Original Article

Salivary Flow Rate, pH, and Buffer Capacity in the Individuals with Obesity and Overweight; A Meta-Analysis

Ö Hatipoğlu, E Maraş[1], FP Hatipoğlu[2], AG Saygın[3]

Departments of Restorative Dentistry and [2]Endodontics, Nigde Omer Halisdemir University, Niğde, [1]Department of Endodontics, Recep Tayyip Erdogan University, Rize, [3]Department of Prosthodontics, Cumhuriyet University, Sivas, Turkey

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Abstract

Background: Weight in individuals can affect the saliva structure, which has an essential role in caries prevention. **Aim:** This meta-analysis aimed to compare individuals with obesity (OB)/overweight (OW) and normal weight (NW) in terms of salivary flow rate (SFR), salivary pH (SpH), salivary buffer capacity (SBC). **Materials and Methods:** After electronic databases (Web of Science, PubMed, Scopus, Cochrane Library, and Open Grey databases) were screened, studies were selected depending on inclusion criteria. The Joanna Briggs Institute Critical Appraisal Checklist was used to assess the risk of bias in individual studies. Mean differences (MD) were used to measure the effect estimates in the comparisons of OB vs NW, OW vs NW, and OB+OW vs NW. Additional analyzes such as subgroup, moderator, sensitivity, and grade were also performed. **Results:** 24 studies and 2072 participants (SFR: 748 OB, 896 NW, SpH: 137 OB, 166 NW, SBC: 62 OB, 63 NW) were included in the quantitative synthesis. Significantly lower SFR was found in the group with OB compared to NW when saliva was stimulated (MD = -0.21, 95% CI [-0.30, -0.12], $P < 0.001$), but no significance was obtained when saliva was unstimulated (MD = -0.02, 95% CI [-0.11, 0.06], $P = 0.55$). No significant difference was found in the group with OB compared to NW in SpH (MD = -0.07, 95% CI [-0.26,0.12], $P = 0.48$) and SBC (MD = -1.10, 95% CI [-2.29,0.09], $P = 0.07$). **Conclusions:** SFR significantly decreases in individuals with OB, notably when saliva is stimulated. Besides, the decrease in SFR is much more prominent in adolescence and adulthood than in childhood. Furthermore, the increase in the severity of OB causes a much greater decrease in SFR. However, regarding SpH and SBC, no significant association exists.

Keywords: *Meta-analysis, obesity, saliva*

Introduction

Obesity (OB), characterized by an excessive fat accumulation in adipose tissue and other organs, is a chronic disease that may impair health. It has increased the prevalence of several chronic conditions, including insulin resistance, thrombosis, hypertension, asthma, dyslipidemia, sleep apnea, metabolic syndrome, heart attack, stroke, and atherosclerosis.[1] Although OB is a risk factor for such serious diseases, its worldwide prevalence is alarming, such that approximately 30% of the world population is either overweight (OW) or OB.[2]

In addition to its impacts on general health, extensive research studies have shown that OB is associated with various oral health problems such as dental caries and periodontitis. A meta-analysis conducted by Hayden, *et al*.[3] revealed that individuals with OB under 18 had a higher prevalence of dental caries than individuals with normal weight (NW); furthermore, a meta-analysis by Chen, *et al*.[4] supported these results. The most recent meta-analysis indicated that individuals with OB under six have higher dental caries experience.[5]

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Address for correspondence: Dr. Ö Hatipoğlu, Department of Restorative Dentistry, Nigde Omer Halisdemir University, Niğde, Turkey. E-mail: ohatipoglu@ohu.edu.tr

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The saliva secreted by the major salivary glands (parotid, submandibular, and sublingual) and minor salivary glands is a complex and dynamic biological fluid. Saliva has many functions such as chewing, defense, tissue lubrication, swallowing, digestion, and taste.[6] Especially in terms of defensive function, buffering capacity provides the ability to dilute and neutralize acids in diets that protect the teeth from dental caries. Its efficiency differs depending on the salivary flow rate (SFR). Saliva also plays a critical role in forming the enamel pellicle, which provides a protective barrier for the teeth.[7]

OB and dental caries have common etiological factors such as dietary habits, stress, and sociodemographic features.[5] In addition to such factors, differences in the saliva structure may also affect the number of dental caries, considering the caries-preventive role of saliva. Although the impacts of OB on saliva adipokines levels were synthesized by a meta-analysis[8] recently, other caries-related salivary factors, including salivary flow rate, pH, and buffer capacity, have not been synthesized by a meta-analysis yet. Proving the relationship between saliva and obesity will enable physicians to take saliva-based measures against dental caries. The present meta-analysis purposed of synthesizing the outcomes of previous observational studies which examined the salivary factors of individuals with OB and/or OW, whether adults or pediatric population. Also, this study aimed to offer a comprehensive conclusion on the association between OB/OW and SFR, salivary pH (SpH), and salivary buffer capacity (SBC) to elucidate the underlying factors of dental caries in OB and OW individuals.

Methods

Guidelines and eligibility criteria

This study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) statement, which includes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyzes.

Inclusion criteria (PICOS)

Population: The research population consisted of OB, OW, and NW subjects regardless of the types of gender, socioeconomic status, ethnicity, and hometown.

Indicator: OB and/or OW

Comparison: NW

Outcomes: SFR, SpH, and SBC, whether stimulated or unstimulated.

Study design: Human observational studies (Longitudinal, cohort, cross-sectional and case-control studies).

Exclusion criteria

The exclusion criteria were as follows: (1) Studies that did not include any salivary parameters including SFR, SpH, and SBC related to obesity and dental caries; (2) Descriptive studies, reviews, case reports, protocols, personal opinions, letters, posters, and laboratory research (in vivo and *in vitro* studies); (3) Full-text not found, (4) Any language other than English or Turkish, (5) No control group.

Information sources and search strategy

Studies published between 2001 and 2020 were distinguished by scanning the following electronic databases: PubMed, Web of Science, Scopus, Cochrane Library, and Open Grey database: PubMed, Web of Science, Scopus, Cochrane Library, and Open Grey databases. Two researchers (E.M and F.P.H) screened all databases individually and completed this on the 15th of December 2020. Filters, limits, and terms used in the screening are listed in Table 1. The reference lists of each collected paper and review were thoroughly critiqued by two authors (E.M and F.P.H) to identify further relevant studies. The authors also sought to reach recent articles that cited the collected papers.

Study selection and data collection

Initially, the title and abstract screening were completed blinded by two independent researchers (E.M and F.P.H) by rating studies as "yes" or "no". Afterward, two independent researchers resolved discrepancies in the studies by consensus when the ratings did not overlap. The level of agreement between researchers was calculated using Kappa, and satisfactory agreement (0.86) was obtained.

Risk of bias in individual studies

The Joanna Briggs Institute Critical Appraisal Checklist for cross-sectional studies was used to assess the risk of bias in individual studies.[9] Two researchers (OH and FPH) conducted the assessment independently and attained an agreement. The Joanna Briggs guidelines scoring system and cut-off points were accepted for risk of bias evaluation. Studies that reached up to 49% of questions scored as "yes" were classified as "high risk of bias"; from 50% to 69% as "moderate risk of bias"; and more than 70% as "low risk of bias."

Summary measures

The primary outcome parameters of interest were SFR, SpH, and SBC. Mean differences (MD) with 95% confidence intervals (CI) were used to measure the effect estimates in comparisons (OB vs NW, OW vs NW, and OB+OW vs NW), where the primary outcome was continuous. Outcomes given as median and interquartile ranges were transformed to mean and standard deviation

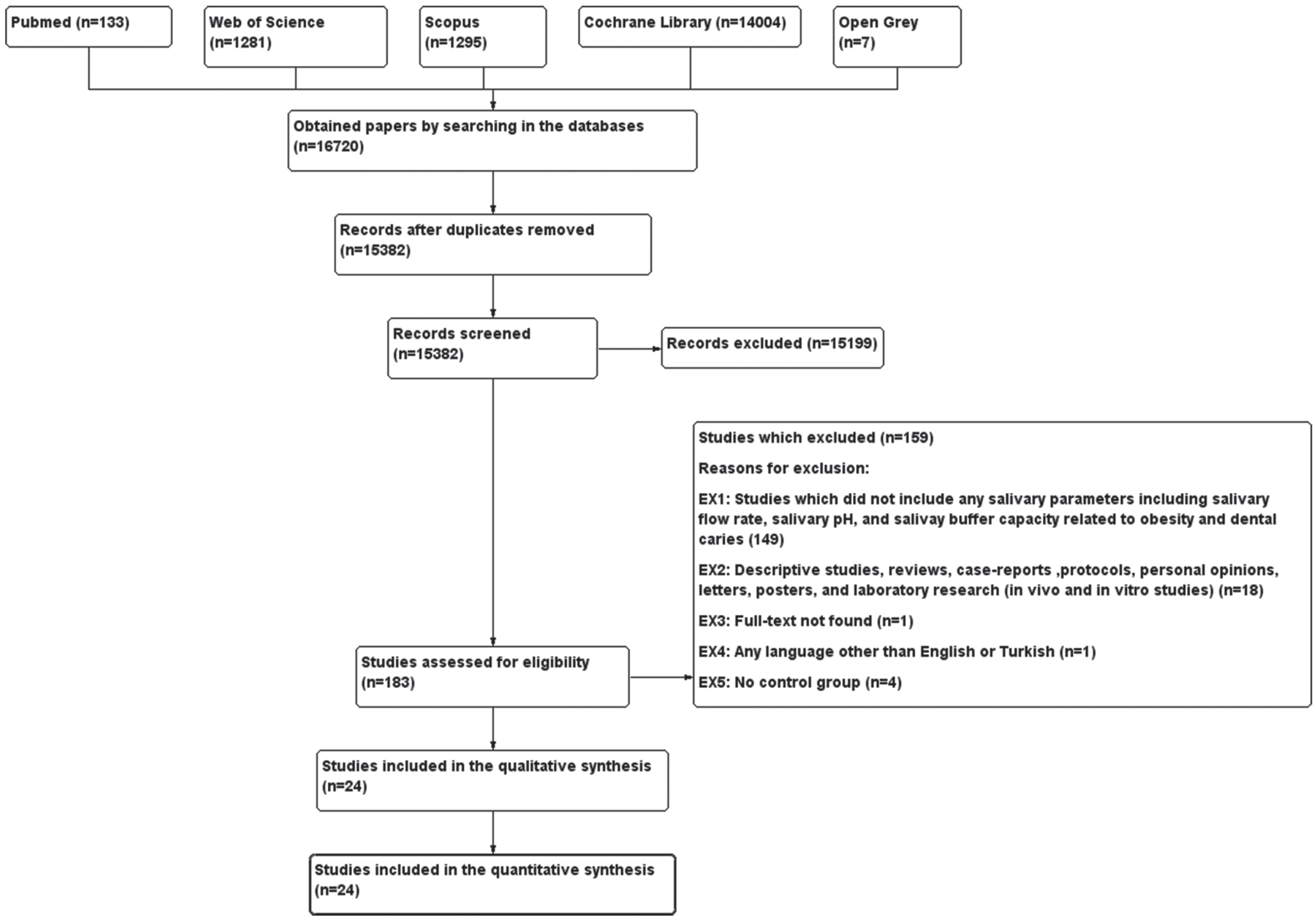


Figure 1: Flow diagram of the studies involved in the qualitative and quantitative analyzes

using methods recommended by Wan, *et al.*[10] and Luo, *et al.*[11]

Synthesis of results

The overall effect estimates were assessed by a meta-analysis software, RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and the forest plots were produced. Methodological heterogeneity was estimated by checking the variabilities in the study design and the risk of bias. Clinical heterogeneity was estimated by evaluating the differences in participant characteristics (e.g., age, sex, ethnicity, obesity severity). Higgins I^2 test was used to estimate the statistical heterogeneity among studies and categorized as not significant (<30%), moderate (30%–50%), substantial (50%–75%), or considerable (75%–100%).[12] Even though statistical homogeneity is identified in a model, applying a random-effects model is suggested over a fixed-effects model if methodological or clinical heterogeneity exists.[13] A random-effects model with 95% CI was preferred as the meta-analysis model due to not achieving methodological, clinical, and statistical homogeneity together. The level of significance was set at $P < 0.05$ in all tests.

Risk of bias across studies

Funnel plots were inspected visually to estimate the publication bias, and their asymmetry was tested with Egger's test. If at least ten studies were not available in the analysis, the analyzes were not conducted. Egger's test was conducted using the David B. Wilson Meta-essentials version 1.2 (http://mason.gmu.edu/~dwilsonb/ma.html).

Additional analyzes

Sensitivity analysis

The robustness of the pooled outcomes was assessed by sensitivity analyzes, applying the leave-one-out method. Sensitivity analysis was completed in two-phase. In the first part, the robustness of the pooled outcomes was evaluated, removing studies with a high and moderate risk of bias from the funnel plots. In the second part, the robustness of the pooled outcomes was evaluated, removing studies whose outcome was transformed to mean and standard deviation from median and interquartile range. Sensitivity analyzes were conducted via web-based software, Review Manager Web (The Cochrane Collaboration, 2019, available at revman.cochrane.org).

Subgroup analysis

Subgroup analyzes were performed to check whether the overall estimate of OB would change according to the types of SFR (stimulated salivary flow rate [SSFR] and unstimulated salivary flow rate [USFR]). Subgroup analysis is critical if there is a suspicion regarding heterogeneity. If at least 10 studies were not available in the analysis, the subgroup analyzes were not conducted.

Moderator analysis

Moderator analysis was conducted using ProMeta 3 Software (IdoStatistics, available from https://idostatistics.com/prometa3/) to identify the influence of the following potential confounders; BMI classification (class 1 [BMI mean value of OB group <35.00], class 2 [BMI mean value of OB group >35.00]), periods of development (Childhood [6-12 yrs], adolescent [12-18 yrs], and adult [>18 yrs]), continental (America, Asia, and Europe), and country classification (Developed and developing countries). Because of the small number of studies (<10) for comparison, only SSFR and USFR were involved in the analysis. Test of differences was calculated using ANOVA Q-Test Random-effects with separate estimates of T2.

GRADE analysis

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system, a certainty assessment method that provides a transparent and structured evaluation of the importance of outcomes, was used. The system also offers comprehensive criteria for downgrading and upgrading certainty in the evidence. A table presenting a summary of the findings was generated and adapted from the online software GRADEpro GDT (The GRADE Working Group).[14]

Results

Study selection

The queries mentioned in Table 1 were used to scan the databases, resulting in 16,720 records (133 in Pubmed, 1281 in Web of Science, 1295 in Scopus, 14004 in Cochrane Library, and 7 in Open Grey). Following duplicate records were eliminated, this number decreased to 15,382. After the abstracts and titles of these studies were screened, 12,217 studies were excluded. Following a thorough review of the full texts of the remaining 183 studies, 159 studies were excluded due to not meeting the eligibility criteria. Twenty-four cross-sectional studies were included in the qualitative synthesis. One study[15] was not included in the quantitative synthesis because no other study had a comparison of OB vs OW+NW [Figure 1]. Characteristics of the included 24 studies[15-38] were displayed in Table 2.

Risk of bias within studies

Sixteen studies were identified as having a low risk of bias.[15,16,19-21,25-28,30,31,33-36,38] Three were identified as having a moderate risk of bias,[17,23,29] and five had a high risk of bias.[18,22,24,32,37] Most of the studies did not identify the confounding factors or the strategies used to deal with the confounding factors stated [Table 3].

Table 1: The used search strategies in information sources

Database	Search strategy
PubMed	#1 ((((Obesity[MeSH Terms]) OR Overweight[MeSH Terms]) OR Adolescent Obesity[MeSH Subheading] OR Childhood Obesity[MeSH Subheading] OR Morbid Obesity[MeSH Subheading]
	#2 ((((Dental Caries[MeSH Terms]) OR Saliva[MeSH Terms]) OR Salivary Proteins[MeSH Subheading]) OR Salivary alpha-Amylases[MeSH Subheading]
	#1AND #2
Web of Science	#1 TS=((Obesity OR Overweight OR Adolescent Obesity OR Childhood Obesity OR Morbid Obesity)
	#2 TS=(Dental Caries OR Saliva OR Salivary Proteins OR Salivary alpha-Amylases)
	#1AND #2
Scopus	#1 TITLE-ABS-KEY (((Obesity) OR (Overweight) OR (Adolescent AND Obesity) OR (Childhood AND Obesity) OR (Morbid AND Obesity)))
	#2 TITLE-ABS-KEY (((dental AND caries) OR (saliva) OR (salivary AND proteins) OR (salivary AND alpha-amylases))))
	#1AND #2
Cochrane Library	#1 MeSH descriptor: [Obesity] explode all trees
	#2 (“Overweight”:ti, ab, kw “)
	#3 (“Adolescent Obesity”:ti, ab, kw “)
	#4 (“Childhood Obesity”:ti, ab, kw “)
	#5 (“Morbid Obesity”:ti, ab, kw “)
	#6 #1 or #2 or #3 or #4 or #5
	#7 MeSH descriptor: [Saliva] explode all trees
	#8 (“Dental Caries”:ti, ab, kw “)
	#9 (“Saliva”:ti, ab, kw “)
	#10 (“Salivary Proteins”:ti, ab, kw “)
	#11 (“Salivary alpha-Amylases”:ti, ab, kw “)
	#12 #7 or #8 or #9 or #10 or #11 or #12
	#13 #6 and #12
Open Grey	((Obesity) OR (Overweight) OR (Adolescent Obesity) OR (Ch Childhood Obesity) OR (Morbid Obesity)) AND ((Dental Caries) OR (Saliva) OR (Salivary Proteins) OR (Salivary alpha-Amylases))

Table 2: Characteristics of the studies included in the qualitative synthesis (*n*=24)

Study	Study Type/ Publication Type	Year	Gender	Country	Age range	BMI values Mean±SD	BMI cut-off points
Ain, *et al.*[16]	Cross-sectional/ Journal Article	2016	NS	India	14-15 yrs	OB: 30.98±0.6 NW: 21.91±1.4	OB: >30 kg/m² NW: 18-25 kg/m²
Al-Juboury, *et al*[17]	Cross-sectional/ Journal Article	2011	F: 0 M: 81	Iraq	30-40 yrs	NS	OB: >30 kg/m² OW: 25-30 kg/m² NW: 18-25 kg/m²
Bud, *et al.*[18]	Cross-sectional/ Journal Article	2017	F: 94 M: 68	Romania	6-12 yrs	OB+OW: 21.32±2.66 NW: 16.37±1.56	OB: >95 kg/cm² OW: 85-95 kg/cm² NW: <85 kg/cm²
de Campos, *et al*[19]	Cross-sectional/ Journal Article	2014	F: 41 M: 27	Brazil	5-12 yrs	OB: 23.32±2.21 OW: 19.20±1.36 NW: 15.92±1.35	OB: >30 kg/m² OW: 25-30 kg/m² NW: 18-25 kg/m²
Fadel, *et al.*[20]	Cross-sectional/ Journal Article	2014	F: 26 M: 29	Sweden	13-18 yrs	OB: 37±4 NW: 20±2	OB: >30 kg/m² NW: 18-25 kg/m²
Fejfer, *et al.*[21]	Cross-sectional/ Journal Article	2017	F: 66 M: 28	Poland	34-55 yrs	OB: 47.10±0.81 NW: 20.61±2.31	OB: >40 kg/m² NW: 18-25 kg/m²
Hartman, *et al.*[22]	Cross-sectional/ Journal Article	2013	F: 33 M: 45	USA	6-12 yrs	OB: 27.4 (7.6) OW: 21.1 (2.4) NW: 17.2 (2.2)	OB: >95 kg/cm² OW: 85-95 kg/cm² NW: <85 kg/cm²
Jassim and Mohammed[23]	Cross-sectional/ Journal Article	2016	F: 22 M: 22	Iraq	18-39 yrs	OB: 38.63±6.391 NW: 23.21±2.85	OB: >30 kg/m² NW: 18-25 kg/m²
Lehmann-Kalata, *et al.*[15]	Cross-sectional/ Journal Article	2018	F: 39 M: 42	Poland	25-40 yrs	OB: 38.7±5.4 OW+NW: 22.1±3.6	OB: >30 kg/m² OW + NW<30 kg/m²
Lindawati, *et al*[24]	Cross-sectional/ Conference proceedings	2017	F: 13 M: 7	Indonesia	18-26 yrs	NS	OB: >27 kg/m² NW: 18-25 kg/m²
Loyola-Rodriguez, *et al.*[25]	Cross-sectional/ Journal Article	2011	F: 56 M: 44	Mexico	12-18 yrs	OB: 29.2±3.1 NW: 19.1±2.2	OB: >95 kg/cm² NW: <85 kg/cm²
Mennella, *et al.*[26]	Cross-sectional/ Journal Article	2014	F: 20 M: 22	Italy	19-54 yrs	OB+OW: 28.5±2.1 NW: 22.2±1.7	OB + OW: >25 kg/m² NW: 18-25 kg/m²
Modéer, *et al.*[27]	Cross-sectional/ Journal Article	2010	NS	Sweden	10-18 yrs	OB: 36.8±5.8 NW: 19.7±2.4	OB: >30 kg/m² NW: 18-25 kg/m²
Mollaasadollah, *et al.*[28]	Cross-sectional/ Journal Article	2020	F: 25 M: 22	Iran	6-12 yrs	NS	OW + OB: >25 kg/m² NW: 18-25 kg/m²
Pannunzio, *et al*[29]	Cross-sectional/ Journal Article	2010	F: 41 M: 49	Brazil	7-10 yrs	NS	OB: >95 kg/cm² OW: 85-95 kg/cm² NW: <85 kg/cm²
Perez, *et al.*[30]	Cross-sectional/ Journal Article	2019	F: 53 M: 38	Brazil	6-12 yrs	OB+OW: 22.81±3.26 NW: 16.11±1.65	OB: >97 kg/cm² OW: 85-97 kg/cm² NW: <85 kg/cm²
Rahmawan, *et al*[31]	Cross-sectional/ Journal Article	2020	F: 76 M: 74	Indonesia	18-21 yrs	NS	OB: >30 kg/m² OW: 25-30 kg/m² NW: 18.5-23 kg/m²
Rodríguez, *et al*[32]	Cross-sectional/ Journal Article	2015	F: 30 M: 30	Argentina	3-6 yrs	NS	BMI Z scores NW: -1.0 to+1.0, OW: ≥ +1.0 y < +2.0, OB: ≥ +2.0
Sawair,*et al.*[33]	Cross-sectional/ Journal Article	2009	F: 134 M: 110	Jordan	15-76 yrs	NS	OB: >30 kg/m² OW: 25-30 kg/m² NW: 18-25 kg/m²

Contd...

Table 2: Contd...

Study	Study Type/ Publication Type	Year	Gender	Country	Age range	BMI values Mean±SD	BMI cut-off points
Şimşek [34]	Cross-sectional/ Thesis	2015	F: 140 M: 0	Turkey	20-40 yrs	OB: 32.5±1.6 NW: 22.6±1.5	OB: >30 kg/m² NW: 18-25 kg/m²
Tong, *et al.*[35]	Cross-sectional/ Journal Article	2014	F: 28 M: 36	U.K	7-15 yrs	OB: 31.12±5.82 NW: 18.13±1.99	OB: >98 kg/cm² NW: <85 kg/cm²
Yamashita, *et al*[36]	Cross-sectional/ Journal Article	2015	F: 121 M: 29	Brazil	30-40 yrs	OB: 50.9±0.9 NW: 21.9±0.3	OB: >40 kg/m² NW: 18-25 kg/m²
Yaseen and Baydaa Hussein[37]	Cross-sectional/ Journal Article	2017	F: 80 M: 0	Iraq	20-22 yrs	NS	OB: >30 kg/m² NW: 18-25 kg/m²
Yomna A, *et al.*[38]	Cross-sectional/ Journal Article	2016	F: 50 M: 50	Egypt	12-15 yrs	OB: 35.62±4.05 NW: 18.55±1.2	OB: >95 kg/cm² NW: <85 kg/cm²

Data are expressed as means±SD or median (interquartile ranges), NS: Not specified

Table 3: Risk of bias summary, assessed by Joanna Briggs Institute Critical Appraisal Checklist for Cross-sectional studies (*n*=24): author's judgments for each included study

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total	Risk of Bias
Ain, *et al*	Y	Y	Y	Y	N	N	Y	Y	75%	Low
Al-Juboury, *et al*	Y	N	Y	Y	N	N	Y	Y	62.5%	Moderate
Bud, *et al*	Y	N	U	Y	N	N	Y	U	37.5%	High
de Campos, *et al*	Y	Y	Y	Y	Y	N	Y	Y	87.5%	Low
Fadel, *et al*	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Fejfer, *et al*	Y	Y	Y	Y	N	N	Y	Y	75%	Low
Hartman, *et al*	N	Y	U	Y	N	N	N	Y	37.5%	High
Jassim and Mohammed	Y	N	Y	Y	N	N	Y	Y	62.5%	Moderate
Lehmann-Kalata, *et al*	Y	Y	Y	Y	Y	N	Y	Y	87.5%	Low
Lindawati, *et al*	Y	N	U	Y	N	N	Y	U	37.5%	High
Loyola-Rodriguez, *et al*	Y	Y	Y	Y	N	N	Y	Y	75%	Low
Mennella, *et al*	Y	Y	Y	Y	Y	N	Y	Y	87.5%	Low
Modéer, *et al*	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Mollaasadollah, *et al*	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Pannunzio, *et al*	Y	N	Y	Y	N	N	Y	Y	62.5%	Moderate
Perez, *et al*	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Rahmawan, *et al*	N	Y	Y	Y	Y	N	Y	Y	75%	Low
Rodríguez, *et al*	Y	N	U	Y	N	N	N	Y	37.5%	High
Sawair, *et al*	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Şimşek	N	Y	Y	Y	Y	N	Y	Y	75%	Low
Tong, *et al*	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Yamashita, *et al*	N	Y	Y	Y	Y	Y	Y	Y	87.5%	Low
Yaseen and Baydaa Hussein	N	N	Y	Y	N	N	Y	U	37.5%	High
Yomna A, *et al*	Y	N	Y	Y	Y	Y	Y	Y	87.5%	Low

Y = Yes; N = No; U = Unclear, NA=Not applicable; Cross-Sectional Study Checklist: Q1- Were the criteria for inclusion in the sample clearly defined? Q2- Were the study subjects and the setting described in detail? Q3- Was the exposure measured in a valid and reliable way? Q4- Were objective, standard criteria used for measurement of the condition? Q5- Were confounding factors identified? Q6- Were strategies to deal with confounding factors stated? Q7- Were the outcomes measured in a valid and reliable way? Q8- Was appropriate statistical analysis used? Total= ΣY/Applicable Items. Risk of bias was categorized as high when the study reaches up to 49% score "yes", moderate when the study reached 50% to 69% score "yes", and low when the study reached more than 70% score "yes

Results of individual studies

SSFR and USFR were significantly lower in the OB group than in the NW group in 9[16,20,21,24,25,27,34,36,38] and 2[21,33] of 18 studies, respectively ($p < 0.05$). Only in one study[37] USFR was significantly higher in the OB group than in the NW group ($p < 0.05$). SSpH was significantly lower in the OB group than in the NW group in one[16] of 5 studies ($p < 0.05$). No significant difference was observed in terms of USpH ($p > 0.05$). SSBC was significantly lower in the OB group than in the NW group in one[16] of 4 studies ($p < 0.05$).

Table 4: Findings of studies included in the qualitative synthesis (*n*=24)

Study	Subject Type	N	SSFR (ml/min)	SSpH	SSBC	USFR (ml/min)	USpH	USBC
Ain, *et al*.[16]	OB	25	0.50±0.1*	6.45±0.3*	6.8±1.8*	-	-	-
	NW	25	0.74±0.1	6.8±0.2	9.6±1.7	-	-	-
Al-Juboury, *et al*.[17]	OB	27	-	-	-	0.42±0.096	-	-
	OW	27	-	-	-	0.37±0.09	-	-
	NW	27	-	-	-	0.33±0.091	-	-
Bud, *et al*.[18]	OB + OW	38	-	7.6±2.19	H (41.66%) M (58.33%) L (0%)	-	-	-
	NW	87	-	8.1±1.95	H (60%) M (40%) L (0%)	-	-	-
de Campos, *et al*.[19]	OB	10	2.20±0.21	7.60±0.25	-	2.11±0.28	7.33±0.22	-
	OW	19	2.21±0.30	7.57±0.29	-	2.02±0.26	7.33±0.43	-
	NW	39	2.29±0.41	7.57±0.25	-	2.06±0.33	7.33±0.35	-
Fadel, *et al*.[20]	OB	27	1.55±0.63*	-	5.3±1.2	0.26±0.18	-	-
	NW	28	2.05±1.05	-	5.6±1.2	0.29±0.19	-	-
Fejfer, *et al*.[21]	OB	47	0.74±0.20*	-	-	0.28±0.04*	-	-
	NW	47	1.21±0.10	-	-	0.41±0.10	-	-
Hartman, *et al*.[22]	OB	26	-	-	-	0.545 (0.46)	-	-
	OW	15	-	-	-	0.672 (0.42)	-	-
	NW	36	-	-	-	0.621 (0.46)	-	-
Jassim and Mohammed[23]	OB	22	-	-	-	0.53±0.26	7.02±0.20	-
	NW	22	-	-	-	0.496±0.29	7.20±0.41	-
Lehmann-Kalata, *et al*.[15]	OB	19	0.85 (0.55-1.30)	7.3 (7.0-7.5)	-	0.25 (0.20-0.38)	6.9 (6.7-7.1)	-
	OW + NW	25	1.30 (0.75-2.13)	7.2 (7.0-7.5)	-	0.30 (0.25-0.50)	6.9 (6.7-7.1)	-
Lindawati, *et al*.[24]	OB	10	0.74±0.21*	-	9±1.2	-	-	-
	NW	10	1.18±0.61	-	9.7±1.3	-	-	-
Loyola-Rodriguez, *et al*.[25]	OB	50	0.86±0.53*	7.31±0.33	-	-	-	-
	NW	50	1.096±0.58	7.29±0.47	-	-	-	-
Mennella, *et al*.[26]	OB + OW	19	-	-	-	0.80±0.09	-	-
	NW	23	-	-	-	0.79±0.14	-	-
Modéer, *et al*.[27]	OB	65	1.2±0.5*	-	-	-	-	-
	NW	65	2.0±0.9	-	-	-	-	-
Mollaasadollah, *et al*.[28]	OB + OW	22	-	-	-	0.3±0.15*	6.41±0.43*	-
	NW	25	-	-	-	0.44±0.14	6.78±0.36	-
Pannunzio, *et al*.[29]	OB	30	0.95±0.47	7.66±0.27	-	-	-	-
	OW	30	0.89±0.54	7.80±0.29*	-	-	-	-
	NW	30	1.06±0.52	7.51±0.22	-	-	-	-
Perez, *et al*.[30]	OB + OW	41	-	-	-	0.65±0.31		
	NW	50	-	-	-	0.67±0.38		
Rahmawan, *et al*.[31]	OB	13	1.46±0.72	-	-	-	-	-
	OW	33	1.41±0.68	-	-	-	-	-
	NW	27	1.48±0.64	-	-	-	-	-
Rodríguez, *et al*.[32]	OB+OW	27	-	-	-	0.439±0.234	-	-
	NW	30	-	-	-	0.534±0.318	-	-
Sawair, *et al*.[33]	OB	20	-	-	-	0.35±0.14*	-	-
	OW	53	-	-	-	0.41±0.22*	-	-
	NW	134	-	-	-	0.50±0.28	-	-
Şimşek[34]	OB	70	1.01±0.38*	-	-	-	-	-
	NW	70	1.39±0.53	-	-	-	-	-

Contd...

Table 4: Contd...

Study	Subject Type	N	SSFR (ml/min)	SSpH	SSBC	USFR (ml/min)	USpH	USBC
Tong, *et al.*[35]	OB	32	0.86±0.54	-	H (78.1%) M (21.9%) L (0%)	-	-	-
	NW	32	0.95±0.47	-	H (71.9%) M (25.0%) L (3.1%)	-	-	-
Yamashita, *et al.*[36]	OB	100	0.6 (0.59)*	-	-	-	-	-
	NW	50	0.9 (0.55)	-	-	-	-	-
Yaseen and Baydaa Hussein[37]	OB	40	-	-	-	0.38±0.04*	-	-
	NW	40	-	-	-	0.34±0.05	-	-
Yomna A, *et al.*[38]	OB	50	1.77±0.7*	-	-	-	-	-
	NW	50	2.84±0.67	-	-	-	-	-

Data are expressed as means±SD or median (interquartile ranges). SSFR: Stimulated salivary flow rate, USFR: Unstimulated salivary flow rate, SSpH: Stimulated salivary pH, USpH: Unstimulated salivary pH, SSBC: Stimulated salivary buffer capacity, USBC: Unstimulated salivary buffer capacity * P<0.05 (Reference: Normal Weight)

Table 5: Assessment of the moderators' effect on the SFR outcome in the comparison of OB vs NW

Moderator	k	N_1	N_2	MD	95% CI		Overall effect Sig.	Heterogenity		Test of differences Sig.
					LL	UL		Sig.	I^2	
BMI classification										
Class 1 (< 35)	7	223	291	-0.17	-0.27	-0.07	<0.001	0.01	64%	0.049*
Class 2 (> 35)	8	385	337	-0.38	-0.56	-0.19	<0.001	<0.001	95%	
Periods of development										
Childhood (<12 yrs)	5	108	176	-0.06	-0.15	0.03	0.20	0.83	0%	0.009*
Adolescent (12-18 yrs)	6	244	246	-0.45	-0.69	-0.21	<0.001	<0.001	93%	
Adult (>18 yrs)	10	396	474	-0.16	-0.28	-0.04	<0.001	<0.001	97%	
Continental type										
America	6	226	244	-0.13	-0.23	-0.02	0.01	<0.001	96%	0.173
Asia	8	207	335	-0.17	-0.31	-0.04	0.01	<0.001	95%	
Europe	7	315	317	-0.32	-0.50	-0.14	<0.001	0.18	34%	
Country classification										
Developed Countries	7	271	283	-0.28	-0.45	-0.10	<0.001	<0.001	95%	0.355
Developing Countries	14	477	613	-0.18	-0.28	-0.07	<0.001	<0.001	94%	

*Significance: 0.049, k: number of studies; N_1: sample size obesity group; N_2: sample size of normal weight group; MD: Mean Differences, 95% CI: confidence interval 95%; Sig.: statistical significance in double tail; I^2: index of heterogeneity I^2

USFR was significantly lower in the OW group than in the NW group in one[33] of three studies. No significant difference was observed in terms of SSFR (p > 0.05). SSpH was significantly higher in the OW group than in the NW group in one[29] of two studies (p < 0.05). No significant difference was observed in terms of USpH (p > 0.05).

USFR and USpH were significantly lower in the OB+OW group than in the NW group in Mollaasadollah, *et al.*[28] No significant difference was observed in terms of SSpH and SSBC (p > 0.05).

No significant difference was observed in terms of SSFR, USFR, SSpH, and USpH in Lehmann-Kalata, *et al.*[15] (p > 0.05) in the comparison of *OB vs OW+NW* [Table 4].

Synthesis of results

Salivary flow rate

Significantly lower SFR was observed in the group with OB than NW (MD = -0.21, 95% CI [-0.30, -0.12], P < 0.001). The highest mean difference in favor of the group with OB (MD = 0.09, 95% CI [0.04, 0.14]) was observed by Al-Juboury, *et al.*[17] The highest mean difference in favor of the group with NW (MD = -1.07, 95% CI [-1.34, -0.80]) was observed in the study by Yomna A, *et al.*[38] Considerable statistical heterogeneity was found for SFR (τ^2 = 0.03, χ^2 = 479.41, I^2 = 94%, P < 0.001) [Figure 2].

Groups with OB and NW did not reveal a significant difference in terms of SFR (MD = -0.03, 95% CI [-0.10, 0.04], P = 0.38). The highest mean difference in favor

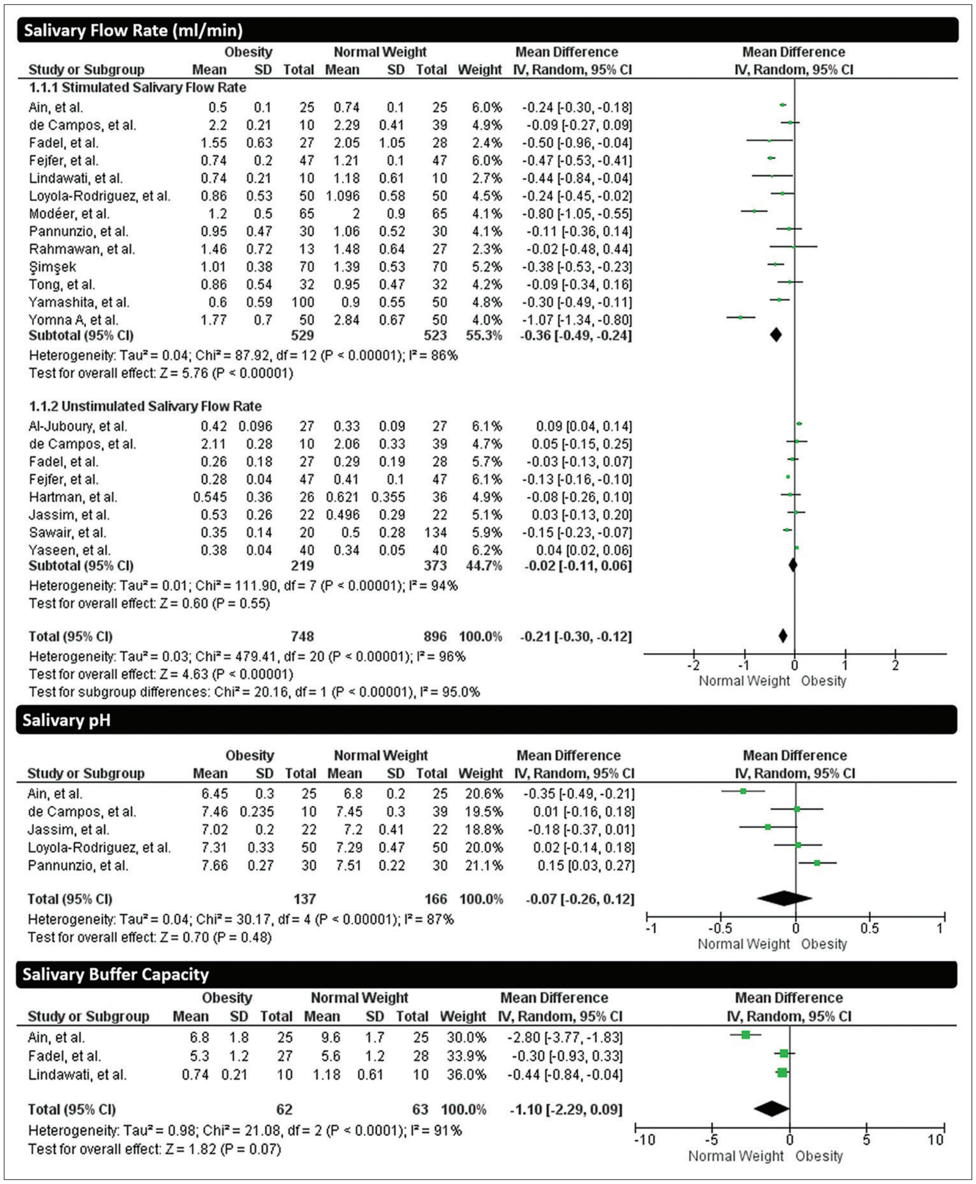


Figure 2: Forest plot presentations of SFR, SpH, and SBC

of the group with OW (MD = 0.04, 95% CI [-0.01, 0.09]) was observed in the study by Al-Juboury, *et al.*[17] The highest mean difference in favor of the group with NW (MD = -0.17, 95% CI [-0.44, 0.10]) was observed in the study by Pannunzio, *et al.*[29] Moderate statistical heterogeneity was found for SFR (τ^2 = 0.00, χ^2 = 10.80, I^2 = 44%, *P* = 0.09) [Figure 3a].

Groups with OB+OW and NW did not reveal a significant difference in terms of SFR (MD = -0.06, 95% CI [-0.14, 0.02], *P* = 0.16). The highest mean difference in favor of the group with OB+OW (MD = 0.01, 95% CI [-0.06, 0.08]) was observed in the study by Mennella, *et al.*[26] The highest mean difference in favor of the group with NW (MD = -0.14, 95% CI [-0.22, -0.06]) was observed in the study by Mollaasadollah, *et al.*[28] Substantial statistical heterogeneity was found for SFR (τ^2 = 0.00, χ^2 = 7.83, I^2 = 62%, *P* = 0.05) [Figure 3b].

Salivary pH

Groups with OB and NW did not reveal a significant difference in terms of SpH (MD = -0.07, 95% CI [-0.26, 0.12], *P* = 0.48). The highest mean difference in favor of the group with OB (MD = 0.15, 95% CI [0.03, 0.27]) was observed in the study by Pannunzio, *et al.*[29] The highest mean difference in favor of the group with NW (MD = -0.35, 95% CI [-0.49, -0.21]) was observed in the study by Ain, *et al.*[16] Considerable statistical heterogeneity was found for SFR ($\tau 2$ = 0.04, $\chi 2$ = 30.17, I^2 = 87%, *P* = p < 0.001) [Figure 2].

Groups with OW and NW did not reveal a significant difference in terms of SpH (MD = 0.15, 95% CI [-0.14,

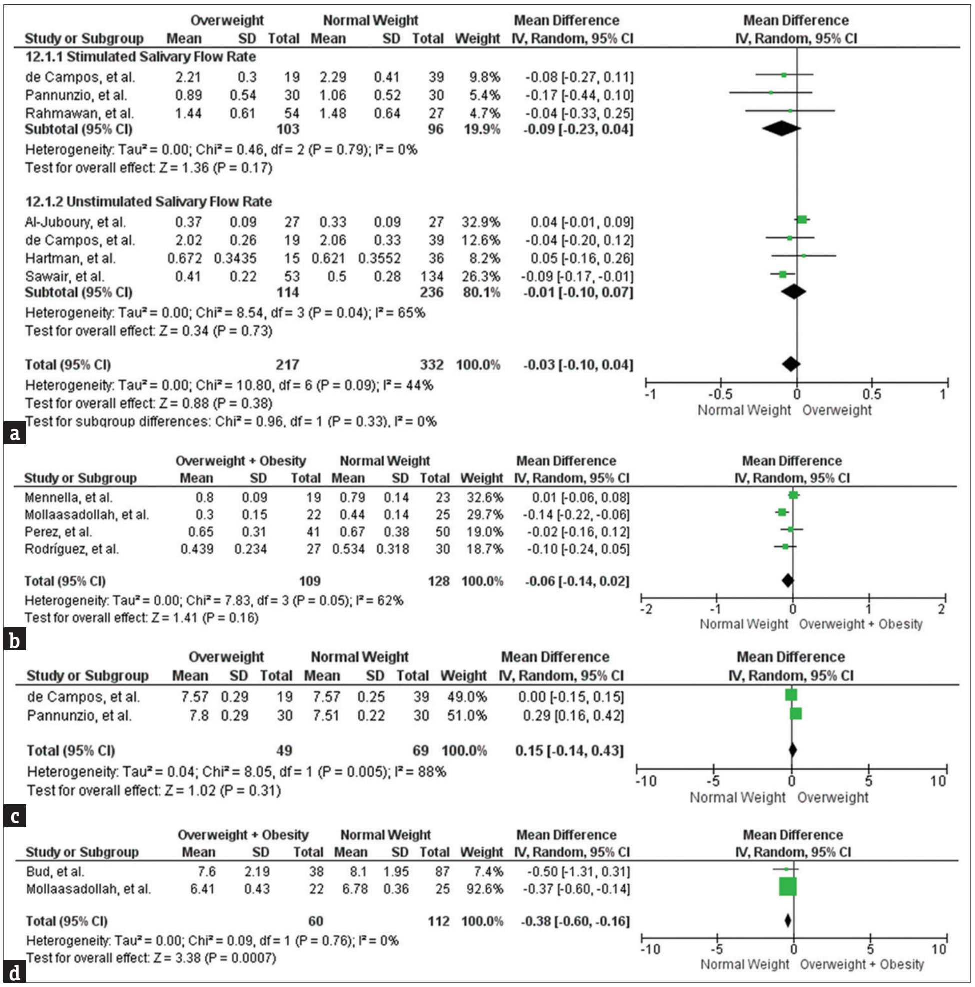


Figure 3: Forest plot presentations of other comparisons (OW vs NW and OB+OW vs NW). (a) Forest plot presentation of SFR for comparison of OW vs NW.(b) Forest plot presentation of SFR for comparison of OB+OW vs NW. (c) . Forest plot presentation of SpH for comparison of OW vs NW. (d) Forest plot presentation of SpH for comparison of OB+OW vs NW

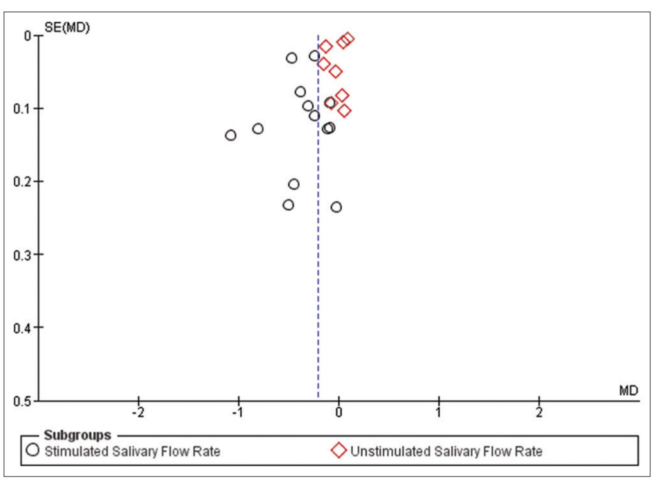


Figure 4: Funnel plots for SFR outcomes

0.43], P = 0.31). The highest mean difference in favor of the group with OW (MD = 0.29, 95% CI [0.16, 0.42]) was observed in the study by Pannunzio, *et al.*[29] Considerable statistical heterogeneity was found for SFR (τ^2 = 0.04, χ^2 = 8.05, I^2 = 88%, P = 0.005) [Figure 3c].

Significantly lower SpH was observed in the group with OB+OW than NW (MD = -0.38, 95% CI [-0.60, -0.16], P < 0.001). The highest mean difference in favor of the group with NW (MD = -0.50, 95% CI [-1.31, 0.31]) was observed in the study by Bud, *et al.*[18] No significant statistical heterogeneity was found for SpH ($\tau 2$ = 0.00, $\chi 2$ = 0.09, I^2 = 0%, P = 0.76) [Figure 3d].

Salivary buffer capacity

Groups with OB and NW did not reveal a significant difference in terms of SBC (MD = -1.10, 95% CI [-2.29, 0.09], P = 0.07). The highest mean difference in favor of the group with NW (MD = -2.80, 95% CI [-3.77, -1.83]) was observed in the study by Ain, *et al.*[16] Considerable statistical heterogeneity was found for SFR (τ^2 = 0.98, χ^2 = 21.08, I^2 = 91%, P < 0.001) [Figure 2].

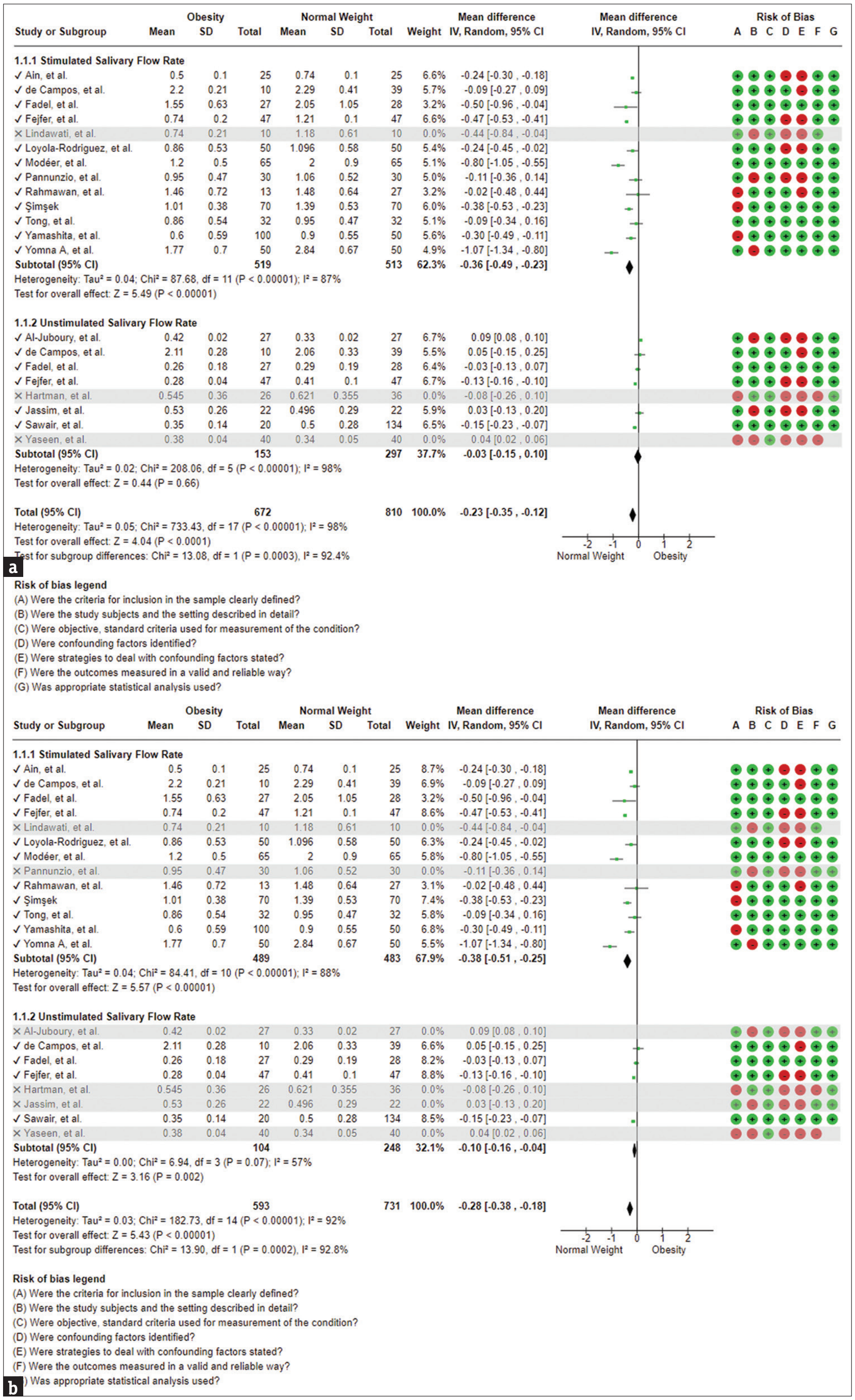
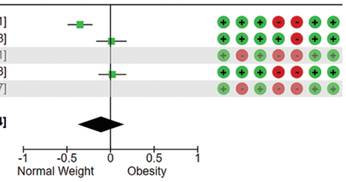


Figure 5: Sensitivity analyzes for outcomes in the comparison of OB vs NW. .(a) Sensitivity analysis for SFR in the comparison of OB vs NW, studies with high risk of bias were removed. (b) Sensitivity analysis for SFR in the comparison of OB vs NW, studies with high and moderate risk of bias were removed. (c) Sensitivity analysis for SpH in the comparison of OB vs NW, studies with moderate risk of bias were removed. (d) Sensitivity analysis for SBC in the comparison of OB vs NW, studies with moderate risk of bias were removed. (e) Sensitivity analysis for SFR in the comparison of OB vs NW, studies whose outcome was transformed to mean and standard deviation from median and interquartile range were removed

Study or Subgroup	Obesity Mean	Obesity SD	Obesity Total	Normal Weight Mean	Normal Weight SD	Normal Weight Total	Weight	Mean difference IV, Random, 95% CI
✓ Ain, et al.	6.45	0.3	25	6.8	0.2	25	34.3%	-0.35 [-0.49 , -0.21]
✓ de Campos, et al.	7.46	0.235	10	7.45	0.3	39	32.5%	0.01 [-0.16 , 0.18]
✕ Jassim, et al.	7.02	0.2	22	7.2	0.41	22	0.0%	-0.18 [-0.37 , 0.01]
✓ Loyola-Rodriguez, et al.	7.31	0.33	50	7.29	0.47	50	33.3%	0.02 [-0.14 , 0.18]
✕ Pannunzio, et al.	7.66	0.27	30	7.51	0.22	30	0.0%	0.15 [0.03 , 0.27]
Total (95% CI)			**85**			**114**	**100.0%**	**-0.11 [-0.36 , 0.14]**

Heterogeneity: Tau² = 0.04; Chi² = 15.22, df = 2 (P = 0.0005); I² = 87%
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable

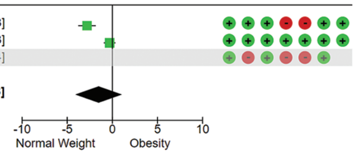


c

Risk of bias legend
(A) Were the criteria for inclusion in the sample clearly defined?
(B) Were the study subjects and the setting described in detail?
(C) Were objective, standard criteria used for measurement of the condition?
(D) Were confounding factors identified?
(E) Were strategies to deal with confounding factors stated?
(F) Were the outcomes measured in a valid and reliable way?
(G) Was appropriate statistical analysis used?

Study or Subgroup	Obesity Mean	Obesity SD	Obesity Total	Normal Weight Mean	Normal Weight SD	Normal Weight Total	Weight	Mean difference IV, Random, 95% CI
✓ Ain, et al.	6.8	1.8	25	9.6	1.7	25	48.9%	-2.80 [-3.77 , -1.83]
✓ Fadel, et al.	5.3	1.2	27	5.6	1.2	28	51.1%	-0.30 [-0.93 , 0.33]
✕ Lindawati, et al.	0.74	0.21	10	1.18	0.61	10	0.0%	-0.44 [-0.84 , -0.04]
Total (95% CI)			**52**			**53**	**100.0%**	**-1.52 [-3.97 , 0.93]**

Heterogeneity: Tau² = 2.95; Chi² = 17.86, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Were the criteria for inclusion in the sample clearly defined?
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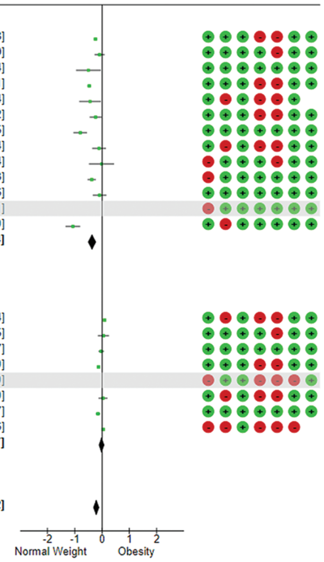
(E) Were strategies to deal with confounding factors stated?
(F) Were the outcomes measured in a valid and reliable way?
(G) Was appropriate statistical analysis used?

d

Study or Subgroup	Obesity Mean	Obesity SD	Obesity Total	Normal Weight Mean	Normal Weight SD	Normal Weight Total	Weight	Mean difference IV, Random, 95% CI
1.1.1 Stimulated Salivary Flow Rate								
✓ Ain, et al.	0.5	0.1	25	0.74	0.1	25	6.7%	-0.24 [-0.30 , -0.18]
✓ de Campos, et al.	2.2	0.21	10	2.29	0.41	39	5.4%	-0.09 [-0.27 , 0.09]
✓ Fadel, et al.	1.55	0.63	27	2.05	1.05	28	2.6%	-0.50 [-0.96 , -0.04]
✓ Fejfer, et al.	0.74	0.2	47	1.21	0.1	47	6.6%	-0.47 [-0.53 , -0.41]
✓ Lindawati, et al.	0.74	0.21	10	1.18	0.61	10	3.1%	-0.44 [-0.84 , -0.04]
✓ Loyola-Rodriguez, et al.	0.86	0.53	50	1.096	0.58	50	5.0%	-0.24 [-0.45 , -0.02]
✓ Modéer, et al.	1.2	0.5	65	2	0.9	65	4.6%	-0.80 [-1.05 , -0.55]
✓ Pannunzio, et al.	0.95	0.47	30	1.06	0.52	30	4.6%	-0.11 [-0.36 , 0.14]
✓ Rahmawan, et al.	1.46	0.72	13	1.48	0.64	27	2.6%	-0.02 [-0.48 , 0.44]
✓ Şimşek	1.01	0.38	70	1.39	0.53	70	5.8%	-0.38 [-0.53 , -0.23]
✓ Tong, et al.	0.86	0.54	32	0.95	0.47	32	4.6%	-0.09 [-0.34 , 0.16]
✕ Yamashita, et al.	0.6	0.59	100	0.9	0.55	50	0.0%	-0.30 [-0.49 , -0.11]
✓ Yomna A, et al.	1.77	0.7	50	2.84	0.67	50	4.4%	-1.07 [-1.34 , -0.80]
Subtotal (95% CI)			**429**			**473**	**56.0%**	**-0.37 [-0.50 , -0.24]**
Heterogeneity: Tau² = 0.04; Chi² = 87.75, df = 11 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 5.44 (P < 0.00001)								
1.1.2 Unstimulated Salivary Flow Rate								
✓ Al-Juboury, et al.	0.42	0.096	27	0.33	0.09	27	6.7%	0.09 [0.04 , 0.14]
✓ de Campos, et al.	2.11	0.28	10	2.06	0.33	39	5.2%	0.05 [-0.15 , 0.25]
✓ Fadel, et al.	0.26	0.18	27	0.29	0.19	28	6.4%	-0.03 [-0.13 , 0.07]
✓ Fejfer, et al.	0.28	0.04	47	0.41	0.1	47	6.8%	-0.13 [-0.16 , -0.10]
✕ Hartman, et al.	0.545	0.36	26	0.621	0.355	36	0.0%	-0.08 [-0.26 , 0.10]
✓ Jassim, et al.	0.53	0.26	22	0.496	0.29	22	5.7%	0.03 [-0.13 , 0.20]
✓ Sawair, et al.	0.35	0.14	20	0.5	0.28	134	6.5%	-0.15 [-0.23 , -0.07]
✓ Yaseen, et al.	0.38	0.04	40	0.34	0.05	40	6.8%	0.04 [0.02 , 0.06]
Subtotal (95% CI)			**193**			**337**	**44.0%**	**-0.02 [-0.10 , 0.07]**
Heterogeneity: Tau² = 0.01; Chi² = 111.32, df = 6 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 0.45 (P = 0.65)								
Total (95% CI)			**622**			**810**	**100.0%**	**-0.21 [-0.31 , -0.12]**

Heterogeneity: Tau² = 0.03; Chi² = 473.08, df = 18 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.44 (P < 0.00001)
Test for subgroup differences: Chi² = 18.78, df = 1 (P < 0.0001), I² = 94.7%



Risk of bias legend
(A) Were the criteria for inclusion in the sample clearly defined?
(B) Were the study subjects and the setting described in detail?
(C) Were objective, standard criteria used for measurement of the condition?
(D) Were confounding factors identified?
(E) Were strategies to deal with confounding factors stated?
(F) Were the outcomes measured in a valid and reliable way?
(G) Was appropriate statistical analysis used?

e

Figure 5: Contd...

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Normal Weight	**Risk with Obesity**				
Salivary flow rate (SFR) assessed with: ml/min	The mean salivary flow rate ranged from **0.29-2.84** ml/min	MD **0.21 ml/min lower** (0.29 lower to 0.13 lower)	-	1644 (21 observational studies)	⊕⊕◯◯ LOW	Obesity may reduce stimulated salivary flow rate, but the evidence is very uncertain about the effect of obesity on unstimulated salivary flow rate.
Salivary pH (SpH) assessed with: pH	The mean salivary pH ranged from **6.8-7.57** pH	MD **0.05 pH lower** (0.21 lower to 0.11 higher)	-	352 (6 observational studies)	⊕◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of obesity on salivary pH.
Salivary Buffer Capacity (SBC) assessed with: pH	The mean salivary Buffer Capacity ranged from **1.18-9.6** pH	MD **1.1 pH lower** (2.29 lower to 0.09 higher)	-	125 (3 observational studies)	⊕◯◯◯ VERY LOW [b]	The evidence is very uncertain about the effect of obesity on salivary Buffer Capacity.

Explanations

a. The quality of evidence was rated down by one level because the point estimates varied widely across studies on these outcomes
b. The quality of evidence was rated down by one level because the CIs failed to exclude important benefits or harms.

Figure 6: Summary of Findings table

Risk of bias across studies

Funnel plots for SFR were evaluated visually and no potential publication bias was observed. This result was verified through Egger's test (p = 0.736). Funnel plot and Egger tests were not performed for other outcomes because of insufficient studies (fewer than 10). The funnel plots were shown in Figure 4.

Additional analyzes

Sensitivity analysis

In the first part, sensitivity analyzes were conducted for SFR, SpH, and SBC. After studies with a high risk of bias were removed, similar estimates were observed in the analysis of SFR (MD = -0.23, 95% CI [-0.35, -0.12], $P < 0.001$) [Figure 5a]. After studies with a high and moderate risk of bias were removed, similar estimates were likewise observed (MD = -0.28, 95% CI [-0.38, -0.18], $P < 0.001$), however, the effect estimate turned into significance from non-significance in USFR (MD = -0.10, 95% CI [-0.16, -0.04], $P = 0.002$) [Figure 5b]. After studies with a moderate risk of bias were removed, similar estimates were observed in the analysis of SpH (MD = -0.11, 95% CI [-0.36, 0.14], $P = 0.39$) [Figure 5c]. After studies with a moderate risk of bias were removed, the significance decreased slightly in the analysis of SBC (MD = -1.52, 95% CI [-3.97, 0.93], $P = 0.22$) [Figure 5d]. In the second part, a sensitivity analysis was conducted for only SFR. After studies whose outcome was transformed to mean and standard deviation from median and interquartile range were removed, similar estimates were observed in the analysis of SFR (MD = -0.21, 95% CI [-0.31, -0.12], $P < 0.001$) [Figure 5e].

Subgroup analysis

Subgroup analysis was conducted for SFR based on stimulated and non-stimulated saliva in the comparisons of OB vs NW, OW vs NW, and OB+OW vs NW. In terms of OB vs NW, SSFR was significantly higher in the NW group than OB (MD = -0.36, 95% CI [-0.49, -0.24], $P < 0.001$), but no significant difference was observed between the groups regarding USFR (MD = -0.02, 95% CI [-0.11, 0.06], $P = 0.55$). A significant difference was found between the subgroups of SFR in the comparison of OB vs NW ($\chi2 = 20.16$, $I^2 = 95\%$, $P < 0.001$) [Figure 2]. In terms of OW vs NW, no significant difference was observed in both SSFR (MD = -0.09, 95% CI [-0.23, 0.04], $P = 0.17$) and USFR (MD = -0.01, 95% CI [-0.10, 0.07], $P = 0.73$). No significant difference was found between the subgroups of SFR in the comparison of OW vs NW ($\chi2 = 0.96$, $I^2 = 0\%$, $P = 0.33$) [Figure 3a].

Moderator analysis

The moderators' effect was assessed on the SFR outcome in the comparison of OB vs NW. In terms of BMI classification, significantly lower SFR was observed in the group with OB than NW in both class 1 (MD = -0.17, 95% CI [-0.27, -0.07], $P < 0.001$) and class 2 (MD = -0.38, 95% CI [-0.56, -0.19], $P < 0.001$). Test differences based on BMI classification indicated that significant difference is available between class 1 and class 2 (p = 0.049). Regarding periods of development, no significant difference in childhood was observed between the groups with OB and NW (MD = -0.06, 95% CI [-0.15, 0.03], $P = 0.20$). However, significantly lower SFR was observed in the group with OB in comparison to the group with NW in both adolescent (MD = -0.45, 95% CI [-0.69, -0.21], $P < 0.001$) and adult (MD = -0.16, 95% CI [-0.28, -0.04], $P < 0.001$). Test differences based on periods of development indicated that significant difference is available between childhood, adolescence, and adulthood (p = 0.009). In terms of continental, significantly lower SFR was observed in the group with OB than NW in both America (MD = 0.01, 95% CI [-0.23, -0.02], $P = 0.01$), Asia (MD = -0.17, 95% CI [-0.31, -0.04], $P = 0.01$), and Europe (MD = -0.32, 95% CI [-0.50, -0.14], $P < 0.001$). Test differences based on continental indicated that no significant difference is available between America, Asia, and Europe ($p = 0.173$). In terms of country classification, significantly lower SFR was observed in the group with OB than NW in both developed (MD = -0.28, 95% CI [-0.45, -0.10], $P < 0.001$) and developing countries (MD = -0.18, 95% CI [-0.28, -0.07], $P < 0.001$). Test differences based on country classification indicated no significant difference between developed and developing countries [Table 5].

Grade analysis

Grade analysis was performed for only the comparison of OB vs NW. Since included studies were observational, scoring the evidence of analyzes started as low quality. In terms of inconsistency, the quality of evidence regarding SpH was rated down by one level because the point estimates varied widely across studies on these outcomes. In terms of imprecision, the quality of evidence regarding SpH and SBC was rated down by one level because the CIs failed to exclude important benefits or harms. Applied GRADE criteria indicated that certainty in the cumulative evidence is low for SFR, and very low for all other outcomes [Figure 6].

Discussion

OB, a predisposing factor for many chronic diseases, also poses a risk for oral health. Various meta-analyzes confirmed the impact of OB on higher dental caries burden regardless of development periods.[3-5] Starch-based consumption and low economic status may be some underlying reasons for higher dental caries experience in OB.[5] Furthermore, the impaired saliva structure and function may also predispose to caries formation.

Pooled estimate indicated that SFR is significantly reduced in individuals with OB. Several theories regarding inflammation, impairment of parasympathetic nerve function, and used medications may reveal the underlying reasons for this issue.[27] Individuals with OB may have increased deposition of adipocytes in the parotid parenchyma, thus enlarging parotid glands. As a result of this enlargement, the number of pro-inflammatory cytokines derived from adipocytes and macrophages stored in adipose tissue may lead to chronic inflammation. As an effect of this inflammation, the function of the salivary glands may be impaired.[27] Dysfunctions in parasympathetic efferent activities, particularly effective in stimulating saliva release in OB, may also reduce SFR.[39-41] Besides, several drugs that cause a decrease in SFR are used to treat many chronic diseases, such as diabetes mellitus, hypertension, and hypercholesterolemia, related to OB.[42]

Subgroup analysis indicated that SFR decreased in individuals with OB when only stimulated. Saliva can be stimulated via some reflexes (masticatory-salivary reflex, gustatory salivary reflex, esophageal-salivary reflex, olfactory-salivary reflex, etc.) that have capabilities to induce parasympathetic efferent activities.[43] However, some studies indicated that parasympathetic nerve function is reduced in individuals with OB.[39,40] The reduction in parasympathetic nerve function may clarify why only stimulated saliva is affected. Despite all the negatives, unstimulated saliva is more critical than stimulated saliva in terms of oral health. Oral tissues, especially teeth, are exposed to primarily unstimulated saliva during the day.[44]

The moderator analysis indicated that no significant difference is available in terms of SFR between OB and NW in childhood; however, it decreased significantly in adolescence and adulthood. The reason may be that both OB and impairment of the salivary gland are slowly cumulative across the lifetime.[45] A meta-analysis by Hayden, *et al*.[3] did not find a relationship between caries and OB in the primary dentition but in the permanent dentition. In addition to possible factors, the decrease in SFR over time may have increased the caries burden, especially in permanent dentition, in the meta-analysis mentioned above.

BMI levels were classified as class 1 (< 35) and class 2 (> 35), and it was found that as the severity of OB increased (from class 1 to class 2), the SFR decreased in the moderator analysis. Moreover, no significant difference was found between individuals with OW and NW in SFR. These findings may suggest that as the severity of OB increases, the salivary gland function's impairment increases simultaneously.

The moderator analysis exhibited no difference in SFR between ON and NW in terms of country classification or continental type. A meta-analysis by Hayden, *et al*.[3] found that individuals with OB had higher caries experience in developed countries compared to developing ones. The finding was attributed to the higher consumption of foods and beverages containing carbohydrates in developed countries. Salivary gland functions are more likely to be unaffected by socioeconomic factors than dental caries.

SpH and SBC are supposed to decrease in individuals with OB due to the hypofunction of the salivary gland.[27] Nevertheless, in the present study, no association was found between SpH or SBC and OB in the comparison of OB vs NW. Due to the insufficient number of studies, no moderator analysis could be performed on these outcomes. However, when the papers regarding SpH and SBC were reviewed, it was noticed that studies that specifically investigate the childhood period[19,29] tend to obtain insignificant effects in comparison to studies that examined adolescent and adult periods.[16,23] This condition may be explained by the hypothesis that salivary gland functions in individuals with OB are not significantly affected in childhood; the findings obtained in SFR also strengthen the hypothesis above. However, in the comparison of OB+OW vs NW, it was found that SpH decreased in favor of OB+OW. Considering all these factors, when the developmental periods could be examined separately, through the increased number of studies, further meta-analyzes may reveal much more certain evidence regarding the effects of OB on SpH and SBC.

The evidence had several limitations; five studies exhibited a high risk of bias individually. Also, the included studies preferred different BMI cut-off points; these different assessment thresholds increased methodological heterogeneity. For instance, Fejfer, *et al*.[21] evaluated only individuals with morbid OB, keeping the BMI cut-off point 40 and above for OB, unlike other studies. Besides, studies of various ethnicities, age periods, and countries, which led to significant clinical heterogeneity, were included. These heterogeneities may decrease the reliability of evidence, although they increase generalizability. Another critical limitation regarding evidence was that included studies were characteristically observational, which is accepted as low quality in terms of certainty of evidence. Moreover, the meta-analysis had a language limitation; a limited number of studies could be screened due to the researchers' language limitations. In addition to these limitations, the meta-analysis had many key strengths. Stimulated and unstimulated saliva was evaluated separately through subgroup analysis, and different effects were observed. The effects of various confounding factors on the pooled estimate were tested by moderator analysis. Furthermore, the effects of studies with a high risk of bias on the pooled estimate were tested by sensitivity analysis. Grade analysis was performed to obtain the certainty level of evidence. Moreover, a deep screening was performed in the literature, and articles and other publication types such as thesis and conference papers were included in the analyzes.

Although several meta-analyzes found an association between OB and dental caries, the underlying reasons have not been clarified yet. This meta-analysis revealed substantial evidence that one of these may be decreasing in the amount of SFR. Clinicians should take measures to increase SFR in patients with OB and be aware of this risk. Much more studies are needed to determine the effects of other potential etiological factors on dental caries in these individuals.

Conclusion

Notwithstanding the study's limitations, the obtained evidence suggested that SFR significantly decreases in individuals with OB. Subgroup analysis showed that this effect is insignificant when the saliva is unstimulated. Besides, the decrease in SFR is more prominent in adolescence and adulthood than in childhood. Furthermore, the increase in the severity of OB causes a much greater decrease in SFR. However, regarding SpH and SBC, no significant association exists. Despite the evidence found, certainty in the evidence was low since the studies were observational and the number of the included studies in the analyzes was small.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, formal consent is not required.

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Conflicts of interest

There are no conflicts of interest.

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