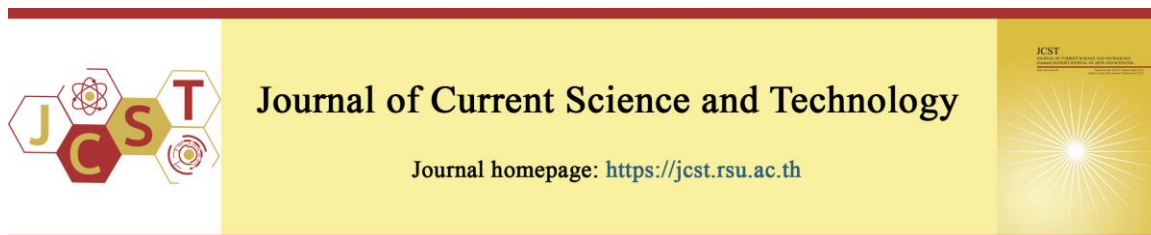


Cite this article: Tiewrungruangsuk, P., Kaewkes, A., Segsarnviriya, C., Lueangarun, S., Prabhakornritta, P., Kupwiwat, R., & Maiprasert, M. (2026). Efficacy of collagen biostimulator injections for facial aesthetics: A systematic review and meta-analysis based on Global Aesthetic Improvement Scale (GAIS) outcomes. *Journal of Current Science and Technology*, 16(3), Article 199. <https://doi.org/10.59796/jcst.V16N3.2026.199>



Efficacy of Collagen Biostimulator Injections for Facial Aesthetics: A Systematic Review and Meta-analysis Based on Global Aesthetic Improvement Scale (GAIS) Outcomes

Punyaporn Tiewrungruangsuk^{1,*}, ORCID: 0009-0003-7221-9802

Arisa Kaewkes², ORCID: 0009-0003-2320-7020

Charnsiri Segsarnviriya³, ORCID: 0000-0002-3939-1964

Suparuj Lueangarun², ORCID: 0000-0002-8121-2982

Peerapong Prabhakornritta², ORCID: 0000-0002-6267-4567

Rosalyn Kupwiwat², ORCID: 0009-0004-3297-2696

Mart Maiprasert², ORCID: 0000-0001-9320-5635

¹Department of Aesthetic Medicine, Dhurakij Pundit University, Bangkok 10210, Thailand

²College of Integrative Medicine, Dhurakij Pundit University, Bangkok 10210, Thailand

³Department of Otorhinolaryngology Head and Neck Surgery, Samitivej Thonburi Hospital, Bangkok 10600, Thailand

*Corresponding author; E-mail: punyaporn.trrs@gmail.com

Received 9 February 2026; Revised 27 March 2026; Accepted 14 April 2026; Published 25 June 2026

Abstract

This systematic review and meta-analysis evaluated the efficacy of injectable collagen biostimulators for facial aesthetic enhancement. The primary outcome was the Global Aesthetic Improvement Scale (GAIS), with adverse events assessed as a secondary outcome. A comprehensive literature search was conducted across five databases (PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL) following the PRISMA 2020 guidelines. Eligible studies included healthy adults receiving facial injections of poly-L-lactic acid (PLLA), polydioxanone (PDO), calcium hydroxylapatite (CaHA), polycaprolactone (PCL), or poly-D,L-lactic acid (PDLLA); however, no eligible PDLLA studies were identified. The included studies consisted of randomized controlled trials and observational studies. Data were synthesized using a random-effects meta-analysis model, and the risk of bias was evaluated using the RoB 2 and ROBINS-I tools. Twenty-four studies were included in the quantitative synthesis. The pooled mean GAIS score was 3.88 (95% CI: 3.63–4.14), indicating moderate to marked aesthetic improvement. Subgroup analysis revealed the highest GAIS scores with PDO (4.20), followed by PLLA (4.13, single study), PCL (4.00), and CaHA (3.33). Reported adverse events were mostly mild and transient, including erythema, swelling, and tenderness. Based on the GRADE assessment, the overall certainty of evidence was low for efficacy and very low for adverse events. Collagen biostimulators demonstrated favorable efficacy profiles for facial rejuvenation. Although all four agents were effective, outcomes varied by product type, suggesting the importance of personalized treatment selection. These findings provide evidence-based support for clinical application and highlight the need for future comparative studies with standardized outcome reporting.

Keywords: adverse events, collagen biostimulators, facial aesthetics, Global Aesthetic Improvement Scale (GAIS), systematic review and meta-analysis.

1. Introduction

Facial aesthetics represents a significant and evolving domain within aesthetic medicine, driven by

the increasing demand for minimally invasive procedures that improve appearance while preserving natural facial expression (Unal et al., 2021). Among

these procedures, injectable collagen biostimulators have garnered substantial attention due to their ability to induce endogenous collagen production and promote long-term dermal remodeling (Scardua et al., 2024). These agents mark a paradigm shift from traditional fillers that provide immediate volumization to regenerative therapies that support sustained improvements in skin structure and quality (Fu et al., 2023; Moers-Carpi et al., 2021).

Currently available collagen biostimulators include poly-L-lactic acid (PLLA), poly-D,L-lactic acid (PDLLA), calcium hydroxylapatite (CaHA), polycaprolactone (PCL), and polydioxanone (PDO). Each of these agents possesses distinct physicochemical properties that influence its biodegradation kinetics, biostimulatory mechanisms, and clinical applications (Bae et al., 2016; Liao et al., 2024; Moon et al., 2020; Park et al., 2022; Preibisz et al., 2022). CaHA offers immediate volumetric correction coupled with fibroblast activation, making it suitable for patients seeking prompt improvement with additional neocollagenesis (Boen et al., 2020). When injected correctly, it has a favorable safety profile; however, superficial placement may lead to the formation of palpable nodules (Bass et al., 2010; Moers-Carpi & Sherwood, 2013). PCL is characterized by a slow biodegradation rate and robust collagen-stimulating capacity, with effects lasting up to 24 months. It is commonly used in areas requiring long-term volume retention, such as the midface and temples (Moers-Carpi & Sherwood, 2013). PDO, traditionally applied in thread-based procedures, exerts a mechanical lifting effect while promoting short-term collagen synthesis. It is frequently selected for the treatment of skin laxity, particularly in patients seeking immediate aesthetic improvement (Khan et al., 2021).

PLLA is well recognized for its gradual onset of action, inducing neocollagenesis over several months. However, it requires meticulous reconstitution and injection techniques to minimize the risk of nodule formation. PDLLA, a newer alternative, incorporates both L and D isomers of lactic acid, resulting in an amorphous structure and consistent degradation kinetics. These properties may contribute to smoother tissue integration and a lower risk of delayed complications compared to PLLA (Trinh et al., 2022). Although preliminary data suggest that PDLLA achieves aesthetic outcomes similar to PLLA with potentially fewer side effects, clinical evidence remains limited and warrants further investigation.

Despite a growing body of literature supporting the use of collagen biostimulators, current evidence

remains fragmented and varies widely in terms of outcome measures, injection techniques, study design, and assessor identity (Corduff, 2020; Galadari et al., 2015; Jeong et al., 2020). Direct comparative trials between products are notably lacking, and ongoing debate persists regarding the relative efficacy and safety of these agents.

Comprehensive quantitative evidence comparing the efficacy and safety of different collagen biostimulators remains limited. To address these gaps, this study aims to systematically evaluate and compare the efficacy and safety of collagen biostimulator injections for facial aesthetics. By synthesizing findings from eligible clinical studies using validated outcome instruments such as the Global Aesthetic Improvement Scale (GAIS), this review seeks to guide evidence-based product selection and inform individualized treatment strategies in aesthetic practice.

2. Objectives

To evaluate the efficacy of collagen biostimulators for facial aesthetics through a systematic review and meta-analysis, with the Global Aesthetic Improvement Scale (GAIS) as the primary outcome and adverse events as secondary outcomes.

3. Materials and Methods

This systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 guidelines (Page et al., 2021) and was prospectively registered in PROSPERO (Registration No. CRD420251020585).

3.1 Eligibility Criteria

The study applied the PICO framework as follows:

1. Population: Healthy adults (≥ 18 years) without chronic dermatological conditions or prior aesthetic interventions within 6 months.

2. Intervention: Injectable collagen biostimulators, including PLLA, PDLLA, PCL, PDO, and CaHA. Studies using combination therapies were excluded.

3. Comparator: No intervention or active comparator.

4. Outcomes: The primary outcome was aesthetic improvement measured using the Global Aesthetic Improvement Scale (GAIS). Secondary outcomes included adverse events.

Only English-language studies published from 2000 onward were included. Eligible designs were

randomized controlled trials (RCTs), prospective and retrospective studies, and observational case series.

3.2 Search Strategy

A comprehensive literature search was conducted on April 17, 2025, across PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search combined controlled vocabulary (e.g., MeSH and Emtree terms) with free-text keywords related to collagen biostimulators, including PLLA, PDLLA, PCL, PDO, and CaHA, as well as synthetic collagen biostimulators and facial aesthetic-related terms (e.g., face, facial, aesthetic). Boolean operators (AND, OR) were used to combine search terms and optimize sensitivity. The search strategies were adapted for each database to account for differences in indexing and syntax while maintaining consistent search concepts. Full search strategies for all databases are provided in Supplementary Appendix 1.

3.3 Study Selection and Data Extraction

Titles and abstracts were screened for relevance, followed by full-text review. A dual-reviewer screening process in Covidence was used to ensure consistency. Discrepancies were resolved through discussion, with consultation of a third reviewer when necessary. Data were independently extracted for authors and year, biostimulator type, study design, injection site, mean age, sample size, follow-up duration, GAIS score, and adverse events.

3.4 Risk of Bias Assessment

The Cochrane RoB 2 tool was applied to RCTs, and ROBINS-I was used for non-randomized studies (Chandler et al., 2019; Sterne et al., 2019). Judgments were made by one reviewer and cross-checked for consistency, with discrepancies resolved through discussion. Results are summarized in both narrative and graphical formats.

3.5 Data Synthesis and Statistical Analysis

Quantitative synthesis was performed using a random-effects DerSimonian–Laird model. The primary outcome (GAIS) was pooled and reported as

mean with 95% confidence intervals. All included studies reported GAIS using a 5-point scale. Outcomes were extracted as reported and were directly comparable across studies. The pooled analysis was performed using a random-effects model to account for between-study heterogeneity. Although GAIS is an ordinal scale, it was treated as a continuous variable for quantitative synthesis, consistent with common practice in meta-analyses of multi-category ordinal outcomes, in which categories are assumed to represent approximately equal intervals (Borenstein et al., 2009; Chandler et al., 2019). This approach enables pooled analysis but may introduce assumptions regarding scale linearity, which are acknowledged as a limitation. Sensitivity analyses were conducted to ensure the robustness of the pooled estimates. Multi-arm studies were treated as independent comparisons based on the reported data structure. Where applicable, potential double counting of participants across comparisons was considered during data extraction and analysis.

Heterogeneity was assessed using I^2 , τ^2 , and Q statistics. Subgroup meta-analyses were performed for CaHA, PCL, and PDO. Meta-regression was used to assess the effect of publication year. Adjustment for follow-up duration was not performed due to inconsistent reporting across included studies. Outcomes were extracted at the most comparable or commonly reported time points where possible.

Funnel plots were used to detect publication bias. Formal statistical tests were not performed because of the limited number of studies. Quantitative synthesis of adverse events was not performed because of heterogeneity in reporting and outcome definitions across studies, which precluded meaningful pooling.

The certainty of evidence was assessed using the GRADE approach.

3.6 Ethical Considerations

Ethical approval was not required for this study because it was based exclusively on previously published data and did not involve human participants or identifiable personal information, as confirmed by the Ethics Committee of Dhurakij Pundit University.

4. Results

4.1 Study Selection

The initial database search yielded 7,186 records from five electronic databases (PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL). After removing 2,776 duplicates, 4,410 records were screened by title and abstract. Of these, 4,209 were excluded, leaving 201 full-text articles assessed for eligibility.

Following full-text review, a total of 176 articles were excluded for the reasons outlined in the

PRISMA flow diagram. Ultimately, 25 studies met the inclusion criteria and were included in the qualitative synthesis (Figure 1). One additional eligible study was identified through reference list screening of relevant systematic reviews, resulting in a total of 26 included studies. However, two studies were systematic reviews and were therefore excluded from quantitative synthesis. Consequently, 24 studies were included in the meta-analysis. The characteristics and outcomes of the included studies are summarized in Table 1.

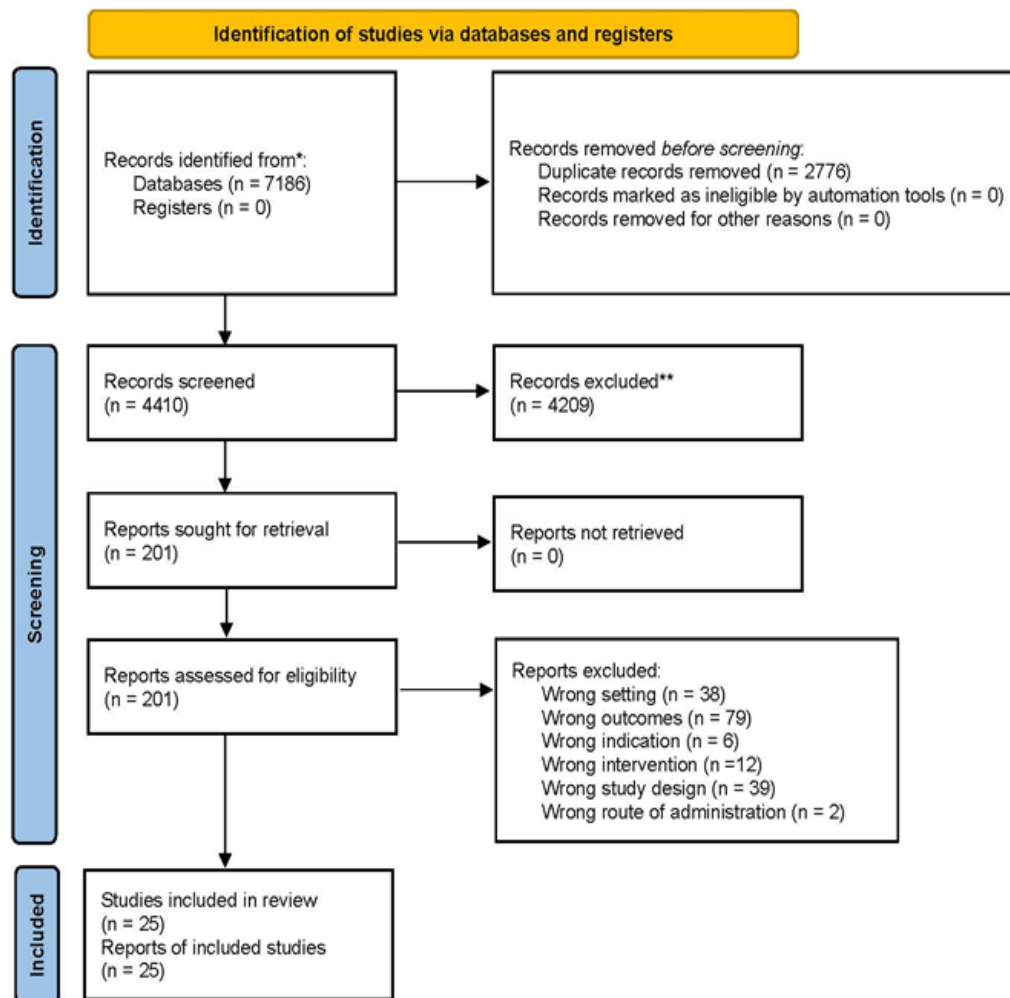


Figure 1 PRISMA 2020 flow diagram

Table 1 Characteristics, efficacy, and safety outcomes of studies on injectable biostimulators

Authors, Year	Biostimulator	Study Type	Injection Site	Mean Age	Sample Size	Follow-up (months)	GAIS	Adverse Events
Trinh et al., 2022	None	Systematic review	Tear trough	52	23	Not reported	Improved	Swelling, bruising
Khan et al., 2022	PDO	Retrospective	Tear trough	49	40	7	3.81	Erythema, bruising
Moers-Carpi & Tufet, 2008	CaHA	RCT	Nasolabia 1 folds	46	60	12	2.94	Nodule formation
Moers-Carpi et al., 2007	CaHA	RCT	Nasolabia 1 folds	48	205	12	2.61	Bruising
Preibisz et al., 2022	PDO	Prospective	Midface, jawline	44	60	6	4.5	Thread palpability
Juhász et al., 2018	CaHA	Prospective	Jawline	45	20	12	3.5	Nodule formation
Juhász et al., 2018	CaHA	Prospective	Temporal fossa	42	20	12	3.74	Not reported
Kang et al., 2019	PDO	Prospective	Upper face	38	33	2	3.7	Swelling, bruising
Amiri et al., 2024	CaHA	Systematic review	Full face	36	1171	1-12	1.8-4.5	Erythema, tissue reaction
Khan et al., 2021	PDO	Prospective	Midface, jawline	39	30	7	3.33	Bruising
Boen et al., 2020	CaHA	RCT	Jawline	42	10	3	3	Bruising, tenderness
Moon et al., 2020	PDO	Prospective	Midface, Lower face	47	21	6	3.62	Mild erythema
Galadari et al., 2015	PCL	RCT	Nasolabia 1 folds	49	40	12	2.73	Swelling, nodules
Park et al., 2022	PCL	RCT	Nasolabia 1 folds	48	59	12	3.63	Site reaction
Moers-Carpi et al., 2021	PCL	Prospective	Nasolabia 1 folds	50	90	12	4.5	Not reported
Fu et al., 2023	PDO	Retrospective	Midface, lower face	38	36	12	4.69	Bruising, swelling
Liao et al., 2024	PLLA	Prospective	Full face	42	30	12	4.13	Swelling, mild discomfort
Barbarino et al., 2021	CaHA	Prospective	Temporal	46	10	1	4	Not reported
Wollina & Goldman, 2020	CaHA	Retrospective	Midface, lower face	51	40	12	2.7	Edema, minor nodules
Unal et al., 2021	PDO	Retrospective	Midface, lower face	43	38	26	4.76	Thread palpability, bruising
Scardua et al., 2024	CaHA	RCT	Forehead	39	132	6	3.71	Not reported
Bae et al., 2016	PCL	Prospective	Forehead	44	58	12	4.45	Swelling
Green et al., 2024	CaHA	Prospective	Jawline	50	175	12	3.23	Not reported
Jeong et al., 2020	PCL	RCT	Crow's feet	Not reported	30	12	3.14	Site edema, erythema
Moers-Carpi & Sherwood, 2013	PCL	Prospective	Nasolabia 1 folds	46	40	12	3.92	Mild swelling, tenderness
Bass et al., 2010	CaHA	RCT	Nasolabia 1 folds	41	102	6	2.31	Swelling, small nodules

4.2 Risk of Bias Assessment

Randomized Controlled Trials (RoB 2)

Across the 8 randomized controlled trials, most domains showed a low risk of bias, with only minor concerns in the selection of reported results and the randomization process. Overall, all trials were judged to have a low risk of bias, with no domains rated as high risk (Figures 2 and 3).

Non-Randomized Studies (ROBINS-I)

For the 16 non-randomized studies, the primary concerns were potential bias from confounding,

outcome measurement, and selection of the reported results. Only 1 study was judged to have a serious risk of bias in confounding and overall risk assessment. The overall judgment for these studies was a moderate risk of bias (Figures 4 and 5).

4.3 Material Properties of Collagen Biostimulators

The key material properties, including mechanisms of action, onset of action, duration of effect, and clinical applications of the included collagen biostimulators, are summarized in Table 2.

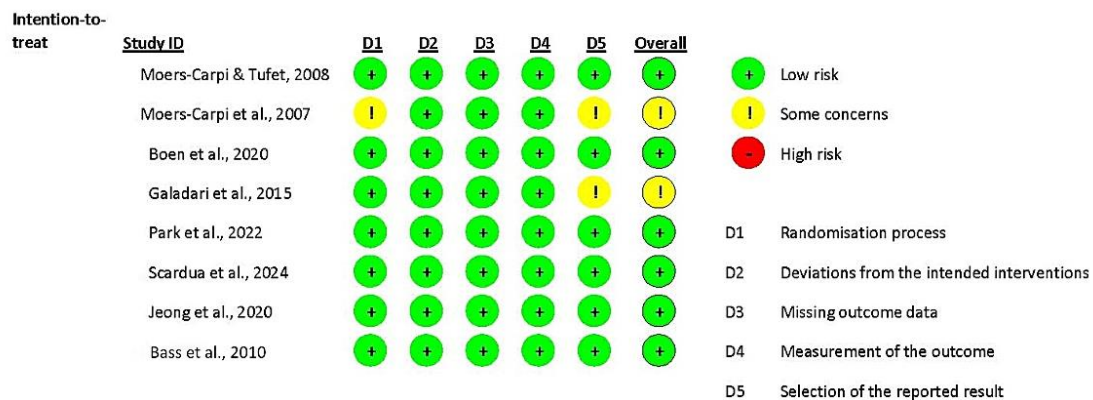


Figure 2 Risk of bias assessment for randomized controlled trials by individual study (RoB 2)

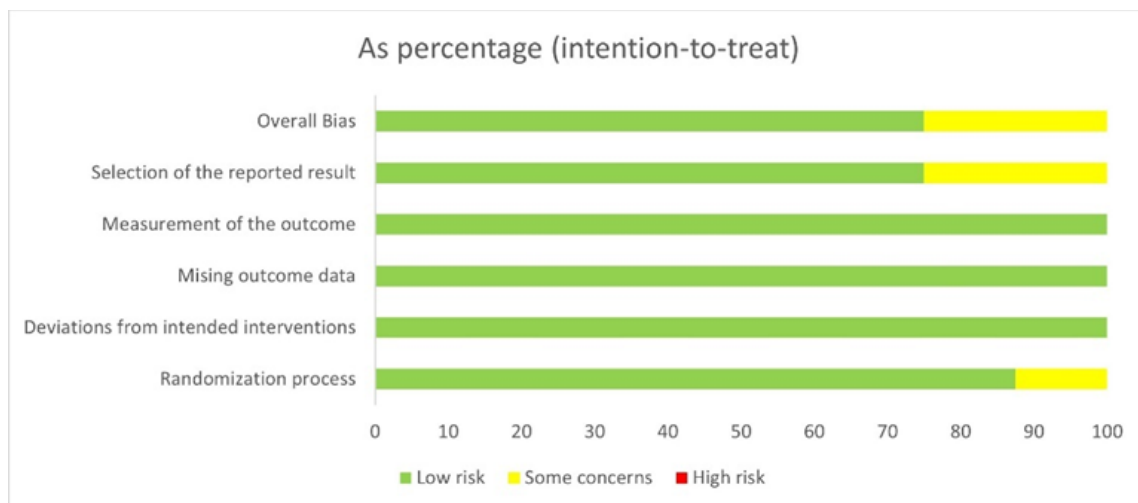


Figure 3 Risk of bias assessment for randomized controlled trials presented as percentages across domains (RoB 2)

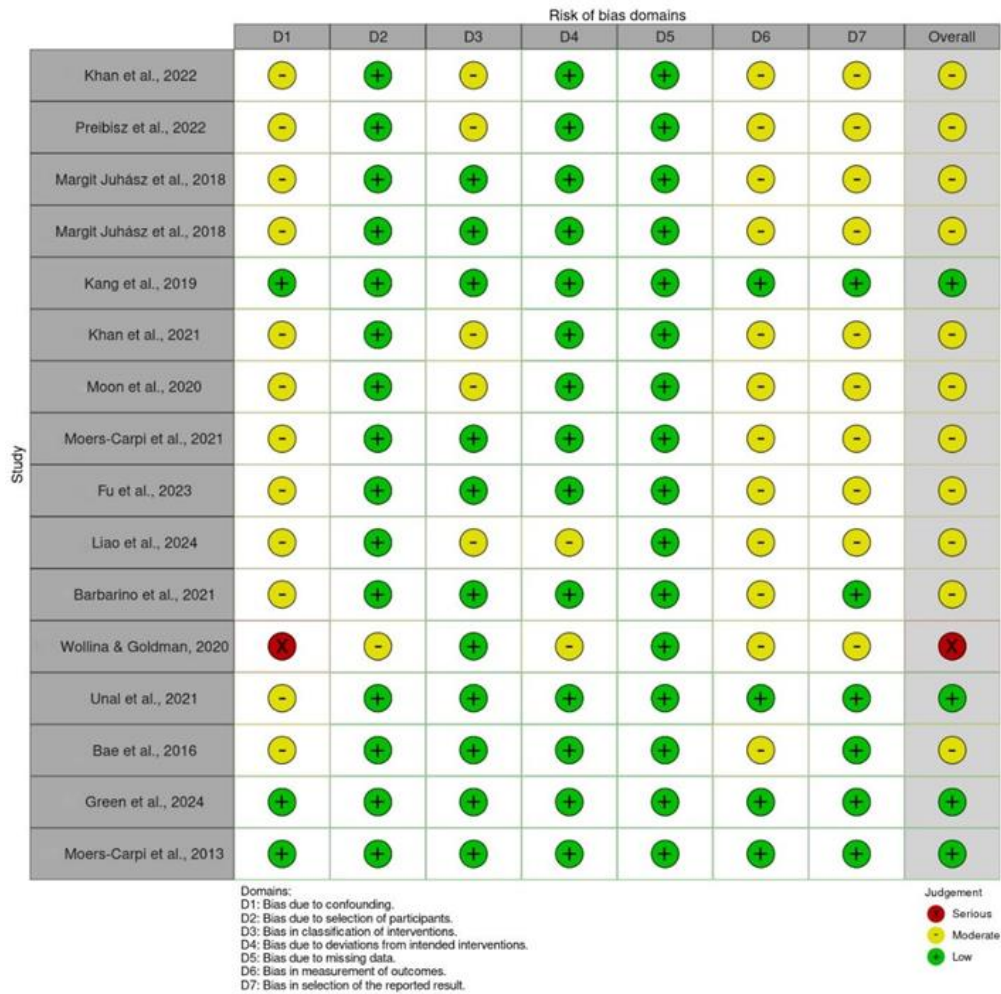


Figure 4 Risk of bias assessment for non-randomized studies by individual study (ROBINS-I)

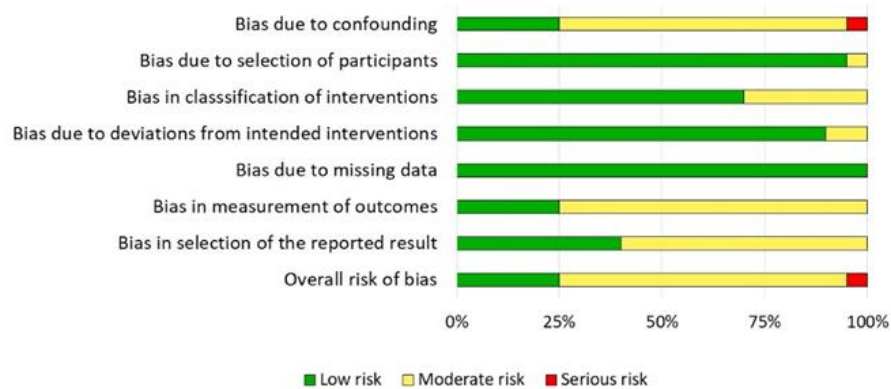


Figure 5 Risk of bias assessment for non-randomized studies presented as percentages across domains (ROBINS-I)

Table 2 Structured comparison of material properties of collagen biostimulators

Biostimulator	Mechanism of Action	Onset of Action	Duration of Effect	Clinical Application	Key Considerations
Poly-L-lactic acid (PLLA)	Scaffold-induced controlled inflammation, macrophage recruitment, fibroblast activation, neocollagenesis	Gradual	Long-term	Skin quality improvement, volume restoration	Injection technique–dependent, risk of nodules
Poly-D,L-lactic acid (PDLLA)	Scaffold-based fibroblast stimulation with more uniform degradation kinetics	Gradual	Long-term	Dermal remodeling, skin rejuvenation	Limited clinical evidence
Calcium hydroxylapatite (CaHA)	Immediate volumization with microsphere-induced fibroblast activation and collagen deposition	Immediate	Intermediate-term	Volume correction, skin tightening	Risk of nodule formation if superficial
Polycaprolactone (PCL)	Prolonged scaffold persistence with sustained mechanical stimulation of fibroblasts	Gradual	Long-term	Long-term volume restoration	Slow biodegradation
Polydioxanone (PDO)	Mechanical tension, mechanotransduction, and localized inflammatory stimulation	Immediate	Short-term	Skin laxity, lifting effect	Primarily used in thread lifting; also included as injectable threads/filaments

4.4 Primary Outcome: Global Aesthetic Improvement Scale (GAIS)

A random-effects meta-analysis was conducted using data from 27 treatment arms derived from 24 original studies included in the quantitative synthesis (Amiri et al., 2024; Trinh et al., 2022). The pooled mean GAIS score was 3.88 (95% CI: 3.63–4.14). Heterogeneity was low ($I^2 = 0.00\%$) (Figure 6).

4.5 Subgroup Analyses

Subgroup analysis based on biostimulator type revealed mean GAIS scores of 3.33 (95% CI: 2.87–3.79) for CaHA, 4.00 (95% CI: 3.48–4.53) for PCL, and 4.20 (95% CI: 3.79–4.62) for PDO. No eligible studies were available for PDLLA because no GAIS data met the inclusion criteria. Only one study was available for PLLA; therefore, no pooled estimate was calculated.

Differences between subgroups were statistically significant (Q-test $p = 0.02$, between-

group heterogeneity). Heterogeneity across all studies was minimal ($I^2 = 1.22\%$, $\tau^2 = 0.01$) (Figure 7).

4.6 Sensitivity Analysis

Leave-one-out sensitivity analysis confirmed the robustness of the pooled estimate, with mean GAIS scores ranging from 3.80 to 3.93 across iterations (Figure 8).

4.7 Meta-Regression

An univariable meta-regression, with year of publication as the sole covariate, demonstrated a non-significant trend toward higher GAIS scores in more recent studies, indicating no statistically meaningful temporal effect (Figure 9).

4.8 Publication Bias

Visual inspection of the funnel plot suggested slight asymmetry. Formal statistical tests for funnel plot asymmetry were not performed due to the limited number of studies per subgroup (Figure 10).

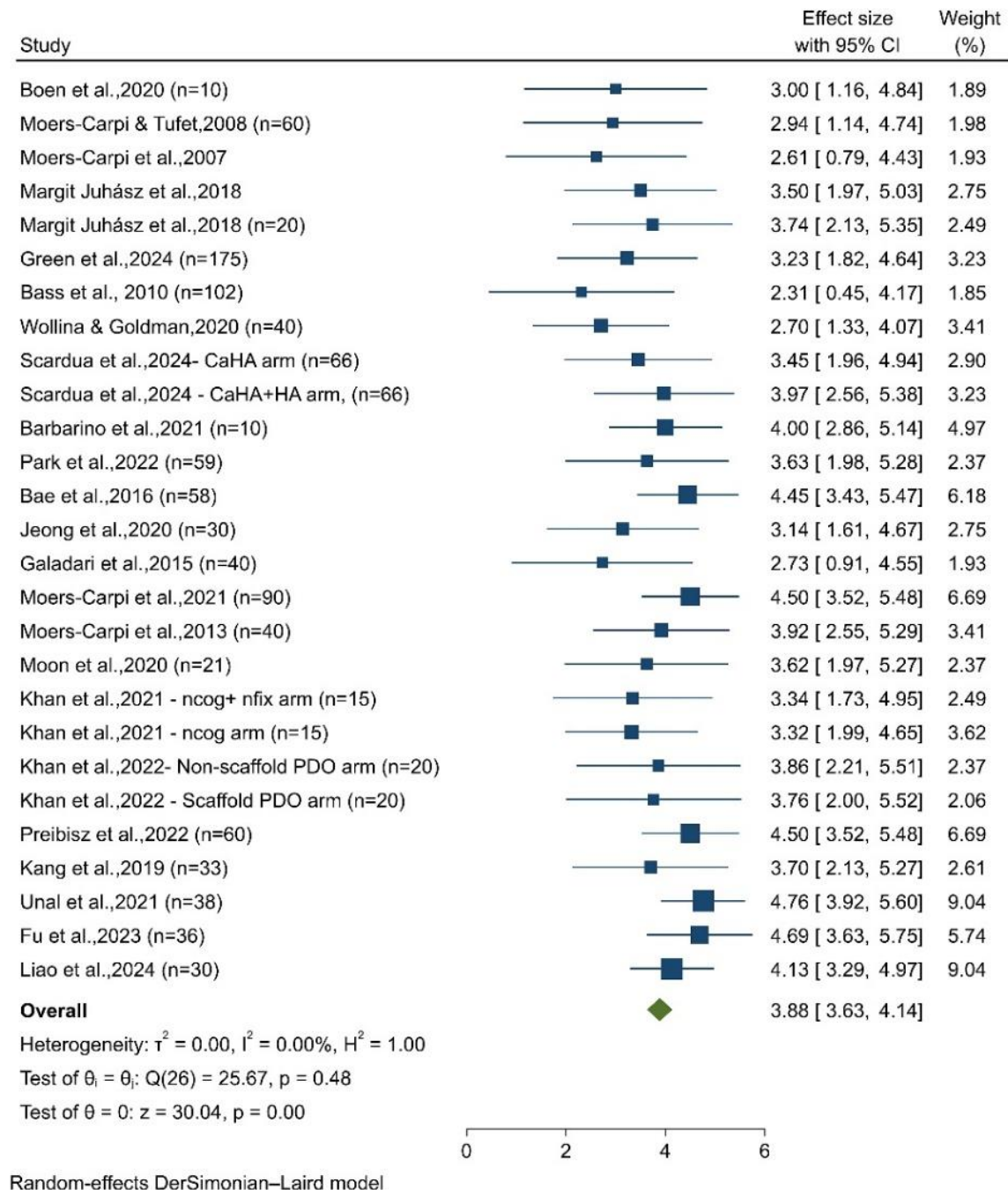


Figure 6 Forest plot of pooled Global Aesthetic Improvement Scale (GAIS) scores from all included studies.

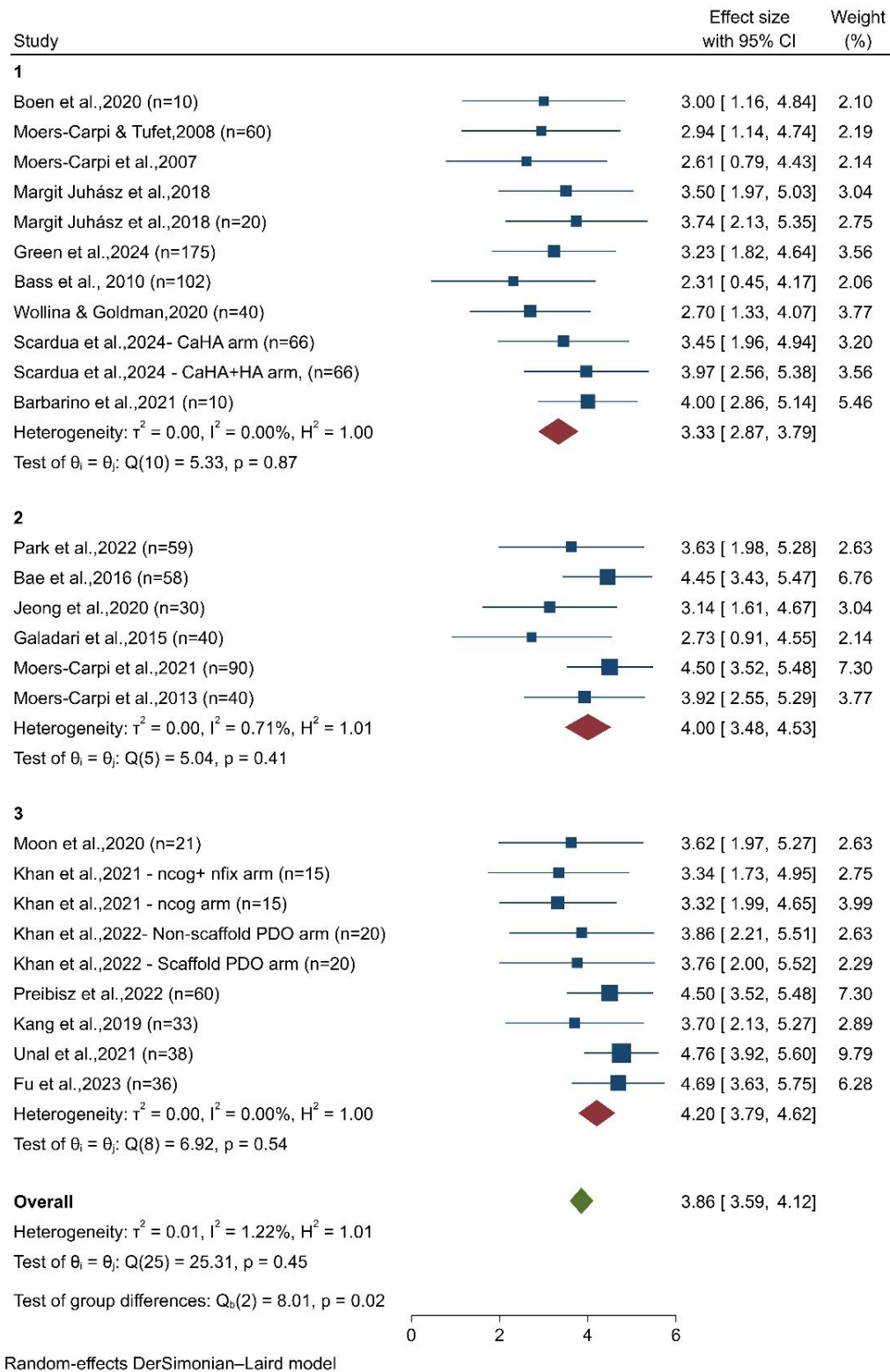


Figure 7 Subgroup meta-analysis of Global Aesthetic Improvement Scale (GAIS) scores by biostimulator type:
Group 1 = CaHA, Group 2 = PCL, Group 3 = PDO

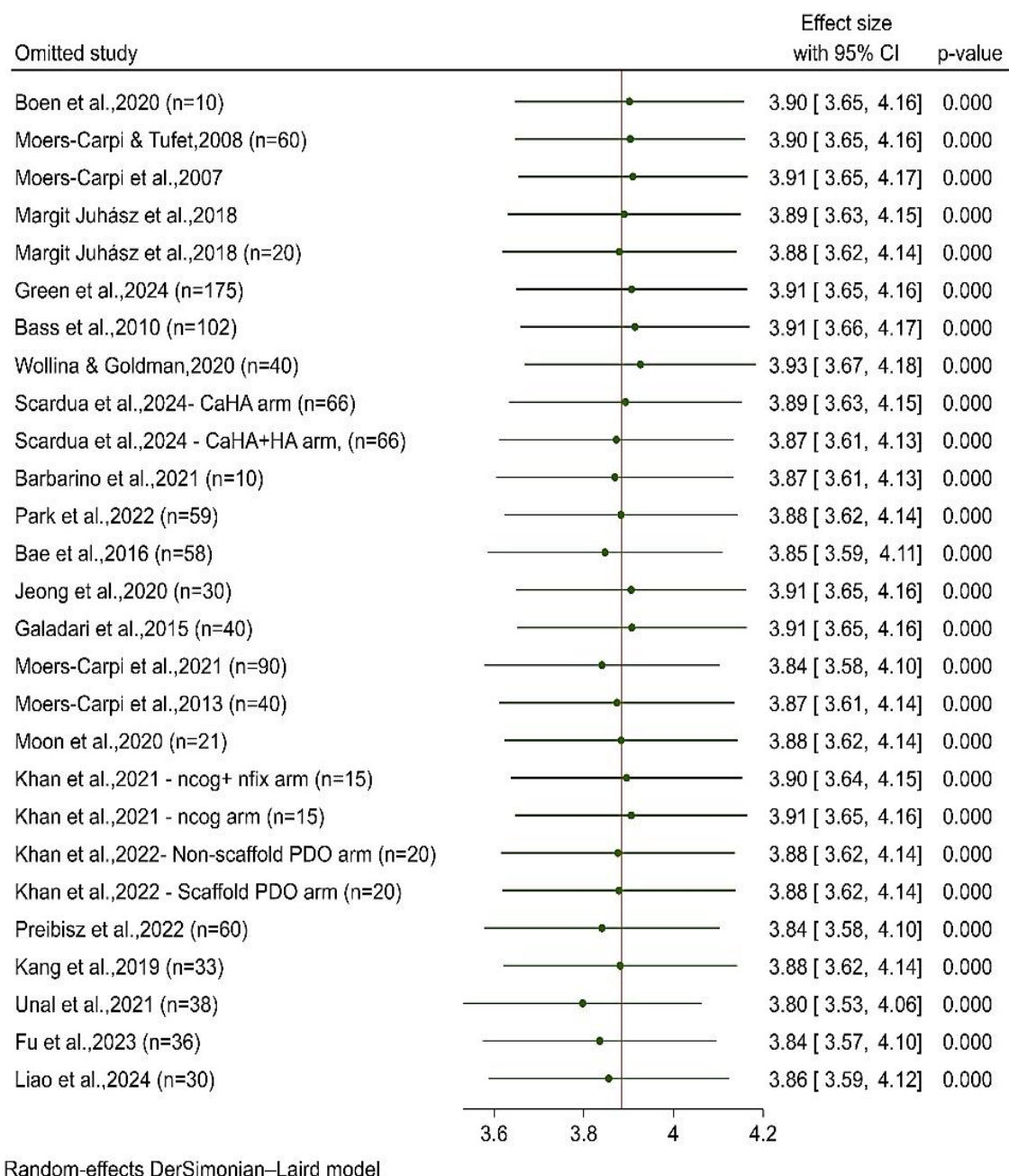


Figure 8 Leave-one-out sensitivity analysis of Global Aesthetic Improvement Scale (GAIS) scores for all included treatment arms

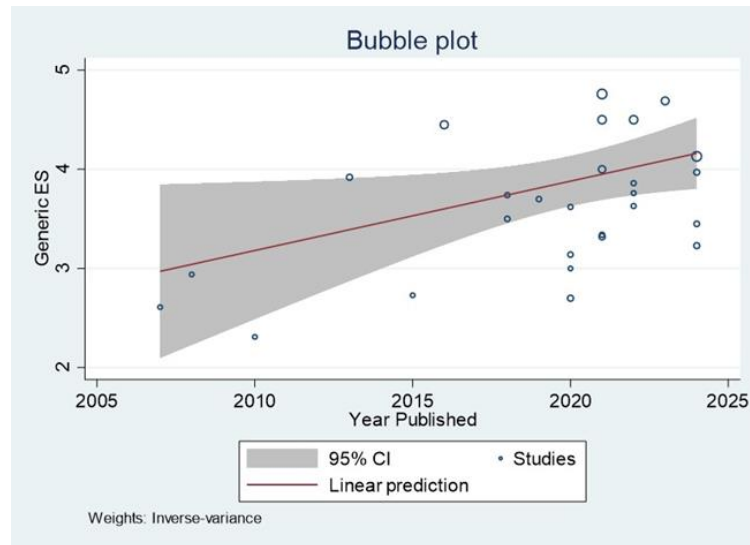


Figure 9 Bubble plot from meta-regression analysis assessing the association between year of publication and Global Aesthetic Improvement Scale (GAIS) scores

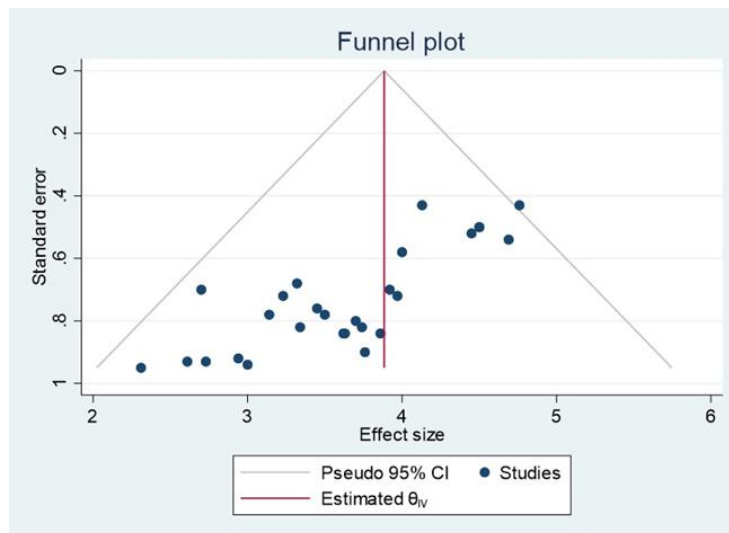


Figure 10 Funnel plot assessing potential publication bias in studies reporting Global Aesthetic Improvement Scale (GAIS) scores

4.9 Certainty of Evidence (GRADE)

The certainty of evidence for the primary outcome (GAIS) was rated as low, primarily due to risk of bias and indirectness. Although statistical heterogeneity was minimal ($I^2 = 0\%$), most included studies were non-randomized, and the outcome was based on a subjective ordinal scale analyzed as a continuous variable, with limited direct comparisons to a no-treatment control.

For adverse events, the certainty of evidence was rated as very low due to risk of bias and indirectness. Adverse events were inconsistently reported across studies, often relying on non-standardized clinical reporting, which limits confidence in the estimates.

A summary of findings table presenting the GRADE assessments is provided in Table 3.

Table 3 Summary of findings: Collagen biostimulators compared with no treatment for facial aesthetic outcomes (GRADE Assessment). Generated using GRADEpro GDT

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No. of participa nts (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no treatment	Risk with Collagen Biostimulators				
Aesthetic improvement (GAIS) assessed with :Global Aesthetic Improvement Scale from :1 to 5 Follow-up :range 1 month to 26 months		Pooled mean GAIS: 3.88 (95% CI 3.63 to 4.14)	-	1379 (24 studies: 8 randomized, 16 non- randomized)	○○⊕⊕ Low ^{a,b}	Collagen biostimulators likely improve aesthetic outcomes, with a mean increase of 3.88 points on the GAIS scale (95 %CI 3.63 to 4.14)
Adverse events (AEs) assessed with : Clinical reporting Follow-up: range 1 to 26 months				952 (19 non- randomized studies)	○○○○⊕ Very low ^{c,d}	Adverse events were generally mild and transient, including swelling, tenderness, bruising, and nodules, with no serious complications consistently reported.

Abbreviation: CI: confidence interval,

Explanations:

- a. Downgraded one level due to risk of bias, as the evidence was predominantly derived from non-randomized studies with moderate overall risk of bias, particularly related to confounding, outcome measurement, and selective reporting.
- b. Downgraded one level due to indirectness, as the primary outcome (GAIS) is a subjective measure and direct comparisons with a no-treatment control were limited or inconsistent across studies.
- c. Downgraded one level due to risk of bias, as the evidence was derived from non-randomized studies with potential underreporting, inconsistent assessment, and selective reporting of adverse events.
- d. Downgraded one level due to indirectness, as adverse events were variably defined and assessed across studies, relying on non-standardized clinical reporting without predefined criteria.

5. Discussion

Collagen biostimulators have become an integral component of aesthetic dermatology due to their regenerative properties and capacity to promote sustained tissue remodeling. Despite their widespread use, comparative evidence across different biostimulators remains limited, underscoring the need for a more comprehensive evaluation.

This systematic review and meta-analysis synthesized evidence from 24 original studies encompassing 27 treatment arms that evaluated the efficacy of collagen biostimulators for facial aesthetics using the Global Aesthetic Improvement Scale (GAIS) as the primary outcome. The pooled GAIS score of 3.88 (95% CI: 3.63–4.14) indicates overall improvements ranging from “improved” to “much improved.”

Statistical heterogeneity was low ($I^2 \approx 0\%$), which is somewhat unexpected given the clinical and methodological variability across the included

studies. This finding should be interpreted with caution. One possible explanation is the use of the Global Aesthetic Improvement Scale (GAIS), which is a subjective and relatively coarse ordinal scale. When treated as a continuous variable, such scales may exhibit ceiling or floor effects and reduced measurement sensitivity, thereby attenuating between-study variability and potentially resulting in artificially low estimates of heterogeneity.

In addition, apparent homogeneity may be influenced by selective outcome reporting across studies, particularly if studies preferentially report favorable or similar results. From a statistical perspective, under the DerSimonian–Laird random-effects model, the estimation of between-study variance (τ^2) may be unstable when true variability is low or when outcome measures lack sufficient dispersion. Furthermore, the Q-statistic used to assess heterogeneity has limited statistical power when the number of included studies is small, increasing the

risk of failing to detect true between-study variability. Consequently, I^2 estimates derived under these conditions should be interpreted with caution, as they may underestimate the true extent of heterogeneity (Borenstein et al., 2009; Higgins et al., 2003).

Therefore, the observed low heterogeneity should not be interpreted as evidence of true clinical or methodological consistency but rather as a reflection of measurement limitations, potential reporting biases, and inherent constraints in heterogeneity estimation.

Subgroup analyses demonstrated differences in mean GAIS scores between products, with higher mean GAIS scores observed for PDO (4.20), PCL (4.00), and CaHA (3.33). However, these findings should be interpreted with caution and considered exploratory, particularly given the limited number of studies for certain subgroups. The comparisons are indirect and may be influenced by multiple confounding factors, including differences in study design, patient characteristics, follow-up duration, injection techniques, and dosing protocols. No eligible PDLA studies and only one PLLA study met the inclusion criteria for quantitative synthesis, highlighting important evidence gaps.

A meta-regression analysis based on publication year demonstrated a slight upward trend in effect size over time; however, this association was not statistically significant. This finding may suggest potential improvements in treatment techniques or patient selection in more recent studies, although the lack of statistical significance limits definitive interpretation.

Differences in observed outcomes may be related to underlying material properties, particularly degradation kinetics and histologic response. CaHA provides an immediate scaffold that stimulates early collagen deposition, whereas PCL undergoes slower degradation, supporting more prolonged collagen remodeling. In contrast, PDO is associated with more rapid resorption and a shorter duration of tissue response. These differences in degradation kinetics and histologic behavior may contribute to variations in clinical outcomes; however, such mechanistic interpretations remain speculative in the absence of direct comparative evidence and should be interpreted with caution.

From a clinical perspective, collagen biostimulators appear to provide meaningful aesthetic improvement across a range of facial indications. Treatment outcomes may vary by anatomical site, as differences in skin thickness, vascularity, and

mechanical stress can influence both efficacy and safety. In the included studies, a range of anatomical regions were treated, including the forehead, midface, lower face, nasolabial folds, temples, jawline, and tear trough. Although consistent site-specific patterns could not be established due to heterogeneous reporting, these regions present distinct structural and aesthetic demands: more delicate areas, such as the tear trough and forehead, may require subtle and controlled tissue responses to avoid visibility or irregularities, whereas volume-deficient regions, such as the midface and nasolabial folds, often benefit from greater volumization and support. In contrast, areas such as the jawline and lower face may prioritize structural definition and contouring. However, the ability to derive site-specific recommendations remains limited by inconsistencies in the available data. Cost-effectiveness was not formally evaluated but is likely to influence clinical decision-making, given differences in product longevity, retreatment intervals, and variability in pricing across settings, which may limit the generalizability of economic comparisons.

The included studies reported follow-up durations ranging from 1 to 26 months, with 12 months being the most frequently reported time point. Overall, a descriptive review of the available data suggests that GAIS outcomes were generally maintained across follow-up periods, although this interpretation is limited by heterogeneity in follow-up duration and reporting.

Although favorable safety profiles were reported, heterogeneity in adverse event definitions and reporting precluded quantitative synthesis, thereby limiting conclusions regarding comparative safety.

This review has several strengths. It was conducted in accordance with the PRISMA guidelines and supported by a comprehensive multi-database search strategy, enhancing the completeness of study identification. The use of validated tools for risk-of-bias assessment (RoB 2 and ROBINS-I) strengthens the methodological rigor of the evaluation. The inclusion of both randomized and non-randomized studies allowed for a broader representation of real-world clinical practice. In addition, the application of random-effects models, subgroup analyses, and sensitivity analyses enhances the robustness and reliability of the findings. The use of a standardized and widely reported outcome measure (GAIS) also facilitated quantitative synthesis across heterogeneous studies.

Several included studies reported commercial or industry support. Specifically, studies by Juhász et al. (2018) and Green et al. (2024) reported funding or support from Merz North America, while Moers-Carpi & Sherwood (2013) reported funding from AQTIS Medical. In addition, Preibisz et al. (2022) reported support from Croma-Pharma GmbH and the provision of study materials by Grand Aespio Inc., indicating further industry involvement. Industry support was not reported in the remaining studies, although the absence of reporting does not necessarily indicate the absence of funding.

A notable proportion of the included studies were supported by industry, which may introduce bias, as industry-sponsored studies are more likely to report favorable efficacy outcomes and may underreport adverse events. This is particularly relevant given that the primary outcome (GAIS) is a subjective measure and therefore susceptible to expectation and reporting bias. Additionally, selective publication of positive findings cannot be excluded.

Consequently, the presence of commercial support across several included studies may have contributed to the relatively high and consistent GAIS scores observed. From a GRADE perspective, this concern further supports downgrading the certainty of evidence to a low level due to risk of bias and potential publication bias and indicates that the observed treatment effects may be overestimated, such that the true effect is likely to be smaller than the pooled estimate; therefore, the findings should be interpreted with caution.

Several limitations should be considered. These include the underrepresentation of certain biostimulators, particularly PDLLA and PLLA, and reliance on a subjective outcome measure (GAIS), which was analyzed as a continuous variable despite its ordinal nature, potentially introducing measurement limitations. Substantial variability in follow-up durations without formal adjustment may have influenced the pooled estimates and contributed to between-study heterogeneity. In addition, the lack of standardization in dosing, injection volume, and technique across studies may have introduced further heterogeneity.

At the study level, variability in methodological quality, potential selective reporting, and the inclusion of non-randomized designs may have introduced bias. In addition, publication bias cannot be excluded. The assessment of publication bias was primarily based on visual inspection of the funnel plot, which is inherently subjective and may

limit the reliability of the interpretation. Furthermore, the influence of industry funding in several included studies may have affected the reported outcomes. These factors may limit the internal validity of the findings.

Overall, this study provides a quantitative synthesis of available evidence on collagen biostimulators in facial aesthetics. These findings suggest clinically meaningful improvement; however, conclusions regarding comparative effectiveness should be interpreted with caution given the low certainty of evidence. Based on the GRADE assessment, the overall certainty for the primary outcome (GAIS) was low, primarily due to risk of bias and indirectness, including reliance on subjective outcome measures and the absence of direct head-to-head comparisons.

For adverse events, the certainty of evidence was very low, reflecting limitations in study design, inconsistent definitions, and non-standardized reporting across studies. These factors substantially limit confidence in safety estimates and highlight the need for more rigorous and standardized adverse event reporting in future studies.

Future research should prioritize head-to-head randomized controlled trials with standardized protocols and outcome measures. Long-term studies are needed to better assess durability, along with standardized reporting of follow-up intervals to facilitate meaningful comparisons across studies. The incorporation of objective assessment tools may improve outcome precision. Broader inclusion of diverse populations will enhance generalizability and support more tailored treatment selection.

6. Conclusion

This systematic review and meta-analysis demonstrate that collagen biostimulators appear to provide clinically meaningful improvements in facial aesthetics, as measured by the Global Aesthetic Improvement Scale (GAIS). Pooled results showed negligible heterogeneity, with PDO and PCL achieving the highest mean GAIS scores, followed by CaHA. Although adverse events were generally reported as mild and transient, heterogeneity in reporting limits definitive conclusions regarding safety. Evidence gaps remain for PDLLA and PLLA. These findings may support the use of collagen biostimulators in individualized treatment planning, with product selection tailored to patient characteristics, desired longevity, and anatomical considerations. Future high-quality, head-to-head

trials with standardized outcome measures, objective assessment tools, and longer follow-up are needed to strengthen the evidence base and inform clinical decision-making in aesthetic dermatology.

7. Supplementary document

Supplementary material for this manuscript can be accessed at the following link:
https://drive.google.com/file/d/1WJDtHqrQTAYFPsdTeT_VQKDDPrAvQFHI/view?usp=sharing

8. Acknowledgements

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. No funding was received for this research. The authors declare no conflict of interest.

9. CRediT Statement

Punyaporn Tiewrungrangsuk: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Arisa Kaewkes: Investigation, Data curation, Supervision.

Charnsiri Segsarnviriya: Validation, Supervision.

Suparuj Lueangarun: Supervision.

Peerapong Prabhakornritta: Validation.

Rosalyn Kupwiat: Supervision.

Mart Maiprasert: Project administration.

10. Abbreviations

Abbreviation	Full Term
AE	Adverse events
CaHA	Calcium hydroxylapatite
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
GAIS	Global Aesthetic Improvement Scale
GRADE	Grading of Recommendations Assessment, Development and Evaluation
PCL	Polycaprolactone
PDLLA	Poly-D,L-lactic acid
PLLA	Poly-L-lactic acid
PDO	Polydioxanone
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
RoB 2	Risk of Bias 2 tool

Abbreviation Full Term

ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
----------	---

11. References

- Amiri, M., Mecani, R., Llanaj, E., Niehot, C. D., Phillips, T. L., Goldie, K., ... & Daughtry, H. (2024). Calcium hydroxylapatite (CaHA) and aesthetic outcomes: A systematic review of controlled clinical trials. *Journal of Clinical Medicine*, 13(6), Article 1686. <https://doi.org/10.3390/jcm13061686>
- Bae, B., Lee, G., & Hong, K. (2016). Safety and long-term efficacy of forehead contouring with a polycaprolactone-based dermal filler. *Dermatologic Surgery*, 42(11), 1256-1260. <https://doi.org/10.1097/DSS.0000000000000913>
- Barbarino, S. C. (2021). Correction of temporal wasting using calcium hydroxylapatite with integral lidocaine: An underused procedure for enhancing overall facial appearance. *Journal of Cosmetic Dermatology*, 20(1), 62-66. <https://doi.org/10.1111/jocd.13505>
- Bass, L. S., Smith, S., Busso, M., & McClaren, M. (2010). Calcium hydroxylapatite (Radiesse) for treatment of nasolabial folds: Long-term safety and efficacy results. *Aesthetic Surgery Journal*, 30(2), 235-238. <https://doi.org/10.1177/1090820X10366549>
- Boen, M., Alhaddad, M., Goldman, M. P., Kollipara, R., Hoss, E., & Wu, D. C. (2020). A randomized, evaluator-blind, split-face study evaluating the safety and efficacy of calcium hydroxylapatite for jawline augmentation. *Dermatologic Surgery*, 48(1), 76-81. <https://doi.org/10.1097/DSS.0000000000002582>
- Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to meta-analysis*. John Wiley & Sons. <https://doi.org/10.1002/9780470743386>
- Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. J. H. W. (2019). Cochrane handbook for systematic reviews of interventions (2nd ed.). *Hoboken: Wiley*, 4(1002), Article 14651858.
- Corduff, N. (2020). An alternative periorbital treatment option using calcium hydroxyapatite for hyperpigmentation associated with the tear trough deformity. *Plastic and Reconstructive Surgery–Global Open*, 8(2), Article e2633. <https://doi.org/10.1097/GOX.0000000000002633>

- Fu, X., Qiao, J., Liu, J., Chen, Y., Jin, Q., Xu, S., ... & Niu, F. (2023). Stab access fascia suspension lift: A facelift technique without skin excision and visible scar. *Journal of Cosmetic Dermatology*, 22(3), 897-906. <https://doi.org/10.1111/jocd.15496>
- Galadari, H., van Abel, D., Al Nuami, K., Al Faresi, F., & Galadari, I. (2015). A randomized, prospective, blinded, split-face, single-center study comparing polycaprolactone to hyaluronic acid for treatment of nasolabial folds. *Journal of Cosmetic Dermatology*, 14(1), 27-32. <https://doi.org/10.1111/jocd.12126>
- Green, J. B., Del Campo, R., Durkin, A. J., Funt, D. K., Nasrallah, N., Martinez, K., & Moradi, A. (2024). Long-term duration and safety of Radiesse (+) for the treatment of jawline. *Journal of Cosmetic Dermatology*, 23(10), 3202-3209. <https://doi.org/10.1111/jocd.16436>
- Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, 327(7414), 557-560. <https://doi.org/10.1136/bmj.327.7414.557>
- Jeong, G. J., Ahn, G. R., Park, S. J., Hong, J. Y., & Kim, B. J. (2020). A randomized, patient/evaluator-blinded, split-face study to compare the efficacy and safety of polycaprolactone and polynucleotide fillers in the correction of crow's feet: the latest biostimulatory dermal filler for crow's feet. *Journal of Cosmetic Dermatology*, 19(7), 1593-1599. <https://doi.org/10.1111/jocd.13199>
- Juhász, M. L., Levin, M. K., & Marmur, E. S. (2018). Pilot study examining the safety and efficacy of calcium hydroxylapatite filler with integral lidocaine over a 12-month period to correct temporal fossa volume loss. *Dermatologic Surgery*, 44(1), 93-100. <https://doi.org/10.1097/DSS.0000000000001268>
- Kang, S. H., Moon, S. H., Rho, B. I., Youn, S. J., & Kim, H. S. (2019). Wedge-shaped polydioxanone threads in a folded configuration ("Solid fillers"): A treatment option for deep static wrinkles on the upper face. *Journal of Cosmetic Dermatology*, 18(1), 65-70. <https://doi.org/10.1111/jocd.12557>
- Khan, G., Ahn, K. H., Kim, S. Y., & Park, E. (2021). Combined press cog type and cog PDO threads in comparison with the cog PDO threads in facial rejuvenation. *Journal of Cosmetic Dermatology*, 20(10), 3294-3298. <https://doi.org/10.1111/jocd.14092>
- Khan, G., Kim, B. J., Kim, D. G., & Park, E. (2022). Retrospective study of the absorbable braided polydioxanone threads' usefulness in the aged lower eyelids' rejuvenation. *Journal of Cosmetic Dermatology*, 21(11), 5952-5956. <https://doi.org/10.1111/jocd.15257>
- Liao, Z. F., She, Y. H., Huang, J. M., Yang, W., Lou, X., Pan, B. H., ... & Luo, S. K. (2024). Cross-linked sodium hyaluronate gel with PLLA-b-PEG microsphere for facial contouring in Chinese: A retrospective study. *Aesthetic Plastic Surgery*, 48(21), 4252-4261. <https://doi.org/10.1007/s00266-024-04195-8>
- Moers-Carpi, M., Christen, M. O., Delmar, H., Brun, P., Bodokh, I., & Kestemont, P. (2021). European multicenter prospective study evaluating long-term safety and efficacy of the polycaprolactone-based dermal filler in nasolabial fold correction. *Dermatologic Surgery*, 47(7), 960-965. <https://doi.org/10.1097/DSS.0000000000002978>
- Moers-Carpi, M. M., & Tufet, J. O. (2008). Calcium hydroxylapatite versus nonanimal stabilized hyaluronic acid for the correction of nasolabial folds: A 12-month, multicenter, prospective, randomized, controlled, split-face trial. *Dermatologic Surgery*, 34(2), 210-215. <https://doi.org/10.1097/00042728-200802000-00010>
- Moers-Carpi, M. M., & Sherwood, S. (2013). Polycaprolactone for the correction of nasolabial folds: A 24-month, prospective, randomized, controlled clinical trial. *Dermatologic Surgery*, 39(3pt1), 457-463. <https://doi.org/10.1111/dsu.12054>
- Moers-Carpi, M. M., Vogt, S., Santos, B. M., Planas, J., Vallve, S. R., & Howell, D. J. (2007). A multicenter, randomized trial comparing calcium hydroxylapatite to two hyaluronic acids for treatment of nasolabial folds. *Dermatologic Surgery*, 33, S144-S151. <https://doi.org/10.1111/j.1524-4725.2007.33354.x>
- Moon, H. J., Chang, D., & Lee, W. (2020). Short-term treatment outcomes of facial rejuvenation using the mint lift fine. *Plastic and Reconstructive Surgery-Global Open*,

- 8(4), Article e2775.
<https://doi.org/10.1097/GOX.0000000000002775>
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372, Article n71. <https://doi.org/10.1136/bmj.n71>
- Park, J. W., Choi, S. Y., Kim, K. R., Jin, M., Seok, J., Yoo, K. H., & Kim, B. J. (2022). A randomized, participant-and evaluator-blinded, matched-pair prospective study to compare the safety and efficacy between polycaprolactone-based fillers in the correction of nasolabial folds. *Dermatologic Therapy*, 35(7), Article e15508. <https://doi.org/10.1111/dth.15508>
- Preibisz, L., Boulmé, F., & Paul Lorenc, Z. (2022). Barbed polydioxanone sutures for face recontouring: six-month safety and effectiveness data supported by objective markerless tracking analysis. *Aesthetic Surgery Journal*, 42(1), NP41-NP54. <https://doi.org/10.1093/asj/sjab359>
- Scardua, N., Rovaris, D. P., Moreira, K. M. S., Guimarães, A. L. S., & Scardua, M. T. (2024). Supraperiosteal technique protocol for forehead filling with a mixture of calcium hydroxyapatite and hyaluronic acid: Double-blind, randomized controlled clinical trial. *Journal of Cosmetic Dermatology*, 23(12), 4116-4122. <https://doi.org/10.1111/jocd.16488>
- Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*, 366, Article 14898. <https://doi.org/10.1136/bmj.14898>
- Trinh, L. N., Grond, S. E., & Gupta, A. (2022). Dermal fillers for tear trough rejuvenation: A systematic review. *Facial Plastic Surgery*, 38(03), 228-239. <https://doi.org/10.1055/s-0041-1731348>
- Unal, M., İslamoğlu, G. K., Ürün Unal, G., & Köylü, N. (2021). Experiences of barbed polydioxanone (PDO) cog thread for facial rejuvenation and our technique to prevent thread migration. *Journal of Dermatological Treatment*, 32(2), 227-230. <https://doi.org/10.1080/09546634.2019.1640347>
- Wollina, U., & Goldman, A. (2020). Long lasting facial rejuvenation by repeated placement of calcium hydroxylapatite in elderly women. *Dermatologic Therapy*, 33(6), Article e14183. <https://doi.org/10.1111/dth.14183>