

Association of Salivary Biomarker Concentration and Activity Between Caries-free and Caries-affected Children: An Umbrella Review

Danial Ahmed, DMD, Yulia Eve, DMD, Nicole Scott, DDS, Amir Yavari, DDS, David Okuji, DDS, MBA, MS
 NYU Langone Hospitals-Advanced Education in Pediatric Dentistry, Brooklyn, NY



NYU Langone Dental Postdoctoral Residency Programs

INTRODUCTION

Dental caries is a prevalent and chronic disease in humans. Dental caries is a highly prevalent multifactorial disease. It afflicts a large proportion of the world's population.

Since teeth are regularly exposed to saliva, the composition and characteristics of this fluid in the mouth are crucial factors influencing the development and advancement of tooth decay.¹

This is because caries results from an imbalance in cariogenic microorganism in the biofilm. This imbalance results in loss of minerals from dental hard tissues.² However, when considering the microorganisms involved in caries progression, one must also exam the environment in which they live. Because teeth are constantly immersed in saliva, the properties and components of this oral fluid are crucial in the onset and advancement of cavities.²

Salivary proteins help maintain tooth health and prevent cavities through various mechanisms, including the production of AEP and the prevention of demineralization on exposed tooth surfaces.²

Numerous salivary proteins play a defensive role in the oral cavity including carbonic anhydrase, lactoferrin, immunoglobulins (Igs), proline-rich proteins (PRPs), and mucins1.

Taking these established, and researched salivary proteins into consideration, examining if there is a relationship in their concentration in caries free vs caries affected patient is plausible.³

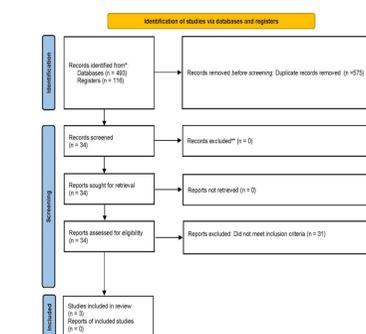
PURPOSE

•Purpose: The purpose of this umbrella review was to retrieve and assess the available systematic reviews reporting on association of salivary biomarker concentration and activity between caries-free and caries-active children.

METHOD

- A literature search was conducted on electronic bibliographic databases to locate systemic reviews reporting on salivary biomarker concentration and activity between caries-free and caries-active children (age 9 and under).
- Literature searches were performed until January 2024 in: PubMed, Embase, CINAHL, Cochrane Library, Prospero, Scopus, Web of Science, Google Scholar, Doss, Health and Psychosocial Instruments (HaPI), Medline.
- Eligible publications were reviewed independently by reviewers and reviews were selected, and their methodological qualities were assessed using Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) tools (16 items) and PRISMA flow diagram.

FIGURES



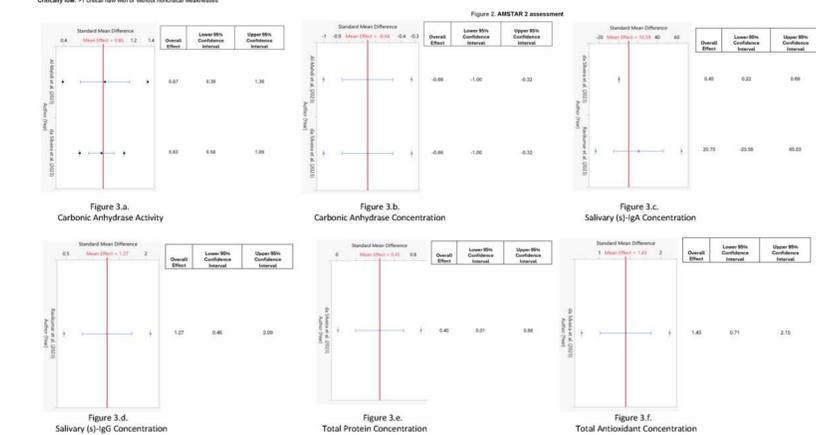
Source: Page MJ, et al. *BMJ* 2021;372:n71. doi:10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>.

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

AMSTAR 2 domain items	Al-Mahdi et al. (2023)	da Silveira et al. (2023)	Ravikumar et al. (2023)
1. Did the research questions and inclusion criteria for the review include the components of PICO?	1	1	1
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	1	1	1
3. Did the reviewer explain their selection of the study designs for inclusion in the review?	1	1	1
4. Did the reviewer authors use a comprehensive literature search strategy?	1	1	1
5. Did the reviewer authors perform study selection in duplicate?	1	1	1
6. Did the reviewer authors perform data extraction in duplicate?	1	1	1
7. Did the reviewer authors provide a list of excluded studies and justify the exclusions?	1	1	1
8. Did the reviewer authors describe the included studies in adequate detail?	1	1	1
9. Did the reviewer authors use a satisfactory technique for assessing the risk of bias (RoB) in individual non-randomized studies of interventions (NRSI) studies that were included in the review?	1	1	1
10. Did the reviewer authors report on the sources of funding for the studies included in the review?	1	1	1
11. If meta-analysis was performed, did the reviewer authors use appropriate methods for statistical combination of non-randomized studies of interventions (NRSI) results?	1	1	1
12. If meta-analysis was performed, did the reviewer authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	1	1	1
13. Did the reviewer authors account for RoB in primary studies when interpreting/summarizing the results of the review?	1	1	1
14. Did the reviewer authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	1	1	1
15. If they performed quantitative synthesis did the reviewer authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	1	1	1
16. Did the reviewer authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	1	1	1
Number of negatively answered domain items (sum of 2,4,7,8,11,13,15)	0	0	0
Final RoB	High	Low	High

Color Code: 1 = Yes, 0 = No, partial yes

Final Rating Assessments: High: 0-1 noncritical weaknesses. Moderate: 2-3 noncritical weaknesses. The systematic review has more than one weakness, but no critical flaws. Low: 4 critical flaws with or without noncritical weaknesses. Critically low: 5+ critical flaws with or without noncritical weaknesses



RESULTS

- A systematic electronic search identified 3 out of 493 articles that met the inclusion criteria and were included in this review (Figure 1).
- AMSTAR 2 assessed two studies as high quality and one as low quality (Figure 2).
- The forest plot (Figure 3) reveals significant variations in salivary biomarkers between caries-affected (CA) and caries-free (CF) children.
- CA children showed:
 - **Higher activity and lower concentration of carbonic anhydrase VI:**
 - Activity: Significant increase (P < 0.0001, Mean Effect: 0.85, CI: [0.39, 1.36]) (Figure 3.a).
 - Concentration: Significant decrease (Mean Effect: -0.66, CI: [-1.00, -0.32]) (Figure 3.b).
 - **Higher salivary (s)-IgA and (s)-IgG concentrations:**
 - (s)-IgA: Significant increase (P = 0.79, Mean Effect: 10.59, CI: [0.22, 0.69]) (Figure 3.c).
 - (s)-IgG: Significant increase (P = 0.02, Mean Effect: 1.27, CI: [0.46, 2.09]) (Figure 3.d).
 - **Higher total protein concentration:** Significant increase (P = 0.0007, Mean Effect: 0.45, CI: [0.01, 0.88]) (Figure 3.e).
 - **Higher total antioxidant concentrations:** Significant increase (P = 0.00001, Mean Effect: 1.43, CI: [0.71, 2.15]) (Figure 3.f).

CONCLUSIONS

Based upon the results of this study, the following conclusions about caries-affected children can be made:

- Higher CA VI activity
- Lower CA VI concentration
- Higher s-IgA concentrations
- Higher s-IgG concentration
- Higher TAC

Salivary biomarker diagnostics is a promising opportunity for dentists to identify children at high risk for caries once commercial clinical laboratories make this service available.

REFERENCES

1. Gao X, Jiang S, Koh D, Hsu CY. Salivary biomarkers for dental caries. *Periodontol* 2000. 2016;70(1):128-141. doi:10.1111/prd.12100
2. Ahmed P, Hussain A, Carrasco-Labra A, Siqueira WL. Salivary Proteins as Dental Caries Biomarkers: A Systematic Review. *Caries Res*. 2022;56(4):385-398. doi:10.1159/000526942
3. Hegde MN, Attavar SH, Shetty N, Hegde ND, Hegde NN. Saliva as a biomarker for dental caries: A systematic review. *J Conserv Dent*. 2019;22(1):2-6. doi:10.4103/JCD.JCD_531_18
4. Al-Mahdi, R., Al-Sharani, H., Al-Haruni, M., & Halboub, E. (2023). Associations of the activity and concentration of carbonic anhydrase VI with susceptibility to dental caries: A systematic review and meta-analysis. *Clinical and Experimental Dental Research*, 9, 358–367. <https://doi.org/10.1002/cre2.723>
5. Silveira EG, Prato LS, Pilati SFM and Arthur RA (2023) Comparison of oral cavity protein abundance among caries-free and caries affected individuals—a systematic review and meta-analysis. *Front. Oral. Health* 4:1265817. doi: 10.3389/froh.2023.1265817
6. Ravikumar D, Ramani P, Gayathri R, Hemashree K, Prabhakaran P. Physical and chemical properties of saliva and its role in Early Childhood caries - A systematic review and meta-analysis. *J Oral Biol Craniofac Res*. 2023;13(5):527-538. doi:10.1016/j.jobcr.2023.05.011