



REVIEW ARTICLE

## A systematic review of differences in outcome between one and two stage palate repair in cleft lip and palate

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### ABSTRACT

The aim of this systematic review was to determine whether one-stage palatoplasty for children born with cleft lip and palate shows overall advantages in outcome compared with two-stage palatoplasty. The included studies were controlled studies of syndromic and non-syndromic children born with unilateral cleft lip and palate, bilateral cleft lip and palate, or isolated cleft palate. The interventions studied were one-stage palatoplasty and two-stage palatoplasty starting with the soft palate. The outcomes were facial growth, speech, hearing, presence of fistulae, other complications related to surgery, health-related quality of life, and health economics. In total, 14 original studies were included. Results were dichotomized into showing advantage for one- or two-stage palatoplasty for the respective outcome and compared with the results from six included systematic reviews. No overall advantage for either surgical strategy was found for any of the outcome measures. The certainty of evidence was highest for the presence of fistulae, followed by facial growth and speech. For several outcomes, the quality of the existing evidence was too low to allow for any conclusions to be drawn. Neither one- nor two-stage palatoplasty showed significant advantages in clinical outcomes compared with the other. Other aspects such as ethics, economics, or surgeon's preference might hence be of more importance. Homogenous choices of outcome measures and defined minimal clinically important differences would facilitate further research.

### ARTICLE HISTORY

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### KEYWORDS

Systematic review; cleft; cleft lip and palate; cleft palate; palatoplasty; palate repair; one-stage; two-stage; outcome

### Introduction

Cleft lip and/or palate (CL/P), in its different variations, is the most common facial congenital malformation worldwide, occurring in approximately 1 in 1,000 live births (1). The malformation can affect several different areas including feeding, dental development, facial growth, speech development, hearing, aesthetics, and psychosocial well-being. Clefts including the palate are typically associated with problems concerning feeding, hearing, speech, and facial growth.

A vast number of techniques for primary palate repair have been described, as well as different strategies regarding the timing of surgery. Although the field has been studied extensively, the optimal technique and timing of surgical palate repair remain in debate. Several studies, both older and more recent ones, have indicated that the palate needs to be closed, at least partly if not completely, before an age of approximately 12–18 months for speech development to be satisfactory (2–5). However, it has also long been known that the surgical trauma and scarring that occurs as a result of the palatoplasty can affect facial growth in a negative way (6, 7). For this reason, staged surgical strategies have been developed more than 100 years ago (6), with one-stage techniques having been described even earlier (8). To facilitate speech development

when using a staged technique, the soft palate is commonly repaired first, and the hard palate repair is delayed to allow optimal facial growth. The timing of both stages has varied greatly over the years (9–12). Today, we remain unsure of the optimal timing for staged palate repair, and whether a staged approach yields different end results compared with one-stage repair.

The aim of this study was to systematically review the existing scientific literature regarding one- versus two-stage palatoplasty. This was done in order to determine whether one strategy has significant advantages over the other, and hence should be preferred in a clinical setting. There are existing systematic reviews on the subject (13–17), but those have mostly focused only on children born with unilateral cleft lip and palate, and on certain outcomes such as fistula formation or facial growth. In this review we aim to include all patients born with a cleft in the palate and several relevant outcomes.

For two-stage palatoplasty, the soft palate is most often closed before the hard palate. Techniques for closing the hard palate first exist, for example through first closing the lip and hard palate with a vomerine flap in the first stage followed by soft palate closure in the second stage (18). In this review, however, only techniques where the soft palate was repaired first were considered.

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## Materials and methods

This review based on the results of a more extensive health technology assessment (HTA) report written by members of the project group and published by HTA Syd, part of the Swedish Agency for Health Technology Assessment and Assessment of Social Service in 2022 (19). The report is written in Swedish but includes a summary in English. The review protocol and data used in this review can be found in the report. The review was not registered.

### Research question

A focused research question was designed using the Patient, Intervention, Comparison and Outcome (PICO) model (20). The research question was: Does one-stage palatoplasty show overall advantages compared with two-stage palatoplasty? To further focus the research question, several inclusion criteria were established. The PICO and inclusion criteria are shown in Table 1. All studies complying with the PICO and inclusion criteria were included. No other outcomes than the ones included in the PICO were studied.

### Literature search

The search strategies were developed by two experienced information specialists in close collaboration with the rest of the project group. Databases used were *Medline*, *Embase* and *Cochrane Library*. The first searches were performed in February 2020 and were last updated in February 2023. Search terms used were the diagnoses of the patient population (*cleft, palate, cleft palate, cleft and palate*), the intervention, and the comparison (*one phase, 1 phase, two phase, 2*

*phase, single stage, single phase, dual stage, dual phase, one stage, 1 stage, two stage, 2 stage, first stage, first phase, second stage, second phase, closure, repair, palate, palatal, palatoplasty, early, late, delayed, timing, first, primary, second, secondary*). Results were limited to controlled human studies and systematic reviews published after 1970 and at the latest in December 2022. More detailed information concerning the search strategies can be found in Appendix B in a Swedish HTA-report written by members of the project group and published by HTA Syd in 2022 (19).

### Study selection

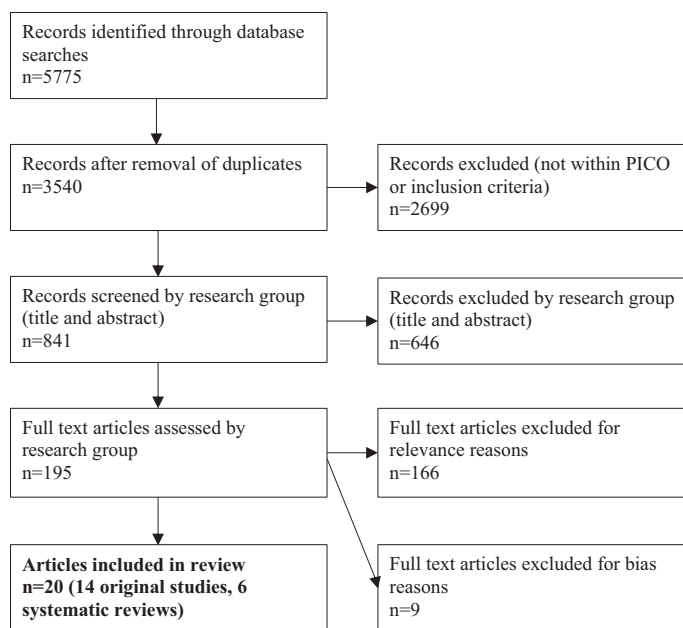
The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21, 22). Database searches generated 5,775 records available for inclusion in the review. This number decreased to 3,540 after removal of duplicates. Two librarians screened the records and removed the obviously irrelevant ones. This left 841 abstracts to be screened by the rest of the project group. The abstracts were divided into two groups and each group was screened by two persons from the project group. The screening was unblinded and done independently using the screening tool Rayyan (23). Senior investigator M.B. screened all records. Consensus decisions in the project group were used for inclusion or exclusion of abstracts when the two persons screening judged the abstract differently. Screening of abstracts resulted in 195 full-text manuscripts for further processing. These full text manuscripts were assessed for relevance by the same project group members who had assessed the abstracts. If the same author had published several studies of the same patient group and outcome, but with

**Table 1.** Research question according to PICO model and inclusion criteria.

PICO	Abbreviation	Meaning
<b>Population (P)</b>		
	P1a	Unilateral cleft lip and palate, without comorbidities/syndromes (UCLP)
	P1b	Unilateral cleft lip and palate, with comorbidities/syndromes (UCLP+)
	P2a	Isolated cleft palate, without comorbidities/syndromes (iCP)
	P2b	Isolated cleft palate, with comorbidities/syndromes (iCP+)
	P3a	Bilateral cleft lip and palate, without comorbidities/syndromes (BCLP)
	P3b	Bilateral cleft lip and palate, with comorbidities/syndromes (BCLP+)
<b>Intervention (I)</b>		
	I	One-stage palatoplasty
<b>Comparison (C)</b>		
	C	Two-stage palatoplasty
<b>Outcome (O)</b>		
	O1	Facial growth
	O2	Speech
	O3	Hearing
	O4	Presence of fistulae
	O5	Other complications related to surgery
	O6	Health-related quality of life
	O7a	Usage of health care resources (surgery, hospital admittance, follow-up visits, etc.)
	O7b	Usage of other supporting resources (parental sick-leave, etc.)
<b>Inclusion criteria</b>		
Study design		Controlled studies (RCTs or non-RCTs) and systematic reviews. At most intermediate overall risk of bias for all included studies
Patient age		Surgical treatment of the cleft palate initiated before two years of age, staged repair completed (stage two) before five years of age
Gender		No limitations
Population size		≥ 25 children per arm (one- vs. two-stage palatoplasty)
Follow-up time		Minimum five years of age follow-up time for O1-O4 and O7. No minimum follow-up time for O5-O6. If the same patient was included in several studies, the result used was taken from the study with the longest follow-up time
Lost to follow-up		<30% of population lost to follow-up. Imputed data not allowed
Date of publication		After 1970 for original studies, after 2005 for systematic reviews
Language		English, French, German, Swedish, Danish, Norwegian, Icelandic, or Finnish for original studies. English, Swedish, Danish, Norwegian, Icelandic, or Finnish for systematic reviews

RCT: randomized controlled trial.

different lengths of follow-up, only the study with the longest follow up was included. A total of 166 full-text manuscripts were deemed irrelevant, as they were outside the PICO and/or inclusion criteria, and were therefore excluded. The remaining 29 articles were assessed for quality including risk of bias according to the Swedish Agency for Health Technology Assessment and Assessment of Social Service's handbook (24). The conventional domains for risk of bias (selection, performance, detection, attrition, reporting bias and conflict of interest) were evaluated on a three-grade scale (high, moderate, or low risk of bias) for each domain. Based on the evaluation from each domain an overall risk of bias for the entire study was obtained in consensus. Only studies with low or moderate total risk of bias were used in the narrative synthesis. Nine studies were excluded due to high overall risk of bias. The remaining 20 studies were included in the review: 14 original studies and six systematic reviews. The screening process is shown in a flowchart in Figure 1 and characteristics of the included studies are shown in Table 2. The table includes the population studied, type of study, and the measure used for a specific outcome. Details regarding the bias assessments of the included studies can be found in Appendix C of the aforementioned HTA report written by HTA Syd (19). Details on the assessment of studies that were excluded can be found in Appendix D in the same report (19). It should be noticed that the searches were updated after the publication of the HTA report, and hence some of the studies assessed in this review were not included in the report.



**Figure 1.** Flowchart illustrating the study selection process.

### Data extraction

All 14 included original studies were thoroughly examined to determine whether they reported any significant differences in between one-and two-stage primary palate repair for the outcomes included in our PICO. This was done by the two project group members who had selected the particular study for inclusion. If a study included several of the included outcomes, assessment was performed separately for every outcome. No data were extracted from the six systematic reviews. The information and conclusions from these reviews were used to mirror and reflect the conclusions drawn from the data synthesis in the present systematic review.

### Data analysis

Due to the nature of the published data, no meta-analysis could be performed (25). The main reasons for this were that many studies did not

report confidence intervals, the heterogeneity in the methods of measuring outcomes, and the lack of definitions of minimal clinically important differences for many outcomes. Hence, a narrative analysis was performed for every outcome separately using the data extracted from the 14 included original publications. This analysis was obtained through extensive discussions within the project group to reach true consensus. The certainty of evidence was determined for every outcome separately using "The Grading of Recommendations Assessment Development and Evaluation System" (GRADE) classification (26).

### Ethics

As the study is a systematic review of the existing scientific literature, meaning no new patients were included, ethical approval has not been obtained.

**Table 2.** List of included studies and study characteristics.

Study	Year of publication	Study type, acronym	Population studied	Number of participants	Outcome studied
Willadsen et al.	2017	RCT, Scandcleft	P1a	399*	O4
Willadsen et al.	2022	RCT, Scandcleft	P1a	399*	O2
Heliövaara et al.	2017	RCT, Scandcleft	P1a	399*	O1
Lohmander et al.	2017	RCT, Scandcleft	P1a	399*	O2, O4
Rautio et al.	2017	RCT, Scandcleft	P1a	399*	O4, O5
Karsten et al.	2020	RCT, Scandcleft	P1a	399*	O1
Küseler et al.	2020	RCT, Scandcleft	P1a	399*	O1
Lundeborg-Hammarström et al.	2020	RCT, subgroup analysis from Scandcleft	P1a	151	O2, O4
Pereira et al.	2018	RCT	P1a	64	O1, O4
Reddy et al.	2018	RCT	P1a	100	O2, O4
Jakobsson & Pontén	1990	Non-RCT	P1a, P1b, P2a, P2b	237	O4, O5
Vedung et al.	1995	Non-RCT	P1a, P2a, P3a	520	O4
Mikoya et al.	2015	Non-RCT	P1a	68	O1
Otsuki et al.	2022	Non-RCT	P1a	86	O1

\*Including Arms A, B, C. Arm D excluded as it does not fulfill this study's PICO.

RCT: randomized controlled trial; P1a: Unilateral cleft lip and palate, without comorbidities/syndromes; P1b: Unilateral cleft lip and palate, with comorbidities/syndromes; P2a: Isolated cleft palate, without comorbidities/syndromes; P2b: Isolated cleft palate, with comorbidities/syndromes; P3a: Bilateral cleft lip and palate, without comorbidities/syndromes; O1: Facial growth; O2: Speech; O4: Presence of fistulae; O5: Other complications related to surgery.

## Results

Characteristics of the included original studies are presented in Table 2. It should be observed that some studies included multiple subpopulations and outcomes, where some of these were relevant for this review while others were outside of our defined PICO. Some studies also included several relevant outcomes but included too small population sizes or had too many patients lost to follow-up for certain outcomes to be included in the narrative analysis. In these cases, the studies were only included in the review for the populations and outcomes fulfilling the inclusion criteria. The study protocol for the Scandcleft trials (27) did not include any results and was hence not included in this study. However, it describes the methodology of the Scandcleft trials and should be read if the other Scandcleft trials are to be fully understood. Statistically significant differences were dichotomized into showing an advantage for either one-stage or two-stage palatoplasty, presented in Table 3. The results found in the included systematic reviews are discussed separately later in this review.

## Outcome O1: Facial growth

Facial growth was reported in six original studies. Three of these were Randomized controlled trials (RCT) within the Scandcleft trials (28–30), one was an independent RCT (31), and two were non-RCTs (32, 33). It is worth observing that the studies that are part of the Scandcleft trials all included the same patient population, although the number of patients lost to follow-up differed slightly. Different outcome measures were used in the studies. Heliövaara et al. (28) and Pereira et al. (31) used 5-year-old index (5Y index) evaluations of dental relationships. Karsten et al. (29) used the Modified Huddart-Bodenham index (MHB index) for evaluating dental relationships and Mikoya et al. (32) used the 5Y index and the Huddart-Bodenham index (HB index). Kùseler et al. (30) evaluated facial growth through cephalometric measurements. Otsuki et al. (33) used both cephalometric measurements and Great Ormond Street, London, and Oslo (GOSLON) yardstick assessments of dental relationships. All studies focused on non-syndromic children born with unilateral cleft lip and

**Table 3.** Dichotomized results from the included original studies.

Outcome	Study	Advantage one-stage	No significant difference	Advantage two-stage	Outcome measure	Comments
O1: Facial growth	Heliövaara et al. 2017		X		5Y index	
	Karsten et al. 2020		X		MHB index	
	Kùseler et al. 2020		X		Cephalometric measurements	
	Pereira et al. 2018			X	5Y index	
	Mikoya et al. 2015			X	HB index and 5Y index	Transversal growth
	Mikoya et al. 2015		X		HB index and 5Y index	Sagittal growth
	Otsuki et al. 2022			X	Cephalometric measurements, GOSLON yardstick	For several relevant outcome measures
O2: Speech	Lohmander et al. 2017		X		Hypernasality, velopharyngeal function	Perceptual speech assessment
	Lundeborg-Hammarström et al. 2020		X		Consonant proficiency, velopharyngeal function	Perceptual speech assessment
	Reddy et al. 2018		X		Hypernasality	Perceptual speech assessment
	Willadsen et al. 2022	X			Consonant proficiency	Perceptual speech assessment
	Willadsen et al. 2022			X	Velopharyngeal function	Perceptual speech assessment
O3: Hearing						No studies reporting this outcome
O4: Presence of fistulae	Willadsen et al. 2017		X		Surgically repaired fistulae	
	Lohmander et al. 2017		X		Surgically repaired fistulae	
	Rautio et al. 2017		X		Surgically repaired fistulae	
	Lundeborg-Hammarström et al. 2020		X		Surgically repaired fistulae	
	Pereira et al. 2018		X		Not specified	
	Reddy et al. 2018		X		All fistulae	
	Jakobsson & Pontén 1990		X		All fistulae	
	Vedung et al. 1995		X		Surgically repaired fistulae	For UCLP (P1a)
	Vedung et al. 1995	X			Surgically repaired fistulae	For ICP (P2a)
Vedung et al. 1995			X	Surgically repaired fistulae	For BCLP (P3a)	
O5: Other complications related to surgery	Rautio et al. 2017	X			Airway complications	
	Rautio et al. 2017		X		Infections, bleeding	
	Jakobsson & Pontén 1990		X		Infections, bleeding, blood transfusion	
O6: HRQoL						No studies reporting this outcome

5Y index: 5 year old's index for dental relationships; (M)HB index: (Modified) Huddart Bodenham index for dental relationships; UCLP: Unilateral cleft lip and palate; P1a: Unilateral cleft lip and palate, without comorbidities/syndromes; ICP: Isolated cleft palate; P2a: Isolated cleft palate, without comorbidities/syndromes; BCLP: Bilateral cleft lip and palate; P3a: Bilateral cleft lip and palate, without comorbidities/syndromes; HRQoL: Health-related quality of life.

palate (UCLP) (P1a). Pereira et al. (31) showed significantly better scores for the 5-year-old index for the two-stage group, as did Mikoya et al. (32). The latter, however, only noticed a difference in transversal growth and not in sagittal growth. Otsuki et al. (33) found longer anterior-posterior length of the maxilla, lower posterior facial height, larger angle between the nasal floor plane and the SN plane, and better GOSLON yardstick scores in the two-stage group. They conclude that the two-stage approach resulted in better dental relationships and anterior-posterior maxillary growth than the one-stage protocol. The three remaining original studies showed no significant differences between one- and two-stage palatoplasty.

### **Narrative synthesis**

Results from the included studies were somewhat disparate. Three out of six showed an advantage for the two-stage group. However, these three studies (31–33) were rather small ( $n = 64$ ,  $n = 68$ , and  $n = 86$ , respectively) and follow-up was limited to between 5 and 8 years of age. Furthermore, in one of them (32) differences were only found for transversal growth. The conclusion drawn by the project group was that no overall advantages were seen for either approach when it comes to growth outcomes in the non-syndromic UCLP population, however a tendency toward favorable results for the two-stage group was seen. As all studies focused on the non-syndromic children born with UCLP, no conclusions could be drawn regarding the other patient groups included in our PICO.

### **Outcome O2: Speech**

Speech outcomes were reported in four original studies. Two of these were RCTs within the Scandcleft trials (34, 35), one was a subgroup analysis within the Scandcleft trials (36), and one was an independent RCT (37). In all the studies, speech was evaluated through perceptual speech assessment. However, the assessments focused on various aspects of cleft palate speech. Willadsen et al. (34) studied consonant proficiency and velopharyngeal competence, Lohmander et al. (35) studied hypernasality and velopharyngeal competence, while Lundeborg-Hammarström et al. (36) evaluated velopharyngeal competency and consonant proficiency. All were part of the Scandcleft trials and included the same patient population, although Lundeborg-Hammarström et al. (36) only focused on a subgroup, namely trial 2 in the Scandcleft trials. Reddy et al. (37) reported hypernasality in an independent RCT. All studies focused on non-syndromic children born with UCLP (P1a). In one of the studies published by Willadsen et al. (34), the one-stage group performed significantly better than the two-stage group when it came to consonant proficiency, but conversely velopharyngeal competence was significantly better in the two-stage group. No significant differences between one- and two-stage palatoplasty were found in the other studies.

### **Narrative synthesis**

In all studies but one, no differences in speech outcomes were seen between one- and two-stage palatoplasty in the UCLP group. One study showed better consonant proficiency in the one-stage group but better velopharyngeal competence in the two-stage group. Hence, the conclusion drawn by the project group was that no overall advantages were seen for either approach when it comes to speech outcomes. No conclusions could be drawn regarding the other patient groups included in our PICO.

### **Outcome O3: Hearing**

Hearing was reported in a few of the screened studies, but none of these fulfilled the other inclusion criteria. Hence, no studies reporting hearing outcomes were included in this review.

### **Narrative synthesis**

No conclusions could be drawn, as no studies reporting hearing outcomes were included.

### **Outcome O4: Presence of fistulae**

Eight original studies reporting the presence of fistulae were included. Of these, three were RCTs within the Scandcleft trials (35, 38, 39), one was a subgroup analysis within the Scandcleft trials (36), two were independent RCTs (31, 37), and two were cohort studies (40, 41). The three studies that were part of the Scandcleft trials reported surgically repaired fistulae (35, 38, 39). So did Lundeborg-Hammarström et al. (36) in a subgroup analysis of the Scandcleft patient population, namely Scandcleft trial 2. Vedung (41) also reported fistulae requiring surgical repair. In Reddy et al. (37) the type of fistula was not specified. The other included studies (31, 40) reported all fistulae (repaired and non-repaired). In all studies, the patient population was non-syndromic children born with UCLP (P1a). Vedung (41) also included children with iCP and BCLP (P1a, P2a and P3a), and Jakobsson & Pontén (40) included both children with UCLP and iCP with and without comorbidities/syndromes (P1a, P1b, P2a, and P2b). Vedung (41) noticed significantly fewer fistulae in the two-stage group for children born with BCLP, but conversely fewer fistulae in the one-stage group for children with iCP. All the other original studies reported no significant differences between one- and two-stage palatoplasty.

### **Narrative synthesis**

The conclusion drawn by the project group was that no clear overall differences in presence of fistulae were seen between one- and two-stage palatoplasty for non-syndromic patients born with UCLP. Other patient groups were included in two of the studies, but the scientific evidence was deemed to be too limited to draw any conclusions for these groups.

### **Outcome O5: Other complications related to surgery**

Complications related to surgery were reported in two studies (39, 40). One was an RCT within the Scandcleft trials (39), and the other was a cohort study (40). In Rautio et al.'s (39) study only children with UCLP (P1a) were included. They reported frequency of perioperative airway problems, bleeding, and rates of infection. Significantly fewer airway problems were seen in the one-stage group, but no differences were seen for the other outcome measures. Jakobsson & Pontén (40) included syndromic and non-syndromic patients with UCLP or iCP (P1a, P1b, P2a, and P2b) and reported bleeding, need for blood transfusion and rates of infection. No statistical analysis was performed in Jakobsson & Pontén's study (40), and hence no statistically significant differences between one- and two-stage palatoplasty were reported in this study.

### **Narrative synthesis**

The conclusion drawn by the project group was that no clear overall differences in rates of complications related to surgery were seen

between one- and two-stage for non-syndromic children born with UCLP. Although one study (39) found a difference in rates of transient airway problems, this was only reported in one single study, and the difference was only seen for one of the studied potential complications. Other patient groups were included in two of the studies, but the scientific evidence was deemed to be too limited to draw any conclusions for these groups.

### Outcome O6: Health-related quality of life

Health-related quality of life was not reported in any of the included studies.

### Narrative synthesis

No conclusions could be drawn, as no studies reporting health-related quality of life were included.

### Outcomes O7a and O7b: Health economics

No aspects of health economics were reported in any of the included studies.

### Narrative synthesis

No conclusions could be drawn, as no studies reporting outcomes related to health economics were included.

### Certainty of evidence according to GRADE

The only patient group included in all studies was children born with UCLP without comorbidities/syndromes (P1a). No other patient group was included in more than two studies. GRADE assessment of the certainty of evidence for the non-syndromic UCLP group for the respective outcomes is shown in Table 4.

The highest certainty of evidence was found for the presence of fistulae (O4). The scientific certainty was deemed to be moderate ( $\oplus\oplus\oplus\circ$ ) for the conclusion that there is no difference in presence of fistulae between groups of children born with UCLP, without comorbidities/syndromes, operated with one- or two-stage palatoplasty. For the outcomes facial growth (O1) and speech (O2), the scientific certainty of the conclusion that there is no difference in these outcomes between groups of children born with UCLP,

without comorbidities/syndromes, operated with one- or two-stage palatoplasty, was deemed to be low ( $\oplus\oplus\circ\circ$ ). The certainty of scientific evidence for the rate of complications related to surgery (O5) was deemed to be very low ( $\oplus\circ\circ\circ$ ). Hence, no conclusions could be drawn regarding the differences between groups of children born with UCLP, without comorbidities/syndromes, operated with one- or two-stage palatoplasty when it comes to complications related to surgery. No conclusions could be drawn regarding hearing (O3), health-related quality of life (HRQoL) (O6), or health economics (O7a and O7b) as these outcomes were not reported in any of the included studies.

### Comparison with results from systematic reviews

The conclusions and quality of evidence presented above were compared with the findings from the included systematic reviews. For facial growth, the two systematic reviews (13, 14) evaluated facial growth using cephalometric measurements, and found no differences between one- and two-stage palatoplasty. This was in accordance with our synthesis. For the presence of fistulae, two systematic reviews (15, 16) showed no differences between one- and two-stage palatoplasty, while one (17) found better results (fewer fistulae) in the one-stage group. This fit well with the conclusions drawn from the original studies. One systematic review by Wadde et al. evaluated several aspects of cleft care (42), with fistula formation and hypernasality being the outcomes relevant to this review. Only one study was included in the review with regard to these outcomes, the RCT performed by Reddy et al. (37), which is also included in our systematic review. The findings from the systematic reviews, and comparisons with the present review, are shown in Table 5.

### Discussion

Whether or not cleft palate should be repaired in one or two stages has been discussed for a long time, with both one- and two-stage techniques being described more than 100 years ago (6, 8). Several studies have indicated that the palate needs to be repaired at least in part before 2 years of age for speech development to be adequate (2–5). It has also been shown that closure of the hard palate in adolescence gives superior results when it comes to facial growth (11), but at the cost of worse speech development (3). However, whether two-stage repair with early closure of the hard palate gives different results than one-stage repair remains a point of discussion. In this review we defined early closure as repairing the hard palate before 5

**Table 4.** GRADE assessment of certainty of evidence in the UCLP group (P1a).

Outcome	Number of studies	Number of unique patients	GRADE score	Difference between groups
O1: Facial growth	6 (3 from the Scandcleft trials)	365	Low $\oplus\oplus\circ\circ$	No
O2: Speech	4 (2 from the Scandcleft trials)	269	Low $\oplus\oplus\circ\circ$	No
O3: Hearing	0	0	N.A.	N.A.
O4: Presence of fistulae	8 (4 from the Scandcleft trials)	637	Moderate $\oplus\oplus\oplus\circ$	No
O5: Other complications related to surgery	2 (1 from the Scandcleft trials)	265	Very low $\oplus\circ\circ\circ$	No
O6: HRQoL	0	0	N.A.	N.A.
O7a: Usage of health care resources	0	0	N.A.	N.A.
O7b: Usage of other supporting resources	0	0	N.A.	N.A.

HRQoL: Health-related quality of life.

years of age. This is older than in many of the included studies, which was a way of ensuring that no relevant studies were excluded.

This review showed no clear advantages in favor of either one- or two-stage palatoplasty with regard to facial growth, speech and presence of fistulae. The evidence was strongest when it came to the presence of fistulae, but weaker for speech and facial growth. For the remaining outcomes; hearing, complications related to surgery, and HRQoL, the available scientific evidence was simply too limited to draw any conclusions. The same went for groups other than UCLP without additional comorbidities/syndromes (P1a), who represent a very limited number of the included patients in this review (15–17, 40, 41). This was in spite of the fact that children with UCLP only represent around 40% of the total CL/P population (43), and that approximately 30% of clefts are associated with additional comorbidities/syndromes (44, 45).

The limited quality of the studies and the relatively small number of studies were the main reasons for the low reliability of the existing scientific evidence. All the included studies were assessed for bias, and only studies that were deemed to have a low or moderate risk of bias were included. In fact, none of the included studies was deemed to have low risk of bias.

The risks of reporting bias, performance bias, and detection bias in particular decreases the quality of the included studies and the scientific evidence. The largest studies were the Scandcleft trials (28–30, 34, 35, 38, 39) and the studies by Jakobsson & Pontén (40) and Vedung (41). Even though these studies are large and ambitious, especially the Scandcleft trials, they are few and not free of risks of bias, which limits the conclusions that can be drawn. This is discussed further next.

The patient selection process was well described in the included RCTs (27, 31, 37) indicating a low risk of selection bias. The non-RCTs were deemed to have a moderate risk of selection bias. Jakobsson & Pontén (40) and Vedung (41) retrospectively assessed patient records and divided the subjects into a one-stage and a two-stage group depending on the surgical technique used. The technique chosen depended on when the patients were operated and the surgical protocol that was in use at that certain point in time. In Mikoya et al. (32) the two groups were treated parallelly, and the technique used depended on to which department the patient was referred, hence there was no randomization.

Many of the studies came from the Scandcleft trials (28–30, 34–36, 38, 39), meaning that many of the included children were the same in several studies, decreasing the number of unique patients. Also, the Scandcleft articles were written by the same research group, increasing the uncertainty of the published data as it is yet to be reproduced by other research groups in different settings.

Several of the included studies were RCTs (28–31, 34–39) but understandably had to use unblinded operators, which inherently increases the risk of performance bias. This is a weakness that is difficult to avoid when conducting research on surgical techniques and outcomes, as it is impossible to use blinded surgeons and patients. Assessors of outcome may be blinded, however this may also be difficult as, for example, the pattern of scarring may provide a hint regarding which technique has been used. Hence, most of the included studies presented with a rather high risk of detection bias. Assessors were blinded in most RCTs, but in one study the surgeon was the one doing the follow-up assessment (37). In the study by Reddy et al. (37) information on documentation of speech was missing, and the methods for calculation of reliability and reporting of hypernasality were vaguely described. One cohort study (40) did not conduct any statistical analysis, and hence the significance of the findings was difficult to assess.

One factor that may influence outcomes, other than the choice of surgical technique, is age at repair(s). The timing of surgery differed between the included studies, and within studies. According to the Scandcleft study protocol (27), one-stage repair was performed at an age of around 12 months. The first stage of two-stage repairs was performed at 3–4 months, and the second stage at 12 months (Arm A) or 36 months (Arm B). A rather similar approach was used by Pereira et al. (31) and Reddy et al. (37) with one-stage repairs being performed at 9–13 months, and 2-stage repairs at approximately 11–13 months (first stage) and 24–39 months (second stage). Mikoya et al. (32) used an approach with later repairs; one-stage surgery and the first stage of two-stage repair at 18 months, and the second surgery of the two-stage repairs at an age of 5–7 years. Jakobsson & Pontén (40) and Vedung (41) presented results from a long period of time, where the surgical strategies had varied. One-stage repair was performed at around 18–24 months, but the timing of the two-stage repairs varied between approximately 6 and 18 months (first stage), and 2 and 6 years (second stage). As it has been shown that a late closure of the palate may lead to better facial growth (11), this may explain the

**Table 5.** Results from included systematic reviews and this review.

Outcome	Study	Advantage one-stage	No significant difference	Advantage two-stage	Outcome measure	Comments
O1: Facial growth	Kappen et al. 2018		X		Cephalometric measurements Cephalometric measurements	
	Salgado et al. 2019		X			
	<i>This review</i>		X			
O2: Speech	Wadde et al. 2022		X		Perceptual speech assessment	
	<i>This review</i>		X			
O3: Hearing						No studies reporting this outcome
O4: Presence of fistulae	Hardwicke et al. 2014		X		All fistulae All fistulae All fistulae	
	Tache et al. 2019		X			
	Stein et al. 2019	X				
	<i>This review</i>		X			
O5: Other complications related to surgery						No studies reporting this outcome
O6: HRQoL						No studies reporting this outcome

HRQoL: Health related quality of life.

superior transversal growth outcomes in the two-stage group shown by Mikoya et al. (32). Unfortunately, neither of the studies where the hard palate was closed at the oldest age reported speech outcomes, which theoretically could have been affected by the late closure (2–5). Interestingly, one of the Scandleft trials saw inferior speech outcomes in the two-stage group where the hard palate was repaired at 36 months (Arm B) compared with when it was repaired at 12 months (Arm A) (38). However, this difference was only seen for one speech outcome, namely PCC score (Percent Consonants Correct).

As argued in the Scandleft trials, the operating surgeon's experience and familiarity with the chosen surgical strategy may play a more important role for the outcome than the choice of surgical technique (46). Furthermore, even though the same technique is used, other factors such as the lines of incision and area of dissection may differ between surgeons. In these trials, many of the operating surgeons had to use one technique they were familiar with, and one new technique (39). The research group tried to minimize the effect of learning curve by allowing the surgeons to use the unfamiliar technique for 1 year before the commencement of the study. However, this relative lack of experience may explain, for example, the higher rates of fistulae when using the unfamiliar technique (although the differences were not statistically significant) (39). When it comes to the other included studies, Mikoya et al. (32), Reddy et al. (37), and Pereira et al. (31) describe the operating surgeons as experienced with the techniques used, whilst the experience is not discussed in Jakobsson & Pontén's (40) and Vedung's (41) studies. Therefore, it is difficult to draw any conclusions regarding the effect of surgical experience on outcomes from these studies.

Factors such as ethics and health economics become more important if, as the present review showed, there are no differences in strictly medical outcome between one- and two-stage palatoplasty. One may claim that it is ethically and economically favorable to repair the palate in one stage rather than two, as the psychological stress on the child is likely to be smaller (47) as well as the costs. Furthermore, another ethical aspect is the displacement effect, meaning that more surgical interventions per patient might restrict other patients' access to surgery even more in a setting where resources are limited.

Difficulties encountered when performing this review included a relatively small number of included studies, that many of the studies were from the same research project and group, the heterogeneity in outcome measures and reporting, and the lack of clearly defined minimal clinically important differences for the studied outcomes. However, this was a calculated risk when forming the research question and inclusion criteria. We chose to only include studies with a minimum of 25 patients in each group (one- and two-stage palatoplasty) as smaller studies are associated with a higher risk of bias (48). Analyzed outcomes were heterogenous. To avoid this, however, we would have had to include only one measurement/assessment method per outcome, which would have decreased the number of appropriate studies even further. Whether, and how, the choice of outcome measures in the included studies might have affected the results is challenging to assess. Certain studies chose to dichotomize results, such as the studies by Lohmander et al. (35) and Lundeborg-Hammarström et al. (36) where velopharyngeal competence was calculated on a 0–4 and 0–6 scale, respectively, but dichotomized into velopharyngeal competence or incompetence. When results are simplified in such a manner, it will be more difficult to detect small statistically significant differences between the groups. On the one hand, when results are simplified in such a manner, it will be more difficult to detect small statistically significant differences between the groups. Comparing completely different measures for the same outcome, such as the cephalometric

measurements presented in one study (30), the (M)HB index scores presented in two studies (29, 32), and the 5Y index scores presented in three studies (28, 31, 32), is even more difficult. The fact that the majority of the included studies did not find any significant differences in outcome between the groups, however, makes this assessment more reliable. Had differences been observed for certain outcome measures, but not for others, one would have had to analyze the reasons for this even more thoroughly. This goes not only for facial growth but also for the other outcomes studied. For instance, when it comes to fistula formation, some studies assessed all fistulae (31, 40), whilst others assessed fistulae requiring surgical repair (35, 36, 38, 39, 41). Whether or not a fistula needs to be surgically repaired is a subjective assessment that can differ from surgeon to surgeon. On the one hand, whether or not a fistula needs to be surgically repaired is a subjective assessment that can differ from surgeon to surgeon.

Another limitation that needs to be addressed is the fact that very few of the included studies had followed the patients through adolescence, and it is known that facial growth continues until 15 years of age or longer (49). Hence, it is possible that a longer follow-up time would show differences in facial growth that were not found in this review.

Strengths include the extensive literature search that was designed by librarians with extensive experience in this type of research and a thorough study selection process that was performed according to well-established guidelines (20–22).

Further research needs to be carried out in the field if reliable conclusions are to be drawn, especially for groups of CLP patients other than UCLP without additional comorbidities/syndromes. A more homogenous choice of outcome measures would greatly facilitate comparisons between studies and metaanalysis, as would clearly defined minimal clinically important outcomes. The Scandleft trials have shown that it is challenging to design an RCT that can answer our research question, and alternative approaches could include, for example, studies that are based on the extensive cleft registries that exist in some countries. Barriers towards conducting further research to try to answer the research question exist. Firstly, in order to assess the final outcomes, very long follow-up times are needed especially for facial growth. This presents a challenge in itself and increases the risk of a large proportion of patients being lost to follow-up, which would in turn decrease the reliability of the scientific evidence. Secondly, deciding on minimal clinically important outcomes is difficult as there are no clear-cut definitions of when, for example, hampered maxillary growth or mild hypernasality affects the daily life of the patient. This is also most certainly dependent on the individual patient's experience. The issue of heterogenous outcome measures is perhaps a bit easier to handle. If the international community of cleft care could agree on certain validated and reliable outcome measures to use, comparison between studies would be greatly facilitated. However, most outcome measures have certain disadvantages, such as subjectivity of assessments or the need of specialized and experienced assessors.

In conclusion, we found some evidence suggesting that there are no differences in facial growth, speech, and presence of fistulae between one- and two-stage palatoplasty for children born with UCLP without comorbidities/syndromes. Other factors such as ethical considerations, health economics, and the surgeons' familiarity with the different techniques may thus play a more important role for a surgeon's choice of surgical strategy.

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