Communication

Repeated Diagnosis of Illnesses Involving Fever or Pain During Early Childhood is Very Strongly Associated with Autism Spectrum Disorder

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Repeated Diagnosis of Illnesses Involving Fever or Pain During Early Childhood is Very Strongly Associated with Autism Spectrum Disorder

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Abstract

A large body of evidence implicates the exposure of susceptible individuals to acetaminophen in the etiology of ASD. We undertook this study to probe the association between ASD and a wide range of childhood diagnoses that would typically warrant acetaminophen use for treatment of pain, fever, or both. The Florida Medicaid database was utilized as the source of medical records. Associations between "acetaminophen exposure surrogates" and ASD were unexpectedly large, with odds ratios of 2.629 (2.343 to 2.949), p-value < 0.0001, for children with at least four diagnoses considered surrogates for acetaminophen use. When fever alone was inspected girls had a statistically different and greater odds ratio 3.663 (3.264 to 4.109), p-value < 0.0001, compared to boys with an odds ratio of 2.844 (2.664 to 3.036), p-value < 0.0001. The greater odds ratios for girls compared to boys appeared to be a consequence of fewer girls without ASD having acetaminophen exposure surrogates. The presence of less than four exposure surrogates was less well associated with ASD, suggesting that multiple exposure surrogates may carry the greatest relative risk of ASD, especially for girls.

Keywords: acetaminophen; paracetamol; ASD; autism spectrum disorder; autism

Introduction

Evidence has emerged over the past two decades pointing toward exposure of susceptible babies and children to acetaminophen as a factor leading to autism spectrum disorder (ASD) [1–7]. The current working model is that neurodevelopmental risks from acetaminophen exposure are greatest during the peripartum period, and decrease over time as the child ages, dissipating by age 6 years [6]. Risk during pregnancy, although possibly lower than post-partum risk, is still probably significant [8]. Unfortunately, many laboratories have underestimated or even overlooked entirely the contribution of acetaminophen to the prevalence of ASD, in large part due to errors in adjusting for confounding factors [7], and due to a focus on pregnancy, when the risks of ASD induction may be lower [6].

The first study probing the connection between acetaminophen use and ASD was published by Schultz in 2008 [9]. That study suggested that the vast majority of all cases of regressive ASD might be attributed to acetaminophen exposure. Although the study has been criticized, a detailed analysis reveals that those criticisms are not valid [5]. The Schultz study adds to independent studies from pregnancy and from the peripartum period, strengthening the link between acetaminophen use and ASD. However, other than the Schultz study, few additional studies have addressed the association between acetaminophen use and regressive ASD, with a major limitation being that the use of acetaminophen in early childhood is often not documented.

In this study, we probed the association between ASD and medical conditions that normally result in acetaminophen exposure during childhood. For this purpose, we evaluated associations between ASD and the occurrence of several conditions involving fever and/or pain using the Florida

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Medicaid database. Here we report initial results from that study, demonstrating remarkably strong associations between repeated documentation of "acetaminophen exposure surrogates" and ASD.

Methods

Data from the Florida Medicaid database was used for the analysis. In all, 674,785 children (Table 1) born between 1990 and 2005 were included if they had at least one Medicaid diagnosis in their first year of life and at or after their 6th year of life. This study is designed to ensure it does not include children who are enrolled in Medicaid but do not interact with it (where diagnoses would not be captured by the system) through the time most likely to receive an ASD diagnosis. This extremely conservative design will inevitably exclude children with a healthy disposition at age 6 and older who do interact with the Medicaid system and do not receive a medical diagnosis between age 6 and the time they leave Medicaid or the study period concludes. Diagnoses for dental work (ICD-9 codes 521, 522, 523), ear ache (ICD-9 codes 381, 382), sinusitis (ICD-9 codes 461, 473), sore throat, tonsillitis or laryngitis (ICD-9 codes 034, 462, 463, 464, 474, 478), upper respiratory tract infection (ICD-9 code 465), fever (ICD-9 codes 780.6 and 078.2) and flu (ICD-9 code 487) were used as surrogates for acetaminophen exposure. All subsequent surrogates were considered providing the first such surrogate was diagnosed before ASD.

Table 1. Study population characteristics.

Category	Sub-Category	N	% of participants
Participants		674,785	
	Male	349,463	51.79%
	Female	325,322	48.21%
Autism diagnosed		8,830	1.31%
	Male	6,769	1.00%
	Female	2,061	0.31%
At least 1 surrogate		624,794	92.59%
	Male	323,883	48.00%
	Female	300,911	44.59%
At least 2 surrogates		578,394	85.72%
	Male	300,218	44.49%
	Female	278,176	41.22%
At least 3 surrogates		533,938	79.13%
	Male	277,477	41.12%
	Female	256,461	38.01%
At least 4 surrogates		493,062	73.07%
	Male	256,582	38.02%
	Female	236,480	35.05%

Results

The associations between acetaminophen exposure surrogates and ASD are shown in Figure 1 and in Table 2. The results of analyses using a minimum of between one and four acetaminophen exposure surrogates are shown. The OR for ASD with one or more surrogates compared to no surrogates was 2.261 (2.016 to 2.536), p-value < 0.0001.

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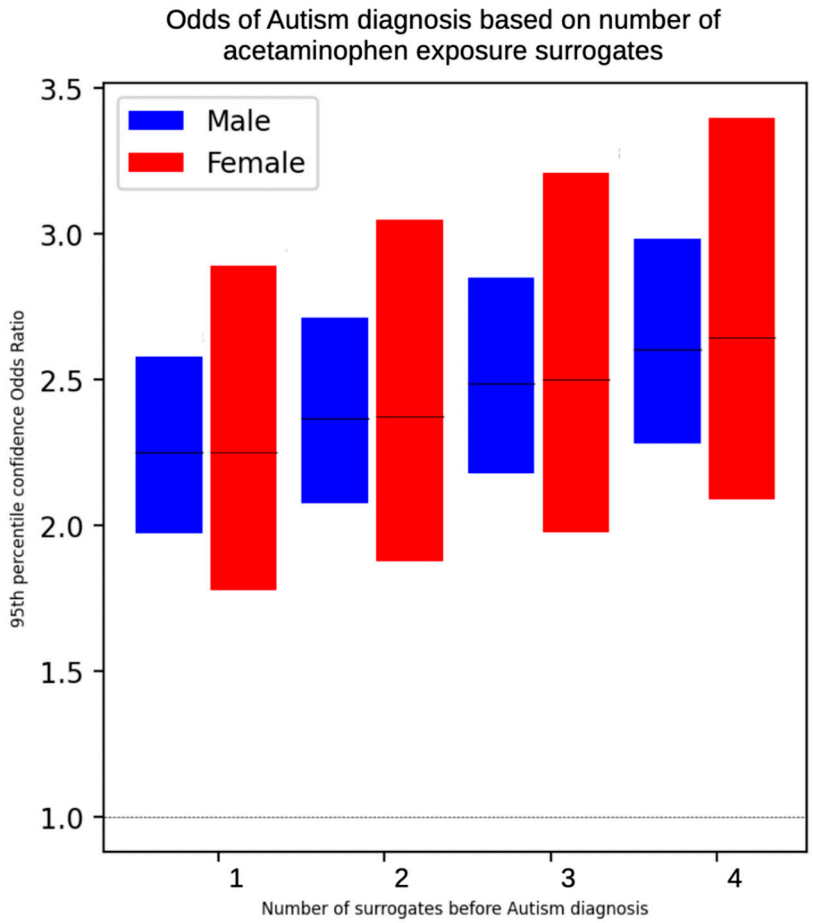

Figure 1. Risk of ASD associated with surrogates for acetaminophen use.

Table 2. Risk of ASD associated with surrogates for acetaminophen use.

surrogates	Boys and Girls		Boys		Girls	
Minimum number of surrogates	ASD (exposed/controls) No ASD (exposed/controls)	OR (+/- 95% CI), p-value	ASD (exposed/controls) No ASD (exposed/controls)	OR (+/- 95% CI), p-value	ASD (exposed/controls) No ASD (exposed/controls)	OR (+/- 95% CI), p-value
1	(8526,304) (616268,49687)	2.2612 (2.0161 to 2.5362), P < 0.0001	(6537, 232) (317346, 25348)	2.2506 (1.9732 to 2.5671), P < 0.0001	(1989, 72) (298922, 24349)	2.2502 (1.7781 to 2.8477), P < 0.0001
2	(8304,304) (570090,49687)	2.3807 (2.1225 to 2.6704), P < 0.0001	(6364, 232) (293854, 25348)	2.3662 (2.0744 to 2.6991), P < 0.0001	(1940, 72) (276236, 24349)	2.3750 (1.8765 to 3.0060), P < 0.0001
3	(8054,304) (525884,49687)	2.5032 (2.2315 to 2.8079), P < 0.0001	(6172, 232) (271305, 25348)	2.4856 (2.1788 to 2.8355), P < 0.0001	(1882, 72) (254579, 24349)	2.5000 (1.9750 to 3.1646), P < 0.0001
4	(7804,304) (485258,49687)	2.6285 (2.3431 to 2.9487), P < 0.0001	(5969, 232) (250613, 25348)	2.6023 (2.2810 to 2.9689), P < 0.0001	(1835, 72) (234645, 24349)	2.6447 (2.0890 to 3.3481), P < 0.0001

The risk did not differ significantly between boys and girls when all surrogates were investigated together, but when fever (one of the most common reasons for childhood acetaminophen use) alone was inspected, girls had a significantly different and greater risk of developing ASD if they were diagnosed with a fever as shown in Figure 2 and Table 3. Boys with one fever diagnosis had a 56% increased risk for ASD (OR 1.562 (1.483 to 1.645), p-value < 0.0001), and a 184% increased risk with four fever diagnoses (OR 2.844 (2.664 to 3.036), p-value < 0.0001). In stark contrast, girls with one

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fever diagnosis had a 79% increased risk for ASD (OR 1.792 (1.631 to 1.970), p-value < 0.0001), and a 266% increased risk with four fever diagnoses (OR 3.663 (3.264 to 4.109), p-value < 0.0001).

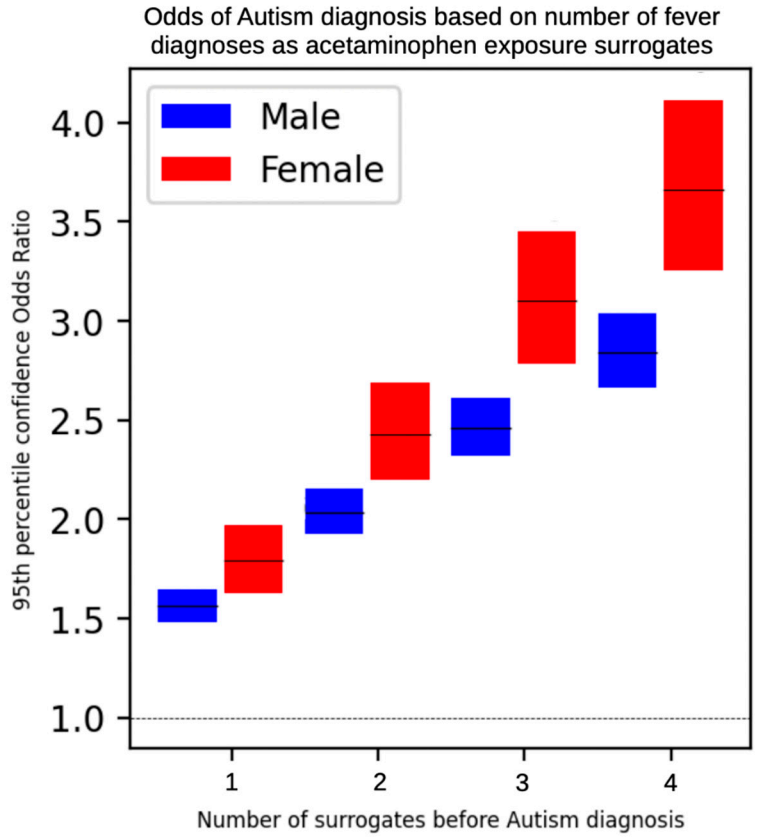

Figure 2. Risk of ASD associated with fever as a surrogate for acetaminophen use.

Table 3. Risk of ASD associated with fever as a surrogate for acetaminophen use.

Fever	Boys and Girls		Boys		Girls	
Minimum number of surrogates	ASD (exposed/controls) No ASD (exposed/controls)	OR (+/- 95% CI), p-value	ASD (exposed/controls) No ASD (exposed/controls)	OR (+/- 95% CI), p-value	ASD (exposed/controls) No ASD (exposed/controls)	OR (+/- 95% CI), p-value
1	(5116, 3015) (339852, 326113)	1.6283 (1.5562 to 1.7036), P < 0.0001	(3893, 2347) (176501, 166193)	1.5618 (1.4832 to 1.6446), P < 0.0001	(1223, 668) (163351, 159920)	1.7924 (1.6307 to 1.9701), P < 0.0001
2	(3807, 3015) (191553, 326113)	2.1497 (2.0487 to 2.2556), P < 0.0001	(2879, 2347) (100128, 166193)	2.0360 (1.9269 to 2.1513), P < 0.0001	(928, 668) (91425, 159920)	2.4300 (2.1992 to 2.6850), P < 0.0001
3	(2799, 3015) (114678, 326113)	2.6400 (2.5065 to 2.7806), P < 0.0001	(2094, 2347) (60250, 166193)	2.4610 (2.3185 to 2.6123), P < 0.0001	(705, 668) (54428, 159920)	3.1009 (2.7883 to 3.4486), P < 0.0001
4	(2054, 3015) (72269, 326113)	3.0742 (2.9049 to 3.2534), P < 0.0001	(1532, 2347) (38148, 166193)	2.8437 (2.6639 to 3.0357), P < 0.0001	(522, 668) (34121, 159920)	3.6625 (3.2643 to 4.1092), P < 0.0001

Increasing the number of minimum acetaminophen exposure surrogates in the analysis increased the OR considerably (Figure 1, Table 2), indicating that multiple surrogates imposed considerably more risk than single surrogates.

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Discussion

The present study was not undertaken to probe the causal relationship between acetaminophen exposure and ASD. A causal relationship has been inferred from a large and robust body of evidence [1–7], and the present study is not designed to address that issue. Rather, this study was conducted to probe the relationships between ASD and the occurrence of childhood illnesses that typically involved treatment with acetaminophen.

The present results demonstrate very strong associations between typical childhood illnesses and ASD, with a very strong sex-linked signal. The stronger association with girls than with boys, appeared to be a result of fewer girls than boys without ASD having documented acetaminophen exposure surrogates (Table 2). However, in this study as in many previous studies, ASD was predominantly observed in males, a fact reflected by several laboratory animal studies showing that males are more susceptible to acetaminophen-mediated neurodevelopmental injury than are females [10–13].

Previous studies have shown that individuals with ASD tend to have more childhood infections than individuals without ASD [14,15]. However, in contrast to the present study, the observed OR's were lower than 2.0 [14,15]. The present study shows that removing individuals with a fewer number of diagnoses from the analysis dramatically increases the risks for ASD. Thus, it seems likely that the higher OR's we observed compared to previous studies are due to multiple occurrences of acetaminophen exposure surrogates, and suggests that multiple exposures to acetaminophen may be important in the etiology of ASD.

A next step in this work will be to evaluate risks of ASD as a function of the number of diagnoses and the type of diagnoses. The current data are sufficient to infer that four or more diagnoses are associated with greater risk than three or less diagnoses, but whether the risk of ASD plateaus with a particular number of diagnoses remains to be seen. Further, it remains unknown whether particular diagnoses (e.g., sinusitis versus ear infection) are associated with more risks than others.

Conclusions

It is recognized that immune activation and oxidative stress render acetaminophen more dangerous due to its pharmacological properties [16]. Unfortunately, individuals with inflammation and oxidative stress are more likely to be exposed to acetaminophen, creating a dangerous situation in which the individuals most likely to be injured by acetaminophen are the individuals most likely to be exposed to the drug. This study adds further to that knowledge, suggesting that individuals with multiple exposures to acetaminophen may be particularly at risk. An important caveat to this view is that limited exposures during the peripartum period may in fact be extremely hazardous [6,17,18].

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Conflicts of Interest: The authors declare no conflicts of interest.

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