EDITORIAL

Moving Beyond a Maternal Perspective to Child Survival

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Notwithstanding the significant improvements in child survival in recent decades [1], India accounts for the largest share of the global burden of under-five mortality with an estimated 1.2-5.9 million child deaths [2]. Consequently, scientific efforts continue to identify factors and interventions that can help improve child survival [3]. An overwhelming majority of studies are informed, almost exclusively, by a 'maternal perspective', such that factors and interventions have largely focused on mothers [3,4]. For instance, increasing educational attainment among women has been identified and targeted as a means to achieve rapid progress towards fourth millennium development goal (MDG-4) [4]. Other maternal specific interventions that have received considerable attention in the literature include family planning and care targeted to mothers in the pre-conception period along with micronutrient and folic acid supplementation and early initiation of breastfeeding during pregnancy and in the postnatal period [5]. In this issue, Sinha, *et al.* [6] consider maternal age at childbirth (hereafter referred to as maternal age) as a potentially modifiable social determinant of child survival within a large prospectively followed cohort. They report that young motherhood is associated with an increase in child mortality, leading to a conclusion that delaying age at pregnancy would confer important survival benefits in this population.

Maternal age at childbirth can influence offspring outcomes, especially survival, in early days after birth through biological and social mechanisms. Specifically, younger age at childbirth could be a marker for biologic vulnerabilities, including short stature, inadequate weight gain during pregnancy and potential difficulties in delivery, leading to adverse outcomes [7]. In addition, women in low- and middle-income countries who have children at younger ages are also more likely to be poor and less educated, implying a social disadvantage leading to adverse outcomes in their offspring [8]. The plausibility of biologic or/and social pathways linking maternal age to child survival provides an important basis for interpreting such epidemiologic associations. However, in the absence of rigorous mediation studies substantiating the mechanisms linking the exposure (maternal age) and child survival, caution and scepticism is warranted before attributing causality to the observed associations. Sinha and colleagues' recommendation to prevent young motherhood as a method of improving child survival implicitly assumes a causal relationship between maternal age and offspring mortality, which given their observational study design, is impossible to ascertain. At the same time, conducting randomized controlled trials on social determinants such as maternal age at child birth are not feasible.

The key question, therefore, is whether the observed association between young motherhood (age <20 y) and an increased risk of post-perinatal mortality is causal? Without the knowledge of whether the observed association is causal, it remains unclear whether maternal age is simply a marker of unmeasured aspects that matter for child survival, or is maternal age truly an independent risk/exposure. In this editorial, we highlight one approach to improving causal inference in observational studies that consider exposures measured on mothers. Using a publicly available national data, we then apply this approach to the case of maternal age at childbirth in India. Based on other studies conducted using this approach, and insights from our own analysis, we conclude that an exclusive maternal focus for improving child survival and development in India may be problematic and misleading.

IMPROVING CAUSAL INFERENCE IN STUDIES WITH MATERNAL EXPOSURES

One approach, which we refer to as 'maternal-paternal comparison' can be considerably useful to improving causal inference in observational epidemiologic studies with an interest in maternal exposures [9,10]. The approach entails comparing the similarity in the effect size of a defined maternal and paternal exposure on the outcome. Under the framework where one anticipates a

unique and substantial maternal mechanism (*e.g.*, intrauterine mechanisms or behavioral mechanisms such as breastfeeding or providing care) – essentially aspects that fathers do not experience or undertake – one should expect that the size of effect for the maternal exposure should be significantly greater than that of the paternal effect size on the same exposure. If evidence supports a larger effect size for mothers as compared to fathers, this substantially increases our belief to attributing a causal interpretation to the maternal exposure. On the other hand, if the effect size associated with maternal and paternal exposures is highly similar, one ought to be sceptical of attributing causality to maternal exposures. Similarity in effect sizes on the same exposure for mothers and fathers are likely to imply residual confounding at the household level, including assortative mating (couples forming partnerships based on similar characteristics) [11]. While the similarity in effect size does not entirely rule out a potential causal effect of the maternal exposure, causal interpretations become highly implausible. For instance, if the effect of paternal and maternal age at childbirth is similar, one would have to believe, somewhat unrealistically, that whatever unique mechanisms that link maternal age to offspring survival are exactly similar in magnitude as the mechanisms that link paternal age to offspring survival.

The maternal-paternal comparison approach has been validated using the example of parental smoking in the Avon Longitudinal Study of Parents and their Children (ALSPAC) [10]. In this study, maternal smoking during pregnancy was inversely and strongly associated, as should be the case given the strong mechanistic linkages, with offspring birthweight while paternal smoking was not, suggesting a clear maternal specific pathway for the effect of smoking on offspring birthweight. Using this approach, studies using data on Indian populations have investigated whether maternal exposures such as Body Mass Index (BMI) [12,13], height [14], education [15], commonly considered to be causally associated with child mortality and undernutrition, are robust to this test of sensitivity. In each of the instances, the maternal effect sizes were found to be no different from the paternal effect size for the same exposure.

It is not clear to us if Sinha, *et al*. [6] can examine this in their data; however, if they can, a supplementary follow-up analysis would be valuable to strengthen the interpretation of their study. Meanwhile, using the publicly available 3rd Indian National Family Health Survey (NFHS) [16], we assessed the similarity in the effect size related to age at birth for both mothers and fathers on child mortality as well as child undernutrition.

MATERNAL AND PATERNAL AGE AT CHILDBIRTH AND CHILD MORTALITY/UNDERNUTRITION

In the NFHS, 50,248 births were available over a 10-year period covering 1995/6 to 2005/6 where maternal and paternal age and other covariates as used by Sinha, *et al*. were available. We used the same age categorizations as used by them for maternal and paternal age at childbirth (<20 y, 20-24 y, 25-29 y, 30-34 y, and ≥35 y), and examined their association with perinatal mortality (<7 d), post-perinatal mortality (7 d-59 mo), child mortality (birth-59 mo), and an additional category for neonatal mortality (<1 mo). We present models with maternal age and paternal age that are further adjusted for child age and sex, household wealth index, maternal and paternal education, and place of delivery, which is a covariate set close to Model 3 specified by Sinha, *et al*. (***Web Fig*. 1*a***).

For perinatal and neonatal mortality, the maternal and paternal effects on offspring mortality were similar. For example, maternal age < 20 y was associated with an odds ratio of 1.31 (95% CI 0.99,1.75) for offspring mortality while paternal age <20 y at child birth had an odds ratio of 1.19 (95% CI 0.77, 1.85), with the test of difference being not statistically significant (P=0.74). Interestingly, the effect for paternal age <20 y was stronger compared to maternal age <20 y for post-perinatal mortality (P=0.006) and child mortality, although the effect for child mortality was not statistically significantly stronger compared to mothers (P=0.08). Younger mothers and fathers at childbirth seemed to show the largest effects on child mortality, with the effects of older ages being less consistent and failed to reach statistical significance.

We further examined associations between maternal and paternal age at childbirth and anthropometric failure, defined according to the 2006 WHO growth standards as stunting, wasting, and underweight (***Web Fig*. 1*b***). First, the magnitude of maternal and paternal effects was very weak, even for the youngest age group, compared to mortality. Second, a comparison of the maternal and paternal effects indicated that the associations were largely similar, with some evidence of maternal effects being stronger than paternal at ages >25 y.

CONCLUSION

In summary, given the similarity of effects of maternal and paternal age at childbirth, it seems that maternal age at childbirth may be more likely a marker than a causal exposure in its own right. Consequently, caution must be exercised while attributing causality to the maternal age at childbirth. As expected, there exists a strong correlation between maternal and paternal age at birth in

India (r=0.72, $P<0.0001$) suggesting substantial residual confounding at the family/household level including support for a strong presence of assortative mating [11]. While it has been hypothesized that there may be mechanisms where paternal age could affect birth outcomes [17] (*e.g.*, quality of sperm, epigenetic or DNA changes), it would mainly be observed among older males (>50 years) [18]. In the absence of any biologic mechanisms for younger fathers, we should expect the maternal effects to be much larger at younger ages.

While improving the conditions of the mother has intrinsic significance (including perhaps delaying age of marriage or childbirth), their instrumental role in improving child outcomes may be exaggerated. Scrutiny and scepticism is warranted on existing observational studies with an interest in maternal exposures. Perhaps most critically, there is an urgent need to move away from an exclusive maternal lens to a more household perspective to addressing child survival and development [19-21], since more often than not, in countries such as India, the vulnerabilities at household level often are considerably greater in magnitude than vulnerabilities between individuals within a household.

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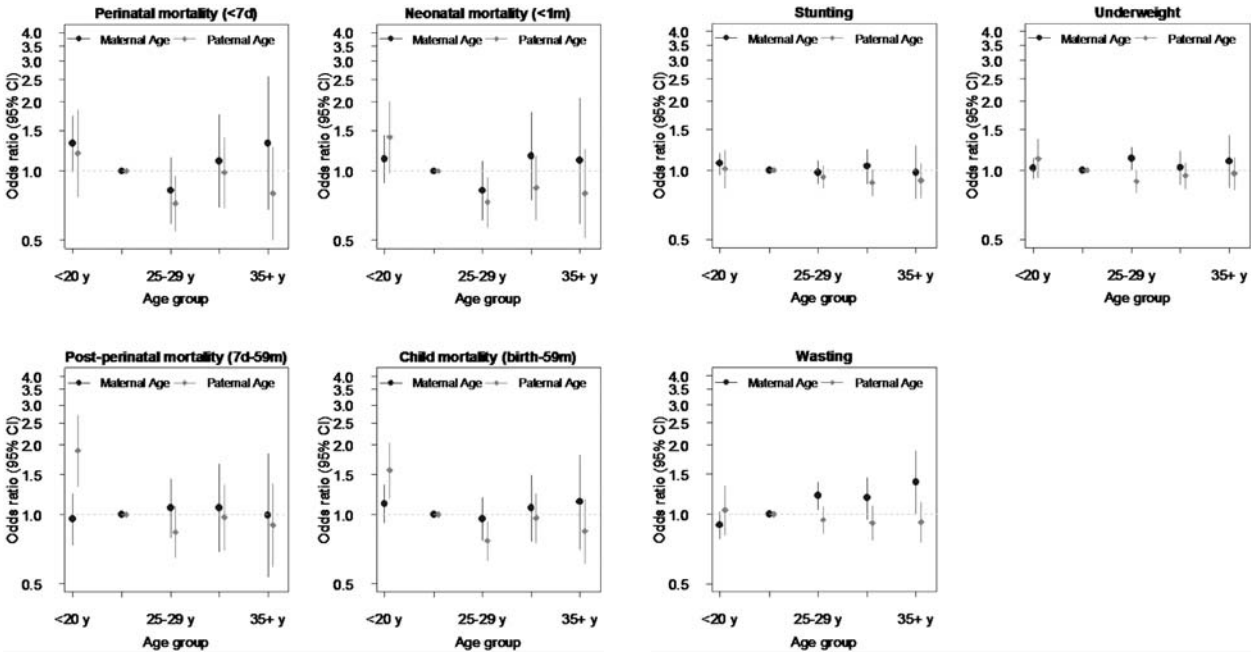
(a) Mortality (b) Anthropometric Failure



Web Fig. 1 *Associations between maternal and paternal age at child birth with (a) perinatal mortality (<7 d), neonatal mortality (<1 mo), post-perinatal mortality (7 d-59 mo) and child mortality (birth-59 mo); and (b) stunting (<-2 SD for length/height-for-age), underweight (<-2 SD for weight-for-age), and wasting (<-2 SD for weight-for-height); National Family Health Survey, India 2005-2006.*

Models adjusted for child age and sex, household wealth index, maternal and paternal education, place of delivery.
Author's calculations from 3rd National Family Health Survey (NFHS), 2005-2006 (India) [16]. NFHS is a multistage stratified national sample survey conducted in all the 29 states of India. We selected a sample of children born within 10 years of the date of interview to women aged 15 to 49 years using the birth history (or 'BR' file) and whose fathers participated (NFHS interviewed a random sample of husbands/partners of selected women in most states and in some states all men were invited). In total 109,999 births were identified although for 59,751 births, fathers were not interviewed by design leaving a sample of 50,248 births available with maternal and paternal ages available. In total, 3,499 child deaths were captured (1,486 in the perinatal period (<7d), 427 in the later perinatal period (7d to <1m) and 1,586 from 1-59m). We defined outcome categories for mortality as perinatal mortality (<7d), post-perinatal mortality (7d-59m), child mortality (birth-59m), and neonatal mortality (<1m). Secondary analyses also examined anthropometric data which was available on children alive, aged <59m at the time of survey, and who participated in the anthropometric measurements for height-for-age (n=19,452), weight-for-age (n=20,068), and weight-for-height (n=19,299). Raw anthropometric data was converted into age and sex-specific SD units (z-scores) using the WHO child growth standards. We defined dichotomous outcomes based on a defined cut-point of less than -2 SD for each anthropometric measure to capture stunting (low height-for-age), underweight (low weight-for-age) and wasting (low weight-for-height), collectively referred to as anthropometric failure. We specified logistic regression models to asses the mutually adjusted association between maternal and paternal age with child mortality and anthropometric failure. We used parental age categories as specified by Sinha and colleages (<20 y, 20-24 y [reference], 25-29 y, 30-34 y, and ≥35 y) and included covariates child age and sex, household wealth index, categories of maternal and paternal education based on years of schooling (no education, primary [1-5y], secondary [6-10y], higher secondary [11-12y], and college [>12y]), place of delivery (home vs. health facility). Household wealth was defined by an index of household asset ownership indicators. The household population was divided along this index into fifths from poorest to richest. All models took account of the multi-stage cluster survey sampling design using sampling weights and survey regression procedures as implemented in Stata (version 13.1/SE).