Contribution of Maternal Antiretroviral Therapy and Breastfeeding to 24-Month Survival in Human Immunodeficiency Virus-Exposed Uninfected Children: An Individual Pooled Analysis of African and Asian Studies

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Contribution of Maternal Antiretroviral Therapy and Breastfeeding to 24-Month Survival in Human Immunodeficiency Virus-Exposed Uninfected Children: An Individual Pooled Analysis of African and Asian Studies


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Background. Human immunodeficiency virus (HIV)-infected pregnant women increasingly receive antiretroviral therapy (ART) to prevent mother-to-child transmission (PMTCT). Studies suggest HIV-exposed uninfected (HEU) children face higher mortality than HIV-unexposed children, but most evidence relates to the pre-ART era, breastfeeding of limited duration, and considerable maternal mortality. Maternal ART and prolonged breastfeeding while on ART may improve survival, although this has not been reliably quantified.

Methods. Individual data on 19 219 HEU children from 21 PMTCT trials/cohorts undertaken from 1995 to 2015 in Africa and Asia were pooled to estimate the association between 24-month mortality and maternal/infant factors, using random-effects Cox proportional hazards models. Adjusted attributable fractions of risks computed using the predict function in the R package “frailtypack” were used to estimate the relative contribution of risk factors to overall mortality.

Results. Cumulative incidence of death was 5.5% (95% confidence interval, 5.1–5.9) by age 24 months. Low birth weight (LBW <2500 g, adjusted hazard ratio (aHR, 2.9), no breastfeeding (aHR, 2.5), and maternal death (aHR, 11.1) were significantly associated with increased mortality. Maternal ART (aHR, 0.5) was significantly associated with lower mortality. At the population level, LBW accounted for 16.2% of 24-month mortality, never breastfeeding for 10.8%, mother not receiving ART for 45.6%, and maternal death for 4.3%; combined, these factors explained 63.6% of deaths by age 24 months.

Conclusions. Survival of HEU children could be substantially improved if public health practices provided all HIV-infected mothers with ART and supported optimal infant feeding and care for LBW neonates.

Keywords. HIV-exposed uninfected; children, infants; mortality; Asia; Africa.

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Antiretroviral therapy (ART) to prevent mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) has dramatically reduced the number of HIV-infected infants [1, 2]. As more women living with HIV survive and become pregnant, the number of HIV-exposed uninfected (HEU) children continues to increase [3]. Several studies have shown that HEU children may experience worse health outcomes than...
HIV-unexposed uninfected (HUU) children in the same setting [4–10], although this has not been confirmed elsewhere [11–14]. Most evidence relates to the era before widespread use of ART for PMTCT and for treatment, when increased mortality in HEU children was associated with poor maternal health and lack of prolonged breastfeeding. Maternal ART for life and prolonged breastfeeding with the protection of ART could ameliorate such negative associations [15, 16], but this has not yet been reliably quantified.

By pooling available individual data on HEU children from clinical trials and observational studies, from both the pre- and post-ART era, we assessed mortality risk in HEU children in Africa and Asia and associated factors. We also estimated the relative importance of identified risk factors in mediating poor outcomes among HEU children.

METHODS

In a recent systematic review [17], we electronically searched 2 bibliographic databases, PubMed and Scopus, for articles published from 2004 to 2015 using the following keywords: HIV, Mortality, and Child or Infant, without restrictions on type or region of study, limited to English and French. Titles and abstracts were assessed; retained articles were subject to full-text reviews with identification of additional references. Additionally, we identified PMTCT trials with potential data on mortality in HEU children. A total of 29 studies were identified, and their principal investigators were contacted. One declined participation [18], 5 were unable to share data [5, 19–22] and 2 did not meet the inclusion criteria [23, 24], leaving 21 studies for the pooled 24-month mortality analysis: 16 from sub-Saharan Africa [4, 8, 25–38] and 5 from Asia [39–42]. Of these, 17 were randomized trials and 4 were observational studies conducted at different times (Supplementary Table S1), with varying sample sizes and follow-up durations (Table 1).

Maternal antiretroviral exposure was categorized as none; single/double peripartum antiretrovirals for PMTCT; 3-drug ART for PMTCT given antenatally and postnatally until cessation of breastfeeding when breastfeeding or until delivery when exclusively formula-fed; or 3-drug ART for life, prescribed beyond breastfeeding cessation per World Health Organization (WHO) HIV treatment and prevention recommendations [43, 44]. Mothers with missing information on antiretroviral use (n = 44) were assumed to have followed the relevant study protocol [28, 35] and thus categorized into the single/double antiretroviral PMTCT. The final HIV status of each child was defined by study-specific criteria. In our analyses, each child contributed from birth to 24 months of age, with right-censoring in case of death, end of study follow-up, and loss to follow-up. We restricted analyses to HEU children with information on breastfeeding and excluded 457 children with unknown infant feeding status. Mortality rates per 100 child-years of follow-up were estimated by maternal and child characteristics. We used the Kaplan–Meier method to estimate survival curves and the log-rank test to test for differences between groups.

Associations between 24-month mortality and the following factors were assessed: residence (rural vs urban/peri-urban), sex, low birth weight (LBW; <2500 g), breastfeeding (ever/never), maternal education (none/primary vs above), maternal age at delivery (5-year categories), maternal antiretroviral exposure (fixed), and maternal vital status (time-dependent). Children known to have initiated breastfeeding but with unknown weaning date (n = 1032) were considered to have been breastfed from birth to either age 6 months per WHO feeding guidance at the time [45], study exit date, or date of mother’s death, whichever occurred first. We used random-effects Cox proportional hazards models to estimate the association between 24-month mortality and potential risk factors, accounting for heterogeneity between studies. The final multivariable model included region (Africa vs Asia) as a fixed effect and adjusted for maternal antenatal CD4 cell count (categorical) because CD4 counts and ART eligibility varied widely between studies. Data from different sites in Kesho Bora [31] and HIVNET024 [30] were treated separately. Missing data were included as a separate category to maintain sample size. We used a stepwise-descending approach for selection of variables in multivariable models, which included variables that were statistically significant in univariate analyses (at a P value < .1, except for maternal antiretroviral exposure, which was maintained in the model independent of statistical significance). In the final model, statistical significance was reached when the P value was < .05. We also analyzed the association between weaning and survival among breastfed children only (n = 13418), with breastfeeding cessation defined in a time-varying manner.

We assessed the combined effects of breastfeeding and maternal 3-drug ART (for PMTCT or for life) on mortality, classifying observation time for each HEU child into 4 categories defined by child being breastfed (yes/no) and mother being on 3-drug ART (yes/no), with breastfeeding and ART variables being time dependent. When the date of ART end was unknown, ART was assumed to have continued until the weaning date or 6 months post-partum [45], whichever came first. The association between 24-month mortality and breastfeeding/maternal 3-drug ART was assessed in multivariable analyses using Cox proportional hazards models and allowing for heterogeneity between studies/trials and adjusting for region as fixed effect and maternal antenatal CD4 cell count and birth weight (<2500 g) as categorical variables.

Finally, to investigate the relative contribution of risk factors to overall 24-month mortality in HEU children, we estimated the adjusted attributable fractions (aAFs) of risks based on our final multivariable model [46, 47]. The AF for a given factor was the number of deaths attributable to the factor divided by the total number of deaths in our population if the prevalence of other factors remained at the same level. To do this, we first
<table>
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<tr>
<th>Trial/Study</th>
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<th>Ever Breastfed</th>
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<th>Antenatal Maternal CD4 (cells/mm³)</th>
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obtained the total number of deaths at a given time by summing the individual predicted probabilities of survival for each child based on the predict function in the R package “frailtypack” [48], then we subtracted this number from the total population to derive the number of deaths. To estimate the number of deaths attributable to the exposure of interest, we computed the number of deaths in the population as if it was not exposed to the factor while exposures to other risk factors were unchanged. Nonexposure was simulated by setting all children to the reference category. For example, for deaths associated with LBW, all children were classified into the category of having birth weight greater than 2500 g. The number of deaths attributable to a specific factor was the difference between the total number of deaths calculated previously and the number of deaths in the unexposed population.

We estimated the aAFs of the identified risk factors at 6, 12, and 24 months of age and computed 95% confidence intervals (CIs) using bootstrapping [49]. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). For the estimates of AF, we used the R package’s “frailtypack” [48] and “boot” [49] using R version 3.3.2 (R Development Core Team, 2004).

RESULTS

A total of 19219 HEU children were part of the analyses (Figure 1). Maternal/child baseline characteristics are shown in Table 2. Median child follow-up was 404 days (interquartile range [IQR], 336–712). More than 75% of children were born in sub-Saharan Africa, mostly Southern Africa; nearly 70% were born prior to 2005. Most children were ever breastfed (69.8%) for a median 181 days (IQR, 126–365). Maternal antiretroviral exposure varied across studies (Supplementary Table S2), reflecting the timing of the study and prevailing ART and PMTCT recommendations [44]. Overall, 23% of mothers received no antiretrovirals, 61% received mono/dual peripartum antiretrovirals for PMTCT, 12% received 3-drug ART for PMTCT, and only 4% were on ART for life. Median antenatal CD4 count was 405 cells/mm³ (IQR, 280–563); 58% of mothers had a CD4 count >350 cells/mm³ at the first antenatal visit. Median antenatal CD4 count in women who received ART for life was low at 214 cells/mm³ (IQR, 147–361). Median duration of ART was 178 (IQR, 152–196) and 443 (IQR, 371–730) days for 3-drug ART for PMTCT and ART for life, respectively. Information on maternal viral load was missing for 16%; among those with available information, median antenatal viral load was 4.0 log_{10} copies/mL (IQR, 3.3–4.6).

HEU Child Mortality

Cumulative incidence of death was 2.1% (394/18012; 95% CI, 1.9–2.3), 3.1% (575/17176; 95% CI, 2.9–3.4), 4.5% (797/12153; 95% CI, 4.2–4.8), and 5.5% (884/4245; 95% CI, 5.1–5.9) by age 3, 6, 12, and 24 months, respectively. Median age at death was 111 days (IQR, 37–244). Mortality varied from 0% in PHPT-5 1st [42] to 17.8% in Ditrame-ANRSb [26] (Table 1). Stratified by geographical region (Figure 2), 24-month survival probability was significantly higher in Asia than in Africa (P < .0001). Of the 300 children whose mothers died, 17% (n = 51) did not survive after mother’s death. Child mortality declined with increasing age at the time of mother’s death: 52% if mother died within 1 month of delivery, 36% if she died between 1 and 3 months, 20% between 3 and 6 months, 6% between 6 and 12 months, and 4% between 12 and 24 months. Mortality was highest among children with mothers not being on any antiretrovirals (6.1/100 child-years), with mortality in single/dual antiretrovirals for PMTCT, 3.1/100; 3-drug ART for PMTCT, 2.7/100; and ART for life, 3.4/100 child-years. Of note, one-third of the single/dual antiretrovirals for PMTCT and the 3-drug ART for PMTCT groups, respectively, were comprised of mothers of children in

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Figure 1. Flow chart of the children included in the pooled analyses. Abbreviations: HIV, human immunodeficiency virus; ID, identification.
PHPT trials where child deaths were rarely observed, which might explain lower mortality rates in these 2 groups.

Association With Maternal/Child Characteristics

Univariously, LBW children were at 3-fold risk of dying as were never-breastfed children (Table 3). Children whose mother had died were 16 times as likely to die compared to children whose mothers survived; maternal antiretroviral exposure was associated with reduced child mortality, but this did not reach statistical significance. Adjusting for region, maternal antenatal CD4 count, maternal antiretroviral exposure, and maternal vital status, LBW and never breastfeeding remained significantly associated with increased mortality (Table 3). The association between maternal ART for life and reduced child mortality became statistically significant (adjusted hazard ratio [aHR], 0.5; 95% CI, 0.3–0.9) after adjusting for maternal CD4 count (HR, 0.72 in univariate analysis, declining to 0.54 after adjusting for maternal CD4 count only). Associations between mortality and the other antiretroviral categories did not reach statistical significance (single/dual antiretrovirals: aHR, 0.78; 95% CI, 0.50–1.22 and 3-drug ART for PMTCT: aHR, 0.66; 95% CI, 0.39–1.13). Children whose mother had died remained at a substantially increased risk of death (aHR, 11.1).

Additional analyses, including ever-breastfed children only (n = 13 418) and treating breastfeeding cessation as a time-dependent variable, showed mortality risk to be significantly increased after breastfeeding cessation. Adjusting for region, birth weight, maternal CD4 count, and maternal antiretroviral exposure, breastfeeding cessation was associated with a 12.5-fold (95% CI, 10.3–15.3) risk of death. In this model, children whose mothers received 3-drug ART (both PMTCT and for life) were at significantly lower risk of death (aHR, 0.51; 95% CI, 0.30–0.85 for 3-drug ART for PMTCT and aHR, 0.45; 95% CI, 0.22–0.92 for ART for life) than children whose mothers did not receive antiretrovirals (ARVs).

Sensitivity Analyses

To investigate the sensitivity of our assumption on 44 women with no information on ARV exposure, we ran the analyses and
excluded these women; the aHRs were virtually unchanged. Further, 2 additional analyses were carried out to verify the effects of the inclusion of 1032 children with no information on weaning date and our assumption on their breastfeeding cessation at 6 months. After excluding these children, in the model with breastfeeding treated as a fixed effect, all aHRs were comparable to results shown in Table 3 (aHR, 3.0; 95% CI, 2.3–3.9 vs aHR, 2.5; 95% CI, 2.0–3.2). When breastfeeding was treated as a time-dependent variable, the risk related to breastfeeding cessation increased slightly but remained comparable to results presented in Table 3 (aHR, 16.9; 95% CI, 13.5–21.1 vs aHR, 13.1; 95% CI, 10.7–16.0).

Combined Effects of Maternal ART and Breastfeeding
Mortality by age 24 months differed significantly by breastfeeding and maternal 3-drug ART status at a given time (P < .0001; Table 4). Compared to not currently breastfed children with mothers not receiving 3-drug ART (category A in Table 4), mortality risk in not currently breastfed children with mothers receiving 3-drug ART (category B) was significantly reduced (HR, 0.6). In the absence of maternal 3-drug ART, currently breastfed children (category C) were significantly less likely to die (HR, 0.07). Currently breastfed children whose mothers were receiving 3-drug ART (category D) had the lowest mortality risk (HR, 0.04).

Adjusted Attributable Fractions of Risks
To investigate the impact of LBW, never breastfeeding, mother not on 3-drug ART for life, and maternal death, we estimated the aAFs of risks based on the parameter estimates obtained from our final model (Table 3). Mother not receiving 3-drug ART for life accounted for 45.6% (95% CI, 19.1–63.9) of child deaths by age 24 months. LBW accounted for an estimated 16.2% of child deaths by age 24 months, never breastfeeding for 10.8%, and maternal death for 4.3%. Combined, these 4 factors explained 63.6% (95% CI, 45.7–76.6) of deaths by age 24 months. The aAFs of risks at 6 and 12 months related to these 4 factors did not significantly differ from those at 24 months (Table 5).

DISCUSSION
Using data from 21 studies/trials undertaken between 1995 and 2015 in Africa and Asia, our findings suggest that where mothers are alive, on ART for life, and breastfeed their infants, 24-month mortality in HEU children is substantially reduced. As reported previously [50–52], LBW, prevalent in 12% of these HEU children, was a major risk factor for mortality. However, the negative consequences of LBW and non-breastfeeding may be even greater in settings outside the context of well-resourced research studies. Almost half of HEU deaths occurred in the first 3 months of life and two-thirds before age 6 months, highlighting the importance of intervening programmatically in this early period.

The survival of mothers living with HIV had a major effect on the survival of HEU children; this association has also been reported among HUU children [53]. In our analyses, the death of a mother shortly after delivery was most hazardous for the survival of her HEU child.

Our results suggest that the risk of mortality in HEU children is reduced when mothers are on ART either until breastfeeding cessation or for life. Mother’s initiation and continuation of ART likely improves her own health, which in turn increases the chances of child survival through better breastfeeding practices, reduced exposure to comorbidities, improved mother’s care capacity, and other unmeasured benefits at the household level.

![Figure 2. Kaplan-Meier estimates of 24-month survival from birth by geographical region.](Image)
The estimated AFs differed from the aHRs. This indicates that the impact at the population level, which reflects prevalence of risk factors, differs from that at the individual level. The CI around the AF estimate of mother not receiving 3-drug ART for life was particularly wide, and caution is required in interpreting this result. Our estimated AFs show that 36% of HEU...
child mortality at age 24 months could not be accounted for by
the 4 risk factors identified and highlight that HEU children are
also at risk of death from other common causes of child mor-
tality. The lack of contemporaneous mortality data from HUU
children meant that we were unable to categorically comment
whether HEU children are at any greater mortality risk if these
4 risk factors are fully addressed.

Although the analyses include a large number of HEU chil-
dren from diverse settings, interpretation of findings is hindered
by lack of detail on potentially important variables including
gestational age, neonatal care practices (early initiation and type
of breastfeeding), and household exposure to opportunistic
infections (such as tuberculosis). These factors may account for
much of the remaining 36% mortality.

Relatively few women were on ART for life, and studies
generally followed earlier WHO guidelines on HIV and infant
feeding, recommending breastfeeding for about 6 months only.
Although we confirm the associations between reduced mor-
tality risk and maternal ART for life and breastfeeding, our
data does not allow us to fully capture the complex associations
between different factors that influence a child's survival out-
come. The women on ART in our study are a highly select pop-
ulation, and we cannot comment on the extent to which such
reductions are facilitated by study-specific factors and whether
such associations would be equally observed in women on ART
in standard-of-care settings. Further, due to lack of data, we
were unable to allow for cotrimoxazole prophylaxis and child-
hood immunization, which are used to prevent infectious mor-
bidity in young children.

We were also unable to differentiate small-for-gestational age
from premature infants in those with LBW. About 11% of all
infants in Eastern and Southern Africa are born with LBW; in
Southeast Asia it is around 28% [54]. LBW has been associated
with HIV infection in pregnant women in sub-Saharan Africa
and with the protease inhibitor class of ART during pregnancy
[55–57]. While the primary drivers for LBW may vary by re-
gion and HIV exposure, the relationship between LBW and
mortality in both HEU and HUU children is clear and strong
and has immediate programmatic implications.

The combination of 3-drug ART was introduced in about the
middle of the timespan covered by the studies included; ART
eligibility criteria varied over time as did inclusion for trials.
Although we could not allow for these trends, these factors
could have introduced selection bias. Each study had its own
criteria for eligibility, including CD4 counts. Data included in
our analyses were heterogeneous in terms of feeding and dur-
ation of follow-up, which limits our ability to generalize the
results beyond these studies. Finally, exclusion of 457 children
whose breastfeeding status was unknown might have led to
underestimation of mortality rates as almost 29% (132/457) of

### Table 4. Multivariate Analysis on the Effects of Breastfeeding and Maternal 3-Drug Antiretroviral Therapy on Child Mortality (n = 24 186 child-years)

<table>
<thead>
<tr>
<th>Category</th>
<th>Child Currently Breastfed</th>
<th>Mother on 3-Drug Antiretroviral Therapy</th>
<th>Number of Child-Years</th>
<th>Number of Deaths</th>
<th>Adjusted Hazard Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No</td>
<td>No</td>
<td>14 119</td>
<td>552</td>
<td>Ref.</td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>B</td>
<td>No</td>
<td>Yes</td>
<td>1027</td>
<td>44</td>
<td>0.63</td>
<td>0.45–0.87</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Yes</td>
<td>No</td>
<td>7874</td>
<td>269</td>
<td>0.08</td>
<td>0.06–0.09</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Yes</td>
<td>Yes</td>
<td>1166</td>
<td>19</td>
<td>0.04</td>
<td>0.03–0.07</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Time-dependent variables.

<sup>b</sup>Variable trial/study was included as random effects. Also adjusted for region, maternal antenatal CD4 count, and birth weight.

### Table 5. Estimated Adjusted Attributable Fractions and 95% Confidence Intervals of Risk Factors for Mortality in Human Immunodeficiency Virus–Exposed Uninfected Children at Different Time Points

<table>
<thead>
<tr>
<th>Expected Number of Deaths Given the Distribution at 6, 12, and 24 Months</th>
<th>0–6 Months</th>
<th>0–12 Months</th>
<th>0–24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Deaths Attributable to the Risk Factor(s)</td>
<td>aAF (%)</td>
<td>95% CI</td>
<td>aAF (%)</td>
</tr>
<tr>
<td>Mother not receiving 3-drug antiretroviral therapy for life</td>
<td>342</td>
<td>47.9</td>
<td>20.0–65.8</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>140</td>
<td>18.5</td>
<td>15.1–21.9</td>
</tr>
<tr>
<td>Breastfeeding never initiated</td>
<td>88</td>
<td>11.7</td>
<td>5.2–19.6</td>
</tr>
<tr>
<td>Mother not being alive</td>
<td>44</td>
<td>5.9</td>
<td>3.1–13.5</td>
</tr>
<tr>
<td>All 4 factors above</td>
<td>486</td>
<td>66.2</td>
<td>48.6–78.4</td>
</tr>
</tbody>
</table>

Abbreviations: aAF; adjusted attributable fraction; CI, confidence interval.
these children died before age 12 months; 105 died before age 1 month, 17 between age 1 and 3 months, and 10 died thereafter. We show substantial regional differences in 24-month mortality, which deserves further investigation, as do the issues surrounding breastfeeding. Explaining the missing fraction of HIV-related and other external mortality risk factors requires prospectively collected data from both HEU and HUU populations. It remains unclear whether HEU infants and children are immunologically impaired at a clinically significant level or whether increased exposure to opportunistic infections because of living in HIV-affected households would explain the missing fraction. Perhaps the most germane question is whether increasing rollout of lifelong ART among women living with HIV and fully supporting optimal infant feeding practices will mitigate the patterns of risks identified in these historical cohorts. With more and more women living with HIV being initiated on ART, understanding the interactions between fetal HIV and ART exposure, the effects of prematurity or small-for-gestational age on mortality, and the effects of other long-term outcomes including early child development, infectious morbidity, and the risk of noncommunicable diseases will be increasingly important.

CONCLUSIONS

Our findings show that not-breastfeeding and LBW were associated with considerable mortality risk and suggest that maternal ART, initiated before or during pregnancy, may substantially reduce child mortality in the first 2 years of life. With increasing numbers of HIV-infected pregnant women being initiated on ART, this would provide hope for reducing overall child mortality in settings of high HIV prevalence. The importance of delivering effective integrated care so that women living with HIV are not only initiated on ART but are also linked with other essential elements of maternal and child healthcare is clear. Eliminating pediatric HIV and improving the survival, health, and development of HEU children should not be separate from improving the well-being of mothers and children not affected by HIV, and our metric of success needs to evolve to “HIV-free survival and development.” While integrated programs and coordinated research and monitoring are unquestionably possible, continued global investment in these responses is perhaps the greatest challenge.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. R. B., M. L. N., and N. R. initiated and set the objectives of the collaboration, defined the statistical analysis plans, and substantially contributed to the writing of the manuscript. S. A. undertook the literature review, managed the data pooling, participated in the definition of the statistical analysis plan, performed statistical analysis, and wrote the first draft of the paper. M. B. and P. J. substantially contributed to the statistical analysis. G. J., J. H., E. F., C. L., B. S. V., T. D., and S. L. C. critically reviewed the manuscript and substantially contributed to the interpretation of the results. All other coauthors reviewed the manuscript.

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