RESEARCH ARTICLE

# Effects of topical application of Virgin Coconut Oil on infection, mortality and dermal maturation in preterm newborns: Systematic review and meta-analysis

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**ABSTRACT**

**Background:** Preterm birth is an important health concern in countries with limited resources and healthcare access. Topical therapy may be effective for improving outcomes in preterm neonates whose skin barriers are compromised due to immaturity.

**Objectives:** To systematically review the topical VCO's effects in preterm infants on infection, mortality, and dermal maturity.

**Methodology:** Systematic review and meta-analysis of RCTs of topical VCO in preterm infants were conducted. Databases included PubMed, Google Scholar, Clinical trials.gov, Trip, Cochrane Library, and Herdin. The risk of bias was assessed by two authors independently. RR with 95% CI was used for the pooled estimate of dichotomous outcomes including infection prevention, mortality reduction, and skin irritation. Mean differences with 95% CI were used for the pooled estimate of weight loss and NSCS.

**Results:** Of 110 records identified, 3 RCTs with 2440 patients were included. Prevention of infection had a trend toward VCO (RR = 0.90, [95% CI: 0.64, 1.27] while the results for mortality reduction were inconclusive (RR = 0.45, [95% CI: 0.06, 3.38]. NSC scores showed a beneficial trend toward VCO (RR = -0.03, [95% CI: -0.16, 0.09]. Both secondary outcomes of skin irritation and weight loss had inconclusive results.

**Conclusions:** This review showed the lack of evidence of the effectiveness of topical VCO in improving various outcomes in premature infants. The effects on infection prevention and dermal maturation were favorable. However, its effects on preventing mortality, skin irritation, and weight loss were inconclusive.

**Keywords:** *meta-analysis, virgin coconut oil, infection, NSCS, mortality, dermal maturation*

## Introduction

Premature birth is a significant public health concern, especially in low-to-middle-income countries where resources and access to healthcare are limited. Preterm births contribute to newborn mortality which is an important indicator of socioeconomic status. The complications of preterm births like increased water loss and infections caused by dermal immaturity, contribute to newborn mortality which is an important indicator of socioeconomic status. Furthermore, a high environmental load of pathogenic organisms and malnutrition of preterm babies contribute to mortality.

The incidence of preterm birth in Africa and Southeast Asia is approximately 60 percent [1]. In the Philippines, the Philippine Pediatric Society has recorded 16253 cases of prematurity since 2017. In our institution, Mary Mediatrix Medical Center in Lipa City, Batangas, 159 cases of premature deliveries were recorded from January 2017 to March 2021. Preterm infants are known to be at risk of various complications like increased water loss and infections caused by dermal immaturity [2]. Neonatal sepsis is one of the major causes of mortality in preterm babies.

The human skin functions as a physical barrier to minimize excessive water loss, prevent the absorption of harmful substances, and protect against microorganisms [3]. However, in preterm, low-birth-weight babies, the skin barriers are critically compromised due to immaturity [4]. The absence of vernix and the partial development of the stratum corneum in extremely preterm infants result in very high transepidermal water loss (TEWL). The vernix which starts to develop during

the last trimester serves as an emollient to maintain hydration that facilitates the formation of the acid mantle for microbial homeostasis and acts as a first-line host defense mechanism [3]. Due to the limited therapeutic options for managing infections in preterm babies, as well as the scarcity of innovative approaches in developing countries, topical therapy may be an effective strategy to improve neonatal outcomes [5]. Neonatal Skin Condition Score (NSCS) is a reliable criterion used to assess neonatal skin conditions. The lower the score on 3 criteria - dryness, erythema, and breakdown, the better is the skin integrity of the neonate. If a neonate scores 3 in any area, the physician should be notified.[8]

Many plant-based oils are used as effective emollients for skin ailments; among them is virgin coconut oil (VCO). VCO is extracted through a low-heat process from fresh coconut oil without the use of chemicals. It is composed of various fatty acids and is widely used in South Asia for food, medical and industrial applications [6]. The assumed benefits of VCO application like the induced tactile kinesthetic stimulation to the newborn skin in the form of improved skin barrier function, thermoregulation, and also a possible positive effect on growth have been documented in previous literature [3,6].

VCO acts by augmenting the skin barrier, supplementing essential fatty acids, and reducing water loss and hypothermia. Lauric acid, its major medium-chain triglyceride, is known to have an effective antimicrobial activity, thereby giving VCO the potential to reduce infections and newborn mortality. Coconut oil application is also affordable and helps promote weight gain.

A meta-analysis in 2018 looked into the efficacy of VCO-supplemented milk in augmenting weight gain of very low birth weight preterm infants. Although oral and not topical VCO was studied here, its safety in this population was established. The population in this meta-analysis included 290 babies. The babies had a statistically significant weight gain after being given VCO-supplemented milk. [7]

This study aimed to systematically review randomized trials assessing the effects of topical VCO application in preterm infants particularly on the prevention of infection and mortality, and on dermal maturity.

## Methodology

*Eligibility Criteria*

This study aimed to investigate the efficacy of topical VCO application on the development of infection, mortality, and dermal maturation in preterm neonates born less than 37 weeks of gestational age as determined by Ballard scoring. Dermal maturation is defined as epidermal maturation based on the Neonatal Skin Condition Score (NSCS), a validated tool for the assessment of neonatal skin conditions. Infections included early- and late-onset sepsis, and nosocomial infection (sepsis, pneumonia).

Following the PICOs approach, we included randomized studies that met the following criteria: (1) preterm neonates <37 weeks gestational age, (2) treatment using VCO topical application, and (3) comparator group composed of other emollients or none. Primary outcomes were infection which includes early/late onset sepsis and pneumonia, all-cause mortality while admitted at the Neonatal Intensive Care Unit (NICU), and dermal maturation as measured by NSCS. NSCS is reliable when used by single and multiple raters to assess neonatal skin conditions, even across weight groups and racial groups. Validity of the NSCS was demonstrated by confirmation of the relationship of the skin condition scores with birth weight, number of observations, and prevalence of infection. [8]

Secondary outcomes were skin irritation and change in weight. Skin irritation is defined as a dermal reaction to any substance applied to the skin. We excluded the following: (1) prospective non-randomized observational studies, case series, and case controls, (2) retrospective observational studies, (3) studies that reported preliminary results, (4) study protocols and ongoing studies, and (5) unpublished manuscripts and conference abstracts.

*Search Strategy*

We conducted this study according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guideline [9]. We searched original articles without language restrictions from their inception until our last search on July 16, 2021 from the following electronic databases: PubMed, Google Scholar, Clinical trials.gov, Trip database, Cochrane Library, and Herdin. We searched for the completeness of the following reference lists of the retrieved studies and relevant reviews (Figure 1).

To search for individual studies, we used the following key and MeSH terms: ((((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR

"trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) and ((virgin coconut oil) or (VCO)) and ((topical application) or (dermal application) or (skin application) or ("Administration, Cutaneous"[Mesh]))) (Table S1. Supplementary Material).

In the first step, 2 reviewers (KQ and DOS) independently screened the titles and abstracts according to the eligibility criteria. The same reviewers retrieved and individually reviewed the full texts of the articles to confirm eligibility in a second step. The 2 reviewers discussed any ambiguities concerning eligibility and in case of disagreement arrived at a consensus (Table S2. Supplementary Material).

*Data extraction*

Two reviewers (KQ and DOS) independently conducted the data extraction. Descriptive data on each article (first author,

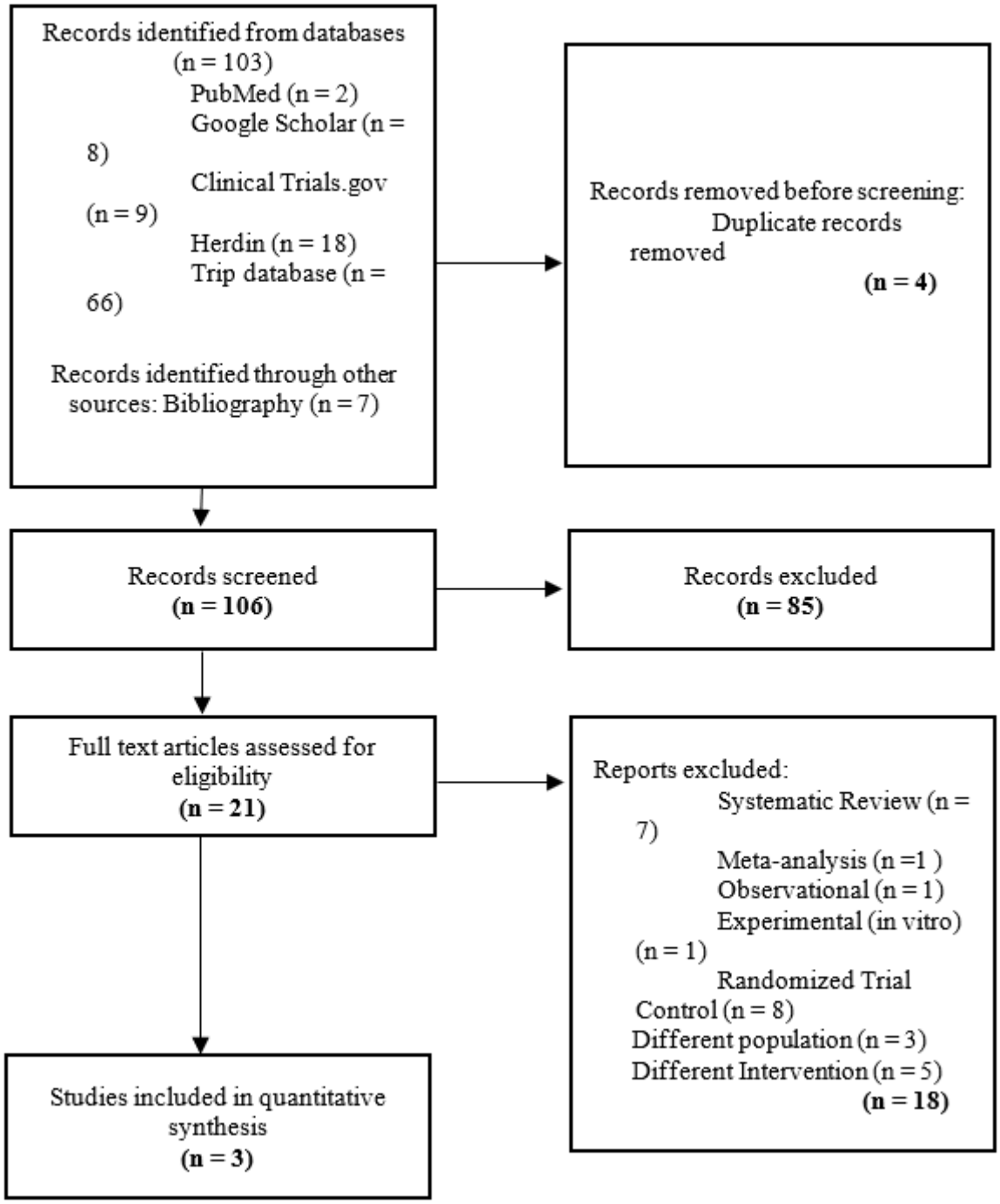



**Figure 1.** *Database search strategy of included studies according to PRISMA guidelines*

publication year), study design, sample size, treatment, country and years conducted, demographic patient characteristics (pediatric age according to Ballard score, sex, weight), infection rate or sepsis, all-cause mortality, skin maturity assessed by Neonatal Skin Condition Score (NSCS), skin irritation and skin infection, and study results (dermal maturation, development of sepsis, weight gain) were collected. The reviewers entered the data into two separate spreadsheets and compared the spreadsheets after data extraction was completed. They resolved the disagreements by discussion.

*Risk of Bias Assessment*

The authors used the Cochrane Risk of Bias Tool 1 to assess the methodological quality of the eligible trials. Disagreements were resolved by discussion between the authors. Selection bias (randomization and allocation concealment), performance bias (blinding of participants and investigators), detection bias (blinding of outcome adjudicators), attrition bias (differential loss to follow-up), and reporting bias (selective outcome reporting) were judged to be of low, unclear, or high risk for each trial. The authors evaluated each trial to ascertain whether the risk of bias was low, unclear, or high, based on the level of bias in the defined domains that could have led to biases in the outcome estimates.

*Statistical Analysis*

We used Review Manager (RevMan 5.4) to compare data from the included studies. Risk ratio (RR with 95% CI) was used for dichotomous data. The heterogeneity among the studies was evaluated using the Cochran Q and chi-squared statistics. In contrast, the I2 statistic was used to determine the percentage of variation across the studies from heterogeneity. An I2 of less than 25% is usually viewed as low heterogeneity, between 25% and 50% as moderate, and over 50% as high heterogeneity." All tests were two-tailed, and a p-value < 0.10 was considered statistically significant [10].

The analysis did not include a trial that did not report the specific outcome. Sources of heterogeneity were explored by looking at the variations in the characteristics of the included patients, interventions, and outcomes.

*Ethical Consideration*

The Ethics and Review Board of the Mary Mediatrix Medical Center reviewed this protocol. The investigators have no conflicts of interest to disclose in this meta-analysis. The investigators applied for a waiver since this meta-analysis and review of published randomized controlled trials pose no risk to patients. This waiver complies with the National Ethical Guidelines for Health and Health-related Research 2017.

## Results

*Study Selection*

We retrieved 110 records up to July 16, 2021. After screening the titles and abstracts, we included 21 studies in a full-text screening, where we removed further 18 studies. The reasons for excluding full-text articles are in Table S2 of the Supplementary Material. We included three trials in the meta-analysis [4,6,11]. The PRISMA flow diagram showed the study selection procedure (Figure 1).

*Characteristics of Included Studies*

Included in this review were three RCTs published between 2004 and 2020. Bautista *et al.* (2004) conducted a study in a Neonatal Intensive Care Unit (NICU) in the Philippines, Konar *et al.* (2020) conducted theirs in a rural field practice area in India, and Strunk *et al.* (2018) conducted theirs in a NICU in Australia [4,6,11]. The rural area trial involved the highest number of patients (n = 2294). Strunk *et al.* (2018) included only 72 and Bautista *et al.* (2004) had 52 patients. Bautista *et al.* (2004) stopped their study before reaching the computed sample size due to adverse outcomes of nosocomial infections [4]. In this review, all three studies reported on infection in general (nosocomial pneumonia, nosocomial sepsis, early and late-onset sepsis) as a clinical outcome. Bautista *et al.* (2004) and Strunk *et al.* (2018) included mortality as an outcome, while Konar *et al.* (2020) and Strunk *et al.* (2018) reported on NSCS as a measure of dermal maturation. For the secondary outcomes, both studies by Konar *et al.* (2020) and Strunk *et al.* (2018) reported skin irritation, rash, and weight loss. Study details such as the country, study design, study period, number of included patients, and the outcomes are in Table 1.

*Patient Characteristics and Outcomes*

The summary of characteristics of patients and reports on outcomes are in Table 2. The pediatric aging of preterm neonates differs from the three trials such that Strunk included a younger age group compared to Bautista and Konar. Konar *et al.* (2020) included older patients who were 34-37 weeks and younger infants who were less than 34 weeks [6]. Bautista *et al.* (2004) also included preterm babies less than 34 weeks [4], while the study of Strunk *et al.* (2018) included much younger preterm infants whose ages ranged from 26.3 to 29.3 weeks

[8]. The amount and frequency of the intervention VCO also differed. Bautista *et al.* (2004) and Strunk *et al.* (2018) specified the body areas where VCO was applied twice a day, while Konar *et al.* (2020) did not indicate the specific areas to which VCO was applied four times a day. Bautista *et al.* (2004) reported nosocomial infection. Strunk *et al.* (2018) reported the timing of sepsis while Konar *et al.* (2020) reported late-onset sepsis only. Only two studies reported on mortality; there was no mortality in the study by Strunk *et al.* (2018), and there were seven in the study of Bautista *et al.* (2004) in the VCO group and 4 in the control group). Bautista reported 12% mortality, whereas Strunk has none. NSC scores were not comparable between the two studies. Overall, 69.3% of the patients in the study of Konar *et al.* (2020) were significantly older (34-37 weeks) and had higher NSC scores compared to the study of Strunk *et al.* (2018) [6, 11].

*Risk of Bias Assessment*

Estimation of the risk of bias for the included studies comparing VCO and no intervention was presented in Figures S1 and S2, and Table S3 (Supplementary Material). Blinding of participants and personnel was impossible due to identifiable emollient types or fragrances. One study reported on the independence of the outcome assessor but did not indicate blinding with the patient assignment. The study of Bautista *et al.* (2004) in which the computed sample size was not reached was given an unclear risk of other biases. The study was prematurely terminated due to harm because interim analysis showed a 10% increased incidence of nosocomial infection and death in the experimental group compared to the control group.

*Primary Outcomes*

*Effect of Topical VCO on the Prevention of Infection*

The three studies reported various types of infections. Bautista *et al.* (2004) reported pneumonia and sepsis while Konar *et al.* (2020) and Strunk *et al.* (2018) reported late-onset sepsis.

The overall pooled effect in the figure touches the no effect line, therefore, we conclude that while the RR indicates that VCO has some effect as the exposure group in lowering the risk, there is no statistical evidence to suggest this as a fact and also the p-value of the test for overall effect is indeed greater than 0.1 also confirms this (Figure 2).

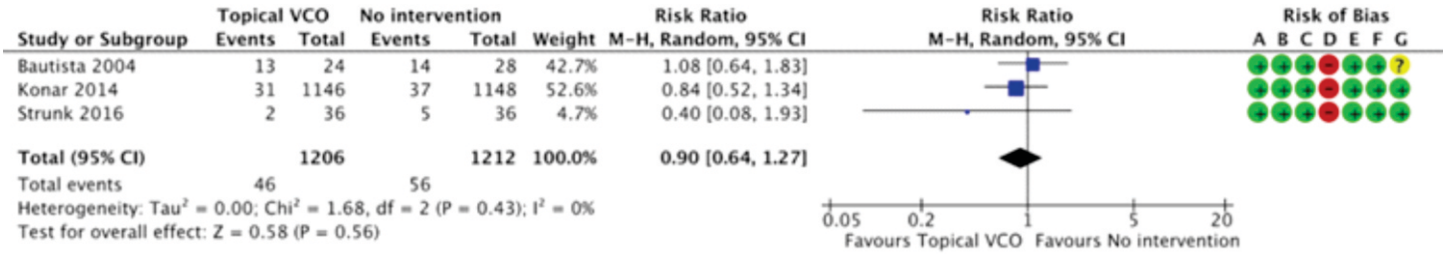
The Q test yielded a p-value of 0.43 indicating that the meta-analysis of the three studies resulted in failing to reject the hypothesis of no heterogeneity. Likewise, the I2 value is 0% showing consistency among the included studies (Figure 2).

*Effect of Topical VCO on the Reduction of Mortality*

The studies of Bautista *et al.* (2004) and Strunk *et al.* (2018) showed that the reduction of mortality by topical application of VCO was inconclusive (RR = 0.45, [95% CI: 0.06, 3.38]). The Q test p-value of mortality reduction was 0.18, and the I2 value was 43%, which indicates low heterogeneity (Figure 3). These two studies reported in-patient mortality (all-cause mortality ).

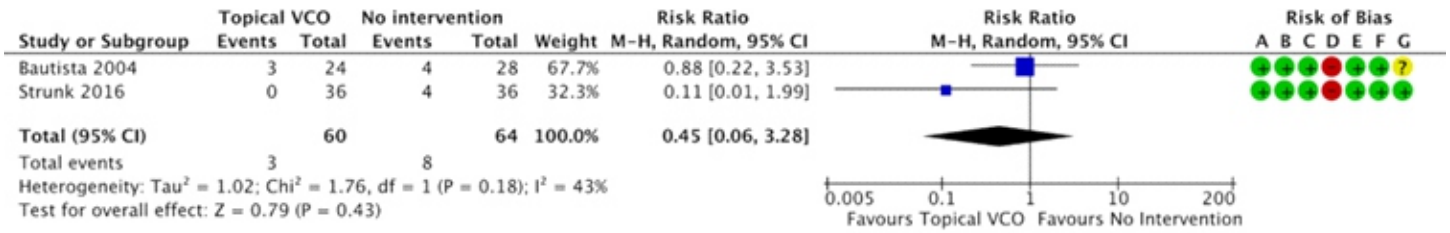
*Effect of Topical VCO on Dermal Maturation*

The meta-analysis of the NSCS results of Konar *et al.* (2020) and Strunk *et al.* (2018) from Day 0 to Day 21 showed a significant trend toward VCO being beneficial as the treatment progressed. Day 0 results indicate heterogeneity and neutrality of the data since the pooled effect is on the no-effect line (Figure 4). Based on the increasing NSCS on Day 7-21, the data showed a significant effect of VCO on the dermal changes (Day 7 MD = -0.62, [95% CI: -0.98, -0.27]; Day 14 MD = -0.68, [95% CI: -1.31, -0.05]; Day 21 MD = -0.89, [95% CI: -1.70, -0.07]). Significant heterogeneity was observed as the intervention proceeded (Day 7 I2 = 96%; Day 14 I2 = 99%; Day 21 I2 = 99%) (Figure 4). The sources of heterogeneity




Risk of Bias Summary Legend: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Blinding of outcome assessment (detection bias); (F) Incomplete outcome data addressed (attrition bias); (G) Other bias

**Figure 2.** *Forest plot showing risk ratio and risk of bias summary for the prevention of infection among Topical VCO and no intervention groups*




Risk of Bias Summary Legend: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Blinding of outcome assessment (detection bias); (F) Incomplete outcome data addressed (attrition bias); (G) Other bias

**Figure 3.** *Forest plot showing risk ratio and risk of bias summary for the prevention of mortality among Topical VCO and no intervention groups*

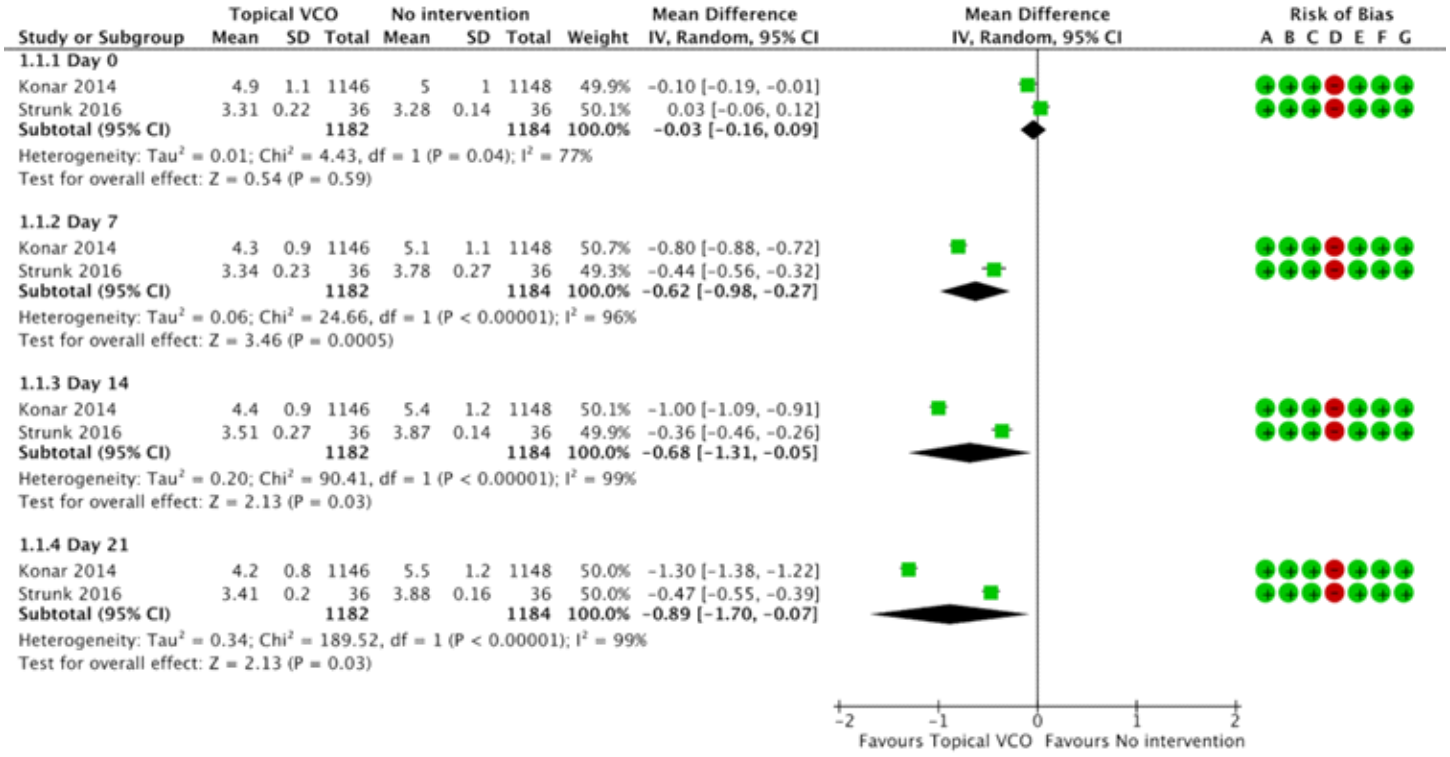



**Figure 4.** *Forest plot showing mean difference and risk of bias summary for Neonatal Skin Condition Score (NSCS) among Topical VCO and no intervention groups*

were the characteristics of included patients such as the age, amount, frequency, and body area of application. There was no subgrouping done in the analysis.

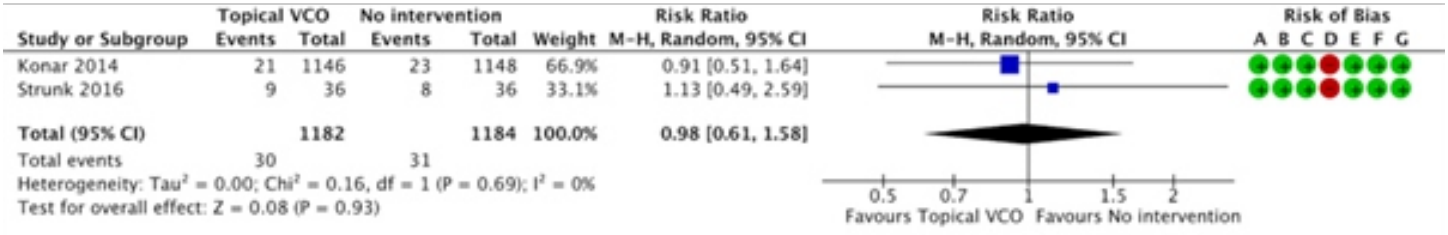
*Secondary Outcomes*

*Effect of Topical VCO on the Prevention of Skin Irritation*

The studies of Konar *et al.* (2020) and Strunk *et al.* (2018) showed inconclusive results on the effect of topical VCO on preventing rash or skin irritation (RR = 0.98, [95% CI: 0.61, 1.58]). The p-value (0.69) indicated no heterogeneity and I2 (0%) indicated consistency between studies (Figure 5).

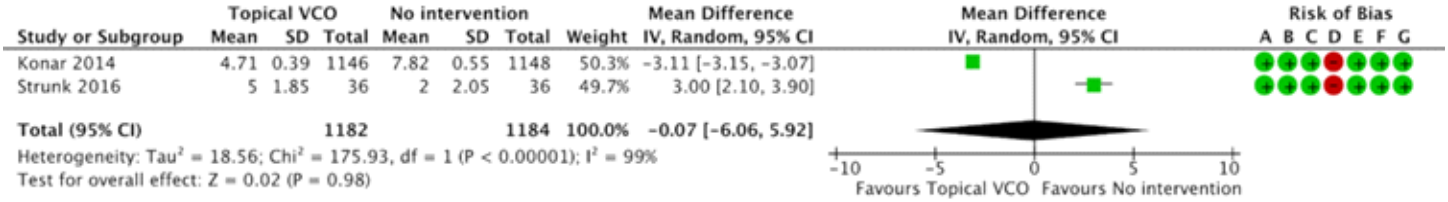
*Effect of Topical VCO on Weight Loss*

The same two studies reported weight loss as an outcome. Weight was measured in grams. and the time point of measurement was from birth to day 7. The results of the meta-analysis were inconclusive (MD = -0.07, [95% CI: -6.06, 5.92]). The studies have significantly very high heterogeneity with a p-value of almost zero, and I2 was 99% (Figure 6).




Risk of Bias Summary Legend: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Blinding of outcome assessment (detection bias); (F) Incomplete outcome data addressed (attrition bias); (G) Other bias

**Figure 5.** *Forest plot showing risk ratio and risk of bias summary for skin irritation among Topical VCO and no intervention groups*




Risk of Bias Summary Legend: (A) Random sequence generation (selection bias); (B) Allocation concealment (selection bias); (C) Blinding of participants and personnel (performance bias); (D) Blinding of outcome assessment (detection bias); (E) Blinding of outcome assessment (detection bias); (F) Incomplete outcome data addressed (attrition bias); (G) Other bias

**Figure 6.** *Forest plot showing mean difference and risk of bias summary for weight loss among Topical VCO and no intervention groups*

## Discussion

The effects of VCO on the prevention of infection and promotion of skin development were inconclusive. Furthermore, the studies lacked the power to detect significant effects on mortality.

*Effects of Topical Application of VCO*

Oil massage has been traditionally practiced for centuries in places like India where it is believed to prevent infection and decrease newborn mortality by augmenting the skin barrier and supplementing essential fatty acids [12]. Virgin coconut oil (VCO) exhibits antibacterial properties and inhibits various inflammatory mediators such as tumor necrosis factor-α, interleukin-5, -6, and -8, and interferon-ɣ [13]. A randomized controlled trial done in Bangladesh involving 212 participants aged 2-24 months with severe acute malnutrition showed that the odds of developing nosocomial infection were reduced by 59% in the emollient therapy group treated with linoleic acid-rich and oleic acid-containing sunflower seed oil [12]. Although VCO is also rich in oleic and linoleic acids [13], in this review, its use to prevent infection was inconclusive. The two studies with 72 and 52 patients in this review did not have enough power to detect any significance in mortality reduction with topical VCO [4,11]. Bautista *et al.* mentioned that for every 56 premature infants given VCO topically, one may have been prevented from dying [4]. Thus, the evidence that topical application of VCO prevents mortality was inconclusive.

Our meta-analysis showed that VCO may enhance dermal maturation, however, the certainty of evidence on skin maturity is low, meaning further research is very likely to have an important impact on our confidence. The significant benefit of topical VCO on dermal maturation was evident in weeks 1 to 3. Topical application of the oil may prevent transepidermal water loss which is one of the significant problems in prematures [14]. Epidermal desquamation occurs more extensively in an older newborn compared to a young preterm, thus, a higher NSC score can be observed in the study by Konar *et al.* from day 7 to 21 days of VCO application [15]. Albeit significant, the evidence showed a risk of bias due to a lack of blinding in outcome assessment, and inconsistency due to the observed considerable heterogeneity. The heterogeneity in the two trials that included NSCS as an outcome may be due to selection bias.

The effect of VCO application on preventing skin rash or irritation in the two studies was inconclusive. As skin

irritation is common in neonates due to the immaturity of their integument, oil is sometimes used to relieve symptoms. In a study done in Nepal, mustard oil massage was done on term and preterm infants to determine skin changes [16]. In the first two weeks of application, rash, and erythema increased, then the skin improved in weeks 3 and 4. This may be explained by the occurrence of a common benign and transient skin condition in newborns called erythema toxicum. This typically regresses after a few weeks of life.

The effect of VCO application on weight loss from birth to 7 days was inconclusive. This may be reflective of the physiologic weight loss of newborns whether they were in the control or the intervention group [17].

## Limitations of the Study

Our study had some limitations. We did not extract data from studies that were not available online for free. Additionally, we included only articles with open access. One of the studies we analyzed was terminated prematurely, leading to a lower number of participants than needed to achieve statistically significant results.

## Conclusion

This meta-analysis aimed to evaluate the effect of topical VCO application on the incidence of infection, mortality, and dermal maturation in prematurely born infants. The results showed inconclusive outcomes in the prevention of infection and the enhancement of dermal maturation with topical VCO. There was insufficient evidence to conclude that VCO application decreased mortality in preterm infants. The secondary outcomes of the effect of topical VCO on preventing skin irritation and weight loss were inconclusive. The evidence of the benefits of topical VCO should be well-established before its inclusion in clinical practice guidelines for the care of premature infants

## References

1. Dey AC, Mannan A, Saha L, Hossain I, Shahidullah M. (2012) Magnitude of problems of prematurity-national and global perspective: a review. Bangladesh J Child Health 36(3):146–52. doi: 10.3329/bjch.v36i3.14288.
2. Debmandal M, Mandal S. (2011) Coconut (Cocos nucifera L.: Arecaceae): In health promotion and disease prevention. Asian Pacific Journal of Tropical Medicine 241-247
3. Dhar S, Banerjee R, Malakar R. (2013) Oil massage in babies: Indian perspectives. Indian Journal of Paediatric Dermatology 14(1-2):1-3. doi: 10.4103/2319-7250.116838
4. Bautista R, Mantaring III JB, Ong-Lim AL. (2004) A Randomized Controlled Trial of Topical Application of Virgin Coconut Oil in the Prevention of Nosocomial Infections in Neonates Born ≤ 34 Weeks Gestational Age. Acta Medica Philippina 46(4 2012)- 47 (1 2013): 18-23.
5. Cleminson J, McGuire W. (2021) Topical emollient for preventing infection in preterm infants. Cochrane Database Syst Rev 5(5): CD001150. doi: 10.1002/14651858.CD001150.pub4. PMID: 33961715; PMCID: PMC8104155.
6. Konar MC, Islam K, Roy A, Ghosh T. (2020) Effect of Virgin Coconut Oil Application on the Skin of Preterm Newborns: A Randomized Controlled Trial. Journal of Tropical Pediatrics 66:129-135. doi: 10.1093/tropej/fmz041
7. Barcelona AD, Resurreccion MM. (2018) Efficacy of Virgin Coconut Oil supplemented-milk feeding in augmenting weight gain among very low birth weight preterm infants: A meta-analysis. The PCMC Journal, 14(2), 1-10
8. Lund CH, Osborne JW. Validity and reliability of the neonatal skin condition score. J Obstet Gynecol Neonatal Nurs. 2004 May-Jun;33(3):320-7. doi: 10.1177/0884217504265174. PMID: 15180195
9. Higgins JP, Green S, *et al.* (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration
10. West SL, Gartlehner G, Mansfield AJ, *et al.* Comparative Effectiveness Review Methods: Clinical Heterogeneity [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Sep. Table 7, Summary of common statistical approaches to test for heterogeneity. https://www.ncbi.nlm.nih.gov/books/NBK53317/table/ch3.t2/]]
11. Strunk T, Pupala S, Hibbert J, Doherty D, Patole S. (2018) Topical Coconut Oil in Very Preterm Infants: An Open-Label Randomized Controlled Trial. Neonatology 113:146–151. doi.org/10.1007/s00431-019-03407-7
12. Ahmed AS, Saha SK, Chowdhury MA, *et al.* (2007) Acceptability of massage with skin barrier-enhancing emollients in young neonates in Bangladesh.

Health Popul Nutr 25(2):236-40. PMID: 17985826; PMCID: PMC2754003

13. Varma SR, Sivaprakasam TO, Arumugam I, *et al.* (2018) *In vitro* anti-inflammatory and skin protective properties of Virgin coconut oil. J Tradit Complement Med 9(1):5-14. doi: 10.1016/j.jtcme.2017.06.012. PMID: 30671361; PMCID: PMC6335493
14. Pupala SS, Rao S, Strunk T, Patole S. (2019) Topical application of coconut oil to the skin of preterm infants: a systematic review. European Journal of Pediatrics. doi:10.1007/s00431-019-03407-7
15. Sarkar R, Podder I, Gokhale N, Jagadeesan S, Garg VK. (2017) Use of vegetable oils in dermatology: an overview. International Journal of Dermatology 56(11):1080–1086. doi:10.1111/ijd.13623
16. Summers A, Visscher MO, Khatry SK, *et al.* (2018) Indicators of skin barrier integrity among newborns massaged with mustard oil in rural Nepal. J Perinatol 38(1):64-70. doi: 10.1038/jp.2017.158. Epub 2017 Nov 9. PMID: 29120456; PMCID: PMC5775032.
17. DiTomasso D, Cloud M. (2019) Systematic Review of Expected Weight Changes After Birth for Full-Term, Breastfed Newborns. J Obstet Gynecol Neonatal Nurs 48(6):593-603. doi: 10.1016/j.jogn.2019.09.004. Epub 2019 Oct 11. PMID: 31610141.

**Table S1.** *PubMed search and Hits*

| | Author (Year of publication) | | | | | |
|---|---|---|---|---|---|---|
| | Bautista (2004) | | Konar (2020) | | Strunk (2018) | |
| **Study Characteristics** | | | | | | |
| **Country** | Philippines | | India | | Australia | |
| **Study period** | 2004 | | March 2014-August 2018 | | March – October 2016 | |
| **Study design** | RCT | | RCT | | RCT | |
| **Outcomes** | • Infection rates<br>• All-cause mortality<br>• Length of stay | | • NSCS on 7th, 14th, 21st, 28th day<br>• Late-onset sepsis<br>• Weight loss<br>• Rash/ skin irritation | | • Safety – skin irritation or local infection<br>• Efficacy – skin condition assessed by NSCS<br>• Weight gain/loss<br>• Late-onset sepsis<br>• Mortality | |
| **Intervention/Dosage** | 4g/kg/day 2x a day for 14 days<br>Control: Minimal to None | | 5ml 4x a day except for face and scalp<br>Control: None | | 5ml every 12 hours for 21 days excluding face and scalp<br>Control: None | |
| Study population | Intervention | Control | Intervention | Control | Intervention | Control |
| **Participants (Total N)** | 24 (52) | 28 (52) | 1146 (2,294) | 1148 (2,294) | 36 (72) | 36 (72) |
| **Sex n M/F** | 15/9 | 16/12 | 584/562 | 572/576 | 13/23 | 19/17 |
| **Pediatric Age by Ballard, N (%)** | ≤ 34 weeks | ≤ 34 weeks and <72 hours | 34 - 37 weeks: 794 | 34 – 37 weeks: 801 | 27.9 (26.3 – 29.3), median (IQR) | 27.9 (25.4 – 29.1), median (IQR) |
| **Birthweight, g** | 1326±318.56, mean±SD | 1212.5±390.07, mean±SD | Not reported | Not reported | 1,070 (879–1202), median (IQR) | 950 (726–1155), median (IQR) |
| **Results** | | | | | | |
| **Weight gain, mean ± SD** | Not reported | Not reported | 1.21±0.17 | 0.89±0.12 | Not reported | Not reported |
| **Weight gain, median (IQR)** | Not reported | Not reported | Not reported | Not reported | Day 7: 1,100 (939-1,257)<br>Day 21: 1,312 (1085-1502) | Day 7: 1,007 (751-1,210)<br>Day 21: 1296 (1066-1492) |
| **Nosocomial Sepsis, N (%)** | 9 (38) | 12 (43) | Not reported | Not Reported | Not reported | Not Reported |
| **Nosocomial pneumonia, N (%)** | 4 (17) | 2 (7) | Not reported | Not reported | Not reported | Not reported |
| **Early Onset Sepsis, N (%)** | Not reported | Not reported | Not reported | Not reported | 0 (0) | 0 (0) |
| **Late Onset Sepsis, N (%)** | Not reported | Not reported | 31 (2.7) | 37 (3.2) | 2 (5.6) | 5 (13.9) |
| **Mortality, N (%)** | 3 (12) | 4 (14) | Not reported | Not Reported | 0 (0) | 4 (11.1) |
| **Skin irritation/Rash, N (%)** | Not reported | Not reported | 21 (1.8) | 23 (2.0) | 9 (25) | 8 (22) |
| **NCSC (Neonatal Skin Cndition Score)** | Not reported | Not reported | mean ± SD<br>Baseline: 4.9±1.1<br>Day 28: 3.9±0.7 | mean ± SD<br>Baseline: 5.0±1.0<br>Day 28: 4.8±1.0 | median (IQR)<br>Baseline: 3.31 (0.89)<br>Day 21: 3.41 (0.81) | median(IQR)<br>Baseline: 3.28 (0.55)<br>Day 21: 3.88 (0.63) |

| Search number | Query | Results | Time |
|---|---|---|---|
| 17 | #1 and #4 and #9 and #16 | 2 | 07:22:39 |
| 16 | "clinical trial"[Publication Type] | 895,725 | 07:22:09 |
| 15 | #1 and #4 and #9 | 2 | 07:21:48 |
| 14 | #1 and #4 and #9 and #13 | 1 | 07:21:24 |
| 13 | #10 or #11 or #12 | 126,807 | 07:20:48 |
| 12 | "Premature Birth"[Mesh] Sort by: Most Recent | 15,527 | 07:20:29 |
| 11 | preterm babies | 75,848 | 07:15:39 |
| 10 | premature neonates | 107,362 | 07:15:29 |
| 9 | #5 or #6 or #7 or #8 | 93,307 | 07:15:13 |
| 8 | "Administration, Cutaneous"[Mesh] Sort by: Most Recent | 22,874 | 07:14:47 |
| 7 | skin application | 53,490 | 07:13:57 |
| 6 | dermal application | 6,935 | 07:13:50 |
| 5 | topical application | 32,886 | 07:13:42 |
| 4 | #2 or #3 | 1,383 | 07:13:31 |
| 3 | VCO | 1,307 | 07:12:28 |
| 2 | virgin coconut oil | 189 | 07:12:23 |
| 1 | ((randomized controlled trial [pt]) OR (controlled clinical trial [pt]) OR (randomized [trial]) OR (placebo [trial]) OR (drug therapy [sh]) OR (randomly [trial]) OR (trial [trial]) OR (groups [trial])) NOT (animals [mh] NOT humans [mh]) - Saved search Sort by Most Recent | 4,435,943 | 07:12:07 |

**Table S2.** *Reasons for exclusion of full-text studies*

| No | Author | Title | Reason for Exclusion and Inclusion |
|---|---|---|---|
| 1 | M. Konar et al. | Effect of Virgin Coconut Oil Application on the Skin of Preterm Newborns: A Randomized Controlled Trial | RCT* |
| 2 | L. Ayuningrum et al. | Effectiveness Of H-Hope Plus Kinesthetic with Virgin Coconut Oil (VCO) On Body Weight in Premature Infants | RCT *Different Intervention: (H-Hope + VCO)* |
| 3 | R. Bautista et al. | A Randomized, Controlled Trial of Topical Application of Virgin Coconut Oil in the Prevention of Nosocomial Infections in Neonates Born <34 Weeks Gestational Age | RCT* |
| 4 | S. Pupala et al. | Topical application of coconut oil to the skin of preterm infants: a systematic review | Systematic Review |
| 5 | K. Koo et al. | The use of complementary and alternative medicine in children with atopic eczema at a tertiary care center in Malaysia | RCT (*Different Population: Eczema Patients)* |
| 6 | M. Alvarez et al. | The effects of massage therapy in hospitalized preterm neonates: A systematic review | Systematic Review |
| 7 | A. Ibrahim et al. | Angiogenic and wound healing potency of fermented virgin coconut oil: in vitro and in vivo studies | Experimental (In Vitro) *Different Population* |
| 8 | L. Ayuningrum et al. | Effectiveness of Massage Therapy for Preterm Infants: A Literature Review | Systematic Review |
| 9 | S. Joshi et al. | Coconut Oil and Immunity: What do we really know about it so far? | Review |
| 10 | M. Frias et al. | The efficacy of virgin coconut oil versus zinc oxide in the treatment of diaper dermatitis among pediatric patients: A randomized controlled trial | RCT *(Different Population: Eczema patients)* |
| 11 | M. Shahunj et al. | Topical emollient therapy in the management of severe acute malnutrition in children under two: A randomized controlled clinical trial in Bangladesh | RCT (*Different Population: Malnourished children Different Intervention: Topical Emollient)* |
| 12 | M. Evangelista et al. | The effect of topical virgin coconut oil on SCORAD index, transepidermal water loss, and skin capacitance in mild to moderate pediatric atopic dermatitis: a randomized, double-blind, clinical trial | RCT (*Different Population: Eczema patients)* |
| 13 | M. Visscher et al. | Update on the Use of Topical Agents in Neonates | Review |
| 14 | T. Strunk et al. | Topical Coconut Oil in Very Preterm Infants: An Open-Label Randomised Controlled Trial | RCT* |
| 15 | R. Salam et al. | Emollient therapy for preterm newborn infants – evidence from the developing world | Systematic Review (*Different Intervention: Emollient Therapy)* |
| 16 | D. Prince et al. | Effectiveness of oil massage on weight gain among pre-term neonates in selected pediatric hospitals, Hyderabad | RCT (*Different Intervention: Oil massage)* |
| 17 | W. Edwards et al. | The Effect of Prophylactic Ointment Therapy on Nosocomial Sepsis Rates and Skin Integrity in Infants with Birth Weights of 501 to 1000 g | RCT (*Different Intervention: Aquaphor ointment)* |
| 18 | A. Kulkarni et al. | Massage and Touch Therapy in Neonates: The Current Evidence | Review |
| 19 | J. Arora et al. | Effect of oil massage on growth and neurobehavior in very low birth weight preterm neonates | RCT (*Different Intervention: Oil Massage)* |
| 20 | A. Barcelona et al. | Efficacy of Virgin Coconut Oil Supplemented-Milk Feeding in Augmenting Weight Gain Among Very Low Birth Weight Preterm Infants: A Meta-Analysis | Meta-analysis (*Different Intervention: Oral VCO)* |
| 21 | C. Lund et al. | Validity and Reliability of the Neonatal Skin Condition Score | Validation Observational Study |

Legend: RCT* - RCT's ncluded in the study

**Table S3.** *Support for judgment on the risk of bias summary*

*Bautista 2004*

| Bias | Authors' judgment | Support for judgment |
|---|---|---|
| Random sequence generation (selection bias) | Low Risk | Randomized according to protocol |
| Allocation concealment (selection bias) | Low Risk | Assignments were placed in sealed opaque envelopes |
| Blinding of participants and personnel (performance bias) | Low Risk | Control intervention involved minimal to no use of topical emollients, blinding might be impossible due to possible identifiable emollient types or fragrances. |
| Blinding of outcome assessment (detection bias) | High Risk | No discussion among attending physicians on their knowledge of patient assignment |
| Incomplete outcome data (attrition bias) | Low Risk | No reported losses to follow up |
| Selective reporting (reporting bias) | Low Risk | Outcomes were reported |
| Other bias | Unclear Risk | Computed sample size was not reached, interim analysis and stopping rules due to harm were pre-specified |

*Konar 2014*

| Bias | Authors' judgment | Support for judgment |
|---|---|---|
| Random sequence generation (selection bias) | Low Risk | Randomization is computer-generated |
| Allocation concealment (selection bias) | Low Risk | Assignments were placed in sealed opaque envelopes |
| Blinding of participants and personnel (performance bias) | Low Risk | Control intervention involved massaging without any application of oil or emollients, blinding might be impossible on the study |
| Blinding of outcome assessment (detection bias) | High Risk | No discussion if outcome assessors or trained personnel were blinded |
| Incomplete outcome data (attrition bias) | Low Risk | No reported losses to follow up |
| Selective reporting (reporting bias) | Low Risk | Outcomes were reported |
| Other bias | Low Risk | None identified |

*Strunk 2016*

| Bias | Authors' judgment | Support for judgment |
|---|---|---|
| Random sequence generation (selection bias) | Low Risk | Randomization is computer-generated |
| Allocation concealment (selection bias) | Low Risk | Assignments were placed in sealed, coded, and opaque envelopes |
| Blinding of participants and personnel (performance bias) | Low Risk | Control intervention was the standard neonatal care, without any application of oil or emollients as blinding is impossible on the study |
| Blinding of outcome assessment (detection bias) | High Risk | Outcome assessor was reportedly independent, but no indication of blinding with the patient assignment |
| Incomplete outcome data (attrition bias) | Low Risk | No reported withdrawals from the study |
| Selective reporting (reporting bias) | Low Risk | Outcomes were reported |
| Other bias | Low Risk | None identified |

**Risk of bias assessment**

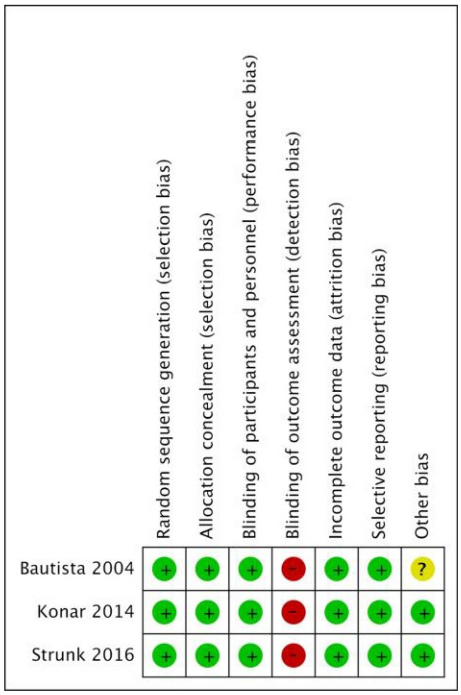



**Figure S1.** *Risk of bias summary for each included study*

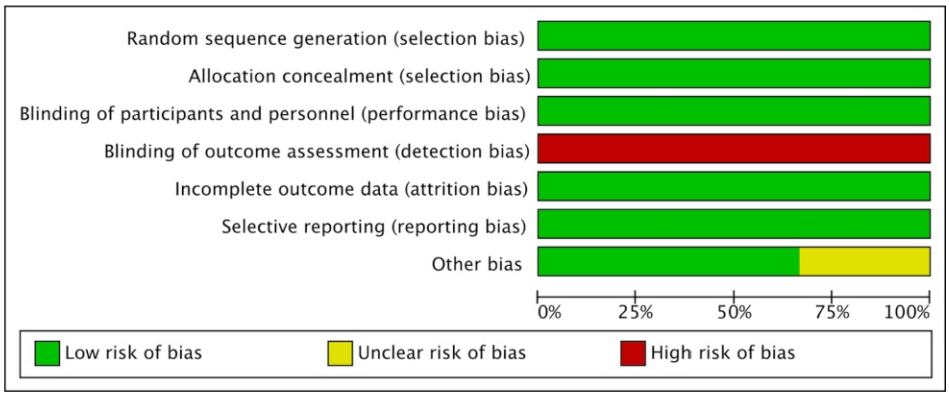



**Figure S2.** *Risk of bias graph for included studies*