Severity of small-for-gestational age and morbidity and mortality among very preterm neonates

Kathleen Minor (minork@stanford.edu)
Stanford University
Katherine Bianco
Lillian Sie
Stanford University https://orcid.org/0000-0003-0069-5028
Maurice Druzin
Henry Lee
Stanford University https://orcid.org/0000-0001-8383-1720
Stephanie Leonard

Article

Keywords:

Posted Date: July 22nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1871875/v1

Version of Record: A version of this preprint was published at Journal of Perinatology on October 27th, 2022. See the published version at https://doi.org/10.1038/s41372-022-01544-w.

Severity of small-for-gestational age and morbidity and mortality among very preterm neonates

Running title: Morbidity and mortality of small for gestational age

Kathleen C. MINOR, MD[1]; Katherine BIANCO, MD[1]; Lillian SIE, MPH[2,3]; Maurice L. DRUZIN, MD[1]; Henry C. LEE, MD[2,3]; Stephanie A. LEONARD, MS, PhD[1]

1 Division of Maternal-Fetal Medicine & Obstetrics, Department of Obstetrics and Gynecology, School of Medicine, Stanford University, Stanford, CA

2 Department of Pediatrics, School of Medicine, Stanford University, Stanford, CA

3 California Perinatal Quality Care Collaborative, Stanford, CA

Corresponding author: Kathleen Minor, Stanford Center for Academic Medicine, 453 Quarry Rd, OB/GYN, Palo Alto, Ca 94304; minork@stanford.edu, 650-724-1824

ABSTRACT:

Objective: Evaluate the association between small for gestational age (SGA) severity and morbidity and mortality in a contemporary, unselected population of very preterm infants.

Study Design: This secondary analysis of a California statewide database evaluated singleton infants born during 2008-2018 at 24-32 weeks' gestation, with a birthweight <15th percentile. We analyzed neonatal outcomes in relation to weight for gestational age (WGA) and symmetry of growth restriction.

Results: An increase in WGA by one z-score was associated with decreased major morbidity or mortality risk (aRR 0.73, 95% CI 0.68-0.77) and other adverse outcomes. The association was most pronounced for WGA percentile <3 and did not differ by fetal growth restriction diagnosis. Symmetric growth restriction was not associated with neonatal outcomes after standardizing for gestational age at birth.

Conclusions: Increasing SGA severity, particularly below the 3rd WGA percentile, had a significant impact on neonatal outcomes among very preterm infants.

INTRODUCTION

Small for gestational age (SGA), defined as a birthweight <10th percentile, and prematurity are leading etiologies of perinatal morbidity and mortality(1). Therefore, SGA in early preterm gestation carries a significant burden of disease. The immediate and longer-term sequalae for SGA and preterm neonates are well characterized, including: stillbirth, neonatal death (2–6), seizures, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, hypoxic ischemic encephalopathy, respiratory distress syndrome, neurodevelopmental disorders, and cardiovascular and metabolic diseases (1–15). Further, the prenatal diagnosis of fetal growth restriction (FGR) by ultrasound and the severity of SGA are known to influence outcomes (4,16–19). However, contemporary, population-based evidence is lacking. Additionally, diagnosis and management of SGA and prematurity has changed dramatically over time and updated evidence is needed.

Prenatal diagnosis of FGR is known to influence outcomes of SGA neonates through enhanced surveillance and delivery timing (20–22). Yet, prenatal identification of FGR in SGA neonates ranges from 10% (23) to 54% (24), depending on the maternal population, severity of SGA and healthcare system (23). This indicates missed opportunities for detection, enhanced surveillance and risk stratification (21,22). Increasing FGR detection must be balanced with the risk of overdiagnosis and iatrogenic preterm birth (3,4). Historically, compared with symmetric growth restriction, asymmetric growth restriction was associated with improved prognosis (7,10,25). However, recent guidelines indicate it should not influence antenatal management (16). There is limited evidence on how symmetry of SGA may be associated with neonatal outcomes (25).

In this context, we sought to characterize the continuum of neonatal morbidity and mortality, according to weight for gestational age (WGA) z-score and determine if there is a clinically relevant WGA inflection point when neonatal risk increases in an early preterm population. We hypothesized that among early preterm infants, <32 weeks' gestation, a lower WGA z-score would be associated with higher neonatal morbidity and mortality. Secondly, we theorized that these associations are attenuated by a prenatal diagnosis of FGR and postnatal asymmetric growth restriction.

MATERIALS/SUBJECTS AND METHODS:

Study Design:

We conducted a secondary analysis of a population-based cohort, the California Perinatal Quality Care Collaborative database (CPQCC), which comprises >90% of neonatal intensive care units (NICUs) in California. The database includes all participating NICU patients who are born 401-1500 grams or $22^{0/7}$ to $31^{6/7}$ weeks gestational age and are admitted on or before 28 days of life (26,27). The CPQCC links NICU data to birth certificate, death certificate and hospital discharge data. This study was approved by the California Committee for the Protection of Human Subjects (IRB #12-06-0393) and the Stanford University Institutional Review Board (IRB #14746).

We included live, singleton neonates born from 2008 to 2018 at early preterm gestational age (24^0-31^6 weeks) births and with a birth WGA <15th percentile (28). Although SGA is defined as <10th percentile, we included WGA up to the 15th percentile to capture the spectrum of risk associated with lower birthweights. Exclusion criteria comprised severe birth anomalies and missing or implausible birthweight, gestational age, sex, or covariates included in analyses.

Implausible was defined as a combination of gestational age and birthweight that were not biologically possible (28).

Definitions:

We calculated a WGA z-score for each infant using sex-specific national reference charts generated with sufficient numbers of early preterm infants (28). We used continuous z-scores for analysis, and converted them to percentiles to assign severity based on clinically relevant cutoffs (16): <3rd, 3rd to <5th, 5th to <10th, and 10 to <15th percentile. Fetal growth restriction (FGR) was defined by the diagnosis being coded antenatally. During the timeframe of this cohort, an estimated fetal weight <10th percentile was used to define FGR.

The CPQCC database provides a population-based repository of head circumference measurements from which we calculated head circumference z-scores. We followed the method described by Bocca-Tjeertes et al.(25) to classify the study participants with postnatal asymmetric growth restriction or symmetric growth restriction. Infants with a birthweight >1 standard deviation less than the corresponding head circumference were classified as asymmetric growth restriction. All other infants were classified as symmetric growth restriction. This method characterizes outcomes based on SGA etiology and the phenomenon known as head sparing (25).

Maternal, fetal and delivery factors known to influence neonatal outcomes were analyzed. Hypertension included chronic hypertension, gestational hypertension and/or pre-eclampsia. Diabetes included pre-existing or gestational diabetes. Antenatal magnesium and steroids included receipt of these treatments and does not always indicate a full course. Covariates were selected *a priori* based on literature review, and included: diabetes (3),

113 hypertension (26), and antenatal steroid administration (3,29). As described below, gestational
114 age at birth (30–32) and FGR diagnosis (3,4,19) were also treated as covariates.

115 Outcomes:

116 The primary outcome was major neonatal morbidity or death. This composite outcome
117 was previously developed by the CPQCC and is defined as the occurrence of any of the
118 following: infant death during birth hospitalization or within 1 year of birth after continuous
119 hospitalization, chronic lung disease, severe intraventricular hemorrhage, infection, necrotizing
120 enterocolitis, severe retinopathy of prematurity (ROP) or ROP surgery and cystic periventricular
121 leukomalacia (33).

122 Secondary outcomes included cesarean birth, the need for neonatal endotracheal tube
123 ventilation in the delivery room, an Apgar score < 4 at 5 minutes, neonatal death in the delivery
124 room and infant death. These were selected due to the objective nature, clinical relevance and
125 prognostic value.

126 Statistical Analysis:

127 We calculated maternal, fetal, delivery, and neonatal characteristics according to WGA
128 groups <3rd, 3rd to <5th, 5th to <10th and 10 to <15th percentile. We then conducted multivariable
129 modified Poisson regression models to estimate relative risks (RR) and 95% confidence intervals
130 (CI) for the associations between WGA z-score, treated as a continuous exposure, and the
131 outcomes of interest. Linear associations between WGA z-score and the outcomes were assessed
132 and verified by fitting WGA z-scores with restricted cubic splines. The multivariable regression
133 models adjusted for gestational age at birth (weeks), FGR (diagnosed antenatally), diabetes,
134 hypertension, and antenatal steroid administration. To aid in interpretation of the primary results,
135 we plotted the incidence of major neonatal morbidity or mortality across WGA percentiles for

136 GA groups: 24-26, 27-28, 29-30, and 30-31 wk. We then replicated these models separately
137 among participants with a diagnosis of FGR and among those without a diagnosis of FGR, based
138 on our hypothesis that an antenatal FGR diagnosis modifies the effect of WGA on neonatal
139 outcomes.

140 We assessed differences for SGA infants with symmetric growth restriction versus
141 asymmetric growth restriction by conducting multivariable modified Poisson regression models
142 for the outcomes of interest, treating asymmetric growth restriction as the reference group. The
143 models adjusted for the same covariates as above. All analyses were conducted in SAS version
144 9.4.

145 **RESULTS:**

146 From 2008-2018, 196,501 neonates were identified within the California NICU database.
147 After exclusions, 4,689 unique singleton neonates, born in early preterm gestation, without
148 severe anomalies, and with a birthweight <15th percentile remained in the cohort (Supplementary
149 Figure). In comparing the WGA categorical groups, maternal co-morbidities were least common
150 and prior cesarean section was most common in those <3rd percentile WGA (**Table 1**). Neonates
151 <5th percentile WGA were more likely to be diagnosed antenatally with FGR when compared to
152 3rd to the <5th or 5th to <10th percentile (82% vs 70% vs 55% respectively). In the 10th to <15th
153 percentiles, 37% were had been diagnosed with FGR. The neonates in lower WGA percentile
154 groups were less likely to receive magnesium, but more likely to require intubation, have Apgar
155 scores <4 at 5 minutes, intraventricular hemorrhage, respiratory distress syndrome, neonatal
156 death in the delivery room, infant death or major morbidity or mortality.

157 The incidence of major neonatal morbidity or mortality was plotted based on WGA
158 percentile and stratified by gestational age. The rate of major morbidity or mortality decreased

with increasing WGA percentile and increasing gestational age (**Figure 1**). Among neonates born 29-32 weeks' gestation, there was an inflection point at <3rd percentile of WGA, below which major morbidity and mortality increased dramatically. In contrast, there was an overall gradual continuum of increasing risk with decreasing WGA percentile among neonates born 24-28 weeks' gestation.

Increasing WGA z-score was associated with improved neonatal outcomes (**Table 2**), before and after adjusting for FGR, maternal diabetes, maternal hypertension, and antenatal steroids. These relationships persisted when adjusting for gestational age. The relative risk of the primary outcome, major morbidity or mortality, decreased with each unit increase in WGA z-score (aRR 0.73, 95% CI 0.68-0.77, p<0.0001). This would be interpreted clinically as a neonate in the 14th percentile WGA having a 27% lower risk of major morbidity or mortality compared to a neonate in the 2nd percentile, independent of confounders. Each increase in WGA z-score also demonstrated a reduction in the relative risk of secondary outcomes including: cesarean birth, need for neonatal endotracheal tube ventilation, Apgar score <4 at 5 minutes, neonatal delivery room death and infant death. The estimated effect of increasing WGA z-score was most pronounced for preventing delivery room death (aRR 0.17, 95% CI 0.12-0.24). Indicating that for one increase in z-score, or from the 2nd to the 14th percentile, there is an 83% reduction in delivery room death. Stratifying outcomes by the prenatal diagnosis with FGR (n=2585) versus without (n=2104) did not alter the relationship of increasing WGA z-score on neonatal outcomes (**Table 3**).

More neonates had asymmetric growth restriction (n=3,257) than symmetric growth restriction (n=1,324), as previously defined by Bocca-Tjeertes et al. (25) (**Table 4**). In the crude regression models, neonates with symmetric growth restriction had an increased risk of major

182 morbidity or mortality, intubation, Apgar <4 at 5 minutes, delivery room and infant death
183 compared with neonates with asymmetric growth restriction. These associations persisted after
184 adjusting for maternal comorbidities, FGR, and antenatal steroid use. Specifically, the most
185 pronounced findings among symmetric growth restriction were an increased risk of delivery
186 room death (aRR 24.6, 95% CI 8.9-68.3) and infant death (aRR 5.8 95% CI 4.8-6.9). However,
187 when gestational age was added to the adjustment model, there were no significant associations
188 between symmetric growth restriction and any of the outcomes. Thus, observed differences in
189 outcomes may be attributed to gestational age differences.

190 **DISCUSSION:**

191 Our study demonstrated four important findings. First, among preterm infants born <32
192 weeks' gestation and <15th percentile WGA, increasing WGA z-score was associated with a
193 decrease in neonatal morbidity and mortality. Second, for neonates born from 29-32 weeks
194 gestational age, the 3rd percentile of WGA was a meaningful inflection point; below the 3rd
195 percentile, the risk of major neonatal morbidity or mortality increased dramatically. Conversely,
196 prior to 29 weeks gestational age, risk of neonatal morbidity or mortality increases gradually
197 across all WGA percentiles. Third, the relationship between WGA z-score and major morbidity
198 or mortality was not modified by the diagnosis of FGR. Lastly, symmetrically growth restricted
199 neonates had worse outcomes, which was explained by earlier gestational age.

200 The degree of protection conferred by an increasing WGA percentile was notable for
201 immediate outcomes, longer-term outcomes, and the composite outcome of major morbidity or
202 mortality. Our results parallel conclusions of a large single center cohort from 1988-1996, which
203 demonstrated an increase in neonatal morbidity and mortality for term neonates ≤3rd percentile,
204 but preterm infants had no inflection point and instead experienced a gradual increase in adverse

205 outcomes (31). Our findings of an inflection point at <3rd percentile of WGA in neonates 29-32
206 weeks' gestation, but not <29 weeks, likely reflects an improvement in outcomes of prematurity
207 since the 1980s and 1990s, particularly for those born very preterm, but not extremely preterm
208 (34).

209 Preterm SGA neonates are affected by both growth restriction and prematurity (31).
210 Prematurity is likely acting as an effect modifier, therefore isolating a relationship between
211 growth restriction and neonatal outcomes in a premature population is challenging (6,31). A
212 recent prospective study combining results from nine Maternal-Fetal Medicine Unit Network
213 studies, found no difference in neonatal morbidity between SGA and appropriate for gestational
214 age (AGA) neonates who were born <32 weeks' gestation (6). This study (6) as well as others
215 (30,35) have hypothesized that gestational age dictates neonatal outcomes more than growth
216 restriction, in a premature population. Specifically, when < 27 weeks, neonatal survival improves
217 by 2% for each day in utero (35). This relationship is also evident in our data, where >80% of
218 SGA neonates <27 weeks experienced major morbidity or mortality, but with one additional
219 week of gestation, outcomes improve and the severity of SGA begins to exhibit an effect (Figure
220 1). We notably isolated the effect of SGA severity on neonatal outcomes by reporting WGA z-
221 scores and adjusting models for gestational age and maternal comorbidities (30). Additionally,
222 we restricted the population to <32 weeks, concentrating on pathologically small neonates, as
223 opposed to constitutional growth restriction from biologic variability (36).

224 Prior studies have found FGR to be more specific for extreme SGA percentiles
225 (4,9,22,37,38). Similarly, our results demonstrate neonates categorized as <5th percentile have a
226 higher likelihood of being diagnosed with FGR compared to the 5 to <10th percentile. In our
227 study, 55-82% of SGA (<10th percentile) neonates were diagnosed with FGR antenatally, which

228 is higher than prior studies (3,4,18,19,22,23). Compared with neonates not diagnosed with FGR,
229 the FGR cohort was more severely growth restricted and had a higher risk of infant death. The
230 FGR paradigm of prenatal diagnosis is that detection of pathologically small fetuses allows for
231 surveillance, expedites intervention and leads to improved outcomes (35). However, studies are
232 conflicting as to whether the diagnosis of FGR affects outcomes (3,4,18,19). Our study showed
233 antenatal FGR diagnosis did not impact the relationship between SGA severity and neonatal
234 outcomes. This finding may stem from FGR not being sensitive or specific for SGA (24,38),
235 FGR being more sensitive for severe fetal growth restriction (22), and the heterogeneity in
236 surveillance protocols for detection and management of FGR.

237 Controversy exists as to the clinical utility of asymmetric growth restriction versus
238 symmetric growth restriction. This dichotomy was intended to stratify risk based on the etiology:
239 symmetric growth restriction is correlated with an early insult (infectious or genetic etiologies)
240 and portends a poorer prognosis, whereas asymmetric growth restriction is an adaptive response
241 to a recent event, often utero-placental insufficiency (7,11,25). This is consistent with our
242 results: compared to asymmetric growth restriction, symmetric growth restriction was associated
243 with an increase in major morbidity and mortality, which was driven by earlier gestational age.
244 Physiologic adaptation to the intrauterine milieu, a lack of reserve and earlier gestation in
245 symmetric growth restriction may contribute to the challenge with immediate transition to extra-
246 uterine life. Similarly, a study of 1,268 SGA neonates, <32 weeks, concluded that asymmetric
247 growth restriction neonates had lower odds of mortality and respiratory complications compared
248 to symmetric growth restriction neonates. Excess mortality in symmetric growth restriction was
249 attributed to respiratory distress (7). Antepartum studies of symmetry of growth using ultrasound
250 and did not demonstrate predictive accuracy (39). Guidelines recommended against using

251 symmetric growth restriction for prognostication and our results support this in a contemporary,
252 very preterm cohort (16).

253 The continuum of risk for SGA neonates is vital to how physicians counsel patients,
254 delivery timing and to the allocation of population-based resources (35). While the birthweight
255 is not known to obstetricians at the time of management decisions, outcomes from SGA neonates
256 can be extrapolated to pregnant patients with suspected FGR for counseling purposes (6,30).
257 Prior studies have challenged whether the categorization of SGA <10th percentile is still a
258 meaningful threshold for defining risk (1,5,6,13,18,20,31,37,40,41). Defining SGA using a high
259 percentile jeopardizes applying interventions without benefit, and possible harm. Conversely,
260 using a lower percentile to define SGA may cause missed surveilling an at-risk population
261 (1,19,38). Some propose different thresholds demarcating interventions, individualized to
262 gestational age (1,42). According to our data, while neonates in the 10-15th percentile are not
263 without risk, defining SGA as <10th percentile is appropriate, with <3rd percentile being the most
264 at-risk cohort. Understanding this spectrum is vital for both the obstetrician and neonatologist.

265 Clinically, patients and providers cannot control severity of SGA, but management
266 decisions often dictate gestational age at delivery. Each week gained in gestation during the very
267 preterm period improves outcomes. For example, our data suggests that an infant born at the 3rd
268 percentile WGA at 29 weeks versus 27 weeks gestation could decrease risk of neonatal
269 morbidity and mortality by approximately 40%. Therefore, a higher threshold for delivery is
270 warranted for growth restricted fetuses <29 weeks' gestation, as composite morbidity and
271 mortality is >50% for all neonates with a WGA <10th percentile.

272 The detection of FGR in the 5th to <10th percentile remains low. Future studies are needed
273 to determine the optimal detection and surveillance protocols that can reduce mortality and

274 morbidity (19,24,43). While we present data on singleton births, twin gestations are
275 disproportionally responsible for the burden of morbidity in a preterm population (44–47).
276 Studies are needed to elucidate how the severity of SGA impacts outcomes by twin status and
277 birth order in a contemporary, very preterm population.

278 Major strengths of our study include the prospectively collected data and the large,
279 population based, sample size. This afforded the statistical power to detect differences in rare
280 outcomes, such as neonatal death, and prevent selection bias. The level of detail in this
281 contemporary cohort has not previously been demonstrated and allows for precision in
282 counseling amongst a unique population of very preterm SGA neonates.

283 A neonatal database has limitations, primarily a lack of depth into antenatal management
284 and maternal characteristics. FGR was based on neonatal chart abstraction and therefore
285 misclassification was possible. It is not recorded in the database when FGR was diagnosed, the
286 nomogram used, antenatal surveillance or delivery decisions. Thus, we cannot elucidate what
287 aspect of care is responsible for our observations. Our database also lacks reliable cord pH,
288 which is an important variable to understanding the maternal-fetal interaction and intrauterine
289 milieu at delivery. Lastly, stillbirth is a major adverse outcome related to severe FGR(1,5,43)
290 that our database could not capture. Therefore, we are not reporting the full affliction of FGR.

291 Across decreasing WGA percentiles, neonatal morbidity and mortality increased in this
292 contemporary, population-based cohort, of very preterm infants. Neonates 24 to <29 weeks'
293 gestation demonstrate a continuum of increasing risk with decreasing WGA percentile, whereas
294 neonates 29 to <32 weeks' gestation, have a substantial increase in risk <3rd percentile.
295 Symmetric growth restriction was less common in preterm gestation and when adjusting for

gestational age, was not associated with poorer outcomes.

REFERENCES:

1. Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. Am J Obstet Gynecol. 2012 Oct;207(4):318.e1-318.e6.

2. Gardosi J, Francis A. Adverse pregnancy outcome and association with small for gestational age birthweight by customized and population-based percentiles. Am J Obstet Gynecol. 2009 Jul;201(1):28.e1-28.e8.

3. Monier I, Ancel PY, Ego A, Jarreau PH, Lebeaux C, Kaminski M, et al. Fetal and neonatal outcomes of preterm infants born before 32 weeks of gestation according to antenatal vs postnatal assessments of restricted growth. Am J Obstet Gynecol. 2017 May 1;216(5):516.e1-516.e10.

4. Chauhan S, Beydoun H, Chang E, Sandlin A, Dahlke J, Igwe E, et al. Prenatal Detection of Fetal Growth Restriction in Newborns Classified as Small for Gestational Age: Correlates and Risk of Neonatal Morbidity. Am J Perinatol. 2013 Apr 16;31(03):187–94.

5. Moraitis AA, Wood AM, Fleming M, Smith GCS. Birth Weight Percentile and the Risk of Term Perinatal Death: Obstet Gynecol. 2014 Aug;124(2, PART 1):274–83.

6. Mendez-Figueroa H, Truong VTT, Pedroza C, Chauhan SP. Morbidity and Mortality in Small-for-Gestational-Age Infants: A Secondary Analysis of Nine MFMU Network Studies. Am J Perinatol. 2017 Mar;34(04):323–32.

7. Hei M, Lee S, Shah P, Jain A, for the Canadian Neonatal Network. Outcomes for Symmetrical and Asymmetrical Small for Gestational Age Preterm Infants in Canadian Tertiary NICUs. Am J Perinatol. 2014 Dec 23;32(08):725–32.

8. McEwen EC, Guthridge SL, He VYF, McKenzie JW, Boulton TJ, Smith R. What birthweight percentile is associated with optimal perinatal mortality and childhood education outcomes? Am J Obstet Gynecol. 2018 Feb;218(2):S712–24.

9. Mlynarczyk M, Chauhan SP, Baydoun HA, Wilkes CM, Earhart KR, Zhao Y, et al. The clinical significance of an estimated fetal weight below the 10th percentile: a comparison of outcomes of <5th vs 5th-9th percentile. Am J Obstet Gynecol. 2017;217(2):198.e1-198.e11.

10. Sharma D, Farahbakhsh N, Shastri S, Sharma P. Intrauterine growth restriction – part 2. J Matern Fetal Neonatal Med. 2016 Dec 16;29(24):4037–48.

11. Sharma D, Shastri S, Farahbakhsh N, Sharma P. Intrauterine growth restriction – part 1. J Matern Fetal Neonatal Med. 2016 Dec 16;29(24):3977–87.

12. Lees CC, Marlow N, van Wassenaer-Leemhuis A, Arabin B, Bilardo CM, Brezinka C, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): a randomised trial. The Lancet. 2015 May;385(9983):2162–72.

13. Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, et al. Optimizing the definition of intrauterine growth restriction: the multicenter prospective PORTO Study. Am J Obstet Gynecol. 2013 Apr;208(4):290.e1-290.e6.

14. Murray E, Fernandes M, Fazel M, Kennedy S, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. BJOG Int J Obstet Gynaecol. 2015;122(8):1062–72.

15. Barker DJP. Adult Consequences of Fetal Growth Restriction. Clin Obstet Gynecol. 2006 Jun;49(2):270–83.

16. Martins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: Diagnosis and management of fetal growth restriction. Am J Obstet Gynecol. 2020 Oct;223(4):B2–17.

17. ACOG Practice Bulletin No. 204: Fetal Growth Restriction. Obstet Gynecol. 2019 Feb;133(2):e97.

18. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol. 2005;25(3):258–64.

19. Verlijsdonk JW, Winkens B, Boers K, Scherjon S, Roumen F. Suspected versus non-suspected small-for-gestational age fetuses at term: perinatal outcomes. J Matern Fetal Neonatal Med. 2012 Jul 1;25(7):938–43.

20. Blue NR, Beddow ME, Savabi M, Katukuri VR, Mozurkewich EL, Chao CR. A Comparison of Methods for the Diagnosis of Fetal Growth Restriction Between the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists: Obstet Gynecol. 2018 May;131(5):835–41.

21. Ludvigsson JF, Lu D, Hammarström L, Cnattingius S, Fang F. Small for gestational age and risk of childhood mortality: A Swedish population study. Smith GC, editor. PLOS Med. 2018 Dec 18;15(12):e1002717.

22. Fratelli N, Valcamonico A, Prefumo F, Pagani G, Guarneri T, Frusca T. Effects of antenatal recognition and follow-up on perinatal outcomes in small-for-gestational age infants delivered after 36 weeks. Acta Obstet Gynecol Scand. 2013;92(2):223–9.

23. Mattioli KP, Sanderson M, Chauhan SP. Inadequate identification of small-for-gestational-age fetuses at an urban teaching hospital. Int J Gynecol Obstet. 2010;109(2):140–3.

24. Roeckner JT, Pressman K, Odibo L, Duncan JR, Odibo AO. Outcome-based comparison of SMFM and ISUOG definitions of fetal growth restriction. Ultrasound Obstet Gynecol. 2021;57(6):925–30.

25. Bocca-Tjeertes I, Bos A, Kerstjens J, de Winter A, Reijneveld S. Symmetrical and Asymmetrical Growth Restriction in Preterm-Born Children. PEDIATRICS. 2014 Mar 1;133(3):e650–6.

26. Gould JB. The Role of Regional Collaboratives: The California Perinatal Quality Care Collaborative Model. Clin Perinatol. 2010 Mar;37(1):71–86.

27. CPQCC. Is That Baby Eligible Final? Birth Year 2022, What eligibility means for NICU, HRIF, CPeTS and VON [Internet]. [cited 2022 Jun 22]. Available from: https://www.cpqcc.org/sites/default/files/Is%20That%20Baby%20Eligible%20Final_1.pdf

28. Talge NM, Mudd LM, Sikorskii A, Basso O. United States Birth Weight Reference Corrected For Implausible Gestational Age Estimates. Pediatrics. 2014 May 1;133(5):844–53.

29. Melamed N, Pittini A, Barrett J, Shah J, Yoon EW, Lemyre B, et al. Antenatal Corticosteroids and Outcomes of Small-for-Gestational-Age Neonates: Obstet Gynecol. 2016 Nov;128(5):1001–8.

30. von Dadelszen P, Magee LA, Taylor EL, Muir JC, Stewart SD, Sherman P, et al. Maternal hypertension and neonatal outcome among small for gestational age infants. Obstet Gynecol. 2005 Aug;106(2):335–9.

31. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth Weight in Relation to Morbidity and Mortality among Newborn Infants. N Engl J Med. 1999 Apr 22;340(16):1234–8.

32. Boghossian NS, Geraci M, Edwards EM, Horbar JD. Morbidity and Mortality in Small for Gestational Age Infants at 22 to 29 Weeks' Gestation. Pediatrics. 2018 Feb;141(2):e20172533.

33. Lee HC, Liu J, Profit J, Hintz SR, Gould JB. Survival Without Major Morbidity Among Very Low Birth Weight Infants in California. Pediatrics. 2020 Jul 1;146(1):e20193865.

34. Manuck TA, Rice MM, Bailit JL, Grobman WA, Reddy UM, Wapner RJ, et al. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. Am J Obstet Gynecol. 2016 Jul;215(1):103.e1-103.e14.

35. Baschat AA, Cosmi E, Bilardo CM, Wolf H, Berg C, Rigano S, et al. Predictors of Neonatal Outcome in Early- Onset Placental Dysfunction: Obstet Gynecol. 2007 Feb;109(2, Part 1):253–61.

36. Ananth CV, Vintzileos AM. Distinguishing pathological from constitutional small for gestational age births in population-based studies. Early Hum Dev. 2009 Oct;85(10):653–8.

37. Zhang-Rutledge K, Mack LM, Mastrobattista JM, Gandhi M. Significance and Outcomes of Fetal Growth Restriction Below the 5th Percentile Compared to the 5th to 10th Percentiles on Midgestation Growth Ultrasonography. J Ultrasound Med Off J Am Inst Ultrasound Med. 2018 Sep;37(9):2243–9.

38. Monier I, Blondel B, Ego A, Kaminiski M, Goffinet F, Zeitlin J. Poor effectiveness of antenatal detection of fetal growth restriction and consequences for obstetric management and neonatal outcomes: a French national study. BJOG Int J Obstet Gynaecol. 2015;122(4):518–27.

39. Hiersch L, Melamed N. Fetal growth velocity and body proportion in the assessment of growth. Am J Obstet Gynecol. 2018 Feb;218(2):S700-S711.e1.

40. Madden JV, Flatley CJ, Kumar S. Term small-for-gestational-age infants from low-risk women are at significantly greater risk of adverse neonatal outcomes. Am J Obstet Gynecol. 2018 May;218(5):525.e1-525.e9.

41. Savchev S, Figueras F, Cruz-Martinez R, Illa M, Botet F, Gratacos E. Estimated weight centile as a predictor of perinatal outcome in small-for-gestational-age pregnancies with normal fetal and maternal Doppler indices. Ultrasound Obstet Gynecol. 2012 Mar;39(3):299–303.

42. Lees CC, Romero R, Stampalija T, Dall'Asta A, DeVore GR, Prefumo F, et al. The diagnosis and management of suspected fetal growth restriction: an evidence-based approach. Am J Obstet Gynecol. 2022 Mar;226(3):366–78.

43. Lees C, Stampalija T, Hecher K. Diagnosis and management of fetal growth restriction: the ISUOG guideline and comparison with the SMFM guideline. Ultrasound Obstet Gynecol. 2021;57(6):884–7.

44. Walker AR, Waites BT, Caughey AB. Twins versus singleton pregnancies: outcomes in small for gestational age late preterm deliveries. J Matern Fetal Neonatal Med. 2020 Mar 18;33(6):895–900.

45. Goldenberg RL, Culhane JF, Iams JD, Romero R. Preterm Birth 1 Epidemiology and causes of preterm birth. Lancet. 2008 Jan;371(5):75–84.

46. Fumagalli M, Schiavolin P, Bassi L, Groppo M, Uccella S, De Carli A, et al. The Impact of Twin Birth on Early Neonatal Outcomes. Am J Perinatol. 2015 Jul 27;33(01):063–70.

47. Multifetal Gestations: Twin, Triplet, and Higher-Order Multifetal Pregnancies: ACOG Practice Bulletin, Number 231. Obstet Gynecol. 2021;137(6):e145–62.

434 **FIGURE LEGEND:**

435

436 **FIGURE 1:** Incidence of major neonatal morbidity or mortality by weight for gestational age

437 percentile among 4,771 early preterm (<32 weeks' gestation) infants after stratifying by gestational

438 age

439

440

441

442

443

444

445

446

447

448

449

450

451

452

453

454

455

456

457

Table 1. Descriptive characteristics by degree of small for gestational age, California singletons born $24^{0/7}$-$31^{6/7}$ weeks' gestation below 15th percentile of weight for gestational age, 2008-2018.

Characteristic	<3rd percentile WGA (n = 906)	3rd to <5th percentile WGA (n = 627)	5th to <10th percentile WGA (n = 1551)	10th to <15th percentile WGA (n = 1605)
Maternal Characteristics				
Maternal age, y	30 (6.4)	30 (6.6)	30 (6.2)	30 (6.6)
Diabetes mellitus (preexisting or gestational)	88 (8)	86 (14)	202 (13)	200 (12)
Hypertensive disorder (chronic, gestational, pre-eclampsia)	549 (61)	433 (69)	1111 (72)	1174 (73)
Prior cesarean	155 (17)	82 (13)	223 (14)	243 (15)
Fetal Characteristics				
Antenatal diagnosis with FGR	745 (82)	441 (70)	847 (55)	599 (37)
Gestational age, weeks	28 (2.3)	29 (2.1)	29 (2.2)	29 (2.0)
-31 weeks	186 (21)	180 (29)	375 (24)	423 (26)
-30 weeks	153 (17)	103 (16)	309 (20)	343 (21)
-29 weeks	112 (12)	81 (13)	200 (13)	238 (15)
-28 weeks	106 (12)	70 (11)	208 (13)	182 (11)
-27 weeks	112 (12)	59 (9)	158 (10)	152 (9)
-26 weeks	82 (9)	56 (9)	123 (8)	111 (7)
-25 weeks	92 (10)	44 (7)	98 (6)	88 (5)
-24 weeks	63 (7)	34 (5)	80 (5)	68 (4)
Male fetal sex	566 (62)	366 (58)	847 (55)	863 (54)
Race				
-Other	23 (3)	9 (1)	50 (3)	38 (2)
-Native American	3 (0.3)	2 (0.3)	2 (0.1)	10 (0.6)
-Asian/Pacific Islander	125 (14)	99 (16)	216 (14)	199 (13)
-Non-Hispanic White	218 (24)	142 (23)	339 (22)	316 (23)
-Hispanic	395 (44)	269 (44)	681 (45)	727 (46)
-Non-Hispanic Black	130 (15)	89 (15)	236 (15)	239 (15)
-Unknown	12 (1)	17 (3)	27 (2)	31 (2)
Antenatal steroid administration	812 (90)	565 (90)	1408 (91)	1460 (91)
Antenatal magnesium[a]	374 (63)	262 (66)	671 (68)	719 (71)
Delivery Characteristics				
Cesarean delivery[b]	870 (96)	595 (95)	1438 (93)	1445 (90)
-Indication: fetal distress	500 (57)	301 (51)	653 (45)	576 (40)
-Indication: hypertension[c]	391 (45)	325 (55)	875 (61)	925 (64)
-Indication: placental problem	117 (13)	68 (11)	157 (11)	166 (11)
-Indication: elective	57 (7)	41 (7)	85 (6)	120 (8)
-Indication: failure to progress	10 (1)	4 (1)	20 (1)	21 (2)
-Indication: malpresentation				
-Indication: other	202 (23)	137 (23)	312 (22)	334 (23)
	236 (27)	129 (22)	254 (17)	287 (20)
Delivery location: outborn	38 (4)	35 (6)	105 (7)	84 (5)

Delivery room intubation	458 (51)	269 (43)	609 (39)	609 (38)
Neonatal Characteristics				
Symmetric growth restriction	253 (29)	151 (25)	450 (30)	470 (30)
Composite of major neonatal morbidity or mortality	475 (56)	282 (46)	640 (42)	557 (35)
Chronic lung disease	307 (44)	196 (35)	429 (31)	385 (26)
Severe IVH	41 (5)	31 (5)	54 (4)	62 (4)
Late bacterial infection	61 (8)	39 (7)	101 (7)	90 (6)
Necrotizing enterocolitis[d]	55 (7)	43 (7)	80 (5)	59 (4)
Infant death	231 (26)	85 (14)	145 (9)	105 (7)
Severe ROP or surgery for ROP	97 (14)	44 (8)	101 (8)	83 (6)
Cystic periventricular leukomalacia	12 (1)	16 (3)	29 (2)	25 (2)
Apgar <4 at 5 min	110 (12)	42 (7)	94 (6)	73 (5)
Birth defect diagnosed post-delivery	90 (10)	48 (8)	101 (7)	78 (5)
Respiratory distress syndrome	627 (74)	420 (69)	1086 (71)	1138 (71)
Delivery room death	60 (7)	13 (2)	18 (1)	10 (0)

Cells show n (%) for categorical variables and mean (SD) for continuous variables
Abbreviations: WGA, Weight for Gestational Age; ROP Retinopathy of Prematurity, IVH Intraventricular Hemorrhage
Composite of major neonatal morbidity or mortality: infant death during birth hospitalization or within 1 year of birth after continuous hospitalization, chronic lung disease, severe intraventricular hemorrhage, infection, necrotizing enterocolitis, severe retinopathy of prematurity or retinopathy of prematurity surgery and cystic periventricular leukomalacia
[a] Added in 2013
[b] Multiple indications possible
[c] Added in 2004
[d] Revised 2009

Table 2. Associations between weight for gestational age z-score and outcomes at birth among early preterm infants born <15th percentile, California (N = 4,689).

Outcome	Incidence n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
Composite major morbidity or mortality	2055 (44)	0.64 (0.60, 0.68)	0.64 (0.60, 0.68)	0.73 (0.68, 0.77)
Cesarean birth	4348 (93)	0.95 (0.93,0.97)	0.96 (0.94, 0.98)	0.96 (0.94, 0.97)
Delivery room endotracheal tube ventilation	1945 (41)	0.79 (0.73, 0.85)	0.76 (0.7, 0.82)	0.85 (0.79, 0.93)
Apgar score at 5 minutes <4	319 (7)	0.4 (0.33, 0.49)	0.38 (0.31, 0.46)	0.45 (0.37, 0.55)
Neonatal delivery room death	101 (2)	0.15 (0.11, 0.2)	0.16 (0.12, 0.22)	0.17 (0.12, 0.24)
Infant death	566 (12)	0.31 (0.27, 0.35)	0.31 (0.27, 0.35)	0.37 (0.32, 0.43)

Abbreviations: RR, relative risk; CI, confidence interval

Composite of major neonatal morbidity or mortality: infant death during birth hospitalization or within 1 year of birth after continuous hospitalization, chronic lung disease, severe intraventricular hemorrhage, infection, necrotizing enterocolitis, severe retinopathy of prematurity or retinopathy of prematurity surgery and cystic periventricular leukomalacia

[a] Adjusted for maternal diabetes, maternal hypertension, antenatal steroid use, and fetal growth restriction diagnosis.

[b] Additionally adjusted for gestational age at birth.

Infant death: all deaths from delivery room to 1 year

Table 3. Associations between weight for gestational age z-score and outcomes at birth among early preterm infants <15th percentile, stratified by the antenatal diagnosis of fetal growth restriction versus no diagnosis, California (N = 4,689).

Diagnosis of fetal growth restriction (n =2585)				
Outcome	**Incidence n (%)**	**Crude RR (95% CI)**	**Adjusted RR (95% CI)[a]**	**Adjusted RR (95% CI)[b]**
Composite major morbidity or mortality	1168 (45)	0.63 (0.59, 0.68)	0.64 (0.59, 0.69)	0.72 (0.67, 0.78)
Cesarean birth	2487 (96)	0.98 (0.96, 1.0)	0.97 (0.95, 0.99)	0.97 (0.95, 0.99)
Delivery room endotracheal tube ventilation	1039 (40)	0.73 (0.67, 0.81)	0.75 (0.68, 0.82)	0.84 (0.76, 0.93)
Apgar score <4	163 (6)	0.35 (0.26, 0.46)	0.35 (0.26, 0.46)	0.45 (0.34, 0.59)
Neonatal delivery room death	51 (2)	0.11 (0.07, 0.17)	0.12 (0.07, 0.18)	0.15 (0.09, 0.24)
Infant death	338 (13)	0.27 (0.23, 0.32)	0.28 (0.23, 0.33)	0.34 (0.28, 0.4)
No diagnosis of fetal growth restriction (n=2104)				
Outcome	**Incidence n (%)**	**Crude RR (95% CI)**	**Adjusted RR (95% CI)[a]**	**Adjusted RR (95% CI)[b]**
Composite major morbidity or mortality	887 (42)	0.59 (0.52, 0.66)	0.61 (0.55, 0.69)	0.73 (0.65, 0.82)
Cesarean birth	1861 (88)	0.98 (0.91, 1.03)	0.95 (0.9, 0.99)	0.94 (0.9, 0.99)
Delivery room endotracheal tube ventilation	906 (43)	0.75 (0.65, 0.86)	0.78 (0.67, 0.9)	0.91 (0.79, 1.04)
Apgar score <4	156 (7)	0.31 (0.23, 0.42)	0.4 (0.3, 0.53)	0.45 (0.34, 0.61)
Neonatal delivery room death	50 (2)	0.11 (0.08, 0.15)	0.21 (0.14, 0.33)	0.19 (0.11, 0.31)
Infant death	228 (11)	0.32 (0.25, 0.4)	0.38 (0.3, 0.48)	0.47 (0.37, 0.61)

Abbreviations: RR, relative risk; CI, confidence interval
Composite of major neonatal morbidity or mortality: infant death during birth hospitalization or within 1 year of birth after continuous hospitalization, chronic lung disease, severe intraventricular hemorrhage, infection, necrotizing enterocolitis, severe retinopathy of prematurity or retinopathy of prematurity surgery and cystic periventricular leukomalacia
[a] Adjusted for maternal diabetes, maternal hypertension, antenatal steroid use, and fetal growth restriction diagnosis.
[b] Additionally adjusted for gestational age at birth.
Infant death: all deaths from delivery room to 1 year

540 **Table 4.** Association between symmetric versus asymmetric growth restriction and outcomes at birth
541 among early preterm infants born <15th percentile WGA, California (N = 4,581, Symmetric growth
542 restriction N=1324, Asymmetric growth restriction N=3257).
543

	Incidence n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
Composite major morbidity or mortality				
Symmetric growth restriction	1003 (76)	2.56 (2.41, 2.73)	2.56 (2.41, 2.72)	1.01 (0.91, 1.11)
Asymmetric growth restriction	962 (30)	Reference	Reference	Reference
Cesarean birth				
Symmetric growth restriction	1213 (92)	0.97 (0.96, 0.99)	0.89 (0.96, 1.0)	0.95 (0.93, 0.97)
Asymmetric growth restriction	3062 (94)	Reference	Reference	Reference
Delivery room endotracheal tube ventilation				
Symmetric growth restriction	922 (70)	2.31 (2.17, 2.46)	2.3 (2.16, 2.45)	0.96 (0.87, 1.06)
Asymmetric growth restriction	981 (30)	Reference	Reference	Reference
Apgar score <4				
Symmetric growth restriction	165 (13)	4.56 (3.55, 5.85)	4.58 (3.57, 5.88)	0.95 (0.65, 1.4)
Asymmetric growth restriction	89 (3)	Reference	Reference	Reference
Neonatal delivery room death				
Symmetric growth restriction	39 (3)	23.98 (8.59, 66.98)	24.64 (8.89, 68.26)	2.08 (0.54, 8.07)
Asymmetric growth restriction	4 (0)	Reference	Reference	Reference
Infant death				
Symmetric growth restriction	344 (26)	5.72 (4.77, 6.86)	5.75 (4.8, 6.89)	1.1 (0.84, 1.45)
Asymmetric growth restriction	148 (5)	Reference	Reference	Reference

544
545 Abbreviations: RR, relative risk; CI, confidence interval
546 Composite of major neonatal morbidity or mortality: infant death during birth hospitalization or
547 within 1 year of birth after continuous hospitalization, chronic lung disease, severe intraventricular
548 hemorrhage, infection, necrotizing enterocolitis, severe retinopathy of prematurity or retinopathy of
549 prematurity surgery and cystic periventricular leukomalacia
550

[a] Adjusted for maternal diabetes, maternal hypertension, antenatal steroid use, and fetal growth restriction diagnosis.
[b] Additionally adjusted for gestational age at birth.
Infant death: all deaths from delivery room to 1 year

SUPPLEMENTARY INFORMATION:

FIGURE: Cohort selection
File type: pdf

ADDITIONAL INFORMATION:

Conflict of interest statement: The authors report no conflict of interest.

Ethics approval and consent to participate: This study was approved by the California Committee for the Protection of Human Subjects (IRB #12-06-0393) and the Stanford University Institutional Review Board (IRB #14746). The Study was performed in accordance with the Declaration of Helsinki.

Funding: No funding was received for this study.

Author Contributions: KM contributed to the concept of the work, drafting and revising the manuscript. SL substantially contributed to the design of the study, analysis and co-wrote the manuscript. LS contributed to design, data analysis and revising of the manuscript. KB, MD and HL substantially contributed to the conception of the work, drafting and revising the manuscript and gave approval of this version.

Acknowledgements: We appreciate the approval from the CPQCC to conduct this investigation.

576

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Figure2.pdf