

# Can Hemophilia Impact on the Oral Health Conditions of Children and Adolescents? A Systematic Review and Metanalysis

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## ABSTRACT

**Objective:** To analyze if the oral health conditions in children and adolescents are associated with hemophilia (PROSPERO-42020168192). **Material and Methods:** The search strategy was performed in PubMed, Scopus, Lilacs/BBO, Web of Science, Cochrane, and Grey literature databases. Two independent researchers assessed the risk of bias in these studies by the Newcastle-Ottawa Scale. For the meta-analysis, the clinical conditions data were extracted as numerical variables according to their indexes, such as dental caries experience (dmft/DMFT), gingival condition (Modified Gingival Index - IGM), and oral hygiene (Plaque Index - PI). The quality of the evidence of the meta-analysis was evaluated by the GRADE tool (GRADEproGDT). **Results:** From a total of 431 studies, 27 were included, and 10 were included in the meta-analysis. The studies presented a moderate risk of bias, ranging from 2 to 7 points. The dental caries experience in primary (-0.62; CI95%: -1.68-0.43) and permanent dentitions (-0.05; CI95%: -0.69-0.59), gingival condition (-0.12; CI95%: -0.27-0.03), and oral hygiene (0.36; CI95%: -0.06-0.77) did not differ between the groups. **Conclusion:** Based on studies with very weak evidence, there were no differences in the oral health conditions of children and adolescents with and without hemophilia.

**Keywords:** Blood Coagulation Disorders; Study Characteristics; Oral Health.

## Introduction

Hemophilia is an X-linked hemorrhagic disease characterized by a coagulation factor deficiency and associated with the male gender. Although rare, there are cases of women with hemophilia that can even present manifestations as severe as in men [1]. Although, it is considered a rare disease, Hemophilia A, is the most frequent, representing about 80% of cases. It is estimated that there are around 195,263 cases of hemophilia in the world [2].

The diagnosis of this alteration is commonly established in childhood. Hemorrhagic areas by the body that can be seen post-trauma are often the first clinical signs [3]. The dentist, as a health professional involved with the dental assistance of children from the first moments of life, can contribute to identify these situations and to help with early diagnosis.

One of the most haemophilic patient's concern about dental treatment is the possibility of oral bleeding, which could be spontaneous due to gum/periodontal disease or caused by some more invasive clinical procedures, such as endodontic treatment, periodontal surgery, or tooth extraction [4]. Due to the high risk of bleeding in more invasive dental procedures, dentists should be in compliance with the appropriate clinical guidelines [1,5].

Studies suggested that hemophiliac patients could have particularities in their oral hygiene habits, presenting negligent or ineffectiveness oral hygiene due to fear of bleeding [6,7]. In addition, some socioeconomical aspects could influence the access to dental assistance for hemophiliacs, such as low income and the lack of public policies for this population. These aspects could impact their oral health condition [8].

The literature presents conflicting data about oral health conditions in hemophiliac patients. For example, some studies indicate that hemophiliacs have a lower prevalence of dental caries [9-11] than individuals without hemophilia, while other authors found no association [4,12-16] or found a positive association [6,7,17] between dental caries and hemophilia. Similar contradictions are found for other oral conditions, such as oral hygiene patterns or periodontal disease [4,6,7,10,13-22].

Further knowledge of the oral conditions of hemophiliac patients is fundamental for the establishment of appropriate politics for improving oral health in hemophiliacs. Although the literature has a lot of studies investigating the oral health conditions in hemophiliac, the evident contradictions of the data make it difficult for clinicians to adopt appropriate strategies for promoting and rehabilitating oral health. Thus, the aim of this systematic review with meta-analysis was to analyze if the oral conditions between children and adolescents are associated with hemophilia.

## Material and Methods

### Protocol and Registration

This systematic review was registered in the PROSPERO database (protocol CRD 42020168192) and reported in compliance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist (PRISMA) [23].

### Search Strategy

The research question was: "Can hemophilia impact on the oral health conditions of children and adolescents?". The acronymous PECO (Population, Exposure, Comparison, Outcome) was used: Population:

children and adolescents (0 to 18 years old); Exposure: Hemophilia; Comparison: without Hemophilia; Outcome: oral health conditions.

Two researchers conducted an electronic search in the databases (L.T.S., J.F.S.): Medline through PubMed ([www.pubmed.gov](http://www.pubmed.gov)), ISI Web of Science ([www.isiknowledge.com](http://www.isiknowledge.com)), Scopus ([www.scopus.com](http://www.scopus.com)), the Cochrane Library ([www.cochrane.org](http://www.cochrane.org)), Lilacs and The Brazilian Library of Dentistry (BBO) through the Virtual Health Library (Bireme, Latin America) ([www.bireme.br](http://www.bireme.br)). The electronic search occurred in 2020 (February to November) without restrictions regarding language and date of publication. The electronic search was updated in June 2021.

To identify studies that might not have been found through the electronic search, manual searches using the reference lists of included studies were also performed.

Abstracts of the International Association for Dental Research (IADR) and its regional divisions (1990–2019) were used. Then, the authors of relevant abstracts were contacted for further information. Also, the grey literature was explored using the Google Scholar database. Dissertations and theses were searched using the ProQuest Dissertations, Theses Full-Text Databases, and the Periodicals Capes Theses Database.

The search strategies were elaborated using a combination of free terms and controlled vocabulary terms of the PECO question, following the particularities of each database [children, adolescents, hemophilia, dental caries, periodontal disease, plaque index]. The detailed search strategy is in the appendices.

#### Criteria for Inclusion

The eligibility criteria considered the type of study, participants, exposure and comparison and outcomes. It was included studies presenting:

- Type of study: analytical observational studies (with comparison group) such as cross-sectional or prevalence, case-control, and cohort studies were included.
- Participants: children and adolescents (0 to 18 years old).
- Exposure: hemophilia (hemophilia A, hemophilia B).
- Comparison: without hemophilia.
- Outcomes: dental cavity, periodontal disease, oral examinations, oral hygiene, dental plaque.

It was excluded according to the type of study: clinical trials, editorial letters, pilot studies, case reports, historical reviews, in vitro studies, experiments in animals, and case series. According to the participants, it was also excluded studies that the participants have HIV and other blood or systemic diseases. In the meta-analysis, only the most frequent index of each oral condition evaluated was used.

#### Studies Selection

A two-step process was used to select the studies by two independent researchers (L.T.S., J.F.S.). In the first step, the studies were screened based on titles and abstracts analysis. Those who did not meet the inclusion criteria were excluded. The full texts of the selected studies were obtained and independently analyzed by the researchers. In the cases of inclusion/disagreement, a consensus between the researchers was used. EndNote X6® software (Clarivate Analytics LLC., Morrisville, Pennsylvania, USA) was used to identify duplicate studies and organize the list of abstracts (Figure 1).

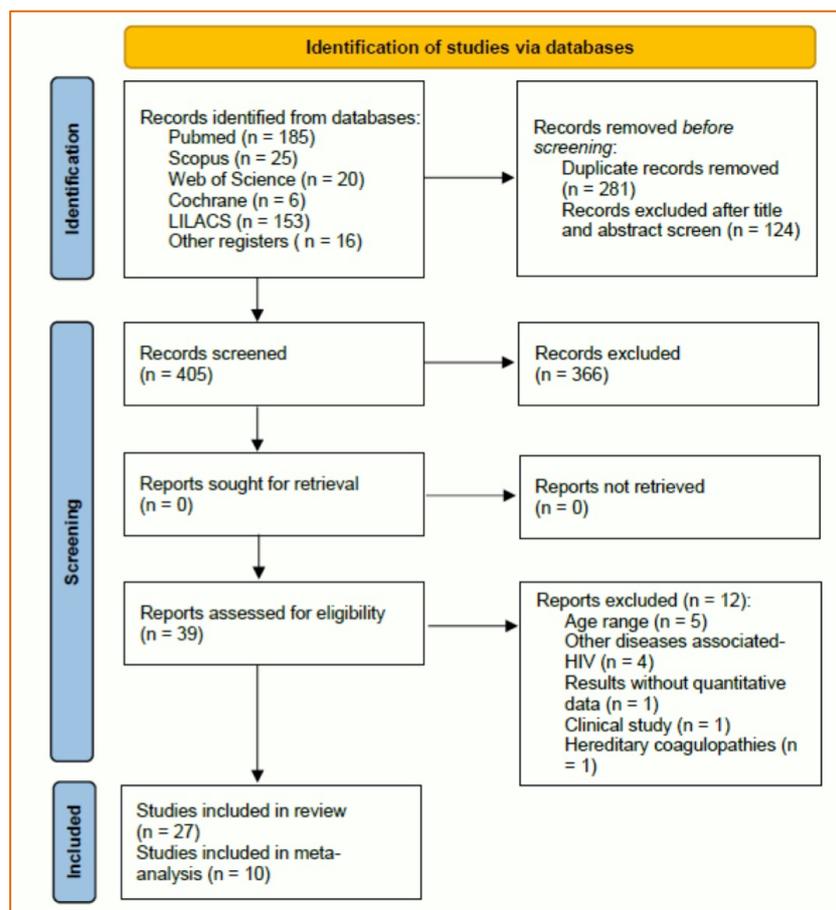


Figure 1. Flow diagram of study (PRISMA 2020).

#### Data Collection Process

The information was extracted from the articles using a previously structured form and included: author, drawing, year and country of study, number of participants, total and groups, place of recruitment, type and classification of hemophilia, and main results (Table 1).

Among the outcomes for the caries experience, the mean and standard deviation values of the decayed, missing and filled teeth (dmft and DMFT) were extracted for the permanent and deciduous dentitions, respectively. Regarding periodontal health results, the mean and standard deviation values of the indexes presented were extracted, such as Modified Gingival Index (MGI), Simplified Gingival Index (GI-S), and Gingival Index. Oral hygiene data were also collected, the mean and standard deviation values of the indices presented as Plaque Index (PI), modification of the O'Leary index, and Oral Hygiene Index (OHI).

#### Evaluation of the Quality of the Studies

The bias risk assessment was performed based on an adapted version of the Newcastle-Ottawa Scale. At this stage, two examiners performed the independent evaluation (L.T.S., J.F.S.). The scale has three main categories: selection (maximum of 4 stars), comparability (maximum of 2 stars), and outcome/exposure (maximum of 3 stars). The range of the scores was from 0 to 9. For the grade analysis, the studies were categorized at a high risk of bias (0-3 points), moderate risk of bias (4-6 points), and low risk of bias ( $\geq 7$  points) [24,25].

**Table 1. Summary of the studies selected for this systematic review.**

Author and Country	Study Design	Subjects' Age (years) mean ± SD [range]	Sampling	Local Setting	Outcomes Evaluated		
					Oral Conditions (Criteria)	Prevalence%; average value ± SD; (range) Case	Control
Al Kubaisi & Alousi, Iraq [30]	Comparative Cross-Section	Total: [5-42]	Total: 314 Hemophilia A and B and Congenital Coagulation Disorders: 157 Control: 157	Case: Al-Mansour Hospital for children in Baghdad City Control: NR	Dental Caries (DMFS/dmfs)	97.8%	91.9%
Baskirt et al., Turkey [7]	Comparative Cross-Section	Total: [6-12] Case: 9.54±2.39 Control: 9.49±1.70	Total: 111 Case: Hemophilia A: 36 (Hemophilia Severity: Mild, 14; Moderate, 12; Severe, 10) Control group: 39	Case: Hemophilia Society of Turkey Control: Istanbul University Faculty of Dentistry, Department of Pedodontics	Gingival Condition (GI- Loe & Silness) Dental Plaque (Plaque Index - PI) Dental Caries (DMFT/S-dmft/s)	0.39±0.48 0.88±0.42 DMFT: 3.44±3.30 DMFS: 5.78±6.64 dmft: 3.44±3.43 dmfs: 5.89±6.57	0.15±0.14 0.72±0.37 DMFT: 1.37±1.62 DFMS: 2.45±4.04 dmft: 3.24±2.62 dmfs: 6.32±6.84
Azhar et al., Pakistan [12]	Comparative Cross-Section	Case: 16.59±3.24 Control: 16.70±2.95	Total: 244 Severe Hemophilia A and B: 52 Control: 192	Case: Hospital of Pakistan Hemophilia Society Control: Lahore students	Dental caries (DMFT) With symptoms of Temporomandibular Joint Dysfunction Syndrome	57.68% 13.45%	40.62% 2.08%
Babu et al., India [5]	Comparative Cross-Section	Total: [6-16]	Total: 200 Hemophilia A: 98 Hemophilia B: 2 (Hemophilia Severity: Mild, 32; Moderate, 20; Severe, 48) Control: 100	Case: Hemophilia Society of Bangalore, India Control: V.S. Dental College and Hospital, Bangalore	Dental Caries (DMFT/dmft) Dental Plaque (Plaque Index - PI) Gingival condition (Modified Gingival Index - MGI)	DMFT: 4.0 (2.0,5.0) dmft: 3.0 (2.0,3.0) 1.0 (1.0,2.0) 2.0 (1.0,2.0)	DMFT: 1.0 (1.0,2.0) dmft: 2.0 (1.0,3.0) 1.0 (1.0,1.0) 0 (0.0,1.0)
Boyd & Kinirons, Northern Ireland [9]	Comparative Cross-Section	Total: [2-15]	Total: NR Hemophilia: 38 Control: NR	Case: Royal Belfast Hospital for Sick Children. Control: Prior published population data for children in Northern Ireland	Dental Caries (DMFT/dmft)	DMFT: 27% dmft: 44%	DMFT: 59% dmft: 55%
Daneswari & Reddy, India [32]	Cross-Sectional	Total: [5-15]	Total: 328 Hemophilia: 328	Mamata Dental College, Khammam	Debris (Debris Index - DI) Calculus (Calculus Index - CI) Oral hygiene (Simplified Oral Hygiene Index - OHI-S) Dental Caries (DMFT/deft)	5-7 years: 1.60 11-15 years: 1.95 5-7 years: 1.61 11-15 years: 1.277 5-7 years: 3.21 11-15 years: 3.22 5-7 years: DMFT: 2.81 deft: 3.23 11-15 years: DMFT: 5.92 deft: 2.27	NR NR NR NR
Dogan et al., Turkey [17]	Comparative Cross-Section	Total: 9.5±3.5 [4-16]	Total: 60 Severe Hemophilia A: 30 Control: 30	Cukurova University, Istanbul	Dental Caries (DMFT/DMFS) Gingival condition (Gingival Index - GI)	DMFT: 5.07±3.5 DMFS: 9.07±0.74 0.66±0.72	DMFT: 4.17±2.5 DMFS: 8.30±5.4 0.32±0.25

Evangelista et al., Brazil [35]	Cross-Sectional	Total: [1-18]	Total: 40 Hemophilia: 40	Hematology and Hemotherapy Center of Piauí (HEMOPI)	Severity of gingival inflammation (NR) Gingival bleeding (Gingival Bleeding Index - GBI) Dental Caries (DMFT/dmft)	2.00±0.74 0-5 years: 18.4% 6-10 years: 42.1% 11-18 years: 39.5% 0-5 years: dmft: 45% 6-10 years: DMFT: 38.5% dmft: 87.5% 11-18 years: DMFT: 73.3%	1.60±0.49 NR NR
Hermida Bruno et al., Uruguay [18]	Retrospective of Cases and Control	Case: 8.62±4.20 [2-15] Control: 6.5±2.88 [3-12]	Total: 117 Hemophilia A: 17 Hemophilia B: 7 Others Congenital Coagulation Disorders: 15 Control: 78	Case: Hemotherapy Service Montevideo Control: Dental Polyclinic of same healthcare center	Dental Caries (DMFT/dmft) Gingivitis (Gingival Index) Malocclusion	DMFT: 1.96±2.59 dmft: 2.85±2.41 43% 39%	DMFT: 2.85±2.41 dmft: 2.13±2.36 NR NR
Jangra & Goswami, India [10]	Case-Control	Total: [2-14]	Total: 110 Hemophilia A: 50 Hemophilia B: 5 Control: 55	Maulana Azad Institute of Dental Sciences, New Delhi- Department of Pedodontics and Preventive Dentistry	Dental Caries (DMFT/S - dmft/s) Dental Plaque (Plaque Index - Silness & Løe)	DMFT: 0.47±0.87 DMFS: 0.56±1.17 dmft: 2.02±2.4 dmfs: 4.71±7.3 1.37±0.56	DMFT: 0.96±1.32 DMFS: 1.60±2.97 dmft: 4.38±4.2 dmfs: 9.85±11.2 1.29±0.52
Kozma et al., Romania [13]	Comparative Cross-Section	Case: Children: 9.4±3.8 Adults: 34.8±9.8 Control: Children: 9.2±3.7 Adults: 38.2±8.5	Total: 94 Hemophilia A: 42 Hemophilia B: 5 (12 children) Control: 47 (12 children)	NR	Dental Caries (DMFT) Dental Plaque (Plaque Index - PI)	3.5±3.5 1.5±0.5	3.8±3.2 0.8±0.7
Kumar et al., India [14]	Case-Control	Case: [2-71] Control: [2-73]	Total: 200 Hemophilia: 100 (41 children) Control: 100 (36 children)	Hemophilia Society, and Oral Diagnosis Clinic	Dental Caries (DMFT - dmft) Oral hygiene/Dental Plaque (OHI-S/PI)	3.51±3.48 2.176±1.58	3.50±3.20 1.721±1.36
Mazzoni & Pignatari, Brazil [15]	Case-Control	Total: 7.24 [3-12]	Total: 58 Hemophilia A: 28 Hemophilia B: 1 (Hemophilia Severity: Mild, 3; Moderate, 10; Severe, 16) Control: 29	Pediatric Otorhinolaryngology Clinic at UNIFESP and Hemophilia Clinic at Faculty of the Paulista School of Medicine	Dental Caries (DMFT/dmft) Gingival Condition (Gingival Bleeding Index - GBI - Ainano Bay) Dental Plaque (Bacterial Plaque Index- O'Leary)	DMFT: 1.05±1.50 dmft: 5.04±4.71 9.47±4.51 55.18±13.63	DMFT: 1.45±2.04 dmft: 4.08±3.45 9.97±6.18 48.13±13.28
Mielnik-Blaszczak, Poland [16]	Comparative Cross-Section	Total: [4-18]	Total: 160 Hemophilia A: 70 Hemophilia B: 7 (Hemophilia Severity: Mild, 5; Moderate, 23; Severe, 49) Others Congenital Coagulation Disorders: 3 Control: 80	Regions of Lublin, Zamosc and Rzeszów	Dental Caries (DMFT/S-dmft/s) Oral hygiene (Simplified Oral Hygiene Index - OHI-S)	DMFT: 5.8 dmft: 4.1 DMFS: 9.6±10.5 dmfs: 10.1±13.0 1.04	DMFT: 5.4 dmft: 4.6 DMFS: 8.5±8.42 dmfs: 10.2±8.62 0.81

Mythri et al., India [33]	Cross-Sectional	Total: [2-15]	Total: 20 Hemophilia A: 11 Hemophilia B: 7 Hemophilia C: 2 (Hemophilia Severity: Mild, 1; Moderate, 9; Severe, 10)	Karnataka hemophilia society at Davangere city	Dental Caries (DMFT/dft)	2-12 years 82.36% 7-15 years 28.52%	NR
Othman et al., Malaysia [4]	Case-Control	Total: [7-16] Case group: 11.74±0.36 Control group: 12.02±0.22	Total: 100 Hemophilia A: 41 Hemophilia B: 8 Other type of hemophilia: 1 Control: 50	Case group: National Blood Centre, Kuala Lumpur Control group: subjects were selected during an oral health-screening program	Dental caries (DMFT/dft) Oral Hygiene (Simplified Oral Hygiene Index - OHI-S) Simplified Debris Index (DI-S) Simplified Calculus Index (CI-S) Gingival Condition (Modified Gingival Index - MGI)	DMFT: 0.66±1.30 dft: 1.71±2.69 1.02±0.86 0.87±0.62 0.15±0.39 0.33±0.39	DMFT: 0.74±1.07 dft: 1.27 ± 1.62 1.23±0.81 0.95±0.51 0.28±0.39 0.50±0.47
Rajantie et al., Finland [38]	Retrospective	Total: 11.4 [5.3-17.4]	Total: 28 Hemophilia A: 21 Hemophilia B: 7 (Hemophilia Severity: Mild, 4; Moderate, 5; Severe, 19) *Group comprised 17.079 boys (public dental clinics in the Helsinki region)	Children's Hospital, Helsinki University Central Hospital	Dental Caries (DMFT/dmft) Periodontal Condition (Community Periodontal Index - CPI) Gingivitis Condition (Community Periodontal Index - CPI)	61% 29% 32%	NR NR NR
Reddy et al., India [34]	Cross-Sectional	Total: [7-16]	Total: 60 Hemophilia: 60	Hyderabad Haemophilic Society	Dental Caries (DMFT/DEFT) Oral Hygiene (Simplified Oral Hygiene Index - OHI-S)	DMFT + DEFT 3.90±1.972 1.52±0.776	NR NR
Rodrigues et al., Brazil [37]	Cross-Sectional	Total: 23.34	Total: 106 Hemophilia A: 81 Others Congenital Coagulation Disorders: 25	Two Blood Centers of the state of Paraíba (cities of João Pessoa and Campina Grande)	Dental Caries (DMFT)	50%	NR
Rodrigues et al., Brazil [36]	Cross-Sectional	Total: [3-12]	Total: 40 Hemophilia: 40	Pernambuco Hemotherapy Center (HEMOPE)	Dental Caries (DMFT/dmft)	DMFT: 0.67±1.22 dmft: 2.00±2.32	NR
Salem & Eshghi, Iran [31]	Comparative Cross-Section	Total: [2-15] Case group: 7.6±4.20 Control group: 7.5±3.4	Total: 92 Hemophilia A: 35 Hemophilia B: 4 Others Congenital Coagulation Disorders: 7 Control: 46	Centre for CBD in Tehran	Dental Caries (DMFT/DMFTS/dmft/dmfs) History of Oral Bleeding Occlusion TJD (WHO) Hypoplasia (WHO) Oral hygiene (Simplified Oral Hygiene Index - OHI-S)	DMFT: 1.13±2.18 dmft: 4.88±4.57 DMFS: 1.30±2.43 dmfs: 10.58±12.23 55% Protusion: 15.2% Retrusion: 0% 8.7% 14.28% 0.82±0.41	DMFT: 1.34±2.08 dmft: 4.95±4.31 DMFS: 1.62±2.7 dfms: 12.71±15.31 NR Protusion: 19.6% Retrusion: 4.3% 13% 17.85% 0.91±0.62

Salem et al., Iran [19]	Case-Control	Total: [2-15]	Total: 106 Hemophilia A: 49 Hemophilia B: 3 Factor XII: 1 (Hemophilia Severity: Mild, 11; Moderate, 14; Severe, 28) Control group: 53	Rasht, Iran	Dental Caries (DMFT/DMFS - dmft/dmfs)	DMFT: 2.75±2.71 dmft: 2.83±3.06 DMFS: 3.79±4.1 dmfs: 4.9±6.2	DMFT: 1.98±2.51 dmft: 3.13±3.21 DMFS: 2.03±4.05 dmfs: 6.58±7.33
					Dental Plaque (Plaque Index - PI - The O'Leary index)	81.87±15.43	72.78±18.94
					Gingival Condition (Modified Gingival Index - Loe and Silness)	1.86±0.8	1.75±1.1
Sonbol et al., England [20]	Case-Control	Case group: 8.8±3.4 [3-13.6]  Control group: 9.8±3.1 [4-15.3]	Total: 60 Severe Hemophilia: 30 Control: 30	Case: Great Ormond Street Hospital for Children Control: Eastman Dental Institute	Dental Caries (DMFT/S-dmft/s)	DMFT: 0.7±1.3 dmft: 2.3±2.8 DMFS: 0.8±1.5 dmfs: 6.1±11.1	DMFT: 2.4±2.8 dmft: 2.9±3.7 DMFS: 3.6±3.8 dmfs: 5.5±6.2
					Dental Plaque (Plaque Index - PI - The O'Leary index)	Primary dentition: 20.8±18.8 Permanent dentition: 15.8±19.5	Primary dentition: 20.5±21.8 Permanent dentition: 34.7±19.9
					Gingivitis (Simplified Gingival Index)	Primary dentition: 1.3±5.4 Permanent dentition: 1.7±5.8	Primary dentition: 2.5±6.5 Permanent dentition: 5±10.7
Vujkov et al., Serbia [39]	Case-Control	[10-25]	Total: 73 Hemophilia: 33 Control: 40	NR	Dental Caries (DMF)	4.21±4.14	4.45±4.19
					Gingival condition (Gingival Index)	1.57±0.77	0.12±0.35
					Oral hygiene (Oral Hygiene Index)	1.54±0.70	0.28±0.48
Yazicioglu et al., Turkey [21]	Comparative Cross-Section	Total: [2-14]	Total: 300 Hemophilia: 76 Control: 224	NR	Dental Caries (DMFT/dmft)	DMFT: 1.30 dmft: 3.5	DMFT: 0.91 dmft: 2.6
					Oral hygiene (NR)	Good: 34.2% Fair: 43.4% Bad: 22.4%	Good: 36.2% Fair: 41.1% Bad: 22.8%
Zaliuniene et al., Lithuania [11]	Case-Control	Total: 26.1±14.4 [4-58]	Total: 155 Hemophilia: 76 (27 children) Control: 79 (30 children)	Case: National Register of Hemophilia patients Control: General population	Dental Caries (DMFT/dft)	DMFT: 9.4±7.6 dft: 2.6±2.6	DMFT: 9.3±7.0 Dft: 6.1±2.5
Zaliuniene et al., Lithuania [22]	Case-Control	Total: 26.1±14.4 [4-58]	Total: 155 Hemophilia: 76 (27 children) Control: 79 (30 children)	Case: National Register of Hemophilia patients Control: General population	Dental Caries (DMFT/dft)	DMFT: 9.4±7.6 dft: 2.6±2.6	DMFT: 9.3±7.0 dft: 6.1±2.5
					Dental Plaque (Quantitative Plaque Percent Index - P% index)	32.0±20.2	28.2±15.2

NR: Unreported; TJD: Temporomandibular Joint Dysfunction.

## Statistic Methods and Data Synthesis

For the meta-analysis, the comparisons were made between the group of individuals with and without hemophilia. The meta-analysis included studies classified as having moderate to low risk of bias, according to the Newcastle Ottawa scale threshold (>5 stars). The outcomes were analyzed as continuous variables for the dental caries experience in primary and permanent dentition (dmft and DMFT), gingival condition (Modified Gingival Index – MGI), and oral hygiene (Plaque Index – PI). Thus, the random effect model was used for meta-analysis and Standard Difference (Std diff) was estimated in all outcomes. For both forest plots, the mean difference, 95% confidence interval (CI), and p-values were calculated.

The heterogeneity of studies was evaluated using the  $I^2$  test and the interval of prediction for metanalysis with more than five studies. The whole analysis was carried out using the Cochrane Collaboration's software for preparing and maintaining Cochrane reviews (RevMan 5.3, Cochrane Collaboration).

## Assessment of the Quality of Evidence Using GRADE

We graded the quality of the evidence for each outcome across studies (the body of evidence) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (<http://www.gradeworkinggroup.org/>) [26,27]. It was analyzed using the GRADEpro/GDT [<https://gdt.gradepro.org/app>]. This technique allows one to determine the overall strength of evidence for each meta-analysis.

The GRADE approach grades the evidence considering the aspects: study design; risk of bias; rating Inconsistency in results; rating imprecision of results; publication bias, rating magnitude of the effect; dose-response gradient; all plausible residual confounding. Then, the quality of evidence was graded in four levels: very low, low, moderate, and high. The "high quality" suggests that we are greatly confident that the true effect lies close to the estimated effect. On the other extreme, "very low quality" suggests that it has very little confidence in the effect estimate and the estimate reported can be substantially different from what was measured [28].

## Results

### Studies Characteristics

Twenty-seven studies were included in this systematic review. Seven studies were included in the meta-analysis for the dental caries experience. For the meta-analysis of the gingival conditions and oral hygiene/dental plaque, two and four studies were included, respectively. The flowchart of the studies is presented in Figure 1 [29].

The studies were conducted in Iraq [30], Turkey [7,17,21], Iran [19,31], Lithuania [11,22], Pakistan [12], India [6,10,14,32-34], Northern Ireland [9], Brazil [15,35-37], Uruguay [18], Romania [13], Poland [16], Malaysia [4], Finland [38], England [20] and Serbia [39].

Sixteen studies involved individuals with hemophilia from hospitals or centers specialized in hematological treatment [4,6,7,9,12,14,18-20,30,31,33-36,38]. Four studies with hemophiliacs from university clinics [10,15,17,32]; two studies that used national records of hemophiliacs [11,22]; two studies did not report such information [13,16,19,21,39]. Two studies showed results from the same sample [11,22]. No study used sample size calculation. The sample size ranged from 20 [33] to 328 [32] individuals, with ages ranging from 1 to 73 years old.

The comparison group was represented by healthy individuals; the majority was from university clinics [6,7,10,12,15,17,20]. Two studies collected data on health promotion actions carried out in hospitals [4,30]. Boyd et al. [9] used an estimate of the population of Northern Ireland. Two studies used national hemophiliac's registers [11,22]. No recruitment data have been reported in three studies [13,19,39].

All studies included evaluated dental caries experience through clinical examination. Sixteen studies endorsed the condition of oral hygiene/dental plaque [4,6,7,10,13-16,19-22,31,32,34,39]. Twelve studies have evaluated the gingival condition [4,6,7,15,17-20,32,35,38,39]. Other aspects such as temporomandibular dysfunction [12,31], malocclusion [18,31], active dental caries in enamel [15], and hypoplasia [31] were evaluated alone.

For the dental caries experience, the dmft/DMFT indexes (WHO) were used in all twenty-seven studies. For the oral hygiene condition, it was used the Plaque Index (PI) [6,7,10,13,14,22], Plaque Index (PI) – The O'Leary Index [19,20], Oral Hygiene Index (OHI) [39], and Simplified Oral Hygiene Index (OHI-S) [4,14,16,31,32,34]. Yazicioglu et al. [21] did not report the index used.

For gingival condition, the indexes used were Gingival Index [GI] [6,7,18,39], Simplified Gingival Index [GI-S] [20], Gingival Bleeding Index [GBI] [15,20], Modified Gingival Index [MGI] [4,19,31], and Periodontal Condition Index [PCI] [38]. The report of symptoms in the temporomandibular joint was used to measure temporomandibular dysfunction [12,31]. The presence of active dental caries in enamel [15], malocclusion [18,31], and hypoplasia [31] were observed by clinical examination; however, the criteria were not reported.

### Quality Assessment

The methodological quality of the studies ranged from 2 [32-34,39] to 7 [4,11,19,22] points (Table 2). The epidemiological designs found were cross-sectional with [9,12,13,15,16,20,21,31] or without [32-36,38] comparison group, and case-control studies [4,6,7,10,11,14,17-19,22,30,39].

Only six studies reported a calibration process [4,12,15,31,35,36]. Regarding the eligibility criteria, nine studies excluded other systemic or blood diseases [10,31,32,34,37], and HIV-positive children [20]. No study reported the rate of non-response.

Nine studies reported pairing the group by age and gender [6,7,10,12-14,16,30,31]. Mazzoni and Pignatari [15] and Othman et al. [4] paired the groups by age. Sonbol et al. [20] paired by age, sex, and ethnicity. Zaliuniene et al. [11] and Zaliuniene et al. [22] paired by age, gender, and place of residence. In contrast, Salem et al. [19] paired by gender, age, socioeconomic status, and education of those responsible.

Some studies were not included on the meta-analysis due to the absence of data such as age groups [14,22,30,36,39] or hematological alteration [16,18,30,31,36].

**Table 2. Summary of methodological quality of studies for this systematic review.**

Study ID and Date	Newcastle–Ottawa Scale			Points
	Selection	Comparability	Outcome	
Al Kubaisi & Alousi (2006) [30]	**	**	**	6
Alpkılıç Baskirt et al. (2010) [7]	**	*	**	5
Azhar et al. (2006) [12]	**	*	**	5
Babu et al. (2016) [5]	**	*	**	5
Boyd & Kinirons (1997) [9]	***		*	4
Daneswari et al. (2017) [32]	*		*	2
Dogan et al. (2010) [17]	**		**	4
Evangelista et al. (2015) [35]	**		*	3

Hermida Bruno et al. (2011) [18]	***		**	5
Jangra & Goswami (2017) [10]	**	*	**	5
Kozma et al. (2019) [13]	**	*	**	5
Kumar et al. (2018) [14]	***	*	**	6
Mazzoni & Pignatari (2009) [15]	**	*	**	5
Mielnik-Blaszczak (1999) [16]	***		**	5
Mythri et al. (2013) [33]	*		*	2
Othman et al. (2015) [4]	****	*	**	7
Rajantie et al. (2013) [38]	**		*	3
Reddy et al. (2019) [34]	*		*	2
Rodrigues et al. (2017) [37]	**	*	****	6
Rodrigues et al. (2008) [36]	**		*	3
Salem & Eshghi (2013) [31]	**	*	**	5
Salem et al. (2018) [19]	****	*	**	7
Sonbol et al. (2001) [20]	**	*	**	5
Vujkov et al. (2014) [39]			**	2
Yazicioglu et al. (2019) [21]	*		**	3
Zaliuniene et al. (2014) [11]	****	*	**	7
Zaliuniene et al. (2015) [22]	****	*	**	7

Number of Stars (\*): Point by Item.

## Data Synthesis

In primary dentition, the matching case-control studies presented conflicting data about the dental caries experience in children with or without hemophilia. Some studies report less dental caries experience in hemophilic individuals [9-11,22]. Others observed less experience of dental caries in healthy individuals [6,15,18,21]. However, the majority of the studies did not report differences between groups [4,7,16,19,20,30,31].

In cross-sectional or prevalence studies, the highest mean of dental caries in primary dentition was reported by Daneswari et al. [32], Mythri et al. [33], and Rajantie et al. [38]. In this meta-analysis, there is no statistical difference on the dmft Index between the groups (-0.62; CI95%: -1.68-0.43) (Figure 2-A) [4,7,10,15,19,20,22].

In permanent dentition, five studies presented a lower mean of dental caries in hemophilic individuals [9,10,15,20,22]. In five other studies, the experience of dental caries was higher in individuals with hemophilia [6,7,12,17,18]. In ten studies no differences were found in the results between the groups [4,11,13,14,16,19,21,30,31,39]. In our meta-analysis for dental caries in permanent dentition, there was no difference on the mean of DMFT index between the groups (-0.05; CI95%: -0.69-0.59) (Figure 2-B) [4,7,10,13,15,19,20].

Kozma et al. [13], Kumar et al. [14], Salem et al. [19], and Vujkov et al. [39] observed a higher dental plaque index in individuals with hemophilia when compared to healthy peers. Of the studies included in this systematic review, only Sonbol et al. [20] reported a significantly lower amount of dental plaque in permanent dentition in hemophilic children, comparing them with a non-hemophilic group. Most studies did not present statistically significant differences between hemophilic children and adolescents and non-hemophilic adolescents for oral hygiene/dental plaque [4,6,7,10,15,21]. In our meta-analysis for oral hygiene, individuals with hemophilia did not present significant differences in the Plaque Index [PI] mean than healthy individuals (0.36; CI95%: -0.06-0.77) (Figure 2-C) [4,7,10,13].

Regarding the gingival condition, some studies found worse gingival indexes in individuals with hemophilia than in the healthy comparison group [6,7]. However, only Othman et al. [4] observed better gingival index values in hemophilic children than in the comparison group. In our meta-analysis, there was no

statistically significant difference in the Modified Gingival Index [MGI] between the groups (-0.12; CI95%: -0.27-0.03) (Figure 2-D) [4,19].

Unclear results and a lack of details about temporomandibular disorders [12,31], malocclusion [18,31], active dental caries in enamel [15], and hypoplasia [31] made the meta-analysis not possible.

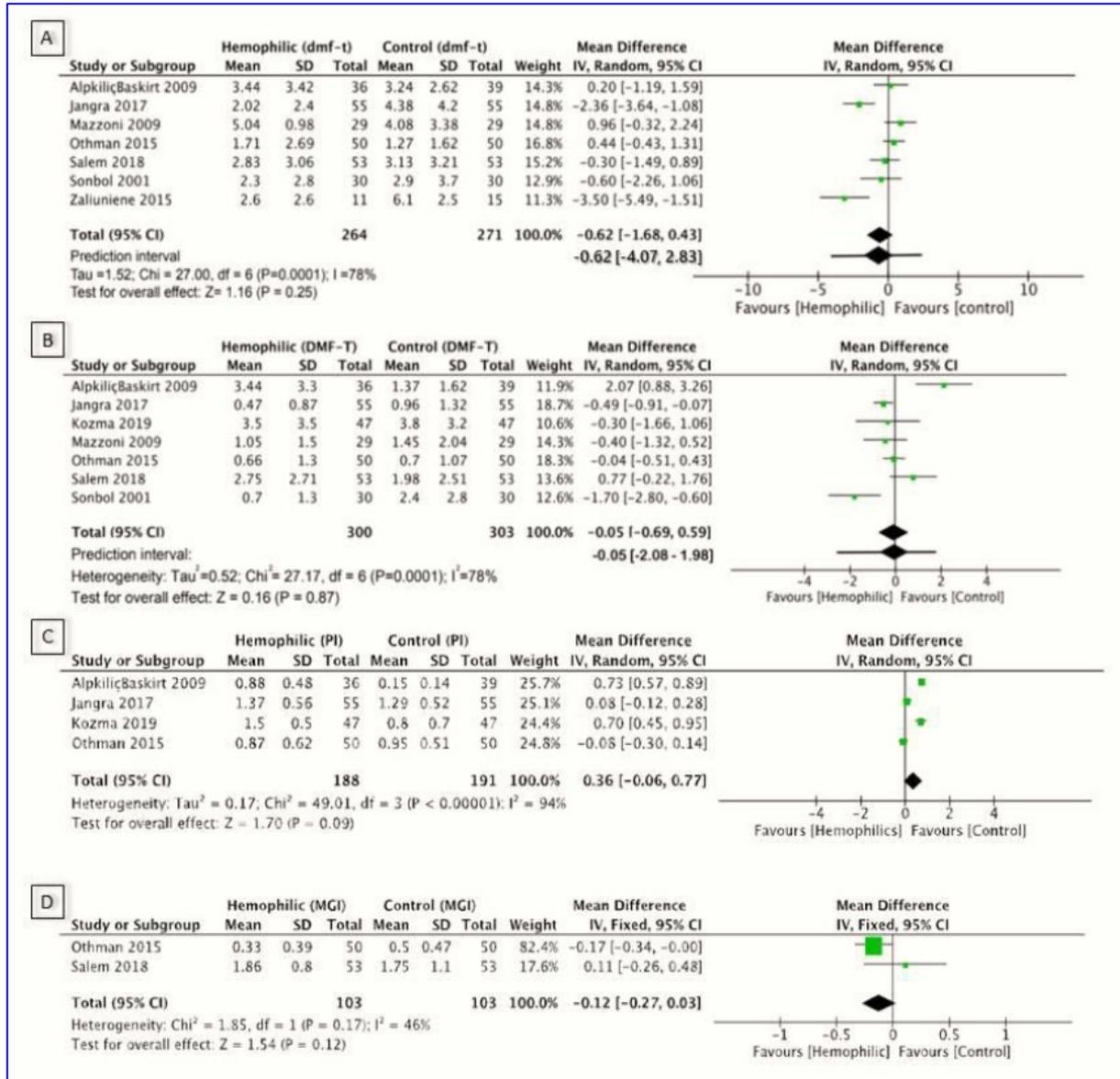


Figure 2. Forest plots of oral conditions (A – dental caries in the primary dentition; B – dental caries in the permanent dentition; C – plaque index; D – modified gingival index).

### GRADE

The analysis of GRADE evidence of meta-analyses was classified as very low for the three oral health outcomes. Among the aspects analyzed that impacted the evidence of the analyses, we noticed the design of the studies, which were observational, mostly cross-sectional with the comparison group, and inconsistency, since the analyses presented substantial heterogeneity, as well as conflicting effects (Table 3).

**Table 3. GRADE summary of findings.**

Outcomes	Study Design (Number of participants)	Effect* MD [SD] (95%CI)	Sample Size per groups	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
DMF-T	7 Case-Control Study (603)	-0.05 [-0.69 to 0.59]	300 HF and 303 controls	Serious <sup>a</sup>	Serious <sup>b</sup>	Not serious	Not serious	none	⊕○○○ VERY LOW <sup>‡</sup>
dmf-t	7 Case-Control Study (535)	-0.62 [-1.68 to 0.42]	264 HF and 271 controls	Serious <sup>a</sup>	Serious <sup>b</sup>	Not serious	Not serious	none	⊕○○○ VERY LOW <sup>‡</sup>
Plaque Index	4 Case-Control (279)	0.36 [-0.06 to 0.77]	188 HF and 191 controls	Serious <sup>a</sup>	Serious <sup>b</sup>	Not serious	Not serious	none	⊕○○○ VERY LOW <sup>‡</sup>
Modified Gingival Index	2 Case-Control (206)	-0.12 [-0.27 to 0.03]	103 HF and 103 controls	Serious <sup>a</sup>	Serious <sup>b</sup>	Not serious	Not serious	none	⊕○○○ VERY LOW <sup>‡</sup>

CI: Confidence Interval; MD: Mean Difference; SD: Standard Deviation; HF: Hemophilia; <sup>a</sup>NOS-T varied from 5 to 7 points; <sup>b</sup>Substantial heterogeneity; Summary of findings table according to the GRADE PRO.

## Discussion

In this study, the metanalysis of the dental caries experience, oral hygiene/dental plaque, and gingival condition data did not differ among children with and without hemophilia. Innumerable aspects could be pointed on the risk of dental caries and periodontal disease. Both conditions are of multifactorial origin with biological, environmental, behavior and socioeconomic components [40-43]. One important point is the access to the health service; our hypothesis was that haemophilics could present worse oral health conditions due to the particularities of their behavior in dental service access. Thus, despite the difficulties faced by this group to ensure access to dental services, according to our metanalysis, this is not reflected by worse oral conditions.

A deep reflection about the methodological aspects of the primary studies should be carefully discussed. For this study, although some confounders were carefully controlled such as age, especially because we analyze diseases with cumulative patterns such as dental caries, the large differences in the population studies could be pointed out. The differences on the demographic aspects could hinder the comparison. The studies did not describe the sample size calculation, non-responded rate, and the methods to select the sample, mainly the comparison group. Thus, the convenience samples could influence the external validity. Although most studies have performed pairing, mainly by age, a few studies bring a representative control of the general population [11,22]. Many studies were performed in groups that received care in health care units, without sample description [4,6,7,9-11,15,17,18,20,22,38].

Concerning the outcomes analyzed, all are associated with socioeconomic factors, such as income, education, and access to health services [41]. It is known that the worst health outcomes are associated with low socioeconomic status or in vulnerable populations [44]. The studies included in this review did not take care to control the socioeconomic differences between the groups. Some studies have been pairing the groups by demographic regions, but the individual's socioeconomic status was not evaluated. It could be a limitation of this systematic review. It is not possible to control the degrees of hemophilia (mild, moderate, and severe) in the studies involved in this systematic review. Yet, all of them were included and discussed in a limits way.

It is important to warn that the quality of the evidence was low, which reflects the methodological issues already described. Thus, it is not possible to state whether children and adolescents with hemophilia have peculiarities in oral health. Therefore, it is of paramount importance that further studies be elaborated and that these have methodological rigidity, as well as analyze the multiple factors already known that are associated with oral health outcomes.

In studies that worse oral health conditions [6,7,10,12,17,29] were observed in hemophiliacs, the authors suggest the presence of fear/anxiety in these individuals regarding to the risk of bleeding during oral health care. On the other hand, when better oral health conditions were observed in hemophiliacs [4,9,30], the authors point out the presence of centers or hospitals promoting dental care and education for this population. Thus, these points should be assessed in future studies.

Besides systematic reviews playing an important role in synthesizing the primary studies, it was also fundamental to synthesizing data from rare conditions increasing the confiability of the effect evaluated in small samples. Knowledge about the oral situation of these will contribute to public policy providers and health providers directing attention to this population [45]. Furthermore, considering the increased incidence of hemophilia in the world population [2] and the importance of instituting an appropriate dental clinical management for its individuals, it is necessary to know whether there is a specificity of oral conditions in this group. According to our knowledge, this systematic review is the first with a meta-analysis that evaluated if children and adolescents with hemophilia have different oral health conditions than individuals without the alteration.

The dental treatment of hemophiliac patients still proves to be a challenge to dentists, because it is an uncommon disease many professionals do not have experience in dealing with the bucco-dental problems of this population [46].

Commonly individuals with hemophilia face access barriers for medical and dental care [8]. Different health systems, geographical and cultural aspects, and budgetary constraints make it difficult for any country to provide comprehensive care to hemophilia patients [47].

Thus, children and adolescents with hemophilia may have an increased need for treatment, generated precisely by the difficulty and delay in intervention in primary dental care [46]. Often these individuals need to move between cities and states. Spatial distance, means of transport, local infrastructure, and financial issues appear as possible contributors to access barriers [8].

This study observed that, especially in the last two decades, an arisen interest in the research on oral conditions in children and adolescents with hemophilia increased. However, the studies should improve some methodological aspects, such as the description of eligibility and pairing criteria, and the calibration of the clinical indexes. In addition, future studies should adopt standard methods to allow the comparison of the clinical indexes in metanalysis.

This systematic review may encourage further studies to assess the oral health of children and adolescents with hemophilia, as well as, other topics involving hemophilia and dentistry, for example, dental anxiety and quality of life-related to oral health.

## Conclusion

The present systematic review demonstrated no differences in oral conditions between groups with and without hemophilia. Thus, hemophilia alone is likely not to impact the degree of oral health. Nonetheless,

caution is necessary once the evidence comes from observational studies with distinct populations, of low methodological quality, and with serious problems of risk of bias and inconsistency.

### Authors' Contributions

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JFS		<a href="https://orcid.org/0000-0001-9969-3721">https://orcid.org/0000-0001-9969-3721</a>	Conceptualization, Methodology and Writing - Review and Editing.
LMW		<a href="https://orcid.org/0000-0002-9696-0406">https://orcid.org/0000-0002-9696-0406</a>	Methodology, Formal Analysis, Data Curation and Writing - Review and Editing.
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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.			

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### Conflict of Interest

The authors declare no conflicts of interest.

### Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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