Supplementary online material

Nasal nitric oxide in chronic rhinosinusitis with or without nasal polyps: a systematic review with meta-analysis.

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Supplemental Table 1. Devices and methods for measurement of nasal nitric oxide (nNO) in included studies.

Study	Analyzer	Technique	Transnasal airflow	Device	Equipment
Alexandersson 2019	Chemiluminescence	Aspiration during breath hold	2000 ml/min	Nasal olive	▪ NIOX®, Aerocrine AB (Solna,Sweden)
Arnal 1999	Chemiluminescence	Aspiration during tidal breath	700 ml/min	Nasal olive	▪ NO analyser, Cosma (Igny, France)
Asano 2008	Chemiluminescence	Nasal exhalation	3000 ml/min	Nasal olive	▪ Sievers NOA-280i®, GE Analytical Instruments (Boulder, USA)
Bae 2014	Electrochemical	Nasal exhalation	-	-	▪ NObreath®, Bedfont Scientific (Rochester, UK)
Bommarito 2008	Chemiluminescence	Aspiration during breath hold	300 ml/min	Nasal olive	▪ NIOX®, Aerocrine AB (Solna,Sweden)
Frendø 2018	Electrochemical	Aspiration during exhalation against resistance	300 ml/min	Nasal olive	▪ NIOX MINO Airway Inflammation Monitor®, Aerocrine AB (Solna,Sweden)
Fu 2015	Electrochemical	Aspiration during tidal breath	300 ml/min	Nasal olive	▪ NIOX MINO Airway Inflammation Monitor®, Aerocrine AB (Solna,Sweden)
Fu 2017	Electrochemical	Aspiration during tidal breath	300 ml/min	Nasal olive	▪ NIOX MINO Airway Inflammation Monitor®, Aerocrine AB (Solna,Sweden)
Gilain 2002	Chemiluminescence	Aspiration during exhalation against resistance	3000 ml/min	Nasal olive	▪ Sievers NOA-280i®, GE Analytical Instruments (Boulder, USA)
Guilemany 2009	Chemiluminescence	Aspiration during breath hold	3000 ml/min	Nasal olive	▪ SIR System N6008 NO tracer®, SIR (Madrid, Spain)
Gupta 2013	Electrochemical	-	300 ml/min	Nasal olive	▪ NIOX MINO Airway Inflammation Monitor®, Aerocrine AB (Solna,Sweden)
Heffler 2013	Chemiluminescence	Aspiration during breath hold	300 ml/min	Nasal olive	▪ NIOX®, Aerocrine AB (Solna,Sweden)
Jeong 2014	Chemiluminescence	Aspiration during exhalation against resistance	700 ml/min	Nasal olive	▪ Sievers NOA-280i®, GE Analytical Instruments (Boulder, USA)
Lee 2015	Chemiluminescence	Aspiration during exhalation against resistance	300 ml/min	Nasal olive	▪ Eco Medics CLD 88sp NO Analyzer®, Eco Physics Inc. (Ann Arbor, USA)
Lindenberg 1997	Chemiluminescence	Aspiration during tidal breath	660 ml/min	Nasal olive	▪ CLD 700 AL Med®, Ecophysics (Durnten, Switzerland)
Liu 2017	Electrochemical	Aspiration during exhalation against resistance	2500-3000 ml/min	Nasal olive	▪ NIOX MINO Airway Inflammation Monitor®, Aerocrine AB (Solna,Sweden)
Noda 2012	Electrochemical	Nasal exhalation	3000 ml/min	Nasal olive	▪ NObreath®, Bedfont Scientific (Rochester, UK)
Ragab 2006	Chemiluminescence	Aspiration during breath hold	250 ml/min	Nasal olive	▪ LR 2000®, Logan Sinclair (Rochester, UK)

Torretta 2015	-	-	-	-	▪ -
Tworek 2012	Electrochemical	-	-	Nasal olive	▪ ExpAir®, Medisoft (Dinant, Belgium)
Weschta 2008	Electrochemical	Nasal exhalation	3000 ml/min	Nasal mask	▪ NIOX MINO Airway Inflammation Monitor®, Aerocrine AB (Solna,Sweden)
Williamson 2010	Chemiluminescence	Aspiration during exhalation against resistance	-	Nasal olive	▪ NIOX®, Aerocrine AB (Solna,Sweden)
Yoshida 2019	Chemiluminescence	Nasal exhalation	3000 ml/min	Nasal olive	▪ Sievers NOA-280i®, GE Analytical Instruments (Boulder, USA)

Supplemental Table S2. 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 on the basis of the design or analysis*	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Quality
Alexandersson 2019	✶	✶	-	✶	-	✶	✶	✶	6
Arnal 1999	✶	-	-	✶	✶	✶	✶	✶	6
Asano 2008	✶	✶	-	✶	-	✶	✶	✶	6
Bae 2014**	-	-	-	-	-	-	-	-	NA
Bommarito 2008	✶	✶	-	✶	-	✶	✶	✶	6
Frendø 2018	✶	✶	✶	✶	-	✶	✶	✶	7
Fu 2015	✶	✶	✶	✶	✶	✶	✶	✶	8
Fu 2017	✶	✶	✶	✶	✶	✶	✶	✶	8
Gilain 2002**	-	-	-	-	-	-	-	-	NA
Guilemany 2009	✶	✶	✶	✶	-	✶	✶	✶	7
Gupta 2013	✶	✶	-	✶	-	✶	✶	✶	6
Heffler 2013	✶	✶	-	✶	-	✶	✶	✶	6
Jeong 2014	✶	-	-	✶	✶	✶	✶	✶	6
Lee 2015	✶	✶	✶	✶	-	✶	✶	✶	7
Lindenberg 1997	✶	-	-	✶	-	✶	✶	✶	5
Liu 2017	✶	✶	-	✶	-	✶	✶	✶	6
Noda 2012	✶	-	-	✶	-	✶	✶	✶	5
Ragab 2006	✶	✶	✶	✶	-	✶	✶	✶	7
Torretta 2015**	-	-	-	-	-	-	-	-	NA
Tworek 2012	✶	-	-	✶	✶✶	✶	✶	✶	7
Weschta 2008	✶	✶	✶	✶	-	✶	✶	✶	7

Williamson 2010	✶	✶	-	✶	✶✶	✶	✶	✶	8
Yoshida 2019	✶	✶	-	✶	-	✶	✶	✶	6

NA: not assessed.

*A maximum of 2 stars can be allotted in this category: ✶if enrolling controls matched to cases for age and sex; ✶✶ if enrolling controls matched to cases for any additional factor.

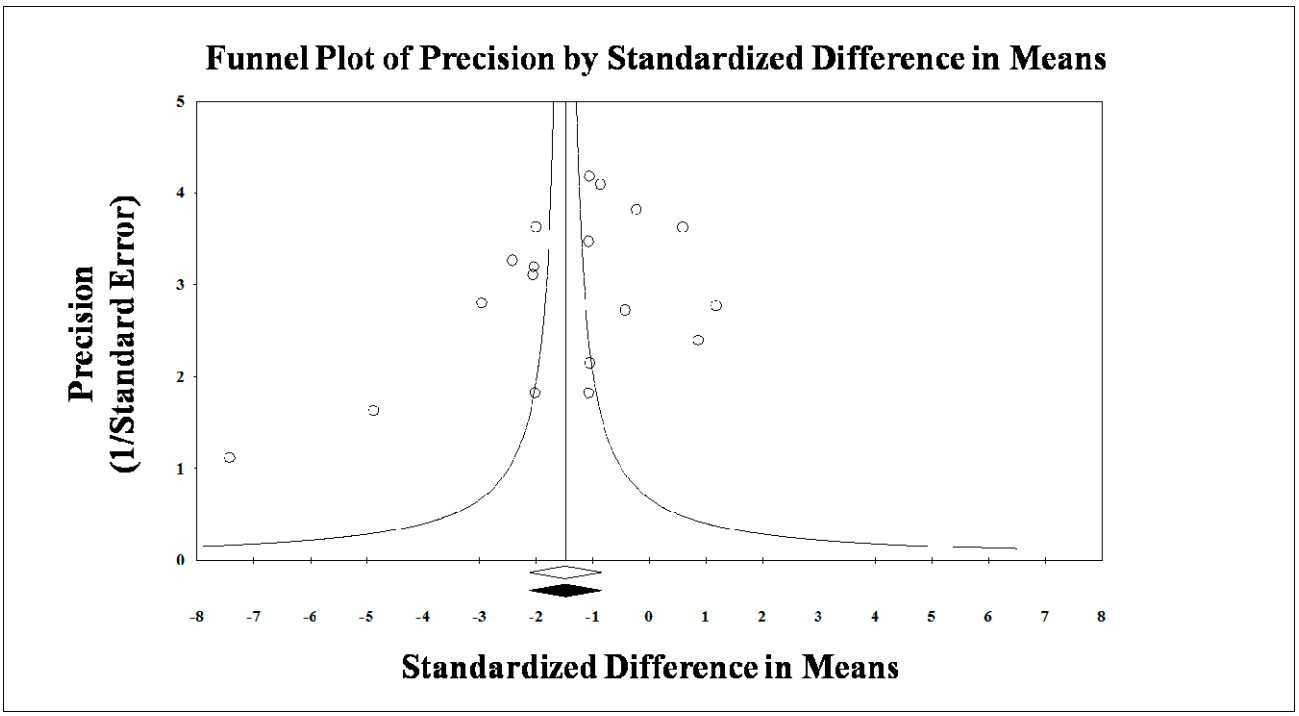
**Only abstract available.

Supplemental Table 3. Meta-regression analyses. Impact of major clinical and demographic variables on nasal nitric oxide (nNO) in cases and control subjects.

	Independent variable	nNO
CRSwNP vs. HEALTHY	% of males	Z-score: 0.115, P=0.908
	Age	Z-score: 1.058, P=0.290
	Smoking	Z-score: 1.707, P=0.088
	Atopy	Z-score: 0.178, P=0.858
	Asthma	Z-score: 1.455, P=0.146
	Lund-Mackay CT score	Z-score: 0.596, P=0.551
	SNOT-22 score	N/A
	FEV_1 (% predicted)	Z-score: 1.401, P=0.161
	FVC (% predicted)	N/A
	FEV_1/FVC	N/A
	Aspiration flow	**Z-score: -4.379, P<0.0001**
CRSsNP vs. HEALTHY	% of males	Z-score: -0.951, P=0.342
	Age	Z-score: 0.484, P=0.629
	Smoking	N/A
	Atopy	Z-score: 1.011, P=0.312
	Asthma	Z-score: 1.975, P=0.050
	Lund-Mackay CT score	**Z-score: -2.123, P=0.034**
	SNOT-22 score	Z-score: -0.455, P=0.649
	FEV_1 (% predicted)	N/A
	FVC (% predicted)	N/A
	FEV_1/FVC	N/A
	Aspiration flow	Z-score: -0.473, P=0.636
CRSwNP vs. CRSsNP	% of males	**Z-score: 2.631, P=0.009**
	Age	Z-score: -0.831, P=0.406
	Smoking	Z-score: 1.576, P=0.115
	Atopy	Z-score: -0.723, P=0.469
	Asthma	Z-score: -1.437, P=0.151
	Lund-Mackay CT score	Z-score: 0.515, P=0.607
	SNOT-22 score	Z-score: -0.613, P=0.540
	FEV_1 (% predicted)	N/A
	FVC (% predicted)	N/A
	FEV_1/FVC	N/A
	Aspiration flow	**Z-score: -4.100, P<0.0001**

CRSwNP: chronic rhinosinusitis with nasal polyps; CRSsNP: chronic rhinosinusitis without nasal polyps; CT: computed tomography; SNOT-22: Sino-Nasal Outcome Test-22; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; N/A: not assessed because of the limited number of studies reporting this covariate.
The overall effect was tested using Z-scores and significance was set at $P < 0.05$. Statistically significant results are shown in bold.

Supplemental Figure 1. Funnel plot of effect size vs. precision (1/standard error) for studies evaluating nasal nitric oxide (nNO) in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and healthy controls.

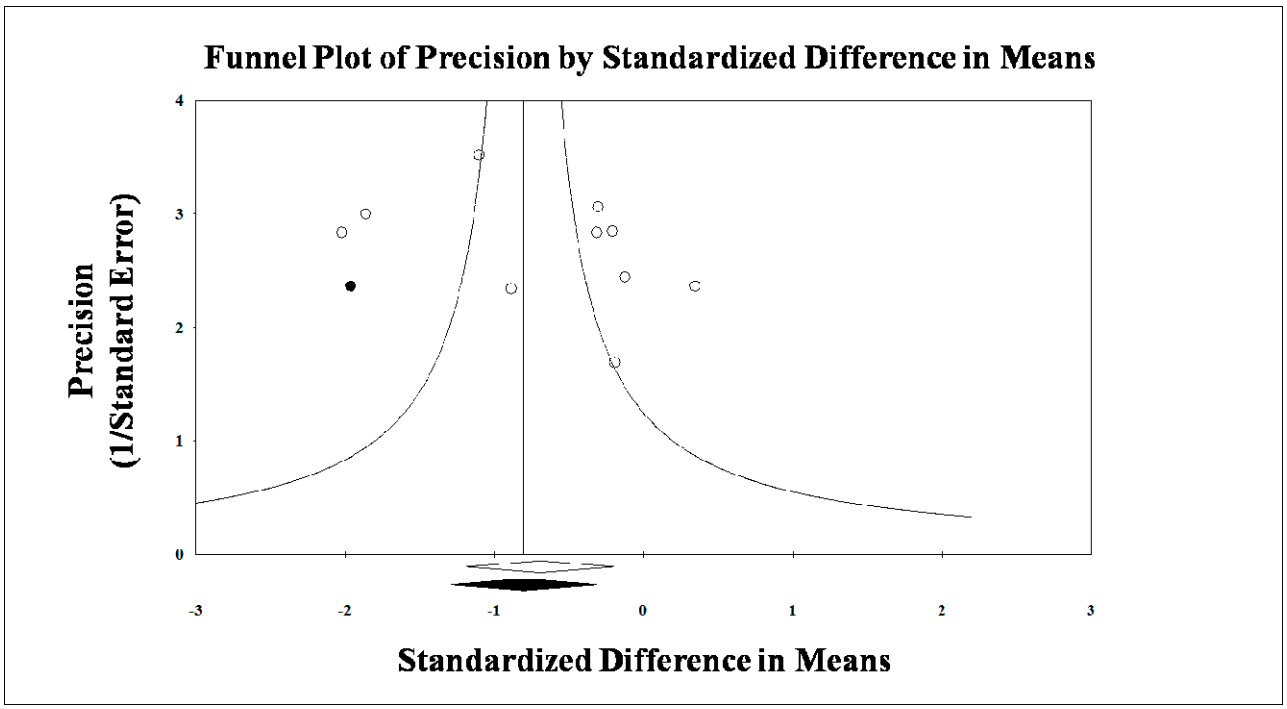


Observed studies and effect size are represented by empty circles and empty square. Imputed studies and adjusted effect size are represented by black circles and black square.

Egger's regression intercept	Intercept	-5.24799
	Standard error	3.13557
	95% lower limit	-11.89511
	95% upper limit	1.39913
	t-value	1.67369
	P value	0.11362
Begg and Mazumdar	**Kendall's S statistic (P-Q)**	-39.00000
	Kendall's tau without continuity correction	
	tau	-0.25490
	Z-value for tau	1.47723
	P-value	0.13961
	Kendall's tau with continuity correction	
	tau	-0.24837
	Z-value for tau	1.43935
	P-value	0.15005

Duvall and Tweedie's trim and fill	Studies trimmed	Point estimate	Lower limit	Upper limit	**Q value**
Observed values	-	-1.495	-2.135	-0.854	270.216
Adjusted values (on the left)	0	-1.495	-2.135	-0.854	270.216
Adjusted values (on the right)	0	-1.495	-2.135	-0.854	270.216

Supplemental Figure 2. Funnel plot of effect size vs. precision (1/standard error) for studies evaluating nasal nitric oxide (nNO) in patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and healthy controls.

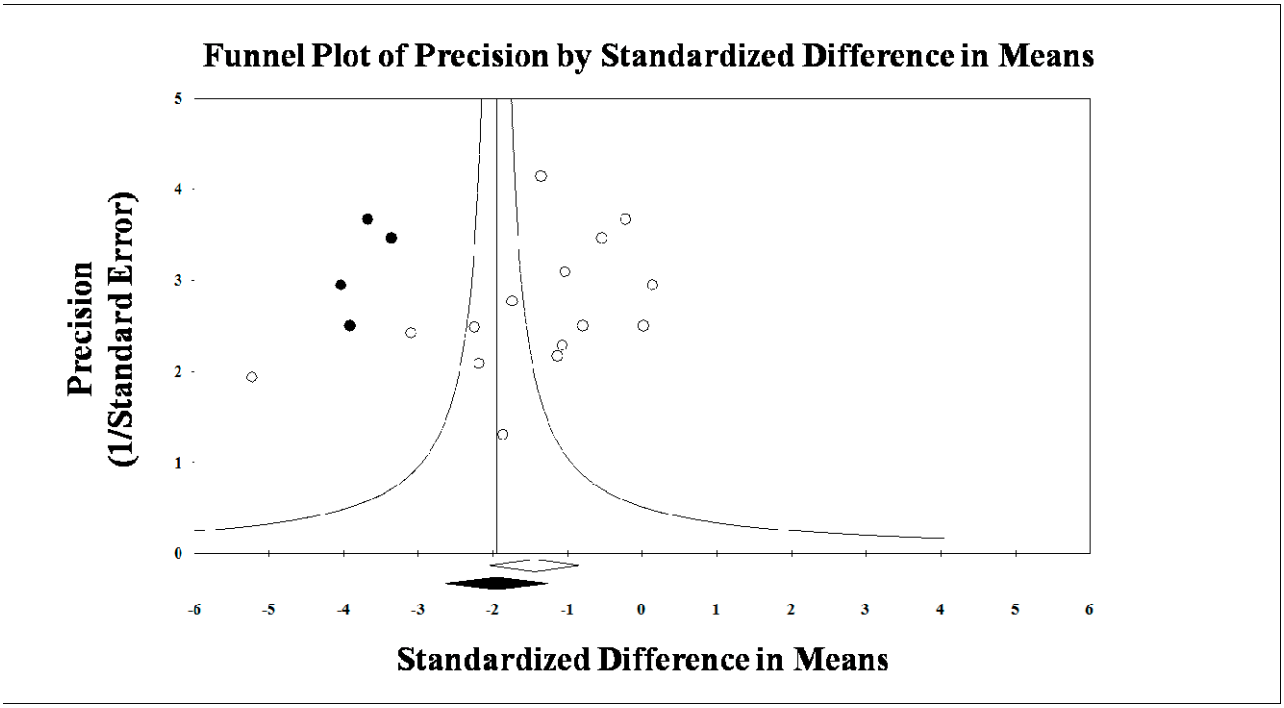


Observed studies and effect size are represented by empty circles and empty square. Imputed studies and adjusted effect size are represented by black circles and black square.

Egger's regression intercept	Intercept	4.45525
	Standard error	3.79837
	95% lower limit	-4.30382
	95% upper limit	13.21431
	t-value	1.17294
	P value	0.27456
Begg and Mazumdar	**Kendall's S statistic (P-Q)**	7.00000
	Kendall's tau without continuity correction	
	tau	0.15556
	Z-value for tau	0.62610
	P-value	0.53125
	Kendall's tau with continuity correction	
	tau	0.13333
	Z-value for tau	0.53666
	P-value	0.59151

Duvall and Tweedie's trim and fill	Studies trimmed	Point estimate	Lower limit	Upper limit	**Q value**
Observed values	-	-0.696	-1.189	-0.202	41.214
Adjusted values (on the left)	1	-0.804	-1.294	-0.315	48.502
Adjusted values (on the right)	0	-0.696	-1.189	-0.202	41.214

Supplemental Figure 3. Funnel plot of effect size vs. precision (1/standard error) for studies evaluating nasal nitric oxide (nNO) in patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and in control subjects with chronic rhinosinusitis without nasal polyps (CRSsNP).



Observed studies and effect size are represented by empty circles and empty square. Imputed studies and adjusted effect size are represented by black circles and black square.

Egger's regression intercept	Intercept	-5.51859
	Standard error	2.94419
	95% lower limit	-11.87912
	95% upper limit	0.84193
	t-value	1.87440
	P value	0.08352
Begg and Mazumdar	**Kendall's S statistic (P-Q)**	-47.0000
	Kendall's tau without continuity correction	
	tau	-0.44762
	Z-value for tau	2.32590
	P-value	0.02002
	Kendall's tau with continuity correction	
	tau	-0.43810
	Z-value for tau	2.27641
	P-value	0.02282

Duvall and Tweedie's trim and fill	Studies trimmed	Point estimate	Lower limit	Upper limit	**Q value**
Observed values	-	-1.448	-2.046	-0.850	140.342
Adjusted values (on the left)	4	-1.955	-2.264	-1.268	328.771
Adjusted values (on the right)	0	-1.448	-2.046	-0.850	140.342