# Determinants of Global Maternal and Neonatal Morbidity and Mortality

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Citable link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:16121139">http://nrs.harvard.edu/urn-3:HUL.InstRepos:16121139</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>
DETERMINANTS OF GLOBAL MATERNAL AND NEONATAL MORBIDITY AND MORTALITY

ELLEN O’NEAL BOUNDY

A Dissertation Submitted to the Faculty of
The Harvard T.H. Chan School of Public Health
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Science
in the Department of Epidemiology
Harvard University
Boston, Massachusetts.
May 2015
Determinants of Global Maternal and Neonatal Morbidity and Mortality

Abstract

In 2013, approximately 289,000 women died from pregnancy-related causes and 2.8 million newborns died within the first 28 days of life. The vast majority of these deaths occur in resource-limited settings. This work examines risk and protective factors for the development of several perinatal complications that put mothers and their infants at risk for adverse health outcomes. We explored determinants of preeclampsia and gestational hypertension among women in Dar es Salaam, Tanzania. We also examined the effects of pregnancy spacing intervals on perinatal outcomes in that group of women. We used log binomial regression to obtain risk ratios and 95% confidence intervals for the development of the adverse pregnancy outcomes of interest. We also looked at the efficacy of an intervention aimed at improving neonatal outcomes by conducting a systematic review and meta-analysis of the effects of kangaroo mother care on neonatal morbidity and mortality.

We found that nulliparity, history of hypertension, urinary tract infection, low calcium intake, history of preeclampsia, and history of preterm birth were associated with an increased risk of developing preeclampsia among women in Dar es Salaam. Risk factors for gestational hypertension included a history of diabetes, elevated blood pressure at study enrollment, increased mid-upper arm circumference, high hematocrit, low mean corpuscular volume, a history of miscarriage or stillbirth, and older age at first pregnancy. Twin gestation and increased body mass index were risk factors for both types of hypertensive disorders of pregnancy among women in Tanzania. After a live birth, inter-pregnancy intervals less than six months were associated with an increased the risk of having a low birth weight baby in the next pregnancy; while after a stillbirth, short inter-pregnancy intervals were associated with increased risk of stillbirth and perinatal death. Providing kangaroo mother care to infants after birth was associated with
decreased neonatal morbidity and mortality and increased likelihood of exclusive breastfeeding when compared to conventional care.

These findings can help identify women and infants at increased risk for developing pregnancy-related complications and contribute to informing development of evidence-based maternal, newborn, and family planning programs and policies.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Page</td>
<td>i</td>
</tr>
<tr>
<td>Abstract</td>
<td>ii</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>iv</td>
</tr>
<tr>
<td>List of Figures</td>
<td>vi</td>
</tr>
<tr>
<td>List of Tables</td>
<td>viii</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>x</td>
</tr>
</tbody>
</table>

## Body of Dissertation

### Paper One: Risk factors for hypertensive disorders of pregnancy among HIV-negative Tanzanian women: a prospective study

- Abstract: 2
- Background: 3
- Methods: 5
- Results: 9
- Discussion: 18
- References: 23

### Paper Two: Inter-pregnancy interval and perinatal outcomes among women in Dar es Salaam, Tanzania

- Abstract: 27
- Background: 28
- Methods: 30
- Results: 34
- Discussion: 42
- References: 45
Table of Contents (Continued)

Paper Three: Kangaroo mother care and neonatal outcomes: a systematic review and meta-analysis

Abstract.........................................................................................................................49
Background..................................................................................................................50
Methods.......................................................................................................................52
Results.........................................................................................................................55
Discussion....................................................................................................................71
References....................................................................................................................74

Supplementary Materials.............................................................................................88
Supplementary Figures (Paper Three)..........................................................................88
Supplementary Tables (Paper Three)........................................................................102
List of Figures

Paper Three: Kangaroo mother care and neonatal outcomes: a systematic review and meta-analysis

Figure 3.1 Flow diagram for identification of included studies........................................56

Figure 3.2 Forest plot for the effect of KMC compared to conventional care on mortality at latest follow-up time, grouped by follow-up time.................................................................65

Supplementary Figure 3.1 Forest plot for effect of KMC compared to conventional care on mortality at latest follow-up time, stratified by skin-to-skin contact initiation criteria........88

Supplementary Figure 3.2 Forest plot for effect of KMC compared to conventional care on mortality at latest follow-up time, stratified by skin-to-skin contact duration promoted, hours per day............................................................................................................................89

Supplementary Figure 3.3 Forest plot for effect of KMC compared to conventional care on exclusive breastfeeding at hospital discharge or 40-41 weeks post-menstrual age..........90

Supplementary Figure 3.4 Forest plot for effect of KMC compared to conventional care on infection, stratified by infection type........................................................................................................91

Supplementary Figure 3.5 Forest plot for effect of KMC compared to conventional care on mean heart rate, beats per minute.................................................................92

Supplementary Figure 3.6 Forest plot for effect of KMC compared to conventional care on mean respiratory rate, breaths per minute.................................................................93

Supplementary Figure 3.7 Forest plot for effect of KMC compared to conventional care on mean oxygen saturation, percent.................................................................94

Supplementary Figure 3.8 Forest plot for effect of KMC compared to conventional care on mean temperature, degrees Celsius.................................................................95

Supplementary Figure 3.9 Forest plot for effect of KMC compared to conventional care on mean length of hospital stay, days.................................................................96

Supplementary Figure 3.10 Forest plot for effect of KMC compared to conventional care on standardized mean weight gain.................................................................97
List of Figures (Continued)

Supplementary Figure 3.11 Forest plot for effect of KMC compared to conventional care on standardized mean pain score………………………………………………………………………………….98

Supplementary Figure 3.12 Risk of bias summary – randomized control trials………………….99

Supplementary Figure 3.13 Risk of bias summary – observational studies……………………100

Supplementary Figure 3.14 Funnel plot for effect of KMC compared to conventional care on mortality at latest follow-up time………………………………………………………………101
# List of Tables

## Paper One: Risk factors for hypertensive disorders of pregnancy among HIV-negative Tanzanian women: a prospective study

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Characteristics of study participants</td>
<td>10</td>
</tr>
<tr>
<td>1.2</td>
<td>Risk factors for preeclampsia</td>
<td>13</td>
</tr>
<tr>
<td>1.3</td>
<td>Risk factors for gestational hypertension</td>
<td>16</td>
</tr>
</tbody>
</table>

## Paper Two: Inter-pregnancy interval and perinatal outcome among women in Dar es Salaam, Tanzania

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Characteristics of participants at study enrollment, by last pregnancy outcome</td>
<td>35</td>
</tr>
<tr>
<td>2.2</td>
<td>Inter-pregnancy interval and perinatal outcomes among women with a live birth last pregnancy</td>
<td>36</td>
</tr>
<tr>
<td>2.3</td>
<td>Inter-pregnancy interval and perinatal outcomes among women with a stillbirth last pregnancy</td>
<td>39</td>
</tr>
</tbody>
</table>

## Paper Three: Kangaroo mother care and neonatal outcomes: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Characteristics of included studies</td>
<td>57</td>
</tr>
<tr>
<td>3.2</td>
<td>Relative risk (RR) and 95% confidence interval (CI) for the effect of KMC compared to conventional care on dichotomous neonatal outcomes</td>
<td>60</td>
</tr>
<tr>
<td>3.3</td>
<td>Mean difference (MD) and 95% confidence interval (CI) for the effect of KMC compared to conventional care on continuous neonatal outcomes</td>
<td>62</td>
</tr>
<tr>
<td>Supplementary 3.1</td>
<td>Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on mortality at latest follow-up</td>
<td>102</td>
</tr>
<tr>
<td>Supplementary 3.2</td>
<td>Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on exclusive breastfeeding during hospital stay or at 40-41 weeks post-menstrual age</td>
<td>105</td>
</tr>
</tbody>
</table>
Supplementary Table 3.3 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on infection…………………………………………………………108

Supplementary Table 3.4 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on heart rate, beats per minute……………………………………110

Supplementary Table 3.5 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on respiratory rate, breaths per minute……………………….112

Supplementary Table 3.6 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on oxygen saturation, percent……………………………………114

Supplementary Table 3.7 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on temperature, degrees Celsius……………………………………117

Supplementary Table 3.8 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on length of hospital stay, days……………………………120

Supplementary Table 3.9 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on weight gain, standardized mean difference………………….123

Supplementary Table 3.10 Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on pain score, standardized mean difference………………….126

Supplementary Table 3.11 Risk of bias for randomized control trials………………………128

Supplementary Table 3.12 Risk of bias for observational studies……………………………130

Supplementary Table 3.13 Studies included in kangaroo mother care systematic review and meta-analysis …………………………………………………………………………..132
Acknowledgments

I would like to express my appreciation and gratitude to my advisor, Dr. Stacey A. Missmer, for the mentorship and support she has given me all the way from my acceptance into the doctoral program in epidemiology through the completion of this degree. I would also like to thank my committee members, Drs. Wafaie W. Fawzi, Ellice Lieberman, and Donna Spiegelman for their insightful and pragmatic guidance in the development of this dissertation. Dr. Fawzi, your expertise in conducting global health research and translation of those findings to impact the public’s health is inspiring. I appreciate you kindly welcoming me into your research group. Dr. Lieberman, I have long admired your work in maternal and child health and feel fortunate for the opportunity to work with you on these projects and benefit from your perspective as a fellow clinician turned researcher. Dr. Spiegelman, learning from your wealth of knowledge in statistical and epidemiologic methods has been instrumental to my development into an epidemiologist, and I will carry those tools with me long into my career.

In addition, I would like to thank my other co-authors, especially Dr. Grace Chan, whose collaboration on the meta-analysis paper was invaluable. I would also like to thank my nurse-midwife colleagues at Mount Auburn Hospital for their encouragement and flexibility which enabled me to continue my clinical work while pursuing this degree.

Very special thanks go out my family and friends, each of whom has cheered me on in their own way and helped me keep perspective and a sense of humor throughout this process. In particular I want to thank my parents who have supported me through every crazy idea, twist, and turn I’ve had in my career and life paths. Finally, I want to express my deep appreciation for my husband, Chris, who I met during the first year of my doctoral program and who has been by my side supporting and encouraging me each and every step of the way since.
Risk factors for hypertensive disorders of pregnancy among HIV-negative Tanzanian women: a prospective study

Ellen Boundy,1 Donna Spiegelman,1,2 Ellice Lieberman,1,4 Stacey A. Missmer,1,5 Willy Urassa,6 Fadhlun M. Alwy,7 Wafaie Fawzi1,3,8

1Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
2Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
3Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
4Department of Pediatric Newborn Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, US
5Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA
6Department of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
7Department of Obstetrics and Gynecology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania
8Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
Abstract

Objective: Identify risk factors for hypertensive disorders of pregnancy among Tanzanian women

Design: Prospective cohort study

Setting: Dar es Salaam, Tanzania, 2001-2004

Population: 8311 pregnant HIV-negative women enrolled at 12-27 weeks gestational age

Methods: Multivariable relative risk regression models to examine risk factors for preeclampsia and gestational hypertension.

Outcome Measures: Risk ratios (RR) and 95% confidence intervals (CI) for preeclampsia and gestational hypertension, compared to women without any hypertensive disorder of pregnancy.

Results: Hypertensive disorders were identified in 7.2% of pregnancies. Twin gestation and increased body mass index were risk factors for both hypertensive disorders. Factors specific to preeclampsia included nulliparity (RR 1.71; 95% CI 1.03, 2.85), history of hypertension (RR 2.19; 95% CI 1.11, 4.31), urinary tract infection (RR 3.11; 95% CI 1.12, 8.65), low calcium intake (trend test p-value = 0.01), history of preeclampsia (RR 6.20; 95% CI 2.08, 18.49), and history of preterm birth (RR 2.60; 95% CI 1.03, 6.56). For gestational hypertension alone, risk factors included history of diabetes (RR 5.64; 95% CI 1.26, 25.11), blood pressure ≥ 120/80 at enrollment (RR 1.78; 95% CI 1.23, 2.58), increased mid-upper arm circumference (trend test p-value = 0.02), high hematocrit (trend test p-value = 0.03), low mean corpuscular volume (trend test p-value = 0.02), history of miscarriage or stillbirth (RR 1.58; 95% CI 1.07, 2.33), and older age at first pregnancy (trend test p-value = 0.03).

Conclusion: In settings similar to Tanzania, these characteristics may warrant closer antenatal surveillance. Interventions related to nutrition and diabetes screening should also be considered.
Background

Hypertension during pregnancy affects approximately 10% of all pregnant women and has a significant impact on maternal and neonatal morbidity and mortality in the short and long term.\(^1\)\(^-\)\(^3\) A 2006 systematic review of the causes of maternal mortality by the World Health Organization found that hypertensive disorders are responsible for 2-43% of maternal deaths across countries, and 9.1% of pregnancy-related deaths in Africa.\(^4\) Hypertensive disorders of pregnancy include preeclampsia and gestational hypertension, or elevated blood pressure before 20 weeks gestation with or without proteinuria, respectively.\(^5\) Eclampsia is defined as onset of seizures in a woman with preeclampsia.\(^5\) Preeclampsia alone accounts for 50-60,000 maternal deaths per year worldwide.\(^6\) A recent review of global estimates of preeclampsia and eclampsia examined 78 datasets and found overall incidence estimates of 4.6% and 1.4% respectively, with wide variation by region.\(^7\) They included seven studies from Africa, with estimates for preeclampsia incidence of 5.6% and eclampsia incidence of 2.9%.\(^7\)

The pathophysiological mechanisms of these disorders are not fully understood, and debate persists on whether gestational hypertension and preeclampsia are two distinct diseases, or one underlying disorder of progressively increasing severity from mild gestational hypertension to eclampsia.\(^2\) Villar et al. explored risk factors for preeclampsia and gestational hypertension in a large cohort of pregnant women from Argentina, Cuba, Saudi Arabia, and Thailand in the WHO Antenatal Care Trial in 2006.\(^2\) They found that these hypertensive disorders shared several risk factors including diabetes, renal diseases, cardiac diseases, previous preeclampsia, urinary tract infections, increased maternal age, twin pregnancy, and obesity.\(^2\) Other risk factors were relevant for only one disease and not the other, including previous large for gestational age birth, antepartum hemorrhage, and reproductive tract infection increasing the risk of gestational hypertension, and primiparity increasing risk for preeclampsia. A task force on hypertension in pregnancy convened by the American College of Obstetrics and Gynecology in 2013 similarly described risk factors for preeclampsia that included primiparity, previous preeclamptic
pregnancy, chronic hypertension, renal disease, thrombophilia, multi-fetal pregnancy, in vitro
fertilization, family history of preeclampsia, diabetes, obesity, lupus, and maternal age over 40 years.\textsuperscript{5}

African American race is also known to increase risk for hypertension in pregnancy, but research on this
topic in sub-Saharan African settings has been limited to date.\textsuperscript{8} The objective of this study was to examine
the incidence and potential risk factors for gestational hypertension and preeclampsia in a cohort of HIV-
seronegative pregnant women in Dar es Salaam, Tanzania.
Methods

Study Design and Population

We examined hypertension during pregnancy in data from a double-blind randomized trial of daily multivitamin versus placebo use during pregnancy among 8428 women attending antenatal clinics in Dar es Salaam, Tanzania between August 2001 and July 2004. Participants in the randomized trial were between 12 and 27 weeks gestational age at enrollment based on their last menstrual period, tested antibody negative for human immunodeficiency virus (HIV) at entry, and planned to continue residing in Dar es Salaam for one year after delivery. All women were given iron and folic acid supplementation at monthly visits during pregnancy and malaria prophylaxis with sulfadoxine-pyrimethamine (Fansidar) at 20 and 30 weeks gestational age. All participants provided written informed consent. The study was approved by the institutional review boards at Muhimbili University of Health and Allied Sciences in Dar es Salaam and at the Harvard School of Public Health in Boston.

Measurements

All women completed a baseline questionnaire that included their socio-demographic characteristics, medical, and obstetric history. A physician performed a clinical exam, and the woman’s height and weight were taken by a nurse. Women were scheduled for monthly visits until 32 weeks gestation, then every two weeks until 36 weeks gestation, then weekly until delivery. Questionnaires were administered to evaluate interim medical problems, and blood pressure was measured by a nurse at each antenatal visit. If blood pressure was elevated, the woman’s urine was to be evaluated by laboratory analysis for the presence of protein to as a sign of preeclampsia or gestational hypertension. Dietary history was obtained with twenty-four hour diet recall questionnaires administered monthly until 36 weeks gestational age. Women who missed antenatal appointments were visited at home when possible. Full-time research midwives attended to the women at delivery and recorded information related to the labor and birth, which was added to the study database.
Preeclampsia was defined as systolic blood pressure greater than or equal to 140mm Hg or diastolic blood pressure greater than or equal to 90mm Hg with proteinuria of 1+ confirmed by laboratory urinalysis after 20 weeks gestation through 48 hours postpartum. Women with eclampsia, defined as seizures or coma in addition to preeclampsia, were also included in the case definition of preeclampsia. Gestational hypertension was defined as a systolic blood pressure greater than or equal to 140mm Hg or diastolic blood pressure greater than or equal to 90mm Hg with negative or trace proteinuria on laboratory urinalysis after 20 weeks gestation through 48 hours postpartum. Physician-diagnosed cases of preeclampsia and gestational hypertension based on blood pressure and urine protein measurement were also included in the case definitions. Women without a urine protein lab test or a physician diagnosis of a hypertensive disorder of pregnancy were excluded from the risk factor analysis.

A variety of potential risk factors for preeclampsia and gestational hypertension were explored in this study. Assessments at the enrollment visit were used for all the variables explored, unless otherwise noted. These included self-reported socio-demographic variables of maternal age, marital status, literacy, education level of the mother and partner, household size, woman having some income of her own, and household food expenditure per person per day. We also looked at Filmer-Pritchett score, a linear index that incorporates asset ownership and household characteristics and can be used as a proxy for long-term household-level wealth. We examined several medical and anthropomorphic factors measured at the enrollment visit, including body mass index (BMI), mid-upper arm circumference (MUAC), hemoglobin, hematocrit, platelet count, mean corpuscular volume (MCV), and blood pressure. Randomization to daily multivitamin use, self-reported alcohol use, personal and family history of hypertension and diabetes, urinary tract infection (UTI) at enrollment, and malaria infection during the current pregnancy but before any hypertension diagnosis were also examined. Calcium intake was explored using the mean intake across 24 hour diet recall questionnaires completed during pregnancy, with nutrient levels calculated using Tanzania Food Composition Tables.
Obstetric and gynecologic factors examined included parity, twin gestation, and history of miscarriage or stillbirth. Vaginal bleeding, nausea and vomiting, and itchy vaginal discharge during the current pregnancy were also assessed at the enrollment visit. Age at first pregnancy, time since last pregnancy, history of preeclampsia, low birth weight (LBW) baby less than 2500g at birth, preterm delivery at less than 37 weeks gestation, and Cesarean section in any previous pregnancy were explored as risk factors among the 4510 multiparous women in the study. Parity was explored for both outcomes as both a dichotomous variable, and as an ordinal variable of parity 0, 1, or 2 or more. The results for women with 2 or more previous births were very similar to women with just 1 previous delivery, so parity was collapsed into a dichotomous variable comparing nulliparous to multiparous women in all analyses.

To examine incident cases of hypertension during pregnancy in the current study, 117 women with systolic blood pressure greater than or equal to 140mm Hg or diastolic blood pressure greater than or equal to 90mm Hg at their enrollment visit, who did not have a urine protein sent or have a subsequent physician diagnosis of preeclampsia or gestational hypertension were excluded from this analysis as likely cases of chronic hypertension. The remaining 8311 women who were normotensive at enrollment were included in the subsequent analyses.

Data analysis
Each potential risk factor for preeclampsia and gestational hypertension was assessed individually in a univariable log-binomial regression model to obtain risk ratios and 95% confidence intervals. Women without any type of hypertensive disorder of pregnancy were used as the comparison group in all analyses. Those variables that were associated with preeclampsia or gestational hypertension at the p-value <0.20 level of significance were then included in multivariable-adjusted models. Poisson regression was used for the multivariable models since the multivariable log-binomial models did not converge. All multivariable models were adjusted for year, district of residence, gestational age at enrollment, and maternal age as confounders defined a priori. Due to high collinearity between BMI and MUAC,
additional multivariable-adjusted models were run entering these variables separately from each other to obtain their effects. The same was done for hemoglobin and hematocrit. Covariates that remained significant at the p-value <0.05 level in the multivariable models were considered independent risk factors for the respective hypertensive disorder of pregnancy.

The indicator method was used to address incomplete covariate information. Continuous variables were categorized at pre-determined cut points to increase interpretability. Calcium intake was divided into quartiles with the highest quartile of intake used as the reference group. Effect estimates for calcium were adjusted for mean total energy intake as a continuous variable across 24 hour recall questionnaires. Wald tests for linear trend were calculated for continuous variables using the median value in each category. Wald tests were also calculated for dichotomous variables. All statistical analyses were performed using SAS software 9.3 (SAS Institute, Inc., www.sas.com, Cary, North Carolina).
Results

Baseline characteristics of the study population are shown in Table 1.1. The mean age of the study participants was 25.1 years (SD 5.1), and the mean gestational age at enrollment to the study was 21.3 weeks (SD 3.5). More than half (56%) of women were multiparous, 2% had twin pregnancies, 88% were married or cohabiting with a partner, and 88% were literate.

Of the 8311 women included in our study, 602 (7%) developed some form of hypertension during pregnancy after 20 weeks gestational age. Of those, 138 (2%) were confirmed as preeclampsia meeting the case definition and 136 (2%) women were confirmed cases of gestational hypertension. 328 women (4%) met the hypertension criteria with systolic blood pressure greater than or equal to 140mm Hg or diastolic blood pressure greater than or equal to 90mm Hg, but did not have a urine sample analyzed in the lab, so we were unable to distinguish them as cases of preeclampsia versus gestational hypertension, so they were excluded from the risk factor analyses. Of the 138 women with preeclampsia, 45(33%) developed eclampsia, and 16 of those women presented with seizures as the first identified symptom of the disease.

Results for the associations between the potential risk factors explored and preeclampsia are shown in Table 1.2, reported as risk ratios and 95% confidence intervals. In the multivariable-adjusted model, BMI greater than 22 at enrollment, history of hypertension, urinary tract infection, calcium intake in the bottom three quartiles, and nulliparity were found to be important independent risk factors for preeclampsia (p <0.05). Women with twin pregnancies had an almost 5-fold increased risk of developing preeclampsia (RR 4.95; 95% CI 2.64, 9.29).

Factors related to previous pregnancy complications were also examined in a separate multivariable analysis of the 4510 multiparous women. History of preeclampsia, low birth weight, preterm birth, and Cesarean section were all associated with current pregnancy risk of preeclampsia in univariable analyses.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographic</strong></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>1335 (16)</td>
</tr>
<tr>
<td>20 - &lt; 25</td>
<td>3305 (40)</td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>2230 (27)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>1399 (17)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>7281 (88)</td>
</tr>
<tr>
<td>Not married or cohabiting</td>
<td>967 (12)</td>
</tr>
<tr>
<td>Illiterate</td>
<td>1020 (12)</td>
</tr>
<tr>
<td>Education, years</td>
<td></td>
</tr>
<tr>
<td>0 – 4</td>
<td>947 (12)</td>
</tr>
<tr>
<td>5 – 7</td>
<td>5499 (67)</td>
</tr>
<tr>
<td>8 – 11</td>
<td>1396 (17)</td>
</tr>
<tr>
<td>≥ 12</td>
<td>432 (5)</td>
</tr>
<tr>
<td>Spouse education, years</td>
<td></td>
</tr>
<tr>
<td>0 – 4</td>
<td>413 (6)</td>
</tr>
<tr>
<td>5 – 7</td>
<td>4284 (59)</td>
</tr>
<tr>
<td>8 – 11</td>
<td>1696 (23)</td>
</tr>
<tr>
<td>≥ 12</td>
<td>884 (12)</td>
</tr>
<tr>
<td>Household size, people</td>
<td></td>
</tr>
<tr>
<td>1 – 2</td>
<td>2819 (34)</td>
</tr>
<tr>
<td>3 – 4</td>
<td>3088 (37)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>2379 (29)</td>
</tr>
<tr>
<td>Woman has some income of her own</td>
<td>2239 (27)</td>
</tr>
<tr>
<td>Filmer-Pritchett wealth score &lt; median</td>
<td>3951 (48)</td>
</tr>
<tr>
<td>Food expenditure/person/day ≤ 500 Tanzanian Shillings#</td>
<td>3009 (40)</td>
</tr>
<tr>
<td><strong>Anthropomorphic/Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
</tr>
<tr>
<td>&lt; 22</td>
<td>1953 (27)</td>
</tr>
<tr>
<td>22 - &lt; 25</td>
<td>2553 (35)</td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>2116 (29)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>670 (9)</td>
</tr>
<tr>
<td>Mid-upper arm circumference, cm</td>
<td></td>
</tr>
<tr>
<td>&lt; 22</td>
<td>340 (4)</td>
</tr>
<tr>
<td>22 - &lt; 26</td>
<td>3481 (43)</td>
</tr>
<tr>
<td>26 - &lt; 28</td>
<td>1960 (24)</td>
</tr>
<tr>
<td>≥ 28</td>
<td>2414 (30)</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td></td>
</tr>
<tr>
<td>&lt; 8.5</td>
<td>863 (12)</td>
</tr>
<tr>
<td>8.5 - &lt; 11.0</td>
<td>3961 (56)</td>
</tr>
<tr>
<td>≥ 11.0</td>
<td>2320 (33)</td>
</tr>
</tbody>
</table>
Table 1.1 (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit, %</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>2295 (32)</td>
</tr>
<tr>
<td>30 - &lt; 33</td>
<td>2138 (30)</td>
</tr>
<tr>
<td>≥ 33</td>
<td>2721 (38)</td>
</tr>
<tr>
<td>Platelet count per µL</td>
<td></td>
</tr>
<tr>
<td>&lt; 150</td>
<td>375 (5)</td>
</tr>
<tr>
<td>≥ 150</td>
<td>6773 (95)</td>
</tr>
<tr>
<td>Mean corpuscular volume, fL</td>
<td></td>
</tr>
<tr>
<td>&lt; 85</td>
<td>3743 (52)</td>
</tr>
<tr>
<td>85 - &lt; 100</td>
<td>3248 (45)</td>
</tr>
<tr>
<td>≥ 100</td>
<td>166 (2)</td>
</tr>
<tr>
<td>Randomized to daily multivitamin</td>
<td></td>
</tr>
<tr>
<td>Calcium intake during pregnancy, mg/day</td>
<td></td>
</tr>
<tr>
<td>&lt; 174</td>
<td>1905 (25)</td>
</tr>
<tr>
<td>174 - &lt; 362</td>
<td>1906 (25)</td>
</tr>
<tr>
<td>362 - &lt; 709</td>
<td>1906 (25)</td>
</tr>
<tr>
<td>≥ 709</td>
<td>1906 (25)</td>
</tr>
<tr>
<td>Alcohol use this pregnancy</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td>Malaria infection during pregnancy</td>
<td></td>
</tr>
<tr>
<td>SBP ≥ 120mm Hg or DBP ≥ 80mm Hg</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td></td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td></td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td></td>
</tr>
<tr>
<td>Obstetric/Gynecologic</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>3759 (46)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>4510 (55)</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>158 (2)</td>
</tr>
<tr>
<td>Vaginal bleeding this pregnancy</td>
<td>366 (4)</td>
</tr>
<tr>
<td>Nausea/vomiting this pregnancy</td>
<td>3322 (40)</td>
</tr>
<tr>
<td>Itchy vaginal discharge this pregnancy</td>
<td>983 (12)</td>
</tr>
<tr>
<td>History miscarriage or stillbirth</td>
<td>1437 (17)</td>
</tr>
<tr>
<td>Age at first pregnancy, years**</td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>2352 (55)</td>
</tr>
<tr>
<td>20 - &lt;30</td>
<td>1902 (44)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>27 (1)</td>
</tr>
<tr>
<td>Time since last pregnancy, years**</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>290 (7)</td>
</tr>
<tr>
<td>1 - &lt; 2</td>
<td>474 (12)</td>
</tr>
<tr>
<td>2 - &lt; 3</td>
<td>813 (20)</td>
</tr>
<tr>
<td>3 - &lt; 10</td>
<td>2411 (58)</td>
</tr>
<tr>
<td>≥ 10</td>
<td>148 (4)</td>
</tr>
<tr>
<td>History of preeclampsia **</td>
<td>62 (1)</td>
</tr>
</tbody>
</table>
Table 1.1 (Continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of low birth weight baby &lt; 2.5kg**</td>
<td>434 (19)</td>
</tr>
<tr>
<td>History of preterm birth &lt; 37 weeks **</td>
<td>213 (10)</td>
</tr>
<tr>
<td>History of Cesarean section **</td>
<td>218 (5)</td>
</tr>
</tbody>
</table>

* All characteristics assessed at study enrollment, unless otherwise noted
* May not sum to 8311 due to incomplete covariate data
** Among multiparous women only (n=4510)
^ Equivalent to approximately 0.50 US dollars in 2004
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n/N</th>
<th>Univariable</th>
<th></th>
<th></th>
<th>Multivariable</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR [95% CI]</td>
<td>p</td>
<td>RR [95% CI]</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Socio-demographic</td>
<td></td>
<td></td>
<td>0.37</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>29/1280</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 - &lt; 25</td>
<td>55/3134</td>
<td>0.77 [0.50, 1.21]</td>
<td>0.69 [0.42, 1.14]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>29/2114</td>
<td>0.61 [0.36, 1.01]</td>
<td>0.65 [0.34, 1.24]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>24/1281</td>
<td>0.83 [0.48, 1.41]</td>
<td>1.09 [0.53, 2.24]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>121/6879</td>
<td>1.00 [REF]</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married or cohabiting</td>
<td>15/910</td>
<td>0.94 [0.55, 1.60]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>13/953</td>
<td>0.75 [0.42, 1.32]</td>
<td>0.32</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, years</td>
<td></td>
<td></td>
<td>0.08</td>
<td>0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 4</td>
<td>9/894</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - 7</td>
<td>92/5205</td>
<td>1.76 [0.89, 3.47]</td>
<td>1.41 [0.68, 2.94]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 - 11</td>
<td>32/1316</td>
<td>2.42 [1.16, 5.04]</td>
<td>1.91 [0.85, 4.29]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 12</td>
<td>4/399</td>
<td>1.00 [0.31, 3.21]</td>
<td>0.93 [0.27, 3.23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse education, years</td>
<td></td>
<td></td>
<td>0.65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 4</td>
<td>7/386</td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - 7</td>
<td>72/4052</td>
<td>0.98 [0.45, 2.11]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 - 11</td>
<td>29/1597</td>
<td>1.00 [0.44, 2.27]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 12</td>
<td>18/838</td>
<td>1.18 [0.50, 2.81]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household size, people</td>
<td></td>
<td></td>
<td>0.05</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 2</td>
<td>58/2674</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - 4</td>
<td>47/2918</td>
<td>0.74 [0.51, 1.09]</td>
<td>0.94 [0.59, 1.48]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5</td>
<td>32/2232</td>
<td>0.66 [0.43, 1.01]</td>
<td>0.75 [0.46, 1.25]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woman has income of her own</td>
<td>32/2118</td>
<td>0.82 [0.55, 1.22]</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealth score &lt; median</td>
<td>72/3763</td>
<td>1.19 [0.85, 1.66]</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food expenditure/person/day ≤ 500</td>
<td>50/2845</td>
<td>0.96 [0.67, 1.36]</td>
<td>0.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzanian Shillings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthropomorphic/Clinical</td>
<td></td>
<td></td>
<td>0.04</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 22</td>
<td>18/1884</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 - &lt; 25</td>
<td>55/2446</td>
<td>2.35 [1.39, 3.99]</td>
<td>2.27 [1.33, 3.87]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>31/1982</td>
<td>1.64 [0.92, 2.92]</td>
<td>1.60 [0.89, 2.89]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>15/573</td>
<td>2.74 [1.39, 5.40]</td>
<td>2.75 [1.36, 5.58]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-upper arm circumference, cm²</td>
<td></td>
<td></td>
<td>0.09</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 22</td>
<td>3/329</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 - &lt; 26</td>
<td>57/3351</td>
<td>1.87 [0.59, 5.92]</td>
<td>1.97 [0.61, 6.29]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 - &lt; 28</td>
<td>30/1860</td>
<td>1.77 [0.54, 5.76]</td>
<td>1.90 [0.58, 6.24]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 28</td>
<td>48/2201</td>
<td>2.39 [0.75, 7.63]</td>
<td>2.52 [0.78, 8.17]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td>0.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8.5</td>
<td>14/824</td>
<td>0.94 [0.51, 1.73]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.5 - &lt;11</td>
<td>57/3756</td>
<td>0.84 [0.56, 1.26]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 11</td>
<td>39/2164</td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td></td>
<td></td>
<td>0.79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>35/2196</td>
<td>0.94 [0.61, 1.47]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 - &lt; 33</td>
<td>32/2018</td>
<td>0.94 [0.60, 1.48]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 33</td>
<td>43/2541</td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt; 150 per µL</td>
<td>7/350</td>
<td>1.24 [0.58, 2.65]</td>
<td>0.57</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>n/N</td>
<td>Univariable RR [95% CI]</td>
<td>p</td>
<td>Multivariable RR [95% CI]</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-----</td>
<td>-------------------------</td>
<td>---</td>
<td>--------------------------</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume, fL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 85</td>
<td>57/3540</td>
<td>1.00 [0.69, 1.47]</td>
<td>0.70</td>
<td>1.00 [REF]</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>85 - &lt; 100</td>
<td>49/3055</td>
<td>1.00 [REF]</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 100</td>
<td>4/163</td>
<td>1.20 [0.86, 1.67]</td>
<td>&lt;0.01</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Randomized to daily multivitamin</td>
<td>75/3889</td>
<td>1.00 [REF]</td>
<td>1.20 [0.86, 1.67]</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium intake during pregnancy, mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 174</td>
<td>41/1802</td>
<td>2.66 [1.49, 4.78]</td>
<td>0.70</td>
<td>2.27 [1.22, 4.25]</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>174 - &lt; 362</td>
<td>31/1795</td>
<td>1.97 [1.08, 3.58]</td>
<td>1.92 [1.03, 3.59]</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>362 - &lt; 709</td>
<td>33/1793</td>
<td>2.05 [1.14, 3.70]</td>
<td>1.81 [0.97, 3.39]</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 709</td>
<td>17/1798</td>
<td>1.00 [REF]</td>
<td>1.00 [REF]</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>20/975</td>
<td>1.19 [0.74, 1.90]</td>
<td>0.47</td>
<td>2.27 [1.22, 4.25]</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4/95</td>
<td>2.45 [0.93, 6.50]</td>
<td>0.07</td>
<td>3.11 [1.22, 4.25]</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Malaria infection during pregnancy</td>
<td>20/752</td>
<td>1.59 [1.00, 2.55]</td>
<td>0.05</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>SBP ≥120mm Hg or DBP ≥80mm Hg</td>
<td>37/1719</td>
<td>1.28 [0.88, 1.85]</td>
<td>0.20</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>12/276</td>
<td>2.60 [1.46, 4.64]</td>
<td>&lt;0.01</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>31/1666</td>
<td>1.06 [0.72, 1.58]</td>
<td>0.02</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>14/722</td>
<td>1.10 [0.64, 1.91]</td>
<td>0.73</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Obstetric/Gynecologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>79/3574</td>
<td>1.61 [1.15, 2.26]</td>
<td>0.04</td>
<td>1.71 [1.03, 2.85]</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>11/141</td>
<td>4.73 [2.62, 8.57]</td>
<td>0.01</td>
<td>4.95 [2.64, 9.29]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>2/344</td>
<td>0.32 [0.08, 1.28]</td>
<td>0.11</td>
<td>0.15 [0.02, 1.09]</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>52/3133</td>
<td>0.90 [0.64, 1.27]</td>
<td>0.56</td>
<td>0.15 [0.02, 1.09]</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Itchy vaginal discharge</td>
<td>25/930</td>
<td>1.64 [1.07, 2.51]</td>
<td>0.09</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>History miscarriage or stillbirth</td>
<td>32/1335</td>
<td>1.48 [1.00, 2.19]</td>
<td>0.18</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Age at first pregnancy ≥ 20 years</td>
<td>28/1806</td>
<td>1.32 [0.78, 2.24]</td>
<td>0.31</td>
<td>1.53 [0.56, 4.19]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Time since last pregnancy, years*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>5/276</td>
<td>1.24 [0.49, 3.16]</td>
<td>0.31</td>
<td>1.24 [0.49, 3.16]</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>1 - &lt; 2</td>
<td>6/442</td>
<td>0.93 [0.39, 2.21]</td>
<td>0.62 [0.28, 1.40]</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 - &lt; 3</td>
<td>7/773</td>
<td>0.93 [0.39, 2.21]</td>
<td>0.62 [0.28, 1.40]</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - &lt; 10</td>
<td>33/2264</td>
<td>1.00 [REF]</td>
<td>1.00 [REF]</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>1/133</td>
<td>0.52 [0.07, 3.74]</td>
<td>0.31</td>
<td>0.52 [0.07, 3.74]</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>History of preeclampsia*</td>
<td>4/53</td>
<td>5.82 [2.19, 15.48]</td>
<td>&lt;0.01</td>
<td>6.20 [2.08, 18.49]</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>History of LBW baby &lt; 2.5kg *&amp;</td>
<td>10/403</td>
<td>2.32 [1.09, 4.94]</td>
<td>0.03</td>
<td>2.08 [0.92, 4.69]</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>History of preterm birth &lt; 37 weeks *&amp;</td>
<td>6/204</td>
<td>2.53 [1.04, 6.16]</td>
<td>0.04</td>
<td>2.60 [1.03, 6.56]</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>History of Cesarean section*&amp;</td>
<td>8/202</td>
<td>3.36 [1.60, 7.06]</td>
<td>&lt;0.01</td>
<td>1.95 [0.82, 4.66]</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

*All characteristics were assessed at study enrollment, unless otherwise noted
+ Adjusted for year, district, gestational age at entry, maternal age, education, household size, BMI, MUAC, mean calcium and energy intake this pregnancy, urinary tract infection at entry, malaria during pregnancy, history hypertension, nulliparity, twins, vaginal bleeding this pregnancy, itchy vaginal discharge this pregnancy, history miscarriage or stillbirth
* BMI and MUAC entered separately in multivariable model
* Among multiparous women only
* Multivariable model additionally adjusted for history of preeclampsia
History of preeclampsia remained the strongest independent risk factor for current preeclampsia in the multivariable model (RR 6.20; 95% CI 2.08, 18.49). After adjusting for preeclampsia history, history of LBW and Cesarean section were no longer significantly independently associated with risk of preeclampsia, but women with a history of preterm delivery remained at more than double the risk (RR 2.60; 95% CI 1.03, 6.56).

Results for the gestational hypertension outcome are shown in Table 1.3. Increasing BMI, increasing MUAC, MCV less than 85 fL, blood pressure greater than 120/80 at enrollment, history of diabetes, twin pregnancy, and history of miscarriage or stillbirth all significantly increased the risk of developing gestational hypertension in the multivariable-adjusted model. Decreasing hematocrit appeared to be associated with a lower risk of gestational hypertension, particularly a hematocrit less than 30%. Among multiparous women, the only pregnancy history variable that appeared important for development of gestational hypertension was age at first pregnancy. Women whose first pregnancy was at age 30 or older had a 5 times higher independent risk of developing gestational hypertension compared to those less than 20 years old.

There were only 10 women in this study who reported having a personal history of any type of diabetes. Although the confidence interval is wide with so few women exposed, diabetes history was still found to be related to gestational hypertension (RR 5.64; 95% CI 1.26, 25.11). None of these 10 women developed preeclampsia.
Table 1.3. Risk factors for gestational hypertension (n/N = 136/7845)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n/N</th>
<th>Univariable</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RR [95% CI]</td>
<td>p</td>
</tr>
<tr>
<td>Socio-demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>19/1270</td>
<td>1.00 [REF]</td>
<td>0.11</td>
</tr>
<tr>
<td>20 - &lt;25</td>
<td>49/3128</td>
<td>1.05 [0.62, 1.77]</td>
<td>0.95 [0.53, 1.64]</td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>40/2125</td>
<td>1.26 [0.73, 2.16]</td>
<td>0.95 [0.48, 1.69]</td>
</tr>
<tr>
<td>≥ 30</td>
<td>28/1285</td>
<td>1.46 [0.82, 2.59]</td>
<td>0.95 [0.48, 1.69]</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or cohabiting</td>
<td>115/6873</td>
<td>1.00 [REF]</td>
<td>0.11</td>
</tr>
<tr>
<td>Not married or cohabiting</td>
<td>21/916</td>
<td>1.37 [0.87, 2.17]</td>
<td>0.19</td>
</tr>
<tr>
<td>Illiterate</td>
<td>21/961</td>
<td>1.30 [0.82, 2.06]</td>
<td>0.26</td>
</tr>
<tr>
<td>Education, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 4</td>
<td>13/898</td>
<td>1.00 [REF]</td>
<td>0.15</td>
</tr>
<tr>
<td>5 – 7</td>
<td>86/5199</td>
<td>1.14 [0.64, 2.04]</td>
<td>0.98 [0.54, 1.78]</td>
</tr>
<tr>
<td>8 - 11</td>
<td>27/1311</td>
<td>1.42 [0.74, 2.74]</td>
<td>1.11 [0.55, 2.24]</td>
</tr>
<tr>
<td>≥ 12</td>
<td>10/405</td>
<td>1.71 [0.75, 3.86]</td>
<td>1.31 [0.53, 3.36]</td>
</tr>
<tr>
<td>Spouse education, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 4</td>
<td>10/389</td>
<td>1.00 [REF]</td>
<td>0.41</td>
</tr>
<tr>
<td>5 – 7</td>
<td>67/4047</td>
<td>0.64 [0.33, 1.24]</td>
<td>0.81 [0.38, 1.70]</td>
</tr>
<tr>
<td>8 - 11</td>
<td>32/1600</td>
<td>0.78 [0.39, 1.57]</td>
<td>0.77 [0.35, 1.70]</td>
</tr>
<tr>
<td>≥ 12</td>
<td>11/831</td>
<td>0.51 [0.22, 1.20]</td>
<td>0.46 [0.18, 1.21]</td>
</tr>
<tr>
<td>Household size, people</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 2</td>
<td>40/2656</td>
<td>1.00 [REF]</td>
<td>0.37</td>
</tr>
<tr>
<td>3 - 4</td>
<td>54/2925</td>
<td>1.23 [0.82, 1.84]</td>
<td>0.77 [0.35, 1.70]</td>
</tr>
<tr>
<td>≥ 5</td>
<td>41/2241</td>
<td>1.21 [0.79, 1.87]</td>
<td>0.51 [0.22, 1.20]</td>
</tr>
<tr>
<td>Has some of her own income</td>
<td>34/2120</td>
<td>0.90 [0.61, 1.32]</td>
<td>0.58</td>
</tr>
<tr>
<td>Wealth score &lt; median</td>
<td>61/3752</td>
<td>0.88 [0.63, 1.23]</td>
<td>0.45</td>
</tr>
<tr>
<td>Food expenditure/person/day ≤ 500 Tanzanian Shillings</td>
<td>56/2851</td>
<td>1.20 [0.85, 1.70]</td>
<td>0.30</td>
</tr>
<tr>
<td>Anthropomorphic/Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m**</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt; 22</td>
<td>21/1887</td>
<td>1.00 [REF]</td>
<td>0.01</td>
</tr>
<tr>
<td>22 - &lt;25</td>
<td>32/2423</td>
<td>1.19 [0.69, 2.05]</td>
<td>1.08 [0.62, 1.88]</td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>43/1994</td>
<td>1.94 [1.15, 3.25]</td>
<td>1.59 [0.93, 2.71]</td>
</tr>
<tr>
<td>≥ 30</td>
<td>29/587</td>
<td>4.44 [2.55, 7.72]</td>
<td>2.91 [1.59, 5.32]</td>
</tr>
<tr>
<td>Mid-upper arm circumference, cm*</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt; 22</td>
<td>4/330</td>
<td>1.00 [REF]</td>
<td>0.02</td>
</tr>
<tr>
<td>22 - &lt;26</td>
<td>40/3334</td>
<td>0.99 [0.36, 2.75]</td>
<td>0.88 [0.31, 2.47]</td>
</tr>
<tr>
<td>26 - &lt;28</td>
<td>28/1858</td>
<td>1.24 [0.44, 3.52]</td>
<td>1.00 [0.35, 2.87]</td>
</tr>
<tr>
<td>≥ 28</td>
<td>63/2216</td>
<td>2.35 [0.86, 6.40]</td>
<td>1.47 [0.53, 4.13]</td>
</tr>
<tr>
<td>Hemoglobin**</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>&lt; 8.5</td>
<td>9/819</td>
<td>0.57 [0.28, 1.16]</td>
<td>0.57 [0.27, 1.24]</td>
</tr>
<tr>
<td>8.5 - &lt; 11</td>
<td>61/3760</td>
<td>0.84 [0.57, 1.24]</td>
<td>0.87 [0.57, 1.34]</td>
</tr>
<tr>
<td>≥ 11</td>
<td>42/2167</td>
<td>1.00 [REF]</td>
<td>1.00 [REF]</td>
</tr>
<tr>
<td>Hematocrit, %**</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>22/2183</td>
<td>0.49 [0.30, 0.79]</td>
<td>0.55 [0.32, 0.94]</td>
</tr>
<tr>
<td>30 - &lt; 33</td>
<td>37/2023</td>
<td>0.88 [0.58, 1.33]</td>
<td>0.92 [0.59, 1.43]</td>
</tr>
<tr>
<td>≥ 33</td>
<td>53/2551</td>
<td>1.00 [REF]</td>
<td>1.00 [REF]</td>
</tr>
<tr>
<td>Platelet count &lt; 150 per μL</td>
<td>4/347</td>
<td>0.68 [0.25, 1.84]</td>
<td>0.45</td>
</tr>
<tr>
<td>Characteristic</td>
<td>n/N</td>
<td>Univariable RR [95% CI]</td>
<td>p</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-------------------</td>
<td>--------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Mean corpuscular volume, fL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 85</td>
<td>66/3549</td>
<td>1.26 [0.87, 1.84]</td>
<td>0.12</td>
</tr>
<tr>
<td>85 - &lt; 100</td>
<td>45/3051</td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>≥ 100</td>
<td>1/160</td>
<td>0.42 [0.06, 3.05]</td>
<td></td>
</tr>
<tr>
<td>Randomized to daily multivitamin</td>
<td>73/3887</td>
<td>1.17 [0.83, 1.63]</td>
<td>0.37</td>
</tr>
<tr>
<td>Calcium intake during pregnancy, mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 174</td>
<td>28/1789</td>
<td>1.05 [0.61, 1.78]</td>
<td>0.37</td>
</tr>
<tr>
<td>174 - &lt; 362</td>
<td>33/1797</td>
<td>1.19 [0.72, 1.97]</td>
<td></td>
</tr>
<tr>
<td>362 - &lt; 709</td>
<td>37/1797</td>
<td>1.31 [0.81, 2.13]</td>
<td></td>
</tr>
<tr>
<td>≥ 709</td>
<td>30/1811</td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>17/972</td>
<td>1.01 [0.61, 1.68]</td>
<td>0.96</td>
</tr>
<tr>
<td>Malaria infection during pregnancy</td>
<td>7/739</td>
<td>0.52 [0.24, 1.11]</td>
<td>0.09</td>
</tr>
<tr>
<td>SBP ≥120 mm Hg or DBP ≥80 mm Hg</td>
<td>47/1729</td>
<td>1.87 [1.31, 2.65]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>11/275</td>
<td>2.41 [1.32, 4.41]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>2/10</td>
<td>11.61 [3.32, 40.57]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>43/1678</td>
<td>1.68 [1.18, 2.40]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>16/724</td>
<td>1.31 [0.78, 2.19]</td>
<td>0.31</td>
</tr>
<tr>
<td>Obstetric/Gynecologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>55/3550</td>
<td>0.81 [0.58, 1.14]</td>
<td>0.24</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>8/138</td>
<td>3.49 [1.74, 6.99]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>6/348</td>
<td>0.99 [0.44, 2.23]</td>
<td>0.98</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>63/3144</td>
<td>1.30 [0.93, 1.82]</td>
<td>0.13</td>
</tr>
<tr>
<td>Itchy vaginal discharge</td>
<td>20/925</td>
<td>1.29 [0.81, 2.07]</td>
<td>0.28</td>
</tr>
<tr>
<td>History miscarriage or stillbirth</td>
<td>37/1340</td>
<td>1.81 [1.24, 2.62]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at first pregnancy, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>35/2221</td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>20 - &lt; 30</td>
<td>39/1794</td>
<td>1.38 [0.88, 2.17]</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>2/25</td>
<td>5.08 [1.29, 19.96]</td>
<td></td>
</tr>
<tr>
<td>Time since last pregnancy, years</td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>3/274</td>
<td>0.59 [0.18, 1.90]</td>
<td></td>
</tr>
<tr>
<td>1 - &lt; 2</td>
<td>11/447</td>
<td>1.33 [0.69, 2.57]</td>
<td></td>
</tr>
<tr>
<td>2 - &lt; 3</td>
<td>15/781</td>
<td>1.04 [0.58, 1.86]</td>
<td></td>
</tr>
<tr>
<td>3 - &lt; 10</td>
<td>42/2273</td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>1/133</td>
<td>0.41 [0.06, 2.93]</td>
<td></td>
</tr>
<tr>
<td>History of preeclampsia</td>
<td>2/51</td>
<td>2.07 [0.53, 8.23]</td>
<td>0.30</td>
</tr>
<tr>
<td>History of LBW baby &lt; 2.5 kg</td>
<td>8/401</td>
<td>1.19 [0.55, 2.57]</td>
<td>0.66</td>
</tr>
<tr>
<td>History of preterm birth &lt; 37 weeks</td>
<td>1/199</td>
<td>0.27 [0.04, 1.98]</td>
<td>0.20</td>
</tr>
<tr>
<td>History of Cesarean section</td>
<td>7/201</td>
<td>1.91 [0.89, 4.11]</td>
<td>0.10</td>
</tr>
</tbody>
</table>

All characteristics were assessed at study enrollment, unless otherwise noted.

+ Adjusted for year, district, gestational age at entry, maternal age, marital status, education, spouse education, BMI, MUAC, hemoglobin, hematocrit, MCV, malaria during pregnancy, baseline BP ≥120/80, history hypertension, history diabetes, family history hypertension, twins, nausea/vomiting during pregnancy, history miscarriage or stillbirth.

* BMI and MUAC entered separately in multivariable model.

** Hemoglobin and hematocrit entered separately in multivariable model.

# Among multiparous women only.

& Multivariable model additionally adjusted for age at first pregnancy and history of Cesarean section.
Discussion

Main findings

We identified incident hypertensive disorders in 7.2% of pregnancies in this population of HIV seronegative women in Dar es Salaam, with 1.7% confirmed cases of preeclampsia, 1.6% confirmed gestational hypertension cases, and 3.9% hypertension of unknown origin. Even in this group of women involved in a randomized control trial with close follow-up, 11.8% of the preeclampsia cases presented with seizures as their first identified symptom of the disease. Work in other developing countries estimated hypertension during pregnancy in 9.2% of women; 2.2% with preeclampsia and 7% gestational hypertension. It is possible that our estimates are slightly lower than these because we excluded women with hypertension at enrollment; including these women gives a similar estimate for prevalence of all types of hypertension in pregnancy of 8.5%. In a randomized trial of multivitamin use in pregnancy among HIV-infected women in the same catchment area in Dar es Salaam, the incidence of any type of hypertension was similar at 8.9%. Some risk factors appeared to be shared between preeclampsia and gestational hypertension, while others were related to only one disorder.

Strengths and limitations

The strength of this study is that it involved a large number of pregnant women with data on a wide variety of risk factors collected in a standardized and detailed fashion throughout their participation in a randomized clinical trial. It also adds to the limited body of evidence available on hypertension during pregnancy among women in sub-Saharan Africa.

The main limitation to our study was that we had a substantial number of women with hypertension during pregnancy whose type could not be confirmed, as urine protein laboratory results were not available. The baseline characteristics of these women appeared to be similar to those in the gestational hypertension cases group, but we cannot be sure which type of hypertension they had without urine protein confirmation. Another limitation was that most women were enrolled in the study about half-way
through pregnancy. Without blood pressure measurements from before pregnancy or prior to 20 weeks gestation in many women, it is difficult to distinguish those women with underlying chronic hypertension from those with hypertensive disorders of pregnancy. We attempted to address with this by excluding women with blood pressure greater than or equal to 140mm Hg systolic or 90mm Hg diastolic at their first visit. The cases we have identified may still include some women who have unidentified chronic hypertension with a super-imposed hypertensive disorder of pregnancy, which could affect the magnitude of the associations observed, but this is unlikely to change the risk factors identified.

Interpretation

Twin pregnancy and body mass index greater than 22 kg/m$^2$ at enrollment were found to be risk factors for both preeclampsia and gestational hypertension. Many of the factors associated with gestational hypertension are similar to risk factors for chronic hypertension outside of pregnancy, while those specific to preeclampsia include several pregnancy-related factors, supporting the idea that these may be two distinct disease processes.

Nulliparity, self-reported history of hypertension prior to pregnancy, and urinary tract infection during pregnancy were associated with an increased risk of developing preeclampsia alone. The relationship with UTI supports the theory of a pathway to preeclampsia where infection may play a role in its development by increasing acute utero-placental atherosis, as well as in its progression by amplifying the maternal systemic inflammatory response. Malaria infection and itchy vaginal discharge during pregnancy, which may be an indicator of genital urinary tract infection, were also associated with increased risk of preeclampsia. Although they did not remain statistically significant in the adjusted model, these relationships lend further support to an infectious pathway to preeclampsia development. This association with malaria has also been found in a few other small studies in sub-Saharan Africa. It is particularly notable here since this population of women was given prophylaxis with sulfadoxine-pyrimethamine (Fansidar).
Although multivitamin supplementation was not associated with either preeclampsia or gestational hypertension, women with calcium intake below 709 mg per day were at 1.8 to 2.3 times higher risk for developing preeclampsia after adjusting for mean daily caloric intake as well as all other variables in the adjusted model (trend test p-value = 0.01). This is consistent with other studies that have found an inverse relationship between calcium supplementation and preeclampsia among populations with low calcium intake, where supplementation was found to decrease the risk of preeclampsia by half.\textsuperscript{21}

History of preeclampsia and previous preterm birth were strong predictors of increased risk of preeclampsia development in the current pregnancy. Adverse prior pregnancy outcomes may act to increase risk of preeclampsia either through a direct mechanism or due to other common causes that increase risk of a variety of complications in pregnancy. For example, preeclampsia in a previous pregnancy may having lingering effects on a woman’s blood vessels, liver, or uterus that are triggered again in subsequent pregnancies, or both cases may be a result of underlying factors that increase women’s risk for preeclampsia in all pregnancies. History of preterm birth remained significantly associated with preeclampsia after adjustment for history of preeclampsia. It is possible that some of this relationship may be explained by residual confounding by other risk factors in previous pregnancies that were not assessed in the current study.

Risk factors specific to gestational hypertension included mid-upper arm circumference of 28cm or higher, mean corpuscular volume less than 85fL, history of diabetes, SBP of 120mm Hg or higher or DBP 80mm Hg or higher at enrollment, and history of miscarriage or stillbirth. Women with a hematocrit less than 30% were at decreased risk compared to women with hematocrit of 33% of higher. Unfortunately, we were unable to distinguish between women who had a history of miscarriage verses stillbirth. This factor was also associated with preeclampsia, but did not remain statistically significant in the adjusted model (RR 1.36; 95% CI 0.87, 2.12). These findings may support a hypothesis of an underlying factor.
affecting implantation and placental function that could increase risk for both pregnancy loss and hypertensive disorders.\textsuperscript{5}

Conclusion

Despite the significant impact of hypertensive disorders of pregnancy on maternal and child health, their pathogenesis and sequelae are not fully understood. There is a particular lack of published evidence in this area from sub-Saharan Africa. Our study in Dar es Salaam found that hypertensive disorders of pregnancy affect approximately 7\% of women in this population. The World Health Organization guidelines for antenatal care recommend at least four visits during pregnancy, with increased surveillance for women at risk for adverse outcomes.\textsuperscript{22} Women with the risk factors identified in this study may be good candidates for closer antenatal surveillance of blood pressure, urine protein, and fetal growth so the development of hypertension during pregnancy can be identified as early as possible and delivery at the appropriate facility level coordinated. The BMI, MUAC, and calcium findings support interventions aimed at diet and lifestyle modifications to help decrease risk of hypertension. There is a need for the implementation of gestational diabetes screening and further research into the impact of diabetes on pregnancy outcomes in resource-limited settings. More investigation into the effects of infections during pregnancy and potential screening or preventative strategies is also warranted.
Acknowledgements

The authors thank the mothers who participated in the study, the field research teams, including nurses, midwives, supervisors, and laboratory personnel, and the administrative staff who made this study possible. We also thank Ellen Hertzmark of Harvard T.H. Chan School of Public Health for her work on the dataset and input into the analysis for this study.

Disclosure of interests

Authors do not have any conflicts of interest to disclose.

Contribution to authorship: EB, WF, DS, EL, SM, WU, FA

EB and WF conceived of the study concept. WF, WU, and FA were part of the research team that conducted the original randomized trial in which the women in the current study participated. EB, WF, DS, EL, and SM made substantial contributions to the design, analysis, and interpretation of the data. EB performed the analyses and drafted the manuscript. WF, DS, EL, SM, WU, and FA contributed to the revisions of the manuscript.

Details of ethics approval

The study was approved by the institutional review boards at Muhimbili University of Health and Allied Sciences in Dar es Salaam and at Harvard School of Public Health in Boston.

Funding

Study supported by a grant from the National Institute of Child Health and Human Development (NICHD R01 37701). EB received research funding support from Training Grant T32HD060454 in Reproductive, Perinatal, and Pediatric Epidemiology from the National Institute of Child Health and Human Development, National Institutes of Health and MCHB Training Grant T76MC00001 from the Maternal and Child Health Bureau.
References


Title
Inter-pregnancy interval and perinatal outcomes among women in Dar es Salaam, Tanzania

Authors
Ellen O. Boundy, Ellice Lieberman, Stacey A. Missmer, Donna Spiegelman, Wafaie W. Fawzi

1 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
2 Department of Pediatric Newborn Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, USA
3 Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
4 Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA
5 Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
6 Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
7 Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Funding
Study supported by a grant from the National Institute of Child Health and Human Development (NICHD R01 37701). EB received research funding support from Training Grant T32HD060454 in Reproductive, Perinatal, and Pediatric Epidemiology from the National Institute of Child Health and Human Development, National Institutes of Health and MCHB Training Grant T76MC00001 from the Maternal and Child Health Bureau.
Abstract

**Background:** Short and long inter-pregnancy intervals have been associated with adverse perinatal outcomes. Research on the effects of pregnancy spacing has been limited in sub-Saharan Africa.

**Methods:** We examined the effect of inter-pregnancy interval on perinatal outcomes in a cohort of 3973 women in Dar es Salaam, Tanzania between 2001 and 2004. Inter-pregnancy interval was defined as time from the end of the previous pregnancy until the last menstrual period of the current pregnancy. An interval of 24 to less than 36 months was used at the reference group based on World Health Organization recommendations for pregnancy spacing.\(^1\) Outcomes included preterm birth, small for gestational age, low birth weight, stillbirth, perinatal death, and maternal anemia. We used log binomial regression to obtain risk ratios and 95% confidence intervals. Results were stratified by last pregnancy outcome of live birth or stillbirth.

**Results:** Following a live birth (n=3732), inter-pregnancy intervals less than six months increased the risk of a low-birth weight infant more than 4-fold (RR 4.63; 95% CI 1.78, 12.03) compared to intervals 24 to less than 36 months. Following a stillbirth (n=241), shorter intervals were associated with increased risk of stillbirth and perinatal death in the subsequent pregnancy (trend test p-values <0.05). A non-statistically significant increase in risk of small for gestational age was also noted for pregnancy intervals less than 12 months after a live birth. We did not find significant evidence for adverse effects of inter-pregnancy intervals longer than 60 months.

**Conclusion:** Family planning counseling should include information on the increased risks of adverse birth outcomes with short inter-pregnancy intervals. Women who are present to antenatal care following a short spacing interval should also be considered at higher risk for these perinatal complications.
Background

Both short and long time intervals between pregnancies have been associated with adverse outcomes for mothers and infants.\textsuperscript{1, 2} A 2006 meta-analysis of 67 studies on birth spacing and perinatal outcomes found that inter-pregnancy intervals less than 18 months and longer than 59 months were associated with increased risk of preterm birth, low birth weight, and small for gestational age, compared to 18 to 23 month intervals.\textsuperscript{2} Shorter inter-pregnancy intervals have also been associated with increased risk of stillbirth, neonatal death, and child under-nutrition.\textsuperscript{3-6} The literature on the effects of pregnancy spacing on maternal outcomes is sparse, but there is some evidence of increased risk of preeclampsia with longer intervals, and mixed findings on the impact of varied intervals on maternal anemia.\textsuperscript{6, 7}

Several biologic mechanisms have been proposed to explain the association between short pregnancy spacing and adverse birth outcomes including maternal nutritional depletion, cervical insufficiency, vertical transmission of infections, suboptimal lactation, sibling competition and infectious disease transmission, and abnormal remodeling of endometrial blood vessels.\textsuperscript{8} One proposed mechanism for the effect of long inter-pregnancy intervals on adverse outcomes is that during pregnancy, a mother may develop physiological changes that support fetal growth, such as increased uterine blood flow, and after delivery those adaptations decline over time.\textsuperscript{9}

The World Health Organization recommends that couples wait at least 24 months after a live birth before attempting the next pregnancy to reduce the risk of adverse maternal and neonatal health outcomes.\textsuperscript{1} Studies on this topic using longitudinal data with adequate control for confounding among populations in sub-Saharan Africa have been limited. The data available from Tanzania indicate that a significant proportion of births do not meet the World Health Organization’s recommended guidelines for pregnancy spacing.\textsuperscript{10, 11} According to the 2010 Demographic and Health Survey, which assesses pregnancy spacing using the time from one birth until the next birth, 16\% of all women in Tanzania and 11\% of those living in urban areas had birth intervals less than 24 months.\textsuperscript{12} There is also limited evidence available
examining potential differences in the effect of pregnancy spacing on perinatal outcomes following a stillbirth compared to a live birth.¹

The objective of this study is to examine the relationship between different inter-pregnancy intervals and perinatal outcomes, including small for gestational age, low birth weight, preterm birth, stillbirth, perinatal death, and maternal anemia in a cohort of multiparous women in Dar es Salaam, Tanzania.
Methods

Study design/population

We examined pregnancy spacing and perinatal outcomes using data from a double-blind randomized trial of daily multivitamin versus placebo use during pregnancy among 8428 women in Dar es Salaam, Tanzania between August 2001 and July 2004. Participants were between 12 and 27 weeks gestational age at enrollment, tested antibody negative for human immunodeficiency virus, and planned to continue residing in Dar es Salaam for one year after delivery. All women were given daily iron and folic acid supplementation and malaria prophylaxis with sulfadoxine-pyrimethamine at 20 and 30 weeks gestational age. All participants provided written informed consent. The study was approved by the institutional review boards at Muhimbili University of Health and Allied Sciences in Dar es Salaam and at the Harvard School of Public Health in Boston.

From that study population, we included all multiparous women with singleton pregnancies whose last pregnancy resulted in a live or stillbirth (n=4436). We then excluded women with missing data for the date of their previous pregnancy outcome (n=439) or last menstrual period prior to the current pregnancy (n=0) from the analysis. We also excluded women whose previous pregnancy outcome was unknown (n=24).

Data collection/measurements

A background questionnaire was administered to all women at study enrollment between 12 and 27 weeks gestation, which included questions on socio-demographic characteristics, medical and obstetric history, and last menstrual period as reported by the participant. For women with an uncertain last menstrual period date, irregular menstrual cycles, last bleeding smaller than usual, or oral contraceptive use in the preceding three months, an ultrasound of the fetal biparietal diameter was performed. When there was a discrepancy of 10 or more days with the last menstrual period dating, the ultrasound estimation of gestational age was used. Women were also asked whether the outcome of their most recent pregnancy
was a live birth, stillbirth, or miscarriage/abortion, and what date that pregnancy ended. The exposure of interest, inter-pregnancy interval, was calculated as the number of days from the end of the previous pregnancy until the first day of the last menstrual period of the current pregnancy.

Women were seen at monthly visits to the antenatal clinic during their pregnancies. Research midwives attended to the women at delivery and recorded information related to the labor, birth, and neonatal outcomes, including birth weight. Women and their babies were then seen in the clinic at six weeks postpartum and at monthly intervals thereafter until the end of the first year of life.

The birth-related outcomes of interest were small for gestational age (SGA) infant, low birth weight (LBW) infant, preterm birth, stillbirth, perinatal death. We also examined maternal anemia at study enrollment as an outcome. SGA was defined as birth weight less than tenth percentile for gestational age according to the INTERGROWTH-21st Project growth standards. LBW was defined as less than 2500 grams. Preterm birth was defined as less than 37 weeks gestational age. Stillbirth was defined as delivery of a baby born at or after 28 weeks gestation without any evidence of life, such as breathing or a heartbeat, at birth. Perinatal death was defined as all stillbirths plus any neonatal deaths within the first 28 days of life. Maternal anemia was defined as hemoglobin less than 8.5 grams per deciliter (g/dL) at study enrollment.

Covariates considered a priori as potential confounders of the relationship between inter-pregnancy interval and the perinatal outcomes of interest were assessed at the enrollment visit, including maternal age, parity, education, marital status, household wealth, preterm birth in a previous pregnancy, and maternal age at first pregnancy. Wealth was assessed using the Filmer-Pritchett score, a linear index that incorporates asset ownership and household characteristics as a proxy for long-term household-level wealth.
Data analysis

We examined the relationship between inter-pregnancy interval and perinatal outcomes among women whose most recent pregnancy resulted in a live birth and those whose last pregnancy resulted in a stillbirth separately. To be able to examine short and long intervals between pregnancies, the exposure was categorized as less than 6 months, 6 to less than 12 months, 12 to less than 24 months, 24 to less than 36 months, 36 to less than 60 months, and 60 months or longer. Twenty-four to less than 36 months was used as the reference group since two or more years is the World Health Organization-recommended spacing between pregnancies.\(^1\) We used log-binomial regression models to obtain univariable and multivariable-adjusted risk ratios (RR) and 95% confidence intervals (CI) for the relationship between pregnancy interval and each perinatal outcome.\(^17\) Poisson regression with robust variance was used in the adjusted models when the log-binomial model did not converge.\(^17\) We examined the SGA and LBW outcomes among term pregnancies of at least 37 weeks gestation. We examined the other outcomes, preterm birth, stillbirth, perinatal death, and maternal anemia, among all women in our study population.

All multivariable models were adjusted for the confounders defined a priori. Continuous variables were categorized at pre-determined cut points to increase interpretability. Parity was categorized as one, two, and three or more previous births. Maternal age at enrollment in years was categorized as less than 20, 20 to less than 25, 25 to less than 30, and 30 or higher. Education in years was categorized as 0 to 4, 5 to 7, 8 to 11, and 12 or more. Marital status was dichotomized as either married/cohabiting or not partnered. History of preterm birth was a dichotomous variable for whether any of a woman’s prior pregnancies resulted in a preterm birth. Body mass index at enrollment, categorized as less than 22, 22 to less than 25, 25 to less than 30, and 30 kg/m\(^2\) or higher, and randomization to multivitamin use during pregnancy were also included in the multi-variable models due to their associations with the outcomes.\(^13, 18\) Additionally, gestational age at enrollment in weeks was included as a continuous variable in the adjusted model for the maternal anemia outcome.
The indicator method was used to address incomplete covariate information.\(^{19}\) Wald tests for linear trend were performed using the median pregnancy interval value in each exposure category. We explored the possibility of a non-linear relationship between inter-pregnancy interval and each birth outcome non-parametrically with restricted cubic splines.\(^{20}\) Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. We also examined potential effect modification by parity, age at first pregnancy, and anemia at study enrollment using likelihood ratio tests. All statistical analyses were performed using SAS software 9.3 (SAS Institute, Inc., www.sas.com, Cary, North Carolina).
Results

Our analysis includes 3973 multiparous women with singleton pregnancies and a live or stillbirth last pregnancy; 3732 (93.9%) following a live birth and 241 (6.1%) following a stillbirth. Characteristics of the included participants, stratified by last pregnancy outcome, are presented in Table 2.1.

Among women with a live birth last pregnancy (n=3732)
The mean age of women with a live birth last pregnancy was 27.5 years and their mean gestational age at enrollment was 21.6 weeks. Approximately half (n=1922, 52%) had one previous birth. The majority of women were married or cohabiting (n=3540, 95%) and had less than eight years of education (n=3053, 82%). About half of women had their first pregnancy before age 20, and 10% had a history of preterm birth. Sixty women (2%) had an inter-pregnancy interval of less than 6 months, 81 (2%) between 6 and less than 12 months, 385 (10%) between 12 and less than 24 months, 753 (20%) between 24 and less than 36 months, 1298 (35%) between 36 and less than 60 months, and 1155 (31%) 60 months or longer.

Among term births, women with inter-pregnancy intervals less than 12 months appeared to be at increased risk of SGA compared to women with intervals 24 to less than 36 months, but this effect was not statistically significant (adjusted RR 1.54; 95% CI 0.70, 3.39 for intervals < 6 months; RR 1.49; 95% CI 0.73, 3.01 for intervals 6 - < 12 months) (Table 2.2). Also among term pregnancies, women with inter-pregnancy intervals less than six months were at 4.6 times higher risk (adjusted 95% CI 1.78, 12.03) of having a LBW baby than women with intervals between 24 and less than 36 months. Among women with intervals 6 to less than 12 months long and those greater than 36 months, the risk of LBW also appeared increased, but the effect was not statistically significant.
Table 2.1. Characteristics of participants at study enrollment (n=3973), by last pregnancy outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Previous live birth (n=3732)</th>
<th>Previous stillbirth (n=241)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) or mean (SD)</td>
<td>n (%) or mean (SD)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>106 (2.9)</td>
<td>26 (10.8)</td>
</tr>
<tr>
<td>20 - &lt; 25</td>
<td>1174 (31.6)</td>
<td>102 (42.3)</td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>1440 (38.7)</td>
<td>67 (27.8)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>998 (26.8)</td>
<td>46 (19.1)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1922 (51.7)</td>
<td>149 (61.8)</td>
</tr>
<tr>
<td>2</td>
<td>1023 (27.5)</td>
<td>50 (20.8)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>772 (20.8)</td>
<td>42 (17.4)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.6 (3.5)</td>
<td>20.9 (3.5)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>3540 (95.4)</td>
<td>225 (93.8)</td>
</tr>
<tr>
<td>Not partnered</td>
<td>170 (4.6)</td>
<td>15 (6.3)</td>
</tr>
<tr>
<td>Education, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 4</td>
<td>506 (13.6)</td>
<td>44 (18.3)</td>
</tr>
<tr>
<td>5 – 7</td>
<td>2547 (68.4)</td>
<td>154 (63.9)</td>
</tr>
<tr>
<td>8 – 11</td>
<td>526 (14.1)</td>
<td>37 (15.4)</td>
</tr>
<tr>
<td>≥ 12</td>
<td>143 (3.8)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Filmer-Pritchett wealth score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; median</td>
<td>1862 (50.1)</td>
<td>131 (54.4)</td>
</tr>
<tr>
<td>≥ median</td>
<td>1855 (49.9)</td>
<td>110 (45.6)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 22</td>
<td>742 (22.9)</td>
<td>54 (25.4)</td>
</tr>
<tr>
<td>22 - &lt; 25</td>
<td>1058 (32.7)</td>
<td>65 (30.5)</td>
</tr>
<tr>
<td>25 - &lt; 30</td>
<td>1039 (32.1)</td>
<td>63 (29.6)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>398 (12.3)</td>
<td>31 (14.6)</td>
</tr>
<tr>
<td>Randomized to multivitamins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1844 (49.5)</td>
<td>127 (52.9)</td>
</tr>
<tr>
<td>No</td>
<td>1878 (50.5)</td>
<td>113 (47.1)</td>
</tr>
<tr>
<td>Age at first pregnancy, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>1957 (54.4)</td>
<td>126 (53.4)</td>
</tr>
<tr>
<td>≥ 20</td>
<td>1641 (45.6)</td>
<td>110 (46.6)</td>
</tr>
<tr>
<td>History of preterm birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>194 (10.1)</td>
<td>29 (22.1)</td>
</tr>
<tr>
<td>No</td>
<td>1720 (89.9)</td>
<td>102 (77.9)</td>
</tr>
<tr>
<td>Pregnancy interval, months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - &lt; 6</td>
<td>60 (1.6)</td>
<td>38 (15.8)</td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>81 (2.2)</td>
<td>31 (12.9)</td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>385 (10.3)</td>
<td>57 (23.7)</td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>753 (20.2)</td>
<td>39 (16.2)</td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>1298 (34.8)</td>
<td>40 (16.6)</td>
</tr>
<tr>
<td>≥ 60</td>
<td>1155 (31.0)</td>
<td>36 (14.9)</td>
</tr>
</tbody>
</table>

*Numbers may not total to 3732 and 241 due to incomplete covariate information*
Table 2.2. Inter-pregnancy interval and perinatal outcomes among women with a live birth last pregnancy (n=3732)

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>7/44 (15.9)</td>
<td>1.56 [0.76, 3.21]</td>
<td>0.79</td>
<td>1.54 [0.70, 3.39]</td>
<td>0.91</td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>9/62 (14.5)</td>
<td>1.42 [0.74, 2.73]</td>
<td>0.69</td>
<td>1.49 [0.73, 3.01]</td>
<td>0.60</td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>27/269 (10.0)</td>
<td>0.98 [0.64, 1.52]</td>
<td>0.60</td>
<td>0.99 [0.63, 1.57]</td>
<td>0.60</td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>58/569 (10.2)</td>
<td>1.00 [REF]</td>
<td>0.60</td>
<td>1.00 [REF]</td>
<td>0.60</td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>119/991 (12.0)</td>
<td>1.18 [0.88, 1.58]</td>
<td>1.00</td>
<td>1.20 [0.87, 1.64]</td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 60</td>
<td>102/942 (10.8)</td>
<td>1.06 [0.78, 1.44]</td>
<td>1.00</td>
<td>1.09 [0.77, 1.53]</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Small for gestational age (<10th percentile) among term births (≥37 weeks), n/N = 322/2877 = 11.2%

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>6/47 (12.8)</td>
<td>4.69 [1.93, 11.42]</td>
<td>0.69</td>
<td>4.63 [1.78, 12.03]</td>
<td>0.62</td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>3/66 (4.6)</td>
<td>1.67 [0.50, 5.58]</td>
<td>0.62</td>
<td>1.85 [0.53, 6.39]</td>
<td>0.56</td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>7/283 (2.5)</td>
<td>0.91 [0.38, 2.18]</td>
<td>0.62</td>
<td>0.90 [0.37, 2.18]</td>
<td>0.62</td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>16/588 (2.7)</td>
<td>1.00 [REF]</td>
<td>0.62</td>
<td>1.00 [REF]</td>
<td>0.62</td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>41/1022 (4.0)</td>
<td>1.47 [0.83, 2.60]</td>
<td>1.04</td>
<td>1.38 [0.77, 2.48]</td>
<td>1.04</td>
</tr>
<tr>
<td>≥ 60</td>
<td>40/982 (4.1)</td>
<td>1.50 [0.85, 2.65]</td>
<td>1.04</td>
<td>1.22 [0.67, 2.25]</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Low birth weight (<2500 g) among term births (≥37 weeks), n/N = 113/2988 = 3.8%

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>10/59 (15.3)</td>
<td>0.97 [0.54, 1.75]</td>
<td>&lt;0.01</td>
<td>0.99 [0.52, 1.89]</td>
<td>0.01</td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>12/77 (15.6)</td>
<td>0.89 [0.52, 1.54]</td>
<td>0.01</td>
<td>0.88 [0.48, 1.59]</td>
<td>0.01</td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>89/368 (24.2)</td>
<td>1.39 [1.09, 1.77]</td>
<td>0.01</td>
<td>1.38 [1.05, 1.81]</td>
<td>0.01</td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>126/723 (17.4)</td>
<td>1.00 [REF]</td>
<td>0.01</td>
<td>1.00 [REF]</td>
<td>0.01</td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>223/1254 (17.8)</td>
<td>1.02 [0.84, 1.24]</td>
<td>0.01</td>
<td>1.04 [0.84, 1.30]</td>
<td>0.01</td>
</tr>
<tr>
<td>≥ 60</td>
<td>145/1111 (13.1)</td>
<td>0.75 [0.60, 0.93]</td>
<td>0.01</td>
<td>0.81 [0.63, 1.04]</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Stillbirth (≥28 weeks gestation), n/N = 96/3688 = 2.6%

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>1/60 (2.5)</td>
<td>0.69 [0.09, 5.05]</td>
<td>0.74</td>
<td>0.62 [0.08, 4.69]</td>
<td>0.68</td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>2/79 (2.5)</td>
<td>1.04 [0.25, 4.41]</td>
<td>0.18</td>
<td>1.08 [0.25, 4.67]</td>
<td>0.16</td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>13/381 (3.4)</td>
<td>1.40 [0.70, 2.84]</td>
<td>0.18</td>
<td>1.35 [0.66, 2.77]</td>
<td>0.16</td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>18/741 (2.4)</td>
<td>1.00 [REF]</td>
<td>0.18</td>
<td>1.00 [REF]</td>
<td>0.18</td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>29/1283 (2.3)</td>
<td>0.93 [0.52, 1.66]</td>
<td>0.18</td>
<td>0.91 [0.50, 1.65]</td>
<td>0.16</td>
</tr>
<tr>
<td>≥ 60</td>
<td>33/1144 (2.9)</td>
<td>1.19 [0.67, 2.09]</td>
<td>0.18</td>
<td>0.96 [0.52, 1.78]</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Perinatal death (stillbirth ≥28 weeks gestation or neonatal death ≤28 days old), n/N = 156/3732 = 4.2%

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>2/60 (3.3)</td>
<td>0.84 [0.20, 3.42]</td>
<td>0.18</td>
<td>0.81 [0.19, 3.39]</td>
<td>0.92</td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>2/81 (2.5)</td>
<td>0.62 [0.15, 2.55]</td>
<td>0.18</td>
<td>0.66 [0.16, 2.76]</td>
<td>0.16</td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>14/385 (3.6)</td>
<td>0.91 [0.49, 1.70]</td>
<td>0.18</td>
<td>0.87 [0.46, 1.64]</td>
<td>0.16</td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>30/753 (4.0)</td>
<td>1.00 [REF]</td>
<td>0.18</td>
<td>1.00 [REF]</td>
<td>0.18</td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>53/1298 (4.1)</td>
<td>1.02 [0.66, 1.59]</td>
<td>0.18</td>
<td>0.96 [0.61, 1.51]</td>
<td>0.16</td>
</tr>
<tr>
<td>≥ 60</td>
<td>55/1155 (4.8)</td>
<td>1.20 [0.77, 1.85]</td>
<td>0.18</td>
<td>0.93 [0.58, 1.50]</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Table 2.2 (Continued)

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal anemia at study enrollment (hemoglobin &lt;8.5 g/dL), n/N = 373/3222 = 11.6%</td>
<td></td>
<td></td>
<td>0.27</td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>2/52 (3.9)</td>
<td>0.30 [0.08, 1.18]</td>
<td>0.31 [0.08, 1.25]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>10/75 (13.3)</td>
<td>1.04 [0.56, 1.91]</td>
<td>1.03 [0.53, 1.99]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>41/333 (12.3)</td>
<td>0.96 [0.68, 1.36]</td>
<td>0.93 [0.64, 1.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>84/655 (12.8)</td>
<td>1.00 [REF]</td>
<td>1.00 [REF]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>132/1110 (11.9)</td>
<td>0.93 [0.72, 1.20]</td>
<td>1.00 [0.76, 1.31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>104/997 (10.4)</td>
<td>0.81 [0.62, 1.07]</td>
<td>0.90 [0.66, 1.22]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p-value for test of trend

+ Adjusted for maternal age (<20, 20 - <25, 25 - <30, ≥30 years), parity (1, 2, ≥3), marital status (married/cohabiting or not partnered), education (0-4, 5-7, 8-11, ≥12 years), wealth score (< or ≥ median), body mass index at enrollment (<22, 22 - <25, 25 - <30, ≥30 kg/m²), randomization to multivitamin use, age at first pregnancy (<20 or ≥20 years), and history of preterm birth

++ Additionally adjusted for gestational age at enrollment (weeks)
Inter-pregnancy intervals of 12 to less than 24 months were associated with an increased risk of preterm birth, compared to 24 to less than 36 month intervals (adjusted RR 1.38; 95% CI 1.05, 1.81). We did not find a significantly increased risk of preterm birth, however, for intervals shorter than 18 months or longer than 36 months. Inter-pregnancy interval was not a significant independent risk factor for stillbirth or perinatal death among women with a live birth in their last pregnancy.

Among women with a stillbirth last pregnancy (n=241)

The distribution of participant characteristics at study enrollment among women with a stillbirth last pregnancy was similar to that of women with a previous live birth in terms of gestational age, marital status, education, body mass index, and age at first pregnancy (Table 2.1). Participants with a stillbirth last pregnancy tended to be younger, primiparous, have a history of a preterm birth, and have shorter inter-pregnancy intervals than women whose previous pregnancy was a live birth. Among women with a previous stillbirth, 38 (16%) had an inter-pregnancy interval of less than 6 months, 31 (13%) between 6 and less than 12 months, 57 (24%) between 12 and less than 24 months, 39 (16%) between 24 and less than 36 months, 40 (17%) between 36 and less than 60 months, and 36 (15%) 60 months or greater.

The likelihood of SGA, LBW, stillbirth, and perinatal death were all higher among women with a stillbirth last pregnancy than those who had a live birth (Tables 2.2 and 2.3). The risk of preterm birth and maternal anemia were similar.

Among women with a stillbirth last pregnancy, inter-pregnancy interval did not significantly affect the risk of SGA or LBW among term births (Table 2.3). Compared to 24 to less than 36 months, women with intervals less than 24 months and those 36 months or greater appeared to be at higher risk of preterm birth, but these associations were not statistically significant. Women with shorter inter-pregnancy intervals were at increased risk of both stillbirth (trend test p-value = 0.03) and perinatal death (trend test p-value < 0.01).
Table 2.3. Inter-pregnancy interval and perinatal outcomes among women with a stillbirth last pregnancy (n=241)

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small for gestational age (&lt;10th percentile) among term births (≥37 weeks), n/N = 26/175 = 14.9%</td>
<td></td>
<td></td>
<td>0.68</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>6/26 (23.1)</td>
<td>1.05 [0.40, 2.75]</td>
<td></td>
<td>0.84 [0.25, 2.81]</td>
<td></td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>0/22 (0)</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>8/35 (22.9)</td>
<td>1.04 [0.43, 2.55]</td>
<td></td>
<td>1.07 [0.35, 3.32]</td>
<td></td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>7/32 (21.9)</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>3/32 (9.4)</td>
<td>0.43 [0.12, 1.51]</td>
<td></td>
<td>0.39 [0.09, 1.71]</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>2/28 (7.1)</td>
<td>0.33 [0.07, 1.45]</td>
<td></td>
<td>0.40 [0.07, 2.27]</td>
<td></td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g) among term births (≥37 weeks), n/N = 16/185 = 8.7%</td>
<td></td>
<td></td>
<td>0.59</td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>2/29 (6.9)</td>
<td>0.55 [0.11, 2.79]</td>
<td></td>
<td>0.41 [0.05, 3.63]</td>
<td></td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>0/24 (0)</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>8/40 (20.0)</td>
<td>1.60 [0.53, 4.84]</td>
<td></td>
<td>1.87 [0.48, 7.36]</td>
<td></td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>4/32 (12.5)</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>1/32 (3.1)</td>
<td>0.25 [0.03, 2.12]</td>
<td></td>
<td>0.25 [0.02, 3.27]</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>1/28 (3.6)</td>
<td>0.29 [0.03, 2.41]</td>
<td></td>
<td>0.40 [0.03, 5.16]</td>
<td></td>
</tr>
<tr>
<td>Preterm birth (≤37 weeks), n/N = 36/222 = 16.2%</td>
<td></td>
<td></td>
<td>0.87</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>4/32 (12.5)</td>
<td>1.19 [0.32, 4.37]</td>
<td></td>
<td>1.44 [0.34, 6.03]</td>
<td></td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>4/27 (14.8)</td>
<td>1.41 [0.39, 5.14]</td>
<td></td>
<td>1.28 [0.31, 5.30]</td>
<td></td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>13/52 (25.0)</td>
<td>2.38 [0.84, 6.72]</td>
<td></td>
<td>2.51 [0.76, 8.26]</td>
<td></td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>4/38 (10.5)</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>5/38 (13.2)</td>
<td>1.25 [0.36, 4.30]</td>
<td></td>
<td>1.30 [0.32, 5.25]</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>6/35 (17.1)</td>
<td>1.63 [0.50, 5.29]</td>
<td></td>
<td>1.69 [0.43, 6.74]</td>
<td></td>
</tr>
<tr>
<td>Stillbirth (≥28 weeks gestation), n/N = 11/233 = 4.7%</td>
<td></td>
<td></td>
<td>0.03</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>4/36 (11.1)</td>
<td>4.33 [0.51, 36.98]</td>
<td></td>
<td>7.81 [0.50, 122.70]</td>
<td></td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>2/29 (6.9)</td>
<td>2.69 [0.26, 28.25]</td>
<td></td>
<td>0.66 [0.03, 16.40]</td>
<td></td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>4/56 (7.1)</td>
<td>2.79 [0.32, 23.98]</td>
<td></td>
<td>0.90 [0.05, 17.37]</td>
<td></td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>1/39 (2.6)</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>0/38 (0)</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>0/35 (0)</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Perinatal death (stillbirth ≥28 weeks gestation or neonatal death ≤28 days old), n/N = 20/241 = 8.3%</td>
<td></td>
<td></td>
<td>0.01</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt; 6</td>
<td>7/38 (18.4)</td>
<td>2.39 [0.67, 8.58]</td>
<td></td>
<td>3.01 [0.66, 13.78]</td>
<td></td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>3/31 (9.7)</td>
<td>1.26 [0.27, 5.81]</td>
<td></td>
<td>1.43 [0.24, 8.31]</td>
<td></td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>6/57 (10.5)</td>
<td>1.37 [0.36, 5.15]</td>
<td></td>
<td>1.36 [0.29, 6.46]</td>
<td></td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>3/39 (7.7)</td>
<td>1.00 [REF]</td>
<td></td>
<td>1.00 [REF]</td>
<td></td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>1/40 (2.5)</td>
<td>0.33 [0.04, 2.99]</td>
<td></td>
<td>0.28 [0.02, 3.21]</td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>0/36 (0)</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2.3 (Continued)

<table>
<thead>
<tr>
<th>Inter-pregnancy interval, months</th>
<th>n/N (%)</th>
<th>Univariable RR [95%CI]</th>
<th>p*</th>
<th>Multivariable RR [95%CI]</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal anemia at study enrollment (hemoglobin &lt;8.5 g/dL), n/N = 22/207 = 10.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>3/33 (9.1)</td>
<td>0.80 [0.19, 3.29]</td>
<td>0.40</td>
<td>1.06 [0.15, 7.45]</td>
<td>0.90</td>
</tr>
<tr>
<td>6 - &lt; 12</td>
<td>3/27 (11.1)</td>
<td>0.97 [0.24, 3.98]</td>
<td>1.23</td>
<td>1.37 [0.22, 6.99]</td>
<td>0.90</td>
</tr>
<tr>
<td>12 - &lt; 24</td>
<td>7/46 (15.2)</td>
<td>1.33 [0.42, 4.19]</td>
<td>2.91</td>
<td>2.91 [0.67, 12.65]</td>
<td>1.00</td>
</tr>
<tr>
<td>24 - &lt; 36</td>
<td>4/35 (11.4)</td>
<td>1.00 [REF]</td>
<td>1.00</td>
<td>1.00 [REF]</td>
<td>1.00</td>
</tr>
<tr>
<td>36 - &lt; 60</td>
<td>3/34 (8.8)</td>
<td>0.77 [0.19, 3.20]</td>
<td>0.69</td>
<td>0.69 [0.11, 4.34]</td>
<td>1.00</td>
</tr>
<tr>
<td>≥ 60</td>
<td>2/32 (6.3)</td>
<td>0.55 [0.11, 2.79]</td>
<td>2.32</td>
<td>2.32 [0.27, 19.92]</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* p-value for test of trend
+ Adjusted for maternal age (<20, 20 - <25, 25 - <30, ≥30 years), parity (1, 2, ≥3), marital status (married/cohabiting or not partnered), education (0-4, 5-7, 8-11, ≥12 years), wealth score (< or ≥ median), body mass index at enrollment (<22, 22 - <25, 25 - <30, ≥30 kg/m²), randomization to multivitamin use, age at first pregnancy (<20 or ≥20 years), and history of preterm birth
++ Additionally adjusted for gestational age at enrollment (weeks)
In the multivariable-adjusted models, women with intervals less than six months were over seven times as likely to have a stillbirth and three times more likely to have a perinatal death than women with 24 to less than 36 month intervals, although these relationships were not statistically significant. Following either a live birth or stillbirth, we did not find an association between inter-pregnancy interval and maternal anemia at study enrollment (hemoglobin < 8.5 g/dL). We also examined this relationship using an anemia definition of hemoglobin less than 11.0 g/dL, and again did not find an association.

Evaluation of non-linear relationships and effect modification

In restricted cubic spline analyses, we did not find evidence of a non-linear relationship between inter-pregnancy interval and any of the outcomes of interest, among women with either a live birth or stillbirth in their last pregnancy (test for curvature p-values ≥ 0.05). We also did not find evidence of effect modification of the relationship between inter-pregnancy interval and any of the perinatal outcomes by parity, age at first pregnancy, or anemia at enrollment (likelihood ratio p-values ≥ 0.05). Women excluded from the analysis due to missing data for inter-pregnancy interval or previous pregnancy outcome had similar baseline characteristics to women included, except that those excluded tended to be slightly older and have higher parity (data not shown).
**Discussion**

In our study population of 3973 women with a prior live or stillbirth, 16% (n=652) had inter-pregnancy intervals shorter than the World Health Organization’s recommended 24 month period. Similar to previous studies, we found that following a live birth, a short inter-pregnancy interval of less than six months significantly increased the risk of having a LBW infant, compared to 24 to less than 36 month intervals. We did not find significant evidence of increased risk of SGA or preterm birth with shorter intervals, as previously noted in other studies and meta-analysis.\(^2\) This could be due to inadequate power to detect the associations or that the effects of pregnancy spacing vary across populations.

Following a stillbirth, we found that the shorter the inter-pregnancy interval, the higher the risk of stillbirth and perinatal death in the subsequent pregnancy. There is little evidence examining this relationship following a stillbirth for comparison to our findings, but the data available also suggest similar associations between short intervals and increased risk of adverse fetal and neonatal outcomes.\(^{21-24}\) The number of cases in each exposure group was small for some outcomes, so it is possible that we did not have adequate statistical power to detect significant effects between some exposure levels and the more rare outcomes.

Using splines, we did not find evidence of a significant non-linear relationship between inter-pregnancy interval and any of the perinatal outcomes examined. We did note, however, that following a live birth, short and long inter-pregnancy intervals were associated with increased risk of LBW, and following a stillbirth, short and long intervals appeared to increase risk of preterm birth compared to the reference group, although these associations were not statistically significant. We did not find increases in risk of other adverse perinatal outcomes with longer intervals of five years or more as noted in some previous studies.
The association between short inter-pregnancy interval and LBW may support a mechanism of maternal nutritional depletion adversely affecting growth of the fetus in utero. It is possible that we did not see a similar relationship following a stillbirth because those pregnancies would have been shorter on average and women would not have had an infant to breastfeed; thus their nutritional reserves may not have been as depleted. After a stillbirth, the association between shorter pregnancy spacing and increased risk of stillbirth and perinatal death may support hypotheses of vertical disease transmission or abnormal remodeling of endometrial blood vessels affecting placentation as biologic mechanisms. We did not find a relationship between pregnancy spacing and maternal anemia at study enrollment, indicating that women’s bodies may be able to re-build their hemoglobin stores relatively quickly after delivery.

We calculated length of inter-pregnancy interval using maternal self-report of pregnancy dating, which may not have been accurately recalled. This is likely minimized since women who were unsure of their last menstrual period dating underwent ultrasound dating confirmation. The dates used to calculate pregnancy interval were obtained at the enrollment visit, prior to the outcomes’ occurrence, so any misclassification of the exposure would likely be non-differential. Ten percent of women were excluded for missing data. The baseline characteristics of these women and those included in the analysis were similar, so their exclusion is unlikely to significantly bias our results.

Unfortunately we did not have information about breastfeeding practices between pregnancies or a detailed history of each of a woman’s previous pregnancies, so we could not adjust for these factors in our analysis. We believe we have addressed many of the major known confounders of the relationship between inter-pregnancy interval and perinatal outcomes, but it is possible that residual confounding by these and other factors remains.

Our analysis is one of a small number of studies examining the effects of pregnancy spacing on perinatal outcomes among women in sub-Saharan Africa. We were able to examine various adverse pregnancy
outcomes using data collected in a standardized, detailed manner for a randomized trial. We prospectively ascertained the exposure and were able to adjust for many important confounding factors. We were also able to examine the relationship between pregnancy spacing and perinatal outcomes taking into account the outcome of the pregnancy that began the interval, which has seldom been done in previous studies. Our results may be generalizable to women in urban settings in developing countries similar to Dar es Salaam. It is possible the relationship between pregnancy spacing and perinatal outcomes varies across populations with differing breastfeeding practices, nutritional intake, and by prevalence of other factors associated with adverse pregnancy outcomes.

Conclusion

In our population of multiparous women in Dar es Salaam, Tanzania, short inter-pregnancy intervals were associated with increased risk of low birth weight following a live birth, and increased risk of stillbirth and perinatal death following a stillbirth. Information about these risks should be provided during family planning counseling. Women with short pregnancy spacing may warrant increased antenatal surveillance in their subsequent pregnancy. Public health programs and policies related to reproductive health should facilitate optimal pregnancy spacing through dissemination of information on the impact of pregnancy spacing and provision of access to effective methods of contraception and family planning services.
References


Title
Kangaroo mother care and neonatal outcomes: a systematic review and meta-analysis

Authors
Ellen O. Boundy,¹ Roya Dastjerdi,² Donna Spiegelman,¹,²,³ Wafaie W. Fawzi,¹,²,⁴ Stacey A. Missmer,¹,⁵
Ellice Lieberman,¹,⁶,⁷ Sandhya Kajeepeta,¹ Stephen Wall,⁸ Grace J. Chan²,⁸,⁹

¹Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
²Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts, USA
³Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
⁴Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
⁵Department of Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts, USA
⁶Department of Pediatric Newborn Medicine, Brigham and Women’s Hospital, Boston, Massachusetts, USA
⁷Department of Social and Behavioral Sciences, Harvard School of Public Health, Boston, Massachusetts, USA
⁸Save the Children, Washington, D.C., USA
⁹Department of Medicine, Boston Children’s Hospital, Boston, Massachusetts, USA

Funding
Bill and Melinda Gates Foundation. EB received research funding support from Training Grant T32HD060454 in Reproductive, Perinatal, and Pediatric Epidemiology from the National Institute of Child Health and Human Development, National Institutes of Health and MCHB Training Grant T76MC00001 from the Maternal and Child Health Bureau.
Abstract

Background: Kangaroo mother care (KMC) is an intervention aimed at preventing deaths among preterm and low birth weight (LBW) newborns. Previous reviews on the effects of KMC have not included observational studies, normal birth weight infants, or physiologic parameter outcomes.

Methods: We conducted a systematic review and meta-analysis of randomized trials and observational studies of KMC and neonatal outcomes through April 2014. Random effects estimates of relative risk (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes.

Findings: 1035 studies were screened; 124 of which met criteria for inclusion. Compared to conventional care, KMC was associated with 36% lower mortality among LBW newborns (<2000 g) (RR 0·64; 95% CI 0·46-0·89), but did not have a significant effect among infants of all birth weights. KMC decreased risk of neonatal sepsis (RR 0·53, 95% CI 0·34-0·83), hypothermia (RR 0·22; 95% CI 0·12-0·41), hypoglycemia (RR 0·12; 95% CI 0·05-0·32), and hospital readmission (RR 0·42; 95% CI 0·23-0·76). KMC increased likelihood of exclusive breastfeeding at hospital discharge (RR 1·50; 95% CI 1·26-1·78). Newborns receiving KMC had lower mean respiratory rate and pain measures, and higher oxygen saturation, temperature, and head circumference growth.

Interpretation: Among newborns who survived to receive KMC, KMC was associated with decreased mortality and morbidity and increased exclusive breastfeeding. Interventions to scale up KMC implementation are warranted.
**Background**

An estimated four million babies die each year during their first four weeks of life.¹ While important progress has been made toward Millennium Development Goal 4 to reduce mortality in children under 5, less improvement has been made in the neonatal period.² Preterm birth is the leading cause of global neonatal mortality, responsible for over one million deaths each year.¹,³ Additionally, LBW infants are at higher risk of neonatal mortality and morbidity, inhibited growth and development, and chronic disease.⁴ Health technologies like incubators can be used to improve outcomes in high-risk infants; however such equipment is not widely available in low- and middle-income countries where 99% of all neonatal deaths occur.¹ Effective and low-cost alternative methods of neonatal care are needed to mitigate this high disease burden.

In 1978, Dr. Edgar Rey Sanabria introduced kangaroo mother care (KMC) in Bogotá, Colombia as an alternative to incubators for LBW infants when such resources were unavailable.⁵ The World Health Organization defines KMC with four main components: early, continuous, and prolonged skin-to-skin contact (SSC) between the newborn and mother, exclusive breastfeeding when possible, early discharge from the health facility, and close follow-up at home.⁶ It is postulated that KMC improves neonatal outcomes by maintaining the newborn’s temperature and other vital sign parameters through SSC.⁵ The infant also benefits from the positive effects of breastfeeding. These mechanisms are thought to improve outcomes in all newborns, but may be especially beneficial in preterm infants.

Several meta-analyses have been published summarizing evidence related to the efficacy of KMC. Lawn et al. reported a reduced the risk of mortality and severe morbidity among preterm infants receiving KMC.⁷ Among LBW infants in randomized control trials (RCTs), KMC has also been found to decrease the risk of mortality, nosocomial infections, hypothermia, and length of hospital stay.⁵ Two Cochrane Database reviews examined the evidence on SSC alone.⁹,¹⁰ Moore et al. found that SSC improved
breastfeeding and cardio-respiratory stability, and decreased infant crying. Johnston et al. reported improved responses to procedural pain among infants in SSC. 

While these meta-analyses have provided important information on the effectiveness of KMC, they are limited to specific outcome measures, exposure measures, study designs, and newborn populations. An inclusive review of the literature on KMC is needed to give a more complete understanding of its benefits and drawbacks. This systematic review and meta-analysis aims to provide a comprehensive summary of observational studies and randomized controlled trials on KMC and neonatal outcomes.
Methods

Search strategy and selection criteria

The literature search for this review included original reports, direct queries of authors of published papers, and program reports with no limitation on year of publication. Studies were included if they reported an association between KMC and any neonatal outcome. We defined KMC as SSC between a caregiver and newborn, often also involving exclusive or nearly exclusive breastfeeding and early discharge from the hospital. We excluded studies with non-human subjects, less than 10 participants, non-primary data collection or analysis, no report of a quantitative effect measure, no comparison group, and no neonatal outcome measure. We did not restrict to a specific gestational age or birth weight of newborns receiving KMC.

Studies were identified through searches of the electronic databases PubMed, Embase, Web of Science, Scopus, AIM, LILACS, IMEMR, IMSEAR, and WPRIM using the search terms ‘kangaroo mother care,’ ‘kangaroo care,’ and ‘skin to skin care’ through April 24, 2014. We also conducted hand-searches of the reference lists of published systematic reviews. To search the “grey literature” for unpublished studies, we explored programmatic reports and requested data from programs implementing KMC.

Data abstraction and synthesis

All abstracts were screened by two independent reviewers. When eligibility for inclusion was unclear from the abstract, two reviewers conducted full-text screens. Two reviewers then abstracted data from the full-text of all articles meeting the inclusion criteria. At each stage, reviewers compared results to ensure agreement. In the case of disagreement, a third party acted as tiebreaker. Data from articles in English, Spanish, and Portuguese were abstracted by two fluent speakers. For articles in less common languages, a single native speaker or online translation software was used for data abstraction. If an article was missing key information, we contacted authors by email to request data or clarification.
We collected information on study design, setting, participant characteristics, components and description of KMC and comparison groups, follow-up time, outcomes, assessment of bias, and measures of association. We collected exposure data on the components of KMC, clinical stabilization criteria for starting KMC, and duration of SSC promoted and practiced. Raw data and relative risk or mean difference effect estimates with 95% confidence intervals were extracted.

Study quality
Two independent reviewers assessed the methodological quality of included studies in five domains: selection bias, information bias, detection bias, attrition bias, and other bias. For observational studies, an additional domain for confounding was assessed. Each domain was categorized as high, low, or unclear risk of bias. We then created an overall assessment of bias for each study. For RCTs, if both selection and information bias were low risk, the overall risk of bias was considered low. If either domain was high risk, the overall risk of bias was designated as high. For observational studies, if selection bias, information bias, and confounding were all low risk, the overall risk of bias was considered low. If any of those three domains was high risk, the overall risk was considered high. Otherwise, the overall risk of bias was considered unclear.

Statistical analysis
We used the random effects estimator to assess the effect of KMC compared to conventional care on each neonatal outcome. For dichotomous outcomes, we report summary estimates as relative risks (RR) and 95% confidence intervals (CI). For studies which did not report a RR, we calculated the RR and standard error from the raw data if available. We excluded studies with zero cells from the summary estimates. For continuous outcomes, we report summary estimates as mean differences (MD) and 95% CI. When outcomes were reported using different units or scales across studies, the standardized mean difference (SMD) was calculated. When available, estimates adjusted for confounding were used rather than crude estimates. We performed sensitivity analyses by restricting to RCTs and adjusted RR estimates for
dichotomous outcomes, and restricting to RCTs and randomized crossover studies for continuous outcomes.

To assess between-study heterogeneity, we report the $I^2$ statistic and the p-value for the Q statistic.$^{12-14}$ The $I^2$ statistic quantifies the amount of variation in the effect estimate attributable to between-study heterogeneity, reported as a percentage. A higher $I^2$ indicates more heterogeneity in the effect across studies. We conducted subgroup analyses and meta-regression for outcomes with data from at least 10 studies. We explored the effect of KMC on neonatal outcomes in the following pre-determined subgroups: year, study type, sample size, location, country-level economy,$^{15}$ country-level neonatal mortality in 2013,$^{16}$ infant gestational age and weight at birth, KMC components, SSC initiation criteria and duration, and study quality classification. In the meta-regression analyses, we report the residual $I^2$, indicating the amount of remaining heterogeneity in the effect estimate after adjusting for a given characteristic. The indicator method was used for missing covariate information in meta-regression analyses.$^{17}$

We assessed publication bias by visual inspection of funnel plots of effect size and standard error for asymmetry and by Begg’s rank correlation and Egger’s linear regression tests.$^{18,19}$ All meta-analyses were conducted using STATA statistical software (version 13·1), and risk of bias figures were created using RevMan software (version 5·3).

Role of the funding source

Financial support was provided by a grant from the Bill and Melinda Gates Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Results

Our search identified 2515 records (Figure 3.1). We then identified 29 additional records related to KMC through crosscheck of reference lists from previous reviews, personal communication with an author, and programmatic reports. After 1006 duplicate records were removed, 1035 underwent initial abstract screening. Of those, 527 did not meet inclusion criteria. Full-text articles for the remaining 508 records were then assessed for inclusion. Of those, 384 did not meet inclusion criteria. This review and meta-analysis includes 124 studies that reported an association between KMC and at least one neonatal outcome. One hundred eleven of the included studies (90%) were in English, seven (6%) in Portuguese, four (3%) in Spanish, and two (2%) in Farsi. We emailed eight authors to obtain additional data or clarification, and received a response with data from two. A description of each study included in this review is in Supplementary Table 3.13 and risk of bias classification for each study is presented in Supplementary Tables 3.11 and 3.12.

Study characteristics

Characteristics of the 124 included studies are presented in Table 3.1. One hundred ten studies (89%) were published between 2000 and 2014. Seventy-six studies (61%) had less than 100 study participants. Fifty-five studies (44%) were RCTs, 8 (6%) were randomized crossover trials, and the remaining 61 studies (49%) were observational or non-randomized intervention studies. The vast majority (n=113, 94%) were conducted in middle or high income countries. One hundred eighteen studies (98%) took place in health facilities, and 3 (2%) were community or population-based.

Among articles reporting gestational age data, the majority (n=61, 68%) were among preterm infants less than 37 weeks gestation at birth, 17 (19%) were of full-term infants defined as 35 to 37 weeks or greater, and 12 (13%) were of infants of all gestational ages.
Figure 3.1 Flow diagram for identification of included studies
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of studies, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year of publication</strong></td>
<td></td>
</tr>
<tr>
<td>1988 - 1999</td>
<td>14 (11)</td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>58 (47)</td>
</tr>
<tr>
<td>2010 - 2014</td>
<td>52 (42)</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>43 (35)</td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>33 (27)</td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>21 (17)</td>
</tr>
<tr>
<td>≥ 200</td>
<td>27 (22)</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td></td>
</tr>
<tr>
<td>Randomized control trial</td>
<td>55 (44)</td>
</tr>
<tr>
<td>Cohort</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Pre-post</td>
<td>23 (19)</td>
</tr>
<tr>
<td>Intervention trial (non-randomized)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Randomized crossover</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Crossover (non-randomized)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Case-control</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Chart review</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Facilities evaluation</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Interview/survey</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Region (World Health Organization)</strong></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Americas</td>
<td>50 (41)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Europe</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Country-level economy (World Bank)</strong></td>
<td></td>
</tr>
<tr>
<td>Low income</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Middle income</td>
<td>65 (54)</td>
</tr>
<tr>
<td>High income</td>
<td>48 (40)</td>
</tr>
<tr>
<td>Multiple</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Country-level neonatal mortality ratio, deaths/1000 live births</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>52 (43)</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>36 (30)</td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>29 (24)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>4 (3)</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>92 (90)</td>
</tr>
<tr>
<td>Rural</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (6)</td>
</tr>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
</tr>
<tr>
<td>NICU or step-down unit</td>
<td>51 (42)</td>
</tr>
<tr>
<td>Health facility</td>
<td>67 (55)</td>
</tr>
<tr>
<td>Community or population based</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Number of studies, n (%)</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Gestational age at birth</strong></td>
<td></td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>34 (38)</td>
</tr>
<tr>
<td>Very preterm &lt; 34 weeks</td>
<td>27 (30)</td>
</tr>
<tr>
<td>Full-term ≥ 35 – 37 weeks</td>
<td>17 (19)</td>
</tr>
<tr>
<td>All gestational ages</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Comparison: preterm vs full term</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
</tr>
<tr>
<td>Low birth weight ≤ 2500 g</td>
<td>47 (58)</td>
</tr>
<tr>
<td>Very low birth weight ≤ 1500 g</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Normal birth weight ≥ 2500 g</td>
<td>9 (11)</td>
</tr>
<tr>
<td>All birth weights</td>
<td>10 (12)</td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
</tr>
<tr>
<td>SSC only</td>
<td>71 (68)</td>
</tr>
<tr>
<td>SSC + EBF</td>
<td>14 (13)</td>
</tr>
<tr>
<td>SSC + EBF + DC</td>
<td>1 (1)</td>
</tr>
<tr>
<td>SSC + EBF + DC + FU</td>
<td>4 (4)</td>
</tr>
<tr>
<td>SSC + DC</td>
<td>1 (1)</td>
</tr>
<tr>
<td>SSC + DC + FU</td>
<td>7 (7)</td>
</tr>
<tr>
<td>SSC + EBF + FU</td>
<td>7 (7)</td>
</tr>
<tr>
<td><strong>SSC initiation time</strong></td>
<td></td>
</tr>
<tr>
<td>Immediately after birth</td>
<td>7 (8)</td>
</tr>
<tr>
<td>After stability criteria met</td>
<td>41 (48)</td>
</tr>
<tr>
<td>After other criteria met</td>
<td>27 (31)</td>
</tr>
<tr>
<td>For a painful procedure</td>
<td>11 (13)</td>
</tr>
<tr>
<td><strong>SSC duration promoted, hours/day</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>38 (48)</td>
</tr>
<tr>
<td>2 – &lt; 4</td>
<td>14 (18)</td>
</tr>
<tr>
<td>4 – &lt; 9</td>
<td>6 (8)</td>
</tr>
<tr>
<td>9 – &lt; 12</td>
<td>0</td>
</tr>
<tr>
<td>12 – &lt; 22</td>
<td>1(1)</td>
</tr>
<tr>
<td>≥ 22</td>
<td>20 (25)</td>
</tr>
<tr>
<td><strong>Number of days of SSC promoted</strong></td>
<td></td>
</tr>
<tr>
<td>1 - 5</td>
<td>47 (75)</td>
</tr>
<tr>
<td>6 - &lt; 30</td>
<td>9 (14)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Dependent on hospital stay</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

NICU: neonatal intensive care unit, g: grams, KMC: kangaroo mother care, SSC: skin-to-skin contact, EBF: exclusive breastfeeding, DC: early discharge, FU: follow-up after discharge
Among articles reporting gestational age data, the majority (n=61, 68%) were among preterm infants less than 37 weeks gestation at birth, 17 (19%) were of full-term infants defined as 35 to 37 weeks or greater, and 12 (13%) were of infants of all gestational ages. Similarly, forty-seven studies (58%) were among LBW infants (≤ 2500 g), an additional 15 (19%) were of very LBW infants (≤ 1500 g), nine (11%) were in normal weight infants, and 10 (12%) were among infants of all birth weights. Forty-three studies (35%) did not specify the birth weight of infants in their study and 34 (27%) did not specify gestational age.

Most studies (n=71, 68%) defined KMC as SSC only. Fourteen studies (13%) defined KMC as SSC plus promotion of exclusive breastfeeding. Twenty studies’ (19%) KMC definition included an early discharge or outpatient follow-up component. Nineteen studies (15%) did not describe the components of their KMC intervention. SSC was initiated immediately after birth in 7 studies (8%), while 41 (48%) had stability criteria to be met before SSC initiation, and 27 (31%) had some other non-stability related criteria. Eleven studies (14%) looking at pain-related outcomes had mothers start SSC around the time of a painful infant procedure. Fifty-two studies (66%) promoted less than 4 hours of SSC per day, 20 (25%) promoted at least 22 hours per day, and few studies (n=7, 9%) had a SSC duration between 4 and 21 hours per day. Thirty-eight studies (31%) did not specify when SSC was initiated, and 45 studies (36%) did not report the daily duration of SSC mothers were instructed to practice. Information on duration of SSC actually practiced, as opposed to promoted or instructed, was only available in 16 studies (13%).

**Meta-analysis**

Results for summary RR estimates for the effect of KMC compared to conventional care on dichotomous outcomes are reported in Table 3.2, and estimates of MD measures for continuous outcomes are reported in Table 3.3. We present the results by outcome type: mortality, breastfeeding, infection, heart rate, respiration and oxygenation, temperature, hypoglycemia and cortisol levels, hospital stay, growth, pain, and other outcomes.
Table 3.2. Relative risk (RR) and 95% confidence interval (CI) for the effect of KMC compared to conventional care on dichotomous neonatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All studies</th>
<th>RCT and adjusted observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>RR [95%CI] ^*</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latest follow-up</td>
<td>16</td>
<td>0·77 [0·60, 0·99]</td>
</tr>
<tr>
<td>≤ 45 days</td>
<td>11</td>
<td>0·79 [0·57, 1·10]</td>
</tr>
<tr>
<td>3 – 12 months</td>
<td>7</td>
<td>0·59 [0·43, 0·82]</td>
</tr>
<tr>
<td>LBW &lt; 2000g</td>
<td>15</td>
<td>0·64 [0·46, 0·89]</td>
</tr>
<tr>
<td>All birth weights</td>
<td>2</td>
<td>1·04 [0·82, 1·33]</td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge or 40-41 weeks</td>
<td>13</td>
<td>1·50 [1·26, 1·78]</td>
</tr>
<tr>
<td>1-4 months old</td>
<td>8</td>
<td>1·39 [1·11, 1·74]</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>12</td>
<td>0·67 [0·43, 1·05]</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8</td>
<td>0·53 [0·34, 0·83]</td>
</tr>
<tr>
<td>NEC</td>
<td>3</td>
<td>0·96 [0·45, 2·04]</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>9</td>
<td>0·22 [0·12, 0·41]</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>3</td>
<td>0·77 [0·59, 1·01]</td>
</tr>
<tr>
<td>Outcome</td>
<td>All studies</td>
<td>RCT and adjusted observational studies</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>RR [95% CI]</td>
</tr>
<tr>
<td>Apnea</td>
<td>6</td>
<td>0.39 [0.13, 1.14]</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2</td>
<td>0.12 [0.05, 0.32]</td>
</tr>
<tr>
<td>Readmission</td>
<td>2</td>
<td>0.42 [0.23, 0.76]</td>
</tr>
</tbody>
</table>

KMC: kangaroo mother care, PMA: post-menstrual age, NEC: necrotizing enterocolitis

^ Random effects estimates

* I-squared: variation in risk ratio or mean difference attributable to heterogeneity
Table 3.3. Mean difference (MD) and 95% confidence interval (CI) for the effect of KMC compared to conventional care on continuous neonatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All studies</th>
<th>RCT and randomized crossover studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>MD [95% CI]^</td>
</tr>
<tr>
<td>Vital signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>15</td>
<td>-0.41 [-2.25, 1.42]</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>12</td>
<td>-3.17 [-5.15, -1.19]</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>14</td>
<td>0.90 [0.35, 1.45]</td>
</tr>
<tr>
<td>Temperature, degrees C</td>
<td>14</td>
<td>0.24 [0.15, 0.33]</td>
</tr>
<tr>
<td>Breastfeeding initiation time, SMD</td>
<td>4</td>
<td>-1.07 [-2.30, 0.17]</td>
</tr>
<tr>
<td>Growth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight change, g</td>
<td>5</td>
<td>3.29 [-4.95, 11.52]</td>
</tr>
<tr>
<td>Weight change, g/day</td>
<td>5</td>
<td>2.58 [-0.51, 5.67]</td>
</tr>
<tr>
<td>Weight change, g/kg/day</td>
<td>2</td>
<td>-0.84 [-3.39, 1.70]</td>
</tr>
<tr>
<td>Weight change, SMD</td>
<td>11</td>
<td>0.16 [-0.08, 0.40]</td>
</tr>
<tr>
<td>Length change, cm/week</td>
<td>2</td>
<td>0.15 [-0.09, 0.39]</td>
</tr>
<tr>
<td>Length change, SMD</td>
<td>3</td>
<td>0.24 [-0.02, 0.49]</td>
</tr>
<tr>
<td>Head circumference change, cm/week</td>
<td>3</td>
<td>0.19 [0.01, 0.37]</td>
</tr>
</tbody>
</table>
Table 3.3 (Continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All studies</th>
<th></th>
<th></th>
<th>RCT and randomized crossover studies</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>MD [95% CI]^</td>
<td>p-value</td>
<td>I^2, %^</td>
<td>n</td>
<td>MD [95% CI]^</td>
</tr>
<tr>
<td>Head circumference change, SMD'^</td>
<td>4</td>
<td>0-61 [0-20, 1-02]</td>
<td>&lt;0-01</td>
<td>77</td>
<td>4</td>
<td>0-61 [0-20, 1-02]</td>
</tr>
<tr>
<td>Pain</td>
<td>10</td>
<td>-0-63 [-1-09, -0-16]</td>
<td>0-01</td>
<td>89</td>
<td>8</td>
<td>-0-75 [-1-28, -0-22]</td>
</tr>
<tr>
<td>Premature Infant Pain Profile score, 0-21'^</td>
<td>3</td>
<td>-1-14 [-2-34, 0-05]</td>
<td>0-06</td>
<td>85</td>
<td>2</td>
<td>-1-21 [-2-88, 0-45]</td>
</tr>
<tr>
<td>Neonatal Infant Pain Scale score, 0-7'^</td>
<td>2</td>
<td>-1-40 [-3-08, 0-28]</td>
<td>0-10</td>
<td>91</td>
<td>2</td>
<td>-1-40 [-3-08, 0-28]</td>
</tr>
<tr>
<td>Crying duration after painful stimulus, sec'^</td>
<td>3</td>
<td>-11-30 [-19-79,-2-80]</td>
<td>0-01</td>
<td>0</td>
<td>3</td>
<td>-11-30 [-19-79,-2-80]</td>
</tr>
<tr>
<td>Heart rate during painful stimulus, beats/min'</td>
<td>3</td>
<td>-7-46 [-12-98, -1-93]</td>
<td>0-01</td>
<td>29</td>
<td>3</td>
<td>-7-46 [-12-98, -1-93]</td>
</tr>
<tr>
<td>Heart rate after painful stimulus, beats/min'</td>
<td>4</td>
<td>-4-00 [-8-93, 0-93]</td>
<td>0-11</td>
<td>87</td>
<td>3</td>
<td>-7-52 [-8-47, -6-58]</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>0-68 [-2-11, 0-75]</td>
<td>0-35</td>
<td>95</td>
<td>5</td>
<td>0-38 [-2-99, 2-23]</td>
</tr>
<tr>
<td>Length of hospital stay, days'^</td>
<td>3</td>
<td>0-44 [-0-94, 0-06]</td>
<td>0-08</td>
<td>54</td>
<td>2</td>
<td>0-58 [-0-88, -0-29]</td>
</tr>
</tbody>
</table>

Min: minute, C: Celsius, SMD: standardized mean difference, g: grams, kg: kilograms, cm: centimeters

^ Random effects mean difference; * I-squared: variation in risk ratio or mean difference attributable to heterogeneity
Mortality

The RR of mortality assessed at each study’s latest follow-up time was 0·77 (n=16; 95% CI 0·60, 0·99); with I²=67%, indicating moderate heterogeneity across studies (Figure 3.2). Eleven studies reported mortality during the first 45 days of life, finding a non-significant decrease in mortality (RR 0·79; 95% CI 0·57, 1·10; I²=77%), while seven studies reporting mortality up to 3, 6, or 12 months of age showed 41% lower mortality in the KMC groups compared to controls (RR 0·59; 95% CI 0·43, 0·82; I²=0%) (Table 3.2). Two studies contributed mortality estimates at both early and later follow-up times.²⁹,³⁰

Among LBW newborns weighing less than 2000 g, KMC decreased mortality at latest follow-up time by 36% (n=15; RR 0·64; 95% CI 0·46, 0·89; I²=72%). In the two studies including infants of all birth weights, KMC did not significantly affect mortality (RR 1·04; 95% CI 0·82, 1·33). Results of the other subgroup analyses of study characteristics and KMC components for mortality at latest follow-up are shown in Supplementary Table 3.1. We did not find important differences in the effect of KMC on mortality by study location or country-level economy or background neonatal mortality rate. The two studies whose KMC intervention included SSC, exclusive breastfeeding, early discharge, and close follow-up showed a stronger protective effect of KMC against mortality (RR 0·43; 95% CI 0·19, 0·98) than studies using other definitions of KMC. Similarly, when mothers were encouraged to provide SSC plus at least one other KMC component, KMC was protective against mortality (n=9; RR 0·65; 95% CI 0·48, 0·89), while studies where KMC was defined as SSC alone did not (n=5; RR 0·71; 95% CI 0·33, 1·52). There was no difference in the mortality outcome among studies which included promotion of exclusive breastfeeding in their KMC definition compared to those who did not.

Studies instructing mothers to start SSC after stability criteria was met showed a similarly protective effect against mortality (n=9, RR 0·57; 95% CI 0·34, 0·97) as those which started SSC immediately (n=3, RR 0·51; 95% CI 0·33, 0·78) (Supplementary Figure 3.1). The 11 studies promoting at least 22 hours of SSC per day showed a protective effect of KMC (RR 0·64; 95% CI 0·44, 0·92) on mortality, while there was no effect in the one study promoting a duration of 4 to 8 hours per day or the four studies which did not define SSC duration. (Supplementary Figure 3.2).
Figure 3.2. Forest plot for effect of KMC compared to conventional care on mortality at latest follow-up time, grouped by follow-up time.
Breastfeeding

KMC increased the likelihood of exclusive breastfeeding at hospital discharge or 40-41 weeks post-menstrual age by 50% (n=13; RR 1·50; 95% CI 1·26, 1·78; I²=93%) (Supplementary Figure 3.3). Among these studies, KMC increased the likelihood of exclusive breastfeeding across nearly all subgroups of study, infant, and KMC characteristics (Supplementary Table 3.2). Studies that encouraged exclusive breastfeeding as part of the KMC intervention showed a 10% stronger effect (n=7; RR 1·46; 95% CI 1·17, 1·82) than the studies that did not have this KMC component (n=4; RR 1·36; 95% CI 1·11, 1·66).

In studies which examined exclusive breastfeeding at longer follow-up times of one to four months, KMC increased its likelihood by 39% (n=8; RR 1·39; 95% CI 1·11, 1·74; I²=60%) (Table 3.2). KMC did not have a significant impact on the standardized mean difference in time to breastfeeding initiation (n=4; SMD -1·07; 95% CI -2·30, 0·17; I²=97%) (Table 3.3). Several studies looked at other feeding outcomes that were too heterogeneous to combine into a summary estimate.\textsuperscript{31-38}

Infection

Risk of infection during study follow-up was not statistically different between the KMC and control groups (n=12; RR 0·67; 95% CI 0·43, 1·05; I²=60%) (Table 3.2). When stratified by infection type, KMC was associated with a 47% decrease in risk of sepsis (n=8; RR 0·53; 95% CI 0·34, 0·83; I²=25%), but did not have an effect on methicillin-resistant staph aureus or other severe infections (n=4; RR 1·00; 95% CI 0·40, 2·46; I²=77%) (Supplementary Figure 3.4). Similarly, KMC did not have a significant effect on risk of necrotizing enterocolitis (n=3; RR 0·96; 95% CI 0·45, 2·04) (Table 3.2). All the studies that examined sepsis and necrotizing enterocolitis were among infants less than 2250 g at birth.

Among RCTs, KMC decreased risk of infection by 49% (n=9; RR 0·51; 95% CI 0·32, 0·81; I²=54%) (Supplementary Table 3.3). The nine studies that had stability criteria before initiating SSC showed a protective
effect of KMC against infection (RR 0.50; 95% CI 0.33-0.77), while the two studies that had other non-stability related criteria before initiation did not show an effect (RR 1.00; 95% CI 0.69-1.45).

Vital signs
Heart rate
KMC did not have a significant effect on mean heart rate (n=15; MD 0.41 beats per minute; 95% CI -2.25, 1.42; I²=46%) (Supplementary Figure 3.5). No statistical or clinically significant differences were noted by subgroup analysis of study, infant, or KMC characteristics (Supplementary Table 3.4).

Respiration/oxygenation
Compared to conventional care, KMC did not significantly reduce the risk of apnea in six studies of LBW infants less than 2000 g (RR 0.39; 95% CI 0.13, 1.14; I²=42%) (Table 3.2). Newborns receiving KMC had a respiratory rate three breaths per minute slower than controls (n=12; MD -3.17; 95% CI -5.15, -1.19; I²=75%) (Supplementary Figure 3.6). KMC was also associated with 0.9% higher oxygen saturation (n=14; MD 0.90; 95% CI 0.35, 1.45; I²=92%) (Supplementary Figure 3.7). In subgroup analyses, KMC was consistently associated with lower respiratory rate and higher oxygen saturation (Supplementary Tables 3.5 and 3.6).

Temperature
KMC was associated with a 78% decrease in hypothermia risk (n=9; RR 0.22; 95% CI 0.12, 0.41; I²=71%) (Table 3.2). KMC also lowered the risk of hyperthermia by 23% (n=3; RR 0.77; 95% CI 0.59, 1.01; I²=0%). The mean body temperature of infants receiving KMC was 0.24 degrees Celsius higher than in controls (n=14; 95% CI 0.15, 0.33; I²=82%) (Supplementary Figure 3.8), and this effect was similar across subgroups of study, infant, and KMC characteristics (Supplementary Table 3.7).
Hypoglycemia and cortisol levels

KMC was strongly protective against hypoglycemia in the two studies reporting this outcome among LBW babies (RR 0.12; 95% CI 0.05, 0.32) (Table 3.2). Standardized mean cortisol levels were not different between KMC and conventional care groups (n=3; SMD -0.44; 95% CI -0.94, 0.06) (Table 3.3).

Hospital stay

KMC decreased the likelihood of hospital readmission by 58% in two studies (95% CI 0.23, 0.76) (Table 3.2). Length of hospital stay in days did not differ between the KMC and control groups (n=12; MD -0.68; 95% CI -2.11, 0.75; \( I^2 = 95\% \)) (Supplementary Figure 3.9). Among these, one study had early discharge as part of their KMC intervention, and they did not report a significant difference in length of stay (MD -3.20; 95% CI -7.51, 1.11) (Supplementary Table 3.8). One study reported mean length of hospital and neonatal intensive care unit stays stratified by birth weight <1201 g, 1201-1500 g, 1501-1800 g, and 1800-2000 g, and found shorter hospital stays in the KMC group compared to controls among babies less than 1500g, and in length of neonatal intensive care unit stay among babies 1201-1500g.\(^{39}\)

Growth

Various infant growth outcomes were examined across studies, including weight, length, and head circumference measures. We looked at the effect of KMC on different measures of weight gain individually and by combining them using the SMD (Table 3.3, Supplementary Figure 3.10). We did not find a significant association between KMC and the SMD in weight gain or body length growth. In three studies of infants less than 2000 g at birth, those receiving KMC had head circumference growth 0.19 cm per week higher than controls (95% CI 0.01, 0.37; \( I^2 = 89\% \)). Among the 11 studies used to estimate the SMD in weight gain, there were no important differences in the effect of KMC by subgroups of study, infant, or KMC characteristics (Supplementary Table 3.9). One additional study examined the risk of being malnourished, overweight, and obese at five to six years old and found no difference between the KMC and control groups.\(^{40}\)
Pain

Several studies examined pain-related outcomes, including crying, heart rate, and pain scores during and after painful procedures (Table 3.3). Seven studies used the Premature Infant Pain Profile scale, which has seven domains and a total score range from 0-21. On average, infants given SSC during a painful procedure scored 0.83 points lower on this pain scale than controls (95% CI -1.53, -0.13; I²=88%). Studies using the Neonatal Infant Pain Scale (n=3) and the Neonatal Facial Coding System (n=2) showed non-significant decreases in pain among infants receiving SSC during painful procedures compared to controls. When pain scores were combined across scales using the SMD, a decrease in pain score was again noted in babies receiving SSC compared to conventional care (SMD -0.63; 95% CI -1.09, -0.16; I²=89%) (Supplementary Figure 3.11). This effect was similar across subgroups (Supplementary Table 3.10).

After a painful stimulus, infants in SSC cried on average 11 seconds less than control group infants (n=3; MD -11.30; 95% CI -19.79, -2.80; I²=0%) (Table 3.3). Three studies looked at infant heart rate during painful stimulus as a proxy pain measure, and mean heart rate was 7 beats per minute slower in the SSC groups than controls (MD -7.46; 95% CI -12.98, -1.93; I²=29%).

Other outcomes

A variety of other neonatal outcomes were reported in a single study or in different ways across studies that could not be combined into a summary measure. Those outcomes related to illness included retinopathy, bronchopulmonary dysplasia, regurgitation, respiratory tract disease, diarrhea, and intraventricular hemorrhage. Other outcomes included hyperbilirubinemia, blood pressure, stratum corneum hydration, oxygen requirement, carbon dioxide production, LF/HF ratio, thyroid measures, water loss, home observation of the environment, stabilization of cardio-pulmonary system, time in incubator, and cost of care, among others. Several studies also examined the effect of KMC on neuro-cognitive outcomes. These data were reported across different scales and endpoints at different ages and thus could not be combined into summary measures. They included assessments of behavior, mental and psychomotor development, reflexes, temperament, brain maturation, and sleep measures.
Estimates that were presented only as medians rather than means with standard deviation, only as odds ratios without raw data, or where with zero cells were excluded from summary measures.62, 86, 89-102

Risk of bias

After evaluating each of the five domains of bias in the 55 RCTs, we classified 25 (45%) as having overall low risk of bias, 14 (25%) as high, and 16 (29%) unclear (Supplementary Figure 3.12). The observational studies were assessed using the same five bias domains as for RCTs plus a domain for confounding. Among these 69 studies, overall risk of bias was considered low in 29 (42%), high in 24 (35%), and unclear in 16 (23%) (Supplementary Figure 3.13). When restricted to studies with low overall risk of bias, the protective effects of KMC on mortality, exclusive breastfeeding, and infection were stronger than results obtained using all studies (Supplementary Tables 1 – 3). Effect estimates for continuous outcomes did not materially change when restricted to studies with low overall risk of bias (Supplementary Tables 3.4 – 3.10).

Publication bias

We assessed publication and small study bias for the mortality at latest follow-up time, exclusive breastfeeding at hospital discharge, and infection outcomes. No significant evidence of publication bias was noted for the mortality outcome by either Begg’s (p=0·89) or Egger’s (p=0·36) tests or by visual inspection of the funnel plot (Supplementary Figure 3.14). Similarly, no evidence of publication bias was found for exclusive breastfeeding (Begg’s p=0·25; Egger’s p=0·12) or infection (Begg’s p=0·45; Egger’s p=0·75).
Discussion

Kangaroo mother care is associated with decreased mortality among newborns who survive to receive KMC, when compared to conventional care, particularly among low birth weight infants. KMC also increases the likelihood of exclusive breastfeeding up to four months of age and decreases risk of sepsis, hypothermia, hypoglycemia, and hospital readmission in newborns. Additionally, infants receiving KMC have improved vital signs, greater head circumference growth, and lower pain responses when experiencing painful stimuli.

We found a similar magnitude in reduction of mortality risk among LBW babies exposed to KMC as that found in prior reviews among LBW and preterm babies.\textsuperscript{7, 8} We did not find a significant difference in mortality for KMC compared to controls in the two studies that included babies of all birth weights. We noted a similar protective effect of KMC against sepsis and hypothermia as previously described.\textsuperscript{8} Some studies have found decreased length of hospital stay among babies receiving KMC, while we did not find a significant difference.\textsuperscript{8} This could be due to differences in study inclusion criteria and infant characteristics. Our results showing an increased likelihood of exclusive breastfeeding among babies receiving KMC were similar to previous reviews.\textsuperscript{8, 9} Like Johnson et al., we found decreased infant pain scores using the PIPP scale.\textsuperscript{10} We found an increase in head circumference growth, but no difference in length or weight gain, with most measurements taken across the hospital stay period. Conde-Agudelo et al. reported an increase in growth parameters for KMC-exposed babies compared to controls at latest follow-up, but similarly to our results, no important differences in growth measured at discharge or 40-41 weeks post-menstrual age.\textsuperscript{8}

The positive effects on respiratory, oxygenation, glycemic, and temperature-related parameters support the hypothesis that KMC can improve physiologic regulation in the neonate. Maintenance of these parameters could also decrease susceptibility to infection. Lower pain parameters among infants receiving KMC indicates that it may be beneficial for LBW and preterm infants who experience numerous blood draws and injections over the course of their hospital stay.
How much of the effect of KMC is through SSC compared to other components of the intervention remains unclear. In many settings, KMC also includes additional teaching and support for new parents from providers and community health workers, which could provide additional benefits. Given the sparsity of details on KMC characteristics, we were unable to fully analyze the individual KMC components’ effects. We were not able to adequately examine the dose-response relationship between duration of SSC and neonatal outcomes because there were few studies with KMC duration between four and 22 hours per day. The effects of KMC may be confounded with breastfeeding as a component of KMC. We attempted to explore this by looking at subgroups of studies that encouraged exclusive breastfeeding as a part of their KMC intervention compared to those which did not. We did not see a consistent difference in effect in those comparisons, which may be related to a lack of data available on breastfeeding.

To summarize all the evidence available to date on KMC and neonatal outcomes, our meta-analysis included both randomized trials and observational studies, and did not limit the gestational age or birth weight of newborns included. This allowed us to look at as many studies as possible for each outcome and perform sensitivity analyses. We were able to assess the effect of KMC on normal weight and term babies albeit with limited data. We collected information on study design, newborn characteristics, and KMC components to look for potential differences in the effect of KMC in subgroups and meta-regression analyses. We also examined several outcomes that have not been included in previous reviews. To obtain summary estimates, we defined our exposure as any form of KMC and our comparison group as any type of conventional care that did not include KMC or SSC. There was heterogeneity in the definition and components of KMC and conventional care across studies. We attempted to address this limitation by looking at subgroup analyses by KMC components, duration, and initiation time.

Conclusion

Kangaroo mother care is protective against a variety of morbidities and mortality and improves physiologic parameters in the neonate. This relatively low cost intervention has the potential to prevent many of the short and long-term complications associated with preterm birth, and may also provide benefits to full-term newborns.
Further research is needed to help determine the ideal duration and components of KMC that provide the most benefit. Additional studies among full term, normal birth weight babies, newborns delivered by Cesarean section, and KMC provided by caregivers other than the mother are also needed to determine the effectiveness of KMC in these populations. Understanding the barriers and facilitators to successful implementation of KMC would also help provide guidance for clinicians and policy-makers focused on improving maternal and newborn health.
References


87. Andrade ISNd, Guedes ZCF. Sucção do recém-nascido prematuro: comparação do método mãe-canguru com os cuidados tradicionais


97. Toma TS, Venâncio SI, Andretto DDA. Maternal perception of low birth weight babies before and following the implementation of the Kangaroo Mother Care in a public hospital, in the city of São Paulo, Brazil. Percepção das mães sobre o cuidado do bebê de baixo peso antes e após implantação do Método Mãe-Canguru em hospital público da cidade de São Paulo, Brasil. 2007; 7(3): 297-307.


104. Blay S. Ghana KMC Study Results. 2009 [cited; Available from:


129. Miltersteiner AR, Miltersteiner DR, Rech VV, Molle LD. Respostas fisiológicas da Posição Mãe-Canguru em bebês pré-termos, de baixo peso e ventilando espontaneamente


Supplementary Figure 3.1. Forest plot for effect of KMC compared to conventional care on mortality at latest follow-up time, stratified by skin-to-skin contact initiation criteria.
Supplementary Figure 3.2. Forest plot for effect of KMC compared to conventional care on mortality at latest follow-up time, stratified by skin-to-skin contact duration promoted, hours per day.
Supplementary Figure 3.3. Forest plot for effect of KMC compared to conventional care on likelihood of exclusive breastfeeding at hospital discharge or 40-41 weeks post-menstrual age
Supplementary Figure 3.4. Forest plot for effect of KMC compared to conventional care on infection, stratified by infection type
Supplementary Figure 3.5. Forest plot for effect of KMC compared to conventional care on mean heart rate, beats per minute.
Supplementary Figure 3.6. Forest plot for effect of KMC compared to conventional care on mean respiratory rate, breaths per minute
### Supplementary Figure 3.7. Forest plot for effect of KMC compared to conventional care on mean oxygen saturation, percent

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali (2009)</td>
<td>1.50 (0.93, 2.07)</td>
<td>8.58</td>
</tr>
<tr>
<td>Bauer (1996)</td>
<td>1.00 (0.16, 1.84)</td>
<td>7.76</td>
</tr>
<tr>
<td>Begum (2008)</td>
<td>-0.50 (-1.55, 0.55)</td>
<td>7.04</td>
</tr>
<tr>
<td>Boju (2012)</td>
<td>1.09 (0.66, 1.52)</td>
<td>8.93</td>
</tr>
<tr>
<td>Collados-Gomez (2011)</td>
<td>0.01 (0.00, 0.02)</td>
<td>9.44</td>
</tr>
<tr>
<td>Kadam (2005)</td>
<td>0.90 (0.52, 1.28)</td>
<td>9.03</td>
</tr>
<tr>
<td>Lee (2011)</td>
<td>3.00 (1.90, 4.10)</td>
<td>6.85</td>
</tr>
<tr>
<td>Legault (1995)</td>
<td>-0.10 (-1.10, 0.90)</td>
<td>7.19</td>
</tr>
<tr>
<td>Ludington-Hoe (2004)</td>
<td>-1.88 (-3.73, -0.03)</td>
<td>4.57</td>
</tr>
<tr>
<td>Maastrup (2010)</td>
<td>0.00 (-1.77, 1.77)</td>
<td>4.78</td>
</tr>
<tr>
<td>Messmer (1997)</td>
<td>0.00 (-1.88, 1.88)</td>
<td>4.51</td>
</tr>
<tr>
<td>Mittersteiner (2003)</td>
<td>1.04 (0.19, 1.89)</td>
<td>7.72</td>
</tr>
<tr>
<td>Sajedi (2007)</td>
<td>2.80 (1.91, 3.69)</td>
<td>7.56</td>
</tr>
<tr>
<td>Tenório (2010)</td>
<td>2.38 (1.04, 3.72)</td>
<td>6.05</td>
</tr>
<tr>
<td>Overall (I-squared = 92.1%, p = 0.000)</td>
<td>0.90 (0.35, 1.45)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Supplementary Figure 3.8. Forest plot for effect of KMC compared to conventional care on mean temperature, degrees Celsius
Supplementary Figure 3.9. Forest plot for effect of KMC compared to conventional care on mean length of hospital stay, days

<table>
<thead>
<tr>
<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acharya (2014)</td>
<td>2.99 (0.62, 5.36)</td>
<td>10.47</td>
</tr>
<tr>
<td>Broughton (2013)</td>
<td>-3.20 (-7.51, 1.11)</td>
<td>6.28</td>
</tr>
<tr>
<td>Gregson (2011)</td>
<td>-0.68 (-0.79, -0.57)</td>
<td>14.71</td>
</tr>
<tr>
<td>Kadam (2005)</td>
<td>-0.80 (-2.65, 1.05)</td>
<td>11.81</td>
</tr>
<tr>
<td>Lamy Filho (2008)</td>
<td>-5.20 (-6.79, -3.61)</td>
<td>12.45</td>
</tr>
<tr>
<td>McMaster (2000)</td>
<td>7.00 (2.24, 11.76)</td>
<td>5.58</td>
</tr>
<tr>
<td>Roberts (2000)</td>
<td>2.00 (-14.95, 18.95)</td>
<td>0.68</td>
</tr>
<tr>
<td>Rodrigues (2009)</td>
<td>1.10 (-2.71, 4.91)</td>
<td>7.18</td>
</tr>
<tr>
<td>Suman (2008)</td>
<td>-0.08 (-1.73, 1.57)</td>
<td>12.31</td>
</tr>
<tr>
<td>Tuoni (2012)</td>
<td>13.71 (3.30, 24.12)</td>
<td>1.67</td>
</tr>
<tr>
<td>Wahlberg (1992)</td>
<td>-7.80 (-16.45, 0.85)</td>
<td>2.30</td>
</tr>
<tr>
<td>Overall (I-squared = 94.8%, p = 0.000)</td>
<td>-0.68 (-2.11, 0.75)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

KMC decreases LOS, days | KMC increases LOS, days
Supplementary Figure 3.10. Forest plot for effect of KMC compared to conventional care on standardized mean weight gain

<table>
<thead>
<tr>
<th>Study ID</th>
<th>SMD (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acharya (2014)</td>
<td>0.68 (0.33, 1.04)</td>
<td>9.79</td>
</tr>
<tr>
<td>Ahn (2010)</td>
<td>0.19 (-0.69, 1.07)</td>
<td>4.68</td>
</tr>
<tr>
<td>Boo (2007)</td>
<td>0.08 (-0.27, 0.43)</td>
<td>9.91</td>
</tr>
<tr>
<td>Broughton (2013)</td>
<td>-0.17 (-0.56, 0.23)</td>
<td>9.34</td>
</tr>
<tr>
<td>Cattaneo (1998)</td>
<td>-0.08 (-0.31, 0.15)</td>
<td>11.22</td>
</tr>
<tr>
<td>Lamy Filho (2008)</td>
<td>-0.20 (-0.33, -0.07)</td>
<td>12.07</td>
</tr>
<tr>
<td>McMaster (2000)</td>
<td>-0.05 (-0.44, 0.34)</td>
<td>9.45</td>
</tr>
<tr>
<td>Roberts (2000)</td>
<td>-0.15 (-0.87, 0.57)</td>
<td>5.91</td>
</tr>
<tr>
<td>Rodrigues (2009)</td>
<td>0.16 (-0.20, 0.52)</td>
<td>9.80</td>
</tr>
<tr>
<td>Rojas (2003)</td>
<td>0.40 (-0.13, 0.92)</td>
<td>7.83</td>
</tr>
<tr>
<td>Suman (2008)</td>
<td>0.91 (0.57, 1.25)</td>
<td>10.00</td>
</tr>
<tr>
<td>Overall (I-squared = 81.6%, p = 0.000)</td>
<td>0.16 (-0.08, 0.40)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Supplementary Figure 3.11. Forest plot for effect of KMC compared to conventional care on standardized mean pain score
Supplementary Figure 3.12. Risk of bias summary for randomized control trials (n=55)
Supplementary Figure 3.13. Risk of bias summary for observational studies (n=69)
Supplementary Figure 3.14. Funnel plot for effect of KMC compared to conventional care on mortality at latest follow-up time
Supplementary Table 3.1. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on mortality at latest follow-up

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95%CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>I², %*</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I², %**</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>16</td>
<td>0·77 [0·60, 0·99]</td>
<td>0·05</td>
<td>&lt;0·01</td>
<td>67</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Confounding adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted/RCT</td>
<td>12</td>
<td>0·95 [0·73, 1·23]</td>
<td>0·69</td>
<td>0·13</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>4</td>
<td>0·54 [0·31, 0·96]</td>
<td>0·04</td>
<td>&lt;0·01</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 45 days post birth</td>
<td>9</td>
<td>0·89 [0·64, 1·22]</td>
<td>0·46</td>
<td>&lt;0·01</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-12 month follow-up</td>
<td>7</td>
<td>0·59 [0·43, 0·82]</td>
<td>&lt;0·01</td>
<td>0·63</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>9</td>
<td>0·91 [0·73, 1·14]</td>
<td>0·40</td>
<td>0·59</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>3</td>
<td>0·90 [0·60, 1·35]</td>
<td>0·61</td>
<td>0·39</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilities evaluation</td>
<td>2</td>
<td>0·26 [0·13, 0·50]</td>
<td>&lt;0·01</td>
<td>0·26</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chart review</td>
<td>2</td>
<td>1·04 [0·63, 1·73]</td>
<td>0·87</td>
<td>&lt;0·01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>1</td>
<td>0·34 [0·16, 0·72]</td>
<td>&lt;0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>4</td>
<td>0·81 [0·72, 0·91]</td>
<td>&lt;0·01</td>
<td>0·93</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>2</td>
<td>0·34 [0·10, 1·14]</td>
<td>0·08</td>
<td>0·03</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>9</td>
<td>1·05 [0·83, 1·31]</td>
<td>0·70</td>
<td>0·19</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 - 1999</td>
<td>4</td>
<td>0·79 [0·47, 1·34]</td>
<td>0·38</td>
<td>0·78</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>11</td>
<td>0·72 [0·52, 1·00]</td>
<td>0·05</td>
<td>&lt;0·01</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 - 2014</td>
<td>1</td>
<td>1·00 [0·63, 1·60]</td>
<td>1·00</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>4</td>
<td>0·77 [0·50, 1·18]</td>
<td>0·23</td>
<td>&lt;0·01</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>5</td>
<td>0·76 [0·47, 1·23]</td>
<td>0·26</td>
<td>0·67</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>1</td>
<td>1·03 [0·15, 6·91]</td>
<td>0·98</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>4</td>
<td>1·02 [0·80, 1·30]</td>
<td>0·86</td>
<td>0·51</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1</td>
<td>0·17 [0·07, 0·44]</td>
<td>&lt;0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple</td>
<td>1</td>
<td>0·91 [0·19, 4·43]</td>
<td>0·91</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economy -World Bank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4</td>
<td>0·74 [0·48, 1·16]</td>
<td>0·19</td>
<td>0·02</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>9</td>
<td>0·73 [0·49, 1·08]</td>
<td>0·11</td>
<td>&lt;0·01</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2</td>
<td>1·24 [0·28, 5·43]</td>
<td>0·78</td>
<td>0·76</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>0·91 [0·19, 4·43]</td>
<td>0·91</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country-level NMR, deaths/1000 live births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>2</td>
<td>1·24 [0·28, 5·43]</td>
<td>0·78</td>
<td>0·76</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>4</td>
<td>0·74 [0·45, 1·20]</td>
<td>0·22</td>
<td>0·58</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>9</td>
<td>0·82 [0·61, 1·12]</td>
<td>0·21</td>
<td>&lt;0·01</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>1</td>
<td>0·34 [0·16, 0·72]</td>
<td>0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Supplementary Table 3.1 (Continued)**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95%CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>I², %*</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I², %**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>10</td>
<td>0.54 [0.37, 0.80]</td>
<td>&lt;0.01</td>
<td>0.20</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>1.06 [0.80, 1.41]</td>
<td>0.69</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>0.82 [0.73, 0.92]</td>
<td>&lt;0.01</td>
<td>0.69</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0.71 [0.12, 4.20]</td>
<td>0.70</td>
<td>0.08</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>12</td>
<td>0.73 [0.54, 0.99]</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>2</td>
<td>0.49 [0.10, 2.42]</td>
<td>0.38</td>
<td>0.26</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>1</td>
<td>1.00 [0.63, 1.60]</td>
<td>1.00</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0.97 [0.45, 2.09]</td>
<td>0.94</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm &lt;34 weeks</td>
<td>1</td>
<td>1.64 [0.16, 17.13]</td>
<td>0.68</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All gestational ages</td>
<td>2</td>
<td>1.04 [0.82, 1.33]</td>
<td>0.73</td>
<td>0.83</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>13</td>
<td>0.67 [0.48, 0.94]</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>11</td>
<td>0.76 [0.55, 1.04]</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>3</td>
<td>0.50 [0.11, 2.33]</td>
<td>0.38</td>
<td>0.08</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BW</td>
<td>2</td>
<td>1.04 [0.82, 1.33]</td>
<td>0.73</td>
<td>0.83</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>5</td>
<td>0.71 [0.33, 1.52]</td>
<td>0.38</td>
<td>0.01</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC / EBF</td>
<td>3</td>
<td>0.64 [0.38, 1.10]</td>
<td>0.11</td>
<td>0.57</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC / EBF/DC/FU</td>
<td>2</td>
<td>0.43 [0.19, 0.98]</td>
<td>0.04</td>
<td>0.27</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC / DC/FU</td>
<td>2</td>
<td>0.55 [0.29, 1.07]</td>
<td>0.08</td>
<td>0.94</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC / EBF/FU</td>
<td>2</td>
<td>0.63 [0.15, 2.63]</td>
<td>0.53</td>
<td>0.15</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>1.04 [0.63, 1.73]</td>
<td>0.87</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC duration promoted, hours/day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - &lt; 9</td>
<td>1</td>
<td>1.64 [0.16, 17.13]</td>
<td>0.68</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 22</td>
<td>11</td>
<td>0.64 [0.44, 0.92]</td>
<td>0.02</td>
<td>0.01</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>4</td>
<td>1.04 [0.66, 1.64]</td>
<td>0.87</td>
<td>&lt;0.01</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC only</td>
<td>5</td>
<td>0.71 [0.33, 1.52]</td>
<td>0.38</td>
<td>0.01</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC+ other components</td>
<td>9</td>
<td>0.65 [0.48, 0.89]</td>
<td>0.01</td>
<td>0.36</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>1.04 [0.63, 1.73]</td>
<td>0.87</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EBF as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF component</td>
<td>7</td>
<td>0.66 [0.42, 1.01]</td>
<td>0.06</td>
<td>0.21</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EBF component</td>
<td>7</td>
<td>0.66 [0.39, 1.14]</td>
<td>0.14</td>
<td>0.02</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>1.04 [0.63, 1.73]</td>
<td>0.87</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Supplementary Table 3.1 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95% CI] *</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>I², % *</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I², % **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSC instructed to start</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately</td>
<td>3</td>
<td>0·51 [0·33, 0·78]</td>
<td>&lt;0·01</td>
<td>0·38</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After stability met</td>
<td>9</td>
<td>0·57 [0·34, 0·97]</td>
<td>0·04</td>
<td>0·18</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>1·04 [0·77, 1·39]</td>
<td>0·81</td>
<td>&lt;0·01</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk of bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
<td>0·65 [0·44, 0·97]</td>
<td>0·04</td>
<td>0·64</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>9</td>
<td>0·72 [0·52, 0·99]</td>
<td>0·04</td>
<td>0·01</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>2</td>
<td>1·35 [1·11, 1·65]</td>
<td>&lt;0·01</td>
<td>0·62</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Random effects estimates  
* I-squared: variation in risk ratio or mean difference attributable to heterogeneity  
** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
Supplementary Table 3.2: Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on exclusive breastfeeding during hospital stay or at 40-41 weeks post-menstrual age

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95% CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>$\Gamma^2$, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $\Gamma^2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>13</td>
<td>1.50 [1.26, 1.78]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>93</td>
<td>-</td>
<td>0.03</td>
</tr>
<tr>
<td>Confounding adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>Adjusted/RCT</td>
<td>8</td>
<td>1.25 [1.10, 1.42]</td>
<td>&lt;0.01</td>
<td>0.02</td>
<td>59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crude</td>
<td>5</td>
<td>1.80 [1.57, 2.07]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>80</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>RCT</td>
<td>7</td>
<td>1.21 [1.07, 1.37]</td>
<td>&lt;0.01</td>
<td>0.04</td>
<td>55</td>
<td>-</td>
<td>67</td>
</tr>
<tr>
<td>Cohort</td>
<td>6</td>
<td>1.80 [1.58, 2.05]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>1</td>
<td>2.50 [1.43, 4.38]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>94</td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>2</td>
<td>1.39 [0.84, 2.29]</td>
<td>0.20</td>
<td>0.08</td>
<td>68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>2</td>
<td>1.38 [0.83, 2.31]</td>
<td>0.22</td>
<td>0.13</td>
<td>57</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 200</td>
<td>8</td>
<td>1.49 [1.21, 1.83]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>1988-1999</td>
<td>3</td>
<td>1.24 [0.99, 1.56]</td>
<td>0.07</td>
<td>0.02</td>
<td>75</td>
<td>-</td>
<td>86</td>
</tr>
<tr>
<td>2000-2009</td>
<td>3</td>
<td>1.19 [0.97, 1.47]</td>
<td>0.10</td>
<td>0.28</td>
<td>22</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2010-2014</td>
<td>7</td>
<td>1.70 [1.42, 2.03]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>91</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHO region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Americas</td>
<td>3</td>
<td>1.33 [0.76, 2.32]</td>
<td>0.32</td>
<td>&lt;0.01</td>
<td>97</td>
<td>-</td>
<td>94</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>1.38 [1.13, 1.70]</td>
<td>&lt;0.01</td>
<td>0.10</td>
<td>52</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>3</td>
<td>1.67 [1.11, 2.51]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>94</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>East Mediterranean</td>
<td>1</td>
<td>1.73 [1.29, 2.32]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1</td>
<td>2.05 [1.01, 4.18]</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Multiple</td>
<td>1</td>
<td>1.25 [1.10, 1.42]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Economy – World Bank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>1.88 [1.74, 2.03]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>90</td>
</tr>
<tr>
<td>Middle</td>
<td>5</td>
<td>1.43 [1.09, 1.88]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>78</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>6</td>
<td>1.53 [1.13, 2.07]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>93</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>1.25 [1.10, 1.42]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Country-level NMR, deaths/1000 live births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>7</td>
<td>1.57 [1.18, 2.08]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>91</td>
<td>-</td>
<td>92</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>2</td>
<td>1.31 [0.78, 2.20]</td>
<td>0.31</td>
<td>&lt;0.01</td>
<td>89</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>4</td>
<td>1.53 [1.13, 2.08]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>94</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>Urban</td>
<td>10</td>
<td>1.56 [1.22, 1.99]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>94</td>
<td>-</td>
<td>94</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>1.40 [0.99, 1.99]</td>
<td>0.06</td>
<td>&lt;0.01</td>
<td>94</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Facility type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>Health facility</td>
<td>9</td>
<td>1.39 [1.09, 1.77]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>3</td>
<td>1.84 [1.42, 2.39]</td>
<td>&lt;0.01</td>
<td>0.54</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Community</td>
<td>1</td>
<td>1.88 [1.74, 2.03]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.2 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95% CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>$\Gamma^2$, %</th>
<th>Univariable meta-regression</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $\Gamma^2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>3</td>
<td>1.51 [1.11, 2.06]</td>
<td>0.01</td>
<td>0.12</td>
<td>54</td>
<td>0.37</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Full term</td>
<td>3</td>
<td>1.76 [1.14, 2.73]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All gestational ages</td>
<td>3</td>
<td>1.69 [1.21, 2.35]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>1.17 [1.02, 1.34]</td>
<td>0.02</td>
<td>0.11</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>3</td>
<td>1.15 [1.02, 1.29]</td>
<td>0.02</td>
<td>0.16</td>
<td>45</td>
<td>0.20</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>1</td>
<td>2.05 [1.01, 4.19]</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BW</td>
<td>3</td>
<td>1.69 [1.21, 2.35]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>1.63 [1.23, 2.17]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>4</td>
<td>1.36 [1.11, 1.66]</td>
<td>&lt;0.01</td>
<td>0.12</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC / EBF</td>
<td>2</td>
<td>1.53 [0.82, 2.87]</td>
<td>0.18</td>
<td>&lt;0.01</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC / EBF / DC / FU</td>
<td>2</td>
<td>1.14 [0.93, 1.39]</td>
<td>0.20</td>
<td>0.06</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC / EBF / FU</td>
<td>3</td>
<td>1.69 [1.16, 2.46]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>2</td>
<td>1.87 [1.27, 2.75]</td>
<td>&lt;0.01</td>
<td>0.28</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC duration promoted, hours/day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>1</td>
<td>2.05 [1.01, 4.18]</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td>0.61</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>2 - &lt; 4</td>
<td>4</td>
<td>1.75 [1.24, 2.47]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>94</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - &lt; 9</td>
<td>1</td>
<td>1.16 [0.99, 1.36]</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 22</td>
<td>3</td>
<td>1.35 [0.92, 1.96]</td>
<td>0.12</td>
<td>&lt;0.01</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>4</td>
<td>1.43 [1.08, 1.88]</td>
<td>0.01</td>
<td>0.12</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC only</td>
<td>4</td>
<td>1.36 [1.11, 1.66]</td>
<td>&lt;0.01</td>
<td>0.12</td>
<td>49</td>
<td>0.59</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>SSC + other components</td>
<td>7</td>
<td>1.46 [1.17, 1.82]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>1.87 [1.27, 2.75]</td>
<td>&lt;0.01</td>
<td>0.28</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EBF as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF component</td>
<td>7</td>
<td>1.46 [1.17, 1.82]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>96</td>
<td>0.59</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>No EBF component</td>
<td>4</td>
<td>1.36 [1.11, 1.66]</td>
<td>&lt;0.01</td>
<td>0.12</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>1.87 [1.27, 2.75]</td>
<td>&lt;0.01</td>
<td>0.28</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC start time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately</td>
<td>2</td>
<td>1.67 [0.85, 3.27]</td>
<td>0.13</td>
<td>0.02</td>
<td>82</td>
<td>0.96</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>After stability met</td>
<td>4</td>
<td>1.33 [1.10, 1.60]</td>
<td>&lt;0.01</td>
<td>0.06</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After other criteria met</td>
<td>3</td>
<td>1.68 [0.92, 3.08]</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>1.51 [1.15, 1.98]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk of bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>2.32 [1.49, 3.60]</td>
<td>&lt;0.01</td>
<td>0.67</td>
<td>0</td>
<td>0.18</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6</td>
<td>1.60 [1.29, 1.97]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>5</td>
<td>1.30 [0.94, 1.80]</td>
<td>0.11</td>
<td>&lt;0.01</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Supplementary Table 3.2 (Continued)**


^ Random effects estimates

* I-squared: variation in risk ratio or mean difference attributable to heterogeneity

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
Supplementary Table 3.3. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on infection

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95%CI]</th>
<th>p</th>
<th>Test for heterogeneity</th>
<th>I², %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>12</td>
<td>0.67 [0.43, 1.05]</td>
<td>0.08</td>
<td>&lt;0.01</td>
<td>60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Confounding adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.30</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Adjusted/RCT</td>
<td>10</td>
<td>0.60 [0.36, 1.01]</td>
<td>0.05</td>
<td>&lt;0.01</td>
<td>65</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crude</td>
<td>2</td>
<td>1.19 [0.56, 2.53]</td>
<td>0.65</td>
<td>0.92</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infection type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>8</td>
<td>0.53 [0.34, 0.83]</td>
<td>0.01</td>
<td>0.23</td>
<td>25</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MRSA or other severe</td>
<td>4</td>
<td>1.00 [0.40, 2.46]</td>
<td>0.99</td>
<td>0.01</td>
<td>77</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>9</td>
<td>0.51 [0.32, 0.81]</td>
<td>&lt;0.01</td>
<td>0.03</td>
<td>54</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cohort</td>
<td>1</td>
<td>3.82 [1.11, 13.14]</td>
<td>0.03</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Facilities evaluation</td>
<td>1</td>
<td>1.16 [0.48, 2.81]</td>
<td>0.74</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intervention</td>
<td>1</td>
<td>1.27 [0.30, 5.46]</td>
<td>0.75</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.83</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>1</td>
<td>1.27 [0.30, 5.47]</td>
<td>0.75</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>3</td>
<td>0.47 [0.28, 0.81]</td>
<td>0.01</td>
<td>0.38</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>4</td>
<td>0.75 [0.33, 1.73]</td>
<td>0.50</td>
<td>0.21</td>
<td>33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 200</td>
<td>4</td>
<td>0.72 [0.27, 1.88]</td>
<td>0.50</td>
<td>&lt;0.01</td>
<td>83</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>1988-1999</td>
<td>2</td>
<td>0.58 [0.18, 1.87]</td>
<td>0.36</td>
<td>0.01</td>
<td>86</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2000-2009</td>
<td>8</td>
<td>0.65 [0.35, 1.21]</td>
<td>0.18</td>
<td>0.01</td>
<td>62</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2010-2014</td>
<td>2</td>
<td>1.15 [0.36, 3.69]</td>
<td>0.81</td>
<td>0.83</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>WHO region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.05</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>3</td>
<td>0.57 [0.25, 1.28]</td>
<td>0.17</td>
<td>0.02</td>
<td>75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>5</td>
<td>0.40 [0.25, 0.64]</td>
<td>&lt;0.01</td>
<td>0.45</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>4</td>
<td>1.65 [0.89, 3.08]</td>
<td>0.11</td>
<td>0.47</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Economy – World Bank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>9</td>
<td>0.56 [0.35, 0.91]</td>
<td>0.02</td>
<td>0.02</td>
<td>58</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>1.30 [0.38, 4.49]</td>
<td>0.68</td>
<td>0.05</td>
<td>68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Country-level NMR, deaths/1000 live births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>4</td>
<td>1.36 [0.49, 3.78]</td>
<td>0.56</td>
<td>0.10</td>
<td>53</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>3</td>
<td>0.48 [0.19, 1.20]</td>
<td>0.12</td>
<td>&lt;0.01</td>
<td>82</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>5</td>
<td>0.58 [0.31, 1.07]</td>
<td>0.08</td>
<td>0.17</td>
<td>38</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.26</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>11</td>
<td>0.73 [0.46, 1.15]</td>
<td>0.17</td>
<td>&lt;0.01</td>
<td>58</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0.27 [0.09, 0.79]</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Facility type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.36</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>7</td>
<td>0.66 [0.42, 1.02]</td>
<td>0.06</td>
<td>0.09</td>
<td>45</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>4</td>
<td>1.17 [0.30, 4.56]</td>
<td>0.82</td>
<td>0.01</td>
<td>72</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0.30 [0.14, 0.67]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.3 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95% CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>I^2, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I^2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm &lt;34 weeks</td>
<td>2</td>
<td>0·68 [0·30, 1·58]</td>
<td>0·37</td>
<td>0·31</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All gestational ages</td>
<td>1</td>
<td>3·82 [1·11, 13·14]</td>
<td>0·03</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>9</td>
<td>0·56 [0·35, 0·91]</td>
<td>0·02</td>
<td>0·02</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>6</td>
<td>0·45 [0·25, 0·81]</td>
<td>0·01</td>
<td>0·01</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>4</td>
<td>0·87 [0·48, 1·59]</td>
<td>0·65</td>
<td>0·58</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BW</td>
<td>1</td>
<td>3·82 [1·11, 13·14]</td>
<td>0·03</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1·27 [0·30, 5·46]</td>
<td>0·75</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>6</td>
<td>0·75 [0·34, 1·68]</td>
<td>0·48</td>
<td>&lt;0·01</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF</td>
<td>2</td>
<td>0·90 [0·40, 2·02]</td>
<td>0·80</td>
<td>0·58</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF/DC/FU</td>
<td>2</td>
<td>1·00 [0·69, 1·45]</td>
<td>0·99</td>
<td>0·98</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF/FU</td>
<td>1</td>
<td>0·27 [0·09, 0·79]</td>
<td>0·02</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>1</td>
<td>0·31 [0·13, 0·72]</td>
<td>0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC duration promoted, hours/day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>2</td>
<td>1·43 [0·41, 4·94]</td>
<td>0·58</td>
<td>0·77</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>5</td>
<td>0·62 [0·32, 1·20]</td>
<td>0·16</td>
<td>0·02</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>3</td>
<td>0·91 [0·24, 3·53]</td>
<td>0·89</td>
<td>&lt;0·01</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC only</td>
<td>6</td>
<td>0·75 [0·34, 1·68]</td>
<td>0·48</td>
<td>0·01</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC + other components</td>
<td>5</td>
<td>0·79 [0·48, 1·28]</td>
<td>0·34</td>
<td>0·24</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>1</td>
<td>0·31 [0·13, 0·72]</td>
<td>0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EBF as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF component</td>
<td>5</td>
<td>0·79 [0·48, 1·28]</td>
<td>0·34</td>
<td>0·24</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EBF component</td>
<td>6</td>
<td>0·75 [0·34, 1·68]</td>
<td>0·48</td>
<td>&lt;0·01</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>1</td>
<td>0·31 [0·13, 0·72]</td>
<td>0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC instructed to start</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After stability met</td>
<td>9</td>
<td>0·50 [0·33, 0·77]</td>
<td>&lt;0·01</td>
<td>0·15</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After other criteria met</td>
<td>2</td>
<td>1·00 [0·69, 1·45]</td>
<td>0·99</td>
<td>0·98</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>3·82 [1·11, 13·14]</td>
<td>0·03</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk of bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>0·47 [0·29, 0·77]</td>
<td>&lt;0·01</td>
<td>0·25</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>1·24 [0·44, 3·53]</td>
<td>0·69</td>
<td>0·05</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>2</td>
<td>0·61 [0·19, 1·95]</td>
<td>0·40</td>
<td>0·04</td>
<td>77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


^ Random effects estimates

* I-squared: variation in risk ratio or mean difference attributable to heterogeneity

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
### Supplementary Table 3.4. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on heart rate, beats per minute

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95%CI] (^a)</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>(I^2, %) *</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual (I^2, %) **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All studies</strong></td>
<td>15</td>
<td>-0·41 [-2·25, 1·42]</td>
<td>0·66</td>
<td>0·03</td>
<td>46</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>1</td>
<td>0·20 [-1·54, 1·94]</td>
<td>0·82</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Randomized crossover</td>
<td>1</td>
<td>-1·20 [-6·06, 3·66]</td>
<td>0·63</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pre-post</td>
<td>12</td>
<td>-0·40 [-2·89, 2·09]</td>
<td>0·75</td>
<td>0·01</td>
<td>55</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intervention</td>
<td>1</td>
<td>3·77 [-11·80, 19·34]</td>
<td>0·64</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>10</td>
<td>0·93 [-1·63, 3·49]</td>
<td>0·48</td>
<td>0·14</td>
<td>33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>4</td>
<td>-3·09 [-5·41, -0·77]</td>
<td>&lt;0·01</td>
<td>0·34</td>
<td>11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>1</td>
<td>0·20 [-1·54, 1·94]</td>
<td>0·82</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 – 1999</td>
<td>3</td>
<td>0·86 [-2·16, 3·88]</td>
<td>0·58</td>
<td>0·46</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2000 – 2009</td>
<td>7</td>
<td>1·46 [-1·62, 4·53]</td>
<td>0·35</td>
<td>0·10</td>
<td>44</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2010 – 2014</td>
<td>5</td>
<td>-3·13 [-5·08, -1·18]</td>
<td>&lt;0·01</td>
<td>0·49</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>WHO region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>4</td>
<td>0·75 [-4·16, 5·65]</td>
<td>0·77</td>
<td>0·06</td>
<td>61</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>2</td>
<td>-1·16 [-4·08, 1·77]</td>
<td>0·44</td>
<td>0·06</td>
<td>73</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Europe</td>
<td>4</td>
<td>-3·95 [-8·53, 0·64]</td>
<td>0·09</td>
<td>0·23</td>
<td>31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1</td>
<td>-1·64 [-8·28, 5·00]</td>
<td>0·63</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Africa</td>
<td>1</td>
<td>1·53 [-7·57, 10·63]</td>
<td>0·74</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2·63 [-0·51, 5·78]</td>
<td>0·10</td>
<td>0·68</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Economy – World Bank</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>1·53 [-7·57,10·63]</td>
<td>0·74</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Middle</td>
<td>4</td>
<td>-0·12 [-3·58, 3·33]</td>
<td>0·94</td>
<td>0·01</td>
<td>74</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>7</td>
<td>-2·62 [-5·19, -0·06]</td>
<td>0·05</td>
<td>0·38</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2·63 [-0·51, 5·78]</td>
<td>0·10</td>
<td>0·68</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Country-level NMR, deaths/1000 live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>7</td>
<td>-2·62 [-5·19, -0·06]</td>
<td>0·05</td>
<td>0·38</td>
<td>6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>2</td>
<td>2·27 [-9·66, 14·20]</td>
<td>0·71</td>
<td>0·01</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>3</td>
<td>-0·94 [-3·38, 1·51]</td>
<td>0·45</td>
<td>0·14</td>
<td>49</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>2·63 [-0·51, 5·78]</td>
<td>0·10</td>
<td>0·68</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>9</td>
<td>-0·90 [-3·77, 1·98]</td>
<td>0·54</td>
<td>0·02</td>
<td>55</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-2·80 [-5·32, -0·28]</td>
<td>0·03</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>1·62 [-1·02, 4·25]</td>
<td>0·23</td>
<td>0·69</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>5</td>
<td>-0·91 [-2·70, 0·89]</td>
<td>0·32</td>
<td>0·27</td>
<td>23</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>9</td>
<td>-0·27 [-3·74, 3·20]</td>
<td>0·88</td>
<td>0·02</td>
<td>56</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>3·00 [-1·62, 7·62]</td>
<td>0·20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Supplementary Table 3.4 (Continued)

| Subgroup | n   | MD [95%CI]
\(^\text{^a}\) | p     | Test for heterogeneity (p) | I\(^2\), % * | Test for heterogeneity by covariate (p) | Residual I\(^2\), % ** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm &lt;34 weeks</td>
<td>6</td>
<td>-1.22 [-5.23, 2.80]</td>
<td>0.55</td>
<td>0.04</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>7</td>
<td>0.02 [-3.04, 3.07]</td>
<td>0.99</td>
<td>0.04</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0.25 [-1.47, 1.96]</td>
<td>0.78</td>
<td>0.78</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>8</td>
<td>-0.17 [-2.63, 2.28]</td>
<td>0.89</td>
<td>0.12</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>2</td>
<td>2.15 [-1.70, 6.01]</td>
<td>0.27</td>
<td>0.51</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non LBW</td>
<td>1</td>
<td>1.53 [-7.57, 10.63]</td>
<td>0.74</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>-1.77 [-5.85, 2.30]</td>
<td>0.39</td>
<td>0.06</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KMC components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>10</td>
<td>0.17 [-1.18, 1.52]</td>
<td>0.80</td>
<td>0.76</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF</td>
<td>2</td>
<td>6.86 [1.90, 11.83]</td>
<td>0.01</td>
<td>0.50</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>-3.62 [-5.74, -1.50]</td>
<td>&lt;0.01</td>
<td>0.39</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC duration promoted, hours/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>12</td>
<td>-0.88 [-3.22, 1.47]</td>
<td>0.46</td>
<td>0.03</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - &lt; 9</td>
<td>1</td>
<td>0.20 [-1.54, 1.94]</td>
<td>0.82</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>2</td>
<td>2.97 [-2.29, 8.24]</td>
<td>0.27</td>
<td>0.46</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC as KMC component</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC only</td>
<td>10</td>
<td>0.17 [-1.18, 1.52]</td>
<td>0.80</td>
<td>0.76</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC + other components</td>
<td>2</td>
<td>6.86 [1.90, 11.83]</td>
<td>0.01</td>
<td>0.50</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>-3.62 [-5.74, -1.50]</td>
<td>&lt;0.01</td>
<td>0.39</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF as KMC component</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF component</td>
<td>2</td>
<td>6.86 [1.90, 11.83]</td>
<td>0.01</td>
<td>0.50</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EBF component</td>
<td>10</td>
<td>0.17 [-1.18, 1.52]</td>
<td>0.80</td>
<td>0.76</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>-3.62 [-5.74, -1.50]</td>
<td>&lt;0.01</td>
<td>0.39</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC start time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After stability met</td>
<td>5</td>
<td>2.01 [-1.29, 5.32]</td>
<td>0.23</td>
<td>0.12</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After other criteria met</td>
<td>6</td>
<td>1.15 [-1.38, 3.68]</td>
<td>0.37</td>
<td>0.93</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>-3.85 [-5.90, -1.81]</td>
<td>&lt;0.01</td>
<td>0.47</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>0.90 [-1.67, 3.47]</td>
<td>0.49</td>
<td>0.06</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>5</td>
<td>-2.30 [-5.48, 0.88]</td>
<td>0.16</td>
<td>0.06</td>
<td>57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


^ Random effects estimates

* I-squared: variation in risk ratio or mean difference attributable to heterogeneity

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
Supplementary Table 3.5. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on respiratory rate, breaths per minute

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95% CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>12</td>
<td>-3·17 [-5·15, -1·19]</td>
<td>&lt;0·01</td>
<td>&lt;0·01</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>2</td>
<td>-6·42 [-10·24, -2·60]</td>
<td>&lt;0·01</td>
<td>&lt;0·01</td>
<td>93</td>
<td>0·03</td>
</tr>
<tr>
<td>Randomized crossover</td>
<td>1</td>
<td>-2·30 [-7·05, 2·45]</td>
<td>0·34</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Pre-post or crossover</td>
<td>9</td>
<td>-2·16 [-4·06, -0·26]</td>
<td>0·03</td>
<td>0·13</td>
<td>36</td>
<td>0·07</td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>7</td>
<td>-2·06 [-4·84, 0·72]</td>
<td>0·15</td>
<td>0·07</td>
<td>49</td>
<td>0·07</td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>4</td>
<td>-3·49 [-4·99, -1·99]</td>
<td>&lt;0·01</td>
<td>0·27</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>1</td>
<td>-8·40 [-10·01, -6·79]</td>
<td>&lt;0·01</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 - 1999</td>
<td>2</td>
<td>-1·91 [-6·06, 2·23]</td>
<td>0·37</td>
<td>0·75</td>
<td>0</td>
<td>0·07</td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>5</td>
<td>-3·65 [-6·90, -0·40]</td>
<td>0·03</td>
<td>&lt;0·01</td>
<td>85</td>
<td>0·07</td>
</tr>
<tr>
<td>2010 – 2014</td>
<td>5</td>
<td>-2·94 [-5·51, -0·36]</td>
<td>0·03</td>
<td>0·05</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td><strong>WHO region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>4</td>
<td>-1·86 [-4·35, 0·63]</td>
<td>0·14</td>
<td>0·53</td>
<td>0</td>
<td>0·10</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>3</td>
<td>-5·43 [-8·50, -2·35]</td>
<td>&lt;0·01</td>
<td>&lt;0·01</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>Europe</td>
<td>2</td>
<td>-0·30 [-3·08, 2·48]</td>
<td>0·83</td>
<td>0·46</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1</td>
<td>-7·82 [-12·03, -3·61]</td>
<td>&lt;0·01</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>-0·95 [-5·41, 3·50]</td>
<td>0·68</td>
<td>0·51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Economy – World Bank</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>5</td>
<td>-4·24 [-6·93, -1·56]</td>
<td>&lt;0·01</td>
<td>&lt;0·01</td>
<td>84</td>
<td>0·38</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>-2·37 [-5·59, 0·85]</td>
<td>0·15</td>
<td>0·06</td>
<td>57</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>-0·95 [-5·41, 3·51]</td>
<td>0·68</td>
<td>0·51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>County-level NMR, deaths/1000 live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>5</td>
<td>-2·37 [-5·59, 0·84]</td>
<td>0·15</td>
<td>0·06</td>
<td>57</td>
<td>0·20</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>2</td>
<td>-1·60 [-6·21, 3·01]</td>
<td>0·50</td>
<td>0·15</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>3</td>
<td>-5·43 [-8·50, -2·35]</td>
<td>&lt;0·01</td>
<td>&lt;0·01</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>-0·95 [-5·41, 3·51]</td>
<td>0·68</td>
<td>0·51</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>7</td>
<td>-3·04 [-5·68, -0·40]</td>
<td>0·02</td>
<td>&lt;0·01</td>
<td>84</td>
<td>0·87</td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>-2·99 [-5·87, -0·11]</td>
<td>0·04</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>-3·33 [-7·63, 0·98]</td>
<td>0·13</td>
<td>0·11</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>5</td>
<td>-4·49 [-7·08, -1·90]</td>
<td>&lt;0·01</td>
<td>&lt;0·01</td>
<td>82</td>
<td>0·37</td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>7</td>
<td>-1·93 [-4·45, 0·60]</td>
<td>0·14</td>
<td>0·09</td>
<td>45</td>
<td>0</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.5 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95% CI]</th>
<th>p</th>
<th>(I^2) (%)</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual (I^2), %**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm &lt;34 weeks</td>
<td>3</td>
<td>-0.19 [-2.70, 2.32]</td>
<td>0.88</td>
<td>0.75</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>7</td>
<td>-3.16 [-5.18, -1.15]</td>
<td>&lt;0.01</td>
<td>0.24</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>-6.42 [-10.24, -2.60]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>7</td>
<td>-4.23 [-6.71, -1.75]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>1</td>
<td>-0.69 [-9.16, 7.78]</td>
<td>0.87</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>-1.68 [-3.61, 0.24]</td>
<td>0.09</td>
<td>0.50</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>6</td>
<td>-3.46 [-7.42, 0.51]</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>SSC/EBF</td>
<td>3</td>
<td>-2.64 [-6.25, 0.98]</td>
<td>0.15</td>
<td>0.10</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>-2.61 [-4.57, -0.65]</td>
<td>0.01</td>
<td>0.60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>SSC duration promoted,</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hours/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>8</td>
<td>-2.56 [-4.43, -0.69]</td>
<td>0.01</td>
<td>0.18</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>4 - &lt; 9</td>
<td>1</td>
<td>-8.40 [-10.01, -6.79]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>3</td>
<td>-2.46 [-6.27, 1.34]</td>
<td>0.20</td>
<td>0.06</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td><strong>SSC as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC only</td>
<td>6</td>
<td>-3.46 [-7.42, 0.51]</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>SSC + other components</td>
<td>3</td>
<td>-2.64 [-6.25, 0.98]</td>
<td>0.15</td>
<td>0.10</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>-2.61 [-4.57, -0.65]</td>
<td>0.01</td>
<td>0.60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>EBF as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF component</td>
<td>3</td>
<td>-2.64 [-6.25, 0.98]</td>
<td>0.15</td>
<td>0.10</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>No EBF component</td>
<td>6</td>
<td>-3.46 [-7.42, 0.51]</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>-2.61 [-4.57, -0.65]</td>
<td>0.01</td>
<td>0.60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>SSC start time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After stability met</td>
<td>5</td>
<td>-4.06 [-7.10, -1.01]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>After other criteria met</td>
<td>4</td>
<td>-2.06 [-6.91, 2.80]</td>
<td>0.41</td>
<td>0.02</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>-2.61 [-4.57, -0.65]</td>
<td>0.01</td>
<td>0.60</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Risk of bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>8</td>
<td>-2.91 [-4.84, -0.98]</td>
<td>&lt;0.01</td>
<td>0.04</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>4</td>
<td>-3.63 [-8.45, 1.18]</td>
<td>0.14</td>
<td>&lt;0.01</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>


**Random effects estimates**

* I-squared: variation in risk ratio or mean difference attributable to heterogeneity

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
Supplementary Table 3.6. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on oxygen saturation, percent

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95% CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>$I^2$, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $I^2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>14</td>
<td>0.90 [0.35, 1.45]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>92</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>3</td>
<td>1.65 [0.72, 2.59]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized crossover</td>
<td>1</td>
<td>-0.10 [-1.10, 0.90]</td>
<td>0.85</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-post</td>
<td>10</td>
<td>0.72 [0.06, 1.38]</td>
<td>0.03</td>
<td>&lt;0.01</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>8</td>
<td>0.74 [-0.24, 1.71]</td>
<td>0.14</td>
<td>&lt;0.01</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>4</td>
<td>0.51 [-0.17, 1.19]</td>
<td>0.14</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>2</td>
<td>2.10 [0.83, 3.37]</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 - 1999</td>
<td>3</td>
<td>0.43 [-0.37, 1.23]</td>
<td>0.29</td>
<td>0.22</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>6</td>
<td>0.85 [0.02, 1.69]</td>
<td>0.05</td>
<td>&lt;0.01</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 - 2014</td>
<td>5</td>
<td>1.26 [0.23, 2.29]</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>4</td>
<td>0.85 [-0.20, 1.91]</td>
<td>0.11</td>
<td>0.02</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>3</td>
<td>1.11 [0.07, 2.13]</td>
<td>&lt;0.01</td>
<td>0.23</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>2</td>
<td>0.01 [0.00, 0.02]</td>
<td>0.05</td>
<td>0.99</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Mediterranean</td>
<td>1</td>
<td>2.80 [1.91, 3.70]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1</td>
<td>3.00 [1.90, 4.10]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>-0.29 [-1.81, 1.23]</td>
<td>0.71</td>
<td>&lt;0.01</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economy – World Bank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>6</td>
<td>1.48 [0.97, 1.98]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>0.61 [-0.53, 1.75]</td>
<td>0.30</td>
<td>&lt;0.01</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>-0.29 [-1.81, 1.23]</td>
<td>0.71</td>
<td>&lt;0.01</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country-level NMR, deaths/1000 live births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>5</td>
<td>0.61 [-0.53, 1.75]</td>
<td>0.30</td>
<td>&lt;0.01</td>
<td>86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>3</td>
<td>2.04 [0.86, 3.23]</td>
<td>&lt;0.01</td>
<td>0.02</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>3</td>
<td>1.11 [0.79, 1.43]</td>
<td>&lt;0.01</td>
<td>0.23</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>-0.29 [-1.81, 1.23]</td>
<td>0.71</td>
<td>&lt;0.01</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>8</td>
<td>1.06 [0.34, 1.78]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>1</td>
<td>1.09 [0.66, 1.52]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>0.42 [-1.09, 1.93]</td>
<td>0.58</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supplementary Table 3.6 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95%CI]^*</th>
<th>p</th>
<th>Test for heterogeneity</th>
<th>I^2, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I^2, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>6</td>
<td>1.32 [0.68, 1.95]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>83</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>7</td>
<td>0.42 [-0.46, 1.30]</td>
<td>0.35</td>
<td>&lt;0.01</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1.00 [0.16, 1.84]</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm &lt; 34 weeks</td>
<td>4</td>
<td>0.15 [-0.41, 0.71]</td>
<td>0.59</td>
<td>0.10</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>7</td>
<td>0.93 [0.04, 1.82]</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full term</td>
<td>1</td>
<td>2.80 [1.91, 3.70]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>1.16 [0.58, 1.75]</td>
<td>&lt;0.01</td>
<td>0.09</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>7</td>
<td>1.13 [0.44, 1.82]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>81</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>2</td>
<td>0.83 [0.07, 1.60]</td>
<td>0.03</td>
<td>0.34</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non LBW</td>
<td>1</td>
<td>2.80 [1.91, 3.70]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>0.11 [-0.77, 0.99]</td>
<td>0.80</td>
<td>&lt;0.01</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KMC components</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>SSC</td>
<td>8</td>
<td>1.05 [0.16, 1.93]</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>84</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>SSC/EBF</td>
<td>3</td>
<td>0.42 [-0.64, 1.47]</td>
<td>0.44</td>
<td>0.01</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>0.98 [-0.08, 2.04]</td>
<td>0.07</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC duration promoted,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>hours/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>10</td>
<td>1.07 [0.36, 1.77]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - &lt; 9</td>
<td>1</td>
<td>1.50 [0.93, 2.07]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>3</td>
<td>-0.14 [-1.78, 1.50]</td>
<td>0.10</td>
<td>0.01</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC as KMC component</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>SSC only</td>
<td>8</td>
<td>1.05 [0.16, 1.93]</td>
<td>0.02</td>
<td>0.01</td>
<td>84</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>SSC + other components</td>
<td>3</td>
<td>0.42 [-0.64, 1.47]</td>
<td>0.44</td>
<td>0.01</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>0.98 [-0.08, 2.04]</td>
<td>0.07</td>
<td>0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF as KMC component</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>EBF component</td>
<td>3</td>
<td>0.42 [-0.64, 1.47]</td>
<td>0.44</td>
<td>0.01</td>
<td>77</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>No EBF component</td>
<td>8</td>
<td>1.05 [0.16, 1.93]</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>3</td>
<td>0.98 [-0.08, 2.04]</td>
<td>0.07</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC instructed start time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>After stability met</td>
<td>5</td>
<td>0.63 [-0.06, 1.32]</td>
<td>0.08</td>
<td>&lt;0.01</td>
<td>76</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>After other criteria met</td>
<td>5</td>
<td>0.76 [-0.54, 2.07]</td>
<td>0.25</td>
<td>&lt;0.01</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For a painful procedure</td>
<td>1</td>
<td>2.80 [1.91, 3.69]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>0.98 [-0.08, 2.04]</td>
<td>0.07</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Supplementary Table 3.6 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95% CI]^</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>$I^2$, %</th>
<th>Univariable meta-regression</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $I^2$, %**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>9</td>
<td>0.93 [0.34, 1.51]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>78</td>
<td>0.24</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>2.80 [1.91, 3.69]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>4</td>
<td>0.42 [-0.52, 1.35]</td>
<td>0.38</td>
<td>&lt;0.01</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


^ Random effects estimates

* I-squared: variation in risk ratio or mean difference attributable to heterogeneity

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
**Supplementary Table 3.7. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on temperature, degrees Celsius**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95% CI]</th>
<th>p</th>
<th>Test for heterogeneity</th>
<th>I²</th>
<th>p</th>
<th>Test for heterogeneity by covariate</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>14</td>
<td>0.24 [0.15, 0.33]</td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
<td>82</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>2</td>
<td>0.31 [0.12, 0.51]</td>
<td>&lt;0-01</td>
<td>0-01</td>
<td>85</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Randomized crossover</td>
<td>1</td>
<td>0.10 [-0.03, 0.23]</td>
<td>0.12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Crossover</td>
<td>1</td>
<td>0.50 [0.39, 0.61]</td>
<td>&lt;0-01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pre-post</td>
<td>10</td>
<td>0.20 [0.10, 0.30]</td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
<td>63</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>10</td>
<td>0.21 [0.09, 0.34]</td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
<td>79</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>2</td>
<td>0.26 [-0.07, 0.59]</td>
<td>0.12</td>
<td>&lt;0-01</td>
<td>88</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>2</td>
<td>0.31 [0.12, 0.51]</td>
<td>&lt;0-01</td>
<td>0-01</td>
<td>85</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 - 1999</td>
<td>2</td>
<td>0.23 [-0.26, 0.72]</td>
<td>0.35</td>
<td>0.19</td>
<td>42</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>7</td>
<td>0.28 [0.17, 0.40]</td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
<td>82</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2010 - 2014</td>
<td>5</td>
<td>0.19 [0.03, 0.35]</td>
<td>0.02</td>
<td>&lt;0-01</td>
<td>76</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>WHO region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>3</td>
<td>0.09 [-0.01, 0.19]</td>
<td>0.08</td>
<td>0.36</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>2</td>
<td>0.40 [0.35, 0.46]</td>
<td>&lt;0-01</td>
<td>0.72</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Europe</td>
<td>2</td>
<td>-0.18 [-0.71, 0.35]</td>
<td>0.50</td>
<td>0.13</td>
<td>57</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>East Mediterranean</td>
<td>1</td>
<td>0.20 [0.06, 0.34]</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1</td>
<td>0.26 [0.17, 0.35]</td>
<td>&lt;0-01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Africa</td>
<td>2</td>
<td>0.35 [0.06, 0.64]</td>
<td>0.02</td>
<td>&lt;0-01</td>
<td>94</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>0.32 [0.18, 0.47]</td>
<td>&lt;0-01</td>
<td>0.68</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Economy – World Bank</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>0.20 [0.09, 0.31]</td>
<td>&lt;0-01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Middle</td>
<td>5</td>
<td>0.35 [0.24, 0.46]</td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
<td>76</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>0.06 [-0.09, 0.22]</td>
<td>0.42</td>
<td>&lt;0-01</td>
<td>74</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>0.32 [0.18, 0.47]</td>
<td>&lt;0-01</td>
<td>0.68</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Country-level NMR, deaths/1000 live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>5</td>
<td>0.06 [-0.09, 0.22]</td>
<td>0.42</td>
<td>&lt;0-01</td>
<td>74</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>2</td>
<td>0.19 [0.07, 0.30]</td>
<td>&lt;0-01</td>
<td>0.74</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>3</td>
<td>0.34 [0.19, 0.49]</td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
<td>82</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 30</td>
<td>1</td>
<td>0.50 [0.39, 0.61]</td>
<td>&lt;0-01</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>0.32 [0.18, 0.47]</td>
<td>&lt;0-01</td>
<td>0.68</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>8</td>
<td>0.21 [0.08, 0.34]</td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
<td>88</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rural</td>
<td>2</td>
<td>0.19 [-0.31, 0.69]</td>
<td>0.45</td>
<td>&lt;0-01</td>
<td>90</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>0.28 [0.20, 0.36]</td>
<td>&lt;0-01</td>
<td>0.73</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## Supplementary Table 3.7 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95% CI]^*</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>I^2, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I^2, % **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>7</td>
<td>0·32 [0·21, 0·43]</td>
<td>&lt;0·01</td>
<td>&lt;0·01</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>6</td>
<td>0·14 [0·03, 0·25]</td>
<td>0·02</td>
<td>0·02</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0·70 [-0·19, 1·59]</td>
<td>0·12</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Gestational age** |     |               |      |                             |        |                                          |                   |
| Very preterm < 34 weeks | 4  | 0·11 [-0·20, 0·42] | 0·50  | 0·01 | 72 |                                           |                   |
| Preterm < 37 weeks | 6   | 0·21 [0·09, 0·33] | <0·01 | 0·01 | 68 |                                           |                   |
| Full Term | 1   | 0·20 [0·06, 0·34] | 0·01  | -   | - |                                           |                   |
| Missing | 3   | 0·37 [0·22, 0·52] | <0·01 | <0·01 | 88 |                                           |                   |

| **Birth weight** |     |               |      |                             |        |                                          |                   |
| LBW < 2500g | 7   | 0·26 [0·14, 0·38] | <0·01 | <0·01 | 86 |                                           |                   |
| Very LBW < 1500g | 2  | 0·03 [-1·22, 1·29] | 0·96  | 0·03 | 79 |                                           |                   |
| Non LBW | 1   | 0·20 [0·09, 0·31] | <0·01 | -   | - |                                           |                   |
| Missing | 4   | 0·24 [0·05, 0·42] | 0·01  | 0·01 | 75 |                                           |                   |

| **KMC components** |     |               |      |                             |        |                                          |                   |
| SSC | 10  | 0·24 [0·13, 0·35] | <0·01 | <0·01 | 84 |                                           |                   |
| SSC/EBF | 3  | 0·14 [-0·07, 0·36] | 0·19  | 0·09 | 60 |                                           |                   |
| Undefined KMC | 1  | 0·43 [0·25, 0·62] | <0·01 | -   | - |                                           |                   |

| **SSC duration promoted, hours/day** |     |               |      |                             |        |                                          |                   |
| < 2 | 8   | 0·23 [0·13, 0·32] | <0·01 | 0·02 | 58 |                                           |                   |
| 2 - < 4 | 2  | 0·09 [-0·17, 0·35] | 0·52  | 0·07 | 70 |                                           |                   |
| 4 - < 9 | 1  | 0·40 [0·04, 0·46] | <0·01 | -   | - |                                           |                   |
| 12 - < 22 | 1 | 0·50 [0·39, 0·61] | <0·01 | -   | - |                                           |                   |
| Undefined | 2  | 0·16 [-0·18, 0·49] | 0·36  | 0·04 | 77 |                                           |                   |

| **SSC as KMC component** |     |               |      |                             |        |                                          |                   |
| SSC only | 10  | 0·24 [0·13, 0·35] | <0·01 | <0·01 | 84 |                                           |                   |
| SSC + other components | 3   | 0·14 [-0·07, 0·36] | 0·19  | 0·09 | 60 |                                           |                   |
| Undefined KMC | 1  | 0·43 [0·25, 0·62] | <0·01 | -   | - |                                           |                   |

| **EBF as KMC component** |     |               |      |                             |        |                                          |                   |
| EBF component | 3   | 0·14 [-0·07, 0·36] | 0·19  | 0·09 | 60 |                                           |                   |
| No EBF component | 10  | 0·24 [0·13, 0·35] | <0·01 | <0·01 | 84 |                                           |                   |
| Undefined KMC | 1  | 0·43 [0·25, 0·62] | <0·01 | -   | - |                                           |                   |

| **SSC start time** |     |               |      |                             |        |                                          |                   |
| After stability met | 6  | 0·29 [0·16, 0·42] | <0·01 | <0·01 | 85 |                                           |                   |
| After other criteria met | 6 | 0·17 [0·06, 0·29] | <0·01 | 0·02 | 62 |                                           |                   |
| Missing | 2   | -0·01 [-1·00, 0·98] | 0·98  | 0·01 | 86 |                                           |                   |
Supplementary Table 3.7 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MD [95% CI]^</th>
<th>p</th>
<th>Test for heterogeneity</th>
<th>I^2, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I^2, %**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>0.20 [0.10, 0.30]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>4</td>
<td>0.31 [0.14, 0.47]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


^ Random effects estimates

* I-squared: variation in risk ratio or mean difference attributable to heterogeneity

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
Supplementary Table 3.8. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on length of hospital stay, days

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95%CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>I², %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I², % **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>12</td>
<td>-0.68 [-2.11, 0.75]</td>
<td>0.35</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>5</td>
<td>-0.38 [-2.99, 2.23]</td>
<td>0.78</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other observational</td>
<td>7</td>
<td>-0.32 [-3.28, 2.64]</td>
<td>0.83</td>
<td>&lt;0.01</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>5</td>
<td>-0.38 [-2.99, 2.23]</td>
<td>0.78</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>4</td>
<td>-1.72 [-5.88, 2.45]</td>
<td>0.42</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chart review</td>
<td>2</td>
<td>-0.93 [-5.13, 3.28]</td>
<td>0.67</td>
<td>0.14</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilities evaluation</td>
<td>1</td>
<td>7.00 [2.24, 11.76]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>1</td>
<td>2.00 [-14.95, 8.95]</td>
<td>0.82</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>3</td>
<td>-2.19 [-5.09, 0.71]</td>
<td>0.14</td>
<td>0.20</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>4</td>
<td>1.67 [-3.04, 6.37]</td>
<td>0.49</td>
<td>&lt;0.01</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>4</td>
<td>-1.01 [-3.81, 1.79]</td>
<td>0.48</td>
<td>&lt;0.01</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 - 1999</td>
<td>1</td>
<td>-7.80 [-16.45, 0.85]</td>
<td>0.08</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>7</td>
<td>-0.96 [-3.01, 1.09]</td>
<td>0.36</td>
<td>&lt;0.01</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 – 2014</td>
<td>4</td>
<td>1.08 [-2.31, 4.46]</td>
<td>0.53</td>
<td>&lt;0.01</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WHO region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>3</td>
<td>-2.68 [-6.61, 1.24]</td>
<td>0.18</td>
<td>0.01</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>4</td>
<td>0.43 [-3.10, 2.24]</td>
<td>0.75</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>3</td>
<td>1.01 [-7.70, 9.71]</td>
<td>0.82</td>
<td>0.01</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Pacific</td>
<td>2</td>
<td>6.63 [2.05, 11.22]</td>
<td>0.01</td>
<td>0.58</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Economy – World Bank</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>2.99 [0.62, 5.36]</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>7</td>
<td>-1.24 [-3.16, 0.68]</td>
<td>0.21</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td>1.01 [-6.31, 8.34]</td>
<td>0.79</td>
<td>0.02</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Country-level NMR, deaths/1000 live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>4</td>
<td>1.01 [-6.31, 8.34]</td>
<td>0.79</td>
<td>0.02</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>3</td>
<td>-2.68 [-6.61, 1.24]</td>
<td>0.18</td>
<td>0.01</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>5</td>
<td>0.64 [-2.17, 3.44]</td>
<td>0.66</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>11</td>
<td>-0.74 [-2.29, 0.81]</td>
<td>0.35</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>-0.08 [-1.73, 1.57]</td>
<td>0.92</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>11</td>
<td>-0.74 [-2.29, 0.81]</td>
<td>0.35</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>1</td>
<td>-0.08 [-1.73, 1.57]</td>
<td>0.92</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Supplementary Table 3.8 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>RR [95% CI] (^\text{a})</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>I(^2), % (^*)</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual I(^2), % (^**)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>5</td>
<td>0.23 [-5.22, 5.68]</td>
<td>0.93</td>
<td>0.02</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All gestational ages</td>
<td>1</td>
<td>-0.68 [-0.79, -0.57]</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>-0.49 [-2.80, 1.83]</td>
<td>0.68</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>7</td>
<td>-1.32 [-3.24, 0.59]</td>
<td>0.18</td>
<td>&lt;0.01</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>2</td>
<td>8.69 [2.98, 14.41]</td>
<td>&lt;0.01</td>
<td>0.25</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BW</td>
<td>1</td>
<td>-0.68 [-0.79, -0.57]</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>-5.72 [-13.57, 2.13]</td>
<td>0.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>7</td>
<td>-0.10 [-2.17, 1.98]</td>
<td>0.93</td>
<td>&lt;0.01</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF</td>
<td>2</td>
<td>-3.03 [-7.34, 1.29]</td>
<td>0.17</td>
<td>&lt;0.01</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF/DC</td>
<td>1</td>
<td>-3.20 [-7.51, 1.11]</td>
<td>0.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF/FU</td>
<td>1</td>
<td>-0.08 [-1.73, 1.57]</td>
<td>0.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>1</td>
<td>2.99 [0.62, 5.36]</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC duration promoted, hours/day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>1</td>
<td>13.71 [3.30, 24.12]</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 - &lt; 4</td>
<td>2</td>
<td>1.14 [-2.57, 4.86]</td>
<td>0.55</td>
<td>0.92</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - &lt; 9</td>
<td>2</td>
<td>-0.24 [-6.34, 5.86]</td>
<td>0.94</td>
<td>&lt;0.01</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 22</td>
<td>3</td>
<td>0.09 [-5.11, 5.29]</td>
<td>0.97</td>
<td>&lt;0.01</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>4</td>
<td>-0.92 [-1.90, 0.06]</td>
<td>0.07</td>
<td>0.27</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC only</td>
<td>7</td>
<td>-0.10 [-2.17, 1.98]</td>
<td>0.93</td>
<td>&lt;0.01</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC+ other components</td>
<td>4</td>
<td>-2.25 [-5.03, 0.54]</td>
<td>0.11</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>1</td>
<td>2.99 [0.62, 5.36]</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EBF as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBF component</td>
<td>4</td>
<td>-2.25 [-5.03, 0.54]</td>
<td>0.11</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EBF component</td>
<td>7</td>
<td>-0.10 [-2.17, 1.98]</td>
<td>0.93</td>
<td>&lt;0.01</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>1</td>
<td>2.99 [0.62, 5.36]</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC start time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After stability met</td>
<td>6</td>
<td>-0.60 [-2.94, 1.75]</td>
<td>0.62</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After other criteria met</td>
<td>3</td>
<td>2.46 [0.46, 4.46]</td>
<td>0.02</td>
<td>0.71</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>-2.08 [-5.07, 0.91]</td>
<td>0.17</td>
<td>0.14</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup</td>
<td>n</td>
<td>RR [95% CI]</td>
<td>p</td>
<td>Test for heterogeneity (p)</td>
<td>I², %</td>
<td>Test for heterogeneity by covariate (p)</td>
<td>Residual I², %**</td>
</tr>
<tr>
<td>-------------------</td>
<td>----</td>
<td>---------------</td>
<td>-----</td>
<td>----------------------------</td>
<td>--------</td>
<td>----------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Risk of bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>-1.49 [-3.78, 0.80]</td>
<td>0.20</td>
<td>&lt;0.01</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>-0.27 [-3.16, 2.62]</td>
<td>0.85</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>1</td>
<td>2.99 [0.62, 5.36]</td>
<td>0.01</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


* I-squared: variation in risk ratio or mean difference attributable to heterogeneity

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate

^ Random effects estimates

^ Random effects estimates

** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
Supplementary Table 3.9. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on weight gain, standardized mean difference (SMD)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>SMD [95%CI] *</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>$I^2$, % *</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $I^2$, % **</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>11</td>
<td>0·16 [-0·08, 0·40]</td>
<td>0·19</td>
<td>&lt;0·01</td>
<td>82</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Study type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>6</td>
<td>0·33 [-0·05, 0·70]</td>
<td>0·09</td>
<td>&lt;0·01</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>2</td>
<td>-0·19 [-0·32, -0·06]</td>
<td>0·01</td>
<td>0·39</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chart review</td>
<td>2</td>
<td>0·01 [-0·31, 0·32]</td>
<td>0·97</td>
<td>0·23</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilities evaluation</td>
<td>1</td>
<td>-0·05 [-0·44, 0·34]</td>
<td>0·81</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>2</td>
<td>-0·01 [-0·57, 0·54]</td>
<td>0·96</td>
<td>0·56</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 - &lt;100</td>
<td>2</td>
<td>0·09 [-0·46, 0·64]</td>
<td>0·76</td>
<td>0·09</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 - &lt;200</td>
<td>4</td>
<td>0·22 [-0·09, 0·54]</td>
<td>0·17</td>
<td>0·03</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>3</td>
<td>0·19 [-0·36, 0·73]</td>
<td>0·50</td>
<td>&lt;0·01</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 - 1999</td>
<td>1</td>
<td>-0·08 [-0·31, 0·15]</td>
<td>0·50</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 - 2009</td>
<td>7</td>
<td>0·17 [-0·16, 0·50]</td>
<td>0·32</td>
<td>&lt;0·01</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 - 2014</td>
<td>3</td>
<td>0·25 [-0·38, 0·87]</td>
<td>0·44</td>
<td>0·01</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>4</td>
<td>-0·02 [-0·27, 0·24]</td>
<td>0·90</td>
<td>0·06</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>2</td>
<td>0·80 [0·56, 1·05]</td>
<td>&lt;0·01</td>
<td>0·37</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Pacific</td>
<td>4</td>
<td>0·02 [-0·22, 0·25]</td>
<td>0·90</td>
<td>0·90</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Regions</td>
<td>1</td>
<td>-0·08 [-0·31, 0·15]</td>
<td>0·50</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economy – World Bank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·36</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>0·68 [0·33, 1·04]</td>
<td>&lt;0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>6</td>
<td>0·12 [-0·22, 0·45]</td>
<td>0·50</td>
<td>&lt;0·01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>0·20 [-0·18, 0·58]</td>
<td>0·30</td>
<td>0·49</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>-0·08 [-0·31, 0·15]</td>
<td>0·50</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country-level NMR, deaths/1000 live births</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·20</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>4</td>
<td>0·13 [-0·12, 0·39]</td>
<td>0·31</td>
<td>0·65</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - &lt;15</td>
<td>3</td>
<td>-0·11 [-0·32, 0·10]</td>
<td>0·29</td>
<td>0·19</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - &lt;30</td>
<td>4</td>
<td>0·36 [-0·15, 0·87]</td>
<td>0·17</td>
<td>&lt;0·01</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·13</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>9</td>
<td>0·09 [-0·13, 0·32]</td>
<td>0·42</td>
<td>&lt;0·01</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>-0·08 [-0·31, 0·15]</td>
<td>0·50</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>0·91 [0·57, 1·25]</td>
<td>&lt;0·01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0·30</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>8</td>
<td>0·06 [-0·16, 0·28]</td>
<td>0·59</td>
<td>&lt;0·01</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>3</td>
<td>0·42 [-0·22, 1·06]</td>
<td>0·19</td>
<td>&lt;0·01</td>
<td>83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Supplementary Table 3.9 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>SMD [95%CI]</th>
<th>p</th>
<th>Test for heterogeneity</th>
<th>$I^2$, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $I^2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm &lt; 34 weeks</td>
<td>1</td>
<td>0.40 [-0.13, 0.92]</td>
<td>0.14</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>4</td>
<td>-0.01 [-0.23, 0.25]</td>
<td>0.95</td>
<td>0.62</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>0.21 [-0.14, 0.56]</td>
<td>0.24</td>
<td>&lt;0.01</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>7</td>
<td>0.20 [-0.13, 0.54]</td>
<td>0.24</td>
<td>&lt;0.01</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very LBW &lt; 1500g</td>
<td>3</td>
<td>0.09 [-0.14, 0.33]</td>
<td>0.43</td>
<td>0.41</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>-0.15 [-0.87, 0.57]</td>
<td>0.69</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>5</td>
<td>0.10 [-0.09, 0.28]</td>
<td>0.32</td>
<td>0.67</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF</td>
<td>1</td>
<td>-0.20 [-0.33, -0.07]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF/DC</td>
<td>1</td>
<td>-0.17 [-0.56, 0.23]</td>
<td>0.41</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF/DC/FU</td>
<td>1</td>
<td>-0.08 [-0.31, 0.15]</td>
<td>0.50</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC/EBF/FU</td>
<td>1</td>
<td>0.91 [0.57, 1.26]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>0.60 [-0.24, 0.96]</td>
<td>&lt;0.01</td>
<td>0.30</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC duration promoted, hours/day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>1</td>
<td>0.08 [-0.27, 0.43]</td>
<td>0.66</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 - &lt; 4</td>
<td>2</td>
<td>0.10 [-0.22, 0.42]</td>
<td>0.55</td>
<td>0.46</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - &lt; 9</td>
<td>2</td>
<td>0.59 [0.30, 0.89]</td>
<td>&lt;0.01</td>
<td>0.37</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 22</td>
<td>4</td>
<td>0.13 [-0.30, 0.56]</td>
<td>0.55</td>
<td>&lt;0.01</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>2</td>
<td>-0.11 [-0.47, 0.25]</td>
<td>0.56</td>
<td>0.47</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>SSC only</td>
<td>5</td>
<td>0.10 [-0.09, 0.28]</td>
<td>0.32</td>
<td>0.70</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC + other components</td>
<td>4</td>
<td>0.10 [-0.33, 0.54]</td>
<td>0.64</td>
<td>&lt;0.01</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>0.60 [0.24, 0.96]</td>
<td>&lt;0.01</td>
<td>0.30</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EBF as KMC component</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>EBF component</td>
<td>4</td>
<td>0.10 [-0.33, 0.54]</td>
<td>0.64</td>
<td>&lt;0.01</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No EBF component</td>
<td>5</td>
<td>0.10 [-0.09, 0.28]</td>
<td>0.32</td>
<td>0.67</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined KMC</td>
<td>2</td>
<td>0.60 [0.24, 0.96]</td>
<td>&lt;0.01</td>
<td>0.30</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC start time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately</td>
<td>1</td>
<td>-0.08 [-0.31, 0.15]</td>
<td>0.50</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After stability met</td>
<td>5</td>
<td>0.21 [-0.22, 0.65]</td>
<td>0.33</td>
<td>&lt;0.01</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After other criteria met</td>
<td>3</td>
<td>0.29 [-0.17, 0.75]</td>
<td>0.21</td>
<td>0.04</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>-0.11 [-0.47, 0.25]</td>
<td>0.56</td>
<td>0.47</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup</td>
<td>n</td>
<td>SMD [95% CI]^</td>
<td>p</td>
<td>Test for heterogeneity (p)</td>
<td>I^2, % *</td>
<td>Test for heterogeneity by covariate (p)</td>
<td>Residual I^2, % **</td>
</tr>
<tr>
<td>-------------------</td>
<td>----</td>
<td>---------------</td>
<td>-------</td>
<td>---------------------------</td>
<td>---------</td>
<td>----------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Risk of bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2</td>
<td>0.50 [-0.32, 1.31]</td>
<td>0.23</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>6</td>
<td>-0.06 [-0.23, 0.12]</td>
<td>0.53</td>
<td>0.18</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear</td>
<td>3</td>
<td>0.26 [-0.32, 0.85]</td>
<td>0.38</td>
<td>&lt;0.01</td>
<td>84</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


^ Standardized mean difference - random effects estimates
* I-squared: variation in risk ratio or mean difference attributable to heterogeneity
** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
### Supplementary Table 3.10. Subgroup analysis and meta-regression for the effect of KMC compared to conventional care on pain score, standardized mean difference (SMD)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>SMD [95% CI]</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>$I^2$, %</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $I^2$, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subgroup analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>6</td>
<td>-0.52 [-1.16, 0.13]</td>
<td>0.12</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Randomized crossover</td>
<td>2</td>
<td>-1.50 [-1.93, -1.06]</td>
<td>&lt;0.01</td>
<td>0.33</td>
<td>0</td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>Crossover</td>
<td>1</td>
<td>-0.53 [-0.93, -0.13]</td>
<td>0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-post</td>
<td>1</td>
<td>0.31 [-0.37, 0.98]</td>
<td>0.37</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>1</td>
<td>0.31 [-0.37, 0.98]</td>
<td>0.37</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 - &lt; 100</td>
<td>7</td>
<td>-0.67 [-1.09, -0.25]</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 - &lt; 200</td>
<td>1</td>
<td>-0.10 [-0.59, 0.39]</td>
<td>0.69</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>1</td>
<td>-1.56 [-1.81, -1.31]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 – 2009</td>
<td>6</td>
<td>-0.59 [-1.31, 0.12]</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
<td>0.21</td>
</tr>
<tr>
<td>2010 – 2014</td>
<td>4</td>
<td>-0.65 [-1.07, -0.22]</td>
<td>&lt;0.01</td>
<td>0.07</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WHO region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>5</td>
<td>-0.89 [-1.58, -0.20]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>3</td>
<td>-0.62 [-1.18, -0.06]</td>
<td>0.03</td>
<td>0.03</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>2</td>
<td>0.02 [-0.43, 0.48]</td>
<td>0.92</td>
<td>0.28</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Economy – World Bank</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>6</td>
<td>-0.65 [-1.25, -0.06]</td>
<td>0.03</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>High</td>
<td>4</td>
<td>-0.59 [-1.44, 0.26]</td>
<td>0.17</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Country-level NMR, deaths/1000 live births</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>4</td>
<td>-0.59 [-1.44, 0.26]</td>
<td>0.17</td>
<td>&lt;0.01</td>
<td>87</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>3</td>
<td>-0.66 [-1.71, 0.39]</td>
<td>0.22</td>
<td>&lt;0.01</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - &lt; 30</td>
<td>3</td>
<td>-0.62 [-1.18, -0.06]</td>
<td>0.03</td>
<td>0.03</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>8</td>
<td>-0.68 [-1.21, -0.14]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>90</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>-0.40 [-1.07, 0.26]</td>
<td>0.23</td>
<td>0.10</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Facility type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>4</td>
<td>-0.87 [-1.60, -0.14]</td>
<td>0.02</td>
<td>&lt;0.01</td>
<td>92</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>NICU/step-down</td>
<td>6</td>
<td>-0.46 [-1.00, 0.08]</td>
<td>0.10</td>
<td>&lt;0.01</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gestational age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm &lt; 34 weeks</td>
<td>3</td>
<td>-0.73 [-1.88, 0.41]</td>
<td>0.21</td>
<td>&lt;0.01</td>
<td>90</td>
<td></td>
<td>0.34</td>
</tr>
<tr>
<td>Preterm &lt; 37 weeks</td>
<td>5</td>
<td>-0.44 [-0.79, -0.08]</td>
<td>0.02</td>
<td>0.04</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Term</td>
<td>1</td>
<td>-1.56 [-1.81, -1.31]</td>
<td>&lt;0.01</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>-0.14 [-0.70, 0.41]</td>
<td>0.62</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

126
### Supplementary Table 3.10 (Continued)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>SMD [95%CI]^</th>
<th>p</th>
<th>Test for heterogeneity (p)</th>
<th>$\tau^2$, %*</th>
<th>Test for heterogeneity by covariate (p)</th>
<th>Residual $\tau^2$, %**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBW &lt; 2500g</td>
<td>5</td>
<td>-0.48 [-0.95, -0.02]</td>
<td>0.04</td>
<td>0.01</td>
<td>70</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Missing</td>
<td>5</td>
<td>-0.76 [-1.50, -0.02]</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KMC components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSC</td>
<td>10</td>
<td>-0.63 [-1.09, -0.16]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>89</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>SSC duration promoted, hours/day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>5</td>
<td>-0.62 [-1.31, 0.08]</td>
<td>0.14</td>
<td>&lt;0.01</td>
<td>86</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>2 - &lt; 4</td>
<td>1</td>
<td>-0.78 [-1.44, -0.12]</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undefined</td>
<td>4</td>
<td>-0.60 [-1.40, 0.19]</td>
<td>0.14</td>
<td>&lt;0.01</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SSC start time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After other criteria met</td>
<td>2</td>
<td>-0.48 [-0.98, 0.03]</td>
<td>0.06</td>
<td>0.22</td>
<td>33</td>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td>For a painful procedure</td>
<td>5</td>
<td>-0.96 [-1.66, -0.26]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>3</td>
<td>-0.19 [-0.65, 0.26]</td>
<td>0.41</td>
<td>0.10</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk of bias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>8</td>
<td>-0.72 [-1.23, -0.20]</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>90</td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Unclear</td>
<td>2</td>
<td>-0.24 [-1.31, 0.83]</td>
<td>0.66</td>
<td>0.02</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


^ Standardized mean difference - random effects estimates
* I-squared: variation in risk ratio or mean difference attributable to heterogeneity
** Residual I-squared: percent residual variation due to heterogeneity after adjustment for covariate
Supplementary Table 3.11. Risk of bias for randomized control trials (n=55)

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Information Bias</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Other bias</th>
<th>Overall Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acharya 2014</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Aghdas 2014</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Ali 2009</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Anderson 2003</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Bergman 2004</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Bier 1997</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Boo 2007</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Carfoot 2004</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Castral 2008</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Cattaneo 1998</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Charpak 1997</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Charpak 2001</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Chermont 2009</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Christensson 1998</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Eka Pratiwi 2009</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Freire 2008</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Gastwala 2008</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Ghavane 2012</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Gray 2000</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Hake-Brooks 2008</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Kadam 2005</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Kashaninia 2008</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Keshavarz 2010</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Ludington-Hoe 2001</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Mahmood 2011</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Marin Gabriel 2008</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Marin Gabriel 2010</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
</tbody>
</table>
Supplementary Table 3.11 (Continued)

![Image showing a table or a diagram related to bias assessment in studies.]
Supplementary Table 3.12. Risk of bias for observational studies (n=69)
Supplementary Table 3.12 (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection Bias</th>
<th>Information Bias</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Confounding</th>
<th>Other bias</th>
<th>Overall Risk of Bias</th>
</tr>
</thead>
</table>
Supplementary Table 3.13. Studies included in kangaroo mother care systematic review and meta-analysis (n=124)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboueffetoh</td>
<td>2011</td>
<td>Effect of skin-to-skin contact on preterm infant skin barrier function and hospital-acquired infection</td>
<td>USA</td>
<td>Pre-post</td>
<td>10</td>
<td>28-30 weeks</td>
<td>SSC</td>
<td>N/A</td>
<td>≥1</td>
<td>5</td>
<td>Lateral/prone position, clothed in diaper &amp; cap</td>
<td></td>
</tr>
<tr>
<td>Acharya</td>
<td>2014</td>
<td>Randomized control trial of Kangaroo Mother Care in low birth weight babies at a tertiary level hospital</td>
<td>Nepal</td>
<td>RCT</td>
<td>126</td>
<td>&lt;2000g</td>
<td>N/A</td>
<td>Once &amp; mother ready</td>
<td>≥6</td>
<td>N/A</td>
<td>Adequately dressed: W, L, A, Ho, Lp, Hg kept with mother or under radiant warmer</td>
<td></td>
</tr>
<tr>
<td>Acosta Diaz</td>
<td>2003</td>
<td>Kangaroo mother care method. Clinical and humoral assessment during the first year of corrected age</td>
<td>Cuba</td>
<td>Intervention</td>
<td>120</td>
<td>N/A</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Re</td>
</tr>
<tr>
<td>Acosta Diaz</td>
<td>2003</td>
<td>Kangaroo mother care method. Evaluation of neurodevelopment at first year of corrected age</td>
<td>Cuba</td>
<td>Intervention</td>
<td>120</td>
<td>N/A</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Acosta Diaz</td>
<td>2003</td>
<td>Kangaroo mother care method. Impact on physical and intellectual development at preschool age</td>
<td>Cuba</td>
<td>Intervention</td>
<td>120</td>
<td>N/A</td>
<td>SSC</td>
<td>Immediately after birth</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Aghdas</td>
<td>2014</td>
<td>Effect of immediate and continuous mother-infant skin-to-skin contact on breastfeeding self-efficacy of primiparous women: A randomized control trial</td>
<td>Iran</td>
<td>RCT</td>
<td>92</td>
<td>≥37 weeks, 2500-4000g</td>
<td>SSC</td>
<td>Once eligible to definition N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Radiant heater immediately after cutting cord, then wrapped in heated blankets &amp; given to mother</td>
<td>Bt</td>
</tr>
<tr>
<td>Ahmed</td>
<td>2011</td>
<td>Community Kangaroo Mother Care: implementation and potential for neonatal survival and health in very low-income settings</td>
<td>Bangladesh</td>
<td>Cohort</td>
<td>4165</td>
<td>All ages</td>
<td>SSC, EBF, FU</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td>M, B</td>
</tr>
<tr>
<td>Ahn</td>
<td>2010</td>
<td>Kangaroo care on premature infant growth and maternal attachment and post-partum depression in South Korea</td>
<td>South Korea</td>
<td>Prospective cohort</td>
<td>20</td>
<td>&lt;36 weeks, &lt;1800g</td>
<td>N/A</td>
<td>N/A</td>
<td>21</td>
<td>N/A</td>
<td>Conventional care</td>
<td>W</td>
</tr>
<tr>
<td>Ali</td>
<td>2009</td>
<td>Kangaroo mother care as compared to conventional care for low birth weight</td>
<td>India</td>
<td>RCT</td>
<td>114</td>
<td>1200-1800g</td>
<td>SSC</td>
<td>N/A</td>
<td>≥4-6</td>
<td>N/A</td>
<td>Conventional care</td>
<td>B, I, H, R, O, T, A, N, Ho</td>
</tr>
<tr>
<td>Almeida</td>
<td>2007</td>
<td>Effects of Kangaroo Mother Care on the vital signs of low-weight preterm newborns</td>
<td>Brazil</td>
<td>Pre-post</td>
<td>22</td>
<td>28-33 weeks</td>
<td>SSC</td>
<td>After first assessment</td>
<td>0.5</td>
<td>3</td>
<td>Cradle, lying on back, wearing diaper x30min</td>
<td></td>
</tr>
<tr>
<td>Almeida</td>
<td>2010</td>
<td>The impact of kangaroo care on exclusive breastfeeding in low birth weight newborns</td>
<td>Brazil</td>
<td>Retrospective cohort</td>
<td>43</td>
<td>&lt;2000g</td>
<td>SSC, EBF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Title</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample size*</td>
<td>Newborn characteristics</td>
<td>KMC components</td>
<td>Onset of SSC</td>
<td>Hours per day of KMC provision**</td>
<td># of days of KMC provision**</td>
<td>Care in comparison group</td>
<td>Outcomes***</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>-----------------------------------------------------------------------</td>
<td>---------</td>
<td>--------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>---------------------------------</td>
<td>----------------------------</td>
<td>--------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Anderson</td>
<td>2003</td>
<td>Mother-newborn contact in a randomized trial of kangaroo (skin-to-skin) care</td>
<td>USA</td>
<td>RCT</td>
<td>91</td>
<td>32–36 weeks, 1300–3000g</td>
<td>DC</td>
<td>Immediately after birth</td>
<td>24</td>
<td>6-May</td>
<td>Wrapped &amp; held by mothers</td>
<td>Conventional care</td>
</tr>
<tr>
<td>Andrade</td>
<td>2005</td>
<td>Sucking of the premature newborn child: comparison between the kangaroo mother method with traditional care</td>
<td>Brazil</td>
<td>Prospective cohort</td>
<td>30</td>
<td>30–35 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Azevedo</td>
<td>2012</td>
<td>Safety of Kangaroo Mother Care in intubated neonates under 1500 g</td>
<td>Brazil</td>
<td>Pre-post</td>
<td>43</td>
<td>Premature: cutoff N/A, &lt;1500 g</td>
<td>SSC</td>
<td>N/A</td>
<td>1</td>
<td>1</td>
<td>Incubator</td>
<td></td>
</tr>
<tr>
<td>Azevedo</td>
<td>2011</td>
<td>Kangaroo mother care in preterm newborns on artificial ventilation: An evaluation of behavior patterns</td>
<td>Brazil</td>
<td>Pre-post</td>
<td>44</td>
<td>Mean 29 weeks &amp; 1096g</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Bauer</td>
<td>1996</td>
<td>Metabolic rate and energy balance in very low birth weight infants during Kangaroo holding by their mothers and fathers</td>
<td>N/A</td>
<td>Pre-post</td>
<td>11</td>
<td>28–32 weeks, 560–1390 g</td>
<td>SSC</td>
<td>8–48 days after birth</td>
<td>1</td>
<td>1</td>
<td>Pre KMC, &amp; paternal KMC</td>
<td>H,O,T</td>
</tr>
<tr>
<td>Begum</td>
<td>2008</td>
<td>Cerebral oxygenation responses during kangaroo care in low birth weight infants</td>
<td>N/A</td>
<td>Pre-post</td>
<td>16</td>
<td>&lt;33 weeks, &lt;1600g</td>
<td>SSC</td>
<td>After 30 min in incubator</td>
<td>1</td>
<td>1</td>
<td>Incubator</td>
<td>H,R,O,T</td>
</tr>
<tr>
<td>Bera</td>
<td>2014</td>
<td>Effect of kangaroo mother care on growth and development of low birth weight babies up to 12 months of age: a controlled clinical trial</td>
<td>India</td>
<td>Intervention</td>
<td>500</td>
<td>&lt;2500 g</td>
<td>SSC, EBF, FU</td>
<td>Once hemo-dynamically stable</td>
<td>1 on 1st day, 2 on 2nd, 3 on 3rd, then as long as mother desires</td>
<td>N/A</td>
<td>Shared same bed as mother, clothed to keep warm, held as long &amp; often as mother desired</td>
<td></td>
</tr>
<tr>
<td>Bergman</td>
<td>2004</td>
<td>Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200–2199 gram newborns</td>
<td>South Africa</td>
<td>RCT</td>
<td>35</td>
<td>1200-2195g</td>
<td>SSC</td>
<td>After infant dried, assessed for anomalies, resuscitated if needed, given eye prophylaxis &amp; vit K &amp; weighed</td>
<td>6</td>
<td>1</td>
<td>Incubator; cap &amp; booties, heat shield over infant, plastic sheet over the foot end if temp &lt;38 deg C</td>
<td></td>
</tr>
<tr>
<td>Bergstrom</td>
<td>2007</td>
<td>Immediate maternal thermal response to skin-to-skin care of newborn</td>
<td>Uganda</td>
<td>Pre-post</td>
<td>39</td>
<td>Non LBW</td>
<td>SSC</td>
<td>Immediately after birth</td>
<td>0.5–1</td>
<td>1</td>
<td>Conventional care</td>
<td>H,T</td>
</tr>
<tr>
<td>Bier</td>
<td>1996</td>
<td>Comparison of skin-to-skin contact with standard contact in low-birth-weight infants who are breast-fed</td>
<td>Colombia</td>
<td>RCT</td>
<td>50</td>
<td>&lt;1500 g</td>
<td>SSC, EBF</td>
<td>N/A</td>
<td>N/A</td>
<td>≤10</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Blay****</td>
<td>2009</td>
<td>Ghana KMC Study Results</td>
<td>Ghana</td>
<td>Chart review</td>
<td>12953</td>
<td>All ages</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>M</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bohnhorst</td>
<td>2001</td>
<td>Skin-to-skin (kangaroo) care, respiratory control, and thermoregulation</td>
<td>Germany</td>
<td>Pre-post</td>
<td>22</td>
<td>&lt;32 weeks</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>2</td>
<td>1</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Boju</td>
<td>2012</td>
<td>Short spell kangaroo mother care and its differential physiological influence in subgroups of preterm babies</td>
<td>India</td>
<td>Pre-post</td>
<td>86</td>
<td>&lt;37 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>1</td>
<td>1</td>
<td>N/A</td>
<td>H,R,O,T</td>
</tr>
<tr>
<td>Boo</td>
<td>2007</td>
<td>Short duration of skin-to-skin contact: Effects on growth and breastfeeding</td>
<td>Malaysia</td>
<td>RCT</td>
<td>126</td>
<td>&lt;1501g</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>1</td>
<td>10</td>
<td>Incubator</td>
<td>B,I,W,Hg</td>
</tr>
<tr>
<td>Bramson</td>
<td>2010</td>
<td>Effect of early skin-to-skin mother–infant contact during the first 3 hours following birth on exclusive breastfeeding during the maternity hospital stay.</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>21842</td>
<td>Full term</td>
<td>SSC, EBF</td>
<td>Immediately after birth</td>
<td>1</td>
<td>3</td>
<td>Mothers with no early SSC contact</td>
<td>B</td>
</tr>
<tr>
<td>Broughton</td>
<td>2013</td>
<td>The cost-savings of implementing kangaroo mother care in Nicaragua</td>
<td>Nicaragua</td>
<td>Chart review</td>
<td>98</td>
<td>&lt;37 weeks, &lt;2500g</td>
<td>SSC, EBF, DC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator</td>
<td>W,L</td>
</tr>
<tr>
<td>Carbaasse</td>
<td>2013</td>
<td>Safety and Effectiveness of Skin-to-Skin Contact in the NICU to Support Neurodevelopment in Vulnerable Preterm Infants</td>
<td>France</td>
<td>Pre-post</td>
<td>96</td>
<td>&lt;33 weeks</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Before SSC</td>
<td></td>
</tr>
<tr>
<td>Carfoot</td>
<td>2004</td>
<td>The value of a pilot study in breastfeeding research</td>
<td>UK</td>
<td>RCT</td>
<td>28</td>
<td>≥36 weeks</td>
<td>SSC</td>
<td>Immediately after birth</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Castral</td>
<td>2008</td>
<td>The effects of skin-to-skin contact during acute pain in preterm newborns</td>
<td>Brazil</td>
<td>RCT</td>
<td>59</td>
<td>30–&lt;37 weeks</td>
<td>SSC</td>
<td>After 2 min of baseline readings</td>
<td>0.283</td>
<td>1</td>
<td>Lateral position in crib or incubator; head elevated, wearing diaper or wrapped in blankets;</td>
<td>P, PF, Hp</td>
</tr>
<tr>
<td>Cattaneo</td>
<td>1998</td>
<td>Kangaroo mother care for low birth weight infants: a randomized controlled trial in different settings</td>
<td>Mexico, Indonesia, Ethiopia</td>
<td>RCT</td>
<td>7354</td>
<td>1000-1999g</td>
<td>SSC, EBF, DC, FU</td>
<td>Immediately after birth</td>
<td>20</td>
<td>N/A</td>
<td>Ethiopia: warm room, open cribs &amp; possibility of rewarming; Indonesia: mothers in separate room; Mexico: mothers not allowed to stay, could visit during the day</td>
<td>M, B, W</td>
</tr>
<tr>
<td>Charpak</td>
<td>1997</td>
<td>Kangaroo mother versus traditional care for newborn infants ≤2000 grams: A randomized, controlled trial</td>
<td>Colombia</td>
<td>RCT</td>
<td>746</td>
<td>&lt;2000g</td>
<td>SSC, EBF, DC, FU</td>
<td>Once eligible: definition N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator</td>
<td>B,I</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charpak</td>
<td>2001</td>
<td>A randomized, controlled trial of kangaroo mother care: results of follow-up at 1 year of corrected age</td>
<td>Colombia</td>
<td>RCT</td>
<td>777</td>
<td>&lt;2000g</td>
<td>SSC, DC, FU</td>
<td>Once eligible: definition N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator</td>
<td>M</td>
</tr>
<tr>
<td>Charpak</td>
<td>1994</td>
<td>Kangaroo Mother Program: an alternative way of caring for low birth weight infants? One year mortality in a two cohort study</td>
<td>Colombia</td>
<td>Prospective cohort</td>
<td>332</td>
<td>≤2000g</td>
<td>SSC, DC, FU</td>
<td>After surviving neonatal period &amp; eligible for minimal care</td>
<td>N/A</td>
<td>28.5</td>
<td>Incubator</td>
<td>M</td>
</tr>
<tr>
<td>Chermont</td>
<td>2009</td>
<td>Skin-to-Skin Contact and/or Oral 25% Dextrose for Procedural Pain Relief for Term Newborn Infants</td>
<td>Brazil</td>
<td>RCT</td>
<td>640</td>
<td>Full term</td>
<td>SSC</td>
<td>2 min before injection</td>
<td>N/A</td>
<td>1</td>
<td>3 comparisons: 1ml P, Pn, P, Hp sterile water on tongue &amp; supine in crib, 1ml 0.25 oral dextrose; SSC &amp; 1ml 0.25 oral dextrose</td>
<td>Heel prick without KMC</td>
</tr>
<tr>
<td>Chidambaram</td>
<td>2013</td>
<td>Effect of Kangaroo mother care in reducing pain due to heel prick among preterm neonates: a crossover trial</td>
<td>India</td>
<td>Crossover</td>
<td>50</td>
<td>32-36 weeks, ≤2500g</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>1</td>
<td>Heel prick without KMC</td>
<td>P, Pp</td>
</tr>
<tr>
<td>Christensson</td>
<td>1998</td>
<td>Randomized study of skin-to-skin versus incubator care for rewarthing low-risk hypothermic neonates</td>
<td>Zambia</td>
<td>RCT</td>
<td>80</td>
<td>All ages, ≥1500g</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator</td>
<td>Heel prick without KMC</td>
</tr>
<tr>
<td>Collados-Gomez</td>
<td>2011</td>
<td>Assessing the impact of kangaroo care on preterm infant stress</td>
<td>Spain</td>
<td>Chart review, pre-post</td>
<td>51</td>
<td>29-34 weeks PMA</td>
<td>N/A</td>
<td>N/A</td>
<td>≥0.5</td>
<td>1</td>
<td>N/A</td>
<td>Conventional care</td>
</tr>
<tr>
<td>Cong</td>
<td>2012</td>
<td>Effects of skin-to-skin contact on autonomic pain responses in preterm infants</td>
<td>USA</td>
<td>Randomized crossover</td>
<td>26</td>
<td>28-33 weeks</td>
<td>SSC</td>
<td>N/A</td>
<td>0.25-0.5</td>
<td>N/A</td>
<td>Incubator</td>
<td>Hp</td>
</tr>
<tr>
<td>Cong</td>
<td>2009</td>
<td>Kangaroo Care modifies preterm infant heart rate variability in response to heel stick pain: pilot study</td>
<td>USA</td>
<td>Randomized crossover</td>
<td>14</td>
<td>30-32 weeks</td>
<td>SSC</td>
<td>After NG tube or bottle feeding completed</td>
<td>1.5</td>
<td>1</td>
<td>Incubator</td>
<td>Hp</td>
</tr>
<tr>
<td>Constantinou</td>
<td>1999</td>
<td>Effects of skin-to-skin holding on general movements of preterm infants</td>
<td>USA</td>
<td>Pre-post</td>
<td>10</td>
<td>33-36 weeks, ≤2000g</td>
<td>SSC</td>
<td>After the first feeding of the day</td>
<td>N/A</td>
<td>1</td>
<td>Isolette</td>
<td>Heel prick without KMC</td>
</tr>
<tr>
<td>Dageville</td>
<td>2008</td>
<td>Very early neonatal apparent life-threatening events and sudden unexpected deaths: incidence and risk factors</td>
<td>France</td>
<td>Case control</td>
<td>62968</td>
<td>&gt;36 weeks</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Case control</td>
<td>Heel prick without KMC</td>
</tr>
</tbody>
</table>
| Eka Pratiwi     | 2009 | Effect of kangaroo method on the risk of hypothermia and duration of birth weight regain in low birth weight infants: A randomized control trial | Indonesia | RCT          | 98           | 1500-2250g         | N/A               | Immediately after birth | N/A                      | N/A                  | Conventional care | I, Ho, He
### Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entringer</td>
<td>2013</td>
<td>Budget impact of using the Kangaroo Method in neonatal care</td>
<td>Brazil</td>
<td>Chart review</td>
<td>1000</td>
<td>All ages, &gt;1250g</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td>H</td>
</tr>
<tr>
<td>Feldman</td>
<td>2003</td>
<td>Skin-to-skin contact (Kangaroo Care) accelerates autonomic and neurobehavioral maturation in preterm infants</td>
<td>Israel</td>
<td>Intervention</td>
<td>70</td>
<td>25-33 weeks, &lt;1650g</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>1</td>
<td>14</td>
<td>Incubator  H</td>
<td>P,Pp</td>
</tr>
<tr>
<td>Freire</td>
<td>2008</td>
<td>Evaluation of analgesic effect of skin-to-skin contact compared to oral glucose in preterm neonates</td>
<td>Brazil</td>
<td>RCT</td>
<td>105</td>
<td>28-36 weeks</td>
<td>SSC</td>
<td>10 min before painful stimulus</td>
<td>N/A</td>
<td>1</td>
<td>Incubator L</td>
<td>I,A,G</td>
</tr>
<tr>
<td>Furman</td>
<td>2002</td>
<td>Correlates of lactation in mothers of very low birth weight infants</td>
<td>USA</td>
<td>Cohort</td>
<td>149</td>
<td>&lt;33 weeks, 600-1499g</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Women who hadn’t heard of or tried KMC</td>
<td>I,A,G</td>
</tr>
<tr>
<td>Gathwala</td>
<td>2008</td>
<td>KMC facilitates mother baby attachment in low birth weight infants</td>
<td>India</td>
<td>RCT</td>
<td>110</td>
<td>≥1800g</td>
<td>SSC</td>
<td>N/A</td>
<td>≥6</td>
<td>N/A</td>
<td>Incubator</td>
<td>I,A,G</td>
</tr>
<tr>
<td>Ghavane</td>
<td>2012</td>
<td>Kangaroo Mother Care in Kangaroo ward for improving the growth and breastfeeding outcomes when reaching term gestational age in very low birth weight infants</td>
<td>India</td>
<td>RCT</td>
<td>149</td>
<td>&lt;1500g</td>
<td>SSC,EBF, DC,FU</td>
<td>Once transferred to KMC ward</td>
<td>8</td>
<td>N/A</td>
<td>Incubator</td>
<td>I,A,G</td>
</tr>
<tr>
<td>Gray</td>
<td>2000</td>
<td>Skin-to-skin contact is analgesic in healthy newborns</td>
<td>USA</td>
<td>RCT</td>
<td>30</td>
<td>Full term</td>
<td>SSC,EBF</td>
<td>10-15 min before heel stick</td>
<td>≤1</td>
<td>1</td>
<td>Swaddled in a crib</td>
<td>I,A,G</td>
</tr>
<tr>
<td>Gregson</td>
<td>2011</td>
<td>Kangaroo care in pre-term or low birth weight babies in a postnatal ward</td>
<td>UK</td>
<td>Prospective cohort</td>
<td>214</td>
<td>All ages</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>In cot beside mother</td>
<td>B,L</td>
</tr>
<tr>
<td>Hale-Brooks</td>
<td>2008</td>
<td>Kangaroo care and breastfeeding of mother-preterm infant dyads 0-18 months: a randomized, controlled trial</td>
<td>USA</td>
<td>RCT</td>
<td>66</td>
<td>32-36 weeks</td>
<td>SSC,EBF</td>
<td>N/A</td>
<td>N/A</td>
<td>5</td>
<td>Conventional care</td>
<td>B</td>
</tr>
<tr>
<td>Heidarazadeh</td>
<td>2013</td>
<td>The Effect of Kangaroo Mother Care (KMC) on Breast Feeding at the Time of NICU Discharge</td>
<td>Iran</td>
<td>Prospective cohort</td>
<td>251</td>
<td>28-&lt;37 weeks</td>
<td>N/A</td>
<td>Immediately after birth</td>
<td>9-Mar</td>
<td>Until discharge</td>
<td>Conventional care B</td>
<td>B</td>
</tr>
<tr>
<td>Helmann</td>
<td>2013</td>
<td>Infrared thermography for detailed registration of thermoregulation in premature infants</td>
<td>Germany</td>
<td>Pre-post</td>
<td>10</td>
<td>&lt;32 weeks, 720-1450g</td>
<td>SSC</td>
<td>N/A</td>
<td>1-1.5</td>
<td>1</td>
<td>Conventional care</td>
<td>T</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Title</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample size*</td>
<td>Newborn characteristics</td>
<td>KMC components</td>
<td>Onset of SSC</td>
<td>Hours per day of KMC provision**</td>
<td># of days of KMC provision**</td>
<td>Care in comparison group</td>
<td>Outcomes***</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------</td>
<td>----------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>---------------------------------</td>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Ibe</td>
<td>2004</td>
<td>A comparison of kangaroo mother care and conventional incubator care for thermal regulation of infants &lt; 2000 g in Nigeria using continuous ambulatory temperature monitoring</td>
<td>Nigeria</td>
<td>Crossover</td>
<td>13</td>
<td>1200-1999g</td>
<td>SSC</td>
<td>After enrollment</td>
<td>12</td>
<td>N/A</td>
<td>Incubator, wearing nappies</td>
<td>T, Ho</td>
</tr>
<tr>
<td>Johnston</td>
<td>2008</td>
<td>Kangaroo mother care diminishes pain from heel lance in very preterm neonates: a crossover trial</td>
<td>Canada</td>
<td>Randomized crossover</td>
<td>61</td>
<td>28-31 weeks</td>
<td>SSC</td>
<td>≥15 minutes prior to heel lance</td>
<td>0.5</td>
<td>N/A</td>
<td>Incubator</td>
<td>P, Pp</td>
</tr>
<tr>
<td>Kadam</td>
<td>2005</td>
<td>Feasibility of kangaroo mother care in Mumbai</td>
<td>India</td>
<td>RCT</td>
<td>89</td>
<td>&lt;1800g</td>
<td>SSC, EBF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Radiant warmer</td>
<td>M, U, R, O, L, A, Ho, He, Bt</td>
</tr>
<tr>
<td>Kaffashi</td>
<td>2013</td>
<td>An analysis of the kangaroo care intervention using Kangaroo care versus incubator care in the management of well preterm infants: a pilot study</td>
<td>USA</td>
<td>Prospective cohort</td>
<td>126</td>
<td>All ages</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>56</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Kambarami</td>
<td>1998</td>
<td>Early skin-to-skin care in extremely preterm infants: thermal balance and care environment</td>
<td>Zimbabwe</td>
<td>Intervention</td>
<td>74</td>
<td>Premature: cutoff N/A, &lt;1600g</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator or cot when incubators crowded</td>
<td></td>
</tr>
<tr>
<td>Karlsson</td>
<td>2012</td>
<td>Early skin-to-skin care in extremely preterm infants: thermal balance and care environment</td>
<td>Sweden</td>
<td>Pre-post</td>
<td>27</td>
<td>&lt;27 weeks</td>
<td>SSC</td>
<td>A few days after birth</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator</td>
<td></td>
</tr>
<tr>
<td>Kashaninia</td>
<td>2008</td>
<td>The effect of Kangaroo Care on behavioral responses to pain of an intramuscular injection in neonates</td>
<td>Iran</td>
<td>RCT</td>
<td>100</td>
<td>Full term, non LBW</td>
<td>SSC</td>
<td>10 min before procedure</td>
<td>N/A</td>
<td>N/A</td>
<td>Placed in quiet room for 10 min</td>
<td></td>
</tr>
<tr>
<td>Keshavaze</td>
<td>2010</td>
<td>Effects of kangaroo contact on some physiological parameters in term neonates and pain score in mothers with cesarean section</td>
<td>Iran</td>
<td>RCT</td>
<td>160</td>
<td>Full term</td>
<td>SSC</td>
<td>2 hours after Cesarean</td>
<td>3</td>
<td>N/A</td>
<td>Conventional care</td>
<td>T, C</td>
</tr>
<tr>
<td>Kostandy</td>
<td>2008</td>
<td>Kangaroo Care (skin contact) reduces crying response to pain in preterm neonates: pilot results</td>
<td>USA</td>
<td>Randomized crossover</td>
<td>10</td>
<td>30-32 weeks</td>
<td>SSC</td>
<td>30 min before heel stick</td>
<td>0.83</td>
<td>1</td>
<td>Incubator</td>
<td></td>
</tr>
<tr>
<td>Lam Filho</td>
<td>2006</td>
<td>Evaluation of neonatal outcomes of the kangaroo mother method in Brazil</td>
<td>Brazil</td>
<td>Prospective cohort</td>
<td>905</td>
<td>500-1749g</td>
<td>SSC, EBF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Facilities without KMC</td>
<td>M, W, L, N</td>
</tr>
<tr>
<td>Lee</td>
<td>2011</td>
<td>The Effects of Kangaroo Care on Maternal Self-esteem and Premature Infants’ Physiological Stability</td>
<td>South Korea</td>
<td>Pre-post</td>
<td>34</td>
<td>&gt;32 weeks, 1000-2000g</td>
<td>SSC</td>
<td>After feeding</td>
<td>0.5</td>
<td>14</td>
<td>Incubator or bassinet</td>
<td>H, R, O, T</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Title</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample size*</td>
<td>Newborn characteristics</td>
<td>KMC components</td>
<td>Onset of SSC</td>
<td>Hours per day of KMC provision**</td>
<td># of days of KMC provision**</td>
<td>Care in comparison group</td>
<td>Outcomes***</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>----------------------------------------------------------------------</td>
<td>----------</td>
<td>--------------</td>
<td>--------------</td>
<td>------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Legault</td>
<td>1995</td>
<td>Comparison of kangaroo and traditional methods of removing preterm infants from incubators</td>
<td>Canada</td>
<td>RCT, pre-post, crossover</td>
<td>61</td>
<td>Premature; cutoff N/A, 1000-1800g</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>0.5</td>
<td>1</td>
<td>Wrapped in blanket, held by mother after removing from incubator</td>
<td>H,R,O,T</td>
</tr>
<tr>
<td>Lincetto</td>
<td>2000</td>
<td>Kangaroo mother care with limited resources</td>
<td>Mozambique</td>
<td>Facility evaluation</td>
<td>32</td>
<td>≤1800g</td>
<td>SSC, EBF, DC, FU</td>
<td>As soon as possible after admission irrespective of health condition</td>
<td>2.5-3.83</td>
<td>1</td>
<td>Conventional care</td>
<td>M</td>
</tr>
<tr>
<td>Ludington-Hoe</td>
<td>2000</td>
<td>Kangaroo care compared to incubators in maintaining body warmth in preterm infants</td>
<td>USA</td>
<td>Randomized pre-post</td>
<td>29</td>
<td>26-35 weeks, 770-2710g</td>
<td>SSC, EBF</td>
<td>Once transferred from incubator to mother seated in upright chair beside incubator</td>
<td>1</td>
<td>10</td>
<td>Incubator</td>
<td>T</td>
</tr>
<tr>
<td>Ludington-Hoe</td>
<td>2001</td>
<td>Kangaroo mother care during phototherapy: effect on bilirubin profile</td>
<td>USA</td>
<td>RCT</td>
<td>30</td>
<td>30-35 weeks, &lt;2500g</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>1</td>
<td>10</td>
<td>One group phototherapy 24 h/day, one group 23h photo-therapy, &amp; 1h prone on neonatal fiber optic photo-therapy panel</td>
<td>H,R,O,T</td>
</tr>
<tr>
<td>Ludington-Hoe</td>
<td>2004</td>
<td>Randomized controlled trial of kangaroo care: cardiorespiratory and thermal effects on healthy preterm infants</td>
<td>N/A</td>
<td>Randomized pre-post</td>
<td>24</td>
<td>32-36 weeks</td>
<td>SSC, EBF</td>
<td>After pretest phase</td>
<td>N/A</td>
<td>1</td>
<td>Lying in open crib, wearing diaper, T-shirt &amp; cap</td>
<td>H,R,O,T</td>
</tr>
<tr>
<td>Lyngstad</td>
<td>2014</td>
<td>Does skin-to-skin contact reduce stress during diaper change in preterm infants?</td>
<td>Norway</td>
<td>Randomized crossover</td>
<td>19</td>
<td>28-34 weeks</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>2</td>
<td>Incubator</td>
<td>H,R,O,T</td>
</tr>
<tr>
<td>Maastrup</td>
<td>2010</td>
<td>Extremely preterm infants tolerate skin-to-skin contact during the first weeks of life</td>
<td>Sweden, Norway, Denmark</td>
<td>Pre-post</td>
<td>22</td>
<td>&lt;28 weeks</td>
<td>SSC</td>
<td>After pre-test</td>
<td>N/A</td>
<td>1</td>
<td>Incubator before KMC</td>
<td>H,R,O,T</td>
</tr>
<tr>
<td>Mahnood</td>
<td>2011</td>
<td>Effect of mother-infant early skin-to-skin contact on breastfeeding status: a randomized controlled trial</td>
<td>Pakistan</td>
<td>RCT</td>
<td>183</td>
<td>≥37 weeks, ≥2500g</td>
<td>SSC, EBF</td>
<td>Once eligible: definition N/A</td>
<td>N/A</td>
<td>30</td>
<td>Radiant warmer immediately after cutting cord</td>
<td>Bt</td>
</tr>
</tbody>
</table>
## Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marin Gabriel</td>
<td>2010</td>
<td>Randomized controlled trial of early skin-to-skin contact: effects on the mother and the newborn</td>
<td>Spain</td>
<td>RCT</td>
<td>274</td>
<td>35-42 weeks</td>
<td>SSC, EBF, FU</td>
<td>Immediately after birth</td>
<td>2</td>
<td>1</td>
<td>Placed on exam table with heater above, dried, dressed in diaper &amp; cap, wrapped in warm blanket, given to parents at ~10 min of life</td>
<td>B</td>
</tr>
<tr>
<td>Marin Gabriel</td>
<td>2008</td>
<td>Evaluation of pain in a neonatal intensive care unit during endocrine-metabolic tests</td>
<td>Spain</td>
<td>RCT</td>
<td>54</td>
<td>Premature: cutoff N/A</td>
<td>SSC</td>
<td>N/A</td>
<td>≤1</td>
<td>1</td>
<td>Place on comparison group</td>
<td>P, Pn</td>
</tr>
<tr>
<td>McMaster</td>
<td>2000</td>
<td>Kangaroo care in Port Moreby, Papua New Guinea</td>
<td>Papua New Guinea</td>
<td>Facility evaluation</td>
<td>109</td>
<td>&lt;1500g</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td>M, I, W, L</td>
</tr>
<tr>
<td>Messmer</td>
<td>1997</td>
<td>Effect of kangaroo care on sleep time for neonates</td>
<td>USA</td>
<td>Pre-post</td>
<td>20</td>
<td>26-37 weeks, 750-1500g</td>
<td>SSC</td>
<td>After pre period 1</td>
<td>1</td>
<td>1</td>
<td>Incubator</td>
<td>H, R, O</td>
</tr>
<tr>
<td>Miles</td>
<td>2006</td>
<td>A controlled trial of skin-to-skin contact in extremely preterm infants</td>
<td>UK</td>
<td>RCT</td>
<td>78</td>
<td>&lt;32 weeks</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>0.33</td>
<td>2B</td>
<td>Incubator</td>
<td>N/A</td>
</tr>
<tr>
<td>Miltesterine</td>
<td>2003</td>
<td>Physiological responses of the kangaroo Mother Position in low birth weight, spontaneous ventilating premature babies</td>
<td>Brazil</td>
<td>Pre-post</td>
<td>23</td>
<td>24-37 weeks, &lt;2000g</td>
<td>SSC, EBF</td>
<td>Once eligible: definition N/A</td>
<td>1</td>
<td>1</td>
<td>Incubator</td>
<td>H, R, O, T</td>
</tr>
<tr>
<td>Mitchell</td>
<td>2013</td>
<td>Does daily kangaroo care provide sustained pain and stress relief in preterm infants?</td>
<td>USA</td>
<td>RCT</td>
<td>54</td>
<td>27-30 weeks, ≥1000g</td>
<td>SSC</td>
<td>5 days of life</td>
<td>≥2</td>
<td>5</td>
<td>Held 15 min daily at parent's request</td>
<td>P, P, C</td>
</tr>
<tr>
<td>Mitchell Al</td>
<td>2013</td>
<td>Effects of daily kangaroo care on cardiorespiratory parameters in preterm infants</td>
<td>USA</td>
<td>RCT</td>
<td>38</td>
<td>27-30 weeks, 1000-1500g</td>
<td>SSC</td>
<td>5 days of life</td>
<td>2</td>
<td>5</td>
<td>Incubator, allowed to be held SSC up to 15 min per day</td>
<td>H, R, O, T</td>
</tr>
<tr>
<td>Mohammed El-Nagger</td>
<td>2013</td>
<td>Effect of kangaroo mother care on premature infants' physiological, behavioral and psychosocial outcomes in Ain Shams maternity and Gynecological Hospital, Cairo, Egypt</td>
<td>Egypt</td>
<td>Pre-post</td>
<td>50</td>
<td>Premature, LBW, cutoff N/A</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>1</td>
<td>1</td>
<td>Incubator</td>
<td>H, O</td>
</tr>
<tr>
<td>Morellus</td>
<td>2005</td>
<td>Salivary cortisol and mood and pain profiles during skin-to-skin care for an unsolicited group of mothers and infants in neonatal intensive care</td>
<td>Sweden</td>
<td>Pre-post</td>
<td>17</td>
<td>33 weeks, 495-2590g</td>
<td>SSC</td>
<td>N/A</td>
<td>1</td>
<td>2</td>
<td></td>
<td>H, P, P, P, N, c</td>
</tr>
<tr>
<td>Morgan</td>
<td>2011</td>
<td>Should Neonates Sleep Alone? South Africa</td>
<td>South Africa</td>
<td>Randomized crossover</td>
<td>16</td>
<td>Full term</td>
<td>SSC</td>
<td>N/A</td>
<td>1</td>
<td>1</td>
<td>Swaddled in open bassinet next to mother's head for 1 hour</td>
<td>A, B, C, D</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanavati</td>
<td>2013</td>
<td>Effect of Kangaroo Mother Care Expressed Breast Milk Administration on Pain Associated with Removal of Adhesive Tapes in Very Low Birth Weight Neonates: A Randomized Controlled Trial</td>
<td>India</td>
<td>RCT</td>
<td>50</td>
<td>LBW, cutoff N/A</td>
<td>SSC</td>
<td>15 min before removal of tape</td>
<td>N/A</td>
<td>N/A</td>
<td>Swab soaked in expressed breast milk in mouth ≥2 min before/during removal of tape</td>
<td>P,Pp</td>
</tr>
<tr>
<td>Neu</td>
<td>2010</td>
<td>Maternal Holding of Preterm Infants During the Early Weeks After Birth and Dyad Interaction at Six Months</td>
<td>USA</td>
<td>RCT</td>
<td>87</td>
<td>32-34 weeks</td>
<td>SSC</td>
<td>4 weeks after birth</td>
<td>≥1</td>
<td>N/A</td>
<td>Wrapped in blanket, held by mother ≥1 h/day without specific direction on holding style or duration</td>
<td>B</td>
</tr>
<tr>
<td>Neu</td>
<td>2013</td>
<td>Influence of holding practice on preterm infant development between a mother and her NICU-infant in two university hospitals in Finland</td>
<td>USA</td>
<td>RCT</td>
<td>87</td>
<td>32-35 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Wrapped in blankets, held by mother</td>
<td>B</td>
</tr>
<tr>
<td>Niets-Vilen</td>
<td>2013</td>
<td>Early physical contact between a mother and her NICU-infant in two university hospitals in Finland</td>
<td>Finland</td>
<td>Prospective cohort qualitative</td>
<td>381 at phase one, 170 at phase two</td>
<td>All NICU newborns</td>
<td>N/A</td>
<td>Immediately after birth</td>
<td>N/A</td>
<td>N/A</td>
<td>No physical contact</td>
<td>B</td>
</tr>
<tr>
<td>Nimbalkar</td>
<td>2013</td>
<td>Kangaroo Mother Care in reducing pain in preterm neonates on heel prick</td>
<td>India</td>
<td>Randomized crossover</td>
<td>50</td>
<td>32-36 weeks, &lt;2500g</td>
<td>SSC</td>
<td>15 min before heel stick</td>
<td>0.5</td>
<td>1</td>
<td>Blanket with cot, prone position</td>
<td>P,Pp</td>
</tr>
<tr>
<td>Nimbalkar</td>
<td>2012</td>
<td>Reduced duration of cpap in preterm babies receiving kangaroo care within an hour of birth - Randomized trial</td>
<td>India</td>
<td>RCT</td>
<td>16</td>
<td>26-32 weeks</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Nimbalkar</td>
<td>2014</td>
<td>Effect of early skin-to-skin contact following normal delivery on incidence of hypothermia in neonates more than 1800g: a randomized control trial</td>
<td>India</td>
<td>RCT</td>
<td>100</td>
<td>≥1800g</td>
<td>SSC, EBF</td>
<td>After post-delivery care, 30min-1hr after birth</td>
<td>N/A</td>
<td>1</td>
<td>Radiant warmer HO post-birth, wearing cap, covered with blanket, bedded with mother for first 48 hours</td>
<td>Incubator</td>
</tr>
<tr>
<td>Ohgi</td>
<td>2002</td>
<td>Comparison of kangaroo care and standard care: behavioral organization, development, and temperament in healthy, low-birth-weight infants through 1 year</td>
<td>Japan</td>
<td>Intervention</td>
<td>53</td>
<td>1501-2099g</td>
<td>SSC, EBF, FU</td>
<td>Tolerated handling outside incubator</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Title</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample size*</td>
<td>Newborn characteristics</td>
<td>KMC components</td>
<td>Onset of SSC</td>
<td>Hours per day of KMC provision**</td>
<td># of days of KMC provision**</td>
<td>Care in comparison group</td>
<td>Outcomes***</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>-----------------------------------------------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Park</td>
<td>2014</td>
<td>Practical application of kangaroo mother care in preterm infants: clinical characteristics and safety of kangaroo mother care</td>
<td>South Korea</td>
<td>Intervention</td>
<td>31</td>
<td>25-32 weeks</td>
<td>SSC, EBF</td>
<td>None or self-limiting apnea, bradycardia, &amp; desaturation, acceptable BP, no arterial line, chest tube, intensive phototherapy, deterioration of condition in past 2 days</td>
<td>0.5-1.5</td>
<td>1-2 times per week until transition</td>
<td>Before KMC</td>
<td>I</td>
</tr>
<tr>
<td>Pattinson</td>
<td>2006</td>
<td>Does kangaroo mother care save lives?</td>
<td>South Africa</td>
<td>Chart review</td>
<td>N/A</td>
<td>1000-1999g</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Before hospital introduced KMC</td>
<td>W</td>
</tr>
<tr>
<td>Priya</td>
<td>2004</td>
<td>Kangaroo care for low birth weight babies</td>
<td>India</td>
<td>Crossover</td>
<td>N/A</td>
<td>LBW: cutoff N/A</td>
<td>SSC</td>
<td>N/A</td>
<td>2</td>
<td>2</td>
<td>Warmer or kept well wrapped</td>
<td>M</td>
</tr>
<tr>
<td>Ramanathan</td>
<td>2001</td>
<td>Kangaroo Mother Care in very low birth weight infants</td>
<td>India</td>
<td>RCT</td>
<td>28</td>
<td>&lt;1500g</td>
<td>N/A</td>
<td>N/A</td>
<td>&gt;4</td>
<td>N/A</td>
<td>Warmer or incubator</td>
<td>W,L</td>
</tr>
<tr>
<td>Roberts</td>
<td>2000</td>
<td>A comparison of kangaroo mother care and conventional cuddling care</td>
<td>Australia</td>
<td>RCT</td>
<td>30</td>
<td>30-&lt;37 weeks, SGA</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>2</td>
<td>5</td>
<td>Swaddled in infant clothing &amp; light blanket on rocking seat</td>
<td>W,L</td>
</tr>
<tr>
<td>Rodrigues</td>
<td>2009</td>
<td>Trial gain of weight and hospital length stay of the low birth weight preterm infant in assistance for kangaroo mother care</td>
<td>Brazil</td>
<td>Chart review</td>
<td>120</td>
<td>&lt;37 weeks, &lt;2000g</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>2</td>
<td>Depends on mother length of stay</td>
<td>Babies denied KMC provision or born before KMC implementation</td>
<td>W,L</td>
</tr>
<tr>
<td>Rojas</td>
<td>2003</td>
<td>Somatic growth of preterm infants during skin-to-skin care versus traditional holding: a randomized, controlled trial</td>
<td>USA</td>
<td>RCT</td>
<td>60</td>
<td>≤32 weeks, ≤1500g</td>
<td>SSC</td>
<td>Once eligible: definition N/A</td>
<td>8</td>
<td>4</td>
<td>Traditional holding: in parent's arms, supine, eye-to-eye contact</td>
<td>M,I,W,A,N,Ha, Lp,Hg</td>
</tr>
<tr>
<td>Saeedi</td>
<td>2011</td>
<td>Effect of kangaroo care method on the pain intensity of vaccination in newborns</td>
<td>Iran</td>
<td>RCT</td>
<td>60</td>
<td>Full term, 2500-4000g</td>
<td>SSC</td>
<td>24h after birth &amp; 230 min since last feeding &amp; 2 min before vaccination</td>
<td>0.5</td>
<td>1</td>
<td>Wrapped in blanket near mother's bed</td>
<td>M,I,W,A,N,Ha</td>
</tr>
<tr>
<td>Saeidi</td>
<td>2010</td>
<td>Kangaroo mother care for infantile colic: A randomized clinical trial</td>
<td>Iran</td>
<td>RCT</td>
<td>48</td>
<td>Full term, &gt;2500g</td>
<td>N/A</td>
<td>2 days old</td>
<td>22</td>
<td>7</td>
<td>Cradle</td>
<td>M,I,W,A,N,Ha</td>
</tr>
<tr>
<td>Saeidi</td>
<td>2011</td>
<td>Use of &quot;kangaroo care&quot; to alleviate the intensity of vaccination pain in newborns</td>
<td>Iran</td>
<td>RCT</td>
<td>60</td>
<td>Full Term, 2500-4000g</td>
<td>SSC</td>
<td>30 min before vaccination</td>
<td>0.5</td>
<td>1</td>
<td>Wrapped in blanket near mother's bed</td>
<td>M,I,W,A,N,Ha</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sajedi</td>
<td>2007</td>
<td>The effect of Kangaroo Care on physiologic responses to pain of an intramuscular injection in neonates</td>
<td>Iran</td>
<td>RCT</td>
<td>100</td>
<td>37-42 weeks, 2500-4000g</td>
<td>SSC</td>
<td>10 min before injection, when quiet &amp; alert</td>
<td>0.21</td>
<td>1</td>
<td>Wrapped in blanket O,Hp in bassinet near mother's bed</td>
<td></td>
</tr>
<tr>
<td>Sakaki</td>
<td>2009</td>
<td>An investigation of the risk factors for infection with methicillin-resistant Staphylococcus aureus among patients in a neonatal intensive care unit</td>
<td>Japan</td>
<td>Prospective cohort</td>
<td>923</td>
<td>All ages</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Conventional care</td>
<td></td>
</tr>
<tr>
<td>Samsa</td>
<td>2012</td>
<td>The effect of kangaroo mother care on the duration of phototherapy of infants re-admitted for neonatal jaundice</td>
<td>Egypt</td>
<td>Intervention</td>
<td>50</td>
<td>35-40 weeks</td>
<td>SSC</td>
<td>≥3</td>
<td>Daily until photo-therapy stopped</td>
<td>Continuous phototherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scher</td>
<td>2009</td>
<td>Neurophysiologic assessment of brain maturation after an 8-week trial of skin-to-skin contact on preterm infants</td>
<td>USA</td>
<td>RCT</td>
<td>134</td>
<td>28-32 weeks, &gt;1000g, &amp; full term</td>
<td>SSC</td>
<td>N/A</td>
<td>1.5</td>
<td>4 per week x 8 weeks</td>
<td>Two comparison groups: preterm non-SSC &amp; full-term non-SSC</td>
<td></td>
</tr>
<tr>
<td>Schneider</td>
<td>2012</td>
<td>Cerebral motor function in very premature-at-birth adolescents: a brain stimulation exploration of kangaroo mother care effects</td>
<td>Colombia</td>
<td>RCT</td>
<td>48</td>
<td>All ages</td>
<td>SSC, DC, FU</td>
<td>Immediately after birth</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubators, N/A for full term infants</td>
<td></td>
</tr>
<tr>
<td>Singh</td>
<td>2012</td>
<td>Utilization of postnatal care for newborns and its association with neonatal mortality in India: an analytical appraisal</td>
<td>India</td>
<td>Case control</td>
<td>145662</td>
<td>All ages</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Mothers who did not receive advice during prenatal care on keeping baby warm</td>
<td></td>
</tr>
<tr>
<td>Sloan</td>
<td>2008</td>
<td>Community-based kangaroo mother care to prevent neonatal and infant mortality: a randomized, controlled cluster trial</td>
<td>Bangladesh</td>
<td>Cluster RCT</td>
<td>4165</td>
<td>All ages</td>
<td>SSC</td>
<td>N/A</td>
<td>2</td>
<td>N/A</td>
<td>N/A</td>
<td>M</td>
</tr>
<tr>
<td>Sloan</td>
<td>1994</td>
<td>Kangaroo mother method: randomized controlled trial of an alternative method of care for stabilized low-birth weight infants</td>
<td>Ecuador</td>
<td>RCT</td>
<td>300</td>
<td>&lt;2000g</td>
<td>SSC</td>
<td>Once tolerating food &amp; weight stabilized</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator or thermal crib with scheduled visits to be breastfed</td>
<td>M,I,Re</td>
</tr>
<tr>
<td>Suman</td>
<td>2008</td>
<td>Kangaroo mother care for low birth weight infants: a randomized controlled trial</td>
<td>India</td>
<td>RCT</td>
<td>206</td>
<td>&lt;2000g</td>
<td>SSC, EBF, FU</td>
<td>Once stable: definition N/A</td>
<td>As long as possible</td>
<td>N/A</td>
<td>Radiant warmer or M,L,W,LA,Ho, He,G,Bt,Lg,Hg lamp</td>
<td></td>
</tr>
<tr>
<td>Suzuki</td>
<td>2013</td>
<td>Effect of early skin-to-skin contact on breast-feeding</td>
<td>Japan</td>
<td>Cohort</td>
<td>470</td>
<td>N/A</td>
<td>SSC, EBF, FU</td>
<td>Immediately after birth</td>
<td>1-1.5</td>
<td>1</td>
<td>Women without early SSC</td>
<td></td>
</tr>
</tbody>
</table>
### Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendrio</td>
<td>2010</td>
<td>Evaluation of physiological parameters in preterm newborns with low weight before and after application of the kangaroo mother care</td>
<td>Brazil</td>
<td>Pre-post</td>
<td>24</td>
<td>&lt;24-36 weeks, &lt;2500g</td>
<td>N/A</td>
<td>N/A</td>
<td>0.33</td>
<td>3</td>
<td>Conventional care</td>
<td>H, R, O</td>
</tr>
<tr>
<td>Tessier</td>
<td>1998</td>
<td>Kangaroo mother care and the bonding hypothesis</td>
<td>Colombia</td>
<td>RCT</td>
<td>488</td>
<td>&lt;2001g</td>
<td>SSC, DC, FU</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator</td>
<td></td>
</tr>
<tr>
<td>Tessier</td>
<td>2009</td>
<td>Kangaroo Mother Care, home environment and father involvement in the first year of life: a randomized controlled study</td>
<td>Colombia</td>
<td>RCT</td>
<td>338</td>
<td>&lt;2001g</td>
<td>SSC, DC, FU</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator, DC at ~1700g, same outpatient care &amp; FU as KMC group, encouraged early breastfeeding</td>
<td></td>
</tr>
<tr>
<td>Tessier</td>
<td>2003</td>
<td>Kangaroo Mother Care: A method for protecting high-risk low-birth-weight and premature infants against developmental delay</td>
<td>Colombia</td>
<td>RCT</td>
<td>431</td>
<td>Premature: cutoff N/A, &lt;1800g</td>
<td>SSC, DC, FU</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator, DC at ~1700g, same outpatient care &amp; FU as KMC group, encouraged early breastfeeding</td>
<td></td>
</tr>
<tr>
<td>Thukral</td>
<td>2012</td>
<td>Early skin-to-skin contact and breast-feeding behavior in term neonates: A randomized controlled trial</td>
<td>India</td>
<td>RCT</td>
<td>41</td>
<td>Full Term</td>
<td>SSC, EBF, FU</td>
<td>Immediately after birth</td>
<td>2</td>
<td>1</td>
<td>Kept by the mother's side, encouraged exclusive breast feeding</td>
<td>B</td>
</tr>
<tr>
<td>Toma</td>
<td>2007</td>
<td>Maternal perception of low birth weight babies before and following the implementation of the Kangaroo Mother Care in a public hospital, in the city of São Paulo, Brazil</td>
<td>Brazil</td>
<td>Focus group/ interview</td>
<td>41</td>
<td>&lt;2000g</td>
<td>N/A</td>
<td>Mean 18 days</td>
<td>N/A</td>
<td>N/A</td>
<td>Before KMC implementation</td>
<td></td>
</tr>
<tr>
<td>Tuoni</td>
<td>2012</td>
<td>Kangaroo Mother Care: four years of experience in very low birth weight and preterm infants</td>
<td>Italy</td>
<td>Retrospective cohort</td>
<td>213</td>
<td>Premature, &lt;1500g SSC</td>
<td>Once eligible: definition N/A</td>
<td>≥1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A, fed by gavage or bottle</td>
<td>L, R, L</td>
</tr>
<tr>
<td>Vesel</td>
<td>2013</td>
<td>Promoting skin-to-skin care for low birth weight babies: findings from the Ghana Newborns cluster-randomized trial</td>
<td>Ghana</td>
<td>Cluster RCT</td>
<td>15615</td>
<td>All ages</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Women who did not receive community based messages about SSC</td>
<td></td>
</tr>
<tr>
<td>Wahlberg</td>
<td>1992</td>
<td>A retrospective, comparative study using the kangaroo method as a complement to the standard incubator care</td>
<td>Sweden</td>
<td>Retrospective cohort</td>
<td>66</td>
<td>Premature: cutoff N/A</td>
<td>SSC</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Holding a dressed baby with blanket or heating pad</td>
<td>B, L</td>
</tr>
</tbody>
</table>
### Supplementary Table 3.13 (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Title</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample size*</th>
<th>Newborn characteristics</th>
<th>KMC components</th>
<th>Onset of SSC</th>
<th>Hours per day of KMC provision**</th>
<th># of days of KMC provision**</th>
<th>Care in comparison group</th>
<th>Outcomes***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weller</td>
<td>2002</td>
<td>Longitudinal assessment of pituitary-thyroid axis and adrenal function in preterm infants raised by 'kangaroo mother care'</td>
<td>Colombia</td>
<td>RCT</td>
<td>87</td>
<td>&lt;37 weeks, &lt;2001g, SSC,DC,FU</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Incubator if available</td>
<td>M</td>
</tr>
<tr>
<td>Whitelaw</td>
<td>1988</td>
<td>Skin to skin contact for very low birth weight infants and their mothers</td>
<td>UK</td>
<td>RCT</td>
<td>71</td>
<td>&lt;1500g, SSC</td>
<td>Once eligible: definition N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Clothed, visited by mother &amp; taken out of incubator to cuddle</td>
<td>M</td>
</tr>
<tr>
<td>Worku</td>
<td>2005</td>
<td>Kangaroo mother care: a randomized controlled trial on effectiveness of early kangaroo mother care for the low birth weight infants in Addis Ababa, Ethiopia</td>
<td>Ethiopia</td>
<td>RCT</td>
<td>123</td>
<td>&lt;2000g, SSC,EBF</td>
<td>Immediately after birth</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Artificial warming system, oxygen therapy, breast feeding, tube, cup, or mixed feeding</td>
<td>M</td>
</tr>
</tbody>
</table>

KMC: kangaroo mother care; LBW: low birth weight; SSC: skin-to-skin contact; EBF: exclusively or near exclusively breast feeding; DC: early discharge from facility; FU: follow up after discharge; N/A: not available or undefined; NG tube: naso-gastric tube; PMA: post menstrual age; min: minutes, h: hours

*Sample size is related to the number of newborns participated in the study only.

**Number of hours per day and number of days of KMC provision were amount of KMC provision promoted by researchers not truly observed.

***Outcomes included in meta-analysis: M: mortality; B: exclusive breastfeeding; I: infection; N: necrotizing enterocolitis; H: hypothermia, He: hyperthermia; A: apnea, G: hypoglycemia; Re: readmission; H: heart rate; R: respiratory rate; O: oxygen saturation; T: temperature; Bt: breastfeeding initiation time; W: weight gain; Lg: length growth; Hg: head circumference growth;
P: pain score; Pp: premature infant pain profile; Pn: neonatal infant pain scale; Pfe: neonatal facial coding system; Hp: heart rate during/after painful procedure; L: length of hospital stay; C: cortisol

**** Program report