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## Association of Maternal Autoimmune Disease With Attention-Deficit/Hyperactivity Disorder in Children.

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**IMPORTANCE:** Maternal autoimmune disease has been associated with increased risk of neurodevelopmental disorders in offspring, but few studies have assessed the association with attention-deficit/hyperactivity disorder (ADHD).

**OBJECTIVE:** To examine the association between maternal autoimmune disease and ADHD within a population-based cohort and combine results in a subsequent systematic review and meta-analysis.

**DESIGN, SETTING, AND PARTICIPANTS:** A cohort study was conducted of singleton children born at term gestation (37-41 weeks) in New South Wales, Australia, from July 1, 2000, to December 31, 2010, and followed up until the end of 2014; and a systematic review evaluated articles from the MEDLINE, Embase, and Web of Science databases to identify all studies published before November 20, 2019. A total of 12 610 children exposed to maternal autoimmune disease were propensity score matched (1:4) to 50 440 unexposed children, for a total cohort of 63 050. A child was considered to have ADHD if they had (1) an authorization or filled prescription for stimulant treatment for ADHD or (2) a hospital diagnosis of ADHD. Children linked to a first ADHD event before 3 years of age were excluded. Data were analyzed from January 13 to April 20, 2020.

**EXPOSURES:** One or more maternal autoimmune diagnoses in linked hospital admission records between July 1, 2000, and December 31, 2012. Thirty-five conditions were considered together and individually.

**MAIN OUTCOMES AND MEASURES:** The main outcome was child ADHD identified from stimulant authorization or prescription data and diagnoses in linked hospital admission records. Multivariable Cox regression was used to assess the association between maternal autoimmune disease and ADHD adjusted for child sex. Pooled hazard ratios (HRs) were calculated using random-effects meta-analysis with inverse-variance weights for each exposure reported by 2 or more studies.

**RESULTS:** In the population-based cohort analysis, 831 718 singleton, term infants born to 831 718 mothers (mean [SD] age, 29.8 [5.6] years) were assessed. Of 12 767 infants (1.5%) who were linked to a maternal autoimmune diagnosis, 12 610 were propensity score matched to 50 440 control infants, for a total study cohort of 63 050 infants. In this cohort, any autoimmune disease was associated with ADHD in offspring (HR, 1.30; 95% CI 1.15-1.46), as was type 1 diabetes (HR, 2.23; 95% CI, 1.66-3.00), psoriasis (HR, 1.66; 95% CI, 1.02-2.70), and rheumatic fever or rheumatic carditis (HR, 1.75; 95% CI, 1.06-2.89). Five studies (including the present study) were included in the meta-analysis. Any autoimmune disease (2 studies: HR, 1.20; 95% CI, 1.03-1.38), type 1 diabetes (4 studies: HR, 1.53; 95% CI, 1.27-1.85), hyperthyroidism (3 studies: HR, 1.15; 95% CI, 1.06-1.26), and psoriasis (2 studies: HR,

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1.31; 95% CI, 1.10-1.56) were associated with ADHD.

**CONCLUSIONS AND RELEVANCE:** In this cohort study, maternal autoimmune diseases were associated with increased ADHD among children. These findings suggest possible shared genetic vulnerability between autoimmune disease and ADHD or a potential role for maternal immune activation in the expression of neurodevelopmental disorders in children. Future studies measuring disease activity, modifiers, and medication use are required to better understand the mechanisms underlying this association.

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