% of predicted.

Methacholine challenge testing

Using a breath-actuated dosimeter Aerosol Provocation System (APS) (Jaeger GmbH, Germany), the subjects inhaled nebulized isotonic saline for baseline measurement followed by 1–5 incremental doses of nebulised Methacholine (0.37 µmol, 0.55 µmol, 0.92 µmol, 1.84 µmol, and 3.68 µmol). Two minutes after each inhaled dose, the subject performed a spirometry. The test was stopped when reaching a decrease in FEV₁ of 20% or more, or after reaching a cumulated maximum of 7.37

μmol inhaled Methacholine. The test was considered positive when reaching a decrease in FEV_1 of at least 20% at an administered cumulated dose of $\leq 7.37 \mu\text{mol}$ Methacholine.

Mannitol bronchial provocation

Performed as described by Anderson et al. [23]. After a baseline dose with an empty capsule, the subject inhaled 1–8 doses of Mannitol dry powder (5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 3×160 mg) until either reaching a decrease in FEV_1 of at least 15% of baseline or reaching a cumulated Mannitol dose of 635 mg. A positive challenge response was defined as a decrease in FEV_1 of at least 15% after inhalation of 635 mg of mannitol or less.

Fractional exhaled nitric oxide (FeNO)

FeNO was analysed using Aerocrine (Solna, Sweden) following the recommendations of the European Respiratory Society and the American Thoracic Society [24]. A positive response was defined as >25 ppb [24].

Continuous laryngoscopy during exercise (CLE)

CLE testing was performed using the protocol previously described by Heimdal et al. [9], excluding ergo-spirometry. In brief, the larynx was visualised during exercise using a flexible video laryngoscope and Visera video recording equipment (Olympus, Tokyo, Japan). Topical Xylometazolinhydrochloride and Lidocaine gel as well as spray was used to prepare the nares prior to inserting the scope [5].

CLE scoring

The video recordings were graded by an asthma specialist with experience in diagnosing EILO (V. B.) using the Norwegian standardized 0–3 scoring system [2] and by the examiner (E. W.), who has 3 years' experience in grading EILO. A diagnosis of EILO was based on a Norwegian grade score of ≥ 2 (i.e., at least moderate) for either glottic or supraglottic obstruction (Maat C and D scores, respectively) [2]. The more conservative (i.e., lowest) score of the two EILO scores (V. B. or E. W.) was used for diagnosis.

Statistical analysis

All data analysis was performed with the statistical software SPSS version 22.0 (Chicago, Illinois). Mean and standard deviations ($\pm\text{SD}$) are reported for normally distributed data, and median and interquartile ranges (IQR) otherwise. For continuous unpaired data, t -test or

Mann–Whitney U-test was used as appropriate. Fischer's Exact test was used to compare categorical, unpaired data. Spearman's ρ was used for testing correlation between continuous and ordinal variables. A p -value of < 0.05 was considered significant. All continuous variables with $p \leq 0.20$ in univariate testing were included in a multiple regression. Using stepwise backward elimination, variables that were not likely to be independent predictors for EILO sum score (i.e., having $p > 0.10$) were excluded from the model.

Results

Subject characteristics

In total, 78 subjects were recruited; however, four were unable to run on a treadmill due to illness or injury and 37 did not wish to undergo CLE. Thus, the remaining 37 subjects completed the full assessment, including CLE testing. Subjects who did not participate in the CLE study were more likely to test positive in the Methacholine challenge test (69% versus 35%, respectively; $p = 0.02$) or have bronchodilator reversibility (27% versus 3%, respectively; $p = 0.03$) compared with the subjects who did participate; whereas there was no difference in other indices including baseline spirometric parameters.

Laryngoscopy findings

Out of the 37 subjects undergoing CLE testing, 8 (22%, all female) had evidence of EILO. Seven of these subjects (88%) had supra-glottic EILO, whereas one had glottic EILO. Subjects with EILO had a lower BMI compared to subjects without EILO (20.2 versus 23.6; $p = 0.04$), and a slightly higher FEV_1/FVC ratio (0.89 versus 0.83; $p = 0.01$). There was however no difference in neither age, level of physical activity, pulmonary function test values, including bronchial provocation test results (Table 1) between subjects with and without EILO.

Clinical questionnaire results

Subjects with EILO reported less frequent use of rescue medication ($p = 0.04$) than subjects without EILO and did not report more symptoms or limitations on daily activities (Table 2). No pattern of symptoms reliably discerned individuals with or without EILO (Table 2). Asthma was diagnosed in a similar proportion of subjects with and without EILO (63% versus 62%, respectively, $p = 1.00$).

Bronchial provocation tests

In total, 23 of the 37 included subjects (62%) were diagnosed with asthma. This was on the basis of consistent

Table 1. Subject characteristics.

	Non-EILO	EILO	<i>p</i>
N (Female/male)	29 (12/17)	8 (8/0)	<0.01*
Age in years ^a	27.0 (22)	22.5 (12)	0.22
Body Mass Index ^a	23.6 (5.1)	20.2 (3.7)	0.04*
Physical activity minutes/day ^a	60 (98)	80 (159)	0.39
FEV ₁ (L) ^a	3.96 (1.4)	3.46 (0.9)	0.39
FEV ₁ percent of predicted ^a	102.08 (20)	97.18 (30)	0.81
FVC (L) ^a	4.530 (1.54)	3.815 (1.23)	0.08
FVC percent of predicted ^a	124.3 (26)	109.4 (36)	0.12
FEV ₁ /FVC ratio ^a	0.832 (0.11)	0.892 (0.11)	0.01 ^a
FeNO > 25 ppb, positive/tested	12/28 (43%)	2/8 (25%)	0.48
Bronchial hyperresponsiveness			
Mannitol positive/tested	11/27 (41%)	4/8 (50%)	0.70
Methacholine positive/tested	10/29 (34%)	4/7 (57%)	0.39
Bronchodilator reversibility positive/tested	1/29 (3%)	1/8 (13%)	0.39
Asthma positive/tested	18/29 (62%)	5/8 (63%)	1.00
Extrathoracic airway hyperresponsiveness			
Mannitol positive/tested	9/24 (38%) ^b	4/8 (50%)	0.68
Methacholine positive/tested	8/29 (28%)	3/7 (43%)	0.65
Positive to both Mannitol and Methacholine	<i>n</i> = 1	<i>n</i> = 0	

Note. **p* < 0.05. ^aReported numbers are median (interquartile range, IQR).

^bIn 3 subjects, forced inspiratory flow at 50% of inspired volume (FIF₅₀) was not recorded due to technical difficulties. EILO: Exercise-induced laryngeal obstruction. FEV₁: forced expiratory volume at 1 second. FVC: forced vital capacity. FeNO: fractional exhaled nitric oxide.

Table 2. Clinical questionnaire results.

	Non-EILO	EILO	<i>P</i>
Clinical interview			
Wheezing at rest (yes/no)	13/16	1/7	0.22
Wheezing during exercise (yes/no)	10/9	3/5	0.12
Respiratory symptoms during inspiration (yes/no)	24/5	6/2	0.63
Respiratory symptoms during expiration (yes/no)	10/19	0/8	0.58
<i>During the last 4 weeks, did you:</i>			
Experience symptoms during daytime at rest? (yes/no)	6/23	0/8	0.31
Experience symptoms during daytime during exercise? (yes/no)	7/22	1/7	0.66
Use rescue medication? (yes/no)	20/8 ^b	2/6	0.04*
Feel limited in your daily activities? (yes/no)	18/11	5/3	1.00
Have nightly symptoms or wake up because of asthma? (yes/no)	6/23	3/5	0.37
Questionnaires			
ACQ score ^c	1.30 (1.40)	1.20 (1.35)	0.77
Mini-AQLQ score ^c	5.93 (1.32)	5.60 (1.22)	0.47
Nijmegen questionnaire^b			
score > = 23, positive/answered	7/29	4/7	0.21
score ^c	13 (16)	27 ^d	0.08

Note. **p* < 0.05. ^aOne subject did not answer the question. ^bSeven subjects did not complete the Nijmegen questionnaire. ^cReported numbers are median (interquartile range, IQR). ^dNot enough observations to calculate IQR. EILO: exercise-induced laryngeal obstruction; ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality-of-Life Questionnaire.

symptoms as well as a positive Methacholine test in 14 subjects and Mannitol test in 15 subjects. Mannitol and Methacholine tests were both positive in 11 subjects. Five subjects were diagnosed with asthma based on a clinical decision allied with peak flow variation while one subject had evidence of bronchodilator reversibility (Table 1).

Evidence of EAHR to either Mannitol or Methacholine tests was found in 21 out of 31 tested subjects (68%); however, there was no relationship between the presence of EAHR and EILO or a difference in the proportion of subjects with and without EILO and EAHR (Table 1).

The percent decrease in FIF₅₀ in Mannitol and Methacholine BPTs is depicted in Figure 1. There was no correlation between the percent decrease in FIF₅₀ and EILO sum score, neither for Methacholine BPT (*r* = −0.15; *p* = 0.38) nor Mannitol BPT (*r* = 0.04; *p* = 0.84). Likewise, no correlation was found for the absolute decrease in FIF₅₀, neither for Methacholine BPT (*r* = −0.21; *p* = 0.2) nor Mannitol BPT (*r* = −0.17; *p* = 0.37).

However, the FIF₅₀ in litres per second after the last dose of inhaled Mannitol was inversely related to the EILO sum score (*r* = −0.46; *p* < 0.01). In the final model, only sex and height remained statistically significant, *F*(2,34) = 8.697, *p* = 0.003, and accounted for 30% of the variance of EILO sum score (*R*² = 0.399; adjusted *R*² = 0.332), whereas use of rescue medication during the last 4 weeks was kept in the model to avoid overfitting (*p* = 0.06) and FIF₅₀ did not remain in the model. Female sex (*b* = 1.200 [95% CI: 0.524 to 1.876]; *p* < 0.001) and short stature (*b* = 0.051 [95% CI: 0.003 to 0.099]; *p* = 0.04) were significant predictors of EILO sum score (Table 3).

Discussion

In young individuals referred with unexplained exertional respiratory symptoms, a change in inspiratory flow parameters, to indicate extra-thoracic hyperresponsiveness during bronchoprovocation testing, proved to be of no diagnostic value when screening for EILO. Specifically, neither a 25% decrease in FIF₅₀, nor the relative decrease in FIF₅₀ or any of the FIF₅₀ measures obtained during bronchoprovocation testing provided diagnostic precision when compared with the gold standard means for diagnosing EILO, i.e., CLE testing. Moreover, although a relationship between FIF₅₀ and EILO severity score was seen for Mannitol provocation, this proved insignificant when sex, age, and height were controlled.

Our findings are in keeping with the recent work published by Christensen et al. [25], demonstrating that spirometric measurements, with detailed assessment of inspiratory flow, performed before and immediately following exercise likewise provided no diagnostic value for EILO. Similarly, Watson et al. [26] found that spirometry was not predictive of vocal cord dysfunction (VCD).

EILO most commonly occurs because of closure at the level of the supra-glottic structures (i.e. above the vocal cords). This differs from VCD or

Table 3. Summary of variables predicting EILO.

	<i>b</i> (95% CI)	<i>SE</i> (<i>b</i>)	β	<i>P</i>
(Constant)	−9.786(−18.987; −0.584)	4.517		$p = 0.04^a$
Sex	1.200(0.524; 0.1876)	0.332	0.686	$p < 0.07^a$
Height in cm	0.051(0.003; 0.099)	0.024	0.400	$p = 0.04^a$
Use of rescue medication during the last 4 weeks	−0.489(−1.005; 0.027)	0.253	0.400	$p = 0.06$

Note. The initial model included sex, height, weight, age, FEV₁/FVC ratio, use of rescue medication during the last 4 weeks, Mannitol and Methacholine FIF₅₀ change in percent from baseline to last measurement, and absolute drop in FIF₅₀ from first to last dose Mannitol. Using stepwise backward elimination of predictors having $p > 0.10$, only the predictors shown above remained in the final model. * $p < 0.05$. CI: confidence intervals; SE(*b*): standard error of the unstandardized coefficients.

laryngeal dysfunction and the VCD overlap syndromes [14,22,27]. The impact of supra-glottic adduction on inspiratory airflow parameters, whether at rest or during exercise, is yet to be fully characterised. Christensen et al. [11] recently evaluated the feasibility of laryngoscopy during eucapnic voluntary hyperpnoea (EVH); however, due to difficulties with the test protocol it remains to be seen whether assessment of laryngeal movement, during a hyperpnoeic challenge provides useful information. It also remains to be established whether other means of establishing changes in inspiratory flow may prove useful in detecting EILO [28,29].

Clinical features of EILO

In keeping with our prior findings [5], we found few clinical features that reliably discern EILO from EIB. Typical features that may be expected to provide discriminatory value (i.e. ‘difficulty breathing in’) again failed to be useful for screening. This may be explained by the fact that, in

the small number of individuals with EILO, 63% also had EIB.

In addition, the sensation of dyspnea is often attributed to a difficulty “breathing in” [30]. This being said, the group with EILO were less likely to utilise reliever inhaler; perhaps because they were less likely to find it clinically beneficial. The presence of EILO might affect how subjects report asthma symptoms, which could lead to incorrect diagnosis and the inappropriate use of medication. This confirms the importance of objective testing in making an accurate diagnosis of asthma [6]; however, further work is needed to understand the consequences of EILO with regards to the use of asthma medication.

In the current study, we found that EILO was exclusively present in females. This is consistent with prior work [3,5,7] and the female preponderance of EILO is yet to be explained.

Despite a comprehensive assessment in the current cohort, one third of the group neither had EILO nor asthma. This is broadly in line with our prior work [5] and highlights the likely fact that although EIB and EILO are key differential diagnoses for unexplained dyspnea in young individuals, it is likely that other conditions play a role. These are likely to include disorders characterised by dysfunctional breathing, i.e., a breathing pattern disorder or hyperventilation [31,32]. In respect to the latter however we found low Nijmegen scores in both groups with few subjects having a ‘positive’ score (i.e., ≥ 23), however further work is needed to explore exercise ventilatory responses in this group of individuals.

Methodological considerations

Only 37 out of 78 referred subjects were CLE tested. This reluctance to participate in exercise laryngoscopy further

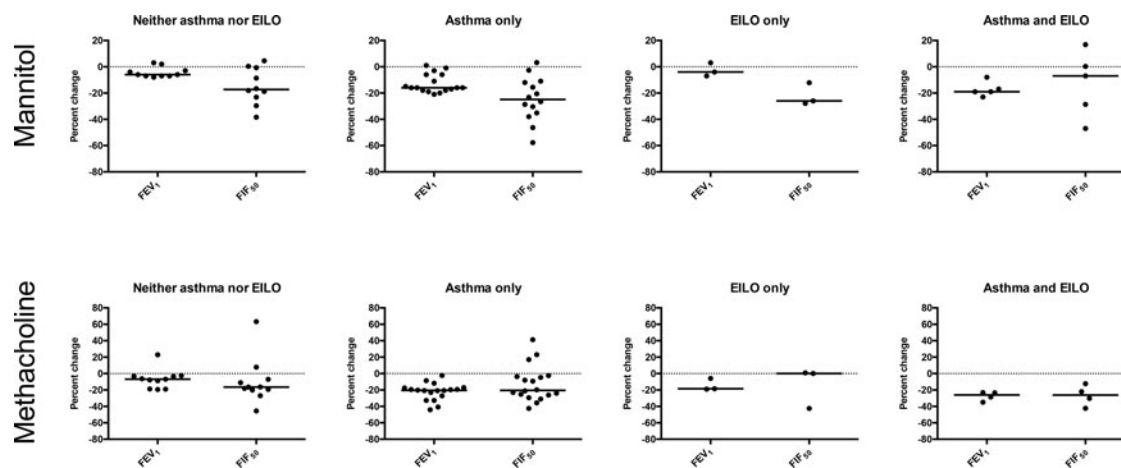


Figure 1. Bronchoprovocation test results grouped by diagnosis. Horizontal lines depict the median. There were no differences between the groups in percent decrease of FIF₅₀ for neither Mannitol test, nor Methacholine test (Kruskal–Wallis; $p > 0.05$). In contrast, FEV₁ differed significantly between the groups (Kruskal–Wallis; $p < 0.01$) for both Mannitol and Methacholine.

emphasises the need for less invasive diagnostic methods and it is possible that the prevalence of EILO in this study has been underestimated. Likewise, we specifically adopted conservative approach to score a diagnosis of EILO, in order to minimize the false positive rate. Thus, the number of subjects who develop EILO may actually be higher than reported.

Conclusion

EILO is an important and prevalent differential diagnosis for asthma-type symptoms, in young individuals presenting with exertional dyspnea. In this study, EILO could not be detected on the basis of either symptom assessment, resting lung function measures or bronchoprovocation testing with evaluation of extra-thoracic hyper-responsiveness. These findings indicate that the CLE test remains a key and important diagnostic test to confirm EILO, yet the reluctance of many subjects to undergo this test, indicates that work is needed to explore other less invasive means for establishing a diagnosis of EILO.

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Declaration of interest

E.S. Walsted contributed substantially to the design of this study, performed data collection and statistical analysis, and had full access to all data. He assumes responsibility for the integrity of data and analysis presented in this study, and for this study as a whole. J.H. Hull, C. Porsbjerg, A. Sverrild, and V. Backer critically revised this manuscript and provided valuable input on study design and data analysis. All authors have given their approval to submission of this manuscript. The authors did not receive any funds from external sources for the present study. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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