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Maternal health conditions during pregnancy and acute leukemia in children with Down syndrome: A Children's Oncology Group study

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Abstract

Background—Children with Down syndrome (DS) have about a 20-fold increased risk of developing leukemia. Early childhood infections may protect against acute lymphoid leukemia (ALL) in children with and without DS. We examined whether maternal infections and health conditions during pregnancy were associated with acute leukemia in children with DS.

Procedure—We conducted a case-control study of 158 children with DS and leukemia (including 97 cases with acute lymphoblastic leukemia (ALL) and 61 cases with acute myeloid leukemia (AML)) and 173 children with DS during the period 1997–2002. Maternal interview included information about fourteen maternal conditions during gestation that are likely to induce an inflammatory response. We evaluated their prevalence in cases and controls. Five of these were common enough to allow analyses by leukemia subtype.

Results—Vaginal bleeding was the most frequent (18% cases, 25% controls) and was associated with a reduced risk (Odds Ratio (OR)=0.57; 95% Confidence Interval (CI)=0.33–0.99) for all cases combined. Other variables, while showing a potential trend toward reduced risk had effect estimates which were imprecise and not statistically significant. In contrast, amniocentesis was marginally associated with an increased risk of AML (OR=2.06, 95%CI=0.90–4.69).

Conclusions—Data from this exploratory investigation suggest that some health conditions during pregnancy may be relevant in childhood leukemogenesis. Larger epidemiologic studies and other model systems (animal, clinical studies) may provide a clearer picture of the potential association and mechanisms.

Keywords

inflammation; Down syndrome; leukemia

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Introduction

Children with Down syndrome (DS) are at 20-fold increased risk of developing leukemia compared to children without DS, and, for acute megakaryocytic leukemia (M7), a subtype of acute myeloid leukemia (AML), this risk may be increased up to 500-fold.[1] AML is more common in children with DS compared to the general population and this phenomenon is strongly dependent on age. In children under 15 years of age, the ratio of acute lymphoblastic leukemia (ALL) to AML in children with DS is 1.7, in contrast to 6.5 in the general population. However, in children younger than 5 years, standardized incidence rates for AML are four times higher than for ALL.[2]

It is not clear why children with DS are at such an increased risk of developing leukemia. Children with DS have trisomy of chromosome 21 leading to overexpression of genes located on this chromosome. Many of these genes have been implicated in leukemia development.[3] Despite these facts, it is estimated that only 2% of children with DS will develop leukemia.[2] Therefore, host genetic susceptibility and environmental exposures likely work together to give rise to leukemia. In the multistep pathway leading to leukemia development, genetic susceptibility due to trisomy 21 in DS children would represent only the first step[4,5] and additional environmental exposures are probably also required.

Several environmental exposures and their associations with risk of leukemia in children without DS have been studied.[6] Among them, *in utero* exposure to X-rays and ionizing radiation, as well as postnatal exposure to ionizing radiation may increase the risk of childhood leukemia. Likewise, chemicals, such as pesticides and benzene have been associated with increased risk. Among lifestyle factors, maternal alcohol consumption may increase the risk of AML in very young children, while maternal and paternal smoking have yielded no clear associations.[6]

Several epidemiological studies have investigated risk factors for leukemia in children with DS.[7–12] In our study, periconceptional vitamin supplementation and early childhood infections showed a protective effect for ALL.[8,12] The latter results support the hypothesis by Greaves that early exposure to infections may enhance normal maturation of immune cells and thereby protect a child from developing ALL, while children whose exposure is delayed would be at comparatively increased risk of ALL.[13–15] A number of studies have supported the role of delayed infections in the etiology of childhood leukemia[16–18] and our recent study confirmed that this may also be true for ALL development among children with DS.[8]

Likewise, some of the genes overexpressed as a result of DS, such as superoxide dismutase-1 and lymphocyte function associated antigen-1, may contribute to the impaired immunity observed in children with DS. Due to impaired immunity, children with DS are more susceptible to infections,[19–21] possibly a consequence of defects in cell-to-cell communication and decreased white cell counts.[22,23] The impaired immunity could make these children more at risk of developing leukemia.

Unlike this well-defined role of the postnatal environment, our knowledge of how the intrauterine environment may impact the risk of leukemia is very limited. Weakened maternal immunity due to thyroid disease may play a role in DS development, although studies have been inconsistent[24–26] and have not addressed the risk of leukemia among children with DS. No studies of other conditions that may affect maternal immune system status have been carried out to date to examine their association with acute leukemia development in children with DS. Our study included a maternal interview with information about fourteen maternal health conditions during gestation. Although these conditions are heterogeneous, each may lead to release of inflammatory mediators, either locally or systemically. We investigated the

prevalence of such maternal health conditions during pregnancy and whether they may be associated with acute leukemia in children with DS.

Methods

Case Identification

A description of the study has been presented in detail elsewhere.[8,12] Briefly, children with DS and a diagnosis of either ALL or AML between January 1997 and October 2002 were identified using the registration files of the Children's Oncology Group (COG). Diagnosis of DS was confirmed by review of cytogenetic data and obstetrical medical charts for both cases and controls. Classification of acute leukemia was made by central review using clinical data, pathologic specimens and reports, and cytogenetic data. Permission to contact the parents was obtained from the child's physician and written consent was obtained from the child's mother. Cases were required to be 19 years of age or less at diagnosis, have a residential telephone, a biological mother available who spoke English, and have resided in the United States or Canada at diagnosis. From 116 COG institutions, 210 cases were identified and 158 mothers (75%) completed interviews (97 ALL and 61 AML). Reasons for not completing the interview included maternal refusal (17%), physician refusal (5%), and not being able to locate the mother (3%).

Control Identification

After the telephone interview, names and addresses of the primary care physician seen by cases before diagnoses of leukemia were obtained from the mothers of the cases. Primary care physicians were contacted and asked to provide a roster that included age and gender of their patients with DS who had no history of leukemia. Controls were randomly selected from the rosters and frequency matched to cases by age and sex. Controls were required to have a telephone in their home, have an English-speaking mother that could be interviewed, and reside in the United States or Canada. Out of the 151 clinics contacted, 77 provided rosters of patients with DS. Using these rosters, 726 potential controls were identified and 329 were randomly selected based on date of birth. Names and addresses were provided by the clinic for 215 of the random sample of controls. Of these, 173 mothers (80.5%) completed telephone interviews.

Data Collection

Data were collected using telephone interviews conducted with mothers of cases and controls and included information about medical and reproductive history, personal habits, and demographics. This was an exploratory case-control study in which the questionnaire was designed to examine a variety of factors. In these analyses, we have identified fourteen maternal health conditions during pregnancy that may induce an inflammatory response and analyzed their reported prevalence among cases and controls. These maternal health conditions during pregnancy of the case or control child included hypertension, preeclampsia or toxemia, heart disease, urinary tract or bladder infection, threatened miscarriage, vaginal bleeding, genital warts, gestational diabetes, insulin use, thyroid medication use, steroid or immunosuppressant use, amniocentesis, and chorionic villus sampling. Among these, the five most prevalent conditions (10% or higher in controls) were hypertension, urinary tract or bladder infection, vaginal bleeding, gestational diabetes and amniocentesis. Variables were created to look at the association between each of these conditions and risk of all leukemia, ALL or AML. Potential confounders identified *a priori* included maternal age (continuous), mother's education (high school or less, more than high school), mother's race (white, non-white), and the index child's sex.

Statistical Analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated from unconditional logistic regression models to examine the relationship between inflammatory conditions and leukemia. In addition to controlling for age of the index child at interview, all models were adjusted for potential confounders including maternal age, race, and education level and index child's sex. Separate models were constructed for each condition/exposure of interest as small sample size could make parameter estimates unstable in full multivariate models. To evaluate potential confounding, separate analyses were performed for the five most common inflammatory conditions after exclusion of cases and controls who received steroids or immunosuppressants. We also evaluated potential confounding by adjusting for early childhood infections. Separate analysis was performed for the ALL and AML subgroups to examine differential effects of the exposures. Since this analysis was exploratory, no adjustment for multiple comparisons was made. A sensitivity analysis was also performed which limited the cases to those for whom physicians provided a roster of controls. All analysis was performed using SAS 9.1 (SAS Institute, Inc., Cary, NC).

Results

The major ALL subtype was L1 (78%) and the major AML subtype was M7 (60%). The high proportion of the M7 subtype was in concordance to previous reports for the DS population. [27] Table I shows demographic information for cases and controls and their mothers. There were some differences in maternal characteristics including race, educational level, and age between cases and controls. Case mothers were more likely to be non-white (OR=1.93, 95% CI=1.05–3.54) and were less likely to have more than a high school education (OR=0.49, 95% CI=0.30–0.78). In addition, case mothers were more likely to be age 35 or older at birth of the index child compared to controls both overall (OR=1.53, 95%CI=0.97–2.41), and for AML specifically (OR=2.09, 95% CI=1.15–3.81) (Table I). However, mean maternal age for cases and controls was 32.5 years and 31.9 years, respectively, with respective standard deviations of 7.1 years and 6.2 years and did not differ significantly (p=0.46).

We examined fourteen common maternal health conditions during pregnancy as shown in Table II. The majority of these conditions/exposures were rare, present in less than five cases of ALL, AML, or controls. Only vaginal bleeding, urinary tract or bladder infection, amniocentesis, gestational diabetes and hypertension were more frequent. Vaginal bleeding was by far the most common characteristic, present in 18% of cases and 25% of controls.

We further examined associations between the five most prevalent maternal health conditions during pregnancy and acute leukemia risk (Table III). Vaginal bleeding, the most common condition in our study, was associated with reduced risk for acute leukemia (all cases combined) (OR=0.57, 95% CI=0.33–0.99). Analyses for each subgroup showed the same trend, but were more imprecise. Three other common maternal conditions showed a potential trend toward reduced risk, although they were associated with wide confidence intervals. In contrast, amniocentesis was associated with a possible increased risk of AML (OR=2.06, 95% CI=0.90–4.69).

We also analyzed whether these exposures were associated with early onset of ALL, diagnosed before the age of 5 years (such analyses were not possible for AML because only one AML case was diagnosed after the age of 5 years). Analyses were possible for only two exposures; vaginal bleeding and urinary tract or bladder infection, but the small number of cases in each group lead to imprecise estimates and little evidence of an age at diagnosis effect (data not shown). Separate analyses were also performed for the five most common conditions after exclusion of cases (n=7) and controls (n=7) who received steroids or immunosuppressants. No differences in the magnitude of the odds ratios were observed after these exclusions (data not

shown). Likewise, the odds ratios remained relatively constant after adjusting for steroid and immunosuppressant use in the analysis. Controlling for subjects who developed infections during the first two years of life did not meaningfully affect the results. Limiting analysis to cases whose primary care clinic provided some controls for the study did attenuate the effect seen for vaginal bleeding (combined cases; OR=0.76, 95% CI=0.38–1.54) and amniocentesis (AML; OR = 1.34, 95% CI = 0.44–4.13), but the overall trend was similar.

Discussion

Based upon published observations that early childhood infections may protect against ALL development in children with and without DS,[8,15] and that such infections are often accompanied by profound inflammatory response, we examined whether *in utero* exposure due to maternal health conditions that may mediate an inflammatory response may similarly affect leukemia risk. From the data collected through our case-control study of DS and leukemia, we identified fourteen of the most commonly reported such maternal health conditions during pregnancy, of which only five were present in at least 5 cases and 5 controls.

Overall, we found little evidence of an association between maternal health conditions during pregnancy and leukemia in children with DS. Although most conditions tended to have OR estimates less than one, these were not precise enough to infer reduced risk. However, two conditions showed some evidence of differential risk. Vaginal bleeding was associated with a reduced risk for leukemia for all cases combined. The same pattern of association was observed among ALL and AML cases. Amniocentesis was marginally associated with an increased risk in the AML subgroup. However, these results should be interpreted with caution due to small sample size and multiple comparisons.

It is plausible that the potential mechanism leading to reduced risk for leukemia associated with vaginal bleeding might involve activation of the maternal immune system. It has been shown in mice that activated maternal T cells can cross the placenta, enter the fetal circulation, and exhibit immune modulation effects in the fetus.[28] It is not clear whether the maternal inflammatory response may lead to enhanced maturation of the fetal immune system. However, it is likely that maternal inflammatory response may induce an inflammatory response in the fetus either directly, by passing of activated maternal lymphocytes[28] or maternally-produced cytokines[29,30] through the placenta and into fetal circulation, or indirectly, by inducing inflammation of the placenta, which in turn produces cytokines released into fetal circulation, as shown in gestational diabetes.[31] The fetal immune system is immature, but it may contribute to maternally-initiated inflammation by releasing pro- and anti-inflammatory cytokines[32]; however, whether it can contribute to elimination of transformed fetal cells remains unknown.

There are several strengths of this study. This is the largest study to focus on childhood leukemia specifically in children with DS. It is also the first study to examine maternal conditions/ exposures during pregnancy that could be associated with an inflammatory response and describe them as such. In addition, we might expect recall bias to be less of a factor in this study since controls also were affected with DS. Mothers of children with DS might have the same propensity to think about potential causes and exposures during pregnancy regardless of whether or not the child also develops leukemia.

One of the limitations of our study is the varying period of time between the index pregnancy and the interview that in some subjects reached 20 years. This is important since we might expect recall accuracy to decline over time. Several papers have examined potential recall bias when assessing conditions during pregnancy. [33–35] One study looked specifically at the effect of length of time since birth on maternal recall and found that many medical conditions

had reduced sensitivity and specificity over time.[35] To attempt to control for this we included the child's age at interview in our analysis. While this does not eliminate the problem of maternal recall bias based on time since birth, it is the best way we could account for it in our study.

Selection bias among controls is another limitation of our study. One third of the clinics refused to provide rosters of potential controls and contact information was not available for one third of the children selected. To attempt to assess this potential bias due to clinic non-participation, a sensitivity analysis was performed limited to cases from whose primary care clinic provided controls. We found some attenuation of the effect of vaginal bleeding and amniocentesis, although this was based on a very small number of cases and the general trends of both of these variables remained consistent. There is also a potential concern about participation bias in this study. Since we could not obtain information on characteristics of non-participating controls we could not fully examine how different the participants were compared to the population of interest. In fact, since many clinics did not provide control information, we could not calculate the overall participation rate for the controls. We did find that the controls mothers who participated were older, more often white, and reported higher education compared to cases. This could indicate participation bias in our study. Since we do not have information about the controls not recruited in our study and we cannot know for sure if we have controlled for all possible factors that could influence our exposure variables, we cannot rule out bias. However, the prevalence of vaginal bleeding, urinary tract or bladder infection, amniocentesis, gestational diabetes and hypertension observed in our study of children with DS was similar to those reported in non-DS pregnancies. For example, gestational diabetes mellitus has recently been shown to be increasing, at least in some population subgroups.[36] This condition was present in 11% of controls in our study. Likewise, hypertension occurs in approximately 8% of non-DS pregnancies[37], 11.6% of controls in our study reported maternal hypertension. Vaginal bleeding is the most common complication of pregnancy occurring in around 25% of non-DS pregnancies[38] and we observed a similar prevalence in our study of children with DS (24.9% in controls).This provides us with at least some evidence that selection bias might not be a large factor in the analysis if mothers of children with DS have the same prevalence of these conditions as mothers of children without DS. For cases, the potential for selection bias was minimal, because case participation was high and the Children's Oncology Group treats 94% of children with leukemia aged 0–14 years and 21% of those aged 15–19 years. [39,40]

Although this is the largest study of leukemia among children with DS to date, the sample size is still small, which leads to imprecise effect estimates. In addition, the maternal health conditions described here represent a limited and heterogeneous group. Other conditions, such as autoimmune disease, trauma, allergies, etc, were not ascertained. We also have not classified the conditions based on their ability to induce systemic or local inflammation. While chronic conditions (hypertension, diabetes, preeclampsia) are known to induce systemic inflammation, it is more likely that the inflammation as part of the wound-healing process (vaginal bleeding, threatened miscarriage and amniocentesis) would be more localized. However, the proximity of such localized inflammation to the developing fetus deems paracrine signaling plausible and therefore such exposures were included in our study.

In conclusion, this study examined at the associations of various health conditions associated with inflammation during pregnancy and the risk of acute leukemia in children with DS. Our data suggest a reduced risk of acute leukemia associated with vaginal bleeding and provide some indication of a positive association between amniocentesis and AML. As these results are based on small numbers, and many comparisons were made, they must be interpreted with caution and await confirmation by other studies.

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Table I

Baseline characteristics by leukemia subtype.

	No. of controls (%)	No. of all cases (%)	OR (95%CI)	No. of ALL cases (%)	OR (95%CI)	No. of AML cases (%)	OR (95%CI)
Mother's Race							
White	152 (88.4)	126 (79.7)	1.0	79 (81.4)	1.0	47 (77.0)	1.0
Non-white	20 (11.6)	32 (20.3)	1.93 (1.05–3.54)	18 (18.6)	1.73 (0.87–3.46)	14 (23.0)	2.26 (1.06–4.83)
Mother's Age							
<35 years	120 (69.8)	95 (60.1)	1.0	63 (64.9)	1.0	32 (52.5)	1.0
≥35 years	52 (30.2)	63 (39.9)	1.53 (0.97–2.41)	34 (35.1)	1.25 (0.73–2.11)	29 (47.5)	2.09 (1.15–3.81)
Mother's Education							
≤High school	41 (23.8)	62 (39.2)	1.0	40 (41.2)	1.0	22 (36.1)	1.0
>High school	131 (76.2)	96 (60.8)	0.49 (0.30–0.78)	57 (58.8)	0.45 (0.26–0.76)	39 (63.9)	0.56 (0.30–1.04)
Household Income							
≤$30,000	57 (33.1)	57 (36.5)	1.0	37 (38.5)	1.0	20 (33.3)	1.0
$30,001–50,000	41 (23.8)	43 (27.6)	1.05 (0.60–1.84)	22 (22.9)	0.83 (0.43–1.60)	21 (35.0)	1.46 (0.70–3.04)
>$50,000	74 (43.0)	56 (35.9)	0.76 (0.46–1.25)	37 (38.5)	0.77 (0.44–1.36)	19 (31.7)	0.73 (0.36–1.50)
Index child's gender							
Male	90 (52.0)	85 (53.8)	1.0	57 (58.8)	1.0	28 (45.9)	1.0
Female	83 (48.0)	73 (46.2)	0.93 (0.60–1.44)	40 (41.2)	0.76 (0.46–1.26)	33 (54.1)	1.28 (0.71–2.30)
Index child's age at interview date*							
< 4 years	52 (30.1)	55 (34.8)		14 (14.4)		41 (67.2)	
4–5 years	39 (22.5)	44 (27.8)		27 (27.8)		17 (27.9)	
6–8 years	29 (16.8)	30 (19.0)		27 (27.8)		3(4.9)	
≥ 9 years	53 (30.6)	29 (18.4)		29 (29.9)		0(0.0)	
Any Inflammation Condition (of 14)							
No	65 (37.6)	70 (44.3)	-	49 (50.5)	-	21 (34.4)	-
Yes	108 (62.4)	88 (55.7)	-	48 (49.5)	-	40 (65.6)	-
Any Inflammation Condition (of 5)							
No	78 (45.1)	81 (51.3)	-	56 (57.7)	-	25 (41.0)	-
Yes	95 (54.9)	77 (48.7)	-	41 (42.3)	-	36 (59.0)	-

* Not evaluated for relationship to leukemia since it was a frequency matching factor

Table II

Prevalence of the maternal health conditions during pregnancy in the case-control study of acute leukemia in children with Down syndrome.

	No. of controls (%)	No. of all cases (%)	No. of ALL cases (%)	No. of AML cases (%)
Hypertension**				
No	153 (88.4)	147 (93.0)	91 (93.8)	56 (91.8)
Yes	20 (11.6)	11 (7.0)	6 (6.2)	5 (8.2)
Preeclampsia or Toxemia				
No	164 (95.3)	154 (98.1)	94 (96.9)	60 (100.0)
Yes	8 (4.7)	3 (1.9)	3 (3.1)	0 (0.0)
Heart Disease				
No	168 (97.1)	154 (97.5)	94 (96.9)	60 (98.4)
Yes	5 (2.9)	4 (2.5)	3 (3.1)	1 (1.6)
Urinary tract or bladder infection**				
No	147 (85.0)	137 (86.7)	85 (87.6)	52 (85.2)
Yes	26 (15.0)	21 (13.3)	12 (12.4)	9 (14.8)
Kidney infection				
No	170 (98.8)	157 (99.4)	96 (99.0)	61 (100.0)
Yes	2 (1.2)	1 (0.6)	1 (1.0)	0 (0.0)
Threatened miscarriage				
No	157 (91.3)	144 (92.3)	89 (91.8)	55 (93.2)
Yes	15 (8.7)	12 (7.7)	8 (8.2)	4 (6.8)
Vaginal bleeding**				
No	130 (75.1)	129 (81.6)	78 (80.4)	51 (83.6)
Yes	43 (24.9)	29 (18.4)	19 (19.6)	10 (16.4)
Genital warts				
No	172 (99.4)	154 (98.7)	96 (99.0)	58 (98.3)
Yes	1 (0.6)	2 (1.8)	1 (1.0)	1 (1.7)
Gestational diabetes**				
No	154 (89.0)	142 (89.9)	87 (89.7)	55 (90.2)
Yes	19 (11.0)	16 (10.1)	10 (10.3)	6 (9.8)
Insulin use during pregnancy				
No	168 (97.1)	154 (98.1)	95 (97.9)	59 (98.3)
Yes	5 (2.9)	3 (1.9)	2 (2.1)	1 (1.7)
Thyroid medication use in pregnancy				
No	165 (95.4)	150 (95.5)	94 (96.9)	56 (93.3)
Yes	8 (4.6)	7 (4.5)	3 (3.1)	4 (6.7)
Steroid/Immunosuppressant use in pregnancy				
No	165 (95.4)	151 (95.6)	92 (94.8)	59 (96.7)
Yes	8 (4.6)	7 (4.4)	5 (5.2)	2 (3.3)

	No. of controls (%)	No. of all cases (%)	No. of ALL cases (%)	No. of AML cases (%)
Amniocentesis**				
No	154 (89.0)	132 (83.5)	88 (90.7)	44 (72.1)
Yes	19 (11.0)	26 (16.5)	9 (9.3)	17 (27.9)
Chorionic Villus Sampling				
No	169 (99.4)	154 (98.1)	95 (97.9)	59 (98.3)
Yes	1 (0.6)	3 (1.9)	2 (2.1)	1 (1.7)

** At least 5 cases of both ALL and AML and 5 controls reported the event.

Table III

Most prevalent maternal health conditions during pregnancy and the risk of acute leukemia in children with Down syndrome.

	No. of controls (%)	No. of all cases (%)	OR*	95% CI	No. of ALL cases (%)	OR*	95% CI	No. of AML cases (%)	OR*	95% CI
Hypertension										
No	153 (88.4)	147 (93.0)	1.0		91 (93.8)			56 (91.8)		
Yes	20 (11.6)	11 (7.0)	0.54	[0.24,1.21]	6(6.2)	0.42	[0.16,1.14]	5(8.2)	0.94	[0.29,2.97]
Urinary tract or bladder infection										
No	147 (85.0)	137 (86.7)	1.0		85 (87.6)			52 (85.2)		
Yes	26 (15.0)	21 (13.3)	0.79	[0.41,1.52]	12 (12.4)	0.73	[0.33,1.59]	9(14.8)	0.95	[0.38,2.40]
Vaginal bleeding										
No	130 (75.1)	129 (81.6)	1.0		78 (80.4)			51 (83.6)		
Yes	43 (24.9)	29 (18.4)	0.57	[0.33,0.99]	19 (19.6)	0.67	[0.35,1.27]	10 (16.4)	0.52	[0.23,1.20]
Gestational diabetes										
No	154 (89.0)	142 (89.9)	1.0		87 (89.7)			55 (90.2)		
Yes	19 (11.0)	16 (10.1)	0.87	[0.42,1.80]	10 (10.3)	0.91	[0.39,2.11]	6(9.8)	0.86	[0.30,2.46]
Amniocentesis										
No	154 (89.0)	132 (83.5)	1.0		88 (90.7)			44 (72.1)		
Yes	19 (11.0)	26 (16.5)	1.46	[0.74,2.87]	9(9.3)	0.93	[0.38,2.25]	17 (27.9)	2.06	[0.90,4.69]

*Logistic regression models were adjusted for child's age at interview (continuous), mother's age (continuous), mother's race (white vs. non-white), child's sex, and education (≤ high school vs. >high school)