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Systematic Review/Meta-analysis

Obstructive Sleep Apnea as a Predictor of Atrial Fibrillation After Coronary Artery Bypass Grafting: A Systematic Review and Meta-analysis

Amro Qaddoura, BHSc,[a] Conrad Kabali, PhD,[b] Doran Drew, BScH,[a] Erik M. van Oosten, MD, MSc,[c] Kevin A. Michael, MBChB, MPhil,[a,d] Damian P. Redfearn, MBChB,[a,d] Christopher S. Simpson, MD,[a,d] and Adrian Baranchuk, MD[a,d]

[a] *Department of Medicine, Queen's University, Kingston, Ontario, Canada*

[b] *Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*

[c] *Department of Medicine, Western University, London, Ontario, Canada*

[d] *Division of Cardiology, Kingston General Hospital, Queen's University, Kingston, Ontario, Canada*

ABSTRACT

Background: Post–coronary artery bypass grafting atrial fibrillation (PCAF) is associated with increased morbidity, mortality, and system costs. Few studies have explored obstructive sleep apnea (OSA) as a risk factor for PCAF. We aimed to systematically review and synthesize the evidence associating OSA with PCAF.

Methods: We conducted a search of MEDLINE, EMBASE, Google Scholar, and Web of Science, as well as abstracts, conference proceedings, and reference lists until June 2014. Eligible studies were in English, were conducted in humans, and assessed OSA with polysomnography (PSG) or a validated questionnaire. Two reviewers independently selected studies, with disagreement resolved by consensus. Piloted forms were used to extract data and assess risk of bias.

RÉSUMÉ

Introduction : La fibrillation auriculaire survenant après un pontage artériel coronarien (FAPP) est associée à une augmentation de la morbidité, de la mortalité, et des coûts du système de santé. Peu d'études ont évalué l'apnée obstructive du sommeil (OSA) comme un facteur de risque pour la FAPP. Nous avons cherché à systématiquement examiner et résumer les évidences associant OSA et FAPP.

Méthodes : Nous avons effectué une recherche à partir de MEDLINE, EMBASE, Google Scholar, et Web of Science, ainsi que de résumés, de comptes rendus de conférences, et de listes de référence jusqu'en juin2014. Les études éligibles étaient en anglais, ont été menées chez l'humain, et ont évalué une OSA par polysomnographie (PSG) ou un questionnaire validé. Deux réviseurs ont indépendamment sélectionné les études, et les désaccords ont été résolus par consensus. Des

Postoperative atrial fibrillation (AF) is the most common complication after cardiac surgery and is associated with longer hospitalization and increased morbidity and mortality.[1,2] It is consistently estimated to affect between 25% and 50% of patients undergoing coronary artery bypass grafting (CABG) and has a substantial impact on hospital resources and costs.[3-7] Risk factors for post-CABG AF (PCAF) have been previously reported.[6-9] Obstructive sleep apnea (OSA) is highly prevalent in patients referred for CABG and is a potential risk factor for PCAF.[10] Few studies have investigated the relationship between OSA and PCAF, and most were not adequately powered to definitively characterize OSA as a predictor of PCAF. If OSA is demonstrated to be a risk factor for PCAF, there may be a role for perioperative OSA therapy such as continuous positive airway pressure (CPAP). Hence, we aimed to conduct a systematic review and meta-analysis to synthesize the evidence for the association between OSA and PCAF.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) statements for reporting our systematic review and meta-analysis.[11,12]

We searched MEDLINE and EMBASE until June 2014 using keywords, MeSH terms, and Emtree headings, including "sleep apnea syndrome," "sleep-disordered

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Corresponding author: Dr Adrian Baranchuk, Electrophysiology and Pacing Training Program, Kingston General Hospital, 76 Stuart St, FAPC 3, Kingston, Ontario, Canada, K7L 2V7. Tel.: +1-613-549-6666 ×3801; fax: +1-613-548-1387.

E-mail: barancha@kgh.kari.net

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Results: Five prospective cohort studies were included (n = 642). There was agreement in study selection (κ statistic, 0.89; 95% confidence interval [CI], 0.75-1.00). OSA was associated with a higher risk of PCAF (odds ratio [OR], 1.86; 95% CI 1.24-2.80; $P = 0.003$; $I^2 = 35\%$). We conducted 3 subgroup analyses. The associations increased for data that used PSG to assess OSA (OR, 2.34; 95% CI, 1.48-3.70), when severe OSA was included from 1 study (OR, 2.59; 95% CI, 1.63-4.11), and when adjusted analyses were pooled (OR, 2.38; 95% CI, 1.57-3.62; $P < 0.001$ in all), with no heterogeneity detected in any subgroup analysis ($I^2 < 0.01\%$ in all).
Conclusions: OSA was shown to be a strong predictor of PCAF.

Résultats : Cinq études de cohortes prospectives ont été incluses (n = 642). Il y a eu une bonne cohérence dans la sélection des études (Statistique κ, 0,89; intervalle de confiance à 95% [IC]: 0,75-1,00). L'OSA a été associée à un risque plus élevé de FAPP (« odds ratio » [OR], 1,86; IC à 95%, 1,24 à 2,80; $P = 0{,}003$; $I^2 = 35\%$). Nous avons effectué des analyses de 3 sous-groupes. Les associations sont majorées pour les données utilisant la PSG pour évaluer l'OSA (OR, 2,34; IC à 95%, 1,48 à 3,70), en cas d'OSA sévère incluse à partir d'une étude (OR, 2,59; IC à 95%, 1,63 à 4,11), et lorsque les analyses ajustées ont été regroupées (OR, 2,38; IC 95%, 1,57 à 3,62; $P < 0{,}001$ au total), sans hétérogénéité détectée dans aucune analyse de sous-groupe ($I^2 < 0{,}01\%$ au total).
Conclusions : L'OSA s'est montré être un facteur fortement prédictif de la FAPP.

breathing," "sleep apnea," "hypopnea," "cardiovascular surgical procedures," "coronary artery bypass graft," "CABG," "arrhythmias," and "atrial fibrillation." In addition, we searched Google Scholar and the Web of Science and examined abstracts, conference proceedings, and reference lists of retrieved articles. Two authors (AQ, AB) independently screened titles and abstracts and retrieved eligible articles if they (1) reported data on the association between OSA and PCAF in humans, (2) assessed OSA by polysomnography (PSG) or a validated method before the patients' elective CABG surgery, and (3) monitored PCAF using a validated method during the postoperative hospital stay. PCAF was defined as an episode of AF from the end of the operation to hospital discharge. We excluded studies not written in English. There was agreement between the 2 reviewers for study screening (κ statistic, 0.89, 95% confidence interval [CI], 0.75-1.00). All disagreements were resolved by consensus. We extracted data in a standardized manner using an ad hoc abstraction form containing study information and quality criteria. We systematically assessed study quality using criteria proposed by the MOOSE statement.[12] We analyzed data with the R package meta for using the DerSimonian-Laird random effects model.[13,14] We evaluated between-study heterogeneity using the I^2 index and set cutoff ranges for low, moderate, and high I^2 values at $< 25\%$, 25%-50%, and $> 50\%$, respectively.[15] We reported associations as odds ratios (ORs) and 95% CIs. We ran a funnel plot to evaluate the risk of publication bias using Egger's test. We included 90% confidence bounds to improve the power of the test of symmetry.

Results

We identified 204 unique records. Five studies comprising 642 patients were eligible for inclusion (Fig. 1).[16-20] All included studies were prospective cohort in design and identified OSA by either PSG or a validated questionnaire (Table 1). Some studies had an imbalance in the measured baseline characteristics. The quality of the included studies is summarized in Table 2.

Primary meta-analysis and subgroup analyses

The OSA group had a higher risk of PCAF than did the non-OSA group (OR, 1.86; 95% CI, 1.24-2.80; $P = 0.003$; $I^2 = 35\%$) (Fig. 2). We performed subgroup analyses that included the following: data that assessed OSA status by PSG, data from 1 study that reported the association with severe OSA,[17] and data that reported associations adjusted by multivariate logistic regression (Fig. 3).[16,20] All 3 analyses increased the association between OSA and PCAF, with no detected heterogeneity in any analysis (OR, 2.34; 95% CI, 1.48-3.70; OR, 2.59; 95% CI, 1.63-4.11; OR, 2.38; 95% CI, 1.57-3.62, respectively; $P < 0.001$ in all; $I^2 < 0.01\%$ in all).

Sensitivity analyses

Two studies used 2 methods to assess OSA status.[16,20] We conducted follow-up sensitivity analyses, including only 1 method from each study in each analysis. We always found results similar to that of the analyses pooling all methods of OSA assessment, with some detected heterogeneity.

Risk of publication bias

The study by Sharma et al.[18] had a data point that fell outside the 90% confidence bounds, suggesting that publication bias cannot be ruled out (Fig. 4).

Discussion

OSA is a common problem in patients undergoing CABG and is frequently undiagnosed. PCAF remains the most common complication after cardiac surgery, with associated negative sequelae.[1,2] Previous studies investigated the relationship between OSA and PCAF but lacked the power to definitively characterize OSA as a risk factor because of small sample size. In this meta-analysis of 5 prospective cohort studies, we found that OSA increased the odds of PCAF approximately 2-fold. PCAF risk increased further in patients with OSA when only data that assessed OSA status using PSG was included, when data from 1 study that reported severe OSA was included, and for associations adjusted by multivariate logistic regression. Our confidence in the validity of results for the unadjusted associations is high because of their similarity to the adjusted associations, especially given the multifactorial risk for PCAF.[6-9]

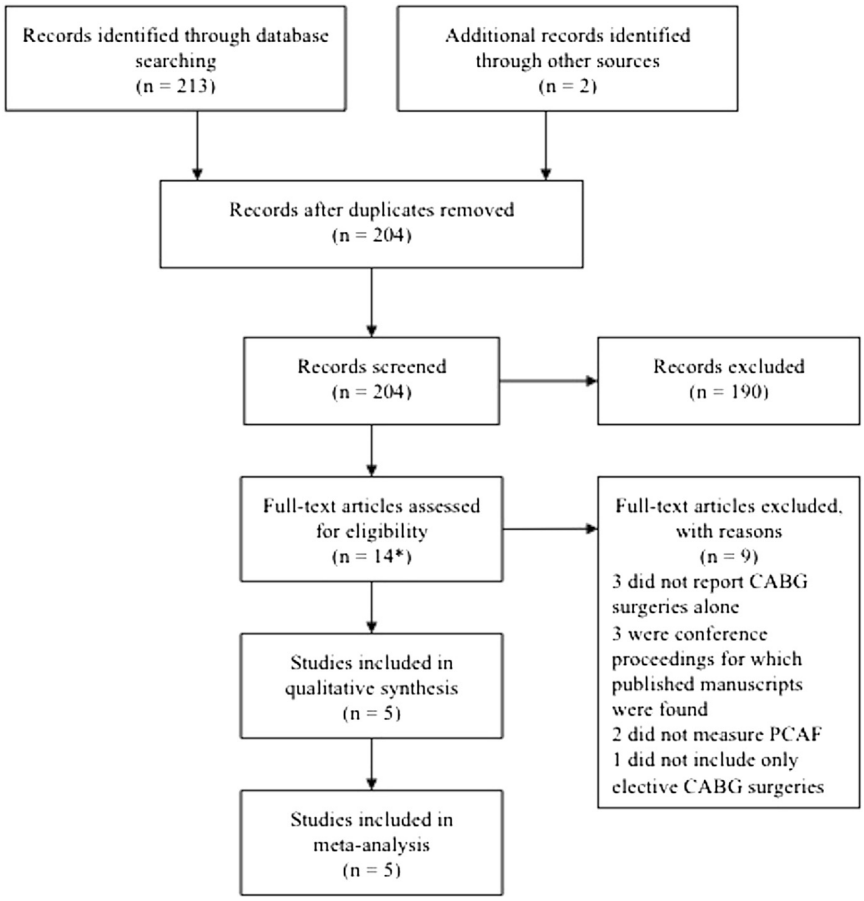

Figure 1. Flow chart summary of study selection. Three of these studies did not have full texts (abstracts or conference proceedings). CABG, coronary artery bypass grafting; PCAF, post–coronary artery bypass graft atrial fibrillation.

Table 1. Characteristics of included studies

Study	Design	OSA groups	N	Age, y mean (SD)	Male no. (%)	Exclude patients with permanent AF at baseline?	Imbalance in baseline factors?
Mooe et al., 1996[16]	PC	Non-OSA (AHI < 5)	39	61.3 (8.7)	?*	Not reported	Age and hospital stay imbalance for PCAF vs no-PCAF groups
		OSA (AHI ≥ 5)	78	62.0 (7.7)	?		
		Non-OSA (ODI < 5)	72	60.6 (8.4)	?		
		OSA (ODI ≥ 5)	49	62.9 (7.8)	?		
Grilli et al., 2007[17]	PC	Non-OSA (AHI < 10)	19	67.8 (9.0)	15 (79)	Not reported	Baseline characteristics seem balanced
		OSA (AHI > 10)	31	68.1 (9.5)	27 (87)		
		Severe OSA (AHI > 30)	10	73.0 (8.0)	9 (90)		
Sharma et al., 2012[18]	PC	Non-OSA (BQ)	40	59.8 (9.7)	26 (65)	Not reported	Baseline characteristics seem balanced
		OSA (BQ)	81	60.2 (9.6)	58 (72)		
Mungan et al., 2013[19]	PC	Non-OSA (BQ)	40	?†	?†	Yes	Cannot be certain, because they did not include these data for OSA vs non-OSA; there seems to be baseline balance for PCAF vs no- PCAF groups, however
		OSA (BQ)	33	?	?		
		Non-OSA (ESS < 10)	45	?	?		
		OSA (ESS ≥ 10)	28	?	?		
van Oosten et al. 2014[20]	PC	Non-OSA (BQ)	145	66.4 (9.9)	110 (76)	Yes	High risk/confirmed vs low risk: age, HTN, BMI, DM, and CPAP use
		High risk/confirmed OSA (BQ/PSG)	132	63.7 (10.7)	106 (80)		
		Confirmed OSA (PSG)	35	63.2 (10.3)	28 (80)		Confirmed vs low risk: BMI, DM, and CPAP use

AF, atrial fibrillation; AHI, apnea-hypopnea index; BMI, body mass index; BQ, Berlin Questionnaire; CPAP, continuous positive airway pressure; DM, diabetes mellitus; ESS, Epworth Sleepiness Scale; HTN, hypertension; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PC, prospective cohort; PCAF, post–coronary artery bypass grafting atrial fibrillation; PSG, polysomnography.

* PCAF vs no-PCAF groups: 27 (84%) vs 69 (78%) men.

† PCAF vs no-PCAF groups: age (SD) of 63.7 y (7.6) vs 62.1 y (9.3), and 20 (61%) vs 24 (59%) men.

Table 2. Quality of included studies

Study	Design	Population clearly identified?	Clear definition of outcome and outcome assessment?	Independent assessment of outcome parameters?	No selective loss of patients during follow-up?	Important confounders and prognostic factors identified?	No other bias?
Mooe, et al., 1996[16]	PC	Yes	Yes	No	Yes	Yes	Baseline imbalance
Grilli et al., 2007[17]	PC	Yes	Yes	Yes	Yes	Yes	No adjusted analyses
Sharma et al., 2012[18]	PC	Yes	Yes	No	No (see other bias column)	Yes	Incomplete questionnaires; no adjusted analyses
Mungan et al., 2013[19]	PC	Yes	Yes	No	Yes	Yes	No adjusted analyses
van Oosten et al., 2014[20]	PC	Yes	Yes	Yes	Yes	Yes	Baseline imbalance

PC, prospective cohort.

A recent meta-analysis conducted by Hernandez et al.[8] identified obesity as a modest risk factor for PCAF (OR, 1.12; 95% CI, 1.04-1.21; $P = 0.002$; I^2, 39%). There is a close association between obesity and OSA, but it is unlikely to have a substantial impact on the association between OSA and PCAF. First, our meta-analysis demonstrated that the magnitude of the association between OSA and PCAF is higher than the reported magnitude with obesity in other studies.[8] Second, we conducted a subgroup analysis including only data that reported an adjusted association between OSA and PCAF, and this increased the magnitude of the association. One of the individual studies from which the data were drawn for this subgroup analysis included obesity as a potential risk factor for PCAF in the multivariate logistic regression model and did not find it to be statistically significant.[20]

Two of the studies assessed OSA using 2 different methods on the same patient sample. One study used the apnea-hypopnea index (AHI) and oxygen desaturation index (ODI),[16] whereas the other used the Berlin Questionnaire (BQ) and Epworth Sleepiness Scale (ESS).[19] We pooled the data together with other studies and performed sensitivity analyses including only 1 method from each study. The sensitivity analyses always showed results similar to those including all methods of OSA assessment, providing assurance for the results pooling all methods. This was expected for the AHI and ODI given their strong correlation,[21-23] and despite limited evidence reporting correlations between the BQ and ESS, this was also expected because they are both validated reliable methods for assessing patients at high risk of OSA.[24-29]

The number of data points was smaller than the minimum recommended threshold of 10 data points for testing the symmetry of the funnel plot and does not allow for effective publication bias assessment.[30] Despite the low power, we ran a funnel plot with the largest number of data points. The test could not rule out the potential for publication bias. However, the lack of symmetry does not necessarily imply publication bias because underlying heterogeneity can also lead to asymmetry.[31] Given that Sharma et al.[18] was the only study that contributed to detected heterogeneity and the only study that fell outside the 90% confidence bounds, we are more confident that the asymmetry was caused by underlying heterogeneity rather than true publication bias.

Previous research demonstrated OSA to be a strong predictor of AF in other clinical scenarios.[32,33] The pathophysiological process has been proposed to involve hypoxia,[34] hypertension,[35,36] negative intrathoracic pressures,[37] inflammation,[38] and autonomic instability.[39-41] OSA may increase the risk for PCAF through similar mechanisms and in addition to the specific triggers associated with CABG (eg, cold cardioplegia, incomplete revascularization, use of inotropic drugs, intracardiac catheters). Future research efforts should aim to assess the effectiveness of OSA management strategies (especially CPAP) in reducing PCAF and other complications in this population.

Limitations

Despite rigorous methodology, our review had some limitations. First, the number of studies included is small. None of the meta-analyses had 10 or more data points, the recommended minimum for testing funnel plot symmetry.[30]

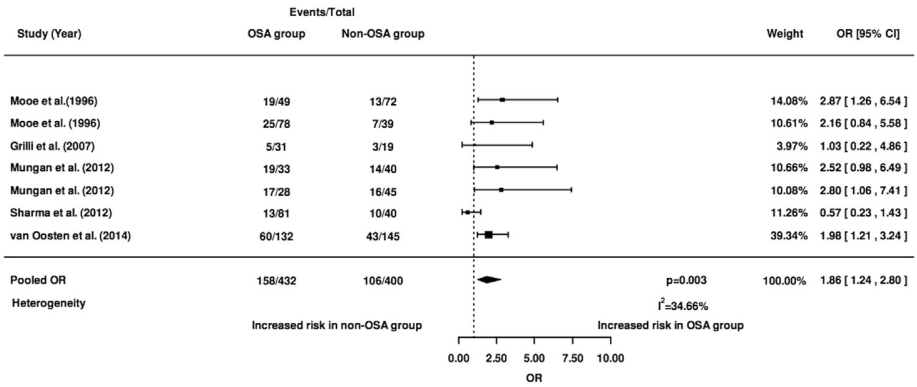

Figure 2. Association between obstructive sleep apnea (OSA) and post–coronary artery bypass graft atrial fibrillation (PCAF). CI, confidence interval; OR, odds ratio.

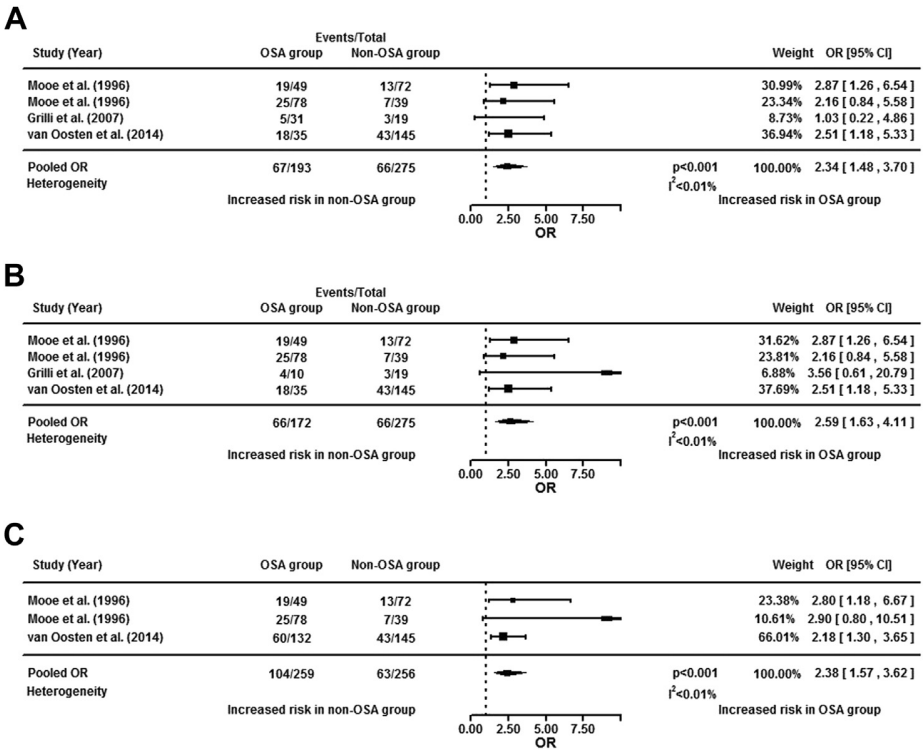

Figure 3. Association between obstructive sleep apnea (OSA) and post–coronary artery bypass graft atrial fibrillation (PCAF) for data that (**A**) used polysomnography (PSG) to assess OSA status, (**B**) assessed OSA with PSG including severe OSA from 1 study, and (**C**) reported an adjusted association. (The events/total for the adjusted association are for illustrative purposes; Their odd ratios (ORs) and standard errors were taken from the studies.) CI, confidence interval; OR, odds ratio.

Second, the impact of the severity of OSA on PCAF was reported in only 1 study with a small sample size.[17] Finally, OSA was reported in studies assessing other risk factors for PCAF. However, these studies did not provide enough information to extract relevant data and usually included AF as a complication after any cardiovascular surgery.

Conclusions

Notwithstanding the aforementioned limitations, this overview of available evidence suggests that OSA appears to be independently associated with the development of AF after elective CABG. Future research efforts should aim to assess the effectiveness of OSA identification and management strategies (especially CPAP) in reducing PCAF and other complications in this population.

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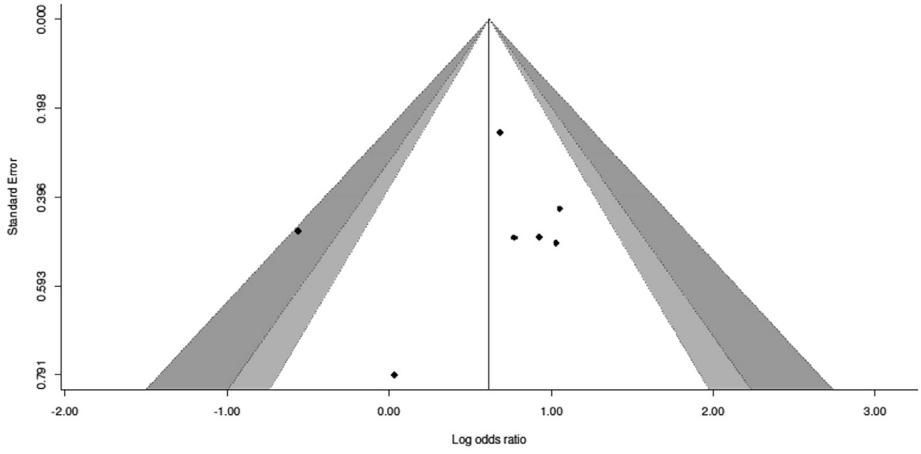

Figure 4. Funnel plot using Egger's test.

the collection, analysis, and interpretation of data; in writing the report; or in the decision to submit the article for publication.

Disclosures

The authors have no conflicts of interest to disclose.

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