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Periconceptional Serum Creatinine and Risk of Childhood Autism Spectrum Disorder: A Research Letter

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental condition that manifests in early childhood, in which the maternal metabolic syndrome may be a risk factor. The kidney is a barometer of maternal metabolic syndrome duration and severity.

Objective: The main objective of this study is to determine whether periconceptional kidney function is associated with ASD in early childhood.

Design, Setting, and Participants: This retrospective population-based cohort study was completed in Ontario, Canada. Included were singleton children born in an Ontario hospital between April 2007 and March 2021, who were alive at age 48 months and whose mother had a recorded prepregnancy body mass index (BMI) and a measured serum creatinine (SCr) between 120 days preconception and 28 days postconception.

Measurement: The main study outcome was a diagnosis of ASD between ages 24 and 48 months.

Methods: Relative risks (RRs) of ASD in association with periconceptional SCr were generated using modified Poisson regression and adjusted for several confounders.

Results: The cohort comprised 86 054 women, who had 89 677 liveborn children surviving to at least 48 months of age. There was no significant association between periconceptional SCr and ASD (RR: 0.86; 95 % confidence interval: [0.67, 1.10]).

Limitations: Selection bias may have arisen had SCr been ordered on clinical grounds.

Conclusions: Further study is warranted to determine whether prepregnancy glomerular hyperfiltration is a marker of ASD and other behavioral conditions in childhood. To do so, a more accurate measure of hyperfiltration is needed than SCr.

Abrégé

Contexte: Des problèmes d'innocuité sont détectés dans environ un tiers des médicaments d'ordonnance au cours des années qui suivent leur approbation par l'organisme de réglementation. Les personnes âgées, en particulier celles qui sont atteintes d'insuffisance rénale chronique, sont particulièrement exposées aux effets indésirables des médicaments d'ordonnance. Ce protocole décrit une nouvelle approche qui, à partir des données administratives du système de santé, pourrait permettre d'identifier plus efficacement les signaux crédibles sur la sécurité des médicaments.

Objectif: Utiliser l'informatique à haut débit et l'automatisation pour mener plus de 700 études de cohorte sur l'innocuité des médicaments chez les adultes âgés résidant en Ontario (Canada). Chaque étude comparera 74 résultats aigus (30 jours) chez des patients qui commencent un nouveau médicament sur ordonnance (nouveaux utilisateurs) à ceux d'un groupe de non-utilisateurs avec des caractéristiques de santé initiales similaires. Les risques seront évalués par strates de la fonction rénale initiale.

Cadre et type d'étude: Études populationnelles de cohortes de nouveaux utilisateurs de médicaments menées à l'aide des bases de données administratives couplées du système de santé ontarien (Canada). Période étudiée: du 1er janvier 2008 au 1er mars 2020. Population source: les Ontariens de 66 ans ou plus ayant rempli au moins une ordonnance pour patient non hospitalisé par l'entremise du Program de médicaments de l'Ontario (PMO) pendant la période de l'étude (tous les résidents de la province bénéficient d'un système de soins de santé universel; les personnes âgées de 65 ans et plus bénéficient d'une couverture universelle des médicaments d'ordonnance par l'intermédiaire du PMO).

Sujets: Nous avons identifié 3,2 millions d'adultes âgés dans la population source au cours de la période d'étude et constitué plus de 700 cohortes de médicaments, chacune contenant des groupes mutuellement exclusifs de nouveaux utilisateurs et de non-utilisateurs. Les non-utilisateurs se sont vu attribuer au hasard des dates d'entrée dans la cohorte qui suivaient les dates

de début d'ordonnance des nouveaux utilisateurs. Les critères d'admissibilité étaient d'avoir une mesure initiale du débit de filtration glomérulaire estimé [DFGe] dans les 12 mois précédant la date d'entrée dans la cohorte (dans le groupe des nouveaux utilisateurs, le délai médian était de 71 jours avant l'entrée dans la cohorte), ne pas suivre de dialyze chronique, ne pas avoir eu de greffe rénale et n'avoir jamais eu de prescription d'un médicament de la même sous-classe que le médicament à l'étude. Les nouveaux utilisateurs et les non-utilisateurs seront jumelés selon environ 400 caractéristiques de santé initiales à l'aide de la probabilité inverse de traitement pondérée selon les scores de propension dans les trois strates de mesure du DFGe initial: ≥60 ml/min/1,73 m^2; 45 à <60 ml/min/1,73 m^2 et <45 ml/min/1,73 m^2.

Résultats: Nous comparerons les groupes de nouveaux utilisateurs et de non-utilisateurs selon 74 critères de jugement cliniquement pertinents (17 critères composites et 57 critères individuels) pendant les 30 jours suivant l'entrée dans la cohorte. Une approche prédéfinie a permis de déterminer ces 74 résultats.

Plan d'analyze statistique: Dans chaque cohorte, nous calculerons les différences de risque (par régression de Poisson) et les rapports de risque (par régression binomiale) pondérés pour chaque strate de DFGe. Les interactions additives et multiplicatives par catégorie de DFGe seront examinées. Les associations médicaments-résultats répondant à des critères prédéfinis (signaux identifiés) seront examinées plus avant dans des analyses supplémentaires (survie, exposition à des témoins négatifs, analyses de la valeur E, etc.) et des visualizations.

Résultats: Dans les cohortes initiales de médicaments, les médianes sont de 6 120 nouveaux utilisateurs (intervalle interquartile de 1 469 à 38 839) et de 1 088 301 non-utilisateurs (intervalle interquartile de 751 697 à 1 267 009). Les médicaments comptant le plus grand nombre de nouveaux utilisateurs sont le trihydrate d'amoxicilline (n = 1 000 032), la céfalexine (n = 571 566), l'acétaminophène sur ordonnance (n = 571 563) et la ciprofloxacine (n = 504 374). De 19 à 29 % des nouveaux utilisateurs dans ces cohortes présentaient un DFGe < 60 ml/min/1,73 m^2.

Limites: Malgré l'utilization de techniques robustes pour équilibrer les indicateurs de base et pour contrôler le risque de confusion par indication, il pourrait subsister des facteurs de confusion résiduels. Seuls les résultats aigus (30 jours) seront examinés. Nos sources de données ne comprennent pas les médicaments sans ordonnance (en vente libre) ni les médicaments prescrits dans les hôpitaux, et n'incluent pas l'utilization de médicaments sur ordonnance en ambulatoire chez les enfants ou les adultes de moins de 65 ans.

Conclusion: Cette approche accélérée pour la réalisation d'études d'innocuité des médicaments après leur mise en marché a le potentiel de détecter efficacement les effets indésirables de ces médicaments dans une population vulnérable. Les résultats de ce protocole serviront à améliorer l'innocuité des médicaments.

Keywords

autism spectrum disorder, periconceptual kidney function, body mass index

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition that manifests in early childhood, traditionally diagnosed starting at age 24 months.[1] Maternal metabolic syndrome (MetSyn) may be one factor influencing the observed rise in ASD.[2,3] The kidney is a barometer of MetSyn duration and severity,[4] manifested by glomerular hyperfiltration and a relative decline in serum creatinine (SCr) in the early phase of MetSyn-related kidney injury.[5] This study determined whether periconceptional kidney function is associated with ASD in early childhood.

Methods

This retrospective population-based cohort study was completed in Ontario, Canada. Hospital birth records are linked to patient-level records across several databases using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). These databases have been previously validated for sociodemographic data, primary diagnoses, laboratory data, and physician billing claims (Supplementary File S1).

Included were singleton children born in an Ontario hospital between April 2007 and March 2021, who were alive at age 48 months (the typical upper age at which ASD is

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diagnosed),[1] and whose mother had a recorded prepregnancy body mass index (BMI) and a measured SCr between 120 days preconception up to 28 days postconception (the latter preceding any measurable decline in SCr in pregnancy).[6] Exclusion criteria are in Supplementary File S1.

The main study outcome was a diagnosis of ASD between ages 24 and 48 months (the recommended age interval across most of the study period), using a validated algorithm (Supplementary File S1).

Relative risks (RRs) of ASD in association with periconceptional SCr were generated using modified Poisson regression and adjusted for several confounders (Supplementary eTable 1). Three different approaches were taken for handling SCr as an exposure, as outlined in Supplementary eAppendix 1, including the possibility that a relatively low SCr might be present in young women with early glomerular injury due to hyperfiltration related to MetSyn.[4,5]

Analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results

The cohort comprised 86 054 women, who had 89 677 liveborn children surviving to at least 48 months of age (Table 1). Mean (SD) maternal age was 30.7 (5.0) years, 54% were multiparous, mean (SD) BMI was 25.7 (6.3) kg/m^2, and 3.8% had diabetes or hypertension before pregnancy.

Approach 1 found no significant association between periconceptional SCr and ASD (Table 2). With Approach 2, an SCr < fifth percentile was associated with a higher rate of childhood ASD (2.4%) than SCr between the fifth to 95th percentile (1.8%)—corresponding to an unadjusted RR of 1.31 (95% confidence interval [CI]: [1.06, 1.62]). As expected, within Approach 2, adjusting for prepregnancy diabetes, hypertension and BMI, among other covariates, attenuated that RR (1.23, 95% CI: [1.00, 1.52]) (Table 2). A similar, but nonsignificant trend was seen with Approach 3 (Table 2).

Table 1. Demographic and Clinical Characteristics of the 89 677 Pregnancies Resulting in Livebirths Among 86 054 Women.

Characteristic	
Maternal, at time of conception	
Mean (SD) age, years	30.7 (5.0)
Residential income quintile	
1 (lowest)	19 360 (21.6)
2	17 948 (20.0)
3	18 753 (20.9)
4	19 118 (21.3)
5 (highest)	14 498 (16.2)
Rural residence	6135 (6.8)
Median (IQR) parity	1 (0-1)
Parity ≥ 1	48 339 (53.9)
Mean (SD) prepregnancy body mass index, kg/m^2	25.7 (6.3)
Pre-pregnancy body mass index category, kg/m^2	
10 to 18.4	4782 (5.3)
18.5 to 24.9	45 376 (50.6)
25 to 29.9	21 930 (24.5)
30 to 49.9	17 054 (19.0)
50 to ≤60	535 (0.6)
Maternal comorbidities within 1 year prior to conception	
Diabetes mellitus	3382 (3.8)
Chronic hypertension	3363 (3.8)
Drug dependence	2439 (2.7)
Systemic lupus erythematosus	1506 (0.7)
Maternal laboratory measures between 120 days prior to conception and up to 28 days after conception	
Mean (SD) periconceptional serum creatinine, μmol/L	60.7 (9.7)
Mean (SD) periconceptional eGFR, mL/min	115.1 (12.5)
Newborn measures at birth	
Mean (SD) newborn gestational age at birth, weeks	38.8 (1.7)
Mean (SD) newborn weight at birth, grams	335 (544)
Female	43 496 (48.5)

Note. All data are shown as a number (%) unless otherwise indicated. A woman may have contributed more than 1 pregnancy. IQR = interquartile range.

Discussion

Elevated periconceptional maternal SCr was not associated with the development of ASD in childhood, but a low SCr posed a marginally higher risk.

Study strengths included the use of a large, diverse cohort within a universal health care system and the ability to account for some important confounders, such as BMI. The study also has some limitations. First, although often part of the routine annual health exam, selection bias may have arisen had SCr been ordered on clinical grounds. Specifically, of the 193 205 women in the original cohort, 107 151 (55%) were excluded for not having an SCr measurement. Second, the broad window period in which the SCr was measured in relation to the estimated date of conception (EDC), as well as the single SCr measurement necessary to be included in the final cohort may not have been reflective of changes in kidney function that may have occurred at the time of conception. Third, a family or sibling history of ASD was not accounted for herein, nor were other environmental or toxicological factors. Finally, it is plausible that some of the low SCr values may have been associated with malnutrition or low muscle mass, rather than hyperfiltration.

Hyperfiltration and reduced SCr are typical early responses of renal injury in young adults with MetSyn, including women of reproductive age.[4,5] Only in later adulthood does SCr begin to rise with ongoing renal injury.[4] It is not surprising that adjusting for prepregnancy diabetes and

Table 2. Periconceptional Maternal Serum Creatinine and Associated Risk of Childhood Autism Spectrum Disorder (ASD), Assessed Between Ages 24 and 48 Months.

Serum creatinine measurement[a]		No. (%) with outcome	Relative risk (95% CI)	
			Unadjusted	Adjusted[b]
Approach 1:	≤95th percentile: 78 µmol/L (N = 85 791)	1592 (1.9)	1.00 (referent)	1.00 (referent)
	>95th percentile: 78 µmol/L (N = 3886)	63 (1.6)	0.87 (0.68-1.12)	0.86 (0.67-1.10)
Approach 2:	<Fifth percentile: 46 µmol/L (N = 3797)	91 (2.4)	1.31 (1.06-1.62)	1.23 (1.00-1.52)
	Fifth to 95th percentile: 46-78 µmol/L (N = 81 994)	1501 (1.8)	1.00 (referent)	1.00 (referent)
	>95th percentile: 78 µmol/L (N = 3886)	63 (1.6)	0.89 (0.69-1.14)	0.86 (0.67-1.11)
Approach 3:[a]	<65 µmol/L (N = 60 976)	1170 (1.9)	1.12 (1.00-1.25)	1.11 (0.99-1.24)
	65-75 µmol/L (N = 22 417)	384 (1.6)	1.00 (referent)	1.00 (referent)
	>75 µmol/L (N = 6284)	101 (1.7)	0.94 (0.76-1.17)	0.91 (0.74-1.14)

Note. Shown are 3 different modeling approaches, using different serum creatinine cut points. CI = confidence interval.
[a]Cut-points were derived based on inspection of the fractional polynomial curve, as shown in the Supplementary eAppendix.
[b]Adjusted for maternal age, residential income quintile, and rural residence—each at the time of conception—as well as pre to pregnancy body mass index, diabetes and chronic hypertension—each within 1 year before the estimated date of conception.

hypertension attenuated the RR because both are on the causal pathway to glomerular injury.[4]

Further study is warranted to determine whether prepregnancy glomerular hyperfiltration is a marker of ASD and other behavioral conditions in childhood. To do so, a more accurate measure of hyperfiltration is needed than SCr.

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Author Contributions

YK 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.

Concept and design and drafting of the manuscript: Z.H. and J.G.R.

Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Kang.

Administrative, technical, or material support: Jeyakumar.

Data Sharing

The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Declaration of Conflicting Interests

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Ethical Considerations

Datasets were linked using unique encoded identifiers and analyzed at ICES. Use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board

Supplemental Material

Supplemental material for this article is available online.

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