



ELSEVIER

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Review

Evaluating the clinical and economic impact of ceramide-infused skin barriers in patients with Intestinal and urinary stomas: A systematic review and meta-analysis

Rosario Caruso, PhD, RN, FESNO, FAAN^{1,2,*}, Silvia Belloni, PhD, RN^{3,#},
Beniamino Schiavone, MD^{4,#}, Gianluca Conte, PhD, RN², Cristina Di Pasquale, RN⁵,
Arianna Magon, PhD, RN², Cristina Arrigoni, RN, MSc³, Giuseppe Candilio, MD⁶,
Francesco Stanzione, MD⁶, Alessandro Stievano, PhD, MSN, MEd, FAAN, FEANS, FESNO,
FFNMRCISI, FTNSS^{7,9}, Gennaro Rocco, PhD, RN, FFNMRCISI, FESNO, FAAN^{8,10}, Maddalena De
Maria, PhD, RN, FESNO¹⁰

¹ Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

² uni, IRCCS Policlinico San Donato, San Donato Milanese, Italy

³ Department of Public Health, Experimental and Forensic Medicine, Section of Hygiene, University of Pavia, Pavia, Italy

⁴ Department of Clinical Pathology and Molecular Biology, Pineta Grande Hospital, Castel Volturno, Italy

⁵ Stomal Therapy Outpatient Service, European Institute of Oncology IRCCS, Milan, Italy

⁶ Department of General Surgery, Pineta Grande Hospital, Castel Volturno, Italy

⁷ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

⁸ Faculty of Medicine, Catholic University "Our Lady of Good Counsel", Tirana, Albania

⁹ Center of Excellence for Nursing Scholarship, OPI of Rome, Rome, Italy

¹⁰ Department of Life Health Sciences and Health Professions, Link Campus University, Rome, Italy

ARTICLE INFO

Key words:

Ceramide-infused skin barriers
Cost-effectiveness
Meta-analysis
Peristomal skin complications
Quality-adjusted life days
Systematic review

ABSTRACT

Purpose: Ceramide-infused skin barriers (CIBs) applied to stoma care hold potential benefits, which are thus far not summarized. This study aims to summarize the literature on CIBs in patients with intestinal and urinary stomas and to quantitatively compare the clinical, economic, and well-being outcomes of CIBs against the standard of care (SOC) in these patients.

Methods: Systematic review and random-effect meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, including meta-regression analyses to explore sources of heterogeneity. PubMed, CINAHL, Scopus, Web of Science, Embase, Google Scholar, and clinicaltrials.gov were searched for studies published up to November 2024. Studies involving patients of any age with intestinal or urinary stomas treated with CIBs or SOC. Outcomes included peristomal skin complications (PSCs), cost-effectiveness, and quality-adjusted life days (QALDs).

Findings: CIBs increased the odds of preventing PSCs by 77% compared to SOC (OR = 1.77, 95% CI: 1.40, 2.23). Cost savings averaged -140,000 USD per patient (95% CI: -142,000 USD, -139,000 USD), although cost-effectiveness varied significantly ($I^2 = 100\%$, $P < 0.001$). Meta-regression identified gross domestic product (GDP) per capita ($\beta = -7.31$, $P = 0.010$) and healthcare expenditure per capita ($\beta = -169.33$, $P < 0.001$) as key contributors to cost variability. CIBs also improved QALDs (MD = 0.35, 95% CI: 0.33, 0.37), enhancing patient quality of life.

Implications: CIBs reduce PSCs, generate cost savings, and improve QALDs, demonstrating potential for widespread clinical adoption. However, economic benefits vary across healthcare systems, warranting further research into their long-term impact and country-specific cost-effectiveness.

* Address correspondence to: Rosario Caruso, Health Professions Research, Department of Biomedical Sciences for Health, University of Milan, Milan, Italy.

E-mail address: rosario.caruso@grupposandonato.it (R. Caruso).

These authors are equally considered second authors.

<https://doi.org/10.1016/j.clinthera.2025.02.001>

Accepted 10 February 2025

Available online xxx

0149-2918/© 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Introduction

Patients with intestinal and urinary stomas, such as colostomies, ileostomies, and urostomies, present significant clinical challenges due to complications like peristomal skin conditions (PSCs), which can seriously affect their quality of life.^{1,2} These procedures are performed for a variety of medical conditions, most notably colorectal cancer, inflammatory bowel disease (IBD), and bladder cancer.^{3–6} Colorectal cancer is one of the most common malignancies requiring colostomy, with surgical resection often necessitating the creation of a permanent or temporary stoma.⁶ Patients with IBD, including Crohn's disease and ulcerative colitis, may require ileostomy formation, particularly in cases of severe disease refractory to medical management or as part of staged surgical interventions.⁷ Bladder cancer is a primary indication for urostomy, often following radical cystectomy when bladder preservation is not feasible.^{4,5} In addition to malignancies and inflammatory conditions, stomas may also be required in cases of traumatic bowel or bladder injury, congenital abnormalities such as Hirschsprung's disease, or severe diverticular disease.^{8–10}

Globally, the number of these surgical procedures is increasing due to rising rates of colorectal cancer, inflammatory bowel disease, and bladder cancer, with approximately 700,000 people in Europe currently living with an ostomy.¹¹ Although stomas are life-saving, they often result in complications that can significantly impact patients' quality of life.^{1,2,11,12} Among the most common of these complications are PSCs, which mainly arise from moisture, digestive enzymes, or mechanical irritation caused by poorly fitting ostomy appliances.^{1,11} The type and permanence of the ostomy influence the impact and severity of PSCs. Ostomies could be classified into temporary and permanent stomas, each with distinct clinical implications.¹³ Temporary stomas, such as diverting ileostomies, are often created to protect anastomosis during bowel resection and are intended for later reversal.¹⁴ Despite their short-term nature, they could still cause significant PSCs due to high-output effluent and increased moisture exposure. Permanent stomas, such as colostomies following cancer resection or urostomies after cystectomy, require lifelong management, making peristomal skin integrity a critical factor in long-term quality of life.¹⁴ Additionally, the anatomical location of the stoma influences the likelihood of developing PSC. Ileostomies are associated with higher leakage rates, as their liquid and enzymatic output increases skin irritation and erosion risk.¹⁴ Colostomies generally produce a more formed stool, reducing excessive moisture exposure, but poorly fitted appliances can still lead to mechanical irritation and chronic PSCs. Urostomies pose unique challenges due to continuous urine flow, which can lead to alkaline encrustation, chronic leakage, and a higher risk of urinary-related PSCs.⁴

Standard skin barriers are widely used to manage PSCs but are often inadequate, leaving patients vulnerable to ongoing skin irritation, discomfort, and infection.¹⁵ The challenges of preventing and managing PSCs underscore the need for more effective interventions that could protect the skin and improve patients' overall well-being.^{16–18} In recent years, ceramide-infused skin barriers (CIBs) have emerged as a promising approach for maintaining the health of the peristomal area, improving skin health, and reducing peristomal complications. These barriers protect the skin from stoma effluent and help prevent PSCs.¹⁹

Ceramides, naturally occurring lipids in the skin, play a critical role in maintaining the skin's barrier function and hydration.^{19,20} Ceramides enhance the skin barrier function by replenishing the natural lipids that form the lamellar structure of the barrier. When incorporated into ostomy skin barriers, ceramides strengthen the skin's protective layer, reduce moisture loss, and lower the risk of irritation, erosion, and infection.²¹ This enhanced barrier function is expected to improve patient comfort, reduce complications, and ultimately contribute to better clinical outcomes. Some clinical research and cost-effectiveness analysis have shown that CIB seems to offer significant benefits over standard skin barriers.^{22–25} Early findings also suggest that these barriers may

provide a longer wear time, leading to fewer appliance changes, reduced healthcare costs, and increased patient convenience.^{24,25}

However, despite these promising results, several gaps remain.^{22–25} Current standard of care (SOC) methods, such as hydrocolloid-based barriers, while effective in some cases, show limitations in preventing PSCs, particularly in high-risk patients.^{22–25} Despite previous studies on CIBs suggesting potential benefits in enhancing skin hydration and barrier function, several gaps remain.²⁵ The overall impact of CIBs on cost-effectiveness, PSC prevention, and quality-adjusted life days (QALDs)—a measure that combines the quantity and quality of life, reflecting both the duration and well-being of patients—has not been comprehensively explored and summarized. QALDs represent a metric that combines both duration and quality of life, conceptually akin to quality-adjusted life years (QALYs) but adapted to assess shorter time frames.²⁶ Unlike QALYs, which assess long-term health outcomes, QALDs provide a more granular assessment of daily well-being, making them particularly relevant for evaluating interventions to improve skin integrity and reduce stoma-related complications in the short term.²⁶

In this context, it is relevant to consider that ostomy care's economic burden is highly variable across healthcare systems, depending on reimbursement policies, healthcare spending, and resource allocation.²⁷ In high-income countries with well-established reimbursement models, the cost-effectiveness of CIBs may be less pronounced due to broader access to standard ostomy care supplies.²⁷ Conversely, in middle-income countries where healthcare resources are more constrained, out-of-pocket expenses for ostomy products may limit patient access to optimal skin barriers, potentially exacerbating PSCs.²⁸ Countries with universal healthcare systems often provide full or partial coverage for ostomy care, whereas private or mixed healthcare systems may require individuals to bear a substantial portion of these costs.^{27,28} Such disparities raise important questions regarding the economic feasibility and equitable distribution of CIBs as a standard intervention across different healthcare settings.^{29–31}

Thus far, existing studies offer limited insight into these outcomes, and the available literature is fragmented.²⁴ As such, a systematic review is needed to consolidate the existing evidence and provide a clearer understanding of the intervention's role in improving patient outcomes and healthcare efficiency. This approach will pave the way for future research to address the current gaps and support clinicians in their decision-making processes, which are currently undermined by a fragmented literature framework. Given these gaps, this systematic review aims to summarize the literature on using CIBs in patients with intestinal and urinary stomas and to quantitatively compare the clinical, economic, and well-being outcomes of CIBs against the SOC in these patients.

Methods

Study Design

This systematic review, including a meta-analysis of outcomes related to the utilization of CIBs, was conducted as part of a predefined protocol registered on PROSPERO (CRD42023492933) and following the Cochrane handbook for systematic review of interventions.³² The review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.³³ The main research question guiding the review was: "What are the clinical, cost-effectiveness, and quality-of-life outcomes associated with using CIBs in patients with intestinal and urinary stomas?"

Search Strategy and Eligibility Criteria

The main research question was framed using the Population, Intervention, Comparison, Outcome, and Study Type (PICOS) framework.³² The population included people of any age with intestinal or urinary stomas. The intervention focused on using CIBs, with comparisons

drawn against standard care without CIBs, alternative interventions, or any other relevant comparators. The primary outcomes were the impact on PSCs as clinical outcomes and cost-effectiveness and well-being outcomes, such as QALDs. The review included primary studies or cost-effectiveness analysis studies.

Two independent reviewers (ADC and MI) independently conducted a systematic and comprehensive literature search across multiple databases, including PubMed, CINAHL, Scopus, Web of Science, Embase, Google Scholar, and clinicaltrials.gov, covering studies up to November 2024. A first discussion meeting was conducted to compare and unify the search strategies of the authors involved in the systematic searches (see Supplementary File 1). The search employed a combination of MeSH terms and free-text keywords developed following the PICOS framework, and the final queries are detailed in Supplementary File 1. Additionally, reference lists from prior systematic reviews and relevant articles were manually reviewed to ensure a thorough search.

The inclusion criteria encompassed studies involving patients with intestinal or urinary ostomies, using CIBs, and evaluating clinical outcomes, well-being measures, or cost-effectiveness data. Articles without empirical or real-world simulation data, such as commentaries, editorials, and perspective papers, were excluded because these types of articles, while valuable for providing opinions and theoretical insights, do not contribute to assessing the clinical and cost-effectiveness of CIBs. Studies that did not report on the specified outcomes of interest were also excluded as well. While no language restrictions were imposed during the search, articles in languages other than English were excluded if their full-text versions were inaccessible online due to the impracticality of translating non-HTML format articles into English. Discrepancies between the two reviewers during the double-blind selection process were resolved through consensus discussions, ensuring that any disagreements were carefully reviewed and reconciled based on the predefined inclusion criteria.

Selection Flow Strategy

The selection flow for this systematic review adhered to the PRISMA guidelines, following the four key phases: identification, screening, eligibility, and inclusion.³³ During the identification phase, comprehensive searches were conducted as detailed in the “Search strategy and eligibility criteria.” After removing duplicates, the titles and abstracts of the remaining studies were screened to assess their relevance based on the inclusion criteria. Studies that did not meet the inclusion criteria were excluded at this stage. In the eligibility phase, the full texts of the remaining studies were thoroughly reviewed to determine whether they reported relevant data on PSCs, cost-effectiveness, or QALDs related to CIBs. Studies that did not report these outcomes or lacked empirical data were excluded. Finally, in the inclusion phase, studies that met all the eligibility criteria were included in the systematic review and, where applicable, in the meta-analysis.

Outcomes

In this review, the primary outcomes of interest were PSCs, cost differences between CIBs and SOC, and QALDs. QALDs were selected as an outcome measure to provide a more sensitive assessment of peristomal skin health-related quality of life over shorter periods.²⁶ While adapted from the concept of QALYs, QALDs allow for a more precise evaluation of interventions targeting immediate improvements in skin integrity and patient comfort.²⁶

PSCs refer to skin issues that arise in the area surrounding the stoma, which could be caused by moisture, digestive enzymes, or mechanical irritation from poorly fitted ostomy appliances.^{15,21} Common PSCs include irritation, redness, inflammation, and skin erosion. These complications significantly impact the comfort and well-being of ostomy patients and frequently lead to infections or the need for frequent appliance changes.^{15,21}

Cost differences between CIBs and SOC assess the economic impact of using CIBs compared to non-CIB products.³⁴ This outcome is key for understanding the financial implications of adopting CIBs in healthcare settings, including direct healthcare costs such as product use, frequency of replacements, and healthcare visits, as well as potential long-term savings from reduced complications. In this study, all cost data were converted into US dollars (USD) by using the exchange rate from September 6th, 2024, to standardize comparisons across studies and ensure consistency in the analysis.

QALDs measure the quality of life adjusted for the time spent in a particular health state.^{35,36} QALDs provide insight into how the use of CIBs impacts patients’ overall health and well-being. An improvement in QALDs indicates that patients live longer and experience a better quality of life, free from significant discomfort or complications caused by PSCs.

Data Extraction

Information from each study was extracted in a tabular format to ensure consistency and clarity. The data extraction was conducted independently by 2 reviewers, and a third reviewer ensured the accuracy and consistency of the extracted information. The following details were recorded: authors, year of publication, country, study design, sample size, sample characteristics, study duration, type of ostomy barriers used, control group (if applicable), primary outcomes, time points assessed, adverse events, and key findings.

In addition, where feasible, data allowing for meta-analysis of (PSCs were extracted as rates of failures (i.e., PSCs) and successes (i.e., no PSCs) in both the intervention (CIB) and control (SOC) arms. For economic analysis, the overall mean cost of CIBs and SOCs was extracted for each country and group, with all cost data converted to USD using the exchange rate from September 6th, 2024. When standard deviations (SDs) were not directly reported, they were estimated using the range divided by four or with algebraic estimations, when feasible, as recommended by recent recommendations to deal with missing variances in meta-analyses.³⁷ Additionally, once the studies were included, we independently retrieved cost-effectiveness analysis data for GDP per capita and healthcare expenditure per capita, specific to the year of each study reporting cost-effectiveness analyses. This data was essential for evaluating potential economic variations between countries. The GDP per capita and healthcare expenditure per capita values were sourced from the following reputable global databases: World Bank (Source: World Bank GDP per capita)³⁸ and Organisation for Economic Co-operation and Development (OECD) (Source: OECD Health Expenditure).³⁹ In addition to extracting cost data from individual studies, we independently retrieved country-specific economic indicators, including GDP per capita and healthcare expenditure per capita, to assess how healthcare system differences influence cost-effectiveness outcomes. These indicators were sourced from the World Bank and the OECD.³⁹ This approach contextualized cost-effectiveness findings within each country’s specific economic and healthcare framework, improving the interpretability of cross-country comparisons.

Data on QALDs were extracted where available, specifically as the mean per group (CIB and SOC), along with the corresponding reported or estimated SDs.

Risk of Bias Assessment

In this study, several tools were employed to assess the risk of bias, which were specific to the study design of the eligible records.

The Risk of Bias 2 (ROB2) tool was used for randomized controlled trials (RCTs).⁴⁰ Developed by the Cochrane Collaboration, ROB2 is a domain-based evaluation tool designed specifically for RCTs. It assesses five key domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selective reporting of results. Each domain is evaluated, and the overall risk of bias for each study is categorized as “low

risk,” “some concerns,” or “high risk” of bias. This tool is widely recognized for its systematic approach to evaluating the internal validity of RCTs.

For non-randomized interventional studies, the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool was applied.⁴¹ ROBINS-I assesses the risk of bias in non-randomized studies that evaluate the effectiveness of interventions. It examines seven domains, including confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and the selection of reported results. Studies are rated as having “low,” “moderate,” “serious,” or “critical” risk of bias based on these domains. This tool is considered essential for evaluating non-randomized studies, where the absence of randomization could introduce systematic biases.⁴¹

For observational studies, including cohort and case-control designs, the Newcastle-Ottawa Scale (NOS) was used.⁴² The NOS evaluates studies based on three broad areas: the selection of study groups, the comparability of groups, and the ascertainment of outcomes. Studies are awarded stars based on the quality of their design, with a higher number of stars indicating a lower risk of bias. This scale is a well-established tool for assessing the quality of non-randomized studies in meta-analyses and systematic reviews.⁴²

In the assessment of economic evaluations, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was employed. CHEERS provides a standardized framework for reporting economic evaluations, ensuring that studies adequately describe the methods, data sources, perspective, comparators, time horizon, and results of the analysis. This checklist promotes transparency and comparability across economic studies, enhancing the reliability and usability of health economic evaluations.⁴³

Data Analysis

This review used random-effects models for all outcomes to account for the variability across studies, given the differences in patient populations and intervention products. These models assumed that variability between studies was not negligible, making them suitable for estimating the effect size for each outcome.

For PSCs, a random-effects restricted maximum likelihood model was applied to calculate the odds ratios (OR) for PSC rates between the intervention and control groups. This model adjusted for potential variations across studies and accounted for the likelihood of PSCs in both arms.

The DerSimonian–Laird random-effects method was used to summarize the results related to cost differences between CIBs and SOC by employing mean difference (MD) as effect size. This model allowed for estimating cost variations between the two interventions while accounting for the heterogeneity across studies. A meta-regression was performed to explore the sources of heterogeneity in the cost analysis. The year of publication, gross domestic product (GDP) per capita, healthcare expenditure per capita, and sample sizes for both CIB and SOC groups were included in the model to assess their impact on cost variations. The meta-regression results were reported using regression coefficients, standard errors, z-values, and 95% confidence intervals (CIs). More precisely, to evaluate how healthcare system variability affects cost-effectiveness, we conducted a meta-regression analysis incorporating GDP per capita and healthcare expenditure per capita as predictors of cost differences between CIBs and SOC. These variables were included to account for differences in purchasing power, healthcare resource allocation, and reimbursement models across countries. To better account for cross-country cost differences, we explicitly modeled economic variability by treating each country as a distinct analytical unit rather than pooling cost-effectiveness data across all settings. This approach prevented overgeneralization and provided a more precise understanding of the cost savings associated with CIBs in diverse healthcare environments.

Sensitivity analyses were conducted to determine each study’s influence on the overall results, and Galbraith plots were used to identify outliers or influential studies. Contour-enhanced funnel plots were generated to visually examine the potential for publication bias. Egger’s regression test was subsequently applied to statistically evaluate the symmetry of the funnel plots, providing a more objective measure of potential bias. For this outcome, it was possible to extract country-specific information included in the meta-analysis by treating countries as distinct units rather than individual studies. To ensure best practices and avoid overrepresentation, specific precautions were taken to handle the multiple inputs appropriately. In cases where multiple country-specific data points originated from the same study, the variance was adjusted to prevent these inputs from inflating the study’s influence. This approach ensured that no single study disproportionately affected the overall effect size, maintaining the integrity and balance of the meta-analysis results.

For the analysis of QALDs, the random-effects model was applied to summarize the mean differences between the CIB and SOC groups. Due to the limited number of studies available for each outcome, specific subgroup analyses outlined in the protocol could not be performed while maintaining statistical robustness.

Heterogeneity across studies was evaluated using Cochran’s Q test, along with measures of between-study variance (τ^2), the proportion of total variation across studies attributable to heterogeneity (I^2), and the ratio of total variation inclusive of heterogeneity to that exclusive of it (H^2). Threshold values were applied to interpret the degree of heterogeneity: I^2 values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively. Additional diagnostics, such as residual variance and likelihood ratio tests, were employed to assess the robustness and fit of the models. All statistical analyses were performed using Stata 18 (StataCorp LLC, College Station, TX, USA).

Results

Study Selection

Figure 1 depicts the flowchart of the selection process. In the identification phase, a total of 3,133 records were identified from seven databases: PubMed (n = 443), CINAHL (n = 191), Scopus (n = 676), Web of Science (n = 242), Embase (n = 927), Google Scholar (n = 645), and Clinicaltrials.gov (n = 9). After removing 1,240 duplicate records, 1,893 records were screened based on titles and abstracts. During the screening phase, 1,851 records were excluded for the following reasons: not focused on ceramides (n = 1,135), not focused on patients with stomas (n = 343), lacking empirical data (n = 356), or being abstracts without sufficient information (n = 17). This left 42 reports for full-text review. In the eligibility phase, 35 reports were excluded due to the lack of empirical data (n = 4), not focusing on ceramides (n = 23), or not involving patients with stomas (n = 8). Additionally, citation searching identified 15 more reports, but all were duplicates. Finally, seven studies were included in the systematic review, as shown in the inclusion phase of the flowchart.^{20,44–49}

Characteristics of the Included Studies

The included studies, as summarized in Table 1, present a variety of designs, sample sizes, and geographic locations, all investigating the clinical and economic impact. Most studies adopted a decision-analytic or cost-effectiveness model,^{44,47,48} while one RCT design,⁴⁹ one a quasi-experimental design,⁴⁶ and one an observational design.⁴⁵ Key outcomes across these studies included preventing PSCs, improving QALDs, and overall cost savings.

Regarding sample sizes, Berger et al.⁴⁸ modeled a hypothetical cohort of 1000 patients, equally split between CIB and SOC users, highlighting the reduction in PSCs and associated costs with CIB use. Berger

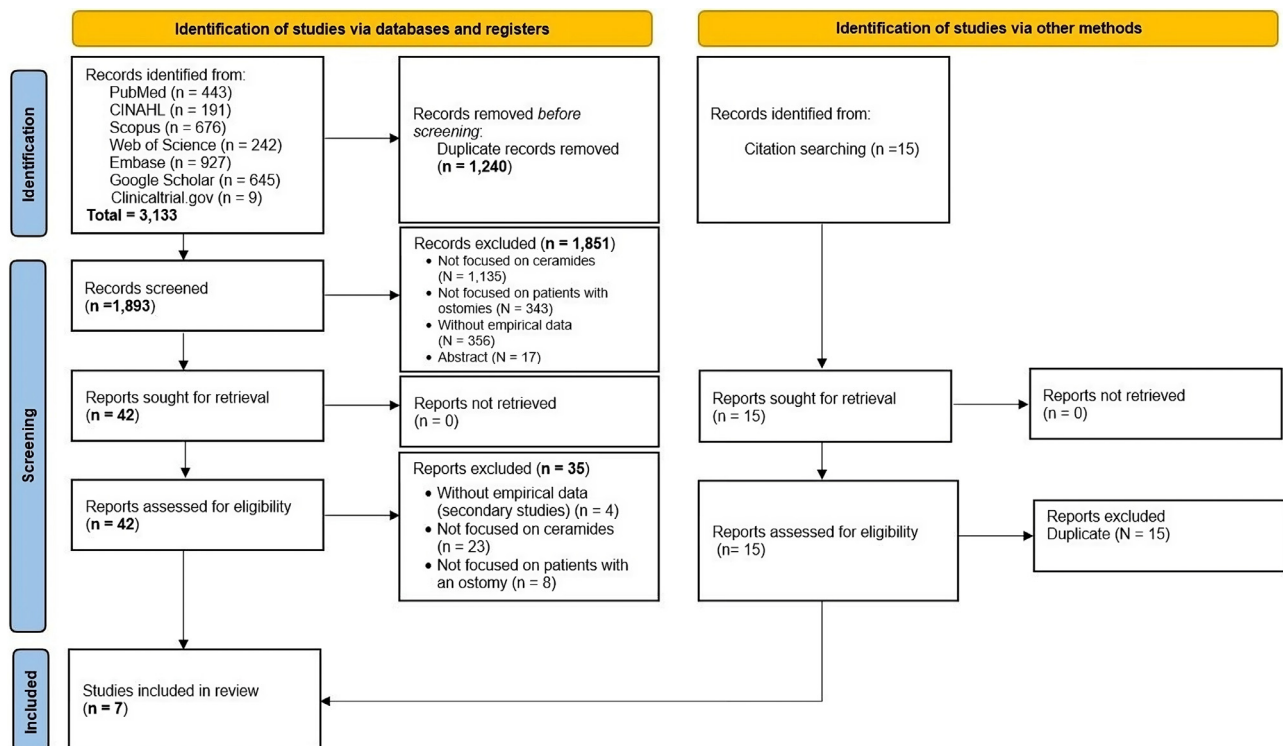


Figure 1. PRISMA 2020 flow chart.

et al.⁴⁷ expanded this model, including data from multiple countries (US, UK, Sweden, Australia, Italy, and Norway) and focusing on cost savings and clinical outcomes in larger cohorts.

Colwell et al.⁴⁹ conducted a more direct RCT with 153 adults, finding significant reductions in PSCs and costs associated with CIB use. Ishii et al. (2016) and Hoeflok (2016) focused on smaller sample sizes and specific patient characteristics, such as skin fragility or transepidermal water loss (TEWL), and both showed that CIB improved peristomal skin health.^{45,46}

Risk of bias

A detailed analysis of the risk of bias is reported in Supplementary File 2. The included RCT was of high quality, with a low risk of bias across most domains, including randomization, allocation concealment, and the measurement of outcomes.⁴⁹ The study's blinding of participants and outcome assessors further reduced the risk of bias, leading to a robust overall assessment.⁴⁹ The Non-randomized study performed by Ishii et al.⁴⁶ presented a moderate risk of bias primarily due to the lack of blinding and potential confounding. In observational studies, which were Hoeflok et al. (2016) and Taggart and Spencer (2018),^{20,45} key limitations were noted, such as the absence of control groups and relatively short follow-up periods. These studies were assessed as having a moderate overall risk of bias, given their design and lack of direct comparators. The economic analyses provided detailed and transparent reporting of cost-effectiveness outcomes.^{44,47,48} However, the need for longer-term analyses and the inclusion of different healthcare perspectives were noted as areas for improvement. Overall, the quality of evidence across studies was acceptable, with most studies providing reliable data, although caution is needed when interpreting findings from nonrandomized and observational designs.

Meta-Analysis on PSCs

In this meta-analysis of PSCs, data were derived from two studies,^{47,48} as shown in Figure 2. The overall OR for preventing PSCs was

1.77 [95% CI: 1.40, 2.23], indicating that the use of CIBs significantly increased the odds by 77% of preventing PSCs compared to SOC ($z = 4.78$, $P < 0.0001$). Both studies presented consistent results, with the OR from each study supporting the overall effect size. Berger et al. (2018) contributed most of the weight to the analysis (86.77%) due to a larger sample size.⁴⁸ No significant heterogeneity was observed between the studies, with $\tau^2 = 0.00$, $I^2 = 0.00\%$, and $H^2 = 1.00$, indicating consistency in the treatment effect across both studies.

Meta-Analysis on Cost-Saving

In this meta-analysis of cost differences between CIBs and SOC, data were retrieved from three primary studies but analyzed across nine different country-specific settings,^{44,47,48} as shown in Figure 3 (quadrant: A). The overall MD in costs per patient was $-140,000$ USD [95% CI: $-142,000$ USD, $-139,000$ USD], demonstrating a statistically significant cost saving associated with the use of CIBs ($z = -182.00$, $P < 0.0001$). The results revealed substantial heterogeneity, with $\tau^2 = 3.21e+06$, $I^2 = 100\%$, and $H^2 = 58181.26$, indicating significant variations in cost savings between countries. For example, Berger et al. (2021), which focused on the United States, contributed the lowest weight (0.49%) to the overall effect due to its extreme outlier status in terms of cost differences. In contrast, studies from other countries, such as Australia and Canada, contributed more consistently to the overall effect. Sensitivity analysis using leave-one-out methods showed no significant changes in terms of effect size and heterogeneity.

Meta-regression analysis was conducted to explore potential sources of heterogeneity, incorporating variables such as GDP per capita, healthcare expenditure per capita, and sample sizes (Wald $\chi^2_{(5)} = 2613.72$, $P < 0.001$). The analysis revealed that both GDP per capita ($\beta = -7.31$, 95% CI: -12.83 , -1.78 , $P = 0.010$) and healthcare expenditure per capita ($\beta = -169.33$, 95% CI: -230.75 , -107.90 , $P < 0.001$) significantly influenced cost variations across the different countries. In contrast, sample sizes in both the CIB and SOC groups did not significantly impact cost differences ($P > 0.1$), indicating that economic factors, rather than sample sizes, were primary drivers of the observed heterogeneity.

Table 1
Summary of included studies.

Authors	Year	Country	Design	Sample	Sample characteristics	Duration	Type of ostomy barriers	Control group (if any)	Outcome	Time points assessed	Adverse events	Key findings
Berger et al.	2018	Australia	Cost-effectiveness analysis using a hypothetical cohort based on available clinical and cost data	Hypothetical cohort of 1000 fecal ostomy patients	Fecal ostomy patients. 500 using ceramide-infused skin barriers (CIB) and 500 using SOC (Standard of Care)	1 y	Ceramide-infused skin barrier	SOC	PSCs, QALDs, healthcare costs	1 y	None	CIB reduces PSCs, increases QALDs, and lowers costs
Berger et al.	2021	US, UK, Sweden, Australia, Italy, Norway	Decision-analytic model based on a hypothetical cohort of patients, incorporating data inputs from clinical trials, observational studies, and cost data	New ostomates (fecal or urinary) - Hypothetical cohorts (1000 in ON, 4000 in AB)	New ostomates. CIB (20%) vs SOC barriers	1 y	Ceramide-infused skin barrier	SOC	PSCs, QALDs, healthcare costs	1 y	None	CIB results in cost savings across all countries
Colwell et al.	2018	US, Canada, Europe	RCT	153 adults with new colostomy, ileostomy, or urostomy	Adults with normal peristomal skin. Patients randomized to CIB or SOC	12 wk	Ceramide-infused skin barrier	SOC	PSCs, costs, quality of life	Baseline and 12 wk	None	CIB reduces stoma-related costs, and PSCs
Ishii et al.	2016	Japan	Quasi-experimental trial	13 patients with colostomy or ileostomy	Colostomy/ileostomy patients aged 52–85. Patients aged 52–85 y using CIB or SOC	1 mo	Ceramide-infused skin barrier	SOC	TEWL, itchiness, wear time	Baseline and 1 mo	None	CIB improves skin barrier function, reduces TEWL
Hoeflok	2016	Canada, Netherlands	Prospective evaluation (Observational study)	111 ostomates	54.6% normal skin, 40% fragile or dry skin. Ileostomy (46.8%), colostomy (41.4%), urostomy (9.9%)	3 wk (minimum)	Ceramide-infused hydrocolloid skin barrier	No control	Peristomal skin condition, satisfaction	End of the evaluation period	None	87.5% satisfaction with CIB, 55.7% skin improvement
LeBlanc et al.	2023	Canada	Cost-effectiveness model	Hypothetical cohort: 1000 (ON) and 4000 (AB)	Ostomy patients in ON and AB. 50% using CIB and 50% using SOC	1 y	Ceramide-infused skin barrier	SOC	Cost savings, PSCs avoided, QALDs	1 y	None	CIB results in significant cost savings and PSC reduction
Taggart and Spencer	2018	US	Case series (Observational study)	2 adult patients with ileostomy or colostomy	Patients with skin damage (discoloration, erosion). Patients with peristomal skin complications using CIB	21 d (Case 1), 14 d (Case 2)	Ceramide-infused hydrocolloid skin barrier	None (case series)	DET score improved (9 to 0, 10 to 0)	Baseline and after 14–21 d	None	CIB improved skin condition and resolved complications

CIB, ceramide-infused barrier; SOC, standard of care; PSCs, peristomal skin complications; QALDs, quality-adjusted life days; RCT, randomized controlled trial; TEWL, transepidermal water loss; DET, discoloration, erosion, tissue overgrowth (scale); ON, Ontario; AB, Alberta; US, United States; UK, United Kingdom.

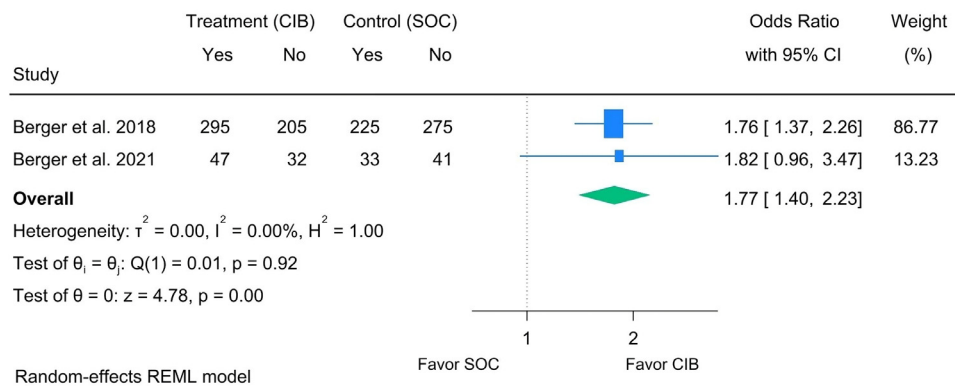


Figure 2. Meta-analysis of PSCs comparing treatment (CIB) and control (SOC) groups, showing the odds ratio with 95% confidence intervals.

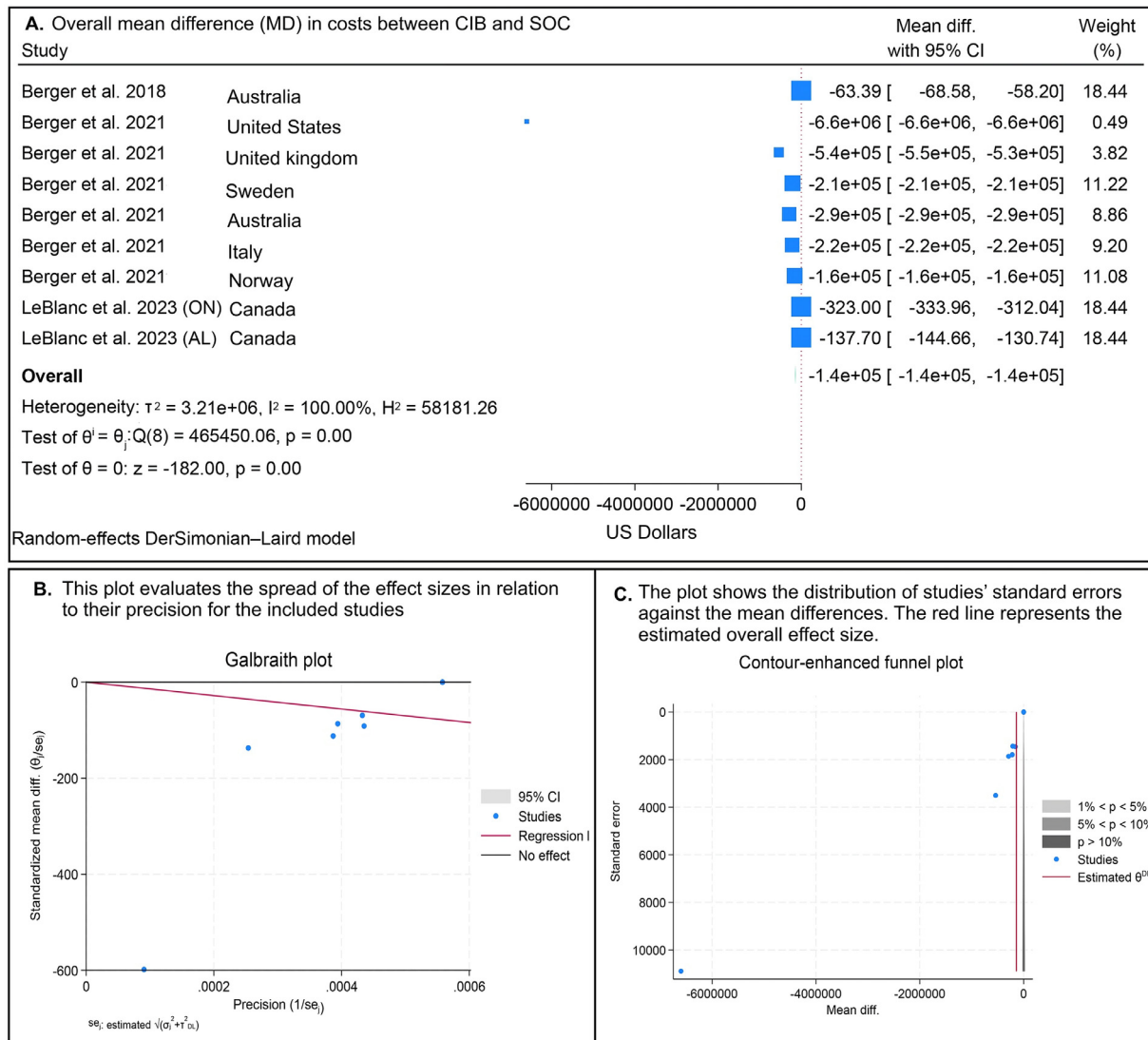


Figure 3. Meta-analysis of cost differences between treatment (CIB) and control (SOC), including a forest plot (A), a Galbraith plot (B) to evaluate the spread of effect sizes, and a funnel plot (C) assessing publication bias.

ity. However, minimal explanatory power for the included covariates in reducing between-study heterogeneity has been observed ($R^2=0.10$), showing that additional, unmeasured factors may also influence the reported heterogeneity.

The Galbraith plot (Fig 3, quadrant: B) visualizes the spread of effect sizes and their precision across the included studies. Studies closer to the

regression line indicate a higher level of precision: the plot shows substantial dispersion, further supporting the existence of between-study variability. Likely, the funnel plot (Fig 3, quadrant: C) assesses the distribution of study standard errors against the mean differences. While the plot suggests asymmetry, the regression-based Egger test confirmed significant small-study effects ($\beta = -269.41, z = -495.33, P < 0.001$),

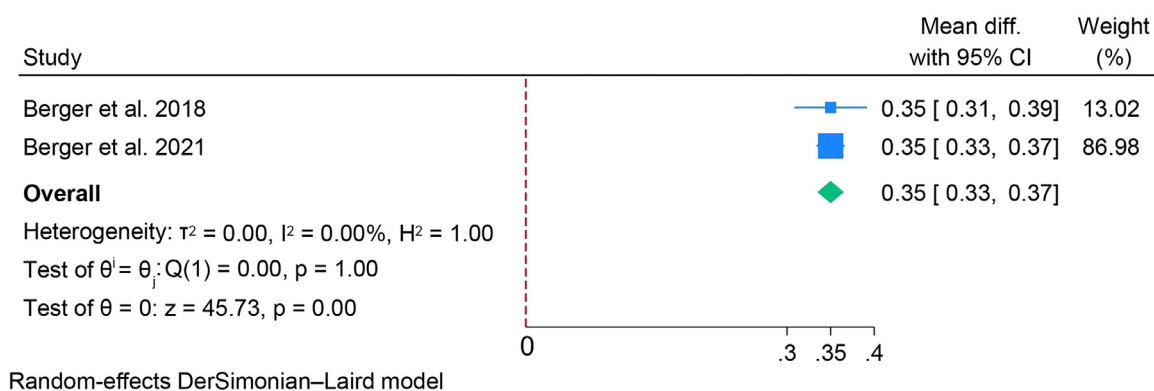


Figure 4. Meta-analysis on QALDs, showing the mean differences with 95% confidence intervals.

implying potential publication bias or other sources of small-study influences.

Meta-Analysis on QALDs

In this meta-analysis of QALDs, data were derived from two studies,^{47,48} as shown in Figure 4. The overall MD in QALDs was 0.35 [95% CI: 0.33, 0.37], indicating a statistically significant improvement in QALDs with the use of CIBs compared to SOC ($z = 45.73$, $P < 0.0001$). Both studies showed consistent results, with no observed heterogeneity between them ($\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$), suggesting that the treatment effect of CIBs on QALDs is homogeneous across the studies. Berger et al. (2021) contributed the largest weight to the analysis (86.98%) due to a larger sample size.⁴⁷

Discussion

This systematic review and meta-analysis provide comprehensive insights into the clinical, economic, and well-being outcomes associated with using CIBs in patients with intestinal and urinary stomas by consolidating evidence in relation to cost-effectiveness,^{20,44–49} prevention of PSCs, and improvements in QALDs.^{15,19,20,23–25,44–52} The results highlight the emerging benefits of CIBs in improving PSCs, reducing healthcare costs, and enhancing patient well-being in terms of QALDs. Results were consistent across included studies concerning PSCs and QALDs but with considerable variability in cost-saving outcomes between countries. This systematic review demonstrated that CIBs significantly increased by 77% the rates of prevented PSCs compared to SOC, with consistency in the results across the included studies. In terms of cost savings, the meta-analysis revealed a significant reduction in healthcare costs associated with CIB use compared to SOC, where the overall MD in costs per patient was $-140,000$ USD [95% CI: $-142,000$ USD, $-139,000$ USD], with high variability across different healthcare systems and countries. For QALDs, CIBs showed a significant improvement compared to SOC, with an overall mean difference of 0.35 days [95% CI: 0.33, 0.37].

Regarding evidence concerning the significant cost savings associated with CIBs, it is relevant to note that as healthcare providers seek cost-effective interventions that deliver high clinical value, CIBs appears to be a suitable option for optimizing the health of the peristomal skin. However, our study also identified substantial heterogeneity in cost savings, which contrasts with the limited available literature on economic outcomes.^{47,48} While Berger et al. reported wide variability in cost-saving potential across different healthcare systems,⁴⁷ our meta-regression further confirmed that factors like GDP per capita and healthcare expenditure per capita significantly influence these variations. These discrepancies may be attributed to differences in healthcare delivery models, cost structures, and reimbursement policies across countries.

Beyond GDP per capita and healthcare expenditure per capita, additional policy-driven factors likely contribute to the observed cost heterogeneity.⁵³ Countries with universal healthcare coverage and centralized reimbursement models may exhibit greater cost absorption for ostomy-related interventions, potentially reducing the relative cost savings associated with CIBs. Conversely, in privately driven or mixed healthcare systems, where out-of-pocket expenses for medical supplies are higher, the cost benefits of CIBs may be more pronounced as they directly translate into financial savings for patients. This distinction is crucial in interpreting cost-effectiveness findings across countries, as the economic impact of adopting CIBs will differ depending on the financial burden shouldered by healthcare providers versus individual patients.⁵⁴ Furthermore, differences in procurement policies and market competition for ostomy supplies across nations may also influence the baseline cost-effectiveness of CIBs. In countries where medical devices and ostomy products undergo competitive pricing negotiations or where centralized purchasing policies regulate costs, the price gap between CIBs and SOC may be smaller, reducing the potential for cost savings. However, in regions where market-driven pricing dominates or where ostomy product reimbursement is limited, cost disparities may be magnified.^{55,56} In this regard, future research should incorporate comparative health policy analyses to better understand how national reimbursement frameworks, procurement strategies, and regulatory policies affect the adoption and cost-effectiveness of CIBs. Specifically, exploring the impact of different insurance models, reimbursement schemes, and subsidy programs on the cost burden of ostomy care could provide a more comprehensive perspective on how policy factors influence economic outcomes.

The coefficient for GDP per capita in our meta-regression analysis was -7.31 (95% CI: -12.83 , -1.78), indicating a statistically significant relationship ($P = 0.010$). This negative coefficient suggests that, on average, for every unit increase in GDP per capita, the cost-saving effect (mean difference) decreases by 7.31 units. This effect implies that countries with higher GDP per capita tend to show smaller cost savings from the use of CIBs. This might be because wealthier countries often have more advanced healthcare infrastructure, which could minimize the marginal benefits of adopting new interventions like CIBs.⁵⁷ In these settings, the baseline costs of care might already be optimized, leading to smaller differences between the intervention and control groups in terms of cost savings.⁵⁸ Likely, the coefficient for healthcare expenditure per capita was -169.33 (95% CI: -230.75 , -107.90), suggesting that for every unit increase in healthcare expenditure per capita, the mean difference in cost savings decreases by 169.33 USD. This could be explained by the fact that in countries where healthcare spending is already high, the incremental cost-saving benefits of interventions like CIBs may be reduced. Higher spending might indicate more comprehensive baseline care, meaning that the introduction of CIBs results in fewer cost differences between the intervention and control groups.^{59,60} These findings emphasize that economic factors, such as national wealth and healthcare expenditure, play significant roles in determining the cost-

saving potential of CIBs across different countries. This variation should be taken into account when generalizing cost-effectiveness findings from one country to another. Further research is warranted to explore additional variables that could explain the observed heterogeneity in cost savings.

The significant 77% increase in the odds of PSC prevention with the use of CIBs compared to SOC has clear and impactful implications for clinical practice. Given the substantial burden of PSCs on patient quality of life and healthcare resources, this finding suggests that CIBs should be considered as a suitable intervention for patients with intestinal and urinary stomas. However, it is important to interpret this result with caution. The available evidence is limited in scope, as CIBs have been consistently compared to SOC without direct comparisons to other types of advanced skin barriers or alternative interventions. This lack of indirect comparisons introduces a degree of uncertainty, making it difficult to determine whether CIBs are superior to other potential options⁶¹. Further research is needed to explore how CIBs perform against other advanced products, ensuring a comprehensive evaluation of their relative efficacy.

The significant improvements in QALDs observed using CIBs have notable clinical relevance. In fact, converting QALDs into Quality-Adjusted Life Years (QALYs) offers a clearer perspective on the magnitude of these benefits.⁶² For example, if a patient gains an additional 35 QALDs from using CIBs, this would equate to approximately 0.096 QALYs (35/365), indicating nearly 10% of a full year of improved quality of life. Although this may seem like a small improvement, the cumulative impact on patient well-being could be significant, particularly for those living with chronic conditions like intestinal or urinary stomas. From a clinical practice standpoint, this improvement in QALYs highlights the potential for CIBs to enhance overall patient outcomes.^{21,50,51,63,64} Better peristomal skin health reduces the risk of infections and complications and leads to fewer interventions, less discomfort, and greater patient satisfaction. These improvements in quality of life are crucial for healthcare providers managing ostomy patients, as they reduce the burden of stoma care, contribute to more efficient resource utilization, and align with broader goals of patient-centered care.^{50,51,64,65}

One of the key strengths of this systematic review lies in its adherence to the rigorous PRISMA statement.³³ Including multiple databases and one register (PubMed, CINAHL, Scopus, Web of Science, Embase, Google Scholar, and Clinicaltrials.gov) provided a comprehensive and exhaustive search, minimizing the risk of missing relevant studies. Additionally, using validated tools to assess the risk of bias in the included studies ensured a thorough and systematic evaluation of the internal validity of the results used to summarize the quantitative estimates in this review. Incorporating meta-regression analysis to explore heterogeneity further strengthened the review by identifying important moderating variables like GDP per capita and healthcare expenditure per capita, providing insights into the economic variations across different countries.

However, several limitations must also be acknowledged. A notable limitation is the relatively small number of studies available for most outcomes, with the exception of the cost-saving analysis. This limited the feasibility of conducting subgroup analyses and performing both qualitative and quantitative assessments of publication bias. Although funnel plots and Egger's test were feasible for the cost-saving analysis, they were not possible for other outcomes, increasing the challenge of assessing potential biases. In this scenario, publication bias must be considered plausible, as the small number of included studies could skew the observed effects and reduce the conclusions' robustness.

A key limitation of this meta-analysis that warrants discussion is the lack of differentiation across critical clinical factors that could influence PSC outcomes and cost-effectiveness estimates. Specifically, the included studies did not stratify patients based on the underlying disease requiring ostomy formation (e.g., colorectal cancer, Crohn's disease, diverticular disease), whether the ostomy was temporary or per-

manent, or the anatomical location of the stoma.^{20,44–49} These distinctions are particularly relevant, as previous research suggests that ileostomies, commonly used for Crohn's disease, are associated with higher complication risks and recurrence rates (30%).⁶⁶ Similarly, diabetes has been identified as a significant risk factor for surgical site infections (OR = 1.53), which could independently affect PSC incidence and outcomes related to CIBs.⁶⁷ Furthermore, anatomical stoma placement plays a well-documented role in determining postoperative complications.⁶⁸ However, the included studies did not report data in a way that would allow for stratified analyses based on these factors. While one included study justified not differentiating ostomy types due to baseline equivalence in the ADVOCATE trial,⁴⁷ no similar justification was provided for the previously included study of the same team,⁴⁸ which accounted for 86.77% of the PSC meta-analysis weight. As such, the applicability of the pooled findings should be interpreted cautiously. Future research should aim to stratify outcomes based on disease type, stoma classification, comorbidities, and surgical factors to enhance the clinical applicability of findings.

Additionally, an important limitation of the PSCs and cost-saving meta-analyses is that the studies contributing to these analyses originate from the same research group.^{44,47,48} For this reason, the risk of bias and limits the independent validation of findings has to be acknowledged when interpreting these findings. The reliance on a single cohort of authors introduces the possibility of reinforcing the same analytical assumptions and methodological frameworks, which may reduce the generalizability of results. Future research should aim to incorporate independent replications of these findings by different research teams using varied methodologies.

Variations in healthcare systems and cost-reporting practices across countries further complicate the estimation and standardization of cost data, potentially limiting the generalizability of the cost-effectiveness outcomes. More precisely, the lack of country-specific policy adjustments in our cost-effectiveness analyses presents a limitation in fully capturing how national healthcare differences impact the economic viability of CIBs. Our meta-regression accounted for GDP per capita and healthcare expenditure per capita, yet policy-level variables such as reimbursement structures, price control mechanisms, and access restrictions were not included due to data limitations. Future studies should explore cross-country policy differences in stoma care financing and procurement to enhance the applicability of cost-effectiveness findings across diverse healthcare settings.

Despite our efforts to explore potential sources of heterogeneity in cost differences using GDP per capita and healthcare expenditure per capita as predictors, our meta-regression analysis demonstrated limited explanatory power ($R^2 = 10\%$). This suggests that additional, unmeasured factors likely contribute to cross-country cost variability. Policy-level variables such as out-of-pocket healthcare expenditure, regulatory pricing controls on ostomy supplies, and national reimbursement structures were not included in our analysis due to data limitations.^{31,53,54} Given the complex nature of healthcare financing and procurement strategies, future research should incorporate a broader range of economic and policy-related regressors to refine cost-effectiveness evaluations and better map inefficiencies across health systems. Integrating such variables would provide a clearer understanding of how different reimbursement models, subsidy schemes, and cost-containment policies influence the economic viability of CIBs in diverse healthcare settings.

Although our systematic review demonstrated a significant reduction in PSCs and cost savings associated with CIBs, we acknowledge the limitation of not conducting subgroup analyses based on stoma type (colostomy, ileostomy, urostomy), anatomical location, or classification (temporary vs. permanent). While such distinctions are clinically relevant, the limited number of included studies and the inconsistent reporting of ostomy characteristics across studies prevented us from performing a statistically meaningful subgroup analysis. Different ostomy types pose varying risks for PSCs, with ileostomies often being more prone to

leakage-related complications and urostomies presenting specific risks such as alkaline encrustation. Furthermore, economic outcomes may vary based on the temporary or permanent nature of the stoma, as temporary stomas often involve reversal surgeries that affect overall cost assessments. Given these considerations, future research should aim to stratify results by stoma type, location, and permanence to provide more precise estimates of the clinical and economic impact of CIBs across diverse patient populations.

Other limitations of this review include the lack of direct comparison between CIBs and other advanced skin barrier technologies beyond SOC, limiting our ability to assess how CIBs perform relative to other interventions. This introduces some degree of indirectness in the findings, which may affect the broader applicability of the results to different clinical settings. While this review primarily compares CIBs to standard ostomy skin barriers, it is important to acknowledge other potential PSC prevention and management interventions warrant further investigation. Emerging alternatives include silicone-based skin barriers, polymer-based protective films, and hydrofiber dressings, which have been explored for their ability to reduce peristomal skin irritation and improve skin adhesion.^{69–74} Additionally, topical treatments such as zinc oxide, corticosteroid creams, and antifungal agents are commonly used adjunct therapies to manage inflammation, infections, and moisture-related complications.⁷⁵ For instance, some studies have also investigated the use of probiotic-infused skin products to enhance skin microbiome balance and improve barrier function.^{76,77} However, direct comparisons between these alternatives and CIBs remain unexplored in the literature. Future research should focus on comparative effectiveness trials evaluating CIBs alongside these alternative treatments to determine their relative clinical benefits, cost-effectiveness, and impact on quality of life in patients with ostomies.

The variation in study designs, such as the inclusion of both randomized and non-randomized trials, may introduce additional heterogeneity despite the use of robust analytical techniques like random-effects models to account for such variability. In addition, the reliance on estimated values for missing data, such as the approximation of standard deviations, may introduce imprecision into the meta-analyses, affecting the confidence in the final effect estimates. Lastly, none of the included studies enrolled patients under 18 years of age, limiting the generability of the emerging findings in this population.

Conclusions

This systematic review and meta-analysis provide valuable insights into the clinical and economic benefits of CIBs for patients with intestinal and urinary stomas. The findings highlight significant improvements in preventing PSCs, notable cost savings, and enhancements in QALDs, even if caution is required when interpreting results for the intrinsic limits related to the heterogeneity of healthcare systems, the limited number of included studies, and the lack of differentiation across key clinical factors such as ostomy type, anatomical location, and underlying conditions. While these promising findings, overgeneralization should be avoided. Further research is needed to explore the long-term effects of CIBs, direct comparisons with other advanced skin barriers, and the factors contributing to the observed variability in cost savings. Future studies should address these gaps to provide a more comprehensive understanding of CIBs' clinical and economic impact. In clinical practice, these findings support using CIBs as an effective and potentially cost-saving intervention for stoma care, emphasizing their role in improving skin health, reducing complications, and enhancing patient quality of life.

Declaration of competing interest

None declared.

CRediT authorship contribution statement

Rosario Caruso: Writing – original draft, Methodology, Formal analysis, Conceptualization, Writing – review & editing. **Silvia Belloni:** Data curation, Software, Methodology, Writing – review & editing. **Beniamino Schiavone:** Data curation, Methodology, Writing – review & editing. **Gianluca Conte:** Data curation, Methodology, Writing – review & editing. **Cristina Di Pasquale:** Data curation, Methodology, Writing – review & editing. **Arianna Magon:** Data curation, Methodology, Writing – review & editing. **Cristina Arrigoni:** Data curation, Methodology, Writing – review & editing. **Giuseppe Candilio:** Data curation, Methodology, Writing – review & editing. **Francesco Stanzione:** Data curation, Methodology, Writing – review & editing. **Alessandro Stievano:** Data curation, Methodology, Writing – review & editing. **Gennaro Rocco:** Data curation, Methodology, Writing – review & editing. **Maddalena De Maria:** Data curation, Methodology, Writing – review & editing, Supervision.

Original Protocol

The original protocol is available on Prospero [Record ID: 492933].

Funding Sources

None.

Acknowledgments

We extend our gratitude to all the study participants of the included studies of this review. We also would like to acknowledge the contribution of the students Marianna Iorio and Ornella Di Costanzo for their support during their internship related to the Master of Science in Nursing course.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.clinthera.2025.02.001](https://doi.org/10.1016/j.clinthera.2025.02.001).

References

1. Tsujinaka S, Tan KY, Miyakura Y, et al. Current management of intestinal stomas and their complications. *J Anus Rectum Colon*. 2020;4(1):25–33. doi:10.23922/jarc.2019-032.
2. Dellafiore F, Caruso R, Bonavina L, et al. Risk factors and pooled incidence of intestinal stoma complications: systematic review and meta-analysis. *Curr Med Res Opin*. 2022;38(7):1103–1113. doi:10.1080/03007995.2022.2081455.
3. Van Hoogstraten LMC, Vrieling A, Van Der Heijden AG, et al. Global trends in the epidemiology of bladder cancer: challenges for public health and clinical practice. *Nat Rev Clin Oncol*. 2023;20(5):287–304. doi:10.1038/s41571-023-00744-3.
4. Marinova P, Marinova R. Patient-centred stoma care support: urostomy patients. *Br J Community Nurs*. 2024;29(12):580–587. doi:10.12968/bjcn.2024.0130.
5. Geng Z, Geng Q. Risk of urinary bladder cancer in patients with inflammatory bowel diseases: a meta-analysis. *Front Surg*. 2021;8:636791. doi:10.3389/fsurg.2021.636791.
6. Roshandel G, Ghasemi-Kebria F, Malekzadeh R. Colorectal cancer: epidemiology, risk factors, and prevention. *Cancers (Basel)*. 2024;16(8):1530. doi:10.3390/cancers16081530.
7. Deputy M, Worley G, Patel K, et al. Long-term outcome and quality of life after continent ileostomy for ulcerative colitis: a systematic review. *Colorectal Dis*. 2021;23(9):2286–2299. doi:10.1111/codi.15788.
8. Pandiaraja J, Chakkarapani R, Arumugam S. A study on patterns, indications, and complications of an enteric stoma. *J Family Med Primary Care*. 2021;10(9):3277–3282. doi:10.4103/jfmpc.jfmpc.123.21.
9. Liu Z, Zhang Y, Sun D, et al. Bowel perforation in neonates with Hirschsprung disease: a case series and literature review. *Pediatr Surg Int*. 2024;41(1):15. doi:10.1007/s00383-024-05907-6.
10. Sacks OA, Hall J. Management of diverticulitis: a review. *JAMA Surg*. 2024;159(6):696. doi:10.1001/jamasurg.2023.8104.
11. Maydick-Youngberg DA. Descriptive study to explore the effect of peristomal skin complications on quality of life of adults with a permanent ostomy. *Ostomy Wound Manage*. 2017;63(5):10–23.
12. Dellafiore F, Manara DF, Arrigoni C, et al. Predictors of adjustment to living with an ostomy: results of a cross-sectional study. *Adv Skin Wound Care*. 2022;35(5):1–6. doi:10.1097/01.ASW.0000823980.15166.35.

13. Jabbal IS, Spaulding AC, Lemini R, et al. Temporary vs. permanent stoma: factors associated with the development of complications and costs for rectal cancer patients. *Int J Colorectal Dis.* 2022;37(4):823–833. doi:10.1007/s00384-022-04116-8.
14. Pine J, Stevenson L, On J. Intestinal stomas. *Surgery (Oxford).* 2023;41(1):55–61. doi:10.1016/j.mpsur.2022.10.010.
15. Schuetz SJ, Sanchez M. Preventive stoma care and peristomal skin conditions. *Semin Colon Rectal Surg.* 2023;34(2):100959. doi:10.1016/j.scrs.2023.100959.
16. Montesinos Gálvez AC, Jódar Sánchez F, Alcántara Moreno C, et al. Value-based healthcare in ostomies. *IJERPH.* 2020;17(16):5879. doi:10.3390/ijerph17165879.
17. Naseh L, Shahriari M, Hayrabadian A, Moeini M. Nurses' viewpoints on factors affecting ostomy care: a qualitative content analysis. *Nursing Open.* 2023;10(8):5261–5270. doi:10.1002/nop2.1764.
18. Li J, Zhang Q, Wu X, Pang D. The quality and clinical applicability of recommendations in ostomy guidelines: a systematic review. *RMHP.* 2022;15:1517–1529. doi:10.2147/RMHP.S378684.
19. Grove G, Houser T, Sibbald G, Salvadale G. Measuring epidermal effects of ostomy skin barriers. *Skin Res Technol.* 2019;25(2):179–186. doi:10.1111/srt.12630.
20. Taggart E, Spencer K. Maintaining peristomal skin health with ceramide-infused hydrocolloid skin barrier. *World Council Enterostomal Therapists J.* 2018;38(1 (Supplement)):58.
21. Guerra E, Denti FC, Di Pasquale C, et al. Peristomal skin complications: detailed analysis of a web-based survey and predictive risk factors. *Healthcare (Basel).* 2023;11(13):1823. doi:10.3390/healthcare11131823.
22. Colwell JC, McNichol L, Boarini J. North America wound, ostomy, and continence and enterostomal therapy nurses current ostomy care practice related to peristomal skin issues. *J Wound Ostomy Continence Nurs.* 2017;44(3):257–261. doi:10.1097/WON.0000000000000324.
23. Black P. Peristomal skin care: an overview of available products. *Br J Nurs.* 2007;16(17):1048–1050, 1052–1054 passim. doi:10.12968/bjon.2007.16.17.27249.
24. Salvadale G, Colwell JC, Skountrianos G, Pittman J. Lessons learned about peristomal skin complications: secondary analysis of the ADVOCATE trial. *J Wound Ostomy Continence Nurs.* 2020;47(4):357–363. doi:10.1097/WON.0000000000000666.
25. Stephen-Haynes J. The outcomes of barrier protection in periwound skin and stoma care. *Br J Nurs.* 2014;23(5):S26–S28–30. doi:10.12968/bjon.2014.23.Sup5.S26.
26. Brennan VK, Dixon S. Incorporating process utility into quality adjusted life years: a systematic review of empirical studies. *Pharmacoeconomics.* 2013;31(8):677–691. doi:10.1007/s40273-013-0066-1.
27. Simoens S, Vanleene V, De Maré L, et al. Ostomy appliance prices in Europe. *J Med Econ.* 2009;12(1):17–24. doi:10.3111/13696990902843338.
28. Lاپtan MCM, Sacdalan MDP, Lopez MPJ, et al. Mixed-methods exploration of challenges to stoma care for ostomates in four low- and middle-income countries: sTomaCare For Improvement reSEARCH (STARFISH) study. *J Global Health Rep.* 2024;8:e2024017. doi:10.29392/001c.117626.
29. Schaum KD. Reimbursement for ostomy supplies and professional services should not be a secret. *Adv Skin Wound Care.* 2021;34(6):290–291. doi:10.1097/01.ASW.0000750852.84867.14.
30. Geisler BP, Cao KN, Ryschon AM, Alavi K, Komen N, Pietzsch JB. Cost associated with diverting ostomy after rectal cancer surgery: a transnational analysis. *Surg Endosc.* 2023;37(10):7759–7766. doi:10.1007/s00464-023-10300-w.
31. Cross HH. CE: nursing care for patients after ostomy surgery. *AJN, Am J Nurs.* 2023;123(8):34–41. doi:10.1097/01.NAJ.0000947460.38199.fe.
32. Higgins JPT, ed. *Cochrane Handbook for Systematic Reviews of Interventions.* 2nd ed. Hoboken, NJ, USA: Wiley-Blackwell; 2020.
33. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *J Clin Epidemiol.* 2021;134:103–112. doi:10.1016/j.jclinepi.2021.02.003.
34. Mishan EJ, Quah E. *Cost-Benefit Analysis.* 6th ed. London, UK: Routledge/Taylor & Francis Group; 2021.
35. Cookson R, Skarda I, Cotton-Barratt O, Adler M, Asaria M, Ord T. Quality adjusted life years based on health and consumption: a summary wellbeing measure for cross-sectional economic evaluation. *Health Econ.* 2021;30(1):70–85. doi:10.1002/hec.4177.
36. Mehrez A, Gafni A. Quality-adjusted life years, utility theory, and healthy-years equivalents. *Med Decis Making.* 1989;9(2):142–149. doi:10.1177/027298898900900209.
37. Weir CJ, Butcher I, Assi V, et al. Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: a systematic review. *BMC Med Res Methodol.* 2018;18(1):25. doi:10.1186/s12874-018-0483-0.
38. World Bank Open Data. World Bank Open Data. Accessed September 7, 2024. <https://data.worldbank.org>.
39. Health at a Glance. Accessed September 7, 2024. https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance_19991312.
40. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;14898. doi:10.1136/bmj.14898.
41. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;14919. doi:10.1136/bmj.14919.
42. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(9):603–605. doi:10.1007/s10654-010-9491-z.
43. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health.* 2013;16(2):231–250. doi:10.1016/j.jval.2013.02.002.
44. LeBlanc K, Furtado S, Mings D, et al. A cost-effectiveness model to determine ostomy-related costs of care and health outcomes among people with an ostomy in Canada using a ceramide-infused skin barrier. *J Wound Ostomy Continence Nurs.* 2023;50(1):31–38. doi:10.1097/WON.0000000000000935.
45. Hoeflok J. Experiences with a ceramide-infused hydrocolloid skin barrier. *World Council Enterostomal Therapists J.* 2016;36(3):16–21.
46. Ishii HN, Komiyama K, Mizokami C, Sinden M, Mizokami Y. Prospective evaluation of skin barriers containing ceramide for stoma patients. *World Council Enterostomal Therapists J.* 2016;36(2):8–13.
47. Berger A, Inglese G, Skountrianos G, Croce D, Oguz M. Budget impact of ceramide-infused skin barriers versus standard of care skin barriers for new ostomates: a six-country analysis. *wcet.* 2021;41(2):22–31. doi:10.33235/wcet.41.2.22-31.
48. Berger A, Inglese G, Skountrianos G, Karlsmark T, Oguz M. Cost-effectiveness of a ceramide-infused skin barrier versus a standard barrier: findings from a long-term Cost-effectiveness analysis. *J Wound Ostomy Continence Nurs.* 2018;45(2):146–155. doi:10.1097/WON.0000000000000416.
49. Colwell JC, Pittman J, Raizman R, Salvadale G. A randomized controlled trial determining variances in ostomy skin conditions and the economic impact (ADVOCATE Trial). *J Wound, Ostomy Continence Nurs.* 2018;45(1):37–42. doi:10.1097/WON.0000000000000389.
50. Alenezi A, McGrath I, Kimpton A, Livesay K. Quality of life among ostomy patients: a narrative literature review. *J Clin Nurs.* 2021;30(21–22):3111–3123. doi:10.1111/jocn.15840.
51. Khalilzadeh Ganjalikhani M, Tirgari B, Roudi Rashtabadi O, Shahaemaeili A. Studying the effect of structured ostomy care training on quality of life and anxiety of patients with permanent ostomy. *Int Wound J.* 2019;16(6):1383–1390. doi:10.1111/iwj.13201.
52. Danielsen AK, Burcharth J, Rosenberg J. Patient education has a positive effect in patients with a stoma: a systematic review. *Colorectal Dis.* 2013;15(6). doi:10.1111/codi.12197.
53. Stjepanović S, Tomić D, Škare M. Policy lessons from green gdp convergence over five decades: enhancing sustainability and economic outcomes. *J Policy Modeling.* 2025;47(1):187–210. doi:10.1016/j.jpolmod.2024.08.002.
54. Kallis G, Hickel J, O'Neill DW, et al. Post-growth: the science of well-being within planetary boundaries. *Lancet Planet Health.* 2025;9(1):e62–e78. doi:10.1016/S2542-5196(24)00310-3.
55. Kittscha J, Fairbrother G, Bliokas V, Wilson V. Adjustment to an ostomy: an integrative literature review. *J Wound, Ostomy Continence Nurs.* 2022;49(5):439–448. doi:10.1097/WON.0000000000000895.
56. Graham LA, Illarino S, Gray CP, et al. Mapping the discharge process after surgery. *JAMA Surg.* 2024;159(4):438. doi:10.1001/jamasurg.2023.7539.
57. Dawkins B, Renwick C, Ensor T, Shinkins B, Jayne D, Meads D. What factors affect patients' ability to access healthcare? An overview of systematic reviews. *Trop Med Int Health.* 2021;26(10):1177–1188. doi:10.1111/tmi.13651.
58. De Siqueira Filha NT, Li J, Phillips-Howard PA, et al. The economics of healthcare access: a scoping review on the economic impact of healthcare access for vulnerable urban populations in low- and middle-income countries. *Int J Equity Health.* 2022;21(1):191. doi:10.1186/s12939-022-01804-3.
59. Liu GG, Guan H, Peng N, et al. Key issues of economic evaluations for health technology assessment in China: a nationwide expert survey. *Value Health.* 2024;27(11):1535–1543. doi:10.1016/j.jval.2024.06.020.
60. Magon A, Caruso R. Addressing a potential crisis in the Italian National Health System. *The Lancet.* 2023;401(10384):1262–1263. doi:10.1016/S0140-6736(23)00450-6.
61. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol.* 2011;64(12):1303–1310. doi:10.1016/j.jclinepi.2011.04.014.
62. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *British Medical Bulletin.* 2010;96(1):5–21. doi:10.1093/bmb/ldq033.
63. Dellafiore F, Conte G, Baroni I, et al. Ostomy adjustment Inventory-23 (OAI-23): development and testing of the Italian version. *J Wound Ostomy Continence Nurs.* 2019;46(1):38–43. doi:10.1097/WON.0000000000000493.
64. Dellafiore F, Pittella F, Arrigoni C, et al. A multi-phase study for the development of a self-efficacy measuring scale for ostomy care nursing management. *J Adv Nurs.* 2020;76(1):409–419. doi:10.1111/jan.14242.
65. Panattoni N, Mariani R, Spano A, et al. Nurse specialist and ostomy patient: competence and skills in the care pathway. A scoping review. *J Clin Nurs.* 2023;32(17–18):5959–5973. doi:10.1111/jocn.16722.
66. Hoentjen F, Colwell JC, Hanauer SB. Complications of peristomal recurrence of Crohn's disease: a case report and a review of literature. *J Wound Ostomy Continence Nurs.* 2012;39(3):297–301. doi:10.1097/WON.0b013e3182487189.
67. Martin ET, Kaye KS, Knott C, et al. Diabetes and risk of surgical site infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol.* 2016;37(1):88–99. doi:10.1017/ice.2015.249.
68. Murken DR, Bleier JIS. Ostomy-related complications. *Clin Colon Rectal Surg.* 2019;32(3):176–182. doi:10.1055/s-0038-1676995.
69. Jeppesen PB, Vestergaard M, Boisen EB, Ajslev TA. Impact of stoma leakage in everyday life: data from the Ostomy Life Study 2019. *Br J Nurs.* 2022;31(6):S48–S58. doi:10.12968/bjon.2022.31.6.S48.
70. Gray M, Bliss DZ, McNichol L. Moisture-associated skin damage: expanding and updating practice based on the newest ICD-10-CM codes. *J Wound Ostomy Continence Nurs.* 2022;49(2):143–151. doi:10.1097/WON.0000000000000865.
71. Meisner S, Lehur PA, Moran B, Martins L, Jemec GBE. Peristomal skin complications are common, expensive, and difficult to manage: a population based cost modeling study. *PLoS One.* 2012;7(5):e37813. doi:10.1371/journal.pone.0037813.
72. Morss-Walton PC, Yi JZ, Gunning M, McGee JS. Ostomy 101 for dermatologists: managing peristomal skin diseases. *Dermatol Ther.* 2021;34(5):e15069. doi:10.1111/dth.15069.
73. Nicholson J, Srisankarajah S, Moore J, Clouston H, Telford K. Aerosol steroids for the treatment of peristomal mucocutaneous breakdown due to severe eczema. *Int J Surg Case Rep.* 2014;5(12):1173–1175. doi:10.1016/j.ijscr.2014.11.015.

74. Swift T. Peristomal skin complications: new materials needed to ease the ostomy care market. *Br J Dermatol*. 2023;188(4):455–456. doi:[10.1093/bjd/ljad006](https://doi.org/10.1093/bjd/ljad006).
75. Nielsen LF, Blume N, Romme T, et al. Skin changes induced by a zinc oxide dressing compared with a hydrocolloid dressing in healthy individuals. *Skin Res Technol*. 2005;11(2):140–151. doi:[10.1111/j.1600-0846.2005.00105.x](https://doi.org/10.1111/j.1600-0846.2005.00105.x).
76. De Almeida CV, Antiga E, Lulli M. Oral and topical probiotics and postbiotics in skin-care and dermatological therapy: a concise review. *Microorganisms*. 2023;11(6):1420. doi:[10.3390/microorganisms11061420](https://doi.org/10.3390/microorganisms11061420).
77. Habeebuddin M, Karnati RK, Shiroorkar PN, et al. Topical probiotics: more than a skin deep. *Pharmaceutics*. 2022;14(3):557. doi:[10.3390/pharmaceutics14030557](https://doi.org/10.3390/pharmaceutics14030557).