

Measles, Mumps, Rubella Vaccination and Autism

A Nationwide Cohort Study

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Background: The hypothesized link between the measles, mumps, rubella (MMR) vaccine and autism continues to cause concern and challenge vaccine uptake.

Objective: To evaluate whether the MMR vaccine increases the risk for autism in children, subgroups of children, or time periods after vaccination.

Design: Nationwide cohort study.

Setting: Denmark.

Participants: 657 461 children born in Denmark from 1999 through 31 December 2010, with follow-up from 1 year of age and through 31 August 2013.

Measurements: Danish population registries were used to link information on MMR vaccination, autism diagnoses, other childhood vaccines, sibling history of autism, and autism risk factors to children in the cohort. Survival analysis of the time to autism diagnosis with Cox proportional hazards regression was used to estimate hazard ratios of autism according to MMR vaccination status, with adjustment for age, birth year, sex, other childhood vaccines, sibling history of autism, and autism risk factors (based on a disease risk score).

Results: During 5 025 754 person-years of follow-up, 6517 children were diagnosed with autism (incidence rate, 129.7 per 100 000 person-years). Comparing MMR-vaccinated with MMR-unvaccinated children yielded a fully adjusted autism hazard ratio of 0.93 (95% CI, 0.85 to 1.02). Similarly, no increased risk for autism after MMR vaccination was consistently observed in subgroups of children defined according to sibling history of autism, autism risk factors (based on a disease risk score) or other childhood vaccinations, or during specified time periods after vaccination.

Limitation: No individual medical charts were reviewed.

Conclusion: The study strongly supports that MMR vaccination does not increase the risk for autism, does not trigger autism in susceptible children, and is not associated with clustering of autism cases after vaccination. It adds to previous studies through significant additional statistical power and by addressing hypotheses of susceptible subgroups and clustering of cases.

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The hypothesized link between the measles, mumps, rubella (MMR) vaccine and autism continues to cause concern and challenge vaccine acceptance almost 2 decades after the controversial and later retracted *Lancet* paper from 1998 (1), even though observational studies have not been able to identify an increased risk for autism after MMR vaccination. In a 2014 meta-analysis, 10 observational studies on childhood vaccines were identified: 5 cohort studies and 5 case-control studies (2). Of these, 2 cohort studies and 4 case-control studies specifically addressed MMR and autism, all reporting no association. This is consistent with more recent studies of note (3, 4).

We previously addressed this issue in a nationwide cohort study of 537 303 Danish children with 738 cases of autism spectrum disorders (5). In our cohort, MMR vaccination was not associated with autistic disorder (rate ratio, 0.92 [95% CI, 0.68 to 1.24]) or other autism spectrum disorders (rate ratio, 0.83 [CI, 0.65 to 1.07]).

In this study, we aimed to evaluate the association again in a more recent and nonoverlapping cohort of Danish children that has greater statistical power owing to more children, more cases, and longer follow-up. A criticism of our and other previous observational studies has been that these did not address the concern that MMR vaccination could trigger autism in specific groups of presumably susceptible children, in contrast to all children (6); the current study addresses this concern in detail. We evaluate the risk for autism after MMR vaccination in subgroups of children defined according to environmental and familial autism risk factors. Another criticism

has been that MMR is associated with a regressive form of autism, leading to a clustering of cases with onset shortly after MMR vaccination (7). We evaluate the risk for autism after MMR vaccination in specific periods in detail.

METHODS

Ethical approval is not needed for register-based research in Denmark. The Danish Data Protection Agency approved the study.

Cohort

We conducted a nationwide cohort study of all children born in Denmark of Danish-born mothers from 1 January 1999 through 31 December 2010. We sourced the study cohort from the Danish Civil Registration System, which assigns a unique personal identification number to all people living in Denmark and keeps track of basic demographic information for each individual (8). This unique identifier is used in all other national registries and allows for individual-level linkage of health-related information, including vaccinations and autism diagnoses.

See also:

Editorial comment	1
Summary for Patients	2
Web-Only Supplement	

MMR and Other Childhood Vaccinations

The Danish childhood vaccination program is voluntary and free of charge. The mainstays of the early part of the Danish program are MMR and a diphtheria, tetanus, acellular pertussis, inactivated polio, and *Haemophilus influenzae* type b (DTaP-IPV/Hib) combination. A first dose of MMR vaccine is offered at 15 months (MMR1), with a second dose (MMR2) at 12 years of age or, since 2008, at 4 years of age. The DTaP-IPV/Hib vaccine is offered in 3 doses at 3, 5, and 12 months. Boosters are offered later in childhood. General practitioners administer all childhood vaccinations and are reimbursed when reporting these to the National Board of Health; these reports are included in the Danish National Health Service Register (9).

We obtained individual-level information on MMR1 and MMR2 vaccinations and other childhood vaccinations administered in the first year of life. There were no thimerosal-containing vaccines in the Danish program during the study period. The specific MMR vaccine used in the study period contained the following vaccine strains: Schwarz (measles, 2000 to 2007) or Ender's Edmonton (measles, 2008–2013), Jeryl Lynn (mumps), and Wistar RA 27/3 (rubella).

Autism

Information on autism spectrum disorder diagnoses in the study period was obtained from the Danish Psychiatric Central Register (10). Child psychiatrists diagnose and assign diagnostic codes for this register, which contains information from psychiatric hospitals and psychiatric wards (inpatients and outpatients in the study period). The coding classification used in the study period was the International Classification of Diseases, 10th Revision; we used the codes F84.0 (autistic disorder), F84.1 (atypical autism), F84.5 (Asperger syndrome), F84.8 (other pervasive developmental disorder), and F84.9 (unspecified pervasive developmental disorder). We defined our main study outcome of autism as a diagnosis of any of these autism spectrum disorders.

From the Danish National Patient Register comprising diagnoses from all somatic departments, we obtained information on several syndromes and conditions with an inherent increased risk for autism (fragile X syndrome, tuberous sclerosis, Angelman syndrome, Down syndrome, DiGeorge syndrome, neurofibromatosis, Prader-Willi syndrome, and congenital rubella syndrome) (11). Children with any of these conditions were excluded from the study if the condition was diagnosed before their first birthday or censored at date of the diagnosis if it was made when the child was older than 1 year (14).

Autism Risk Factors

We included many autism risk factors for stratification and confounder adjustment, on the basis of a literature review on environmental autism risk factors and availability of data in our registers (12); these were maternal age, paternal age, smoking during pregnancy, method of delivery, preterm birth, 5-minute Apgar score, low birthweight, and head circumference. For variables with missing values, we included a missing value category in the analyses. Table 1 of the Supple-

ment (available at Annals.org) provides a complete list of variables with categorizations). These variables were obtained from the Danish Medical Birth Registry, which includes information on the parents and the newborn, pregnancy, date of birth, multiple births, gestational age, and vital status and other physical characteristics of the newborn (13).

From the Danish Civil Registration System, we obtained parental links to identify siblings (defined as common father and mother) for each cohort child. Cases of autism among siblings were identified similarly to the main study outcome.

Statistical Analysis

The main goal of our modeling strategy was to evaluate whether the MMR vaccine increases the risk for autism in children, subgroups of children, and time periods after vaccination. We defined subgroups according to 1) sibling history of autism ("genetic susceptibility"), sex, birth cohort, and prior vaccinations in the first year of life and 2) a summary index estimated from a disease risk model combining multiple environmental risk factors. The motivation for a summary index was that the combination of several factors each associated with only a moderate risk increase in autism had the potential of identifying children at higher risk through multiple risk factors, in contrast to many stratified analyses of single moderate risk factors.

We analyzed the study cohort by using survival analysis (14). Children in the cohort contributed person-time to follow-up from 1 year of age and until a first diagnosis of autism, death, emigration, unexplained disappearance from the source registers, diagnoses of autism-associated conditions or syndromes, or end of the study on 31 August 2013.

The MMR vaccination status was considered a time-varying variable; children could contribute time as both unvaccinated and vaccinated in our study. Using the cases of autism among siblings, we constructed a time-varying variable summarizing each child's sibling history of autism with the states "no siblings," "siblings without autism," or "siblings with at least one case of autism"; a missing value category covered the children who had unknown fathers. We used sibling history at study entry unless otherwise specified.

In a preliminary analysis based on maternal age, paternal age, smoking during pregnancy, method of delivery, preterm birth, 5-minute Apgar score, low birthweight, and head circumference, we estimated a disease risk score (15) (termed "autism risk score" throughout) for each child in the cohort. The autism risk score was derived in the complete study cohort by fitting a proportional hazards model of autism risk with attained age as underlying time-scale comprising the preselected variables as covariates. For each child, a score (in the form of a hazard ratio [HR] relative to a child with reference values for all variables included) was calculated as the exponential of the sum of the estimated regression coefficients corresponding to the characteristics of the child. The score was categorized according to deciles which were combined into 4 risk

groups: very low (first to third decile), low (fourth to sixth decile), moderate (seventh to ninth decile), or high (10th decile).

Survival times were then analyzed by using Cox regression with attained age as underlying time scale, producing HRs according to vaccination status. For fully adjusted models, the baseline hazard function was stratified on birth year, sex, other childhood vaccines received, sibling history of autism and autism risk score (in deciles). We evaluated the proportional hazards assumption of the main analysis by a joint test of homogeneity allowing the effect of vaccination to vary between the age intervals 1 to 3 years, 3 to 5 years, 5 to 7 years, 7 to 10 years, and more than 10 years (16).

We estimated autism HRs (aHRs) according to MMR vaccination status (yes or no), overall in the cohort and in several subanalyses: 4 analyses, each restricting risk time to young children by censoring observed survival times at 3, 5, 7, or 10 years of age; in subgroups characterized by sex, birth cohort, other childhood vaccines received, autism risk score, or autism history in siblings (joint tests for homogeneity of aHRs between levels of each factor were carried out [16]); and in specific periods after vaccination (comparing the hazard rates of autism in the first, second, third, and fourth year after vaccination and more than 4 years after vaccination, respectively, with the rate among unvaccinated children. A test for homogeneity of aHRs between intervals was conducted using a type 3 test (16).

We conducted several sensitivity analyses. To increase the validity of our autism case definition further, we conducted a main analysis with a case definition requiring at least 2 autism diagnosis registrations; an event was defined at date of second autism diagnosis. We evaluated specific autism phenotypes by conducting main analyses of autistic disorder and other autism spectrum disorder separately (with right censoring of other autism spectrum disorder when analyzing autistic disorder and vice versa). We conducted a dose-dependent fully adjusted analysis taking the second MMR dose into account by estimating the increase in HR per vaccination. Instead of adjusting for birth year, sex, other childhood vaccines received, sibling history of autism, and autism risk score by stratification of the baseline hazard, we included these as covariates. Finally, we replaced the autism risk score of the previous model with the 8 variables on which it was based.

Crude associations between variables included in the analyses and autism were estimated in proportional hazards models with attained age as underlying time-scale and autism as outcome, including only the specific variable of interest as a covariate.

Data management and statistical analyses were conducted by using SAS, version 9.4; the figures were created by using R, version 3.5.1. All Cox regressions were fitted by using the SAS PHREG procedure with the Breslow option for handling ties. Cumulative risks were calculated from the Kaplan-Meier estimates using the survfit function in R with the log-log option for confidence limits.

Role of the Funding Source

The study was supported by a grant from the Novo Nordisk Foundation and the Danish Ministry of Health. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Dr. Hviid had full access to all of the data in the study and had overall responsibility for the decision to submit for publication.

RESULTS

We identified 663 236 children born to Danish-born mothers from 1 January 1999 through 31 December 2010 (Figure 1). We excluded 5775 children; 1498 had no registration in the Danish Medical Birth Registry, and 4277 were unavailable for follow-up at study entry (1 year of age) because of death ($n = 2673$), emigration ($n = 770$), unexplained disappearance from the source registers ($n = 203$), an autism diagnosis ($n = 11$), or an exclusionary diagnosis ($n = 620$). This resulted in a study cohort of 657 461 children contributing 5 025 754 person-years of follow-up during 1 January 2000 through 31 August 2013.

Figure 1. Study flow diagram.

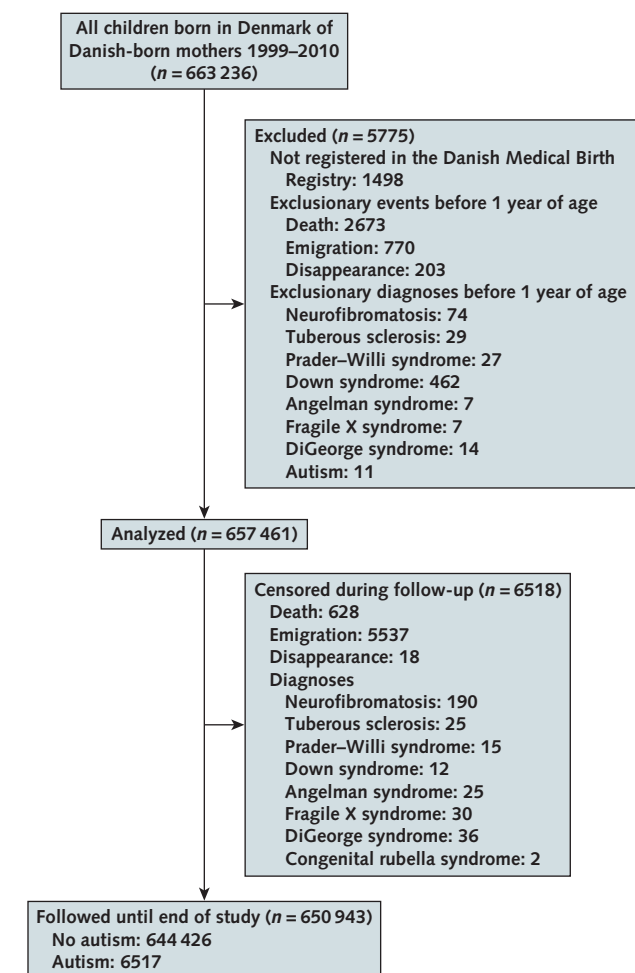


Table. Study Population Characteristics*

Characteristic	Overall (n = 657 461)†	Vaccinated Children (n = 625 842)‡	Unvaccinated Children (n = 31 619)‡
Sex			
Male	336 949 (0.51)	320 038 (0.95)	16 911 (0.05)
Female	320 512 (0.49)	305 804 (0.95)	14 708 (0.05)
Birth cohort			
1999-2001	168 350 (0.26)	162 513 (0.97)	5837 (0.03)
2002-2004	163 478 (0.25)	153 439 (0.94)	10 039 (0.06)
2005-2007	165 064 (0.25)	159 059 (0.96)	6005 (0.04)
2008-2010	160 569 (0.24)	150 831 (0.94)	9738 (0.06)
Other early childhood vaccines§			
None	11 571 (0.02)	6842 (0.59)	4729 (0.41)
1 DTap-IPV/Hib	60 306 (0.09)	54 686 (0.91)	5620 (0.09)
≥2	585 584 (0.89)	564 314 (0.96)	21 270 (0.04)
Autism risk score			
Very low risk	191 261 (0.29)	183 671 (0.96)	7590 (0.04)
Low risk	203 219 (0.31)	194 384 (0.96)	8835 (0.04)
Moderate risk	197 220 (0.30)	186 491 (0.95)	10 729 (0.05)
High risk	65 761 (0.10)	61 296 (0.93)	4465 (0.07)
Autism history in siblings§			
No siblings	319 936 (0.49)	306 642 (0.96)	13 294 (0.04)
No siblings with autism	331 994 (0.50)	314 362 (0.95)	17 632 (0.05)
Siblings with autism	838 (0.001)	759 (0.91)	79 (0.09)
Father unknown	4693 (0.007)	4079 (0.87)	614 (0.13)

DTaP-IPV/Hib = diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine.

* Data are numbers (percentages).

† Column proportions are in parentheses. Proportions may not sum to 1 due to rounding.

‡ Status at end of follow-up. Row proportions are in parentheses. Proportions may not sum to 1 due to rounding.

§ Status at study entry.

During follow-up, 6517 children were diagnosed with autism (incidence rate, 129.7 per 100 000 person-years), and 6518 children were censored (335 had an autism-associated syndrome or condition, 628 had died, 5537 had emigrated, and 18 had disappeared from the source registers for unknown reasons). The number of children and autism cases in the study according to age and vaccination status are presented in **Figure 1 of the Supplement** (available at [Annals.org](#)).

The mean attained age in the study was 8.64 years (SD, 3.48). The first autism-related diagnoses among included autism cases were autistic disorder ($n = 1997$), atypical autism ($n = 537$), Asperger syndrome ($n = 1098$), other pervasive developmental disorder ($n = 576$), and unspecified pervasive developmental disorder ($n = 2309$). The mean age at first autism diagnosis was 7.22 years (SD, 2.86), and the mean age among autistic disorder cases was 6.17 years (SD, 2.65). Uptake of the MMR1 vaccine was 95.19%, with a median age at vaccination of 1.34 years (interquartile range, 0.24 years). There were no appreciable differences in vaccine uptake according to sex, birth cohort, autism risk score, or autism history in siblings; MMR vaccinations were more common among children previously vaccinated in early childhood (**Table**).

The variables used to construct the autism risk score are presented in **Table 1 of the Supplement** (available at [Annals.org](#)). The largest single risk factors for autism were

an older or unknown father, an older mother, poor Apgar score, low birthweight, preterm birth, large head, assisted birth, and smoking in pregnancy (**Table 1 of the Supplement**). The crude hazard ratios associated with the deciles of the autism risk score ranged from 0.73 (first versus fifth decile) to 1.62 (10th versus fifth decile) (**Table 2 of the Supplement**, available at [Annals.org](#)). The Harrell C-statistic for the autism risk score was 0.57.

Comparing MMR-vaccinated with MMR-unvaccinated children yielded a fully adjusted aHR of 0.93 (95% CI, 0.85 to 1.02). The test for homogeneity of aHRs in the age intervals 1 to 3, 3 to 5, 5 to 7, 7 to 10, and more than 10 years of age yielded a P value of 0.138. Crude cumulative incidences of autism in MMR-vaccinated and MMR-unvaccinated children are presented in **Figure 2**. Ending follow-up at 5, 7, and 10 years of age produced similar aHRs (0.97 [CI, 0.81 to 1.15], 0.96 [CI, 0.84 to 1.09], and 0.97 [CI, 0.87 to 1.07], respectively). Ending follow-up at 3 years of age yielded a slightly lower aHR (0.73 [CI, 0.53 to 1.00]).

We compared MMR-vaccinated with MMR-unvaccinated children in subgroups characterized by sex, birth cohort, other childhood vaccines received, autism risk score, or autism history in siblings (**Figure 3**). Receipt of MMR vaccination reduced the risk for autism in girls (aHR, 0.79 [CI, 0.64 to 0.97]) and in the 1999-2001 birth cohort (aHR, 0.84 [CI, 0.73 to 0.96]). The MMR vaccination did not increase the risk for autism in children characterized by other early childhood vaccinations, high risk

for autism, or having autistic siblings (Figure 3). When sibling history of autism was treated as a time-varying covariate, MMR vaccination was also not associated with autism among children with autistic siblings (aHR, 1.15 [CI, 0.71 to 1.87]). Cumulative incidences of autism according to age and MMR vaccination status, stratified by sex and sibling history, are presented in Figure 2 of the Supplement (available at Annals.org). Cumulative incidences of autism according to age stratified on autism risk score groups are presented in Figure 3 of the Supplement (available at Annals.org).

The crude effect sizes of sex, birth cohort, other early childhood vaccinations, sibling history of autism, and autism risk score are presented in Tables 2 and 3 of the Supplement (available at Annals.org). The highest risk for autism was conferred by being a boy (HR, 4.02 [CI, 3.78 to 4.28]), being born in a late birth cohort (2008-2010; HR, 1.34 [CI, 1.18 to 1.52]), having no early childhood vaccinations (HR, 1.17 [CI, 0.98 to 1.38]), and having siblings with autism at study entry (HR, 7.32 [CI, 5.29 to 10.12]). The autism risk score had a modest

effect on autism risk compared with sex and sibling history of autism (highest-risk group versus moderate-risk group; HR, 1.38 [CI, 1.28 to 1.48]).

We evaluated HRs in 1-year risk periods after MMR vaccination; we identified no period after MMR vaccination with an increased aHR (Figure 3).

The analysis requiring at least 2 autism diagnosis registrations for case ascertainment resulted in similar results as the main analysis (aHR, 0.99 [CI, 0.88 to 1.11]). Using autistic disorder cases or other autism spectrum cases only resulted in aHRs of 0.96 (CI, 0.81 to 1.13) and 0.91 (CI, 0.82 to 1.02), respectively. In an analysis taking the second MMR dose into account, there was no evidence of a dose-response (increase in aHR per dose, 0.90 [CI, 0.85 to 0.95]). Adjustment for the potential confounders as covariates instead of stratification of the baseline hazard function did not affect the result (aHR, 0.93 [CI, 0.84 to 1.02]). Replacing the autism risk score with the individual covariates used to estimate it in the above model yielded an aHR of 0.94 (CI, 0.85 to 1.03).

Figure 2. Cumulative incidences of autism (unadjusted and with 95% CI bands) in 657 461 children born in Denmark between 1 January 1999 and 31 December 2010, by vaccination status and age.

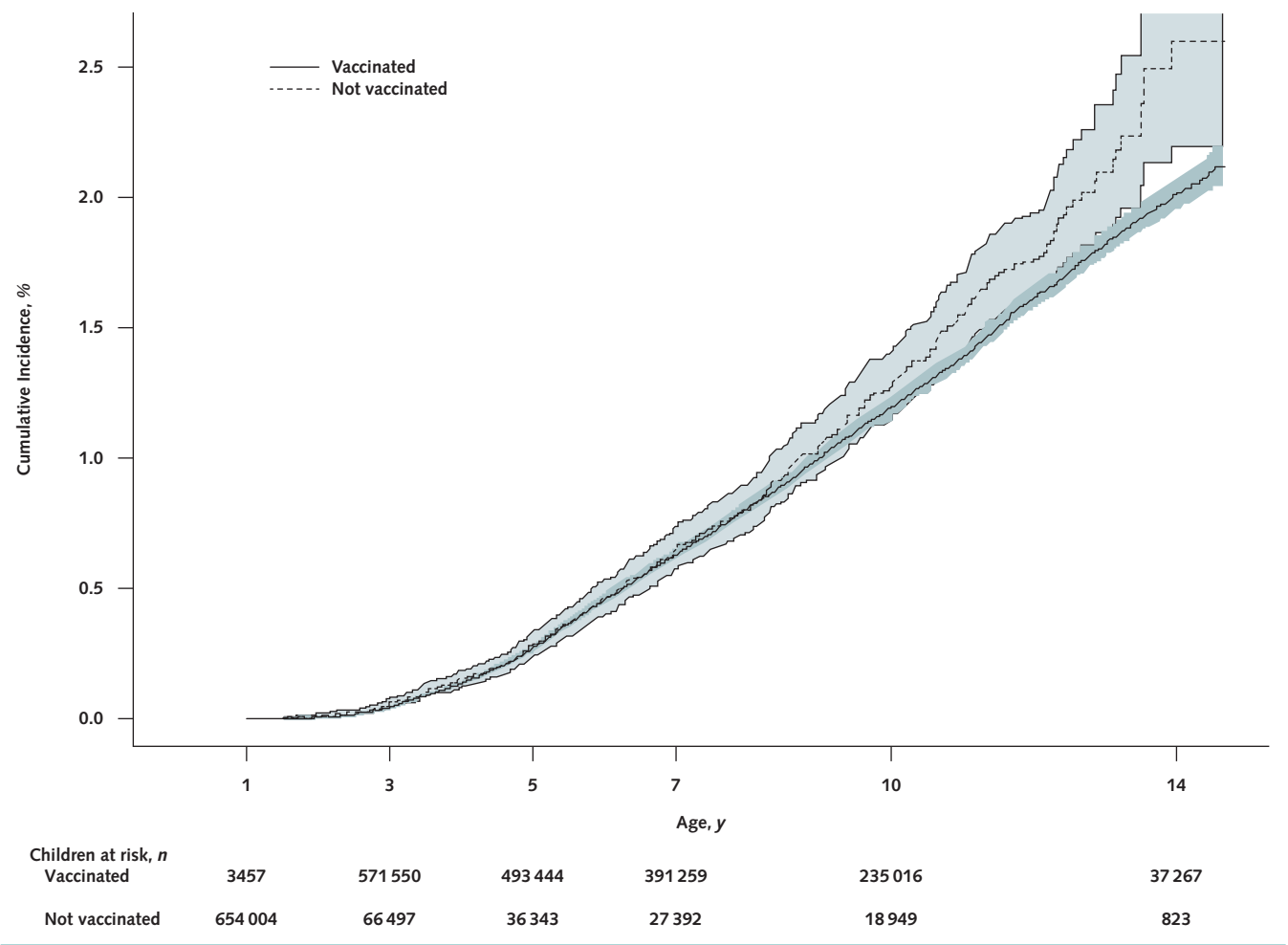
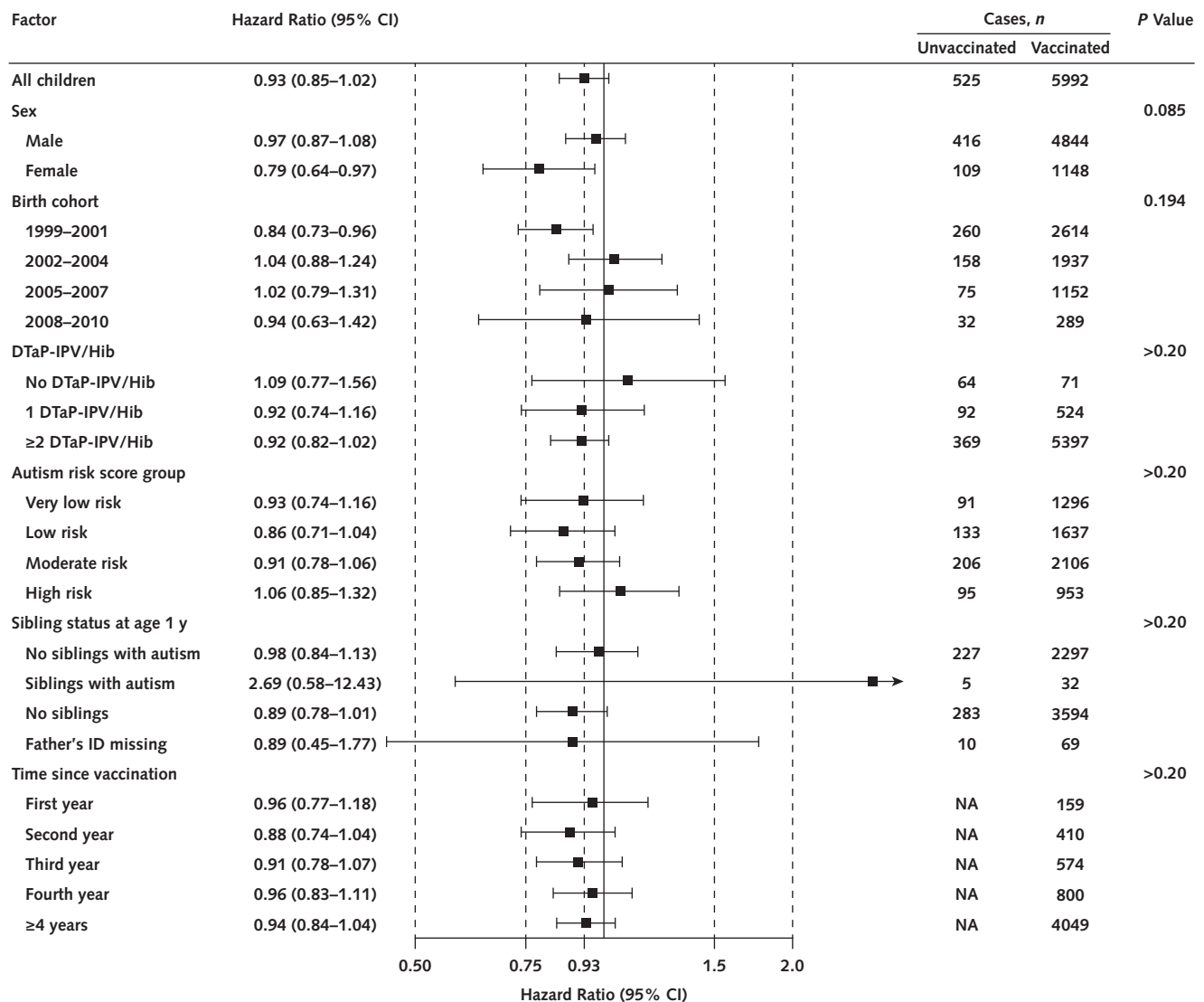


Figure 3. Association between measles, mumps, rubella vaccination and autism in subgroups of 657 461 children born in Denmark between 1 January 1999 and 31 December 2010.



Fully adjusted autism hazard ratios comparing children who received measles, mumps, rubella vaccine with those who did not. The hazard ratios are depicted on a logarithmic scale, with bars representing 95% CIs. *P* values are from a test of homogeneity of effect. DTaP-IPV/Hib = diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and *Haemophilus influenzae* type b vaccine; NA = not applicable.

DISCUSSION

We found no support for the hypothesis of increased risk for autism after MMR vaccination in a nationwide unselected population of Danish children; no support for the hypothesis of MMR vaccination triggering autism in susceptible subgroups characterized by environmental and familial risk factors; and no support for a clustering of autism cases in specific time periods after MMR vaccination.

We previously addressed this issue in a similar but nonoverlapping nationwide cohort study of 537 303 Danish children (5). Reassuringly, the main results are similar between the 2 studies, which supports the internal and external validity of both. The major difference between our studies is a significant increase in statisti-

cal power and additional susceptible subgroup and clustering analyses. In a 2014 meta-analysis of MMR vaccination and autism studies, 2 cohort and 4 case-control studies were identified from Denmark (5), Poland (17), Japan (4, 18), the United Kingdom (19), and the United States (20), with no support for an association—for example, a pooled odds ratio from cohort studies of 0.84 (CI, 0.70 to 1.01) (2).

A concern about observational studies is that they do not often take into account the possibility of MMR vaccination triggering autism in susceptible subgroups of children. The large number of cases in our study allowed us to define subgroups with sufficient statistical power for useful inference. Specific definitions of susceptible subgroups have been lacking. We defined

subgroups according to environmental and familial risk factors for autism. We are only aware of 1 previous study taking a similar approach: A U.S. study by Jain and colleagues (3) evaluated the association between MMR and autism according to sibling history of autism. Those researchers found no support for an association in children with a sibling history of autism, but identified lower MMR uptake rates in children with affected siblings, a potentially important public health issue with increasing autism prevalence and supported by other studies (21).

Another frequent criticism of observational studies of MMR vaccination and autism is a perceived failure to take into account the existence of specific autism phenotypes associated with vaccination, such as regressive autism. Our analysis of specific time periods after vaccination does not support a regressive phenotype triggered by vaccination with excessive clustering of cases in the subsequent period, and no other studies have been able to substantiate the existence of this phenotype (22).

A general criticism of observational vaccine effect studies is that they do not include a completely unvaccinated group of children (23). The number of children completely unvaccinated throughout childhood will be low in a country such as Denmark. We evaluated the association between MMR and autism in children with no DTaP-IPV/Hib vaccinations in the first year of life; we found no support for an association in this vaccine-naïve subpopulation.

Our study has several strengths. Comprising 6517 cases, it is by far the largest single study to date and adds significantly to our knowledge on the issue, in that it allows us to conclude from one study that even minute increases in autism risk after MMR vaccination are unlikely, assuming unbiased results. We evaluated the hypothesis in an unselected setting with a nationwide cohort from an ethnically and socioeconomically homogeneous population. We obtained independent and prospectively collected information on vaccination and autism from nationwide health registries with mandatory reporting reducing concern about ascertainment and recall bias. We included information on a range of environmental and familial risk factors, which allowed us to consider their potential confounding effect.

We obtained autism cases from the Danish Psychiatric Central Register, which has previously been used extensively for autism research in Denmark. This register has a high degree of validity; an earlier medical record review revealed a positive predictive value of 92.5% (5), and our study prevalence of 1.0% is similar to that found in other studies (24) and the estimated general U.S. prevalence of 1.5% (25).

A limitation of our study is that we used date of first diagnosis of autism, which is probably delayed compared with the age at onset of symptoms. This can be a source of information bias—for example, in the case where symptoms precede vaccination and diagnosis occurs after vaccination. This will result in misclassification of autism cases as vaccinated, biasing the hazard ratio toward an effect. If onset of symptoms results in

avoidance of vaccination, or conversely if symptoms increase the probability of vaccination through increased health care utilization, bias in either direction is possible. During the study period, the measles strain in the vaccine changed in 2008 from Schwarz to Ender's Edmonston. However, birth cohort-specific HRs were homogeneous, suggesting that the change in composition had no effect on autism risk.

Measles outbreaks are not uncommon in Europe and in the United States, and vaccine hesitancy or avoidance has been identified as a major cause (26). In a mathematical modeling study, U.S. researchers concluded that even a 5% reduction in vaccination coverage would triple measles cases, with significant health economic costs (27). A main reason that parents avoid or are concerned about childhood vaccinations has been the perceived link to autism (28). Our study adds to previous studies through significant additional statistical power and by addressing hypotheses of susceptible subgroups and clustering of cases. We believe that our results offer reassurance and provide reliable data on which clinicians and health authorities can base decisions and public health policies.

In conclusion, our study does not support that MMR vaccination increases the risk for autism, triggers autism in susceptible children, or is associated with clustering of autism cases after vaccination.

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