Published in final edited form as:

Eur J Epidemiol. 2018 June ; 33(6): 523–530. doi:10.1007/s10654-018-0373-0.

Two denominators for one numerator: The example of neonatal mortality

Quaker E Harmon¹, Olga Basso², Clarice R Weinberg³, and Allen J Wilcox¹

¹Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, North Carolina

²Department of Obstetrics and Gynecology, Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec

³Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, Durham, North Carolina

Abstract

Preterm delivery is one of the strongest predictors of neonatal mortality. A given exposure may increase neonatal mortality directly, or indirectly by increasing the risk of preterm birth. Efforts to assess these direct and indirect effects are complicated by the fact that neonatal mortality arises from two distinct denominators (i.e. two risk sets). One risk set comprises fetuses, susceptible to intrauterine pathologies (such as malformations or infection), which can result in neonatal death. The other risk set comprises live births, who (unlike fetuses) are susceptible to problems of immaturity and complications of delivery. In practice, fetal and neonatal sources of neonatal mortality cannot be separated – not only because of incomplete information, but because risks from both sources can act on the same newborn. We use simulations to assess the repercussions of this structural problem. We first construct a scenario in which fetal and neonatal factors contribute separately to neonatal mortality. We introduce an exposure that increases risk of preterm birth (and thus neonatal mortality) without affecting the two baseline sets of neonatal mortality risk. We then calculate the apparent gestational-age-specific mortality for exposed and unexposed newborns, using as the denominator either fetuses or live births at a given gestational age. If conditioning on gestational age successfully blocked the mediating effect of preterm delivery, then exposure would have no effect on gestational-age-specific risk. Instead, we find apparent exposure effects with either denominator. Except for prediction, neither denominator provides a meaningful way to define gestational-age-specific neonatal mortality.

Corresponding Author: Quaker Harmon, National Institute of Environmental Health Sciences, P.O Box 12233, MD A3-05, 111 T.W. Alexander Drive, Durham, NC 27709, Telephone: 984-287-3747, eFax: (301) 480-3290, quaker.harmon@nih.gov, ORCID 0000-0002-5866-848X.

The authors report no conflicts of interest.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Informed Consent: Publicly available data with no identifying details were used. For this type of study formal consent is not required.

Keywords

Neonatal mortality; fetal pathology; preterm delivery; gestational-age paradox

Neonatal mortality is a commonly studied perinatal outcome. Rates of neonatal mortality (usually death of a liveborn infant within the first 28 days) vary widely among countries and even within high-income countries [1]. One of the most powerful predictors of neonatal mortality is gestational age at birth. Mortality can vary 400-fold or more between babies born at 24 weeks and those born at 40 weeks [2], reflecting strong effects of immaturity on newborn survival. An exposure that increases preterm births will therefore increase neonatal mortality. The same exposure may also increase mortality directly, for example by damaging fetal development. These two distinct pathways of effect have different clinical implications: an exposure that works only through an increase in preterm delivery could in principle be nullified by an intervention that prevents those preterm births. Such an intervention, however, would not completely remove the effect of an exposure that also damages the fetus. Unfortunately, appropriate methods for estimating week-specific effects, as an attempt to distinguish direct from indirect (gestational-age-mediated) effects on neonatal mortality have proven contentious, with no consensus on the correct analytic strategy – or whether a correct strategy even exists [3–10].

One common approach attempts to block the indirect pathway that works through effects of gestational age on neonatal mortality by stratifying live births by gestational age – that is, to compare the mortality of exposed and unexposed live births at each gestational age. A second approach is to use fetuses (rather than live births) as the denominator of gestational-age-specific rates [5, 4] and model the composite outcome of birth followed by neonatal death. An argument supporting the “fetuses-at-risk” approach is that it removes an apparent “paradox” that can occur with live births as the denominator. In this paradox, lower rates of neonatal mortality can be found in some preterm weeks among the exposed “higher-risk” group [11–14].

In this paper, we point out a problem common to both approaches. The choice of an appropriate denominator (risk set) depends on the cause of the neonatal death. Fetuses are vulnerable to intrauterine pathologies that can cause death after delivery. Live births are additionally vulnerable to problems that can arise during labor and following birth. In principle, each type of neonatal death should be assessed in reference to its own risk set. In practice, fetal causes and birth-dependent causes of death (e.g. those related to immaturity) cannot be distinguished, and neonatal mortality is therefore analyzed as a single combined outcome. We explore how this structural property of neonatal risk influences etiologic studies. Specifically, we assess whether it is possible to estimate interpretable rates of neonatal mortality at a given gestational age.

Causes and rates of neonatal death

Intrauterine pathologies

Intrauterine determinants of neonatal mortality are chiefly fetal or placental pathologies. Examples include fetal malformations, infection of fetal membranes, and preeclampsia. These intrauterine pathologies may kill a fetus outright (stillbirth) or precipitate delivery of a distressed newborn at increased risk of dying neonatally. Nearly any intrauterine pathology that causes fetal death is also a plausible cause of neonatal death [15, 16]. Whether a death is a stillbirth or a neonatal death is a matter of the timing of death in relation to delivery [17]. To further complicate matters, not all intrauterine pathologies are identified or recorded. Cause of death remains unknown for more than a quarter of stillbirths [18–20] and, presumably, also for a substantial proportion of neonatal deaths. For example, a common recorded “cause” of neonatal death is low birth weight, which may reflect unspecified intrauterine causes.

Birth-dependent pathologies

The second major contributor to neonatal mortality comprises conditions contingent on labor or delivery. Immaturity of the newborn is the chief example. While immaturity poses no threat to the fetus, it contributes to neonatal death among infants born preterm. Other examples of birth-dependent causes of death are birth trauma, birth asphyxia, and hospital-acquired infection [21].

Estimating gestational-age specific rates

If the sources of neonatal mortality were all intrauterine, the appropriate risk set (denominator) for the estimation of gestational-age specific mortality rates (the composite outcome of birth that week followed by death within 28 days) would be all fetuses (all ongoing pregnancies). Analogously, if all neonatal mortality were due to birth-dependent causes, the appropriate denominator would be all live births at that gestational age. Both approaches use the same numerator (neonatal deaths among babies born at that week). The two denominators (fetuses and live births) however, can differ strikingly in number – particularly at preterm weeks, when fetuses vastly outnumber live births.

Not only do intrauterine pathologies and birth-dependent factors both contribute to neonatal mortality, they are also hard to distinguish. This is in part due to limited clinical information on causes of neonatal death. More importantly, the two types of mortality can – and often do – act on the same infant. For example, a preterm infant with a malformation will be subject to risk from both fetal and neonatal sources.

It is a common analytic procedure to either stratify on gestational age or adjust neonatal risk by gestational age (by means of logistic regression modeling or other methods). We use simulations to explore how the structural properties of neonatal mortality play out in the analysis of gestational-age-specific risk.

Separating intrauterine pathology and birth-dependent pathology: A simulation

We construct a simulation in which we specify (under reasonable -if somewhat arbitrary- assumptions) two sources of neonatal mortality. We start with US vital statistics data from 2006 [22, 23], with minor exclusions to clean the data [24, 25] (see Online Resource 1 for a description of this step). Our simulation parameters are derived from observed gestational-week-specific fetal deaths, live births, and neonatal deaths (within 28 days) among singleton, non-Hispanic white births at 22–44 weeks (Figures present only 28–42 weeks).

We simulate two hypothetical sets of neonatal deaths at each gestational week. One set dies solely of intrauterine causes, and the other dies of causes that can occur only during or after birth. For simplicity, infants in our simulation die from one or the other, but not both. We also assume there are no competing risks between stillbirths and neonatal death related to exposure.

Estimation of simulation parameters

The simulation uses empirical data as a starting point to construct 3 sets of gestational-age-specific rates: fetal mortality, neonatal mortality due to intrauterine causes, and neonatal mortality due to birth-dependent causes. The derivation of each is described below (and, in more detail, in Online Resource 1).

1. **Fetal mortality.** Fetal mortality at each gestational week was calculated using observed fetal deaths in a given week divided by the number of ongoing pregnancies (fetuses) at the beginning of that week.
2. **Neonatal mortality due to intrauterine causes.** Fetal deaths (stillbirths) provide an indicator of intrauterine pathology. We assume that the forces causing fetal death also damage a portion of fetuses who survive labor and then die after birth. Although the rate of fetal mortality increases with advancing gestation [26] the majority of stillbirths occur preterm [20]. We therefore assume most neonatal deaths due to intrauterine pathologies also take place among preterm births. Specifically, we assume that, for every four fetal deaths at a given week, an additional afflicted fetus is born and dies within 28 days. (Results are qualitatively unchanged with proportions as low as one neonatal death per 10 fetal deaths.) We assume that mortality for these affected infants is 100%. (This mortality rate can also be reduced without affecting the conclusions.) We calculate the rate of neonatal mortality due to intrauterine causes in a given week by assuming that the number of neonatal deaths from intrauterine causes is 25% of the number of fetal deaths observed in that week. This mortality rate is calculated using fetuses *in utero* at the start of that week as the denominator (Figure 1, dotted curve). The risk of neonatal mortality due to intrauterine pathology (in contrast with the absolute number of those neonatal deaths) gradually increases as pregnancy progresses.

3. **Neonatal mortality due to birth-dependent causes.** In order to estimate mortality due to birth-dependent causes, we first removed live births with any evidence of intrauterine pathology by excluding babies born of pregnancies with gestational diabetes, preeclampsia, eclampsia, or chronic hypertension, babies with severe birth defects, and small-for-gestational-age babies (<5th percentile birth weight for sex/gestational week [25]). (These exclusions are admittedly imperfect because of incomplete information on prenatal pathologies). We then calculate neonatal mortality as deaths among the remaining “healthy” live births (Figure 1, dashed curve). The resulting mortality curve for birth-dependent causes is biologically plausible: neonatal mortality is highest at the earliest weeks (in large part due to immaturity), falls steeply with advancing gestational age, and plateaus at a low level among term births (when immaturity is no longer an issue and only other delivery-dependent causes remain).

Simulation procedure

Given this framework, we now address a key issue: how do the separate contributions from two risk sets affect the estimation of exposure effects on neonatal mortality? As a motivating example, we consider an exposure known to increase the risk of preterm delivery. Can we estimate the unbiased direct effect of the exposure on neonatal mortality by adjusting (stratifying) by gestational age?

As an exposure we use pregestational diabetes (referred to hereafter simply as diabetes), which is an established cause of preterm delivery and neonatal mortality [27–29]. For the purpose of this example, we impose the further simplifying assumption that diabetes affects mortality exclusively by causing earlier delivery, with no direct effect on survival. This assumption is likely untrue, but useful for this thought experiment.

1. **Exposure cohorts.** We first establish exposed and unexposed cohorts based on singleton, non-Hispanic white births (live and stillbirths) at 22–44 weeks from the US in 2006. The exposed cohort is the subset of these births to mothers who had pregestational diabetes while the unexposed cohort is all other births.
2. **Calculation of the number at risk each week.** We used the observed numbers of live and still births at each week to generate the number of ongoing pregnancies in each week for each exposure cohort (Figure 2A dotted red and black lines). The rate of fetal mortality calculated above was applied to ongoing pregnancies in each week to calculate the number of fetal deaths in that week. Even though the same *rates* of fetal mortality were applied to both cohorts, the *number* of fetal deaths at each gestational age differed by exposure, due to the varying number of ongoing pregnancies at risk in a given gestational week. The number of fetal deaths was then subtracted from the weekly total births to generate the number of live births at each week (Figure 2A dashed black and red lines). The effect of diabetes on preterm delivery is clear (Figure 2A dashed lines). The proportion of live births less than 37 weeks is 8% in the unexposed (black dashed line) and 21% in the exposed (red dashed line) population.

3. **Calculation of the number of neonatal deaths each week.** We now apply the week-specific mortality rates for each of the two sources of mortality (from Figure 1) to the appropriate population at risk for each exposure group. For neonatal deaths due to intrauterine pathology, the population at risk is ongoing pregnancies, while for neonatal deaths due to birth-related causes, only live births are at risk. We then admix these two subsets of neonatal death (as happens in the real world) by pooling them to produce the combined number of neonatal deaths in each week. These provide the outcome (numerators) for further analysis. In this simulation, overall neonatal mortality is increased in the exposed (pregestationally diabetic) population by 75% (2.8 per 1000 live births, compared with 1.6 per 1000 in the unexposed).
4. **Calculation of week-specific rates.** Once the two types of neonatal death are combined, a gestational-age-specific analysis requires choosing a single denominator (fetuses or live births) to calculate mortality at a given gestational age. Both calculations use the same number of neonatal deaths per week in the numerator. It is only the denominator that varies: neonatal mortality is expressed either per 1000 fetuses or per 1000 live births in a given week.

Simulation Results

The gestational-week-specific rates of neonatal mortality for exposed and unexposed babies are presented in Figures 2B and 2C. It should be noted that although the X-axes appear similar in Figures 2B and 2C, there are important differences. In Figure 2B the X-axis refers to fetuses *in utero* at the start of a specific gestational week. In Figure 2C the X-axis refers to infants born in a specific gestational week. Consider first the unexposed (black lines). The black curves in Figures 2B and 2C are strikingly different, even though both are based on the same number of neonatal deaths. The black curve in Figure 2B would accurately describe the mortality caused by fetal pathology if all neonatal deaths were due exclusively to intrauterine causes. Correspondingly, the black curve in Figure 2C would accurately describe the mortality due to immaturity and other post-delivery hazards if all neonatal deaths were due exclusively to factors dependent on birth. However, given the underlying framework, in which neonatal deaths arise from both sources, neither curve accurately captures the mortality rates that generated these neonatal deaths. Only one useful interpretation is possible, and it is predictive rather than causal – neonatal mortality rates based on live births (Figure 2C) represent an unbiased and clinically relevant predictor of gestational-age-specific mortality, given a live birth. (Everything said here about the unexposed babies would apply equally to the exposed babies (red curves).)

Now consider the apparent effects of the exposure. Recall that, under the assumptions of the simulated data, diabetes does not directly affect the gestational-age-specific neonatal mortality of either fetuses or live births. However, when the two types of neonatal deaths are combined and a single denominator is (inevitably) chosen, diabetes appears to affect gestational-age-specific mortality (Figure 2B, 2C). Differences between the red and black mortality curves in each panel suggests direct effects of the exposure on neonatal mortality, where none in fact exists.

Even more surprising, the apparent direct effects are in opposite directions depending on the chosen denominator. Maternal diabetes is associated with higher neonatal mortality at preterm weeks when fetuses provide the denominator, and with lower mortality at preterm weeks when live births provide the denominator. Since the “truth” (in our simulation) is that week-specific mortality is identical for babies of diabetic and non-diabetic mothers, the differences between exposed and unexposed babies in Figures 2B and 2C reflect bias. (Online Resource 1 and 2 shows the arithmetic basis for these results, and allows the interested reader to explore the robustness of the results by modifying the assumptions.)

Discussion

Adjustment for gestational age is widely practiced in the analysis of neonatal mortality. Adjustment requires calculation of gestational-age-specific risk, which in turn requires selection of a numerator and denominator. While the numerator (neonatal deaths) is seemingly straightforward, the appropriate denominator is debatable. Commonly, live births at a given gestational age are used as the denominator. This approach has come under criticism because of the apparent “paradox” that can result, in which preterm babies in the exposed group have better survival despite having worse survival overall. A plausible explanation for this paradox is the presence of rare unmeasured factors that cause both preterm delivery and neonatal mortality [3, 24, 30, 10]. Such factors lead to collider stratification bias when stratifying by gestational age.

An alternative analytic approach is to select as the denominator ongoing fetuses at a given gestational age [4, 5]. This “fetuses-at-risk” approach removes the apparent paradox, but has been criticized for a different reason. When fetuses are the denominator, neonatal mortality rates are a composite of the probabilities of birth and death in a given week [7]. As a result, any exposure that increases the risk of preterm delivery will increase the apparent probability of death at a given preterm week. Thus, direct and indirect effects are indistinguishable and only questions regarding total effects can be answered [31].

We suggest that an additional underlying problem with both approaches is the compound nature of neonatal mortality. Neonatal deaths arise from two distinct sets of risk, one acting on fetuses and the other acting on newborns. Our simulations show that no single denominator (neither fetuses nor live births) generates causally interpretable estimates of gestational-age-specific mortality. Neither approach provides a sound basis for gestational-age adjustment and neither enables modeling that can block the indirect effects of preterm birth on neonatal mortality.

In one sense, this is a simple arithmetic problem. Two fractions with different denominators cannot be meaningfully combined by summing the numerators and choosing a single denominator (Online Resources 1 provides an example). Neither denominator represents the relevant population at risk, and therefore neither denominator is appropriate when combined week-specific neonatal mortality is the outcome of interest. Further, each denominator represents a different unit of measure which precludes summation. When the outcome of interest is perinatal mortality (stillbirth plus neonatal deaths) [4] another layer of complexity is introduced. There is now an additional outcome in the numerator. Although the rate of

stillbirth is correctly estimated using fetuses as the denominator [26], there is still no single suitable gestational-length-specific denominator for the outcome of neonatal death.

This methodologic problem extends beyond neonatal mortality. It seems plausible that at least some of the morbidity observed with preterm delivery (cerebral palsy, mental retardation, and other developmental problems [32]) is the result of intrauterine pathology. To the extent that this is true, adjustment for gestational age is problematic for these outcomes as well.

While we are not aware of previous discussion of two distinct risk sets giving rise to a single outcome, this problem may occur elsewhere in epidemiology. Consider mortality among early retirees as an example. Young retirees may have unexpectedly high mortality if their early retirement was prompted by failing health (work-related or other). Given this possibility, age-specific mortality rates among retirees for certain causes of death (e.g., work-site injury or exposure-induced health problems) should arguably be calculated with workers as the denominator, while mortality rates from causes unrelated to work history should be calculated among those already retired.

Strengths and weaknesses

A strength of our simulation is that it was derived from empirical data, with reasonable extensions. Furthermore, the distortions we observed in our analysis of exposure effects are qualitatively consistent with those reported in the literature. With a fetuses-at-risk approach, we found higher preterm mortality among the exposed (Figure 2B), as observed in the literature [33], which is to be expected whenever an exposure causes preterm delivery (all else being equal) [7]. When gestational-age-specific neonatal mortality was based on live births, we observed a paradoxically lower mortality among the preterm exposed infants (Figure 2C), again reflecting what is seen in the literature when live births are the denominator [11–14].

Furthermore, our simulations suggest that intrauterine pathology can act as the unknown factor causing collider bias when live births are the denominator. Figure 3 provides the directed acyclic graph corresponding to the conditions of our simulation (see Supplement 1 for an annotated DAG that more explicitly connects to the simulation). Intrauterine pathology is a strong cause of both gestational age at delivery and neonatal death; thus, stratifying on gestational age (preterm delivery) causes strong collider bias.

Our scenario (like most didactic simulations) does over-simplify reality. Nevertheless, our results were qualitatively consistent under a range of assumptions about the balance between intrauterine pathology and birth-dependent pathology. Still, it is unlikely that we have pursued all reasonable possibilities. Readers are invited to use our spreadsheets (provided in the electronic appendix) to explore the consequences of alternative assumptions about the size and balance of the two types of mortality.

Possible methodologic solutions

This simulation exposes the structural problem that occurs when two indistinguishable risk sets contribute cases – each risk set is legitimate for a subset of cases, but neither is

appropriate when applied to all. This problem may be overcome if neonatal deaths could be unequivocally assigned to either intrauterine or birth-dependent causes. This is unfeasible, both for lack of the necessary information and because the two sources of mortality can act (and interact) in one baby. Even precise clinical information on intrauterine pathology will not improve estimation of mortality if that baby is also preterm. Additionally, premature birth seldom (if ever) occurs in the absence of some underlying pathology, making the effect of immaturity itself frustratingly difficult to measure. Analytic methods have been proposed to address the mediating effects of gestational age [6, 34], but none can estimate direct effects [35].

Sometimes, direct effects are estimated even in the presence of unmeasured collider bias. Such analysis, however, requires strong assumptions and rely on sensitivity analysis [34, 36]. A typical mediation sensitivity analysis would rarely (if ever) consider an unmeasured confounder with the strength we have assumed for intrauterine pathology [24, 30, 3]. In our simulation, intrauterine pathology increased the risk of preterm birth almost eight-fold. Among live births in this population, 8% were preterm, while, among fetal deaths (the risk set for infant born with intrauterine pathology), 61% occurred in the preterm weeks (Online Resource 2 Fetal Deaths Sheet). The relative risk of mortality was even more extreme: in our simulated unexposed population, overall neonatal mortality was 1.6 per thousand while among births with intrauterine pathology it was 1000 per thousand. If true mortality were one-tenth that level, the relative risk would still exceed sixty-fold. As a further complication, we have not included effects of the exposure on intrauterine pathologies. Any exposure that increases preterm delivery may do so through an increase in intrauterine pathology. Such effects only add to the complexities of disentangling direct and indirect effects on neonatal mortality.

Conclusion

The assessment of causal pathways leading to neonatal mortality is more complex than epidemiologists have generally appreciated. Preterm delivery (and the consequent immaturity of the neonate) is a powerful cause of neonatal mortality, but not the only one. Intrauterine direct causes of neonatal mortality have long been recognized (for example, birth defects, genetic abnormalities), but we have not fully come to terms with the extent to which such prenatal sources of mortality may undermine our analytic tools. Investigators often stratify neonatal mortality by gestational age, choosing either fetuses or live births as the denominator. Whatever effects real-world exposures might have on neonatal mortality, our simulation suggests that neither denominator can provide an unbiased estimate of those effects – in either magnitude or direction. As unpalatable as this conclusion may be, we know of no valid way, at present, to estimate the effect of a prenatal exposure on neonatal mortality except by foregoing stratification on gestational age and, instead, restricting analysis to overall effects and using the total number of pregnancies as the denominator.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the comments on earlier drafts by Dr. Donna Baird, Dr. David Umbach, and anonymous reviewers. This research has been supported in part by the Intramural Program of the National Institute of Environmental Health Sciences, National Institutes of Health.

Funding: This research has been supported in part by the Intramural Research Program of the National Institute of Environmental Health Sciences, National Institutes of Health.

References

1. Wang H, Liddell CA, Coates MM, Mooney MD, Levitz CE, Schumacher AE, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014; 384(9947):957–79. [PubMed: 24797572]
2. [Accessed: Aug 28, 2015] Linked Birth / Infant Death Records 2007–2013, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program, on CDC WONDER On-line Database [database on the Internet]2015. Available from: <http://wonder.cdc.gov/lbd-current.html>
3. Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. *Am J Epidemiol*. 2011; 174(9):1062–8. [PubMed: 21946386]
4. Kramer MS, Zhang X, Platt RW. Analyzing risks of adverse pregnancy outcomes. *Am J Epidemiol*. 2014; 179(3):361–7. [PubMed: 24287468]
5. Platt RW, Joseph KS, Ananth CV, Grondines J, Abrahamowicz M, Kramer MS. A proportional hazards model with time-dependent covariates and time-varying effects for analysis of fetal and infant death. *Am J Epidemiol*. 2004; 160(3):199–206. [PubMed: 15257989]
6. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology*. 2012; 23(1):1–9. [PubMed: 22157298]
7. Basso O. Implications of Using a Fetuses-at-Risk Approach When Fetuses Are Not at Risk. *Paediatr Perinat Epidemiol*. 2016; 30(1):3–10. [PubMed: 26768054]
8. Joseph KS. Incidence-based measures of birth, growth restriction, and death can free perinatal epidemiology from erroneous concepts of risk. *J Clin Epidemiol*. 2004; 57(9):889–97. [PubMed: 15504632]
9. Wilcox AJ, Weinberg CR, Basso O, Harmon QE. Re: “Analyzing risks of adverse pregnancy outcomes”. *Am J Epidemiol*. 2015; 181(3):218.
10. Ananth CV, Schisterman EF. Confounding, causality, and confusion: the role of intermediate variables in interpreting observational studies in obstetrics. *Am J Obstet Gynecol*. 2017; 217(2): 167–75. [PubMed: 28427805]
11. Chen XK, Wen SW, Smith G, Yang Q, Walker M. Pregnancy-induced hypertension is associated with lower infant mortality in preterm singletons. *BJOG*. 2006; 113(5):544–51. [PubMed: 16579801]
12. Papiernik E, Alexander GR, Paneth N. Racial differences in pregnancy duration and its implications for perinatal care. *Med Hypotheses*. 1990; 33(3):181–6. [PubMed: 2292982]
13. Cheung YB, Yip P, Karlberg J. Mortality of twins and singletons by gestational age: a varying-coefficient approach. *Am J Epidemiol*. 2000; 152(12):1107–16. [PubMed: 11130615]
14. Ananth CV, Smulian JC, Vintzileos AM. The effect of placenta previa on neonatal mortality: a population-based study in the United States, 1989 through 1997. *Am J Obstet Gynecol*. 2003; 188(5):1299–304. [PubMed: 12748502]
15. Naeye RL. Causes of perinatal mortality in the US Collaborative Perinatal Project. *JAMA-J Am Med Assoc*. 1977; 238(3):228–9.
16. Silver RM, Varner MW, Reddy U, Goldenberg R, Pinar H, Conway D, et al. Work-up of stillbirth: a review of the evidence. *Am J Obstet Gynecol*. 2007; 196(5):433–44. [PubMed: 17466694]
17. Smith GCS. Quantifying the Risk of Different Types of Perinatal Death in Relation to Gestational Age: Researchers at Risk of Causing Confusion. *Paediatr Perinat Epidemiol*. 2016; 30(1):18–9. [PubMed: 26768056]

18. The Stillbirth Collaborative Network Writing Group. Causes of death among stillbirths. *JAMA-J Am Med Assoc.* 2011; 306(22):2459–68.
19. Wou K, Ouellet MP, Chen MF, Brown RN. Comparison of the aetiology of stillbirth over five decades in a single centre: a retrospective study. *BMJ Open.* 2014; 4(6):e004635.
20. Hoyert DL, Gregory EC. Cause of Fetal Death: Data From the Fetal Death Report, 2014. *Natl Vital Stat Rep.* 2016; 65(7):1–25.
21. Heron M, Hoyert DL, Murphy SL, Xu J, Kochanek KD, Tejada-Vera B. Deaths: final data for 2006. *Natl Vital Stat Rep.* 2009; 57(14):1–134.
22. [Accessed: July 10 2015] Birth Cohort Linked Birth-Infant Death Data Files [database on the Internet]. 2006. Available from: http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm
23. [Accessed: July 16 2015] Fetal Death Data File [database on the Internet]. 2006. Available from: http://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm
24. Basso O, Wilcox A. Mortality risk among preterm babies: immaturity versus underlying pathology. *Epidemiology.* 2010; 21(4):521–7. [PubMed: 20407380]
25. Talge NM, Mudd LM, Sikorskii A, Basso O. United States birth weight reference corrected for implausible gestational age estimates. *Pediatrics.* 2014; 133(5):844–53. [PubMed: 24777216]
26. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet.* 1987; 1(8543):1192–4. [PubMed: 2883499]
27. Sibai BM, Caritis SN, Hauth JC, MacPherson C, VanDorsten JP, Klebanoff M, et al. Preterm delivery in women with pregestational diabetes mellitus or chronic hypertension relative to women with uncomplicated pregnancies. The National Institute of Child Health and Human Development Maternal- Fetal Medicine Units Network. *Am J Obstet Gynecol.* 2000; 183(6):1520–4. [PubMed: 11120521]
28. Feig DS, Hwee J, Shah BR, Booth GL, Bierman AS, Lipscombe LL. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996–2010. *Diabetes Care.* 2014; 37(6):1590–6. [PubMed: 24705609]
29. Knorr S, Stochholm K, Vlachova Z, Bytoft B, Clausen TD, Jensen RB, et al. Multisystem Morbidity and Mortality in Offspring of Women With Type 1 Diabetes (the EPICOM Study): A Register-Based Prospective Cohort Study. *Diabetes Care.* 2015; 38(5):821–6. [PubMed: 25710920]
30. Basso O, Wilcox AJ. Might rare factors account for most of the mortality of preterm babies? *Epidemiology.* 2011; 22(3):320–7. [PubMed: 21372718]
31. Platt, RW. The Fetuses-at-Risk Approach: An Evolving Paradigm. In: Louis, GB., Platt, RW., editors. *Reproductive and perinatal epidemiology.* Oxford: Oxford University Press; 2011.
32. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med.* 2008; 359(3):262–73. [PubMed: 18635431]
33. Lisonkova S, Paré E, Joseph K. Does advanced maternal age confer a survival advantage to infants born at early gestation? *BMC Pregnancy Childbirth.* 2013; 13(1):87. [PubMed: 23566294]
34. Ananth CV, VanderWeele TJ. Placental abruption and perinatal mortality with preterm delivery as a mediator: disentangling direct and indirect effects. *Am J Epidemiol.* 2011; 174(1):99–108. [PubMed: 21430195]
35. Auger N, Naimi AI, Fraser WD, Healy-Profitos J, Luo ZC, Nuyt AM, et al. Three alternative methods to resolve paradoxical associations of exposures before term. *Eur J Epidemiol.* 2016; 31(10):1011–9. [PubMed: 27325162]
36. VanderWeele TJ. Commentary: Resolutions of the birthweight paradox: competing explanations and analytical insights. *Int J Epidemiol.* 2014; 43(5):1368–73. [PubMed: 25301862]

FIGURE 1.

Simulated gestational-week-specific rates for two subsets of neonatal mortality. Mortality due to intrauterine pathology (dotted line) expressed per 1000 fetuses. Mortality due to birth-dependent pathology (dashed line) expressed per 1000 live births. Based on live births, fetal deaths and neonatal deaths to singleton non-Hispanic white mothers in the United States 2006.

FIGURE 2.

Simulated week-specific rates of neonatal mortality Distribution of live births (dashed lines) and fetuses (dotted lines) for an exposed (red) and unexposed (black) cohort (Panel A). Subset mortality rates (Figure 1) are applied to each gestational age distribution in Panel A. The pooled neonatal mortality (solid line) is expressed per 1000 fetuses at risk (Panel B) or per 1000 live births (Panel C). Based on live births, fetal deaths and neonatal deaths observed in the United States 2006.

FIGURE 3.

Directed acyclic graph for effects of an exposure (E) on neonatal mortality through effects on gestational age at birth (“preterm delivery”) in the presence of an intrauterine pathology (previously “unmeasured confounder” U) that causes both preterm delivery and neonatal mortality. In the simulation, the exposure (pregestational diabetes) affects only preterm delivery. The gestational-age-specific effects of preterm delivery do not vary by exposure status. Intrauterine pathology is assumed to have gestational-age-specific effects on neonatal mortality proportional to its effects on fetal death, and these are also independent of exposure. In the simulation, intrauterine pathology is strongly associated with preterm delivery (61%) and neonatal mortality (100%), but not with E.