Respiratory Medicine 220 (2023) 107457

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

The acute effects of endurance exercise on epithelial integrity of the airways in athletes and non-athletes: A systematic review and meta-analysis

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ABSTRACT

Introduction: Acute endurance exercise may induce airway epithelium injury. However, the response of epithelial integrity markers of the airways including club cell secretory protein (CC16) and surfactant protein D (SP-D) to endurance exercise have not been systematically reviewed. Therefore, the aim of this systematic review and meta-analysis was to assess the acute effects of endurance exercise on markers of epithelial integrity of the airways (CC16, SP-D and the CC16/SP-D ratio) in athletes and non-athletes.

Methods: A systematic search was performed utilizing PubMed/Medline, EMBASE, Web of Science, and hand searching bibliographies of retrieved articles through to September 2022. Based on the inclusion criteria, articles with available data about the acute effects of endurance exercise on serum or plasma concentrations of CC16, SP-D and CC16/SP-D ratio in athletes and non-athletes were included. Quality assessment of studies and statistical analysis were conducted via Review Manager 5.4 software.

Results: The search resulted in 908 publications. Finally, thirteen articles were included in the review. Acute endurance exercise resulted in an increase in CC16 ($P = 0.0006$, n = 13) and CC16/SP-D ratio ($P = 0.005$, n = 2) whereas SP-D ($P = 0.47$, n = 3) did not change significantly. Subgroup analysis revealed that the type ($P = 0.003$), but not the duration of exercise ($P = 0.77$) or the environmental temperature ($P = 0.06$) affected the CC16 response to endurance exercise.

Conclusions: Acute endurance exercise increases CC16 and the CC16/SP-D ratio, as markers of epithelial integrity, but not SP-D in athletes and non-athletes.

1. Introduction

Endurance exercise training reduces the risk of diabetes, cardiovascular disease, stroke and morbidity and mortality [1,2]. However, endurance exercise could also exert considerable stress on the body, especially the respiratory system [3]. For example, during high-intensity exercise, minute ventilation increases up to 20–30 times of what it is at rest and individuals can be chronically exposed to unfavorable conditions including cold dry air, airborne pollutants, chlorinated indoor pools or allergens [4,5]. These conditions could cause airway damage and lead to the development of airway hyperresponsiveness, exercise-induced bronchoconstriction and/or respiratory symptoms [4–7].

High minute ventilation during prolonged endurance exercise can result in dehydration and cooling of the airway mucosa that increase shear stress on the airway epithelium [4]. The epithelial cells respond to these conditions by releasing mediators including club cell secretory protein (CC16) and alveolar surfactant-associated serum protein D (SP-D) which are used as markers of airway epithelial barrier integrity damage [8–11]. CC16 is a secretory protein (16 KD) that is released from non-ciliated cells of the bronchioles and is a stress biomarker of the respiratory system [12–14]. CC16 has anti-inflammatory, anti--oxidative, and anti-infectious properties [15,16]. SP-D is a collagenous glycoprotein (43 KD) that belongs to the family of collectin proteins and has a significant impact on innate immune defense, regulating pulmonary surfactants, maintaining lipid homeostasis, tumor proliferation and metastasis in the lungs [8,17,18]. SP-D deficiency in the lungs causes alveolar macrophage activation, inflammation, and oxidative stress in the respiratory system [19,20].

There are conflicting data on how the concentrations of CC16, SP-D and the CC16/SP-D ratio respond to acute endurance exercise in athletes and non-athletes. Further, the response of these epithelial integrity markers of the airways to acute endurance exercise has not been systematically reviewed. This information is important to understand

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https://doi.org/10.1016/j.rmed.2023.107457
Received 28 August 2023; Received in revised form 22 October 2023; Accepted 3 November 2023
Available online 10 November 2023

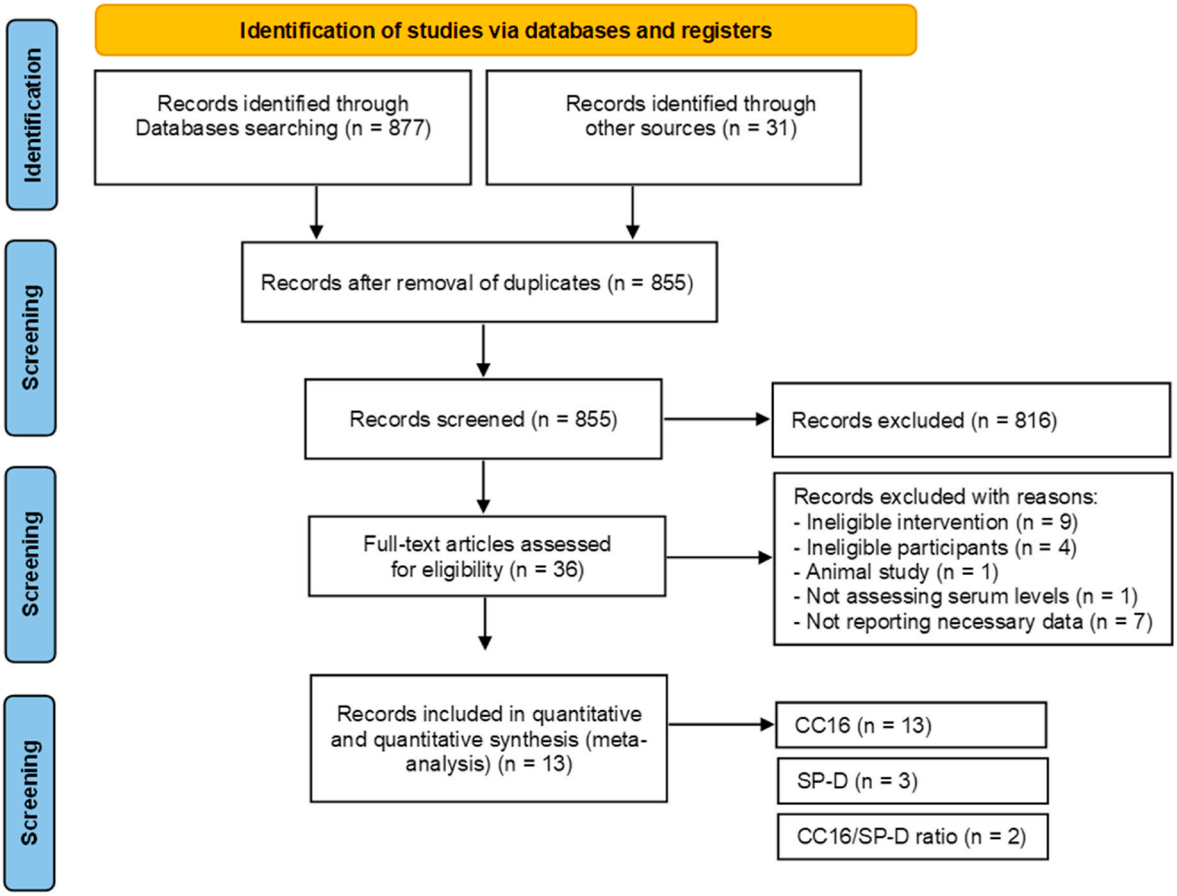

Fig. 1. PRISMA flow chart for search and selection of the included studies.

whether acute endurance exercise results in epithelial integrity damage to the airways.

Accordingly, the aim of this systematic review and meta-analysis was to examine the acute effects of endurance exercise on epithelial integrity markers of the airways (CC16, SP-D and the CC16/SP-D ratio) in athletes and non-athletes.

2. Methods

The systematic review and meta-analysis was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21]. A comprehensive search to identify clinical trials that assessed the responses of serum or plasma concentrations of epithelial integrity markers of the airways (CC16, SP-D and the CC16/SP-D ratio) after acute endurance exercise in athletes and non-athletes was undertaken. The protocol was registered on PROSPERO (ID: CRD42022352403).

2.1. Search strategy

PubMed/Medline, Web of Science, EMBASE, Google Scholar, and hand-searched bibliographies of retrieved articles were searched for articles that were in English through September 2022. Medical subject headings (MeSH) were utilized to search the controlled vocabulary terms and text words including the following main terms: endurance, physical endurance, endurance training, endurance exercise, endurance exercise training, endurance training, endurance workout, endurance-type exercise, endurance-type training, stamina, physical, aerobic exercise, aerobics, low impact aerobic exercise, low impact aerobics, step aerobics, aerobic training, and also, epithelia cell, epithelial cells, epitheliocyte, epitheliocytes, epitheliocytus, epithelium cell, cell damage, cell injury, cell lesion, cell trauma, cellular damage, cellular injury, CC16, SP-D.

2.2. Interventions and outcome measures

A continuous or interval endurance exercise session (any kind of sport and activity with durations of more than 8 min) was considered as an intervention in this review. The outcome measurement was the serum or plasma concentration of CC16, SP-D and the CC16/SP-D ratio.

2.3. Inclusion and exclusion criteria

Inclusion criteria were considered as follows: (1) clinical studies eligible up to September 2022; (2) articles with available data about the acute effects of endurance exercise on epithelial cell damage (serum or plasma concentrations of CC16, SP-D and the CC16/SP-D ratio) in athletes and non-athletes aged between 18 and 60 years. Two reviewers determined the final inclusion of the studies (VS and RA) that independently made the final decision on the inclusion of the articles. For studies that had reported in more than one publication, we performed data abstraction using all publications; however, just one report was included.

The articles that met the following criteria were excluded: (1) case reports, review articles, and conference abstracts; (2) animal studies; (3) original articles not containing data of CC16, SP-D, and CC16/SP-D ratio; (4) inaccessible articles after mailing (two times) for paper request from the corresponding author; (5) unclear data description articles; (6) non-English articles; (7) articles with participants over 60 and under 18 years of age.

Table 1
Characteristics of included studies.

Author (year)	Country	Sample size (Male/Female)	Age (years)	Physical fitness	Study design	Exercise			Results
						Type	Intensity	Duration (min)	
Broeckaert (2000) [42]	Belgium	24 (9/15)	29 ± 3	Trained	Crossover	Cycling	HR: 122 ± 12 beats/min	120	↑ Serum CC16 (μg/L) concentration
Nanson (2001) [40]	USA	10 (9/1)	NR	Untrained	RCT	Interval treadmill running	HR_{max}: 98 ± 5 %	60	↑ Serum CC16 (μg/L) concentration
Carbonnelle (2002) [38]	Belgium	13 (6/7)	37 ± 10	Active	RCT	Swimming	HR: 170 ± 12 beats/min	120	↔ Serum CC16 (μg/L) concentration
Carbonnelle (2008) [39]	Belgium	11 (4/7)	M: 22 ± 2 F: 22 ± 1	Active	Crossover	Swimming	NR	45	↔ Serum CC16 (μg/L) concentration
Jacobs (2010) [47]	Belgium	38 (28/10)	43 ± 9	Active	Crossover	Cycling	HR_{max}: 74 ± 9 %	20	↔ Serum CC16 (μg/L) concentration
Font-Ribera (2010) [43]	Spain	48 (31/17)	30 ± 6	Untrained	Crossover	Swimming	Speed: 22.5 ± 9.7 m/min	40	↑ Serum CC16 (μg/L) concentration ↔ Serum SP-D (μg/L) concentration
Tufvesson (2013) [41]	Sweden	18 (9/9)	25	Untrained	RCT	Treadmill running	HR_{max}: 90 %	8	↑ Plasma CC16 (ng/mL) concentration
Combes (2019) [9]	France	16 (16/-)	24 ± 5	Active	Crossover	Continuous and intermittent cycling (ergometry)	HR_{max}: 90 ± 9 % CE HR_{max}: 70 ± 2 % IE	30	↑ Serum CC16 (μg/L) and SP-D (μg/L) concentration and CC16/SP-D ratio
Font-Ribera (2019) [44]	Spain	116 (56/60)	24	Active	Non-RCT	Swimming	EE: 205 kcal	40	↔ Serum CC16 (ng/mL) concentration
Pourmanaf (2020) [8]	Iran	10 (10/-)	26 ± 3	Trained and active	RCT	Running	HR: 156 ± 3 beats/min	30	↑ Serum CC16 (ng/mL) and SP-D (ng/mL) concentration and CC16/SP-D ratio
Eklund (2021) [45]	Sweden	31 (16/15)	M: 38 F: 43	Untrained	Crossover	Interval treadmill running at +10 °C and −10 °C	$\dot{V}O_2max$: 70 %	50	↑ Plasma CC16 (ng/mL) concentration
Stenfors (2022) [48]	Sweden	23 (8/15)	31 ± 8	Trained	Crossover	Incremental and maximal treadmill running at −15 °C	$\dot{V}O_2peak$: 65–90 % incremental	30	↑ Plasma CC16 (ng/mL) concentration
Eklund (2022) [46]	Sweden	29 (18/11)	38	Untrained	Crossover	Interval treadmill running at −15 °C	$\dot{V}O_2max$: 85 %	35	↑ Plasma CC16 (ng/mL) concentration

CC16, club cell secretory protein; EE, energy expenditure; F, Female; HR, heart rate; HR_{max}, maximum heart rate; M, male; NR, not reported.
RCT, randomized control trial; SP-D, surfactant-associated serum protein D; $\dot{V}O_2max$, maximal oxygen uptake; $\dot{V}O_2peak$, peak oxygen uptake; %, percentage of maximum heart rate or peak/maximal oxygen uptake.

2.4. Selection process

Duplicate citations were initially removed. Subsequently, the titles, abstracts keywords of the studies were screened by two reviewers (VS and JV) independently for inclusion based on the selection criteria. Any discrepancies between reviewers were resolved through discussion. Finally, the full text of the remaining articles were read and the final list of studies was included in the study.

2.5. Literature quality assessment

Two independent reviewers (VS and JV) assessed the quality of the included studies using the Cochrane risk of bias tool in Review Manager 5.4 [22]. According to the tool, we focused on the following seven items: randomized sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting, and other biases. In times of disagreement, the final decision was made after consulting with the other authors.

2.6. Data extraction

Two authors conducted the data extraction from the text and tables, independently (SN and HP). The author's names, publication date, the country of the study, number of participants, age, physical fitness, study type, the types of exercise, the intensity of exercise, the duration of exercise, results, and mean and standard deviation of the CC16, SP-D, and CC16/SP-D ratio were extracted. In case of lacking essential data in the text and tables, we contacted the corresponding author of the original articles.

2.7. Statistical analysis

The meta-analysis was conducted to compare the serum or plasma concentration of CC16, SP-D and the CC16/SP-D ratio before (baseline) and after the intervention (acute exercise) by calculating the mean difference (MD), with a 95 % confidence interval (CI). To examine the effect of heterogeneity between studies, the I_2 ($I_2 = 100\,\% \times (Q - df)/Q$) method was used. When I_2 was more than 50 %, it is considered as the presence of heterogeneity [23]. In addition, the Random Effect Model was applied for data analysis [24]. For statistical analysis, Review Manager 5.4 software (version 5.4) was used. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Description of studies

The PRISMA flow chart is shown in Fig. 1 and 908 publications (records identified through database searching and other sources) were found after a comprehensive search. Fifty-three duplicate studies were excluded and 855 studies were recorded for screening. The titles and

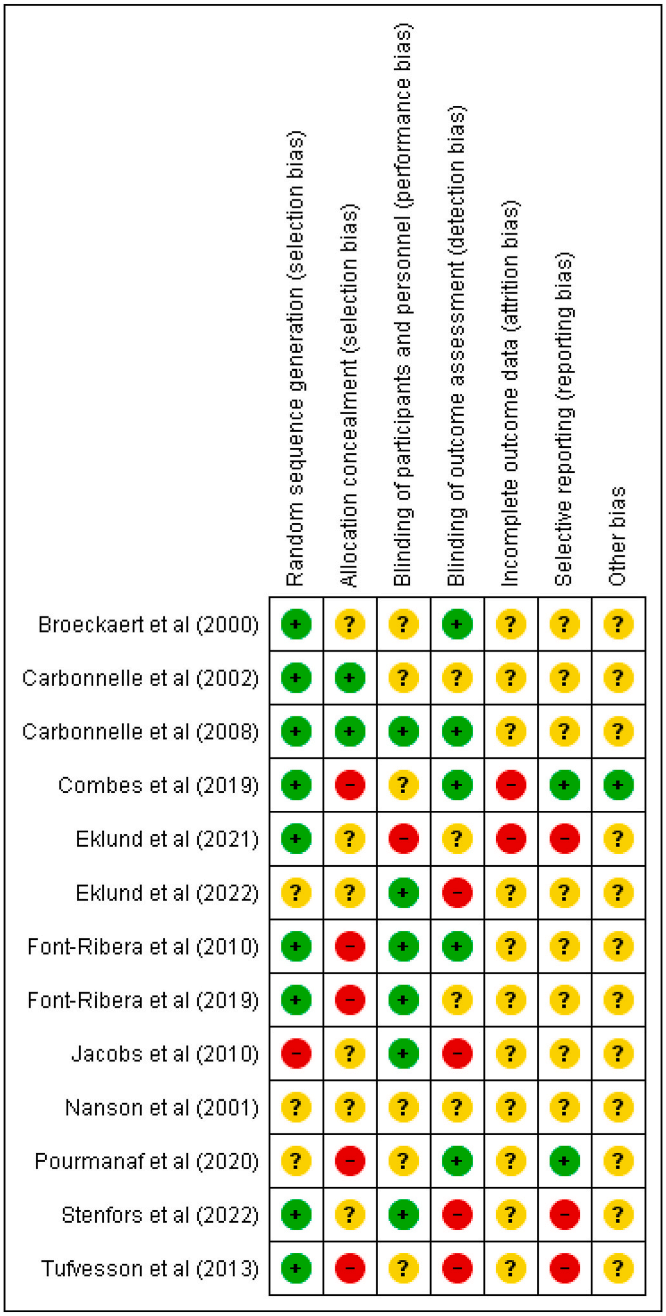

Fig. 2. Risk of bias in included studies.

abstracts of these articles were investigated and 816 of them were removed for not meeting the exclusion and inclusion criteria. The reasons included irrelevant purposes, unclear indicators, review articles, case reports and conference abstracts. Abstracts of the remaining 36 potentially related studies that met the inclusion criteria were kept. Subsequently, full-text of the articles was reviewed carefully and 16 of 36 studies were omitted because one was performed on rats [25], nine had used ineligible interventions [10,14,16,26–31], two did not examine serum or plasma concentrations of outcomes [32,33] and four applied ineligible participants [34–37]. Of the remaining 20 studies, 13 were included in the systematic review and meta-analysis [8,9,38–48] because the other seven studies did not report necessary information for the meta-analysis and the corresponding authors of these studies did not respond to our emails [49–55].

3.2. Characteristics of included studies

Characteristics of the included studies are shown in Table 1. The 13 articles included were published between 2000 and 2022. Eleven were undertaken in Europe [9,38,39,41–48], one in Iran [8], and one in the United States [40]. The participants of these 13 studies were 387 individuals (male = 220 and female = 167) aged 18–60 years. Participants in eight of the studies were recreationally active or trained athletes [8,9,38,39,42,44,47,48] and participants in the remaining five studies were untrained adults [40,41,43,45,46]. The types of endurance exercise utilized in the studies were running [8,40,41,45,46,48], cycling [9,42,47], and swimming [38,39,43,44]. The duration of the exercise was between 8 and 120 min. Of the 13 studies, ten were performed in an environment with a temperature above 0 °C [8,9,38–44,47] and three in a temperature below 0 °C [45,46,48]. All included studies assessed CC16 [8,9,38–48], three assessed CC16 and SP-D [8,9,43] and only two studies examined all of the outcomes (CC16, SP-D and the CC16/SP-D ratio) [8,9].

3.3. Risk of bias of the included studies

Fig. 2 demonstrates the risk of bias of the included studies. Nine articles had a low risk of bias in random sequence generation. However, most of the included studies did not report allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, and selective reporting or had high risk of selection bias.

3.4. Meta-analysis

3.4.1. Heterogeneity

There was significant heterogeneity among the studies for CC16 ($Tau^2 = 0.78$, $Chi^2 = 65.55$, df = 12, $P = 0.00001$, $I^2 = 82$ %) and SP-D ($Tau^2 = 3.88$, $Chi^2 = 2.27$, df = 2, $P = 0.32$, $I^2 = 12$ %), but there was not heterogeneity among the studies for the CC16/SP-D ratio ($Tau^2 = 0.00$, $Chi^2 = 0.80$, df = 1, $P = 0.37$, $I^2 = 0$ %).

3.4.2. Club cell secretory protein

Nine of the 13 studies reported a significant post-exercise increase in CC16 concentrations compared to baseline [8,9,40,42,43,47,48]. The meta-analysis demonstrated that CC16 concentrations increased after exercise (MD = 1.12, 95 % CI = 0.48 to 1.77, $P = 0.0006$) (Fig. 3).

Subgroup analysis based on the environmental temperature revealed that there was not a difference in CC16 concentrations ($P = 0.06$) after exercise between temperatures below 0 °C and above 0 °C (<0 °C: MD = 4.26, 95 % CI = 0.43 to 8.9, $P = 0.03$) (>0 °C: MD = 0.53, 95 % CI = 0.05 to 1.01, $P = 0.03$) (Fig. 4), but there was a trend to statistical significance.

There was no difference in CC16 concentrations ($P = 0.77$) after exercise between shorter (<60 min: MD = 1.23, 95 % CI = 0.28 to 2.17, $P = 0.01$) and longer duration exercise (≥60 min: MD = 1.51, 95 % CI = −0.10 to 3.12, $P = 0.07$) (Fig. 5).

There was a difference in CC16 concentrations ($P = 0.003$) after exercise based on the types of endurance exercise (Running: MD = 3.48, 95 % CI = 1.42 to 5.53, $P = 0.0009$) (Swimming: MD = 0.01, 95 % CI = 0.-0.71 to 0.74, $P = 0.97$) (Cycling: MD = 0.91, 95 % CI = 0.70 to 1.12, $P = 0.00001$) (Fig. 6) and only running and cycling increased CC16 concentrations.

3.4.3. Surfactant protein D

Two of the three studies reported a significant increase in SP-D concentrations after exercise compared to baseline [8,9], but when the data from these three studies was pooled, the differences between baseline and post-exercise were not significant (MD = 1.78, 95 % CI = -3.02 to 6.59, $P = 0.47$) (Fig. 7).

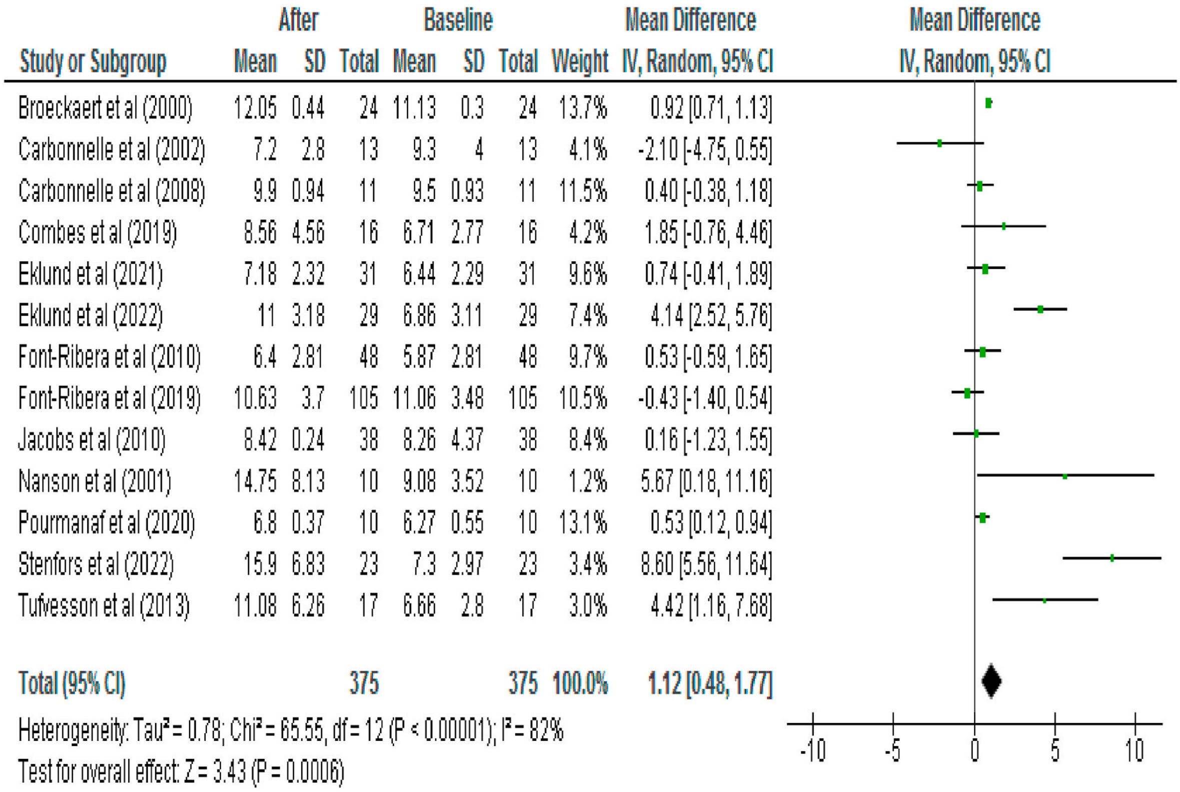

Fig. 3. Forest plots of the effect of endurance exercise on club cell secretory protein compared with baseline.

3.4.4. Club cell secretory protein/surfactant protein D ratio

Two studies reported an increase in the CC16/SP-D ratio after exercise compared to baseline, and when the information from these two studies was pooled, the differences between the baseline and post-exercise were significant (MD = 0.01, 95 % CI = 0.00 to 0.01, P = 0.005) (Fig. 8).

4. Discussion

The aim of this systematic review and meta-analysis was to examine the acute effects of endurance exercise on markers of epithelial integrity of the airways (CC16, SP-D and the CC16/SP-D ratio) in athletes and non-athletes. Out of 908 articles included from different databases, 13 publications, with a total of 376 participants, had sufficient information to be included in the meta-analysis, and the data from these articles revealed that endurance exercise increases the serum or plasma concentrations of CC16 and CC16/SP-D ratio, but SP-D did not change after exercise.

The present study focused on the changes in the serum or plasma concentrations of CC16 after endurance exercise compared to baseline. Out of the 13 articles included in the review, nine reported that the intervention (i.e., exercise) can increase the serum or plasma concentrations of CC16 in comparison with baseline. Moreover, the forest plot revealed that endurance exercise may lead to damage to airway epithelial integrity. This finding may indicate that acute endurance exercise may induce airway epithelium injury and supports several studies that have confirmed that endurance exercise increases the leakage of CC16 into the blood [32,41,45,46,49,50]. Previous studies have reported that endurance exercise can exert stress and pressure on the airways due to the increase in minute ventilation [5,6]. This condition is associated with the release of inflammatory factors, epithelial damage, and plasma exudation [5,6]. If this process is repeated, it can affect the contractile properties of the bronchial smooth muscle and possibly result in airway hyperresponsiveness, exercise-induced bronchoconstriction and respiratory symptoms [5,6]. CC16 is a protein, which is secreted from the epithelial cells during stress and pressure, and could be used as a marker of epithelial integrity of the airways [15].

The results of the subgroup analyses showed that the type of endurance exercise influences the serum or plasma concentrations of CC16 after exercise. Running and cycling increased CC16 concentrations compared to baseline, but swimming had no significant effect. This issue might be related to the intensity of exercise in swimmers because in three included studies, low intensity exercise or free activity was used as an intervention.

The results of the subgroup analyses showed that there were no differences between studies with the duration of exercise and both <60 min and ≥60 min durations increased the serum or plasma concentrations of CC16 after exercise. Other factors such as exercise intensity, the type of exercise (continuous or interval) and the physical fitness of participants could have an impact on these results.

Some studies have reported that performing endurance exercise in cold environments aggravates airway epithelial damage because the temperature and humidity of the inspired air must be increased more [56,57]. This condition exposes the airway epithelium to more damage and dehydration during exercise [5,57]. Probably, these results are due to the type of exercise (continuous or interval). Recently, Combs et al. confirmed that interval training caused less damage to the integrity of the airway [9], and in this review, three studies that were conducted at sub-zero temperatures from interval exercises were used, but further studies are needed to confirm these issues. In addition to temperature, air pollution, indoor exposures to chlorine compounds and other environmental factors may also affect the epithelial integrity of the airways in response to acute exercise. However, we could not carry out a subgroup analysis on these factors because most of the included studies did not report data related to these.

Out of the 13 studies in the present systematic review and meta-analysis only three [8,9,43] and two studies [8,9] evaluated SP-D and CC16/SP-D ratio after endurance exercise, respectively. All studies were

	After			Baseline				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.2.1 <0 °C								
Eklund et al (2021)	7.18	2.32	31	6.44	2.29	31	9.6%	0.74 [-0.41, 1.89]
Eklund et al (2022)	11	3.18	29	6.86	3.11	29	7.4%	4.14 [2.52, 5.76]
Stenfors et al (2022)	15.9	6.83	23	7.3	2.97	23	3.4%	8.60 [5.56, 11.64]
Subtotal (95% CI)			**83**			**83**	**20.4%**	**4.26 [0.43, 8.09]**
Heterogeneity: Tau² = 10.39; Chi² = 28.40, df = 2 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 2.18 (P = 0.03)								
1.2.2 >0 °C								
Broeckaert et al (2000)	12.05	0.44	24	11.13	0.3	24	13.7%	0.92 [0.71, 1.13]
Carbonnelle et al (2002)	7.2	2.8	13	9.3	4	13	4.1%	-2.10 [-4.75, 0.55]
Carbonnelle et al (2008)	9.9	0.94	11	9.5	0.93	11	11.5%	0.40 [-0.38, 1.18]
Combes et al (2019)	8.56	4.56	16	6.71	2.77	16	4.2%	1.85 [-0.76, 4.46]
Font-Ribera et al (2010)	6.4	2.81	48	5.87	2.81	48	9.7%	0.53 [-0.59, 1.65]
Font-Ribera et al (2019)	10.63	3.7	105	11.06	3.48	105	10.5%	-0.43 [-1.40, 0.54]
Jacobs et al (2010)	8.42	0.24	38	8.26	4.37	38	8.4%	0.16 [-1.23, 1.55]
Nanson et al (2001)	14.75	8.13	10	9.08	3.52	10	1.2%	5.67 [0.18, 11.16]
Pourmanaf et al (2020)	6.8	0.37	10	6.27	0.55	10	13.1%	0.53 [0.12, 0.94]
Tufvesson et al (2013)	11.08	6.26	17	6.66	2.8	17	3.0%	4.42 [1.16, 7.68]
Subtotal (95% CI)			**292**			**292**	**79.6%**	**0.53 [0.05, 1.01]**
Heterogeneity: Tau² = 0.24; Chi² = 23.87, df = 9 (P = 0.005); I² = 62%								
Test for overall effect: Z = 2.18 (P = 0.03)								
Total (95% CI)			**375**			**375**	**100.0%**	**1.12 [0.48, 1.77]**
Heterogeneity: Tau² = 0.78; Chi² = 65.55, df = 12 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 3.43 (P = 0.0006)								
Test for subgroup differences: Chi² = 3.58, df = 1 (P = 0.06), I² = 72.0%								

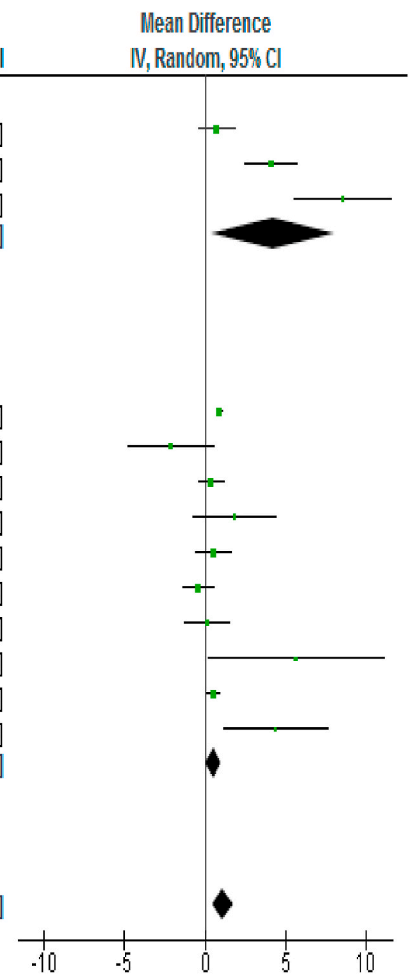

Fig. 4. Subgroup analysis of the effect of environmental temperature on club cell secretory protein compared with baseline.

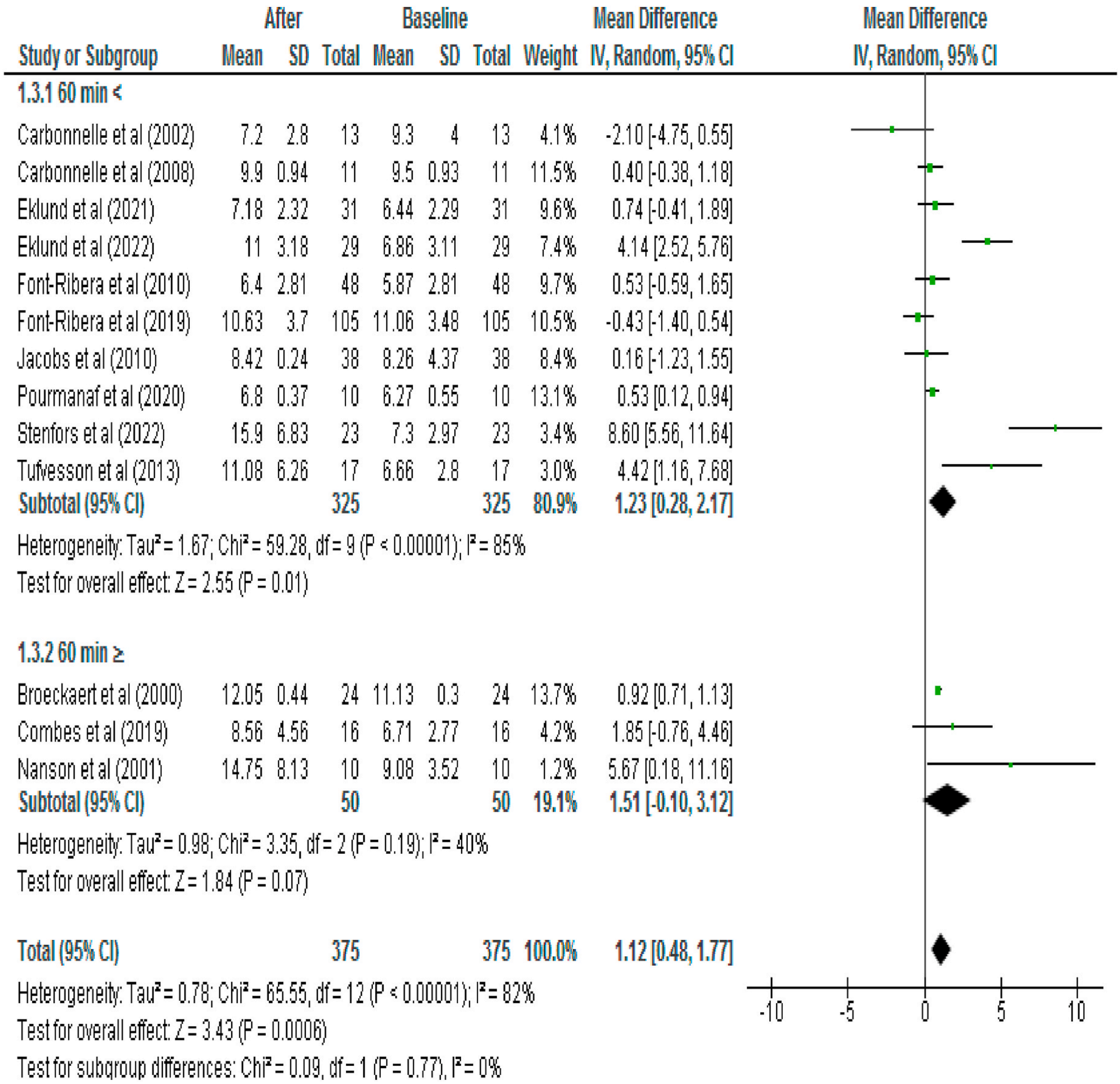

Fig. 5. Subgroup analysis of the effect of exercise duration on club cell secretory protein compared with baseline.

pooled into the meta-analysis and the results demonstrated that the changes in CC16/SP-D ratio were significant after exercise. Moreover, the results from the forest plot demonstrated that the concentrations of SP-D were increased after exercise, but it was not significant.

The results of this systematic review and meta-analysis should be interpreted considering the limitations. First, there were differences between included publications in terms of type, intensity, and duration of endurance exercise. Second, exercise interventions have been performed in discrepant environmental and temperature conditions. Third, the participants in the studies did not have the same physical fitness. Fourth, given the number of studies was insufficient on SP-D and the CC16/SP-D ratio, we could not carry out subgroup analysis for them. Finally, we only included published articles that were in English in this review.

We are the first to undertake a systematic review and meta-analysis on the acute effects of endurance exercise on the epithelial integrity of the airways in athletes and non-athletes. Our findings demonstrate that acute endurance exercise resulted in an increase in CC16 and CC16/SP-D ratio, whereas SP-D did not change significantly. Given the limited current evidence of the CC16/SP-D ratio and SP-D, further studies are needed to confirm or refute these findings. There is also a need to examine the effects of acute endurance exercise on airway epithelial integrity markers in patients with respiratory disease. This could assist with examining the responses of the airways to therapeutic interventions including pulmonary rehabilitation, nutrition, and pharmacological treatments which could help guide clinical practice.

Our subgroup analysis also revealed that the type, but not the duration of exercise or the environmental temperature affected the CC16 response to endurance exercise. Further studies are required to specifically examine how exercise intensity, exercise duration, environmental factors, and aerobic fitness affect the response of airway epithelial integrity markers to acute endurance exercise.

5. Conclusion

The aim of this systematic review and meta-analysis was to examine the acute effects of endurance exercise on markers of epithelial integrity of the airways (CC16, SP-D and the CC16/SP-D ratio) in healthy athletes and non-athletes. We found that acute endurance exercise increases CC16 and the CC16/SP-D ratio, but not SP-D in healthy athletes and non-athletes. Subgroup analysis revealed that the type, but not the duration of or the environmental temperature, increased CC16 after exercise. In

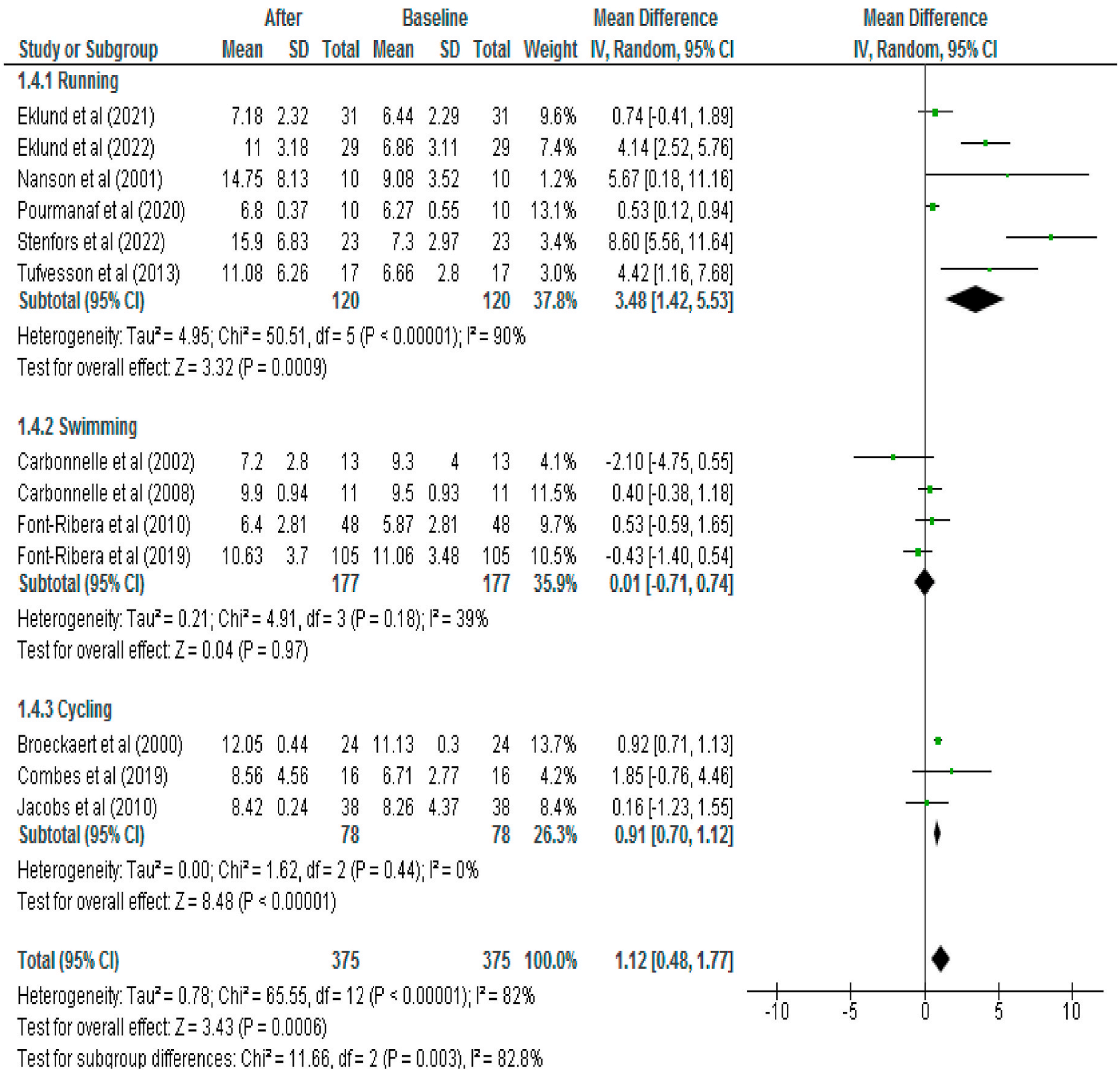

Fig. 6. Subgroup analysis of the effect of the exercise type on club cell secretory protein compared with baseline.

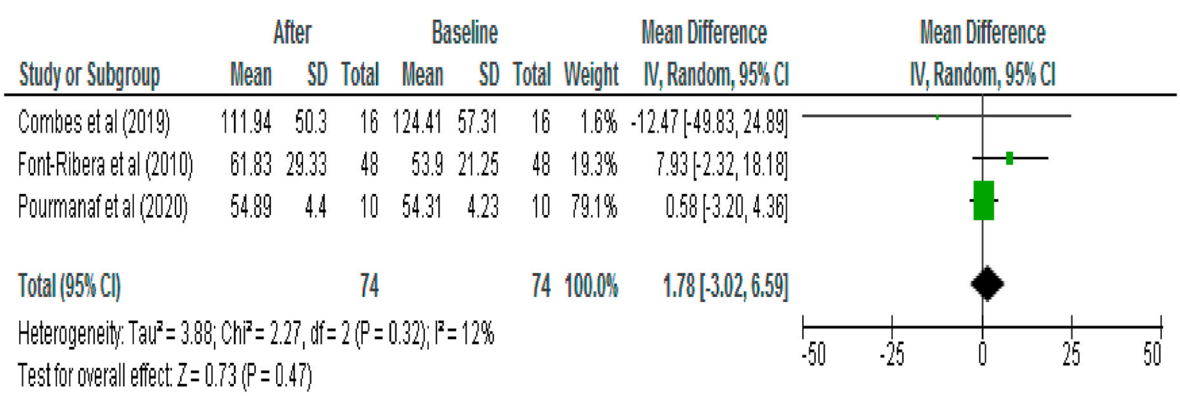

Fig. 7. Forest plots of the effect of endurance exercise on surfactant protein D compared with baseline.

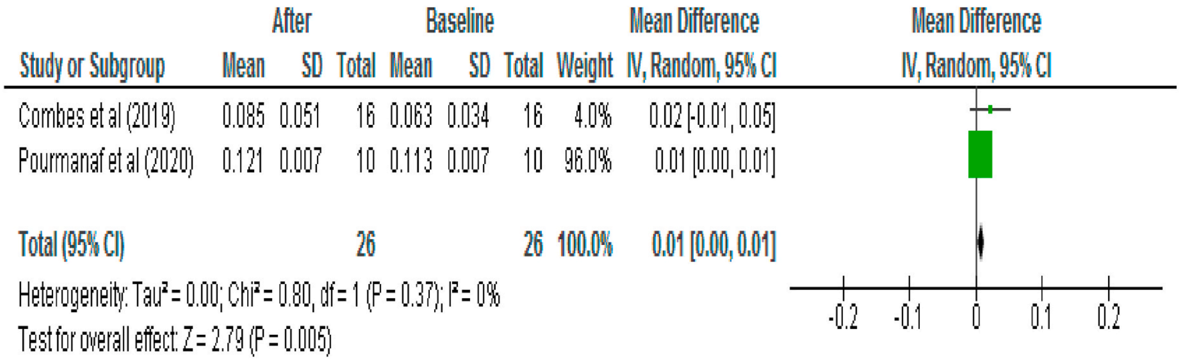

Fig. 8. Forest plots of the effect of endurance exercise on club cell secretory protein/surfactant protein D compared with baseline.

conclusion, acute endurance exercise increases CC16 and the CC16/SP-D ratio, markers of epithelial integrity, but not SP-D.

Funding

No funding

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors' contributions

Study concept and design: SN and HP; Collection and assembly of data: SN, VS, RA, and JV; Data analysis and interpretation: HP, SN and DM; Manuscript writing and review: HP, SN and DM. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Acknowledgements

Not applicable.

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