Appendix 1. NBDPS Eligibility

The National Birth Defects Prevention Study (NBDPS) is a population-based case-control study with two data sources: clinical information and interview. Clinical information was obtained from the birth or fetal death certificate as well as by through medical records abstraction and submitted on all identified cases with eligible birth defects. This information was then reviewed by clinical geneticists to determine if the case met study clinical eligibility criteria. Those meeting the study criteria for the birth defect and with an eligible pregnancy outcome (live birth, stillbirth, termination) were included in a clinical database. Controls were liveborn infants without major birth defects randomly select from the underlying population. Trained interviewers contacted mothers of eligible cases and controls by phone to determine if they met the eligibility criteria for the interview (e.g., mother not incarcerated, speaks English or Spanish; see Yoon et al., and Reefhuis et al., for details) and conduct the interview using a computer-assisted telephone interview.[2,3] Our analysis includes all eligible cases regardless of eligibility for, or participation in, the interview portion of NBDPS.

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Appendix 2. NBDPS Eligible Birth Defects

Birth defects eligible for participation in the NBDPS. For further details, see Yoon et al 2001 and Reefhuis et al., 2015.[2,3]

- Anencephaly and craniorachischisis
- Spina bifida
- Encephalocele, cranial meningocele, encephalomyelocele
- Holoprosencephaly
- Hydrocephalus
- Dandy-Walker malformation
- Anophthalmia/microphthalmia
- Cataracts, glaucoma, and related eye defects
- Anotia/microtia
- Conotruncal heart defects
- Single ventricle
- Septal heart defects (atrial septal defects, ventricular septal defects)
- Atrioventricular septal heart defects
- Ebstein malformation
- Obstructive heart defects (right and left ventricular outflow defects)
- Anomalous pulmonary venous return
- Heterotaxia
- Choanal atresia
- Cleft lip with and without palate
- Cleft palate
- Esophageal atresia with and without tracheoesophageal fistula
- Intestinal atresia/stenosis
- Biliary atresia
- Hypospadias (third or second degree)
- Bilateral renal agenesis or hypoplasia
- Limb deficiency, intercalary
- Limb deficiency, longitudinal
- Limb deficiency, transverse
- Limb deficiency, not elsewhere classified
- Craniosynostosis
- Diaphragmatic hernia
- Sacral agenesis
- Omphalocele
- Extrophy, bladder
- Extrophy, cloacal
- Gastroschisis
- Amniotic band syndrome

Appendix 3. Data Review and Cleaning

Pregnancy Outcome

Pregnancy outcome is based on medical records. When pregnancy outcome was missing for those who were interviewed, outcome from medical records was substituted when available. Those without a pregnancy outcome were excluded from analyses. If, after gestational age and birthweight cleaning, the pregnancy outcome was discrepant with gestational age or birthweight, abstracted medical records were reviewed to determine the outcome, as described below.

Gestational Age and Birth Weight

There were multiple sources of gestational age available in this study: maternal report (interviewed participants only), ultrasound, last menstrual period (LMP), and clinical estimate. All available gestational age values were checked for consistency with birthweight and pregnancy outcome.

To identify records with potential errors, we calculated the absolute difference in available gestational estimates using the following hierarchy: 1. Maternal report and clinical estimates 2. LMP and ultrasound estimates (if maternal or clinical estimate missing) 3. Clinical and LMP estimates (if maternal and ultrasound missing).

We reviewed individual records where birthweight was missing if any of the following conditions were met: >5 week difference in gestational age estimates, difference in gestational age estimate which bridged the 20 week cut point, and a single gestational age estimate which was inconsistent with the reported pregnancy outcome. For records where birthweight was not missing, individual records were reviewed if the absolute value of the z-scores for all birthweight estimates (described below) were greater than 5 standard deviation units from the mean. All records with a birth weight of <50 g or >10000g or with a gestational age of <10 weeks' were reviewed. Identified errors were then corrected.

To evaluate the consistency of gestational age estimates with the reported birthweight, we calculated sex and gestational age specific z-scores for each available gestational age source using reference values from Talge et al 2014.[1] To estimate z-scores for records with a gestational age below 22 weeks (the lowest value in the reference) we estimated the mean birth weight and standard deviation for weeks 20 (female = 299, 70; male = 350, 60) and 21 (female = 370, 80; male = 400, 75).

For records where a z-score was calculated, we used the following hierarchy to select the first gestational age estimate with a z-score within 5 standard deviations of the mean for the final gestational age: 1. Maternal report, 2. Ultrasound, 3. LMP, 4. Clinical estimate.

For records where no z-score could be calculated (i.e., no birthweight or all gestational age estimates <20 weeks'), if all gestational age estimates were within 4 weeks of each other we used the following hierarchy to choose the best gestational age: 1. Ultrasound, 2. Maternal Report, 3. LMP, 4. Clinical estimate. If any gestational age estimate was more than 4 weeks different than the other, records were individually reviewed to determine gestational age.

Following these procedures, individual records were reviewed if the selected gestational age value was inconsistent with pregnancy outcome (e.g., termination ≥30 weeks) or if there was an unknown pregnancy outcome. Errors were corrected when identified. If the discrepancy could not be resolved, the gestational age or pregnancy outcome was set to missing.

Records where a single best gestational age could not be determined were considered to be at risk for stillbirth if either all gestational age values were ≥20 weeks' or birthweight was ≥500 g. Those who had all gestational age values <20 weeks and a birthweight of <500 g were considered to not be at risk of stillbirth and excluded from the main analyses.

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Appendix 4. Pregnancy Outcome Among Multiple Birth Defect Cases for Specific Birth Defects

Body System	Birth Defect	Stillbirths (N)	Live Births (N)	Termination (N)	Grand Total
Amniotic Band Syndrome	ABS: Limb anomalies only	29	154	1	184
	ABS: Craniofacial disruptions ± limb anomalies	3	36	9	48
	ABS: Limb-body-wall complex	16	20	16	52
Facial	Cleft palate	22	464	8	494
	Cleft lip with cleft palate	34	391	18	443
	Cleft lip without cleft palate	14	109	4	127
Gastrointestinal	Esophageal atresia	8	558	4	570
	Duodenal atresia or stenosis	7	119	1	127
	Cloacal exstrophy	4	77	6	87
Genitourinary	Bladder exstrophy	1	24		25
	Bilateral renal agenesis or hypoplasia	20	78	22	120
Muskuloskeletal	Longitudinal limb deficiency	13	299	19	331
	Transverse limb deficiency	19	145	16	180
	Intercalary limb deficiency	2	26	7	35
	Diaphragmatic hernia	13	307	7	327
	Omphalocele	34	211	21	266
	Gastroschisis	14	178	6	198
	Sacral agenesis or caudal dysplasia	2	133	6	141
Neurological	Anencephaly and craniorachischisis	27	37	33	97
	Spina bifida	17	206	18	241
	Encephalocele	12	70	10	92
	Hydrocephaly	7	219	9	235
	Dandy-Walker malformation	2	94	4	100
	Holoprosencephaly	5	64	8	77

There were 3, 972 fetuses and infants with multiple birth defects. Fetuses and infants are included in each birth defect category for which they met the study criteria. There were no terminations for fetuses with bladder extrophy.

Some fetuses are included in multiple categories. Some fetuses will only be included in one category because their other major birth defects were not included in the analyses (e.g., heart defects) or their other birth defects were not included in the NBDPS.

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Appendix 5. Stillbirth Risk Among Fetuses With Nonfatal Birth Defects

Body System	Birth Defect	Stillbirth Risk (per 1000)	Lower Risk Bound (per 1000)	Upper Risk Bound (per 1000)	Lower 95% CI (per 1000)	Upper 95% CI (per 1000)
Amniotic Band Syndrome	ABS: Limb anomalies only	137	136	142	10.2	17.8
	ABS: Craniofacial ± limb anomalies	125	110	250	6.0	22.4
Facial	Cleft palate	12	12	15	0.8	1.7
	Cleft lip with cleft palate	19	19	22	1.4	2.5
	Cleft lip without cleft palate	12	12	13	0.7	1.8
Gastrointestinal	Esophageal atresia	13	13	17	0.7	2.2
	Duodenal atresia or stenosis	37	37	40	2.0	6.3
	Cloacal exstrophy	65	61	121	2.8	12.3
Muskuloskeletal	Longitudinal limb deficiency	21	20	49	1.1	3.5
	Transverse limb deficiency	36	35	52	2.5	5.0
	Intercalary limb deficiency	34	32	104	0.7	9.5
	Diaphragmatic hernia	23	22	39	1.5	3.3
	Omphalocele	105	100	146	8.1	13.3
	Gastroschisis	45	45	50	3.7	5.5
	Sacral agenesis	7	7	40	0.0	3.8
Neurological	Spina bifida	31	29	113	2.3	4.1
	Encephalocele	74	68	158	4.8	10.9
	Hydrocephaly	19	19	37	1.1	3.2
	Dandy-Walker malformation	27	26	59	1.1	5.4
	Holoprosencephaly	43	39	135	2.1	7.7

Stillbirth risks and bounds are reported per 1000 affected fetuses. Two-tailed 95% confidence intervals (95% CIs) using the Poisson distribution when there were fewer than 20 stillbirths and using the exact binomial method otherwise. Infants and fetuses with multiple birth defects are included in each defect category for which they have an eligible primary birth defect. Within a defect category, each infant or fetus is represented only once. ABS = amniotic band syndrome.

Total Births = Stillbirths + Livebirths

Risk of Stillbirth = Stillbirths / Livebirths + Stillbirths

Upper Risk Bound = Stillbirth + Terminations / Livebirths + Stillbirths + Terminations

Lower Risk Bound = Stillbirth / Livebirths + Stillbirths + Terminations

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Appendix 6. Number of Elective Terminations by Gestational Age at Termination and Specific Birth Defect

		Gestational Age at Termination		
Body System	Birth Defect	< 20 Weeks'	≥20 Weeks'	Grand Total
Amniotic Band Syndrome	ABS: Limb anomalies only	0	2	2
	ABS: Craniofacial ± limb anomalies	11	12	23
	ABS: Limb-body-wall complex	12	33	45
Facial	Cleft palate	5	8	13
	Cleft lip with cleft palate	7	18	25
	Cleft lip without cleft palate	4	4	8
Gastrointestinal	Duodenal atresia or stenosis	0	1	1
	Esophageal atresia	1	4	5
	Cloacal exstrophy	3	9	12
Genitourinary	Bilateral renal agenesis or hypoplasia	11	55	66
Musculoskeletal	Longitudinal limb deficiency	6	24	30
	Transverse limb deficiency	10	22	32
	Intercalary limb deficiency	3	7	10
	Diaphragmatic hernia	6	21	27
	Omphalocele	15	32	47
	Gastroschisis	8	11	19
	Sacral agenesis	2	7	9
Neurological	Anencephaly	258	251	509
	Spina bifida	56	144	200
	Encephalocele	25	33	58
	Hydrocephaly	5	16	21
	Dandy-Walker malformation	3	9	12
	Holoprosencephaly	3	25	28

Fetuses with multiple birth defects are included in each category for which they had an eligible birth defect. There were no terminations for bladder exstrophy. ABS = amniotic band syndrome.

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Appendix 7. Difference in Risk Bounds When Including Terminations Before 20 Weeks of Gestation

Body System	Birth Defect	Stillbirth Risk	Lower Risk Bound Including <20 Weeks	Lower Risk Bound	Absolute Difference in Lower Risk Bounds	Upper Risk Bound Including <20 weeks'	Upper Risk Bound	Absolute Difference in Upper Risk Bounds
Amniotic Band Syndrome	ABS: Limb anomalies only	137	136	136	0	142	142	0
	ABS: Craniofacial ± limb anomalies	125	95	107	-12	337	250	87
	ABS: Limb-body-wall complex	492	283	319	-36	708	670	37
Facial	Cleft palate	13	13	13	0	18	16	2
	Cleft lip with cleft palate	21	21	21	0	30	27	2
	Cleft lip without cleft palate	14	13	13	0	19	16	3
Gastrointestinal	Esophageal atresia	14	13	13	0	19	18	1
	Duodenal atresia or stenosis	37	37	37	0	40	40	0
	Cloacal exstrophy	63	58	59	-1	145	126	19
Genitourinary	Bladder exstrophy	11	11	11	0	11	11	0
	Bilateral renal agenesis	232	187	193	-6	380	360	21
Musculoskeletal	Longitudinal limb deficiency	25	24	24	0	66	58	8
	Transverse limb deficiency	41	39	40	0	70	61	9
	Intercalary limb deficiency	34	30	31	-1	131	104	27
	Diaphragmatic hernia	25	25	25	0	46	41	5
	Omphalocele	115	107	110	-3	181	161	20
	Gastroschisis	46	46	46	0	54	51	3
	Sacral agenesis	13	12	13	0	68	57	12
Neurological	Anencephaly	418	230	298	-68	679	584	94
	Spina bifida	32	28	29	-1	141	113	28
	Encephalocele	74	63	67	-4	215	160	55
	Hydrocephaly	19	19	19	0	45	39	6
	Dandy-Walker malformation	27	26	26	0	69	59	10
	Holoprosencephaly	42	38	38	0	144	134	10

Stillbirth risks and bounds are reported per 1000 affected fetuses. Infants and fetuses with multiple birth defects are included in each defect category for which they have an eligible primary birth defect. Within a defect category, each infant or fetus is represented only once. ABS = amniotic band syndrome.

Risk = Stillbirths / Live births + Stillbirths;

Upper Risk Bound = Stillbirth + Terminations (≥20 Weeks') / Livebirths + Stillbirths + Terminations (≥20 Weeks');

Upper Risk Bound Including <20 Weeks' = Stillbirth + Terminations (all gestational ages) / Livebirths + Stillbirths Terminations (<20 Weeks');

Lower Risk Bound = Stillbirths / Livebirths + Stillbirths + Terminations (≥20 Weeks');

Lower Risk Bound Including <20 Weeks' = Stillbirths / Livebirths + Stillbirths + Terminations (all gestational ages)

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