A Meta-analysis on the Effect of Kangaroo Mother Care on Preterm Mortality

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ABSTRACT

Background. Kangaroo mother care (KMC) is a low-cost but high-impact intervention for preterm and low birth weight (LBW) infants.

Objectives. To determine the effect of KMC on in-hospital mortality among preterm and LBW infants, taking into consideration their gestational age, birth weight, income category of the country of birth, and medical stability.

Materials and Methods. A comprehensive search of several databases, as well as local listings of research papers, was performed to look for randomized controlled studies with KMC as intervention, and mortality and length of hospitalization as outcome measures. The risk of bias and publication bias was assessed. We did subgroup analyses based on income category of the country of birth, gestational age, birth weight, and medical stability of the infants.

Results. Sixteen randomized controlled trials (RCTs) with 1738 infants in the KMC group and 1674 infants in the control group were included. Based on the GRADE approach, although all the studies were RCTs, the evidence is assessed as moderate certainty due to the nature of the intervention (KMC) that prevented blinding. There was a 41% reduction in risk of dying among preterm and low birth weight infants who received KMC compared to conventional medical care (3.86%% vs 6.87%; RR = 0.59, 95% CI 0.44, 0.79; I^2 = 0%; number needed to treat for additional benefit (NNTB) = 34; 16 RCTs; 3,412 infants). Furthermore, there were also reductions in the risk of dying among infants who were <34 weeks AOG (KMC: 4.32% vs CMC: 8.17%, RR = 0.55, 95% CI 0.38, 0.79; I^2 = 0%; NNTB = 26; 10 RCTs; 1795 infants), with birthweight of >1500 g (KMC: 3.97% vs CMC: 6.83%, RR = 0.60; 95% CI 0.45, 0.82; I^2 = 0%; NNTB = 35; 10 RCTs; 2960 infants), and born in low- and middle income countries (LMIC) (3.77% vs 6.95%; RR = 0.57, 95% CI 0.43, 0.77; I^2 = 0%; NNTB = 32; 14 RCTs; 3281 infants). There was a significant reduction in mortality (KMC: 11.05% vs CMC: 20.94%; RR = 0.54; 95% CI 0.34, 0.87; I^2 = 0%; NNTB = 11; 5 RCTs; 387 infants) even among medically unstable infants who received KMC compared to those who did not. The length of hospitalization did not significantly differ between the KMC and the control groups. Due to high heterogeneity, subgroup analyses were performed, which showed a trend towards a shorter length of hospital stay among preterm infants <34 weeks AOG, with birthweight ≥1500 g, medically unstable during admission, and belonging to LMIC but did not reach statistical significance.

Conclusion. There was moderate certainty evidence that KMC can decrease mortality among preterm and LBW infants. Furthermore, KMC was beneficial among relatively more premature, bigger, medically unstable preterm infants and born in low to middle-income countries.

Key Words: kangaroo mother care, preterm, low birth weight, mortality, hospital stay

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INTRODUCTION

Description of the condition

The first month of the life of a newborn is considered the toughest period for childhood survival. In 2019, the global average neonatal mortality rate (NMR) is 17 deaths per 1,000 live births. Although there has been a significant reduction in neonatal mortality rate (NMR) from 38 deaths per 1000 live births in 1990, NMR remains a major contributor to childhood mortality.[1] Neonatal death comprises 47% of under-5 childhood mortality. Of these deaths, 99% occur in low to middle-income countries and most of these are considered preventable deaths.[2] In 2019, 1/3 of newborns died in the first 24 hours of life and 3/4 died within the first week.[3] Neonates predominantly die of complications of preterm births (35%), intrapartum events (24%), infections (15%), and congenital anomalies (11%).[4]

WHO initiatives, such as *A Promise Renewed* and *Every Newborn Action Plan*, set specific targets also reflected in the Sustainable Development Goals (SDGs) that aim to end preventable deaths of newborn babies and children younger than 5 years by 2030. SDG 3.2 stipulates that all countries shall aim to reduce neonatal mortality to 12 deaths per 1000 live births or fewer.[5]

Although substantial progress has been made in reducing neonatal mortality over the past years, there is still a need to accelerate all efforts in the next 5 years to achieve the SDG target by 2030. Faster improvements are much desired in the regions with high NMR, especially in sub-Saharan Africa and South Asia.[5]

Description of the intervention

Kangaroo Mother Care (KMC) started in the 1970s in Bogota, Colombia, and has been considered as an innovative and daring intervention to care for low-birth-weight (LBW) infants.[6]

In 2015, the World Health Organization (WHO) has recommended that KMC should be routine care for newborn infants weighing 2000 g or less and initiated once the infants are clinically stable.[7] Aside from assurance of thermoregulation among the lower birth weight or preterm infants, KMC has been proven to significantly improve preterm survival. The meta-analysis of Aguedo-Conde in 2016 showed a reduction in the risk of dying by 40% among infants who received KMC. An apparent dose-response relationship was likewise observed with KMC, wherein earlier initiation and a longer duration rendered led to a greater reduction in mortality.[8]

KMC is comprised of prolonged skin-to-skin contact between the baby and the mother, exclusive breastmilk feeding, and early discharge.[7] However, in a recent review of publications, there seem to be variable definitions of the KMC intervention with 71% defining KMC in terms of skin-to-skin contact only. Only a few publications included the other integral components of the KMC intervention, namely exclusive breastfeeding (16%), early discharge (7%), and follow-up (12%).[9] In this review, the skin-to-skin component of the KMC intervention is considered.

How the intervention might work

The reasons for the significant reduction in mortality among preterm or LBW infants who received KMC are multifactorial. Foremost, KMC has been shown to ensure better thermoregulation among these high-risk infants. In a small randomized controlled trial (RCT) comparing KMC and conventional care (infant inside an incubator), there was more than a 90% reduction in hypothermia among infants <2000 g birth weight.[10] Hypothermia is recognized to be associated with higher morbidities such as arrhythmia, bleeding, thrombosis, intraventricular hemorrhage, and sepsis.[11]

In a small randomized study of 52 very preterm infants randomized to KMC < 3 hours/day versus KMC ≥ 3 hours/day, there was a significantly lower incidence of nosocomial sepsis among those provided longer KMC sessions. Other preterm complications like bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and growth parameters were the same between the two groups. The reduction in sepsis rates was hypothesized to be due to the higher frequency of infants breastfed in the KMC group compared to the control.[12] A meta-analysis in 2019 concurred and showed higher breastfeeding rates among KMC mothers.[13] Likewise, in another meta-analysis, KMC mothers were able to initiate breastfeeding earlier than the non-KMC mothers.[14] Breastmilk has been shown to not only contain optimal nutrition but also bioactive reagents that are known to fight infections. Exclusive breastfeeding, as mentioned earlier, is an integral part of the KMC intervention.

In a randomized trial, infants have better physiologic parameters (heart rate, respiratory rate, and oxygen saturation) while on KMC compared with baseline (pre-KMC session) and compared with infants on conventional care.[15] This may indicate a calmer preterm infant. This may have led to faster growth velocities observed among KMC infants.[16] In another randomized controlled trial, infants randomized to KMC have lower levels of the stress hormone, cortisol, in their saliva at 1 month. Furthermore, even the mothers' salivary cortisol levels correlated with those of their infants at 4 months, which may also indicate a more relaxed mother. The fathers of KMC mother-infant dyads also seem to be in a more comfortable relationship with their wives as they scored lower in the questionnaire on spouse relationship problems.[17] It seems that there is less stress not only among the preterm infants on KMC but also among their mothers and their family in general.

There is a more rapid improvement among KMC infants on respiratory support. In a retrospective cohort of 145 extremely LBW infants, the duration of non-invasive ventilation and oxygen support were significantly shorter among infants provided with KMC. Similarly, episodes of

apnea were also less among the preterm infants on KMC. All these may lead to a short hospital stay.[18]

Aside from increased survival, KMC infants were found to fare better in terms of neurobehavioral performance. In a RCT, preterm infants in the KMC group scored higher for attention, quality of movements, and lower scores on asymmetry and signs of stress and abstinence while in the hospital.[19] Aside from having better short-term outcomes among the KMC infants, a 20-year follow up of these infants showed that they were more employable, more socially adaptable, and had more stable homes compared with those who were not provided KMC.[20]

Why it is important to do this review?

KMC is a cost-effective and efficacious intervention in preventing preterm mortality in in-hospital deliveries.[21] Despite the robust evidence of multiple benefits of KMC to both the mothers and the babies, the number of hours KMC rendered is usually only from 3–5 hours/day, which is much less than the recommended for intermittent KMC (≥ 8 hours/day) and continuous KMC (≥ 20 hours/day).[22] Furthermore, the quality of KMC implementation in developing countries is poor, with only 59.0% of the facilities ready to provide KMC service and only 46% of the eligible infants receiving KMC.[23]

Several factors influence the uptake of KMC, which include context-specific interventions such as the development of guidelines, behavior change materials, training curriculum, and job aids. Societal and cultural norms are also taken into consideration. The barriers identified have been the perception that KMC is not based on scientific fact, the inconsistent application of KMC within the facilities, the lack of leadership and support from management, and the perception of non-priority of newborn care in the health system. There is also the perception that KMC is only safe for stable LBW infants.[24]

In a meta-analysis by Boundy (2016), pooled estimates from 24 studies showed a 36% reduction in mortality (RR 0.64; 95 CI 0.46, 0.89), a 47% lower risk of neonatal sepsis (RR 0.53; 95% CI 0.34, 0.83), a 78% reduction in hypothermia (RR 0.22; 95% CI 0.12, 0.41), a 92% reduction in hypoglycemia (RR 0.12; 95% CI 0.05, 0.32), and a 1.5-fold increase in the chance of exclusive breastfeeding (RR 1.50; 95% CI 1.26, 1.78). However, there have been no further analyses using states of medical stability and geographical regions as subgroups.[25]

An updated meta-analysis of 21 studies by Conde-Agudelo (2016) showed a 40% reduction in the risk of dying, a 65% reduction in the risk of sepsis, and a 72% reduction in the risk of hypothermia. The weight, length, and head circumference increment rates are faster among the KMC group. However, only one study on KMC provided to infants before stabilization has been analyzed and has not shown any significant reduction in mortality. No subgroup analyses on the gestational age and birthweight were done.[8]

Although the 2015 recommendation of WHO[7] is to provide KMC as part of neonatal care for clinically stable infants, in recent years, KMC has been provided even in unstable preterm or LBW infants. A mixed-method study by Morgan on the feasibility and acceptability of KMC provided to unstable infants < 2000 grams has shown that 75% of the mothers agreed that KMC may be provided to medically unstable infants. Clinical instability among infants is defined as receiving ≥ 2 medical therapies.[26]

Providing evidence of the benefits of KMC among preterm and LBW infants may further influence clinicians and policymakers in improving KMC implementations in both stable and unstable infants.

SIGNIFICANCE

The implementation of KMC programs has faced challenges over the years. Providing additional information on its benefits on preterm mortality and hospital cost may further motivate stakeholders in the acceptance of the KMC programs.

OBJECTIVE

To determine if KMC provided among preterm or LBW infants will decrease in-hospital neonatal mortality and length of hospital stay.

MATERIALS AND METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled single-blind studies were eligible for inclusion in this review. Studies that were not intention-to-treat or permitted cross-over to other study groups were also not included. There were no restrictions imposed in terms of language and publication status. Google Translate was used for foreign-language publications.

Types of participants

This review included only studies that involve preterm infants (< 37 completed weeks) or LBW infants (< 2,500 g birth weight).

Types of interventions

Only studies with interventions stated as KMC, kangaroo mother care, or skin-to-skin contact, started only during the hospital stay, were included in this review. Studies in which KMC was in combination with other interventions, or was started post-discharge or in the community were not included. Control group infants were those who received conventional care such as placement inside an incubator, a radiant warmer, or a bassinet. Traditional holding was also considered an acceptable control intervention.

Types of outcome measures

The primary outcome of interest was in-hospital mortality. A secondary outcome variable was the length of hospitalization. These outcome measures would reflect the effectiveness of KMC in reducing deaths (mortality) as well as in facilitating faster improvement from preterm complications (length of hospitalization). Studies, where outcome variables did not include mortality, were not included in the review.

Search methods used to identify the studies

Electronic searches

The following databases were searched thoroughly: Cochrane Central Register of Controlled Trials (CENTRAL), U.S. National Library of Medicine via PubMed, Scopus, LILACS (Latin American and Caribbean Health Sciences Literature), Embase (Excerpta Medica Database), and CINAHL (Cumulative Index to Nursing and Allied Health Literature). The Cochrane Database of Systematic Reviews was also searched for reviews or meta-analyses. The WHO International Clinical Trials Registry Platform and ClinicalTrials.gov were also searched for ongoing clinical trials. The authors also searched for local studies from the Health Research and Development Information Network (HERDIN), Philippine Index Medicus, and the Philippine Journal of Pediatrics. There were no restrictions imposed on language or year of publication. The last update was performed in September 2020. The search strategy for "CENTRAL" and "MEDLINE" used the MeSH terms 'kangaroo mother care', 'skin to skin contact', 'low birth weight', and 'preterm neonates' and 'randomized controlled trials.'

Searching other resources

The citation list of eligible trials was explored to find other studies. The Philippine General Hospital Department of Pediatrics Research Inventory from 2011 to 2018 was likewise searched for published and unpublished studies. Inquiry into the list of submitted research studies (published and unpublished) to the Philippine Society of Newborn Medicine, as well as studies funded by the Kangaroo Mother Care Foundation Philippines, were also done. Some authors were contacted by e-mail regarding the possible eligibility of their studies for this review.

Data collection and analysis

We utilized the standard methods of the Cochrane Neonatal Review Group and The Cochrane Collaboration.

Selection of studies

Only randomized controlled trials that fulfilled set criteria and included hospital mortality were reviewed. Duplicate publications were removed.

Data extraction and management

Two authors independently extracted and assessed the accuracy of data from the clinical trials. Disparities between the two authors were resolved by discussion among the authors. Data input was through the Review Manager Version 5.3 (RevMan) software.

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias of all included trials as outlined in the Cochrane Handbook for Systematic Reviews of Intervention.[27] Assessments were specified as 'low risk,' 'high risk,' or 'unclear.' Any disparity was resolved by discussion among the authors.

1. Sequence generation

Selection bias was assessed as a) Low risk – application of randomization such as random number via a table or computer-generated; b) High risk – any non-random process, e.g., hospital number; or c) Unclear.

2. Allocation concealment

The allocation concealment methods were assessed as a) Low risk – telephone or central randomization, consecutively numbered-sealed envelopes, coding by the third party; b) High risk – unsealed or non-opaque envelopes, alternation; or c) Unclear.

3. Blinding

The methods for blinding affect performance and detection bias. Trials were assessed as low risk if the process of blinding was defined in the included trials. Otherwise, the trials were assessed as either high risk (no blinding) or unclear. The blinding assessment included both the research personnel and the outcome assessor.

4. Incomplete outcome data

The completeness of data was assessed based on the number of participants included in the analysis compared with the total randomized participants to check for possible attrition bias. The methods were assessed as a) Low risk (< 20% missing data); b) High risk (≥ 20% missing data); or c) Unclear.

5. Selective reporting bias

This bias was assessed as a) Low risk – if the study reported all pre-specified outcomes and all expected outcomes of interest, b) High risk – if not all of the study's pre-specified outcomes were reported, outcomes of interest were incompletely reported and thus could not be used, or non-inclusion of the results of an important outcome expected to have been reported; or c) Unclear.

6. Other sources of bias

The included studies were assessed for other sources of bias such as imbalances in baseline data, possible reports

of fraudulence, issues with sample size, and the presence of conflicts of interest. As with the other biases listed under the Cochrane Handbook for Systematic Reviews of Intervention, these other biases will be judged as 'low risk' (no evidence of such biases), 'high risk' (clear evidence of such biases), or 'unclear' (insufficient data to assess bias).

7. Overall risk of bias

The authors assessed the trials based on the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions. The direction and magnitude of the bias, and whether it was likely to impact the results were assessed.

Measures of treatment effect

The statistical analyses were based on the standard methods of the Cochrane Neonatal Review Group. Continuous data were analyzed using mean differences (MD) while dichotomous data were reflected on summary risk ratios (RR). All the point estimates were reported together with the 95% confidence intervals (CI). The number needed to treat (or harm) was also calculated.

Unit of analysis issues

Included studies were randomized controlled trials, with the unit of analysis being preterm or LBW infants admitted in the hospital.

Assessment of heterogeneity

To be able to assess the appropriateness of pooling data, heterogeneity between studies was evaluated using the I-squared (I^2) statistic. The degree of heterogeneity was categorized based on the following ranges as suggested by Higgins et al.[27]: <25% = none, 25-49% = low, 50-74% = moderate, >75% = high.

Assessment of reporting bias

A search for unpublished studies was conducted in the following trial registries: ClinicalTrials.gov (n=7), ISRCTN (International Standard Randomized Controlled Trial Number) (n=7), and ICTRP (International Clinical Trials Registry Platform of the World Health Organization) (n=137). A similar search was likewise conducted among the list of local Neonatology Fellowship unpublished research papers. Outcome estimates from all included studies (published and unpublished) were encoded in the Review Manager software (RevMan version 5.3) and the appropriate funnel plot was generated and inspected for symmetry.

Data synthesis

Statistical analysis was performed using RevMan version 5.3. Outcomes were analyzed on an intention-to-treat basis. The random-effects model was used to pool the data for meta-analysis. The Mantel-Haenszel method was used for approximations of risk ratios for categorical outcomes (in-hospital mortality). For continuous outcomes (length of hospital stay), the inverse variance method was employed to determine the pooled mean difference. A p-value of <0.05 was considered statistically significant.

Quality of Evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, as outlined in the GRADE Handbook[28] was used to assess the quality of evidence contained within the included studies. Results of randomized trials are considered high-quality evidence by default. For some of the included studies, however, downgrading by one to two levels has occurred after considering the following: publication bias, risk of bias, directness of evidence, and consistency across the studies.

Subgroup analysis and investigation of heterogeneity

For the primary outcome of in-hospital mortality, analyses were performed on the following pre-specified subgroups: economic status of the country of birth (high income vs low-to-middle income), gestational age (<34 weeks vs ≥34 weeks), birth weight (<1500 g vs ≥1500 g) and medical stability (unstable vs stable). Medical instability was defined as infants requiring respiratory support (oxygen, CPAP [continuous positive airway pressure], HFNC [high-flow nasal cannula], NIPPV [non-invasive positive pressure ventilation] and IPPV [invasive positive pressure ventilation]).

Sensitivity analysis

In the event of moderate to high heterogeneity, we planned to do sensitivity analysis by excluding the following studies that may be deemed problematic: studies with inadequate randomization; studies with unclear or disputed concealment of allocation; or studies with significant loss to follow up.

RESULTS

Results of the search

There were 1,207 records obtained using the following search strategy: MeSH words ["kangaroo mother care" OR "skin to skin"] AND ["preterm infants" OR "low birth weight"] AND "randomized controlled trial." Databases searched were PubMed®, Embase (Excerpta Medica Database), LILACS (Latin American and Caribbean Health Sciences Literature), CINAHL (Cumulative Index to Nursing and Allied Health Literature), SCOPUS, ClinicalTrials.gov. and the local database, HERDIN (Health Research and Development Information Database). Three studies were obtained from the Philippine Society of Newborn Medicine list of researches submitted by Neonatology Fellowship graduates as part of their requirements for board eligibility. Only 519 studies were screened after removing duplicates. There were 116 studies that were assessed for

eligibility. Excluded studies mostly did not include or report mortality as the outcome variable. Most RCTs were on the effect of KMC on pain. Studies with interventions of KMC plus another intervention (touch therapy, music, early family intervention, sucrose, breastfeeding) were not included. Studies where skin-to-skin contact was not a daily intervention for some time, but rather just one session during resuscitation, were not included. Comparison studies of early and late KMC were also not considered. Ultimately, only 16 RCTs were included in the review (Figure 1).

Description of included studies

There were 15 single center RCTs and 1 multicenter RCT involving Ethiopia, Mexico and Indonesia. There were 1738 infants who were randomized to the KMC group and 1674 infants to the conventional medical care (CMC) group.

With regards to the subgroups on the economic status of the country of birth, two RCTs were from high-income countries, namely, UK (Whitelaw) and USA (Rojas), while the remaining 14 RCTs were from the following

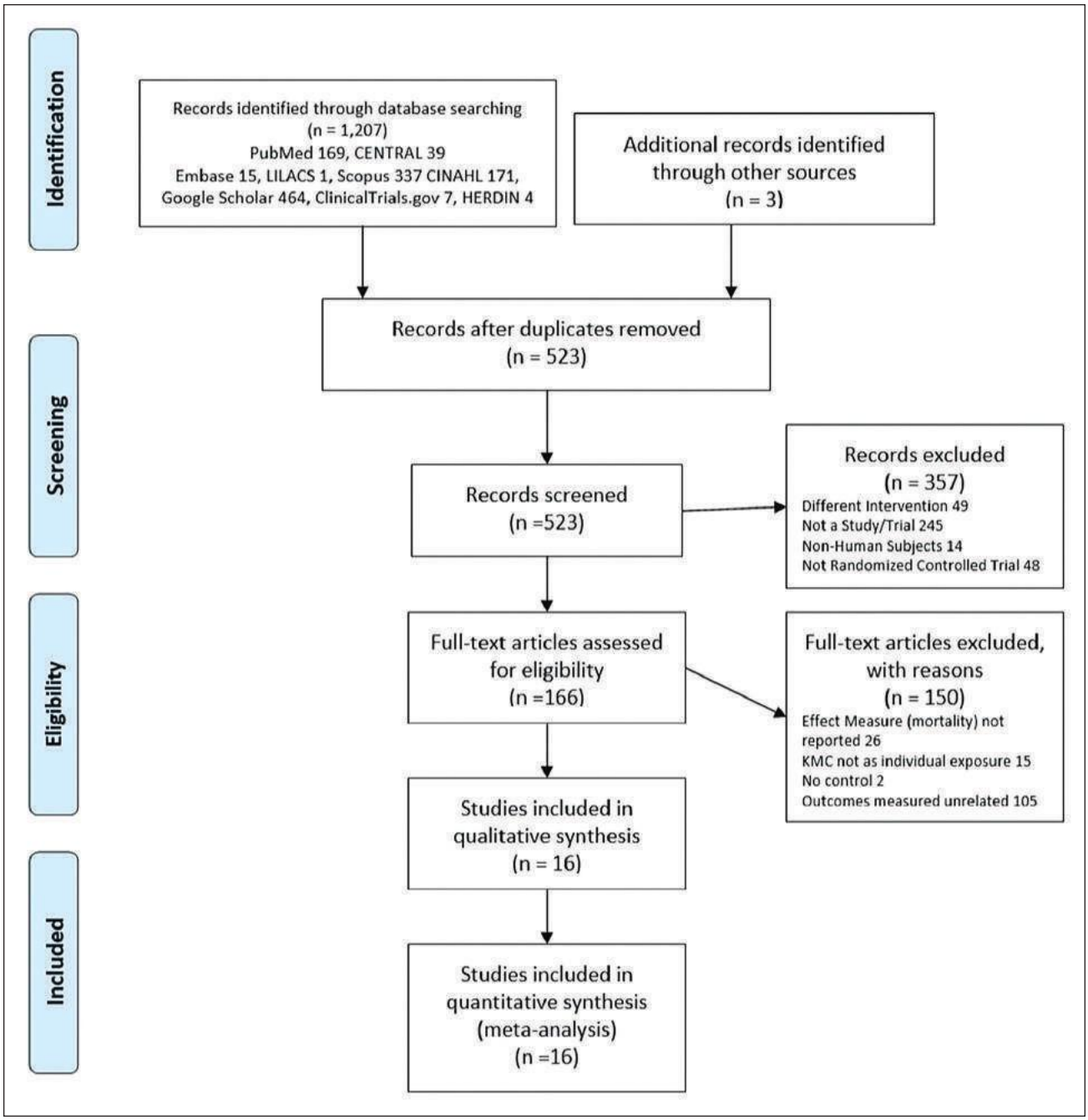

Figure 1. Study flow diagram.

low-to-middle income countries: India (Kadam; Rao), Ethiopia (Cattaneo; Worku), Mexico (Cattaneo), Indonesia (Cattaneo), Kenya (Mwendwa), Ecuador (Sloan), Colombia (Charpak [1997]; Charpak [2001]; Tessier), Nepal (Acharya), Philippines (Baton; Fortifaes; Luistro) and Zimbabwe (Kambarami). For the subgroups of gestational age at birth, 2 RCTs recruited infants with AOG ≥34 weeks (Rao; Sloan), while 14 RCTs recruited infants with AOG <34 weeks (Acharya; Baton; Cattaneo; Charpak [1997]; Charpak [2001]; Fortifaes; Kadam; Luistro; Mwendwa; Rojas; Tessier; Whitelaw; Worku). Ten RCTs recruited infants with birthweights <1500 g (Acharya; Baton; Kadam; Kambarami; Luistro; Mwendwa; Rojas; Tessier; Whitelaw; Worku) while 6 RCTs recruited infants who weight ≥1500 g at birth (Cattaneo; Charpak [1997]; Charpak [2001]; Fortifaes; Rao; Sloan). Five RCTs enrolled medically unstable infants (Baton; Fortifaes; Luistro; Rojas; Worku). A summary of the study characteristics and a detailed description of the included studies are provided in Tables 1 and 2.

Table 1. Summary of characteristics of the included studies

Characteristics of included studies	N=16
Year of publication	
<1990	1
1990-1999	4
2000-2009	6
2010+	6
Sample size	
<50	1
50-99	4
100-199	4
200-299	2
300-399	3
400+	2
Study site	
Single	1
Multiple	3
Country	
Colombia	3
Ecuador	1
Ethiopia	2*
Kenya	1
Indonesia	1*
India	2
Mexico	1*
Nepal	1
Philippines	3
United Kingdom	1
United States	1
Medical Stability	
Stable	11
Unstable	5
Duration of KMC/day (hours)	
<3	2
3-6	3
6-12	3
12-18	1
>18	6
Not stated	1

**Countries included in the multi-country study of Cattaneo 1998.*

Risk of bias assessment of the included studies (Figure 2)

Allocation (selection bias)

Four RCTs allocated their infants randomly to either KMC or control groups using random number tables

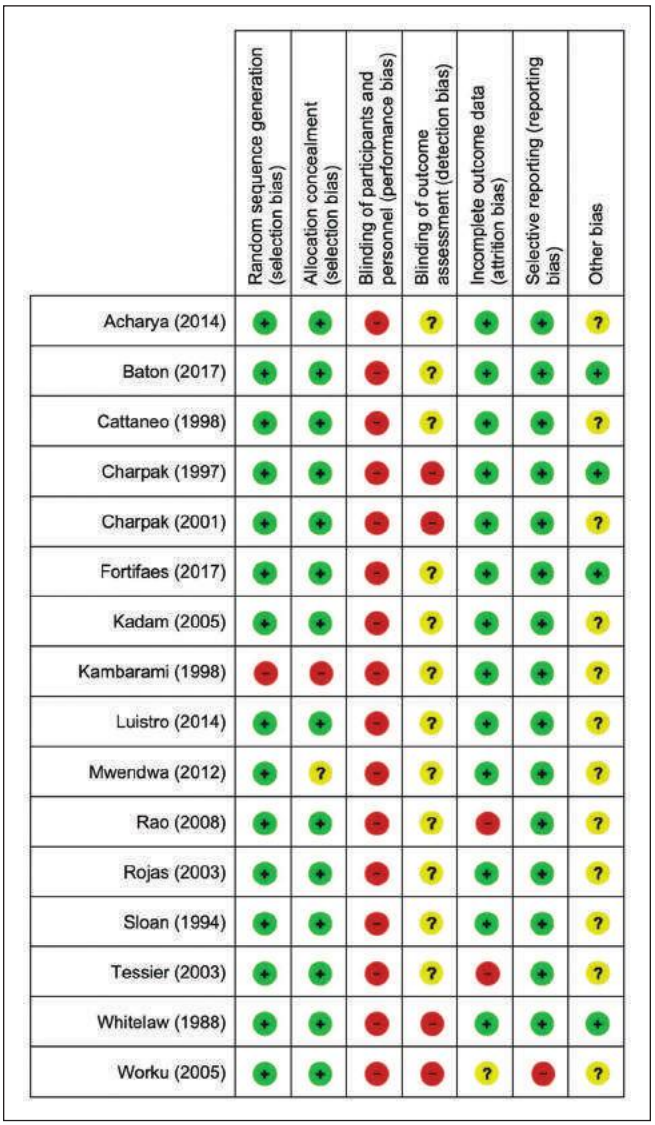

Figure 2. Risk of bias summary.

Table 2. Characteristics of Included Studies Comparing KMC and Conventional Care on Premature, LBW Infants

Study, Year, and Design (n)	Inclusion and Exclusion Criteria	Study Groups	Description of Infants Included in the Study	Outcomes Measured
Acharya, 2014 Single-center RCT (n = 126)	*Inclusion:* Neonates with birth weight <2000 g. *Exclusion:* Critically ill infants requiring ventilatory or inotropic support or radiant warmer; chromosomal and life-threatening congenital abnormalities; babies whose mothers are critically ill; parental refusal.	*KMC (n = 63):* KMC duration at least 6 hours per day in not more than 4 sittings, each sitting lasting at least 1 hour. Mothers wore a loose blouse covering the infant's trunk and extremities but not the head, with the baby was held upright between the breasts and supported by 3-meter long flannel clothes. Babies wore only diaper and a cap during the period of KMC. Infants requiring phototherapy were withdrawn from the group and reintroduced afterwards. *Control (n = 63):* Babies were adequately clothed, covered and kept with their mother. If they did not maintain temperature, they were kept under radiant warmer.	• Medically stable upon entry into study. • Birth weight: 1385.87 ± 234.12 g for KMC group vs 1458.57 ± 172.66 g for CMC group (p = 0.05) • Weight at recruitment: 1458.57 ± 172.66 g for KMC group, 1385.87 ± 234.12 g for CMC group.	• Average weight gain • Head circumference • Length • Hypothermia • Apnea • Duration of hospital stay
Baton, 2017 Single-center RCT (n = 32)	*Inclusion:* All preterm neonates aged 28 to 36 weeks, weighing 600 to 2000 g, admitted at the NICU, requiring intubation and mechanical ventilation due to respiratory distress, but with stable heart rate, BP within normal range for weight and age of gestation, oxygen saturation > 90% and no adverse respiratory events requiring emergent interventions during the previous 12 hours. *Exclusion:* Age <28 weeks and birthweight <600g; presence of severe respiratory distress (FiO_2 >50%), persistent pulmonary hypertension, intraventricular hemorrhage ≥ grade 3, shock state as seen in severe sepsis, and major congenital abnormalities.	*KMC (n = 16):* KMC was provided to all preterm neonates as soon as the infant demonstrated stable vital signs while on the ventilator. The infant and parent were kept on the KMC position intermittently for 2 to 4 hours daily, until they were extubated. *Control (n = 16):* The participants were provided care inside an incubator. All preterm neonates in both groups were managed similarly except for the KMC position in the intervention group. Since KMC is the standard of care for all preterm and low birthweight neonates in the study facility, all neonates in both groups were enrolled to the KMC program as soon as they were extubated.	• Mechanically ventilated by medically stable. • No statistically significant difference between the two groups in terms of pregnancy, maternal, and infant demographic characteristics.	• Mortality rate • Morbidity (sepsis, pneumonia, necrotizing enterocolitis, hypothermia) • Number of days intubated • Duration of hospitalization
Cattaneo, 1998 Multicenter RCT (n = 285)	*Inclusion:* Infants with birth weight between 1000 and 1999 g, regardless of gestational age, without oxygen and/or IV fluid requirement, free of any visible major malformation, able to feed, and mother is present and willing to collaborate *Exclusion:* None stated	*KMC (n = 149):* Continuous skin-to-skin contact between mother's breasts, with diaper and a hat with their mother's clothes, for an average of about 20 hours/d, even during mother's sleep. KMC assistant replaces mothers on occasion *Control (n = 136):* Infants were kept in a warm room, with open cribs and the possibility of rewarming in a bulb-heated cot, and in incubators in the other 2 hospitals.	• Medically stable upon entry into study. • Infants <32 weeks GA: 24 (16%) for KMC group vs 14 (10%) for CMC group (p = 0.02) • Breastfeeding at hospital admission: 63 (48%) for KMC group vs 49 (40%) for CMC group (p = 0.001) • Breastfeeding at study enrollment: 100 (67%) for KMC group vs 75 (55%) for CMC group (p = 0.003)	• Severe illness • Hypothermia • Hyperthermia • Breastfeeding • Weight gain • Neonatal death • Acceptability to health workers • Acceptability to mothers • Costs

Table 2. Characteristics of Included Studies Comparing KMC and Conventional Care on Premature, LBW Infants *(continued)*

Study, Year, and Design (n)	Inclusion and Exclusion Criteria	Study Groups	Description of Infants Included in the Study	Outcomes Measured
Charpak, 1997 Single-center RCT (n = 709)	*Inclusion:* Infants with birth weights ≤2000 g born to mothers who consented to participating in the study and understand protocol instructions. *Exclusion:* Refusal to comply with specifics of the instructions (for KMC group), referral to another institution, plans to leave Bogotá in the near future, life-threatening or major malformations, early detected major conditions arising from perinatal problems, parental or family refusal to comply with the follow-up program	*KMC (n = 396 randomized, 364 analyzed for mortality, 343 analyzed for hospital length of stay):* Firm skin-to-skin contact to mother's chest was maintained 24 hours a day with infants in a strict upright position. Breastfeeding was done regularly; premature formula supplements were administered if necessary. *Control (n = 381 randomized, 345 analyzed for mortality, 320 analyzed for hospital length of stay):* Infants were kept in an incubator until they were able to regulate temperature and were thriving. Parents' access to them was severely restricted.	• Medically stable upon entry into study. • No statistically significant difference between the two groups in terms of pregnancy, maternal, and infant demographic characteristics.	• Mortality • Infant growth • Length of hospital stay • Infection • Breastfeeding • Mother-infant attachment • Neurodevelopmental disability, and social and home environment
Charpak, 2001 Single-center RCT (n = 663)	*Inclusion:* Regardless of actual weight or gestational age, infants became eligible as soon as they overcame major problems of adaptation to extrauterine life, had any infection or concomitant condition treated properly, started sucking and swallowing properly, and had daily weight changes appropriate for gestational and chronological age. *Exclusion:* Referral of infants to another institution, parent/s with plans to leave Bogotá in the near future, lethal or major malformations, early conditions arising from perinatal problems (e.g., severe hypoxic ischemic encephalopathy, pulmonary hypertension), and parental or family refusal to comply with the follow-up program or with the (KMC) intervention.	*KMC (n = 339):* Infants were kept in an upright position, in skin-to-skin contact, firmly attached to the mother's chest for 24 hours a day. They were breastfed regularly; premature formula supplements were likewise given if necessary, to guarantee adequate weight gain. They were examined daily until they had a weight gain of at least 20 g/day. *Control (n = 324):* Infants were kept in incubators until they could regulate their temperature and showed appropriate weight gain. While the infants were in the neonatal care unit, their parents' access to them was severely restricted. They were discharged when they weight approximately 1700 g.	• Medically stable upon entry into study. • Compared to CMC infants, KMC infants weighed significantly lighter at time of eligibility (1678 ± 226 g vs 1715 ± 228 g; p = 0.01) and at discharge from their respective treatment arms (1685 ± 216 g vs 1756 ± 190 g; p = 0.01).	• Morbidity • Mortality • Growth • Development • Breastfeeding • Hospital stay • Sequelae at 12 months of corrected age (cerebral palsy, psychomotor delay, visual or hearing impairment)
Fortifaes, 2017 Single-center RCT (n = 100)	*Inclusion:* Birthweight 1500-2500 g; APGAR score >5 at 1 minute of life; placed on NIPPV; physiologically stable (no desaturations, apnea, bradycardia, tachycardia, hypothermia, hyperthermia, cyanosis) *Exclusion:* Presence of cardiac or surgical conditions; permanent neurologic abnormality affecting respiration (e.g., hydrocephalus, intraventricular hemorrhage, nerve injury); multiple congenital abnormalities	*KMC (n = 50):* Infants were placed in the kangaroo position on a parent intermittently for a minimum of 1 hour to maximum of 4 hours per session, to be done 3 to 4 times a day every day until they were weaned from NIPPV *Control (n = 50):* Infants wore a cap and diaper while placed in a bassinet. Thermoregulation was done using a droplight or application of plastic wraps as necessary.	• Medically stable on NIPPV. • The baseline maternal and neonatal characteristics were comparable on both groups.	• Physiologic parameters (heart rate, respiratory rate, oxygen saturation, temperature) • Hospital length of stay • Adverse events (hypothermia, hyperthermia, feeding difficulty, seizures, skin color changes) • Mortality

Table 2. Characteristics of Included Studies Comparing KMC and Conventional Care on Premature, LBW Infants *(continued)*

Study, Year, and Design (n)	Inclusion and Exclusion Criteria	Study Groups	Description of Infants Included in the Study	Outcomes Measured
Kadam, 2005 Single-center RCT (n = 89)	*Inclusion:* Infants with birth weight <1800 g, stable cardiopulmonary status, Apgar score ≥7 at 5 minutes, and on feeds (breastfeeding or spoon feeding of expressed breast milk) *Exclusion:* Sick and unstable infants; presence of major congenital malformations; refusal of parents to consent	*KMC (n = 44):* Infants kept in skin-to-skin contact between mother's breasts (minimum of 1 hour at a stretch, continued for as long as comfortable), in vertical position supported by dupatta cloth, with mothers seating in a semi-reclining position. Crossover to conventional care allowed in case of any problems that arose; infant transferred back to the KMC group after stabilization, and treatment continued thereafter until discharge. *Control (n = 45):* Infants kept in radiant warmers Handling of babies, diaper changes, and breastfeeding by mothers were allowed at any hour of the day in both groups.	• Medically stable upon entry into study. • No statistically significant difference between the two groups in terms of baseline characteristics.	• Mortality • Hypothermia • Hyperthermia • Sepsis • Apnea • Onset of breastfeeding • Duration of hospital stay • Weight at discharge
Kambarami, 1998 Single-center RCT (n = 74)	*Inclusion:* Preterms <7 days old, birth weight <1600 g, able to suck; mothers willing to participate in the study. Singletons only. *Exclusion:* Twin births, presence of major congenital anomalies, recovery from major illness	*KMC (n = 37):* Infants, wearing only a nappy, in skin-to-skin contact between mother's breasts in an upright position. A cover was put around mother and infant. KMC was carried out in a 12-bed KMC unit. All infants were entirely breastfed. *Control (n = 37):* Infants were placed in incubators and received standard care. They were fed either formula or breast milk, or both. When incubators were overcrowded, some infants in this group were moved onto cots to make room for sicker infants requiring incubators. They were then returned to the incubators as soon as they became available again.	• Medically stable upon entry into study. • Median weight study entry: 1460 g (range 1400–1545 g) for KMC group vs 1400 g (range 1260–1450 g) for CMC group (p = 0.004) • Median age on study entry: 5 days (range 4–7 days) for KMC group vs 3 days (range 1–6 days) for CMC group (p = 0.002)	• Mean daily weight gain • Incidence of intercurrent illness in hospital • Mean duration of hospital stay • Survival
Luistro, 2014 Single-center RCT (n = 70)	*Inclusion:* Preterm neonates (<36 weeks) admitted at the neonatal intensive care unit weighing 1000–2000 g, with Apgar score >7 at the first and fifth minute of life and requiring RAM cannula CPAP support due to respiratory distress. *Exclusion:* Babies with major congenital abnormalities, especially facial and gastrointestinal anomalies. Pediatric aging below 28 weeks and birth weight <1000 g were likewise excluded.	*KMC (n = 35):* KMC was done to all participants starting at 24 hours of life intermittently for 4 hours daily until they are discharged. *Control (n = 35):* The participants in the control group were donned with a cap and diaper, were placed inside an incubator and were given conventional care.	• Infants requiring RAM cannula CPAP support due to respiratory distress upon entry into study • Proportion of obstetric comorbidities: 16 (45.71%) with KMC group vs 8 (22.86%) with CMC group (p = 0.04) • Apgar score at 1 minute: 8.83 ± 0.51 for KMC group vs 8.37 ± 1.19 for CMC group (p = 0.04)	• Length of RAM cannula CPAP use • Length of oxygen support • Morbidity • Mortality • Sepsis • Length of hospital stay
Mwendwa, 2012 Single-center RCT (n = 166)	*Inclusion:* Medically stable LBW infants with birth weights of 1000–1750 g *Exclusion:* None stated	*KMC (n = 85):* KMC was practiced over an 8-hour period per day *Control (n = 81):* Infants remained in incubators or cots Mothers in both groups were encouraged to breastfeed, or feed expressed breast milk to their babies. Supplementation with infant formula was used when mothers were not producing enough breast milk.	• Medically stable upon entry into study. • Median maternal age: 26 years (range 17–34 years) for KMC group vs 24.5 years (range 15–33 years) for CMC group (p = 0.04).	• Weight • Head circumference • Mid-upper arm circumference • Major illness • Duration of stay

Table 2. Characteristics of Included Studies Comparing KMC and Conventional Care on Premature, LBW Infants *(continued)*

Study, Year, and Design (n)	Inclusion and Exclusion Criteria	Study Groups	Description of Infants Included in the Study	Outcomes Measured
Rao, 2008 Single-center RCT (n = 206)	*Inclusion:* Singleton infants with birth weight <2000 g *Exclusion:* Critical illness in infant, requiring ventilatory or inotropic support; presence of chromosomal and life-threatening congenital anomalies; infants requiring transfer, or whose mothers were critically ill or unable to comply with the follow-up schedule	*KMC (n = 108):* Infants kept in skin-to-skin contact in semi-upright position using a "kangaroo bag" made of soft flannel cloth. Mothers were encouraged to keep infant in this position as long as possible during the day and night, for a minimum period of 1 to 2 hours at a time. When not in KMC, infants were placed under a servo-controlled radiant warmer or in a cradle under a hot lamp, clothed and covered. *Control (n = 112):* Infants were placed under a servo-controlled radiant warmer or in a cradle under a hot lamp in the NICU adequately clothed and covered.	• Medically stable upon entry into study. • Age at enrollment: 3.7 ± 2.8 days for KMC group vs 2.3 ± 1.9 days for CMC group (p <0.01) • Weight at enrollment: 1607.6 ± 278 for KMC group vs 1690.5 ± 273 g, for CMC group (p = 0.03) • Gestational age: 35.3 ± 2.3 weeks for KMC group vs 35.9 ± 2.1 weeks for CMC group (p = 0.05)	• Gain in weight, length, head, chest, mid-arm circumference, and foot length • Mortality • Morbidity • Duration of hospital stay
Rojas, 2003 Single-center RCT (n = 60)	*Inclusion:* Hemodynamically stable infants with birth weight <1501 g, gestational age ≤32 weeks, with minimal ventilatory support or extubated on nasal CPAP or nasal cannula *Exclusion:* Maternal age <18 years, maternal history of illicit drug use during pregnancy, clinical evidence of perinatal asphyxia, potential transfer within the first month after birth, presence of major congenital abnormalities, planned adoption, Grade III or IV intraventricular hemorrhage, fetal growth restriction, or suspected sepsis	*KMC (n = 33):* Infants (who wore only a diaper, with their backs were covered with a blanket) were held in a prone semi-upright position at approximately a 45° angle, in direct skin-to-skin contact with the parent's chest. *Control (n = 27):* Infants in this group received conventional care. Parents were allowed to remove them from the incubator and held them in their arms in supine position with eye-to-eye contact. Infants wore diapers and T-shirts and were wrapped in a blanket.	• Medically stable upon entry into study. • No statistically significant difference between the two groups in terms of baseline characteristics.	• Weight gain • Head circumference growth Breastfeeding • Length of hospital stay • Mortality • Occurrence of sepsis, necrotizing enterocolitis, intraventricular hemorrhage
Sloan, 1994 Single-center RCT (n = 300)	*Inclusion:* Singleton infants weighing < 2000 g with acceptable food tolerance; no serious congenital abnormalities; no respiratory, metabolic, or infectious disease. Infants' temperature had to be stabilized between 36.5°C and 37.0°C for 24 hours before enrollment. *Exclusion:* None stated	*KMC (n = 140):* Infants were kept in an upright position, in skin-to-skin contact against the mother's breasts and were frequently breastfed. Infants were allowed to wear diaper. *Control (n = 160):* Infants were kept in incubators or thermal cribs and were breastfed at scheduled times	• Medically stable upon entry into study. • No statistically significant difference between the two groups in terms of baseline characteristics.	• Illness severity (severe: lower respiratory tract disorder, apnea, aspiration, pneumonia, septicemia, general infection; moderate: urinary tract infection; mild: upper respiratory tract disorder, dermatitis, jaundice, hip displacement) • Diarrhea • Weight gain, length gain, upper arm and head circumference gain • Post-eligibility mortality • Hospital length of stay (only the difference between groups reported) • Re-admission, Costs of care

Table 2. Characteristics of Included Studies Comparing KMC and Conventional Care on Premature, LBW Infants *(continued)*

Study, Year, and Design (n)	Inclusion and Exclusion Criteria	Study Groups	Description of Infants Included in the Study	Outcomes Measured
Tessier, 2003 Single-center RCT (n = 336)	*Inclusion:* Birth weight <2000 g, mother or relative understand and willing to follow instructions *Exclusion:* Infant referred to another institution, had lethal or major malformations, had sequelae from perinatal problems, abandoned or given up for adoption	*KMC (n = 183):* Infants were maintained in kangaroo position continuously, 24 hours a day, until they manifest behaviorally that they are ready to be separated, usually around 37–38 weeks of gestational age. Other carers (i.e., the father and grandmother) were allowed to alternate with the mother in providing skin-to-skin contact. Besides breastmilk, infants may receive preterm formula and vitamin supplements when necessary *Control (n = 153):* Infants were kept in incubators until they could self-regulate their temperature and had appropriate weight gain. Mothers were encouraged to breastfeed their infants as soon as possible.	• Medically stable upon entry into study. • No statistically significant difference between the two groups in terms of baseline characteristics.	• This study is part of the RCT by Charpak et al. (1997). Besides outcomes measured for that particular RCT, developmental scores (Griffiths) at 12 months were likewise measured.
Whitelaw, 1988 Single-center RCT (n = 71)	*Inclusion:* Infants with birth weight <1500 g, having stable breathing with no oxygen requirement, and with ≥1 parent speaking fluent English. *Exclusion:* Presence of congenital malformations (e.g., hydronephrosis or scoliosis), or intracranial lesions (e.g., periventricular leukomalacia, ventricular dilatation)	*KMC (n = 35):* Infants were kept in an upright position, in skin-to-skin contact between the mother's breasts, with a cardiac or respiration monitor attached. *Control (n = 36):* Mother was encouraged to visit as much as she liked and helped to take her baby out of the incubator for a cuddle. However, baby and mother remained clothed.	• Medically stable upon entry into study. • No statistically significant difference between the two groups in terms of maternal and infant baseline characteristics.	• Breastfeeding • Infant's behavior at 6 months of age (hours sleeping, feeding, being held, playing per day, minutes crying per day) • Mother's feelings about the infant at discharge and at 6 months of age
Worku, 2005 Single-center RCT (n = 165)	*Inclusion:* Birth weight <2000 g; singletons only, unless 1 of the twins died; no major congenital malformations; mother healthy and willing to participate *Exclusion:* None stated	*KMC (n = 62):* Continuous skin-to-skin contact between mother and infant starting during the first 24 hours of life. The mother kept her newborn infant between the breasts, in close contact with her body and covered with her clothes day and night. Breastfeeding was the standard feeding method, but the mother can also feed her baby with formula milk using tube or cup when needed. *Control (n =61):* Routine care offered in the neonatal unit to LBW infants, which included an artificial warming system (heated room overhead lamp warmers), oxygen therapy, breast, tube, cup, or mixed feeding.	• Medically unstable infants allowed to be recruited into the study. • The demographic and socioeconomic characteristics for both groups are comparable.	• Death • Serious illness (sepsis, diarrhea, pneumonia, aspiration, pneumonia) • Mothers' feeling about the method of care

(Acharya, Cattaneo, Sloan, and Worku). Random allocation was carried out in 7 RCTs using brown, numbered, or sealed envelopes (Baton, Fortifaes, Kadam, Luistro, Rao, Rojas, and Whitelaw), while block randomization was done in the RCTs by Charpak, Tessier, and in the Yogyakarta arm of the multi-country RCT by Cattaneo. On the other hand, Kambarami et al. openly stated in their study that their infants were allocated consecutively without any concealment. Since consecutive allocation invariably does not reflect any randomization, there is a substantial risk that the resultant comparator groups would be significantly heterogeneous in terms of both measured and unmeasured confounders. In Mwendwa's study, details on the method of allocation were not explicitly described and only mentioned randomization to each group.

Blinding (performance bias and detection bias)

Due to the nature of the intervention (KMC), patient blinding is not possible in all the included studies. Furthermore, blinding of the assessor was not done in the 4 included studies. In the remaining 12 studies, it was not explicitly mentioned whether the assessors were blinded or not.

Incomplete outcome data (attrition bias)

The outcomes of interest were ascertained in all infants in most of the included studies, except for Rao et al. and Tessier et al. The former reported losses to follow-up of 11 and 38 in the KMC and control groups, respectively. Comparably, with Tessier et al., 32 and 30 infants (KMC and control groups, respectively) were pulled out from the study by their mothers. For both of these studies, reasons

for these losses/dropouts were not disclosed, with these losses/dropouts likely to influence the final results.

On the other hand, Worku reported in their study that 91% and 88% of babies in the KMC and control groups, respectively, were discharged from the study during the first 7 days of life. It is unclear, however, whether the total number of infants used to compute the percentage for each group excluded the mortalities or not. It was likewise not explicitly mentioned if any outcome was ascertained with the remaining 9% of the infants in the KMC group and the remaining 12% in the control group.

Selective reporting (reporting bias)

Although Worku intended and designed their study as an RCT to compare the effectiveness of KMC compared to conventional care, it was unclear what parameters they based effectiveness on. Similarly, outcomes of interest were not clearly defined in their methodology, with infant mortality as the only outcome reported per study group in the results. For that matter, we assess this study to have a substantial risk of selective reporting bias.

For all other studies, their outcomes of interest were pre-specified and comprehensively reported in their results. Only the studies by Charpak et al. (1997, 2001) performed an intention-to-treat analysis.

Other potential sources of bias

Studies that were deemed to have an unclear risk for other biases are those that either had significant differences in baseline characteristics between-participant study groups (Acharya, Charpak [2001], Cattaneo, Kambarami, Luistro, and Rao reported significant differences in birthweight between study groups) or failed to include key baseline characteristics that may be associated with the outcomes of interest (Kadam did not include maternal baseline characteristics); and those that either did not provide statistical bases for their sample sizes (Acharya, Cattaneo, Kadam, Kambarami, Mwendwa, Rojas, Sloan, Tessier, and Worku) or had sample sizes that were found to have underpowered their respective studies on posthoc power analysis (Rojas and Sloan).

Publication bias (Figure 3)

On visual inspection, the funnel plot appears symmetrical; albeit intuitive and subjective, this indicates an absence of publication bias. The Egger test, which regresses the included studies' standardized effect sizes on their standard errors, was performed additionally to objectively assess for any publication bias. It tests the null hypothesis that no small-study effects (i.e., no indications of publication bias) are present. Yielding a p-value of 0.868, the Egger test showed no substantial evidence to claim that publication bias exists among the studies included in this review.

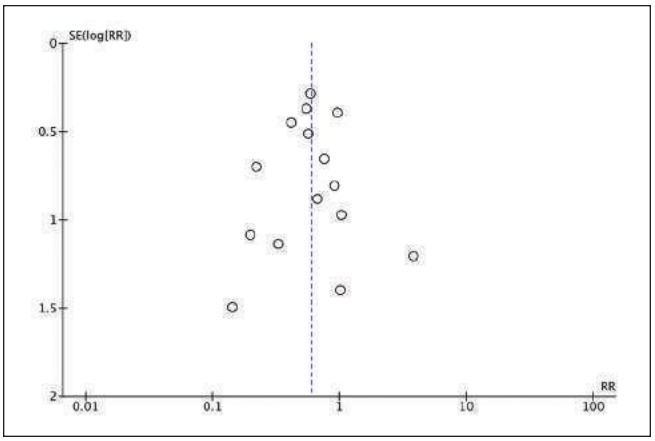

Figure 3. Funnel plot for studies reporting mortality.

Effects of interventions

Primary Outcome: In-hospital mortality

There was a significant reduction in the risk of dying by 41% among infants to whom KMC was rendered, compared with control (3.86%% vs 6.87%; RR = 0.59, 95% CI 0.44, 0.79; I^2 = 0%; number needed to treat for additional benefit (NNTB) = 34; 16 RCTs; 3,412 infants). Of note, Acharya did not have any mortalities in both groups because no sick babies were included at the beginning of the study (Figure 4).

Income category of the country of birth

In a subgroup analysis of in-hospital mortality based on the economic status or income category of the country of birth, only two studies were classified under the high-income country (HIC) subgroup. There was a low pooled sample of 131 and thus, the confidence interval of the diamond was wide and crossed the line of no significance (KMC: 5.88% vs CMC: 4.76%; RR = 1.24, 95% CI 0.28, 5.42; I^2 = 0%; 2 RCTs; 131 infants). However, in RCTs carried out in low to middle income countries (LMIC), there was a significant reduction in mortality among infants on KMC compared with controls (3.77% vs 6.95%; RR = 0.57, 95% CI 0.43, 0.77; I^2 = 0%; NNTB = 32; 14 RCTs; 3281 infants). Again, Acharya did not have any mortalities for both groups so that there was no estimable measure of association for this study (Figure 5).

Gestational age

In the subgroup analysis on gestational age, only 15 RCTs were analyzed, since Kambarami's study did not have information on the AOG of the infants. For both groups, the estimates are consistently on the side favoring KMC. However, the ≥ 34-week-AOG subgroup's pooled estimate did not reach statistical significance (KMC: 3.48% vs CMC: 5.34%; RR = 0.7, 95% CI 0.43, 1.13; I^2 =0%; 5 RCTs; 1543 infants). Among infants < 34 weeks, there was a significant reduction in mortality among those who were provided KMC compared with control (KMC: 4.32%

vs CMC: 8.17%, RR = 0.55, 95% CI 0.38, 0.79; I^2 = 0%; NNTB = 26; 10 RCTs; 1795 infants) (Figure 5).

Birth weight

In the subgroup analysis on birth weight, a 40% reduction in the risk of dying (KMC: 3.97% vs CMC: 6.83%, RR = 0.60; 95% CI 0.45, 0.82; I^2 = 0%; NNTB = 35; 10 RCTs; 2960 infants) was demonstrated among infants belonging to the ≥ 1500 g subgroup who were provided KMC. Similarly, the pooled estimate for the < 1500 g subgroup was on the side favoring KMC, but it did not reach statistical significance. Again, this could be due to the much smaller sample size of this subgroup (n=452) compared with the bigger infants (n=2960). If both subgroups had comparable sample sizes, they would most probably have the same point estimate (Figure 5).

Medical stability

Among infants who were medically stable, there was a significant reduction in the risk of dying by 38% among those receiving KMC (KMC: 2.98% vs CMC: 5.22%; RR = 0.62; 95% CI 0.43, 0.89; I^2 = 0%; NNTB = 45; 11 RCTs; 3025 infants). Analysis was also done among infants assessed to be medically unstable (intubated [Baton]; requiring nasal CPAP [Luistro]; requiring NIPPV [Fortifaes]; on minimal ventilatory support, and if extubated, on CPAP/O_2 support [Rojas]; on oxygen or IV support [Worku]), which likewise showed a significant reduction in

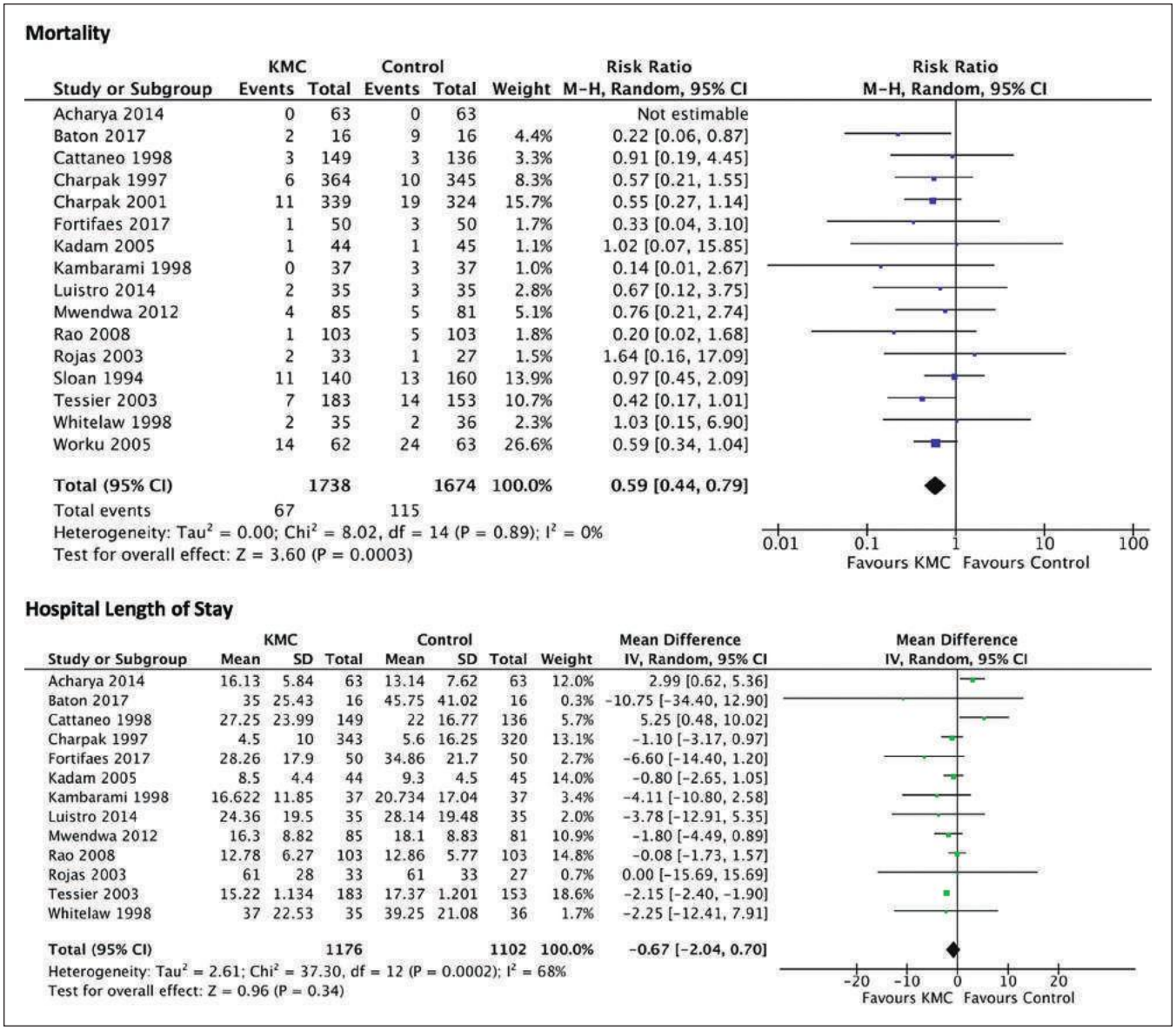

Figure 4. Forest plots for the outcomes of interest (infant mortality reported as risk ratios, and hospital length of stay reported as risk differences).

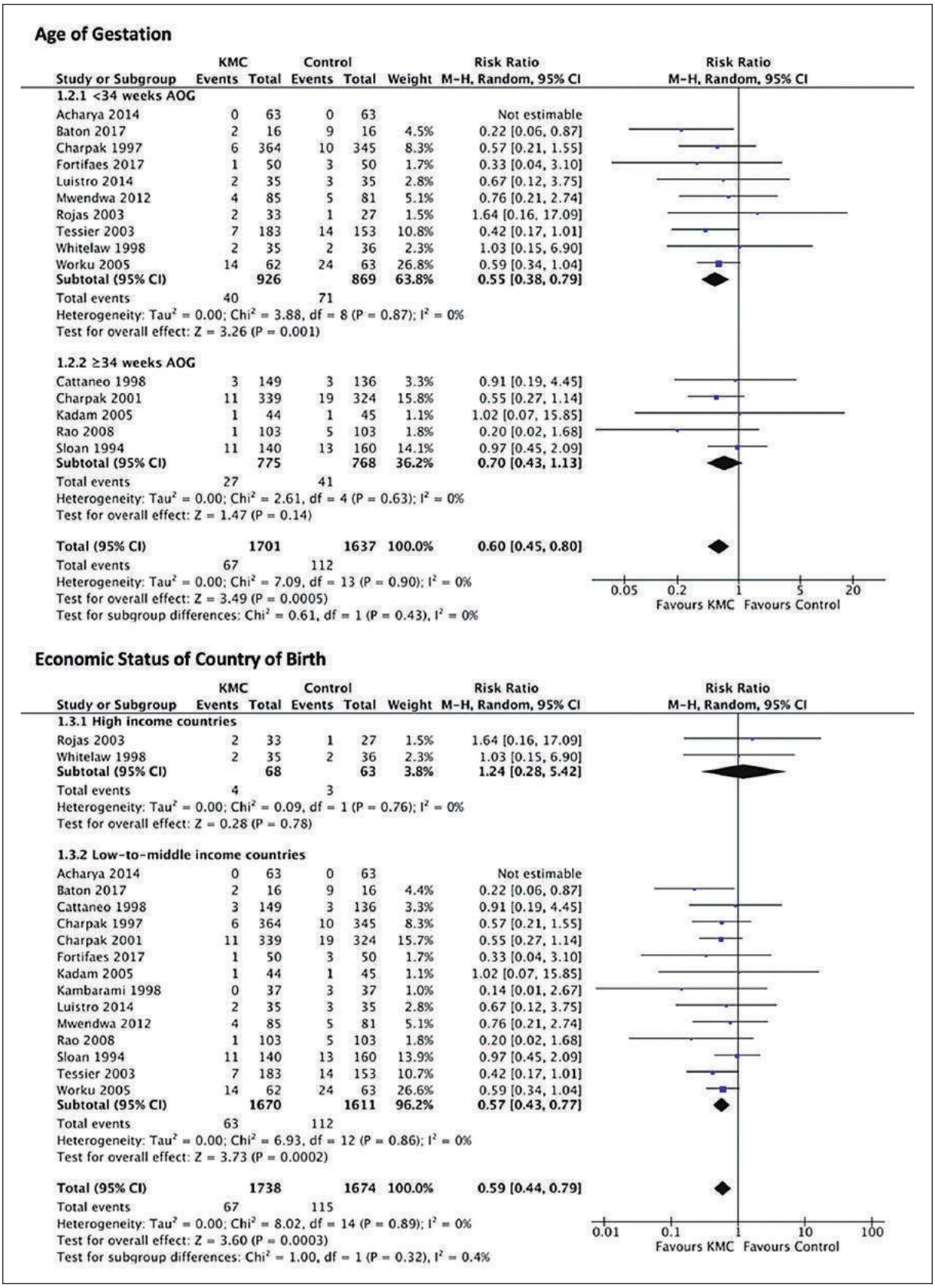

Figure 5. Forest plots for the subgroup analyses on infant mortality (age of gestation, economic status of country of birth, birthweight and medical stability).

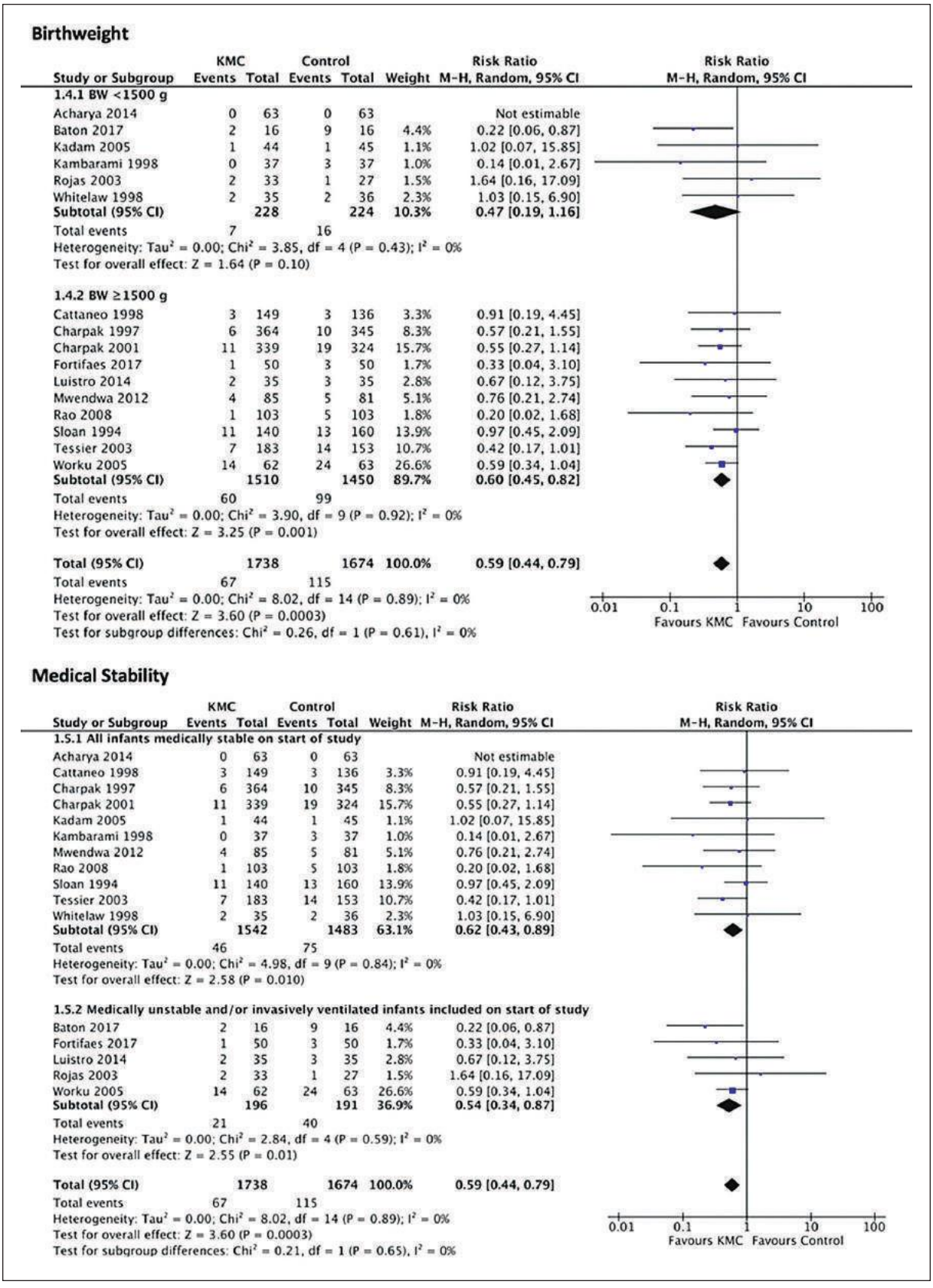

Figure 5. Forest plots for the subgroup analyses on infant mortality (age of gestation, economic status of country of birth, birthweight and medical stability). *(continued)*

the risk of dying by 46% in favor of those rendered KMC compared with the control group (KMC: 11.05% vs CMC: 20.94%; RR = 0.54; 95% CI 0.34, 0.87; I^2 = 0%; NNTB = 11; 5 RCTs; 387 infants) (Figure 5).

Secondary Outcome: Hospital Length of Stay

Of the 16 studies included, only 13 had data on hospital length of stay (HLOS). Charpak (2001) did not report the mean and standard deviation of HLOS for each intervention group but instead reported the mean HLOS by birthweight classifications with age-corrected to term, 3, 6, and 9 months. The study of Samra reported NICU length of stay rather than the total HLOS. Sloan merely reported the mean difference of 2 days between intervention groups with a longer stay among those on KMC, without providing information on means and standard deviations. Some of the studies included in this analysis reported median and range (Baton, Cattaneo, Kambarami, and Whitelaw). In such cases, the mean and standard deviation were estimated based on the method devised by Hozo, Djulbegovic, and Hozo.[29]

For studies that reported mean and range instead of standard deviation (Charpak, 1997), the standard deviation was estimated by using the formula: (max-min)/4. For studies that reported mean and interquartile range (IQR) instead of standard deviation (Kambarami), the standard deviation was estimated by using the formula: $(Q_3 - Q_1)/1.35$. For studies that reported mean and sample size but no standard deviation (Tessier), the pooled standard deviation was computed instead. Overall, the pooled estimated did not reach statistical significance (mean difference: –0.67; 95% CI –2.04, 0.70; p = 0.34). Of note, the I^2 statistic is quite high (68%), warranting subgroup analysis to explain this heterogeneity (Figure 4).

Income category of country of birth

The respective pooled estimates of infants born in HIC and LMIC did not reach statistical significance, although infants born in LMIC have a tendency towards benefit. However, the I^2 in the LMIC subgroup is higher than the overall I^2 at 68%. Therefore, this particular subgroup analysis did not explain the heterogeneity between studies (Figure 6).

Gestational age

Kambarami did not have any information on the age of gestation. Thus, only 12 studies were included in this subgroup analysis. Point estimates of the pooled effects of the subgroups were divergent (one on each side of the null value of 0). The <34-week-AOG subgroup pooled estimate suggested a tendency towards benefit but was not statistically significant. Moreover, I^2 values remained high, indicating that this subgroup analysis did not explain the heterogeneity from earlier (Figure 6).

Birth weight

The ≥ 1500-g birth weight subgroup appeared to be at an advantage in terms of having shorter HLOS compared to the <1500-g subgroup, though this was not statistically significant. Furthermore, this subgroup analysis did not explain the high I^2 from the overall analysis on the effect of KMC on HLOS (Figure 6).

Medical stability

There was a tendency towards a shorter HLOS among medically unstable infants treated with KMC, though this was not statistically significant. Notable also was that the I^2 was 0% for this subgroup. KMC could have a potential for a shorter HLOS among infants who were medically unstable upon NICU admission (Figure 6).

RESULTS AND DISCUSSION

Sixteen trials comparing the effect on in-hospital mortality of infants who were provided KMC versus control among 3,412 LBW or preterm infants showed a significant reduction in the risk of dying by 41%. Similarly, the reduction in the risk of dying among those on KMC was 40% in the updated 2016 meta-analysis by Conde-Agudelo[8] and 36% in the 2016 meta-analysis by Boundy.[25] This meta-analysis showed a larger reduction in the risk of dying among KMC infants in low-to-middle income countries at 43%, compared to 35% in the 2016 meta-analysis by Conde-Agudelo. This meta-analysis likewise included a set of subgroup analyses based on gestational age, showing a significant reduction in mortality among infants less than 34 weeks AOG. Of note as well, KMC infants with birthweight ≥ 1500 g had a significant reduction in mortality compared to lighter infants. This may be due to lighter infants having more preterm comorbidities compared with slightly heavier ones. An important finding in this review was the significant reduction in the risk of dying by 44% with a low number needed to treat at 11.

KMC has been found to significantly reduce the risk of sepsis and hypothermia, as well as increase breastfeeding success. All these KMC benefits contribute to the overall reduction in neonatal mortality. However, despite the solid evidence shown by several studies on the benefits of KMC, uptake of the program is still far from ideal. Every Newborn Tracking Tool maps the coverage of four essential newborn care interventions, namely antenatal steroids, resuscitation, management of sepsis, and KMC. Sadly, only 11 out of 51 countries include KMC in their health management information system.[30]

Most notable in this meta-analysis was the reduction in the risk of dying when KMC is provided to medically unstable infants requiring respiratory support ranging from oxygen administration via nasal cannula to invasive positive pressure ventilation. As pointed out earlier, the number

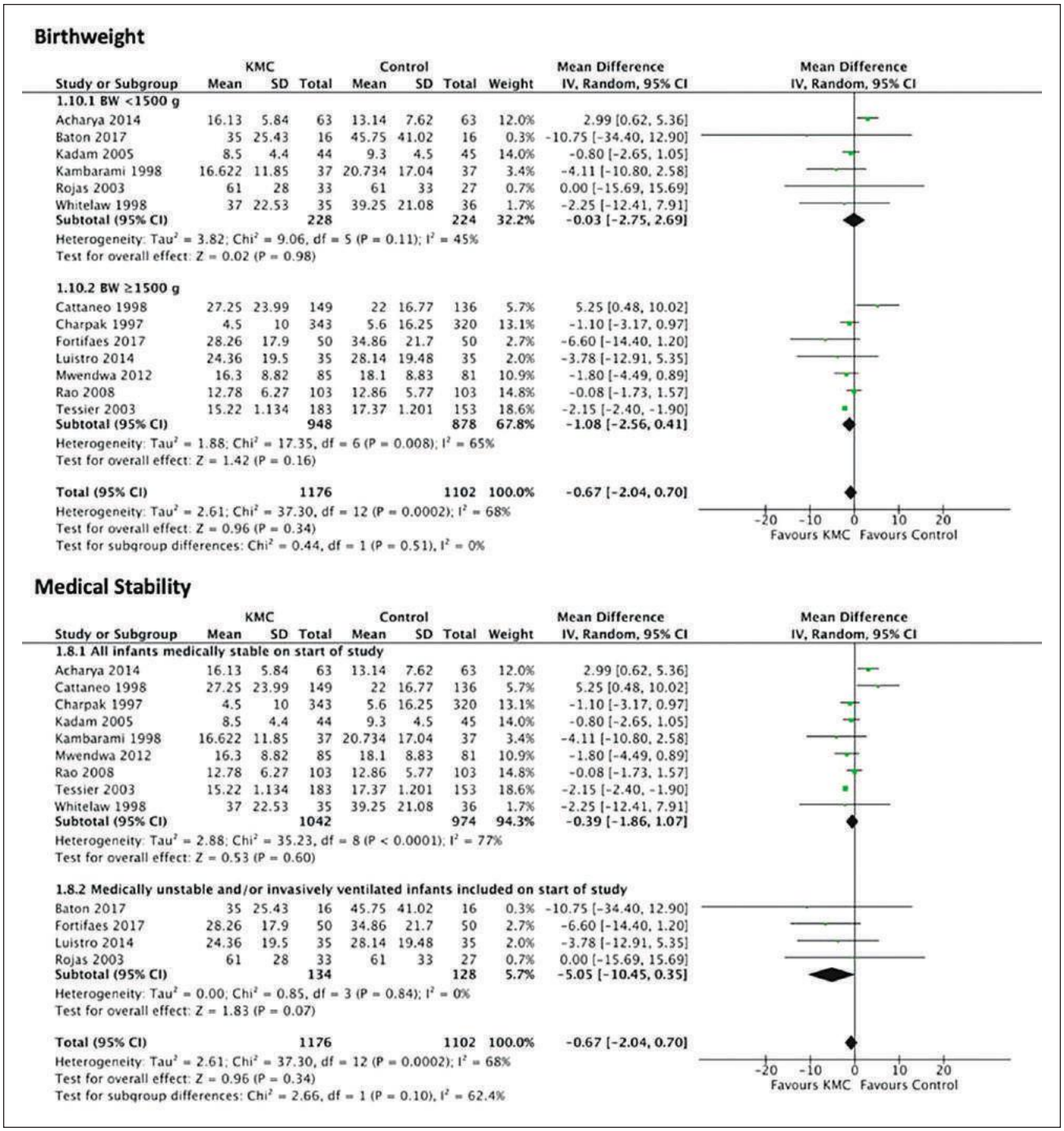

Figure 6. Forest plots for the subgroup analyses on hospital length of stay (age of gestation, economic status of country of birth, birthweight and medical stability).

needed to treat among these infants was the lowest in this review, at 11. These findings should encourage better uptake of the KMC program not only among stable preterm or LBW infants but also among the sicker ones who could potentially benefit from this more. WHO recommends scaling up KMC programs, commencing at birth and continuing well into the period when the infant is already at home. This would mean an earlier start and a longer duration of KMC among infants who have respiratory distress at birth. In the study by Morgan et al., the mothers were agreeable to start the KMC in the first 24 hours. Other identified factors that are believed to significantly improve uptake

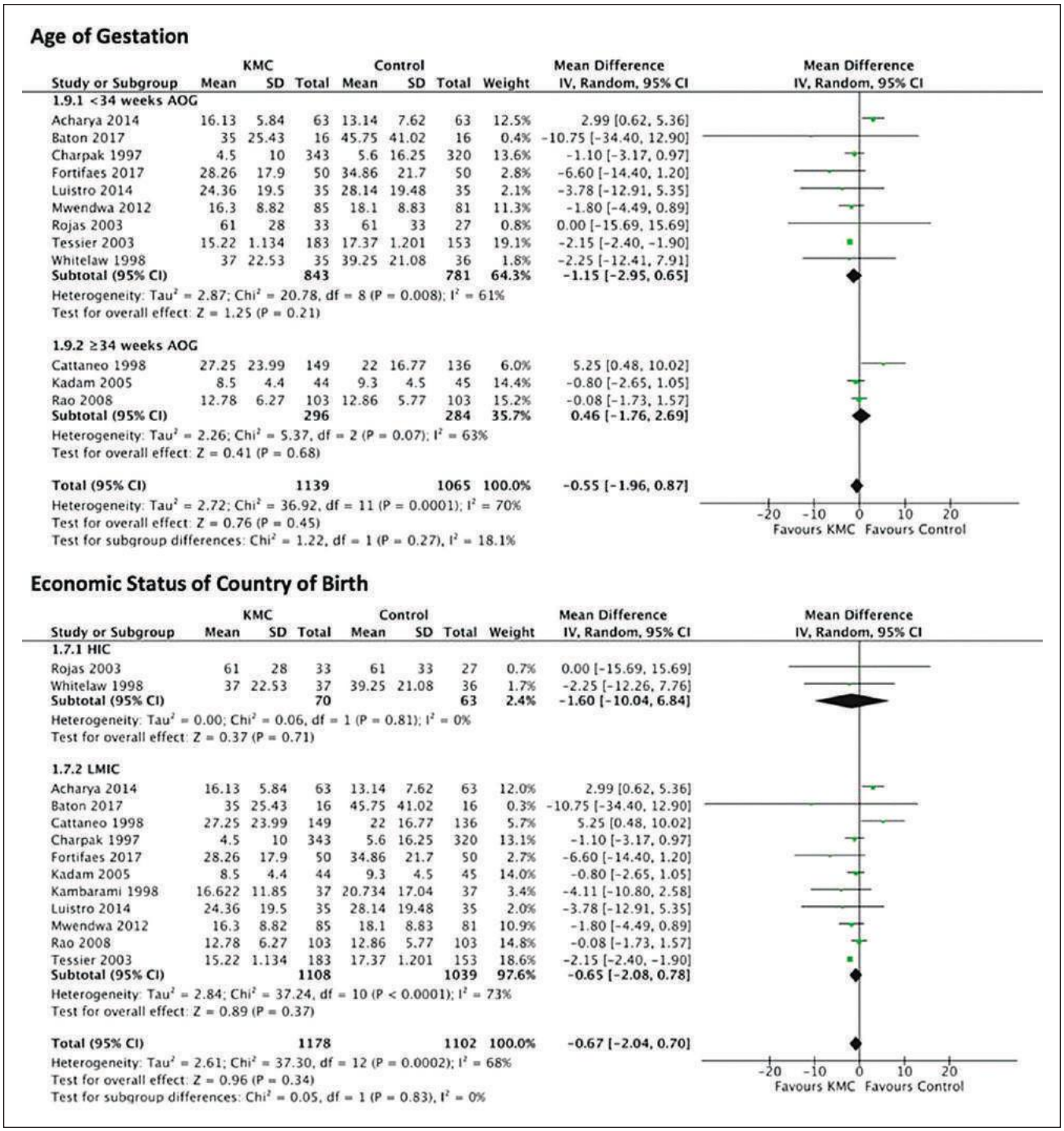

Figure 6. Forest plots for the subgroup analyses on hospital length of stay (age of gestation, economic status of country of birth, birthweight and medical stability). *(continued)*

of the KMC program are improvement of the following: knowledge about KMC in the family and the community, staff counseling, infant monitoring, and family support. Conversely, barriers to universal KMC uptake that need to be overcome are: stigmatization of preterm birth, poor infant monitoring, lack of family support, finances and time away from work, lack of beds and spaces for KMC in the NICU, and lack of KMC education.[26]

In this meta-analysis, an assessment of the duration of hospitalization among infants provided KMC was performed. HLOS as an outcome measure was used as a surrogate to faster improvement or recovery from preterm

or LBW complications, ultimately leading to better survival. Analysis of the pooled estimates showed no difference in the length of hospital stay between infants provided KMC and those who were not. A possible reason for this is that not all of the studies included in this review that report in-hospital mortality as outcomes likewise report HLOS. Per the criteria for studies to be included in this meta-analysis, the primary outcome is in-hospital mortality; data on length of hospital stay were extracted only from the already-included studies, even though there were more RCTs on KMC that were retrieved on an initial search that report length of hospital stay. Overall, only 13 out of the 16 included studies reported length of hospital stay. There were trends towards a shorter hospital stay among infants in the KMC group who were younger albeit heavier, unstable, and born in LMIC; these were the same subgroups found to have a significant reduction in in-hospital mortality in this meta-analysis. If studies that did not report in-hospital mortality but reported HLOS were allowed to be included in the analysis, this could have possibly led to pooled estimates that would demonstrate findings of a significant reduction in hospital stay in the KMC group. Another possible reason for the finding of no difference in the length of hospital stay between the KMC and the control groups might be that the infants in the control group who survived tended to be more stable, bigger, and physiologically more mature so that their hospital stay was generally shorter. On the other hand, the infants who survived in the KMC group were found to be younger (albeit relatively heavier) and more clinically unstable; such characteristics inadvertently translated to having a longer hospital course. A third possible reason was that since the majority of (medically unstable premature and LBW) infants would tend to die during the first week of life,[3] a technically shorter length of hospital stay would be recorded. Since the control group overall reported more infant deaths compared to the KMC group, an overall shorter HLOS spuriously resulted.

Overall completeness and applicability of evidence

Besides the differences mentioned previously under the section of 'Other potential sources of bias,' the study participants in both treatment groups among the RCTs included generally had comparable baseline characteristics. All outcome measures were analyzed and presented. The results of this review applied to the different subgroups included in the trials.

Quality of the evidence

All the included studies, which were of the randomized controlled trial design, were individually appraised by two authors. Recommended methods of allocation concealment (i.e., block randomization, use of opaque brown envelopes, use of random number tables) were noted with the included studies, except for the RCT by Kambarami, which allocated their study participants via alternation. Due to the nature of the intervention (KMC), blinding was not possible. Although outcome assessors in the studies included were also not blinded, the outcomes of interest in this meta-analysis (in-hospital mortality and HLOS) were hard objective outcomes that are easy to ascertain.

The overall quality of evidence for outcomes in this review was considered moderate.

Potential biases in the review process

The eligibility and exclusion criteria in all RCTs were both specified. There was a systematic and comprehensive search strategy used in the identification and retrieval of pertinent studies included in this review. The authors reviewed the articles and extracted data independently. Any disparity was resolved through consensus.

Agreements and disagreements with other studies or reviews

This review added three local clinical trials. The magnitude of the reduction in mortality among the KMC infants found in this meta-analysis was similar to those seen in the reviews by Conde-Agudelo[8] and Boundy.[25] Similar to the meta-analysis by Conde-Agudelo, there was also a significant reduction in mortality among KMC infants in low-to-middle income countries. In addition, this review analyzed the effect of KMC on mortality according to subgroups of gestational age and infant birth weight. Furthermore, this meta-analysis reported a significant reduction in the risk of dying among medically unstable infants.

CONCLUSIONS

Implications for practice

This review demonstrated that there was a significant reduction in mortality by 41% among infants who were rendered KMC. Furthermore, there was also a significant benefit of KMC among younger infants and those born in low-to-middle income countries. More importantly, this review demonstrated the medically unstable infants (i.e., requiring respiratory support) significantly benefitted from KMC.

Implications for research

Due to the findings of benefit among younger and medically unstable preterm infants, further studies on these subgroups of preterm and LBW infants should be undertaken. Assessment of the implementation of scaled-up KMC programs that start from birth would further provide evidence of KMC's benefit. Additionally, long-term outcomes on neurologic development and catch-up growth would also be important to pursue.

Statement of Authorship

This meta-analysis was principally conceived by EVU and MVH as part of their requirement in their Masters'

class. Both likewise conducted the search process. EVU excluded duplicate articles. EVU and MVH independently reviewed the full text of the remaining articles to determine their eligibility based on the set inclusion criteria. SLM was the third author to break the tie and resolve any disagreement. The PRISMA diagram was done by ESK.

Author Disclosure

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