

RESEARCH LETTER

Unadjusted Analysis of a Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism

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Abstract

Madsen et al.'s unadjusted results do not support rejecting the causal link between the MMR (measles, mumps, and rubella) vaccine and autism. The summary statistics and errors in the original publication warrant

the release of the raw data. Madsen et al. is a cornerstone publication that forms the basis of the claim that vaccines do not cause autism, and thus, correctness and transparency need to be ensured.

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Introduction

On November 7, 2002, *The New England Journal of Medicine*, a journal of the Massachusetts Medical Society published an article by Madsen et al., titled "A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism."¹ The original research article concludes that the "study provides strong evidence against the hypothesis that MMR vaccination causes autism."

Madsen has been cited prolifically by over a hundred PubMed-indexed publications² and more than a thousand in Google Scholar,³ many of which address vaccine "hesitancy." *The New England Journal of Medicine* is widely regarded as one of the most prestigious medical journals globally. With its support, Madsen has become a cornerstone publication that forms the basis of the claim that vaccines do not cause autism.

What Does Strong Evidence Look Like?

Madsen states, "[t]his study provides strong evidence against the hypothesis that MMR (measles, mumps, and rubella) vaccination causes autism." The authors further state, "[t]he power of the study is reflected in the narrow 95 percent confidence intervals." A study that provides strong evidence against a causal association would have a relative risk close to 1.00 and tight confidence intervals that overlap 1.00 (e.g., 1.01 (0.98-1.04)). It is striking just how wide the authors' confidence intervals are for the purported strong evidence against the causation of autistic

disorder, 0.92 (0.68-1.24). In lay terms, this means that the authors are 95% confident that recipients of the MMR vaccine are anywhere from 47% less likely to 24% more likely to be harmed by autistic disorder. This is "strong evidence" of the need for more evidence.

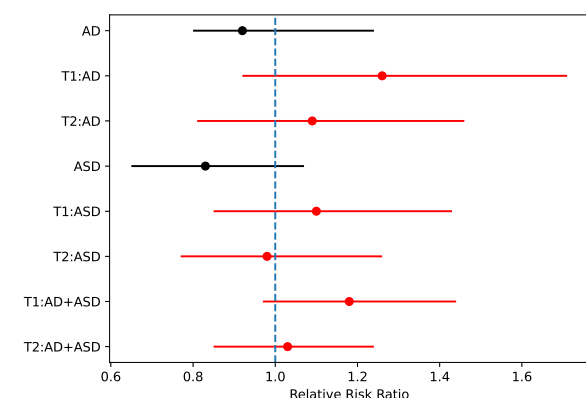
It is problematic in a study purporting a lack of causation if the relative risk is further away from 1.00, either high or low. The null hypothesis is that vaccination does not affect autism. The detachment from the null hypothesis, as exhibited in Madsen, concludes either that vaccination is protective against an autism diagnosis (a claim the authors do not make) or that there is a fault in the analysis, which invalidates the study.

Adjustment Inversion

Madsen's Table #2 demonstrates, with statistical adjustment, that the authors calculate the relative risk of autistic disorder for MMR vaccination as 0.92 (0.68-1.24), or non-significantly beneficial against autism [Figure 1]. Without statistical adjustment, we can calculate the relative risk⁴ of the 263 autistic disorders from the 440 655 vaccinated and the 53 autistic disorders from the 96 648 unvaccinated children to be 1.09 (0.81-1.46, *P* value = .574), or non-significantly harmful. Likewise, Madsen calculates the adjusted 'other autistic-spectrum disorders' relative risk to be 0.83 (0.65 - 1.07), whereas unadjusted, we calculate the relative risk of the 345 vaccinated and 77 unvaccinated diagnosed children to be 0.98 (0.77-1.26, *P* value = .890).

Considering the adjustment inversion, regarding the switch from vaccine 'favoring harm' to 'favoring protection' from autistic disorder upon adjustment, it would be appropriate to share the detailed model used for statistical adjustment, which the authors did not provide. The authors do not share the relevant data. It is, therefore, impossible to determine if the authors performed good-faith analyses or selected confounding variables for

Figure 1. Relative Risk Ratios and 95% Confidence Intervals as Derived from Madsen et al.



Note: Statistical Adjustment Relative Risk Ratios (Black) Have Been Plotted with the Unadjusted Relative Risk Ratios (Red). For the Same Cohort, Madsen et al. Produced Different Disease Outcome Summary Statistics in Table 1 (T1) Than in Table 2 (T2). The Disease Outcomes are ‘Autistic Disorder’ (AD) and ‘Other Autism-Spectrum Disorder’ (ASD). Both AD and ASD are Exclusive Groups and May be Combined (AD+ASD), an Analysis not Performed in the Original Publication.

adjustment for a specific outcome. The authors obtained “[i]nformation on potential confounders, including socioeconomic status (as indicated by the employment status of the head of the household) and mother’s education was obtained from Statistics Denmark from the time when the child was 15 months of age.” Table 1 shows that the vaccinated child’s family socioeconomic status is more likely to be either high or medium, and their mother’s education is more likely to be college or vocational training. No other variables were inspected by “Statistics Denmark.” In contrast, Hviid et al.,⁵ which includes 3 of the same authors and much of the same data, additionally included the child’s place of birth, 5-minute Apgar score, mother’s age at birth of child, and mother’s country of birth as confounding variables and excluded mother’s education, and socioeconomic status of the family as confounding variables. The authors “determined MMR-vaccination status on the basis of vaccination data reported to the National Board of Health.” Although the source contains records of the previously recommended 3 doses each of polio, diphtheria, tetanus, pertussis (as demonstrated in Hviid et al.), and *Haemophilus influenzae* type b (Hib) for each child, the authors did not entertain these as potential confounding variables.

Cohort Confusion

The disposition of the unvaccinated autistic population forms the baseline of this study, and the authors are confused about how many there are. In Table 1, the sum of ‘age at diagnosis of autistic disorder’ has 269 (48+187+34) vaccinated and 47 (9+31+7) unvaccinated children. This contrasts with Table 2, which has 263 vaccinated and 53 unvaccinated children. This implies a 12.3% increase in the unvaccinated baseline population. In

Table 1, the sum of ‘age at diagnosis of other autistic-spectrum disorder’ has 352 (32+202+118) unvaccinated and 70 (3+37+30) vaccinated children. This starkly contrasts with Table 2, which contains 345 vaccinated and 77 unvaccinated children. This implies a 10% increase in the unvaccinated baseline population. This confusion was neither resolved in peer review nor in the following 23 years.

The authors’ confusion about the total number of autistic and autism-spectrum disorder children makes a huge difference. Although a swing of merely 13 children, the overall diagnosis is 1 in 728 children (738/537,303) in the study, so it represents a foundational swing. As expected, Figure 1 shows that relative risks are higher for Table 1-derived ratios (with 13 fewer autism-diagnosed unvaccinated children) than for Table 2-derived ratios.

Madsen’s study does not double-count autistic disorder and autism spectrum disorder. Therefore, we can calculate them in total. The study has a total cohort size of 440,655 vaccinated and 96,648 unvaccinated children. According to the Table 2 summary statistics, there are 608 vaccinated and 130 unvaccinated children with either autistic disorder or other autism-spectrum disorder. This yields a relative risk of 1.03 (0.85-1.24) and a *P* value of .792, implying statistical insignificance. However, by Table 1 summations, there are 631 vaccinated and 117 unvaccinated children with either autistic disorder or other autism-spectrum disorder. This yields a relative risk of 1.18 (0.97-1.44) and a *P* value of .095. While some researchers would opine a *P* value below .1 to be significant, most would find it noteworthy, but none would say it is strong evidence against causation.

Historical Significance

For a brief period, there were a few countries or healthcare organizations in the world capable of studying the effects that vaccines have on autism with such clarity. The beginning of the exponentially exploding epidemic is when other theorized toxic exposures are at a minimum. During the time of the Madsen study, the other vaccines on the Danish recommended schedule before 2 years of age were polio, diphtheria, tetanus, pertussis, and Hib. Additionally, the current CDC-recommended immunizations include respiratory syncytial virus, hepatitis A, hepatitis B, rotavirus, pneumococcal, initial and booster COVID-19, and biannual influenza.

The best circumstances with the clearest signals would require a population-wide standardized autism screening program and a population-wide healthcare surveillance program. Denmark had both at the right time. The now quarter-century-old raw data must be made publicly available for scientific discourse to resolve the noted issues and contribute to the advancement of our understanding of the pathophysiological development of disease.

Conclusion

Madsen's results do not support rejecting the causal link. The girth of the confidence intervals can only be resolved with more evidence. The adjustment inversion casts doubt on the adjustment model, a doubt that can only be resolved by the authors making the original data public. The autism diagnoses do not add up between Tables 1 and 2, resulting in drastically different interpretations. Unbiased authors would implore the world over to replicate the study.

Author Disclosure Statement

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