

Clinical application of nasal nitric oxide measurement in allergic rhinitis

A systematic review and meta-analysis

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ABSTRACT

Background: Nasal nitric oxide (nNO) is considered a biomarker of nasal inflammation.

Objective: To perform a systematic review with meta-analysis and meta-regressions on the association between nNO levels and allergic rhinitis (AR).

Methods: PubMed, Web of Science, Scopus, and EMBASE databases were systematically searched. Differences between cases and controls were expressed as standardized mean differences (SMD) with 95% confidence intervals (CI).

Results: Overall, 39 articles were included: 30 containing data on nNO measured by nasal aspiration (1881 patients with AR and 1337 controls) and 12 assessing nNO by nasal exhalation (525 patients with AR and 350 controls). Compared with controls, AR presented significantly higher nNO values both during nasal aspiration (SMD, 1.309; 95% CI, 0.841–1.777; $P < .001$) and nasal exhalation (SMD, 0.708; 95% CI, 0.303–1.114; $P = .001$). Sensitivity and subgroup analyses confirmed that the results for the evaluated outcomes were not affected by the presence of clinical confounding factors (asthma, nasal polyps, inhaled corticosteroids, smoking history), this being valid for both perennial and seasonal diseases during exposure to allergens. For the aspiration method, meta-regressions indicated that older age and a better pulmonary function were associated with a lower difference in nNO levels between patients with AR and controls, whereas an increasing aspiration flow was associated with a high effect size.

Conclusion: nNO levels are higher in AR, particularly when using high aspiration flows and in younger patients, who often perceive this condition as a source of disability. Further studies are needed to evaluate the usefulness of this biomarker for monitoring airway disorders and optimizing strategies in different settings (community, hospital, rehabilitation).

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Introduction

The studies on the role of nitric oxide (NO) in the airways have witnessed a growing interest during the previous decades.¹ Though only considered as a vasodilator at first,² in recent years, several functions have been recognized for NO in the upper and lower

respiratory tract.^{3–5} It is well known that in chronic inflammatory lung diseases, the NO concentration in exhaled air is generally augmented.⁶ Thus, measuring the fractional exhaled NO (FeNO) has become an important unbiased method to monitor drug compliance and response to different therapeutic interventions (eg, steroids, rehabilitation) in chronic airway diseases, especially asthma.^{7–12}

The observation that NO can also easily be quantified in the nasal airways suggested that nasal NO (nNO) could become a noninvasive means for monitoring nasal inflammation.⁵ To date,

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the European Respiratory Society and the American Thoracic Society have only agreed on a highly standardized FeNO procedure,^{13–15} whereas no single standardized method has been defined for nNO assessment so far among the several techniques used for evaluating nNO. The current approaches of measuring nNO include sampling the nasal air either directly from one nostril (aspiration method) or during a nasal single-breath exhalation using a nasal mask (exhalation method).

In recent years, both procedures have been applied to assess the relationship between allergic rhinitis (AR) and nNO levels. However, controversial results have been reported because some prospective studies found increased nNO levels in AR during exposure to allergens,^{16–19} whereas others observed no differences.²⁰ This could be related to the presence of comorbidities and other confounding factors, such as the occlusion of the sinus ostia, the use of intranasal corticosteroids, and differences in detection methods.²¹ In general, there is disagreement on the effect of AR on nNO levels, and no meta-analytical data providing a comprehensive information about this issue currently exists.

In this article, we aimed at performing a systematic review and meta-analysis of data assessing the relationship between AR and nNO levels measured by either nasal aspiration or nasal exhalation methods. We also carried out meta-regression models to account for the effects of some clinical and demographic variables on the evaluated outcomes.

Methods

For this systematic review, we prospectively developed a protocol specifying the goals, the principles for selecting the studies, the procedure to assess study quality, the outcomes, and the statistical methods.

Search Strategy

In agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,²² we carried out a systematic search in the electronic databases (PubMed, Web of Science, Scopus, EMBASE). The search terms “allergic rhinitis” and “nasal nitric oxide” were used in all possible combinations without any language restriction. We performed the final search on March 16, 2020.

In addition, the lists of the retrieved articles were manually reviewed. In the case of missing data, the authors were contacted by email to acquire the original data. Two investigators (Drs Parella and Motta) independently analyzed the studies and carried out data extraction. For divergent opinions, a third investigator was consulted (Dr Formisano). Discrepancies were resolved by consensus. Selection results presented a high interreader agreement ($\kappa = 1.00$) and have been detailed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig 1).

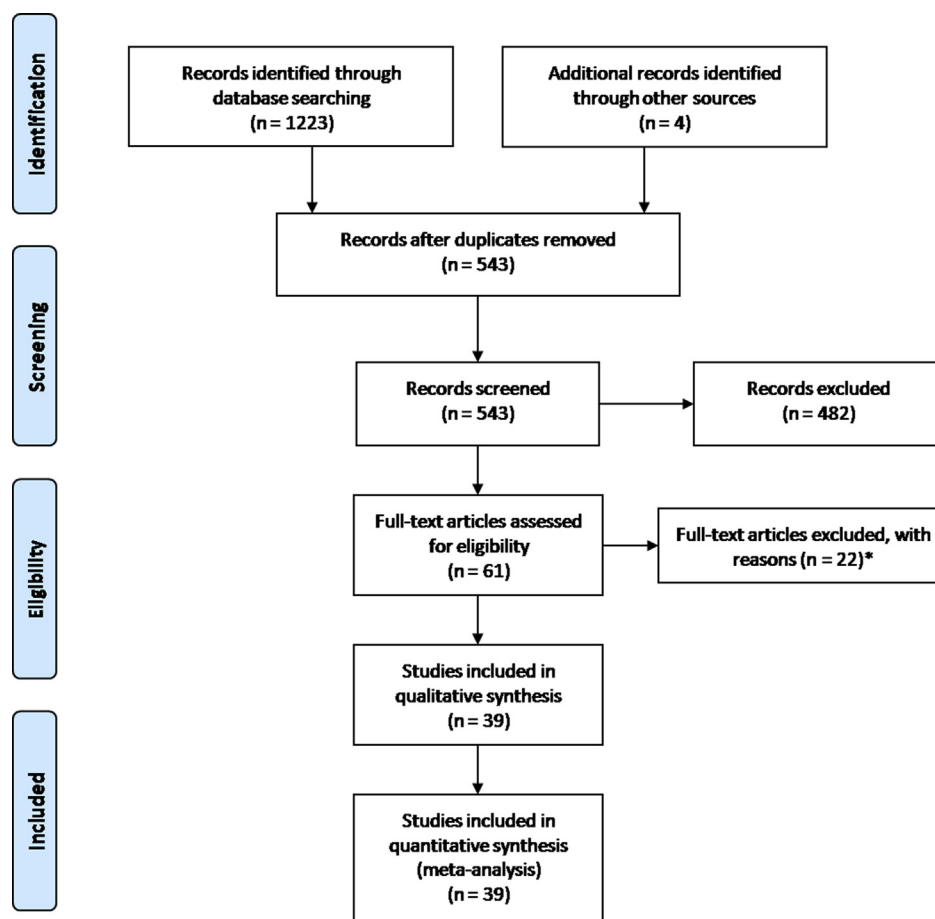


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for study selection. The * symbol indicates 13 studies without a control group, 3 studies with patients having nonallergic rhinitis being the control group, and 6 studies only reporting *P* values without mean values with SD or SE.

Data Extraction and Quality Assessment

In accordance with the established protocol, all studies evaluating nNO levels in patients with AR and controls were considered. Case reports, case series without a control group, reviews, and animal studies were not considered. Abstracts and citations from scientific conferences were also evaluated. To be included in the analysis, a study had to contain nNO values (mean with SD or SE) measured in patients with AR and controls. In accordance with the study design, articles were classified as either prospective or retrospective.

From each study, we extracted data on sample size, major clinical and demographic variables, nNO values in patients with AR and controls. The diagnosis of AR and the definition of controls have been reported in [eTable 1](#). Data on patients with rhinitis etiology other than allergic were excluded.

In [eTable 2](#), we reported the devices and methods used for nNO evaluation in the selected studies. Data obtained with nasal aspiration or nasal exhalation were separately analyzed. The methodological quality of each study was evaluated using the Newcastle-Ottawa Scale (NOS), which was specifically designed to assess the quality of nonrandomized observational studies.²³ The scoring system considered the following 3 major domains: selection (4 items), comparability (1 item), and exposure (3 items). A maximum score of 1 was graded for each item, except for that linked to comparability, which allowed for a score of 2. Total scores were calculated by adding the results from each item with a final score comprised between 0 and 9; higher value represented better methodological quality. The results of the NOS quality assessment are reported in [eTable 3](#).

Statistical Analysis and Risk of Bias Assessment

Statistical analysis was performed using Comprehensive Meta-analysis (version 2, Biostat Inc, Englewood, New Jersey). Differences between cases and controls were reported as standardized mean difference (SMD) with pertinent 95% confidence interval (CI). A different variance of the estimator among studies was assumed for the analyses.

The overall effect was tested using z-scores, with $P < .05$ considered as statistically significant. We evaluated statistical heterogeneity among studies using χ^2 Cochran's Q test and I^2 index. The latter measures the inconsistency across study results and describes the proportion of total variation in study estimates, which is because of heterogeneity rather than sampling error. In detail, I^2 values of 0% indicate no heterogeneity, 25% low, 25%–50% moderate, and more than 50% high heterogeneity.²⁴

Publication bias was evaluated by Egger's test and depicted graphically by funnel plots reporting the standard difference in mean values vs the SE. By visual inspection of funnel plot asymmetry, we addressed possible small-study effect, and Egger's and Begg and Mazumdar tests were applied to assess publication bias over and above any subjective evaluation. A $P < .10$ was considered statistically significant.²⁵ Moreover, the Duval and Tweedie's trim-and-fill analysis was used to evaluate an adjusted effect size after trimming and imputing studies.²⁶

To be as conservative as possible, we considered the variability among included studies by using the random-effects method.

Sensitivity Analyses

Potential sources of heterogeneity were investigated by repeating the analyses with the inclusion of only "high-quality" studies according to NOS (ie, NOS $\geq$ median value found among included studies). A separate analysis was also planned for studies systematically performing the skin prick test or the

allergen-specific immunoglobulin E (IgE) test to distinguish patients with AR from healthy controls.

To avoid data overlap, we performed a sensitivity analysis after excluding data obtained from patients recruited in the same centers and in the same period as other included studies.

Because of the possible effects of nasal polyposis and asthma on nNO levels, we carried out separate analyses explicitly excluding patients with such comorbidities. Similarly, we separately analyzed studies excluding the use of intranasal corticosteroids and those excluding patients with a smoking history.

Subgroup Analyses

For data on perennial AR and seasonal disease, subgroup analyses were also carried out. An additional stratification was performed for studies on seasonal AR by separately analyzing those quantifying nNO levels in-season and those estimating it off-season.

Additional sensitivity analysis was also planned after stratifying studies according to design (prospective or retrospective).

Meta-Regression Analyses

We also considered the effect of the following on the difference in nNO between cases and controls: (1) demographic variables (mean age, male sex); (2) pulmonary function measures (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], and FEV1/FVC); and (3) transnasal airflow during nNO measurement. For this, we performed meta-regression analyses after implementing a regression model that considered changes in nNO as dependent variables (y) and the abovementioned covariates as independent variables (x). Such analysis was carried out using the software Comprehensive Meta-analysis (version 2, Biostat Inc, Englewood, New Jersey).

Results

After the elimination of duplicate results, the search retrieved 543 articles. Of those, we excluded 368 (because they were off-topic after scanning the title or the abstract) and an additional 114 reviews, comments, case reports or studies owing to the lack of information on variables of interest. Another 22 studies were eliminated after a full evaluation of the texts. As a result, for the final analysis, we considered 39 articles^{16–20,27–60} ([Fig 1](#)). Of these, 30 studies (37 data sets on 1881 patients with AR and 1337 controls) contained data on nNO measured by nasal aspiration and 12 (18 data sets on 525 patients with AR and 350 controls) by nasal exhalation.

Study Characteristics

The studies included had prospective designs. The major characteristics of study populations are reported in [Table 1](#) and [eTable 1](#). The number of patients ranged between 5 and 267, the mean age between 6.1 and 64.1 years, and the male sex prevalence between 25% and 85.7%. The prevalence of asthma or nasal polyps and the use of intranasal corticosteroids among patients with AR varied from 0% to 100%. The mean values of FEV1 comprised between 77% and 101.2%, predicted; FVC between 82% and 95%, predicted; and FEV1/FVC between 86 and 100.8.

A total of 4 studies^{34,35,37,52} reported separate data for patients with AR with or without asthma, and 1 study⁴⁷ for patients with or without nasal polyps. Notably, 2 studies^{39,52} reported different analyses for seasonal and perennial AR, 4 studies^{27,30,36,52} for in-season and off-season evaluation of nNO in patients with seasonal disease, 1 study¹⁸ stratified results according to the presence or absence of ongoing steroid treatment, and 1 study⁵⁷

Table 1
Demographic and Clinical Data of Patients With Allergic Rhinitis and Control From the Included Studies

Study	Pop (n)	Males (%)	Age (y)	Smoking (%)	Perennial (%)	Seasonal (%)	In or off-season (%)	Nasal polyps (%)	Asthma (%)	Intranasal CCS (%)	FEV ₁ (% predicted)	FVC (% predicted)	FEV ₁ /FVC
Aggelides et al ^{27,a}													
AR	18	50.0	25.5	0	0	100	Both	-	-	0	97.1	-	-
Healthy	10	50.0	36.5	0	NA	NA	NA	NA	NA	NA	106.1	-	-
Arnal et al ¹⁶													
AR	36	55.5	-	-	66.6	33.3	-	-	36.1	25.0	-	-	-
Healthy	19	52.6	42.0	-	NA	NA	NA	NA	NA	NA	-	-	-
Asano et al ²⁸													
AR	20	-	-	0	-	-	-	0	100	0	-	-	-
Healthy	10	-	-	0	NA	NA	NA	NA	NA	NA	-	-	-
Baraldi et al ²⁹													
AR	21	80.9	9.6	-	100	0	NA	-	-	0	-	-	-
Healthy	21	85.7	10.5	-	NA	NA	NA	NA	NA	NA	-	-	-
Bozek et al ³⁰													
AR	248	33.5	64.1	-	0	100	Both	-	0	0	-	-	-
Healthy	196	38.8	65.0	-	NA	NA	NA	NA	NA	NA	-	-	-
Chen et al ³¹													
AR	55	52.7	-	0	-	-	-	-	-	-	-	-	-
Healthy	50	-	-	0	NA	NA	NA	NA	NA	NA	-	-	-
Colantonio et al ³²													
AR	82	-	39.0	0	-	-	-	46.3	-	100	-	-	-
Healthy	20	-	36.9	0	NA	NA	NA	NA	NA	NA	-	-	-
Djupestrand et al ³³													
AR	5	-	37.0	-	0	100	-	-	-	-	-	-	-
Healthy	8	50.0	38.1	0	NA	NA	NA	NA	NA	NA	-	-	-
Duong-Quy et al ³⁴ —Asthma													
AR	243	47.3	31.0	-	-	-	-	0	100	0	77.0	82.0	86.0
Healthy	217	52.5	37.0	-	NA	NA	NA	NA	NA	NA	97.0	98.0	88.0
Duong-Quy et al ³⁴ —No asthma													
AR	168	54.8	36.0	-	-	-	-	0	0	0	93.0	95.0	87.0
Healthy	217	52.5	37.0	-	NA	NA	NA	NA	NA	NA	97.0	98.0	88.0
Galiniak et al ³⁵ —Asthma													
AR	58	50.0	10.9	0	-	-	-	-	100	0	81.6	-	-
Healthy	25	56.0	10.1	0	NA	NA	NA	NA	NA	NA	87.5	-	-
Galiniak et al ³⁵ —No asthma													
AR	47	55.3	11.0	0	-	-	-	-	0	0	87.4	-	-
Healthy	25	56.0	10.1	0	NA	NA	NA	NA	NA	NA	87.5	-	-
Gratziou et al ³⁶													
AR	32	40.0	37.0	0	0	100	Both	0	40.6	0	>80%	-	100.8
Healthy	80	31.3	32.0	0	NA	NA	NA	NA	NA	NA	105.0	-	102.0
Gupta et al ³⁷ —Asthma													
AR	25	56.0	23.8	0	-	-	-	-	100	0	-	-	-
Healthy	15	66.7	25.5	0	NA	NA	NA	NA	NA	NA	-	-	-
Gupta et al ³⁷ —No asthma													
AR	25	56.0	24.7	0	-	-	-	-	0	0	-	-	-
Healthy	15	66.7	25.5	0	NA	NA	NA	NA	NA	NA	-	-	-
Henriksen et al ¹⁷													
AR	46	-	-	0	58.7	100	Both	-	0	0	-	-	-
Healthy	12	41.7	17.8	0	NA	NA	NA	NA	NA	NA	122.0	114.0	-
Hou et al ³⁸													
AR	75	61.3	36.2	0	0	100	In-season	-	0	-	-	-	-
Healthy	31	62.5	35.3	0	NA	NA	NA	NA	NA	NA	-	-	-
Irander et al ³⁹ —Perennial													
AR	13	-	-	0	100	0	NA	-	-	0	-	-	-
Healthy	7	-	-	0	NA	NA	NA	NA	NA	NA	-	-	-
Irander et al ³⁹ —Seasonal													
AR	5	-	-	0	0	100	Off-season	-	-	0	-	-	-

Healthy	7	-	-	0	NA	NA	NA	NA	NA	NA	-	-	-
Jeong et al ⁴⁰													
AR	27	77.8	33.4	-	-	-	-	100	0	0	-	-	-
Healthy	30	50.0	27.3	-	NA	NA	NA	NA	NA	NA	-	-	-
Kharitonov et al ¹⁸ —Steroid treated													
AR	10	40.0	31.0	0	0	100	In-season	0	0	100	92.0	94.0	-
Healthy	46	86.9	32.0	0	NA	NA	NA	NA	NA	NA	95.0	96.0	-
Kharitonov et al ¹⁸ —Steroid untreated													
AR	12	41.7	37.0	0	0	100	In-season	0	0	0	94.0	95.0	-
Healthy	46	86.9	32.0	0	NA	NA	NA	NA	NA	NA	95.0	96.0	-
Klak et al ⁴¹													
AR	30	53.3	27.3	-	40.0	60.0	-	0	0	-	-	-	-
Healthy	30	-	-	-	NA	NA	NA	NA	NA	NA	-	-	-
Lee et al ⁴²													
AR	35	71.4	22.7	-	-	-	-	-	0	0	-	-	-
Healthy	34	50.0	26.9	-	NA	NA	NA	NA	NA	NA	-	-	-
Liu et al ⁴⁴													
AR	30	80.0	-	0	-	-	-	-	0	-	-	-	-
Healthy	15	73.3	-	0	NA	NA	NA	NA	NA	NA	-	-	-
Liu et al ⁴³													
AR	48	35.4	31.9	-	-	-	-	0	-	0	-	-	-
Healthy	46	21.7	30.7	-	NA	NA	NA	NA	NA	NA	-	-	-
Maniscalco et al ⁴⁶													
AR	7	85.7	28.1	0	0	100	Off-season	0	0	0	-	-	-
Healthy	9	55.6	26.7	0	NA	NA	NA	NA	NA	NA	-	-	-
Maniscalco et al ⁴⁷ —Nasal polyps													
AR	5	80.0	37.6	0	-	-	-	100	0	0	-	-	-
Healthy	18	38.9	28.0	0	NA	NA	NA	NA	NA	NA	-	-	-
Maniscalco et al ⁴⁷ —No nasal polyps													
AR	15	46.7	26.3	0	-	-	-	0	0	0	-	-	-
Healthy	18	38.9	28.0	0	NA	NA	NA	NA	NA	NA	-	-	-
Maniscalco et al ⁴⁵													
AR	15	40.0	32.6	46.6	0	100	Off-season	0	0	0	-	-	-
Healthy	15	33.3	27.9	33.3	NA	NA	NA	NA	NA	NA	-	-	-
Martin et al ¹⁹													
AR	32	-	30.4	0	0	100	In-season	-	0	0	-	-	-
Healthy	18	-	30.2	0	NA	NA	NA	NA	NA	NA	-	-	-
Nesic et al ⁴⁸													
AR	23	65.2	33.4	0	47.8	52.2	Off-season	-	0	0	-	-	-
Healthy	10	30.0	33.3	0	NA	NA	NA	NA	NA	NA	-	-	-
Palm et al ^{49,a}													
AR	11	-	-	-	-	-	-	-	-	0	-	-	-
Healthy	9	-	-	-	NA	NA	NA	NA	NA	NA	-	-	-
Palm et al ²⁰													
AR	18	50.0	32.0	0	0	100	In-season	0	0	0	-	-	-
Healthy	18	50.0	30.0	0	NA	NA	NA	NA	NA	NA	-	-	-
Suojalehto et al ⁵⁰													
AR	89	41.6	32.9	6.7	-	-	-	-	42.7	0	-	-	-
Healthy	42	40.5	33.5	11.9	NA	NA	NA	NA	NA	NA	-	-	-
Takahara et al ⁵¹													
AR	25	72.0	30.5	-	100	0	N/A	0	0	0	-	-	-
Healthy	10	80.0	35.9	-	NA	NA	NA	NA	NA	NA	-	-	-
Takeno et al ⁵² —Perennial (asthma)													
AR	18	61.1	31.5	-	100	0	NA	0	100	0	-	-	-
Healthy	30	56.7	34.9	-	NA	NA	NA	NA	NA	NA	-	-	-
Takeno et al ⁵² —Perennial (no asthma)													
AR	56	58.9	32.0	-	100	0	N/A	0	0	0	-	-	-
Healthy	30	56.7	34.9	-	NA	NA	NA	NA	NA	NA	-	-	-
Takeno et al ⁵² —Seasonal													
AR	12	50.0	33.3	-	0	100	Both	0	0	0	-	-	-

(continued on next page)

Table 1 (continued)

Study	Pop (n)	Males (%)	Age (y)	Smoking (%)	Perennial (%)	Seasonal (%)	In or off-season (%)	Nasal polyps (%)	Asthma (%)	Intranasal CCS (%)	FEV ₁ (% predicted)	FVC (% predicted)	FEV ₁ /FVC
Healthy	30	56.7	34.9	-	NA	NA	NA	NA	NA	NA	-	-	-
Tsuburai et al ^{53,a}													
AR	9	-	-	-	-	-	-	-	0	-	-	-	-
Healthy	9	-	-	-	NA	NA	NA	NA	NA	NA	-	-	-
Tworek et al ⁵⁴													
AR	24	66.7	24.5	0	0	100	Off-season	0	0	0	-	-	-
Healthy	24	66.7	27.1	0	NA	NA	NA	NA	NA	NA	-	-	-
Vass et al ⁵⁵													
AR	27	35.0	33.3	11.1	-	-	-	-	0	22.2	97.2	-	-
Healthy	15	25.7	60.0	0	NA	NA	NA	NA	NA	NA	96.3	-	-
Vo-Thi-Kim et al ⁵⁶													
AR	267	54.7	36.0	31.7	100	0	NA	0	0	0	91.0	89.0	87.0
Healthy	234	56.4	37.0	32.6	NA	NA	NA	NA	NA	NA	92.0	91.0	82.0
Wang et al ⁵⁷ —Mild AR													
AR	50	36.0	6.1	0	-	-	-	0	0	0	-	-	-
Healthy	49	44.9	7.2	0	NA	NA	NA	NA	NA	NA	-	-	-
Wang et al ⁵⁷ —Moderate/severe AR													
AR	44	25.0	6.8	0	-	-	-	0	0	0	-	-	-
Healthy	49	44.9	7.2	0	NA	NA	NA	NA	NA	NA	-	-	-
Wen et al ⁵⁸													
AR	90	67.8	9.7	0	100	0	NA	0	0	0	-	-	-
Healthy	79	69.6	10.1	0	NA	NA	NA	NA	NA	NA	-	-	-
Williamson et al ⁵⁹													
AR	52	44.2	40.0	-	-	-	-	0	0	0	101.2	-	-
Healthy	41	46.3	27.0	-	NA	NA	NA	NA	NA	NA	98.4	-	-
You et al ^{60,a}													
AR	51	-	-	-	-	-	-	-	0	-	-	-	-
Healthy	96	-	-	-	NA	NA	NA	NA	NA	NA	-	-	-

Abbreviations: AR, allergic rhinitis; CCS, corticosteroids; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; n, number; NA, not applicable; Pop, population.

NOTE: Continuous data are expressed as mean values unless otherwise indicated.

^aOnly an abstract is available.

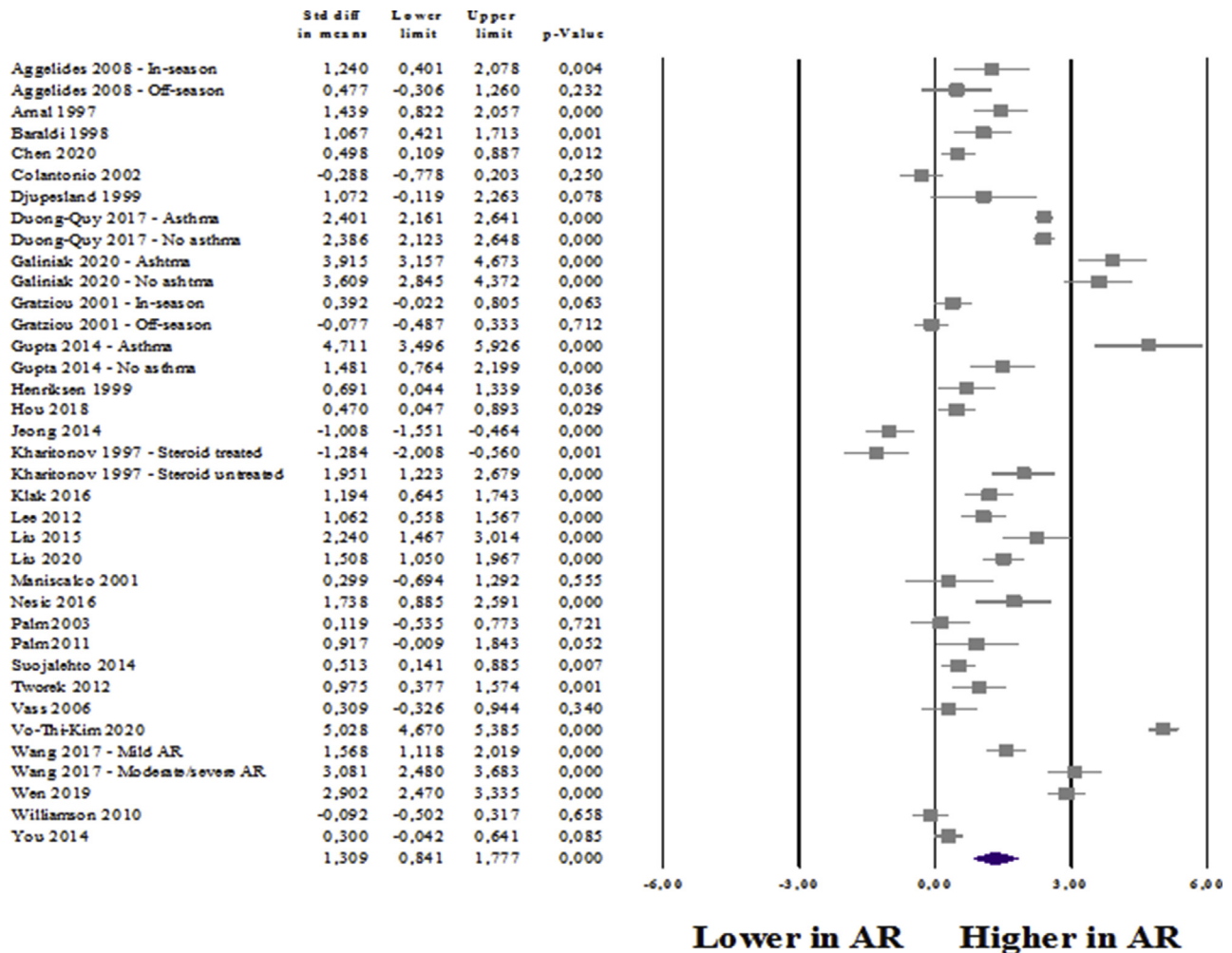


Figure 2. Forest plot of the standardized mean difference in nasal nitric oxide levels measured by nasal aspiration method between patients with AR and controls. AR, allergic rhinitis.

according to disease severity. In all these cases, the different groups were evaluated as different data sets.

With the exception of only 4 studies^{20,33,47,49} reporting nNO values in nanoliters per minute, all included studies measured nNO in parts per billion.

All but 1 study³³ based the diagnosis of AR on medical history with a positive reaction to at least 1 allergen at skin prick test or at allergen-specific IgE test. For 3 studies^{49,53,60} in which only abstract was available, the definition of cases was not clearly reported.

The NOS for quality assessment of included studies had a median value of 6.

Nasal Nitric Oxide—Aspiration Method

In 30 studies^{16–18,20,27,29,31–38,40–44,46,48–50,54–60} (37 data sets), the 1881 patients with AR indicated significantly higher nNO values than 1337 healthy controls (SMD, 1.309; 95% CI, 0.841–1.777; $P < .001$) (Fig 2). Heterogeneity among the studies was statistically significant ($I^2 = 96.9\%$; $P < .001$) and did not diminish after excluding 1 study at a time.

Nasal Nitric Oxide—Exhalation Method

In 12 studies^{19,20,28,30,39,45,47–49,51–53} (18 data sets) with 525 cases and 350 controls, the nNO levels in patients with AR, measured by nasal exhalation, was significantly higher than those of controls (SMD, 0.708; 95% CI, 0.303–1.114; $P = .001$, Fig 3). These

data had a high heterogeneity ($I^2 = 89.9\%$; $P < .001$), which did not degrade after excluding 1 study at a time.

Publication Bias

Because publication bias is known to affect meta-analysis, we evaluated such a potential bias using funnel plots analysis (eFig 1).

Visual inspection of funnel plots reporting effect size vs SE for studies evaluating nNO by nasal aspiration and nasal exhalation methods suggested the absence of bias and of small-study effect. Egger's and Begg and Mazumdar tests consistently confirmed the absence of publication bias. Moreover, application of the Duval and Tweedie's trim-and-fill analysis confirmed the results after trimming and imputing studies.

Sensitivity Analyses

Because the median value of NOS quality assessment was 6, the analyses were repeated by including only the 23 “high-quality” studies^{17,20,28–30,34,35,38,39,43–48,50–52,54,56–59} (NOS ≥ 6) (eTable 3). For 4 studies,^{27,49,53,60} data were extracted from the abstract; thus, no quality assessment could be performed. Interestingly, after excluding “low-quality” studies^{16,18,19,31–33,36,37,40–42,55} and those in which only the abstracts were available,^{27,49,53,60} all the results were largely confirmed (Table 2A). Similar results were also obtained by only including studies that systematically performed the skin prick test or the allergen-specific IgE test to distinguish patients with AR

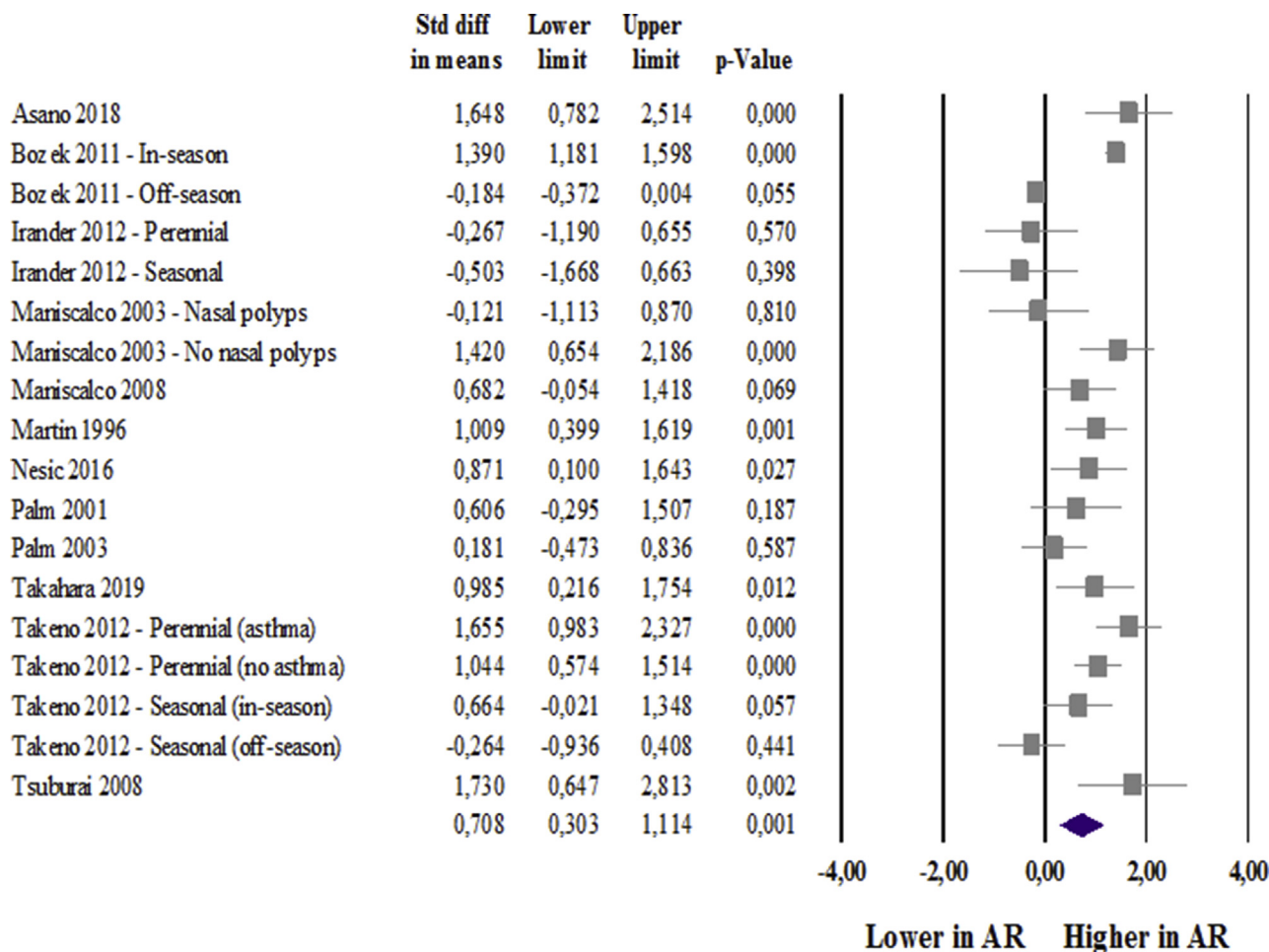


Figure 3. Forest plot of the standardized mean difference in nasal nitric oxide levels measured by nasal exhalation method between patients with AR and controls. AR, allergic rhinitis.

from healthy controls^{16-19,27,35-37,39,42,43,45-48} (Table 2B), and after excluding studies^{34,42,49,60} potentially reporting the same population as other included studies^{20,40,56,57} (Table 2C).

Sensitivity analyses were further applied to studies that explicitly excluded populations with concomitant clinical confounding factors, possibly affecting nNO values. Interestingly, all results were substantially confirmed when separately analyzing studies on patients with AR without asthma^{17-20,30,34,35,37,38,40-42,44-48,51-60} (Table 2D), without nasal polyps^{18,20,28,34,36,41,43,45-47,51,52,54,56-59} (Table 2E), or not receiving intranasal corticosteroids^{17,18,20,27-30,34-37,39,40,42,43,45-49,50-52,54,56-59} (Table 2F). Likewise, results were unaffected when specifically considering patients without a smoking history^{17-20,27,28,31,32,35-39,44,46-48,54,57,58} (Table 2G). Unfortunately, separate analyses of studies on patients with such clinical confounding factors could not be carried out because of the limited number of studies.

Subgroup Analyses

For studies on perennial AR,^{29,39,51,52,56,58} we confirmed all results for both aspiration and exhalation methods (Table 3A). In contrast, when evaluating 14 studies on seasonal disease,^{17-20,27,30,33,36,38,39,45,46,52,54} a significant difference in nNO values between cases and controls was found only for nasal aspiration method ($P = .02$), and not for nasal exhalation ($P = .23$) (Table 3B). Interestingly, when analysis was repeated on only 9 studies^{17-20,27,30,36,38,52} carried out during the pollen season, a significant difference between seasonal AR and healthy subjects was further confirmed for both

aspiration (SMD, 0.865; 95% CI, 0.351-1.379; $P = .001$, $I^2 = 77.1\%$; $P = .001$) and exhalation (SMD, 0.862; 95% CI, 0.288-1.436; $P = .003$, $I^2 = 80.2\%$; $P = .002$) methods (Table 3C). On the contrary, no significant difference in nNO levels between cases and controls was found in 9 studies^{17,27,30,36,39,45,46,52,54} on seasonal AR far from the pollen season (Table 3D).

Because the included studies were all prospective, subgroup analysis considering the study design (prospective or retrospective) was not performed.

Meta-Regression Analyses

Regression models for studies comparing patients with AR and healthy controls indicated that age, FEV1 and FEV1/FVC significantly affected nNO levels when measured by nasal aspiration (z-score, -2.250 ; $P = .02$ [Fig 4A]; z-score, -2.132 ; $P = .03$ [Fig 4B]; and z-score, -3.744 ; $P < .001$ [Fig 4C], respectively). Furthermore, an increasing aspiration flow was linked to a higher difference in nNO levels between cases and controls (z-score, 3.827 ; $P < .001$, Fig 4D).

No other demographic and clinical variables influenced the observed results (eTable 4).

Discussion

Our meta-analysis results consistently indicate that AR is associated with increased nNO levels when measured by both aspiration and exhalation methods. Furthermore, sensitivity and subgroup analyses confirmed that the results were not affected by

Table 2
Sensitivity Analyses

	Number of studies	Number of patients	Effect size SMD (95% CI)
High-quality studies			Panel A
nNO—aspiration	16 (19 data sets)	1400 AR 873 healthy	SMD, 1.815 (1.168–2.462); <i>P</i> < .001 <i>I</i> ² = 97.3%; <i>P</i> < .001
nNO—exhalation	9 (15 data sets)	472 AR 314 healthy	SMD, 0.636 (0.181–1.092); <i>P</i> = .006 <i>I</i> ² = 91.4%; <i>P</i> < .001
Prick test or IgE test			Panel B
nNO—aspiration	11 (16 data sets)	440 AR 306 healthy	SMD, 1.412 (0.781–2.043); <i>P</i> < .001 <i>I</i> ² = 93.5%; <i>P</i> < .001
nNO—exhalation	5 (7 data sets)	109 AR 68 healthy	SMD, 0.534 (0.035–1.034); <i>P</i> = .04 <i>I</i> ² = 61.1%; <i>P</i> = .02
Exclusion of duplicate populations			Panel C
nNO—aspiration	26 (32 data sets)	1373 AR 981 healthy	SMD, 1.292 (0.742–1.843); <i>P</i> < .001 <i>I</i> ² = 96.8%; <i>P</i> < .001
nNO—exhalation	11 (17 data sets)	514 AR 341 healthy	SMD, 0.713 (0.292–1.135); <i>P</i> = .001 <i>I</i> ² = 90.5%; <i>P</i> < .001
No asthma			Panel D
nNO—aspiration	20 (22 data sets)	1158 AR 1030 healthy	SMD, 1.323 (0.636–2.010); <i>P</i> < .001 <i>I</i> ² = 97.5%; <i>P</i> < .001
nNO—exhalation	9 (14 data sets)	306 AR 268 healthy	SMD, 0.714 (0.240–1.187); <i>P</i> = .003 <i>I</i> ² = 91.8%; <i>P</i> < .001
No nasal polyps			Panel E
nNO—aspiration	12 (16 data sets)	927 AR 873 healthy	SMD, 1.411 (0.652–2.169); <i>P</i> < .001 <i>I</i> ² = 97.9%; <i>P</i> < .001
nNO—exhalation	5 (9 data sets)	154 AR 73 healthy	SMD, 0.874 (0.458–1.290); <i>P</i> < .001 <i>I</i> ² = 70.1%; <i>P</i> = .001
No intranasal CCS			Panel F
nNO—aspiration	19 (27 data sets)	1448 AR 1054 healthy	SMD, 1.577 (1.009–2.146); <i>P</i> < .001 <i>I</i> ² = 97.1%; <i>P</i> < .001
nNO—exhalation	10 (16 data sets)	470 AR 308 healthy	SMD, 0.635 (0.199–1.071); <i>P</i> = .004 <i>I</i> ² = 90.8%; <i>P</i> < .001
No smoking			Panel G
nNO—aspiration	16 (22 data sets)	771 AR 493 healthy	SMD, 1.369 (0.816–1.922); <i>P</i> < .001 <i>I</i> ² = 94.8%; <i>P</i> < .001
nNO—exhalation	6 (8 data sets)	131 AR 81 healthy	SMD, 0.586 (0.070–1.102); <i>P</i> = .03 <i>I</i> ² = 68.8%; <i>P</i> = .002

Abbreviations: AR, allergic rhinitis; CCS, corticosteroids; CI, confidence interval; IgE, immunoglobulin E; N, number; nNO, nasal nitric oxide; SMD, standardized mean difference.

NOTE: Panel A includes “high-quality” studies (Newcastle-Ottawa Scale ≥ 6); Panel B includes studies systematically performing the skin prick test or the allergen-specific IgE test to distinguish cases from controls; Panel C includes an exclusion of studies potentially reporting on the same population in different included studies; Panel D includes an exclusion of studies reporting on patients with asthma; Panel E includes an exclusion of studies reporting on patients with nasal polyps; Panel F includes an exclusion of studies reporting on patients receiving intranasal corticosteroids; Panel G includes an exclusion of studies reporting on patients with a smoking history.

Bold indicates statistical significance *P* values for SMD.

the presence of clinical confounding factors (asthma, nasal polyps, inhaled corticosteroids, smoking history), this being valid for both perennial and seasonal disease during exposure to allergens. When the aspiration method was considered, meta-regressions revealed that older age and a better pulmonary function were associated with a lower difference in nNO levels between patients with AR and controls, whereas an increasing aspiration flow during nNO assessment was associated with a high effect size.

Overall, our results provide support to the hypothesis that, for patients with AR, nNO could become a marker of inflammation, just like FeNO is considered an established and recognized tool for the diagnosis and monitoring of asthma.^{7,8,10} The potential role of nNO in AR can be better appreciated if we analyze the results of the subgroup analyses, which indicated that patients with AR exhibit increased levels of nNO as compared with controls only during exposure to the allergens. In fact, we were not able to find any correlation between AR and nNO levels in patients with seasonal diseases when measurements were performed far from the pollen season.

In line with previous studies, this may be considered as indirect evidence that nNO production in the nasal mucosa of patients with AR is triggered by allergen exposure and consequent inflammation.^{61,62} Inflammation in the human nose and paranasal sinuses originates from the activation of mast cells and antigen-specific T_H2 cells with the simultaneous production of cytokines, such as interleukin 4 (IL-4), IL-5, and IL-13.³ In asthma, the release of these

inflammatory factors can modulate the expression of the inducible isoform of NO synthase, thus favoring an increased NO production.⁶³ Similar results have been recently reported for AR, which found increased expression of inducible isoform of NO synthase in epithelial cells of patients with rhinitis when exposed to allergens.^{62,64,65} Moreover, elevated neuronal NO synthase immunoreactivity around mucosal glands in patients with AR⁶⁶ and overexpression of endothelial NO synthase in the mucosal epithelium of patients with rhinitis⁶⁷ have also been found. Accordingly, a relationship between the increased expression of the different isoforms of NO synthase and the anatomic damage of the nasal mucosa in AR has been put forward.⁶⁸ Based on the above findings, a strict link can be hypothesized between inflammation and NO production in the nose and paranasal sinuses, with a principal pathogenic role for inducible isoform of NO synthase and a not-yet-fully-understood role for other NO synthase isoforms.²¹

Our findings are consistent with a great number of both in vitro and clinical studies, suggesting that measuring nNO can objectively reflect inflammation in patients with AR. Our systematic literature search confirms that many authors tried to evaluate the impact of AR on nNO levels over time, with conflicting results. This may be because of the heterogeneous populations enrolled in each study, often presenting several concomitant clinical confounding factors, such as asthma, nasal polyps, use of intranasal corticosteroids, and smoking history, which are known to potentially affect nNO levels.^{69,70} Accordingly, we performed a series of sensitivity

Table 3
Subgroup Analyses

	Number of studies	Number of patients	Effect size MD (95% CI)
Panel A			
Perennial AR			
nNO—aspiration	3 (3 data sets)	378 AR 232 healthy	SMD, 3.012 (0.868–5.157); <i>P</i> = .006 <i>I</i> ² = 98.5%; <i>P</i> < .001
nNO—exhalation	3 (5 data sets)	117 AR 47 healthy	SMD, 0.915 (0.261–1.570); <i>P</i> = .006 <i>I</i> ² = 72.5%; <i>P</i> = .012
Panel B			
Seasonal AR			
nNO—aspiration	9 (12 data sets)	247 AR 236 healthy	SMD, 0.500 (0.098–0.902); <i>P</i> = .02 <i>I</i> ² = 75.5%; <i>P</i> < .001
nNO—exhalation	6 (8 data sets)	342 AR 284 healthy	SMD, 0.402 (–0.252 to 1.057); <i>P</i> = .23 <i>I</i> ² = 94.7%; <i>P</i> < .001
Panel C			
Seasonal AR (in-season)			
nNO—aspiration	6 (6 data sets)	183 AR 197 healthy	SMD, 0.865 (0.351–1.379); <i>P</i> = .001 <i>I</i> ² = 77.1%; <i>P</i> = .001
nNO—exhalation	4 (4 data sets)	310 AR 262 healthy	SMD, 0.862 (0.288–1.436); <i>P</i> = .003 <i>I</i> ² = 80.2%; <i>P</i> = .002
Panel D			
Seasonal AR (off-season)			
nNO—aspiration	5 (5 data sets)	99 AR 135 healthy	SMD, 0.436 (–0.012 to 0.884); <i>P</i> = .06 <i>I</i> ² = 55.7%; <i>P</i> = .060
nNO—exhalation	4 (4 data sets)	280 AR 248 healthy	SMD, –0.065 (–0.465 to 0.335); <i>P</i> = .75 <i>I</i> ² = 45.4%; <i>P</i> = .14

Abbreviations: AR, allergic rhinitis; CI, confidence interval; MD, mean difference; N, number; nNO, nasal nitric oxide; ppb, parts per billion.

NOTE: Panel A includes studies on perennial allergic rhinitis (AR), Panel B includes studies on seasonal AR, Panel C includes studies on seasonal AR measuring nNO levels in-season, and Panel D includes studies on seasonal AR measuring nNO levels off-season.

Bold indicates statistical significance *P* values for SMD.

analyses that substantially confirmed all findings and excluded that our results could be somehow affected by comorbidities or treatments for nasal symptoms. Moreover, our meta-regression analyses were able to further refine results, showing that a better pulmonary function (as expressed by higher FEV1 and FEV1/FVC values) is associated with a lower difference in nNO levels between patients with AR and controls. This may be in line with a number of previous studies reporting an inverse correlation between lung function and nNO levels.^{71,72}

The other important factor that could explain the high heterogeneity among study results is the fact that several techniques for measuring nNO have been used so far. In contrast with FeNO, which is typically used for monitoring asthma, no single standardized method for nNO assessment has been defined yet. Thus, in our meta-analysis, we analyzed studies adopting different approaches. Obviously, differences in the assessment techniques and devices may account for the discrepancies observed across studies.⁷³ By using SMD instead of mean difference, and by separately analyzing results from studies on aspiration and those on exhalation method, we were able to (partially) overcome such heterogeneity among studies. However, another technical aspect that can markedly affect nNO levels is the transnasal airflow.⁷⁴ Because the nNO concentration is inversely related to transnasal airflow, different flows produce different nNO values.⁷⁵ Thus, we hypothesized that transnasal airflow might affect our findings; in fact, we found that an increasing aspiration flow is associated with a higher difference in nNO values in patients with AR compared with controls. However, because most studies on the exhalation method used a constant flow of 50 mL/s, transnasal airflow did not

influence our results for this technique. The higher diagnostic value of high aspiration flows during nNO assessment has also been hypothesized in a recent meta-analysis on the use of nNO in patients with chronic rhinosinusitis with or without nasal polyps.²¹

Overall, these findings suggest that higher aspiration flows should be used to amplify the difference in nNO values between patients with AR and healthy individuals. Moreover, an important role of nNO in younger patients with rhinitis emerged from our regression models, thus suggesting a greater relevance for those with chronic disease belonging to pediatric populations who often perceive this respiratory disorder as a source of disability because of the number of invalidating symptoms (eg, shortness of breath, wheezing, reduced exercise tolerance).^{76–81} At present, nNO is routinely used only to identify individuals with primary ciliary dyskinesia,^{82,83} in which it is currently considered a useful screening test regardless of the method used.⁸⁴ In contrast, the lack of normal reference values for the different techniques has limited its utility in other clinical settings. In line with previous evidence,²¹ our meta-analysis further supports the role of nNO as a potentially useful biomarker to monitor inflammation in upper airway disorders, in the same way as FeNO can be used to monitor treatment response, optimize interventional strategies (eg, pharmacological, rehabilitation), and identify non-adherence to therapies in chronic respiratory diseases.^{7–12} However, the presence of only indirect evidence prompts the need for large long-term prospective studies to better define a potential clinical use of nNO assessment for patients with AR and other airway disorders. In this regard, one single standardized method for nNO measurement should be characterized.

Some potential limitations of our study need to be discussed.

Considering that meta-analyses are carried out on aggregate data, the multivariate approach may favor the adjustment of some (but not all) demographic and clinical confounders.^{85–89} Thus, although meta-regression analyses were able to refine analyses by evaluating the influence of most variables on the observed results, care should be taken for results interpretation.

Second, our results were affected by a generally high heterogeneity. The fact that the skin prick test or the allergen-specific IgE test were not systematically performed in all studies to distinguish cases from controls may contribute to the high heterogeneity affecting our results. However, although it was not possible to definitively ascertain sources of such heterogeneity, all findings were substantially confirmed by appropriate sensitivity and subgroup analyses. Moreover, the impact of clinical and demographic variables on results was evaluated by means of meta-regression models. Finally, publication bias was ruled out by using different methods.

Other important aspects are the differences among measuring techniques and devices, the lack of a standardized method for nNO evaluation, and the lack of comparable age-adjusted normal values, all of which may reduce the clinical application of our results. Besides the sampling method (aspiration or exhalation), there are a number of other technical features significantly influencing nNO levels (eg, transnasal airflow, method of exclusion of the lower respiratory tract).^{90–93} In an attempt to partially overcome these limitations, we separately analyzed data from studies on nasal aspiration and those on nasal exhalation. Moreover, we performed our analyses by using SMD instead of mean difference, given that this method is useful when different techniques are analyzed together.²⁴ This allowed for consistent meta-analytical information with an appropriate statistical methodology, but we were unable to perform a meta-analysis of diagnostic accuracy at different cutoff values. This partially limits the clinical relevance of our results.

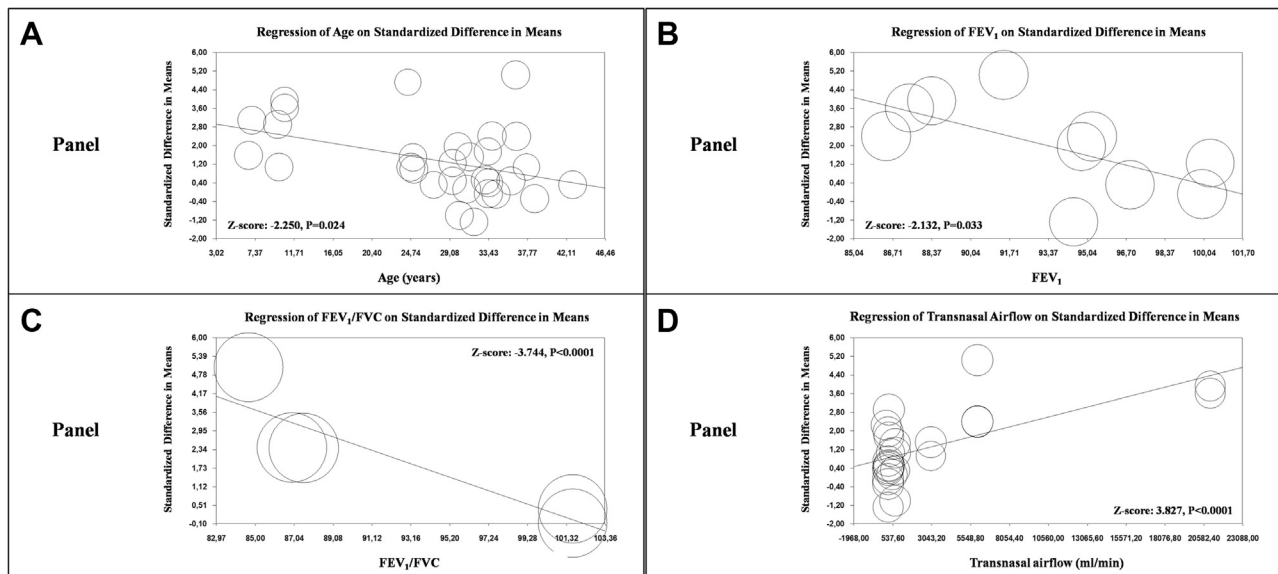


Figure 4. Meta-regression analyses. (A), Impact of age, (B), FEV₁, (C) FEV₁/FVC, and (D), transnasal airflow on the standardized mean difference in nNO levels measured by nasal aspiration method in patients with AR and controls. AR, allergic rhinitis; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; nNO, nasal nitric oxide.

Taken together, our meta-analysis results indicate that AR is associated with increased nNO levels, particularly in younger patients, and when using higher aspiration flows. Additional and specifically designed studies are needed to define whether nNO assessment may have a potential role in the monitoring of chronic airway diseases and optimization of interventional strategies in different settings (community, hospital, rehabilitation). One single standardized technique and normal reference values for nNO need to be defined.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jana.2020.07.003>.

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Supplementary Data

eTable 1

Diagnosis of AR and Definition of Controls in Included Studies

Study	AR	Controls
Aggelides et al ^{27,a}	Medical history + prick test ⁺	No medical history + prick test ⁻
Arnal et al ¹⁶	Medical history + prick test ⁺	No medical history + prick test ⁻
Asano et al ²⁸	Medical history + IgE ⁺	No medical history
Baraldi et al ²⁹	Medical history + prick test ⁺	No medical history
Bozek et al ³⁰	Medical history + prick test ⁺	No medical history
Chen et al ³¹	Medical history + prick test ⁺	No medical history
Colantonio et al ³²	Medical history + prick test ⁺	No medical history
Djupestrand et al ³³	Medical history	No medical history
Duong-Quy et al ³⁴	Medical history + prick test ⁺	No medical history
Galiniak et al ³⁵	Medical history + prick test ⁺ + IgE ⁺	No medical history + prick test ⁻ + IgE ⁻
Gratziou et al ³⁶	Medical history + prick test ⁺	No medical history + prick test ⁻
Gupta et al ³⁷	Medical history + prick test ⁺ + IgE ⁺	No medical history + prick test ⁻
Henriksen et al ¹⁷	Medical history + IgE ⁺	No medical history + IgE ⁻
Hou et al ³⁸	Medical history + IgE ⁺	No medical history
Irandar et al ³⁹	Medical history + prick test ⁺	No medical history + prick test ⁻
Jeong et al ⁴⁰	Medical history + prick test ⁺ or IgE ⁺	No medical history
Kharitonov et al ¹⁸	Medical history + prick test ⁺	No medical history + prick test ⁻
Klak 2016 ⁴¹	Medical history + prick test ⁺	No medical history
Lee 2012 ⁴²	Medical history + prick test ⁺ or IgE ⁺	No medical history + prick test ⁻ or IgE ⁻
Liu et al ⁴⁴	Medical history + prick test ⁺ + IgE ⁺	No medical history
Liu et al ⁴³	Medical history + prick test ⁺ + IgE ⁺	No medical history + prick test ⁻ + IgE ⁻
Maniscalco et al ⁴⁶	Medical history + prick test ⁺	No medical history + prick test ⁻
Maniscalco et al ⁴⁷	Medical history + prick test ⁺	No medical history + prick test ⁻
Maniscalco et al ⁴⁵	Medical history + prick test ⁺	No medical history + prick test ⁻
Martin et al ¹⁹	Medical history + prick test ⁺	No medical history + prick test ⁻
Nesic et al ⁴⁸	Medical history + IgE ⁺	No medical history + IgE ⁻
Palm et al ^{49,a}	-	-
Palm et al ²⁰	Medical history + prick test ⁺	No medical history
Suojalehto et al ⁵⁰	Medical history + prick test ⁺ or IgE ⁺	No medical history
Takahara et al ⁵¹	Medical history + prick test ⁺ or IgE ⁺	No medical history
Takeno et al ⁵²	Medical history + IgE ⁺	No medical history
Tsuburai et al ^{53,a}	-	-
Tworek et al ⁵⁴	Medical history + IgE ⁺	No medical history
Vass et al ⁵⁵	Medical history + prick test ⁺	No medical history
Vo-Thi-Kim et al ⁵⁶	Medical history + prick test ⁺	No medical history
Wang et al ⁵⁷	Medical history + prick test ⁺	No medical history
Wen et al ⁵⁸	Medical history + IgE ⁺	No medical history
Williamson et al ⁵⁹	Medical history + prick test ⁺	No medical history
You et al ^{60,a}	-	-

Abbreviations: AR, allergic rhinitis; IgE: allergen-specific immunoglobulin E test.

^aOnly abstract available.

eTable 2

Devices and Methods for Measurement of Nasal Nitric Oxide in Included Studies.

Study	Analyzer	Technique	Transnasal airflow (mL/min)	Device	Equipment
Aggelides et al ²⁷	Chemiluminescence	Aspiration	-	-	□ Eco Screen, Jaeger (Höechberg, Germany)
Arnal et al ¹⁶	Chemiluminescence	Aspiration during tidal breath	700	Nasal olive	□ NO analyzer, Cosma (Igny, France)
Asano et al ²⁸	Chemiluminescence	Nasal exhalation	3000	Nasal olive	□ Sievers NOA-280i, GE Analytical Instruments (Boulder, Colorado)
Baraldi et al ²⁹	Chemiluminescence	Aspiration during breath hold	-	Nasal olive	□ Rotork 447, Orion (Bath, United Kingdom)
Bozek et al ³⁰	Electrochemical	Nasal exhalation	3000	Nasal mask	□ NIOX MINO Airway Inflammation Monitor, Aerocrine AB (Solna, Sweden)
Chen et al ³¹	-	Aspiration during breath hold	-	Nasal olive	□ NO Analyzer, Sunvou Medical Electronics Co Ltd (Wuxi, People's Republic of China)
Colantonio et al ³²	Chemiluminescence	Aspiration during breath hold	250	Nasal olive	□ LR 2000, Logan Sinclair (Rochester, United Kingdom)
Djupestrand et al ³³	Chemiluminescence	Aspiration during tidal breath	2400	Nasal olive	□ Sievers NOA-280i, GE Analytical Instruments (Boulder, Colorado)
Duong-Quy et al ³⁴	Electrochemical	Aspiration during exhalation against resistance	6000	Nasal olive	□ Hypair FeNO + Device, Medisoft (Dinant, Belgium)
Galiniak et al ³⁵	Electrochemical	Aspiration	21,000	Nasal olive	□ Hypair FeNO + Device, Medisoft (Dinant, Belgium)
Gratziou et al ³⁶	Chemiluminescence	Aspiration during exhalation against resistance	250	Nasal olive	□ LR 2000, Logan Sinclair (Rochester, United Kingdom)
Gupta et al ³⁷	Chemiluminescence	Aspiration	-	-	□ NIOX, Aerocrine AB (Solna, Sweden)
Henriksen et al ¹⁷	Chemiluminescence	Aspiration during breath hold	250	Nasal olive	□ LR 2000, Logan Sinclair (Rochester, United Kingdom)
Hou et al ³⁸	Chemiluminescence	Aspiration during exhalation against resistance	300	Nasal olive	□ NIOX MINO 09-1000, Aerocrine AB (Solna, Sweden)
Irandar et al ³⁹	Chemiluminescence	Nasal exhalation	3000	Nasal mask	□ NIOX, Aerocrine AB (Solna, Sweden)
Jeong et al ⁴⁰	Chemiluminescence	Aspiration during exhalation against resistance	700	Nasal olive	□ Sievers NOA-280i, GE Analytical Instruments (Boulder, Colorado)
Kharitonov et al ¹⁸	Chemiluminescence	Aspiration during breath hold	250	Nasal olive	□ LR 2000, Logan Sinclair (Rochester, United Kingdom)
Klak et al ⁴¹	Electrochemical	Aspiration during exhalation against resistance	-	Nasal olive	□ Hypair FeNO + Device, Medisoft (Dinant, Belgium)
Lee 2012 ⁴²	Chemiluminescence	Aspiration during exhalation against resistance	700	Nasal olive	□ Sievers NOA-280i, GE Analytical Instruments (Boulder, Colorado)
Liu et al ⁴⁵	Electrochemical	Aspiration during tidal breath	120	Nasal olive	□ NIOX MINO Airway Inflammation Monitor, Aerocrine AB (Solna, Sweden)
Liu et al ⁴³	Chemiluminescence	Aspiration during exhalation against resistance	3000	Nasal olive	□ NIOX, Aerocrine AB (Solna, Sweden)

(continued on next page)

eTable 2 (continued)

Study	Analyzer	Technique	Transnasal airflow (mL/min)	Device	Equipment
Maniscalco et al ⁴⁶	Chemiluminescence	Aspiration during breath hold	700	Nasal olive	□ Model 42, Thermo Electron (Warrington, United Kingdom)
Maniscalco et al ⁴⁷	Electrochemical	Nasal exhalation	12,000	Nasal mask	□ NIOX MINO Airway Inflammation Monitor, Aerocrine AB (Solna, Sweden)
Maniscalco et al ⁴⁵	Chemiluminescence	Nasal exhalation	3000	Nasal mask	□ Sievers NOA-280i, GE Analytical Instruments (Boulder, Colorado)
Martin et al ¹⁹	Chemiluminescence	Nasal exhalation	-	Nasal mask	□ NO analyzer Model 9841A, Siemens (Plessey, Dorset, United Kingdom)
Nesic et al ⁴⁸	Electrochemical	Aspiration during breath hold	300	Nasal olive	□ NIOX MINO Airway Inflammation Monitor, Aerocrine AB (Solna, Sweden)
Nesic et al ⁴⁸	Electrochemical	Nasal exhalation	3000	Nasal mask	□ NIOX MINO Airway Inflammation Monitor, Aerocrine AB (Solna, Sweden)
Palm et al ⁴⁹	Chemiluminescence	Nasal exhalation	3000	Nasal mask	□ Aerocrine NO system, Aerocrine AB (Solna, Sweden)
Palm et al ⁴⁹	Chemiluminescence	Aspiration during exhalation against resistance	3000	Nasal olive	□ Aerocrine NO system, Aerocrine AB (Solna, Sweden)
Palm et al ²⁰	Chemiluminescence	Nasal exhalation	3000	Nasal mask	□ Aerocrine NO system, Aerocrine AB (Solna, Sweden)
Palm et al ²⁰	Chemiluminescence	Aspiration during exhalation against resistance	3000	Nasal olive	□ Aerocrine NO system, Aerocrine AB (Solna, Sweden)
Suojalehto et al ⁵⁰	Chemiluminescence	Aspiration during breath hold	300	Nasal olive	□ NIOX, Aerocrine AB (Solna, Sweden)
Takahara et al ⁵¹	Electrochemical	Nasal exhalation	3000	Nasal olive	□ Nobreath, Bedfont Scientific (Rochester, United Kingdom)
Takeno et al ⁵²	Electrochemical	Nasal exhalation	3000	Nasal olive	□ Nobreath, Bedfont Scientific (Rochester, United Kingdom)
Tsuburai et al ⁵³	-	Nasal exhalation	-	-	□ -
Tworek et al ⁵⁴	Electrochemical	Aspiration	-	Nasal olive	□ ExpAir, Medisoft (Dinant, Belgium)
Vass et al ⁵⁵	Chemiluminescence	Aspiration during breath hold	250	Nasal olive	□ LR 2000, Logan Sinclair (Rochester, United Kingdom)
Vo-Thi-Kim et al ⁵⁶	Electrochemical	Aspiration during exhalation against resistance	6000	Nasal olive	□ Hypair FeNO + Device, Medisoft (Dinant, Belgium)
Wang et al ⁵⁷	Electrochemical	Aspiration during exhalation against resistance	-	Nasal olive	□ Nanocoulomb Breath Analyzer, Sunvou Medical Electronics (Jiangsu, People's Republic of China)
Wen et al ⁵⁸	Electrochemical	Aspiration during breath hold	300	Nasal olive	□ NIOX MINO Airway Inflammation Monitor, Aerocrine AB (Solna, Sweden)
Williamson et al ⁵⁹	Chemiluminescence	Aspiration	-	Nasal olive	□ NIOX, Aerocrine AB (Solna, Sweden)
You et al ⁶⁰	Electrochemical	Aspiration	-	-	□ NIOX MINO Airway Inflammation Monitor, Aerocrine AB (Solna, Sweden)

eTable 3
Assessment of Quality of Studies (Newcastle-Ottawa Scale)

Study	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls based on the design or analysis ^a	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Quality
Aggelides et al ^{27,b}	-	-	-	-	-	-	-	-	NA
Arnal et al ¹⁶	*	-	-	*	-	*	*	*	5
Asano et al ²⁸	*	*	-	*	-	*	*	*	6
Baraldi et al ²⁹	*	*	-	*	*	*	*	*	7
Bozek et al ³⁰	*	-	-	*	*	*	*	*	6
Chen et al ³¹	*	-	-	*	-	*	*	*	5
Colantonio et al ³²	*	-	-	*	-	*	*	*	5
Djupesland et al ³³	-	-	-	*	-	*	*	*	4
Duong-Quy et al ³⁴	*	*	-	*	*	*	*	*	7
Galiniak et al ³⁵	*	-	-	*	**	*	*	*	7
Gratziou et al ³⁶	*	-	-	*	-	*	*	*	5
Gupta et al ³⁷	*	-	-	*	-	*	*	*	5
Henriksen et al ¹⁷	*	*	*	*	**	*	*	*	9
Hou et al ³⁸	*	*	-	*	**	*	*	*	8
Irander et al ³⁹	*	*	*	*	-	*	*	*	7
Jeong et al ⁴⁰	*	-	-	*	-	*	*	*	5
Kharitonov et al ¹⁸	*	-	-	*	-	*	*	*	5
Klak 2016 ⁴¹	*	-	-	*	-	*	*	*	5
Lee 2012 ⁴²	*	-	-	*	-	*	*	*	5
Liu et al ⁴⁴	*	*	-	*	-	*	*	*	6
Liu et al ⁴³	*	*	-	*	-	*	*	*	6
Maniscalco et al ⁴⁶	*	-	*	*	-	*	*	*	6
Maniscalco et al ⁴⁷	*	-	*	*	-	*	*	*	6
Maniscalco et al ⁴⁵	*	-	*	*	**	*	*	*	8
Martin et al ¹⁹	*	-	-	*	-	*	*	*	5
Nesic et al ⁴⁸	*	*	-	*	-	*	*	*	6
Palm et al ^{49,b}	-	-	-	-	-	-	-	-	NA
Palm et al ²⁰	*	-	-	*	**	*	*	*	7
Suojalehto et al ⁵⁰	*	*	*	*	*	*	*	*	8
Takahara et al ⁵¹	*	*	-	*	**	*	*	*	8
Takeno et al ⁵²	*	-	-	*	**	*	*	*	7
Tsuburai et al ^{53,b}	-	-	-	-	-	-	-	-	NA
Tworek et al ⁵⁴	*	*	-	*	**	*	*	*	8
Vass et al ⁵⁵	*	-	-	*	-	*	*	*	5
Vo-Thi-Kim et al ⁵⁶	*	-	-	*	**	*	*	*	7
Wang et al ⁵⁷	*	*	-	*	-	*	*	*	6
Wen et al ⁵⁸	*	*	-	*	**	*	*	*	8
Williamson et al ⁵⁹	*	*	-	*	**	*	*	*	8
You et al ^{60,b}	-	-	-	-	-	-	-	-	NA

Abbreviation: NA, not assessed.

^aA maximum of 2 stars can be allotted in this category as follows: *if enrolling controls matched to cases for age and sex and ** if enrolling controls matched to cases for any additional factor.

^bOnly an abstract is available.

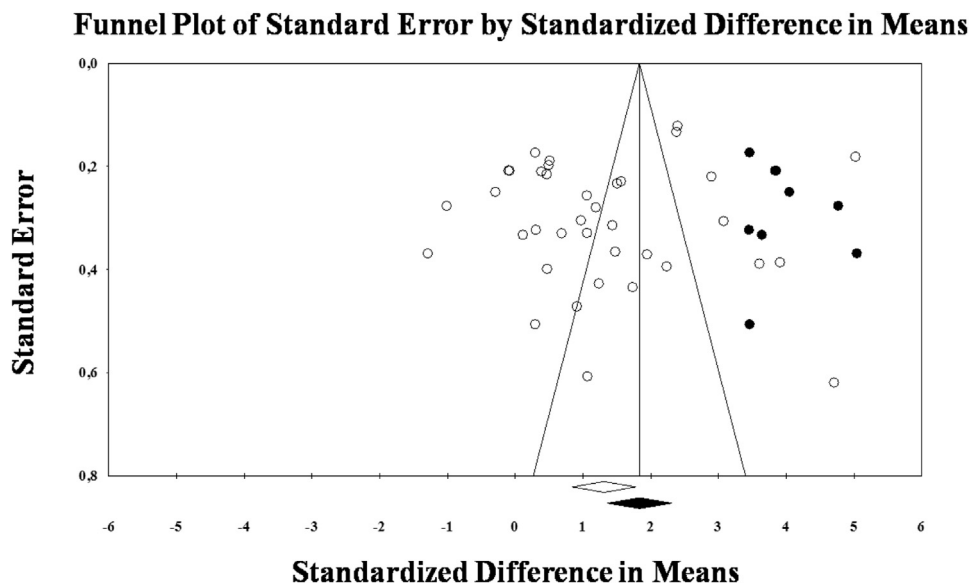
eTable 4

Meta-Regression Analyses on the Impact of Major Clinical and Demographic Variables on nNO Measured by Nasal Aspiration and Nasal Exhalation Methods in Patients With Allergic Rhinitis and Controls

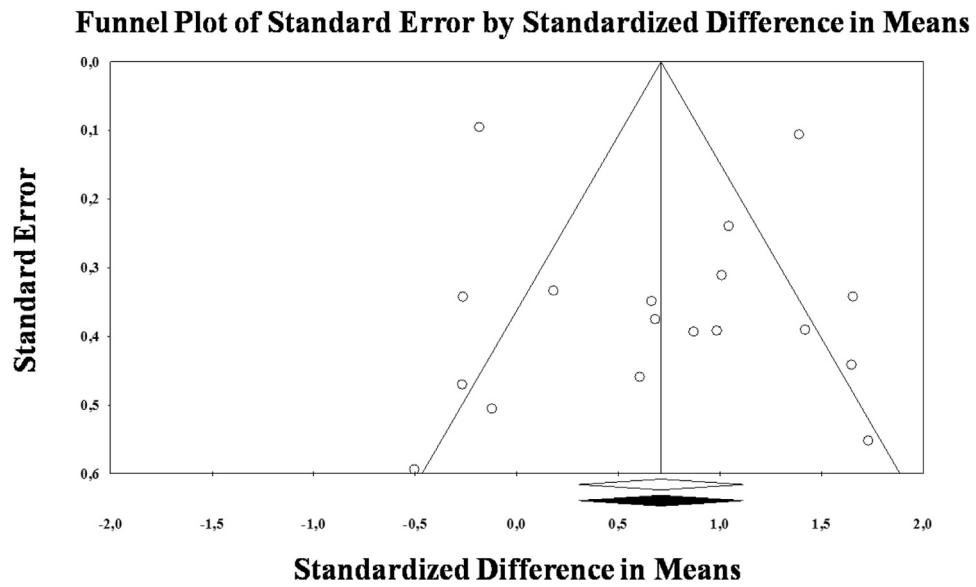
Independent variable	nNO
Nasal aspiration	
% of males	z-score: 0.145, $P = .89$
Age	z-score: -2.250, $P = .03$
FEV ₁ (% predicted)	z-score: -2.132, $P = .03$
FVC (% predicted)	z-score: -1.322 , $P = .19$
FEV ₁ /FVC	z-score: -3.744, $P < .001$
Transnasal airflow	z-score: 3.827, $P < .001$
Nasal exhalation	
% of males	z-score: 0.368, $P = .71$
Age	z-score: -0.204 , $P = .84$
FEV ₁ (% predicted)	N/A
FVC (% predicted)	N/A
FEV ₁ /FVC	N/A
Transnasal airflow	z-score: 0.137, $P = .89$

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; N/A, not assessed because of the limited number of studies reporting this covariate; nNO, nasal nitric oxide.

Bold indicates statistical significant P values.



efigure 1. Funnel plots of effect size vs SE for studies evaluating nNO measured by nasal aspiration (Panel A) and by nasal exhalation method (Panel B) in patients with allergic rhinitis and controls. Observed studies and effect sizes are represented by empty circles and empty square. Imputed studies and adjusted effect sizes are represented by black circles and black squares. nNO, nasal nitric oxide.



eFigure 1. (continued).