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The Effect of Tongue Volume and Adipose Content on Obstructive Sleep Apnea: Meta-analysis & Systematic Review

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Abstract

Objective. Macroglossia is a risk factor for obstructive sleep apnea (OSA) and has been linked to an elevated apnea-hypopnea index (AHI). Obesity may contribute to macroglossia, but its exact relationship is unknown and likely multifactorial, and the degree to which increased adiposity of the tongue affects the development of OSA is not understood. The primary objective of this study was to evaluate how tongue fat and volume relate to the presence and severity of OSA.

Data Sources. Studies reporting the impact of tongue fat or volume were identified using predefined inclusion criteria from September 2002 to 2022.

Review Methods. All studies underwent a 2-stage blinded screening, extraction, and evaluation process. Primary outcomes were the effect of tongue fat and volume on OSA severity and evaluation of study quality. Secondary outcomes included the impact of obesity on tongue fat distribution and OSA severity.

Results. Out of 930 studies, 6 studies with 219 patients and 133 controls were included in meta-analysis. All 6 studies were case-control designs. Included studies showed low (4) and moderate (2) risks of bias. All studies compared tongue volume with an observed significant increase in tongue volume in OSA patients ($P < .00001$) with a weighted mean difference of 19.00 cm^3 [15.53, 22.47]. Two studies compared tongue fat, and there was a significant increase in tongue fat in patients with OSA ($P < .00001$) with a weighted mean difference of 8.04 cm^3 [4.25, 11.82].

Conclusion. This meta-analysis supports increased tongue volume and tongue adipose as important risk factors associated with OSA. Larger studies investigating tongue fat distribution and the effect of weight changes on tongue fat and volume and OSA severity are needed to characterize this relationship better.

Keywords

macroglossia, obstructive sleep apnea, tongue fat, tongue volume

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Obstructive sleep apnea (OSA) is a condition associated with numerous health consequences that is estimated to affect almost one billion people worldwide.[1] The underlying pathophysiology is related to the intermittent collapse of upper airway structures during the sleep state, leading to episodes of hypoxia, hypercapnia, and arousal from sleep that may go unnoticed by patients.[2] In addition to having significant impacts on quality of life,[3] long-term consequences of OSA include increased risk of cardiovascular disease,[4] stroke, diabetes, and hyperlipidemia.[5] The primary symptoms of OSA include snoring and excessive daytime sleepiness. One of the most important risk factors for OSA is obesity, with other risk factors including male sex, increased age, as well as certain anatomical variations of the upper airway.[6] Major anatomical variants associated with increased risk of OSA include micrognathia and retrognathia, maxillary hypoplasia, tonsillar hypertrophy, and macroglossia.[7]

Macroglossia is considered a risk factor for OSA and is correlated with increased severity as characterized by the apnea-hypopnea index (AHI),[8] but macroglossia may occur for a variety of reasons. One such cause may be obesity in the form of increased adipose deposition in the tongue. Previous autopsy studies have shown increased

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tongue fat in obese patients,[9] and prior clinical trials have shown that tongue fat volume as measured by magnetic resonance imaging (MRI) is decreased following weight loss in persons with diagnosed OSA.[10] While the exact nature of the relationship between obesity and OSA severity has not yet been clearly established and is almost certainly multifactorial, there is likely an impact on the anatomical structures of the upper airway that results in increased propensity for airway narrowing.[11]

Case-control studies have shown that increased tongue fat may be associated with increased severity of OSA.[12] Given the extremely high incidence of OSA, the profound consequences of the disease, and the role of obesity as a primary yet reversible risk factor, investigating the relationship between obesity and OSA severity as it relates to tongue fat volume could have important clinical implications. Despite pre-existing research on this subject, there is currently no systematic reviews or meta-analyses of studies examining the relationship between tongue fat and OSA severity. Given this finding, we conducted a meta-analysis of case-control studies to evaluate the relationship between tongue fat volumes and OSA severity. This study examines the effects of tongue fat and volume on the presence and severity of OSA and evaluates study quality using the NIH quality assessment tool. Secondary outcomes included the impact of obesity on tongue fat distribution on OSA severity.

Materials and Methods

The design of this systematic review and meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and was subsequently registered in the PROSPERO database (ID CRD42022359253).

Search Strategy

Relevant studies were identified using a search strategy conducted using the PubMed, Embase, Ovid, Scopus, and Cochrane databases. The search terms included "obstructive sleep apnea" OR "sleep apnea, obstructive" OR "OSA" OR "apnea" OR "apneic" OR "hypopneas" OR "AHI" OR "sleep apnea-hypopnea syndrome" AND "macroglossia" OR "tongue size" OR "Mallampati score" OR "lingual fat" OR "tongue fat" OR "tongue adipose" OR "upper airway fat". Relevant studies published from September 2002 to 2022, were extracted.

Eligibility Criteria

The following inclusion criteria were established: (i) studies specifically measuring the impact of tongue fat on the severity of OSA; (ii) studies with more than 1 human participant; and (iii) retrospective cohort studies, randomized control trials, and case-control studies. PICO (participants, intervention, comparator, outcome) framework and detailed inclusion and exclusion criteria are shown in **Figure 1**.

Data Collection

A multi-stage screening process was conducted as illustrated in **Figure 2**. Duplicate articles were removed prior to abstract screening by 3 independent reviewers (EB, JB, CN). Articles selected at this stage underwent full-text screening by 2 independent reviewers (CN, JB). In addition to the predefined inclusion criteria, studies were selected at this stage by computed tomography (CT) or MRI to quantify overall tongue volume and fat content. Studies selected during the full-text review were subjected to a risk of bias analysis prior to data extraction. Data extraction was carried out by 2 independent reviewers using Covidence. The data collected from each publication included: author, publication date, study type, number of subjects and controls, age range, and gender of participants. Tongue volume, tongue fat, and tongue fat as a percentage of

Criteria Category	Inclusion Criteria	Exclusion Criteria
Participants	Children and adults subjects with a diagnosis of OSA by overnight PSG	• Non-human participants
Interventions/ Investigations	Studies evaluating tongue volume or tongue fat percentage by CT or MRI	• Studies that do not report tongue fat and/or volume as measured by CT/MRI
Comparator (control)	Individuals without OSA	• No control group
Outcome	Presence and severity of OSA	• Studies not specifically looking at tongue fat and/or volume and their relationship with OSA
Study design	Retrospective cohort studies Case-control studies Prospective cohort studies Randomized control trials	• Reviews • Case reports/case series • Systematic reviews • Meta-analysis • Not in English language • Full text not available

Abbreviations: OSA: Obstructive sleep apnea; PSG: Polysomnography; CT: Computed tomography; MRI: Magnetic resonance imaging

Figure 1. Inclusion and exclusion criteria for studies being extracted from databases.

total tongue volume were extracted as outcome measures.

Quality Assessment of Included Studies

For assessing the quality of the studies included in the analysis, we used the National Institute of Health Quality Assessment Tool for Case Control Studies Checklist. This tool is comprised of this 12-question questionnaire that can be answered “yes,” “no,” and “unclear.” All responses other than a “yes” indicate risk of bias. All studies were reviewed and given an overall score which were categorized based on scores as Good: 9 to 12, Fair: 5 to 8, and Poor 1 to 4 (**Table 1**).

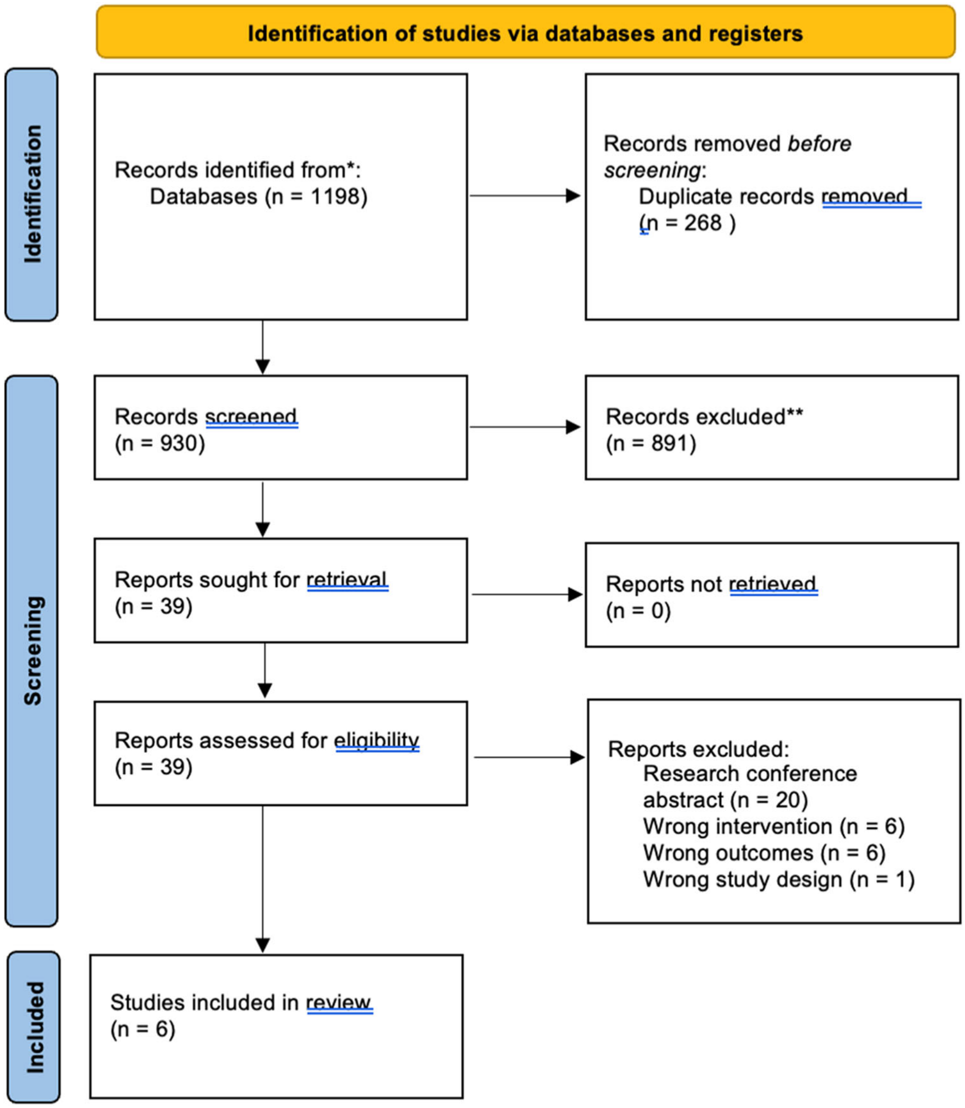

Figure 2. PRISMA 2020 flow diagram for study selection.

Table 1. National Institute of Health Quality Assessment of Case-Control Studies

First author—Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Quality Score	RoB
Lin—2020	Y	N	N	Y	N	Y	N	U	Y	Y	N	Y	6/12, 1U	Fair
Li—2010	Y	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y	10/12, 1U	Good
Kim—2014	Y	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y	10/12, 1U	Good
Schwab—2003	Y	Y	N	Y	Y	Y	N	U	Y	Y	N	Y	8/12, 1U	Fair
Jugé—2021	Y	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y	10/12, 1U	Good
Do—2000	Y	Y	N	Y	Y	Y	N	U	Y	Y	Y	Y	9/12, 1U	Good
Subtotal														

Abbreviations: N, no; RoB, Risk of Bias; U, unclear; Y, yes.

Statistical Analysis

A conventional pair-wise meta-analysis was done in the weighted mean difference (WMD). Statistical heterogeneity was assessed via I^2 and Cochrane's Q-test whereby a heterogeneity level of 0% to 40% low importance, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity, and 75% to 100% considerable heterogeneity.[13] Random effects models were used in all analyses regardless of heterogeneity given that it provides more robust outcome measures, the results are intended to be applied beyond the study (ie, generalization inference), and heterogeneity present amongst the different studies.[14] Therefore, this model was used to meaningfully estimate the proportion of patients with changes in either tongue volume or tongue fat composition with respect to patients with OSA versus patients without OSA. A forest plot was used to graphically display the primary analysis and subsequent analyses outcomes. Statistical analyses were 2-tailed and $P < .05$ were considered statistically significant. Data analyses were performed using Revman 5.4.1.

Results

Search Process and Study Selection

The combined searches yielded 1198 records from which 268 duplicates were removed. The remaining 930 abstracts were screened, and 897 of these were excluded based on title and abstract (**Figure 1**). Therefore, 39 full-text articles were assessed for eligibility. In total, 33 articles were excluded: 20 studies were a research conference abstract, 6 studies were the wrong intervention, 6 studies were the wrong outcomes, and one study was the wrong study design. In total, 6 studies were included in the systematic review and meta-analysis.

Study Characteristics

The characteristics of the 6 selected studies are summarized in **Figure 3**.[12,15–19] All included studies were case-control studies that included measurement of total tongue volume in patients with OSA compared to control patients without OSA. Two of the 6 included studies specifically measured the volume adipose tissue in the tongue as a percentage of total tongue volume.[12,19] There were a total of 219 cases diagnosed with OSA of which 132 were male and 87 were females. There were 133 within the control group, consisting of individuals without OSA diagnosis. The control group consisted of 60 males and 54 females. All studies were matched by age and gender, and all studies used MRI as the imaging modality in determining the dimensions and volume of the tongue. Five of the 6 selected studies controlled for BMI.

Quality Assessment

The quality assessment of each study is summarized in **Table 1**. Of the 6 studies in our review, 4 studies were determined to Good, while 2 were determined to contain a Fair risk of bias based on the National Institute of Health (NIH) Quality Assessment Tool for Case-Control Studies. The main sources of bias arose from convenience sampling, and a paucity of justification for the sample size. All studies had a clearly described research question or objective. All except one study had a clearly defined study population. Only 3 studies included a sample size justification. Furthermore, all studies had controls

Author/Year	N (Gender- M:F)		Controls matched to BMI	Imaging modality	Outcome measure(s)	Tongue Volume Mean (SD) [cm^3]		Tongue Fat % Mean (SD)	
	OSA	Control				OSA	Control	OSA	Control
Lin et al. 2020	18 (18:0)	20 (20:0)	Yes	MRI	Tongue volume	138.23 (13.79)	119.21 (12.64)	NA	NA
Li et al. 2012	14 (11:3)	14 (11:3)	Yes	MRI	Tongue volume	94.69 (14.96)	79.49 (11.82)	NA	NA
Do et al. 2000	9 (9:0)	10 (10:0)	No	MRI	Tongue volume	150 (23.7)	130 (20.47)	NA	NA
Schwab et al. 2003	48 (21:27)	48 (21:27)	Yes*	MRI	Tongue volume	112.45(16.21)	90.25(18.10)	NA	NA
Jugé et al. 2021	40 (31:9)	10 (7: 3)	Yes	MRI	Tongue volume; Tongue fat %	169 (26)	143 (12)	30.4 (9.4)	25.1 (7.3)
Kim et al. 2014	90 (42:48)	31 (10:21)	Yes	MRI	Tongue volume; Tongue fat %	101.20 (17.65)	85.54 (13.81)	32.80 (9.20)	23.40 (5.51)

Abbreviations: OSA: obstructive sleep apnea; BMI: Body mass index; MRI: Magnetic resonance imaging.

*The authors of this study chose to control patients by visceral neck fat measurement in place of BMI

Figure 3. Characteristics of included studies.

selected from the same population as the cases. Aside from 1 study, each one implemented a consistent and systematic basis for including cases and controls. Furthermore, each study clearly differentiated cases from controls. However, none of the studies randomly selected the cases or controls. Moreover, it was unable to determine if any of the studies implemented concurrent controls. All studies were able to confirm that the exposure occurred prior to the development of the condition in each case, and the implementation of risk/exposure was clearly defined, valid, and systematically implemented for all study participants, and key confounding variables were adjusted for in the statistical analysis. Finally, 4 studies had blinded outcome assessors.

Outcomes

The primary outcome measured was total tongue volume. All 6 studies were included in this analysis, and it was found that there was a significant increase in tongue volume in patients with OSA compared to those without OSA ($P < .00001$). The weighted mean difference in tongue volume between the 2 cohorts was 19.00 cm^3 (95% CI: 15.53, 22.47; $I^2 = 0\%$) (**Figure 4**). The 2 studies which investigated tongue fat composition showed that there was a significant increase in tongue fat in patients with OSA compared to those without OSA ($P < .0001$). The weighted mean difference in tongue fat composition between the 2 cohorts was 8.04 cm^3 (95% CI: 4.25, 11.82; $I^2 = 44.0\%$) (**Figure 5**). Due to a limited number of included studies that reported data on tongue fat composition and severities of OSA our ability to evaluate the relationship of tongue fat and volume on the severity of OSA was limited.

Discussion

This meta-analysis showed that patients who have increased tongue volume and tongue fat distribution were associated with an increased risk of OSA when compared to control subjects. In the studies that controlled patients based on baseline variables and BMI, it was found that tongue volume was significantly increased in subjects with OSA compared to subjects without OSA. This indicates a relationship between macroglossia and OSA independent from obesity. Although we were not able to investigate the impact of tongue fat and volume on the severity of OSA in this study, macroglossia is a known risk factor for OSA severity,[8] making it relevant to examine the factors that may be contributing to macroglossia in these patients.

Macroglossia can be caused by congenital, acquired, and transient physiological status. One of the most common causes of macroglossia is obesity, a strong risk factor predisposing OSA diagnosis. Since the prevalence of OSA has been increasing due to the obesity epidemic, it is anticipated that more patients will present with macroglossia due to increased visceral fat of the neck and increase in adipose accumulation in deeper structures of the airway.[20] When fat is deposited in the upper airway, the soft tissue structures such as the tongue, tongue base, soft palate, and epiglottis will become enlarged and can contribute to obstruction of the airway with subsequent development of OSA.[8,21] Increases in tongue adipose tissue can affect many structures that correlate to the severity of OSA, such as hyoid bone positioning, tongue size, tongue volume, and pharyngeal tissue collapsibility. An increase in tongue adiposity positively correlates to an increase in tongue volume and size. The increased size of the tongue may caudally displace the hyoid bone and epiglottis, increasing the pharyngeal length while narrowing airway diameter resulting in increased airway collapsibility during sleep.[22] Increased tongue volume is associated with narrowing of the airway lumen in the retroglossal region which is associated with the severity of OSA.[23] Tongue volume and size are factors that should be monitored in obese patients with OSA, as adipose accumulations in the tongue may increase or decrease with changes in weight thereby affecting the severity of OSA.[24] In some cases, patients who were diagnosed with OSA had more tongue fat than those who did not regardless of obesity and BMI.[12] Fat accumulations within the tongue can disrupt the normal architecture of the tongue which may affect the function of the tongue is its role as a pharyngeal dilator, leading to increased collapsibility of the airway.[12]

Other factors that cause macroglossia include congenital syndromes, muscular hypertrophy, tissue overgrowth, hypothyroidism, and more rare clinical diagnoses such as amyloidosis, acromegaly, lymphatic malformations, and chronic inflammation.[25,26] These conditions

Study or Subgroup	OSA Tongue Volume Mean [cm^3]	SD [cm^3]	Total	Non-OSA Tongue Volume Mean [cm^3]	SD [cm^3]	Total	Weight	Mean Difference IV, Random, 95% CI
Do 2000	150	23.7	9	130	20.47	10	3.0%	20.00 [−0.02, 40.02]
Jugé 2021	169	26	40	143	12	10	10.0%	26.00 [15.03, 36.97]
Kim 2014	101.193	17.651	90	85.542	13.813	31	32.6%	15.65 [9.57, 21.73]
Li 2010	94.69	14.96	14	79.49	11.82	14	12.1%	15.20 [5.21, 25.19]
Lin 2020	138.23	13.79	18	119.21	12.64	20	16.9%	19.02 [10.58, 27.46]
Schwab 2003	112.4465	16.2065	48	90.254	18.0943	48	25.5%	22.19 [15.32, 29.06]
Total (95% CI)			219			133	100.0%	19.00 [15.53, 22.47]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.13$, df = 5 ($P = 0.53$); $I^2 = 0\%$
Test for overall effect: Z = 10.73 ($P < 0.00001$)

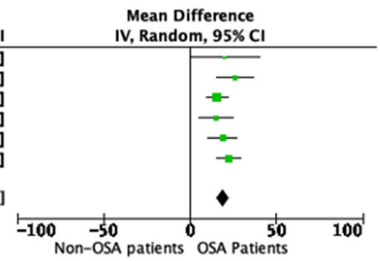

Figure 4. Forest plot analysis depicting the pooled comparison of tongue volume in patients with and without OSA (black diamond). The mean tongue volume difference between the 2 cohorts was 19.00 cm^3 (95% CI: 15.53, 22.47). CI, confidence interval.

	OSA Tongue Fat			Non-OSA Tongue Fat				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Jugé 2021	30.4	9.4	40	25.1	7.3	10	33.3%	5.30 [−0.08, 10.68]
Kim 2014	32.791	9.175	90	23.39	5.511	31	66.7%	9.40 [6.69, 12.11]
Total (95% CI)			130			41	100.0%	8.04 [4.25, 11.82]

Heterogeneity: $Tau^2 = 3.68$; $Chi^2 = 1.78$, $df = 1$ ($P = 0.18$); $I^2 = 44\%$
Test for overall effect: $Z = 4.16$ ($P < 0.0001$)

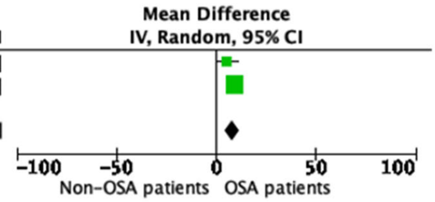

Figure 5. Forest plot analysis depicting the pooled comparison of tongue fat.

can result in disruption of tongue function increasing the collapsibility of the airway, and increased density and weight of the tongue which narrow the airway especially during supine sleep. Different physiological states and differing genetic patterns of adipose distribution could explain the observation that macroglossia is independently related to OSA regardless of BMI.[26]

Recognizing the effect that tongue size on upper airway function in patients with OSA is an important factor to consider in the workup and management of OSA. Recent advances in sleep surgery have included procedures and neurostimulators that alter the anatomy and function of the tongue to treat OSA. One recent advancement is upper airway stimulation (UAS) which involves stimulating the hypoglossal nerve to activate the intrinsic and extrinsic muscles of the tongue to dilate the airway.[27,28] In those who undergo UAS, or any other kind of non-CPAP OSA treatment, higher BMI is associated with reduced treatment success.[29,30] Increased adipose deposits in those with higher BMI will increase the risk of perioperative morbidity and mortality and postoperative complications in those who undergo operative procedures.[31]

Although there are several strengths to this meta-analysis, there were also some limitations that were present. The studies included in this study did not consistently collect information about BMI, AHI, and CPAP, thus preventing comparing fat accumulation in the tongue to OSA severity and obesity. More research is needed to develop a comprehensive report on how tongue fat accumulation relates to obesity and its effect on OSA severity, to fill this gap in research. Only some of the included studies examined tongue fat percentage as a variable, making the sample size for this analysis smaller. Additionally, the data used in the analysis was pooled from studies with varying gender ratios. One study did not include females, which may have introduced bias and influenced the findings.

Conclusions

This meta-analysis supports the conclusion that tongue volume and fat are associated with the development of OSA independent of BMI. Larger studies that examine the distribution of fat within the tongue and the severity of OSA as measured by polysomnography are needed to further characterize this relationship. Additionally, studies that examine how tongue fat changes in response to reduction in body weight, upper airway exercises, and targeted fat removal are needed to investigate the therapeutic opportunities related to the association between tongue fat and OSA.

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Author Contributions

Emily Baker, conception and design of work, data acquisition, data analysis, interpretation of data, drafting and revision of manuscript; **Meghana Chanamolu**, conception and design of work, data acquisition, data analysis, interpretation of data, drafting and revision of manuscript; **Chad Nieri**, conception and design of work, data acquisition, data analysis, interpretation of data, drafting and revision of manuscript; **Stephen F. White**, conception and design of work, data acquisition, data analysis, interpretation of data, drafting and revision of manuscript; **Josiah Brandt**, conception and design of work, data acquisition, data analysis. **Marion Boyd Gillespie**, conception and design of work, data acquisition, data analysis, interpretation of data, drafting and revision of manuscript.

Disclosures

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