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# Association between risk of infant death and birth-weight *z* scores according to gestational age: A nationwide study using the Finnish Medical Birth Register

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## Abstract

**Objective:** To investigate the association between infant mortality and birth weight using estimated fetal weight (EFW) versus birth-weight charts, by gestational age (GA).

**Methods:** This nationwide population-based study used data from the Finnish Medical Birth Register from 2006 to 2016 on non-malformed singleton live births at 24–41$^{+6}$ weeks of gestation ($N = 563\,630$). The outcome was death in the first year of life. Mortality risks by birth-weight *z* score, defined as a continuous variable using Maršál's EFW and Sankilampi's birth-weight charts, were assessed using generalized additive models by GA (24–27$^{+6}$, 28–31$^{+6}$, 32–36$^{+6}$, 37–38$^{+6}$, 39–41$^{+6}$ weeks). We calculated *z* score thresholds associated with a two- and three-fold increased risk of infant death compared with newborns with a birth weight between 0 and 0.675 standard deviations.

**Results:** The *z* score thresholds (with corresponding centiles in parentheses) associated with a two-fold increase in infant mortality were: −3.43 (<0.1) at 24–27$^{+6}$ weeks, −3.46 (<0.1) at 28–31$^{+6}$ weeks, −1.29 (9.9) at 32–36$^{+6}$ weeks, −1.18 (11.9) at 37–38$^{+6}$ weeks, and −1.34 (9.0) at 39–41$^{+6}$ weeks according to the EFW chart. These values were −2.43 (0.8), −2.62 (0.4), −1.34 (9.0), −1.37 (8.5), and −1.43 (7.6) according to the birth-weight chart.

**Conclusion:** The association between birth weight and infant mortality varies by GA whichever chart is used, suggesting that different thresholds for the screening of growth anomalies could be used across GA to identify high-risk newborns.

KEYWORDS
birth-weight chart, estimated fetal weight chart, fetal growth restriction, growth reference, infant mortality, intrauterine growth restriction, large for gestational age, small for gestational age

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## 1 | INTRODUCTION

Fetal growth restriction (FGR) is a complication of pregnancy with multiple etiologies, but is most commonly due to placental dysfunction.[1] FGR is associated with an increased risk of stillbirth, infant death, neonatal morbidity, and neurodevelopmental and metabolic disorders.[2,3] Therefore, accurate identification of fetuses and newborns with FGR is vital to enable appropriate surveillance and intervention.

Although FGR is defined in relation to individual growth potential, this cannot be measured. Current screening strategies rely on comparing the fetus or newborn to a reference population using centiles or *z* scores to identify those who are small-for-gestational-age (SGA), usually defined as an estimated fetal weight (EFW) or an abdominal circumference less than the 10th centile during pregnancy or a birth weight below the 10th centile for newborns.[4] Measurements below the 3rd centile represent severe SGA. Clinical criteria (i.e. maternal hypertensive disorder, Doppler measurements) and the longitudinal evaluation of fetal growth are then used to distinguish constitutionally small fetuses from those with FGR.[5,6]

Despite wide consensus on these screening thresholds, there is debate on the references used to define them. Findings from some studies suggest that the choice of growth chart can substantially impact the estimated prevalence of SGA and the predictive value for identifying newborns at risk.[7,8] Another question concerns the application of the same centile thresholds throughout gestation.

The 10th and 3rd thresholds have been defined based on studies in the general population, where most births occur at term. However, preterm births before 37 weeks of gestation, which make up about 10% of births globally and 6.9% in Europe,[9] significantly contribute to the burden of severe infant complications associated with FGR.[10] Previous work has shown a varying impact of SGA status on neonatal morbidity by gestational age (GA), suggesting that normative references for identifying newborns at risk due to growth anomalies should consider the possibility of differential effects by GA.[11,12]

Specifically, in evaluations of appropriate norms, preterm births should be analyzed separately because there are major differences between EFW charts, built from EFW, and birth-weight charts, constructed from birth weights, in this population.[13] Because of the strong association between prematurity and FGR, birth weights before 37 weeks of gestation tend to be lower than EFW measures.[14,15] Using birth-weight charts versus EFW charts could therefore significantly impact the identification of appropriate screening thresholds.

This study aims to evaluate the association between infant mortality and birth-weight *z* scores by GA in a high-resource setting, and to examine whether the use of birth-weight charts versus EFW charts modifies this association.

## 2 | MATERIALS AND METHODS

This nationwide population-based study used data from the Finnish Medical Birth Register. This register collects data on all births with a GA of at least 22 weeks or a birth weight of at least 500 g in Finland. We used data for births between 2006 and 2016, period over which the data structure was consistent ($N = 644\,073$).

The study population was singleton live births without major congenital malformations between 24 and 41 completed weeks of gestation. This GA range was selected because clinical practices have evolved significantly during the study period for births less than 24 weeks and post-term births. Births with major congenital malformations, as defined by the European Registration of Congenital Anomalies (EUROCAT),[16] were identified using linked data from the Finnish Register of Congenital Malformations. We also excluded births with missing birth weight or GA and birth weight outliers (<300 g or <6 standard deviations [SD] according to the Sankilampi chart[17]). Finally, we excluded infants who emigrated before 1 year of age, using linked data from the Finnish Population Information System.

The primary outcome was infant mortality, defined as death up to 1 year of age. The main exposure was GA at birth and sex-specific birth-weight *z* scores. In Finland, pregnancy dating is confirmed by ultrasound, and GA was used in exact weeks and days. We used *z* scores rather than centiles because centiles have finite values (0 and 100) at each end of the birth-weight spectrum, which limits the ability to investigate mortality risk in infants with extreme values. This is important for high-risk populations, such as very preterm infants, where extreme values of birth weight can be observed.

*Z* scores were calculated using two sex-specific references constructed from Nordic birth samples and therefore adapted to this population: Maršál's EFW chart[18] and Sankilampi's birth-weight chart, which publishes norms for primiparous and multiparous women separately.[17] To compute the *z* scores, we calculated individual birth-weight centiles using formulae and coefficients published for each chart.[17,18] These centile values were then converted to *z* scores using the inverse normal distribution function. *Z* scores were used as a continuous and categorical variable (<−1.28 SD [<10th centile], ≥−1.28 SD and ≤1.28 SD [≥10th and ≤90th centile], >1.28 SD [>90th centile]).

Other variables were mother's age, country of birth, parity, smoking status, mode of onset of labor, mode of delivery, and maternal diabetes and hypertensive disorder during pregnancy.

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We described maternal, pregnancy and neonatal characteristics overall and by five GA groups: 24–$27^{+6}$, 28–$31^{+6}$, 32–$36^{+6}$, 37–$38^{+6}$, and 39–$41^{+6}$ weeks. We compared the birth-weight *z* score distributions with histograms for each GA group. We used generalized additive models to investigate the association of birth-weight *z* scores calculated using the EFW and birth-weight charts with the risk of infant death by GA category. The choice of the type of model (generalized additive model vs spline) and the number of knots to use was based on the lowest Bayesian Information Criterion. Finally, to quantify differences across GA in the relationship between the birth-weight *z* score and infant mortality, we calculated the *z* score threshold corresponding to a two- and three-fold increase in the infant mortality risk compared with newborns with a birth-weight *z* score between 0 and 0.675 SD, corresponding to the 50th and 75th centiles, who are considered to be at the lowest level of risk.[19] This was done for each GA group and for each chart.

In order to examine the robustness of our models at the extremes of the growth spectrum, where numbers of births are smaller, we carried out sensitivity analyses to examine the shape of our models and the *z* score thresholds after excluding newborns with birth weight up to −4 SD and 4 or more SD according to the birth-weight chart. A second sensitivity analysis used narrower 2-week bands to explore the progressive impact of GA in more detail.

Analyses were carried out using R Studio software version 4.3.2.

The study protocol was approved by the Research Ethics Board and Finnish Institute for Health and Welfare. The pseudonymized data were used with permission from the register holder, the Finnish Institute for Health and Welfare, in accordance with national data protection legislation. In Finland, individual informed consent is not required for the use of pseudonymized register data for research purposes.

## 3 | RESULTS

There were 594 492 live singleton births in Finland between 24 and 41 weeks of gestation in 2006–2016. We excluded 555 (0.1%) and 952 (0.2%) births with missing data on birth weight or GA, 4 (<0.01%) birth-weight outliers, 729 (0.1%) infants who emigrated before 1 year of age, and 28 622 (4.8%) infants with major congenital malformations. The final study population comprised 563 630 births (Figure S1).

Maternal, pregnancy, and neonatal characteristics are shown in Table 1. Overall, the infant mortality rate was 1.1 per 1000 births. Risks of infant death were higher at earlier gestations, with 144 deaths (169.8‰) at 24–$27^{+6}$ weeks, 52 (27.6‰) at 28–$31^{+6}$ weeks, 87 (4.1‰) at 32–$36^{+6}$ weeks, 98 (1.0‰) at 37–$38^{+6}$ weeks and 227 (0.5‰) at 39–$41^{+6}$ weeks.

Birth-weight *z* scores calculated using the EFW chart were normally distributed among babies born between 32 and 41 weeks of gestation, but their distribution was skewed towards lower weights among babies born before 32 weeks (Figure 1a–e). Results using the birth-weight chart were similar, but the skewedness appeared less pronounced (Figure 2a–e).

Figures 1 and 2 show the probability of infant death and 95% confidence interval (CI) by birth-weight *z* score based on the EFW and birth-weight charts, respectively, for each GA category. For all charts and categories, the probability of infant death was maximal for the lowest birth-weight *z* scores and progressively decreased to a minimum close to 0 SD before rising up again at the other birth-weight extreme. Also, the slope in the probability of infant death between −6 SD and 0 SD was steeper with a longer duration of pregnancy.

We estimated the *z* score thresholds within each category associated with a two- and three-fold increase in the infant death risk, compared with newborns with a *z* score between 0 and 0.675 SD (Table 2). The mean probability of infant death for these newborns with optimum birth-weight *z* scores decreased from 141.6‰ at 24–$27^{+6}$ weeks to 0.4‰ at 39–$41^{+6}$ weeks when using the EFW chart and from 133.0‰ to 0.4‰ when using the birth-weight chart. *Z* score thresholds of the EFW chart (corresponding centile value) associated with a two- and three-fold increased risk were −3.43 (<0.1) and −4.39 (<0.1) at 24–$27^{+6}$ weeks, then rose up to −1.18 (11.9) and −1.74 (4.1) at 37–$38^{+6}$ weeks. At term, these results were stable around −1.28 (10.0) and −1.88 (3.0), respectively. The pattern was similar when using the birth-weight chart, with values at −2.43 (0.8) and −3.63 (<0.1) at 24–$27^{+6}$ weeks, and −1.37 (8.5) and −1.91 (2.8) at 37–$38^{+6}$ weeks.

In sensitivity analyses excluding newborns with *z* scores under −4 SD and over 4 SD, results were similar (Figures S2 and S3; Table S1). *Z* score thresholds associated with a two- and three-fold increased risk of infant death followed the same pattern with smaller GA groups (Figures S4 and S5; Table S2).

## 4 | DISCUSSION

Our results illustrate the variation in the distribution of birth-weight *z* scores by GA, with a more pronounced left-skewedness before 32 weeks of gestation, especially when using an EFW chart. The increase in infant mortality associated with lower birth-weight *z* scores was more marked with longer duration of pregnancy and seemed to stabilize after 37 weeks. Differences in the relationship between infant mortality and birth-weight *z* scores defined either by an EFW or a birth-weight chart were small and mainly concerned GAs before 32 weeks.

Limitations of this study include the use of observational data, which may be more prone to measurement or pregnancy dating errors, especially for extreme values of birth weight for GA. However, over the study period, pregnancy dating in Finland was mostly carried out using early ultrasound, which is known to be the most accurate method.[20] Moreover, results were stable after excluding birth-weight *z* scores under −4 and over 4 SD. Another limitation is that we were unable to study the impact of clinical practices on our results, including antenatal corticosteroid administration or

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**TABLE 1** Population characteristics.[a]

| | Total population ($n=563630$) | 24–27$^{+6}$ weeks ($n=848$) | 28–31$^{+6}$ weeks ($n=1887$) | 32–36$^{+6}$ weeks ($n=21302$) | 37–38$^{+6}$ weeks ($n=98443$) | 39–41$^{+6}$ weeks ($n=441150$) | Missing data |
|---|---|---|---|---|---|---|---|
| Maternal characteristics | | | | | | | |
| Age, years | 30.2 ± 5.3 | 31.0 ± 6.0 | 30.8 ± 5.8 | 30.4 ± 5.6 | 30.6 ± 5.5 | 30.2 ± 5.3 | 3157 (0.6) |
| Multiparous | 59.3 | 52.7 | 49.9 | 50.5 | 61.7 | 59.2 | 84 (0.0) |
| Maternal smoking status during pregnancy | 15.4 | 20.0 | 20.4 | 18.4 | 15.8 | 15.1 | 13398 (2.4) |
| Born outside Finland | 10.1 | 15.8 | 11.4 | 10.1 | 10.3 | 10.1 | 3157 (0.6) |
| Pregnancy characteristics | | | | | | | |
| Diabetes | | | | | | | |
| Pre-existing type 1 | 0.6 | 1.4 | 2.7 | 5.4 | 1.7 | 0.1 | 1 (0.0) |
| Pre-existing type 2 | 0.2 | 0.1 | 0.6 | 0.4 | 0.4 | 0.1 | |
| Gestational | 14.0 | 9.1 | 13.6 | 16.5 | 18.4 | 12.9 | |
| Hypertensive disorders[b] | | | | | | | |
| Without proteinuria | 4.6 | 3.7 | 4.9 | 5.5 | 6.0 | 4.2 | 1 (0.0) |
| With proteinuria | 2.8 | 18.0 | 27.9 | 12.9 | 4.9 | 1.7 | |
| Delivery by cesarean section | 15.2 | 61.1 | 65.7 | 32.1 | 19.4 | 13.1 | 2 (0.0) |
| Induction of labor | 17.4 | 7.0 | 6.9 | 21.8 | 24.3 | 15.7 | 0 (0.0) |
| Neonatal characteristics | | | | | | | |
| Sex (female) | 48.9 | 47.4 | 45.4 | 43.5 | 46.5 | 49.7 | 0 (0.0) |
| Birth weight, g | 3518 ± 522 | 856 ± 210 | 1413 ± 341 | 2648 ± 561 | 3298 ± 473 | 3623 ± 438 | 0 (0.0) |
| Under −1.28 SD (10th centile) according to EFW chart | 9.4 | 34.9 | 45.2 | 18.9 | 9.7 | 8.7 | 0 (0.0) |
| Under −1.28 SD (10th centile) according to birth-weight chart | 11.9 | 20.8 | 28.0 | 20.6 | 14.9 | 10.8 | 0 (0.0) |
| Over 1.28 SD (90th centile) according to EFW chart | 10.7 | 1.9 | 2.4 | 12.6 | 16.0 | 9.5 | 0 (0.0) |
| Over 1.28 SD (90th centile) according to birth-weight chart | 8.3 | 18.8 | 13.8 | 11.9 | 10.4 | 7.7 | 0 (0.0) |
| Gestational age, exact weeks | 39.7 (1.6) | 26.2 (1.1) | 30.3 (1.1) | 35.5 (1.2) | 38.2 (0.5) | 40.3 (0.8) | 0 (0.0) |
| Infant deaths at <1 year of life (per 1000 live births) | 1.1 | 169.8 | 27.6 | 4.1 | 1.0 | 0.5 | 0 (0.0) |

Abbreviations: EFW, estimated fetal weight; SD, standard deviation.

[a]Data are presented mean ± standard deviation, percentage or number (percentage).

[b]Hypertensive disorders without proteinuria include gestational or chronic hypertension, and hypertensive disorders with proteinuria include pre-eclampsia or eclampsia.

medically indicated preterm birth, because these data were not available. Finally, we did not have information on ultrasound or Doppler measurements carried out during pregnancy, which have been proposed to improve definitions of FGR.[5,6] However, these definitions have not proven superior for identifying morbidity risks than birth-weight centiles alone.[21]

This study's strengths include the use of high-quality data from nationwide registers, with under 0.5% of births excluded for missing or discordant data. These data were population-based and covered an 11-year period, which enabled the investigation of a rare outcome. However, confidence intervals remained large for birth weights at the extremes of the spectrum, especially before 32 weeks. In a sensitivity analysis we repeated our approach with smaller GA categories, which confirmed the tendency of the relative impact of birth-weight *z* score on infant mortality to gradually increase at later gestations. Finally, the use of *z* scores instead of centiles to express birth weight allowed accurate evaluation of its association with infant mortality for extreme weights.

These findings corroborate the results of previous studies showing a skewed distribution of birth weight at earlier gestations, which

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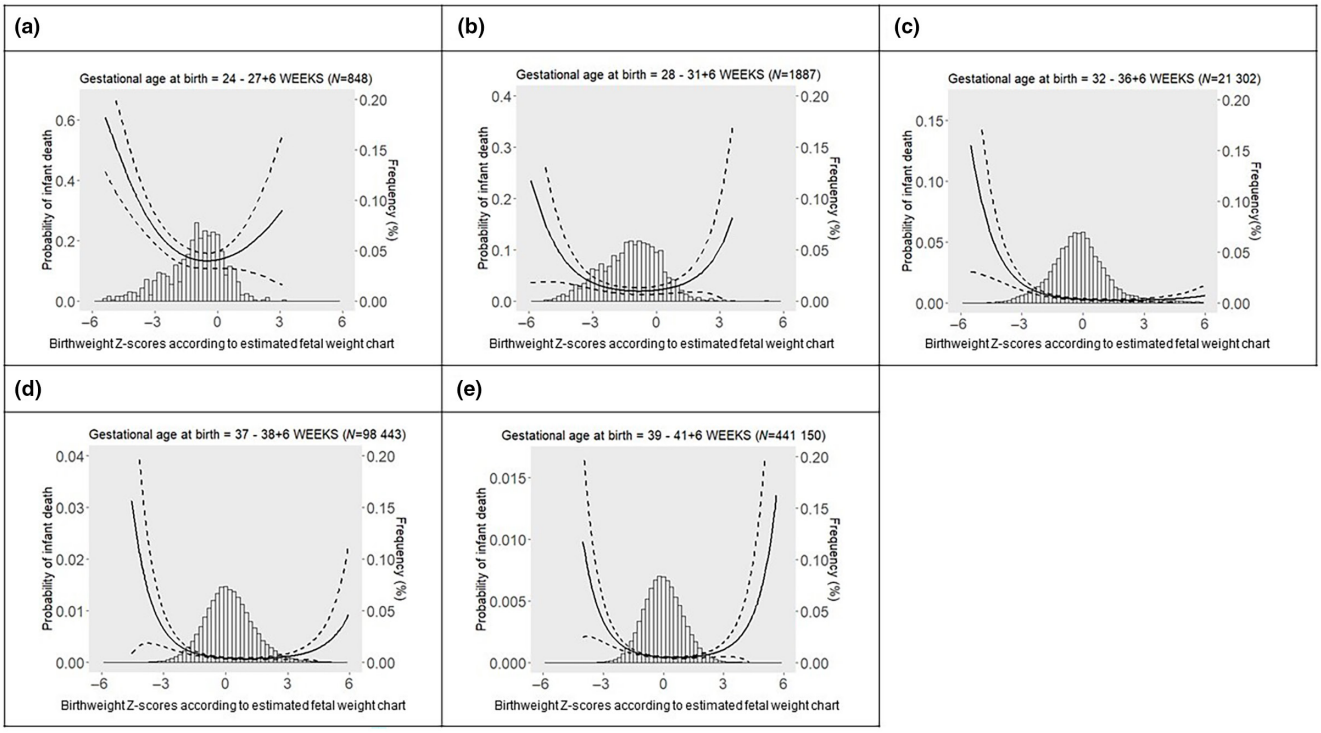


**FIGURE 1** (a–e) Histograms of birth-weight *z* score and probability of infant death according to birth-weight *z* scores (based on the estimated fetal weight chart) by gestational age categories.

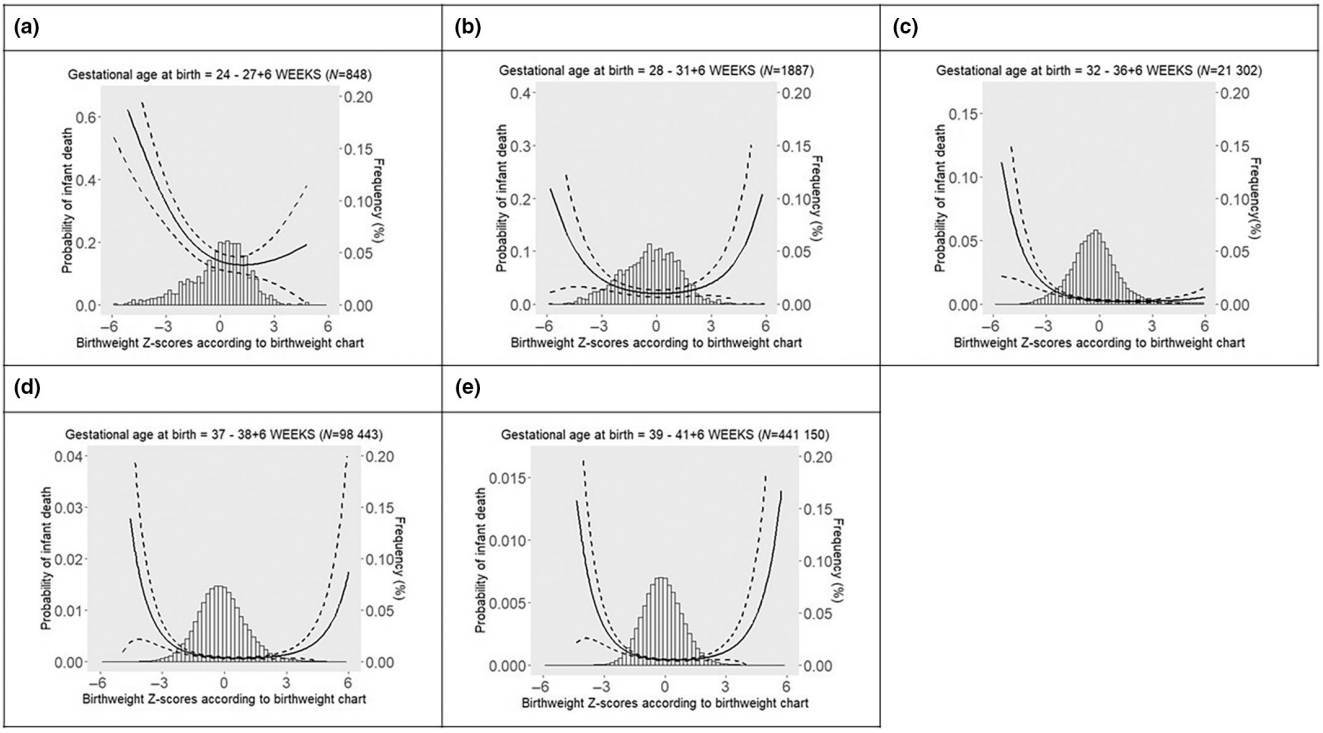


**FIGURE 2** (a–e) Histogram of birth-weight *z* score and probability of infant death according to birth-weight z scores (based on the birth-weight chart) by gestational age categories.

can be explained by the strong association between FGR and prematurity.[13,14] This skewedness is artificially reduced when using birth-weight rather than EFW charts to calculate the *z* score.

Birth-weight charts in preterm gestations are, by definition, based on infants who were born preterm, which is an abnormal condition and associated with FGR.[14] Therefore, birth-weight chart

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**TABLE 2** Mean probability of infant death for newborns with a birth weight between 0 SD and 0.675 SD according to estimated fetal weight and birth-weight charts by gestational age categories, and thresholds associated with a two-fold and three-fold increased risk compared with this group.

| | 24–27$^{+6}$ weeks | | 28–31$^{+6}$ weeks | | 32–36$^{+6}$ weeks | | 37–38$^{+6}$ weeks | | 39–41$^{+6}$ weeks | |
|---|---|---|---|---|---|---|---|---|---|---|
| | EFW | Birth weight | EFW | Birth weight | EFW | Birth weight | EFW | Birth weight | EFW | Birth weight |
| Mean probability of infant death for birth weight between 0 and 0.675 SD (per 1000) | 141.6 | 133.0 | 22.7 | 19.5 | 2.4 | 2.4 | 0.7 | 0.7 | 0.4 | 0.4 |
| SD threshold (equivalence in centiles) associated with a risk increased by | | | | | | | | | | |
| 2× | −3.43 (<0.1) | −2.43 (0.8) | −3.46 (<0.1) | −2.62 (0.4) | −1.29 (9.9) | −1.34 (9.0) | −1.18 (11.9) | −1.37 (8.5) | −1.34 (9.0) | −1.43 (7.6) |
| 3× | −4.39 (<0.1) | −3.63 (<0.1) | −4.09 (<0.1) | −3.45 (<0.1) | −1.94 (2.6) | −2.00 (2.3) | −1.74 (4.1) | −1.91 (2.8) | −1.77 (3.8) | −1.96 (2.5) |

Abbreviations: EFW, estimated fetal weight; SD, standard deviation.

centile thresholds are lower than those from EFW charts, constructed from ultrasound data on fetuses in utero.[15] EFW charts are recommended for the surveillance of fetal growth during pregnancy for this reason[4] and our study underlines the need for further thought about their use for the identification of preterm newborns with impaired growth.

A stronger association between infant mortality and birth-weight *z* scores with increasing GA has been documented in previous studies.[3,11,12] Xu et al.[12] showed that risk ratios for neonatal death associated with a birth weight below the 10th centile rose from 2.3 (95% CI 2.2–2.4) among preterm births to 3.5 (95% CI 3.3–3.7) among term births and this increase was also observed when looking at 2-week GA categories. McIntire et al.[3] found term newborns with a birthweight under the 3rd centile to be at higher risk of neonatal mortality, while this was not significant for preterm births.

Other authors have suggested using risk curves to identify newborns at a 2-, 2.5-, or 3-fold increased risk of adverse outcomes rather than traditional centile charts.[11] Our study suggests that this may be of value for the preterm population, whereas the thresholds for term newborns associated with a two- and three-fold increased risk in infant mortality were close to the 10th and 3rd centile thresholds currently recommended in clinical practice.[4] These previous studies, in addition to our own, used birth-weight data which limit direct extrapolation of results to surveillance of fetal growth. However, they bring forward new arguments and approaches that could also contribute to improvements in screening for FGR during pregnancy.

One hypothesized explanation for the stronger association of birth-weight *z* scores with infant mortality as gestation progresses is the evolution of the fetus's nutritional and gas exchange demands, which are impacted in case of placental dysfunction, the major etiology for FGR.[1] In early pregnancy, placental disorders will affect fetal nutrition and impact growth rather than gas exchange demands, which are still fairly low before 32 weeks of gestation.[22] However, late-onset placental dysfunction will have a larger effect on rapidly increasing fetal gas exchange demands near term, potentially leading to a more severe impact on morbidity and mortality.

This stronger association also reflects lower absolute risks of infant mortality later in gestation.[23] Babies born very preterm experience severe complications, regardless of growth restriction. Therefore, the risk increase at these gestations is less marked when expressed as a ratio, although there is still a substantial absolute difference.

The increased mortality risk at the higher end of the *z* score spectrum should be interpreted with caution given the large confidence intervals, but is concordant with the literature.[24,25] Variation across GA categories may be explained by differences in the causes of death, with higher risks of delivery complications and perinatal asphyxia among pregnancies at later gestations. However, further comparative studies are needed to explore these hypotheses. Also, despite the exclusion of all congenital anomalies from our study population, some remaining conditions could be associated both with

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elevated birth-weight *z* score and higher risks of mortality, such as large tumors, which are rare but lead to extreme weights.

In conclusion, the association between birth-weight *z* scores and infant mortality varies by GA and was stronger among term births, where the 10th centile threshold (−1.28 SD), used in current screening practices, corresponds to a two-fold increase in the risk of infant death. Lower thresholds may be more appropriate for screening at preterm gestations, supporting the use of risk curves with different thresholds across gestations to permit better identification of newborns at risk.

## AUTHOR CONTRIBUTIONS

AH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. AH, EK, and JZ conceived and designed the study and drafted the manuscript; AH, AP, KH, JM, EK, and JZ contributed to data acquisition and interpretation, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript. Data management and statistical analysis were by AH, AP, and JM.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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