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Rhinology

Nasal nitric oxide measurement in allergic rhinitis and non-allergic rhinitis: a meta-analysis

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SUMMARY

The goal of this meta-analysis was to study nasal nitric oxide (nNO) measurements in allergic rhinitis (AR) and non-allergic rhinitis (non-AR). The protocol was registered with PROSPERO (no: CRD4202124828). Electronic databases from PubMed, Google Scholar, Scopus, Web of Science, and Cochrane were all thoroughly searched and studies were chosen based on the qualifying requirements. The quality of the studies was evaluated by Joanna Briggs Institute evaluation tools, and publication bias using funnel plots. The meta-analysis included 18 studies, whereas the systematic review included 20 studies, totaling 3097 participants (1581 AR, 458 non-AR, and 1058 healthy/control). Patients with AR had significantly greater nNO levels than the control group, although this did not change significantly before or after treatment. AR patients had significantly greater nNO levels than non-AR patients, but there was no significant difference between non-AR patients and healthy controls. Nineteen of the studies were of high quality and the remaining one was of moderate quality. nNO measurement has a promising role in the management of AR and non-AR patients, but more investigations are needed to document clinical benefits.

KEY WORDS: allergic rhinitis, non-allergic rhinitis, nitric oxide, nasal nitric oxide, fractional exhaled nitric oxide, bronchial asthma

Introduction

Allergic rhinitis (AR) is characterised as inflammation of the nasal mucosa brought on by type 2 helper T (Th2) cells [1]. Due to immunoglobulin (Ig)E-mediated reactions (type 1 hypersensitivity) to inhaled allergens, AR results in sneezing, nasal pruritus, nasal obstruction, and primarily clear nasal discharge. Most symptoms start to show up within minutes and can linger for hours. When AR affects children, it has a negative impact on their physical, social, and psychological well-being, which indirectly affects parents and/or other family members [2]. AR can disrupt sleep and increase everyday weariness, which can impair academic and professional performance [3]. Clinical and nasoendoscopic examination, and evidence of sensitisation – measured either by the presence of allergen-specific IgE in serum or by positive skin prick tests (wheal and flare responses to allergen extracts) – are used to make the diagnosis of AR [4]. Nitric oxide (NO) is an important element in the airways. It governs bronchial muscle tone, blood flow, and immunological response in the lower airways, as well as cilia motility and defence mechanisms in the upper airways [5].

Nasal NO (nNO) levels associate well with inflammatory biomarkers such as eosinophil and eosinophil cationic protein levels and constitute a low-cost, non-invasive technique to identify airway inflammation [6]. nNO measurement is a validated test that has been shown to be effective in the diagnosis and

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monitoring of asthma, as well as having a potential role in the management of AR.

Airway NO levels are measured using various parameters such as oral fractional exhaled NO (FeNO), nasal FeNO, and nNO. While oral FeNO is typically prescribed for bronchial asthma, nasal FeNO and nNO have also been suggested for AR patients [7]. When the measurement is taken through nasal exhalation, it is referred to as nasal FeNO. It is termed as nNO if it is acquired through transnasal flow in series. nNO levels are typically measured by a single experienced operator in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) standards [7]. Parts per billion (ppb) are the units of measurement. Aspiration at constant flow rate from one naris with gas entrained via the other naris (transnasal flow in series) is the currently advised technique for measuring nNO [7]. This technique measures nNO in isolation from the lower respiratory tract and is the most widely used and most thoroughly validated. To prevent nNO leakage through the posterior velopharyngeal gap, the velum must be closed. The preferred technique has been determined to be slow oral exhalation against a resistance of at least 10 cm H_20 since it has been demonstrated to consistently shut the velum [7]. The measurement of NO levels as oral FeNO, nasal FeNO, and nNO differs, and thus a consistent approach is required to avoid misinterpretation. We conducted a systematic review and meta-analysis to evaluate the use of nNO measurements in AR and non-AR patients.

Methods

Reporting guidelines and protocol registration

The systematic review and meta-analysis were conducted according to the protocol registered in PROSPERO (CRD42021248288). The updated guideline of preferred reporting items for systematic reviews and meta-analyses (PRISMA) served as the framework for the methodology and reporting [8].

Criteria for eligibility

The search was done to find relevant studies that looked at nNO levels in individuals with AR and non-AR in both the paediatric and adult age without limiting them to any particular gender or race.

Literature search

PubMed, Google Scholar, Scopus, Web of Science, and Cochrane were screened, with the final search performed on August 24, 2022, and no language constraints. The terms "allergic rhinitis", "non-allergic rhinitis", "exhaled nitric oxide", and "nasal nitric oxide" were specifically searched for using the "Advanced" and "Expert" search modes, together with the Boolean logical operators ('AND' & 'OR') (Supplementary Table I). To ensure a thorough search, the references of the studies included were also examined. Duplicate studies were managed and filtered using EndNote X8 software.

Study selection

A literature search was carried out independently by two authors (AFD and BA) by first screening the study's title and abstract, then retrieving the full texts of any matching papers that met the inclusion requirements. All age groups with a physician-confirmed diagnosis of AR and non-AR fulfilled the inclusion criteria. Excluded studies included bronchial asthma research, review articles, case studies, non-human studies, views, and viewpoints. Disagreements over inclusion were discussed and resolved (consensus between two authors, BA and MAI).

All studies examining nNO levels in AR and non-AR patients with controls, as well as pre- and post-treatment, were considered. The information retrieved included the nNO analyser, sampling technique, sample rate, and diagnostic criteria. Studies were excluded if any of the following were found: (1) number of AR patients was less than 10; (2) the procedure of nNO measurement did not follow the ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005 [7]; and (3) AR diagnosis did not meet criteria described in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [9].

Data extraction

The data from the studies included was accessed independently by two authors (AFD and MAI). The essential data and information were obtained from each qualified study and entered into a preset Excel spreadsheet. The following information was collected from the studies chosen: type of study, country, number of patients, number of controls, age of participants, diagnosis, analyser used to detect nNO, and last observation of each study. A consensus was reached among the authors regarding any discrepancies, ambiguities, or missing data. The corresponding or first author of the relevant studies was emailed for clarification if the issue persisted.

Quality assessment and publication bias

The critical assessment tools developed by the Joanna Briggs Institute were used to assess the quality of the included studies. The studies were classified as poor quality (high risk of bias), moderate quality (moderate risk of bias), or high quality (low risk of bias) if the overall score

was 50 percent, 50-70 percent, or > 70 percent[10,11]. A publication bias evaluation using a funnel plot would be carried out if there were 10 or more studies.

Data analysis

Parts per billion (ppb) was used as the standard for all nNO level measurement units. The nNO levels were evaluated using mean differences (MDs) and their corresponding 95% confidence intervals (CI). The random-effects model and the I^2 statistic were employed to measure trial heterogeneity ($I^2 > 75\%$ indicating significant heterogeneity). The significance of the heterogeneity test was evaluated using the Cochran's Q test. A sensitivity analysis was also carried out to assess the accuracy of the findings and possible sources of heterogeneity. All analyses were completed using RevMan software (version 5.3.5). A p value of 0.05 or less was considered statistically significant.

Results

Study selection

561 articles were initially identified from the five databases (Fig. 1). Following the removal of 229 duplicates and another 32 studies (non-human subjects, review articles, case reports, editorials, and comments), 267 studies were excluded from the remaining articles based on title and/or abstract evaluation, as they did not meet the criteria. Finally, the meta-analysis comprised 18 studies [6,12-21,24-30] and the systematic review included 20 studies [6,12-30].

Characteristics of the included studies

All studies measured the nNO levels in AR, non-AR and healthy (control) individuals, with a total of 3097 participants (1581 AR, 458 non-AR, 1058 healthy/control). The investigations were done in different nations, including China (n = 8), Sweden (n = 3), Korea (n = 1), Finland (n = 1), Taiwan (n = 1), Vietnam (n = 1), Czech Republic (n = 1), USA (n = 1), Turkey (n = 1), Italy (n = 1) and Greece (n = 1).

Except for three cross-sectional studies [26-28], all papers were case control studies [6,12-25,29,30]. The NO analysers used were made by Sievers 280i, NIOX, NIOX MINO, HypAir, Analyser CDL 88, Nano Coulomb Breath Analyzer CA2122. Apart for two studies [15,21], which employed chemiluminescence analysers, all studies [6,12-14,16-20,22-30] used electrochemical analysers. Conventional clinical criteria, including symptoms, examination, and allergy testing, were used to confirm AR diagnosis in accordance with guidelines [9]. Skin prick testing and serum specific IgE were procedures employed for confirmatory allergy testing. Online measurement techniques were applied in all testing.

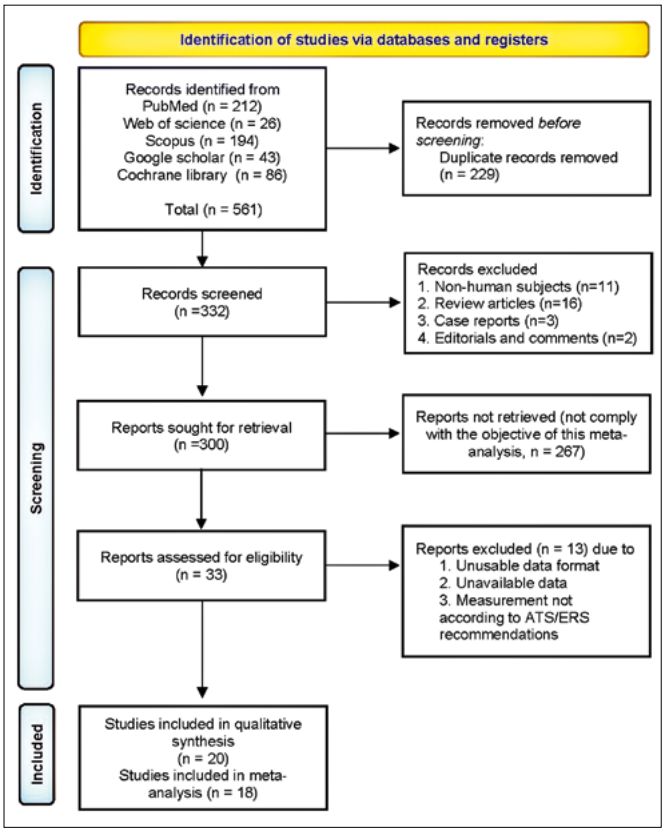

Figure 1. PRISMA flow-chart depicting the study selection process.

In seven studies [12,13,17,18,21,23,24], patients were not given intranasal corticosteroids or oral antihistamines for their AR; in three studies [6,14,30], a combination of oral antihistamines and intranasal corticosteroids with or without a leukotriene receptor antagonist was given; two studies [27,29] used only oral antihistamines; one study [28] used sublingual immunotherapy; one study [25] used subcutaneous immunotherapy; six studies did not provide this information [15,16,19,20,22,26]. The length of treatment varied, ranging from two weeks to a year. AR with bronchial asthma was included in three studies [13,18,26], while AR with nasal polyps was included in one study[18]. Table I summarises the characteristics of the studies included.

Outcomes

A. nNO levels in AR patients

Patients with AR were compared to controls in 13 studies [6,12-21,24,25]. The nNO levels were substantially greater in AR patients than healthy subjects (MD: 296.18, 95% CI: 118.18 to 474.17; p = 0.001) (Fig. 2A).

B. nNO levels in pre- and post-treated patients

Six studies [6,25,27-30] investigated nNO levels in AR patients

Table I. Main characteristics of the studies included.

No.	Study	Country	No. of participants	Age (years)	Diagnosis of AR	Type of AR	Severity of AR	Comorbid condition	Analyser	Treatment	Outcomes
1	Lee, 2012 [15]	Korea	AR: 35	AR: 22.7 ± 8.7	Skin prick test	Intermittent and persistent	Mild to severe	No	Sievers 280i (Ge Analytical Instruments, Colorado)	NR	nNO levels significantly higher in AR compared to control
			C: 34	C: 26.9 ± 11.0							
2	Hou, 2018 [12]	China	AR: 75	AR: 36.2 ± 10.9	Serum IgE measurement	Intermittent only	Mild to severe	No	NIOX (Aerocrine AB, Solna Sweden)	None	Compared with controls, nNO levels were significantly higher in AR patients
			C: 31	C: 35.3 ± 12.1							
3	Suojalehto, 2014 [18]	Finland	AR: 89	AR: 32.9 ± 1.3	Skin prick test, serum IgE measurement	NR	NR	1. bronchial asthma	NIOX (Aerocrine AB, Solna Sweden)	None	1.nNO levels were elevated in AR compared to controls
			Non-AR: 44	Non-AR: 33.2 ± 1.5				2. nasal polyps			2. nNO levels did not differ between non-AR and control groups or between non-AR and AR groups
			C: 42	C: 33.5 ± 1.8							
4	Irander, 2012 [13]	Sweden	AR: 18	AR: 18 ± NR	Skin prick test	Intermittent and persistent	NR	Bronchial asthma	NIOX (Aerocrine AB, Solna Sweden)	None	Higher levels of nNO were found in AR compared to control
			C: 7	C: 18 ± NR							
5	Wen, 2019 [19]	Taiwan	AR: 90	AR: 9.7 ± 2.4	Allergen specific IgE testing	Persistent only	NR	No	NIOX MINO (Aerocrine AB, Solna Sweden)	NR	Significantly higher nNO levels and total nasal resistance in children with AR than normal children
			C: 79	C: 10.1 ± 1.9							
6	Kim, 2020 [14]	Vietnam	AR: 267	AR: 36.0 ± 17.0	Skin prick test	Persistent only	Mild to severe	No	HypAir (Medisoft, Belgium)	Desloratadine combined with montelukast, or with intranasal fluticasone propionate x 6/12	nNO levels of persistent AR patients were higher than controls
			C: 234	C: 37.0 ± 18.0							
7	Palm, 2003 [17]	Sweden	AR: 18	AR: 32 (21-50)	Skin prick test	Intermittent only	Mild to moderate	No	NIOX (Aerocrine AB, Solna Sweden)	None	Patients with AR have higher and larger interindividual spread in nNO levels compared to controls
			C: 18	C: 30 (20-46)							
8	Maniscalco, 2008 [16]	Sweden	AR: 15	AR: 36.0 ± 13.9	Skin prick test	NR	NR	No	NIOX MINO (Aerocrine AB, Solna Sweden)	NR	nNO levels were slightly higher in AR compared to control group
			C: 15	C: 27.9 ± 2.3							

continues ▶

Table I. *follows.*

No.	Study	Country	No. of participants	Age (years)	Diagnosis of AR	Type of AR	Severity of AR	Comorbid condition	Analyser	Treatment	Outcomes
9	Antosova, 2020 [6]	Czech Republic	AR: 50	AR: Men 42.5 ± 15.3, Women: 39.0 ± 10.9	Skin prick test	Intermittent only	NR	No	NIOX MINO (Aerocrine AB, Solna Sweden)	Oral antihistamine and intranasal steroids x 3/52	1. AR patients may frequently have high nNO values
			C: 50	C: Men 21.3 ± 1.7, Women: 21.0 ± 3.7							2. No significant differences in nNO after three weeks of treatment
10	Liu, 2015 [20]	China	AR: 30	NR	Skin prick test	NR	NR	No	NIOX MINO (Aerocrine AB, Solna Sweden)	NR	1. nNO levels were significantly higher in children with AR compared to healthy children
			Non-AR: 10								
			C: 25								2. Non-AR children had higher nNO levels than healthy children, although the levels were lower than AR children
11	Makris, 2011 [21]	Greece	AR: 26	AR: 28.4 (16-47)	Skin prick test	Intermittent only	NR	No	Analyser CDL 88 sp (ECO MEDICS, Duernten, Sweden)	None	nNO levels were increased during pollen season only in patients with bronchial hyper-responsiveness
			C: 15	C: 37.1 (31-43)							
12	Ren, 2019 [22]	China	AR: 151	AR: 45 (18-63)	Skin prick test	NR	NR	No	NIOX MINO (Aerocrine AB, Solna Sweden)	NR	1. nNO levels were significantly higher in AR patients than in healthy and asymptomatic atopic subjects
			Non-AR: 298	Non-AR: 47 (19-64)							
			C: 328	C: 45 (18-68)							2. nNO levels were not substantially different in non-AR patients compared to AR or non-AR patients compared to normal subjects.
13	Zhao, 2022 [23]	China	AR: 60	AR: 25.0 ± 6.3	Skin prick test, serum IgE measurement	NR	Mild, moderate severe	No	Nano Coulomb Breath Analyzer CA2122 (Sunvou Medical Electronics, China)	None	The nNO in the AR group was higher than in healthy people
			C: 30	C: 27.0 ± 8.4							

continues ▶

Table I. *follows.*

No.	Study	Country	No. of participants	Age (years)	Diagnosis of AR	Type of AR	Severity of AR	Comorbid condition	Analyser	Treatment	Outcomes
14	Li, 2021 [24]	China	AR: 30	AR: 37.6 ± 14.76	Skin prick test	Persistent only	NR	No	Nano Coulomb Breath Analyzer CA2122 (Sunvou Medical Electronics, China)	None	The levels of nNO in AR group were higher than in the control group
			C: 30	C: 33.43 ± 16.2							
15	Wen, 2023 [25]	China	AR: 120	AR: 31.7 ± 10.6	Skin prick test, serum IgE measurement	NR	Moderate to severe	No	Nano Coulomb Breath Analyzer CA2122 (Sunvou Medical Electronics, China)	SCIT Novo-Helisen Depot (NHD) allergen extracts (Allergopharma, Reinbek, Germany) x 1 year	1. nNO levels were higher in AR patients than in controls
			C: 40	C: 30.4 ± 7.6							2. Higher nNO is seen with symptomatic reduction after subcutaneous injections immunotherapy
16	Kalpaklioglu, 2021 [26]	Turkey	Non-AR: 106	Non-AR: 28 (22-39)	Skin prick test, serum IgE measurement	Intermittent and persistent	Mild, moderate-severe	Bronchial asthma	NIOX MINO (Aerocrine AB, Solna Sweden)	NR	AR had significantly higher nNO levels compared to NAR (370 ppb *vs* 290 ppb
			AR: 337	AR: 25 (20-33)							
17	Luo, 2021 [27]	China	AR: 61	AR: 7.5 ± 2.18	Serum IgE measurement	NR	NR	No	Nano Coulomb Breath Analyzer CA2122 (Sunvou Medical Electronics, China)	Oral loratadine for 3 weeks	nNO values were higher after treatment. Possible reasons were:
											1. anti-inflammatory drugs do not work efficiently due to reduced diffusion capacity
											2. airway remodeling may interfere with nNO levels
18	Parisi, 2021 [28]	Italy	AR: 34	AR: 10.1 ± 3.2	Skin prick test, serum IgE measurement	Persistent only	NR	No	HypAir FeNO (Medisoft, Belgium)	House dust mite sublingual immunotherapy x 6/12	Significant nNO value was reached when the patients completed the 6 months of treatment

continues ▶

Table I. *follows.*

No.	Study	Country	No. of participants	Age (years)	Diagnosis of AR	Type of AR	Severity of AR	Comorbid condition	Analyser	Treatment	Outcomes
										plus oral antihistamines, intranasal corticosteroids, montelukast	
19	Bautista, 2011 [29]	USA	AR: 31	AR: 29 (13-45)	Skin prick test	Persistent only	NR	No	NIOX (Aerocrine AB, Solna Sweden)	Oral levocetirizine x 2/52	Significant difference pre & post, and treatment with placebo
			C: 31	C: 29 (13-45)							
20	Wang, 2017 [30]	China	AR: 44	AR: 6.8 ± 2.3	Skin prick test, serum IgE measurement	Persistent only	Mild, moderate severe	No	Nano Coulomb Breath Analyzer CA2122 (Sunvou Medical Electronics, China)	Mometasone furoate alone or mometasone furoate combined with oral antihistamine x 1/12	Significant difference in nNO levels after treatment
			C: 49	C: 7.2 ± 1.9							

AR: allergic rhinitis; non-AR: non-allergic rhinitis; C: control; nNO: nasal nitric oxide; IgE: immunoglobulin E; NR: not reported.

before and after treatment, but no studies for non-AR patients were found. nNO levels in AR patients did not change substantially before or after treatment (MD: 146.35, 95% CI: -16.28 to 308.97; p = 0.08) (Fig. 2B).

C. nNO levels in non-AR patients

nNO levels in non-AR patients were compared to controls in two studies [18,20], and to AR patients in three studies [18,20,26]. Compared to non-AR patients, AR patients had higher nNO levels (MD: 78.06, 95% CI: 33.20 to 122.91; p < 0.001) (Fig. 2C). There was no difference in nNO levels between non-AR patients and healthy controls (MD: 58.09, 95% CI: -29.12 to 145.31; p = 0.19) (Fig. 2D).

Quality assessment and publication bias

The quality assessment of the case-control studies can be seen in Supplementary Table II and the cross-sectional studies in Supplementary Table III. Ninety-five percent (n = 19) of the included studies were of high quality (low risk of bias) and the remaining 5% (n = 1) were of moderate quality (moderate risk of bias). The funnel plot revealed the possibility of publication bias in estimating the mean difference of nNO levels between AR patients and controls, as well as nNO levels in AR patients before and after treatment (Supplementary Figure 1).

Sensitivity analysis

We determined that Kim et al. [14] and Wen et al. [19] were outlier studies using the leave-one-out method, and when these two studies were excluded the MD became 25.87 ppb lower than the overall value (Supplementary Table IV). The difference of nNO levels between the AR and control participants, however, remained statistically significant.

Discussion

The use of FeNO as a measurement technique in bronchial asthma has been demonstrated to have high accuracy regardless of the type of instrument utilised [31]. With such precision, it can be used as a screening and diagnostic tool for the allergic airway condition. The NO analysis method for nNO in patients with AR, chronic rhinosinusitis, or primary ciliary dyskinesia has been developed and evaluated.

The current meta-analysis observed that nNO levels in AR patients were considerably higher than in the control group. There are two outlier studies with extraordinarily high nNO values. Due to the existence of numerous confounding factors that contribute to the formation or exacerbation of AR, such as cigarette smoking, frequent exposure to allergens such as pollen, home dust mites, dog and cat hairs, and cockroaches, the level of nNO was exceedingly high in the study by Kim et al. [14] even after treatment. Wen et al. [19] reported a very high nNO level since they included AR patients who had severe sinusitis.

The concurrent occurrence of AR in asthma patients, known as the one airway theory, is characterised by eosinophil inflow, mast cell degranulation, and an increase in Th2-related cytokine release from lymphocytes [32]. AR patients with

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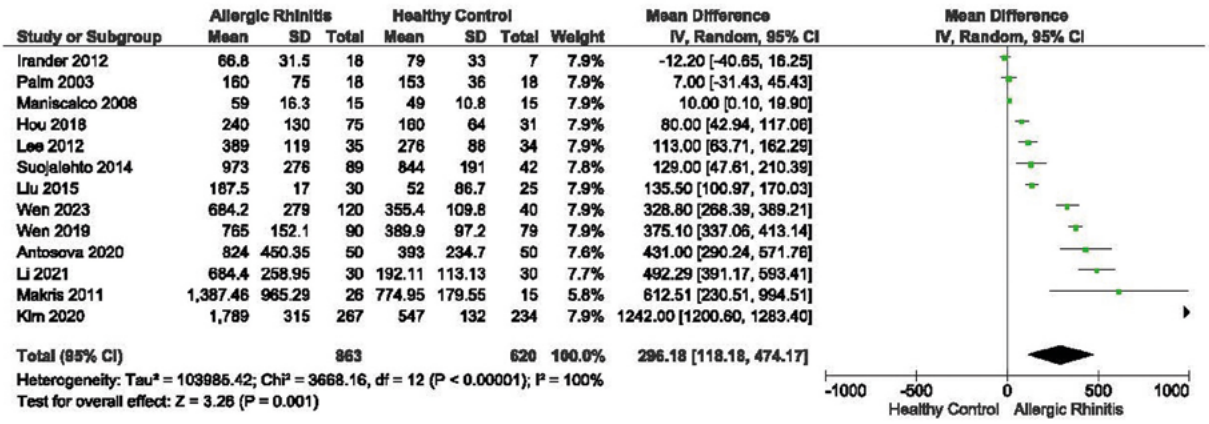

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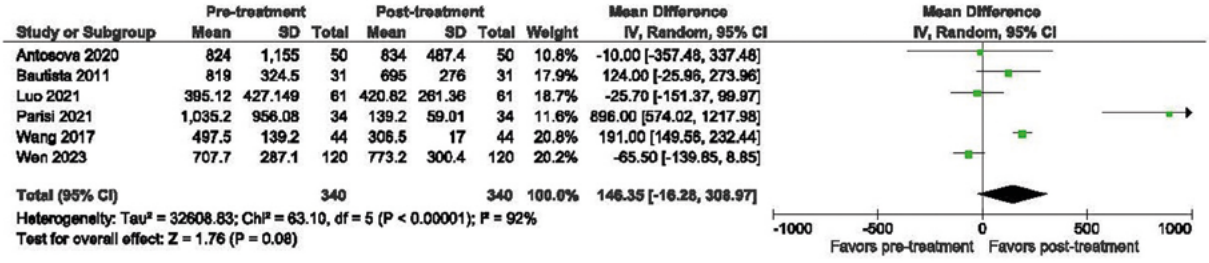

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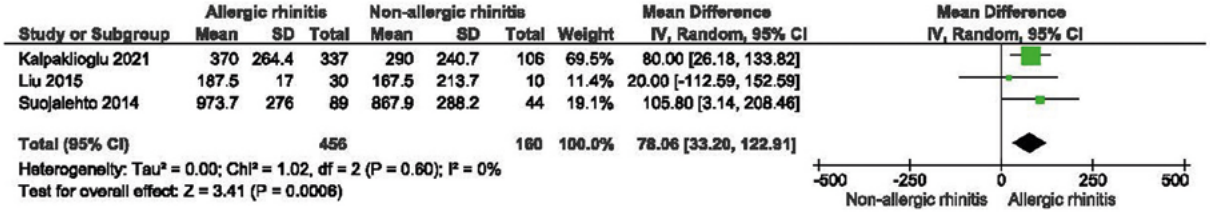

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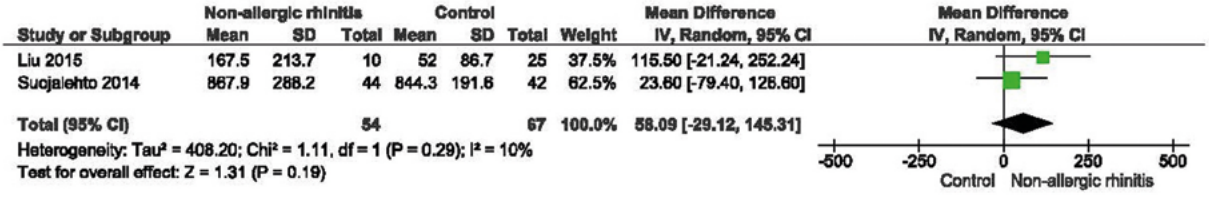

Figure 2. Forest plot representing the (**A**) nNO levels between patients with allergic rhinitis and controls and (**B**) pre- and post-treatment; (**C**) allergic rhinitis and non-allergic rhinitis and (**D**) non-allergic rhinitis vs controls.

and without asthma are frequently evaluated for airway hyper-responsiveness, spirometry, allergen skin testing, total and specific IgE, and NO measurement. A study by Duong-Quy et al. [33] found that nasal FeNO levels were not substantially different between AR and AR-asthma participants, but were significantly greater in AR and AR-asthma subjects than in control subjects. This suggests that nasal FeNO levels and AR symptoms in people with or without asthma were substantially correlated. This finding implies that NO measurement may be used as a tool in the management of AR when combined with clinical symptoms. Additionally, Nesic et al. [34] showed that nasal FeNO was very reliable in differentiating between AR patients and healthy individuals. In light of this finding, the authors proposed NO measurement as an objective and independent metric in the identification of AR patients with or without additional respiratory comorbidities like asthma.

In another investigation, it was reported that the nNO levels varied in accordance with the intensity of the clinical symptoms in people with seasonal AR during the pollen season [35]. The increased production of nNO brought on by airborne allergens (pollens, house dust mites, or cat or dog hairs) is the reason for the greater levels of nNO in AR compared to healthy people. In comparison to FeNO levels in the lower airway, nNO levels in the upper airway are significantly higher. The observation that nNO levels are significantly greater than FeNO may be due to the high NO production by the sinus epithelium [36]. Exhaled nNO is generated not only by gradient diffusion from the sinuses, but also by NO produced by nasal mucosal membranes (epithelium) and inflammatory cells (eosinophils) in response to iNOS overexpression [13,29,37,38]. Thus, in patients with AR, nNO measurement shows eosinophilic inflammation with a strong link to clinical symptoms and airway inflammation.

While nNO is more established in AR, its role in non-AR, and especially in certain subtypes like vasomotor rhinitis, is not as well-defined. In vasomotor rhinitis, there is evidence of neurogenic dysregulation, contributing to nasal hyperreactivity and increased nasal congestion [39]. In other cases, the exact cause is unknown, leading to the term idiopathic rhinitis. While the exact mechanisms can vary, some forms of non-AR may involve nasal inflammation [40]. NO measurements may provide insights into the underlying pathophysiology and guide treatment strategies. Furthermore, nNO measurement can assist in differentiating between allergic and non-allergic forms of rhinitis. The measurement might augment skin prick testing, which is the main clinical diagnostic tool to identify AR and non-AR [40]. In the present meta-analysis, we found that nNO differs between non-AR and AR with the latter having higher nNO levels. Interestingly, there is no difference in nNO levels between non-AR and controls. These results appear to indicate nNO levels would be effective in distinguishing non-AR from AR, but not in distinguishing non-AR from healthy people. The evaluation of the efficacy of anti-inflammatory therapies is another use for nNO measurement; documenting the levels of nNO before and after treatment can be invaluable in determining how well each therapeutic approach works. However, this meta-analysis found that using nNO in AR patients to determine therapeutic efficacy may not be helpful, and caution is advised when interpreting the results. Similarly, it is unclear whether monitoring therapy in non-AR patients with nNO will be beneficial, given no studies have documented such measurement. In addition to evaluating the measurement of nNO in diagnosing non-AR patients and its significance in monitoring therapeutic effectiveness, the results of this meta-analysis support those of two earlier meta-analyses [41,42].

Limitations of the study

The findings from our study may have some limitations. The literature search was restricted to research reports, with conference abstracts, review papers, case studies, non-human studies, views, and viewpoints removed while the subgroup's sample size was moderate, and several of the studies used a variety of confounding variables that might influence the nNO levels. The inclusion of diverse types of AR patients with varying severity, AR patients with or without concomitant diseases, and AR patients receiving therapy or not are most likely contributing factors for the extremely high heterogeneity among studies. Variability in the technique of measurement and the device used can impact the reliability and reproducibility of results. Lack of standardised protocols for nNO measurement can hinder comparisons between studies and limit the establishment of universal diagnostic criteria. nNO may not predict treatment response uniformly across all patients, and its role as a predictor of therapeutic outcomes remains an area of investigation.

Conclusions

The outcomes of this meta-analysis indicate that while nNO measurement can discriminate between AR and healthy individuals, it is unable to distinguish non-AR from healthy individuals. Additionally, nNO measurement can identify AR patients from non-AR individuals. Caution should be taken when interpreting nNO levels to monitor the efficacy of treatment in AR patients. nNO measurement has a promising role in the management of AR and non-AR patients, but more investigations are needed to document clinical benefits.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

AFD, MAI, NMS, BA: made a substantial contribution to the conception and design of the article, to the acquisition, analysis and interpretation of data. All authors critically revised the article and gave the final approval of the version to be published.

Ethical consideration

The systematic review and meta-analysis design of this article does not require ethical approval from our institution. This article does not involve generation of new data from human or animal and no consent is necessary.

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Table SI. Search strategies.

Databases	Search strategies
PubMed	(allergic rhinitis, non-allergic rhinitis, treatment [Title/Abstract]) AND (nasal nitric oxide[Title/Abstract] OR nNo[Title/Abstract])
Scopus	TITLE-ABS ("allergic rhinitis", "non-allergic rhinitis", "treatment") AND TITLE-ABS ("nasal nitric oxide" OR nNo)
Web of Science	TI= (allergic rhinitis, non-allergic rhinitis, treatment) AND TI= (nasal nitric oxide OR nNo) Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI Timespan: all years
Cochrane Library	(allergic rhinitis, non-allergic rhinitis, treatment) AND (nasal nitric oxide OR nNo): ti,ab,kw
Google Scholar	All in title: ("allergic rhinitis") ("non-allergic rhinitis") ("treatment") ("nasal nitric oxide" OR nNo)

Table SII. Quality assessment of the case-control studies.

No.	Study ID	Questions assessing included case-control studies										Yes (%)
		1	2	3	4	5	6	7	8	9	10	
1	Lee, 2012 [15]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90
2	Hou, 2018 [12]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90
3	Suojalehto, 2014 [18]	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	80
4	Irander, 2012 [13]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	80
5	Wen, 2019 [19]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90
6	Kim, 2020 [14]	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	90
7	Palm, 2003 [17]	Y	Y	Y	Y	Y	U	U	Y	Y	Y	80
8	Maniscalco, 2008 [16]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	90
9	Antosova, 2020 [6]	Y	Y	Y	Y	Y	U	U	Y	Y	Y	80
10	Liu, 2015 [20]	Y	Y	Y	Y	Y	Y	U	Y	N	Y	80
11	Makris, 2011 [21]	Y	Y	Y	Y	Y	U	U	Y	Y	Y	80
12	Ren, 2019 [22]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	80
13	Li, 2021 [24]	Y	Y	Y	Y	Y	U	U	Y	U	Y	70
14	Wen, 2023 [25]	Y	Y	Y	Y	Y	U	U	Y	Y	Y	80
15	Zhao, 2022 [23]	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	90
16	Bautista, 2011 [29]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	90
17	Wang, 2017 [30]	Y	Y	Y	Y	Y	U	U	Y	Y	Y	80

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls? 2. Were cases and controls matched appropriately? 3. Were the same criteria used for identification of cases and controls? 4. Was exposure measured in a standard, valid and reliable way? 5. Was exposure measured in the same way for cases and controls? 6. Were confounding factors identified? 7. Were strategies to deal with confounding factors stated? 8. Were outcomes assessed in a standard, valid and reliable way for cases and controls? 9. Was the exposure period of interest long enough to be meaningful? 10. Was appropriate statistical analysis used? Y: yes; N: no; U: unclear.

Table SIII. Quality assessment of the cross-sectional studies.

No.	Study ID	Questions assessing included cross-sectional studies								Yes (%)
		1	2	3	4	5	6	7	8	
1	Kalpaklioglu, 2021 [26]	Y	Y	Y	Y	U	U	Y	Y	60
2	Luo, 2021 [27]	Y	Y	Y	Y	Y	N	Y	Y	70
3	Parisi, 2021 [28]	Y	Y	Y	Y	Y	Y	Y	Y	80

1. Were the criteria for inclusion in the sample clearly defined? 2. Were the study subjects and the setting described in detail? 3. Was the exposure measured in a valid and reliable way? 4. Were objective, standard criteria used for measurement of the condition? 5. Were confounding factors identified? 6. Were strategies to deal with confounding factors stated? 7. Were the outcomes measured in a valid and reliable way? 8. Was appropriate statistical analysis used? Y: yes; N: no; U: unclear.

Table SIV. Sensitivity analyses.

Strategies of sensitivity analyses	MD [95% CI]	Difference of MD compared to the main result	Overall effect (p value)	Number of studies analysed	Total number of participants	Heterogeneity	
						I^2	p value
Excluding outlier studies	270.31 [170.37, 370.26]	25.87 lower	< 0.00001	11	891	96%	< 0.00001
Excluding small studies (n < 50)	390.09 [122.44, 657.74]	93.91 higher	0.004	10	1392	100%	< 0.00001

MD: mean difference, CIs: confidence intervals.

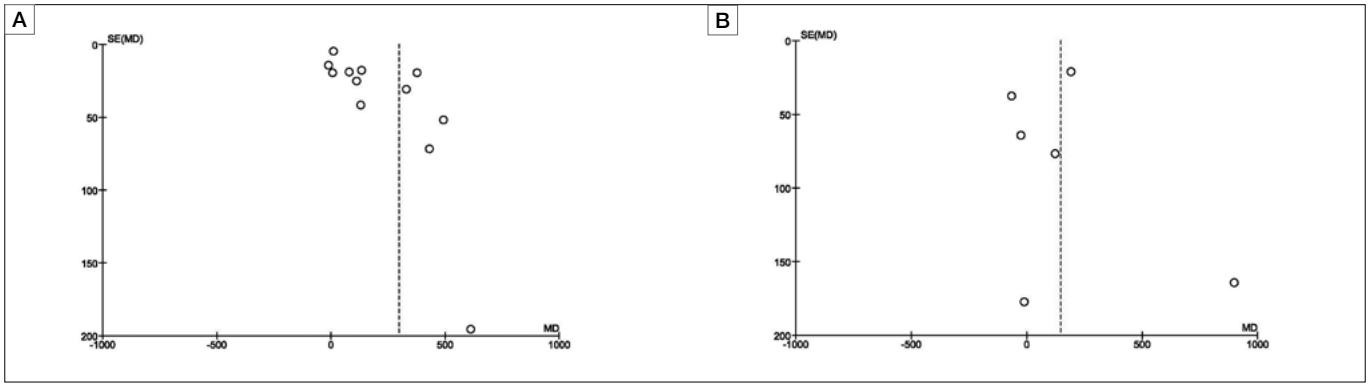

Figure S1. Funnel plot showing potential presence of publication bias representing the (**A**) nNO levels between patients with allergic rhinitis and controls and (**B**) pre- and post-treatment.