Association between interpregnancy interval and subsequent stillbirth in 58 low-income and middle-income countries: a retrospective analysis using Demographic and Health Surveys

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Summary

Background About 3 million stillbirths occur each year, 98% of which are in low-income and middle-income countries (LMICs). Interpregnancy interval is a key risk factor of interest, because it is modifiable. We aimed to investigate whether there is a causal relationship between the length of interpregnancy interval and risk of subsequent stillbirth.

Methods We used Demographic and Health Surveys (2002–18) from 58 LMICs to study reproductive histories of women and to identify livebirths and stillbirths in the preceding 5 years. Countries were selected on the basis of the availability of interpregnancy interval data and other covariates of interest (age, education, urban or rural residence, and wealth) in surveys done since 2002. Exclusion criteria were being nulliparous, having missing parity data, and not having had at least two births (livebirth or stillbirth) in the 5 years before the survey. We combined two analytic approaches: one that analyses intervals between all births and another that analyses intervals within mothers. We report stratified estimates for the first, second, and third intervals, controlling for all past birth outcomes and intervals in a 5-year period, and other socioeconomic covariates. We also explored effect heterogeneity across key cohort subgroups.

Findings Between July, 1997, and April, 2018, we identified 716 478 births from 338 223 women in 123 Demographic and Health Surveys from 58 LMICs, of which 9647 were stillbirths. Intervals of less than 6 months were associated with an increased risk of stillbirth in the between-mother models when considering the first interval (risk difference [RD] 0·0096, 95% CI 0·008–0·011). This association was slightly attenuated when considering only the second interval (RD 0·0054, 95% CI 0·0010 to 0·0099) and substantially attenuated when considering only the third interval (0·0007, –0·037 to 0·039). Within-mother modelling showed a null association with intervals of 24–59 months when considering the first and second (RD 0·007, 95% CI –0·001 to 0·016) and first and third (0·040, –0·422 to 0·501) intervals.

Interpretation Although interpregnancy intervals of less than 12 months were associated with increased risk of stillbirth, these effects were attenuated when considering second and third intervals, suggesting the association in the first interval might not be causal. Future studies should use generalisable cohorts with longitudinal data, and report estimates stratified by birth order.

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Introduction

About 3 million stillbirths—defined as fetal deaths after 28 weeks' gestation—occur each year,[1] 98% of which are in low-income and middle-income countries (LMICs).[2] Although previous research has primarily focused on socioeconomic and biological risk factors for stillbirth,[3,4] interpregnancy interval is a key variable of interest because it is easier to modify than other risk factors, such as genetic disorders and socioeconomic status.[5] There is little research on modifying interpregnancy intervals; possible strategies to change such intervals could include educational programmes, cash transfer programmes, and contraception provision programmes, which have been shown to reduce pregnancy rates in LMICs.[6,7]

Several studies have examined the association between interpregnancy interval and subsequent adverse perinatal and maternal outcomes, such as small-for-gestational-age birth,[8] preterm birth,[9] low birthweight,[10] child mortality,[11,12] maternal death,[13] and, to a lesser extent, stillbirth.[14] Although many of these studies have found strong associations between short interpregnancy intervals and adverse birth outcomes, there is ongoing debate regarding whether or not the relationship is causal.[15] In particular, failure to appropriately control for confounding, inappropriate statistical modelling, data scarcity, and inconsistent variable definitions are some of the difficulties of using observational data to study the effects of the interpregnancy interval.[16]

A systematic review[17] of 58 studies examined 10 proposed mechanisms for the effect of birth spacing on maternal and newborn outcomes. Although there was insufficient evidence to clearly support any single hypothesis, the study

Research in context

Evidence before this study
We searched PubMed on Aug 30, 2018 for English articles published using the search terms: "poor birth outcomes" OR "adverse birth outcomes" OR "stillbirth" AND "interpregnancy interval" OR "birth spacing". We included the reference lists of selected articles. Past research has found that short (<6 months) and long (>60 months) interpregnancy intervals are associated with increased risk of adverse birth outcomes, including small for gestational age, preterm birth, low birthweight, maternal death, and, to a lesser extent, stillbirth. Despite robust associations, the causality of the relationship between interpregnancy interval and adverse birth outcomes is unclear. Studies from low-income and middle-income countries (LMICs) have typically drawn from small samples, and few studies have exclusively studied stillbirth as the outcome.

Added value of this study
This study was the first to assess the association of interpregnancy interval on stillbirth using data from 123 large international health surveys representative of 58 LMICs. Generalisability to LMICs is important given that the majority of stillbirths occur in LMICs. We compared several distinct analytic

approaches to estimate the association, controlled for a wide range of covariates (including past pregnancy outcomes and past intervals over 5 years), and considered heterogeneity of the exposure effect by providing stratified estimates by wealth, outcome of previous pregnancy, and region of the world. Notably, controlling for past pregnancy outcomes and past interpregnancy intervals has not been done in previous studies owing to the scarcity of data on stillbirth. Our methods follow recommendations of several expert working groups for observational studies of interpregnancy interval. Although previous studies of interpregnancy interval have included a diverse range of perinatal outcomes, this study is the first to focus solely on stillbirth.

Implications of all the available evidence
Although our findings show that short interpregnancy intervals were associated with greater risk of stillbirth in some models, this effect—and others—were attenuated when considering the interval preceding a mother's third or fourth birth. These findings suggest a non-causal association between interpregnancy interval and stillbirth. Future research should assess whether any association with stillbirth is robust across all birth orders.

noted growing evidence in support of the folate depletion hypothesis.[18] Depleted maternal folate concentrations, especially during the second and third trimesters, can weaken connective tissue by preventing collagen cross-linking, thus increasing the risk of adverse pregnancy outcomes after a short interpregnancy interval. Other hypotheses with varying amounts of supporting evidence propose an association between short interpregnancy interval and adverse outcomes, such as the maternal depletion, transmission of infection, and sibling competition hypotheses; there is scarce evidence that physiological regression could explain the association between long interpregnancy intervals and adverse birth outcomes.[17]

We aimed to use nationally representative samples from 58 LMICs to apply and compare diverse analytic approaches to estimate the association of interpregnancy interval with stillbirth.

Methods

Study design and data collection
The Demographic and Health Surveys (DHS) are nationally representative household surveys that have been done in over 85 LMICs. The DHS's high response rates, high quality interviewer training, and standardised data collection procedures make it a uniquely valuable dataset for analysing health outcomes across LMICs.[19] We assembled DHS data on 2 987 618 women from 67 countries; countries were selected on the basis of the availability of interpregnancy interval data and other covariates of interest in surveys done since 2002. Exclusion criteria were being nulliparous, having missing parity data, and not having had at least two births (livebirth or

stillbirth) in the 5 years before the survey. After we applied our exclusion criteria, data on the 338 223 remaining women from 58 countries were reshaped such that each row of data represented one birth (appendix 2 p 3). The resulting 716 478 rows of data represented the total number of births from 338 223 mothers; every mother had at least two rows in the final dataset because of the inclusion criterion of having had at least two births in the 5-year period preceding the survey (ie, July, 1997, to April, 2018, for DHS surveys done between July, 2002, and April, 2018). After extracting and recording birth outcomes and birth event dates, we excluded all first order births, since first order births do not have a preceding interpregnancy interval. The remaining 377 691 births were analysed in between-mother models. We also fit within-mother models on a sample of 77 600 births after excluding 300 091 births to mothers who did not have at least three births (and therefore two interpregnancy intervals) in the 5 years before the survey.

This study was approved by the Ottawa Health Science Network Research Ethics Board and the Children's Hospital of Eastern Ontario Research Ethics Board.

The DHS reproductive calendar
The DHS reproductive (or contraceptive) calendar, distinct from the DHS birth history questionnaire, is a monthly history collected for women which details pregnancy, birth outcomes, and contraceptive use. Collected during interviews, the self-reported calendar data are cross-checked with the data collected during the birth history portion of the DHS interview. The

respondent is asked to recall a monthly reproductive and contraception history for several years (up to 80 months) preceding the month of the interview.[20] In the present study, we considered only reproductive histories of 5 years (up to 59 months) before the interview owing to varying availability of birth histories beyond 5 years, and to minimise self-reporting errors.

Previous studies have used the DHS reproductive calendar to study contraceptive histories[21] and to calculate population estimates of birth outcomes, such as stillbirth.[22] Although we found two studies that used DHS birth history data to study birth intervals (which end at a birth event),[23,24] to our knowledge, this study is the first to use the DHS reproductive calendar to study interpregnancy intervals (which end at the start of a pregnancy). Studies have shown that these DHS contraceptive histories are fairly accurate in aggregate, but less so when detailing complex individual histories.[25] We aimed to assess data quality by comparing associations between interpregnancy interval and stillbirth found in DHS data with correlations in previous studies.

Outcomes
The primary outcome was stillbirth. Definitions of stillbirth vary greatly across countries, ranging from fetal death after 12 weeks' gestation to after 28 weeks' gestation.[26] The WHO definition of stillbirth for international comparisons is fetal death occurring after 28 weeks' gestation or in fetuses weighing at least 1000 g.[1] Because the DHS reproductive calendar data records outcomes on a monthly basis, we define stillbirth here as a fetal death occurring after at least 7 months of pregnancy, which is consistent with the definition of stillbirth used by DHS[27] and is comparable to the WHO definition for international comparisons.

Interpregnancy interval
Although studies have historically used both interbirth interval and interpregnancy interval to study the effects of birth spacing on pregnancy outcomes, more recent studies[10,16] suggest that using interbirth interval should be avoided. This change in thinking is because an interbirth interval contains both an interpregnancy interval and a pregnancy, rendering it impossible to determine whether a poor pregnancy outcome after a short interbirth interval is a result of a short interpregnancy interval or a short pregnancy. We used interpregnancy interval as our exposure of interest, defined as the number of months between the end of a pregnancy (ie, a livebirth or stillbirth) to the start of the subsequent pregnancy. Important edge cases—instances where interpregnancy interval could be calculated in various ways—are shown in the appendix 2 (p 20).

Based on current recommendations,[16] we treated interpregnancy interval as categorical and used five groupings (months <6, 6–11, 12–17, 18–23, and 24–59), with 18–23 months as the reference group. As a sensitivity

analysis, we also considered interpregnancy interval as continuous and report these results in the appendix (pp 9, 11).

Covariates
We used several socioeconomic, demographic, and environmental covariates. Certain covariates, such as wealth quintile, education, and household location (urban *vs* rural), did not vary according to time, birth, or mother because they were only measured at the time of the survey and were not provided retrospectively for the duration of the reproductive calendar.

Covariates that varied across births from the same mother include past pregnancy outcomes (binary, either livebirth or stillbirth), past interpregnancy intervals (categorical, birth order 3 or greater), birth order of the child, and mother's age at the start of the interval. We created a directed acyclic graph depicting the theorised causal mechanism of preceding interpregnancy interval and stillbirth on the basis of a literature review (appendix 2 p 3).

Statistical analyses
We used two distinct methods to estimate the association between interpregnancy interval and stillbirth. The first method, the between-mother model, was a multivariable linear regression model with stillbirth as a binary outcome, interpregnancy interval (categorical) as the exposure, and mother-level characteristics as covariates. This approach assumed all births to be independent, thus disregarding the effect of any specific mother (or household or family) on all of her births. This method requires controlling for as many confounders as possible at the mother level. Our mother-level covariates were restricted to socioeconomic indicators; we did not have access to mothers' medical history or genetic information that could affect both interpregnancy interval and birth outcomes. For example, a mother who has difficulty getting pregnant might have involuntarily long intervals, and her fertility issues could also affect the health of her pregnancy. Fertility information is an example of an unobserved confounder that would likely bias the results of this analytical approach. To assess the extent to which unobserved confounders could have biased our estimates, we did positive control analyses.

We explored the robustness of our main findings by fitting three separate models where mothers' first, second, and third interpregnancy intervals were separately modelled as the exposure. Although we also fit an aggregate model which includes all intervals of all mothers, we present only the results of the disaggregated models in the main text to emphasise the importance of presenting disaggregated results, and because the results of the aggregate model were dominated by births after mothers' first intervals. In each of these models, we controlled for mothers' previous birth outcomes and previous interpregnancy intervals in those models where

the exposure is the second or third interval. These models essentially served as positive controls. Hence, if we see an effect of interpregnancy interval when only considering mothers' first intervals, we should expect to see the same effect when only considering their second or third intervals assuming that the effect is not modified by birth order. If we see attenuation of the effect across these models, it is an indication that the relationship is not causal, or that unmeasured time-varying covariates could be biasing our results. We report estimates of incremental probability of a subsequent stillbirth, with 95% CIs.

Finally, we did cross tabulations of interpregnancy interval and covariates to assess the extent to which some covariate subgroups did not experience certain inter-pregnancy interval lengths (positivity violations). We present an example scenario that shows how positivity violations can threaten the validity of statistical inference and why they are important to consider. Consider an imaginary scenario where all births in our sample from central Asia were preceded by an interpregnancy interval of less than 6 months. If we run our model using births from all regions of the world and find a protective effect for interpregnancy intervals 6–11 months, this protective effect for intervals 6–11 months must have been estimated using data from births from regions other

than central Asia, since no births in central Asia were preceded by an interval of 6–11 months—a positivity violation. Thus, it is impossible to know whether intervals 6–11 months are truly protective in births from central Asia. The positivity violation prevents us from making a generalisable inference across certain covariate sub-groups—in this case, births from central Asia.

The second method, the within-mother model, was a multivariable linear regression with stillbirth as the outcome, interpregnancy interval as the exposure, and a fixed effect term for the mother. By including a fixed-effect term for the mother, we can analyse how the different interpregnancy intervals of a single mother affected her birth outcomes. This method eliminates the necessity to control for time-invariant mother-level covariates—both observed and unobserved confounders—since they would be absorbed within the fixed-effect term. Although this outcome is a clear advantage of the within-mother model, there are several assumptions and limitations that affect the interpretability and generalisability of results.[16] First, only mothers who have had at least two interpregnancy intervals (at least three births) can be included in this model, reducing the sample size from 377 691 births to 77 600 and thus affecting the generalisability of our results.

Second, this method still requires controlling for time-varying confounders, many of which are not measured in our cohort. Examples of these include maternal smoking status, maternal bodyweight, social support, living conditions, maternal medical history, and pregnancy intention. The time-varying covariates that we controlled for were mother's age at the start of the interval, birth order, year of birth, month of birth, outcome of previous birth (binary), and previous interpregnancy interval (categorical). For second order births, previous inter-pregnancy interval was excluded from the model.

Third, this design assumes independence of births within mothers. That is, an interval of 12 months following a mother's first birth is assumed to have the same effect as an interval of 12 months following a mother's second, third, or fourth birth. We assessed the validity of this assumption by repeating our analysis within subsets of the data that only included two of the three possible birth intervals of a given mother. If the effect of interpregnancy interval is causal, we expected to see the same effect size when a mother's first and second are compared as to when her second and third intervals are compared, etc.

Finally, this design guarantees violations of the positivity assumption, which states that observed expo-sure levels (in our case interpregnancy interval length) should vary within covariate subgroups.[16] By control-ling for time-varying covariates like maternal age and parity, it becomes impossible to find two or more births belonging to the same mother that have the same covariate values. Although this is an example of deterministic positivity violation, we attempt to test the extent of random positivity violation by calculating
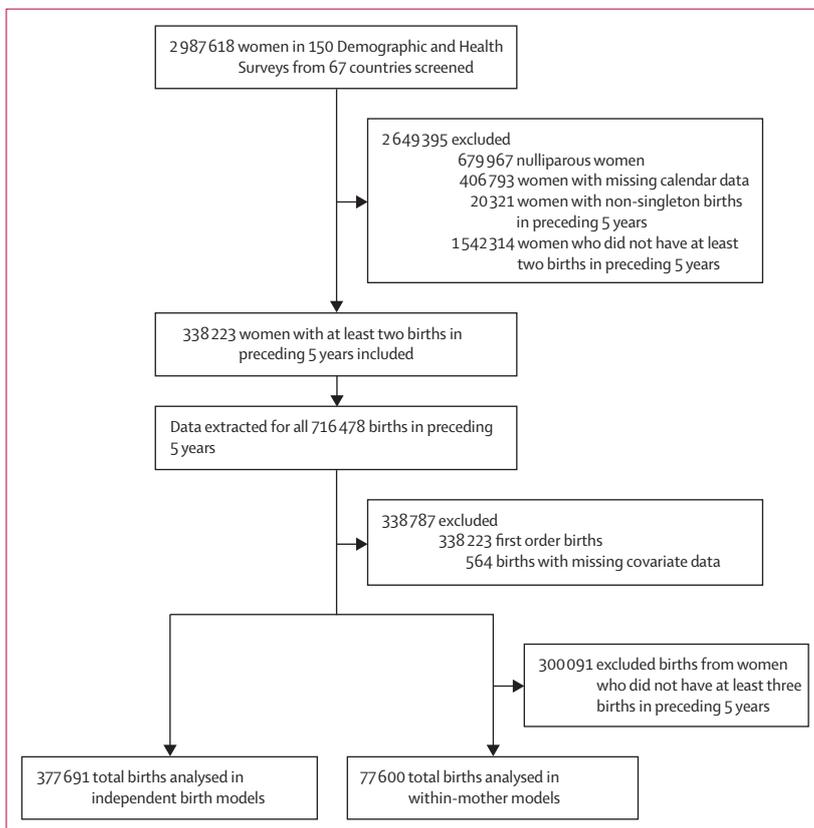

Figure 1: Study profile

cross-tabulations of interpregnancy interval with various covariates. We report estimates of incremental absolute probability of a subsequent stillbirth, with 95% CI.

Understanding the heterogeneity in the exposure effect for different demographic subgroups of our international cohort is important for two reasons. First, as discussed above, most stillbirths occur in LMICs,[2] thus highlighting the need to understand the effect of interpregnancy intervals in geographically and socioeconomically diverse populations. Second, wealth and previous pregnancy outcomes—which are known risk factors for adverse pregnancy outcomes—are associated with interpregnancy interval, thus bringing into question whether interpregnancy interval is merely a marker of at-risk women.[28] Subgroup analyses are important for understanding whether interpregnancy interval exerts a consistent effect on stillbirth across these key covariates. Therefore, we repeated our between-mother analyses stratified by region, wealth, and outcome of previous pregnancy and report the interaction term between interpregnancy interval and these mediating variables. For subgroup analyses by region, we focused on sub-Saharan Africa and south and southeast Asia, since these two regions have the highest rates of stillbirth worldwide.[4] For wealth, we used a dichotomous grouping of low wealth (bottom two quintiles) and high wealth (top three quintiles). Our analyses are consistent with recommendations that subgroup analyses should be theoretically motivated, have high power, and report interaction terms and subgroup effects.[29,30]

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Of 338 223 unique mothers with data collected between July 2002, and April, 2018, 9647 (2·9%) had at least one stillbirth in the 5 years preceding the survey (ie, July, 1997, to April, 2018; figure 1; table). 128 923 (38·1%) mothers had no formal education, 99 648 (29·5%) were in the lowest wealth quintile in their country, and 243 562 (72·0%) lived in a rural area (table). The top five countries represented in the cohort were India, Nigeria, Senegal, Jordan, and Malawi. The distribution of covariates did not differ substantially between women who had no history of stillbirth and those who did. Of the 377 691 births with a preceding interpregnancy interval, the mean preceding interval determined by the reproductive calendar was 17·9 months (IQR 11–24) and mean maternal age at the start of the interval was 27·3 years (22·9–30·8; figure 2).

We plotted the cumulative incidence of stillbirth by the interpregnancy interval and saw a U-shaped association,

	Entire cohort (n=338 223)	No previous stillbirth (n=328 576)	Previous stillbirth (n=9647)
Age at first delivery, years*			
<15	14 584 (4·3%)	14 176 (4·3%)	408 (4·2%)
15–19	162 991 (48·2%)	158 427 (48·2%)	4564 (47·3%)
20–34	159 677 (47·2%)	155 044 (47·2%)	4633 (48·0%)
35–39	892 (0·3%)	853 (0·3%)	39 (0·4%)
40–50	79 (<0·1%)	76 (<0·1%)	3 (<0·1%)
Education			
No formal	128 923 (38·1%)	125 171 (38·1%)	3752 (38·9%)
Some primary	101 148 (29·9%)	98 038 (29·8%)	3110 (32·2%)
Some secondary	64 230 (19·0%)	62 439 (19·0%)	1791 (18·6%)
Some higher	43 922 (13·0%)	42 928 (13·1%)	994 (10·3%)
Household location			
Urban	94 661 (28·0%)	92 175 (28·1%)	2486 (25·8%)
Rural	243 562 (72·0%)	236 401 (71·9%)	7161 (74·2%)
Wealth quintile			
1 (lowest)	99 648 (29·5%)	96 925 (29·5%)	2723 (28·2%)
2	80 061 (23·7%)	77 726 (23·7%)	2335 (24·2%)
3	66 635 (19·7%)	64 629 (19·7%)	2006 (20·8%)
4	53 039 (15·7%)	51 563 (15·7%)	1476 (15·3%)
5 (highest)	38 840 (11·5%)	37 733 (11·5%)	1107 (11·5%)
Country			
India	72 834 (21·5%)	70 541 (21·5%)	2293 (23·8%)
Nigeria	18 081 (5·4%)	17 727 (5·4%)	354 (3·7%)
Senegal	15 643 (4·6%)	15 021 (4·6%)	622 (6·5%)
Jordan	12 871 (3·8%)	12 671 (3·9%)	200 (2·1%)
Malawi	11 679 (3·5%)	11 306 (3·4%)	373 (3·9%)
Egypt	10 904 (3·2%)	10 682 (3·3%)	222 (2·3%)
Peru	10 605 (3·1%)	10 338 (3·2%)	267 (2·8%)
Benin	10 603 (3·1%)	10 395 (3·2%)	208 (2·2%)
Indonesia	10 279 (3·0%)	9988 (3·0%)	291 (3·0%)
Uganda	9491 (2·8%)	9185 (2·8%)	306 (3·2%)
Other	155 233 (45·9%)	150 722 (45·9%)	4511 (46·8%)

Data are n (%). *Includes stillbirths and livebirths.

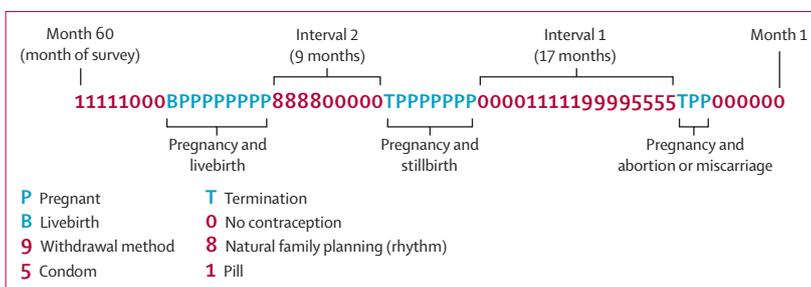*Table:* **Demographic data for mothers, Demographic and Health Surveys 2002–17**

Figure 2: **The structure of the Demographic and Health Surveys reproductive calendar string for one woman**

indicating that our data were detailed enough to capture this non-linear relationship (appendix 2 p 22).

The between-mother models provided varying estimates of the effect of interpregnancy interval (figure 3;

appendix 2 p 8). When only considering women's first interpregnancy interval (n=337721), the probability of a subsequent stillbirth increased (absolute increase) by 0·0096 (95% CI 0·008–0·011) for intervals of less than 6 months and by 0·0039 (0·003–0·005) for intervals of 6–11 months, although the magnitude was small. When only considering women's second interval (n=38482), the increase in the probability of subsequent stillbirth for intervals of less than 6 months was 0·0054 (95% CI 0·0010–0·0099) and for 6–11 months was 0·0015 (–0·0025 to 0·0054). When only considering women's third interval (n=1448), the increase in the probability of subsequent stillbirth was 0·0007 (–0·037 to 0·039) for intervals of less than 6 months. The estimates of risk difference (RD) from these two models considering the first and second intervals showed a J-curved association between interval length and additional risk of stillbirth, where the smallest risk was at intervals between 12–17 months. This relationship and all effect sizes were attenuated in the model that considered only the third interval, while controlling for all previous pregnancy outcomes and intervals (n=1448). Positivity violations for these models were minor (appendix 2 p 7), suggesting that our results are representative of births with diverse

confounding. Analyses treating interpregnancy interval as a continuous variable yielded comparable results (appendix 2 p 9).

77600 births met the selection criteria for the within-mother model. We report the country-wise count and proportion of births in both analytic samples (appendix 2 pp 4–5). The correlation in the country-wise proportion of births between the sample used for the between-mother models and for the within-mother models was high (r=0·985), suggesting that the additional selection criteria did not cause a notable loss of generalisability with regard to country of origin.

All models using the within-mother approach yielded smaller estimates of RD with wider 95% CIs than did the independent-birth models (figure 4; appendix 2 p 10). The RD for intervals of less than 6 months, which was the most positive in the between-mother models, was no longer significantly different from 0 when we considered the first and second intervals (0·003, 95% CI –0·003 to 0·009), second and third intervals (–0·009, –0·113 to 0·095), or first and third intervals (0·006, –0·136 to 0·148). Within-mother modelling showed a null association with intervals of 24–59 months when considering the first and second intervals (RD 0·007, 95% CI –0·001 to 0·016) and first and third intervals (0·040, –0·422 to 0·501). Notably, the p values for all estimates of RD were greater than 0·50 in the first and third interval model and in the second and third interval model. Positivity violations for these models were minor (appendix 2 p 7). Analyses treating interpregnancy interval as continuous yielded similar results (appendix 2 p 11).

Between-mother modelling was repeated for subgroups of our sample based on region, wealth, and outcome of previous birth (figure 5; appendix 2 p 13). Births in sub-Saharan Africa had an increased risk for stillbirth after intervals of less than 6 months (RD 0·015, 95% CI 0·012–0·017) and 6–11 months (0·006, 0·004–0·0007), and these risks were higher than the risk of stillbirth in other world regions ($p_{interaction}$<0·001 for <6 months and $p_{interaction}$<0·0001 for 6–11 months). These additional risks
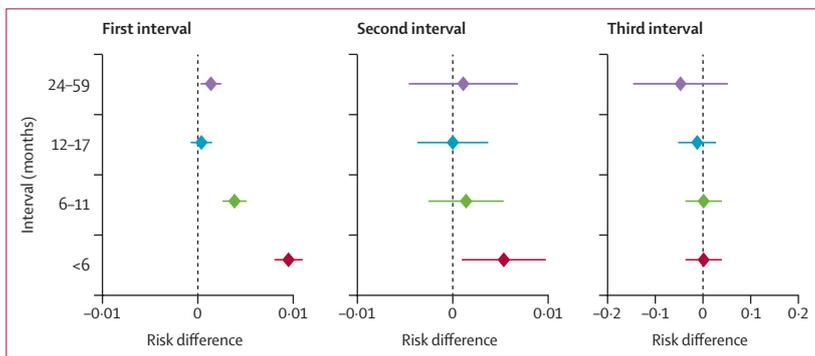

Figure 3: Estimates of risk difference by interval, between-mother models
Data are compared with the reference of 18–23 months. Error bars are 95% CIs. Models were adjusted for wealth, age, region (urban *vs* rural), education, outcomes of previous pregnancies, and previous interpregnancy interval duration.
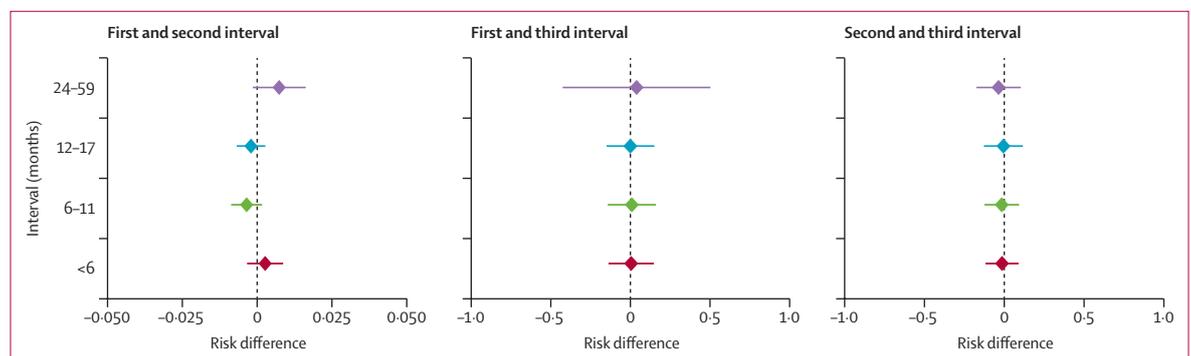

Figure 4: Estimates of risk difference by interval, within-mother models
Data are compared with the reference of 18–23 months. Error bars are 95% CIs. Models were adjusted for age, birth order, previous pregnancy outcomes, and previous interpregnancy interval duration.
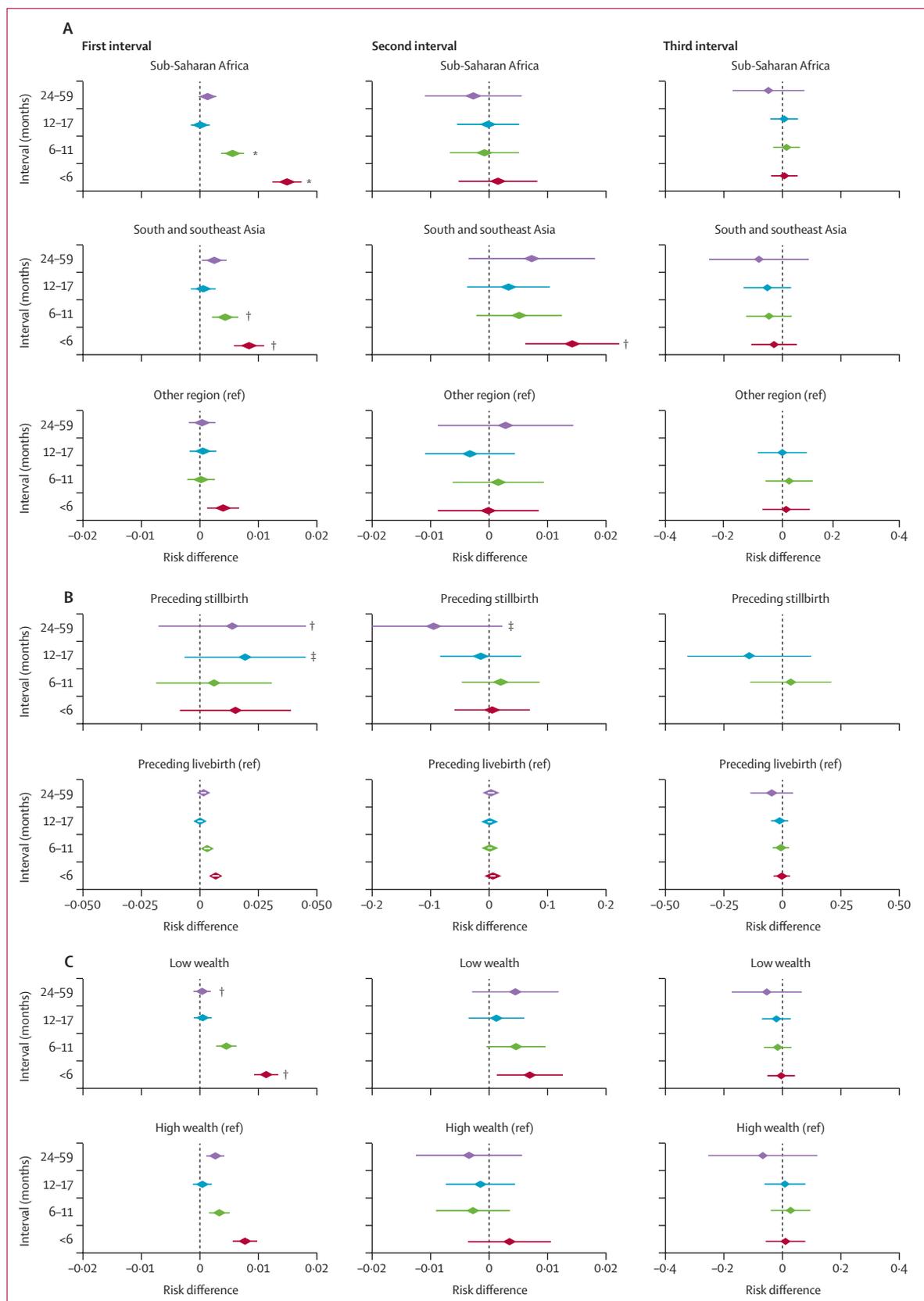
Figure 5: **Estimates of risk difference by interval, between-mother models**
Data are interval-specific risks compared with the reference of 18–23 months. Error bars are 95% CIs. Stratified by region (A), outcome of previous pregnancy (B), and wealth quintile (C). Models were adjusted for wealth, age, region (urban *vs* rural), education, outcomes of previous pregnancies, and previous interpregnancy interval duration. When considering the third interval, insufficient data were available for other region and preceding stillbirth in some interval groups. p values show the significance of the interaction term between interval and subgroup, compared with the reference categories. *p<0·001, †p<0·05, and ‡p<0·01.

were attenuated when considering the second and third intervals.

In births from south and southeast Asia, first intervals of less than 6 months (RD 0·008, 95% CI 0·006 to 0·01) and 6–11 months (0·004, 0·002 to 0·007) were associated with increased risk of stillbirth, and these risks were higher than those in other world regions ($p_{interaction}$<0·001 for <6 months and $p_{interaction}$<0·001 for 6–11 months). When considering only the second interval, intervals of less than 6 months were still associated with an increased risk of stillbirth (RD 0·014, 95% CI 0·006 to 0·022), and this risk was higher than that in other world regions ($p_{interaction}$<0·05).

When considering only the first interval, women with a preceding stillbirth had a higher risk of subsequent stillbirth than did women with a preceding livebirth, although these differences were not always substantial. In women with a preceding stillbirth, first intervals of 12–17 months (RD 0·019, 95% CI –0·006 to 0·045; $p_{interaction}$<0·01) and 24–59 months (0·014, –0·017 to 0·045, $p_{interaction}$<0·1) were associated with an increased risk of stillbirth, and these risks were higher than those in women with a preceding livebirth $p_{interaction}$<0·01 for 12–17 months and $p_{interaction}$<0·1 for 24–59 months). When considering only the second interval, the effect of intervals 12–17 months was completely attenuated (RD –0·015, 95% CI –0·084 to 0·054), and the effect of intervals 24–59 months changed from increasing risk to reducing risk of stillbirth (–0·096, –0·213 to 0·021, $p_{interaction}$<0·01; appendix 2 p 14).

When considering the first interval, in women of low wealth (bottom two quintiles), intervals of less than 6 months were associated with an increased risk of stillbirth (RD 0·011, 95% CI 0·009 to 0·013) and intervals of 24–59 months were associated with a decreased risk of stillbirth (0·000, –0·001 to 0·002); these risk were higher than that of women of high wealth (top three quintiles; $p_{interaction}$<0·05 for both intervals). When considering the second interval, among women of low wealth, intervals of less than 6 months were associated with an increased risk of stillbirth (0·007, 0·001 to 0·012). An interval of 6–11 months was associated with an increased risk of stillbirth (RD 0·004, 95% CI –0·001 to 0·010) in women of low wealth, and this risk was higher than the corresponding risk in women of high wealth ($p_{interaction}$<0·1), for whom intervals of 6–11 months were protective.

Discussion

This study of a large international cohort of women from 58 LMICs found little evidence of a causal association between interpregnancy interval and stillbirth. In between-mother models, short interpregnancy intervals (<12 months) between the first and second pregnancy were associated with a higher probability of stillbirth than intervals of 18–23 months; however, the magnitude of these associations was small and these effects were attenuated in intervals between subsequent pregnancies.

If the association between interpregnancy interval and stillbirth was causal and unaffected by birth order, we would have seen a consistent and unchanged effect, regardless of interval. Our findings suggest that the effects seen in the first interval models could be a result of unobserved confounding, or that the association between interpregnancy interval and stillbirth is modified by birth order. We found that in the within-mother models, which account for some potential unobserved confounding, the association for intervals of less than 6 months was notably attenuated, which is consistent with previous findings.[31,32]

Our heterogeneity analyses revealed several important trends across subgroups. First, analyses of women from sub-Saharan Africa and south and southeast Asia showed increased risk of stillbirth for intervals of less than 12 months in south and southeast Asia, suggesting the association between interpregnancy interval and stillbirth was not consistent by region. Second, the association of interpregnancy interval differed when comparing mothers who had a preceding stillbirth and a preceding livebirth. Among women with a preceding stillbirth, longer intervals (12–17 months and 24–59 months) were associated with a greater risk of stillbirth compared with women with a previous livebirth, although these findings are not highly reliable owing to a small sample size. Overall, women with a preceding stillbirth were at higher risk of subsequent stillbirth than were those with a preceding livebirth, regardless of interpregnancy interval, which is similar to previous findings.[14] Finally, intervals shorter than 12 months in women of low wealth were associated with greater risk of stillbirth compared with women of high wealth. Despite this heterogeneity in the association of interpregnancy interval, the additional risk of stillbirth did not exceed 2% in any of the subgroups we considered. Taken together and given the small magnitude of RD, it is likely that the observed differences in subgroups were non-casual and further research is needed on effect heterogeneity in these three subgroups (region, previous pregnancy outcome, and wealth).

Previously, the minimum recommended interpregnancy interval was 24 months after a livebirth and 6 months after a miscarriage, abortion, or stillbirth.[33] Shorter interpregnancy intervals, coupled with high parity and prolonged breastfeeding, could lead to nutritional depletion in mothers in resource-limited settings.[34] This reduction can influence maternal body mass, micronutrient reserves, and can lead to adverse pregnancy and neonatal outcomes.[18] Duration of breastfeeding and exclusive breastfeeding might be related to interpregnancy interval.[35] If a woman remains amenorrheic, this state could increase intervals between pregnancies and reduce resource competition among siblings, although it is not clear if this method is reliable as contraception beyond 6 months.[36]

Despite existing recommendations, we did not find a consistent reduced risk of stillbirth for intervals greater than 24 months or an elevated risk of stillbirth for intervals of less than 6 months after a previous stillbirth across all models.

Although our multi-faceted approach suggests the absence of a robust association between interpregnancy interval and stillbirth, our study had several limitations. First, there are several potential sources of confounding that were not captured in our data. One notable variable is pregnancy intention, which is collected by DHS for livebirths but not for stillbirths. Residual confounding by these variables might have led to overestimation of the effect of interpregnancy interval on subsequent risk of stillbirth.[16]

Second, the accuracy of the DHS reproductive calendar for the calculation of interpregnancy interval has not been formally assessed. Although it has been concluded that the contraceptive histories are acceptably detailed,[25] more investigation is needed on the quality of interpregnancy interval data and individual birth histories. Research shows that the reproductive calendar underestimates stillbirth, which is indicative of a larger trend of stillbirth being underestimated in survey data.[25] If the true number of stillbirths to the mothers in our sample was greater than those recorded in our data, our estimates of risk of stillbirth could be too low.

One possible solution to the data quality limitations of the DHS reproductive calendar—besides globally standardised clinical recording of stillbirth—is to use DHS pregnancy history data, which contain detailed reports of every pregnancy in the relevant countries.[37] Pregnancy histories are superior to reproductive calendars in capturing incidence of stillbirth[25] and neonatal mortality.[38] In addition, surveys that only contain reproductive calendars do not collect information on important risk factors for stillbirths, such as antenatal care, emergency obstetric care, and other health service utilisation.[37] The availability of these additional data might reduce bias from confounding if these potential risk factors were not considered. Despite clear advantages of using pregnancy histories, less than 20% of DHS surveys (2005–15) contain complete pregnancy history data, compared with over 85% of DHS surveys (2005–15) that contain reproductive calendar data.[37] Prioritisation of the collection of complete pregnancy histories in future DHS surveys could substantially improve the quality of data on stillbirth.

Third, athough our assessments of data quality suggested that our data replicated a previously reported[10,16] U-shaped association between interpregnancy interval and stillbirth, the self-reported nature of the DHS reproductive calendar, combined with that stillbirth was a rare outcome (2·9% of women), leads to inherent bias. Another shortcoming of the reproductive calendar is that it does not contain data about spontaneous miscarriages that occurred without the mother knowing; however, early miscarriage is notoriously difficult to capture in any perinatal study.

Finally, time-invariant covariates, including socioeconomic status, education, and household location, were measured at the time of the survey and could have potentially changed throughout the 5-year period we considered—although previous studies on DHS have suggested that the wealth index variable is relatively stable over time.[39] Finally, in models where we only consider the third interval, the samples sizes were smaller, which might have affected the precision of the estimates. For example, in the between-mother analysis, sample size decreased from 38482 to 1448 when going from the second to third interval. This smaller sample size, along with the rarity of stillbirth as an outcome, could have led to imprecise estimates.

Notwithstanding these limitations, we address several methodological issues in previous observational analyses of interpregnancy interval. Our use of a robust and generalisable cohort from LMICs, controlling for past pregnancy outcomes, application of two distinct analytic methods, and inclusion of abortions in the calculation of interval advance the exploration of interpregnancy intervals in LMICs.

Although associations between interpregnancy interval and stillbirth found in this study might not be causal, additional evidence is required to inform guidelines for global family planning. Future analyses might wish to investigate other pregnancy outcomes, population heterogeneity, and the effect of higher-order intervals in datasets with at least four births per woman.

References
1   Cousens S, Blencowe H, Stanton C, et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet* 2011; **377:** 1319–30.
2   Mullan Z, Horton R. Bringing stillbirths out of the shadows. *Lancet* 2011; **377:** 1291–92.
3   Flenady V, Koopmans L, Middleton P, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011; **377:** 1331–40.
4   Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; **387:** 587–603.
5   Kirby D. Emerging answers: research findings on programs to reduce teen pregnancy (summary). *Am J Health Educ* 2001; **32:** 348–55.

6   Hindin MJ, Kalamar AM, Thompson T-A, Upadhyay UD. Interventions to prevent unintended and repeat pregnancy among young people in low- and middle-income countries: a systematic review of the published and gray literature. *J Adolesc Health* 2016; **59** (suppl)**:** S8–15.

7   McQueston K, Silverman R, Glassman A. The efficacy of interventions to reduce adolescent childbearing in low- and middle-income countries: a systematic review. *Stud Fam Plann* 2013; **44:** 369–88.

8   Schummers L, Hutcheon JA, Hernandez-Diaz S, et al. Association of short interpregnancy interval with pregnancy outcomes according to maternal age. *JAMA Intern Med* 2018; **178:** 1661–70.

9   Klerman LV, Cliver SP, Goldenberg RL. The impact of short interpregnancy intervals on pregnancy outcomes in a low-income population. *Am J Public Health* 1998; **88:** 1182–85.

10 Zhu BP. Effect of interpregnancy interval on birth outcomes: findings from three recent US studies. *Int J Gynaecol Obstet* 2005; **89** (suppl 1)**:** S25–33.

11 Kozuki N, Walker N. Exploring the association between short/long preceding birth intervals and child mortality: using reference birth interval children of the same mother as comparison. *BMC Public Health* 2013; **13** (suppl 3)**:** S6.

12 Molitoris J, Barclay K, Kolk M. When and where birth spacing matters for child survival: an international comparison using the DHS. *Demography* 2019; **56:** 1349–70.

13 Conde-Agudelo A, Belizán JM. Maternal morbidity and mortality associated with interpregnancy interval: cross sectional study. *BMJ* 2000; **321:** 1255–59.

14 DaVanzo J, Hale L, Razzaque A, Rahman M. Effects of interpregnancy interval and outcome of the preceding pregnancy on pregnancy outcomes in Matlab, Bangladesh. *BJOG* 2007; **114:** 1079–87.

15 Klebanoff MA. Interpregnancy interval and pregnancy outcomes: causal or not? *Obstet Gynecol* 2017; **129:** 405–07.

16 Hutcheon JA, Moskosky S, Ananth CV, et al. Good practices for the design, analysis, and interpretation of observational studies on birth spacing and perinatal health outcomes. *Paediatr Perinat Epidemiol* 2019; **33:** O15–24.

17 Conde-Agudelo A, Rosas-Bermudez A, Castaño F, Norton MH. Effects of birth spacing on maternal, perinatal, infant, and child health: a systematic review of causal mechanisms. *Stud Fam Plann* 2012; **43:** 93–114.

18 King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. *J Nutr* 2003; **133** (suppl 2)**:** 1732–36S.

19 Corsi DJ, Neuman M, Finlay JE, Subramanian SV. Demographic and health surveys: a profile. *Int J Epidemiol* 2012; **41:** 1602–13.

20 USAID. DHS contraceptive calendar tutorial. The Demographic and Health Surveys Program. Sept 2, 2018. https://www.dhsprogram.com/data/calendar-tutorial/upload/DHS-Contraceptive-Calendar-Tutorial.pdf (accessed Nov 14, 2019).

21 Ali MM, Cleland JG, Shah IH; WHO. Causes and consequences of contraceptive discontinuation: evidence from 60 Demographic and Health Surveys. 2012. https://www.who.int/reproductivehealth/publications/family_planning/9789241504058/en/ (accessed Jan 25, 2019).

22 Stanton C, Lawn JE, Rahman H, Wilczynska-Ketende K, Hill K. Stillbirth rates: delivering estimates in 190 countries. *Lancet* 2006; **367:** 1487–94.

23 Baschieri A, Hinde A. The proximate determinants of fertility and birth intervals in Egypt: an application of calendar data. *Demogr Res* 2007; **16:** 59–96.

24 Rutstein SO. Effects of preceding birth intervals on neonatal, infant and under-five years mortality and nutritional status in developing countries: evidence from the demographic and health surveys. *Int J Gynecol Obstet* 2005; **89** (suppl 1)**:** S7–24.

25 Bradley S, Winfrey W, Croft T. Contraceptive use and perinatal mortality in the DHS: an assessment of the quality and consistency of calendars and histories. DHS methodological report no. 17. Calverton, MD: ICF International, 2015.

26 Joseph KS, Basso M, Davies C, et al. Rationale and recommendations for improving definitions, registration requirements and procedures related to fetal death and stillbirth. *BJOG* 2017; **124:** 1153–57.

27 USAID. Guide to DHS statistics. DHS-7. August, 2018. https://dhsprogram.com/pubs/pdf/DHSG1/Guide_to_DHS_Statistics_DHS-7.pdf (accessed April 26, 2019).

28 Gemmill A, Lindberg LD. Short interpregnancy intervals in the United States. *Obstet Gynecol* 2013; **122:** 64–71.

29 Fernandez Y Garcia E, Nguyen H, Duan N, Gabler NB, Kravitz RL. Assessing heterogeneity of treatment effects: are authors misinterpreting their results? *Health Serv Res* 2010; **45:** 283–301.

30 Lagakos SW. The challenge of subgroup analyses—reporting without distorting. *N Engl J Med* 2006; **354:** 1667–69.

31 Hanley GE, Hutcheon JA, Kinniburgh BA, Lee L. Interpregnancy interval and adverse pregnancy outcomes: an analysis of successive pregnancies. *Obstet Gynecol* 2017; **129:** 408–15.

32 Ball SJ, Pereira G, Jacoby P, de Klerk N, Stanley FJ. Re-evaluation of link between interpregnancy interval and adverse birth outcomes: retrospective cohort study matching two intervals per mother. *BMJ* 2014; **349:** g4333.

33 WHO. Report of a WHO technical consultation on birth spacing. June 13–15, 2005. Geneva: World Health Organization, 2007.

34 Winkvist A, Rasmussen KM, Habicht JP. A new definition of maternal depletion syndrome. *Am J Public Health* 1992; **82:** 691–94.

35 Howie PW. Natural regulation of fertility. *Br Med Bull* 1993; **49:** 182–99.

36 Kennedy KI, Rivera R, McNeilly AS. Consensus statement on the use of breastfeeding as a family planning method. *Contraception* 1989; **39:** 477–96.

37 Christou A, Dibley MJ, Raynes-Greenow C. Beyond counting stillbirths to understanding their determinants in low- and middle-income countries: a systematic assessment of stillbirth data availability in household surveys. *Trop Med Int Health* 2017; **22:** 294–311.

38 Espeut D, Becker S. The validity of birth and pregnancy histories in rural Bangladesh. *J Health Popul Nutr* 2015; **33:** 17.

39 Filmer D, Pritchett LH. Estimating wealth effects without expenditure data—or tears: an application to educational enrollments in states of India. *Demography* 2001; **38:** 115–32.