

# **Effect of surgery-first orthognathic approach on oral health-related quality of life:**

## ***A systematic review***

**Ke Yao<sup>a</sup>; Guanyin Zhu<sup>a</sup>; Miao Chen<sup>a</sup>; Bo Zhang<sup>a</sup>; Yongzhi Wu<sup>a</sup>; Peilin Li<sup>b</sup>**

### **ABSTRACT**

**Objectives:** To systematically evaluate the effect of the surgery-first approach (SFA) on oral health-related quality of life (OHRQoL) in patients with dentofacial deformities.

**Materials and Methods:** An electronic database search and hand search of selected journals and references were carried out. Studies investigating the OHRQoL of patients receiving SFA with or without a control group were included. The risk of bias was assessed by the Cochrane risk of bias tool in randomized clinical trials (RCTs) and the Newcastle-Ottawa Scale in non-RCTs.

**Results:** A total of seven articles met the eligible criteria and were included, of which six were cohort studies and one was an RCT, and six assessed the OHRQoL of the SFA with conventional orthodontic–surgical treatment (COST) as a control and one without. A total of 214 patients were examined, with sample sizes in studies ranging from 9 to 50. A total of 3 articles successfully measured the OHRQoL both before and after treatment in both the SFA and conventional orthodontic–surgical treatment groups. A total of six cohort studies were classified as low to moderate risk of bias, and the RCT was classified as high.

**Conclusions:** The SFA could improve the OHRQoL of patients with dentofacial deformities similar to conventional orthodontic–surgical treatment at the end of complete treatment. In addition, it increases OHRQoL immediately at the beginning of treatment without a deterioration. (*Angle Orthod.* 2020;90:723–733.)

**KEY WORDS:** Malocclusion; Orthodontics; Orthognathic surgery; Surgery-first approach; Quality of life

### **INTRODUCTION**

Individuals with dental deformities often suffer from impaired oral function and inharmonious facial profile, thereby having lower quality of life (QoL).<sup>1,2</sup> However, it is estimated that approximately 5% of the general population have dentofacial deformities that are not amenable to orthodontic treatment only.<sup>3</sup> For these patients, therapy that combines orthodontic treatment and orthognathic surgery is required to obtain an ideal facial profile and stable occlusion.

The “orthodontic-first” concept has been the generally accepted dogma in combined orthodontic–surgical treatment for decades. This results in a long treatment duration and also leads to several disadvantages, including gingival recession, oral functional deterioration, and subsequent psychological disorders. In addition, patients have to endure a deteriorated facial profile during the presurgical preparation, which has a negative effect on QoL.<sup>4</sup>

<sup>a</sup> Postgraduate Student, State Key Laboratory of Oral Diseases, National Clinical Research Center of Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China.

<sup>b</sup> Research Assistant, State Key Laboratory of Oral Diseases, National Clinical Research Center of Oral Diseases, Department of Orthodontics, West China Hospital of Stomatology, Sichuan University, Chengdu, China.

Corresponding author: Dr Peilin Li, Research Assistant, State Key Laboratory of Oral Diseases, National Clinical Research Center of Oral Diseases, Department of Orthodontics, West China Hospital of Stomatology, Sichuan University, No. 14, 3rd Section, Renminnan Road, Chengdu 610041, China (e-mail: lipeilin@scu.edu.cn)

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Recently, a combined orthodontic–surgical treatment characterized by the surgery-first approach (SFA) was introduced into clinical practice.<sup>5</sup> In the SFA, orthognathic surgery is carried out first without the usual presurgical orthodontic phase, followed by comprehensive postoperative orthodontic treatment. The SFA is suggested to have faster improvement of facial profile and less treatment duration than conventional orthodontic–surgical treatment (COST). It also may bring about higher patient satisfaction from the beginning of treatment and better cooperation during postoperative orthodontics.<sup>6</sup>

The oral health-related QoL (OHRQoL) refers to the QoL concerning the stomatognathic system. It assesses the particular effect of oral health conditions, such as oral functional limitations, symptoms, and social and emotional well-being, on daily life.<sup>7</sup> In the past, a few clinical trials have found that the OHRQoL of patients receiving COST show great improvement after treatment.<sup>8</sup> However, a recent review demonstrated that patients suffered an exacerbation of OHRQoL deterioration during presurgical orthodontic treatment in COST.<sup>4</sup> The SFA is supposed to avoid this problem and thus has the potential to achieve better OHRQoL than COST. However, there are a few evidence-based studies supporting this viewpoint.

Recently, a meta-analysis<sup>9</sup> comparing the OHRQoL of SFA with COST after treatment concluded that SFA was better with regard to its effect on OHRQoL. However, inappropriate data extraction may have contributed to a controversial conclusion. In addition, in that review, emphasis on the OHRQoL at the end of treatment resulted in less understanding of the changes of OHRQoL throughout the entire treatment. Hence, considering the urgent demand for a comprehensive analysis and more evidence for the SFA, the current study aimed to systematically assess the impact of SFA on OHRQoL and its difference from COST in patients with dentofacial deformities to provide an evidence-based reference for clinicians and promote its clinical application.

## MATERIALS AND METHODS

### Protocol and Registration

This systematic review was conducted and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>10</sup> The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019131116).

### Eligibility Criteria

The following eligibility criteria were based on the participants, intervention, comparators, outcomes,

and study designs (PICOS) strategy: (1) participants were patients aged older than 16 years who were treated with orthognathic surgery to correct dentofacial deformities; (2) the intervention was a SFA; (3) comparators were that the studies should include patients with COST as a control or investigate the OHRQoL before and after the SFA; (4) the primary outcome was the OHRQoL evaluated by validated instruments, with at least one time point after surgery-first orthognathic surgery, and secondary outcomes were the treatment duration, skeletal stability and relapse rate, complications, and other changes that might affect patients' QoL; and (5) the study designs were randomized clinical trials (RCTs), controlled clinical trials, and cohort studies.

The exclusion criteria were (1) patients with cleft lip or palate, or with syndromes or systemic diseases related to bone metabolism or the maxillofacial region, or with a previous orthodontic or orthognathic treatment history; (2) OHRQoL only assessed before treatment; and (3) cross-sectional studies, case reports, review articles, abstracts, editorials, or opinions.

### Information Sources, Search Strategy, and Study Selection

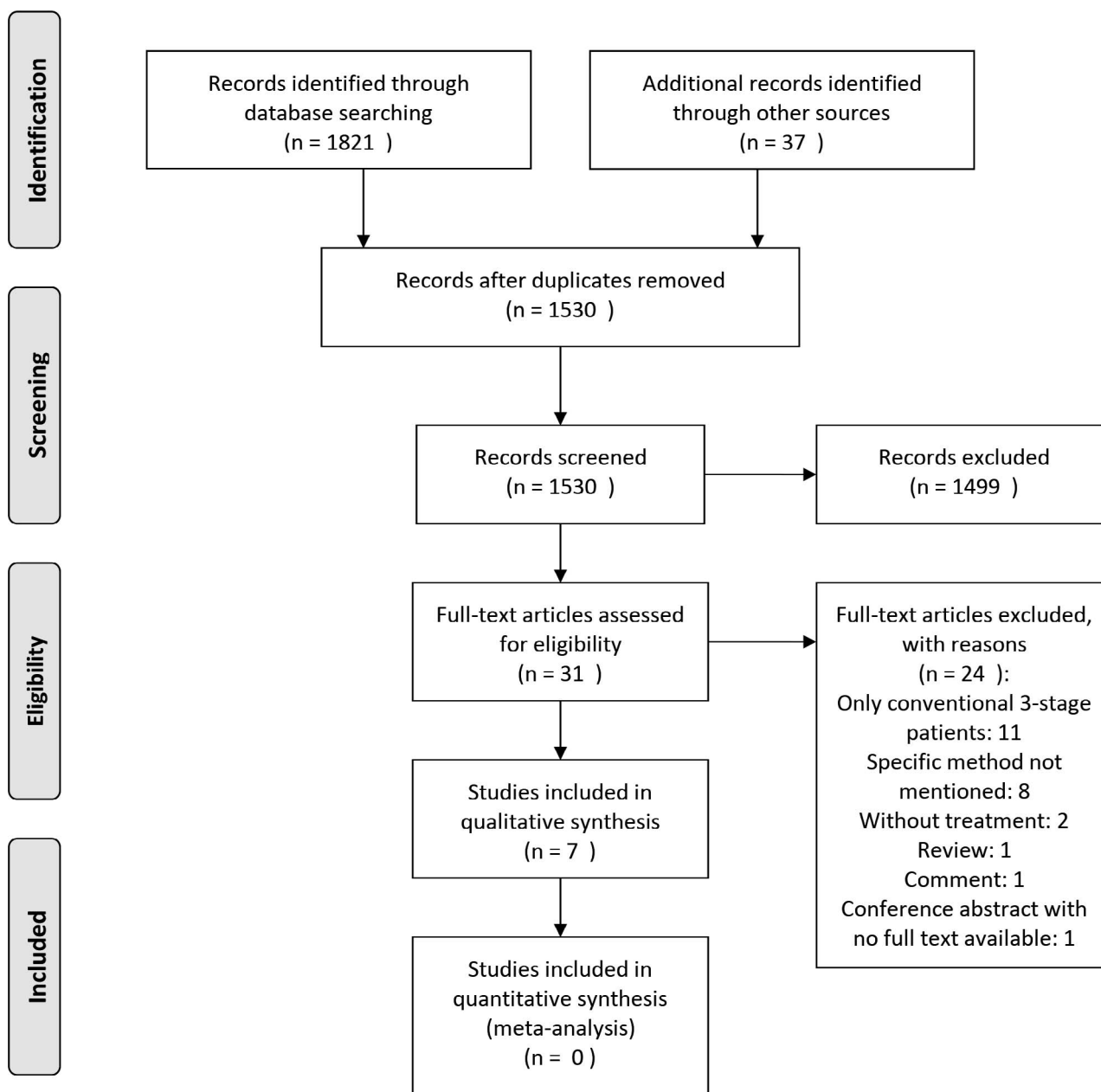
The electronic search was conducted including PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, EMBASE, Web of Science, SCOPUS, ProQuest Dissertation & Theses Database, System for Information on Grey Literature in Europe, ClinicalTrials.gov, and the following two Chinese databases: China National Knowledge Infrastructure and Chinese Biomedical Literature Database. The search strategy in PubMed combined the medical subject headings terms with free-text words and was adjusted for each database (Supplementary Table 1).

A hand search was undertaken in orthodontic journals. In addition, the reference lists of all eligible studies and related review articles were checked. The searches were conducted in April 2019 with no restriction on language, date, or status of publication.

Two authors selected the studies for eligibility independently and in duplicate. Any disagreements where no decision could be made were resolved by a third author.

### Data Extraction and Data Items

Studies that fulfilled the eligibility criteria were collected for data extraction. Two piloted data collection forms were used to record the quantitative and qualitative information. Two authors extracted the desired information independently and in duplicate. Disagreements were resolved by discussing



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart diagram of literature selection.

with a third author. Finally, the following items were collected: author, year of publication, country of study, study design, demographic characteristics, dentofacial deformities, treatment protocols, assessment instruments, results, additional outcomes, and conclusion.

#### Risk of Bias in Individual Studies

The Cochrane collaboration risk-of-bias tool was used to assess the risk of bias of RCTs.<sup>11</sup> For nonrandomized clinical trials, the Newcastle-Ottawa Scale was adopted.<sup>12</sup> Two authors assessed the risk of

bias independently and in duplicate, and disagreements were resolved with a third author.

#### Summary Measures, Synthesis of Results, and Quality of Evidence

Because of the lack of extensive data with regard to OHRQoL as well as the heterogeneity in methodology and clinical features, quantitative analysis was not feasible. As a result, the primary outcome was qualitatively analyzed and summarized, with comparisons of OHRQoL conducted between the SFA and COST or before and after surgery-first surgery. The

**Table 1.** Characteristics of Included Studies<sup>a</sup>

	Study	Origin	Study Design	Participants	Malocclusion	Pre operative Orthodontic Preparation
1	Brucoli et al., <sup>19</sup> 2019	Italy	Prospective cohort study	(SFA vs COST) N: 8 vs 25, F: 4 vs 19, M: 4 vs 6 Age: 35.63 ± 13.45 years vs 25.04 ± 5.58 years	Class II (8) Class III (25)	Not recorded
2	Feu et al., <sup>14</sup> 2017	Brazil	Prospective cohort study	(SFA vs COST) N: 8 vs 8, F: 5 vs 5, M: 3 vs 3 Age: 22.9 ± 5.4 years vs 26.8 ± 7.1 years	Class III	0.022-in to 0.028-in preadjusted Roth appliances SFA: no adjustment and orthodontic appliances were placed 1–2 weeks before surgery COST: dental alignment and leveling was performed
3	Huang et al., <sup>13</sup> 2016	China	Prospective cohort study	(SFA vs COST) N: 25 vs 25, F: 12 vs 13, M: 13 vs 12 Age: 18–25 years: 5 vs 4, 25–30 years: 15 vs 15, 30–35 years: 5 vs 6	Class III	Not recorded
4	Wang et al., <sup>18</sup> 2017	China	Prospective cohort study	(SFA vs COST) N: 25 vs 25, F: 12 vs 13, M: 13 vs 12 Age: 25 years (25.4 ± 6.4 years) vs 25 years (25.1 ± 6.8 years)	Class III	Not recorded
5	Park et al., <sup>15</sup> 2015	South Korea	Retrospective cohort study	(SFA vs COST) N: 11 vs 15, F: 9 vs 12, M: 2 vs 3 Age: 26.27 ± 4.45 years vs 25.00 ± 3.25 years	Class III	SFA: less than 100 days COST: 100 days or more
6	Pelo et al., <sup>17</sup> 2017	Italy	RCT	(SFA vs COST) N: 15 vs 15, F: 20, M: 10 Age: 30.2 ± 4.3 years	Class II (15) Class III (15)	SFA: orthodontic brackets placed only 3 days before surgery COST: 20.6 ± 1.9 months
7	Zingler et al., <sup>16</sup> 2017	Germany	Prospective cohort study	N: 9, F: 6, M: 3 Age: 26.7 ± 8.4 years	Class II (7) Class III (2)	Brackets (0.022 slot preadjusted edgewise brackets; Synthesis, Ormco Corp., West Collins, Orange, Calif) were banded 1 week before surgery. The molars were banded at the same time. Initial orthodontic wire was 016*022 stainless steel (Remanium, Dentaaurum, Ispringen, Germany) and was annealed and inactive

<sup>a</sup> BSSRO indicates bilateral sagittal splint ramus osteotomy; COST, conventional orthodontic–surgical treatment; F, female; HSSO, high oblique sagittal split osteotomy; M, male; N, total number; OHIP-14, 14-item Oral Health Impact Profile; OHRQoL, oral health-related quality of life; OQLQ, Orthognathic Quality of Life Questionnaire; RCT, randomized clinical trial; SFA, surgery-first approach.

secondary outcomes were also summarized qualitatively. The overall quality of evidence was rated according to the Grading of Recommendations, Assessment, Development, and Evaluation approach.

## RESULTS

### Study Selection and Characteristics

A total of 31 articles were reserved after screening the titles and abstracts of initially retrieved literature. Of

**Table 1.** Extended.

Type of Orthognathic Surgery	Method of Fixation	Postoperative Orthodontic Protocol	OHRQoL Measures	Assessment Timing
Not recorded	Not recorded	Not recorded	OHIP-14	T0: before surgery; T1: 1 month after surgery; T2: 6 months after surgery
Bimaxillary orthognathic surgery (the SFA used flexible wires and Kobayashi-type hooks; COST used rectangular 0.019*0.025-in wires with hooks welded to the arch)	Surgical splint for 4 weeks	0.022-in to 0.028-in preadjusted Roth appliances. Postoperative orthodontics began 4 weeks after placement of splint and lasted for 12 months. Final occlusion was refined	OQLQ OHIP-14	T0: before treatment; T1: 1 month after appliance placement T2/T3/T4: 3/6/12 months after treatment initiation T5: 24 months after treatment initiation or end of treatment T6: 2–3 weeks after orthognathic surgery
BSSRO	Not recorded	Not recorded	OHIP-14	T0: before treatment T1: 1 month after surgery (SFA) T2: 6 months after treatment initiation T3/T4: 12/18 months after treatment initiation (1/6 months after COST surgery) T5: finished treatment (12 months after COST surgery)
BSSRO	Rigid fixation and interocclusal splint for 2 weeks, then light training elastics for 2 weeks	Not recorded	OHIP-14	T0: before treatment T1/T2/T3: 1/6/12 month after surgery vs 1/6/12 month after treatment initiation T4: end of treatment
Bimaxillary orthognathic surgery (one-piece Le Fort I osteotomy, BSSRO)	Not recorded	Not recorded	OQLQ	T0: before treatment T1: before surgery T2: 3 months after surgery T3: After treatment
Bimaxillary orthognathic surgery (Le Fort I osteotomy, BSSOR)	Not recorded	Not recorded	OQLQ OHIP-14	T0: before treatment T1: 1 month before surgery T2: 1 month after surgery
Monomaxillary orthognathic surgery (4) Bimaxillary orthognathic surgery (5) (maxilla: Le Fort I osteotomy; mandible: HSSO and BSSRO; genioplasties were performed in classic sliding way)	Internal fixation by miniplates; intermaxillary fixation used orthodontic elastics (Dentaurum, Inspingen, Germany); final occlusion was supported by the final splint for the first week postoperatively	Active orthodontic treatment was resumed after splint removal and continued until final settling of occlusion was achieved	OQLQ	T0: before treatment T1: 3 months after surgery

these, 24 articles were excluded with reasons (Supplementary Table 2). Seven articles fulfilled the eligibility criteria and were included in this systematic review.<sup>13–19</sup> Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart diagram of literature selection.

The characteristics of the included studies are presented in Table 1. Six articles were cohort studies,<sup>13–16,18,19</sup> and one was an RCT.<sup>17</sup> Six articles compared the different effects on OHRQoL between the SFA and COST.<sup>13–15,17–19</sup> The other study investigated the change of OHRQoL before and after the SFA treatment.<sup>16</sup> In total, 214 participants were examined,



**Table 2.** Risk of Bias Assessment of Nonrandomized Clinical Trials by NOS<sup>a</sup>

Study	Selection				Comparability	Outcome			NOS Score	Overall Risk of Bias
	Represent Activeness of Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at the Start of the Study	Comparability of the Cohorts	Assessment of Outcome	Was Follow-Up Long Enough	Adequacy of Follow-Up		
1 Brucoli et al., <sup>19</sup> 2019	b*	a*	a*	a*	a*	c	b	d	5	Moderate
2 Feu et al., <sup>14</sup> 2017	b*	a*	a*	a*	a*	c	a*	a*	7	Low
3 Huang et al., <sup>13</sup> 2016	b*	a*	a*	a*	a*	c	a*	d	6	Moderate
4 Wang et al., <sup>18</sup> 2017	b*	a*	a*	a*	a*	c	a*	d	6	Moderate
5 Park et al., <sup>15</sup> 2015	b*	a*	a*	a*	a*	c	a*	c	6	Moderate
6 Zingler et al., <sup>16</sup> 2017	b*	a*	a*	a*	a*	c	b	d	5	Moderate

<sup>a</sup> NOS indicates Newcastle-Ottawa Scale.

\* a study could be awarded a maximum of 1 star for each numbered item within the selection and outcome categories, and a maximum of 2 stars for comparability, different letters mean different options of NOS, asterisks are the star given by these options.

with the sample sizes in individual studies ranging from 9 to 50. Three studies used a generic measure named the 14-item Oral Health Impact Profile (OHIP-14) questionnaire,<sup>13,18,19</sup> 2 studies used a condition-specific Orthognathic Quality of Life Questionnaire (OQLQ),<sup>15,16</sup> and two studies employed both.<sup>14,17</sup> The time points of assessment varied from 2 to 3 weeks after surgery to 2 years after treatment initiation.

### Risk of Bias Within Studies

The Newcastle-Ottawa Scale scores of six cohort studies differed from five to seven (Table 2). Five studies had moderate risk of bias,<sup>13,15,16,18,19</sup> and the other one had low risk of bias.<sup>14</sup> The RCT<sup>17</sup> was ranked as high risk of bias (Table 3).

### Results of Individual Studies

The results of the included studies are summarized in Table 4. All studies showed that patients had lower scores of OHRQoL after combined surgical–orthodontic treatment, whether by the SFA or COST.<sup>13–19</sup> In addition, the effects of complete treatments of the SFA

and COST seemed similar, as the OHRQoL in both groups either before or after treatment showed no statistically significant difference.<sup>13,15,18</sup> However, differences were detected during treatment. The OHRQoL of patients treated with the SFA displayed an immediate improvement at the beginning of treatment, and this trend continued throughout the evaluation periods.<sup>13–19</sup> However, in the COST group, the OHRQoL showed a deterioration in the preoperative orthodontic phase, which was followed by progressive improvement after orthognathic surgery.<sup>13–15,17,18</sup>

When comparing the OHRQoL of the same time after surgery in the SFA and COST groups, Huang et al.<sup>13</sup> demonstrated that the changes did not show any significant difference in total scores and each domain of OHIP-14. Park et al.<sup>15</sup> found similar results: the SFA and COST did not produce any significant difference in each domain of OQLQ 3 months after surgery. Pelo et al.,<sup>17</sup> by using the OQLQ and OHIP-14 instruments, noted that these two procedures resulted in no difference in OHRQoL 1 month after surgery.

Huang et al.<sup>13</sup> and Wang et al.<sup>18</sup> reported that the average treatment duration in the SFA group was 16.6

**Table 3.** Risk of Bias Assessment of Randomized Controlled Trial by Cochrane Handbook for Systematic Reviews of Interventions

Study	Domain	Risk of Bias	Quote and Comment
Pelo et al., <sup>17</sup> 2017	Random sequence generation	Unclear	"Patients were randomly assigned to 2 groups," but without more detail
	Allocation concealment	Unclear	Not mentioned
	Blinding of participants and personnel	High	Although not mentioned, it is hardly to blind
	Blinding of outcome assessment	High	Self-reported by patients
	Incomplete outcome data	Low	"All 30 patients included in the study were analyzed"
	Selective reporting	Low	Results reported all needed data (mean and standard deviation) at three time points of two questionnaires of two groups
	Other bias	Low	
	Overall risk of bias	High	

**Table 4.** Results of Included Studies<sup>a</sup>

Study	OHRQoL Measures	Assessment Timing	Results	Additional Outcomes	Conclusion
1 Brucoli et al., <sup>19</sup> 2019	OHIP-14	T0: before surgery T1: 1 month after surgery T2: 6 months after surgery	Both groups showed improvements from T0 to T2, with a great worsening at T1 in COST. The SFA presented an impressive preoperative discomfort at T0 and a higher score at T2 ( $P < .001$ )	Quality of life (36-item Short Form Health Survey): In four domains (bodily pain, vitality, social functioning, mental health), COST presented better scores at T0, with a postoperative decrease at T1 and a final improvement at T2, whereas the SFA progressively improved to reach higher levels than COST at T1 and T2 ( $P < .05$ )	The SFA allowed a precocious re-establishment of harmonic esthetics of face, thus positively influencing the compliance and psychological status
2 Feu et al., <sup>14</sup> 2017	OQLQ OHIP-14	T0: before treatment T1: 1 month after appliance placement T2/T3/T4: 3/6/12 months after treatment initiation T5: 24 months after treatment initiation or end of treatment T6: 2–3 weeks after orthognathic surgery	(SFA vs COST) OQLQ T0: $21.5 \pm 1.1$ vs $17.6 \pm 2.5$ T1: $20.4 \pm 3.8$ vs $18.0 \pm 3.3$ T2: $11.5 \pm 7.2$ vs $19.5 \pm 3.0$ T3: $10.9 \pm 6.4$ vs $17.6 \pm 5.6$ T4: $6.1 \pm 3.6$ vs $18.5 \pm 4.0$ T5: $7.4 \pm 3.5$ vs $20.6 \pm 1.7$ T6: $12.6 \pm 5.3$ (SFA) OHIP-14 T0: $25.4 \pm 5.6$ vs $21.5 \pm 9.0$ T1: $26.9 \pm 10.6$ vs $20.4 \pm 4.6$ T2: $17.0 \pm 9.7$ vs $15.0 \pm 6.7$ T3: $14.9 \pm 11.0$ vs $11.1 \pm 8.7$ T4: $7.5 \pm 6.6$ vs $14.1 \pm 11.3$ T5: $8.1 \pm 5.7$ vs $22.1 \pm 11.8$ T6: $20.1 \pm 8.0$ (SFA)	1. Duration: average duration of high complexity COST is 6 years, but five patients had completed and three had not at T5 in the SFA group 2. Malocclusion: significantly improved in the SFA group, but deteriorated in COST group 3. Esthetics: significantly improved in normative and self-perceived IOTN in the SFA group, whereas significantly deteriorated in normative IOTN in COST	OHRQoL improved significantly in a linear trend in the SFA group after surgery through 2 years of follow-up and worsened in COST group as they all remained in the presurgical orthodontic phase
3 Huang et al., <sup>13</sup> 2016	OHIP-14	T0: before treatment T1: 1 month after surgery (SFA) T2: 6 months after treatment initiation T3/T4: 12/18 months after treatment initiation (1/6 months after COST surgery) T5: finished treatment (12 months after COST surgery)	(SFA vs COST) T0: $38.68 \pm 4.35$ vs $39.55 \pm 4.15$ T1: $27.72 \pm 3.26$ vs $41.67 \pm 4.14$ T2: $13.94 \pm 2.13$ vs $48.48 \pm 3.91$ T3: $6.90 \pm 1.39$ vs $28.86 \pm 3.83$ T4: $4.11 \pm 0.49$ vs $15.61 \pm 2.49$ T5: $3.89 \pm 1.02$ vs $8.68 \pm 1.65$	1. Duration: $16.6 \pm 2.4$ months vs $25.3 \pm 2.4$ months (SFA vs COST) 2. Satisfaction (Dental Impact on Daily Living questionnaire): scores were lower in the SFA group than COST group (no significance)	Although OHRQoL was not significantly different, SFA significantly reduced treatment duration and showed no deterioration stage, which lead to better satisfaction

Table 4. Continued

Study	OHRQoL Measures	Assessment Timing	Results	Additional Outcomes	Conclusion
4 Wang et al., <sup>18</sup> 2017	OHIP-14	T0: before treatment T1/T2/T3: 1/6/12 month after surgery vs 1/6/12 month after treatment initiation (SFA vs COST) T4: end of treatment	Both OHRQoL significantly improved after treatment. Scores were highest before treatment in the SFA group, but increased significantly from T0 to T2 and then significantly decreased after surgery in COST group. The SFA showed lower scores than COST at T0, T3, T4 ( $P > .05$ )	Duration: $16.6 \pm 2.4$ months vs $25.3 \pm 2.4$ months (SFA vs COST)	Both treatment methods can obtain the same results; time of the orthognathic approach did not affect the final OHRQoL
5 Park et al., <sup>15</sup> 2015	OQLQ	T0: before treatment T1: before surgery T2: 3 months after surgery T3: After treatment	(SFA vs COST) T0: $51.64 \pm 19.27$ vs $53.87 \pm 17.81$ T1: $58.07 \pm 18.18$ (COST) T2: $23.09 \pm 22.41$ vs $23.53 \pm 9.28$ T3: $11.36 \pm 14.15$ vs $11.60 \pm 8.20$	Not recorded	SFA might have an advantage over COST in terms of no deterioration stage of OQLQ score
6 Pelo et al., <sup>17</sup> 2017	OQLQ OHIP-14	T0: before treatment T1: 1 month before surgery T2: 1 month after surgery	(SFA vs COST) OQLQ T0: $57 \pm 10$ vs $52 \pm 10$ T1: $60 \pm 9$ (COST) T2: $22 \pm 3$ vs $29 \pm 9$ OHIP-14 T0: $16 \pm 6$ vs $13 \pm 5$ T1: $18 \pm 6$ (COST) T2: $2 \pm 1$ vs $3 \pm 2$	Not recorded	SFA provided an immediate improvement of quality of life and avoided the worsening and discomfort caused by presurgical treatment in COST
7 Zingler et al., <sup>16</sup> 2017	OQLQ	T0: before treatment T1: 3 months after surgery	T0: $36 \pm 17.24$ T1: $18 \pm 12.69$	1. Duration: $15.7 \pm 3.31$ months, with the time until final splint removal was $30 \pm 11.2$ days 2. Complication: two patients receiving BSSRO showed postoperative hypesthesia of lower lip for 4–6 weeks 3. Sense of coherence: improved by nine points ( $P = .029$ ), indicating patients experiencing more meaningfulness, intelligibility, and self-efficacy 4. Esthetics: most (eight of nine) reported favorable facial changes after surgery; most prominent changes were experienced during the first week	Score reducing by more than 50% indicated patients experienced a significant improvement in quality of life after surgery-first orthognathic treatment

<sup>a</sup> BSSRO indicates bilateral sagittal splint ramus osteotomy; COST, conventional orthodontic-surgical treatment; IOTN, Index of Orthodontic Treatment Need; OHIP-14, 14-item Oral Health Impact Profile; OHRQoL, oral health-related quality of life; OQLQ, Orthognathic Quality of Life Questionnaire; SFA, surgery-first approach.



**Table 5.** GRADE<sup>a</sup> Summary of Findings Table for the Effects of Surgery-First Approach on Patients With Dentofacial Deformities<sup>b</sup>

Outcome and No. of Participants (Studies)	Impact	Certainty
Final OHRQoL 126 (3)	The total OHRQoL scores and the scores of every domain did not show any difference between patients treated with the SFA and COST.	⊕○○○ Very low <sup>c</sup>
Presurgical deterioration of OHRQoL 214 (7)	OHRQoL of patients in the SFA group improved immediately after orthognathic surgery, whereas patients treated by COST suffered a significant presurgical deterioration of OHRQoL.	⊕⊕⊕○ Moderate <sup>c</sup>
Treatment duration 125 (4)	Two studies showed average treatment duration were 16.6 months and 25.3 months in the SFA and COST groups, respectively. One study showed that the SFA treatment lasted for 15.7 ± 3.31 months. In another study, five of eight SFA patients completed treatment after 2 years, whereas the whole patients in COST were still in preoperative orthodontic phase.	⊕⊕○○ Low <sup>d,e</sup>

<sup>a</sup> GRADE Working Group grades of evidence: high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate—the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty: our confidence in the effect estimate is limited—the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

<sup>b</sup> COST indicates conventional orthodontic–surgical treatment; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; OHRQoL, oral health-related quality of life; SFA, surgery-first approach.

<sup>c</sup> Nonrandomized cohort studies were conducted without blinding and outcomes were assessed by self-reported questionnaires.

<sup>d</sup> Treatment time is an objective outcome hardly affected by the nonrandomized cohort study design.

<sup>e</sup> One study had ceased before all patients completed treatment. One study was conducted without a COST group.

months, whereas patients in the COST group were treated for an average of 25.3 months. Feu et al.<sup>14</sup> showed that five of eight participants in the SFA group had completed treatment 2 years later, but participants in the COST group were still in the preoperative phase. In another study recruiting SFA patients, treatment lasted for 15.7 ± 3.31 months until postorthodontic bracket removal.<sup>16</sup>

In addition, other pertinent results were also retrieved. One study reported the complication in SFA patients of two patients who suffered from postoperative hypesthesia of the lower lip for 4 to 6 weeks.<sup>16</sup> Two studies found a favorable perception of facial changes of SFA patients after surgery.<sup>14,16</sup> Two studies noted improved psychological parameters in the SFA group.<sup>13,16</sup> Brucoli et al.,<sup>19</sup> using a generic questionnaire named the 36-item Short Form Health Survey, found a similar result to that of the OHIP-14. No information about skeletal stability or relapse rate could be extracted from the included studies.

Finally, the evidence for three significant outcomes was rated as very low to moderate quality by the Grading of Recommendations, Assessment, Development, and Evaluation system (Table 5, Supplementary Table 3).

## DISCUSSION

### Summary of Evidence

The surgery-first orthognathic approach has been recently accepted as an alternative to COST. However,

the actual impact of SFA on patients' OHRQoL remained unclear. This study was an evidence-based review on this topic.

All included studies reported the improvement of OHRQoL in patients treated with combined orthodontic–surgical treatment whether by SFA or COST,<sup>13–19</sup> demonstrating the necessity and effectiveness of this procedure in patients with dentofacial deformities. Patients seek treatment mostly for improvements in esthetics, function, and psychology. Therefore, the improved facial and dental esthetics, oral masticatory function, self-esteem, and interpersonal relationships after combined treatment may account for this change.

The assessment time points of OHRQoL differed in the included studies, making it unsuitable to quantitatively synthesize the data. Three studies successfully evaluated the patients' OHRQoL both before and after treatment in the SFA and COST groups.<sup>13,15,18</sup> They found that scores of OHRQoL in both the SFA and COST groups showed no significant differences before or after treatment, implying the similar effects of complete treatment by the SFA and COST approaches on OHRQoL. In addition, the most affected domains of the two approaches showed the same descending order according to the OQLQ questionnaire: facial esthetics, oral function, social relationship, and awareness of dentofacial deformity.<sup>15,16</sup> Generally, the two approaches were not different in terms of OHRQoL, and patients with dentofacial deformities would gain a similar improvement in OHRQoL after treatment either by the SFA or COST.

However, differences emerged when the OHRQoLs were compared at different stages during the entire treatment. In the SFA group, because of the elimination of preoperative orthodontic treatment, an immediate improvement was observed at the initiation of treatment.<sup>13–19</sup> By contrast, in the COST group, patients experienced a presurgical deterioration, which was followed by an improvement after surgery.<sup>13–15,17,18</sup> The preoperative deterioration of patients' OHRQoL treated with COST was realized in different studies and could be attributed to the worsening of malocclusion and psychological disadvantages.<sup>20</sup> Dental decompensation in the presurgical phase had a negative impact on facial esthetics, and most patients considered it as the most stressful period during treatment.<sup>21</sup> Therefore, dental professionals should be aware of the harmful changes during presurgical orthodontic treatment and inform their patients what to expect and, if necessary, help them to overcome the negative effects.<sup>21</sup>

Three studies evaluated the OHRQoL of two groups at the same time after surgery and found no significant difference.<sup>13,15,17</sup> Although the presurgical orthodontic treatment in COST worsened the OHRQoL, the orthognathic surgery improved it to the same level as the postoperative OHRQoL in the SFA. This result indicated the critical role of orthognathic surgery in combined orthodontic–surgical therapy. Regarding the effects on OHRQoL, it can be hypothesized that the SFA may be similar to the last two phases of COST: the combination of surgery and postsurgical orthodontics.

Another advantage of the SFA was the reduction of total treatment duration. In the review, three studies recorded this outcome and found a significantly decreased treatment duration in the SFA group.<sup>13,14,18</sup> It was reported that the presurgical orthodontics in COST lasted for an average of 17 months, followed by orthognathic surgery and approximately 6 to 12 months of postsurgical orthodontic treatment.<sup>22</sup> The recent study focusing on treatment time revealed that the total duration for the SFA averaged 14.6 months compared with 22.0 months for COST.<sup>23</sup>

The SFA seemed to have an advantage for the prevention of presurgical deterioration of OHRQoL and the reduction of treatment time in comparison with COST, but more issues should be considered before choosing this procedure. For example, the skeletal stability of the SFA and its difference from COST remains inconclusive.<sup>1,24</sup> The exact psychological effects of extended postsurgical orthodontics in the SFA need to be further investigated in the future. Emphasis should be placed on the criteria of patient selection for the SFA. The SFA is primarily indicated for patients with (1) well-aligned to mild crowding of anterior teeth, (2) flat to mild curve of Spee, (3) normal

to mild proclination/retroclination of incisors, and (4) minimal transverse discrepancy.<sup>25</sup>

## Limitations

Inadequate reporting hindered the accurate assessment of bias and comprehensive data collection. For example, exact treatment details, numerical data of every domain, total treatment time, and complications were often missing. In addition, heterogeneity in methodology, statistics, and clinical features made it unreliable to quantitatively analyze the results. Each study had different assessment time points, and the measurement methods also varied. All cohort studies were evaluated as having low to moderate risk of bias, and the RCT was evaluated as high. Therefore, additional well-designed, standardized, properly reported prospective trials with homogeneous patients and adequate duration are necessary to provide the best evidence.

## CONCLUSIONS

- Treatment with the SFA improves OHRQoL in patients with dentofacial deformities and has a similar effect to conventional, combined three-stage orthodontic–surgical treatment at the end of complete treatment.
- Compared with the conventional strategy, the SFA increases OHRQoL immediately after surgery, and the trend continues throughout the entire course of treatment, with no presurgical deterioration.
- Clinicians could consider the surgery-first orthognathic approach as an alternative protocol in eligible patients.

## REFERENCES

1. Wei H, Liu Z, Zang J, Wang X. Surgery-first/early-orthognathic approach may yield poorer postoperative stability than conventional orthodontics-first approach: a systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;126(2):107–116.
2. Ribeiro-Neto CA, Ferreira G, Monnazzi GCB, Gabrielli MFR, Monnazzi MS. Dentofacial deformities and the quality of life of patients with these conditions: a comparative study. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;126(6):457–462.
3. Harrington C, Gallagher JR, Borzabadi-Farahani A. A retrospective analysis of dentofacial deformities and orthognathic surgeries using the index of orthognathic functional treatment need (IOFTN). *Int J Pediatr Otorhinolaryngol.* 2015;79(7):1063–1066.
4. Yi J, Lu W, Xiao J, Li X, Li Y, Zhao Z. Effect of conventional combined orthodontic–surgical treatment on oral health-related quality of life: a systematic review and meta-analysis. *Am J Orthod Dentofacial Orthop.* 2019;156(1):29–43.e25.

5. Nagasaka H, Sugawara J, Kawamura H, Nanda R. "Surgery first" skeletal class III correction using the Skeletal Anchorage System. *J Clin Orthod.* 2009;43(2):97–105.
6. Hernandez-Alfaro F, Guijarro-Martinez R, Peiro-Guijarro MA. Surgery first in orthognathic surgery: what have we learned? A comprehensive workflow based on 45 consecutive cases. *J Oral Maxillofac Surg.* 2014;72(2):376–390.
7. Sischo L, Broder HL. Oral health-related quality of life: what, why, how, and future implications. *J Dent Res.* 2011;90(11):1264–1270.
8. Emadian Razvadi ES, Soheilifar S, Esmaeelinejad M, Naghdi N. Evaluation of the changes in the quality of life in patients undergoing orthognathic surgery: a multicenter study. *J Craniofac Surg.* 2017;28(8):e739–e743.
9. Huang X, Cen X, Sun W, et al. The impact of surgery-first approach on the oral health-related quality of life: a systematic review and meta-analysis. *BMC Oral Health.* 2019;19(1):136.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
11. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(9):603–605.
13. Huang S, Chen W, Ni Z, Zhou Y. The changes of oral health-related quality of life and satisfaction after surgery-first orthognathic approach: a longitudinal prospective study. *Head Face Med.* 2016;12:2.
14. Feu D, de Oliveira BH, Palomares NB, Celeste RK, Mendes Miguel JA. Oral health-related quality of life changes in patients with severe class III malocclusion treated with the 2-jaw surgery-first approach. *Am J Orthod Dentofacial Orthop.* 2017;151(6):1048–1057.
15. Park J-K, Choi J-Y, Yang I-H, Baek S-H. Patient's satisfaction in skeletal class III cases treated with two-jaw surgery using orthognathic quality of life questionnaire: conventional three-stage method versus surgery-first approach. *J Craniofac Surg.* 2015;26(7):2086–2093.
16. Zingler S, Hakim E, Finke D, et al. Surgery-first approach in orthognathic surgery: Psychological and biological aspects—a prospective cohort study. *J Craniomaxillofac Surg.* 2017;45(8):1293–1301.
17. Pelo S, Gasparini G, Garagiola U, et al. Surgery-first orthognathic approach vs traditional orthognathic approach: oral health-related quality of life assessed with 2 questionnaires. *Am J Orthod Dentofacial Orthop.* 2017;152(2):250–254.
18. Wang J, Chen W, Ni Z, et al. Timing of orthognathic surgery on the changes of oral health-related quality of life in Chinese orthognathic surgery patients. *Am J Orthod Dentofacial Orthop.* 2017;151(3):565–571.
19. Brucoli M, Zeppegno P, Benech R, Boffano P, Benech A. Psychodynamic features associated with orthognathic surgery: a comparison between conventional orthognathic treatment and "surgery-first" approach. *J Oral Maxillofac Surg.* 2019;77(1):157–163.
20. Tachiki C, Nishii Y, Takaki T, Sueishi K. Condition-specific quality of life assessment at each stage of class iii surgical orthodontic treatment—a prospective study. *Bull Tokyo Dent Coll.* 2018;59(1):1–14.
21. Esperao PT, de Oliveira BH, de Oliveira Almeida MA, Kiyak HA, Miguel JA. Oral health-related quality of life in orthognathic surgery patients. *Am J Orthod Dentofacial Orthop.* 2010;137(6):790–795.
22. Luther F, Morris DO, Hart C. Orthodontic preparation for orthognathic surgery: how long does it take and why? A retrospective study. *Br J Oral Maxillofac Surg.* 2003;41(6):401–406.
23. Jeong WS, Choi JW, Kim DY, Lee JY, Kwon SM. Can a surgery-first orthognathic approach reduce the total treatment time? *Int J Oral Maxillofac Surg.* 2017;46(4):473–482.
24. Soverina D, Gasparini G, Pelo S, et al. Skeletal stability in orthognathic surgery with the surgery first approach: a systematic review. *Int J Oral Maxillofac Surg.* 2019;48(7):930–940.
25. Liou EJ, Chen PH, Wang YC, Yu CC, Huang CS, Chen YR. Surgery-first accelerated orthognathic surgery: orthodontic guidelines and setup for model surgery. *J Oral Maxillofac Surg.* 2011;69(3):771–780.

## Erratum

The supplemental tables were not included in “**Effect of surgery-first orthognathic approach on oral health-related quality of life: A systematic review,**” by Ke Yao, Guanyin Zhu, Miao Chen, Bo Zhang, Yongzhi Wu, and Peilin Li. *Angle Orthod.* 2020;90:723–733. They are provided here:

**Supplementary Table 1.** Search Strategies of Each Database

Electronic Database	Search Strategy	Hits
PubMed	(Orthodontics[MeSH Terms] OR orthodont*) AND (Orthognathic Surgery[MeSH Terms] OR orthognathic OR surgery OR surgical OR osteotomy OR Le Fort OR sagittal split ramus OR intraoral vertical ramus) AND (Quality of Life[MeSH Terms] OR quality of life OR oral health-related quality of life OR OHRQoL)	404
Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Library	([mh Orthodontics] OR orthodont*) AND ([mh “Orthognathic Surgery”] OR [mh “Orthognathic Surgical Procedures”] OR orthognathic OR surgery OR surgical OR osteotomy OR Le Fort OR sagittal split ramus OR intraoral vertical ramus) AND ([mh “Quality of Life”] OR quality of life OR oral health-related quality of life OR OHRQoL)	26
Cochrane Database of Systematic Reviews (CDSR) via The Cochrane Library	([mh Orthodontics] OR orthodont*) AND ([mh “Orthognathic Surgery”] OR [mh “Orthognathic Surgical Procedures”] OR orthognathic OR surgery OR surgical OR osteotomy OR Le Fort OR sagittal split ramus OR intraoral vertical ramus) AND ([mh “Quality of Life”] OR quality of life OR oral health-related quality of life OR OHRQoL)	67
EMBASE via Ovid	(exp orthodontics/ OR orthodont*) AND (exp orthognathic surgery/ OR orthognathic OR surgery OR surgical OR osteotomy OR Le Fort OR sagittal split ramus OR intraoral vertical ramus) AND (exp “quality of life”/ OR quality of life OR oral health-related quality of life OR OHRQoL)	220
Web of Science	TS=(orthodont*) AND TS=(orthognathic OR surgery OR surgical OR osteotomy OR Le Fort OR sagittal split ramus OR intraoral vertical ramus) AND TS=(quality of life OR life quality OR oral health-related quality of life OR HRQOL OR OHRQoL)	259
SCOPUS	TITLE-ABS-KEY(orthodont*) AND TITLE-ABS-KEY(orthognathic OR surgery OR surgical OR osteotomy OR (Le Fort) OR (sagittal split ramus) OR (intraoral vertical ramus)) AND TITLE-ABS-KEY((quality of life) OR (life quality) OR (oral health-related quality of life) OR HRQOL OR OHRQoL)	228
China National Knowledge Infrastructure (CNKI)	SU=‘orthodont*’ AND SU=‘(orthognathic+‘surgery’+‘osteotomy’) AND SU=‘(quality of life’+‘HRQOL’+‘OHRQoL’)	11
Chinese Biomedical Literature Database (CBM)	(“Orthodontics”[MeSH Terms] OR “orthodont*”) AND (“Orthognathic Surgery”[MeSH Terms] OR “Orthognathic Surgical Procedures”[MeSH Terms] OR “orthognathic” OR “surgery” OR “osteotomy”) AND (“Quality of Life”[MeSH Terms] OR “quality of life” OR “HRQOL” OR “OHRQoL”)	141
ProQuest Dissertation & Theses Database	(mainsubject(orthodontics) OR orthodont*) AND (orthognathic OR surgery OR surgical OR osteotomy OR “Le Fort” OR “sagittal split ramus” OR “intraoral vertical ramus”) AND (“quality of life” OR “life quality” OR “oral health-related quality of life” OR HRQOL OR OHRQoL)	442
System for Information on Grey Literature in Europe (SIGLE)	(orthodont*) AND (orthognathic OR surgery OR surgical OR osteotomy OR Le Fort OR sagittal split ramus OR intraoral vertical ramus) AND (quality of life OR life quality OR oral health-related quality of life OR HRQOL OR OHRQoL)	2
ClinicalTrials.gov		21

**Supplementary Table 2.** Summary of Excluded Studies

	Author and Year	Title	Reason
1	Peter 2017	Oral health-related quality of life in surgery-first vs traditional orthognathic approach	Comment
2	Gambaro 2016	Surgery-first or orthognathic surgery approach: Psychosocial and physical changes	Conference abstract with no full text available
3	Alanko 2017	A longitudinal study of changes in psychosocial well-being during orthognathic treatment	Only conventional three-stage patients
4	Asada 2015	Satisfaction with orthognathic surgery of skeletal Class III patients	Only conventional three-stage patients
5	Baherimoghaddam 2016	Assessment of the changes in quality of life of patients with class II and III deformities during and after orthodontic-surgical treatment	Only conventional three-stage patients
6	Eslamipour 2017	Impact of orthognathic surgery on quality of life in patients with dentofacial deformities	Only conventional three-stage patients
7	Kavin 2012	Changes in quality of life and impact on patients' perception of esthetics after orthognathic surgery	Only conventional three-stage patients
8	Kurabe 2016	Impact of orthognathic surgery on oral health-related quality of life in patients with jaw deformities	Only conventional three-stage patients
9	Murphy 2011	The clinical relevance of orthognathic surgery on quality of life	Only conventional three-stage patients
10	Razvadi 2017	Evaluation of the changes in the quality of life in patients undergoing orthognathic surgery: a multicenter study	Only conventional three-stage patients
11	Rustemeyer 2012	Quality of life in orthognathic surgery patients: post-surgical improvements in aesthetics and self-confidence	Only conventional three-stage patients
12	Silva 2013	Evaluation of life quality of patients submitted to orthognathic surgery	Only conventional three-stage patients
13	Silva 2016	Quality of life in patients undergoing orthognathic surgery—a two-centered Swedish study	Only conventional three-stage patients
14	Le Gall 2015	First-line surgery: indications, advantages and drawbacks	Review
15	Antoun 2015	Oral health-related quality of life changes in standard, cleft, and surgery patients after orthodontic treatment	Specific method not mentioned
16	Azuma 2008	Beneficial effects of orthodontic treatment on quality of life in patients with malocclusion	Specific method not mentioned
17	Choi 2010	Change in quality of life after combined orthodontic-surgical treatment of dentofacial deformities	Specific method not mentioned
18	Nichols 2018	Long-term changes in oral health-related quality of life of standard, cleft, and surgery patients after orthodontic treatment: a longitudinal study	Specific method not mentioned
19	Schmidt 2013	Survey of oral health-related quality of life among skeletal malocclusion patients following orthodontic treatment and orthognathic surgery	Specific method not mentioned
20	Silvola 2014	Dental esthetics and quality of life in adults with severe malocclusion before and after treatment	Specific method not mentioned
21	Silvola 2016	Do changes in oral health-related quality-of-life, facial pain and temporomandibular disorders correlate after treatment of severe malocclusion?	Specific method not mentioned
22	Tamme 2017	Correlation of general and oral health-related quality of life in malocclusion patients treated with a combined orthodontic and maxillofacial surgical approach	Specific method not mentioned
23	Bock 2009	Assessment of quality of life in patients undergoing orthognathic surgery	Without treatment
24	Jung 2016	Quality of life and self-esteem of female orthognathic surgery patients	Without treatment



**Supplementary Table 3.** GRADE Evidence Profile for the Effects of a Surgery-First Approach on Patients With Dentofacial Deformities

Outcome No. of Participants (Studies)	Certainty Assessment					Summary of Findings	
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Overall Certainty of Evidence	Impact
Final OHRQoL 126 (3)	Serious <sup>a</sup>	Not serious	Not serious	Not serious	None	⊕○○○ VERY LOW	The total OHRQoL scores and the scores of every domains did not show any difference between patients treated with SFA and COST.
Presurgical deterioration of OHRQoL 214 (7)	Serious <sup>a</sup>	Not serious	Not serious	Not serious	Very strong association	⊕⊕⊕○ MODERATE	OHRQoL of patients in the SFA group improved immediately after orthognathic surgery, while patients treated by COST suffered a significant presurgical deterioration of OHRQoL.
Treatment duration 125 (4)	Not serious <sup>b</sup>	Not serious	Serious <sup>c</sup>	Not serious	Strong association	⊕⊕○○ LOW	Two studies showed an average treatment duration of 16.6 months and 25.3 months in the SFA and COST groups, respectively. One study showed that the SFA treatment lasted for 15.7 ± 3.31 months. In another study, 5 of 8 patients completed treatment after 2 years, while all patients in the COST group were still in the preoperative orthodontic phase.

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

<sup>a</sup> Nonrandomized cohort studies were conducted without blinding, and outcomes were assessed by self-reported questionnaires.

<sup>b</sup> Treatment time is an objective outcome hardly affected by the nonrandomized cohort study design.

<sup>c</sup> One study had ceased before all patients completed treatment. One study was conducted without the COST group.