

# Long-term Risk of Neuropsychiatric Disease After Exposure to Infection In Utero

Benjamin J. S. al-Haddad, MD, MSc, PhD; Bo Jacobsson, MD, PhD; Shilpi Chabra, MD; Dominika Modzelewska, MS; Erin M. Olson, PhD; Raphael Bernier, PhD; Daniel A. Enquobahrie, MD, PhD; Henrik Hagberg, MD, PhD; Svante Östling, MD, PhD; Lakshmi Rajagopal, PhD; Kristina M. Adams Waldorf, MD; Verena Sengpiel, MD, PhD

 Supplemental content

**IMPORTANCE** The developmental origins of mental illness are incompletely understood. Although the development of autism and schizophrenia are linked to infections during fetal life, it is unknown whether more common psychiatric conditions such as depression might begin in utero.

**OBJECTIVE** To estimate the risk of psychopathologic conditions imparted from fetal exposure to any maternal infection while hospitalized during pregnancy.

**DESIGN, SETTING, AND PARTICIPANTS** A total of 1791 520 Swedish children born between January 1, 1973, and December 31, 2014, were observed for up to 41 years using linked population-based registries. Children were excluded if they were born too late to contribute person-time, died before being at risk for the outcome, or were missing particular model data. Infection and psychiatric diagnoses were derived using codes from hospitalizations. Directed acyclic graphs were developed from a systematic literature review to determine Cox proportional hazards regression models for risk of psychopathologic conditions in the children. Results were evaluated using probabilistic and simple bias analyses. Statistical analysis was conducted from February 10 to October 17, 2018.

**EXPOSURES** Hospitalization during pregnancy with any maternal infection, severe maternal infection, and urinary tract infection.

**MAIN OUTCOMES AND MEASURES** Inpatient diagnosis of autism, depression, bipolar disorder, or psychosis among offspring.

**RESULTS** A total of 1791 520 Swedish-born children (48.6% females and 51.4% males) were observed from birth up to age 41 years, with a total of 32 125 813 person-years. Within the directed acyclic graph framework of assumptions, fetal exposure to any maternal infection increased the risk of an inpatient diagnosis in the child of autism (hazard ratio [HR], 1.79; 95% CI, 1.34-2.40) or depression (HR, 1.24; 95% CI, 1.08-1.42). Effect estimates for autism and depression were similar following a severe maternal infection (autism: HR, 1.81; 95% CI, 1.18-2.78; depression: HR, 1.24; 95% CI, 0.88-1.73) or urinary tract infection (autism: HR, 1.89; 95% CI, 1.23-2.90; depression: HR, 1.30; 95% CI, 1.04-1.61) and were robust to moderate unknown confounding. Within the directed acyclic graph framework of assumptions, the relationship between infection and depression was vulnerable to bias from loss to follow-up, but separate data from the Swedish Death Registry demonstrated increased risk of suicide among individuals exposed to pregnancy infection. No evidence was found for increased risk of bipolar disorder or psychosis among children exposed to infection in utero.

**CONCLUSIONS AND RELEVANCE** These findings suggest that fetal exposure to a maternal infection while hospitalized increased the risk for autism and depression, but not bipolar or psychosis, during the child's life. These results emphasize the importance of avoiding infections during pregnancy, which may impart subtle fetal brain injuries contributing to development of autism and depression.

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**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Kristina M. Adams Waldorf, MD, Center for Innate Immunity and Immune Disease, Department of Obstetrics & Gynecology, University of Washington, PO Box 356460, Seattle, WA 98195 (adamsk@uw.edu).

**A** large body of evidence indicates that particular infections in pregnancy lead to fetal brain injury, neurodevelopmental abnormalities, and an elevated lifelong risk for certain psychiatric disorders in the children.<sup>1-4</sup> Early epidemiologic evidence for an association between infection in pregnancy and psychopathologic conditions was evident in Scandinavian studies on the risk of schizophrenia after exposure to influenza in utero<sup>3</sup> and subsequent studies have demonstrated similar associations with other viral (measles, rubella, varicella-zoster, polio, and herpes), bacterial, and parasitic infections during pregnancy.<sup>5-7</sup> Other studies found associations between maternal infection and development of bipolar disorder and autism.<sup>8-10</sup> Although compelling, these studies have focused mainly on linking specific infections with a particular psychopathologic condition, with few exceptions,<sup>11</sup> rather than determining a generalized effect of infection and inflammation during pregnancy on a broad spectrum of psychopathologic conditions.

Whether maternal infection and inflammation can alter fetal neurodevelopment to a degree that imparts risk for a broad spectrum of psychopathologic conditions across the child's lifetime is unknown. Several mechanisms of neuronal injury have been postulated to occur in the developing brain as a result of inflammation and glial production due to activation of mast cells, microglia, and astrocytes.<sup>7-23</sup> Maternal and fetal inflammatory responses to infection may alter fetal neurodevelopment, as suggested in some children with autism, who display a chronic state of inflammation in the periphery as well as in the brain.<sup>10,24-26</sup> Furthermore, changes in placental serotonin production due to maternal inflammation have been suggested to lead to aberrant neurodevelopment.<sup>27</sup> Finally, the idea that some psychiatric disorders have a common mechanism of pathogenesis is supported by recent evidence implicating shared molecular pathways of transcriptional dysregulation and a common polygenic origin for autism, schizophrenia, and bipolar disorder.<sup>28,29</sup>

We hypothesized that fetal exposure to maternal infection or associated inflammation increases the future risk for the child of a broad scope of psychopathologic conditions such as autism spectrum disorder, bipolar disorder, depression, and psychosis, including schizophrenia. We further hypothesized that the magnitude of risk for psychopathologic conditions in the child differs by the type and severity of the maternal infection.

## Methods

### Study Design

We obtained data on all births between January 1, 1973, and December 31, 2014, in the Swedish population-based birth registry, which was linked to hospital inpatient, demographic, education, and death registries by each person's unique identification number.<sup>30</sup> Raw data included some births in 1972 and 2015 that were excluded. Statistics Sweden deidentified the data to maintain confidentiality; therefore, informed consent was not required. Ethical approval was obtained to link birth and registry data from the regional

### Key Points

**Question** Does exposure to maternal infection during pregnancy increase the long-term risk for major psychiatric disorders in the child?

**Findings** In this Swedish population-based cohort study of children born between 1973 and 2014, exposure to infection in pregnancy significantly increased the risk for autism spectrum disorder and depression.

**Meaning** Maternal infection during pregnancy may be responsible for some portion of autism and depression in childhood and adulthood among the exposed offspring.

ethical review board of the University of Gothenburg (Gothenburg, Sweden; 437-15) and reciprocally at Seattle Children's Hospital (Seattle, Washington; STUDY00000634).

### Exposure

Fetal exposure to maternal infection was defined using the Swedish *International Classification of Diseases, Eighth Revision (ICD-8)*, *International Classification of Diseases, Ninth Revision (ICD-9)*, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* hospitalization codes. Three prespecified exposure categories were used in pregnant women hospitalized with a diagnosis of (1) any maternal infection (eTable 1 in the *Supplement*); (2) severe infections, which included sepsis, meningitis or encephalitis, pneumonia, influenza, pyelonephritis, or chorioamnionitis (eTable 2 in the *Supplement*); and/or (3) urinary tract infection (eTable 2 in the *Supplement*). We used both primary and secondary infection diagnosis codes that occurred during any hospitalization during pregnancy except the admission for delivery, because we could not determine that infection preceded the birth for this admission. There was one exception to this rule: we used a chorioamnionitis diagnosis from the delivery admission because chorioamnionitis could have only occurred before delivery.

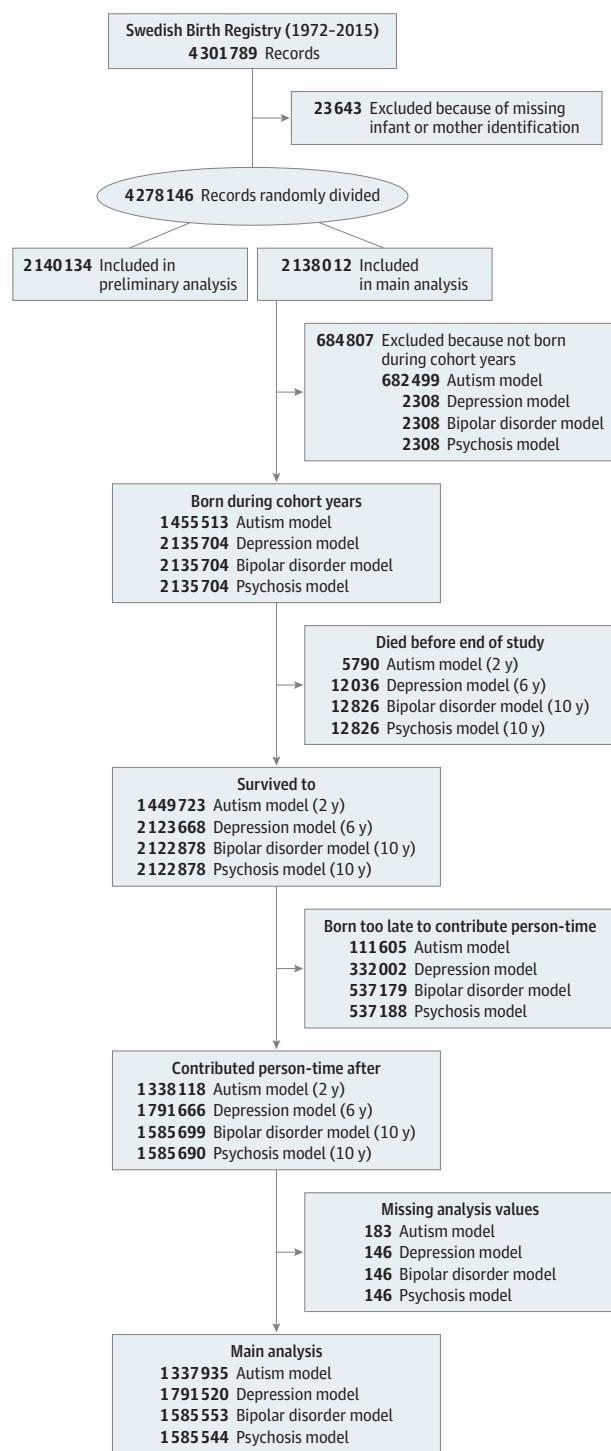
### Primary Outcomes

Primary study outcomes were autism, bipolar disorder, depression, and psychosis (including schizophrenia), which were defined by Swedish *ICD-8*, *ICD-9*, and *ICD-10* codes during an inpatient hospitalization (eTable 3 in the *Supplement*).

### Inclusion and Exclusion Criteria

We included all children born in Sweden from January 1, 1973, to December 31, 2014, for our models with depression, bipolar disorder, and psychosis (**Figure 1**). In the autism model, we included all children born in Sweden from January 1, 1987, to December 31, 2014, because 1987 coincided with the introduction of autism as a new diagnosis and implementation of *ICD-9* coding. As diagnoses of psychopathologic conditions are unusual prior to certain ages, children were considered at risk for autism only after age 2 years, depression only after age 6 years, and psychosis and bipolar disorder only after age 10 years.

**Figure 1. Inclusions and Exclusions by Psychopathologic Condition Outcome**



This diagram shows cohort numbers used to analyze fetal exposure to infection and each type of psychopathologic condition, which varied owing to differing inclusion and exclusion criteria.

### Statistical Analysis

Statistical analysis was conducted from February 10 to October 17, 2018. All tests were 2-sided. We reviewed 12 264 ab-

stracts and articles to develop a series of directed acyclic graphs (DAGs) to characterize the relationships among maternal infection during pregnancy, diagnosis of psychopathologic conditions in the child, and other important variables. These models were based on the best available evidence and subject area expertise when evidence was not available. We reviewed and approved the final DAG models (eAppendix and eFigures 1-12 in the *Supplement*).

On the basis of these DAGs, we used established analytic rules with the Dagitty web application<sup>31</sup> and the R package (R Foundation for Statistical Computing) to determine whether a given variable should be considered as a confounder, collider, or neither a confounder nor collider. These tools were also used to establish the minimally sufficient adjustment sets of variables for regression to estimate the total effects of exposure to infection during fetal life on subsequent development of psychopathologic conditions in childhood and adulthood.<sup>32</sup> If there was disagreement about a variable's status, we performed the analysis with and without the variable to determine how the effect estimate changed (eg, maternal mental health; eTable 4 in the *Supplement*). Statistically equivalent DAG models were also evaluated for alternate frameworks.

According to best practice and consistent with study power, we split the data in half; one half was used for preliminary power analyses to determine whether there was sufficient power to examine infections by trimester as well as to examine asymptomatic bacteriuria and vaginal tract infections as separate categories. The second half of the data was used for 8 prespecified analyses with Bonferroni correction (type I error rate of 0.05 adjusted after correction to 0.0063). In the first 4 analyses, we investigated the relationship between any maternal infection and bipolar disorder, psychosis (including schizophrenia), autism, or depression. The final 4 analyses studied the effect of a severe maternal infection with the diagnosis of autism and depression or the effect of a maternal urinary tract infection (UTI) on the diagnosis of autism or depression. Based on the DAG models, we used Cox proportional hazards regression to generate hazard ratios (HRs). We ensured that the proportional hazards assumption was met using individual and global  $\chi^2$  tests and examination of Schoenfeld residual plots. In most models, delivery year and maternal tobacco use violated the proportional hazards assumption; therefore, we estimated HRs with maternal tobacco use and 10-year birth epoch as strata. We also adjusted for maternal age, maternal asthma, maternal diabetes, and premature rupture of membranes. Other variables examined are shown in eFigures 1 to 12 in the *Supplement*. To account for nonindependence of siblings, we used robust sandwich variance estimators. Unadjusted cumulative hazards were also plotted for each exposure and outcome.

### Bias Analyses

We used the following 2 methods of bias analysis to interrogate our results: probabilistic bias analysis to assess for an unknown confounder and simple bias analysis to assess for outcome misclassification (differential loss to follow-up) and exposure misclassification (inaccurate infection coding).<sup>33</sup>

**Table 1. Maternal, Delivery, and Infant Characteristics by Infection Status**

Characteristic	Value <sup>a</sup>	
	No Infection (n = 2 108 156)	Any Infection (n = 29 856)
<b>Maternal characteristics</b>		
Age, mean (SD), y	28.7 (5.3)	27.6 (5.6)
Tobacco use <sup>b</sup>	324 493 (15.4)	5671 (19.0)
Asthma	4844 (0.2)	158 (0.5)
Seizures	3592 (0.2)	106 (0.4)
Hypertension	53 314 (2.5)	1007 (3.4)
Diabetes	6358 (0.3)	291 (1.0)
Mental health diagnosis	15 820 (0.75)	596 (2.0)
<b>Delivery characteristics</b>		
Gestational age, mean (SD), wk	39.4 (1.9)	39 (2.4)
Prolonged labor	27 456 (1.3)	493 (1.7)
Preterm premature rupture of membranes	3216 (0.2)	138 (0.5)
Antepartum hemorrhage	35 748 (1.7)	1045 (3.5)
<b>Infant characteristics</b>		
Birth weight, mean (SD), g	3508 (579)	3415 (643)
Female sex	1 024 770 (48.6)	14 474 (48.5)
Small for gestational age <sup>c</sup>	66 785 (3.2)	1201 (4.0)
Large for gestational age <sup>c</sup>	67 774 (3.2)	1057 (3.5)
Bronchopulmonary dysplasia or respiratory distress syndrome	5666 (0.3)	171 (0.6)
Intraventricular hemorrhage	5666 (0.3)	171 (0.6)
Hyperbilirubinemia	69 750 (3.3)	1495 (5.0)
Fetal alcohol syndrome	6679 (0.3)	195 (0.7)
<b>Outcomes</b>		
Bipolar disorder	4402 (0.2)	71 (0.2)
Psychosis, including schizophrenia	4307 (0.2)	75 (0.3)
Autism	5003 (0.2)	133 (0.5)
Depression	20 749 (1.0)	409 (1.4)

<sup>a</sup> Data are presented as number (percentage) of patients unless otherwise indicated.

<sup>b</sup> Tobacco status is not known for women who gave birth before 1982.

<sup>c</sup> Numbers to indicate neonates who were either large or small for gestational age were estimated using the method of Marsál et al.<sup>34</sup>

## Results

### Study Population and Cumulative Hazard Curves

We analyzed linked Swedish pregnancy and birth records for 4 278 146 neonates, as well as subsequent hospitalization records for the children up to 41 years after birth. We used half the data for preliminary power analyses and the second half (2 138 012 records) for the main analysis (Figure 1). Study population characteristics are reported in Table 1.<sup>34</sup>

To evaluate the risk of psychopathologic conditions in the child after fetal exposure to any maternal infection during hospitalization, unadjusted cumulative hazard curves were generated by infection status for each outcome (Figure 2). The risk for hospital admission with psychosis and bipolar disorder appeared to be similar between children exposed and not exposed in utero to any maternal infection during hospitalization (Figure 2A and B). However, compared with children not

exposed in utero to maternal infection during hospitalization, the cumulative hazard for hospital admission with autism was significantly greater by age 7 years and the cumulative hazard for hospital admission with depression was significantly greater by age 21 years (Figure 2C and D). The number of outcomes, person-years, and unadjusted rate ratios for any maternal infection and risk for a neuropsychiatric disorder are presented in eTables 5 to 8 in the Supplement.

To determine if the type of maternal infection changed the risk of autism or depression, we modeled the risk of the psychopathologic condition imparted by a composite of severe maternal infections (sepsis, pneumonia, pyelonephritis, meningitis or encephalitis, influenza, and chorioamnionitis) vs UTI, which may represent a more limited infection. In unadjusted cumulative hazard curves, children or adults exposed to severe maternal infections during fetal life had similar magnitudes of increased risk for autism and depression compared with children exposed to a maternal UTI (Figure 3). The number of outcomes, person-years, and unadjusted rate ratios for severe maternal infections or UTI and risk for a neuropsychiatric disorder are presented in eTables 9 to 12 in the Supplement.

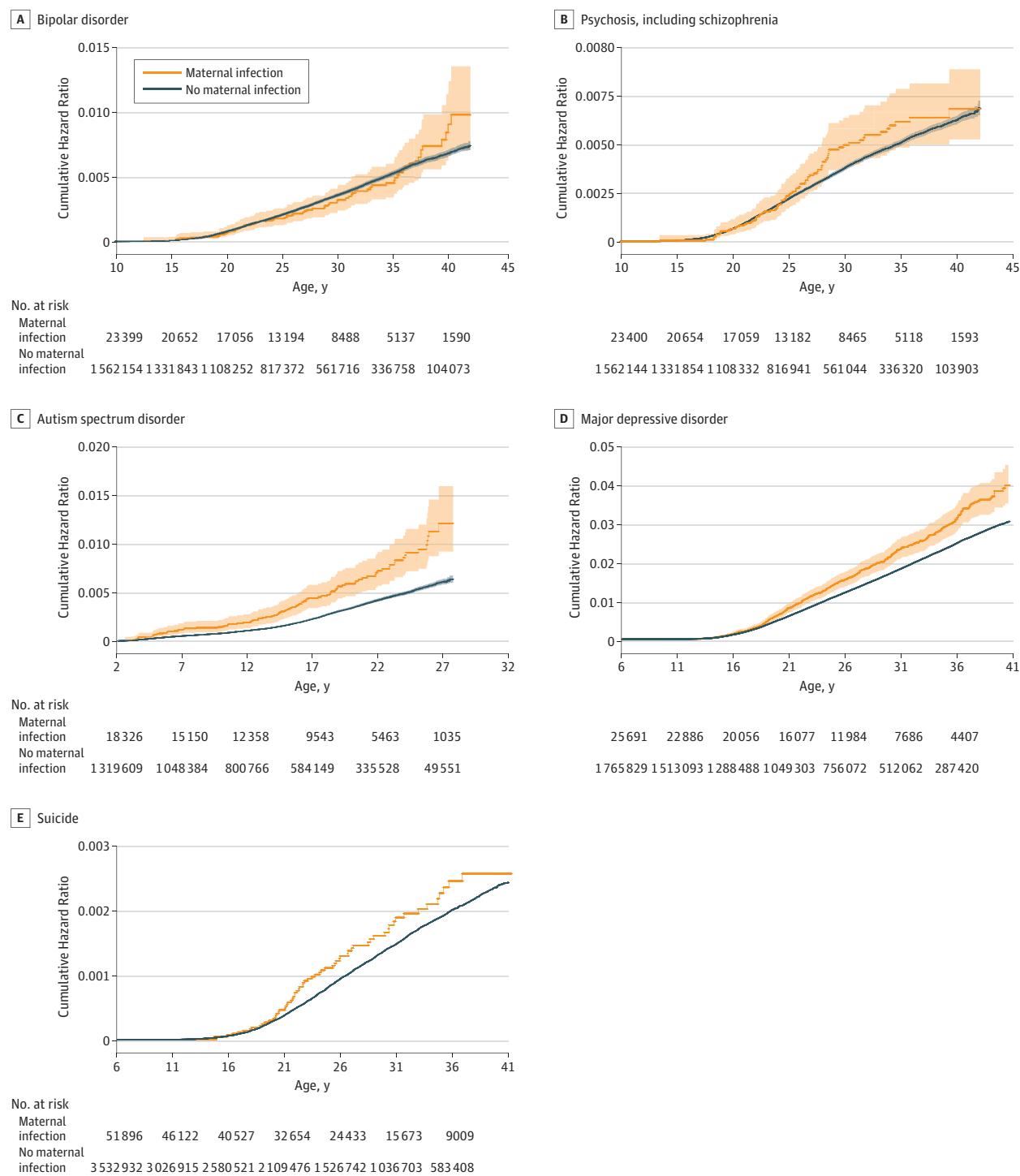
### Cox Proportional Hazards Regression Cumulative

Directed acyclic graph models informed a minimally sufficient adjustment set for estimating the effect of infections during pregnancy with future risk of psychopathologic conditions in the child, which included 10-year epoch of delivery and specific maternal exposure variables (age, tobacco use, asthma, diabetes, and premature rupture of membranes). In Cox proportional hazards regression models, there was a 79% increased risk of an autism diagnosis (HR, 1.79; 95% CI, 1.34-2.40) and a 24% increased risk of a depression diagnosis (HR, 1.24; 95% CI, 1.08-1.42) among children and adults exposed to any maternal infection during pregnancy (Table 2 and eFigures 7-13 in the Supplement). There was no apparent increased risk of bipolar disorder (HR, 0.99; 95% CI, 0.71-1.38) or diagnoses of psychosis, including schizophrenia (HR, 1.14; 95% CI, 0.83-1.57), in childhood or adulthood after fetal exposure to maternal infection (eFigures 1-6 in the Supplement). Additional analyses with maternal mental health as a confounder did not yield significantly different effect estimates (eTable 4 in the Supplement). When we analyzed the risk for psychopathologic conditions by type of infection, we found similar magnitudes of increased risk for autism and depression regardless of whether the exposure was a severe maternal infection or UTI (Table 2). For example, the HR for hospital admission with an autism diagnosis in childhood or adulthood after exposure to infection during fetal life was 1.81 (95% CI, 1.18-2.78) for a maternal severe infection and 1.89 (95% CI, 1.23-2.90) for a maternal UTI.

### Bias Analyses

We used 2 methods of bias analysis to evaluate result sensitivities to introduction of an unknown confounder and loss to follow-up bias. First, we used probabilistic bias analysis to introduce a hypothetical moderate confounder to determine the sensitivity of the results (eFigure 14 in the Supplement).<sup>33</sup>

Figure 2. Lifetime Risk for Psychopathologic Conditions in the Child After Fetal Exposure to Maternal Infection



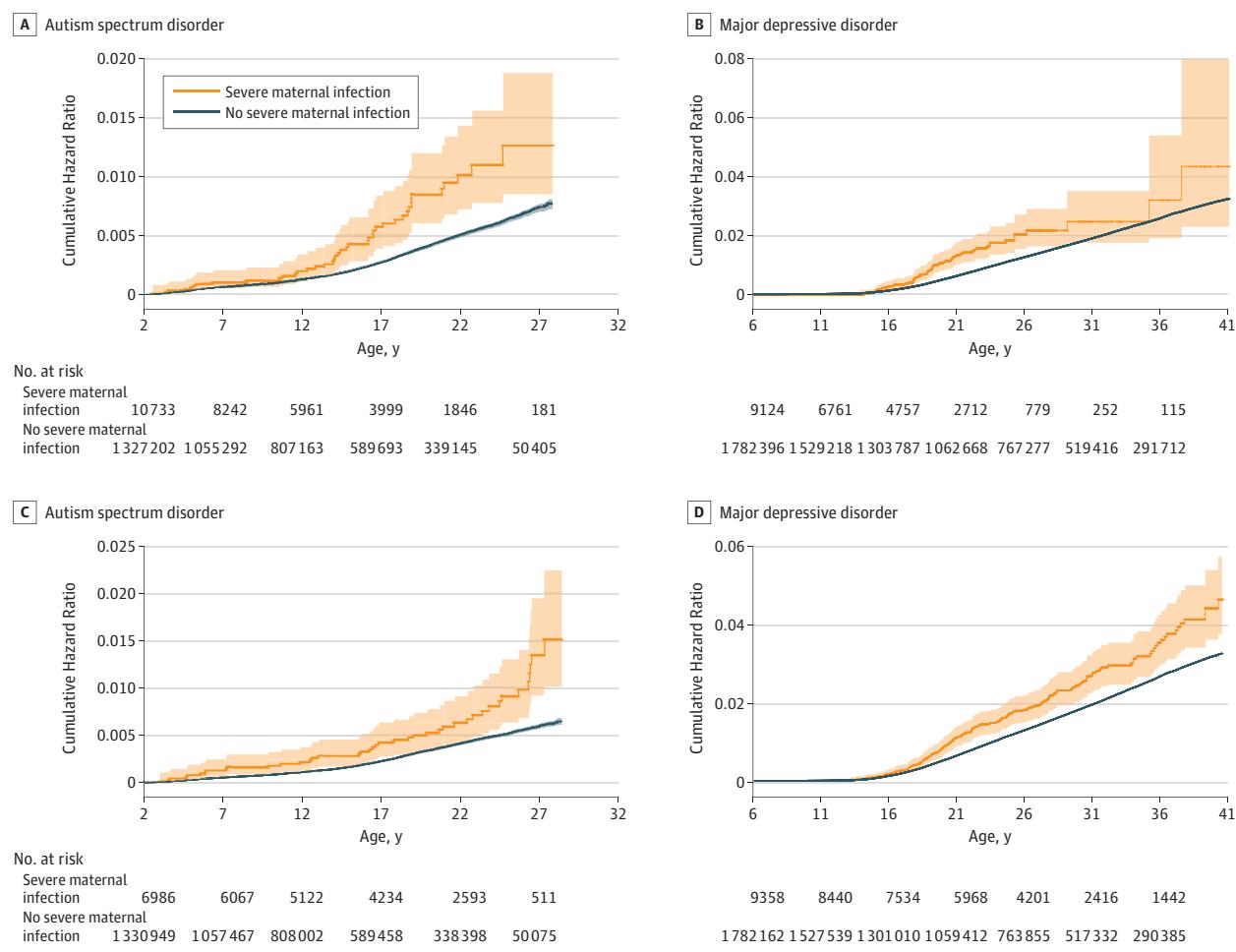
A, Unadjusted cumulative hazard curves demonstrate the risk for bipolar disorder among individuals exposed and not exposed to infection in utero. B, Risk for psychosis, including schizophrenia, among individuals exposed and not exposed to infection in utero. C, Risk for autism spectrum disorder among

individuals exposed and not exposed to infection in utero. D, Risk for major depressive disorder among individuals exposed and not exposed to infection in utero. E, Risk for death by suicide among individuals exposed and not exposed to infection in utero. Shading around the lines indicates the 95% CI.

However, measures of effect remained significant and only slightly decreased for all statistically significant results for the development of autism or depression.

Second, we used simple bias analysis<sup>33</sup> to determine the effect of misclassification of outcome bias from loss to follow-up, which would occur when a child received a diagnosis of a

Figure 3. Lifetime Risk for Autism or Depression in the Child After Fetal Exposure to Maternal Infection by Type of Infectious Exposure



A, Unadjusted cumulative hazard curves demonstrate the risk for autism spectrum disorder across the child's lifetime by fetal exposure to severe maternal infection (sepsis, meningitis or encephalitis, pneumonia, influenza, pyelonephritis, or chorioamnionitis). B, Risk for major depressive disorder across the child's lifetime by fetal exposure to severe maternal infection.

C, Risk for autism spectrum disorder across the child's lifetime by fetal exposure to maternal urinary tract infection (UTI). D, Risk for major depressive disorder across the child's lifetime by fetal exposure to maternal UTI. Shading around the lines indicates the 95% CI.

psychopathologic condition (ie, autism) but was never admitted to the hospital during the study period. Inpatient admission was required in our study to capture diagnoses of psychopathologic conditions through the Swedish Inpatient Health Registry. Our findings suggest that a population prevalence of autism spectrum disorder between 2% and 3% would be required to negate these results based on a misclassification of outcome bias (eTable 13 in the *Supplement*). Although estimates of the prevalence of autism have increased over time, with the highest estimates of prevalence in Stockholm published in 2012 at 2.5%,<sup>35</sup> prior studies in Sweden encompassing most of the study period estimated the prevalence of autism between 0.2% and 1%.<sup>36</sup>

For the outcome of depression, when we assumed a population prevalence of only 5%, there was no increased risk of depression among children and adults who were exposed to any maternal infection or UTI during fetal life (eTable 14 in the *Supplement*). Estimates of depression in

Sweden are higher than 5%, suggesting that this analysis is vulnerable to a misclassification of outcome bias from loss to follow-up.<sup>37</sup> To interrogate these results with external data, we used the Swedish National Death Registry to examine cumulative hazard curves for suicide among individuals who were exposed during fetal life to a maternal infection during hospitalization. As the National Death Registry is inclusive of the entire Swedish population, it is not vulnerable to bias from loss to follow-up like the inpatient registry. The cumulative hazard for death by suicide among adults exposed to infection during fetal life was significantly greater compared with unexposed individuals starting at age 21 years, which mirrored the results from the inpatient registry for depression (Figure 2E). Although the Cox proportional hazards regression models for depression using inpatient data were vulnerable to a misclassification of outcome bias, descriptive suicide data supported the results and were not subject to the same bias.

**Table 2. Hazard Ratios for Development of Psychopathology by Infection Type in Pregnancy<sup>a</sup>**

Infection Type	Psychopathologic Condition	Adjusted Hazard Ratio (95% CI) <sup>b</sup>
Any maternal infection	Autism	1.79 (1.34-2.40)
	Depression	1.24 (1.08-1.42)
	Psychosis	1.14 (0.83-1.57)
	Bipolar disorder <sup>c</sup>	0.99 (0.71-1.38)
Severe maternal infection	Autism	1.81 (1.18-2.78)
	Depression	1.24 (0.88-1.73)
Maternal urinary tract infection	Autism	1.89 (1.23-2.90)
	Depression	1.30 (1.04-1.61)

<sup>a</sup> All models included maternal age, maternal asthma, maternal diabetes, premature rupture of membranes, maternal tobacco status, and robust sandwich variance estimators for lack of independence among sibling births. For all models, stratification was used for 10-year epoch of birth and maternal tobacco status to avoid violating the proportional hazard assumption.

<sup>b</sup> Bonferroni correction was used to adjust 95% CIs for 8 prespecified comparisons shown in the table.

<sup>c</sup> Stratification was used for premature rupture of membranes and maternal age because of proportional hazards assumption violations.

Finally, we did a series of analyses to examine whether our results were sensitive to a misclassification of exposure bias, which may occur when maternal infection is misdiagnosed or miscoded during pregnancy. We found that the risk ratios corrected for misdiagnosis or miscoding were larger than the original effect estimates for maternal infection on autism and depression, severe maternal infection (autism only), or maternal UTI (eTables 15-19 in the *Supplement*). This finding suggests that our results are robust to possible bias from misclassification of exposure.

## Discussion

The effect of infection during pregnancy on the fetal brain and risk for subsequent development of neuropsychiatric disorders is understudied. In the Swedish population, we found compelling evidence that fetal exposure to infection (or inflammation) when the mother was hospitalized increased the risk for the child of hospital admission with autism during childhood and adulthood. These effects were observed irrespective of whether the exposure was a maternal severe infection (sepsis, influenza, pneumonia, meningitis or encephalitis, chorioamnionitis, and pyelonephritis) or UTI during pregnancy. Bias analyses revealed that autism results were robust to adjustment for a moderate unknown confounder, but that the depression results were vulnerable to bias from our inability to capture diagnoses among those who were never admitted to the hospital after birth (loss to follow-up). However, separate descriptive data from the National Death Registry, which was not subject to loss to follow-up, supported the depression results by demonstrating an increased risk of suicide among adults who were exposed to infection during fetal life. We did not find convincing evidence that maternal infection during gestation increased the lifetime risk of bipolar disorder or psychosis, including schizophrenia. Overall, our

findings provide evidence for a fetal origin of some portion of autism and depression across a spectrum of maternal infections in pregnancy.

The earliest evidence for a fetal origin of psychiatric disease came from correlations of birth season with the incidence of schizophrenia and later through associations with maternal influenza infection.<sup>3</sup> Subsequent studies have yielded mixed results<sup>38,39</sup> and recent evidence suggests that the relationship with inflammatory exposures in pregnancy may be complicated by genetic susceptibility for both schizophrenia and autism.<sup>29,40-42</sup> Unlike prior epidemiologic studies, our work used a literature-based variable framework (DAG models) and descriptive cumulative hazard curves to demonstrate that maternal infection during pregnancy increased the risk not only for autism but also possibly for depression. A few studies have investigated the lifetime risk of depression for the child after exposure to particular infections, but they have yielded mixed results.<sup>43,44</sup> Although vulnerable to possible loss to follow-up bias, our study provides suggestive evidence for a fetal origin for depression, with separate support using suicide data from the Swedish National Death Registry. Although little is known about the scientific basis to link aberrant fetal neurodevelopment with subsequent risk for depression, infection and inflammation in the pregnant mouse lead to alterations in placental serotonin production and dysgenesis of serotonergic neurons in the fetal brain.<sup>27</sup> These new findings suggest an important possible biological basis for a fetal origin for depression and suicide.

Our results of increased risk of autism after fetal exposure to infection are consistent with other epidemiologic and animal studies, which suggest that inflammation during gestation alters brain architecture or transcriptional programs.<sup>1,8,11</sup> Similar to results from another study from Sweden, we found no evidence that maternal infection increased the lifetime risk of psychosis or bipolar disorder.<sup>45</sup> However, the descriptive cumulative hazard curve for admission with psychosis suggests that infection may increase the risk earlier, but not later, in the child's lifetime. Our results cannot exclude the possibility of increased risk for psychopathologic conditions as a result of a dual "hit": an inflammatory fetal brain injury on a background of genetic susceptibility.

Although we expected that fetal exposure to severe infection would increase the risk for psychopathologic conditions compared with limited infections such as UTIs, we did not find a difference in these models. The effect of UTIs on uterine and placental inflammation during pregnancy is unknown but may be sufficient to alter neuropsychiatric risk for the fetus. A few studies of UTIs in pregnancy have found increased risk of fetal morbidity and developmental delay.<sup>46</sup> Although it is possible that the diagnosis of a UTI in hospitalized women may have reflected a more severe infection (eg, pyelonephritis), our findings suggest that further study is warranted to quantify the inflammatory effects of a UTI in pregnancy on the fetus.

## Strengths and Limitations

A clear strength of the study was the conservative nature of our analysis and use of mechanistic DAG models to specify a priori the complicated relationships among maternal, pater-

nal, perinatal, and psychiatric outcome variables. We also interrogated the sensitivity of our results to potential biases. Directed acyclic graph modeling is limited by the degree to which variables are included and relationships appropriately specified. Although the DAGs did not indicate that adjustment for socioeconomic status was required, further analysis adjusting for occupation, educational level, or income would have enriched the study; however, income variables were incomplete in our data set. As our study was restricted to pregnancies in Swedish women, it is possible that findings may not be generalizable to other populations. Finally, we acknowledge that data on maternal infection and psychiatric outcomes from birth and health registries were derived only from inpatient hospitalizations. Our results may not translate to infections diagnosed in the outpatient setting. Bias analyses and suicide data from the death registry suggest that our results are somewhat robust to the probable underestimate of psychiatric dis-

orders in our study, which occurred when participants were not admitted to the hospital after birth (lost to follow-up).

## Conclusions

Overall, we found evidence that exposure to maternal infection during fetal life increased the risk of autism and possibly of depression in the child within our DAG model assumptions. Although the individual risk appears to be small, the population effects are potentially large. Our findings amplify the urgency to better understand the role of maternal infection during pregnancy on fetal brain development and suggest that prevention of infection (eg, influenza vaccination) or anti-inflammatory therapies<sup>47,48</sup> may be important strategies for the primary prevention of some portion of autism and depression.

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**Author Affiliations:** Department of Pediatrics, Seattle Children's Hospital and University of Washington, Seattle (al-Haddad, Chabra, Rajagopal); Centre for Perinatal Medicine & Health, Department of Obstetrics & Gynecology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (Jacobsson, Modzelewska, Hagberg, Adams Waldorf, Sengpiel); Division of Health Data and Digitalisation, Department of Genetics and Bioinformatics, Norwegian Institute of Public Health, Oslo, Norway (Jacobsson); Department of Epidemiology, School of Public Health, University of Washington, Seattle (Olson, Enquobahrie); Department of School Psychology, College of Education, University of Washington, Seattle (Olson); Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle (Bernier); Centre for the Developing Brain, King's College, London, United Kingdom (Hagberg); Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (Östling); Center for Global Infectious Disease Research, Seattle Children's Research Institute, Seattle, Washington (Rajagopal); Department of Global Health, University of Washington, Seattle (Rajagopal); Center for Innate Immunity and Immune Disease, Department of Obstetrics & Gynecology, University of Washington, Seattle (Adams Waldorf).

**Author Contributions:** Dr al-Haddad had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Adams Waldorf and Sengpiel contributed equally to this work.

**Concept and design:** al-Haddad, Jacobsson, Chabra, Olson, Bernier, Adams Waldorf, Sengpiel.

**Acquisition, analysis, or interpretation of data:** al-Haddad, Jacobsson, Modzelewska, Bernier, Enquobahrie, Hagberg, Östling, Rajagopal, Adams Waldorf, Sengpiel.

**Drafting of the manuscript:** al-Haddad, Hagberg, Rajagopal, Adams Waldorf.

**Critical revision of the manuscript for important intellectual content:** al-Haddad, Jacobsson, Chabra, Modzelewska, Olson, Bernier, Enquobahrie,

Hagberg, Östling, Sengpiel.

**Statistical analysis:** al-Haddad, Modzelewska.

**Obtained funding:** Jacobsson, Chabra, Adams Waldorf, Sengpiel.

**Administrative, technical, or material support:** Jacobsson, Bernier, Enquobahrie, Hagberg, Östling, Rajagopal, Sengpiel.

**Supervision:** Jacobsson, Adams Waldorf, Sengpiel.

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### REFERENCES

1. Limperopoulos C, Bassan H, Sullivan NR, et al. Positive screening for autism in ex-preterm infants: prevalence and risk factors. *Pediatrics*. 2008;121(4):758-765. doi:10.1542/peds.2007-2158
2. Canetta SE, Bao Y, Co MDT, et al. Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring. *Am J Psychiatry*. 2014;171(5):557-563. doi:10.1176/appi.ajp.2013.13070943
3. Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry*. 1988;45(2):189-192. doi:10.1001/archpsyc.1988.0180026010903
4. Machón RA, Mednick SA, Huttunen MO. Adult major affective disorder after prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry*. 1997;54(4):322-328. doi:10.1001/archpsyc.1997.01830160040006
5. Brown AS, Cohen P, Harkavy-Friedman J, et al. A.E. Bennett Research Award: prenatal rubella, premorbid abnormalities, and adult schizophrenia. *Biol Psychiatry*. 2001;49(6):473-486. doi:10.1016/S0006-3223(01)01068-X
6. Meyer U, Feldon J. Neural basis of psychosis-related behaviour in the infection model of schizophrenia. *Behav Brain Res*. 2009;204(2):322-334. doi:10.1016/j.bbr.2008.12.022
7. Brown AS, Vinogradov S, Kremen WS, et al. Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. *Am J Psychiatry*. 2009;166(6):683-690. doi:10.1176/appi.ajp.2008.08010089
8. Lee BK, Magnusson C, Gardner RM, et al. Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders. *Brain Behav Immun*. 2015;44:100-105. doi:10.1016/j.bbi.2014.09.001
9. Avramopoulos D, Pearce BD, McGrath J, et al. Infection and inflammation in schizophrenia and bipolar disorder: a genome wide study for interactions with genetic variation. *PLoS One*. 2015;10(3):e0116696. doi:10.1371/journal.pone.0116696

10. Desmond MM, Montgomery JR, Melnick JL, Cochran GG, Verniaud W. Congenital rubella encephalitis. Effects on growth and early development. *Am J Dis Child.* 1969;118(1):30-31. doi:10.1001/archpedi.1969.02100040032005
11. Atladóttir HO, Thorsen P, Østergaard L, et al. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J Autism Dev Disord.* 2010;40(12):1423-1430. doi:10.1007/s10803-010-1006-y
12. Pratt L, Ni L, Ponzio NM, Jonakait GM. Maternal inflammation promotes fetal microglial activation and increased cholinergic expression in the fetal basal forebrain: role of interleukin-6. *Pediatr Res.* 2013;74(4):393-401. doi:10.1038/pr.2013.126
13. Theoharides TC, Angelidou A, Alysandratos KD, et al. Mast cell activation and autism. *Biochim Biophys Acta.* 2012;1822(1):34-41. doi:10.1016/j.bbadi.2010.12.017
14. Angelidou A, Asadi S, Alysandratos KD, Karagkouni A, Kourembanas S, Theoharides TC. Perinatal stress, brain inflammation and risk of autism—review and proposal. *BMC Pediatr.* 2012;12:89. doi:10.1186/1471-2431-12-89
15. Ni L, Acevedo G, Muralidharan B, Padala N, To J, Jonakait GM. Toll-like receptor ligands and CD154 stimulate microglia to produce a factor(s) that promotes excess cholinergic differentiation in the developing rat basal forebrain: implications for neurodevelopmental disorders. *Pediatr Res.* 2007;61(1):15-20. doi:10.1203/01.pdr.0000249981.70618.18
16. McAdams RM, Juul SE. The role of cytokines and inflammatory cells in perinatal brain injury. *Neurology Int.* 2012;2012:561494. doi:10.1155/2012/561494
17. Oskvig DB, Elkahloun AG, Johnson KR, Phillips TM, Herkenham M. Maternal immune activation by LPS selectively alters specific gene expression profiles of interneuron migration and oxidative stress in the fetus without triggering a fetal immune response. *Brain Behav Immun.* 2012;26(4):623-634. doi:10.1016/j.bbi.2012.01.015
18. Wu WL, Adams CE, Stevens KE, Chow KH, Freedman R, Patterson PH. The interaction between maternal immune activation and alpha 7 nicotinic acetylcholine receptor in regulating behaviors in the offspring. *Brain Behav Immun.* 2015;46:192-202. doi:10.1016/j.bbi.2015.02.005
19. Zeidán-Chuliá F, Salmina AB, Malinovskaya NA, Noda M, Verkhratsky A, Moreira JCF. The glial perspective of autism spectrum disorders. *Neurosci Biobehav Rev.* 2014;38:160-172. doi:10.1016/j.neubiorev.2013.11.008
20. Meyer U, Nyffeler M, Engler A, et al. The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology. *J Neurosci.* 2006;26(18):4752-4762. doi:10.1523/JNEUROSCI.0099-06.2006
21. Hagberg H, Gressens P, Mallard C. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. *Ann Neurol.* 2012;71(4):444-457. doi:10.1002/ana.22620
22. Meyer U, Murray PJ, Urwyler A, Yee BK, Schedlowski M, Feldon J. Adult behavioral and pharmacological dysfunctions following disruption of the fetal brain balance between pro-inflammatory and IL-10-mediated anti-inflammatory signaling. *Mol Psychiatry.* 2008;13(2):208-221. doi:10.1038/sj.mp.4002042
23. Dammann O, Leviton A. Intermittent or sustained systemic inflammation and the preterm brain. *Pediatr Res.* 2014;75(3):376-380. doi:10.1038/pr.2013.238
24. Malik M, Sheikh AM, Wen G, Spivack W, Brown WT, Li X. Expression of inflammatory cytokines, Bcl2 and cathepsin D are altered in lymphoblasts of autistic subjects. *Immunobiology.* 2011;216(1-2):80-85. doi:10.1016/j.imbio.2010.03.001
25. Jyonouchi H, Sun S, Le H. Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. *J Neuroimmunol.* 2001;120(1-2):170-179. doi:10.1016/S0165-5728(01)00421-0
26. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol.* 2005;57(1):67-81. doi:10.1002/ana.20315
27. Goeden N, Velasquez J, Arnold KA, et al. Maternal inflammation disrupts fetal neurodevelopment via increased placental output of serotonin to the fetal brain. *J Neurosci.* 2016;36(22):6041-6049. doi:10.1523/JNEUROSCI.2534-15.2016
28. Gandal MJ, Haney JR, Parikhshak NN, et al; CommonMind Consortium; PsychENCODE Consortium; iPSYCH-BROAD Working Group. Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. *Science.* 2018;359(6376):693-697. doi:10.1126/science.aad6469
29. Meyer U, Feldon J, Dammann O. Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? *Pediatr Res.* 2011;69(5, pt 2):26R-33R. doi:10.1203/PDR.0b013e318212c196
30. Ludvigsson JF, Andersson E, Ekblom A, et al. External review and validation of the Swedish National Inpatient Register. *BMC Public Health.* 2011;11:450. doi:10.1186/1471-2458-11-450
31. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol.* 2016;45(6):1887-1894. doi:10.1093/ije/dyw341
32. Textor J, Hardt J, Knüppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* 2011;22(5):745. doi:10.1097/EDE.0b013e318225c2be
33. Lash T, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data.* New York, NY: Springer US; 2009. doi:10.1007/978-0-387-87959-8
34. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr.* 1996;85(7):843-848. doi:10.1111/j.1651-2227.1996.tb14164.x
35. Idring S, Rai D, Dal H, et al. Autism spectrum disorders in the Stockholm Youth Cohort: design, prevalence and validity. *PLoS One.* 2012;7(7):e41280. doi:10.1371/journal.pone.0041280
36. Lundström S, Reichenberg A, Anckarsäter H, Lichtenstein P, Gillberg C. Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples. *BMJ.* 2015;350:h1961. doi:10.1136/bmj.h1961
37. Johansson R, Carlbring P, Heedman Å, Paxling B, Andersson G. Depression, anxiety and their comorbidity in the Swedish general population: point prevalence and the effect on health-related quality of life. *PeerJ.* 2013;1:e98. doi:10.7717/peerj.98
38. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry.* 2010;167(3):261-280. doi:10.1176/appi.ajp.2009.09030361
39. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol Med.* 2013;43(2):239-257. doi:10.1017/S0033291712000736
40. van Os J, Rutten BPF, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr Bull.* 2008;34(6):1066-1082. doi:10.1093/schbul/sbn117
41. Karl T, Arnold JC. Schizophrenia: a consequence of gene-environment interactions? *Front Behav Neurosci.* 2014;8:435. doi:10.3389/fnbeh.2014.00435
42. Ursini G, Punzi G, Chen Q, et al. Convergence of placenta biology and genetic risk for schizophrenia. *Nat Med.* 2018;24(6):792-801. doi:10.1038/s41591-018-0021-y
43. Simanek AM, Meier HCS. Association between prenatal exposure to maternal infection and offspring mood disorders: a review of the literature. *Curr Probl Pediatr Adolesc Health Care.* 2015;45(11):325-364. doi:10.1203/cppeds.2015.06.008
44. Murphy SK, Fineberg AM, Maxwell SD, et al. Maternal infection and stress during pregnancy and depressive symptoms in adolescent offspring. *Psychiatry Res.* 2017;257:102-110. doi:10.1016/j.psychres.2017.07.025
45. Blomström Å, Karlsson H, Gardner R, Jörgensen L, Magnusson C, Dalman C. Associations between maternal infection during pregnancy, childhood infections, and the risk of subsequent psychotic disorder—a Swedish cohort study of nearly 2 million individuals. *Schizophr Bull.* 2016;42(1):125-133. doi:10.1093/schbul/sbv112
46. McDermott S, Daguisse V, Mann H, Szwejbka L, Callaghan W. Perinatal risk for mortality and mental retardation associated with maternal urinary-tract infections. *J Fam Pract.* 2001;50(5):433-437.
47. Giovanoli S, Engler H, Engler A, et al. Preventive effects of minocycline in a neurodevelopmental two-hit model with relevance to schizophrenia. *Transl Psychiatry.* 2016;6:e772. doi:10.1038/tp.2016.38
48. Vuillermot S, Luan W, Meyer U, Eyles D. Vitamin D treatment during pregnancy prevents autism-related phenotypes in a mouse model of maternal immune activation. *Mol Autism.* 2017;8:9. doi:10.1186/s13229-017-0125-0