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Supporting information – Association between preeclampsia and autism spectrum disorder: a population-based study – by Maher *et al.*

Appendix S1. Supplementary methods

Confounding variables

Maternal and paternal depression: ICD-8: 29600, 3004; ICD-9: 296B, 311, 300E; ICD-10: F32, F33.

Maternal and paternal bipolar disorder: ICD-8: 29610-29630; ICD-9: 296A,C-E; ICD-10: F30-31.

Maternal and paternal non-affective psychiatric disorders: ICD-8: 295, 297, 298 [excluding 29800 and 29810], 29999; ICD-9: 295, 297, 298 [excluding 298A and 298B]; ICD-10: F20-29.

Maternal smoking status: Categorised as “no smoking,” “smoking 1-9 cigarettes a day,” and “smoking ≥ 10 cigarettes a day”.

Optimal gestational weight gain: This was established for each maternal BMI category based on significant risk estimates of adverse maternal and fetal outcomes (Cedergren, 2007).

Family income: Disposable income in the household the year the child was born. This was divided into quintiles, ranging from “low income” to “high income”.

Parental level of education: Available since 1990, parental level of education was categorised as “pre-high school,” “high school,” and “post high school”.

Appendix S2. Supplementary results.

Sensitivity analyses

Table S1: When the study population was restricted to 1987-2010, preeclampsia was associated with a 25% increase in the likelihood of ASD, compared to those unexposed to preeclampsia (HR: 1.25, 95% CI: 1.19, 1.31). Similarly, excluding births after 2006 did not materially change results (HR: 1.24, 95% CI: 1.18, 1.30).

Fully adjusted results of the sensitivity analysis suggested that preeclampsia in those born at ≥ 34 weeks’ gestational age was associated with an 18% increase in the likelihood of ASD (HR: 1.18, 95% CI: 1.13, 1.24) when compared to those unexposed to preeclampsia, and born at a similar gestational age. The fully adjusted result for preeclampsia in those born at < 34 weeks’ gestational age (used as a proxy for preeclampsia with severe features) was 2.04 (95% CI: 1.81, 2.30) when compared to non-exposure to preeclampsia in those born at ≥ 34 weeks’ gestation. The HR for a preeclampsia-ASD relationship, excluding those with chronic hypertension, was 1.26 (95% CI: 1.20, 1.31); and including those with both preeclampsia and chronic

hypertension: 0.91 (95% CI: 0.63, 1.31). The fully adjusted HR for preeclampsia (excluding those with family history of mental illness) was 1.28 (95% CI: 1.22, 1.35). Including caesarean section in the multivariate model resulted in a HR of 1.21 (95% CI: 1.15, 1.26). Preeclampsia with a low/intermediate APGAR score at five minutes increased the likelihood of ASD by 30% compared to non-exposure to preeclampsia and low/intermediate score. Finally, preeclampsia among mothers <20 years of age and mothers with a BMI of <20 was associated with the highest odds of ASD (HR: 1.37 and 1.29 respectively) compared to those of similar maternal age and BMI at first antenatal visit.

Subgroup analyses

Table S2: Adjusted subgroup analysis suggested an increase in the likelihood of ASD at all gestational ages when compared to non-exposure to preeclampsia in those born at ≥ 37 weeks' gestation. When adjusted for potential confounders, exposure to preeclampsia was associated with a 25% increase in the odds of ASD in both male and female offspring (HR: 1.25, 95% CI: 1.18, 1.32) and (HR: 1.25, 95% CI: 1.16, 1.35 respectively).

Figure S1. Directed acyclic graph used to identify potential confounders.

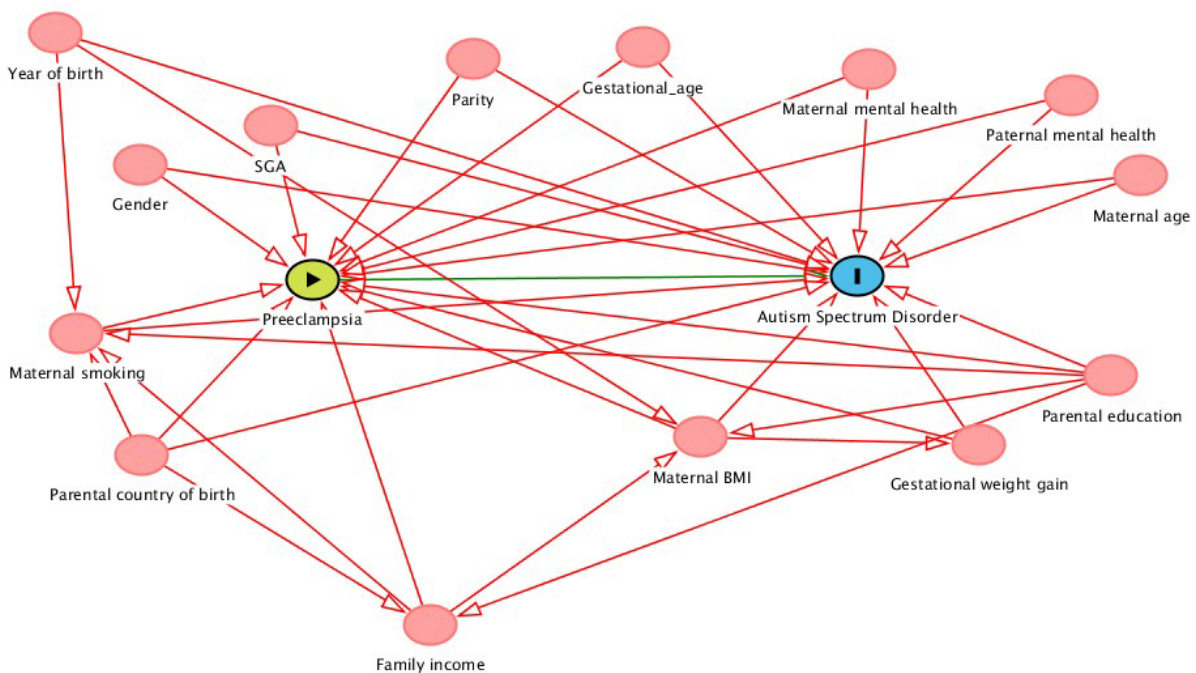


Table S1. Sensitivity analyses examining the association between preeclampsia and autism spectrum disorder among singleton live births in Sweden between 1982 and 2010

Variable	Exposed cases	Model 1 (95% CI) ^a	Model 2 (95% CI) ^b
Preeclampsia (Study population restricted to 1987-2010)	1843	1.37 (1.31, 1.44)	1.25 (1.19, 1.31)
Preeclampsia (excluding births after 2006)	1830	1.35 (1.29, 1.41)	1.24 (1.18, 1.30)
Preeclampsia (born ≥ 34 weeks' gestational age) ^c	1755	1.30 (1.24, 1.36)	1.18 (1.13, 1.24)
Preeclampsia (born < 34 weeks' gestational age) ^c	269	2.23 (1.97, 2.51)	2.04 (1.81, 2.30)
Preeclampsia without chronic hypertension ^f	1996	1.37 (1.31, 1.43)	1.26 (1.20, 1.31)
Preeclampsia with chronic hypertension ^f	28	1.03 (0.71, 1.49)	0.91 (0.63, 1.31)
Preeclampsia excluding those with family history of mental illness ^g	1575	1.40 (1.33, 1.48) ^c	1.28 (1.22, 1.35) ^c
Preeclampsia-ASD (+adjusted for caesarean section)	2024	1.36 (1.31, 1.43)	1.21 (1.15, 1.26) ^d
Preeclampsia with low/intermediate APGAR at 5 minutes ^h	87	1.35 (1.09, 1.69)	1.30 (1.04, 1.62)
<i>Preeclampsia by maternal ageⁱ</i>			
<20	99	1.46 (1.19, 1.79)	1.37 (1.12, 1.68)
20-29	1053	1.32 (1.24, 1.40)	1.22 (1.15, 1.30)
30-39	798	1.41 (1.31, 1.51)	1.29 (1.20, 1.38)
≥ 40	74	1.19 (0.94, 1.50)	1.11 (0.88, 1.40)
<i>Preeclampsia by BMI at first antenatal visit^j</i>			
<20	117	1.31 (1.09, 1.57)	1.29 (1.07, 1.55)
20-24.9	606	1.33 (1.22, 1.44)	1.27 (1.17, 1.38)
25-29.9	392	1.16 (1.04, 1.28)	1.11 (1.01, 1.23)
≥ 30	372	1.22 (1.09, 1.35)	1.18 (1.06, 1.31)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index.

^aAdjusted for year of birth.

^bAdjusted for year of birth, infant sex, maternal age, maternal and paternal country of birth, birth order, parental depression, bipolar disorder and non-affective psychiatric disorders, maternal smoking status, BMI at first antenatal visit, gestational weight gain, family income and parental level of education.

^cAdjusted for same potential confounders as above with the exception of parental mental health.

^dAdjusted for same potential confounders as 'b' above, in addition to adjusting for caesarean section.

^eReference=deliveries ≥ 34 weeks' gestational age in mothers with no preeclampsia.

^fReference=no preeclampsia/no chronic hypertension. ^gReference=no preeclampsia/no family history of mental illness. ^hReference=no preeclampsia/low/intermediate APGAR.

ⁱReference=no preeclampsia at corresponding maternal age. ^jReference=no preeclampsia with corresponding BMI.

Table S2. Association between preeclampsia and autism spectrum disorder among singleton live births in Sweden between 1982 and 2010 by gestational age and infant sex

Variable	Total Population	Exposed Cases	Partially Adjusted HR (95% CI)^a	Fully Adjusted HR (95% CI)^b
Gestational age^c	N (%)		Preeclampsia	Preeclampsia
<34 weeks	32,332 (1.1)	269	2.25 (2.00, 2.54)	2.05 (1.82, 2.31)
34 weeks	17,162 (0.6)	57	1.32 (1.02, 1.71)	1.19 (0.92, 1.54)
35 weeks	29,982 (1.1)	83	1.44 (1.16, 1.78)	1.32 (1.06, 1.64)
36 weeks	60,016 (2.1)	153	1.57 (1.34, 1.84)	1.42 (1.21, 1.67)
37 weeks	141036 (5.0)	226	1.41 (1.24, 1.61)	1.29 (1.13, 1.47)
38 weeks	386963 (13.6)	319	1.37 (1.23, 1.53)	1.26 (1.13, 1.41)
39 weeks	657765 (23.2)	351	1.28 (1.15, 1.42)	1.17 (1.06, 1.30)
40 weeks	799752 (28.2)	316	1.21 (1.08, 1.35)	1.12 (1.00, 1.25)
>40 weeks	712440 (25.1)	240	1.18 (1.04, 1.34)	1.03 (0.91, 1.17)
Infant sex				
Male ^d	1460940 (51.4)	1386	1.36 (1.29, 1.43)	1.25 (1.18, 1.32)
Female ^e	1381290 (48.6)	638	1.36 (1.26, 1.47)	1.25 (1.16, 1.35)

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

^aAdjusted for year of birth.

^bAdjusted for year of birth, infant sex, maternal age, maternal and paternal country of birth, birth order, parental depression, bipolar disorder and non-affective psychiatric disorders, maternal smoking status, BMI at first antenatal visit, gestational weight gain, family income and parental level of education.

^cReference=no preeclampsia/born at ≥ 37 weeks' gestation.

^dReference=no preeclampsia in males.

^eReference=no preeclampsia in females.

References

CEDERGREN, M. I. (2007). Optimal gestational weight gain for body mass index categories. *Obstetrics and Gynecology*, 110, 759-764.