Using The National Children's Study in Analyses of Maternal Autoimmune Disorders and Developmental Disorders in Offspring

Social & Scientific Systems, Inc.

Jodi Anne Cisewski, MPH

Public Health Sciences, Social & Scientific Systems, Inc., Silver Spring, Maryland, USA

BACKGROUND

The National Children's Study (NCS) Vanguard Study was a pilot study for a planned large-scale epidemiological birth cohort of children (and their parents) to examine environmental influences on child health and development. Between 2009 and 2014, the study enrolled and followed over 5,400 birth families in 43 counties across 31 states throughout the United States. At protocol-specified study visits, data concerning a wide variety of health-related topics were collected including basic demographics, medical conditions and history, physical measures, infant feeding, cognitive assessments, childcare arrangements and more. This information and material is available through the NCS Archive (https://ncsarchive.s-3.net) for approved research projects by qualified investigators. The NCS Archive contains study visit data from preconception to 42 months post birth, as well as a sample repository of over 220,000 biological and environmental samples (1). The NCS Archive is free for researchers to use exclusive of sample shipping and handling costs. This presentation is an example of the use of the NCS Archive data for pediatrics research, in this case with respect to maternal autoimmune disorders and risk of autism in offspring. In addition, this presentation describes several childhood developmental screening tools used in The National Children's Study, data from which are available for researchers.

METHODS

Data Source and Study Sample

The NCS Vanguard Study sample was a prospective, longitudinal cohort of mother-child pairs residing in the U.S. Potential mothers were recruited to NCS pre-conception, during pregnancy or at childbirth and followed for up to 4 years. Information concerning the mother's medical history was collected during the first pregnancy visit. Health information such as 1) whether she has an autoimmune disorder; 2) if she was ever told she has diabetes (not gestational), hyperthyroidism, hypothyroidism; and 3) if she received treatment in the past 12 months for diabetes (excluding gestational diabetes), hypothyroidism or a thyroid problem, were used to derive whether a mother had an autoimmune disorder during pregnancy. Mothers were classified as having an autoimmune disorder if they reported having (or receiving treatment for) rheumatoid arthritis, diabetes (excluding gestational), lupus, multiple sclerosis, Graves' disease, hyperthyroidism, hypothyroidism, or "other" autoimmune disorder prior to giving birth.

During the 24-month visit, children underwent developmental screening to assess for the risk of autism using the Modified Checklist of Autism in Toddlers (M-CHAT) (2). The M-CHAT is a validated developmental screening tool that consists of a 23-item checklist, which was completed by the primary caregiver during the visit or mailed back at a later date*. Scoring for the M-CHAT is described elsewhere (3).

Demographic characteristics of NCS mothers and children such as age at birth of first NCS child**, maternal education, maternal employment status at childbirth, yearly household income, sex of the child, gestational age at birth, and child's birthweight were collected during the study. Maternal education and household income were reported prior to childbirth during the pregnancy visits.

**The 24-Month in-person interview window was between 23 and 29 months of age – some M-CHAT self-administered questionnaires were mailed back outside this age window.*

***For the analyses in this presentation, 51 out of 2,244 (2.27%) children had an NCS sibling from a separate birth.*

Statistical Analysis

The analyses for this presentation investigated the effect of the exposure of interest, presence of an autoimmune disorder during pregnancy, on the outcome of interest, offspring who are at risk for autism. Descriptive analyses of maternal education, yearly household income, and child's sex among children who were at risk and those not at risk of autism were examined using Rao-Scott Chi-Square test; while mean maternal age at childbirth, gestational age at birth, and birthweight were examined using t-tests. The association between autoimmune disorders and risk of autism was explored using logistic regression analyses and adjusted for *a priori* covariates. All analyses were performed using SAS SURVEY procedures to account for non-response and clustered sampling design in SAS Version 9.4 (SAS Institute Inc., Cary, NC) at 5% level of significance. Sampling weights were not used in analysis due to unavailability of weights with the NCS Vanguard Study sample. Graphics were prepared using R version 3.4.1 (RStudio, Inc., Boston, MA).

RESULTS

Study Cohort

The study sample included 2,244 women who responded to medical history questions at the pregnancy visit and whose child was screened for risk of autism using the M-CHAT instrument. Compared with children not at risk, children at risk for autism were more likely to have a mother with a high school diploma or less, who was unemployed at the time of birth, and come from lower income families. Additional demographic characteristics are displayed in Table 1. The distribution of child's age at the time of the M-CHAT screening is shown in Figure 1.

Table 1. Distribution of Demographic Characteristics among Study Participants

Demographic Characteristics[a]	Risk of Autism Status based on M-CHAT			
	Total	At Risk	Not At Risk	
	(N=2,244)	(N=156)	(N=2,088)	P-Value
Parental Characteristics				
Maternal Age (years) at Child's Birth, Mean (SD)	29.6 (5.4)	28.2 (5.9)	29.7 (5.3)	0.004[c]
Maternal Education, N (%)				<0.0001[b]
High School Diploma, GED or less	548 (24.6)	88 (56.8)	460 (22.2)	
Associate Degree, Some College	597 (26.8)	35 (22.6)	562 (27.2)	
Bachelor's Degree	641 (28.8)	22 (14.2)	619 (29.9)	
Post Graduate Degree	438 (19.7)	10 (6.4)	428 (20.7)	
Maternal Employment Status, N (%)				0.0001[b]
Employed	1151 (53.1)	49 (33.1)	1102 (54.5)	
Not Employed	1018 (46.9)	99 (66.9)	919 (45.5)	
Yearly Household Income, N (%)				<0.0001[b]
Less than $50,000	1013 (49.34)	98 (75.38)	915 (47.58)	
$50,000 or more	1040 (50.66)	32 (24.62)	1008 (52.42)	
Child Characteristics				
Sex of Child, N (%)				0.224[b]
Female	1097 (48.9)	69 (44.2)	1028 (49.2)	
Male	1147 (51.1)	87 (55.8)	1060 (50.8)	
Gestational Age (wks), Mean (SD)	38.7 (1.9)	38.2 (2.3)	38.7 (1.8)	0.003[c]
Birthweight (g), Mean (SD)	3371.2 (535.5)	3278.3 (650.9)	3377.7 (526)	0.110[c]

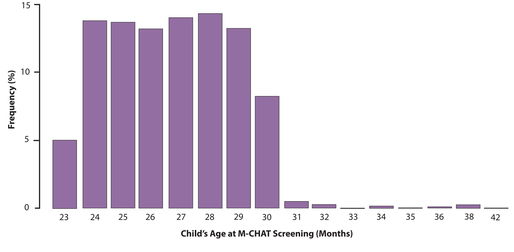
Sample Sizes and proportions are based on unweighted data.

[a]The number of responses for some variables diverged due to missing data (non-responses).

[b]Rao-Scott Chi-Square Test at level of significance 5%.

[c]T Test at level of significance 5%.

Figure 1. Distribution of Child's Age at M-CHAT Screening



Maternal Autoimmune Disorder and Risk of Autism

Eighteen out of 156 (12%) women whose children were at risk for autism had an autoimmune disorder during pregnancy, while 198 out of 2,088 (9%) women whose children were not at risk for autism had an autoimmune disorder during pregnancy. The association between maternal autoimmune disorder during pregnancy and offspring at risk for autism was weak and non-significant (odds ratio [OR] 1.245; 95% confidence interval [CI] 0.720 to 2.154; P = 0.422). The OR, after adjusting for maternal age at childbirth, education, employment, income, sex of child, gestational age and birthweight, also revealed no significant relationship between maternal autoimmune disorder during pregnancy and offspring at risk for autism (adjusted odds ratio [aOR], 1.348; 95% confidence interval [CI] 0.714 to 2.546; P = 0.347) (Table 2).

Table 2. Association Between Maternal Autoimmune Disorder and Risk of Autism in Offspring

Model	Exposure	At-Risk for Autism	Not at Risk for Autism	OR (95% CI)	P-Value
		N (%)	N (%)		
Crude	Autoimmune Disorder				
	Yes	18 (12)	198 (9)	1.245 (0.720, 2.154)	0.422
	No	138 (88)	1890 (91)	1[a]	
Adjusted[b]	Autoimmune Disorder				
	Yes	18 (12)	198 (9)	1.348 (0.714, 2.546)	0.347
	No	138 (88)	1890 (91)	1[a]	

[a]Reference group

[b]Adjusted for maternal age at childbirth, education, employment, income, sex of child, gestational age and birthweight.

CONCLUSIONS

The National Children's Study, a prospective study of environmental influences on child health and development, recruited 5,420 mothers during pre-conception, pregnancy, or at childbirth — the mother-child pairs were followed for up to the 42-month interview. Using the 156 children (7% of the 2,244 administered the M-CHAT) identified as "at risk" for autism, the relationship between the risk of autism and mothers who self-identified as having an autoimmune disorder during the pregnancy visit was explored. The data did not provide evidence of a significant association between having an autoimmune disorder during pregnancy and children at-risk of autism, at level of significance 5%. The association between maternal autoimmune disorder and reported diagnosis of autism spectrum disorder (ASD) was not explored in this presentation due to small sample sizes. Limitations of the NCS data should be noted. As the purpose of the NCS Vanguard Study was to pilot procedures for use in a larger study, identical evaluations were not conducted on all participants.

This presentation illustrates how researchers can use the newly released developmental screening data from The National Children's Study (Table 3). While the focus here was on autoimmune disorders during pregnancy, the NCS Archive contains a plethora of familial information such as demographics of the father, child medications, physical measures, tobacco smoke exposure, insurance status, breastfeeding, childcare arrangements, and home exposures, for future exploration.

Table 3. Developmental Screening Tools Administered to NCS Children

Developmental Screening Tool	Time point Administered	Number of Records
Modified Checklist for Autism in Toddlers (M-CHAT)	24-Month Visit	2244
Ages & Stages Questionnaires Third Edition (ASQ™)	18-Month Visit 24-Month Visit	5826[a]
Brief Infant Toddler Social Emotional Assessment (BITSEA)	12-Month Visit 30-Month Visit	2430[a]
Infant/Toddler Sensory Profile® (ITSP)	30-Month Visit	1622
Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scales (SWAN)	36-Month Visit	535
NIH Toolbox®	36-Month Visit	632
Infant Behavior Questionnaire (IBQ)	6-Month Visit	70

[a]Indicates children may have multiple records

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3 Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in Toddlers: An Initial Study Investigating the Early Detection of Autism and Pervasive Developmental Disorders. J Autism Dev Disord. 2001 Apr; 31(2):131-44.

For more information, please contact:

NICHD Website https://www.nichd.nih.gov/research/NCS/

NCS Archive Website https://ncsarchive.s-3.net/

Archive Email NCSArchive@s-3.net

THE NATIONAL CHILDREN'S STUDY

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