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Gastroschisis and Cumulative Stressor Exposures

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Abstract

Background: Gastroschisis, a congenital defect of the abdominal wall, occurs disproportionately more in offspring of young mothers and has been increasing in prevalence over the past decades. A wide range of exposures have been reported in association with an increased gastroschisis risk, independent of mother's age; many have also been correlated with stress responses.

Methods: We explored cumulative exposures to such stressor exposures among 1,261 mothers of gastroschisis cases and 10,682 mothers of controls in the National Birth Defects Prevention Study (1997–2011). We considered 16 exposures as stressors in the first trimester: fever, genitourinary infection, anti-herpetic medication use, injury, bronchodilator use, cigarette smoking, alcohol intake, illicit drug use, prescription opioid use, oral contraceptive use, interpregnancy interval < 12 months, residential move, aspirin use, ibuprofen use, venlafaxine use, and paroxetine use.

Results: Mothers of cases reported more stressor exposures than controls. For 1, 2, 3, and ≥ 4 stressor exposures compared with none, the age-adjusted odds ratios (95% confidence interval) were 1.3 (1.1, 1.6), 1.7 (1.4, 2.1), 2.5 (2.0, 3.1), and 3.6 (2.9, 4.4), respectively. When we weighted cumulative stress scores according to the magnitude of stressor-specific odds ratios, similar associations were observed. Cumulative stressor exposure did not account for the strong inverse association between age and gastroschisis risk.

Conclusions: These findings show that gastroschisis risk appears to increase with accumulation of widely different types of exposures, consistent with the hypothesis that stress-induced inflammation might play an etiologic role.

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The process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html.

Coding of drug information in NBDPS used the Slone Drug Dictionary, under license from the Slone Epidemiology Center at Boston University, Boston, MA.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Keywords

Stressor; Gastroschisis; Pregnancy; Epidemiology

Gastroschisis is an abdominal wall defect in which the contents of the abdomen protrude outside the body at birth. Several pathogenetic pathways are proposed for the development of gastroschisis, with those involving abnormalities of vessels garnering most attention.[1,2] The epidemiology of gastroschisis stands out from other congenital malformations due to its higher birth prevalence in young mothers and its increasing prevalence over the past decades.[3] A myriad of epidemiologic studies have explored pregnancy risk factors and, unlike most other malformations, a wide range of exposures have been reported in association with an increased gastroschisis risk independent of mother's age. For example, maternal cigarette smoking, asthma, illicit and therapeutic medication use, genitourinary infection, alcohol, and residential moves have each been suggested to increase gastroschisis risk even after controlling for confounding by maternal age.[4–12] These findings raise the question of whether there might be a common underlying factor that explains this pattern of risk factors. If this set of exposures acts through a common pathogenetic pathway that produces gastroschisis, we hypothesize that accumulation of exposures will be associated with increasingly greater risks of this abdominal wall defect. Many of the observed risk factors for gastroschisis have been shown to induce stress responses, including inflammation, cytokine production, oxidative stress, DNA damage, and mitochondrial dysfunction, all of which appear to be involved in fetal development in animal models.[13–16] In the absence of early pregnancy biomarker data, we sought to evaluate the hypothesis that accumulation of stressor exposures is associated with increasing risks of gastroschisis, using data from the National Birth Defects Prevention Study (NBDPS).

METHODS

From 1997 to 2011, the NBDPS ascertained population-based cases with birth defects and liveborn controls without birth defects for the purpose of identifying potential teratogenic risk factors. Livebirths, stillbirths, and terminations were identified from birth defect registries in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) and were classified by clinical geneticists using standardized criteria. Controls were infants born without any major structural malformation and were selected randomly from the source population. We interviewed mothers of cases and controls by telephone within 2 years after their due date (median 8 months). The standardized, computerized questionnaire asked about demographic, reproductive, medical, and behavioral factors. The study was approved by the institutional review boards at the Centers for Disease Control and Prevention and each of the participating states. All participating mothers provided informed consent. Details on study design have been reported previously.[17,18]

Cases were liveborn, stillborn, or terminations with gastroschisis in the absence of any known chromosomal or genetic defect, amniotic band sequence, or limb–body wall complex. Intestinal atresia is considered to be a common sequela of gastroschisis and

therefore cases of gastroschisis with accompanying intestinal atresia were classified as isolated. Multiple cases had 1 or more additional major malformations.

STRESSOR EXPOSURES

Potential stressor exposures for this study included factors previously reported to be associated with gastroschisis risk in NBDPS publications. Based on the published findings, we considered the number of exposed cases and magnitude of associations in our selection of stressor exposures. Exposures with a reported odds ratios < 1.30 were not studied, including dietary factors,[19–21] bathing habits,[22] pesticides,[23] occupation as an entertainer,[24] caffeine,[25] acetaminophen,[26] obesity,[27] and anti-bacterials.[28] Although the reported odds ratio for polycyclic hydrocarbon exposure was > 1.30, exposure was based on industrial hygienist review of individual maternal reports of job titles and classification[29]; because exposure classification was not available for data collected during the most recent 10 years, we omitted polycyclic hydrocarbon as a potential stressor. Sixteen exposures were considered as potential stressor exposures for this analysis, including fever,[4,30] genitourinary infection,[6,10] anti-herpetic medication use,[10] injury,[31] bronchodilator use,[5] cigarette smoking,[4] alcohol intake,[7] illicit drug use,[4] prescription opioid use,[32] oral contraceptive use,[8] inter-pregnancy interval of less than 12 months,[33] residential move,[12] venlafaxine,[9] paroxetine,[11] aspirin,[34] and ibuprofen.[34] For each of these exposures, we considered any reported exposure for the interval beginning 1 month before through 3 months after an approximate date of conception (14 days after the last menstrual period). Further details on exposure definitions have previously been reported.

The cumulative stress score was the sum across all 16 exposures with yes valued as 1 and no valued as 0 (range, 0–16). We also created a weighted stress score, using our calculated exposure-specific fully adjusted odds ratio as the weighted value for exposed women and 0 for unexposed women and summing weights across all exposures (range, 0–25.92). Because only gravid women would have an interpregnancy interval, we assigned nulligravid women as unexposed for the full group analysis. We also conducted subanalyses restricted to gravid women only.

Odds ratios and 95% confidence intervals were estimated with logistic regression for each exposure and for each cumulative stress score. We adjusted for maternal age (< 20, 20–24, 25–29, and ≥ 30 years) in all models and for the other “stressors” in exposure-specific models to produce independent odds ratios to serve as weights. Maternal age was examined as a potential effect modifier. Departure from additive effects was evaluated, using odds ratios as estimators of relative risk,[35] to measure whether gastroschisis risk associated with joint exposure (younger age and high number of stressors) was greater than expected, given the individual effects of each exposure. The group we considered doubly exposed comprised women with ≥ 4 stressors in each of the younger age strata (≤ 20, 20–24, 25–29 years) and the common unexposed group comprised women aged ≥ 30 with no stressors.

To determine whether the strong inverse association with maternal age was explained by these stressor exposures, we compared crude odds ratios for categories of maternal age to adjusted odds ratios for the same age categories with 16 potential stressors were included in the model.

RESULTS

Among the 1,450 mothers of cases and 11,829 mothers of controls, information was missing on at least 1 stressor exposure for 189 cases and 1,147 controls. Table 1 shows demographic factors for study subjects overall, and for the 1,261 case and 10,682 control mothers with no missing data. Analyses were confined to those with complete data. Mothers of cases were younger and had less education and lower gravidity than mothers of controls. Short interpregnancy interval and cigarette smoking, alcohol use, and ibuprofen use in early pregnancy were the most common stressors (Table 2). As expected, each stressor was more common among case mothers than control mothers with age-adjusted odds ratios ranging from 1.2 (1.0, 1.5) (short interpregnancy interval) to 6.7 (2.1, 21) (antiherpetics). Some attenuation of odds ratios was due to correlations between stressors when all other stressors were included in the fully adjusted model.

The mean number of stressor exposures was 2.2 among cases and 1.5 among controls. More than half (57%) of control mothers had 0 or 1 stressor, whereas the majority (63%) of case mothers had 2 or more stressors (Table 3). As the number of stressors increased, age-adjusted odds ratios increased; they were 1.3 (1.1, 1.6), 1.7 (1.4, 2.1), 2.5 (2.0, 3.1), and 3.6 (2.9, 4.4) for 1, 2, 3, and ≥ 4 stressors, respectively. Weighted stressor scores showed a similar pattern. Both stressor counts and weighted scores assumed nulligravid women did not have a short interpregnancy interval. Among the subgroup of 631 case and 7450 control women with a previous pregnancy, the patterns of increasing odds ratios with number of stressors or score of weighted stressors were even more apparent.

Among control mothers, having *four or more* stressors was most common in < 20 year olds (11.9%) and least common in ≥ 30 year olds (4.9%) (Table 4). In contrast, *four or more* stressors was prevalent in at least 16% of case mothers across all age groups. Odds ratios were strongest among older women, driven by the lower prevalence of *four or more* stressors in the older control group. Departure from additive effects, as estimated by the relative excess risk due to interaction for *four or more* stressors in each age stratum compared with no stressors in ≥ 30 year olds were 27.6 (−0.2, 55.4) for women under 20, 29.7 (5.8–53.7) for those 20–24, and 11.9 (−0.8, 24.6) for those 25–29.

To determine whether the strong inverse association with maternal age was explained by these exposures, we calculated unadjusted and adjusted odds ratios as shown in Table 5. The 20.3-fold unadjusted odds ratio for maternal age < 20 years relative to ≥ 30 years was only slightly attenuated after adjustment for the 16 stressor exposures, the stressor exposure count, or the weighted score.

DISCUSSION

A wide range of risk factors have been reported for gastroschisis, independent of the strong inverse association with maternal age.[36] It has long been hypothesized that gastroschisis is caused by exposures that are more common in adolescent pregnancies, but no epidemiologic data to date have supported this hypothesis. In the present study, we sought to determine if accumulation of risk factors might shed some light on the pathogenesis of gastroschisis. We

observed a strong dose–response association of these so-called stressors with gastroschisis risk, where odds ratios increased monotonically for 1, 2, 3, and 4 or more stressors. Women who reported this highest level of stressors were estimated to be 3.6 times more likely to have a baby with gastroschisis, after adjusting for age. The combination of being less than 25 years old and having more than 3 stressor exposures increased gastroschisis risk more than expected, given individual associations for each factor. Even though younger women had higher counts of stressors, accumulating stressors did not explain the strong inverse association with maternal age.

Based on previous publications from the NBDPS,[4–12,30–34] we identified 16 risk factors for gastroschisis, and all were associated with increased crude and age-adjusted odds ratios in the present analysis. The 16 risk factors vary in the strength of the association with gastroschisis, consistency of evidence from other studies, and evidence as biologic stressors. Maternal fever, genitourinary infection, and injury each involves pathophysiologic responses, including inflammation and oxidative stress, whereas uses of anti-herpetic medication serves as a marker for underlying herpes infection, bronchodilator for asthma, analgesic for pain, and antidepressants for depression/anxiety, all of which are also associated with these stress responses.[37–41] In consideration of the other potential stressors that are related to lifestyle, links to inflammation and oxidative stress are less direct, but have been observed. For example, markers of inflammation and oxidative stress levels are higher in users of oral contraceptives,[42–44] cigarettes,[45–48] alcohol,[49–51]and illicit drugs.[52–55] Residential moves are counted as a major life-event stressor associated with adverse health outcomes.[56] High levels of inflammatory cytokines are associated with higher cumulative life-event stressor scores in pregnant women[56] and in adolescent boys,[57] but to our knowledge have not been explored in relation to residential moves, specifically. Short interpregnancy interval is considered to be a marker of nutritional depletion and nutritionally poor diets are known to raise levels of markers of inflammation and oxidative stress.[58,59] Short interpregnancy interval might also be considered a psychosocial stressor resulting from competing demands of being pregnant while caring for an infant.[60] In any case, biomarkers of inflammation and oxidative stress have not, to our knowledge, been examined in relation to interpregnancy interval.

Across all stressor exposures, the biologic evidence of stress response is strongest for the inflammation and oxidative stress pathways, which may well be inter-related along with DNA damage and mitochondrial dysfunction. At present, the developmental process that leads to gastroschisis is not known, leaving open the possibility that any or all of these stress responses are involved.

In our overall analysis, we assigned women with no previous pregnancies as unexposed for short interpregnancy interval. When we restricted to gravid women to avoid this assumption, odds ratios were stronger across the all stressor scores. Thus, artificial inflation of the unexposed group for short interpregnancy interval induced a downward bias. It is also possible, however, that gravid women are different than nulligravid women and that the stronger odds ratios in gravid women may reflect this difference. Nevertheless, short interpregnancy interval was observed to be positively associated with gastroschisis and may be an important contributor to cumulative stress.

We defined a stressor as an exposure reported to increase the risk for gastroschisis from the NBDPS and for which there is some biologic evidence of oxidative or inflammatory stress response. Our definition encompasses the environmental and biologic perspectives of stress.[61] This is in contrast to most epidemiologic studies of stress during pregnancy, which examined the effects of stressful major life-events. Carmichael et al.[62] examined major stress life-events in NBDPS for the 6 years when data were collected on a set of psychosocial stressors, including relationship difficulties, legal/financial problems, violence crime, illness/injury, relative's death, residential move, and job change. For gastroschisis, they did not observe an association in teenaged mothers, but a greater than 3-fold increase in risk was associated with 3 or more stress events in mothers ≥ 20 years of age.[62] We observed a clear trend of increasing gastroschisis risk across cumulative "stressors" in all age groups, including teenagers, suggesting that our empirically and biologically based definition may better represent the underlying developmental pathogenetic mechanism of stress. Palmer et al.,[63] on the other hand, used the Carmichael definition of stressors and reported an age-adjusted 4.9-fold increased risk of gastroschisis for ≥ 2 stressful life events in the first trimester, but they did not estimate age-specific risks. One paradox of a putative cumulative stress etiology for gastroschisis is obesity. Data from NBDPS and other studies show that obesity is associated with reduced risk of gastroschisis[27,63] despite observed increases in inflammatory cytokine levels with increasing body mass index.[64]

Correlations between and among the 16 stressors in our study were apparent, based on the observed attenuation of odds ratios when all stressors were included in logistic models, though independent associations of at least 1.3-fold remained for all but 2 stressors. However, correlations were not strong enough to greatly destabilize effect estimates from these models. Further, elevated odds ratios for increasing numbers of stressors could not be attributed to any specific combinations of stressors.

Many different metabolites have served as biomarkers of stress, including cortisol, CRP, cytokines, and 8-isoprostanes commonly measured in epidemiologic studies of pregnant women.[65,66] Epstein-Barr virus (EBV) reactivation has also been explored in pregnant women as a novel biomarker of stress.[66] EBV is in the herpes family and therefore typically remains in a latent state after initial infection in humans. Because stress can trigger reactivation of latent herpes virus[67] and over 85% of women of childbearing age have been exposed to EBV, serologic evidence of EBV reactivation is a useful marker of stress.[66] To date, to our knowledge, EBV serotype is the only early pregnancy biomarker studied in relation to gastroschisis.[68] That study reported increased associations for serotypes that are consistent with reactivated EBV infections based on small numbers. Such an association might represent an inflammatory response from circulating virus, from stressors that induced the reactivation, or from both. Only 1 sample of serum was collected in the first trimester in that study, which likely would not capture all reactivations during the etiologically relevant time frame. Nevertheless, the approximate 4-fold increased risk for women with a serotype suggestive of reactivation is compatible with findings in the present study that stress may play a role in the etiology of gastroschisis.

Early pregnancy biomarkers were not available in the NBDPS. Because gastroschisis occurs in approximately 1 in 5000 pregnancies, prospective data collection on hundreds

of thousands of pregnant women is necessary for sufficient numbers of cases. The NBDPS case–control design is efficient for studying risk factors for gastroschisis, but precludes collection of early pregnancy biomarkers. The case–control design is also vulnerable to inaccurate recall of exposures. If recall error is not differential for cases versus controls, odds ratios would likely be underestimates of the true associations. We did not take levels of the individual stressor exposures into account in this analysis; rather, we used dichotomous exposure based on NBPDS publications for these stressors. It is possible that further refinement of each stressor exposure might have been more revealing with regard to clues about gastroschisis etiology. The case–control design also precludes calculation of absolute risks; however, we were able to calculate departure from additive effects with odds ratios as estimators of relative risk and show a strong interaction between young maternal age and 4 or more stressors.

In summary, 1 in 5 mothers of infants with gastroschisis reported at least 4 stressors compared with 1 in 14 control mothers. In the absence of confounding, selection, or recall bias, the observed 3.6-fold increased risk for this high level of stressors would account for approximately 16% of cases. These findings provide support for a role of stress-induced inflammation in the pathogenesis of gastroschisis. The results are consistent with the hypothesis that accumulation of different types of stressor exposures in early pregnancy increases the risk of gastroschisis in offspring.

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Table 1.

Distributions of Demographic Factors among Gastroschisis Cases and Controls, National Birth Defects Prevention Study, 1997–2011

	Overall Study Population				Study Population with No Missing Data			
	Cases (n = 1450)		Controls (n = 11,829)		Cases (n = 1261)		Controls (n = 10,682)	
Factor	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**	**Number**	**(%)**
Age (y)								
< 20	628	43	1519	13	545	43	1332	13
20–24	547	38	2775	23	482	38	2497	23
25–29	190	13	3331	28	157	13	3028	28
≥ 30	85	5.9	4204	36	77	6.1	3825	36
Education (y)								
0–11	373	26	1905	16	345	27	1738	16
12	539	37	2725	23	484	38	2476	23
13+	465	32	6854	58	425	34	6436	60
Missing	73	5.0	345	2.9	7	0.6	32	0.3
Gravidity								
0	696	48	3471	29	630	50	3232	30
1	400	28	3347	28	347	28	3056	29
≥ 2	349	24	4960	42	284	23	4394	41
Missing	5	0.3	51	0.4				
Study site								
Arkansas	197	14	1471	12	179	14	1345	13
California	286	20	1263	11	255	20	1147	11
Georgia	154	11	1267	11	138	11	1148	11
Iowa	133	9.2	1300	11	116	9.2	1182	11
Massachusetts	119	8.2	1402	12	105	8.3	1307	12
New Jersey	47	3.2	578	4.9	42	3.3	533	5.0
New York	80	5.5	989	8.4	73	5.8	884	8.3
North Carolina	105	7.2	1016	8.6	95	7.5	928	8.7
Texas	176	12	1416	12	143	11	1216	11
Utah	153	11	1127	9.5	115	9.1	992	9.3

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	Overall Study Population				Study Population with No Missing Data			
	Cases (n = 1450)		Controls (n = 11,829)		Cases (n = 1261)		Controls (n = 10,682)	
Factor	Number	(%)	Number	(%)	Number	(%)	Number	(%)
Year (due date)								
1997–2001	339	23	3434	29	308	24	3155	30
2002–2006	514	35	4271	36	460	37	3911	37
2007–2011	597	41	4124	35	493	39	3616	34

Table 2.

Specific Maternal Stressor Exposures in Relation to Gastroschisis, National Birth Defects Prevention Study, 1997–2011

			Odds Ratio (95% Confidence Interval)	
Stressor	**Cases, n (%) (N = 1,261)**	**Controls, n (%) (N = 10,682)**	**Age-adjusted**	**Fully-adjusted[a]**
Fever	41 (3.3)	211 (2.0)	1.5 (1.0, 2.1)	1.1 (0.7, 1.6)
Genitourinary infection	225 (18)	1054 (9.9)	1.5 (1.3, 1.8)	1.3 (1.1, 1.6)
Antiherpetic use	6 (0.5)	12 (0.1)	6.7 (2.1, 21)	6.0 (1.9, 19)
Injury	52 (4.1)	214 (2.0)	1.7 (1.2, 2.4)	1.5 (1.0, 2.1)
Bronchodilator use	50 (4.0)	331 (3.1)	1.3 (0.9, 1.7)	1.1 (0.8, 1.5)
Opioid use	42 (3.3)	226 (2.1)	1.8 (1.3, 2.6)	1.3 (0.9, 1.9)
Smoking	437 (35)	1869 (18)	1.8 (1.5, 2.0)	1.4 (1.2, 1.6)
Alcohol	527 (42)	4004 (38)	1.6 (1.4, 1.8)	1.3 (1.1, 1.5)
Illicit drug use	171 (14)	445 (4.2)	2.1 (1.7, 2.6)	1.5 (1.2, 1.8)
Oral contraceptive use	157 (13)	791 (7.4)	1.5 (1.2, 1.8)	1.3 (1.1, 1.6)
Interpregnancy interval < 12 mo[b]	243 (39)	2038 (27)	1.2 (1.0, 1.5)	1.3 (1.1, 1.6)
Residential move	361 (29)	1542 (14)	1.5 (1.3, 1.7)	1.3 (1.1, 1.5)
Aspirin	64 (5.1)	445 (4.2)	1.3 (1.0, 1.8)	1.1 (0.9, 1.5)
Ibuprofen	387 (31)	2453 (23)	1.6 (1.4, 1.9)	1.4 (1.2, 1.6)
Venlafaxine	9 (0.7)	25 (0.2)	5.0 (2.2, 12)	3.5 (1.4, 8.4)
Paroxetine	13 (1.0)	57 (0.5)	2.4 (1.2, 4.6)	1.8 (0.9, 3.5)

[a]Adjusted for maternal age and all other stressor exposures in this table.

[b]Restricted to 631 gravid cases and 7450 gravid controls.

Table 3.

Unweighted Counts and Weighted Scores of Stressor Exposures in Relation to Gastroschisis, National Birth Defects Prevention Study, 1997–2011

Stressor exposure	All			Gravid		
	Cases, n (%) (n = 1,261)	Controls, n (%) (n = 10,682)	Age-adjusted OR (95% CI)[a]	Cases, n (%) (n = 631)	Controls, n (%) (n = 7,450)	Age-adjusted OR (95% CI)[a]
Unweighted count[b]						
Mean (max)	2.2 (8)	1.5 (9)		2.5 (8)	1.5 (9)	
0	185 (15)	2703 (25)	1.0 (reference)	66 (11)	1828 (25)	1.0 (reference)
1	288 (23)	3395 (32)	1.3 (1.1, 1.6)	134 (21)	2418 (33)	1.4 (1.0, 1.9)
2	288 (23)	2557 (24)	1.7 (1.4, 2.1)	142 (23)	1764 (24)	2.0 (1.4, 2.7)
3	248 (20)	1243 (12)	2.5 (2.0, 3.1)	137 (22)	882 (12)	3.2 (2.3, 4.4)
≥ 4	252 (20)	784 (7.3)	3.6 (2.9, 4.4)	152 (24)	558 (7.5)	5.0 (3.6, 6.8)
Weighted score[c]						
Mean (max)	3.0 (14)	2.0 (13)		3.3 (14)	2.0 (13)	
0	185 (15)	2703 (25)	1.0 (reference)	66 (11)	1828 (25)	1.0 (reference)
1.1–1.9	287 (23)	3387 (32)	1.3 (1.1, 1.6)	134 (21)	2413 (32)	1.4 (1.0, 1.9)
2–3.9	346 (27)	2944 (28)	1.7 (1.4, 2.1)	178 (28)	2039 (27)	2.1 (1.5, 2.8)
4–5.9	322 (26)	1375 (13)	2.8 (2.3, 3.5)	178 (28)	971 (13)	3.7 (2.7, 5.0)
≥ 6	121 (31)	273 (2.6)	4.6 (3.5, 6.1)	75 (12)	199 (2.7)	6.2 (4.3, 9.1)

[a] OR (95% CI), odds ratio (95% confidence interval).

[b] Count of stressor exposures.

[c] Sum of OR-based scores (from Table 2).

CI indicates confidence interval; OR, odds ratio.

Table 4.

Count of Maternal Stressor Exposures in Relation to Gastroschisis, Stratified by Maternal Age, National Birth Defects Prevention Study, 1997–2011

Maternal Age	Stressor Count	Cases, n (%)	Controls, n (%)	OR (95% CI)[a]	OR[b]
< 20 y	0	93 (17)	326 (25)	1.0 (reference)	
	1	131 (24)	377 (23)	1.2 (0.9, 1.7)	
	2	117 (22)	287 (22)	1.4 (1.0, 2.0)	
	3	112 (21)	184 (14)	2.1 (1.5, 3.0)	
	≥ 4	92 (17)	158 (12)	2.0 (1.4, 2.9)	71.4[c]
20–24y	0	63 (13)	571 (23)	1.0 (reference)	13.5
	1	100 (21)	727 (29)	1.2 (0.9, 1.7)	
	2	112 (23)	591 (24)	1.7 (1.2, 2.4)	
	3	97 (20)	349 (14)	2.5 (1.8, 3.6)	
	≥ 4	110 (23)	259 (10)	3.8 (2.7, 5.4)	52.1[d]
25–29y	0	21 (13)	824 (27)	1.0 (reference)	3.1
	1	42 (27)	1007 (33)	1.6 (1.0, 2.8)	
	2	31 (20)	692 (23)	1.8 (1.0, 3.1)	
	3	28 (18)	325 (11)	3.4 (1.9, 6.0)	
	≥ 4	35 (22)	180 (5.9)	7.6 (4.3, 13)	23.9[e]
≥ 30 y	0	8 (10)	982 (26)	1.0 (reference)	1.0 (reference)
	1	15 (20)	1284 (34)	1.4 (0.6, 3.4)	
	2	28 (36)	987 (26)	3.5 (1.6, 7.7)	
	3	11 (14)	385 (10)	3.5 (1.4, 8.9)	
	≥ 4	15 (20)	187 (4.9)	9.8 (4.1, 24)	9.8

[a] OR (95% CI), odds ratio (95% confidence interval), within age strata.

[b] OR, odds ratio using > 30 years, 0 stressor exposures as the common referent group for calculation of relative excess risk due to interaction (RERI).

[c] RERI, 71.4–35.0–9.8 = 27.6; (95% confidence bounds, −0.2, 55.4).

[d] RERI, 52.1–13.5–9.8 = 29.7; (95% confidence bounds, 5.8, 53.7).

[e] RERI, 23.9–3.1–9.8 = 11.9; (95% confidence bounds, −0.8, 24.6).

Table 5.

Assessment of Confounding of Inverse Associations between Maternal Age and Gastroschisis by Stressor Exposures, National Birth Defects Prevention Study, 1997–2011

	Odds Ratio (95% Confidence Interval)			
Maternal age (y)	**Unadjusted**	**Fully-adjusted[a]**	**Adjusted for Unweighted Count[b]**	**Adjusted for Weighted Score[c]**
< 20	20 (16, 26)	18 (14, 24)	19 (15, 24)	19 (15, 24)
20–24	9.6 (7.5, 12)	8.6 (6.7, 11)	8.6 (6.7, 11)	8.6 (6.7, 11)
25–29	2.6 (2.0, 3.4)	2.5 (1.9, 3.4)	2.5 (1.9, 3.4)	2.5 (1.9, 3.3)
> 30	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)

[a] Adjusted for all stressor exposures in Table 2.

[b] Adjusted for count of stressor exposures in Table 3.

[c] Adjusted for weighted scores of stressors in Table 3.