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Association between Preeclampsia and Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder: An Intergenerational Analysis

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Using a large Swedish-based registry cohort, we estimated that preeclampsia is associated with a 25% increase in the likelihood of autism spectrum disorder (ASD), and a 15% increase in the likelihood of attention deficit hyperactivity disorder (ADHD) (n=2,842,230 and 2,047,619 respectively)(1, 2). Evidence suggests that certain non-communicable diseases may have an effect across several generations(3, 4). However, whether there is any intergenerational link between preeclampsia exposure and ASD or ADHD outcome in the child is unknown. Therefore, we conducted a cross family analysis to examine the intergenerational association between preeclampsia and ASD and ADHD using a large population-based cohort.

The Swedish Medical Birth Register was founded in 1973, and includes information on prenatal care, delivery, neonatal care and maternal socio-demographic and lifestyle factors(5). When a woman is discharged from hospital after giving birth, a doctor reviews her discharge records and notes any diagnoses during pregnancy using a standard form. These are forwarded to the National Board of Health and Welfare for inclusion in the Medical Birth Register(6). Therefore, for any children born from 1973 onwards, data on preeclampsia-exposure can be obtained from the Medical Birth Register, classified according to ICD-coding. As a result, our study population consisted of mothers of females who were born in Sweden from 1973 onwards, and their grandchildren. This allowed us to link each child to their mother and maternal grandmother, and identify mothers and children who were born to preeclamptic pregnancies.

There were 1,816,118 female singleton children born between 1973-2010. These females were tracked to childbearing age using personal identification numbers assigned to Swedish residents. For ASD, we identified 340,809 women who subsequently became mothers to children born between 1987-2010. While our original preeclampsia-ASD study consisted of births from 1982-2010(1), only children born from 1987 could be linked for the current study. For ADHD, we identified 339,724 women who subsequently became mothers to children born between 1990-2010.

In sum, the Medical Birth Register provided information on preeclampsia-exposure from 1973 (i.e. during maternal grandmother's pregnancy), and information on preeclampsia-exposure from 1987 for ASD, and 1990 for ADHD (i.e. during mother's pregnancy). This data was linked to the National Patient Register and the Prescribed Drug Register to obtain information on ASD and ADHD in the child. For a full description of data sources, see Maher et al(1, 2).

Data were analysed using Stata/MP 14.2. We conducted multivariate Cox proportional hazards regression to analyse time-to-event data, calculating hazard ratios (HR) and 95% confidence intervals (CI). This allowed for individuals within the cohort to enter and exit the study at different times. We adjusted for several perinatal and sociodemographic factors including year of birth, infant sex, maternal age, maternal and paternal country of birth, parity, parental mental health, family income, maternal smoking status, maternal BMI at first antenatal visit, maternal gestational weight gain, parental level of education, and grandmother's age at time of her pregnancy. Follow-up began from the child's first birthday for ASD, and third birthday for ADHD. Data were censored at first diagnosis of ASD/ADHD, death, migration or end of study period (31st December 2016). We examined **1)** preeclampsia in the grandmother only and likelihood of ASD and ADHD in the child; **2)** preeclampsia in the child's mother only and likelihood of ASD and ADHD in the child; and **3)** preeclampsia in both the mother and the grandmother combined and likelihood of ASD and ADHD in the child.

ASD Results: We linked 591,085 children to their mother and grandmother. We excluded 2,349 children whose mother had ASD, resulting in 10,930 children with ASD. Preeclampsia in the grandmother only was not significantly associated with ASD in the child (adjusted HR: 1.04, 95% CI: 0.89-1.20). The adjusted HR for preeclampsia in the mother only and ASD in child was 1.31 (95% CI: 1.19-1.43). The adjusted HR for preeclampsia in both the grandmother and mother and ASD in child was 1.58 (95% CI: 1.02-2.46) (Table 1).

ADHD Results: We linked 588,853 children to their mother and grandmother. We excluded 13,778 children whose mother had ADHD, resulting in 31,041 children with ADHD. The adjusted HR for preeclampsia in the grandmother only and ADHD in the child was 1.08 (95% CI: 0.99-1.18). The adjusted HR for preeclampsia in the mother only and ADHD in the child was 1.23 (95% CI: 1.16-1.30). Finally, the adjusted HR for preeclampsia in both the grandmother and mother and ADHD in child was 1.34 (95% CI; 1.01-1.80) (Table 1).

Exposure to preeclampsia was associated with an increased likelihood of ASD and ADHD in offspring. However, if both a child's mother and grandmother had preeclampsia, this increased the likelihood of ASD and ADHD in the child, suggesting an intergenerational link between preeclampsia and ASD and ADHD.

However, this may also suggest the presence of a 'dose response' effect as previous literature suggests women with preeclampsia (with severe features) are more likely to have been born of a pregnancy complicated by preeclampsia(7). Therefore, it is also possible that a more "severe" phenotype of preeclampsia could be leading to the stronger intergenerational association in our study.

This study is not without its limitations however. For example, ICD codes for ASD and ADHD only became available in 1987 and 1997 respectively; therefore data on ASD/ADHD status in the grandmother was not available. Furthermore, a lack of quality data on factors such as grandmother's BMI may have had an impact on findings. Finally, while data were prospectively obtained from national registers, ensuring a large sample size and minimising the likelihood of recall and selection bias, it is important to note that data were not collected for research purposes specifically. Therefore, we cannot be certain of the exact processes or level of accuracy involved when recording data. However, several validation studies of inpatient data in the National Patient Register have been conducted, and a review of these studies suggests high validity, concluding a positive predictive value of 85-95% for most diagnoses(8).

In conclusion, while unravelling the influences of genetics in this intergenerational association warrants further investigation, our findings suggest that obtaining information on the history of preeclampsia in the mother *and* the grandmother, may allow for more detailed risk stratification for ASD or ADHD in the child(9).

Table 1: Cross Family Analyses Examining the Association between Preeclampsia and ASD and ADHD Among Singleton Live Births in Sweden

	ASD cases	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI)‡**
Grandmother only had preeclampsia and likelihood of ASD in child§	175	1.10 (0.95, 1.28)	1.04 (0.89, 1.20)
Mother only had preeclampsia and likelihood of ASD in child§	473	1.35 (1.23, 1.48)	1.31 (1.19, 1.43)
Both mother and grandmother had preeclampsia and likelihood of ASD in child§	20	1.62 (1.05, 2.52)	1.58 (1.02, 2.46)
	ADHD cases	**Model 1 HR (95% CI)†**	**Model 2 HR (95% CI)‡**
Grandmother only had preeclampsia and likelihood of ADHD in child§	506	1.15 (1.05, 1.25)	1.08 (0.99, 1.18)
Mother only had preeclampsia and likelihood of ADHD in child§	1223	1.22 (1.15, 1.29)	1.23 (1.16, 1.30)
Both mother and grandmother had preeclampsia and likelihood of ADHD in child§	45	1.31 (0.98, 1.76)	1.34 (1.01, 1.80)

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

†Adjusted for year of birth.

‡Adjusted for year of birth, infant sex, maternal age, maternal and paternal country of birth, firstborn, parental mental health, family income, maternal smoking status, maternal BMI at first antenatal visit, maternal gestational weight gain, parental level of education and grandmother's age at time of her pregnancy.

§Reference= neither mother nor grandmother had preeclampsia.

Bibliography

1. MAHER GM, O'KEEFFE GW, DALMAN C, et al. Association between preeclampsia and autism spectrum disorder: a population-based study. Journal of child psychology and psychiatry, and allied disciplines. 2020 Feb;61:131-9.
2. MAHER GM, DALMAN C, O'KEEFFE GW, et al. Association between Preeclampsia and Attention Deficit Hyperactivity Disorder: A Population-Based and Sibling-Matched Cohort Study. Acta Psychiatrica Scandinavica. 2020 doi:10.1111/acps.13162 2020/02/13.
3. WIJNANDS KP, OBERMANN-BORST SA, SIJBRANDS EJ, WILDHAGEN MF, HELBING WA, STEEGERS-THEUNISSEN RP. Cardiovascular diseases in grandparents and the risk of congenital heart diseases in grandchildren. Journal of developmental origins of health and disease. 2014 Apr;5:152-8.
4. MCCARRON P, DAVEY SMITH G, HATTERSLEY AT. Type 2 diabetes in grandparents and birth weight in offspring and grandchildren in the ALSPAC study. Journal of epidemiology and community health. 2004 Jun;58:517-22.
5. NATIONAL BOARD OF HEALTH AND WELFARE (SOCIALSTYRELSEN). In English – the Swedish Medical Birth Register. 2019 [updated 2019; cited 2019 30th August]; Available from: https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/medicinska-fodelseregistret/.
6. ROS HS. Preeclampsia and other circulatory diseases during pregnancy – etiological aspects and impact on female offspring. [PhD dissertation]. Stockholm, Sweden: Karolinska Institutet; 2001.
7. SKJÆRVEN R, VATTEN LJ, WILCOX AJ, RØNNING T, IRGENS LM, LIE RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. BMJ. 2005;331:877.
8. LUDVIGSSON JF, ANDERSSON E, EKBOM A, et al. External review and validation of the Swedish national inpatient register. BMC public health. 2011 Jun 9;11:450.
9. KOLLINS SH. Editorial: From risk prediction to action: leveraging electronic health records to improve pediatric population mental health. Journal of Child Psychology and Psychiatry. 2020 2020/02/01;61:113-5.