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Overweight and exercise-induced bronchoconstriction – Is there a link?

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Abstract

Background: The objective of this study was to evaluate the role of body mass index with regard to exercise performance, exercise-induced bronchoconstriction (EIB), and respiratory symptoms in 7- to 16-year-old children.

Methods: A total of 1120 outdoor running exercise challenge test results of 7- to 16-year-old children were retrospectively reviewed. Lung function was evaluated with spirometry, and exercise performance was assessed by calculating distance per 6 minutes from the running time and distance. Respiratory symptoms in the exercise challenge test were recorded, and body mass index modified for children (ISO-BMI) was calculated for each child from height, weight, age, and gender according to the national growth references.

Results: Greater ISO-BMI and overweight were associated with poorer exercise performance ($P < .001$). In addition, greater ISO-BMI was independently associated with cough ($P = .002$) and shortness of breath ($P = .012$) in the exercise challenge. However, there was no association between ISO-BMI and EIB or with wheeze during the exercise challenge.

Conclusion: Greater ISO-BMI may have a role in poorer exercise performance and appearance of respiratory symptoms during exercise, but not in EIB in 7- to 16-year-old children.

KEYWORDS

asthma, BMI, cough, exercise-induced bronchoconstriction, pediatrics, physical fitness, shortness of breath, wheeze

Key Message

In this so far largest study of 7- to 16-year-old children with asthmatic symptoms undergoing exercise challenge tests, we found no association between overweight and exercise-induced bronchoconstriction. However, overweight contributed significantly to exercise-induced respiratory symptoms as well as poor exercise performance which may lead to misinterpretation in the clinical evaluation, unless the diagnosis is based on objective lung function measurements.

1 | INTRODUCTION

The association between asthma, poor physical fitness, and overweight has been investigated in various studies in adults, but among children the issue has been evaluated inconclusively.[1] Overweight is supposed to increase the risk of asthma,[2–4] but the findings on its effects on bronchial hyper-responsiveness have been incoherent.[5–7] Overweight has also been associated with poor physical fitness,[1,8] which can be one of the reasons for exercise-induced respiratory symptoms eliciting asthma investigations. Exercise-induced cough, wheeze, and shortness of breath are often interpreted as signs of asthma, but the correlation between the symptoms and actual bronchial hyper-responsiveness has proven to be poor.[9,10]

Children with asthma may also suffer from impaired physical fitness.[11] Regular exercise seems to be positively associated with milder bronchial hyper-responsiveness in asthmatic children,[12] but it is not clear whether this is due to good cardiorespiratory fitness or other benefits of exercise.

The goal of this study was to evaluate the role of body mass index (BMI) with regard to exercise performance, respiratory symptoms, and exercise-induced bronchoconstriction (EIB), in a large sample of children with respiratory symptoms suggestive of asthma.

2 | METHODS

2.1 | Study design, participants, and setting

This was a cross-sectional retrospective study based on reviewing 1120 documented outdoor free-running test results of 7- to 16-year-old children performed in a tertiary hospital in 2014-2015. During the study period, a small number of children (n = 60) were referred to exercise challenge test two times for their clinical assessment and follow-up. Most of the children were referred to clinical assessment by primary care doctors or specialists working as private consultants. Among those tested children, there was no one with severe heart disease or chronic disease other than asthma that might exacerbate during exercise, as those conditions were considered a contraindication for an outdoor running test. Patients with no recordings of running time or distance, or those with uncertain asthma diagnosis (n = 100) were excluded from the analyses. As the free-running test was included as a part of routine asthma investigations, no separate visits or examinations were required from patients for this study.

2.2 | Definition of asthma diagnosis

According to current GINA guidelines, children were diagnosed with asthma, if they presented with a typical symptom history, and showed evidence of variable airflow obstruction or bronchial hyper-responsiveness, by using the following tests: spirometry with a bronchodilator test, an outdoor running test, a provocation test with histamine or methacholine, and/or a 2-week peak expiratory flow (PEF) surveillance.

2.3 | Ethics

The study was conducted according to the principles of the Declaration of Helsinki. As the study was a retrospective review of medical records and exercise challenge measurements, according to institutional principles, permission for the study was requested from the institutional board, but no review from ethics committee was considered to be needed.

2.4 | Outdoor free-running test

The exercise test was performed on a running track near the tertiary hospital. To avoid bias caused by asthma medication, patients were advised not to use long-acting beta-agonists (LABAs) for 48 hours and short-acting beta-agonists (SABAs) for 24 hours before the exercise test. A total of 113 subjects were using inhaled corticosteroids at the time of the test. The test consisted of outdoor running on the track for 6-8 minutes, while heart rate was monitored (Vantage NV, Polar Ltd). Running distance was measured and recorded along with the running time. Outdoor temperature was recorded. Possible respiratory symptoms were observed by the physician overseeing the test and/or reported by the patient.

2.5 | Lung function

Lung function was evaluated with spirometry according to standard principles,[13,14] with a pneumotachograph-based flow-volume spirometer (MasterScreen Pneumo, CareFusion, Hoechberg, Germany). The following parameters were recorded: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio. Spirometric raw values were transformed into z-scores based on national reference values.[15] Z-score values of ≤ −1.65 standard deviation (SD) were considered abnormal.

During the running test, spirometric measurements were repeated before the exercise and immediately, 5 minutes, and 10 minutes after the exercise. After this, inhaled salbutamol was administered, and the final spirometric measurements were performed. A fall of 15% or more in FEV1 after the exercise was considered indicative of significant EIB.

2.6 | Exercise performance

Exercise performance was measured by calculating the running speed and distance per 6 minutes from the running time and distance in the outdoor free-running test. To ensure that patients would give their maximal exercise performance, they were urged to reach at least 85% of their predicted maximum heart rate (calculated with the formula 208 - (0.7 × age)[16] during a 2-3 minutes acceleration phase and maintain the target heart rate at least for 4 minutes.

2.7 | BMI

As BMI (ie, weight divided by square of height) is not well suited for evaluating children's body composition, we used ISO-BMI, that is, BMI modified for children. ISO-BMI gives values that are better comparable to those of adults; for example, ISO-BMI ≥25 is considered overweight. ISO-BMI was calculated for each child from height, weight, age, and gender according to the national growth references.[17]

2.8 | Statistical analysis

Normality of continuous variables was evaluated using Kolmogorov-Smirnov's test. The effects of continuous baseline variables on maximal fall in FEV1 and on running distance per 6 minutes were evaluated using Pearson's correlation test (r < .40 meaning weak correlation, r = .40-.59 moderate correlation, and r ≤ .60 strong correlation). t test was used to evaluate differences in maximal fall in FEV1 and in running distance per 6 minutes in two different groups. Adjusted analyses were performed by linear regression used for determining variables independently associated with maximal fall in FEV1 and exercise performance and by logistic regression used for determining variables independently associated with exercise-induced respiratory symptoms and EIB. Variables for the multivariate models were chosen with the backward selection method. P-value of <.05 was considered statistically significant. IBM SPSS Statistics version 22 was used for statistical analyses.

3 | RESULTS

3.1 | Baseline characteristics

Baseline characteristics of the children in the exercise tests are presented in Table 1. A total of 555 children were diagnosed with asthma. A significant EIB was observed in 189 outdoor running tests. In 212 cases, the child was overweight, and their age and gender distribution were similar to children with normal weight. There were no statistically significant differences in ISO-BMI or being overweight between the children with and those without asthma (data not shown).

3.2 | Exercise performance

Results of univariate analyses implied that higher age (r = .442, P < .001) and outdoor temperature (r = .123, P < .001) were associated with better exercise performance, and greater ISO-BMI (r = -.211, P < .001) and overweight (Figure 1) with poorer exercise performance, that is, shorter running distance in 6 minutes. In addition, males ran farther than females (mean 978.6 m (SD 6.0 m) vs 929.6 m (SD 6.1 m), P < .001), and those with any respiratory symptoms during the

TABLE 1 Baseline characteristics, lung function parameters, and physical performance of the children in 1020 exercise tests

Baseline characteristics	n = 1020
Age, years, mean (SD)	11.1 (2.6)
Males, n (%)	616 (60)
ISO-BMI, kg/m^2, geometric mean (95% CI)	22.1 (21.9; 22.4)
ISO-BMI ≥ 25 kg/m^2, n (%)	212 (21)
Lung function parameters Pre-exercise	
FVC, l, geometric mean (95% CI)	2.7 (2.6; 2.7)
FVC z-score, SD, mean (SD)	−0.4 (1.2)
Abnormal FVC z-score, n (%)	138 (14)
FEV1, l, geometric mean (95% CI)	2.3 (2.2; 2.3)
FEV1 z-score, SD, mean (SD)	−0.8 (1.1)
Abnormal FEV1 z-score, n (%)	228 (22)
FEV1/FVC, %, mean (SD)	85.3 (6.6)
FEV1/FVC z-score, SD, mean (SD)	−0.7 (1.1)
Abnormal FEV1/FVC z-score, n (%)	201 (20)
Performance in exercise challenge Post-exercise	
Maximal FEV1 change, %, median (min; max)	−6.7 (-74.6; 17.9)
EIB, n (%)	189 (19)
Distance / 6 min, m, mean (SD)	959.2 (141.2)

Abbreviations: EIB, exercise-induced bronchoconstriction; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ISO-BMI, body mass index modified for children according to national growth references; SD, standard deviation.

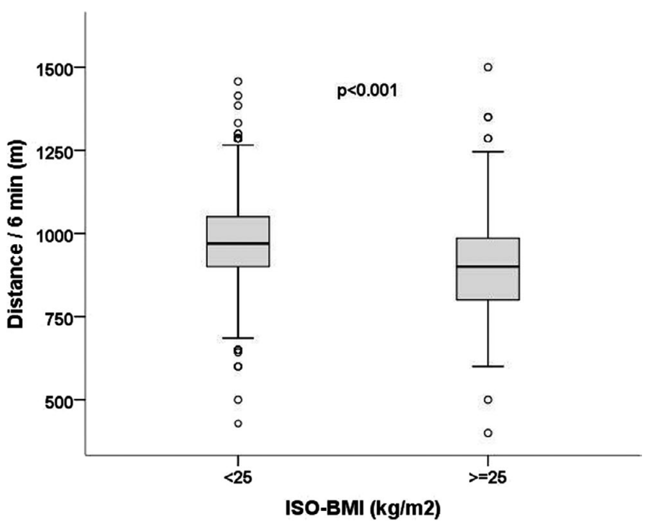

FIGURE 1 Physical performance (ie, running distance in meters per 6 minutes) was better in children (n = 808) with ISO-BMI < 25 kg/m^2 than in those (n = 212) with ISO-BMI ≥ 25 kg/m^2

TABLE 2 Multivariate model including variables independently associated with poorer physical performance

	Distance / 6 min β (SE)	*P*
Age	0.47 (1.48)	<.001
Male gender	0.23 (7.90)	<.001
ISO-BMI	−0.27 (1.03)	<.001
Outdoor temperature	0.12 (0.50)	<.001
Pre-exercise FEV1 z-score	0.07 (3.42)	.008
Respiratory symptoms during the exercise	−0.06 (7.86)	.023
R^2 for the model	0.321	

Abbreviations: FEV1, forced expiratory volume in 1 second; ISO-BMI, body mass index modified for children according to national growth references; R^2, coefficient of determination; SE, standard error;β, beta-coefficient.

exercise challenge test ran shorter distance (mean 938.3 m, SD 6.3 m) than those without symptoms (mean 975.5 m, SD 6.1 m) ($P < .001$). However, no statistically significant correlation was seen between baseline lung function and exercise performance ($P > .05$).

Multivariate linear regression analysis including the entire study group showed that variables independently associated with poorer exercise performance were younger age, female gender, greater ISO-BMI, lower outdoor temperature, lower FEV1 z-score, and appearance of any respiratory symptoms during the running test, as presented in Table 2.

In the linear regression analysis including only the non-asthmatic children, age, weight, height, and gender were the variables independently associated with exercise performance (data not shown). This gave us the following regression model equation for predicting exercise performance (distance per 6 minutes) in non-asthmatic children: $y = A + B \times \text{age} + C \times \text{height} + D \times \text{weight} + E \times \text{gender}$ ($A = -127.375$, $B = 21.488$, $C = 6.993$, $D = -6.733$, $E = 67.185$, male = 1, female = 0). The adjusted *R* square for this model was .414.

3.3 | EIB

In the univariate analyses, younger age ($r = .157$, $P < .001$), lower outdoor temperature ($r = .135$, $P < .001$), poorer exercise performance ($r = .161$, $P < .001$), and a lower pre-exercise FEV1/FVC z-score ($r = .141$, $P < .001$) were associated with a greater fall in FEV1. Neither pre-exercise FEV1 z-score nor ISO-BMI had statistically significant association with a maximal change in FEV1 ($P > .05$). Moreover, EIB was more commonly observed in those with abnormal FEV1/FVC z-score (27.4% vs 16.4% in those with normal FEV1/FVC z-score) and any respiratory symptoms (36.8% vs 4.2%) during the running test. In addition, children with EIB were younger (mean 10.3 years (SD 0.2 years) vs 11.3 years (SD 0.1 years)) and ran shorter distance in 6 minutes (916.3 m (SD 8.4 m) vs 969.0 m (SD 5.0 m)) in lower outdoor temperature (6.5°C (SD 0.6°C) vs 8.9°C (SD 0.3°C)) ($P < .001$ for all univariate comparisons).

In the multivariate logistic regression analysis, variables independently associated with EIB were younger age, lower outdoor temperature, abnormal FEV1/FVC z-score, and any respiratory symptoms during the running test, as presented in Table 3.

3.4 | Exercise-induced respiratory symptoms

A total of 572 children were symptomless, 219 had cough, 140 had wheeze, and 299 experienced shortness of breath during or after the exercise challenge. Fifty children had both cough and shortness of breath, 15 had cough and wheeze, 69 had wheeze and shortness of breath, and 38 experienced all three symptoms.

In the univariate analysis, greater ISO-BMI (geometric mean 22.6 kg/m^2 (min 15.8 kg/m^2, max 34.7 kg/m^2), $P < .001$), poorer exercise performance (mean 925.2 m (SD 128.9 m), $P < .001$), lower outdoor temperature (mean 7.0°C (SD 7.3°C), $P < .001$), lower FEV1/FVC z-score (mean −0.8 (SD 1.1), $P = .05$), a greater fall in FEV1 (median −9.2% (min −74.6%, max 3.9%), $P < .001$), and EIB (38% vs 18% of those without EIB, $P < .001$) were associated with an increased risk for cough.

Greater ISO-BMI (geometric mean 22.4 kg/m^2 (min 15.9 kg/m^2, max 34.7 kg/m^2), $P = .041$), poorer exercise performance (mean 920.6 m (SD 132.7 m), $P < .001$), lower outdoor temperature (mean 6.3°C (SD 7.2°C), $P < .001$), lower FEV1 z-score (mean −1.0 (SD 1.2), $P = .039$), lower FEV1/FVC z-score (mean −1.1 (SD 1.3), $P < .001$), a greater fall in FEV1 (median −21.6% (min −74.6,% max −1.2%), $P < .001$), and EIB (53% vs 4.8% in those without EIB, $P < .001$) were associated with an increased risk for wheeze.

TABLE 3 Multivariate model including variables independently associated with EIB

	EIB OR (95% CI)	*P*
Age	0.80 (0.74; 0.87)	<.001
Outdoor temperature	0.97 (0.95; 1.00)	.026
FEV1/FVC z-score <-1.65	1.75 (1.14; 2.69)	.011
Respiratory symptoms during the exercise	12.25 (8.68; 19.56)	<.001
R^2 for the model	0.317	

Abbreviations: CI, confidence interval; EIB, exercise-induced bronchoconstriction; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; R^2, coefficient of determination.

TABLE 4 Multivariate models for predicting symptoms in exercise challenge in the study children

	Cough OR (95% CI)	Shortness of breath OR (95% CI)	Wheeze OR (95% CI)
Age	-	1.14 (1.06; 1.22)	-
ISO-BMI	1.08 (1.03; 1.13)	1.06 (1.01; 1.10)	-
Outdoor temperature	0.96 (0.94; 0.99)	0.96 (0.94; 0.99)	0.96 (0.92; 0.99)
EIB	8.95 (5.35; 14.99)	19.11 (11.60; 31.48)	48.97 (27.93; 85.87)
R^2 for the model	0.195	0.329	0.530

Abbreviations: CI, confidence interval; EIB, exercise-induced bronchoconstriction; ISO-BMI, body mass index modified for children according to national growth references; OR, odds ratio; R^2, coefficient of determination.

Greater ISO-BMI (geometric mean 22.3 kg/m^2 (min 14.8 kg/m^2, max 34.7 kg/m^2), P = .002), poorer exercise performance (mean 945.0 m (SD 133.8 m), P = .002), lower outdoor temperature (mean 6.9°C (SD 7.6°C), P < .001), lower FEV1 z-score (mean −1.0 (SD 1.2), P = .017), lower FEV1/FVC z-score (mean −0.9 (SD 1.2), P = .003), a greater fall in FEV1 (median −13.4% (min −74.6%, max 17.9%), P < .001), and EIB (70% vs 20% in those without EIB, P < .001) were associated with an increased risk for shortness of breath.

Multivariate models for predicting exercise-induced respiratory symptoms are presented in Table 4. Variables independently associated with cough were greater ISO-BMI, lower outdoor temperature, and EIB. Variables independently associated with shortness of breath were older age, greater ISO-BMI, lower outdoor temperature, and EIB. Variables independently associated with wheeze were lower outdoor temperature and EIB.

4 | DISCUSSION

To our knowledge, this is the largest study investigating the interrelationships of overweight, exercise performance, and EIB in children with respiratory symptoms suggestive of asthma. A greater ISO-BMI was associated with poorer exercise performance and appearance of cough and shortness of breath during the exercise, but not with EIB or wheeze induced by the exercise. We found also a significant association between lower outdoor temperature and EIB.

Our study shows a correlation between greater ISO-BMI and poorer exercise performance in the outdoor free-running test. This result is easily rationalized, as physical inactivity can cause both increase in weight and decrease in physical fitness. However, as our study is cross-sectional and does not include records of physical activity habits, we cannot speculate the reasons for overweight in our study material. Ferreira et al. found that obese subjects walked shorter distances during a 6-minute walk test.[1] Obese children also performed poorly on a treadmill challenge compared to lean children.[9] Özgen et al. even found BMI standard deviation score to be the only independent factor influencing exercise performance in a 6-minute indoor walk test,[8] whereas in our study with a larger sample, also age, gender, outdoor temperature, and FEV1 z-score were found as independent factors associated with exercise performance, in addition to ISO-BMI.

Obesity and overweight have been associated with EIB in some studies.[6,8] The connection is suggested to be due to inflammatory mechanisms involving both conditions.[18] Experimental evidence shows that changes in lung mechanics in obesity may predispose to bronchial hyper-responsiveness.[19] In our study, ISO-BMI was not associated with EIB. Equal findings have been observed by others as well.[7] However, in most longitudinal studies, asthma and BMI have been associated, and the opposing results have only come from cross-sectional studies.[4] Obesity has been found to increase the risk of developing asthma in children,[2] but from epidemiologic studies, it is difficult to conclude whether clinical assessments leading to diagnosis of asthma have been biased by the increased amount of respiratory symptoms due to obesity per se, and what has been the role of lung function measurements.

In our study, poorer exercise performance was correlated with a maximal fall in FEV1. Similarly, poorer physical fitness in childhood has been found to increase the risk of hyper-responsiveness to methacholine and the risk of developing asthma.[11,12] However, it is not clear whether poor physical fitness contributes to the development of asthma and bronchial hyper-responsiveness or whether poor physical fitness is caused by exercise avoidance due to unpleasant exercise-induced respiratory symptoms in asthmatic children.

As expected, EIB had an independent association with all three symptoms. However, exercise-induced cough, wheeze, and shortness of breath have been found to be poor predictors for a diagnostic fall in FEV1.[9,10] Our observations support the concept that the symptoms are not specific for EIB, but also affected by ISO-BMI and outdoor temperature.

Even though exercise performance was found to have an association with all the exercise-induced respiratory symptoms in the univariate analysis, it was not independently associated with the symptoms in the multivariate regression analysis. In contrast, ISO-BMI was an independent factor associated with both cough and shortness of breath; for wheeze, this association was not evident. Overweight predisposes to breathlessness by increasing metabolic demands for running and increasing breathing work.[20] Susceptibility for wheezing is higher in overweight subjects due to lower functional residual capacity (FRC) which increases airway resistance and promotes intrathoracic airway closure[21] and due to extrathoracic airway obstruction caused by fat deposition.[22] Scholtens et al. concluded that dyspnea and wheeze were associated with a greater BMI in children.[23] However, there is also evidence that lean subjects experience more dyspnea after exercise challenge compared to obese subjects.[8]

The outdoor free-running test has been found to mimic real-life EIB and may give positive test results when other bronchial challenges do not.[24] The outdoor free-running test enables the evaluation of patient's physical fitness, as the running time and distance are recorded. Compared to, that is, treadmill test in the laboratory, the outdoor running test is more feasible to investigate larger samples of subjects such as in the current study, but the inherent weakness is that the outdoor conditions (temperature, humidity) cannot be standardized. In this study, outdoor temperature was an independent factor associated with all three symptoms in the analyses including the entire study population. Respiratory symptoms are common in cold temperatures,[25] especially in those with asthma.[26] It is thought that exercise-induced hyperpnea causes drying and cooling of airway surface liquid, which triggers respiratory symptoms and EIB via vagal reflex mechanisms and by mast cell degranulation.[27] Shortness of breath during exercise has been found to be more common in cold temperature than in normal room temperature, or simply during exposure to cold air.[28] Accordingly in our series, lower outdoor temperature was not only associated with exercise-induced respiratory symptoms, but also with a greater maximal fall in FEV1 and EIB. Similar results have also been reported in preschool children with asthma.[29]

Assessment of exercise-induced respiratory symptoms suggesting asthma in children is a common clinical problem. Considering the reliability of our results, this retrospective study has a reasonably good-sized cohort and well-documented data, as the running test was conducted in a standardized manner, including quantification of performance and high-quality spirometric recordings. On the other hand, cross-sectional retrospective design of our study unfortunately limited the amount of data available on the study subjects, which may have caused residual confounding. Even though maximal performance was not measured, the running pace was adjusted to be symptom-limited and by monitoring the heart rate. The observational period after the exercise test was short compared to recommendations concerning assessment of EIB, but there is evidence that in children the nadir for maximal bronchoconstriction occurs significantly earlier (3-6 min post-exercise) than in adults[30], and therefore, it is unlikely that the shorter follow-up time would have had large impact on the diagnosis of EIB in this study. One limitation is the lack of a proper control group. Children referred to exercise challenge test are always in some way symptomatic, and although those children in whom during careful assessment of symptoms and objective lung function tests asthma could not be confirmed, this group was biased and not necessarily composed of "healthy" individuals. Also, parental smoking was not considered in the exclusion criteria. We also acknowledge that ISO-BMI has its limitations in describing body composition.

In conclusion, greater ISO-BMI was associated with exercise-induced cough, shortness of breath, and poorer exercise performance, but not with wheeze or EIB. Respiratory symptoms in overweight children may be misinterpreted as asthmatic, unless objective lung function measurements are conducted. There was also a significant association between lower outdoor temperature and EIB. The conflicting findings in other studies call for more evidence on the matter, as well as better understanding on the underlying mechanisms linking obesity and asthma. Controlled intervention studies on the effects of improving physical performance in preventing and controlling overweight and asthma in children should be done.

CONFLICT OF INTEREST

There is no conflict of interest concerning the authors of this manuscript. Study sponsors had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the manuscript for publication.

AUTHOR CONTRIBUTION

Maiju Malmberg: Data curation (equal); Formal analysis (lead); Writing-original draft (lead). **Anne Kotaniemi-Syrjänen:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Supervision (equal); Writing-original draft (equal); Writing-review & editing (equal). **Pekka Malmberg:** Conceptualization (equal); Funding acquisition (equal); Methodology (equal); Supervision (equal); Writing-review & editing (equal). **Anna Susanna Pelkonen:** Conceptualization (equal); Investigation (equal); Resources (equal); Supervision (equal); Writing-review & editing (equal). **Mika Juhani Makela:** Conceptualization (equal); Funding acquisition (equal); Writing-review & editing (equal).

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