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Survival of infants with spina bifida and the role of maternal prepregnancy body mass index

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Abstract

Objective: To investigate first-year survival of infants born with spina bifida, and examine the association of maternal prepregnancy body mass index (BMI) with infant mortality.

Methods: This is a retrospective cohort study of 1,533 liveborn infants with nonsyndromic spina bifida with estimated dates of delivery from 1998 to 2011 whose mothers were eligible for the National Birth Defects Prevention Study (NBDPS). NBDPS data were linked to death records to conduct survival analyses. Kaplan–Meier survival functions estimated mortality risk over the first year of life. Cox proportional hazards models estimated hazard ratios (HRs) for maternal prepregnancy BMI categorized as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obese (≥30).

Results: Infant mortality risk among infants with spina bifida was (4.4% [3.52, 5.60%]). Infants with multiple co-occurring defects, very preterm delivery, multiple gestation, high-level spina bifida lesions, or non-Hispanic Black mothers had an elevated risk of infant mortality. Maternal prepregnancy underweight and obesity were associated with higher infant mortality (15.7% [7.20,

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SUPPORTING INFORMATION

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32.30%] and 5.82% [3.60, 9.35%], respectively). Adjusted HR estimates showed underweight and obese mothers had greater hazard of infant mortality compared to normal weight mothers (HR: 4.5 [1.08, 16.72] and 2.6 [1.36, 8.02], respectively).

Conclusion: The overall risk of infant mortality for infants born with spina bifida was lower than most previously reported estimates. Infants born with spina bifida to mothers who were underweight or obese prepregnancy were at higher risk of infant mortality. This study provides additional evidence of the importance of healthy maternal weight prior to pregnancy.

Keywords

birth defects; body mass index; mortality; obesity; spina bifida

1 | INTRODUCTION

Birth defects are a leading cause of infant mortality in the United States accounting for one in every five infant deaths (Xu, Murphy, Kochanek, & Bastian, 2016). Spina bifida is a congenital anomaly characterized by the protrusion of the spinal cord through a bony defect in the vertebral column. It is the most common neural tube defect (NTD), occurring in approximately 1 out of every 3,000 live births (Parker et al., 2010). Over time, mortality among infants with spina bifida has greatly declined; however, recent estimates of approximately 8% (Wang et al., 2015) are still 13 times higher than the national average for all U.S. births (Mathews, MacDorman, & Thoma, 2015).

Identified risk factors for infant mortality among infants born with spina bifida include young maternal age, non-Hispanic Black race, low birth weight for gestational age, existence of multiple co-occurring birth defects (non-isolated defects), nativity, and parity (Bol, Collins, Kirby, & Network, 2006; Davidoff, Petrini, Damus, Russell, & Mattison, 2002; Wang, Hu, Druschel, & Kirby, 2011; Williams, Rasmussen, Flores, Kirby, & Edmonds, 2005; Wong & Paulozzi, 2001). Furthermore, lesions located higher on the spine are associated with higher mortality compared to lower lesions (Wong & Paulozzi, 2001).

Recent estimates indicate that among U.S. women ages 20–39, 24% are overweight and 32% are obese (Ogden, Carroll, Kit, & Flegal, 2014). Prepregnancy obesity, defined as a body mass index (BMI) greater than or equal to 30 at the start of pregnancy, is common, occurring in more than one in five pregnant women in the United States (21% in 2009) with increases in prevalence during the last decade (Dawson et al., 2015; Fisher, Kim, Sharma, Rochat, & Morrow, 2013). Over-weight and obese prepregnancy BMI has been associated with infant mortality, preterm birth, stillbirth, and longer duration in neonatal intensive care (Schummers, Hutcheon, Bodnar, Lieberman, & Himes, 2015). A recent meta-analysis showed a 42% increased odds of infant mortality among infants born to mothers who were obese relative to normal weight women (95% confidence interval [CI]: 1.24–1.63) with an even greater elevated odds among the most obese category (>35 BMI) (odds ratio: 2.03, CI: 1.61–2.56) (Meehan, Beck, Mair-Jenkins, Leonardi-Bee, & Puleston, 2014). Underweight prepregnancy BMI (<18.5) has also been associated with negative infant outcomes (e.g., indicated preterm delivery, neonatal intensive care, and infant mortality) (Declercq, MacDorman, Cabral, & Stotland, 2016; Schummers et al., 2015). One large study of the

association of maternal prepregnancy BMI in women from 38 U.S. states demonstrated a "J"-shaped pattern, with infants of underweight mothers having births with higher infant mortality (5.4/1,000 live births) compared to births of mothers with normal prepregnancy weight (4.2/1,000 live births) and infant mortality sharply increasing with severity of maternal prepregnancy obesity: (5.9/1,000 for 30 ≤ BMI < 35; 6.8/1,000 for 35 ≤ BMI < 40; 8.2/1,000 for BMI≥40 among live births) (Declercq et al., 2016).

Prior research suggests that maternal prepregnancy obesity is associated with increased risk of spina bifida (Anderson et al., 2005; Marengo, Farag, & Canfield, 2013; Waller et al., 2007; Watkins, Rasmussen, Honein, Botto, & Moore, 2003; Watkins, Scanlon, Mulinare, & Khoury, 1996). However, no prior studies, to our knowledge, have examined the influence of maternal prepregnancy BMI in relation to infant mortality among infants with spina bifida. The purpose of this study is to investigate the first-year survival of infants born with spina bifida and examine the association of prepregnancy BMI with infant mortality.

1.1 | Materials and methods

We conducted a retrospective cohort study using data on liveborn infants with spina bifida from the National Birth Defects Prevention Study (NBDPS), a multi-state, population-based, case–control study of more than 30 major structural birth defects to define our cohort. Population-based surveillance programs in each participating site (entire state: Arkansas, Iowa, Utah; selected counties: California, Georgia, Massachusetts, North Carolina, New York, and Texas) were used to identify eligible cases of spina bifida among livebirths, stillbirths, and induced abortions. Details of the NBDPS design and data collection protocol are published elsewhere (Reefhuis et al., 2015). This analysis used only data from liveborn infants with spina bifida born between January 1, 1998 and December 31, 2011.

In the NBDPS, maternal interviews were conducted via telephone using a standardized computer-assisted interview available in either English or Spanish. The interview collected self-reported sociodemographic, health, and dietary information, among other exposures, before and during pregnancy. Interviews were administered after 6 weeks or more had passed since the infant's estimated date of delivery and no later than 2 years after the estimated date of delivery. Average time to interview for these mothers was 9.0 months.

The NBDPS and this analysis, which, in particular, used data from both interviewed and non-interviewed mothers and their infants, were approved by the institutional review boards of the Centers for Disease Control and Prevention, the University of North Carolina at Chapel Hill, and all other participating study centers.

1.2 | Prepregnancy BMI assessment

BMI was calculated from self-reported prepregnancy height and weight as mass (kilograms) divided by height^2 (meters^2) (National Institutes of Health, 1998). Height was recorded in feet and inches or in centimeters in response to the interview question: What is your height without shoes? Weight was recorded in pounds or kilograms in response to the question: How much did you weigh before your pregnancy? Appropriate unit conversions were done to then calculate BMI. Since the components for this calculation were gathered via maternal interview, BMI information was not available for non-interviewed mothers. BMI was

categorized into four groups: Underweight (BMI < 18.5), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), and obese (BMI ≥ 30) (National Institutes of Health, 1998). Both categorical and continuous measures of BMI were used in the analysis.

1.3 | Spina bifida classification

Potential cases of spina bifida were ascertained by the population-based birth defect surveillance registry of each NBDPS center. Potential cases were screened for eligibility by clinical geneticists at each center. Data collection for eligible cases involved comprehensive abstraction of medical records to capture detailed clinical information including spina bifida phenotype and diagnostic test results. Eligible cases were then recruited to participate in the NBDPS. Following recruitment, clinical information about spina bifida cases from all centers was systematically reviewed by a team of study-wide clinical geneticists to ensure consistency across study sites and to assign one of the following categories: isolated defect (one major birth defect), multiple (≥2 major yet unrelated birth defects), or complex (≥2 major birth defects which are suspected to be related) (Rasmussen et al., 2003). For spina bifida co-occurring with other NTDs, there was an established hierarchy in which each infant was only classified under the highest-ranking NTD. The hierarchy was, highest to lowest: anencephaly, encephalocele, and spina bifida. Infants with spina bifida in this analysis did not have co-occurring anencephaly or encephalocele. Details were also provided on anatomical location of the lesion along the vertebral column: cervical, thoracic, lumbar, and sacral. Cases with chromosomal abnormalities or with recognized or strongly suspected single-gene disorders or syndromes were excluded from the NBDPS by design (Reefhuis et al., 2015).

1.4 | Infant death ascertainment

Our primary outcome of interest was time to infant mortality, defined as death in the first year of life, among infants with spina bifida. We also assessed neonatal mortality and early neonatal mortality, defined as death before 28 days of age and before 7 days of age, respectively, as well as death within the first 24 hr. NBDPS data and accompanying clinical files containing medical record data were linked to vital statistics data from each participating study center to provide infant mortality data. When the medical record, NBDPS, or vital statistics data were discordant in regard to the primary outcome, that record was examined to determine whether death did occur and if so when. In situations in which two sources agreed on this information, the conclusion shared by the two sources was considered the correct information in the analytic data set. For most discordant information, the correct conclusion was obvious (i.e., the discordant record indicated the date of death was prior to the date of birth). Cause of death was recorded for some infants though this information was missing for most records; therefore, infant mortality in this analysis was defined as all-cause mortality during the first year of life. There were two infants for which records indicated that the infant had died though no exact date of death was recorded. For these two observations the date of death was imputed using fully conditional specification (van Buuren, 2007) which has been shown to be generally less subject to bias than complete-case analysis (Lee & Carlin, 2010).

1.5 | Statistical analysis

Infant mortality among infants with spina bifida was calculated as the complement of the Kaplan–Meier survival probability at 1 year of life. Twenty-four hour, early neonatal (<7 days) and neonatal (<28 days) mortality was calculated by the same method. We further constructed and plotted cumulative incidence (1 - S_{KM}) curves from the Kaplan–Meier survival estimate (S_{KM}) for the entire study sample as well as by interview status and, among women who were interviewed, prepregnancy BMI. Stratified infant mortality estimates are presented by isolated versus multiple defect(s), BMI category, gestational age category, maternal race, plurality, and spina bifida anatomical location. The standard error and corresponding pointwise CIs for the Kaplan–Meier survival probabilities were estimated using Greenwood's formula (Greenwood, 1926). The log-rank test was used to test infant mortality differences across strata.

We used Cox proportional hazards models to adjust for potential confounding. We report corresponding hazard ratios (HRs) and 95% CIs for the association of BMI with infant survival at 1year. Cox models included a semi-Bayes approach by including a weak Bayesian prior of no association (i.e., a null prior) for BMI with infant survival via data augmentation (Sullivan & Greenland, 2013). This approach allowed us to reduce potential sparse-data bias (Cole, Chu, & Greenland, 2014). Sparse-data bias arises from a lack of adequate events (i.e., deaths) for one or more combinations of the exposure (i.e., BMI) and the outcome (i.e., survival) (Sander Greenland, Mansournia, & Altman, 2016). The proportional hazards assumption for all covariates in the model was assessed by visual inspection of log cumulative hazard by BMI categories. The plot showed parallel lines for all the BMI categories suggesting no issues of nonproportional hazards. Cox models included a minimally sufficient set of covariates (i.e., confounders) to reduce the potential for bias in estimation of HRs representing BMI's association with survival. Covariates (maternal age, education, race/ethnicity, smoking, alcohol consumption, periconceptional folic acid consumption, and gestational age) were selected using a Directed Acyclic Graph (Greenland, Pearl, & Robins, 1999; Pearl, 1995) constructed based on evidence from the scientific literature and subject matter expertise (Figure S1). To address limited sample size, covariate selection was complemented by backward selection—removing variables contributing less than a 10% change in the main effect estimate were dropped from the model (Weng, Hsueh, Messam, & Hertz-Picciotto, 2009). When determining appropriate covariates for the adjusted Cox model, we examined maternal smoking and alcohol consumption. These variables had no substantial impact on the parameter estimate (change <10%) and were therefore excluded from the adjusted model.

As part of a sensitivity analysis to test the robustness of the relation between prepregnancy BMI and infant survival, we used Cox proportional hazards models with continuous BMI and allowed for model flexibility with first and second order polynomials as well as cubic splines. We also tested models without the weak null prior to check consistency of results.

Though self-reported information on BMI and other factors collected via interview were not available for infants whose mothers were not interviewed, clinical information from abstracted medical records of clinically eligible infants were used to apply the same systematic case classification and the same methods were used to link to vital statistics data

to ascertain first-year deaths. To address the potential for selection bias due to interview status and to produce estimates representative of the underlying population (Haneuse, 2013), we weighted data from infants with maternal interview data to reflect the combined sample of both subjects with and without maternal interview. Weighting involved the use of inverse probability weights (IPWs) (Robins, Hernán, & Brumback, 2000) to make interviewed study participants reflect the overall population based on variables available in both groups (i.e., birth defect classification, gestational age, plurality, maternal age, and race/ethnicity) (Appendix). Corresponding 95% CIs were then generated for weighted model parameter estimates using Efron's non-parametric bootstrap (Efron & Tibshirani, 1993).

2 | RESULTS

All analyses excluded infants with spina bifida classified as having a complex birth defect (n = 9) or not a live birth (n = 252; i.e., fetal death, induced abortion, spontaneous abortion, or missing pregnancy outcome information). Based on these restrictions, we reduced our sample size to 1,533 infants (1,080 [70%] with maternal interview and 453 [30%] without maternal interview) from the original sample size of 1,793 infants (1,228 [68%] with maternal interview and 565 [32%] without maternal interview). In our analytical sample, 1,336 (87%) infants had isolated spina bifida and 197 (13%) infants had nonisolated spina bifida (i.e., other co-occurring defects).

Among interviewed mothers, 3 % (n = 36) were underweight prior to pregnancy, 40% (n = 431) had normal BMI, 24% (n = 260) were overweight, and 25% (n = 274) were obese; 7 % of interviewed mothers did not supply information that allowed us to calculate BMI (Table 1) and were excluded from analyses requiring BMI. Among interviewed mothers, slightly more than half of mothers had greater than a high school education and the majority of mothers (82%) took folic acid sometime between 2 months prior to pregnancy and the first trimester. BMI, maternal education, and folic acid use data were not available for non-interviewed mothers. Similar distributions of maternal age, sex, gestational age, and plurality were observed for infants with maternal interview data and those without interview data. Interviewed mothers were more likely to be non-Hispanic White and to have infants with isolated spina bifida compared to non-interviewed mothers and their infants.

For the first study aim to estimate first-year mortality among infants with spina bifida, we included both interviewed and non-interviewed mothers. Overall, infant mortality at 1 year was 4.4%, though infant mortality was 3.7% among infants whose mothers were interviewed compared to 6.2% among infants whose mothers were not interviewed (log-rank test: p = .03, Figure 1). This difference in survival was distinct in the first week of life after which a very similar survival trajectory followed for the two groups. There were 68 infant deaths among infants with and without maternal interview data, 40 of which were among infants with maternal interview data. We observed that approximately half of infant deaths among infants born with spina bifida occurred within the first 24 hr after birth (n = 35).

Infants with spina bifida with another co-occurring defect (multiple/nonisolated defects) had higher infant mortality (17.9%; 95% CI: 13.23, 24.09%) than infants with isolated spina bifida (2.5%; 95% CI: 1.76, 3.46%), more than seven times the risk of death at 1 year (Table

2). Infant mortality was much greater among very preterm (<32 weeks) infants (38.0%; 95% CI: 27.89, 50.35%) compared to preterm (32−−36 weeks) and term (≥37 weeks) infants (7.2%; 95% CI: 4.17, 12.38% and 1.6%; 95% CI: 1.06, 2.52%, respectively). Among race/ethnicity groups, infants of non-Hispanic Black mothers had the highest infant mortality (7.7%; 95% CI: 4.34, 13.46%) and infants of non-Hispanic White mothers had the lowest (3.3%; 95% CI: 2.22, 4.74%). This racial/ethnic disparity was observed for the first day and week of life and gradually increased over the first year. Twins had infant mortality four times that of singletons within 1 day (8.7% vs. 2.1%), though this difference nar rowed at 1 year after birth to slightly more than double the risk. Anatomical location of the lesion was strongly associated with mortality risk with infants with thoracic lesions having notably elevated infant mortality compared to lumbar and sacral lesions; there was only one infant death among those with a cervical lesion. We also noted temporal trends of improving survival. Infants with an estimated day of delivery within the following year categories, 1998–2000, 2001–2003, 2004–2006, and 2007–2011, experienced 5.5, 4.3, 4.0, and 3.0% infant mortality, respectively (data not shown).

For the second aim to assess whether prepregnancy BMI is associated with infant mortality, data were limited only to interviewed mothers and their infants, but we accounted for possible selection bias using inverse probability weights (IPW). Infant mortality differed by maternal prepregnancy BMI. Risk of infant mortality for those born to mothers who were underweight, normal weight, underweight, or obese prepregnancy was 16, 2, 4, and 6%, respectively. Compared to normal weight mothers, underweight and obese mothers had 7 times and 2.6 times the risk of infant mortality, respectively (Table 2). A less distinct but also elevated risk for infant mortality was seen in overweight mothers. Cumulative incidence curves showed clearly different mortality risk by BMI category (Figure 2; log-rank test, $p < .01$). The greatest difference in survival between maternal BMI categories was observed for 24-hr survival while afterward similar incidence curves were followed (see Figure 2). Infants with underweight mothers had a hazard of infant mortality 7.6 times (95% CI: 2.20, 21.80) that of infants with normal weight mothers during the first year of life (Table 3). Infants born to obese mothers also had a hazard of infant mortality significantly greater (HR: 2.6; 95% CI: 1.25, 6.94) than those born to normal weight mothers. After adjusting estimates for potential confounding by maternal age, education, race/ethnicity, and periconceptional folic acid supplementation, infants with spina bifida born to underweight and obese mothers still had significantly greater hazard of infant mortality compared to infants with spina bifida born to normal weight mothers (HR: 4.5; 95% CI: 1.08, 16.72 and HR: 2.6; 95% CI: 1.36, 8.02, respectively). The estimates were imprecise as indicated by the wide CIs. Use of a cubic spline modeling of BMI showed a similar pattern of exposure-outcome relation (Figure 3) with a sharp increase of the HR with greater severity of underweight and a progressively more gradual increase in the HR as BMI exceeds 22, although the lower bound included the null value of one across most BMI values over 20.

When looking at infants with isolated spina bifida only, we found a similar pattern of results, though with less precision due to decreased sample size (Table 3). Infants with isolated defects of underweight mothers had 4.7 times the hazard of infant mortality compared to normal weight mothers (adjusted HR: 4.7; 95% CI: 1.21, 29.48). We do not report HRs and

CIs for infants with nonisolated spina bifida (multiple defects) due to model nonconvergence because of a limited sample size.

3 | DISCUSSION

Mortality in the first year of life among infants with spina bifida has greatly decreased in the past several decades. Lorber (1971) observed a 50% two-year infant mortality from 1959 to 1963 and a 36% two-year infant mortality from 1967 to 1968. A study from 1999 to 2007 showed an infant mortality of babies with spina bifida of 8.1% (Wang et al., 2015). Improvements in clinical care and medical technology have paved the way for this reduction in mortality (Pruitt, 2012). In this study, a temporal trend of reduced infant mortality was also seen. Overall, infant mortality in this study of 4.4% (CI: 3.52, 5.60%) represents one of the lowest infant mortality risks among infants born with spina bifida reported to date. The exclusion of infants with chromosomal anomalies or with recognized or strongly suspected single-gene disorders or syndromes may relate to the differences in infant mortality estimates between this study and others covering similar time periods without such exclusions (Bol et al., 2006; Shin et al., 2012; Wang et al., 2015).

The unambiguous difference in mortality between interviewed and non-interviewed has not previously been noted in this study or in others to our knowledge. Since most deaths occurred in the first month, in almost all instances, the death of the child would have preceded nonparticipation and may have had an influence on participation. As the difference is primarily in the neonatal deaths, it does not appear that infants of non-interviewed mothers were more ill and thereby illness would have inhibited the mothers from participation. One could conjecture that for mothers whose infant had recently passed away, discussing the environment and factors related to that child may be a painful experience and therefore avoided. An awareness of this difference in mortality should be had for future mortality studies with accompanying analytic adjustments as needed.

We found that infants with spina bifida born to mothers with prepregnancy underweight or obesity had poorer survival trajectories than infants of normal weight mothers. This association was strongest for underweight mothers. In the general population there appears to be a J-shaped pattern between prepregnancy BMI and infant mortality, specifically infants of underweight and obese mothers have a higher likelihood of morality (Declercq et al., 2016). There is also literature that observed some of the same associations among infants without a cause of death attributed to congenital anomalies. The results in Declercq et al. (2016) support this. That said, infants with birth defects are often born preterm (another common cause of infant mortality). Although we cannot directly address a comparison, based on our results, the association between maternal prepregnancy BMI and infant mortality among children with spina bifida may be stronger than in the general population.

The mechanism by which prepregnancy BMI might alter the risk of infant mortality in infants born with spina bifida is uncertain and may be different for underweight versus obese women. If the association we observed is of a causal nature, one pathway by which maternal adiposity might increase mortality risk is through stored yet less accessible nutrients in obese mothers or deficient nutrients in underweight mothers, such as reduced folate or iron

levels among women at extreme BMI categories (Bird et al., 2015; Casanueva, Drijanski, Fernández-Gaxiola, Meza, & Pfeffer, 2000). Both extremes of BMI would be related to greater risk of nutritional deficiency increasing both the risk of certain birth defects and setting up an infant for poorer chance of survival. Other mechanisms may include compromised immune system functioning or inflammation related to maternal adiposity that thereby also effects the health of the developing fetus. The effect of maternal prepregnancy BMI on survival among infants with spina bifida may be mediated by higher risk of preterm birth. Underweight mothers are at higher risk of spontaneous preterm birth (Liu et al., 2016) and obese women are at higher risk for indicated preterm birth due to co-morbidities such as hypertension and diabetes (Marchi, Berg, Dencker, Olander, & Begley, 2015). A mediation analysis of length of gestation suggested only some of the association of BMI with survival is attributable to gestational age at birth (data not shown). Type 2 diabetes is strongly associated with obesity (Ford, Williamson, & Liu, 1997). The incidence of Type 2 diabetes often follows weight gain (Colditz, Willett, Rotnitzky, & Manson, 1995; Hanson et al., 1995; Resnick, Valsania, Halter, & Lin, 2000) and can be thought of as another potential mediator in this analysis. A similar analysis for diabetes provided little evidence to suggest diabetes mediates the association of BMI with survival.

Other results from our analysis support previous observations. The disparities in infant mortality among infants born with spina bifida by race and ethnicity followed patterns recorded in prior literature (Wang et al., 2015) with non-Hispanic Whites having the lowest infant mortality, followed by Hispanics, and with non-Hispanic Blacks having the highest infant mortality. Prior literature also indicated an increased risk of mortality with higher anatomical location (Wong & Paulozzi, 2001). To our knowledge, information on infant mortality of spina bifida cases has not previously been presented by plurality.

This analysis had several limitations, including the self-reported nature of the questionnaire, which may have led to misclassification due to inaccurate recall. The exposure, prepregnancy BMI, calculated from self-reported recall of height and weight, has been shown to be a valid measure of BMI; prior research has shown that prepregnancy weight by recall was highly correlated with weight recorded in clinical records (Shin, Chung, Weatherspoon, & Song, 2014). Also, while BMI is used as a proxy for body fat, it more accurately represents excess weight given one’s height (Daniels, 2009). That said, this measure is inexpensive, easily obtainable, and predicts body fat percentage well (Hu, 2008). BMI was missing for all non-interviewed mothers and 7.3% of interviewed mothers and as BMI is more likely to be missing for Hispanic women, underrepresentation of Hispanic mothers may have resulted (Razzaghi et al., 2016). Residual confounding may also be present due to imperfect covariate measures and unknown confounders. Induced abortions could impact our analysis. For instance, one might anticipate that fetuses with more severe spina bifida or with co-occurring defects were more likely to be aborted than those with a less severe form of spina bifida. In addition, prenatal detection of spina bifida by ultrasound could be more difficult in obese women (Dashe, McIntire, & Twickler, 2009), though obese women are at greater risk of an affected pregnancy and may therefore be more likely to receive prenatal testing. We recognize the potential impact on survival if BMI is associated with prenatal ascertainment of spina bifida and subsequent pregnancy termination. That said,

prior research suggests that the impact on infant survival would likely be minimal if this were truly the underlying relation (Howards, Johnson, Honein, Flanders, &, 2015).

Some of our estimates were imprecise and limited sample size prevented us from examining mortality by subtype (meningocele, myelocele, myelomeningocele, lipomeningocele, and lipomyelomeningocele). Lastly, due to the fairly large number of models that were fit, the chance of a Type 1 error owing to multiple comparisons is elevated above 5%; however, the consistent trend of association we saw of increasing risk and hazard as BMI goes from normal weight to overweight to obese would not be likely if significant associations were due to chance.

This study had several strengths. NBDPS data, which combine data from population-based birth defects surveillance and a comprehensive maternal questionnaire, allow for prepregnancy BMI to be examined in relation to the risk of infant mortality among infants with spina bifida. NBDPS data used in this analysis are from sites covering nine distinct regions of the United States, increasing the generaliz-ability of results to multiple regions of the United States.

Second, inverse probability weighting applied to the interviewed sample corrected for some of the bias due to nonparticipation—making the results more representative of the source population (e.g., non-Hispanic Blacks were underrepresented among participating mothers though IPWs made estimates more accurately representative). While IPW allowed for the results to better represent the study base, an accompanying assumption was made that known characteristics about nonparticipating mothers were sufficient to weight participating mothers to accurately represent them and that association between BMI and infant mortality was the same for infants born to mothers who did and did not participate. Clear differences in key characteristics between infants with and without maternal interview substantiated this approach.

Third, the spina bifida case definition was based on strict inclusion or exclusion criteria. Individual case review by a clinical geneticist limits the potential for outcome misclassification. Exclusion of infants with recognized or strongly suspected single-gene disorders or syndromes makes our study sample more homogeneous with respect to underlying etiology and presence of major comorbid conditions.

Analyses in which our models included a continuous measure of BMI allowed for additional flexibility of exposure modeling, demonstrating stability of the exposure-outcome relation. When the null prior was removed from the proportional hazards model, conclusions remained the same. Only in one case did the determination of a statistically significant relation change (i.e., the HR for underweight compared to normal weight among infants with isolated spina bifida no longer included the null value of one) suggesting very minor sparse-data bias if results omitted the inclusion of a null prior.

Currently maternal obesity is a major obstetrical risk factor for several adverse maternal and infant conditions (American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women, 2010; Marchi et al., 2015). The risk of spina bifida is increased among women with a higher BMI (Anderson et al., 2005; Marengo et al., 2013;

Waller et al., 2007; Watkins et al., 2003; M. L. Watkins et al., 1996). Underweight women represent a small fraction of the population with prevalence around 3%; the benefits of achieving a healthy weight may be greatest in this group. Our findings and previous work suggest that policy and behavioral interventions for weight control may both prevent spina bifida (Honein et al., 2013) as well as reduce mortality among infants born with spina bifida.

In conclusion, findings from this analysis suggest that infants born with spina bifida to mothers considered underweight or obese prior to pregnancy have an elevated risk of infant mortality, particularly for underweight mothers. These findings add further evidence to the importance of a woman's healthy prepregnancy weight in reducing the occurrence of poor neonatal and infant outcomes. Further investigation of potential causal mechanisms by which maternal prepregnancy BMI may increase mortality risk in infants with spina bifida is warranted. We encourage replication of this research in other studies to examine the consistency of results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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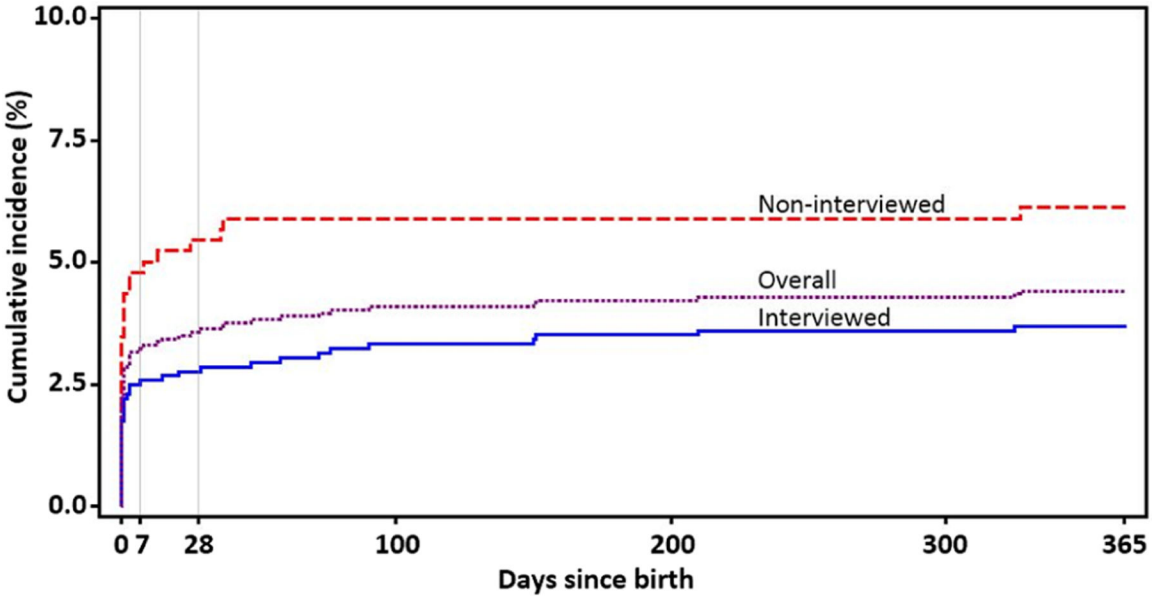

FIGURE 1.

Crude risk of infant mortality during the first year of life among infants born with spina bifida by interview status (National Birth Defects Prevention Study, 1998–2011)

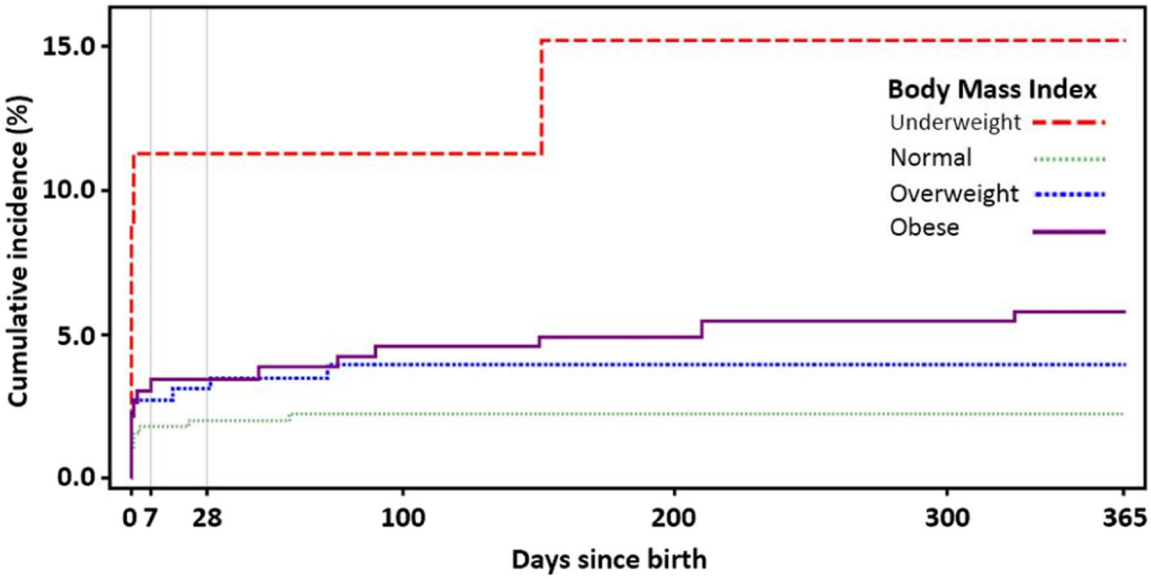

FIGURE 2.

Weighted crude risk of infant mortality during the first year of life among infants born with spina bifida by maternal category of prepregnancy body mass index (National Birth Defects Prevention Study, 1998–2011)

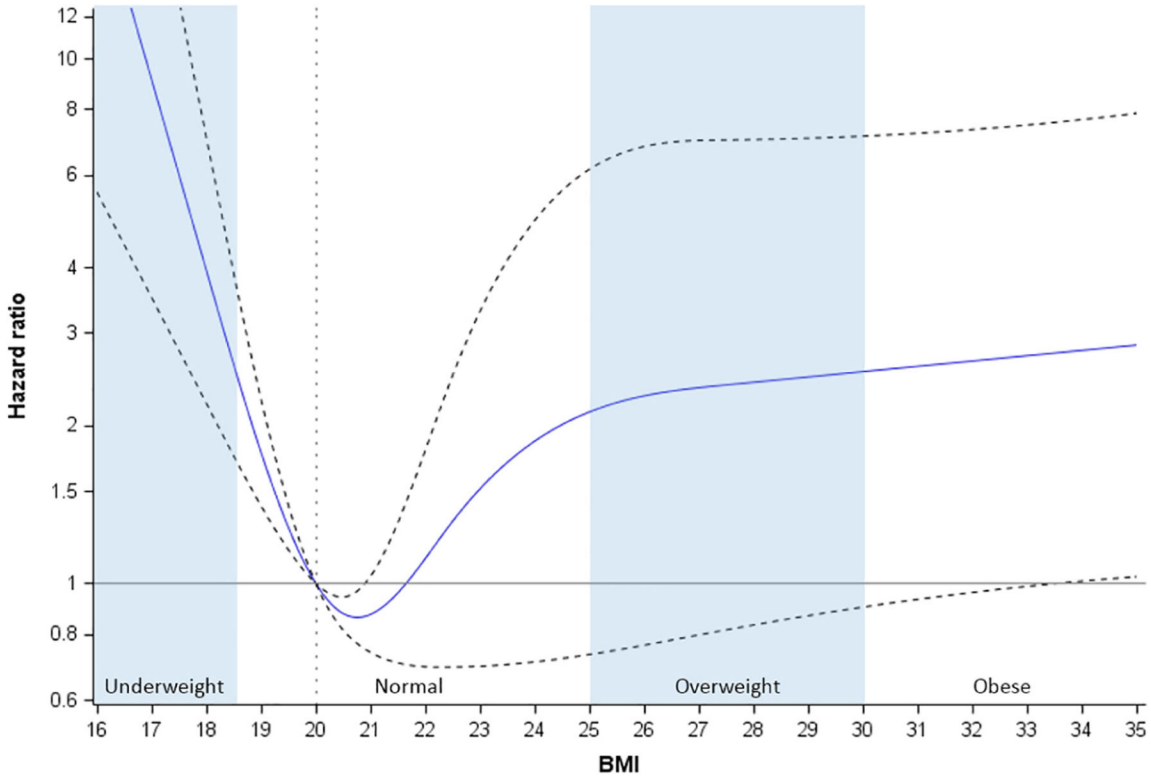

FIGURE 3.

Weighted hazard ratio and 95% confidence intervals for infant mortality by prepregnancy body mass index (BMI) relative to a body mass index of 20 (National Birth Defects Prevention Study, 1998–2011). Note: *Y*-axis values for hazard ratios are plotted on the log-scale

TABLE 1

Characteristics of liveborn infants with spina bifida eligible for the National Birth Defects Prevention Study by maternal interview status, 1998–2011[a]

Characteristic	Interviewed (*n* = 1,080) *n* (%)	Non-interviewed (*n* = 453) *n* (%)
Body mass index (kg/m^2)[b]		
Underweight (<18.5)	36 (3.3)	-
Normal (18.5–24.9)	431 (39.9)	-
Overweight (25–29.9)	260 (24.1)	-
Obese (≥30)	274 (25.4)	-
Missing	79 (7.3)	
Maternal education[b]		
0–12 years	487 (45.1)	-
>12 years	557 (51.6)	-
Folic acid supplementation[b,c]		
Yes	885 (81.9)	-
No	181 (16.8)	-
Maternal age, mean (SD)	27.3 (6.0)	26.9 (6.3)
Male Sex	557 (51.6)	239 (52.8)
Race		
Non-Hispanic White	590 (54.6)	212 (46.8)
Non-Hispanic Black	92 (8.5)	51 (11.3)
Hispanic	379 (35.1)	160 (35.3)
Other	19(1.8)	22 (4.9)
Center		
Arkansas	130 (12.0)	47 (10.4)
California	200 (18.5)	90 (19.9)
Iowa	120 (11.1)	58 (12.8)
Massachusetts	73 (6.8)	55 (12.1)
New York	70 (6.5)	44 (9.7)
Texas	141 (13.1)	66 (14.6)
Georgia	126 (11.7)	37 (8.2)
North Carolina	94 (8.7)	33 (7.3)
Utah	126 (11.7)	23 (5.1)
Gestational age, mean (*SD*)	38.0 (3.6)	37.9 (3.9)
Plurality		
Singleton	1,044 (96.7)	433 (95.6)
Twin	30 (2.8)	16 (3.5)
Defects classification		
Isolated	961 (89.0)	375 (82.8)
Multiple	119(11.0)	78 (17.2)

Characteristic	Interviewed (*n* = 1,080) *n* (%)	Non-interviewed (*n* = 453) *n* (%)
Anatomical location		
Cervical	11(1.0)	5(1.1)
Thoracic	65 (6.0)	50(11.0)
Lumbar	835 (77.3)	313 (69.1)
Sacral	133 (12.3)	62 (13.7)
Infant deaths (<1 year)	40 (3.7)	28 (6.2)

Abbreviation: *SD* = standard deviation.

[a] Small discrepancies between totals cases and summed categories are a result of missing data.

[b] BMI, maternal education, and folic acid supplementation were not recorded for non-interviewed cases.

[c] Any periconceptional use (2 months prior to conception through the 1st trimester) of folic acid supplements.

TABLE 2

Number of deaths (*n*) and infant mortality (IM) estimates (IM = 1 - S_{KM}) with 95% CIs by selected maternal and infant characteristics among infants born with spina bifida[a], National Birth Defects Prevention Study, 1998–2011 (*N* = 1,533)

	<1 day				<7 days				<28 days				<1 year			
Characteristic[b,c]	***n***	**IM (%)**	**95% CI (%)**		***n***	**IM (%)**	**95% CI (%)**		***n***	**IM (%)**	**95% CI (%)**		***n***	**IM (%)**	**95% CI (%)**	
All infants	35	2.3	1.65	3.17	49	3.2	2.43	4.21	55	3.6	2.77	4.65	68	4.4	3.52	5.60
Body mass index (kg/m^2)[d]																
Underweight (<18.5)	3	9.3	3.30	24.84	4	11.7	4.67	27.66	4	11.7	4.67	27.66	6	15.7	7.20	32.30
Normal (18.5–24.9)	4	1.0	0.41	2.63	8	1.8	0.90	3.64	9	2.0	1.04	3.91	9	2.2	1.19	4.18
Overweight (25–29.9)	6	2.3	1.01	5.10	7	2.7	1.30	5.69	8	3.2	1.59	6.24	10	4.0	2.16	7.27
Obese (≥30)	6	2.	0.97	4.79	8	3.1	1.56	5.93	9	3.5	1.85	6.47	16	5.8	3.60	9.35
Defect classification																
Isolated	11	0.8	0.46	1.48	19	1.4	0.91	2.22	24	1.7	1.15	2.58	33	2.5	1.76	3.46
Multiple	24	12.3	8.42	17.80	30	15.4	11.02	21.26	31	16.4	11.90	22.40	35	17.9	13.23	24.09
Gestational age (weeks)																
<32	13	18.3	11.07	29.43	19	26.8	17.99	38.69	23	32.4	22.85	44.60	27	38.0	27.89	50.35
32–36	8	4.8	2.44	9.41	10	6.0	3.29	10.91	10	6.0	3.29	10.91	12	7.2	4.17	12.38
≥37	8	0.7	0.33	1.30	12	1.0	0.56	1.72	13	1.1	0.62	1.82	20	1.6	1.06	2.52
Race																
Non-Hispanic White	13	1.6	0.95	2.78	16	2.0	1.23	3.24	19	2.4	1.52	3.70	26	3.3	2.22	4.74
Non-Hispanic Black	5	3.5	1.47	8.20	7	4.9	2.36	9.99	7	4.9	2.36	9.99	11	7.7	4.34	13.46
Hispanic	16	3.0	1.83	4.80	24	4.5	3.01	6.57	26	4.8	3.31	7.00	28	5.2	3.62	7.44
Other																
Plurality																
Singleton	31	2.1	1.48	2.98	45	3.1	2.29	4.07	50	3.4	2.58	4.45	63	4.3	3.35	5.44
Twin	4	8.7	3.36	21.53	4	8.7	3.36	21.53	5	10.9	4.67	24.16	5	10.9	4.67	24.16
Spina bifida location																
Cervical	0	0.0	0.00	0.00	0	0.0	0.00	0.00	0	0.0	0.00	0.00	1	6.3	0.91	36.77
Thoracic	5	4.3	1.83	10.13	8	7.0	3.54	13.43	10	8.7	4.78	15.56	13	11.3	6.73	18.67
Lumbar	20	1.7	1.13	2.69	29	2.5	1.77	3.62	32	2.8	1.98	3.93	40	3.5	2.57	4.73
Sacral	6	3.1	1.39	6.72	7	3.6	1.73	7.38	7	3.6	1.73	7.38	7	3.6	1.73	7.38

Abbreviations: CI = confidence interval; IM = infant mortality; SKM = Kaplan–Meier Survival estimate.

[a] Excludes spina bifida cases with co-occurring anencephaly, encephalocele, but with or without hydrocephalus.

[b] All characteristics, apart from BMI, include all interviewed and non-interviewed mother-infants pairs collectively.

[c] Log-rank test of differences in survival across strata was conducted for each characteristic and yielded $p < .05$ for all characteristics.

[d] BMI data were only available for interviewed mothers. Estimates and number of deaths were weighted to reflect the entire sample population.

TABLE 3

Weighted[a] hazard ratios and 95% CIs for survival of infants born with spina bifida by category of prepregnancy maternal body mass index in the National Birth Defects Prevention Study, 1998–2011

	All Spina Bifida (*n* = 961)			Isolated Spina Bifida (*n* = 854)		
Model	**HR**	**95% CI**		**HR**	**95% CI**	
Unadjusted model						
BMI						
Underweight	7.6	2.20	21.80	4.1	1.30	25.50
Normal	Reference			Reference		
Overweight	1.8	0.62	4.71	0.9	0.19	3.89
Obese	2.6	1.25	6.94	2.0	0.65	7.83
Adjusted model[b]						
BMI						
Underweight	4.5	1.08	16.72	4.7	1.21	29.48
Normal	Reference			Reference		
Overweight	1.9	0.68	5.44	1.1	0.24	4.76
Obese	2.6	1.36	8.02	2.1	0.59	8.19

Abbreviations: BMI = body mass index; CI = confidence intervals; HR = hazard ratios.

[a]Data from interviewed mothers were weighted to reflect the entire eligible sample population (interviewed and non-interviewed mothers).

[b]Adjusted for maternal age, education, race/ethnicity, and periconceptional folic acid use.