Effects of emollient therapy with sunflower seed oil on neonatal growth and morbidity in Uttar Pradesh, India: a cluster-randomized, open-label, controlled trial

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ABSTRACT
Background: Newborn oil massage is a widespread practice. Vigorous massage with potentially harmful products and forced removal of vernix may disrupt skin barrier integrity. Hospitalized, very-preterm infants treated with sunflower seed oil (SSO) have demonstrated improved growth but community-based data on growth and health outcomes are lacking.

Objectives: We aimed to test whether SSO therapy enhances neonatal growth and reduces morbidity at the population level.

Methods: We conducted an open-label, controlled trial in rural Uttar Pradesh, India, randomly allocating 276 village clusters equally to comparison (usual care) and intervention comprised of promotion of improved massage practices exclusively with SSO, using intention-to-treat and per-protocol mixed-effects regression analysis.

Results: We enrolled 13,478 and 13,109 newborn infants in demographically similar intervention and comparison arms, respectively. Adherence to exclusive SSO increased from 22.6% of intervention infants enrolled in the first study quartile to 37.2% in the last quartile. Intervention infants gained significantly more weight, by 0.94 g·kg⁻¹·d⁻¹ (95% CI: 0.07, 1.82 g·kg⁻¹·d⁻¹; P = 0.03), than comparison infants by intention-to-treat analysis. Restricted cubic spline regression revealed the largest benefits in weight gain (2–4 g·kg⁻¹·d⁻¹) occurred in infants weighing <2000 g at birth. Weight gain in intervention infants was higher by 1.31 g·kg⁻¹·d⁻¹ (95% CI: 0.17, 2.46 g·kg⁻¹·d⁻¹; P = 0.02) by per-protocol analysis. Morbidities were similar by intention-to-treat analysis but in per-protocol analysis rates of hospitalization and of any illness were reduced by 36% (OR: 0.64; 95% CI: 0.44, 0.94; P = 0.02) and 44% (OR: 0.56; 95% CI: 0.40, 0.77; P < 0.001), respectively, in treated infants.

Conclusions: SSO therapy improved neonatal growth, and reduced morbidities when applied exclusively, across the facility–community continuum of care at the population level. Further research is needed to improve demand for recommended therapy inside hospital as well as in community settings, and to confirm these results in other settings. This trial was registered at www.isrctn.com as ISRCTN38965585 and http://ctri.nic.in as CTRI/2014/12/005282. Am J Clin Nutr 2022;115:1092–1104.

Keywords: newborn growth, neonatal growth, neonatal health, neonatal morbidity, newborn morbidity, emollient, skin barrier

Introduction
The epidermal barrier of the skin—the largest organ of the newborn infant—is developmentally compromised and easily injured at birth, especially in preterm infants, posing risks of accelerated water and heat loss, growth faltering, systemic infection, and mortality (1–5). High environmental pathogenic load in tropical settings, poor hygiene, and forceful, injurious
removal of vernix at birth may all place newborn infants at risk (6–9).

Oil massage of newborns is a widespread practice throughout Africa, Asia, and the Mediterranean region (10–15). Application of high-linoleate sunflower seed oil (SSO) was found in mouse models of human infant skin to enhance skin barrier repair and integrity, whereas local products and oils routinely applied to newborns in high-mortality regions in South Asia—including mustard oil—and sub-Saharan Africa showed harmful effects (15–17). Mustard oil can have high concentrations of proinflammatory erucic acid, causing keratinocyte toxicity and skin and gastrointestinal tract inflammation (17, 18), and contamination with seeds of Argemone mexicana can cause epidemic dropsy (19). However, skin barrier integrity was similar in newborns massaged with SSO or mustard oil in the community in Nepal (20).

Before the advent of intralipids, topical applications of SSO, leading to absorption of fatty acids (21), were used in preterm infants to support growth and prevent or treat essential fatty acid deficiencies (22–26). Furthermore, linoleic acid (18:2n−6)—an essential fatty acid abundant in SSO—binds specifically to receptors on keratinocytes to accelerate and bolster skin development (27–29).

In low-resource settings, emollient therapy in preterm infants has been shown to increase fatty acid concentrations in blood (30, 31), improve thermoregulation (30, 32) and skin barrier condition and function (33–37), reduce the risk of serious infections (33–39) and mortality (39–41), enhance neurodevelopment (42–44), and improve growth (31, 35, 37, 39, 42, 44–54) during the neonatal period at high cost-effectiveness (55). Research on health benefits of emollient therapy in term infants is scarce, demonstrating transcutaneous absorption of lipids (56) and improvement in growth in 2 studies (44, 45) but not significantly in another (57).

Despite the risks due to compromised skin barrier function and the growing evidence for improved neonatal outcomes from emollient therapy, data are scarce regarding its utility as a public health strategy for improving newborn health. Previously we examined the impacts of gentle massage with SSO compared with usual skin care practices in a population-based cohort of newborn infants in a rural community in Uttar Pradesh, India. We showed no overall effect on neonatal mortality but a significant 52% reduction in mortality among the subgroup of very-low-birth-weight (VLBW) infants ≤1500 g (41). Here we examine the effects of SSO treatment on the neonatal growth and morbidity of the infants in that trial.

Methods

Study design

The study was a 2-arm, cluster-randomized, open-label, controlled public health intervention trial conducted in 276 contiguous village administrative units or clusters, each with an average population of ~3000 in a rural community of 818,000 inhabitants of the Rae Bareli and Amethi districts of Uttar Pradesh. The intervention was aimed to modify pre-existing, nearly universal practices of newborn oil massage governed by social norms and conducted by traditional massueses with defined service areas; thus, randomization was done at the cluster level. The primary outcome of the parent trial was neonatal mortality rate (NMR), which was reported separately (41). The sample size for the parent trial was calculated to enable measurement of a ≥15% reduction in NMR at a 5% level of significance with 90% power, as detailed previously (41, 58). Secondary outcomes included changes in oil massage practices, adherence to treatment, weight gain, and morbidities, and are the focus of this report.

Ethical review and trial registration

The study received ethical clearance from an independent Institutional Ethics Committee at the Community Empowerment Lab and the Ethics Review Committee at the WHO, Geneva. The trial was registered at the ISRCTN (ISRCTN38965585) and the Clinical Trials Registry—India (CTRI) (CTRI/2014/12/005282) registries with WHO UNT # U1111-1158-4665. The trial protocol can be found at https://doi.org/10.7910/DVN/TGNC9H, Harvard Dataverse, V1.

Randomization, allocation, and eligibility

Randomization was conducted at WHO Geneva to allocate 276 clusters equally to the 2 arms, as described in detail previously (41). Randomization was done at the cluster level to minimize contamination of the intervention into comparison clusters. Because allocation to the intervention or comparison arms could not be concealed from the implementation teams owing to the visible nature of the intervention, various measures were adopted to minimize contamination and observer bias. The intervention and evaluation teams were independent, with separate lines of management and no formal communication between them in order to ensure unbiased data collection. Data management protocols masked the cluster allocation from monitoring and analysis teams, which ensured that during execution of the study, data were never accessed or reported separately for the 2 study groups.

Following a community-consenting process with community leaders from each of the study clusters, a surveillance system was established for identifying pregnancies and births through 2-monthly cycles of door-to-door visitations, supported by a social network of key informants to notify project staff of births as early as possible. Pregnant women who planned to stay within their intervention cluster through the newborn period were provided informed consent and provisionally enrolled. All newborn infants identified in study clusters within 7 d of birth were eligible for inclusion in the study, enrolled after gaining informed consent from their mother, and analyzed as part of the cluster where they were first identified, irrespective of cross-migration. There were no prespecified exclusion criteria.

Intervention and delivery strategy

Home visitations were the mainstay of intervention promotion and consisted of an antenatal interaction between intervention workers and families of pregnant women identified through demographic surveillance in their 25th week of pregnancy. The first postnatal interaction was targeted for the first day (i.e., the day of birth) and the second postnatal visit was targeted for the seventh day after birth. The median time when the first
postnatal visit occurred was day 2 (the day after birth) (IQR: days 1–3) for both intervention and comparison groups, as reported previously (41). Thus, the first-visit weight appears to be a good approximation for birth weight.

We promoted exclusive use of SSO as the emollient for massage during the neonatal period, including 3-times daily applications of ∼10 g SSO using gentle massage with washed hands. The usual practice of applying mustard oil 2–4 times daily, sometimes infused with herbs and often with vigorous massage (7–9), was not intervened upon in the comparison clusters. Infants in the intervention and comparison arms were treated with emollient an average of 2.7 and 2.4 times/d, respectively (41). The intervention delivery strategy was developed through a community-centric design process and trials of improved practices aimed to ensure early and exclusive applications of SSO.

The SSO supplied to families was cold-pressed and each batch of oil was quality tested in an accredited laboratory (SGS India Private Limited) to ensure high linoleic acid content (>60%) and purity from harmful chemicals. The oil was packaged into light-and-heat-protected sterile bottles with packaging that was designed through a participatory branding exercise and distributed under the label “Saksham Sneh [literally, “empowerment and maternal affection”] Newborn Baby Oil” to enhance its desirability and adoption.

Intervention workers had ≥12 y of education and were provided an initial 3-d classroom and 7-d on-the-job training on the intervention and behavior change management approach. They were each allocated an area covering an average of 1200 households. Intervention supervisors each covered 10–12 workers for mentoring, supervision, and resolution of ongoing field issues. A team of remote guidance assistants centrally scheduled and monitored intervention visitations through a call center.

Intervention workers received no training on newborn care and were instructed to not counsel families on other aspects of newborn care besides the intervention. Although washing of hands before SSO application was part of the recommended massage practices, overall benefits of handwashing and its practice beyond massage were not discussed with families. Recognizing that there were no corresponding visits in the comparison clusters which were comparable with the intervention worker visits, data collector visitations were scheduled on the same days as the intervention worker visits to mitigate any potential “Hawthorne effect” (59).

Intervention workers promoted but did not apply SSO; skin care practices remained under the management of families with support from traditional masseuses. During the antenatal interaction mothers received behavioral counseling on oil application and massage and a 100-mL bottle of SSO to facilitate early application as soon as possible after birth, whether the birth occurred at home or in a health facility. During the first postnatal interaction, intervention workers reinforced emollient practices provided a 200-mL bottle of SSO for use during the remainder of the first week. The second postnatal interaction involved provision of the rest of the monthly supply of three 200-mL bottles of SSO and addressing any remaining queries of the families. Traditional masseuses (n = 1189) who serviced the intervention clusters were engaged to ensure that they acted as promoters of rather than barriers to intervention adoption and were trained and accredited on emollient application practices.

In addition, monthly community meetings were conducted to reinforce the early and exclusive application of SSO with the recommended massage technique.

Data collection and management

Data collectors had ≥12 y of education and received an initial 7-d classroom and 3-d on-the-job training on the questionnaires and their administration, pregnancy surveillance, use of electronic tablet devices, and weight measurement to the nearest 10 g using the American Weigh Scales AMW-SR-20 digital hanging scale. Each data collector was allocated an area covering ∼1000 households (4 clusters).

A baseline questionnaire for gathering data on socioeconomic status and pregnancy history was administered in the antenatal period during week 25 of gestation on the same day as the antenatal intervention visit. Data on handwashing, newborn oil massage practices (oil additives and use), morbidities (hospitalization, illness, skin infection, umbilical cord infection), and survival status were collected at the first visit (with the recall period from birth to the first postnatal visit), which occurred at a median of day 2 (IQR: days 1–3) (41); on the day 7 visit (with the recall period from the first to the second visit); and on the third visit targeted for day 29 (with the recall period from the second to the third visit). Data from the 3 visits were combined to generate measures over the neonatal period. Infants were weighed at the first visit and at the third visit.

Proprietary software on electronic tablet devices was utilized for data collection, and data were synchronized from the cloud to a MySQL database on a daily basis. The software included built-in checks for logical inconsistencies, skips, missing values, and range limits. Data collection home visitations were centrally scheduled and appointments were dispatched to data collectors’ tablet devices and monitored through a call center by a team of remote guidance assistants who also tracked the Global Positioning System locations of workers and data collection points. Quality checks consisted of in-the-field spot-checks and back-checks for 5% of all visits. All stillbirths and neonatal deaths were verified by a team of supervisors who were each responsible for 10 data collectors. Two data analysts who were blinded to group allocation reviewed the data quality regularly and provided interviewer- and data-specific feedback for improving data quality.

Ethics and trial oversight

Consent was obtained from leaders in each of the study clusters, and written informed consent was obtained from the parents/guardians of all infants before enrollment. Procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

A group of expert child health clinical trialists from the WHO assisted in overseeing the conduct of the trial, coordinated the ethical review process at WHO Geneva, convened the Technical Advisory Group and the Data Safety Monitoring Board (DSMB), and coordinated the reporting of severe adverse events to the DSMB as described previously (41). The role of the DSMB in monitoring the trial based on mortality outcomes was described in detail previously (41).
Statistical analysis
Analyses were done in SAS version 9.0 (SAS) and replicated in STATA version 13.0 (StataCorp LLC) for verification.

Adherence to treatment
Analysis of adherence to exclusive use of emollient (SSO in the intervention arm, mustard oil in the comparison arm) as a measure of treatment fidelity utilized individual-level data without adjustment for either cluster-size variation or covariates.

Intention-to-treat analysis
We had intended to compare cluster-level measures of changes in practices (addition of *bukwa* to oil, handwashing), growth (g·kg⁻¹·d⁻¹, g/kg), and morbidities (hospitalization, illness, skin infection, umbilical cord infection) across groups using a 2-sample *t* test. Owing to wide variation in cluster sizes we applied a more statistically efficient method of individual-level analysis comparing infants randomly assigned to the intervention group with infants randomly assigned to the comparison group, adjusting for within-cluster variations using mixed-effects regression [linear for continuous outcome (growth) or logistic for binary outcome (practices, morbidities) as appropriate] with group (intervention and comparison group) as a fixed effect and cluster as a random effect (58), as described previously (41). Given the large sample size and randomization, we present crude estimates for intention-to-treat analyses without adjusting for any baseline covariates except that the SE of the parameter estimates was adjusted for within-cluster variations via random-effects modeling. As a sensitivity analysis, multivariate mixed-effects regression analyses were repeated with adjustment for selected covariates. Specifically, caste, first-visit weight (as a proxy for birth weight), delivery attendant, gravidity, maternal age, maternal education, sex of the infant, and multiple births were included in logistic regression analyses of practices and morbidities; sensitivity linear regression analysis for growth, expressed as g·kg⁻¹·d⁻¹ or g/kg, did not include first-visit weight as a covariate. Intention-to-treat mixed-effects regression analyses which were adjusted for covariates are presented in Supplemental Tables 1 and 2. In the analysis for growth, we examined the potentially heterogenous treatment effect according to the first-visit weight and the analyses were adjusted for the same set of covariates as aforementioned (except for first-visit weight), because the effective sample size was smaller for subgroups of infants with specific first-visit weights and there was a chance of imperfect randomization. The outcome for the analysis for growth was the average weight gain per day per first-visit weight and the association between the first-visit weight and outcome was modeled via a nonparametric restricted cubic spline regression with 4 preselected knots within each study group (60). ORs and 95% CIs for practices and morbidities were calculated using mixed-effects logistic regression, with comparison infants as the reference. *P* values for the morbidity analysis were also adjusted using the linear step-up, false discovery rate (FDR) controlling procedure of Benjamini and Hochberg (61) and the results are reported in the text. Type I error, *α*, was controlled at 0.05.

Per-protocol analysis
To further assess the impacts of SSO therapy, we conducted per-protocol analysis of data on growth and morbidities using data on adherence to treatment. The follow-up period was from birth (day 1) to death or 28 completed days after birth. Complete adherence to SSO was defined as using SSO to initially cleanse the newborn infant, applying SSO at the first application during the first 6 h after birth, and subsequently applying SSO exclusively during the entire follow-up period. An analogous definition was used to identify newborn infants who were treated exclusively with mustard oil. Infants treated with additional regimens (e.g., >1 oil) were not included owing to the biased association of increased likelihood of alternative regimens with increased survival time and potential for morbidities. We compared growth and morbidities of infants who had been randomly assigned to the intervention group and whose caregivers strictly adhered to the exclusive use of SSO ("exclusive SSO") with those in the comparison group who received massage with mustard oil exclusively ("exclusive mustard oil") using the same regression methods as for the intention-to-treat analysis, i.e., individual-level analysis accounting for within-cluster variations using mixed-effects regression. Given that a subset of infants in the intervention and comparison groups were selected for these analyses based on treatment adherence criteria rather than randomized group assignment, we present estimates that are adjusted for covariates. Crude estimates of growth and morbidity effects based on per-protocol analyses unadjusted for covariates are shown in Supplemental Tables 1 and 2.

Results
Study population
A total of 13,478 live-born infants in the intervention clusters and 13,109 infants in the comparison clusters were followed up from birth to death or 28 completed days during November 2014–October 2016 for measures of weight and morbidity (Figure 1). Among infants randomly assigned to the intervention arm, 4096 infants (30.4%) received SSO therapy exclusively, whereas 4720 infants (36.0%) who were randomly assigned to the comparison arm received mustard oil exclusively.

Infants randomly assigned to the 2 study groups were comparable in baseline characteristics (Table 1) (41). Briefly, mothers had a mean age of 25.4 y, most (86.7%) were Hindu and about one-third (35.9%) were from scheduled castes, one-third (33.3%) were illiterate, and most (84.8%) gave birth in a health care facility with a skilled birth attendant (83.1%). Characteristics were also similar for the participants in the intervention arm who adhered to exclusive use of SSO and those in the comparison arm who practiced exclusive use of mustard oil (Table 1).

Adherence to treatment
Over the course of implementation, increasing proportions of infants in the intervention clusters were treated exclusively with SSO as recommended (Table 2). Adherence to exclusive SSO increased from 22.6% of infants enrolled in the first quartile to 37.2% of infants enrolled in the last quartile. In contrast, exclusive use of mustard oil for massage of newborn infants in
the comparison clusters showed less change, ranging from 32.4% in the first quartile of the study to 38.3% in the final quartile.

**Intention-to-treat analysis**

**Practices.**

About 28% of infants in comparison clusters were massaged with *bukwa*, a mixture of oil and ground-up grains infused with herbs (Table 3). This potentially harmful practice was reduced to ~6% of infants in the intervention clusters, a significant 88% (OR: 0.12; 95% CI: 0.08, 0.18; \( P < 0.0001 \)) reduction. The odds of handwashing before caring for the infant, including oil application, were increased by 78% over the neonatal period (OR: 1.78; 95% CI: 1.01, 3.13; \( P < 0.0001 \)).

**Growth.**

Significantly higher weight gain velocity by a difference of 0.94 g · kg\(^{-1} \) · d\(^{-1} \) (95% CI: 0.07, 1.82 g · kg\(^{-1} \) · d\(^{-1} \); \( P = 0.03 \)) was found among infants in the intervention clusters, who gained 13.60 g · kg\(^{-1} \) · d\(^{-1} \) (95% CI: 12.98, 14.22 g · kg\(^{-1} \) · d\(^{-1} \)).
| Characteristic                              | Intention-to-treat | Per-protocol                          |
|--------------------------------------------|-------------------|---------------------------------------|
|                                            | Comparison        | Intervention                          |
|                                            | 458 (208–2286)    | 477 (210–3061)                        |
| Households per cluster, median n (range)   | Total live births | 13,109 (49.3)                         | 13,478 (50.7)                         | 4720 (53.5)                          | 4096 (46.5)                          |
|                                            | Singleton         | 12,840 (97.9)                         | 13,146 (97.5)                         | 4617 (97.8)                          | 3994 (97.5)                          |
|                                            | Multiple          | 269 (2.1)                             | 332 (2.5)                             | 103 (2.2)                            | 102 (2.5)                            |
|                                            | Male              | 6820 (52.0)                           | 7042 (52.3)                           | 2431 (51.5)                          | 2114 (51.6)                          |
|                                            | Religion          | Hindu (86.6)                           | 16,756 (86.6)                         | 4185 (88.7)                          | 3502 (85.5)                          |
|                                            |                   | Muslim (13.3)                          | 1787 (13.3)                           | 532 (11.3)                           | 588 (14.4)                           |
|                                            |                   | Other (0.1)                            | 13 (0.1)                              | 3 (0.1)                              | 6 (0.1)                              |
|                                            | Maternal age, y   | 25.3 ± 3.7                            | 25.4 ± 3.7                            | 25.4 ± 3.8                           | 25.5 ± 3.7                           |
|                                            | Caste             | General (15.6)                         | 2084 (14.9)                           | 676 (14.3)                           | 560 (13.7)                           |
|                                            |                   | Other backward caste (48.6)            | 6622 (49.1)                           | 2165 (45.9)                          | 2003 (48.9)                          |
|                                            |                   | Scheduled caste/scheduled tribe (35.8)| 4852 (36.0)                           | 1879 (39.8)                          | 1533 (37.4)                          |
|                                            | Maternal education| Illiterate (33.0)                      | 4531 (33.6)                           | 1536 (32.5)                          | 1416 (34.6)                          |
|                                            |                   | Primary completed (22.2)               | 3215 (23.9)                           | 1050 (22.2)                          | 949 (23.2)                           |
|                                            |                   | Tenth grade completed (29.3)          | 3720 (27.6)                           | 1451 (30.7)                          | 1168 (28.5)                          |
|                                            |                   | Secondary and above completed (15.4)   | 2009 (14.9)                           | 683 (14.5)                           | 563 (13.7)                           |
|                                            | Delivery place    | Health facilities (84.2)               | 11,497 (85.3)                         | 3878 (82.2)                          | 3558 (86.8)                          |
|                                            |                   | On the way to a facility from home     | 30 (0.2)                              | 19 (0.4)                             | 7 (0.2)                              |
|                                            |                   | Home (15.5)                            | 1949 (14.5)                           | 823 (17.4)                           | 531 (13.0)                           |
|                                            | Delivery attendant| Physician (31.0)                       | 4931 (36.6)                           | 1420 (30.1)                          | 1228 (30.0)                          |
|                                            |                   | Auxiliary Nurse (51.2)                 | 6397 (47.5)                           | 2374 (50.3)                          | 2273 (55.5)                          |
|                                            |                   | Midwife/staff nurse (51.2)            | 2148 (15.9)                           | 926 (19.6)                           | 595 (14.5)                           |
|                                            | Delivery type     | Normal (92.6)                          | 12,407 (92.1)                         | 4396 (93.1)                          | 3891 (95.0)                          |
|                                            |                   | Assisted (forceps) or episiotomy       | 704 (5.2)                             | 201 (4.5)                            | 135 (3.3)                            |
|                                            |                   | Cesarean (2.3)                         | 325 (2.4)                             | 113 (2.4)                            | 70 (1.7)                             |
|                                            | Gravidity         | 1 (39.0)                               | 5282 (39.2)                           | 1841 (39.0)                          | 1594 (38.9)                          |
|                                            |                   | 2–3 (41.9)                             | 5470 (40.6)                           | 1972 (41.8)                          | 1660 (40.5)                          |
|                                            |                   | ≥4 (19.1)                              | 2723 (20.2)                           | 907 (19.2)                           | 842 (20.6)                           |
|                                            | Toilet type       | Open defeation (89.4)                  | 12,203 (90.6)                         | 4223 (89.5)                          | 3767 (92.0)                          |
|                                            |                   | Latrine/toilet (10.6)                  | 1272 (9.4)                            | 497 (10.5)                           | 329 (8.0)                            |
|                                            |                   | First-visit weight, g                  | 2575 ± 521                            | 2570.96 ± 530.5                     | 2575.67 ± 493.0                     |
|                                            |                   | Age at measurement of first-visit weight, d | 2.6 ± 1.5 | 2.6 ± 1.5 | 2.6 ± 1.6 | 2.5 ± 1.5 |

1Adapted from Kumar et al. (41). Values are n (%) or mean ± SD unless indicated otherwise.

whereas infants in the comparison clusters gained 12.65 g · kg⁻¹ · d⁻¹ (95% CI: 12.04, 13.27 g · kg⁻¹ · d⁻¹), over the neonatal period (Table 4). Exploratory analysis by sex revealed similar results for emollient-treated male and female infants who gained a mean of 0.92 g · kg⁻¹ · d⁻¹ (95% CI: −0.01, 1.85 g · kg⁻¹ · d⁻¹; P = 0.05) and 1.00 g · kg⁻¹ · d⁻¹ (95% CI: 0.04, 1.96 g · kg⁻¹ · d⁻¹; P = 0.04) more weight, respectively, than infants in the comparison group. The difference in weight gain velocity between SSO-treated and comparison infants reached a mean of 4.21 g · kg⁻¹ · d⁻¹ (95% CI: −3.44, 11.87 g · kg⁻¹ · d⁻¹) in infants born weighing ≤1500 g. The difference in weight gain over the neonatal period was also significantly greater, by 28.43 g/kg (95% CI: −0.46, 57.32 g/kg; P = 0.05), among infants in the intervention (400.82 g/kg; 95% CI: 380.39, 421.24 g/kg) than in the comparison (372.39 g/kg; 95% CI: 351.95, 392.82 g/kg) group (Table 4). Similar results were found
for covariate-adjusted analyses (Supplemental Table 1). Spline analysis revealed significantly higher weight gain velocity in infants in the intervention than in the comparison group, which was accentuated to \( \sim 2.5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \) for infants who had a first-visit weight below \( \sim 2000 \text{ g} \) (Figure 2).

**Morbidity.**

Across both the intervention and comparison groups, \( \sim 2.5\% \) of infants were hospitalized and 11%–12% developed any illness during the neonatal period, by care-giver self-report (Table 5). Skin infections were reported in 3%–4% of infants and umbilical cord infections occurred in 8%–9%. There were no significant differences in measures of morbidity by care-giver self-report between infants in the intervention and comparison groups (Table 5).

**Per-protocol analysis**

**Growth.**

Weight gain velocity was significantly higher, by a mean difference of 1.31 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \) (95% CI: 0.17, 2.46 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \); \( P = 0.02 \)), in infants in the intervention group who were treated exclusively with SSO (14.61 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \); 95% CI: 13.32, 15.90 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \)) than in infants in the comparison group who were massaged exclusively with mustard oil (13.29 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \); 95% CI: 12.01, 14.58 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \)) (Table 4). Exploratory analysis by sex found that the difference in weight gain velocity in intervention infants exclusively treated with SSO compared with comparison infants exclusively treated with mustard oil was significantly higher for females (1.49 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \); 95% CI: 0.18, 2.80 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \); \( P = 0.03 \)) and showed a trend in males (1.20 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \); 95% CI: −0.08, 2.48 \( \text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \); \( P = 0.07 \)). SSO-treated infants showed greater weight gain by 32.24 \( \text{g} \cdot \text{kg}^{-1} \) (95% CI: 3.13, 61.34 \( \text{g} \cdot \text{kg}^{-1} \)) over the neonatal period than mustard oil–treated infants. Similar results were found for crude estimates unadjusted for covariates (Supplemental Table 1).

**Morbidity.**

Rates of morbidities among infants in the intervention clusters who were treated exclusively with SSO as recommended (i.e., per protocol) were generally lower than among infants in the intervention clusters (i.e., intention to treat) and than among the infants in the intervention clusters who did not adhere to the recommended therapy with SSO (Table 5). For example, 1.8% (75 of 4096) of intervention infants who were treated per-protocol with SSO, 2.5% (339 of 13,478) of all infants in intervention clusters, and 2.8% (339 – 75/13478 – 4096) of infants in intervention clusters who were not treated per-protocol were hospitalized. Similarly, 6.8% of intervention infants treated exclusively with SSO, compared with 10.8% of all infants in intervention clusters and 12.6% of infants in intervention clusters who did not receive exclusive SSO, developed any illness during the neonatal period (Table 5). Similar beneficial patterns were seen for these same intervention subgroups for skin infections (2.7%, 3.8%, and 4.3%, respectively) and umbilical cord disorders (6.1%, 8.7%, and 9.9%, respectively). In contrast, there were little differences in rates of morbidities for infants...
in the comparison clusters who were massaged exclusively with mustard oil compared with all infants in the comparison clusters or with infants in comparison clusters who were not treated exclusively with mustard oil (Table 5). For example, among infants in the comparison group, hospitalization was reported in 2.9% of infants who received oil massage exclusively with mustard oil, 2.4% (1082 of 6876) of all infants in the comparison group, and 2.2% of infants who did not receive mustard oil exclusively. Any illness was reported in 10.4% of infants in the comparison groups who received oil massage exclusively with mustard oil, 10.8% of all infants in the comparison group, and 13.6% of infants who did not receive mustard oil exclusively. Weaker patterns were also seen for these same comparison subgroups for skin infections (3.5%, 3.6%, and 3.7%, respectively) and umbilical cord disorders (7.2%, 8.5%, and 9.3%, respectively).

Significant reductions by per-protocol regression analysis were found among infants in the intervention clusters who were treated exclusively with SSO compared with infants in the comparison clusters who were massaged exclusively with mustard oil in rates of hospitalization (OR: 0.64; 95% CI: 0.44, 0.94; P = 0.022) and any illness (OR: 0.56; 95% CI: 0.40, 0.77; P < 0.001) (Table 5). A trend was found for reduction in umbilical disorders (OR: 0.68; 95% CI: 0.45, 1.04; P = 0.073) and no significant difference was found for skin infections. Similar results were found for crude estimates unadjusted for covariates (Supplemental Table 2). After multiple-test adjustment, the FDR P value for hospitalization was 0.11 and any illness remained statistically significant with a FDR P value of 0.005.

There were no severe adverse events or unintended effects, as reported previously (41).

Discussion

To our knowledge, this is the first study to examine population-level impacts of topical emollient therapy along the facility–community continuum of care in which treatment was initiated as

| Practice | Comparison n [% of total – (missing + died)] (total n = 13,109) | Intervention n [% of total – (missing + died)] (total n = 13,478) | OR1 (95% CI) | P value |
|----------|---------------------------------------------------------------|---------------------------------------------------------------|---------------|--------|
| Addition of bukwa | 3457 (28.4) | 798 (6.4) | 0.12 (0.08, 0.18) | <0.0001 |
| No | 8696 (71.6) | 11,621 (93.6) | 1.78 (1.01, 3.13) | <0.0001 |
| Died before visit | 732 | 740 | 1.81 (1.03, 3.19) | <0.0001 |
| Missing | 224 | 319 | 1.92 (1.03, 3.55) | <0.0001 |
| Handwashing before caring for the newborn (including oil application) | 3766 (33.5) | 5256 (46.1) | 1.78 (1.01, 3.13) | <0.0001 |
| No | 7466 (66.5) | 6135 (53.9) | 1.81 (1.03, 3.19) | <0.0001 |
| Died before visit | 732 | 740 | 1.81 (1.03, 3.19) | <0.0001 |
| Missing | 1145 | 1347 | 1.81 (1.03, 3.19) | <0.0001 |

1Individual-level analysis showing crude estimates accounting for within-cluster variations using mixed-effects logistic regression. Additional adjustment for covariates (caste, first-visit weight, delivery attendant, gravidity, maternal age, maternal education, sex of the infant, multiple births) produced similar results for addition of bukwa (adjusted OR: 0.12; 95% CI: 0.09, 0.18; P < 0.0001) and for handwashing (adjusted OR: 1.81; 95% CI: 1.03, 3.19; P < 0.0001).

| Practice | Comparison n [% of total – (missing + died)] (total n = 3,534) | Intervention n [% of total – (missing + died)] (total n = 3,782) | Mean difference |
|----------|---------------------------------------------------------------|---------------------------------------------------------------|----------------|
| Add. bukwa | 732 | 740 | 1.81 (1.03, 3.19) | <0.0001 |
| No | 3457 (28.4) | 798 (6.4) | 0.12 (0.08, 0.18) | <0.0001 |
| Died before visit | 732 | 740 | 1.81 (1.03, 3.19) | <0.0001 |
| Missing | 224 | 319 | 1.92 (1.03, 3.55) | <0.0001 |
| Handwashing before caring for the newborn (including oil application) | 3766 (33.5) | 5256 (46.1) | 1.78 (1.01, 3.13) | <0.0001 |
| No | 7466 (66.5) | 6135 (53.9) | 1.81 (1.03, 3.19) | <0.0001 |
| Died before visit | 732 | 740 | 1.81 (1.03, 3.19) | <0.0001 |
| Missing | 1145 | 1347 | 1.81 (1.03, 3.19) | <0.0001 |

1Individual-level analysis showing adjusted estimates accounting for within-cluster variations using mixed-effects linear regression. Infants who died or for whom weight data were missing were excluded from analysis. Comparison, n = 10,834; intervention, n = 11,118.
Neonatal weight gain \((g \cdot kg^{-1} \cdot d^{-1})\) as a function of first-visit weight (a proxy for birth weight) in infants in intervention and comparison clusters in Uttar Pradesh, India, modeled via a nonparametric restricted cubic spline regression with 4 preselected knots within each study group, adjusted for covariates as described in the Methods. \(n = 11,118\), intervention; \(n = 10,834\), comparison. ∗Indicates a statistically significant difference in weight gain between infants in the intervention vs. comparison clusters.

![Graph showing weight gain](image)

As part of this same trial, we found that mortality risk was reduced by 52% in the subgroup of highly vulnerable VLBW infants (≤1500 g) and by per-protocol analysis mortality risk was reduced by 58% for infants (regardless of birth weight) in the intervention arm who received exclusive SSO treatments compared with infants in the comparison arm who received mustard oil massage exclusively (41). We attempted to conduct a post hoc analysis of the connection between neonatal weight gain and mortality using residual inclusion modeling to isolate
| Morbidity outcomes                  | Total, n | No, n | Yes, n (% of total) | OR 2 | P value 2 |
|------------------------------------|----------|-------|---------------------|------|----------|
| **Hospitalization**                |          |       |                     |      |          |
| Intention-to-treat                 |          |       |                     |      |          |
| Intervention                       | 13,478   | 13,139| 339 (2.5)           | 0.99 | 0.901    |
| Comparison                         | 13,109   | 12,789| 320 (2.4)           |      |          |
| Per-protocol                       |          |       |                     |      |          |
| Exclusive SSO in intervention      | 4096     | 4021  | 75 (1.8)            | 0.64 | 0.022    |
| Exclusive MO in comparison         | 4720     | 4584  | 136 (2.9)           |      |          |
| **Any illness**                    |          |       |                     |      |          |
| Intention-to-treat                 |          |       |                     |      |          |
| Intervention                       | 12,449   | 11,103| 1346 (10.8)         | 0.85 | 0.176    |
| Comparison                         | 12,180   | 10,657| 1523 (12.5)         |      |          |
| Per-protocol                       |          |       |                     |      |          |
| Exclusive SSO in intervention      | 3838     | 3576  | 262 (6.8)           | 0.56 | <0.001   |
| Exclusive MO in comparison         | 4222     | 3781  | 441 (10.4)          |      |          |
| **Skin infection**                 |          |       |                     |      |          |
| Intention-to-treat                 |          |       |                     |      |          |
| Intervention                       | 13,478   | 12,966| 512 (3.8)           | 1.16 | 0.416    |
| Comparison                         | 13,109   | 12,630| 479 (3.6)           |      |          |
| Per-protocol                       |          |       |                     |      |          |
| Exclusive SSO in intervention      | 4096     | 3987  | 109 (2.7)           | 0.92 | 0.764    |
| Exclusive MO in comparison         | 4720     | 4553  | 167 (3.5)           |      |          |
| **Umbilical disorder**             |          |       |                     |      |          |
| Intention-to-treat                 |          |       |                     |      |          |
| Intervention                       | 12,443   | 11,359| 1084 (8.7)          | 1.02 | 0.902    |
| Comparison                         | 12,188   | 11,146| 1042 (8.5)          |      |          |
| Per-protocol                       |          |       |                     |      |          |
| Exclusive SSO in intervention      | 3832     | 3600  | 232 (6.1)           | 0.68 | 0.073    |
| Exclusive MO in comparison         | 4218     | 3914  | 304 (7.2)           |      |          |

1. MO, mustard oil; SSO, sunflower seed oil.
2. For intention-to-treat models, crude estimates are shown from individual-level mixed-effects logistic regression analysis accounting for within-cluster variances. For per-protocol models, adjusted estimates are shown from individual-level mixed-effects logistic regression analysis accounting for within-cluster variations and adjusting for covariates (caste, first-visit weight, delivery attendant, gravidity, maternal age, maternal education, sex of the infant, and multiple births).
3. "Was the baby ever hospitalized?"
4. "Did the baby ever suffer from any health problem?"
5. "Did the baby ever have any boil on the skin with pus in it?"
6. "Did the baby ever suffer from a cord problem?"

Variation in the outcome of mortality (64). Data on growth—which were limited to first-visit weight and weight at the third (day 29) visit and were missing for most deaths—were insufficient, however, to enable such an analysis. We found no prior reports quantifying the relation between change in growth in the neonatal period and mortality risk, but before the introduction of WHO growth standards for children in 2006–2009, studies generally showed an exponential increase in risk of child death with anthropometric z-scores below $-2$, as well as increased risk of child death after periods of growth deceleration (65–69). More recently, with the availability of WHO standards for child growth velocity, analysis of longitudinal growth monitoring data from a cohort of children aged 3–24 mo in the Democratic Republic of Congo demonstrated that a weight velocity z-score of $-3$ was associated with a 7.9-fold increase in RR of mortality in the subsequent 3-mo period (70). Young age (e.g., <1 y) was the strongest predictor for mortality risk (71) and growth velocity z-scores reflecting recent weight loss were particularly useful in predicting death in the short term (i.e., within 3 mo).

Risk of neonatal mortality is greatest in the first week after birth, owing to a complex, often interacting mix of direct and indirect causes (72). Although nutrition of the mother and the newborn modifies the risk of various causes of neonatal mortality (73), susceptibility to mortality is in part independent of nutritional status; moreover, anthropometry incompletely characterizes newborn nutritional status (71,74). However, body composition of the newborn infant (e.g., high skin surface area and low muscle mass compared with total body weight) may compound the effects of undernutrition, resulting in higher vital risk in association with poor growth than in older children. Muscle energy and protein reserves are a smaller proportion of total body weight, and fluid and heat losses are exponentially higher with increasing degrees of prematurity and potentially with undernutrition too, and thus may reach critical levels more easily (1, 4, 75,76).
effect; 2) collection of intermediate growth data in addition to birth weight and day 29 weight measures; 3) collection of weight, when possible, at the time of death; and 4) additional information about other causal pathways from the treatment to the outcomes of interest (i.e., to mitigate challenges to the exclusion restriction assumption).

Further research is needed on potential approaches to improving adherence to recommended therapy, particularly in community settings. In this study, intervention workers had only 3 communication-based interactions aimed to enable families to initiate, adhere to, and sustain the therapy. Although this optimized feasibility and scalability, the community’s inherent belief in the goodness of mustard oil appeared to be strong, suggesting that more intensive behavior change management is required to shift deeply entrenched community norms (8, 9, 77). Further research is also warranted on interactions of emollients, massage technique, and environmental conditions on skin barrier function in newborn infants (20, 78).

The mechanism of growth promotion by topical treatment with SSO likely occurred through a combination of local and systemic effects, including improved barrier integrity, reduced transdermal water and heat loss, enhanced innate antimicrobial barrier defense, and reduced pathogen entry and immune activation, thus preserving energy (36, 38, 79–81). In addition, linoleic acid binds to peroxisome proliferator–activated receptor α receptors on keratinocytes to accelerate skin development, which is particularly important for preterm and undernourished infants (28, 29). Absorption of fatty acids provides building blocks and energy for growth (21, 22, 30, 31, 36), and emollient therapy may modulate the skin microbiome, as seen in young children with severe acute malnutrition in Bangladesh (82, 83).

This study had several limitations. Intervention workers could not be blinded to treatment group allocation; however, data collection workers had no information on group assignment. The study was not designed to distinguish the impacts of improved oil as opposed to improved application practices. Limitations in adherence to recommended treatment may have limited the impact of the intervention. Finally, limited data on growth ultimately precluded causal insight into the relation between growth and mortality.

In conclusion, considering the population-level reduction in mortality (41) along with increased growth of the subgroup of VLBW infants (41), there is an emerging evidence base for promotion of improved emollient therapy in the most highly vulnerable VLBW infants along the facility–community continuum of care. Research on integration of emollient therapy with KMC in infants born weighing <2000 g in facility and community settings is recommended (84). Treatment at the population level is not currently recommended. Further research is warranted to develop innovative approaches to improving adherence to recommended practices, and to exploring improvements in emollient composition (16, 17, 85), to optimize health benefits of emollient therapy for all newborn infants, including in sub-Saharan Africa where data are scarce.

We thank the National Health Mission, Uttar Pradesh, and in particular Dr. Anil Kumar Verma for his cooperation and support. We are thankful to the WHO and the Bill & Melinda Gates Foundation for funding this work, in particular, Dr. Rajiv Bahl and Dr. Jose Martines at the WHO and Janna Patterson at the Bill & Melinda Gates Foundation for their support throughout the study. We are immensely grateful to the late Prof. Maharaj Kishan Bhan as the chair of the Technical Advisory Group for critical inputs in the design and conduct of the trial. We express our appreciation to the DSBM chaired by Dr. Vinod Paul with participation from Drs. Nita Bhandari, CM Pandey, and Sunil Sazawal, for monitoring the conduct and safety of the trial. We are immensely grateful to Dr. Sanjeev Agarwal for coordinating the supply of cold-pressed SSO. We thank Prof. Jai Vir Singh and Prof. Monica Agarwal for their valuable support in the coding of verbal autopsies. We thank Sachio Yoshida at the WHO for her support with data management. We thank Raja Rakesh Pratap Singh of Shivgarh for his mentorship and guidance. We are also grateful to Dr. Ramesh C. Ahuja and Dr. Girdhar G. Agarwal for their mentorship and inputs. We thank Hitesh Mahajan, Ranjit Kumar, and Col. Fasihuddin Ahmed for their significant contributions, and Sharat Pradhan for his invaluable support. Our entire field operations team led by Adil Hussain Khan, Abbashek Singh, and Satyaparakash Shukla did a stellar job toward the successful completion of the trial. We thank Amit Tandon for his work ethic and commitment in managing the study database, and Deepak Sahu for coordinating the entire hardware and tablet deployment. We thank Poonam Tiwari for leading engagement and training of maeusees, Dr. Swati Dixit for his support in training of data collectors, and Arpit Singh for data quality assurance. The Shivgarh Emollient Research Group membership is as follows: Sana Ashraf, Gary L. Darmstadt, Peter M Elias, Amin Murtuza, Peiyi Kan, Raghav Krishna, Aarti Kumar, Alka Agarwal, Vishwaajit Kumar, Hina Mehrotra, Shamshabbi Mishra, Pawankumar Patil, Arti Sahu, Pramod Singh, Shamshabbi Singh, Vivek Singh, David K Stevenson, Lu Tian, and Ranjana Yadav.

The authors’ responsibilities were as follows—VK and AK: as coprincipal investigators, conceived the research question, designed the trial, and developed the study protocol; VK: oversaw the implementation of the intervention; AK: oversaw trial evaluation; RK: was responsible for the design and implementation of intervention protocols; SS: participated in the design of evaluation protocols and coordinated evaluation activities; SM and SA: were responsible for data management and quality assurance; PK: conducted quantitative analysis with input from SM and SA, technical and scientific guidance from GLD and DKS, and statistical guidance from LT; MB and ML: explored residual inclusion modeling analysis relating growth velocity to mortality; KJHB: reviewed the literature on growth effects of emollient therapy and the association of child growth and mortality; AKG and Alok K: guided program implementation and contributed to interpretation of study findings; GLD: prepared the first draft and coordinated revisions of the manuscript; GLD and AK: had primary responsibility for the final content; and all authors: read and approved the final manuscript. GLD was an employee of the Bill and Melinda Gates Foundation when this study was funded. All other authors report no conflicts of interest.

Data Availability
Data described in the article, code book, and analytic code will be made publicly and freely available without restriction at https://stanfordmedicine.app.box.com/folder/127704102699. The trial protocol can be found at Harvard Dataverse, V1, https://doi.org/10.7910/DVN/TGNC9H.

References
1. Kalia YN, Nonato LB, Lund CH, Guy RH. Development of skin barrier function in premature infants. J Invest Dermatol 1998;111(2):320–6.
2. Williams M. Skin of the premature infant. In: Eichenfield L, Frieden I, Esterly N, editors. Textbook of neonatal dermatology. Philadelphia, PA: WB Saunders Co.; 2001. p. 46–61.
3. Darmstadt GL, Saha SK, Ahmed A, Khautum M, Chowdhury M. The skin as a potential portal of entry for invasive infections in neonates. Perinatology 2003;5(5):205–12.
4. Darmstadt GL. The skin and nutritional disorders in the newborn. Eur J Pediatr Dermatol 1998;8(4):221–8.
5. Visscher MO, Adam R, Brink S, Odio M. Newborn infant skin: physiology, development, and care. Clin Dermatol 2015;33(3):271–80.
6. Winch PJ, Alam MA, Akther A, Afroz D, Ali NA, Ellis AA, Baqui AH, Darmstadt GL, El Arifeen S, Seraji MHR, et al. Local understandings of vulnerability and protection during the neonatal period in Sylhet District, Bangladesh: a qualitative study. Lancet 2005;366(9484):478–85.
7. Kumar V, Mohantsy S, Kumar A, Misra RP, Santoshm M, Awashis S, Baqui AH, Singh P, Singh V, Ahuja RC, et al. Effect of community-based behaviour change management on neonatal mortality in Shighar, Uttar Pradesh, India: a cluster-randomised controlled trial. Lancet 2008;372(9644):1151–62.
8. Kumar V, Kumar A. Darmstadt GL. Behavior change for newborn survival in resource-poor community settings: bridging the gap between evidence and impact. Semin Perinatol 2010;34(6):446–61.
9. Kumar V, Kumar A, Ghosh AK, Sampelh R, Yadav R, Yeung D, Darmstadt GL. Enculturating science: community-centric design of behavior change interactions for accelerating health impact. Semin Perinatol 2015;39(5):393–415.
10. Darmstadt GL, Saha SK. Traditional practice of oil massage of neonates in Bangladesh. J Health Popul Nutr 2002;20(2):184–8.
11. Darmstadt GL, Saha SK. Neonatal oil massage. Indian Pediatr 2002;39(11):1098–9.
12. Mullany LC, Darmstadt GL, Khatri SK, Tielsch JM. Traditional massage of newborns in Nepal: implications for trials of improved neonatal care practices. J Trop Pediatr 2005;51(2):82–6.
13. Ahmed AS, Saha SK, Chowdhury MA, Law PA, Black RE, Santoshm M, Darmstadt GL. Acceptability of massage with skin barrier-enhancing emollients in young neonates in Bangladesh. J Health Popul Nutr 2007;25(2):236–40.
14. Duffy JL, Ferguson RM, Darmstadt GL. Opportunities for improving, adapting and introducing emollient therapy and improved newborn skin care practices in Africa. J Trop Pediatr 2012;58(2):88–95.
15. Man M-Q, Sun R, Man G, Lee D, Hill Z, Elias PM. Commonly employed African neonatal skin care products compromise epidermal function in mice. Pediatr Dermatol 2016;33(5):493–500.
16. Man M-Q, Feingold KR, Thornfeldt CR, Elias PM. Optimization of physiological lipid mixtures for barrier repair. J Invest Dermatol 1996;106(5):1096–100.
17. Darmstadt GL, Man M-Q, Chi E, Saha SK, Ziboh VA, Black RE, Santoshm M, Elias PM. Impact of topical oils on the skin barrier: possible implications for neonatal health in developing countries. Acta Paediatr 2002;91(5):546–54.
18. Inoue H, Asaka T, Nagata N, Koshihara Y. Mechanism of mustard oil-induced skin inflammation in mice. Eur J Pharmacol 1997;333(2–3):231–40.
19. Sood NN, Sachdev MS, Mohan M, Gupta SK, Sachdev HPS. Epidemic drop following transcutaneous absorption of Argemone mexicana oil. Trans R Soc Trop Med Hyg 1985;79(4):510–12.
20. Summers A, Visscher MO, Khatri SK, Shercand JB, LeClerq SC, Katz J, Tielsch JM, Mullany LC. Impact of sunflower seed oil versus mustard seed oil on skin barrier function in newborns: a community-based, cluster-randomized trial. BMC Pediatr 2019;19:512.
21. Procter C, Hartop PJ, Press M. Correction of the cutaneous manifestations of essential fatty acid deficiency in man by application of sunflower-seed oil to the skin. J Invest Dermatol 1975;64(4):228–34.
22. Friedmann Z, Shochat SJ, Maisels J, Marks KH, Lambeth EL Jr. Correction of essential fatty acid deficiency in newborn infants by cutaneous application of sunflower seed oil. Pediatrics 1976;58(5):650–4.
23. Field T, Scafidi FA, Shanbarg S. Massage of preterm newborns to improve growth and development. Pediatr Nurs 1987;13:385–7.
24. Scafidi FA, Field TM, Shanbarg SM, Baur CR, Tucci K, Roberts J, Morrow C, Kuhn CM. Massage stimulates growth in preterm infants: a randomized controlled trial. BMC Pediatr 2019;19:512.
25. Procter C, Hartop PJ, Press M. Correction of the cutaneous manifestations of essential fatty acid deficiency in man by application of sunflower-seed oil to the skin. J Invest Dermatol 1975;64(4):228–34.
26. Friedmann Z, Shochat SJ, Maisels J, Marks KH, Lambeth EL Jr. Correction of essential fatty acid deficiency in newborn infants by cutaneous application of sunflower seed oil. Pediatrics 1976;58(5):650–4.
27. Field T, Scafidi FA, Shanbarg S. Massage of preterm newborns to improve growth and development. Pediatr Nurs 1987;13:385–7.
28. Field T, Scafidi FA, Shanbarg S, Emory EK, Redzepi M. Stable preterm infants gain more weight and sleep less after five days of massage therapy. J Pediatr Psychol 2003;28(6):403–11.
29. Schourer N, Schliep V, Williams ML. Differential utilization of linoleic and arachidonic acid by cultured human keratinocytes. Skin Pharmacol Physiol 1995;8(1–2):30–40.
30. Schourer N, Schliep V, Williams ML. Differential utilization of linoleic and arachidonic acid by cultured human keratinocytes. Skin Pharmacol Physiol 1995;8(1–2):30–40.
1104 Kumar et al.

47. Kumar J, Upadhyay A, Dwivedi AK, Gothwal S, Jaiswal V, Aggarwal S. Effect of oil massage on growth in preterm neonates less than 1800 g: a randomized control trial. Indian J Pediatr 2013;80(6):465–9.

48. Jabareen M, Rasooly AS, Farshi MR, Malakouti J. Effect of olive oil massage on weight gain in preterm infants: a randomized controlled clinical trial. Niger Med J 2016;57(3):160–3.

49. Saeedi R, Ghorbani Z, Shapouri Moghadam A. The effect of massage with medium-chain triglyceride oil on weight gain in premature neonates. Acta Med Iran 2015;53(2):134–8.

50. Taheri PA, Goudarzi Z, Shariat M, Nariman S, Matin EN. The effect of a short course of moderate pressure sunflower oil massage on the weight gain velocity and length of NICU stay in preterm infants. Infant Behav Dev 2018;50:22–7.

51. Zhao J, Pi GH, Chen YR. Sunflower oil massage’s effect on greater preterm infants weight. J Southeast Univ (Med Sci Ed) 2014;33(6):710–12.

52. Konar MC, Islam K, Roy A, Ghosh T. Effect of virgin coconut oil application on the skin of preterm newborns: a randomized controlled trial. J Trop Pediatr 2020;66(2):129–35.

53. Li X, Zhong Q, Tang L. A meta-analysis of the efficacy and safety of using oil massage to promote infant growth. J Pediatr Nurs 2016;31(5):e313–e22.

54. Clemenson J, McGuire W. Topical emollient for preventing infection in preterm infants. Cochrane Database Syst Rev 2016;(1):CD001150.

55. Lefere A, Shillcutt SD, Saha SK, Ahmed A, Ahmed S, Chowdhury M, Law PA, Black R, Santosh M, Darmstadt GL. Cost-effectiveness of skin-barrier-enhancing emollients among preterm infants in Bangladesh. Bull World Health Organ 2010;88(2):104–12.

56. Solanki K, Matmani M, Kale M, Joshi K, Bavekar A, Bhave S, Pandit A. Transcutaneous absorption of topically massaged oil in neonates. Indian Pediatr 2005;42(10):998–1005.

57. Aggarwal KN, Gupta A, Pushkarna R, Bhargava SK, Faradi MM, Prabh MK. Effects of massage & use of oil on growth, blood flow & sleep pattern in infants. Indian J Med Res 2000;112:212–17.

58. Hayes R, Moulton L. Cluster randomised trials. Vol. 65. Boca Raton, FL: CRC; 2009.

59. Monson RT, Fisher JA. Benefits of “observer effects”: lessons from the field. Qual Res 2010;10(3):357–76.

60. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ Jr. Splines for trend analysis and continuous confounder control. Epidemiology 2011;22(6):874–5.

61. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 1995;57(1):289–300.

62. Arora J, Kumar A, Ramji S. Effect of oil massage on growth and neurobehavior in very low birthweight preterm neonates. Indian Pediatr 2005;42(11):1092–100.

63. Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce mortality-discriminating power in children with medium-chain triglyceride oil. Acta Medica Scandinavica 2015;33(2):96–102.

64. Bairagi R, Koenig MA, Mazummer KA. Mortality-discriminating power of some nutritional, sociodemographic, and diarrheal disease indices. Am J Epidemiol 1993;138(5):310–17.

65. WHO Expert Committee on Physical Status. Physical status: the use and interpretation of anthropometry: report of a WHO expert committee. Geneva, Switzerland: WHO; 1995.

66. Schwingier C, Fadnes LT, Van den Broeck J. Using growth velocity to predict child mortality. Am J Clin Nutr 2016;103(3):801–7.

67. O’Neill SM, Fitzgerald A, Briend A, Van den Broeck J. Child mortality as predicted by nutritional status and recent weight velocity in children under two in rural Africa. J Nutr 2012;142(3):520–5.

68. Oza S, Cousins SN, Lawn JE. Estimation of daily risk of neonatal death, including the day of birth, in 186 countries in 2013: a vital registration and modelling-based study. Lancet Glob Health 2014;2(11):e635–e44.

69. Saeedi R, Ghorbani Z, Shapouri Moghadam A. The effect of massage with medium-chain triglyceride oil on weight gain in premature infants. Acta Med Iran 2015;53(2):134–8.

70. Zakariaz H, Rong J, Gershon R, Shapouri M, Matin EN. The effect of oil massage to promote infant growth. J Pediatr Nurs 2016;31(5):e313–e22.

71. Lefere A, Shillcutt SD, Saha SK, Ahmed A, Ahmed S, Chowdhury M, Law PA, Black R, Santosh M, Darmstadt GL. Cost-effectiveness of skin-barrier-enhancing emollients among preterm infants in Bangladesh. Bull World Health Organ 2010;88(2):104–12.

72. Solanki K, Matmani M, Kale M, Joshi K, Bavekar A, Bhave S, Pandit A. Transcutaneous absorption of topically massaged oil in neonates. Indian J Med Res 2000;112:212–17.

73. Hayes R, Moulton L. Cluster randomised trials. Vol. 65. Boca Raton, FL: CRC; 2009.

74. Monson RT, Fisher JA. Benefits of “observer effects”: lessons from the field. Qual Res 2010;10(3):357–76.

75. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ Jr. Splines for trend analysis and continuous confounder control. Epidemiology 2011;22(6):874–5.

76. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc B 1995;57(1):289–300.

77. Arora J, Kumar A, Ramji S. Effect of oil massage on growth and neurobehavior in very low birthweight preterm neonates. Indian Pediatr 2005;42(11):1092–100.

78. Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev 2016;(1):CD001150.

79. Terzza JV. Two-stage residual inclusion estimation in health services research and health economics. Health Serv Res 2018;53(3):1890–9.

80. Kasongo Project Team. Growth decelerations among under-5-year-old children in Kasongo (Zaire). II. Relationship with subsequent risk of dying, and operational consequences. Bull World Health Organ 1986;64(5):703–9.

81. Briend A, Bari A. Critical assessment of the use of growth monitoring for identifying high risk children in primary health care programmes. BMJ 1989;298(6688):1607–11.

82. Bairagi R, Chowdhury MK, Kim YJ, Curlin GT. Alternative anthropometric indicators of mortality. Am J Clin Nutr 1985;42(2):296–306.

83. Mazumder S, Taneja S, Dube B, Bhatia K, Ghosh R, Shekhar M, Sinha B, Bahl R, Martines J, Bhan MK, et al. Effect of community-initiated kangaroo mother care on survival of infants with low birthweight: a randomized controlled trial. Lancet 2019;394(10210):1724–36.

84. Man G, Cheung C, Crumrine D, Hupe M, Hill Z, Man M-Q, Elias PM. An optimized inexpensive emollient mixture improves barrier repair in murine skin. Dermatologica Sinica 2015;33(2):96–102.