14-348R1
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Birth weight percentile and the risk of term perinatal death not due to congenital anomaly

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Supported by the NIHR Cambridge Comprehensive Biomedical Research Centre.

Shortened running title: Birth weight percentile and perinatal death at term

Word count: Text: 2,806 words.

Précis

One in 3 antepartum stillbirths and 1 in 6 delivery-related perinatal deaths at term could be related to birth weight percentile outside the range 21st to 97th percentile.

Abstract

Objective To estimate the association between birth weight percentile and the risk of perinatal death at term in relation to the cause of death.

Methods. We performed a retrospective cohort study of all term singleton births in delivery units in Scotland between 1992 and 2008 (n=784,576), excluding perinatal deaths ascribed to congenital anomaly.

Results There were 1,700 perinatal deaths in the cohort which were not due to congenital anomaly (21.7 per 10,000 women at term). We observed a reversed J-shaped association between birth weight percentile and the risk of antepartum stillbirth in all women, but the associations significantly differed (P<.001) according to smoking status. The highest risk (adjusted odds ratio referent to 21st–80th percentile, 95% confidence interval) among nonsmokers was for birth weight ≤3rd percentile (10.5, 8.2-13.3), but there were also positive associations for birth weight percentiles 4th-10th (3.8, 3.0–4.8), 11th-20th (1.9, 1.5–2.4) and 98th-100th (1.8, 1.3–2.4). Among smokers, the associations with being small were weaker and the associations with being large were stronger. We also observed a reversed J-shaped association between birth weight percentile and the risk of delivery-related perinatal death (i.e. intrapartum stillbirth or neonatal death), but there was no interaction with smoking. The highest risk was for birth weight >97th percentile (2.3, 1.6–3.3), but there were also associations with ≤3rd percentile (2.1, 1.4–3.1), 4th-10th (1.8, 1.4–2.4) and 11th-20th (1.5, 1.2–2.0). Analysis of the attributable fraction indicated that approximately 1 in 3 antepartum stillbirths and 1 in 6 delivery-related deaths at term could be related to birth weight percentile outside the range 21st to 97th percentile.

Conclusions Effective detection of variation in fetal size at term has potential as a screening test for the risk of perinatal death.

Level of evidence: II

Introduction

Approximately 5 to 6 per 1,000 pregnancies end in stillbirth in the United States and the UK(1,2), with some of the variability due to different definitions. Multiple maternal and obstetric characteristics are associated with the risk of stillbirth but, collectively, they explain less than 20% of the variance in the incidence of stillbirth(3). Hence, making significant impact into overall rates of stillbirth will likely require better methods of screening and intervention in the general population. Approximately one third of all stillbirths and neonatal deaths occur at term(2). Previous studies have shown that growth restricted fetuses are at increased risk of stillbirth(4,5). One potential approach to population based screening for stillbirth would be to assess fetal size prior to term. Women who are found to have growth restricted fetuses could then be offered increased surveillance, with the ultimate intervention of earlier delivery for those thought to be high risk. However, it has been argued that being growth restricted is not a major determinant of the risk of perinatal morbidity and mortality at term(6). Moreover, studies that have described associations between SGA and the risk of perinatal death at term have generally lacked detailed information on the cause of death. The aim of the present study was to estimate the relationship between birth weight percentile at term and the risk of perinatal death. We excluded deaths related to fetal anomaly as these are unlikely to be preventable in the majority of cases.

Materials and Methods

The work was approved by the Privacy Advisory Committee of the Information Services Division of NHS Scotland. We linked data from the Scottish Morbidity Record 02 (SMR02), which collects information on clinical and demographic characteristics and outcomes of all patients discharged from Scottish maternity hospitals, to the Scottish Stillbirth and Infant Death Survey (SSBIDS), a national registry which routinely classifies all perinatal deaths in Scotland and is described elsewhere(7).

We conducted a population based, retrospective cohort study composed of all singleton term pregnancies between 1992 and 2008. The exclusion criteria were multiple pregnancy, perinatal death ascribed to congenital abnormality or Rh isoimmunization, delivery outside the range 37 to 43 weeks of gestation, birth weight less than 500 grams, and records with missing values for certain maternal variables (see below).

The prespecified main outcomes were: (i) antepartum stillbirth, both all causes and sub-divided by cause (see below); and, (ii) delivery related perinatal death (i.e. intrapartum stillbirth or neonatal death), both all causes and subdivided by whether the death was ascribed to intrapartum anoxia. The cause of stillbirth was classified using a modification of the Wigglesworth classification(8) which is a hierarchical system and is described elsewhere(7). Deaths were classified according to direct obstetric causes (in order): congenital abnormality, isoimmunization, toxemia (pre-eclampsia/eclampsia), hemorrhage (antepartum), mechanical, maternal, miscellaneous, and unexplained. Intrauterine growth restriction is not regarded as a cause of death in this classification system. All deaths were classified by a single, medically qualified individual with access to autopsy results where available. The definition of delivery related perinatal death has been described in detail elsewhere(7) and it includes intrapartum stillbirth and neonatal death (i.e. death of a liveborn

infant in the first 4 weeks). The definition of anoxia employed is broad and includes hypoxia, acidosis, and asphyxia.

The main exposure variable in our study was birth weight percentile. Sex and gestational age specific percentiles of birth weight were calculated within the cohort and infants were categorized into the following groups: ≤3rd percentile, 4th to 10th, 11th to 20th, 21st to 80th (referent), 81st to 90th, 91st to 97th and 98th to 100th respectively, as previously described(9). The gestational age at birth was defined as the completed weeks of gestation based on the estimated date of delivery in each woman's clinical record and has been confirmed by ultrasound in the first half of the pregnancy in more than 95% of the women in United Kingdom since the early 1990s(10). Maternal age was defined as the age of the mother at the time of delivery. Socio-economic status was estimated based on the postcode of residence, using Carstairs socio-economic deprivation categories(11). Finally smoking status (current, past, never) was defined by self reported at the first antenatal visit.

Continuous variables were compared using the Kruskal-Wallis test and categorical data were compared using the χ^2 test. All P values are 2-sided, and P<.05 was considered to indicate statistical significance. However, the primary exposure (birth weight percentile) had 6 categories and addressed two main outomes (antepartum stillbirth and delivery-related perinatal death). Hence, particular emphasis is placed on results where P<0.004 (Bonferroni corrected for 12 comparisons), although this is extremely conservative given that the groups of 6 categories are not independent. The risk of stillbirth was modeled using univariate and multivariate logistic regression. We assessed interactions using the likelihood-ratio test(12). Given that 5 tests of interaction were performed, the threshold for significance for interaction terms was reduced to P<.01. Multiple imputation was used to impute missing values for height, as missing values were likely to be missing at random(13). Individuals with missing values in variables with <1% of missing records were excluded for simplicity. Individuals with missing smoking status were also excluded, since it was inappropriate to impute smoking

status due to an interaction with both birth weight percentile and stillbirth. Five imputations were created using a set of appropriate imputation models constructed from all the covariates (including interactions as appropriate) and outcome variables. We estimated attributable fractions using the method by Greenland and Drescher(14). We calculated attributable fractions for those birth weight categories with significant positive associations(15). Analyses were performed at the level of individual pregnancies. As many women had more than one birth in the study period, the assumption of independence of observations was violated. However, we have previously found that correction of standard errors for clustering was without material effect in other analyses of this dataset(7). All statistical analyses were performed using Stata version 12.1 (StataCorp LP, College Station, Texas).

Results

The linked SMR02 and SSBIDS databases contained 937,739 records of singleton births between 1992 and 2008. We excluded 57,760 records where delivery was before 37 weeks (6.2%). Out of the remaining 879,979 records we excluded 4,700 where delivery was beyond 43 weeks (0.5%), 5,001 with birth weight less than 500g or missing (0.6%), 7,664 with missing parity (0.9%), 3,645 with missing maternal age (0.4%), 3,364 with missing deprivation category (0.4%), 3,836 with missing mode of delivery (0.4%), 3,674 with missing infant sex (0.4%), 87,061 with missing smoking status (9.9%), and 1,539 where perinatal death was ascribed to congenital abnormality or Rh isoimmunization (0.2%). In total 95,403 records were excluded for one or more missing values (10.8%) leaving a study cohort of 784,576. There were 1,157 antepartum stillbirths (0.15%). Out of these, 31 (2.7%) were ascribed to pre-eclampsia or eclampsia, 111 (9.6%) to antepartum hemorrhage, 29 (2.5%) to a mechanical cause, 44 (3.8%) to maternal disease (principally diabetes mellitus), 13 (1.1%) to miscellaneous causes and 929 (80.3%) were unexplained. There were 162 intrapartum stillbirths (0.02%) and 381 neonatal deaths (0.05%).

The maternal characteristics of the cohort are tabulated by outcome (Table 1). Women with pregnancies resulting in antepartum stillbirth were older, more likely to smoke, and more likely to be nulliparous or in their third or subsequent pregnancy. They also delivered earlier and the birth weight of their infants was significantly smaller than women whose infants survived. Women with pregnancies resulting in delivery related perinatal death were more likely to be nulliparous and to undergo emergency cesarean delivery.

The overall association between birth weight percentile and risk of antepartum stillbirth and delivery related perinatal death had a reverse J-shaped distribution (Figure 1). Very small infants (≤3rd percentile) had the highest relative risk of antepartum stillbirth (Table 2) and the absolute risk of stillbirth in this group was approximately 1 in 100. The odds ratio declined

with increasing birth weight but remained significantly elevated for the infants between the 11th to 20th birth weight percentile. The trends were similar for stillbirths whether the death was attributed to hemorrhage, toxemia or was unexplained (Figure 2). The risk of stillbirth was also increased where the birth weight percentile was very large for gestational age (98th to 100th percentile). This was particularly marked for stillbirths where the death was attributed to maternal causes (unadjusted odds ratio [OR] 19.0, 95% confidence interval [CI] 9.2–32.3), and this was explained by increased losses attributed to maternal diabetes. However, it was also significantly elevated for apparently unexplained stillbirth (OR 1.9, 95% CI 1.3–2.6). Deaths ascribed to mechanical or miscellaneous causes were not associated with extreme birth weight percentile (data not shown), although the numbers were too small to exclude clinically important associations. There were also independent and significant associations between antepartum stillbirth and maternal age of ≥35 years, nulliparity and parity greater than 2 (Table 2).

The risk of antepartum stillbirth was higher among mothers who smoked compared to nonsmokers. Moreover, there was a significant (P<.001) interaction between smoking and birth weight percentile in relation to the risk of antepartum stillbirth (there were no other statistically significant interactions). Hence, we stratified the analysis of birth weight and the risk of antepartum stillbirth by maternal smoking status (Table 2). The adjusted odds ratio for stillbirth for low birth weight percentile (≤3rd and 4th–10th) was almost twice as high in women who were not current smokers compared to smokers. Conversely, a high birth weight percentile (98th–100th percentile) was more strongly associated with stillbirth among smokers than nonsmokers. However, the infants of mothers who smoked were more likely to be small for gestational age than the infants of nonsmokers or ex-smokers. Hence, the attributable fractions associated with extremely low birth weight percentiles (1st–3rd) were higher for smokers compared to nonsmokers or ex- smokers (17.2% and 11.5% respectively). The attributable fraction of the 4th–10th, 11th–20th, and 98th–100th birth weight percentile

categories was 10.4%, 5.0%, and 2.8% respectively for smokers and 9.3%, 6.2% and 3.5% respectively for non-/ex- smokers. The sum of the attributable fractions of birth weight categories significantly associated with antepartum stillbirth was 31.6% (95% CI 27.7–35.3%; 33.5% for smokers and 30.5% for non-/ex- smokers).

There was also a reversed J shaped relationship between birth weight percentile and the risk of delivery related perinatal death (Figure 3, Table 3). There were no statistically significant interactions between birth weight percentile and any maternal characteristic (including smoking: P=.17) in relation to the risk of delivery-related perinatal death. Infants with a birth weight percentile less than the 20^{th} percentile had an increased risk of delivery related perinatal death. When analyzed by cause, the association between 1^{st} to 20^{th} birth weight percentile and delivery related perinatal death was significant both for deaths attributed to intrapartum anoxia and deaths not attributed to intrapartum anoxia. The risk was also higher for infants between the 98^{th} and 100^{th} percentile, but this association was significant only for deaths attributed to intrapartum anoxia. The absolute and relative risks were similar for infants belonging to the bottom and top 3% (Figure 1, Table 3). The overall attributable fraction for delivery related perinatal deaths was 16.7% (95% CI 11.2–23.2%). Other factors which were found to be significantly associated with delivery related perinatal deaths were nulliparity and maternal age ≥40 years (both associated with deaths due to intrapartum anoxia, Table 3).

Discussion

The main finding of the current analysis is that approximately 1 in 3 antepartum stillbirths and 1 in 6 delivery-related deaths at term could be attributed to the increased risk of loss among infants with a birth weight percentile outside the range 20th to 97th. There was evidence of a reverse J-shaped association between birth weight percentile and the risk of perinatal death, which is consistent with previous studies(16). As our study was focused on term perinatal death it is unlikely that the interval between the time of intrauterine fetal death and the time of delivery would be sufficiently prolonged to bias our analysis of stillbirth risk. Moreover, we also saw the same pattern of association with delivery-related death (i.e. intrapartum stillbirth and neonatal death) where post mortem changes in birth weight caused by maceration would have no potential to influence the results. Our findings underline the importance of identifying fetal growth restriction at term, as prenatal identification of abnormal growth could inform interventions which might mitigate the increased risk of perinatal death. They also indicate that further research would be justified in order to evaluate the routine assessment of fetal size in an unselected population as a screening test which could be coupled with interventions to reduce the risk of perinatal death at term.

We found a complex pattern of association between birth weight percentile, maternal smoking and the risk of antepartum stillbirth. Overall, we found that the risk of term antepartum stillbirth was increased by 60% among mothers who smoked. However, we also found that the relative risk of antepartum stillbirth associated with being SGA was lower among women who were current smokers than among women who were not. We interpret these findings as indicating that SGA caused by maternal smoking increases the risk of antepartum stillbirth. However, among the population of SGA infants, the risk of antepartum stillbirth was greater among the infants of non-smoking mothers, which is in keeping with a previous study(17). We speculate that a given degree of smallness is more strongly

associated with antepartum stillbirth in nonsmokers because small size due to other etiologies is a greater risk factor for stillbirth than small size caused by smoking.

The strength of our study is the large, routinely collected database that covers a whole country over a period of 17 years. However, approximately 10% of the records were excluded because of missing values in any of the covariates, mainly smoking status. This rate of missing values is similar to other high quality national pregnancy registries. For example, a recent study(18) using data from the Swedish Medical Birth Registry, which is internationally highly regarded, reported a 6.4% rate of missing data for smoking. The marginal advantage of the lower rate of smoking non-ascertainment should be set against the fact that the Swedish registry has much less information on the timing and cause of perinatal death.

A Cochrane review evaluated the effect of routine ultrasound at or after 24 weeks gestational age(19) and failed to demonstrate any improvement in outcome, including perinatal mortality. However, a detailed systematic review of the evidence around the diagnostic effectiveness of routine ultrasound to detect growth restricted fetuses by the UK National Institute for Clinical Excellence drew the following conclusion: "poor fetal growth is undoubtedly a cause of serious perinatal mortality and morbidity…. unfortunately, the methods by which the condition can be identified antenatally are poorly developed or not tested by rigorous methodology"(20). A more recent review by leading US academics also identified a lack of evidence in this area(21). Hence, the trials of screening were designed in the absence of high quality information on the diagnostic effectiveness of the screening test. Moreover, none of the nine trials included in the meta-analysis had a standardized intervention, other than revealing the result and, in some trials, recommending further scans. Furthermore, it has been shown that even the meta-analysis is under powered to detect significant effects on perinatal mortality (see Smith(22) for detailed review). Hence, the negative result of the Cochrane review may reflect the methodological weaknesses of the

evidence base and does not justify a view that further evaluation of screening using routine ultrasound is futile.

Despite the fact that intervention at early weeks of gestational age at term carries less risk of neonatal morbidity and mortality than preterm delivery, delivery at 37 weeks is still associated with risks, including neonatal mortality(23) and morbidity(24) plus long term effects on the child such as an increased risk of having special educational needs(9). The population of SGA infants is heterogeneous. Many SGA babies are "healthy small". If screening for stillbirth risk was based wholly on estimates of fetal size, it is likely that many healthy small babies may be delivered at early term, and that this could cause harm. Conversely, the current findings indicate that identifying infants who are growth restricted but whose birth weight percentile is less extremely deviated from the normal range may be useful (e.g. a baby on the 15^{th} percentile may have been genetically determined to be on the 90^{th} percentile and is, in fact, extremely growth restricted). Multiple methods have been described to differentiate between healthy and pathologically growth restricted fetuses, such as assessment of fetal growth velocity(25), analysis of ratios of biometric measurements(26), analysis of utero-placental Doppler flow velocimetry(27), use of customization of measurements for parental characteristics(28), and analysis of placentally derived biomarkers(29). However, many of these have been evaluated in the context of early onset growth restriction. We conclude that further research on existing and novel methods to identify abnormal fetal growth at and near term could yield useful screening tools for population based screening to prevent perinatal death.

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Legends for figures

Figure 1 Absolute risk per 10,000 pregnancies (95% binomial confidence intervals) of term perinatal death by birth weight percentile: **A.** Antepartum stillbirth, and **B.** Delivery related perinatal death (i.e. intrapartum stillbirths and neonatal deaths).

Figure 2 Univariate analysis of the association between birth weight percentile and the risk of antepartum stillbirth ascribed to each cause: **A.** Unexplained (Odds ratio [OR], 95% confidence intervals), **B.** Toxemia (No events within the 91^{st}–97^{th} and 98^{th}–100^{th} birth weight percentile categories), **C.** Antepartum hemorrhage, and **D.** Maternal disease (including diabetes).

Figure 3 Univariate analysis of the association between birth weight percentile and the risk of delivery related perinatal death by cause: **A.** All delivery related perinatal deaths, **B.** Delivery related perinatal deaths ascribed to anoxia, **C.** Delivery related perinatal deaths ascribed to other causes (non-anoxia)

Table 1. Characteristics of the cohort by pregnancy outcome.

Characteristics	Antepartum stillbirths (n=1,157)	Delivery related perinatal deaths (n=543)	Survived to 4 weeks of age (n=782,876)	P*
Maternal				
Age, median (IQR), y	29 (24–34)	28 (24–32)	28 (24–32)	.003
Age category, No. (%)				
<25	292 (25.2)	161 (29.7)	212,041 (27.1)	<.001
25–34	638 (55.2)	302 (55.6)	455,246 (58.1)	
>35	227 (19.6)	80 (14.7)	115,589 (14.8)	
Height, median (IQR), cm	163 (158-167)	162 (157-166)	163 (158-167)	.06
Missing value, No. (%)	179 (15.8)	82 (15.1)	115,428 (14.7)	.76
Smoking status, No. (%)				
Non-smoker	617 (53.3)	310 (57.1)	493,348 (63)	<.001
Smoker	437 (37.8)	179 (33.0)	217,123 (27.7)	
Ex-smoker	103 (8.9)	54 (9.9)	72,405 (9.3)	
Parity, No. (%)				
0	599 (51.8)	300 (55.3)	350,065 (44.7)	<.001
1–2	453 (39.2)	207 (38.1)	382,448 (48.9)	
3–4	85 (7.3)	33 (6.1)	44,575 (5.7)	
>4	20 (1.7)	3 (0.6)	5,788 (0.7)	
Deprivation category, No. (%)				
1–2 (Least deprived)	186 (16.1)	91 (16.7)	152,188 (19.4)	.02
3–5	750 (64.8)	349 (64.3)	482,426 (61.6)	
6–7 (Most deprived)	221 (19.1)	103 (19.0)	148,262 (19.0)	

Fetal/Neonatal				
Male sex, No. (%)	608 (52.6)	268 (49.4)	399,076 (51.0)	.42
Birth weight, median (IQR), g	3,060 (2,620–3,500)	3,280 (2,980–3,770)	3,450 (3,130–3,780)	<.001
Gestational age (wk), median (IQR)	39 (38–40)	40 (39–41)	40 (39–41)	<.001
Gestational age at delivery No. (%)				
37	228 (19.7)	56 (10.3)	40,363 (5.2)	<.001
38	271 (23.4)	77 (14.2)	104,588 (13.3)	
39	244 (21.1)	99 (18.2)	171,611 (21.9)	
40	255 (22.0)	155 (28.6)	251,098 (32.1)	
41	139 (12.0)	128 (23.4)	184,092 (23.5)	
42–43	20 (1.8)	28 (5.1)	31,124 (4.0)	
Obstetric				
Mode of delivery, No. (%)				
Spontaneous vaginal	943 (81.5)	234 (43.1)	537,511 (68.7)	<.001
Assisted vaginal	76 (6.6)	89 (16.4)	96,543 (12.3)	
Breech	35 (3.0)	5 (0.9)	1,719 (0.2)	
Planned cesarean	22 (1.9)	16 (3.0)	58,890 (7.5)	
Emergency cesarean, pre-labor†	45 (3.9)	76 (14.0)	18,204 (2.3)	
Emergency cesarean, labor†	36 (3.1)	123 (22.6)	70,009 (9.0)	

IQR, interquartile range
*Kruskal-Wallis and χ^2 tests, as appropriate
†Pre-labour: before the onset of labour; Labour: after the onset of labour

Table 2. Univariate and multivariate analysis of risk factors associated with antepartum stillbirth (all causes).

Variables	Univariate (n= 1,157 stillbirths)			Multivariate* Smokers† (n=437)			Multivariate* Non/Ex smokers (n=720)		
	OR	95% CI	P	OR‡	95% CI	P	OR‡	95% CI	P
Birth weight percentiles									
1–3	8.0	6.8–9.5	<.001	5.5	4.2–7.2	<.001	10.5	8.2–13.3	<.001
4–10	3.2	2.7–3.8	<.001	2.4	1.8–3.1	<.001	3.8	3.0–4.8	<.001
11–20	1.7	1.4–2.1	<.001	1.4	1.1–2.0	.02	1.9	1.5–2.4	<.001
21–80	Referent			Referent			Referent		
81–90	0.8	0.6–1.0	.10	1.0	0.6–1.7	.89	0.8	0.6–1.0	.08
91–97	0.7	0.5–1.0	.03	1.3	0.8–2.3	.30	0.6	0.4–0.8	.004
98–100	2.2	1.7–2.9	<.001	4.7	2.9–7.8	<.001	1.8	1.3–2.4	.001
Age category									
<20	1.0	0.8–1.3	.97	0.7	0.5–1.0	.05	0.8	0.6–1.1	.21
20–24	1.0	0.8–1.2	.84	0.8	0.6–1.1	.11	0.9	0.7–1.1	.40
25–29	Referent			Referent			Referent		
30–34	1.0	0.9–1.2	.93	1.4	1.1–1.8	.01	1.0	0.8–1.2	.63
35–39	1.4	1.2–1.7	<.001	1.4	1.0–1.9	.08	1.6	1.3–1.9	<.001
≥40	1.3	0.9–1.9	.12	1.4	0.7–2.8	.29	1.3	0.8–2.0	.28
Height category, cm									
<150	1.2	0.8–2.1	.39	1.0	0.5–1.9	.95	0.8	0.4–1.6	.46
150–154	1.0	0.8–1.3	.83	0.7	0.4–1.2	.15	0.9	0.7–1.3	.74
155–159	1.2	1.0–1.5	.04	1.1	0.8–1.4	.57	1.1	0.9–1.5	.37
160–164	Referent			Referent			Referent		
165–169	1.2	1.0–1.4	.04	1.0	0.8–1.3	.86	1.5	1.2–1.8	<.001
170–174	1.0	0.8–1.2	.70	1.0	0.7–1.4	.86	1.2	0.9–1.5	.30

≥175	1.1	0.8–1.5	.67	1.0	0.5–1.9	.97	1.4	0.9–2.1	.10
Deprivation category									
1 (Least deprived)	0.8	0.6–1.0	.08	0.8	0.4–1.7	.53	0.8	0.6–1.1	.21
2	0.8	0.6–0.9	.01	1.1	0.8–1.6	.56	0.7	0.6–0.9	.008
3	1.0	0.8–1.1	.57	1.0	0.7–1.3	.83	1.0	0.8–1.2	.85
4	Referent			Referent			Referent		
5	1.0	0.8–1.2	.94	1.1	0.8–1.4	.58	0.9	0.7–1.1	.36
6	0.9	0.8–1.2	.56	0.9	0.6–1.2	.41	0.9	0.7–1.2	.59
7 (Most deprived)	0.9	0.7–1.2	.62	1.0	0.7–1.3	.82	0.7	0.5–1.1	.13
Parity									
0	1.4	1.3–1.6	<.001	1.7	1.4–2.2	<.001	1.2	1.0–1.4	.01
1–2	Referent			Referent			Referent		
3–4	1.6	1.3–2.0	<.001	1.2	0.9–1.7	.26	1.5	1.1–2.1	.01
>4	2.9	1.9–4.6	<.001	1.5	0.7–3.1	.26	3.1	1.7–5.6	<.001
Sex									
Female	Referent			Referent			Referent		
Male	1.1	0.9–1.2	.28	1.1	0.9–1.3	.29	1.0	0.9–1.2	.63
Smoking status									
Non smoker	Referent								
Smoker	1.6	1.4–1.8	<.001						
Ex smoker	1.1	0.9–1.4	.23						

OR, odds ratio; CI, confidence intervals

* The multivariate analysis was stratified to smokers and non/ex smokers as there is effect modification between smoking and birth weight.
†There were 217,739 (27.8%) smokers and 566,837 (72.2%) non/ex smokers.
‡Adjusted for birth weight percentile, age, height, parity, deprivation category,and sex.

Table 3. Multivariate analysis of risk factors associated with delivery related perinatal deaths, subdivided to deaths ascribed to intrapartum anoxia and non-anoxia.

Variables	All (n= 543 delivery related perinatal deaths)			Anoxia (n=311)			Non-anoxia (n=232)		
	OR*	95% CI	P	OR*	95% CI	P	OR*	95% CI	P
Birth weight percentiles									
1–3	2.1	1.4–3.1	<.001	2.2	1.3–3.7	.003	2.0	1.1–3.6	.02
4–10	1.8	1.4–2.4	<.001	1.6	1.1–2.4	.02	2.0	1.3–3.0	.001
11–20	1.5	1.2–2.0	.002	1.5	1.0–2.1	.03	1.6	1.1–2.4	.02
21–80	Referent			Referent			Referent		
81–90	1.0	0.7–1.4	.94	1.2	0.8–1.8	.38	0.8	0.4–1.3	.35
91–97	1.2	0.9–1.7	.22	1.1	0.7–1.8	.64	1.4	0.9–2.4	.17
98–100	2.3	1.6–3.3	<.001	2.9	1.9–4.6	<.001	1.3	0.6–2.8	.49
Age category									
<20	0.9	0.6–1.2	.39	0.8	0.5–1.2	.23	1.0	0.6–1.7	.87
20–24	1.0	0.8–1.3	.95	0.6	0.4–0.9	.008	1.7	1.2–2.3	.005
25–29	Referent			Referent			Referent		
30–34	1.0	0.8–1.3	.72	1.1	0.8–1.5	.57	1.0	0.7–1.4	.90
35–39	1.1	0.8–1.4	.74	1.2	0.8–1.7	.37	0.9	0.5–1.4	.58
≥40	1.7	1.0–2.8	.04	2.4	1.3–4.2	.003	0.7	0.2–2.4	.62
Height category, cm									
<150	1.1	0.5–2.2	.83	0.9	0.3–2.4	.79	1.3	0.5–3.7	.60
150–154	1.2	0.8–1.6	.37	1.2	0.8–1.9	.34	1.1	0.6–1.8	.76
155–159	1.2	0.9–1.5	.27	1.2	0.8–1.7	.30	1.1	0.7–1.7	.64

160–164	Referent			Referent			Referent		
165–169	1.0	0.8–1.3	.89	0.9	0.7–1.3	.58	1.2	0.8–1.7	.45
170–174	0.8	0.6–1.2	.32	1.0	0.7–1.5	.94	0.6	0.3–1.1	.08
≥175	0.7	0.4–1.2	.15	0.7	0.3–1.5	.35	0.6	0.2–1.5	.25
Deprivation category									
1 (Least deprived)	0.8	0.5–1.2	.27	0.4	0.2–0.9	.03	1.3	0.8–2.3	.33
2	0.9	0.7–1.2	.35	0.9	0.6–1.4	.73	0.8	0.5–1.3	.32
3	0.9	0.7–1.1	.35	1.0	0.7–1.3	.81	0.8	0.5–1.2	.26
4	Referent			Referent			Referent		
5	1.0	0.8–1.3	.81	1.3	0.9–1.8	.14	0.8	0.5–1.1	.18
6	1.0	0.8–1.3	.97	1.1	0.7–1.6	.67	0.9	0.6–1.4	.67
7 (Most deprived)	0.7	0.5–1.0	.08	0.6	0.3–1.1	.10	0.8	0.5–1.3	.34
Parity									
0	1.6	1.3–1.9	<.001	1.9	1.5–2.5	<.001	1.3	1.0–1.7	.08
1–2	Referent			Referent			Referent		
3–4	1.2	0.9–1.8	.27	1.2	0.8–2.0	.41	1.3	0.7–2.3	.39
>4	0.8	0.3–2.5	.68	1.3	0.4–4.0	.68	0		
Sex									
Female	Referent			Referent			Referent		
Male	0.9	0.8–1.1	.45	1.0	0.8–1.3	.87	0.8	0.6–1.1	.18
Smoking status									
Non smoker	Referent			Referent			Referent		
Smoker	1.2	1.0–1.8	.04	1.1	0.8–1.4	.61	1.4	1.1–1.9	.02
Ex smoker	1.1	0.9–1.5	.37	1.2	0.8–1.7	.31	1.1	0.7–1.7	.84

OR, odds ratio; CI, confidence intervals
*Adjusted for birth weight percentile, age, height, parity, smoking, sex and deprivation category.