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# Association of Family History of Autoimmune Diseases and Autism Spectrum Disorders

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## KEY WORDS

autistic disorder, autoimmune diseases, autoimmunity

## ABBREVIATIONS

ASD—autism spectrum disorder  
AD—autoimmune disease  
RA—rheumatoid arthritis  
T1D—type 1 diabetes  
CPR—Central Person Register  
ICD—*International Classification of Diseases*  
DPCR—Danish Psychiatric Central Register  
DNHR—Danish National Hospital Register  
IRR—incidence rate ratio  
CI—confidence interval

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**WHAT'S KNOWN ON THIS SUBJECT:** A number of epidemiological studies have investigated the association between autism and family history of autoimmune diseases; however, results have been inconsistent, and there is a need for a confirmatory study.



**WHAT THIS STUDY ADDS:** This study uses nationwide registers, and the study sample is  $\geq 10$  times larger than study samples used in previous studies. We confirm associations found in previous studies, and we explore the relationship between family history of other ADs and autism.

## abstract

**OBJECTIVES:** Recent studies suggest that familial autoimmunity plays a part in the pathogenesis of ASDs. In this study we investigated the association between family history of autoimmune diseases (ADs) and ASDs/infantile autism. We perform confirmatory analyses based on results from previous studies, as well as various explorative analyses.

**METHODS:** The study cohort consisted of all of the children born in Denmark from 1993 through 2004 (689 196 children). Outcome data consisted of both inpatient and outpatient diagnoses reported to the Danish National Psychiatric Registry. Information on ADs in parents and siblings of the cohort members was obtained from the Danish National Hospital Register. The incidence rate ratio of autism was estimated by using log-linear Poisson regression.

**RESULTS:** A total of 3325 children were diagnosed with ASDs, of which 1089 had an infantile autism diagnosis. Increased risk of ASDs was observed for children with a maternal history of rheumatoid arthritis and celiac disease. Also, increased risk of infantile autism was observed for children with a family history of type 1 diabetes.

**CONCLUSIONS:** Associations regarding family history of type 1 diabetes and infantile autism and maternal history of rheumatoid arthritis and ASDs were confirmed from previous studies. A significant association between maternal history of celiac disease and ASDs was observed for the first time. The observed associations between familial autoimmunity and ASDs/infantile autism are probably attributable to a combination of a common genetic background and a possible prenatal antibody exposure or alteration in fetal environment during pregnancy. *Pediatrics* 2009;124:687–694

Autism spectrum disorders (ASDs) are complex neurodevelopmental disorders characterized by a combination of deficits in communication and social interaction and repetitive, stereotyped behavior and interests.<sup>1</sup> Recent research has focused on the possible association between maternal autoimmunity and the development of ASDs.<sup>2</sup> Antibodies specific for fetal brain proteins have been found in the plasma of mothers to children with ASDs.<sup>3–5</sup> However, maternal sensitization does not seem to fully explain the development of ASDs, because mothers with unaffected children can have a similar antibody profile. Hence, a complex relationship between maternal antifetal brain antibodies, in utero environmental factors, and genetics is likely to predispose to the development of ASDs.<sup>6,7</sup> A number of epidemiologic studies have investigated the association between ASDs and family history of autoimmune diseases (ADs). Croen et al<sup>8</sup> found an increased risk of ASDs in the child if the mother was diagnosed with psoriasis. Comi et al<sup>9</sup> found a statistically significant association between ASDs and family history of all ADs combined, as well as a family history of rheumatoid arthritis (RA), specifically. Sweeten et al<sup>10</sup> found a higher frequency of overall autoimmunity and, specifically, thyroid gland AD in families of children with pervasive developmental disorder. Mouridsen et al<sup>11</sup> performed a cross-sectional, case-control study on Danish register data using case records of 111 individuals diagnosed with infantile autism between 1960 and 1984. They found an association between maternal diagnosis of ulcerative colitis and paternal diagnosis of type 1 diabetes (T1D) and infantile autism. Micali et al<sup>12</sup> found no increased prevalence of any AD among parents of children with pervasive developmental disorder compared with normally developed children. In each

of the studies, numerous ADs were investigated independently for an association with ASDs/infantile autism.

The previous studies have several limitations, such as relatively small study samples,<sup>8–12</sup> the use of self-response questionnaires,<sup>10</sup> recall bias,<sup>9</sup> a possible misclassification of autism cases,<sup>8</sup> and exposure status.<sup>12</sup> The present study uses nationwide registers based on standardized diagnostic procedures to find case subjects with ASDs and family members diagnosed with AD. We included only diagnoses reported by medical doctors, and by using registers we avoided recall bias and reliance on self-response questionnaires. Furthermore, the study sample in this study is  $\geq 10$  times larger than study samples used in previous studies. The aim of this study was to confirm the above-mentioned associations found in previous studies, as well as to explore the relationship between family history of other ADs and ASDs/infantile autism. For all of the ADs, we differentiated between maternal history of AD (representing possible exposures in the fetal environment or prenatal antibody exposure, as well as a potential genetic exposure) and paternal history of AD (representing only potential genetic exposure).

## METHODS

### Study Population

We used data from the Danish Civil Registration System<sup>13</sup> to identify all of the children born in Denmark from January 1, 1993, through December 31, 2004, who survived the first year of life and whose mother was born in Denmark (689 196 children). All live-born children and new residents in Denmark are assigned a unique personal identification number (Central Person Register [CPR] number), which is stored in the Danish Civil Registration System. The CPR number is used as a key to individual information in all of

the national registers, ensuring accurate linkage of information between registers.

### Diagnostic System

The Danish modification of the *International Classification of Diseases, Eighth Revision* (ICD-8), was introduced as a diagnostic instrument in Denmark in 1969 and used until 1993. In 1994, ICD-8 was replaced by the 10th revision (ICD-10). Health care service in Denmark is free of charge and easily accessible for the whole population.

### Autism in Cohort Members

The study population was linked with the Danish Psychiatric Central Register (DPCR).<sup>14</sup> The DPCR includes information on all inpatient admissions to psychiatric hospitals and psychiatric wards in general hospitals in Denmark since 1969 and all outpatient contact since 1995. The DPCR includes the CPR number, diagnosis, dates of admission and discharge, and terms of admission. All of the diagnoses registered in the DPCR are made by psychiatrists.

Cohort members were classified with ASDs if they had been admitted or been in outpatient care with a diagnosis in the autism spectrum (ICD-10 diagnostic codes as follows: infantile autism, F84.0; atypical autism, F84.1; Asperger syndrome, F84.5; and pervasive developmental disorder, not otherwise specified, F84.8 and F84.9). The study population was followed from age 1 year until date of first diagnosis of ASDs (or infantile autism), death, emigration from Denmark, or December 31, 2006.

### ADs in Parents and Siblings

Information on AD in parents and siblings of the cohort members was obtained from the Danish National Hospital Register (DNHR).<sup>15</sup> The DNHR was initiated in 1977 and includes detailed information on all hospital admissions in the entire country. The recorded information includes the CPR number,

**TABLE 1** Diagnostic Codes of Autoimmune Diseases

Variable	ICD-8	ICD-10	No. of Exposed ASDs <sup>a</sup>
All autoimmune diseases combined	All below	All below	227
Endocrine autoimmune diseases			68
T1D	249	E10	46
Thyrotoxicosis	242.00	E05.0	16
Autoimmune thyroiditis	245.03	E06.3	5
Primary adrenocortical insufficiency	255.1	E27.1	<5
Connective tissue autoimmune diseases			47
RA	712.19, 712.39, 712.59	M05, M06	26
Juvenile arthritis	712.09	M08	10
Dermatopolymyositis	716	M33	<5
Polymyalgia rheumatica/temporal arteritis	446.3	M31.5, M31.6, M35.3	<5
Scleroderma	734.0	M34 (except M34.2)	<5
Systemic lupus erythematosus	734.19	M32.1, M32.9	<5
Sjögren syndrome	734.90	M35.0	<5
Ankylosing spondylitis	712.49	M45.9	<5
Wegener granulomatosis	446.29	M31.3	<5
Gastrointestinal autoimmune diseases			69
Celiac disease	269.00	K90.0	10
Crohn disease	563.01	K50	23
Ulcerative colitis	563.19	K51	44
Blood autoimmune diseases			8
Pernicious anemia	281.0	D51.0	<5
Autoimmune hemolytic anemia	283.90, 283.91	D59.1	<5
Idiopathic thrombocytopenic purpura	446.49	D69.3	<5
Nervous system autoimmune diseases			21
Multiple sclerosis	340	G35	16
Guillain-Barré syndrome	354	G61.0	<5
Myasthenia gravis	733.09	G70.0	<5
Skin autoimmune diseases			34
Pemphigus	694	L10 (except L10.5)	<5
Psoriasis vulgaris	696.09, 696.10, 696.19	L40 (except L40.4)	30
Alopecia areata	704.00	L63	<5
Vitiligo	709.01	L80.9	<5

<sup>a</sup> Data show the number of subjects with ASDs exposed to a family history of AD; mother, father, or sibling diagnosed with AD.

diagnosis, hospital, and dates of admission and discharge. Inpatient visits have been included since 1977, whereas outpatient and emergency department visits have been included since 1995. Parents and siblings were classified with a history of AD if they had been admitted or been in outpatient care with 1 of the 26 AD diagnoses included in the study (Table 1).

### Analytic Approach

The incidence rate ratio (IRR) of ASDs was estimated by log-linear Poisson regression<sup>16</sup> with the GENMOD procedure in SAS 9.1 (SAS Institute, Inc, Cary, NC). Calendar year, age at diagnosis for ASDs, and its interaction with gender, place of birth, and age of the

mother and father at the time of the child's birth were regarded as possible confounders, and all of the IRRs were adjusted for these variables. We included information of AD in the family as a time-dependent covariate, because otherwise exposure status and results would depend on the total length of follow-up time included in the study. Including AD in the family as a time-dependent covariate implies that only ADs diagnosed before the date of diagnosis of ASDs in the child are included in the analysis. Age and calendar year were also treated as time-dependent variables,<sup>17</sup> whereas all of the other variables were treated as independent of time. Calendar year was categorized in 1994–1996 in the earliest period

and then in 1-year periods afterward. Age was categorized in 6-month periods from 1 to 3 years of age, and thereafter 1-year periods were used. Maternal age at the time of the child's birth was categorized with cutoff points at 12, 20, 25, 30, 35, and 40 years, and paternal age had cutoff points of 12, 25, 30, 35, 40, and 45 years or unknown father. The difference in age categorization for mothers and fathers is to avoid age groups with very few observations (there are more mothers in the younger categories and more fathers in the older categories). *P* values and 95% confidence limits were based on likelihood ratio tests.<sup>17</sup> The adjusted-score test<sup>18</sup> suggested that the regression models were not subject to overdispersion. No adjustment was made for multiple testing.

Primary analyses involve investigating significant findings from previous studies, that is, the relationship between ASDs or infantile autism and (1) family history of all ADs combined, (2) family history of RA, (3) maternal psoriasis, (4) paternal T1D, (5) maternal ulcerative colitis, and (6) family history of AD in the thyroid gland. Analyses on the association between other ADs and ASDs/infantile autism are regarded as exploratory and, thus, secondary. For all ADs, we estimated the IRR of ASDs/infantile autism after the mother, father, or sibling was diagnosed with AD (reference group: children with no family history of AD); using exclusively the maternal history of AD (reference group: children with no parental history of AD); or using exclusively the paternal history of AD (reference group: children with no parental history of AD). An IRR estimate was not calculated if fewer than 5 case subjects were exposed.

We performed a stratified analysis including children with a gestational age of  $\geq 37$  weeks, a birth weight of  $>2500$  g, and a 5-minute Apgar score of  $>6$ . This analysis was performed in an attempt to

adjust for prenatal and/or perinatal complications that children born by women with AD may experience, such as asphyxia, low birth weight, or low gestational age. Data on these perinatal variables were obtained from the Danish Medical Birth Registry.<sup>19</sup> This study was approved by the Danish Data Protection Agency and the Danish National Board of Health.

## RESULTS

### Primary Analyses

A total of 3325 children were diagnosed with ASDs, of which 1089 had an infantile autism diagnosis (Table 2). No statistically significant association was found between all of the ADs combined and ASDs (Table 3) or infantile autism (Table 4). Endocrine AD in the father was found to be associated with a higher IRR of infantile autism, probably caused by the significant association between T1D and infantile autism (family history of T1D: IRR: 1.78 [95% confidence interval (CI): 1.16–2.61] (Table 4); maternal history of T1D: IRR: 2.14 [95% CI: 1.07–3.77 (Table 4)]; paternal history of T1D: IRR: 1.85 [95% CI: 1.02–3.06 (Table 4)]). Thyrotoxicosis in the family and the mother, specifically, were related to lower risk of ASDs. Connective tissue diseases in the mother were related to ASDs, presumably explained by the significant relationship between RA in the mother and ASDs (IRR: 1.70 [95% CI: 1.07–2.54 (Table 3)]). No statistically significant association was found between ulcerative colitis or psoriasis and ASDs or infantile autism.

### Secondary Analyses

No other group of diseases, or any specific disease, showed a significant relationship with ASDs/infantile autism, with the exception of celiac disease (maternal history of celiac disease: IRR: 2.97 [95% CI: 1.27–5.75 (Table 3)]). When data were limited to children with a gestational age of  $\geq 37$  weeks, a

**TABLE 2** Characteristics of the Study Population

Variable	ASD		Infantile Autism	
	No. of Cases	Incidence <sup>a</sup>	No. of Cases	Incidence <sup>a</sup>
Gender				
Male	2788	111.2	893	35.5
Female	537	22.5	196	8.2
Gestational age				
<37 wk	234	82.2	91	31.9
$\geq 37$ wk	3056	67.1	989	21.7
Unknown	35	73.8	9	18.9
Birth weight				
$\leq 2500$ g	226	96.5	87	37.1
>2500 g	3057	66.5	989	21.5
Unknown	42	72.1	13	22.3
Apgar score				
$\leq 6$	48	100.6	15	31.3
>6	3237	67.7	1063	22.2
Unknown	40	77.7	11	21.3
Mothers age				
<25 y	569	74.6	158	20.7
25–34 y	2252	64.3	736	21.0
$\geq 35$ y	504	81.0	195	31.3
Fathers age				
<25 y	246	66.2	68	18.3
25–34 y	2069	64.6	665	20.7
$\geq 35$ y	971	75.8	348	27.1
Unknown father	39	117.6	8	24.1
Place of birth				
Capital with suburbs	1257	102.7	429	35.0
Provincial city/town	1208	62.0	397	20.4
Rural area	860	50.1	263	15.3

<sup>a</sup> The incidence measures the number of new case subjects diagnosed per 100 000 person-years at risk.

**TABLE 3** Adjusted IRRs (95% CIs) of ASDs After Family History of AD

AD	Previous AD		
	Parent or Sibling, IRR (95% CI) <sup>a</sup>	Mother Only, IRR (95% CI) <sup>b</sup>	Father Only, IRR (95% CI) <sup>c</sup>
All ADs combined	1.04 (0.91–1.19)	1.02 (0.85–1.22)	1.04 (0.83–1.29)
Endocrine AD	0.92 (0.72–1.17)	0.71 (0.48–1.01)	1.33 (0.94–1.83)
Thyrotoxicosis	0.61 (0.36–0.96) <sup>d</sup>	0.58 (0.32–0.95) <sup>d</sup>	NA
Autoimmune thyroiditis	1.21 (0.43–2.60)	NA	NA
T1D	1.04 (0.77–1.38)	0.93 (0.52–1.51)	1.32 (0.90–1.85)
Connective tissue AD	1.20 (0.89–1.58)	1.56 (1.08–2.17) <sup>d</sup>	0.59 (0.25–1.13)
RA	1.32 (0.88–1.90)	1.70 (1.07–2.54) <sup>d</sup>	NA
Juvenile arthritis	1.10 (0.55–1.92)	NA	NA
Gastrointestinal AD	1.05 (0.82–1.33)	1.05 (0.74–1.43)	1.02 (0.67–1.46)
Celiac disease	1.73 (0.87–3.04)	2.97 (1.27–5.75) <sup>d</sup>	NA
Crohn disease	0.96 (0.62–1.41)	0.76 (0.38–1.33)	1.09 (0.55–1.92)
Ulcerative colitis	1.02 (0.75–1.36)	1.05 (0.68–1.53)	0.99 (0.60–1.52)
Blood AD	1.30 (0.59–2.43)	NA	NA
Nervous system AD	1.14 (0.72–1.71)	1.35 (0.78–2.16)	0.76 (0.27–1.64)
Multiple sclerosis	1.19 (0.70–1.88)	1.36 (0.73–2.28)	NA
Skin AD	1.30 (0.91–1.80)	1.44 (0.87–2.21)	1.42 (0.82–2.27)
Psoriasis vulgaris	1.41 (0.96–1.98)	1.55 (0.91–2.45)	1.43 (0.78–2.35)

IRRs were adjusted for age and its interaction with gender, calendar year, place of birth, and ages of the mother and father at the time of the child's birth. NA indicates not applicable.

<sup>a</sup> Data show IRRs of ASDs associated with a history of the specific AD in a parents or sibling. People with no such history were chosen as reference category.

<sup>b</sup> Data show IRRs of ASDs associated with a history of the specific AD in the mother. People with no such history were chosen as a reference group. People with the ADs in both parents were not included.

<sup>c</sup> Data show IRRs of ASDs associated with a history of the specific AD in the father. People with no such history were chosen as a reference group. People with the AD in both parents were not included.

<sup>d</sup>  $P < .05$ .

**TABLE 4** Adjusted IRRs (95% CIs) of Infantile Autism After Family History of ADs

AD	Previous AD		
	Parent or Sibling, IRR (95% CI) <sup>a</sup>	Mother Only, IRR (95% CI) <sup>b</sup>	Father Only, IRR (95% CI) <sup>c</sup>
All ADs combined	1.20 (0.95–1.50)	1.07 (0.76–1.46)	1.42 (0.99–1.97)
Endocrine AD	1.28 (0.86–1.81)	0.95 (0.51–1.61)	1.97 (1.15–3.12) <sup>d</sup>
Thyrotoxicosis	0.62 (0.22–1.33)	NA	NA
T1D	1.78 (1.16–2.61) <sup>d</sup>	2.14 (1.07–3.77) <sup>d</sup>	1.85 (1.02–3.06) <sup>d</sup>
Connective tissue AD	1.29 (0.74–2.07)	1.47 (0.70–2.65)	NA
RA	1.04 (0.41–2.11)	NA	NA
Gastrointestinal AD	1.28 (0.84–1.84)	1.21 (0.67–2.00)	1.23 (0.62–2.17)
Crohn disease	0.93 (0.40–1.81)	NA	NA
Ulcerative colitis	1.41 (0.87–2.16)	1.40 (0.70–2.46)	1.39 (0.63–2.60)
Nervous system AD	1.28 (0.55–2.48)	1.81 (0.72–3.67)	NA
Multiple sclerosis	1.27 (0.46–2.74)	NA	NA
Skin AD	1.25 (0.63–2.20)	NA	2.16 (0.92–4.19)
Psoriasis vulgaris	1.23 (0.56–2.29)	NA	2.15 (0.85–4.37)

IRR was adjusted for age and its interaction with gender, calendar year, place of birth, and ages of the mother and father at the time of the child's birth. NA indicates not applicable.

<sup>a</sup> Data show IRRs of infantile autism associated with a history of the specific AD in a parent or sibling. People with no such history were chosen as a reference category.

<sup>b</sup> Data show IRRs of infantile autism associated with a history of the specific AD in the mother. People with no such history were chosen as a reference group. People with the AD in both parents were not included.

<sup>c</sup> Data show IRRs of infantile autism associated with a history of the specific AD in the father. People with no such history were chosen as a reference group. People with the AD in both parents were not included.

<sup>d</sup>  $P < .05$ .

birth weight of  $>2500$  g, and an Apgar score  $>6$ , a total of 2886 children were diagnosed with ASDs, of which 933 had an infantile autism diagnosis. No major change in results was found by performing this stratification (data not shown). Family history of T1D was still found to be statistically significantly associated with infantile autism (IRR: 1.76 [95% CI: 1.11–2.81]). Both the group of maternal AD in connective tissue (IRR: 1.72 [95% CI: 1.20–2.46]) and RA in the mother (IRR: 1.79 [95% CI: 1.14–2.81]) were found to be associated with ASDs. Celiac disease in the mother (IRR: 3.52 [95% CI: 1.67–7.38]) was found to be associated with ASDs.

## DISCUSSION

The study confirms previous findings of an increased risk of ASDs for children with a family history of RA.<sup>9</sup> We add to previous knowledge by suggesting that this increased risk is possibly limited to maternal history of RA. This suggests that the association between RA and ASDs is caused by a prenatal exposure to maternal antibodies or fetal environment during gestation. It is

well known that autoantibodies can transfer from the mother to the fetus in women affected by certain ADs in connective tissue.<sup>20</sup> However, it is known that pregnancy exerts a beneficial effect on the symptoms and signs of RA:  $\sim 75\%$  of patients experience improvement or even remission of arthritis during gestation,<sup>21</sup> and studies of pregnant patients with RA have shown a cytokine expression similar to that found in healthy pregnant women.<sup>22</sup> Also, the recommended treatment of disease flare-ups during pregnancy is considered safe for the fetus and child during the period of breastfeeding.<sup>23</sup> Warren et al<sup>24</sup> found that the third hypervariable region on the HLA-DR B1 gene is associated with both RA and infantile autism, implying that RA and infantile autism may have some common genetic background. Other immune-based genes found associated with ASDs include HLA-DR4,<sup>25,26</sup> HLA-DR13,<sup>25</sup> and HLA-A2.<sup>27</sup>

Another previous finding was confirmed concerning increased risk of infantile autism for children with a paternal history of T1D.<sup>11</sup> We found,

however, an association between both paternal and maternal history of T1D, suggesting a common genetic factor. Limited research has been done on a possible common genetic profile of infantile autism and T1D, but an increased frequency of complement C4B null allele has been found in both diseases.<sup>28,29</sup> Several studies have suggested a greater prevalence of ASDs in children with diabetes compared with the general population.<sup>30,31</sup> The observed increased risk of ASDs after a history of maternal T1D could possibly be caused by comorbidities with the mother's condition. For example, a state of hypoglycemia or long-standing hyperglycemia in the fetus of a diabetic mother has serious effects for the developing brain.<sup>32</sup> However, this would not explain the increased risk associated with paternal T1D.

Maternal diagnosis of celiac disease was found to be associated with ASDs. Previous studies have found associations between undiagnosed celiac disease in pregnancy and intrauterine growth reduction of the fetus,<sup>33,34</sup> low birth weight,<sup>33,34</sup> and early gestational age,<sup>34</sup> which also are risk factors for ASDs.<sup>35</sup> However, celiac disease diagnosed before pregnancy does not seem to constitute a risk of adverse fetal outcome, indicating the importance of treatment of pregnant women with celiac disease.<sup>33,34</sup> Previous studies have suggested an association between celiac disease and psychiatric diseases. Eaton et al<sup>36</sup> found an increased risk of schizophrenia for individuals with a parental history of celiac disease. Previous studies investigating celiac disease in the child itself and autism have not found a significant association.<sup>37,38</sup> The present study is the first to investigate the association between family history of celiac disease and autism, and this finding needs replication in other study populations.

We found no general association between all ADs combined and ASDs or infantile autism. However, this was not a surprising result, because different pathogenesis and etiologies apply for different ADs. No statistically significant association was found between ulcerative colitis and infantile autism, as suggested by Mouridsen et al<sup>11</sup> in a previous study, a surprising result, because the previous study also used Danish register data. The studies differ, however, in the time period in which infantile autism case subjects are identified; Mouridsen et al<sup>11</sup> included case subjects seen from 1960 to 1984, in contrast to the present study, which includes children born from 1993 to 2004. The registration of infantile autism in Denmark is considered more complete after the introduction of ICD-10 in 1994.<sup>39</sup> No statistically significant association was found between psoriasis and ASDs, as suggested by Croen et al.<sup>8</sup> This could be explained by the use of data on hospital contact (excluding primary care) in the present study as opposed to data on all medical contacts (including primary care) in the study by Croen et al.<sup>8</sup> In the present study, limited completeness of exposure data possible resulted in a weaker observed association between familial AD and ASDs. The significantly lower risk of ASDs after family history of thyrotoxicosis is contradictory to results from most other studies<sup>9–11</sup>; however, Croen et al<sup>8</sup> found an odds ratio of 0.6 (95% CI: 0.3–1.2) of ASDs after including maternal autoimmune thyroid diseases.

We had no data on potential exacerbation of AD activity during pregnancy or the probable use of medication during pregnancy. Previous studies have suggested that women with AD have an increased risk of developing certain obstetric complications, such as preterm birth, fetal growth restriction, or as-

phyxia,<sup>32,40,41</sup> factors that also increase the risk of autism in the child.<sup>35</sup> However, results from the stratified analyses conducted in this study, including only children born at term with a normal birth weight and an Apgar score of >6, were similar to the general results, suggesting that the association between maternal history of AD and autism can not be entirely explained by prenatal or perinatal factors, such as low birth weight, low gestational age, and low Apgar score.

The results of the study were based on an ethnically homogeneous population of children born in Denmark in 1993–2004 by Danish-born mothers. The diagnostic data were obtained from nationwide registers, based on standardized diagnostic reporting procedures. The use of register data made it possible to include a large number of individuals and to thereby obtain optimal statistical power. However, there was not enough statistical power to address possible gender or sibling effects in the risk estimates. The certainty of the risk estimates can be assessed using the CIs; wide CIs indicate an uncertain estimate, whereas narrow CIs indicate a more precise and reliable estimate.

The quality of infantile autism diagnoses found in the DPCR has been validated (M. Lauritsen, DrMedSc, M. Jørgensen, MD, K. Madsen, PhD, et al., unpublished data, 2009). In an evaluation of >500 medical charts of children registered with infantile autism in the DPCR, 94% of the children met the criteria for that diagnosis. The completeness of ASDs diagnosis in the Danish register is assumed to be good; the prevalence of ASDs for 9-year-old children is reported to be 5.1 per 1000,<sup>42</sup> an estimate similar to the American prevalence of 4.2 per 1000 for 8-year-old children living in metropolitan Atlanta, Georgia.<sup>43</sup> The completeness of AD diagnoses is unknown;

however, diagnostic accuracy is informed by a small validation of 2 ADs. We reviewed medical charts on 40 women registered in the DNHR as having RA and 40 women registered in the DNHR as having T1D. Half of the women were diagnosed at a university hospital, and the other half were diagnosed at a regional hospital. Seventy-five percent of the women registered with RA met the operational criteria for RA according to the 1987 Criteria for the Classification of Acute Arthritis of RA from the American College of Rheumatology.<sup>44</sup> Ninety-five percent of the women registered with T1D met the operational criteria for T1D from the American Diabetes Association.<sup>45</sup>

## CONCLUSIONS

The results from this study suggest a complex form of association between family history of certain ADs and ASDs/infantile autism. Findings from previous studies concerning the association between RA and ASDs and T1D and infantile autism are confirmed. Furthermore, this study suggests a probable genetic susceptibility in the case of T1D and a potential prenatal antibody exposure or altered fetal environment in the case of RA. Moreover, a new finding concerning maternal celiac disease and ASDs was presented in this study. More detailed research on the possible common genetic background of ASDs and these specific ADs is suggested. Also, the effect of AD activity during pregnancy on the fetal environment and the potential transfer of maternal antibodies to the fetus are relevant and should be investigated further.

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