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IMPLICATION OF PERSONALIZED MEDICINE IN MAXILLOFACIAL SURGERY

Ph.D. Thesis

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Budapest

2026

“A human often feels quite transformed, when treated humanely and warmly adored.”

(“Ein Mensch fühlt oft sich wie verwandelt, sobald man menschlich ihn behandelt.”)
Eugen Roth (German poet, 1895-1976)

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1. LIST OF ABBREVIATIONS

AB	Autologous bone
CaP-Ti	Calcium phosphate-titanium
CENTRAL	Cochrane central register of controlled trials
CI	Confidence interval
CP	Cranioplasty
GRADE	Grading of recommendations assessment, development and evaluation
HA	Hydroxyapatite
HK	Hartung–Knapp adjustment
HM	Handmolded
IPD	Individual patient data
MD	Mean difference
MINORS	methodological index for non-randomized studies
MMO	Maximal mouth opening
MRAW	Raw mean
N	number
NA	Not available
OR	Odds ratio
PEEK	Polyetheretherketone
PICO	Population; Intervention; Comparison; Outcomes
PMMA	Polymethylmethacrylate
PP	Porous polyethylene
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSI	Patient-specific implant
RoB-2	risk of bias tool for randomized trials
ROBINS-I	Risk of bias in non-randomized studies of interventions
SD	Standard deviation
SE	Standard error
SSI	Surgical side infection
Ti	Titanium
TMJ	Temporomandibular joint

VAS	Visual analogue scale
WK	week

2. STUDENT PROFILE

2.1. Vision, mission, and specific goals

My vision is to improve the care and outcomes of patients with head and neck reconstruction through personalized solutions and evidence-based approaches. To achieve this, my mission is to establish the clinical importance of patient-specific implants (PSI) and provide better clinical decisions based on research. As my specific goal towards this, I aim to compare the safety and effectiveness of PSI with non-customized Implants.

2.2. Scientometrics

Number of all publications:	4
Cumulative IF:	11,83
Av IF/publication:	2,96
Ranking (SCImago):	D1:1, Q1:2, Q4:1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	5,6
Av IF/publication:	2,8
Ranking (SCImago):	Q1:2
Number of citations on Google Scholar:	16
Number of citations on MTMT (independent):	8
H-index:	2

The detailed bibliography of the student can be found on pages 75 and 76.

2.3. Future plans

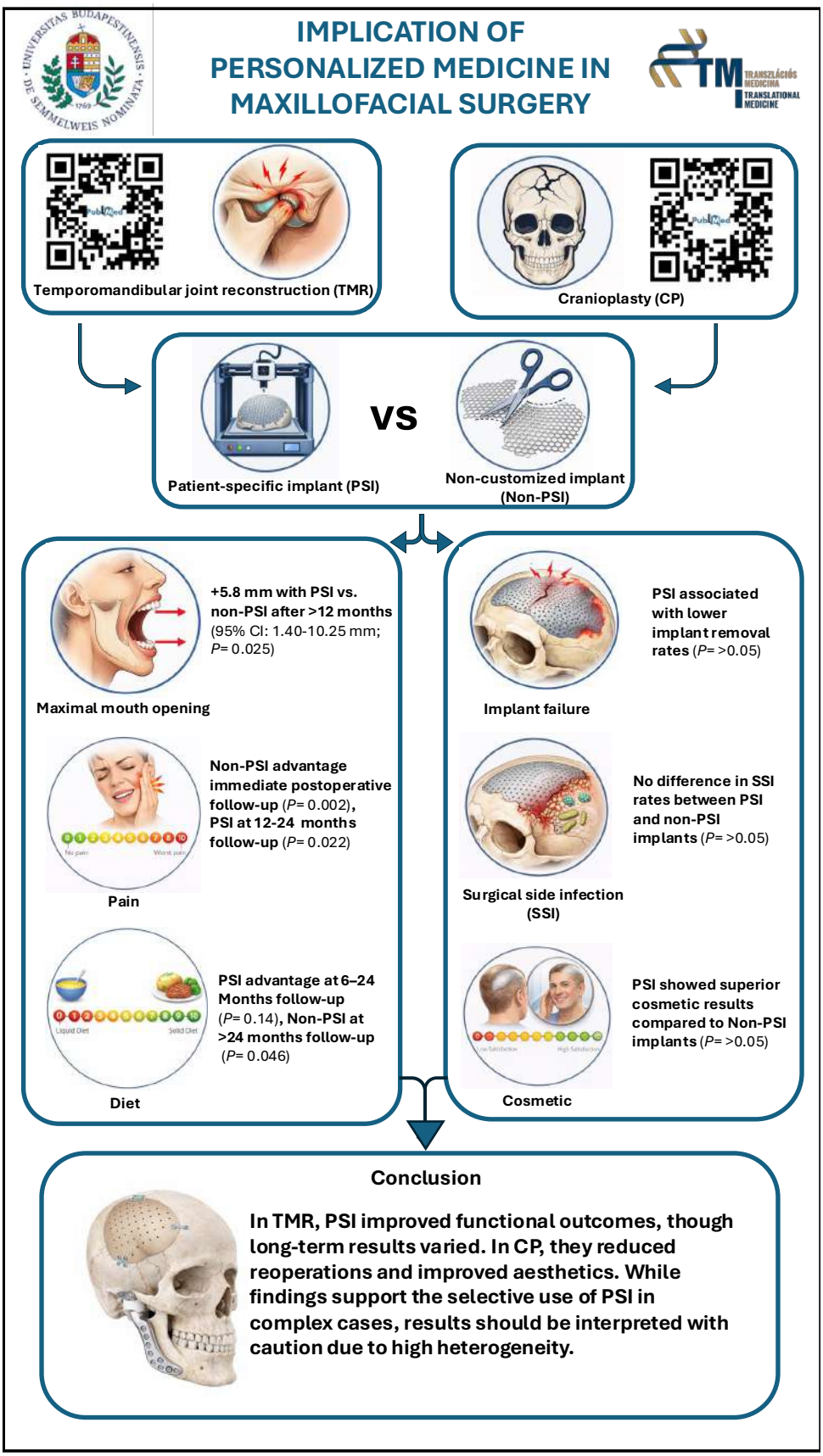
In the short run, my future plan is to complete my residency training in the field of oral and maxillofacial surgery to gain hands-on experience in the area where I aim to make an impact. In the long term, with this new clinical input and understanding, I will continue to advance my scientific career in the field of head and neck reconstruction. As a next step, I also consider it important to pass this knowledge on to future students by engaging in teaching.

3. SUMMARY OF THE THESIS

This thesis examines the clinical implications of personalized medicine in maxillofacial surgery, focusing on the role of patient-specific implants (PSI) in temporomandibular joint (TMJ) replacement and cranioplasty (CP). Through two comprehensive systematic reviews and meta-analyses, the thesis evaluates whether anatomical customization leads to improved functional outcomes, reduced complications, enhanced surgical efficiency, and better patient-centered results compared with conventional, non-customized implant systems. Despite their increasing adoption, robust evidence guiding their clinical indication remains limited. This thesis addresses this gap by synthesizing available evidence in two reconstructive fields where anatomical precision is essential. The first study compares PSI and stock implants in TMJ reconstruction. By analyzing the largest patient cohort reported to date and applying narrow postoperative follow-up intervals, the study provides a detailed assessment of functional recovery over time. PSI demonstrated a significant long-term improvement in maximum mouth opening beyond 12 months, suggesting biomechanical advantages of customization. Pain and dietary outcomes varied over time, with no consistent overall superiority of either implant type. These findings indicate that personalization in TMJ reconstruction offers selective benefits, particularly for patients with severe functional impairment or complex joint anatomy, while stock implants remain effective for pain control and standard indications. The second study evaluates PSI versus hand-molded implants in CP across a wide range of materials and clinical settings. PSI were associated with shorter operative times, lower reoperation and explantation rates, and superior cosmetic outcomes across most materials. Infection rates were comparable between implant types, indicating that customization does not increase infectious risk. Overall, the findings support personalized medicine as a targeted, indication-driven approach rather than a universal replacement for conventional implants.

PSI provide clear advantages in anatomically complex reconstructions, while standard implant systems remain appropriate in less demanding settings. This thesis contributes evidence-based guidance for implant selection and supports a rational, patient-centered integration of personalized medicine into maxillofacial surgery

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Personalized medicine in maxillofacial surgery

Personalized medicine is increasingly redefining head and neck reconstructive strategies in maxillofacial surgery. As digital imaging, computer-aided design, and additive manufacturing technologies grow, patient-specific implants (PSI) have become promising alternatives to conventional non-customized implants (1). These technological advances offer the possibility of tailoring the implant to the individual patient's anatomy, thereby potentially enhancing functional outcomes, reducing complications, and improving esthetic satisfaction (2, 3).

Despite this promise, current clinical practice still lacks clear, evidence-based guidance on when personalized implants offer meaningful advantages over standard systems (4). The literature remains heterogeneous with surgical indications vary widely, patient cohorts differ substantially, and outcome reporting is inconsistent across centers (5).

5.2. PSI in TMJ and CP reconstruction

PSI have gained increasing relevance in maxillofacial reconstruction, particularly in temporomandibular joint (TMJ) replacement and cranioplasty (CP). Two procedures where anatomical precision is essential for restoring both function and quality of life (6, 7).

End-stage TMJ disease represents a growing clinical burden, with the number of total joint replacement surgeries projected to increase by 58% by 2030 due to rising demand and improved indications for alloplastic reconstruction. This growth underscores the need for optimized implant solutions capable of improving long-term functional outcomes, such as mouth opening, pain, and mastication function (8).

CP, on the other hand, is performed at high frequency in trauma and neurosurgery. It is crucial not only for restoring cranial integrity but also for improving cerebral hemodynamics, neurological function, and cosmetic appearance, all of which significantly influence patient rehabilitation and self-image (9). However, CP is

associated with an exceptionally high complication rate of 20–50%, including surgical site infection (SSI), extrusion, wound breakdown, and frequent revision surgeries, complication levels far exceeding most neurosurgical procedures (10).

These two fields were therefore chosen as focal points for investigating PSI, as both face rising clinical demand, depend heavily on precise anatomical reconstruction, and continue to struggle with significant complication rates and heterogeneity in outcomes.

5.3. Towards evidence-based personalized surgeries

By systematically examining the role and efficacy of PSI across two major reconstructive domains, this thesis aims to clarify their contribution to postoperative function, complication profiles, esthetic satisfaction, and surgical efficiency. Generating robust comparative evidence will not only inform about personalized implant selection but may also support the development of future clinical guidelines. Ultimately, a better understanding of the clinical implications of personalized implant design has the potential to refine surgical planning, reduce complication-related morbidity, and advance the broader adoption of evidence-based personalized medicine in maxillofacial surgery.

6. OBJECTIVES

6.1. Study I. – Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: systematic review and meta-analysis

We aimed to systematically evaluate the current evidence on PSI in TMJ reconstruction and to clarify whether PSI provide measurable advantages over stock implants in the rehabilitation of the stomatognathic system. Given the limitations of previous studies, including heterogeneous follow-up periods, insufficient separation between custom and non-custom prostheses, and restricted datasets, we sought to generate a comprehensive and updated synthesis of clinical outcomes (11-13). We hypothesized that PSI would demonstrate superior performance compared with stock implants, particularly in functional recovery and long-term postoperative results.

6.2. Study II. – Comparative efficacy of patient-specific versus hand-molded implants in cranioplasty: systematic review and meta-analysis

Given the increasing clinical demand for CP and the rise in personalized implant technologies, we aimed to systematically assess the performance of fully customized PSI compared to hand-molded (HM) across postoperative outcomes. Previous reviews have often grouped synthetic materials together or failed to analyze fully customized PSI separately, leaving uncertainty regarding their influence on complications (10, 14, 15). Through this updated systematic review and meta-analysis, we sought to clarify whether different PSI materials affect clinical performance. We hypothesized that PSI would demonstrate superior outcomes compared with conventional implants, leading to reduced complication rates, improved surgical efficiency, and enhanced esthetic results.

7. METHODS

Study I. and II. were performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 (16, 17) and followed the recommendations of the Cochrane Handbook (17). The study protocols are registered in PROSPERO (study I.: CRD42023479644 and study II.: CRD42024582985).

7.1. Study I. – Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: systematic review and meta-analysis

7.1.1. Eligibility criteria

The research question was formulated using the PICO framework, where the population (P) comprised patients undergoing unilateral or bilateral TMJ Reconstruction, the intervention (I) was the use of PSI, the comparison (C) was the use of stock system implants, and the outcomes (O) were maximum mouth opening (MMO), pain, and diet. Eligible studies were required to report on human patients receiving total TMJ prostheses, either custom made (PSI) or stock and to present postoperative changes in at least one of these outcomes over a defined follow-up period. No restrictions were placed on follow-up duration to ensure comprehensive data collection. However, pediatric cohorts were excluded. To reduce heterogeneity, two-arm comparative studies were evaluated separately from single-arm cohorts. Both prospective and retrospective observational designs were included. Case reports, small case series, conference abstracts, studies lacking original data, or publications with overlapping patient populations were excluded. In cases where overlap was suspected, only the study with the larger sample size was retained. Mixed populations combining pediatric and adult patients were also excluded to maintain consistency in demographic characteristics.

7.1.2. Selection process and search strategy

A systematic search was performed in MEDLINE (via PubMed), Embase, and the cochrane central register of controlled trials (CENTRAL) on November 5, 2023. No restrictions were applied regarding publication date or study type. Although the search

itself was conducted without language filters, full-text articles not available in English, German, or Hungarian were excluded. The predefined search strategy was ("temporomandibular" OR "TMJ" OR ((mandib* OR "Jaw") AND Joint*) OR "articulatio temporomandibularis" OR "TMD") AND (prosthes* OR implant* OR repla*). Study selection was carried out independently by two reviewers, with duplicates removed both automatically and manually. Titles and abstracts were first screened for relevance, followed by full-text assessment. Discrepancies were resolved through discussion. Inter-reviewer reliability was evaluated using Cohen's kappa, yielding values of $\kappa = 0.97$ after title and abstract screening and $\kappa = 0.95$ after full-text review.

7.1.3. Study selection and data extraction

Data extraction was carried out independently by two reviewers, with disagreements resolved through discussion. The extracted variables included: 1. study characteristics (first author, year, design, sample size, age, sex assigned at birth, study period, country, institution, diagnosis, implant type, and follow-up duration); 2. MMO; 3. pain; and 4. diet. MMO was consistently defined as the inter-incisal distance in millimeters. Pain and diet were assessed using a visual analogue scale (VAS, 0–10), where 10 indicated the most severe pain or a fully liquid diet, and 0 indicated no pain or a normal solid diet. When necessary, alternative scales were converted to a 0–10 VAS. Seven studies used non-standard measures, but their descriptions allowed reliable conversion (18-24). To avoid duplication, study populations were examined for overlap, and several authors were contacted for clarification. Consequently, not all publications by Mercuri, Wolford, Zheng, and Saeed were included (19, 23, 25, 26), and in cases where overlapping cohorts were identified (Gruber with Sidebottom, Brierly with Dimitroulis, and Amarista with Brown (21, 24, 27-30)), only the article with the larger sample size was retained.

7.1.4. Risk of bias and quality of evidence assessment

Risk of bias was independently assessed by two reviewers in accordance with the Cochrane Handbook, using the risk of bias in non-randomized studies of interventions (ROBINS-I) (17) and methodological index for non-randomized studies (MINORS) (31) tools. Any discrepancies were resolved through discussion. The certainty of evidence was

evaluated using the grading of recommendations assessment, development and evaluation (GRADE) framework (32), and was completed using the GRADEpro GDT software (version 2013) (33).

7.1.5. Data synthesis and analysis

Statistical analyses were performed in R (v4.3.2) (34) using the meta and metafor packages for standard (v6.5.0) (35) and multivariate meta-analytic modelling (v4.4.0) (36). Because substantial heterogeneity was expected across studies, random-effects models were applied throughout. When available, changes from baseline were used. Otherwise, pre- and postoperative means and standard deviations (SD) were extracted, and mean change values were calculated. In cases where SD were missing, they were estimated from paired t-test p-values, individual patient data (IPD), derived correlation coefficients, or summary statistics (medians, quartiles, minima/maxima) using validated methods. For pooled analyses combining single- and two-arm studies, raw means with 95% confidence intervals (CI) were used as effect measures.

Two-arm studies contributed data to multiple follow-up subgroups, and although each subgroup represented a different patient interval, the corresponding random effects were correlated within the same study. To account for this dependence, multivariable random-effects models with an unstructured variance–covariance matrix were fitted using the rma.mv function from the metafor (v4.4.0 R) package (36). Mean differences (MD) with 95% CI were used as effect measures, calculated by subtracting the control (stock) group mean from the experimental (PSI) group mean. Thus, all MD are reported as "PSI minus stock," where positive values favor PSI. Statistical significance was assumed when the CI did not include zero. Forest plots were generated for visualization, and heterogeneity was quantified using the Higgins–Thompson I^2 statistic (37). To examine the influence of demographic factors (age, sex), a hierarchical linear mixed-effects model was applied to the available IPD. When SD were missing, they were reconstructed from standard errors (SE) or estimated from quartile-based summary statistics using established methods (Luo et al. (38), Shi et al. (39)). These conversions introduce some approximation, representing a limitation of the analysis.

Pooled MD were calculated using inverse-variance weighting. Between-study variance (τ^2) was estimated with the restricted maximum-likelihood method, and CI were derived using the Q-profile approach (40, 41). For individual study MD, t-distribution–based CI were applied, and the Hartung–Knapp adjustment was used to improve the robustness of pooled estimates (42, 43). When studies reported multiple follow-up times within the same category, the earliest value was selected due to higher attrition at later intervals. Follow-up trends were visualized using ggplot2 (44), with LOESS smoothing applied separately for PSI and stock implants (45). IPD from ten studies were analyzed to assess the influence of demographic factors on changes in MMO. A linear mixed-effects model (lme, nlme package, v3.1.163) was fitted, with rows containing missing values removed (46, 47). The outcome variable was the postoperative change in MMO. Explanatory variables included implant type, preoperative MMO, sex, age, laterality (unilateral/bilateral), and follow-up time group (preoperative, immediate postoperative, 3–6 months, 6–12 months, 1–2 years, 2–4 years, and >4 years), along with two-way interaction terms. Interaction terms involving laterality, preoperative MMO, and age were removed due to insignificance based on ANOVA results. The final model retained device type, preoperative MMO, sex, age, laterality, follow-up time group, and the device–sex interaction. Follow-up time group was kept for clinical relevance despite statistical non-significance.

Group differences and contrasts for continuous variables were estimated using the emmeans and pairs functions from the emmeans v1.10.3 package (48). Model assumptions were evaluated by inspecting residual plots for homogeneity of variance and QQ plots for normality of random effects.

7.2. Study II. – Comparative efficacy of patient-specific versus hand-molded implants in cranioplasty: systematic review and meta-analysis

7.2.1. Eligibility criteria

The research question was formulated using the PICO framework, with (P) defined as patients undergoing CP, (I) as PSI, (C) as intraoperatively HM implants, and (O) including postoperative complications (SSI, implant failure, reoperation rate), operation

time, cosmetic results, and implant cost. Studies were eligible if they involved human participants receiving CP with either a PSI or an HM implant and reported at least one of these predefined outcomes. No restrictions were placed on follow-up duration to ensure comprehensive data capture. To reduce demographic heterogeneity, studies exclusively involving pediatric populations or mixed adult were excluded. Both comparative (two-arm) and single-arm observational cohorts were included. Two-arm studies, defined as those comparing PSI and HM implants made from the same material, contributed direct comparative estimates (odds ratios (OR)). Single-arm studies, reporting only one implant type or multiple materials without a direct comparison, contributed pooled proportions and meta-regression analyses. Studies had to provide raw data for at least one endpoint. Case reports, small series, conference abstracts, and studies without original data were excluded. In cases of overlapping cohorts, only the study with the largest sample size was retained.

7.2.2. Selection process and search strategy

A comprehensive literature search was conducted on 25 August 2024 in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). No restrictions were applied regarding publication date or study type. Although the search itself was unrestricted by language, full-text articles not available in English, German, or Hungarian were excluded. The full search strategy was: (“cranioplasty” OR “cranial” OR “skull” OR “craniofacial” OR “face” OR “calvarial”) AND (“reconstruction” OR “implant” OR prosthes* OR “replacement”) AND (“alloplastic material” OR “autologous material” OR titanium* OR “PEEK” OR “polyetheretherketone” OR “PMMA” OR “polymethylmethacrylate” OR “bone cement” OR “porous polyethylene” OR “calcium phosphate” OR “vascularized bone” OR “non vascularized bone” OR “CAD” OR “computer aided design” OR “CAM” OR “computer aided manufacturing” OR “custom” OR “patient specific” OR “bone graft” OR “hydroxyapatite” OR “composite” OR “bone matrix” OR “polyethylene”). Three reviewers independently screened titles and abstracts, followed by full-text evaluation. Duplicates were removed both automatically and manually. Disagreements were resolved by consensus. Inter-rater reliability was high, with Cohen’s kappa values of $\kappa = 0.96$ for abstract screening and $\kappa = 0.97$ for full-text review.

7.2.3. Study selection and data extraction

Data extraction was performed independently by three reviewers, with disagreements resolved through discussion. Extracted variables included: 1. study characteristics, first author, publication year, design, sample size, age, sex assigned at birth, study period, country, institution, diagnosis, implant type, and follow-up duration; 2. postoperative complications; 3. operative time; and 4. cosmetic outcomes. Because outcome definitions varied across studies, standardized definitions were applied to ensure consistency. SSI included superficial wound infections, deep soft-tissue or bony infections, and intracranial or organ-space infections when linked to the implant or surgical site. Implant failure was defined as implant removal or revision due to postoperative complications. Reoperation referred to any subsequent surgical or ambulatory intervention following the initial procedure. Implant removal and total reoperation were analyzed separately to distinguish implant-specific failure from soft-tissue related revisions. Operation time was defined as the duration from skin incision to final wound closure. Cosmetic outcomes were assessed using a 0–10 VAS, where 10 indicated the best aesthetic result.

7.2.4. Risk of bias and quality of evidence assessment

Risk of bias was independently assessed by three reviewers using the risk of bias tool for randomized trials (RoB 2) tool (49) for randomized studies and the ROBINS-I (17) and MINORS (31) instruments for non-randomized designs. Disagreements were resolved through discussion. The certainty of evidence for each outcome was evaluated using the GRADE framework (32), following the GRADE handbook, and processed with GRADEpro GDT (version 2013) (33).

7.2.5. Data synthesis and analysis

This meta-analysis examined differences in outcomes between PSI and HM implants in CP. Six outcomes (three continuous and three dichotomous) were available across the included studies. Ten distinct material design combinations were identified, although not all materials permitted both PSI and HM fabrication, limiting direct same-material comparisons. Where such direct comparisons were possible, two-arm studies were analyzed separately using OR for dichotomous outcomes. Single-arm studies without a

comparator were synthesized using pooled proportions and meta-regression within a multilevel random-effects framework. Sample size and event counts were extracted to calculate OR or proportions. OR reflected the odds of an event in the PSI group relative to the HM group. Proportions were logit-transformed, applying a continuity correction of 0.5 where needed. Because studies shared no controls and each patient could only receive one implant type, independence of sampling errors was assumed. Material and design combinations were treated as a single factor variable. Two outcomes required additional processing: implant prices were converted to USD using mid-study exchange rates and adjusted for inflation (but not pooled), and cosmetic scores were standardized to a 0–10 scale. When studies contributed more than one result for different material/design subgroups, multivariate meta-analysis (rma.mv, metafor) was used to account for within-study correlation of random effects, employing a two-level hierarchical structure with effect sizes nested within studies. Statistical analyses were conducted in R (v4.4.3), following established recommendations (40). Between-study heterogeneity was quantified using tau and Higgins–Thompson I^2 statistics (37).

8. RESULTS

8.1. Study I. - Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: systematic review and meta-analysis

8.1.1. Study search and selection

Of 4,812 screened articles, 402 underwent full-text review, and 42 met the inclusion criteria (Figure 1). The analysis included 18 studies evaluating PSI, 14 evaluating stock implants, and 10 observational studies assessing both. Data from 2,221 patients were analyzed, comprising 1,002 in the PSI group and 1,219 in the stock implant group. Baseline characteristics are presented in Tables 1 (a–f).

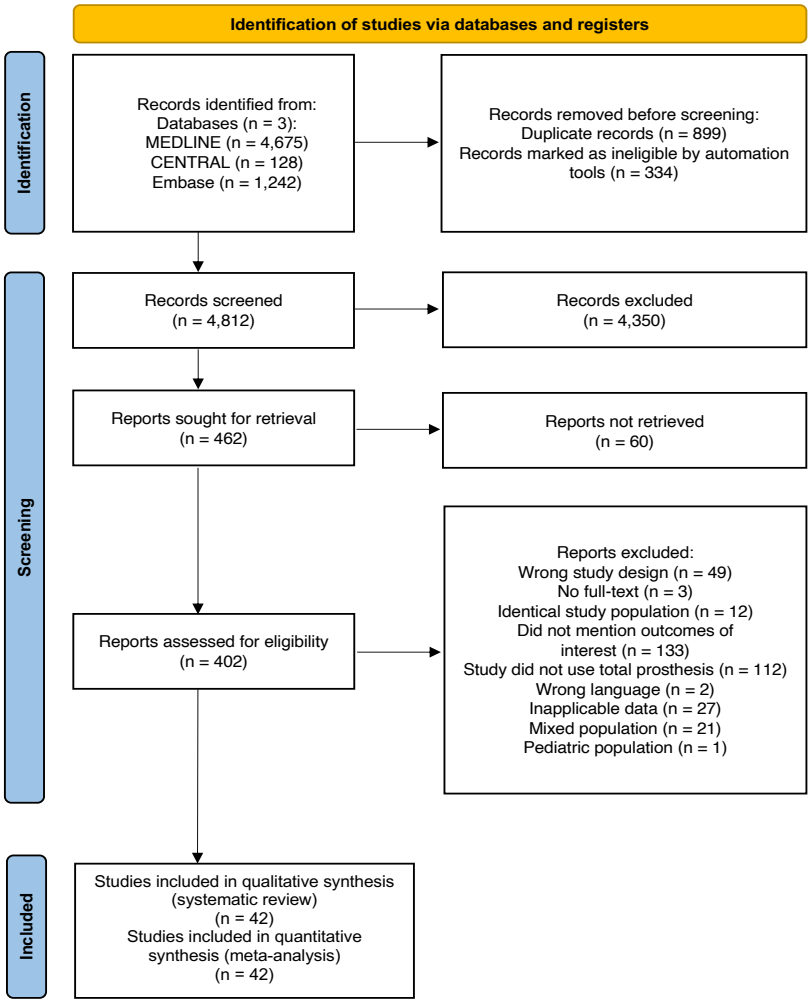


Figure 1. *PRISMA 2020 flowchart representing the study selection process (study I).*

Table 1. (a) Demographic data of the patients with custom PSI (study I).

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Aagaard 2014 (50)	Biomet	64	81	91.4	41 (16)	3, 6, 12, 24, 36	3, 12, 24, 36	NA
Amarista 2022 (21)	TMJ Concepts	28	52	75	42	Mean 46	Mean 46	Mean 46
Bhargava 2020 (51)	DARSN	20	20	40	28.75	12	NA	12
Boyo 2019 (52)	Biomet	33	62	81.8	40.4	12–35, 36–59, 60–122.4	12–35, 36–59, 60–122.4	NA
Brierly 2023 (28)	OMX-TMJ	151	206	90.7	44.8	Mean 36	Mean 18	NA
Briceño 2013 (53)	TMJ Concepts	27	41	92.6	42	Direct	Direct	NA
Burgess 2014[a] (54)	TMJ Concepts	48	NA	84.6[b]	48[b]	NA	Mean 46.3	Mean 46.3
Dowgierd 2022[a] (55)	NA	15	18	53	15	Direct	NA	NA
Gerbino 2016[a] (56)	Biomet	6	12	66	45.16	12, 18	18–24	Mean 20.4
Gonzalez-Perez 2016[a] (57)	Biomet	5	7	66.7[b]	51.8	3, 6, 12, 24, 36	3, 6, 24, 36	NA
Gupta 2020 (18)	TMJ Concepts	36	NA	89	44.5	NA	12	NA
Jones 2011[a] (58)	TMJ Concepts	2	3	71[b]	55.7[b]	12	Mean 10.5	NA

Table 1. (b) Demographic data of the patients with custom PSI - continued (study I).

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Kanatas 2012 (59)	Christensen	30	NA	71	45	Direct, 1, 6, 12	Direct, 1, 6	NA
Kanatsios 2022[a] (60)	OMX	63	79	92	48.87	Median 12 wks, median 2.95 years	Median 12 wks, median 2.95 years	NA
Kozakiewicz 2017 (61)	NA	11	11	36	54	Mean 35.2	NA	NA
Machon 2012[a] (62)	Biomet	4	4	75	33	Direct	Direct	NA
Mani 2020 (63)	NA	10	10	20	17.8	Direct, 60	NA	NA
Mehra 2016 (64)	NA	21	NA	100	25.6	Mean 6.2 years	Mean 6.2 years	Mean 6.2 years
Mercuri 2007 (19)	TMJ Concepts	59	NA	93.4	41.3	12, 24, 36, 60	12, 24, 36, 60	12, 36
Murdoch 2014 (65)	TMJ Concepts	42	63	69	47	Mean 43	Mean 43	NA
Neuhaus 2021 (66)	Biomet	16	NA	NA	Median 44.7	Mean 15.3	Mean 15.3	NA
Perez 2016 (67)	TMJ Concepts	61	61	77	38.6	Mean 44	Mean 44	Mean 44
Sahdev 2019 (68)	TMJ Concepts	93	NA	90	44.3	Mean 4.48 years	Mean 4.48 years	NA
Siegmund 2019[a] (69)	Biomet	16	16	56	46	3 days, 3, 6	3 days, 3, 6	NA
Sidebottom 2013 (24)	TMJ Concepts	74	103	88	47	6 wks, 6, 12	6 wks, 6	12

Table 1. (c) Demographic data of the patients with custom PSI - continued (study I).

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Vorrasi 2023[a] (70)	TMJ Concepts	8	13	87	43	Direct	3, 6	NA
Wolford 2003[a] (6)	TMJ Concepts	22	38	82	38.5	Mean 33	Mean 33	6
Zheng 2022 (71)	NA	37	45	62	43.4	Mean 28.5	Mean 28.5	NA

Table 1. (d) Demographic data of the patients with stock joints (study I).

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Balon 2019 (72)	Biomet	12	12	83	49.2	Mean 39.5	Mean 39.5	Mean 39.5
Burgess 2014[a] (54)	Biomet	4	NA	84.6[b]	48[b]	NA	Mean 46.3	Mean 46.3
Dowgierd 2022[a] (55)	NA	5	5	60	16.4	Direct	NA	NA
Gerbino 2016[a] (56)	Biomet	6	10	33	43.5	12, 18	Mean 46, 108	Mean 74
Giannakopoulos 2012 (73)	Biomet	288	442	89	41.4	36	36	36
Gonzalez-Perez 2016[a] (57)	Biomet	52	68	66.7[b]	52.6	3, 6, 12, 24, 36	3, 6, 24, 36	NA
Gonzalez-Perez 2019 (74)	Biomet	70	91	65	52	3, 6, 12, 24, 36, 60	3, 6, 24, 36, 60	NA

Table 1. (e) Demographic data of the patients with stock joints - continued (study I).

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Jones 2011[a] (58)	Biomet	5	9	71[b]	55.7[b]	12	Mean 10.5	NA
Kanatsios 2018 (75)	Biomet	60	67	97	53.5	Median 6 wks, median 5.2 years	Median 6 wks, median 5.2 years	NA
Kanatsios 2022[a] (60)	Biomet	54	60	96	54.15	Median 6 wks, median 5 years	Median 6 wks, median 5 years	NA
Kunjur 2016 (76)	Biomet	18	NA	83	50	Mean 30	Mean 30	NA
Leandro 2013 (22)	Biomet	300	399	40	NA	Direct, 1 wk, 6, 12, 24, 36, 60	1 wk, 1, 6	6, 36
Machoň 2020 (77)	Biomet	45	62	60	40.56	12, 24	12, 24	NA
Machon 2012[a] (62)	Biomet	23	34	83	NA	Direct	Direct	NA
Roychoudhury 2021 (78)	Biomet	41	54	34	25.12	1 wk, mean 31.71	NA	NA
Saeed 2002 (23)	Christensen	50	68	80	38	Mean 43	Mean 43	Mean 43
Sanovich 2014 (20)	Biomet	36	42	100	49.4	Mean 30	Mean 30	Mean 30
Siegmund 2019[a] (69)	Biomet	12	12	92	44	3 days, 3, 6	3 days, 3, 6	NA

Table 1. (f) Demographic data of the patients with stock joints - continued (study I).

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Vorrasi 2023[a] (70)	Biomet	8	12	88	43	Direct	3, 6	NA
Westermark 2010 (79)	Biomet	12	19	75	29	Mean 42, mean 84	NA	NA
Wolford 2003[a] (6)	TMJ Concepts	23	40	96	38.89	Mean 20.8	Mean 20.8	6
Zou 2018 (80)	Biomet	33	38	85	51.5	Mean 21.48	Mean 21.48	Mean 21.48
Zou 2019 (81)	Biomet	35	44	NA	NA	Mean 15.13	Mean 15.13	Mean 15.13
Zou 2021 (82)	NA	27	NA	100	50.5	1, 3, 6, 12	12	12

MMO: maximum mouth opening; NA: not available; PSI: Patient-specific implant; SD: standard deviation; wk: week.

[a]Two-arm studies. [b]Number represents both arms.

8.1.2. Primary outcome - MMO

In a separate analysis of two-arm studies, five studies enabled direct comparison between PSI and stock implants for MD in MMO (Figure 2) (6, 56, 57, 60, 69). At 1.5–3 months postoperatively (84 PSI vs 118 stock patients), the MD favored PSI by 3.82 mm (95% CI −3.51 to 11.15; P = 0.15). At 3–6 months (27 PSI vs 70 stock), the MD was 4.69 mm in favor of PSI (95% CI −6.16 to 15.55; P = 0.20). Neither comparison was statistically significant. Beyond 12 months, a significant improvement in MMO was observed for PSI, with an MD of 5.83 mm between 96 PSI and 135 stock patients (95% CI 1.40 to 10.25; P = 0.025).

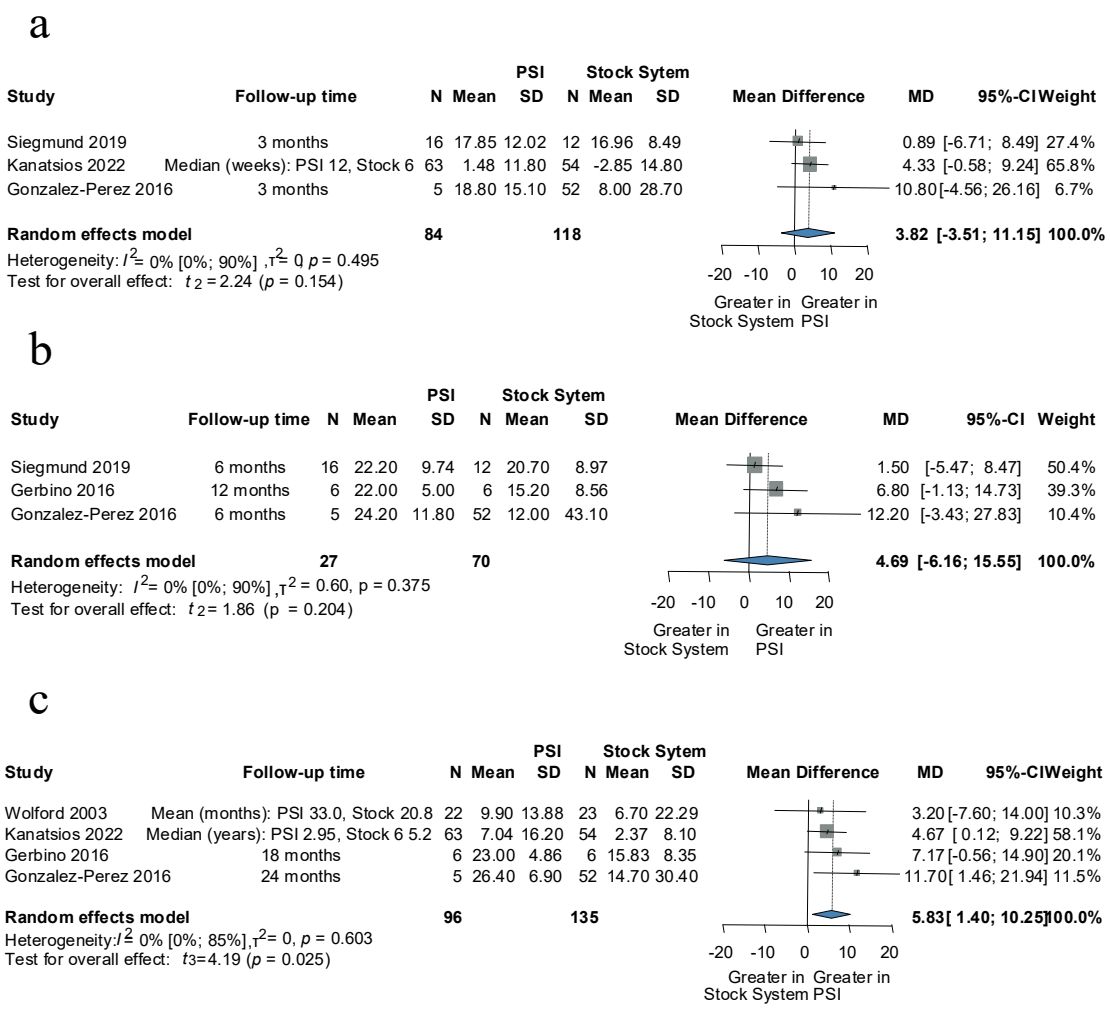


Figure 2. *Forest plots of the MD in MMO between the custom PSI and stock implants, in two-arm studies only: (a) at 1.5–3 months; (b) at 3–12 months; (c) at >12 months.*

CI: confidence interval; MD: mean difference; N: number of patients; PSI: Patient-specific implant; SD: standard deviation.

MD in MMO across all follow-up periods are summarized in Table 2. No analysis was possible for the 1-week to 1-month period due to limited data. Except for the 24–48 month interval, all time points favored PSI, although statistical significance was not reached. Summary plots and the visualization of MMO change are shown in Figure 3 and 4 a.

Table 2. MD in MMO (mm), pain (VAS), and diet (VAS) for all included studies, between custom PSI and stock implants. MD are consistently reported as 'PSI minus stock'.

Outcome	Follow-up	Favouring	MD	95% CI		SE	*z*-value	*P*-value
				Lower	Upper			
MMO	Direct–3 days	Custom	1.05	−2.73	4.83	1.92	0.55	0.59
MMO	6 weeks–3 months	Custom	3.39	−0.41	7.17	1.93	1.75	0.079
MMO	6 months	Custom	3.02	−2.77	8.80	2.95	1.02	0.31
MMO	12 months	Custom	4.16	−2.43	10.75	3.36	1.24	0.22
MMO	12–24 months	Custom	2.02	−4.49	8.53	3.32	0.61	0.54
MMO	24–48 months	Stock	−4.01	−10.71	2.71	3.42	1.17	0.24
MMO	>48 months	Custom	0.52	−14.01	15.05	7.41	0.07	0.94
Pain	Direct–1 week	Stock	−1.23	−2.08	−0.46	0.41	3.09	0.002*
Pain	6 weeks–3 months	Custom	0.63	−0.40	1.67	0.53	1.20	0.23
Pain	6–12 months	Custom	0.84	0.01	1.67	0.42	1.97	0.048*
Pain	12–24 months	Custom	1.90	0.28	3.52	0.83	2.29	0.022*
Pain	24–48 months	Stock	−0.05	−0.98	0.88	0.48	0.12	0.91
Pain	>48 months	Stock	−1.17	−3.39	1.05	1.13	1.03	0.30
Diet	6–24 months	Custom	0.96	−0.32	2.24	0.65	1.47	0.14
Diet	>24 months	Stock	−1.12	−2.34	−0.02	0.59	1.99	0.046*

CI: confidence interval; MD: mean difference; MMO: maximum mouth opening; PSI: Patient-specific implant; SE: standard error; VAS: visual analogue scale. *Significant result.

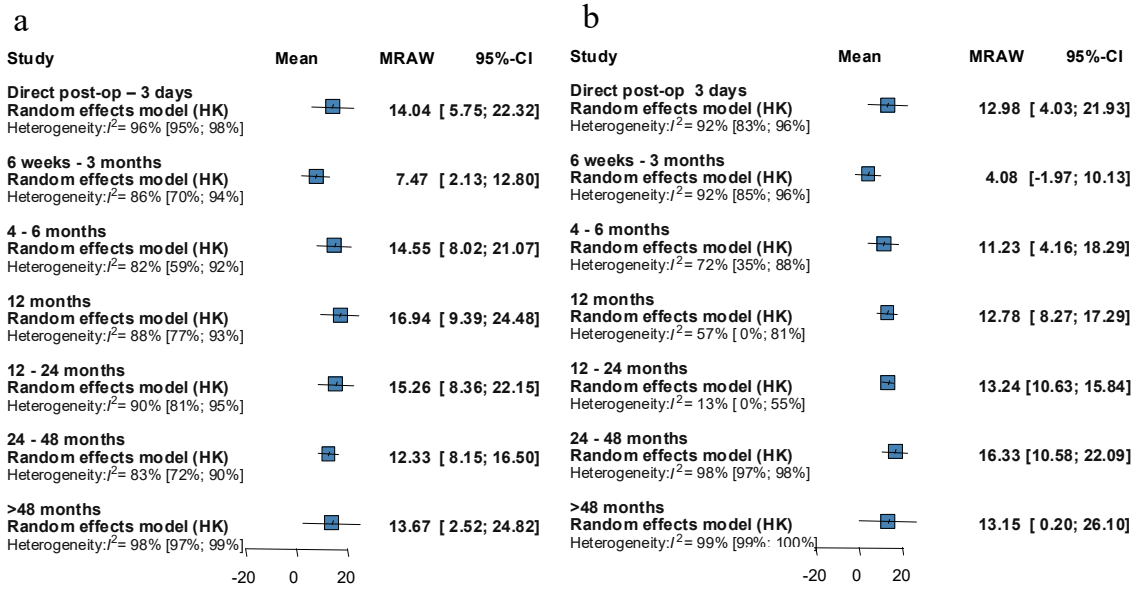


Figure 3. *Summary plots of the change in mean MMO in single-arm and two-arm studies combined, for: (a) custom PSI implants; (b) stock implants.*

CI: confidence interval; HK: Hartung–Knapp adjustment; MRAW: raw mean; PSI: Patient-specific implant.

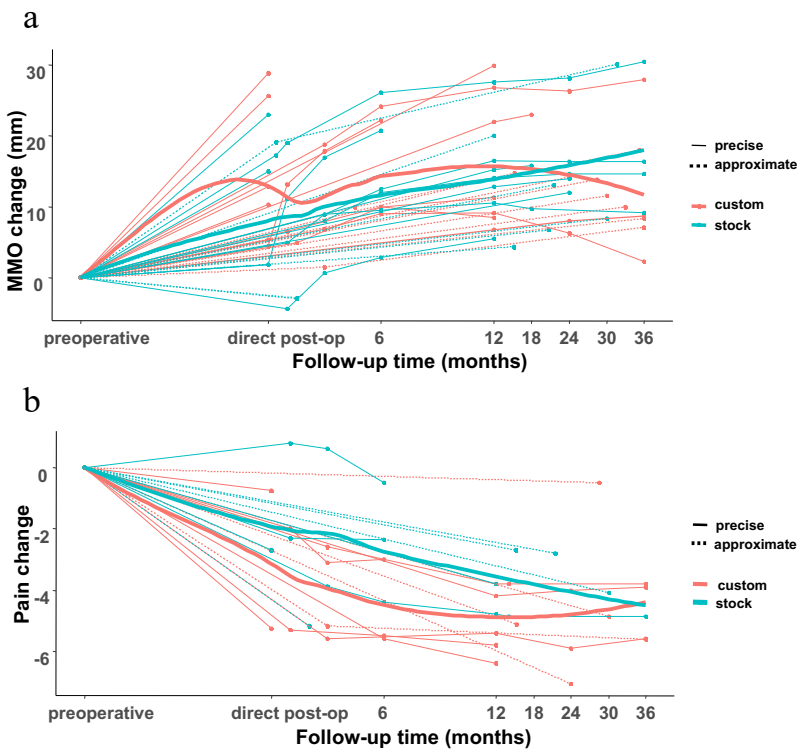


Figure 4. *Visualization of the change in (a) MMO and (b) pain, during follow-up.*

An IPD model assessed the effects of sex, age, and preoperative MMO (Table 3). Male patients showed a significantly greater MMO increase with PSI compared with stock implants (MD 4.99 mm; 95% CI 1.28 to 8.69; P = 0.009), whereas no difference was observed in females. Increasing age was associated with reduced postoperative MMO (−1.01 mm per 10 years; P = 0.015), and higher preoperative MMO predicted a smaller postoperative gain (−4.12 mm per 5 mm increase; P < 0.001).

Table 3. Estimated effects of implant type and patient characteristics on the postoperative change in MMO from the mixed-effects model fitted to individual patient data.

	Estimate	*P*-value	95% CI	
			Lower	Upper
Female	0.35	0.83	−2.78	3.47
Male	4.99	0.009	1.28	8.69
Age: per 10-year increase	−1.01	0.015	−1.82	−0.20
MMO: per 5-mm increase preoperative	−4.12	<0.001	−4.66	−3.58

The first two rows show the estimated difference in MMO between custom and stock implants (including a sex interaction), with positive values favoring custom. The other rows reflect the effects of patient characteristics on the postoperative change in MMO, not implant comparisons. Positive values indicate greater increases in MMO postoperatively and negative values reflect smaller improvements.

8.1.3. Secondary outcomes – pain and diet

Pain was assessed using a 0–10 VAS. Results varied over time, favoring stock implants in the early postoperative period and beyond 24 months, and custom PSI during intermediate follow-up. Statistically significant differences favored stock implants up to 1 week postoperatively (MD −1.23; 95% CI −2.08 to −0.46; P = 0.002), while PSI showed significantly lower pain at 6–12 months (MD 0.84; 95% CI 0.01 to 1.67; P = 0.048) and 12–24 months (MD 1.90; 95% CI 0.28 to 3.52; P = 0.022) (Table 2) also visualized in Figure 4 b.

In a separate analysis of eight two-arm studies, direct comparisons of pain between PSI and stock implants showed no statistically significant differences (6, 54, 56, 57, 60, 62, 69, 70). Pain favored PSI within the first 3 months (MD 0.62; 95% CI −1.62 to 2.85; P =

0.49) and stock implants beyond 3 months (MD −0.24; 95% CI −0.82 to 0.34; P = 0.36) (Figure 5).

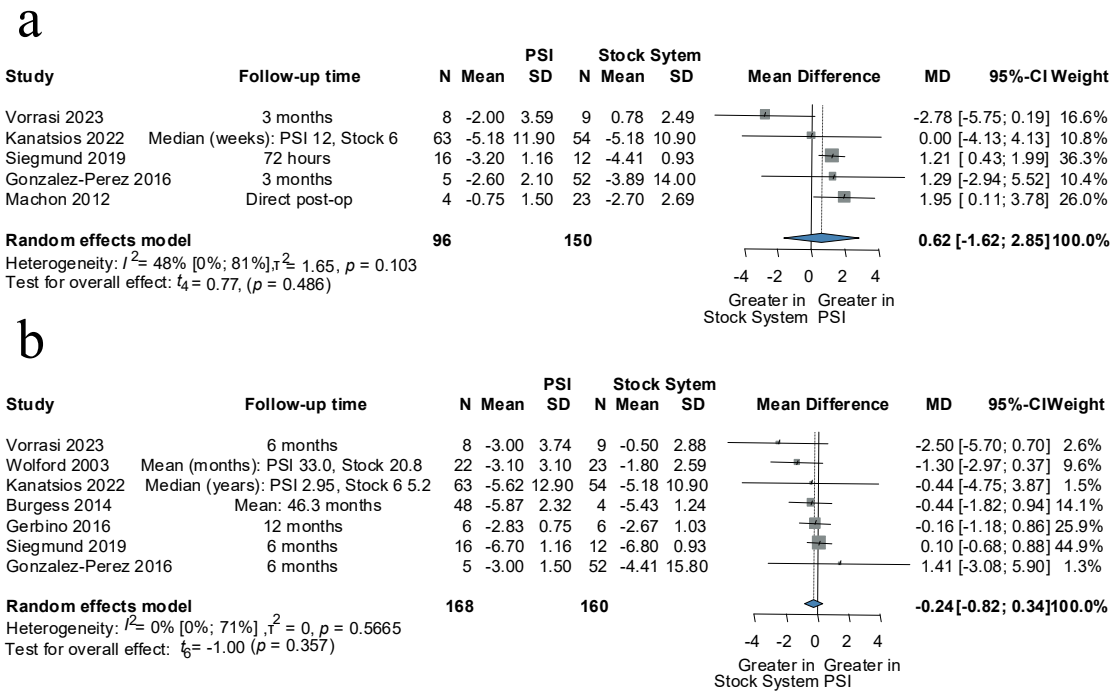


Figure 5. *Forest plots of the mean difference in pain between the custom and stock implants, in two-arm studies only: (a) at <3 months; (b) at >3 months.*
CI: confidence interval; MD: mean difference; N: number of patients; PSI: Patient-specific implant; SD: standard deviation.

Dietary function, assessed on a 0–10 VAS (0 = solid food; 10 = liquid food), showed a non-significant improvement in favor of PSI at 6–24 months (MD 0.96; 95% CI −0.32 to 2.24; P = 0.14). At follow-up beyond 24 months, outcomes significantly favored stock implants (MD −1.12; 95% CI −2.34 to −0.02; P = 0.046).

8.1.4. Risk of bias assessment and quality of evidence

Single-arm studies assessed with the MINORS scale showed mostly moderate risk of bias, mainly due to lack of blinding, absence of prospective sample size calculations, and follow-up losses exceeding 5% in some studies (19, 50, 77). Among the 10 two-arm studies, ROBINS-I indicated predominantly moderate risk of bias, with some serious

risks related to confounding, subjective outcome assessment, and missing data (54, 58, 62). Overall certainty of evidence, assessed using GRADE, was rated as low.

8.2. Study II. - Comparative efficacy of patient-specific versus hand-molded implants in cranioplasty: systematic review and meta-analysis

8.2.1. Study search and selection

Following title and abstract screening of 7,461 records, 902 articles were reviewed in full, resulting in 125 studies meeting the inclusion criteria (Figure 6). Among these, 98 studies reported outcomes for PSI and 69 for HM implants, with overlap across several publications. In total, outcomes from 10,034 patients were included, comprising 6,170 treated with PSI and 3,864 with HM implants. Baseline patient and study characteristics are summarized in Table 4 (a-g).

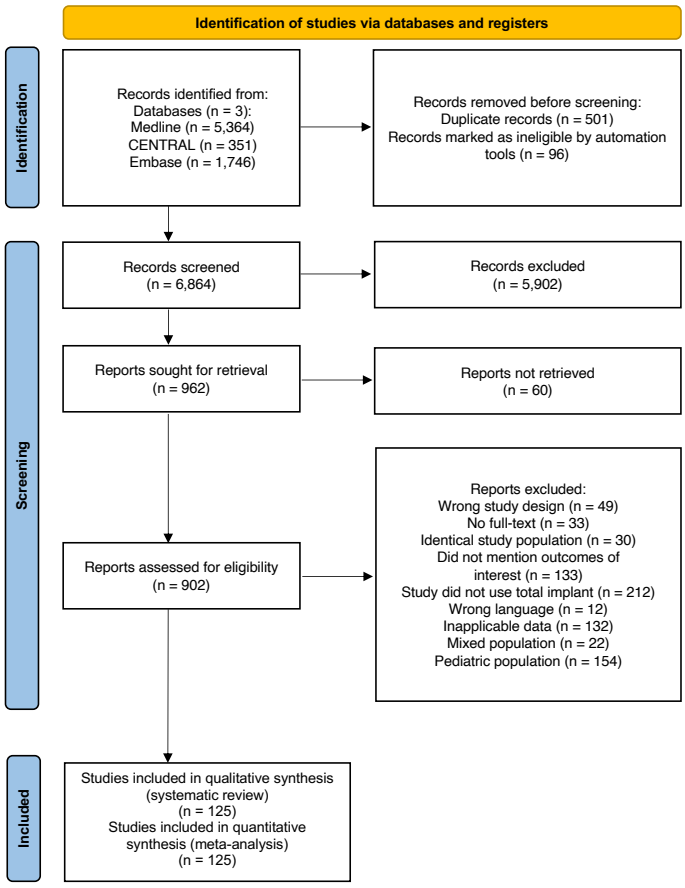


Figure 6. *PRISMA 2020 flowchart representing the study selection process (study II).*

Table 4. (a) Demographic data of the patients (study II).

First author and Year	Country	Patient number and Material	Reported outcomes for Meta-Analysis		
			Postoperative Complications	Surgery time	Cosmetic Score
Akan et al. 2010 (83)	Turkey	10[a], 7[b] PMMA	Yes	No	No
Alawi et al. 2024 (84)	Oman	28 AB; 14 PEEK	Yes	No	No
Alves Junior et al. 2018 (7)	Brazil	11 AB; 3[a], 5[b] PMMA	Yes	Yes	No
Amin et al. 2024 (85)	Bangladesh	11 PEEK	Yes	No	No
Anele et al. 2024 (86)	Nigeria	8[b] Ti	Yes	No	No
Anto et al. 2019 (87)	India	72 AB	Yes	No	No
Ashraf et al. 2022 (88)	Pakistan	10[a] PMMA	Yes	No	Yes
Baldia et al. 2022 (89)	India	46[a], 24[b] PMMA	Yes	No	Yes
Basu et al. 2021 (90)	India	10[a] PMMA	Yes	Yes	No
Bianchi et al. 2019 (91)	Italy	6 PEEK	Yes	Yes	No
Binhammer et al. 2020 (9)	Canada	23[a], 25[b] Ti; 26[a] PMMA; 13 AB; 11 PEEK	Yes	Yes	No
Brandicourt et al. 2017 (92)	France	37 PEEK	Yes	No	Yes
Brie et al. 2013 (93)	France	8[a] HA	Yes	Yes	No
Cabraja et al. 2009 (94)	Germany	26[a] Ti	Yes	Yes	No
Caro-Osorio et al. 2013 (95)	Mexico	26[a] PMMA	Yes	Yes	No
Champeaux et al. 2019 (96)	France	19[a] Ti	Yes	No	No
Chen et al. 2015 (97)	Taiwan	7[a] Ti	Yes	Yes	No
Chen et al. 2018 (98)	China	57[a] HA	Yes	No	No
Cheng et al. 2008 (99)	Taiwan	52 AB; 23[b] PMMA	Yes	No	No

Table 4. (b) Demographic data of the patients - continued (study II).

First author and Year	Country	Patient number and Material	Reported outcomes for Meta-Analysis		
			Postoperative Complications	Surgery time	Cosmetic Score
Cheng et al. 2018 (100)	Taiwan	10[a] PMMA	Yes	Yes	No
Clynch et al. 2023 (101)	United Kingdom	12[a], 4[b] PMMA; 4[a], 10[b] Ti; 2[a] HA	Yes	No	No
Couldwell et al. 1994 (102)	USA	25 PP	Yes	No	No
Csámer et al. 2023 (103)	Hungary	52[a] PMMA	Yes	No	No
Da Silva Júnior et al. 2021 (104)	Brazil	16[a] PMMA	Yes	No	No
Desai et al. 2019 (105)	India	30[a] PMMA	Yes	Yes	Yes
Di Rienzo et al. 2021 (106)	Italy	4[a], 9[b] Ti; 9[a] PMMA; 5[b] HA; 21 PEEK	Yes	No	No
Duric et al. 2019 (107)	Croatia	29[a] PMMA	Yes	Yes	Yes
Eom et al. 2020 (108)	South Korea	19[b] Ti	Yes	No	No
Eufinger et al. 1998 (109)	Germany	22[a] Ti	Yes	No	No
Fong et al. 2015 (110)	USA	13 AB	Yes	No	No
Fountain et al. 2021 (111)	United Kingdom	35 AB; 17 PEEK; 8 PP	Yes	Yes	No
Francaviglia et al. 2017 (112)	Italy	10[a] Ti	Yes	No	No
Ganau et al. 2020 (113)	France	92[a] HA; 89[a] PMMA	Yes	No	No
Giese et al. 2019 (114)	Germany	67[a] PMMA	Yes	No	Yes
Gilardino et al. 2015 (115)	Canada	7 PEEK	Yes	No	No
Goh et al. 2010 (116)	Taiwan	31[a] PMMA	Yes	No	No
Hamböck et al. 2020 (117)	Austria	119 AB; 37[b] PMMA	Yes	No	No
He et al. 2022 (118)	China	104 PEEK	Yes	No	No

Table 4. (c) Demographic data of the patients - continued (study II).

First author and Year	Country	Patient number and Material	Reported outcomes for Meta-Analysis		
			Postoperative Complications	Surgery time	Cosmetic Score
Heissler et al. 1998 (119)	Germany	15[a] Ti	Yes	No	No
Hoffmann et al. 2005 (120)	Germany	15[a] Ti	Yes	Yes	No
Honeybul et al. 2012 (121)	Australia	156 AB	Yes	No	No
Hosameldin et al. 2021 (122)	Egypt	33 PEEK; 33[b] HA	Yes	Yes	Yes
Huang et al. 2015 (123)	USA	20[a] PMMA	Yes	No	No
Iaccarino et al. 2015 (124)	Italy	31 AB; 50[a] HA; 13[a] PMMA; 2 PEEK	Yes	No	No
Inoue et al. 1995 (125)	Japan	8 AB	Yes	No	No
Iratwar et al. 2024 (126)	India	10[a] PMMA	Yes	Yes	No
Jaberi et al. 2013 (127)	USA	70[a] PMMA	Yes	No	No
Jin et al. 2016 (128)	China	39[a] Ti	Yes	Yes	No
Jonkergouw et al. 2016 (129)	Netherlands	38 PEEK	Yes	Yes	No
Kim et al. 2012 (130)	South Korea	16[a] PMMA	Yes	Yes	No
Kim et al. 2018 (131)	South Korea	45 AB; 31[a] Ti; 32 PP	Yes	Yes	Yes
Kim et al. 2023 (132)	South Korea	35[a] Ti	Yes	Yes	No
Kiyokawa et al. 1998 (133)	Japan	12 AB	Yes	No	No
Kohan et al. 2013 (134)	USA	28 AB; 11[b] Ti; 13 PEEK	Yes	Yes	No
KungA et al. 2012 (135)	Taiwan	40[a] Ti	Yes	Yes	No
KungB et al. 2012 (136)	Taiwan	9[b] PMMA	Yes	Yes	No
Kwiecien et al. 2018 (137)	USA	36 AB; 130[b] Ti	Yes	No	No
Lee et al. 2009 (138)	Taiwan	91 AB; 17[a] , 23[b] PMMA	Yes	Yes	No
Lee et al. 2012 (139)	South Korea	118 AB	Yes	Yes	No
Lee et al. 2014 (140)	South Korea	18 AB	Yes	No	No

Table 4. (d) Demographic data of the patients - continued (study II).

First author and Year	Country	Patient number and Material	Reported outcomes for Meta-Analysis		
			Postoperative Complications	Surgery time	Cosmetic Score
Lemée et al. 2013 (141)	France	5 AB; 7[a] HA	Yes	No	No
Lethaus et al. 2014 (142)	Netherlands	16 AB	Yes	Yes	No
Linder et al. 2019 (143)	Sweden	50 CaP-Ti	Yes	No	No
Lindner et al. 2017 (144)	Germany	24[a] Ti; 26[a] HA	Yes	Yes	No
Luo et al. 2012 (145)	China	83[a], 78[b] Ti	Yes	Yes	No
Maenhoudt et al. 2018 (146)	Belgium	16[a] HA	Yes	No	No
Marbacher et al. 2012 (147)	Switzerland	27[a] PMMA	Yes	No	No
Maricevich et al. 2019 (148)	Brazil	63[a] PMMA	Yes	No	No
Marlier et al. 2017 (149)	France	23 PP	Yes	No	No
Matsuno et al. 2006 (150)	Japan	54 AB; 3[a], 55[b] PMMA; 77[a] Ti	Yes	No	No
Moellmann et al. 2022 (1)	Germany	39 PEEK	Yes	Yes	No
Moles et al. 2018 (151)	France	44 AB; 48[a] HA	Yes	Yes	Yes
Morales-Gómez et al. 2018 (152)	Mexico	22[a] PMMA	Yes	Yes	No
Moreira-Gonzalez et al. 2003 (153)	USA	312 AB; 58[b] HA; 75[b] PMMA	Yes	No	No
Morina et al. 2011 (154)	Kosovo	75 AB	Yes	No	No
Morton et al. 2016 (155)	USA	532 AB; 151 PEEK; 23 PP	Yes	No	No
Moser et al. 2017 (156)	Switzerland	17[a] PMMA	Yes	Yes	No

Table 4. (e) Demographic data of the patients - continued (study II).

First author and Year	Country	Patient number and Material	Reported outcomes for Meta-Analysis		
			Postoperative Complications	Surgery time	Cosmetic Score
Mrad et al. 2017 (157)	Canada	10 AB; 9 PEEK	Yes	Yes	No
Nagarjuna et al. 2015 (158)	India	5[a] Ti	Yes	No	No
Ng et al. 2014 (159)	Singapore	7[b] PMMA; 5[b] Ti; 12 PEEK	Yes	Yes	No
Nguyen et al. 2021 (160)	Vietnam	35[a] Ti	Yes	No	No
O Reilly et al. 2015 (161)	USA	19 PEEK	Yes	No	No
Ou et al. 2019 (162)	China	107 AB; 136[b] PMMA	Yes	No	No
Pfnür et al. 2024 (163)	Germany	25 AB; 35 PEEK; 2[a] HA; 21 CaP-Ti	Yes	Yes	No
Piitulainen et al. 2015 (164)	Finland	20 AB; 31[b] HA; 11[b] PMMA	Yes	No	No
Policicchio et al. 2020 (165)	Italy	10[a], 13[b] Ti	Yes	Yes	Yes
Pöppe et al. 2022 (166)	Austria	14[a] PMMA	Yes	Yes	No
Rammos et al. 2015 (167)	USA	11 PEEK	Yes	No	No
Ridwan-Pramana et al. 2019 (168)	Netherlands	16[a] PMMA	Yes	No	No
Rosenthal et al. 2014 (169)	Israel	65 PEEK	Yes	No	No
Rosinski et al. 2020 (170)	USA	21 PEEK; 61[b] Ti	Yes	Yes	No
Rotaru et al. 2012 (171)	Romania	10[a] PMMA	Yes	No	No
Sahoo et al. 2010 (172)	India	11 AB; 6[b] Ti; 5[a] PMMA	Yes	No	No
Sahoo et al. 2019 (173)	India	12 AB	Yes	No	No
Saxena et al. 2023 (174)	India	5 AB; 5[a] Ti; 5 PEEK	Yes	No	No

Table 4. (f) Demographic data of the patients - continued (study II).

First author and Year	Country	Patient number and Material	Reported outcomes for Meta-Analysis		
			Postoperative Complications	Surgery time	Cosmetic Score
Schoekler et al. 2014 (175)	Austria	45 AB	Yes	No	No
Schön et al. 2021 (176)	Switzerland	16[a] PMMA	Yes	Yes	No
Sharavanan et al. 2015 (177)	India	29[a] PMMA	Yes	No	No
Shay et al. 2020 (178)	USA	55[a] PMMA	Yes	No	No
Shi et al. 2023 (179)	China	89[b] Ti; 66 CaP-Ti	Yes	No	No
Soto et al. 2022 (180)	USA	27 AB	Yes	No	No
Splavski et al. 2022 (181)	Croatia	5[a] PMMA	Yes	Yes	No
Staffa et al. 2007 (182)	Italy	25[a] HA	Yes	Yes	No
Stefini et al. 2015 (183)	Italy	2489[a] HA	Yes	No	No
Stieglitz et al. 2014 (184)	Switzerland	28[a] PMMA	Yes	No	No
Sun et al. 2019 (185)	China	207[a] Ti	Yes	No	No
Sundseth et al. 2013 (186)	Norway	13 PP	Yes	Yes	No
Tehli et al. 2023 (187)	Turkey	26[a] Ti	Yes	No	No
Tel et al. 2021 (188)	Italy	7[a] PMMA	Yes	No	No
Thien et al. 2015 (189)	Singapore	24 PEEK; 108[a] Ti	Yes	No	No
Unterhofer et al. 2017 (190)	Austria	46[a] PMMA	Yes	No	Yes
Van Gool et al. 1985 (191)	Netherlands	45[a] PMMA	Yes	No	No
Vargo et al. 2020 (192)	USA	11 PEEK; 10[b] Ti	Yes	No	No
Velnar et al. 2022 (193)	Slovenia	12[b] PMMA	Yes	No	No
Vince et al. 2018 (194)	Germany	221 AB; 65[b] PMMA	Yes	No	No

Table 4. (g) Demographic data of the patients - continued (study II).

First author and Year	Country	Patient number and Material	Reported outcomes for Meta-Analysis		
			Postoperative Complications	Surgery time	Cosmetic Score
Vlok et al. 2018 (195)	South Africa	30[a] PMMA	Yes	No	No
Wang et al. 2012 (196)	China	23 PP	Yes	No	No
Wesp et al. 2022 (197)	Germany	43[a] PMMA; 39 CaP-Ti	Yes	No	No
Williams et al. 2015 (198)	United Kingdom	149[a] Ti	Yes	No	No
Yao et al. 2022 (199)	China	106 PEEK; 105[b] Ti	Yes	Yes	No
Yoon et al. 2021 (3)	South Korea	40[a] Ti	Yes	Yes	No
Zegers et al. 2017 (200)	Netherlands	8[a] Ti; 21 PEEK	Yes	No	Yes
Zhang et al. 2015 (201)	China	8[a] Ti	Yes	No	No
Zhang et al. 2018 (202)	China	75 PEEK; 110[b] Ti	Yes	Yes	No
Zoli et al. 2020 (203)	Italy	84[a], 59[b] PMMA	Yes	No	No

a: Patient-specific implant; b: Hand-molded; NA: Not available; PMMA: Polymethylmethacrylate; AB: Autologous Bone; PEEK: Polyetheretherketone; Ti: Titanium; HA: Hydroxyapatite; PP: Porous polyethylene; CaP-Ti: Calcium Phosphate-Titanium.

8.2.2. Primary outcomes – implant removal and SSI

Eight comparative two-arm studies evaluated implant removal rates between PSI and HM implants, with material-specific subgroup analyses for titanium (Ti) and PMMA (Figure 7) (7, 83, 89, 101, 106, 145, 165, 203). Among 101 PSI and 110 HM Ti implants, the OR for removal was 0.34 in favor of PSI (95% CI 0.11–1.03; P = 0.053). In PMMA implants (155 PSI vs 99 HM), the OR was 0.56 (95% CI 0.21–1.54; P = 0.188), indicating fewer removals with PSI, although neither comparison reached statistical significance. One-arm analyses (Figure 8 a) showed consistently lower explantation probabilities for PSI compared with HM implants of the same material. Across all studies, PSI was associated with reduced postoperative removal risk, particularly for Ti. In pooled analyses, CaP–Ti and hydroxyapatite PSI had the lowest explantation rates (<6%), whereas HM PMMA showed the highest rate (14.2%).

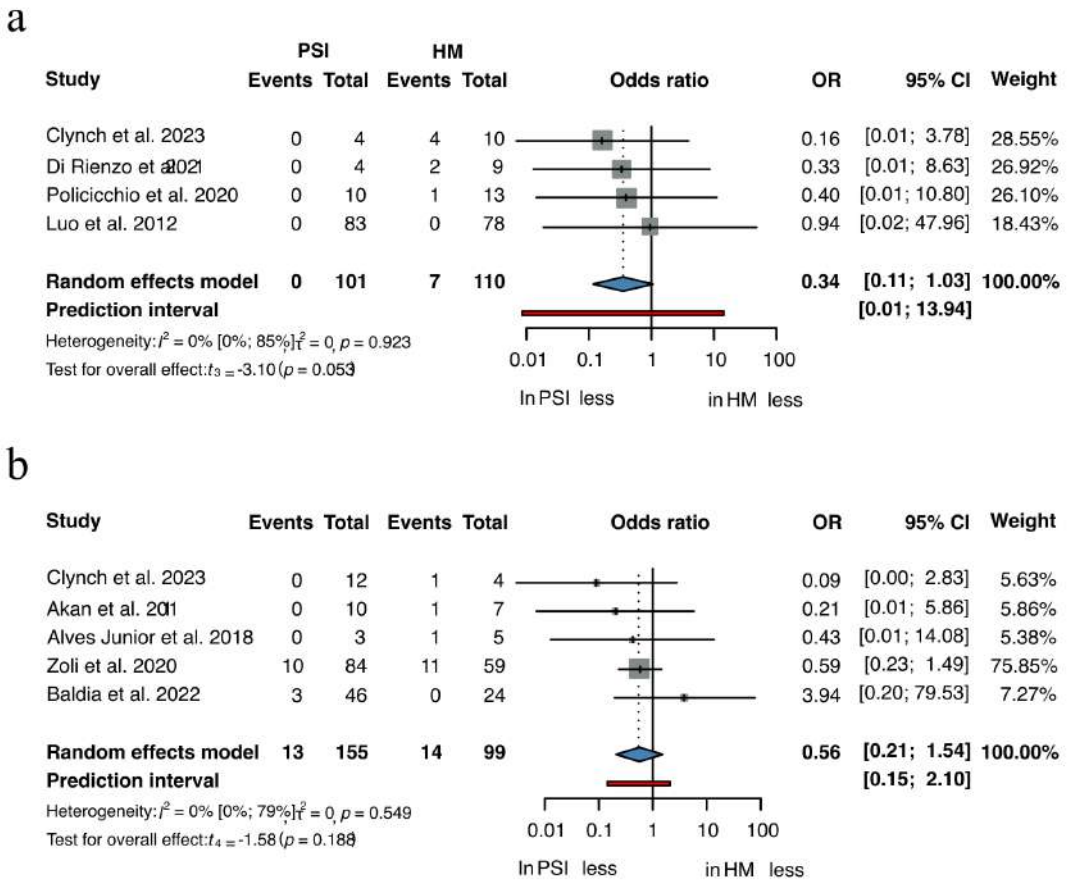


Figure 7. *Removal of (a) Titanium and (b) PMMA implants across all two-arm studies. PSI: Patient-specific Implant; HM: Hand-molded; PMMA: Polymethylmethacrylate; OR: Odds ratio.*

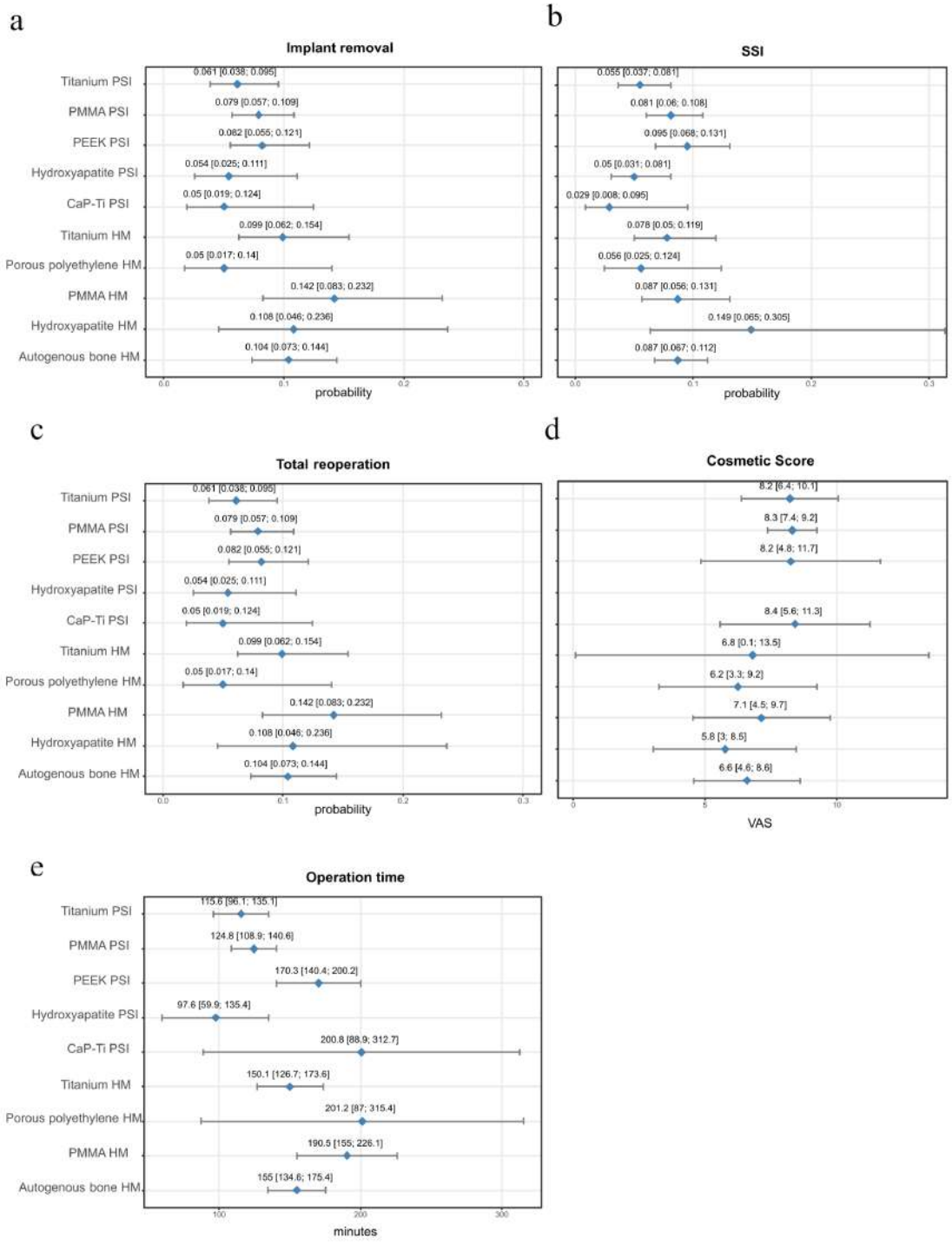


Figure 8. *Visualized Meta-Regression estimates with 95% CI for implant materials. None of the single-arm analyses reached statistical significance. (a) Implant removal; (b) SSI; (c) Total re-operation; (d) Cosmetic Score; (e) Operation time. PSI: Patient-specific implant; HM: Hand-molded; SSI: Surgical Side Infection; CI: Confidence Interval; VAS: Visual Analogue Scale; PMMA: Polymethylmethacrylate; PEEK: Polyetheretherketone; CI: Confidence Interval.*

SSI was directly compared in ten studies, with material-based subgroup analyses shown in Figure 9 (7, 83, 89, 101, 106, 138, 145, 150, 165, 203). For Ti implants (101 PSI vs 110 HM), the OR for SSI was 0.89 (95% CI 0.31–2.57; P = 0.757), while in PMMA implants (175 PSI vs 199 HM) the OR was 0.88 (95% CI 0.31–2.44; P = 0.762). Although differences were not statistically significant, point estimates slightly favored PSI. One-arm SSI analyses (Figure 8 b) demonstrated variability by material, with CaP–Ti, hydroxyapatite, and Ti PSI showing infection rates below 6%. PMMA and PEEK PSI showed rates between 8.1% and 9.5%. Among HM implants, autologous bone (AB) and PMMA had infection rates of 8.7%, while hydroxyapatite exhibited the highest rate (14.9%).

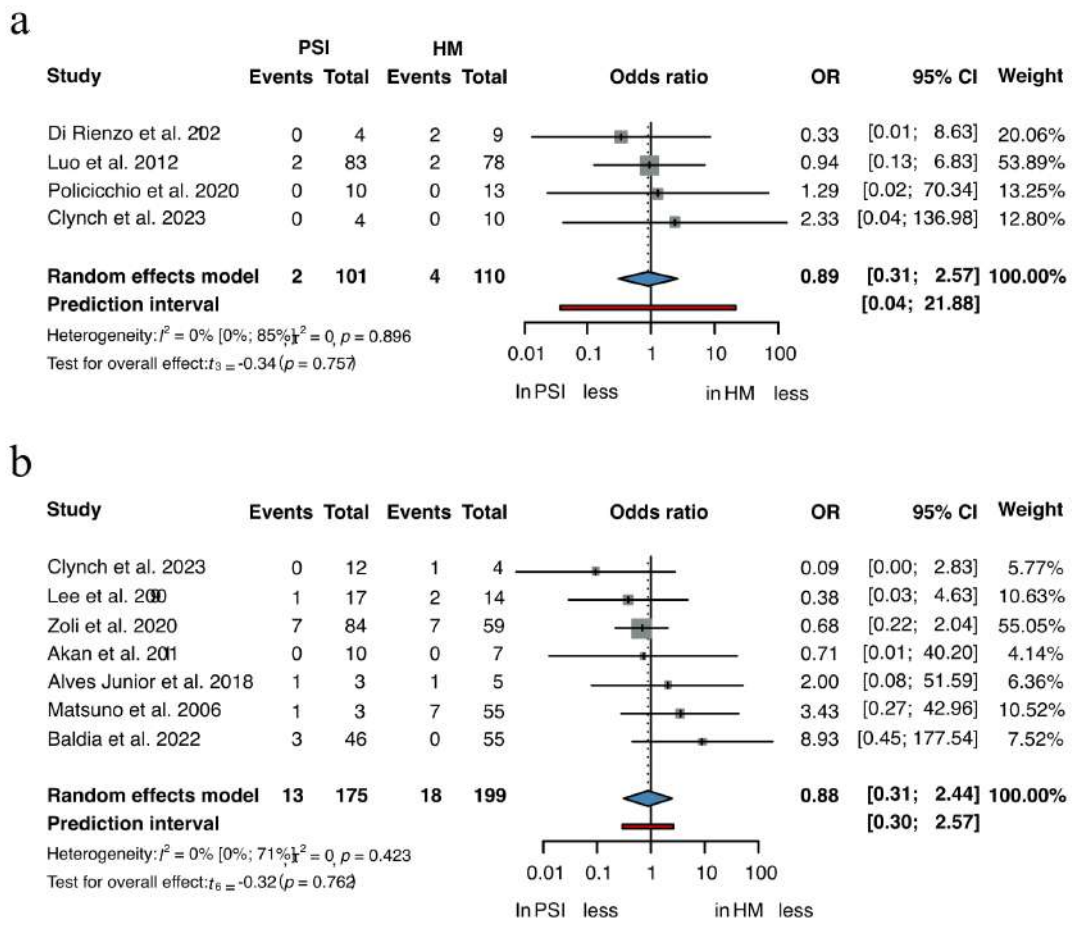


Figure 9. *SSI of (a) Titanium and (b) PMMA. PSI: Patient-specific implant; HM: Hand-molded; SSI: Surgical Side Infection; PMMA: Polymethylmethacrylate; OR: Odds ratio.*

8.2.3. Secondary outcomes – total reoperation, operation time, cosmetic score and implant price

Results of the one-arm analyses for total reoperations are summarized in Figure 8 c. Across most materials, PSI implants were associated with lower reoperation rates than HM implants. The lowest rates among PSI were observed for CaP–Ti (4.7%) and hydroxyapatite (6.7%), while higher rates were noted for PEEK (10.6%) and PMMA (10.8%). Among HM implants, reoperation rates were approximately 11% for hydroxyapatite, AB, and PMMA, with Ti showing the highest rate (12.6%).

Cosmetic outcomes assessed using a 0–10 VAS are summarized in Figure 8 d. PSI implants consistently achieved higher aesthetic scores than HM implants, with mean values ranging from 8.2 to 8.4 across materials. HM implants generally scored between 5.8 and 7.1, indicating lower patient satisfaction. The largest difference was observed for PMMA, where PSI reconstructions averaged approximately 8.3 compared with about 7.1 for HM. Although absolute differences were modest (~1.2 VAS points), this improvement represents a clinically meaningful shift toward near-optimal esthetic outcomes in CP.

Pooled operation times by material are presented in Figure 8 e. Procedures using PSI implants were consistently shorter than those using HM implants. Mean operative times for PSI ranged from 98 minutes for hydroxyapatite to 201 minutes for porous polyethylene, with Ti and PMMA averaging 116 and 125 minutes, respectively. In contrast, HM implants required longer times, averaging 151 minutes for Ti, 156 minutes for AB, and nearly 191 minutes for PMMA. Overall, PSI use reduced surgical duration by approximately 35–65 minutes compared with HM implants, particularly for Ti and PMMA.

Reported implant costs are summarized in Table 5 and varied widely by material and implant type. Among PSI implants, PEEK was the most expensive (approximately USD 14,414–27,902), followed by Ti (USD 5,627–7,858), while PMMA was considerably less costly (USD 398–5,565). HM Ti implants were reported at lower costs, ranging from USD 2,143 to 2,893.

Table 5. CP implant price in USD.

Study	Mean Implant Price in USD
PEEK (PSI)	
Brandicourt et al. 2017	14921.47
Mrad et al. 2017	27902.64
O Reilly et al. 2015	14414.09
Zhang et al. 2018	23810.20
PMMA (PSI)	
Caro-Osorio et al. 2013	1267.86
Ganau et al. 2020	5565.59
Morales-Gómez et al. 2019	398.48
Pöppe et al. 2021	447.67
Titanium (PSI)	
Cabraja et al. 2009	7339.70
Kim et al. 2018	5627.82
Policicchio et al. 2020	7858.36
Titanium (HM)	
Policicchio et al. 2020	2143.19
Zhang et al. 2018	2893.81

PSI: Patient-specific implant; HM: Hand-molded; PMMA: Polymethylmethacrylate; PEEK: Polyetheretherketone; USD: US-Dollar.

8.2.4. Risk of bias assessment and quality of evidence

Risk of bias in single-arm studies was assessed using the MINORS tool and was generally low to moderate, largely reflecting unblinded outcome assessment, lack of prospective sample size justification, and follow-up attrition above 5% in several studies. The ten two-arm studies were appraised with ROBINS-I and were mostly judged to have a moderate risk of bias, although some demonstrated serious concerns related to confounding, subjective outcome measures, and incomplete data. The lone randomized controlled trial, evaluated with the ROB2 tool, raised some concerns due to missing outcome data.

Certainty of evidence for the two-arm studies was evaluated using the GRADE framework and was rated as low overall.

9. DISCUSSION

9.1. Personalized medicine in maxillofacial reconstruction: The role of PSI

This thesis investigated the implications of personalized medicine in maxillofacial surgery, with a particular focus on the clinical performance of PSI in CP and TMJ reconstruction. By synthesizing evidence from two large systematic reviews and meta-analyses, the present work provides a comprehensive overview of how customization influences surgical efficiency, functional outcomes, complication profiles, and clinical decision-making in complex cranio-maxillofacial reconstructions.

In CP, the findings consistently demonstrated that PSI are associated with favorable perioperative and postoperative trends when compared with HM implants. Across a large and heterogeneous patient population, PSI showed reduced implant removal rates, fewer total reoperations, and markedly shorter operative times across most materials, including Ti and PMMA. These advantages appear to stem primarily from the improved anatomical fit and preoperative planning inherent to PSI fabrication, which reduces intraoperative manipulation and technical uncertainty (83). Cosmetic outcomes also consistently favored PSI, underscoring the relevance of personalized reconstruction for patient satisfaction and psychosocial rehabilitation following cranial defect repair. Importantly, infection rates did not differ significantly between PSI and HM implants across most materials, suggesting that customization alone does not increase infectious risk. Instead, material properties and patient-related factors appear to play a more decisive role. Notably, CaP-Ti and hydroxyapatite PSI demonstrated the lowest explantation and reoperation probabilities, highlighting the potential synergy between personalization and biologically favorable materials (163).

In contrast, the analysis of TMJ reconstruction revealed a more nuanced and indication-dependent role for personalization. While patient-specific TMJ implants did not demonstrate universal superiority over stock systems, they showed a consistent trend toward improved MMO, reaching statistical significance beyond 12 months in direct comparative studies. This finding suggests that anatomical customization may be particularly beneficial for restoring joint biomechanics and long-term mobility, especially

in patients with severe deformities or restricted preoperative function. Pain and dietary outcomes after TMJ replacement displayed a time-dependent pattern. Stock implants were associated with greater immediate postoperative pain relief and improved long-term dietary outcomes, whereas PSI were favored during intermediate follow-up periods. These mixed results indicate that the benefits of personalization in TMJ reconstruction are not uniform across all clinical endpoints and should be interpreted within the context of patient characteristics, surgical goals, and functional priorities.

Taken together, the findings of this thesis support the concept that personalized medicine in maxillofacial surgery offers its greatest value in anatomically complex reconstructions, where precision, implant fit, and biomechanical alignment are critical. In CP, PSI appear to provide consistent advantages across efficiency, durability, and esthetic outcomes. In TMJ reconstruction, personalization offers selective benefits while stock systems remain a valid and effective option for pain control and cost-conscious care.

Overall, these results reinforce the notion that PSI should not be viewed as a universal replacement for conventional systems, but rather as a targeted strategy within a personalized treatment algorithm. The integration of PSI into maxillofacial surgery represents a meaningful step toward individualized care, provided that implant selection is guided by evidence, patient-specific anatomy, and clearly defined clinical objectives.

9.2. International comparison, guidelines, and evidence from previous meta-analyses

The global adoption of PSI in maxillofacial surgery reflects a broader shift toward personalized medicine. However, international evidence remains heterogeneous, and current guidelines have not yet fully endorsed customization as a universal standard of care. Both TMJ replacement and CP illustrate the complex interplay between technological innovation, clinical outcomes, patient selection, and healthcare system constraints.

9.2.1. International evidence and guideline perspectives in TMJ replacement

Despite substantial technological advances in computer-aided design and manufacturing, international studies have not conclusively demonstrated the superiority of patient-specific TMJ implants over conventional stock systems. This finding is consistent across several single-center cohort studies and systematic reviews, which report comparable functional and patient-reported outcomes despite increased costs and preoperative planning requirements associated with PSI (12, 56, 57). Consequently, guidelines acknowledge the availability of both customized and stock systems but refrain from recommending one implant type over the other as a universal solution (204). One of the principal challenges in interpreting international TMJ replacement data lies in the broad heterogeneity of surgical indications. Across studies, TMJ replacement has been performed for conditions ranging from inflammatory arthritis and ankylosis to congenital deformities such as hemifacial microsomia and oncologic resections. This diagnostic diversity introduces substantial selection bias and complicates direct comparisons between implant systems (28, 52, 53, 66). Although the Wilkes classification is widely accepted for grading internal TMJ derangement, its inconsistent application across studies limits its usefulness as a unifying stratification tool. Even when authors restricted inclusion to advanced disease stages (Wilkes IV–V), substantial variability in disease severity and patient characteristics persisted, resulting in non-significant differences between implant types in multiple comparative analyses (60, 69). Beyond diagnosis, international data consistently highlight the influence of patient-specific factors on postoperative outcomes. Age-related decline in healing capacity, sex-related differences in joint pathology, and baseline functional status, particularly preoperative MMO, emerge as critical determinants of surgical success (59). Our IPD analyses demonstrate that younger patients and those with more restricted preoperative MMO derive greater functional gains, while patients with higher baseline function exhibit limited postoperative improvement regardless of implant type. These findings suggest that personalization in TMJ reconstruction may be most effective when applied selectively to patients with severe anatomical or functional compromise rather than as a routine alternative to stock implants. Complication profiles reported internationally further emphasize the difficulty of drawing definitive conclusions. Previous meta-analyses indicate that facial nerve dysfunction, sensory disturbances, heterotopic bone formation,

and infection occur at comparable rates in custom and stock systems (205). However, patient demographics and surgical history often differ significantly between groups. Studies reporting higher complication rates in stock implants frequently included older patients and individuals with multiple prior surgeries, confounding implant-related interpretations (60). Although reduced operative time is frequently cited as an advantage of PSI, inconsistent reporting standards and variability in surgical expertise have thus far precluded robust statistical confirmation.

9.2.2. International evidence and guideline perspectives in CP

International evidence and previous meta-analyses in CP demonstrate that, although PSI require greater preoperative planning and higher initial costs, their clinical performance is strongly influenced by material properties, surgical factors, and patient-related variables rather than customization alone (101, 162, 193, 203). Historically, HM PMMA implants have been widely used due to their low cost and immediate intraoperative availability, particularly in resource-limited settings. However, large-scale analyses increasingly associate HM PMMA with higher explantation and reoperation rates, largely attributable to material-specific limitations such as residual monomer toxicity, exothermic polymerization, and intraoperative handling near the dura (83, 138). In contrast, PSI PMMA benefits from controlled industrial manufacturing and improved anatomical fit, resulting in superior outcomes in direct comparisons. Other PSI materials show variable performance: PEEK implants are frequently used in complex, high-risk reconstructions and therefore exhibit relatively higher infection and removal rates, while CaP-Ti and PSI consistently demonstrate lower complication and reoperation probabilities, reflecting their favorable biomechanical stability and osseointegrative potential. Beyond material choice, international meta-analyses highlight the importance of surgical timing, anatomical location, and prior treatments, particularly radiotherapy, which markedly increases postoperative complication risk by impairing tissue healing and vascularity (163). Although early versus delayed CP does not appear to significantly affect overall complication rates, prolonged operative time and extensive intraoperative manipulation remain important risk factors, both of which are reduced by PSI through precise preoperative planning and improved implant fit (206). From a biological perspective, implant–host interaction plays a critical role in long-term success: bioinert

materials such as PEEK lack osseointegration and may predispose implants to migration and infection, CaP-Ti–based and hydroxyapatite implants promote bone ingrowth, neovascularization, and improved stability (163). Economically, while PSI are associated with higher upfront costs, reduced operative time, fewer reoperations, and lower explantation rates may offset these expenses in high-resource healthcare systems, whereas HM techniques continue to offer a viable alternative in settings where affordability and immediate availability are prioritized (145). Overall, international data support a personalized, indication-driven approach to CP, in which implant selection is guided by defect complexity, biological compatibility, patient risk factors, and healthcare system constraints rather than by customization alone.

9.3. Strengths and limitations (study I.)

The main strength of this study is the use of narrow follow-up intervals, which allowed a more detailed assessment of postoperative changes over time. This provided a clearer picture of recovery patterns and differences between patient-specific and stock implants. In addition, this analysis included the largest patient cohort reported to date for TMJ replacement, increasing the robustness of the findings and supporting their relevance to a broad patient population.

Several limitations should be considered. The study population was highly heterogeneous, with a wide range of underlying pathologies that were not consistently classified or graded, limiting comparability between groups. Key outcomes such as pain and diet were based on subjective patient reports, which may introduce reporting bias. Information on postoperative rehabilitation was inconsistently reported, despite its known influence on outcomes. Furthermore, all comparative studies were observational, with no randomized controlled trials available. Differences in baseline characteristics and treatment approaches across studies introduce potential selection bias and confounding, limiting causal interpretation of the results.

9.4. Strengths and limitations (study II.)

The main strength of this study lies in its broad scope and structured methodology. By including all major implant materials and clearly separating PSI from HM implants, the analysis allowed a more transparent comparison than previous reviews. The large dataset represents the most extensive synthesis of CP outcomes to date, supporting the general applicability of the findings across different clinical settings.

However, important limitations remain. The included studies showed substantial heterogeneity in surgical techniques, patient populations, and outcome definitions, which complicates direct comparisons. Most evidence was derived from observational studies, with only one randomized controlled trial available, increasing the risk of bias and limiting the strength of conclusions. In addition, the literature provides limited guidance on how implant choice was made in clinical practice, restricting the ability to draw clear, practice-oriented recommendations.

10. CONCLUSION

This thesis assessed the role of personalized medicine in maxillofacial surgery by evaluating PSI in TMJ replacement and CP. In TMJ replacement, PSI showed a significant long-term improvement in mouth opening beyond 12 months, while pain and dietary outcomes varied over time, with no clear overall superiority of one system. These findings indicate that implant choice should be tailored to individual clinical goals and patient characteristics. In CP, PSI were associated with shorter operative times, fewer reoperations and explantations, and better cosmetic outcomes compared with HM implants. However, as most evidence was observational, these results should be interpreted as associative rather than definitive.

Overall, the findings support personalized medicine as a targeted approach in maxillofacial surgery. PSI offer advantages in selected indications, while conventional systems remain effective in other settings. Careful patient selection is needed to define optimal indications for customization.

11. IMPLICATIONS FOR PRACTICE

11.1. Study I. – Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: systematic review and meta-analysis

Applying research findings in daily clinical practice is essential for improving patient outcomes. The results of this study show that there is no single best implant for all patients undergoing TMJ replacement. Instead, implant selection should be based on the main clinical problem and the individual needs of the patient. For patients with severely limited jaw movement or complex joint anatomy, PSI may be the better option. Their customized design allows for a more accurate fit, improved surgical precision, and better postoperative mouth opening. This makes them particularly suitable when improving joint mobility is the main treatment goal. Stock implants remain an effective and practical alternative, especially when pain relief is the primary concern. They are readily available, less expensive, and can be used without delay, which is important in cases requiring rapid treatment or in settings with limited resources. Both patient-specific and stock implants are effective in restoring chewing ability and meeting dietary needs after surgery.

11.2. Study II. - Comparative efficacy of patient-specific versus hand-molded implants in cranioplasty: systematic review and meta-analysis

The findings of this study suggest that PSI should be preferred when sufficient financial resources and technical infrastructure are available in CP. The customized design of PSI allows for greater intraoperative precision, shorter operative times, and a lower risk of implant-related complications. These advantages are particularly relevant in complex reconstructions, large cranial defects, frontal bone reconstructions with limited soft tissue coverage, and cases where accurate anatomical restoration is essential for both protection and cosmetic outcome. HM implants remain an important and practical alternative in selected situations. They are especially useful for smaller defects, emergency cases, or settings where custom fabrication is not feasible due to time or cost constraints.

12. IMPLICATIONS FOR RESEARCH

12.1. Study I. – Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: systematic review and meta-analysis

The findings of this study highlight several areas where future research is needed to strengthen the evidence base for TMJ replacement. First, greater transparency in patient reporting is essential. Studies should consistently report raw outcome data and use standardized outcome measures to improve comparability and allow more robust secondary analyses. Future research should focus on the further development and direct comparison of personalized TMJ implants, with particular attention to pain control and functional outcomes such as mouth opening and chewing ability. In addition, standardized reporting of patient characteristics, surgical indications, and postoperative rehabilitation protocols would help identify which patient groups benefit most from personalized implant solutions.

12.2. Study II. - Comparative efficacy of patient-specific versus hand-molded implants in cranioplasty: systematic review and meta-analysis

Future research should continue to directly compare patient-specific and HM implants across different materials, while also aiming to define clearer criteria for implant selection in clinical practice. In addition, although materials were analyzed separately in this study, further analyses exploring relationships between different materials may help identify broader patterns in implant performance. Such approaches could support more evidence-based decision-making and contribute to clearer clinical guidelines.

13. IMPLICATIONS FOR POLICY MAKERS

The results of this thesis provide practical guidance for policymakers responsible for healthcare planning, reimbursement, and clinical guideline development in maxillofacial surgery. PSI are an important innovation, but current evidence does not support their routine use in all patients. Policy decisions should therefore focus on selective and justified use rather than broad implementation. Evidence from TMJ replacement and CP indicates that PSI are most beneficial in complex cases, such as large cranial defects, irregular anatomy, or severe functional impairment. Policymakers should ensure that healthcare systems allow clinicians the flexibility to use personalized implants when clearly indicated, while continuing to support conventional implants where outcomes are similar and costs are lower. Reimbursement models based on case complexity rather than implant type alone may help balance clinical benefit with responsible resource use.

The lack of standardized reporting and high-quality comparative studies limits evidence-based decision-making. Policymakers can play an important role by supporting national and international registries that collect uniform data on indications, implant types, complications, and long-term outcomes. Such registries would improve transparency, enable continuous monitoring of implant performance, and support future updates of clinical guidelines.

Cost considerations remain central. Although PSI involve higher upfront expenses, reduced operative time, fewer reoperations, and lower implant removal rates suggest that they may be cost-effective in selected patient groups. Policymakers should encourage health-economic evaluations that consider long-term outcomes and patient quality of life, rather than focusing only on initial implant costs.

Finally, policies that support training in digital planning, interdisciplinary collaboration, and equitable access to personalized technologies are essential. By promoting evidence-based use of PSI and aligning innovation with clinical need, policymakers can help integrate personalized medicine into maxillofacial surgery in a sustainable and patient-centered manner.

14. FUTURE PERSPECTIVES

Personalized medicine is expected to play an increasingly important role in maxillofacial surgery as digital planning, implant design, and biomaterials continue to evolve. Future developments are likely to focus on improving implant biocompatibility, optimizing biomechanical performance, and integrating biological concepts such as osseointegration and tissue regeneration into patient-specific designs. At the same time, advances in imaging, virtual surgical planning, and additive manufacturing will further improve accuracy, reduce operative time, and support more predictable clinical outcomes. An important future direction will be the generation of higher-quality clinical evidence to better define which patients benefit most from personalized approaches. Greater emphasis on cost-effectiveness and value-based care will also be required to ensure that personalized solutions remain sustainable within different healthcare systems.

From a personal perspective, I aim to contribute to this field by combining clinical training with continued scientific research. By starting my residency in oral and maxillofacial surgery, I will gain hands-on experience in complex reconstructive procedures, including TMJ reconstruction and CP. This clinical exposure will allow me to better identify practical challenges, refine research questions, and contribute to studies that bridge the gap between technological innovation and real-world surgical practice. Through this combined clinical and academic pathway, I aim to support the responsible and evidence-based integration of personalized medicine into maxillofacial surgery.

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16. BIBLIOGRAPHY

16.1. Publications Related to the Thesis

1.

Nolden, E-L; Carvalho, B K G; Wenning, A S; Kiss-Dala, S; Hegyi, P; Bródy, A; Rózsa, N K; Végh, D; Köles, L**; Vaszilkó, M**

Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: a systematic review and meta-analysis

INTERNATIONAL JOURNAL OF ORAL AND MAXILLOFACIAL SURGERY (2025)

DOI: 10.1016/j.ijom.2025.06.021

Journal subject: Scopus - Oral Surgery Rank: Q1

Journal subject: Scopus - Otorhinolaryngology Rank: Q1

Journal subject: Scopus - Surgery Rank: Q1

IF: 2.7

2.

Nolden, Elias-Leon; Guimarães Carvalho, Bruna Katherine; Barkovskij-Jakobsen, Katarina Sofia; Wenning, Alexander Schulze; Szentes, Boglárka Lilla; Agócs, Gergely; Németh, Zsolt; Kivovics, Márton; Hegyi, Péter; Köles, László**; Vaszilkó Mihaly**

Comparative Safety and Efficacy of Patient-Specific Versus Hand-Molded Implants in Cranioplasty: A Systematic Review and Meta-Analysis

JOURNAL OF CLINICAL MEDICINE 14 : 24 Paper: 8655 , 21 p. (2025)

DOI: 10.3390/jcm14248655

Journal subject: Scopus - Medicine (miscellaneous) Rank: Q1

IF: 2.9

**Authors are considered as shared Last-Author

16.2. Publications not Related to the Thesis

1.

Carvalho, Bruna Katherine Guimarães; **Nolden, Elias-Leon;** Wenning, Alexander Schulze; Kiss-Dala, Szilvia; Agócs, Gergely; Róth, Ivett; Kerémi, Beáta; Géczi, Zoltán; Hegyi, Péter; Kivovics, Márton

Diagnostic Accuracy of Artificial Intelligence for Approximal Caries on Bitewing Radiographs: A Systematic Review and Meta-analysis

JOURNAL OF DENTISTRY 151 Paper: 105388 , 9 p. (2024)

DOI: 10.1016/j.jdent.2024.105388

Journal subject: Scopus - Dentistry (miscellaneous) Rank: D1

IF: 5.5

2.

Csókay, Gergely; Würsching, Tamás; Szentpéteri, Szófia; **Nolden, Elias-Leon**; Vaszilkó, Mihály; Bogdán, Sándor

Páciensspecifikus implantátumok használata arckoponya-rekonstrukció során

ORVOSI HETILAP 165 : 40 pp. 1594-1600. , 7 p. (2024)

DOI: 10.1556/650.2024.33111

Journal subject: Scopus - Medicine (miscellaneous) Rank: Q4

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Meta-analysis

TMJ

Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: a systematic review and meta-analysis

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E.-L. Nolden, B. K.G. Carvalho, A. S. Wenning, S. Kiss-Dala, P. Hegyi, A. Bródy, N. K. Rózsa, D. Végh, L. Köles, M. Vaszilkó: Comparative efficacy of patient-specific and stock implants in temporomandibular joint replacement: a systematic review and meta-analysis. Int. J. Oral Maxillofac. Surg. 2025; xx: 1–11. © 2025 Published by Elsevier Inc. on behalf of International Association of Oral and Maxillofacial Surgeons.

Abstract. Evidence for the superiority of patient-specific implants (PSI) over stock implants in temporomandibular joint (TMJ) replacement remains inconclusive. The objective of this study was to provide guidance for clinical decisions by evaluating whether PSI offer advantages over stock systems in rehabilitation of the TMJ. A systematic search was performed in three databases to identify studies reporting mouth opening, pain, and diet outcomes for PSI and/or stock TMJ implants. Two-arm studies were analysed separately from pooled single- and two-arm studies; studies with comparable follow-up times were compared. Forty-two observational studies involving 2221 patients were included. PSI showed a consistent trend towards greater mouth opening across most follow-up times; however, a significant difference in favour of PSI was only observed in two-arm studies at > 12 months (mean difference 5.83 mm; $P = 0.025$). Pain outcomes were mixed: stock implants favored early pain and late diet change, while PSI favored pain relief at 6–24 months. The findings suggest PSI should be considered for movement restrictions, while stock implants may provide an alternative for pain and dietary needs. Due to the observational nature of the included studies and differences in study populations across arms, the findings should be interpreted with caution.

Keywords: Temporomandibular joint; Temporomandibular joint disorders; Joint prosthesis; Prostheses and implants; Maxillofacial surgery.

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[1] László Köles and Mihály Vaszilkó contributed equally to this study.

End-stage temporomandibular joint (TMJ) disease manifests through structural changes to the joint, leading to functional impairments such as orofacial pain, difficulties in mastication, and speech issues. Alloplastic TMJ replacement (TMJR), which entails the surgical reconstruction of the condyle and fossa components of the joint, is considered the final therapeutic option for such severe conditions. TMJR is generally recommended for cases including bony ankylosis, unsuccessful previous reconstructions, irreparable damage to the condyle post-trauma, needs following tumour excision, severe inflammatory joint diseases that do not respond to conservative treatments, and congenital–developmental anomalies[1].

The number of TMJR procedures performed continues to increase and is projected to grow by 58% by 2030[2]. Moreover, the field of surgery is currently experiencing rapid technological advancements. These developments have introduced new personalized treatment options such as patient-specific implants (PSI). By merging medical imaging with computer-aided design and manufacturing (CAD/CAM) technologies, a unique implant can be precisely engineered to match the anatomy of the individual patient. This stands in contrast with the traditional stock TMJR systems, where there is a choice of standardized implants[3,4].

While these recent and upcoming technologies aim to improve TMJ implant outcomes, the evidence supporting the superiority of PSI over stock systems in terms of postoperative outcomes is still inconclusive. The current UK National Institute for Health and Care Excellence guidelines on TMJR note that various prosthetic options are available, each differing in long-term safety and efficacy, but they stop short of recommending a specific type[5]. The need for a comprehensive update is underscored by limitations in previous studies, which have lacked differentiation in follow-up times, failed to separate custom from non-custom implants in their analyses, and been constrained by limited datasets.[6–8] Consequently, it is crucial to conduct a new systematic review and meta-analysis to refresh and expand the current understanding of these treatments. The aim of this study was to provide comprehensive insights and an evidence-based analysis to inform clinical decisions in TMJR, evaluating whether PSI offer advantages over stock implants in the rehabilitation of the stomatognathic system.

Materials and methods

The study was performed in accordance with the PRISMA 2020 Statement[9] and followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[10]. The study protocol is registered in PROSPERO (registration number CRD42023479644).

Eligibility criteria

The research question was formulated using the PICO framework, where the population (P) comprised patients undergoing unilateral or bilateral TMJR, the intervention (I) was the use of PSI, the comparison (C) was the use of stock system implants, and the outcomes (O) were maximum mouth opening (MMO), pain, and diet. For an article to be included, it had to report human patients who had received either unilateral or bilateral TMJ implants (total prostheses) from a custom (PSI) or stock system. The article had to evaluate the change in at least one of the outcomes mentioned, over a defined follow-up period. For the most detailed results, no limitation on follow-up time was applied; however, studies including paediatric populations were excluded. To minimize heterogeneity in patient demographics, data from articles reporting two-arm studies were analysed separately. Prospective and retrospective cohort studies that met the inclusion criteria were included. Studies were considered eligible for synthesis if they satisfied the inclusion criteria and reported raw data for any or all outcomes under investigation as per the pre-registered study protocol. However, case reports, smaller case series, conference abstracts, and articles with no original data were excluded from this systematic review. Publications with overlapping populations were excluded; where populations were identical, only the article with the larger sample size was included. Studies involving mixed populations, such as those combining paediatric and adult patients, were also excluded.

Selection process and search strategy

A systematic search was conducted in three databases: MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) on November 5, 2023. No filters or restrictions were applied regarding the date of publication or article type. Although no language filters were applied during the search, articles not available in English, German, or Hungarian were excluded at the full-text review stage. A predefined search key was applied, which is given in Supplementary material Appendix S1. Two independent review authors performed the selection process (E.L.N. as reviewer 1; B.K.G.C. as reviewer 2). Duplicates were removed automatically and manually. The two reviewers then assessed the results for inclusion, first by title and abstract selection and then by full-text evaluation. As agreed beforehand, any conflict was resolved by discussion. To assess inter-reviewer agreement, Cohen's kappa was calculated first following title and abstract selection and then after full-text selection, resulting in $\kappa = 0.97$ and $\kappa = 0.95$, respectively.

Data collection process and data items

The study data were collected independently from the eligible articles by the two reviewers (E.L.N., B.K.G.C.). Disagreements were resolved by discussion between the reviewers. The following data were extracted: (1) study characteristics, including the first author, year of publication, study design, study population (number, age, and sex assigned at birth), study period, study country, institute, diagnosis, implant brand, and follow-up time (in months); (2) MMO; (3) pain; (4) diet. For further details of the data used to assess the outcomes, see Supplementary material Appendix S2.

Assessment of the risk of bias and certainty of the evidence

The two reviewers (E.L.N., B.K.G.C.) independently conducted a risk of bias assessment following the recommendations of the Cochrane handbook, using the ROBINS-I[10] and MINORS[11] tools. Any disagreements were resolved through discussion between the authors. The certainty of the evidence was evaluated using the GRADE assessment, following the GRADE handbook guidelines [12], and performed using the online software GRADEpro GDT version 20[13].

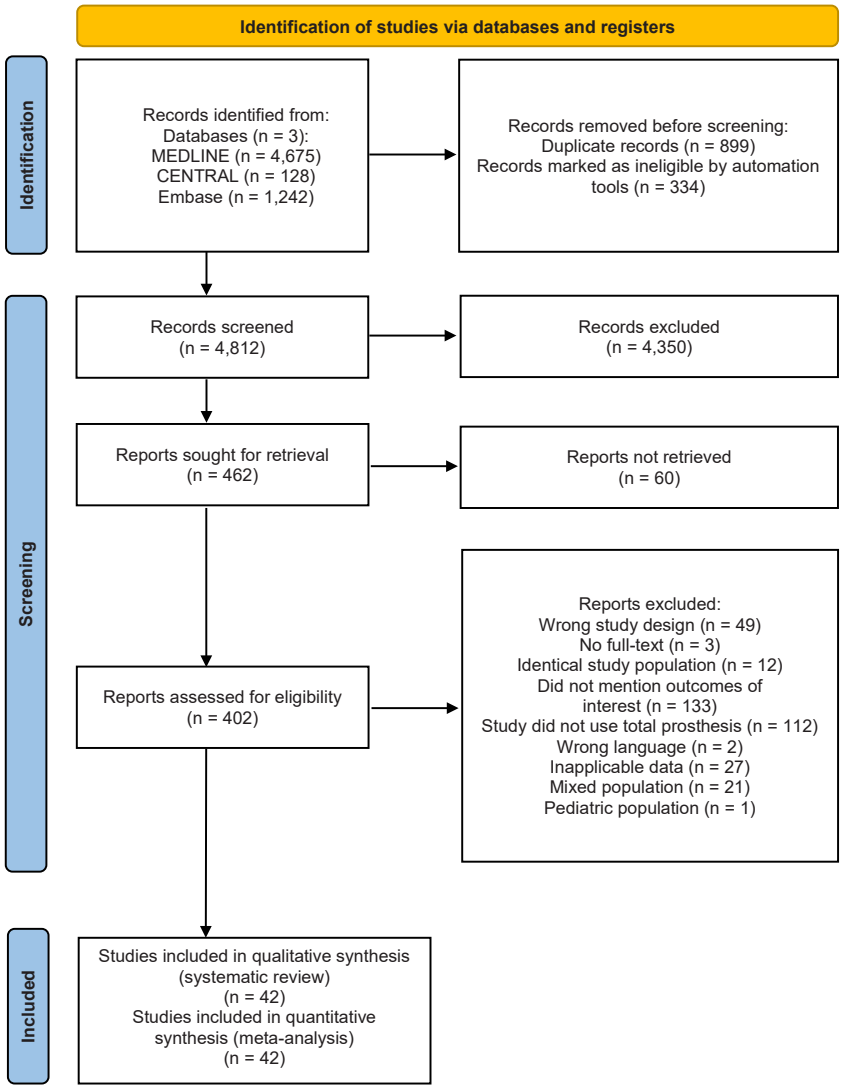

Fig. 1. PRISMA flowchart of the study selection process.

Statistical analysis

The statistical analysis was conducted using R version 4.3.2[14], the meta package for basic meta-analysis calculations and plots (v6.5.0[15]), and the metafor package for multivariate models (v4.4.0[16]). As considerable between-study heterogeneity was assumed in all cases, a random-effects model was used to pool effect sizes. Changes from baseline values were included in the pool where available. Most studies reported only preoperative and postoperative mean and standard deviation (SD) values, so the mean change was calculated by subtracting preoperative values from postoperative values. In a few cases, where the preoperative and postoperative mean and/or SD were not available, they were estimated using median, quartiles, minimum and maximum values. The SD of change was calculated from *P*-values of paired *t*-tests where available. In other cases, it was estimated by imputing correlation coefficients estimated from individual patient data (IPD), and as several studies reported IPD, the lowest correlation values were chosen for analysis to keep the estimate conservative. When single- and two-arm studies were analysed together, raw means were used as effect size measures with 95% confidence intervals (CI). PSI and stock implants were compared as subgroups, as detailed in Supplementary material Appendix S3.

Results

Study selection and main characteristics of the included studies

Of the 4812 articles screened, 402 underwent full-text review, of which 42 met the inclusion criteria (Fig. 1). The analysis included 18 studies that assessed PSIs, 14 that assessed stock implants, and 10 observational studies that assessed both. Data from 2221 patients were analysed, with 1002 in the PSI group and 1219 in the stock implant group. Baseline characteristics are detailed in Tables 1A–D.[1,17–57]

Risk of bias assessment

The MINORS scale was used to evaluate the single-arm studies, with most showing a moderate risk of bias, primarily due to the lack of blinded assessments and the absence of prospective sample size calculations. Some studies also had follow-up losses of over 5%[17–19]. For the 10 two-arm studies, the ROBINS-I tool indicated a mostly moderate risk of bias, with some showing serious risks due to confounding, subjective measurement methods, and missing data[20–22]. Detailed results are available in Supplementary material Table S1 and Fig. S1.

MMO

In the separate analysis of two-arm studies, five studies allowed for direct comparison of PSI with stock systems and evaluation of the mean difference (MD) in MMO[1,23,24,30,41], as shown in Fig. 2. For the initial 1.5–3 months postoperative follow-up, with 84 patients enrolled for PSI reconstruction and 118 patients for stock implant reconstruction, the MD in mouth opening was 3.82 mm in favour of PSI (95% CI −3.51 to 11.15 mm; $P = 0.15$). At 3–6 months postoperative, with 27 patients in the PSI group and 70 in the stock group, the MD in mouth opening was 4.69 mm in favour of PSI (95% CI −6.16 to 15.55 mm; $P = 0.20$). However, neither of these analyses reached statistical significance. Examination of postoperative follow-up data extending beyond 12 months revealed a statistically significant result for MMO in favour of the PSI group: the MD in mouth opening between 96 patients with PSI and 135 patients with stock implants was 5.83 mm (95% CI 1.40 to 10.25 mm; $P = 0.025$).

Table 2 presents the MD in MMO during follow-up for all included studies. No statistical analysis of the period from 1 week to 1 month could be performed as there was only one article reporting this period for the PSI

Table 1A. Demographic data of the patients with custom PSIs.

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Aagaard[18] 2014	Biomet	64	81	91.4	41 (16)	3, 6, 12, 24, 36	3, 12, 24, 36	NA
Amarista[31] 2022	TMJ Concepts	28	52	75	42	Mean 46	Mean 46	Mean 46
Bhargava[32] 2020	DARSN	20	20	40	28.75	12	NA	12
Boyo[25] 2019	Biomet	33	62	81.8	40.4	12–35, 36–59, 60–122.4	12–35, 36–59, 60–122.4	NA
Brierly[27] 2023	OMX-TMJ	151	206	90.7	44.8	Mean 36	Mean 18	NA
Briceño[26] 2013	TMJ Concepts	27	41	92.6	42	Direct	Direct	NA
Burgess[20] 2014[a]	TMJ Concepts	48	NA	84.6[b]	48[b]	NA	Mean 46.3	Mean 46.3
Dowgierd[33] 2022[a]	NA	15	18	53	15	Direct	NA	NA
Gerbino[23] 2016[a]	Biomet	6	12	66	45.16	12, 18	18–24	Mean 20.4
Gonzalez-Perez[24] 2016[a]	Biomet	5	7	66.7[b]	51.8	3, 6, 12, 24, 36	3, 6, 24, 36	NA
Gupta[34] 2020	TMJ Concepts	36	NA	89	44.5	NA	12	NA
Jones[22] 2011[a]	TMJ Concepts	2	3	71[b]	55.7[b]	12	Mean 10.5	NA

MMO, maximum mouth opening; NA, not available; PSI, patient-specific implant; SD, standard deviation.
[a]Two-arm studies.
[b]Number represents both arms.

Table 1B. Demographic data of the patients with custom PSIs—continued.

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Kanatas[29] 2012	Christensen	30	NA	71	45	Direct, 1, 6, 12	Direct, 1, 6	NA
Kanatsios[30] 2022[a]	OMX	63	79	92	48.87	Median 12 wks, median 2.95 years	Median 12 wks, median 2.95 years	NA
Kozakiewicz[35] 2017	NA	11	11	36	54	Mean 35.2	NA	NA
Machon[21] 2012[a]	Biomet	4	4	75	33	Direct	Direct	NA
Mani[36] 2020	NA	10	10	20	17.8	Direct, 60	NA	NA
Mehra[37] 2016	NA	21	NA	100	25.6	Mean 6.2 years	Mean 6.2 years	Mean 6.2 years
Mercuri[17] 2007	TMJ Concepts	59	NA	93.4	41.3	12, 24, 36, 60	12, 24, 36, 60	12, 36
Murdoch[38] 2014	TMJ Concepts	42	63	69	47	Mean 43	Mean 43	NA
Neuhaus[28] 2021	Biomet	16	NA	NA	Median 44.7	Mean 15.3	Mean 15.3	NA
Perez[39] 2016	TMJ Concepts	61	61	77	38.6	Mean 44	Mean 44	Mean 44
Sahdev[40] 2019	TMJ Concepts	93	NA	90	44.3	Mean 4.48 years	Mean 4.48 years	NA
Siegmund[41] 2019[a]	Biomet	16	16	56	46	3 days, 3, 6	3 days, 3, 6	NA
Sidebottom[42] 2013	TMJ Concepts	74	103	88	47	6 wks, 6, 12	6 wks, 6	12
Vorrasi[43]2023[a]	TMJ Concepts	8	13	87	43	Direct	3, 6	NA
Wolford[1] 2003[a]	TMJ Concepts	22	38	82	38.5	Mean 33	Mean 33	6
Zheng[44] 2022	NA	37	45	62	43.4	Mean 28.5	Mean 28.5	NA

MMO, maximum mouth opening; NA, not available; PSI, patient-specific implant; SD, standard deviation; wks, weeks.
[a]Two-arm studies.

group. In all time categories except for the period of 24–48 months, the MD was in favour of the custom implants. However, none of the analyses achieved statistical significance. Individual forest plots, showing the postoperative changes in MMO for each time period in each group (custom PSI and stock implants), are available in Supplementary material Figs. S2–S4; the results are provided in summary plots in Fig. 3 and can be visualized in Fig. 4a.

A model using IPD was also developed to assess the effects of sex assigned at birth, age, and preoperative MMO on outcomes (Table 3). Male patients showed a significant increase in MMO of 4.99 mm when a custom prosthesis was used rather than a stock one (95% CI 1.28 to 8.69 mm; P = 0.009). In contrast, no significant difference in the change in MMO was observed between the implant types for female patients (change in MMO 0.35 mm, 95% CI −2.78 to 3.47 mm; P = 0.83). An increase in age by 10 years at the time of surgery was associated with a reduction in MMO by 1.01 mm (95% CI −1.82 to −0.20 mm; P =

Table 1C. Demographic data of the patients with stock joints.

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Balon[45] 2019	Biomet	12	12	83	49.2	Mean 39.5	Mean 39.5	Mean 39.5
Burgess[20] 2014[a]	Biomet	4	NA	84.6[b]	48[b]	NA	Mean 46.3	Mean 46.3
Dowgierd[33] 2022[a]	NA	5	5	60	16.4	Direct	NA	NA
Gerbino[23] 2016[a]	Biomet	6	10	33	43.5	12, 18	Mean 46, 108	Mean 74
Giannakopoulos[46] 2012	Biomet	288	442	89	41.4	36	36	36
Gonzalez-Perez[24] 2016[a]	Biomet	52	68	66.7[b]	52.6	3, 6, 12, 24, 36	3, 6, 24, 36	NA
Gonzalez-Perez[47] 2019	Biomet	70	91	65	52	3, 6, 12, 24, 36, 60	3, 6, 24, 36, 60	NA
Jones[22] 2011[a]	Biomet	5	9	71[b]	55.7[b]	12	Mean 10.5	NA
Kanatsios[48] 2018	Biomet	60	67	97	53.5	Median 6 wks, median 5.2 years	Median 6 wks, median 5.2 years	NA
Kanatsios[30] 2022[a]	Biomet	54	60	96	54.15	Median 6 wks, median 5 years	Median 6 wks, median 5 years	NA
Kunjur[49] 2016	Biomet	18	NA	83	50	Mean 30	Mean 30	NA
Leandro[50] 2013	Biomet	300	399	40	NA	Direct, 1 wk, 6, 12, 24, 36, 60	1 wk,1, 6	6, 36
Machoň[19] 2020	Biomet	45	62	60	40.56	12, 24	12, 24	NA
Machon[21] 2012[a]	Biomet	23	34	83	NA	Direct	Direct	NA

MMO, maximum mouth opening; NA, not available; SD, standard deviation; wks, weeks.
[a]Two-arm studies.
[b]Number represents both arms.

Table 1D. Demographic data of the patients with stock joints—continued.

First author Year	Implant brand	Patients (*n*)	Replaced joints (*n*)	Sex, female (%)	Age (years), mean (SD)	Follow-up in months		
						MMO	Pain	Diet
Roychoudhury[51] 2021	Biomet	41	54	34	25.12	1 wk, mean 31.71	NA	NA
Saeed[52] 2002	Christensen	50	68	80	38	Mean 43	Mean 43	Mean 43
Sanovich[53] 2014	Biomet	36	42	100	49.4	Mean 30	Mean 30	Mean 30
Siegmund[41] 2019[a]	Biomet	12	12	92	44	3 days, 3, 6	3 days, 3, 6	NA
Vorrasi[43] 2023[a]	Biomet	8	12	88	43	Direct	3, 6	NA
Westermark[54] 2010	Biomet	12	19	75	29	Mean 42, mean 84	NA	NA
Wolford[1] 2003[a]	TMJ Concepts	23	40	96	38.89	Mean 20.8	Mean 20.8	6
Zou[55] 2018	Biomet	33	38	85	51.5	Mean 21.48	Mean 21.48	Mean 21.48
Zou[56] 2019	Biomet	35	44	NA	NA	Mean 15.13	Mean 15.13	Mean 15.13
Zou[57] 2021	NA	27	NA	100	50.5	1, 3, 6, 12	12	12

MMO, maximum mouth opening; NA, not available; SD, standard deviation; wk, week.
[a]Two-arm studies.

0.015). In addition, for every 5-mm increase in preoperative MMO, the total change after surgery was reduced by 4.12 mm (95% CI −4.66 to −3.58 mm; $P < 0.001$).

Pain

Pain was assessed on a visual analogue scale (VAS) with a score range of 0–10 (0, no pain; 10, worst pain). The results for this outcome were mixed and were in favour of stock implants in the early postoperative period and at >24 months, and for custom implants during the intermediate period. Statistical significance was observed in favour of stock implants up to 1 week postoperatively (PSI compared to stock: MD −1.23, 95% CI −2.08 to −0.46; $P = 0.002$) and in favour of custom PSI at 6–12 months (MD 0.84, 95% CI 0.01 to 1.67; $P = 0.048$) and 12–24 months (MD 1.90, 95% CI 0.28 to 3.52; $P = 0.022$) (Table 2).

In the separate analysis of two-arm studies, eight studies allowed for direct comparison of PSI with stock systems and evaluation of the MD in pain[1,20,21,23,24,30,41,43]. In the first 3 months postoperative, the results for pain were in favour of the custom PSI (MD 0.62, 95% CI −1.62 to 2.85; $P = 0.49$); in contrast, at >3 months, the results were in favour of stock implants (PSI compared to stock: MD −0.24, 95% CI −0.82 to 0.34; $P = 0.36$) (Fig. 5). However, neither result was statistically significant.

Individual forest plots, showing the postoperative changes in pain for each time period in each group (custom PSI and stock implants), are available in Supplementary material Figs. S5 and S6; the results are provided in summary

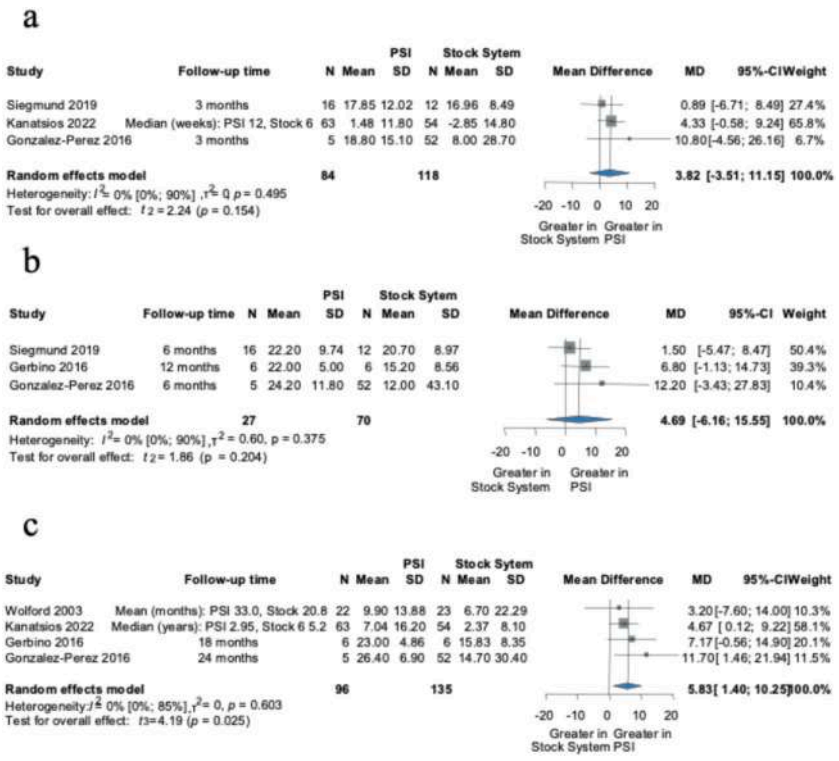

Fig. 2. Forest plots of the mean difference in MMO between the custom PSI and stock implants, in two-arm studies only: (a) at 1.5–3 months; (b) at 3–12 months; (c) at > 12 months. CI: confidence interval; MD: mean difference; *N*: number of patients; PSI, patient-specific implant; SD: standard deviation.

plots in Fig. 6 and can be visualized in Fig. 4b.

Diet

Regarding the dietary outcome, which was assessed on a VAS of 0–10 (0, solid food; 10, liquid food), the results showed a MD in favour of the custom PSI group at 6–24 months (MD 0.96, 95% CI −0.32 to 2.24), however this was not statistically significant (P = 0.14). At > 24 months, the results were significantly in favour of stock implants (PSI compared to stock: MD −1.12, 95% CI −2.34 to −0.02; P = 0.046) (Table 2, Supplementary material Fig. S7).

Certainty of the evidence

The level of certainty of the evidence for the studies was assessed using the GRADE assessment system. Overall, the certainty of the evidence was rated as low. A detailed assessment is provided in Supplementary material Fig. S8.

Discussion

This study presents the largest and most comprehensive systematic review and meta-analysis comparing PSI and non-customized implants in TMJR surgeries to date. Both PSI and stock implants are effective for TMJR. The analysis indicated possible advantages for PSI with regard to mouth opening within the first 6 months and a significant improvement in MMO over stock implants at > 12 months, based on the separate two-arm analysis. Pain outcomes were mixed: a greater pain reduction was observed immediately postoperative for stock implants, whereas custom implants were favoured at 6–24 months postoperative. Significant differences in dietary outcomes were observed after 24 months, in favour of stock implants. These results should be interpreted with caution due to the heterogeneity in the patient population.

Despite the increased cost and effort associated with new customized

Table 2. Mean difference in MMO (mm), pain (VAS), and diet (VAS) for all included studies, between custom PSI and stock implants. MD are consistently reported as 'PSI minus stock'.

				95% CI				
Outcome	Follow-up	Favouring	MD	Lower	Upper	SE	*z*-value	*P*-value
MMO	Direct–3 days	Custom	1.05	−2.73	4.83	1.92	0.55	0.59
MMO	6 weeks–3 months	Custom	3.39	−0.41	7.17	1.93	1.75	0.079
MMO	6 months	Custom	3.02	−2.77	8.80	2.95	1.02	0.31
MMO	12 months	Custom	4.16	−2.43	10.75	3.36	1.24	0.22
MMO	12–24 months	Custom	2.02	−4.49	8.53	3.32	0.61	0.54
MMO	24–48 months	Stock	−4.01	−10.71	2.71	3.42	1.17	0.24
MMO	> 48 months	Custom	0.52	−14.01	15.05	7.41	0.07	0.94
Pain	Direct–1 week	Stock	−1.23	−2.08	−0.46	0.41	3.09	0.002*
Pain	6 weeks–3 months	Custom	0.63	−0.40	1.67	0.53	1.20	0.23
Pain	6–12 months	Custom	0.84	0.01	1.67	0.42	1.97	0.048*
Pain	12–24 months	Custom	1.90	0.28	3.52	0.83	2.29	0.022*
Pain	24–48 months	Stock	−0.05	−0.98	0.88	0.48	0.12	0.91
Pain	> 48 months	Stock	−1.17	−3.39	1.05	1.13	1.03	0.30
Diet	6–24 months	Custom	0.96	−0.32	2.24	0.65	1.47	0.14
Diet	> 24 months	Stock	−1.12	−2.34	−0.02	0.59	1.99	0.046*

CI, confidence interval; MD, mean difference; MMO, maximum mouth opening; PSI, patient-specific implant; SE, standard error; VAS, visual analogue scale.
*Significant result.

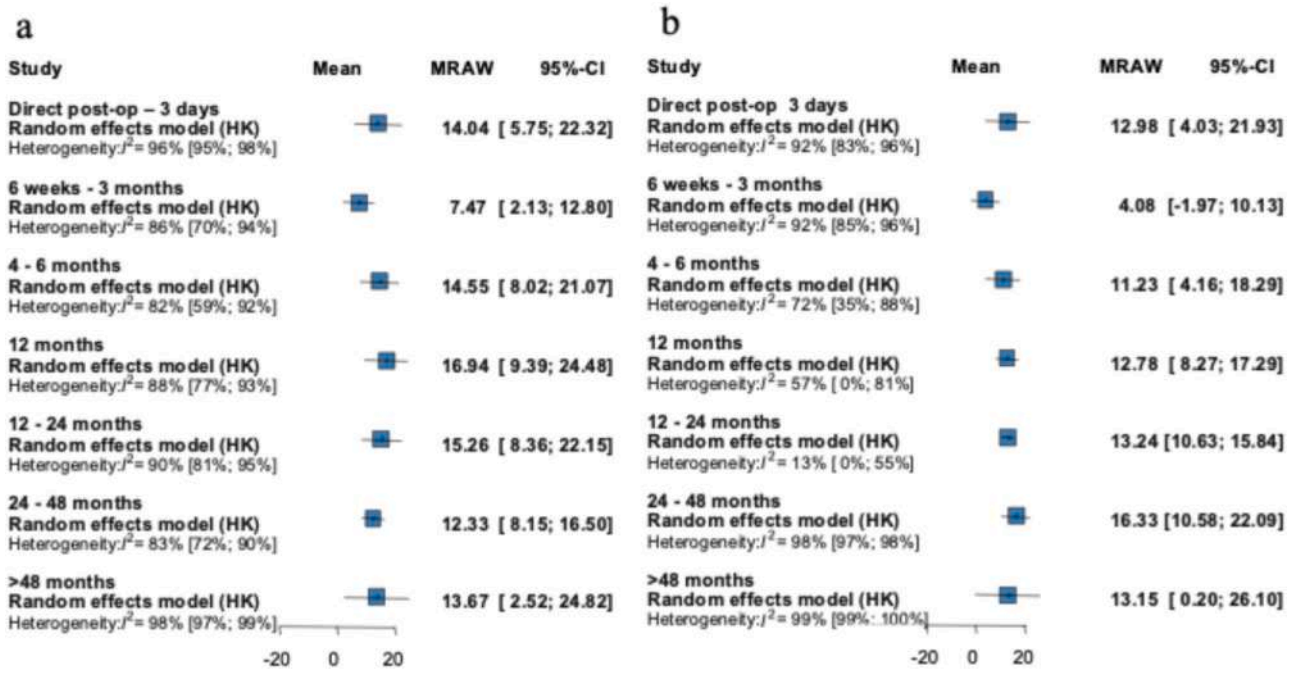

Fig. 3. Summary plots of the change in mean MMO in single-arm and two-arm studies combined, for: (a) custom PSI implants; (b) stock implants. CI: confidence interval; HK, Hartung–Knapp adjustment; MRAW: raw mean; PSI, patient-specific implant.

implant technologies, they have not yet demonstrated a clear superiority over standard stock systems. This lack of clear advantage has been explored in several single-centre studies[7,23,24]. In previous studies, indications for TMJR have been reported for a wide spectrum of severe conditions, from end-stage joint diseases such as inflammatory arthritis and ankylosis, to congenital abnormalities such as hemifacial microsomia and even malignancies within the joint[25–28]. This diversity in patient diagnoses across studies leads to potential biases. Consequently, the use of standardized tools is crucial for effectively addressing and managing these diagnostic variations. The assessment of internal TMJ derangement often utilizes the Wilkes scale; however this has been adopted by only a minority of authors in their studies. Siegmund et al.[41] used the Wilkes classification, focusing on patients with stages IV and V; however, this did not minimize heterogeneity in patient demographics, and they obtained non-significant results for the comparison between the different implant types. Kanatsios et al.[30] included only patients with Wilkes stage V, and their study did not yield significant findings. It is important to note that as the Wilkes classification is based on clinical and radiological criteria, stage V can indicate varying degrees of severity.

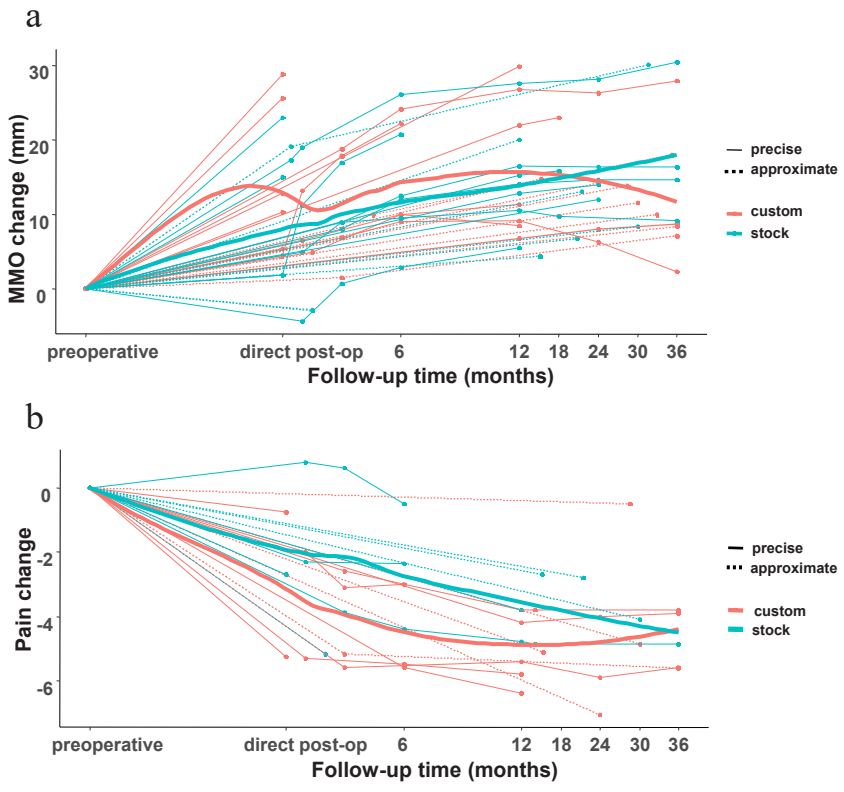

Fig. 4. Visualization of the change in (a) MMO and (b) pain, during follow-up.

Besides the diagnosis, patient characteristics such as age, sex assigned at birth, and preoperative mouth opening may also determine postoperative outcomes (Table 3). In terms of age, the study findings indicate that with every 10-year increase in age, MMO decreases by 1.01 mm after TMJR. This can be explained by the decrease in overall age-dependent healing capacity

Table 3. Estimated effects of implant type and patient characteristics on the postoperative change in MMO from the mixed-effects model fitted to individual patient data.

			95% CI	
	Estimate	*P*-value	Lower	Upper
Female	0.35	0.83	−2.78	3.47
Male	4.99	0.009	1.28	8.69
Age: per 10-year increase	−1.01	0.015	−1.82	−0.20
MMO: per 5-mm increase preoperative	−4.12	< 0.001	−4.66	−3.58

The first two rows show the estimated difference in MMO between custom and stock implants (including a sex interaction), with positive values favouring custom. The other rows reflect the effects of patient characteristics on the postoperative change in MMO, not implant comparisons. Positive values indicate greater increases in MMO postoperatively and negative values reflect smaller improvements.

and reduced compliance of patients with rehabilitation after surgery. Women are often more prone to degenerative joint diseases with systemic influences that make the healing process more difficult[29]. The IPD showed that men could expect an increase in MMO of nearly 5 mm when choosing a custom prosthesis over a stock one. For women, the increase was less than 0.5 mm. In addition, the preoperative MMO is crucial for its outcome. For every 5-mm increase in preoperative MMO, the total change after surgery was found to be reduced by 4.12 mm. Patients with an initially higher MMO had less potential for improvement compared to those with an initially lower MMO.

Given these variations in treatment efficacy and the challenges in determining the optimal implant type, it is essential to consider the complications associated with each type of prosthesis. A meta-analysis by Peres Lima et al.[58] found that common complications in TMJR for both custom and stock implants included paralysis of the facial branch nerves, sensory disturbances, heterotopic bone formation, and infection. However, patient demographics, such as age and prior surgeries, complicate comparisons between custom and stock implants. For example, Kanatsios et al.[30] reported higher complication rates for stock implants, partly due to older age and more previous surgeries in this group. Custom implants, tailored to fit the anatomy of the patient, reduce risks such as alveolar nerve damage and material stress, and are often made of titanium, which has fewer hypersensitivity issues compared to cobalt–chromium stock implants[17,58]. In addition, PSI may shorten the surgery time, although this outcome has not been analysed statistically due to variability in study definitions and surgeon experience.

The main strength of this study lies in the narrower follow-up intervals used

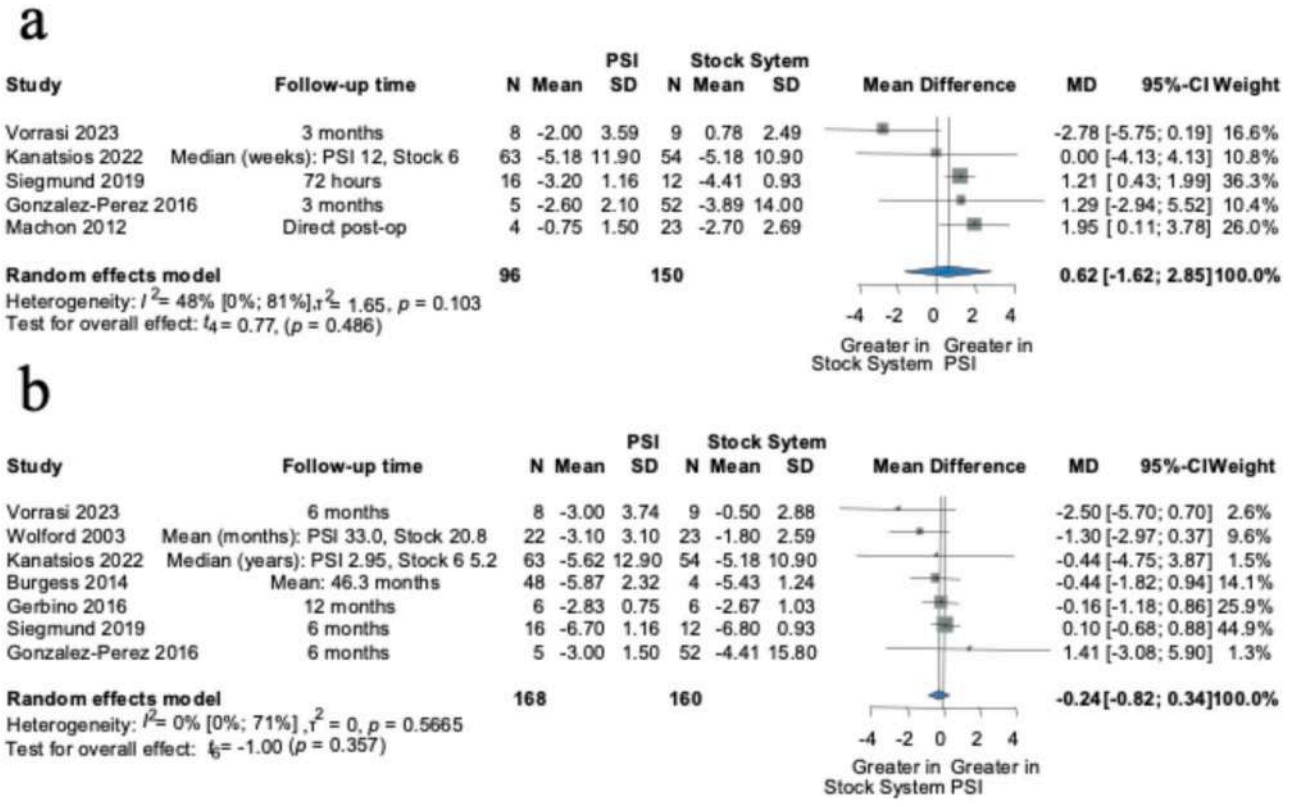

Fig. 5. Forest plots of the mean difference in pain between the custom and stock implants, in two-arm studies only: (a) at < 3 months; (b) at > 3 months. CI: confidence interval; MD: mean difference; *N*: number of patients; PSI, patient-specific implant; SD: standard deviation.

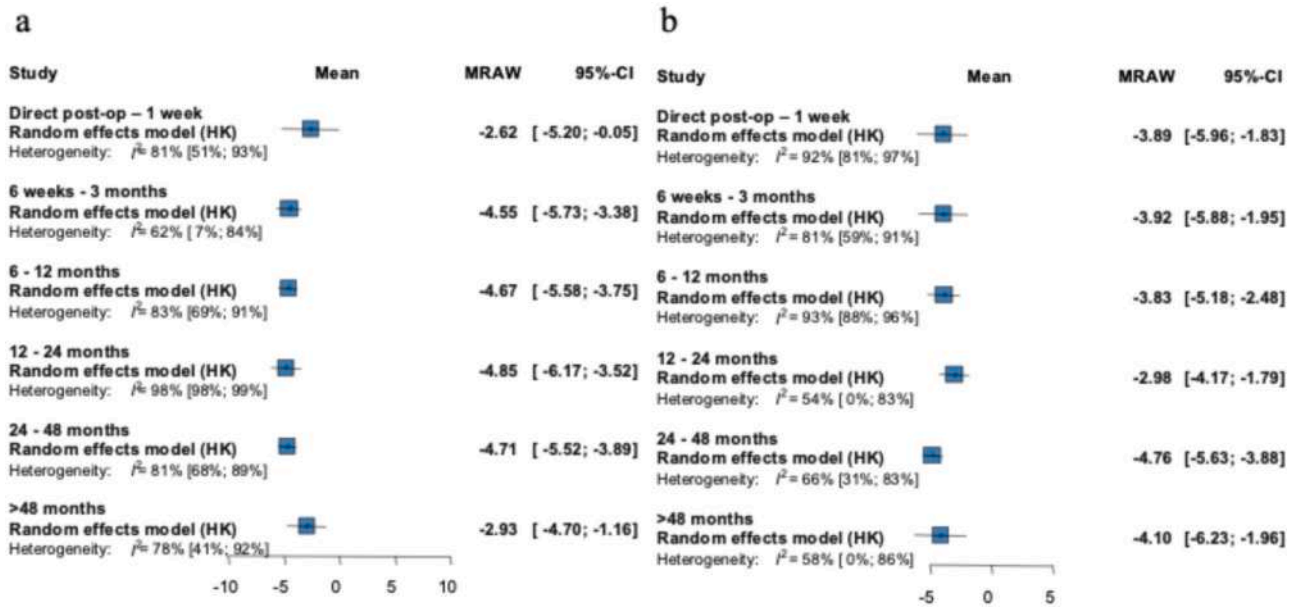

Fig. 6. Summary plots of the change in mean pain in single-arm and two-arm studies combined, for: (a) custom implants; (b) stock implants. CI: confidence interval; HK, Hartung–Knapp adjustment; MRAW: raw mean; PSI, patient-specific implant.

in the analysis, allowing for a more precise and detailed evaluation of outcomes at various stages post-operatively. This methodological approach leads to a clearer understanding of patient recovery dynamics and the effectiveness of different implant types. Furthermore, the analysis is the most comprehensive in terms of TMJR, involving the largest number of patients reported in such research. The large sample size not only adds to the robustness of the study findings, but also supports the generalizability of the results across a broader patient demographic.

Despite the robust data and comprehensive nature of the study, several limitations must be acknowledged. The patient population is highly heterogeneous, with diverse underlying pathologies that have not been graded or uniformly categorized. This variability may complicate the interpretation of the results and affect the comparability of outcomes between custom and stock implants. Key outcome measures such as pain and dietary adaptations could only be assessed subjectively. This subjectivity may introduce biases in how patients perceive and report improvements or declines. There is a lack of consistent information on postoperative rehabilitation protocols followed by patients, which can significantly influence recovery and functional outcomes. Notably, all comparative studies in this meta-analysis were observational; there were no randomized controlled trials. In both the pooled and two-arm analyses, the patient groups originated from different studies, which may vary in baseline characteristics and treatment approaches. These differences introduce the potential for selection bias and uncontrolled confounding, limiting causal interpretation of implant-related outcomes. While these limitations do not undermine the value of the findings, they highlight the need for cautious interpretation and for future high-quality, randomized studies to validate the results.

Bringing scientific results to the bedside is key[59,60]. For patients with restricted jaw movements, a PSI may be recommended over stock systems, offering tailored solutions that improve functional outcomes. These implants improve surgical precision and post-operative range of motion, making them ideal for severe anatomical deformities. On the other hand, stock implants may serve as a cost-effective option for pain management, offering a practical solution that can be deployed quickly. They are especially useful in circumstances where cost concerns or immediate needs prioritize rapid treatment. Both types of TMJ implant effectively meet the dietary needs of patients, helping to restore the jaw functions that are essential for eating.

Based on the results, it is suggested that patient reporting should be more transparent and that raw data be made available. Further research should concentrate on developing and comparing personalized TMJ implants to better manage pain and enhance functionality in patient outcomes.

This study is novel in showing a significant improvement in MMO at > 12 months for PSIs when compared to stock implants, as revealed in the separate meta-analysis of two-arm studies; this was the only statistically significant finding for MMO. Trends suggested potential benefits of PSI in both the separate and pooled analyses of MMO, although these did not reach statistical significance. Meanwhile, the results were in favour of stock implants over PSI in terms of pain immediately postoperative and dietary outcomes after 24 months. However, the overall results for pain were mixed, with PSI implants showing better results between 6 and 24 months. The variability in patient responses necessitates cautious interpretation of these findings. This study underscores the importance of customizing implant selection based on clinical goals and individual patient profiles.

Ethical approval

Not applicable.

Patient consent

Not applicable.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT-4 only for sentence rephrasing and grammar correction. After utilizing this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Competing interests

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ijom.2025.06.021.

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Systematic Review

Comparative Safety and Efficacy of Patient-Specific Versus Hand-Molded Implants in Cranioplasty: A Systematic Review and Meta-Analysis

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Abstract

Background/Objectives: Cranioplasty (CP) is associated with high complication rates (20–50%), and the optimal choice between patient-specific implants (PSIs) and hand-molded (HM) alternatives remains debated. This systematic review and meta-analysis aims to compare surgical and postoperative outcomes between PSIs and HM implants. **Methods:** A systematic search was performed in three databases to identify studies reporting surgical site infection (SSI), implant removal, reoperation, operative time or cosmetic outcome for PSIs and/or HM implants. Two-arm studies of the same material were analyzed separately from pooled single- and two-arm studies. **Results:** 125 observational studies involving 10,034 patients were included. In two-arm comparisons, PSIs reduced implant removal for titanium (OR 0.34, $p = 0.053$) and PMMA (OR 0.56, $p = 0.188$), while SSI rates showed no meaningful difference between groups. In one-arm analyses, PSIs demonstrated lower explantation probabilities (titanium 6.1%, PMMA 7.9%) compared with HM alternatives (titanium 9.9%, PMMA 14.2%), alongside shorter operation times and fewer reoperations. Cosmetic outcomes consistently favored PSIs. **Conclusions:** PSIs demonstrate advantages in efficiency, durability, and esthetics compared with HM implants, supporting their preferential use where resources allow. HM implants remain a cost-effective option in resource-limited settings. Due to the observational nature of the included studies and differences in study populations across arms, the findings should be interpreted with caution.

Keywords: cranioplasty; cranial reconstruction; prostheses and implants; maxillofacial surgery

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1. Introduction

Cranioplasty (CP) is a surgical procedure performed to repair cranial defects, most commonly following decompressive craniectomy, which is used as a life-saving intervention in cases of traumatic brain injury, stroke, or intracranial hypertension [1]. Beyond restoring

skull integrity and protecting the underlying brain, CP also contributes to improved cerebral hemodynamics and neurological function, as well as providing critical cosmetic reconstruction, which can greatly affect patient self-image and quality of life [2]. As a result, timely and effective CP is now regarded as a critical component in supporting neurological recovery and overall rehabilitation. The growing use of CP in both emergency and elective neurosurgical procedures has led to a rising clinical demand for better implant solutions [3].

However, CP is not without risks. Despite being a reconstructive and life-saving operation, CP carries an unusually high complication rate ranging from 20 to 50%–higher than most other neurosurgical procedures [3,4]. Complications include surgical site infection (SSI), implant extrusion, wound breakdown, and the need for revision surgeries, which often come with prolonged operation time and poor cosmetic outcome. These risks are strongly influenced by multiple factors, including the material used, the timing of surgery, and the precision of implant fit [5].

To address these challenges, the use of patient-specific implants (PSIs)–fully customized prostheses designed using 3D printing and computer-aided design and computer-aided manufacturing technology–has gained momentum. Materials commonly used in PSIs include titanium, polyetheretherketone (PEEK), and polymethylmethacrylate (PMMA), each with distinct biological, mechanical, and clinical profiles [6–9].

Despite these developments, there remains no clear consensus on the optimal implant material or the superiority of PSIs over traditional techniques [10,11]. Current literature is fragmented, often limited to small, retrospective series with heterogeneous patient populations and inconsistent outcome reporting. Prior reviews have largely grouped synthetic materials together or failed to isolate fully customized PSIs for head-to-head comparison across critical endpoints like SSI, implant failure and cosmetic success [4,12,13]. Given the increasing adoption of patient-specific technology, the rising demand for CP and the lack of high-level comparative data, an updated systematic review and meta-analysis is urgently needed.

The primary aim of this study is to systematically evaluate the current evidence regarding the use of fully customized PSIs in CP. We aim to compare postoperative outcomes, including SSI, implant failure, total reoperation rate, operation time, and cosmetic results across these materials. Through a meta-analytic approach, we seek to clarify whether the type of PSI material influences complication rates and patient outcomes and to guide future clinical decision-making and standardization in CP practices.

2. Materials and Methods

This systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 guidelines [14] and adhered to the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions [15] (Supplementary Material Table S1). The review protocol was registered prospectively with PROSPERO (registration number: CRD42024582985). This work was carried out as part of the Systems Education Program [16].

2.1. Eligibility Criteria

The research question was structured using the PICO framework, where the population (P) consisted of patients undergoing CP, the intervention (I) was the use of PSI, the comparison (C) was the use of intraoperative HM implants, and the outcomes (O) were postoperative complications (SSI, implant failure, total reoperation rate), operation time, cosmetic score and implant cost. To be eligible, studies had to involve human participants who received a CP using either a PSI or a HM implant and had to report on at least one of the predefined outcomes. No restriction was placed on the length of follow-up

time to ensure comprehensive inclusion of outcome data. However, studies exclusively involving pediatric populations or mixed adult-pediatric cohorts were excluded to reduce demographic heterogeneity. Eligible studies included both comparative (two-arm) and single-arm observational cohorts. Two-arm studies were defined as those comparing PSIs and HM implants made of the same material within the same study, and these contributed to direct comparisons (odds ratios (OR)). Single-arm studies were defined as those reporting only one implant type and/or multiple materials without a direct PSI–HM comparison, and these contributed to pooled proportions and meta-regression analyses. Eligible articles needed to report raw outcome data for at least one of the prespecified endpoints. Case reports, small case series, conference abstracts, and studies lacking original data were excluded. Where multiple studies reported on the same patient cohort, only the publication with the largest sample size was included.

2.2. Selection Process and Search Strategy

A comprehensive literature search was carried out on 25 August 2024, using three electronic databases: MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search was conducted without any limitations on publication date or study type. Although language restrictions were not applied during the initial search, studies unavailable in English, German, or Hungarian were excluded during full-text screening. The complete search strategy is outlined in Supplementary Material (Supplementary Material Text S1). Three reviewers (ELN, BKGC and KSBJ) independently screened titles and abstracts, followed by full-text assessment for final inclusion. Duplicate entries were removed both automatically and manually. Any disagreement between reviewers was resolved through consensus. Inter-rater agreement was assessed using Cohen's kappa, yielding high concordance scores ($\kappa = 0.96$ for abstract screening and $\kappa = 0.97$ for full-text selection).

2.3. Data Collection Process and Extracted Variables

Three reviewers (ELN, BKGC, and KSBJ) independently extracted data from all eligible studies. Any discrepancies were resolved through discussion to reach consensus. The extracted information included: (1) study details—such as first author, publication year, design, study population (sample size, age, and sex assigned at birth), study period, country, institution, diagnosis, implant type, and follow-up duration (in months); (2) postoperative complications; (3) operative time; and (4) cosmetic outcomes. In this study, outcome definitions were standardized across all included articles. Outcome definitions varied across studies. SSI was defined as any postoperative infection involving the incision, soft tissues, or deeper cranial compartments related to the cranioplasty procedure. This included superficial wound infections, deep infections involving soft tissues or bone, and intracranial or organ-space infections when explicitly attributed to the implant or surgical site. These categories were harmonized under a unified SSI outcome to enable consistent extraction across studies. Implant failure was defined as the removal or revision of the implant due to postoperative complications. Reoperation was defined as any subsequent ambulatory or surgical intervention following the initial implantation. Implant removal and total reoperation were analyzed separately to capture the full burden of complications, as "implant removal" reflects material- or implant-specific failure, while "reoperation" includes wound revisions or soft-tissue procedures not necessarily requiring explantation. Operation time was measured from the initial skin incision to the final closure of the surgical site. Cosmetic outcomes were reported using a VAS ranging from 0 to 10, with 10 representing the best possible esthetic result and 0 the poorest.

2.4. Assessment of the Risk of Bias and Certainty of the Evidence

The risk of bias in the included studies was independently assessed by three reviewers (ELN, BKGC, and KSBJ) using the RoB 2 tool for randomized studies, the ROBINS-I tool and the methodological index for non-randomized studies (MINORS) [15,17]. Any discrepancies in scoring were resolved through discussion. The certainty of evidence across outcomes was rated using the GRADE framework, in line with the GRADE handbook [18], and processed using GRADEpro GDT software (version 2013) [19].

2.5. Synthesis Methods

This meta-analysis investigated the differences in various outcomes with PSIs and HM implants in patients with CP. Data for 6 different outcomes were available in the studies: 3 continuous and 3 dichotomous. The main focus was on the different design and material combinations, from which we could identify 10 different ones. Since not every material allows for both PSI and HM design, direct comparisons across methods were not always feasible. For designs where a direct same-material comparison between PSIs and HM implants was possible, the corresponding two-arm studies were analyzed separately using OR for dichotomous outcomes. All single-arm studies lacking direct comparators, were synthesized in pooled proportion analyses and meta-regression using a multilevel random-effects model. To calculate the proportion or the OR, sample size and number of events were extracted from the manuscript. OR were reported as the odds of the event in the PSI group against the odds of the event in the HM group. Otherwise, proportions and mean values were calculated, respectively. Proportions were logit transformed before running the meta regression using the escalc() function. Continuity correction of 0.5 for 0 or 100% proportions was applied and the corresponding sample variance was used with a diagonal variance-covariance matrix. This error structure implies the statistical independence of sampling errors, which can be justified since there are no shared controls, repeated measures, or one patient cannot get multiple different treatments. Material and design were used as a combined factor variable using every combination as a single level. Two outcomes needed data modifications. Implant prices extracted from the studies in their original currency, exchanged for USD at the exchange rate from the middle of the study period, were inflation-adjusted but were not pooled. Cosmetic scores were pooled, but because of the differing scales used, the scales were converted to a 0 to 10 scale before the analysis. Some studies reported more than one results for the same outcomes for different material/design combinations. Although the studies reported average measurement values and standard errors corresponding to distinct combinations, i.e., the correlations among the within-study error terms can be assumed to be 0; the random-effect terms within a single study are correlated when a study contributes to the pooled results with more than one measurement result. For this reason, to calculate pooled results we used multivariate meta-analysis with the rma.mv() function of the metafor R package (version 4.8.0). A two-level hierarchical structure was employed for the random effect terms. We assumed that effect sizes are nested within studies. Statistical analysis was conducted using R version 4.4.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) based on the recommendations from Harrer et al. [20]. Absolute between-study heterogeneity was expressed by tau, and relative between-study heterogeneity was described by Higgins and Thompson's I squared statistics [21].

3. Results

3.1. Search and Selection

Of the 7461 articles screened, 902 underwent full-text review, of which 125 met the inclusion criteria (Figure 1). A total of 98 studies evaluated PSI, and 69 evaluated HM

implants, with several studies assessing both. Data from 10,034 patients were analyzed, with 6170 in the PSI group and 3864 in the HM implant group. Baseline characteristics are detailed in Table 1.

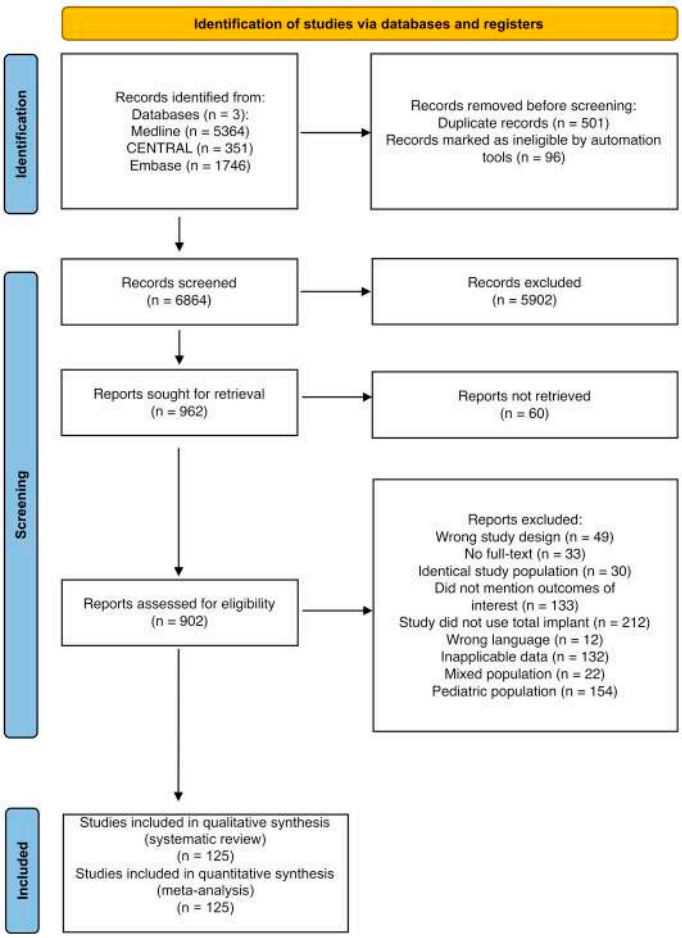

Figure 1. PRISMA flowchart of the study selection process.

Table 1. Demographic data of the patients. [a] Patient-Specific Implant, [b] Hand-molded, NA: Not available, PMMA: Polymethylmethacrylate, AB: Autologous Bone, PEEK: Polyetheretherketone, Ti: Titanium, HA: Hydroxyapatite, PP: Porous polyethylene, CaP-Ti: Calcium Phosphate-Titanium.

First Author and Year	Country	Patient Number and Material	Reported Outcomes for Meta-Analysis		
			Postoperative Complications	Surgery Time	Cosmetic Score
Akan et al., 2011 [22]	Turkey	10 [a], 7 [b] PMMA	Yes	No	No
Alawi et al., 2024 [23]	Oman	28 AB; 14 PEEK	Yes	No	No
Alves Junior et al., 2018 [3]	Brazil	11 AB; 3 [a], 5 [b] PMMA	Yes	Yes	No
Amin et al., 2024 [24]	Bangladesh	11 PEEK	Yes	No	No
Anele et al., 2024 [25]	Nigeria	8 [b] Ti	Yes	No	No
Anto et al., 2017 [26]	India	72 AB	Yes	No	No
Ashraf et al., 2022 [27]	Pakistan	10 [a] PMMA	Yes	No	Yes
Baldia et al., 2022 [28]	India	46 [a], 24 [b] PMMA	Yes	No	Yes
Basu et al., 2021 [29]	India	10 [a] PMMA	Yes	Yes	No
Bianchi et al., 2019 [30]	Italy	6 PEEK	Yes	Yes	No
Binhammer et al., 2020 [2]	Canada	23 [a], 25 [b] Ti; 26 [a] PMMA; 13 AB; 11 PEEK	Yes	Yes	No
Brandicourt et al., 2017 [31]	France	37 PEEK	Yes	No	Yes
Brie et al., 2013 [32]	France	8 [a] HA	Yes	Yes	No

Table 1. *Cont.*

First Author and Year	Country	Patient Number and Material	Reported Outcomes for Meta-Analysis		
			Postoperative Complications	Surgery Time	Cosmetic Score
Cabraja et al., 2009 [33]	Germany	26 [a] Ti	Yes	Yes	No
Caro-Osorio et al., 2013 [34]	Mexico	26 [a] PMMA	Yes	Yes	No
Champeaux et al., 2019 [35]	France	19 [a] Ti	Yes	No	No
Chen et al., 2015 [36]	Taiwan	7 [a] Ti	Yes	Yes	No
Chen et al., 2018 [37]	China	57 [a] HA	Yes	No	No
Cheng et al., 2008 [38]	Taiwan	52 AB; 23 [b] PMMA	Yes	No	No
Cheng et al., 2018 [39]	Taiwan	10 [a] PMMA	Yes	Yes	No
Clynch et al., 2023 [40]	United Kingdom	12 [a], 4 [b] PMMA; 4 [a], 10 [b] Ti; 2 [a] HA	Yes	No	No
Couldwell et al., 1994 [41]	USA	25 PP	Yes	No	No
Csámer et al., 2023 [42]	Hungary	52 [a] PMMA	Yes	No	No
Da Silva Júnior et al., 2021 [43]	Brazil	16 [a] PMMA	Yes	No	No
Desai et al., 2019 [44]	India	30 [a] PMMA	Yes	Yes	Yes
Di Rienzo et al., 2021 [45]	Italy	4 [a], 9 [b] Ti; 9 [a] PMMA; 5 [b] HA; 21 PEEK	Yes	No	No
Duric et al., 2019 [46]	Croatia	29 [a] PMMA	Yes	Yes	Yes
Eom et al., 2020 [47]	South Korea	19 [b] Ti	Yes	No	No
Eufinger et al., 1998 [48]	Germany	22 [a] Ti	Yes	No	No
Fong et al., 2015 [49]	USA	13 AB	Yes	No	No
Fountain et al., 2021 [50]	United Kingdom	35 AB; 17 PEEK; 8 PP	Yes	Yes	No
Francaviglia et al., 2017 [51]	Italy	10 [a] Ti	Yes	No	No
Ganau et al., 2020 [52]	France	92 [a] HA; 89 [a] PMMA	Yes	No	No
Giese et al., 2020 [53]	Germany	67 [a] PMMA	Yes	No	Yes
Gilardino et al., 2015 [54]	Canada	7 PEEK	Yes	No	No
Goh et al., 2010 [55]	Taiwan	31 [a] PMMA	Yes	No	No
Hamböck et al., 2020 [56]	Austria	119 AB; 37 [b] PMMA	Yes	No	No
He et al., 2022 [57]	China	104 PEEK	Yes	No	No
Heissler et al., 1998 [58]	Germany	15 [a] Ti	Yes	No	No
Hoffmann et al., 2005 [59]	Germany	15 [a] Ti	Yes	Yes	No
Honeybul et al., 2012 [60]	Australia	156 AB	Yes	No	No
Hosameldin et al., 2021 [61]	Egypt	33 PEEK; 33 [b] HA	Yes	Yes	Yes
Huang et al., 2015 [62]	USA	20 [a] PMMA	Yes	No	No
Iaccarino et al., 2015 [63]	Italy	31 AB; 50 [a] HA; 13 [a] PMMA; 2 PEEK	Yes	No	No
Inoue et al., 1995 [64]	Japan	8 AB	Yes	No	No
Iratwar et al., 2024 [65]	India	10 [a] PMMA	Yes	Yes	No
Jaberi et al., 2013 [66]	USA	70 [a] PMMA	Yes	No	No
Jin et al., 2016 [67]	China	39 [a] Ti	Yes	Yes	No
Jonkergouw et al., 2016 [68]	Netherlands	38 PEEK	Yes	Yes	No
Kim et al., 2012 [69]	South Korea	16 [a] PMMA	Yes	Yes	No
Kim et al., 2018 [70]	South Korea	45 AB; 31 [a] Ti; 32 PP	Yes	Yes	Yes
Kim et al., 2023 [71]	South Korea	35 [a] Ti	Yes	Yes	No
Kiyokawa et al., 1998 [72]	Japan	12 AB	Yes	No	No
Kohan et al., 2015 [73]	USA	28 AB; 11 [b] Ti; 13 PEEK	Yes	Yes	No
Kung et al., 2012a [74]	Taiwan	40 [a] Ti	Yes	Yes	No
Kung et al., 2012b [75]	Taiwan	9 [b] PMMA	Yes	Yes	No
Kwiecien et al., 2018 [76]	USA	36 AB; 130 [b] Ti	Yes	No	No
Lee et al., 2009 [77]	Taiwan	91 AB; 17 [a], 23 [b] PMMA	Yes	Yes	No
Lee et al., 2012 [78]	South Korea	118 AB	Yes	Yes	No
Lee et al., 2014 [79]	South Korea	18 AB	Yes	No	No
Lemée et al., 2013 [80]	France	5 AB; 7 [a] HA	Yes	No	No
Lethaus et al., 2014 [81]	Netherlands	16 AB	Yes	Yes	No
Linder et al., 2019 [82]	Sweden	50 CaP-Ti	Yes	No	No

Table 1. *Cont.*

First Author and Year	Country	Patient Number and Material	Reported Outcomes for Meta-Analysis		
			Postoperative Complications	Surgery Time	Cosmetic Score
Lindner et al., 2017 [5]	Germany	24 [a] Ti; 26 [a] HA	Yes	Yes	No
Luo et al., 2012 [83]	China	83 [a], 78 [b] Ti	Yes	Yes	No
Maenhoudt et al., 2018 [84]	Belgium	16 [a] HA	Yes	No	No
Marbacher et al., 2012 [85]	Switzerland	27 [a] PMMA	Yes	No	No
Maricevich et al., 2019 [86]	Brazil	63 [a] PMMA	Yes	No	No
Marlier et al., 2017 [87]	France	23 PP	Yes	No	No
Matsuno et al., 2006 [88]	Japan	54 AB; 3 [a], 55 [b] PMMA; 77 [a] Ti	Yes	No	No
Moellmann et al., 2022 [9]	Germany	39 PEEK	Yes	Yes	No
Moles et al., 2018 [89]	France	44 AB; 48 [a] HA	Yes	Yes	Yes
Morales-Gómez et al., 2018 [90]	Mexico	22 [a] PMMA	Yes	Yes	No
Moreira-Gonzalez et al., 2003 [91]	USA	312 AB; 58 [b] HA; 75 [b] PMMA	Yes	No	No
Morina et al., 2011 [92]	Kosovo	75 AB	Yes	No	No
Morton et al., 2016 [93]	USA	532 AB; 151 PEEK; 23 PP	Yes	No	No
Moser et al., 2017 [94]	Switzerland	17 [a] PMMA	Yes	Yes	No
Mrad et al., 2017 [95]	Canada	10 AB; 9 PEEK	Yes	Yes	No
Nagarjuna et al., 2015 [8]	India	5 [a] Ti	Yes	No	No
Ng et al., 2014 [96]	Singapore	7 [b] PMMA; 5 [b] Ti; 12 PEEK	Yes	Yes	No
Nguyen et al., 2021 [97]	Vietnam	35 [a] Ti	Yes	No	No
O Reilly et al., 2015 [98]	USA	19 PEEK	Yes	No	No
Ou et al., 2019 [99]	China	107 AB; 136 [b] PMMA	Yes	No	No
Pfnür et al., 2024 [100]	Germany	25 AB; 35 PEEK; 2 [a] HA; 21 CaP-Ti	Yes	Yes	No
Piitulainen et al., 2015 [101]	Finland	20 AB; 31 [b] HA; 11 [b] PMMA	Yes	No	No
Policicchio et al., 2020 [102]	Italy	10 [a], 13 [b] Ti	Yes	Yes	Yes
Pöppe et al., 2022 [103]	Austria	14 [a] PMMA	Yes	Yes	No
Rammos et al., 2015 [104]	USA	11 PEEK	Yes	No	No
Ridwan-Pramana et al., 2019 [105]	Netherlands	16 [a] PMMA	Yes	No	No
Rosenthal et al., 2014 [106]	Israel	65 PEEK	Yes	No	No
Rosinski et al., 2020 [107]	USA	21 PEEK; 61 [b] Ti	Yes	Yes	No
Rotaru et al., 2012 [108]	Romania	10 [a] PMMA	Yes	No	No
Sahoo et al., 2010 [109]	India	11 AB; 6 [b] Ti; 5 [a] PMMA	Yes	No	No
Sahoo et al., 2019 [110]	India	12 AB	Yes	No	No
Saxena et al., 2023 [7]	India	5 AB; 5 [a] Ti; 5 PEEK	Yes	No	No
Schoekler et al., 2014 [111]	Austria	45 AB	Yes	No	No
Schön et al., 2021 [112]	Switzerland	16 [a] PMMA	Yes	Yes	No
Sharavanan et al., 2015 [113]	India	29 [a] PMMA	Yes	No	No
Shay et al., 2020 [114]	USA	55 [a] PMMA	Yes	No	No
Shi et al., 2023 [115]	China	89 [b] Ti; 66 CaP-Ti	Yes	No	No
Soto et al., 2022 [116]	USA	27 AB	Yes	No	No
Splavski et al., 2022 [117]	Croatia	5 [a] PMMA	Yes	Yes	No
Staffa et al., 2007 [118]	Italy	25 [a] HA	Yes	Yes	No
Stefini et al., 2015 [119]	Italy	2489 [a] HA	Yes	No	No
Stieglitz et al., 2014 [120]	Switzerland	28 [a] PMMA	Yes	No	No
Sun et al., 2019 [121]	China	207 [a] Ti	Yes	No	No
Sundseth et al., 2013 [122]	Norway	13 PP	Yes	Yes	No
Tehli et al., 2023 [123]	Turkey	26 [a] Ti	Yes	No	No
Tel et al., 2021 [124]	Italy	7 [a] PMMA	Yes	No	No
Thien et al., 2015 [125]	Singapore	24 PEEK; 108 [a] Ti	Yes	No	No
Unterhofer et al., 2017 [126]	Austria	46 [a] PMMA	Yes	No	Yes
Van Gool et al., 1985 [127]	Netherlands	45 [a] PMMA	Yes	No	No
Vargo et al., 2020 [128]	USA	11 PEEK; 10 [b] Ti	Yes	No	No
Velnar et al., 2022 [129]	Slovenia	12 [b] PMMA	Yes	No	No

Table 1. *Cont.*

First Author and Year	Country	Patient Number and Material	Reported Outcomes for Meta-Analysis		
			Postoperative Complications	Surgery Time	Cosmetic Score
Vince et al., 2019 [130]	Germany	221 AB; 65 [b] PMMA	Yes	No	No
Vlok et al., 2018 [131]	South Africa	30 [a] PMMA	Yes	No	No
Wang et al., 2012 [132]	China	23 PP	Yes	No	No
Wesp et al., 2022 [133]	Germany	43 [a] PMMA; 39 CaP-Ti	Yes	No	No
Williams et al., 2015 [134]	United Kingdom	149 [a] Ti	Yes	No	No
Yao et al., 2022 [135]	China	106 PEEK; 105 [b] Ti	Yes	Yes	No
Yoon et al., 2021 [6]	South Korea	40 [a] Ti	Yes	Yes	No
Zegers et al., 2017 [1]	Netherlands	8 [a] Ti; 21 PEEK	Yes	No	Yes
Zhang et al., 2015 [136]	China	8 [a] Ti	Yes	No	No
Zhang et al., 2018 [137]	China	75 PEEK; 110 [b] Ti	Yes	Yes	No
Zoli et al., 2020 [138]	Italy	84 [a], 59 [b] PMMA	Yes	No	No

3.2. Risk of Bias Assessment

Single-arm studies were evaluated using the MINORS scale, with most demonstrating a low to moderate risk of bias, mainly due to the lack of blinded assessments and the absence of prospective sample size calculations. Several studies also reported follow-up losses exceeding 5%. Among the ten two-arm studies, the ROBINS-I tool identified a generally moderate risk of bias, with some studies showing serious risks related to confounding factors, subjective outcome measurements, and missing data. The single randomized controlled trial was assessed using the ROB2 tool and rated as having some concerns due to missing outcome data. Detailed results are provided in Supplementary Material (Supplementary Material Table S2 and Figures S1 and S2).

3.3. Implant Removal

A total of eight comparative two-arm studies allowed for the evaluation of implant removal rates between PSIs and HM implants [3,22,28,40,45,83,102,138]. Separate subgroup analyses were performed for titanium and PMMA implants, as illustrated in Figure 2. Across studies including 101 patients treated with PSIs and 110 patients with HM titanium implants, the OR for implant removal was 0.34 in favor of PSIs (95% CI 0.11–1.03; $p = 0.053$). In studies involving 155 patients in the PMMA PSI group and 99 in the HM group, the OR was 0.56 (95% CI 0.21–1.54; $p = 0.188$), again indicating a trend toward fewer removals in the PSI group, though not statistically significant. Table S3 summarizes the results of the one arm analyses for implant removal, showing that all PSI materials demonstrated lower probabilities of explantation compared to HM implants of the same material. Across all included studies, PSIs consistently reduced the risk of postoperative removal, with titanium and PMMA PSIs showing lower rates than their HM counterparts, with the strongest effect being observed for titanium (Figure 3a). In pooled analyses, PSI materials such as CaP-titanium and hydroxyapatite exhibited the lowest explantation rates (<6%), whereas HM PMMA showed the highest rate (14.2%). These findings indicate a consistent advantage of PSIs across materials, although statistical significance was not uniformly achieved in the two-arm subgroup comparisons.

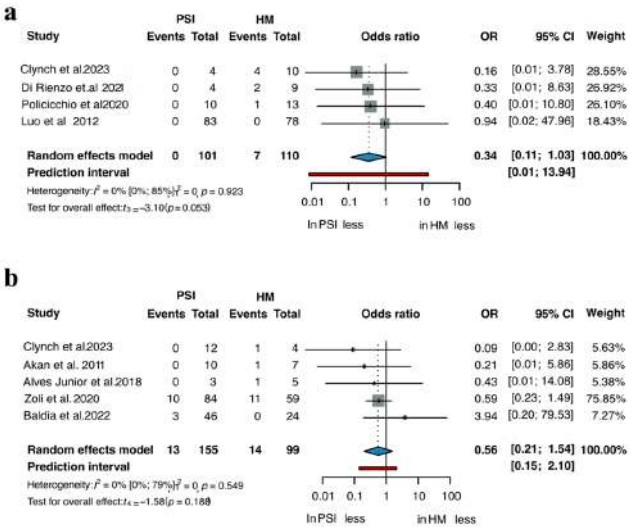

Figure 2. Removal of (**a**) Titanium and (**b**) PMMA implants across all two-arm studies [3,22,28,40,45,83,102,138].

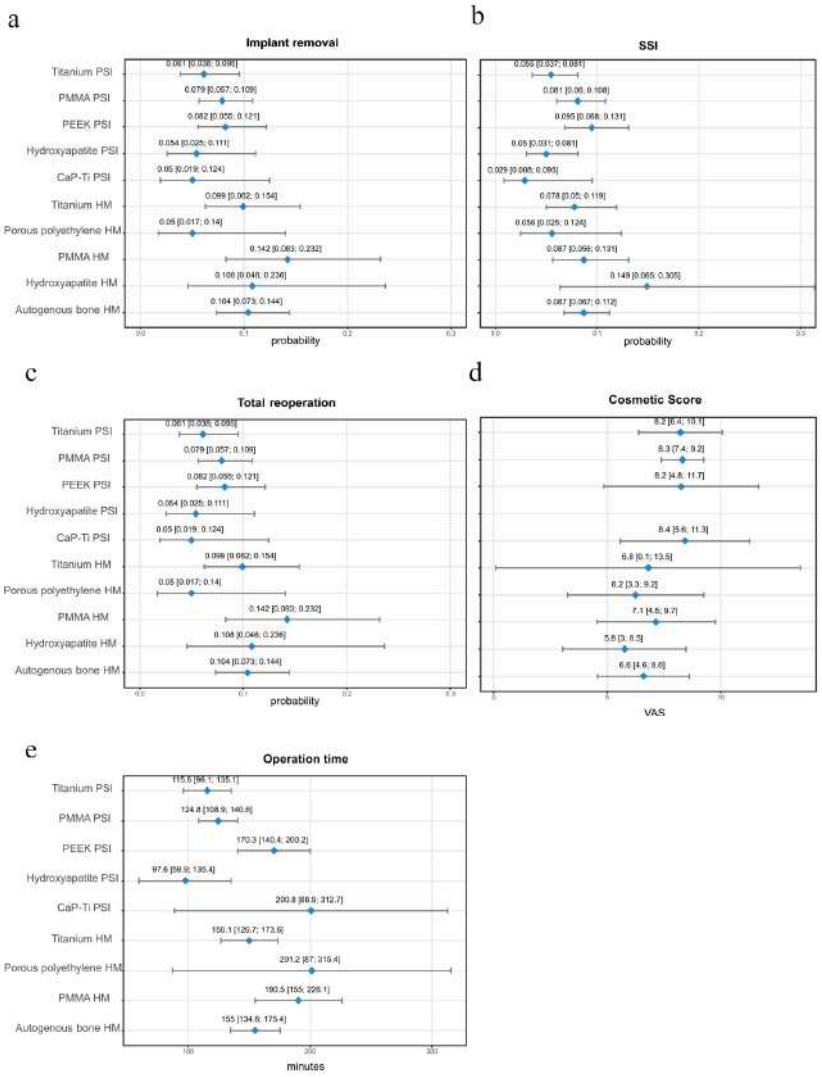

Figure 3. Visualized Meta-Regression estimates with 95% CI for implant materials. None of the single-arm analyses reached statistical significance. (**a**) Implant removal; (**b**) SSI; (**c**) Total reoperation; (**d**) Cosmetic Score; (**e**) Operation time. PSI: Patient-Specific Implant, HM: Hand-molded, SSI: Surgical Side Infection, CI: Confidence Interval, VAS: Visual Analogue Scale, PMMA: Polymethylmethacrylate, PEEK: Polyetheretherketone, CI: Confidence Interval.

3.4. SSI

Ten studies enabled direct comparison of SSI between PSIs and HM implants. Subgroup analyses by material are shown in Figure 4 [3,22,28,40,45,77,83,88,102,138]. Among 101 patients treated with PSIs and 110 with HM titanium implants, the OR for SSI was 0.89 in favor of PSIs (95% CI 0.31–2.57, $p = 0.757$). In the PMMA group, which included 175 PSI cases and 199 HM, the OR was 0.88 (95% CI 0.31–2.44, $p = 0.762$). In both comparisons, the differences in infection rates were not statistically significant, although the point estimates slightly favored PSI.

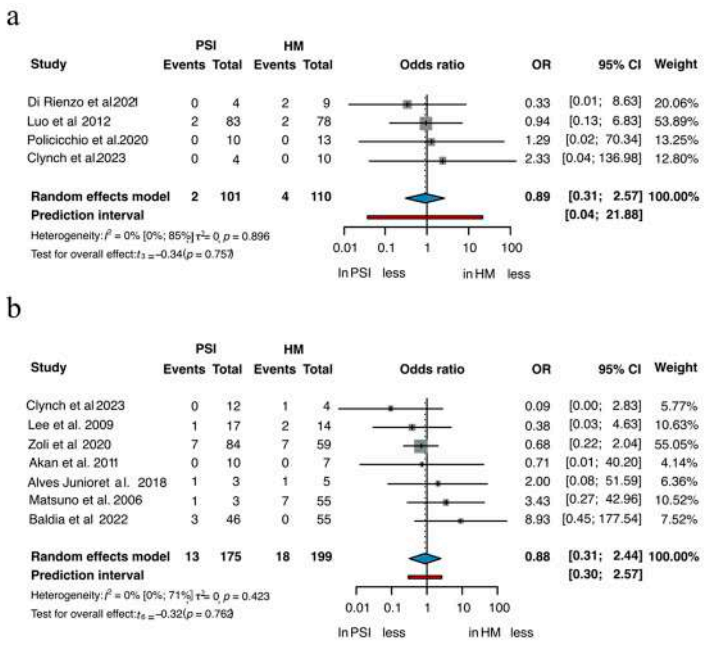

Figure 4. SSI of (**a**) Titanium and (**b**) PMMA [3,22,28,40,45,77,83,88,102,138].

Table S4 summarizes the one-arm analyses of SSI. Infection rates varied across materials, with several PSIs, including CaP-titanium, hydroxyapatite, and titanium, showing postoperative infection probabilities below 6%. PMMA and PEEK PSIs demonstrated infection rates between 8.1% and 9.5%. Among the HM implants, autologous bone and PMMA showed infection rates of 8.7%, while hydroxyapatite reached the highest proportion at 14.9% (Figure 3b).

3.5. Total Reoperation

Table S5 summarizes the results of the one-arm analyses for total reoperations. PSIs showed lower reoperation proportions across most materials compared to HM implants (Figure 3c). The lowest PSI reoperation rates were observed for CaP-Ti (4.7%) and Hydroxyapatite (6.7%), while higher rates were found for PEEK (10.6%) and PMMA (10.8%). Among the HM implants, hydroxyapatite, autologous bone and PMMA exhibited reoperation rates of 11%, with titanium reaching the highest value at 12.6%.

3.6. Operation Time

Table S6 presents the pooled analysis of operation times across materials. Procedures performed with PSIs were generally shorter than those with HM implants. The mean duration for PSIs ranged from 98 min for hydroxyapatite to 201 min for Porous polyethylene, with titanium and PMMA PSIs averaging around 116 and 125 min, respectively (Figure 3e). In contrast, HM implants required longer operative times, with titanium averaging 151 min, autologous bone 156 min, and PMMA nearly 191 min, representing the longest recorded

duration among all materials. These findings highlight a consistent reduction in surgical time when using PSI, particularly for titanium and PMMA, where differences exceeded 35–65 min compared to their HM counterparts.

3.7. Cosmetic Score

Table S7 displays the cosmetic outcomes assessed by visual analogue scale (VAS, 0–10, with 10 indicating the highest satisfaction). Across the included studies, PSIs consistently achieved higher cosmetic ratings compared to HM implants (Figure 3d). Mean scores for PSI materials generally ranged between 8.2 and 8.4, reflecting favorable esthetic outcomes across titanium, PMMA, PEEK, and hydroxyapatite reconstructions. By contrast, HM implants more frequently scored between 5.8 and 7.1, indicating moderate satisfaction but a clear reduction compared with PSI. The widest gap was observed for PMMA, where PSI reconstructions approached VAS scores of 8.3, whereas HM PMMA averaged closer to 7.1. Although the mean differences often appear small (1.2 VAS points), this shift typically represents the transition from "acceptable" to "near-perfect" esthetics in CP, where psychosocial reintegration and patient self-image are central, such improvements are clinically meaningful.

3.8. Implant Price

Table S8 summarizes the reported implant costs across included studies. Prices varied substantially depending on material and implant type. Among PSI materials, PEEK showed the highest average costs, ranging from approximately USD 14414 to 27902 per implant. Titanium PSIs were reported between USD 5627 and 7858, while PMMA PSIs were substantially lower, with reported prices ranging from USD 398 to 5565. HM titanium implants were less expensive, reported between USD 2143 and 2893.

3.9. Certainty of Evidence

The certainty of evidence for the two-arm studies was evaluated using the GRADE system and was overall rated as low. A detailed assessment is presented in Supplementary Material (Supplementary Material Figure S3).

4. Discussion

4.1. Summary of Key Findings

This study presents the most comprehensive systematic review and meta-analysis to date comparing PSIs and HM implants in CP. Overall, the findings suggest that PSI, regardless of the material used, may offer superior outcomes in terms of surgical efficiency and postoperative complications. Specifically, PSIs were associated with shorter operation times, reduced odds of implant removal and fewer overall secondary operations compared to HM alternatives. These trends were observed consistently across materials such as titanium, PMMA, and hydroxyapatite, highlighting the potential benefits of preoperative customization in cranioplasty procedures. However, these results should be interpreted with caution due to the high heterogeneity among the included studies, including variations in surgical technique, patient populations and follow-up duration. Moreover, none of the single-arm analyses reached statistical significance.

4.2. Material-Specific Considerations

Although customized implant technologies involve greater cost and effort, their superiority over conventional HM systems has not been clearly demonstrated, a finding similar to that in several single-center studies [40,99,129,138]. HM PMMA implants gained popularity for decades as a practical and inexpensive option in CP. Their widespread use

was driven by immediate intraoperative availability, low material cost, and the relative ease of shaping PMMA directly at the surgical site to match the defect. Several single-center reports emphasized its value as a rapid solution, especially in settings with limited resources or when custom-made prostheses were not accessible [77,138]. Despite these advantages, however, outcomes varied considerably depending on defect size, anatomical location, and the surgeon's experience, underlining both the appeal and the limitations of this technique [139]. In our analysis, the two-arm comparison favored PSI PMMA, and the meta-regression estimated the explantation probability of HM PMMA at 14.2%. The high rate of explantation seen with HM PMMA can be attributed to its material-specific limitations, particularly residual monomer toxicity arising from intraoperative polymerization. The exothermic reaction and the use of autopolymerizing PMMA, often with suboptimal ratios of monomer to powder, can lead to excess unreacted monomers. These substances have been shown to cause cytotoxic effects, inflammatory responses, and even neurotoxicity when monomers are inadvertently dispersed into the brain during cooling with saline [22]. Moreover, direct contact with the dura and the need for intraoperative shaping and drilling may further increase the risk of foreign body responses, ultimately contributing to implant failure and removal [140]. PEEK was also associated with relatively high rates of both implant removal (8.2%) and SSI (9.5%) compared to other PSI, which likely reflects its frequent use in complex, high-risk reconstructions [23,31]. PEEK is often chosen for more complex or high-risk cases, such as large cranial defects, syndromic conditions, or tumor resections, where PSIs are preferred for their precise fit.

4.3. Influence of Surgical and Patient Factors

The timing between craniectomy and CP appears to have a notable influence on postoperative outcomes. Performing CP too early may increase the risk of complications such as infection and inflammation, likely due to residual contamination, incomplete resolution of cerebral edema, or compromised wound healing. Conversely, delayed CP can lead to extensive dural scarring, bone resorption or brain atrophy, which may complicate implant integration [141]. However, according to a recent meta-analysis by Malcolm et al., no significant difference in postoperative complication rates was observed when comparing early (<90 days) versus delayed (>90 days) CP [142]. Anatomical factors may also influence complication rates. Frontal bone defects, which were present in several included studies, are associated with thinner soft tissue coverage, potentially increasing the risk of implant exposure and chronic inflammatory response, particularly when using materials with known toxicity profiles. Moreover, preoperative radiotherapy is a well-documented factor that significantly worsens surgical outcomes, increasing the risk of postoperative complications by up to sevenfold [143]. Radiation alters local vascularity, impairs tissue regeneration, and induces chronic inflammation, all of which can compromise wound healing and promote implant-related complications, including implant failure. These patients typically present with longer operative times and higher complication risks, both contributing to elevated postoperative infection rates [100]. This trend is consistent with our findings of PEEK PSIs having one of the longest average operation times (170.34 min). In contrast, other PSI, such as hydroxyapatite, titanium, and PMMA demonstrated shorter operation times, which is likely due to their precise preoperative planning and optimal fit, reducing the need for intraoperative adjustments. On the other end of the spectrum, HM PMMA showed one of the longest overall operation time (190.54 min), which may be explained by the intraoperative polymerization process and the need for manual sculpting and fitting during surgery, steps that can be time-consuming and technically demanding [22]. The 35–65 min reduction observed with titanium and PMMA PSIs may have broader consequences, including shorter anesthesia duration, reduced intraoperative blood loss, and potentially

fewer infection-related complications, which are particularly relevant in critically ill or polytrauma patients [144].

4.4. Biological and Biomechanical Factors Underlying Outcomes

Infection rates in our analysis ranged from a postoperative probability of 2.9% to 14.9%, with the highest observed in HM hydroxyapatite implants (14.9%). The elevated infection rate in HM hydroxyapatite may be attributed to challenges in intraoperative handling, increased porosity, and suboptimal fit, all of which can compromise soft tissue closure and increase contamination risk [101]. By contrast, CaP-Ti PSIs demonstrated the lowest infection probability (2.9%), followed by titanium PSIs (5.5%) and PMMA PSIs (8.1%). PEEK PSIs showed relatively high infection rates (9.5%), consistent with its bioinert, non-osseointegrating properties, while autologous bone and PMMA HM also demonstrated elevated risks (8.7% each). When considering overall reoperations, a similar pattern emerged. Beyond infection and revision rates, the biological interaction between implant and host tissue provides further explanation. PEEK, while widely used, is hydrophobic and bioinert, limiting osteoblast adhesion and preventing osseointegration, which may predispose it to implant migration and infection. In contrast, CaP-Ti implants promote neovascularization and bone ingrowth, enhancing stability, wound healing, and even allowing local antibiotic release when pre-soaked in gentamicin [100]. Similarly, hydroxyapatite supports osseointegration, although its brittleness can increase fracture susceptibility [5]. These findings highlight that, in addition to mechanical properties and surgical handling, implant biocompatibility plays a critical role in long-term CP outcomes.

4.5. Economic Considerations

Titanium has long been a favored material for CP due to its biocompatibility, strength, and ease of shaping. HM titanium meshes offer a relatively inexpensive solution, with costs reported around USD 1500 for large implants, whereas computer-aided patient-specific titanium implants are typically two to three times more expensive (USD 2700–7800 depending on size and manufacturer). Despite the higher cost, PSIs reduce implant removals and secondary reoperations, potentially offsetting expenses in high-resource healthcare systems, while HM meshes remain attractive in resource-limited settings where affordability is a primary concern [83].

4.6. Strengths and Limitations

The main strength of this study lies in its comprehensive scope and methodological detail. By including all major implant materials and explicitly separating patient-specific from HM implants, this analysis provides a more precise and transparent comparison than previous reviews. This approach allows for a clearer understanding of recovery dynamics and the relative effectiveness of different implant types. Furthermore, the breadth of the dataset, which represents the largest synthesis of CP outcomes to date, enhances the robustness of the findings and supports their applicability across a wide clinical spectrum. Despite these strengths, several limitations should be acknowledged. The included studies demonstrated a high degree of heterogeneity, with notable variation in surgical techniques, patient populations, and the way outcomes were reported. In addition, differences in how studies defined and classified events likely introduced further residual heterogeneity. Together, these factors complicate direct comparability across studies. Importantly, nearly all of the available evidence derives from observational studies, with only a single randomized controlled trial included. This reliance on non-randomized data increases the risk of bias and limits the strength of causal inferences. Additionally, the literature provides little clarity on the clinical decision-making process regarding when a PSI or HM implant should be preferred, restricting the ability to draw practice-oriented recommendations.

While these limitations do not diminish the relevance of the findings, they emphasize the need for cautious interpretation and for future high-quality prospective studies to establish clearer guidance.

4.7. Implications for Practice and Implications for Research

Translating scientific evidence into daily surgical decision-making is essential [145,146]. Where financial resources and technical infrastructure allow, PSIs should be prioritized. Their tailored design improves intraoperative precision, reduces operative time, and lowers the likelihood of complications, making them particularly valuable in complex reconstructions, frontal bone reconstructions with limited soft tissue coverage, or in cases where anatomical accuracy is critical. Conversely, HM implants remain an important option in situations for smaller defects or in emergency situations where custom fabrication is not feasible.

From a research perspective, greater transparency in reporting is required, including the consistent provision of raw outcome data and standardized definitions of complications. Future studies should not only compare patient-specific and HM implants across different materials but also aim to establish clearer criteria for implant selection in clinical practice. Although materials were analyzed separately to avoid inappropriate cross-material pooling, exploring correlations or hierarchical relationships between materials may help identify broader patterns of implant performance. Such analyses represent an important direction for future research.

5. Conclusions

Across materials, PSIs were associated with favorable trends in shorter operative time, less explantations, fewer reoperations, and better cosmetic satisfaction compared with HM implants, highlighting the benefits of preoperative customization. However, most data derive from observational cohorts, and many direct comparisons were not statistically significant. Therefore, these findings should be interpreted as associative rather than demonstrating proven superiority.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm14248655/s1, Text S1: Predefined search key, Figure S1: RoB 2 assessment, Figure S2: ROBINS-I. assessment for (a) implant removal and (b) SSI, Figure S3: GRADE assessment for all subgroups, Table S1: PRISMA Checklist, Table S2: MINORS assessment for single-arm studies, Table S3: Implant removal across all one-arm studies, Table S4: SSI across all one-arm studies, Table S5: Total number of reoperations across all one-arm studies, Table S6: Operation time in minutes, Table S7: Cosmetic Score on VAS (0–10), Table S8: Implant Price in USD.

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