# Salivary IgA as a Useful Biomarker for Dental Caries in Down Syndrome Patients: A Systematic Review and Meta-analysis

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## Abstract

The objective of this systematic review and meta-analysis is to critically analyze and summarize studies reporting association of salivary immunoglobulin A (IgA) levels as a biomarker for dental caries in Down syndrome (DS) patients. Using the keywords salivary [All Fields] AND IgA [All Fields] AND ("down syndrome" [MeSH Terms] OR ("down"[All Fields] AND "syndrome" [All Fields]) OR "down syndrome" [All Fields]), an electronic search was conducted via PubMed and Scopus databases by two authors, H. H. and Z. K. independently. Retrieved studies were screened against the predefined exclusion and inclusion criteria. To estimate the risk of bias, quality assessment of included studies was carried using the Newcastle–Ottawa quality assessment scale for observational studies. Primary search resulted in 10 articles from PubMed and 13 articles from Scopus. Ten studies fulfilled the defined selection criteria and evaluated the salivary IgA (sIgA) level in DS patients with dental caries. Five articles were further analyzed in a quantitative synthesis presented in the meta-analysis. Due to a modified lifestyle and compromised oral hygiene in DS patients, understandably, it is still postulated in the literature that the presence of sIgA can have a protective effect on the occurrence of dental caries as compared with healthy counterparts. As indicated by the present meta-analysis, no conclusions can be drawn as to definitively label sIgA as a biomarker for dental caries. Further, well-designed longitudinal clinical studies and translational research are therefore required before the benchmarking of sIgA as a useful biomarker for dental caries in DS patients with preferable molecular insights.

### Keywords
► saliva
► dental caries
► salivary IgA
► Down syndrome

## Introduction

Down syndrome (DS) is one of the most prevalent genetic disorders occurring among humans resulting from a trisomy of chromosome 21. The incidence of DS is estimated to be around 1 in 1,000 to 1 in 1,100 live births globally, and believed to be relatively common in children born to women older than 35 years.[1,2] Suffering from this syndrome emanates multiple

issues, including those of mental retardation, congenital heart disease, hearing deficits, skeletal problems and skin disorders, along with physical anomalies, majorly around the stomatognathic system, temporomandibular joint dysfunction, a small maxilla thus a flat face, delayed tooth eruption, malocclusion, dental agenesis, macroglossia, and increased occurrence of dental diseases, particularly periodontal disease. Other signs include cardiovascular and nervous system aberrations, decreased muscle tone, slanting eyes, and misshapen ears.[1-5] It has been postulated in previous literature that DS individuals have a prevalence of dental caries much lower than normal individuals.[5] This could be due to delayed teeth eruption, less complicated tooth morphology with less pronounced pits and fissures, and a difference of microbiota present in the oral biofilm.[5-7] It has also been determined that this could be due to various environmental factors[8] and a different salivary composition with altering flow rates.[8-10]

Saliva plays a major role in the prevention of dental caries, essentially being one of its functions. Salivary pH ranges between 6.2 and 7.6, maintained near neutrality with the average pH of saliva being 6.7.[11] Human saliva contains proteins and peptides for the defense and maintenance of oral health dynamics.[12] The intracellular and extracellular pathways of saliva secretion in the oral cavity make it a diagnostic medium for many diseases such as oral cancer, periodontal diseases, dental caries, oral lichen planus, and systemic diseases.[13,14] Also, saliva has been proven as a detecting biofluid for viruses such as human immunodeficiency virus, human papillomavirus, hepatitis A, hepatitis C, Ebola, Zika, and the severe acute respiratory syndrome virus family.[15,16] Saliva contains a host of antimicrobial factors including enzymes and antibodies such as salivary immunoglobulin A (sIgA).[8] It is reported that sIgA is one of the main immunoglobulins in the line of defense against pathogens invading mucosal surfaces,[17] enhancing oral immunity by preventing microbial adhesion and bacterial colonization.[5,8] Several studies have similarly demonstrated that the presence of high numbers of sIgA correlates with a low incidence of dental caries.[17-19]

To the best of our knowledge, however, there has been no previous review investigating the role of sIgA as an indicator for dental caries in patients of DS, as it can be a very useful biomarker for dental caries occurrence in individuals of DS moving toward prevention and oral care.

The aim of this systematic analysis is to review the studies reporting sIgA as a biomarker for dental caries incidence in DS patients and to possibly conclude whether sIgA can be used as a useful biomarker for dental caries in DS patients.

## Materials and Methods

The protocol for this systematic review has not been published prior to its completion. The present systematic review and meta-analysis were performed according to the guidelines Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[20] PECO question (Patient, Exposure, Comparator, and Outcome) was applied.

A. Patients in the included studies should be between 3 and 29 years
B. Dental caries and DS
C. Stimulated saliva, whole mouth saliva, and unstimulated saliva
D. Level of sIgA levels.

### Search Strategies

A systematic literature search was performed from two databases: Scopus and PubMed, searching for journal articles from January 2000 to December 2018 addressing the focused research question. For the PubMed library, the following MeSH terms were used: ("saliva"[MeSH Terms] OR "saliva"[All Fields]) AND ("down syndrome"[MeSH Terms] OR ("down"[All Fields] AND "syndrome"[All Fields]) OR "down syndrome"[All Fields]) AND IgA [All Fields]. Only articles reported in the English language were included (►Table 1). The search strategies followed the PRISMA guidelines (►Fig. 1).

### Study Selection

Exclusion criteria for the included studies were case reports, review article, studies reporting incidence or prevalence, studies without statistical analysis, studies without control group, and outcome different from sIgA levels. After the removal of duplicates, studies were assessed for inclusion and exclusion criteria by two independent investigators. Any disagreement was resolved by discussion until consensus was reached.

### Data Extraction

The relevant data extracted from each included study were the author's name, publication year, country, study designs, age range, biochemical analysis, sample size (number of patients with DS [cases] and number of healthy controls), mean sIgA levels in cases and controls, statistical technique applied, and results obtained (►Table 1). Five studies were included in meta-analysis. The articles were divided into two groups (cases and controls) in accordance with the description given by the authors. A comparative analysis was done between patients with DS and healthy controls.

### Quality Assessment of the Studies

The quality of studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) for observational studies. The following criteria were assessed: selection of study groups (diagnosed cases of DS by genetic testing, selection of cases with DS from referral centers, healthy controls from same community without any disabilities); control for confounding variable (such as socioeconomic status, medications, or any other potential factor); and outcome assessment (assessment of sIgA levels by a previously calibrated examiner; clinical evaluation of tooth decay; same evaluation method was used for case and controls; and nonresponse rate). Each item scored 1 star if sufficiently reported, and each study scored from 0 to 8 stars.

**Table 1** Study characteristics of nine included studies

| Author (year of publication) | Country | Study design | Age range | Sample size | Assessment of salivary IgA | Statistics | p-Value |
|---|---|---|---|---|---|---|---|
| Chaushu et al (2002) | Israel | CC | 11–24 y DS, 16–24 y controls | 39 (29 with DS, 10 controls) | Salivary IgA was determined by ELISA, measured in μg/mL | Wilcoxon's rank-sum test | NS |
| Chaushu et al (2003) | Israel | CS | 11–22 y | 23 (14 institutionalized DS subjects, 9 noninstitutionalized DS subjects) | Salivary IgA was determined by ELISA, measured in μg/mL | Wilcoxon's rank-sum test | NS |
| Lee et al (2004) | Korea | CC | 8–17 y | 69 (28 cases with DS, 41 matched controls) | Salivary IgA was determined by ELISA, measured in μg/mL | Student's t-test | NS |
| Cogulu et al (2006) | Turkey | CC | 7–12 y | 143 (73 with DS, 70 controls) | Salivary IgA was determined by radial immunodiffusion technique, measured in mg/L | Student's t-test | Sig |
| Chaushu et al (2007) | Israel | CC | Not given | 79 (40 cases with DS, 39 controls) | Salivary IgA was determined by ELISA, measured in EU/mL | Wilcoxon's rank-sum test | Sig between YC and YDS, Sig between YC and OC, Sig between OC and ODS |
| Areias et al (2012) | Portugal | CC | 6–18 y | 90 (45 cases with DS, 45 matched sibling controls) | Salivary IgA was determined by ELISA, measured in mg/L | Student's t-test | NS |
| Fornieles et al (2014) | Spain | Int | 19–26 y | 40 male adults with DS (24 DS in exercising group [Int], 16 DS in control group) | Salivary IgA was determined by ELISA, measured in μg/mL | Two-way ANOVA | Sig in exercising group, NS in control group |
| Balaji et al (2016) | New Zealand | CC | 2–12 y | 50 (20 cases with DS, 10 siblings, 20 parents) | Salivary IgA was determined by ELISA, measured in μg/mL | ANOVA | Sig |
| Hashizume et al (2017) | Brazil | CC | 6–14 y | 113 (61 with DS, 52 controls) | Salivary IgA was determined by ELISA, measured in μg/mL | Mann–Whitney's U test | Sig |

Abbreviations: ANOVA, analysis of variance; CC, case–control; CS, cross-sectional; DS, Down syndrome; ELISA, enzyme-linked immunosorbent assay; Int, interventional; NS, not significant; OC, old controls; ODS, old Down syndrome; Rev, review article; Sig, significant; YC, young controls; YDS, young Down syndrome.

## Statistical Analysis

The software STATA (version 14.2) was used for the meta-analysis. Meta-analyses were performed for the mean sIgA levels in cases and controls. Q-statistic and $I^2$-statistic were used to assess the heterogeneity of the included studies. For the Q-statistic, heterogeneity was supposed statistically significant if $p \leq 0.05$. The forest plot was computed reporting weighted mean differences WMD of sIgA levels and 95% confidence interval (CI). The $p \leq 0.05$ was taken as statistically significant for the pooled effect. Data which were not suitable for quantitative analysis were evaluated descriptively. Moreover, funnel plot was generated to assess publication bias. If the plot was asymmetrical, then it was suggested as a publication bias.

## Results

### Study Selection

A total of 9 and 12 study titles and abstracts were first identified on PubMed and Scopus, respectively. After the removal of the duplicates ($n = 12$), preliminary screening of titles and abstracts was done, and two articles (one case report and one review article) were excluded because they were not meeting the eligibility criteria and were irrelevant to the focused question. A total of 10 articles were selected for full-text reading. Of these 10 studies, 1 study was further excluded because focused question was not answered in it. At final stage, all four articles were selected for qualitative synthesis (one cross-sectional study, one interventional study, and two case–control studies in which mean and standard deviation values were not reported for sIgA levels), whereas five case–control studies were included in quantitative synthesis (►Fig. 1).

### Study Characteristics

All studies ($n = 9$) included in systematic review were observational studies, in which one study was cross-sectional study,[21] one was interventional study,[22] and seven were case–control studies.[2,3,8,10,23-25] These studies were from Israel,[21,23,24] Korea,[10] Turkey,[2] Portugal,[3] Spain,[22] New Zealand,[25] and Brazil.[8] In all of these studies, the number of participants ranged from 23 to 143 individuals with age range of 2 to 26 years. Only one study did not report the age range of the participants.[24]
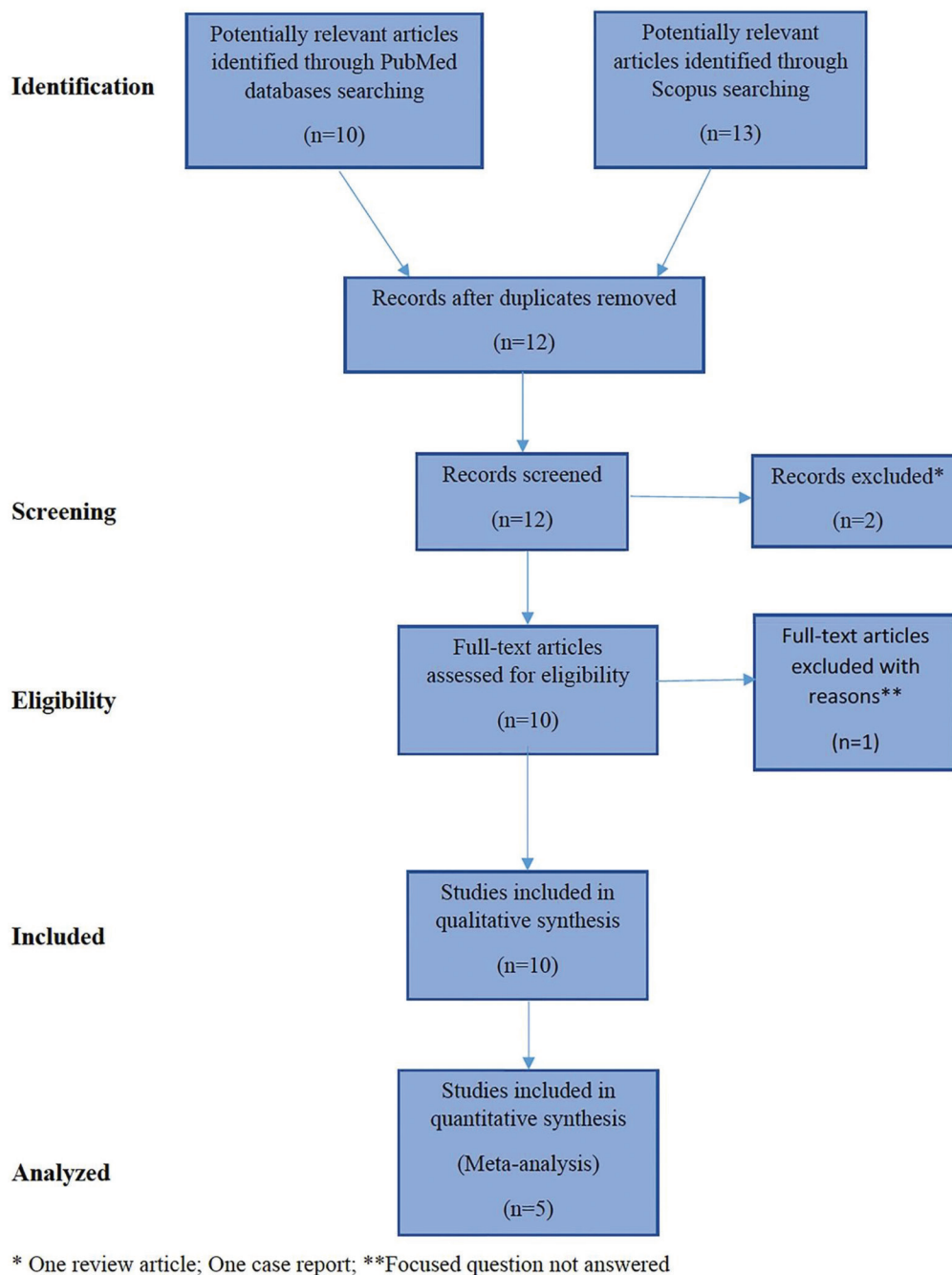
**Fig. 1** Flowchart of the study.

In eight studies, sIgA levels were determined by enzyme-linked immunosorbent assay and in one study by radial immunodiffusion technique.[2] In two case–control studies,[2,25] significant difference was found in mean sIgA levels between cases and controls ($p < 0.05$). In another case–control study,[24] statistical significant difference was found in mean sIgA levels between young DS and young controls ($p < 0.05$), young controls and old controls ($p < 0.05$), and old controls and old DS patients ($p < 0.05$). In an interventional study,[22] statistically significant difference was found in mean sIgA levels before and after 12-week resistance circuit training program in male adults with DS (►**Table 1**).

### Results of Literature Search

Primary search resulted in 156 studies. After exclusion of duplicates, abstracts and titles of 145 studies were read to include studies relevant to this review. After exclusion of 132 irrelevant studies, full texts of 13 studies were read (►**Fig. 1**). After further exclusion of five studies, only eight studies met the inclusion criteria for this review.[9-16] No studies were found in the bibliographies of the included articles during manual search. The included articles consisted of six case reports,[10-14,16] a retrospective study,[9] and a prospective study.[15]

## Main Outcome of the Studies

The comparison of salivary levels of IgA in DS patients as compared with the healthy controls is shown in ►**Table 2**. The pooled MDs of sIgA was 0.433 µg/mL (95% CI: −0.160 to 1.026). A high degree of heterogeneity was found among both the groups of 85.6% and a significant associated p-value of < 0.05. The forest plot showed several nonoverlapping CIs, which also indicated the heterogeneity of the studies (►**Fig. 2**).

## Quality Assessment of Included Studies

The assessment of the quality of the studies was done on the NOS[26] ranging from four to six points. A mean score of 5 was achieved for the included studies (►**Tables 2** and **3**).

## Discussion

The present analysis was undertaken to explicate on the investigation and possible determination of sIgA as a useful biomarker for dental caries in DS children. Various studies have predicated a lower prevalence of dental caries in DS children as compared with their normal counterparts,[2-5,8,17,25] included in this analysis.[2-4,8,10] The occurrence of dental caries and levels of sIgA in children with DS is ascertained, compared with matching controls to balance for confounders.

It has been hypothesized that many environmental factors come into play for the suggested lower prevalence of dental caries in DS children, including a delayed eruption of teeth, congenital oligodontia, a diet differing in sugary components compared with normal individuals, and a contrasting salivary composition.[2] A variety of environmental factors come into play which can alter the salivary physiology, such as oral hygiene and dietary habits.[8]

Immune defenses against dental caries may be enhanced by the presence of increased amounts of sIgA in DS children. Studies have tried to associate the presence of sIgA as a significant factor for a relatively lower frequency of occurrence of dental caries in DS patients.[27,28] IgA antibodies within the saliva may tend to create a neutralizing effect on the toxins and enzymes thus inactivating them, hindering the adherence of bacteria,[8] creating an inhibition of streptococcal accretion on the tooth surfaces[29] necessary to kick start the carious process.[30] Variable salivary flow rates in DS individuals as compared with their normal counterparts also add to a rather low prevalence of dental caries. Coupled with certain eruptive and morphologic traits pertaining to teeth imminent in DS patients; late eruption in the oral cavity, less pronounced pits and fissures; and the incidence of dental caries is thus found to be low.[3,31]

As apparent in our article search, a restricted number of studies were eligible according to our eligibility criteria, highlighting the limited amount of research that has been done focusing on this topic. Adding to that, the small sample sizes that have been used in the studies for evaluating the occurrence of dental caries in DS patients ultimately show insubstantial conclusive evidence of using sIgA as a biomarker for dental caries.

It has been hypothesized that sIgA present in saliva hinders the adherence of bacteria causative of dental caries to the tooth surface, neutralizing the extracellular enzymes in the process as well.[2,30] Moreover, Lee et al[10] and Areias et al[3] also found increased levels of *Streptococcus mutans*-specific sIgA in DS patients as compared with their controls. Areias et al[3] also found low counts of *S. mutans* in DS children when compared with their sibling controls. sIgA usually plays a crucial role in protecting the structures in the oral cavity including the mucosa against a probable bacterial invasion. Doing so, it also protects against dental caries and diseases of the periodontium.[25]

Heterogeneity across results is marked with a total heterogeneity of 85.6% (p = 0.001). Even though studies posit the hypothesis that high sIgA levels reduce the occurrence of caries,[2-5,8,17,25] Lee et al,[10] among other studies,[32,33] nonetheless, stated the opposite that sIgA levels have no significant impact on the incidence of caries in DS individuals. This is believed to be based on the different age groups and ranges assessed within the differing studies of DS participants. As also reported by Balaji et al,[25] children with DS and their parents had higher amounts of sIgA levels as compared with siblings of the DS participants, showing a

**Table 2** Weighted mean difference of salivary IgA levels in cases and controls of studies included in meta-analysis

| No. | Study ID | Cases | | | Controls | | | Weighted mean difference IV, random, 95% CI |
|-----|----------|-------|---|----|----------|---|----|---------------------------------------------|
| | | *n* | Mean | SD | *n* | Mean | SD | |
| 1 | Balaji et al (2016) | 19 | 95.1 | 48.4 | 20 | 92.5 | 46.5 | 0.05 (−0.57, 0.68) |
| 2 | | | | | 10 | 48.3 | 25.7 | 1.11 (0.29,1.93) |
| 3 | Chaushu et al (2003) | 14 | 112 | 34 | 9 | 121 | 30 | −0.28 (−1.12, 0.56) |
| 4 | Lee et al (2004) | 19 | 24 | 10 | 41 | 22 | 6 | 0.27 (−0.28, −0.81) |
| 5 | Areias et al (2012) | 45 | 0.08 | 0.04 | 45 | 0.08 | 0.04 | 0.00 (−0.41, −0.41) |
| 6 | Cogulu et al (2006) | 73 | 0.37 | 0.24 | 70 | 0.13 | 0.06 | 1.36 (1.00, 1.72) |
| | Total | 170 | | | 195 | | | 0.43 (−0.16, 1.03) |
| | Total heterogeneity: I² = 85.6%, p = 0.001 | | | | | | | |

Abbreviations: CI, confidence interval; IV, independent variable; SD, standard deviation.
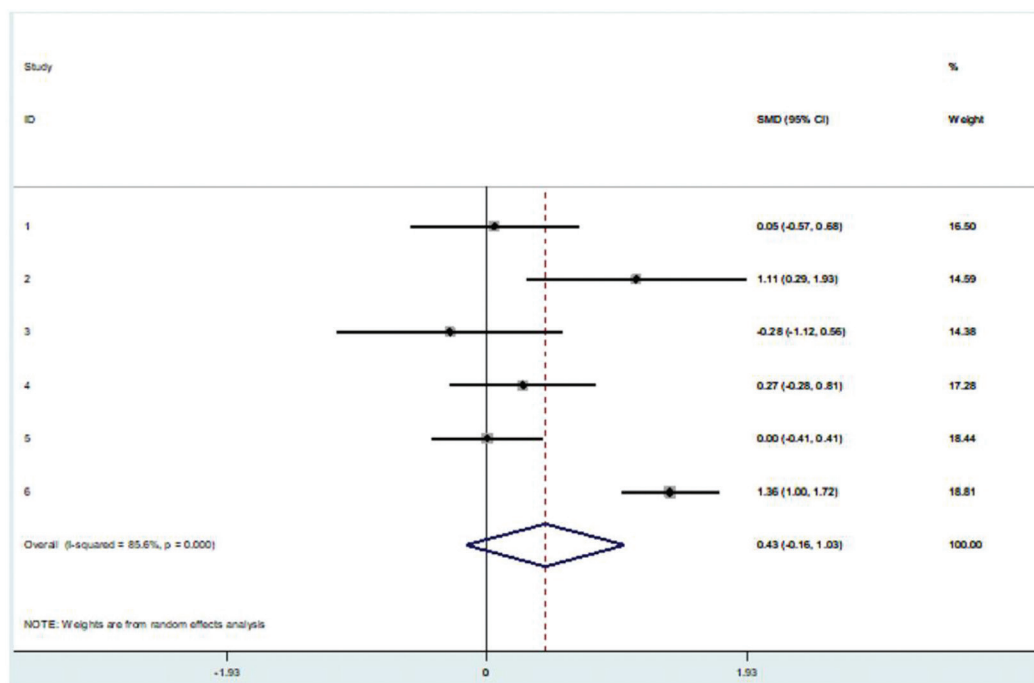
**Fig. 2** Forest plot of random effects of salivary immunoglobulin A levels in Down syndrome patients versus controls. Study ID number in this figure correlates with No. column in Table 2 for understanding.

**Table 3** Quality assessment of included studies

| Author (year of publication) | Selection | Comparability | | Newcastle–Ottawa quality (total) |
|---|---|---|---|---|
| Chaushu et al (2002) | ★  ★ | ★  ★ | ★  ★ | Six |
| Chaushu et al (2003) | ★ | ★  ★ | ★  ★ | Five |
| Lee et al (2004) | ★  ★ | | ★  ★ | Four |
| Cogulu et al (2006) | ★  ★  ★  ★ | | ★  ★ | Six |
| Chaushu et al (2007) | ★  ★ | | ★  ★ | Four |
| Areias et al (2012) | ★  ★ | | ★  ★ | Four |
| Fornieles et al (2014) | ★  ★  ★ | | ★  ★  ★ | Six |
| Balaji et al (2016) | ★  ★ | | ★  ★ | Four |
| Hashizume et al (2017) | ★  ★ | ★  ★ | ★  ★ | Six |

consequential effect of a wide age gap on the sIgA secretion concentrations.

Marked heterogeneity and low samples in studies which were included in the quantitative synthesis limit to draw any significant conclusive evidence of sIgA as an identifying factor for dental caries in patients with DS. Many other confounding factors are hypothesized to be possible not limited to environmental factors, oral hygiene measures, and differing dietary habits of DS patients compared with their healthy counterparts.

## Conclusion

Patients with DS are believed to be at a higher risk of dental caries due to malocclusion and the quality of lifestyle that is understandably compromised compared with healthy children. However, the reason for the low occurrence of dental caries is not very well understood in DS patients, despite availability of a finite amount of literature. Further, well-designed and long-term clinical studies and translational research are required before benchmarking sIgA as a useful biomarker for dental caries in DS patients. There is a dire need of more longitudinal clinical studies on DS patient saliva with preferably large sample sizes requiring advanced molecular attention.

**Conflict of Interest**
None declared.

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