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POPULATION STUDY ARTICLE

Observational study of birth outcomes in children with inborn errors of metabolism

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BACKGROUND: We examined the birth outcomes of children with inborn errors of metabolism detected at birth or later in life.
METHODS: We carried out a retrospective cohort study of 1733 children with inborn errors of metabolism and 1,033,693 unaffected children born in Canada between 2006 and 2019. Primary outcomes included preterm birth, low birth weight, congenital anomalies, and other neonatal complications. We estimated adjusted risk ratios (RR) and 95% confidence intervals (CI) for the association of inborn errors of metabolism with each outcome.
RESULTS: Children with inborn errors of metabolism had 2.51 times the risk of preterm birth (95% CI 2.27–2.77) and 3.08 times the risk of low birth weight (95% CI 2.77–3.42) compared with unaffected children. Disorders of mineral and lipoprotein metabolism were more strongly associated with adverse birth outcomes. Inborn errors of metabolism were associated with congenital anomalies (RR 2.62; 95% CI 2.36–2.90), particularly abdominal wall defects (RR 8.35; 95% CI 5.18–13.44). Associations were present for errors of metabolism diagnosed both at birth and later in life.
CONCLUSIONS: Children with inborn errors of metabolism, whether detected at birth or later, are at high risk of adverse birth outcomes and congenital anomalies.

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IMPACT:

- Inborn errors of metabolism may affect fetal development, but the association with adverse birth outcomes is not well characterized.
- This study indicates that children with inborn errors of metabolism are at risk of preterm birth, neonatal jaundice, congenital anomalies, and a range of other adverse birth outcomes.
- Mothers of children with inborn errors of metabolism are at risk of preeclampsia and cesarean delivery.
- Adverse birth outcomes may be a first sign of inborn errors of metabolism that merit increased screening.

INTRODUCTION

Inborn errors of metabolism affect an estimated 50 live births per 100,000 and are responsible for 0.4% of childhood deaths.[1] However, few studies have examined the birth outcomes of newborns with inborn errors of metabolism. Newborn screening programs and advances in therapy have improved long-term outcomes and survival,[2,3] but early detection is often not possible for rare errors of metabolism that are not part of neonatal screening panels.[1] Diagnosis is frequently delayed as many errors of metabolism have clinical manifestations similar to other common illnesses.[1] Signs and symptoms occur in the neonatal period for only a quarter of cases,[4] suggesting the vast majority of children with errors of metabolism are only diagnosed later in life. Hence, the birth outcomes of these children are rarely studied.

Inborn errors of metabolism encompass over 1000 genetic disorders that inhibit the proper functioning of a biochemical pathway.[5,6] Although symptoms may take time to manifest, inborn errors of metabolism are present from conception and could potentially be associated with adverse birth outcomes. While the delay in diagnosis of these disorders has made it challenging to assess birth outcomes, studies suggest that low birth weight may be a common characteristic of children with selected errors of metabolism.[7,8] A few studies have described the outcomes of children with inborn errors of metabolism who required intensive care,[4,9–11] but the majority of outcomes remain unknown. We investigated birth outcomes of children who were diagnosed with inborn errors of metabolism before 14 years of age in the province of Quebec, Canada.

METHODS

Study population and inclusion criteria

We performed a retrospective cohort study of 1,035,426 children born in Quebec hospitals between 2006 and 2019. We obtained data for the

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cohort from hospital discharge records collected by the province's Ministry of Health and Social Services within the Maintenance and Use of Data for the Study of Hospital Clientele registry.[12] The registry allowed us to identify all children who were diagnosed with inborn errors of metabolism at any time between birth and March 2020. Screening and detection of inborn errors of metabolism were performed independently of study outcomes. We did not include children whose mothers had inborn errors of metabolism in the analysis.

Inborn errors of metabolism

The primary exposure measure was the presence of an inborn error of metabolism diagnosed at birth or during childhood. We used diagnostic codes from the 10th revision of the International Classification of Diseases to identify inborn errors of metabolism (Supplementary Table S1). We investigated subtypes including disorders of aromatic amino acid; branched-chain amino acid and fatty acid; other amino acid; carbohydrate; sphingolipid and other lipid storage; glycosaminoglycan; glycoprotein; lipoprotein and other lipidemia; purine and pyrimidine; porphyrin and bilirubin; and mineral metabolism. We also investigated specific errors of metabolism that were present in the population, such as pure hyperglyceridemia and glycogen storage disease.

Birth outcomes

We selected birth outcomes that are commonly examined in the literature.[7,8,13–15] Primary outcomes were preterm birth (<37 weeks), low birth weight (<2500 g), and small and large-for-gestational age birth (below the lowest and above the highest 10th percentiles, respectively, for birth weight according to sex and gestational age).[16] Secondary birth outcomes were neonatal sepsis, jaundice, congenital anomalies, birth trauma, respiratory disorders, cardiovascular disorders, metabolic disorders, severe preterm morbidity (necrotizing enterocolitis, intracranial hemorrhage, bronchopulmonary dysplasia, respiratory distress syndrome, retinopathy of prematurity, patent ductus arteriosus), blood transfusion, intubation, and admission to an intensive care unit. We identified birth outcomes using diagnostic codes from the 10th revision of the International Classification of Diseases and intervention codes from the Canadian Classification of Health Interventions.[14]

We included defects that are part of the Canadian Congenital Anomalies Surveillance System: central nervous system; eye, ear, and nose; orofacial clefts; heart; respiratory; digestive system; abdominal wall; urinary; genital; musculoskeletal; and chromosomal defects.[15,17] We also examined specific birth defects, such as microcephaly, gastroschisis, and other anomalies. We grouped anomalies that were too rare to analyze individually.

Maternal outcomes

We investigated maternal complications and outcomes of pregnancy, including preeclampsia, gestational diabetes, premature rupture of membranes, cesarean delivery, instrumental delivery, placental abruption, placenta previa, oligohydramnios, polyhydramnios, infection and sepsis, antepartum and postpartum hemorrhage, severe maternal morbidity, and admission to an intensive care unit. Severe maternal morbidity included disorders such as acute renal failure, cerebrovascular accidents, cardiac conditions, and shock, as outlined by the Canadian Perinatal Surveillance System.[18] We identified maternal outcomes using diagnostic and intervention codes from the 10th revision of the International Classification of Diseases and the Canadian Classification of Health Interventions.[14]

Covariates

We selected confounders that are associated with adverse birth outcomes and errors of metabolism.[2,19–23] Boys are at greater risk of inborn errors such as Lesch–Nyhan and Hunter syndrome,[19] as well as adverse birth outcomes.[20] Some inborn errors of metabolism and adverse birth outcomes are more frequent in rural areas of Quebec.[21,22] Screening for errors of metabolism has improved over time,[2] as has the prevalence of some perinatal outcomes.[23] These factors may increase the chance of detecting errors of metabolism. To account for such confounders, we included maternal age (<25, 25–34, ≥35 years), parity (0, 1, ≥2 previous deliveries), sex of the child (male, female), multiple births (yes, no), socioeconomic deprivation (yes, no, unknown), place of residence (rural, urban, unknown), and time period (2006–2010, 2011–2015, 2016–2019). Socioeconomic deprivation corresponded to the lowest quintile of the population according to a composite index of neighborhood employment rates, education levels, and annual income.[24]

Table 1. Prevalence of inborn errors of metabolism according to patient characteristics.

	No. of children	No. of inborn errors of metabolism	Prevalence of inborn errors of metabolism per 100,000 children (95% confidence interval)
Maternal age, years			
<25	158,458	363	229.1 (205.5–252.6)
25–34	690,014	1107	160.4 (151.0–169.9)
≥35	186,954	263	140.7 (123.7–157.7)
Parity			
0	508,186	879	173.0 (161.5–184.4)
1	359,212	549	152.8 (140.1–165.6)
≥2	168,028	305	181.5 (161.2–201.9)
Child sex			
Male	531,343	984	185.2 (173.6–196.8)
Female	504,083	749	148.6 (138.0–159.2)
Multiple births			
Yes	20,499	51	248.8 (180.6–317.0)
No	1,014,927	1682	165.7 (157.8–173.6)
Socioeconomic deprivation			
Yes	207,716	450	216.6 (196.6–236.6)
No	786,126	1209	153.8 (145.1–162.5)
Residence			
Rural	189,072	375	198.3 (178.3–218.4)
Urban	828,861	1332	160.7 (152.1–169.3)
Time period			
2006–2010	369,357	717	194.1 (179.9–208.3)
2011–2015	404,940	672	166.0 (153.4–178.5)
2016–2019	261,129	344	131.7 (117.8–145.6)
Total	1,035,426	1733	167.4 (159.5–175.2)

Statistical analysis

We computed the prevalence of inborn errors of metabolism per 100,000 children. We estimated risk ratios with 95% confidence intervals (CI) for the association between inborn errors of metabolism and study outcomes using log-binomial regression models adjusted for maternal age, parity, child sex, multiple births, socioeconomic deprivation, place of residence, and time period. We applied generalized estimating equations with robust error estimators to account for children with the same mother.

We conducted a sensitivity analysis using solely children with inborn errors of metabolism diagnosed after the birth hospitalization, to rule out the possibility that study outcomes were influenced by knowledge of the exposure at the time of birth. We also analyzed inborn errors of metabolism diagnosed the first year of life versus later in childhood. We adjusted for preterm birth as this outcome may cluster with other birth outcomes. Finally, we stratified results by sex and singleton birth.

We performed statistical analyses in SAS v9.4 (SAS Institute Inc., Cary, NC). Since we conducted the study using de-identified data, the Institutional Review Board of the University of Montreal Hospital Centre waived the requirement for ethics review and informed consent.

RESULTS

Among 1,035,426 children born between 2006 and 2019, 1733 (0.2%) had inborn errors of metabolism (Table 1). The majority of children with inborn errors of metabolism were diagnosed after the birth hospitalization (85.8%). Errors of metabolism were more

Table 2. Birth outcomes of children with inborn errors of metabolism.

Outcome	No. of children with outcome		Prevalence per 1000 children (95% confidence interval)		Risk ratio (95% confidence interval)	
	Inborn error of metabolism	No error of metabolism	Inborn error of metabolism	No error of metabolism	Unadjusted	Adjusted[a]
Infant outcomes						
Preterm birth[b]	332	69,766	191.6 (173.0–210.1)	67.5 (67.0–68.0)	2.64 (2.39–2.93)	2.51 (2.27–2.77)
Low birth weight[c]	303	52,615	174.8 (157.0–192.7)	50.9 (50.5–51.3)	3.20 (2.88–3.56)	3.08 (2.77–3.42)
Small-for-gestational age[d]	256	88,530	147.7 (131.0–164.4)	85.6 (85.1–86.2)	1.71 (1.53–1.92)	1.70 (1.52–1.90)
Large-for-gestational age[d]	153	87,266	88.3 (74.9–101.6)	84.4 (83.9–85.0)	1.04 (0.90–1.21)	1.04 (0.90–1.21)
Neonatal sepsis	126	23,021	72.7 (60.5–84.9)	22.3 (22.0–22.6)	3.22 (2.72–3.82)	3.11 (2.63–3.69)
Neonatal jaundice	432	143,073	249.3 (228.9–269.6)	138.4 (137.7–139.1)	1.75 (1.61–1.90)	1.65 (1.52–1.80)
Birth trauma	82	48,676	47.3 (37.3–57.3)	47.1 (46.7–47.5)	1.01 (0.81–1.24)	0.99 (0.80–1.22)
Respiratory disorders	412	112,500	237.7 (217.7–257.8)	108.8 (108.2–109.4)	2.16 (1.99–2.35)	2.10 (1.93–2.28)
Cardiovascular disorders	212	59,530	122.3 (106.9–137.8)	57.6 (57.1–58.0)	2.11 (1.86–2.40)	2.10 (1.86–2.38)
Metabolic disorders	312	70,563	180.0 (161.9–198.1)	68.3 (67.8–68.7)	2.61 (2.36–2.88)	2.59 (2.34–2.87)
Severe preterm morbidity	98	5605	56.5 (45.7–67.4)	5.4 (5.3–5.6)	10.12 (8.29–12.35)	9.42 (7.76–11.43)
Blood transfusion	104	4247	60.0 (48.8–71.2)	4.1 (4.0–4.2)	14.24 (11.75–17.25)	13.22 (10.89–16.04)
Intubation	154	10,714	88.9 (75.5–102.3)	10.4 (10.2–10.6)	8.45 (7.25–9.84)	7.84 (6.74–9.13)
Intensive care unit	319	52,642	184.1 (165.8–202.3)	50.9 (50.5–51.4)	3.44 (3.11–3.81)	3.34 (3.02–3.69)
Maternal outcomes						
Preeclampsia	111	39,680	65.1 (53.4–76.8)	38.5 (38.2–38.9)	1.62 (1.35–1.93)	1.53 (1.27–1.83)
Gestational diabetes	142	83,900	83.3 (70.2–96.4)	81.5 (81.0–82.0)	0.96 (0.82–1.13)	1.02 (0.88–1.19)
Premature rupture of membranes	226	113,863	132.6 (116.5–148.6)	110.6 (110.0–111.2)	1.19 (1.05–1.34)	1.21 (1.08–1.37)
Cesarean delivery	515	248,052	302.1 (280.3–323.8)	241.0 (240.2–241.8)	1.17 (1.10–1.24)	1.18 (1.11–1.25)
Instrumental delivery	267	149,893	156.6 (139.3–173.8)	145.6 (144.9–146.3)	1.07 (0.96–1.20)	1.05 (0.94–1.17)
Placental abruption	70	25,184	41.1 (31.6–50.5)	24.5 (24.2–24.8)	1.66 (1.31–2.10)	1.69 (1.34–2.14)
Placenta previa	27	7090	15.8 (9.9–21.8)	6.9 (6.7–7.0)	2.30 (1.59–3.34)	2.46 (1.69–3.56)
Oligohydramnios	44	19,812	25.8 (18.3–33.3)	19.2 (19.0–19.5)	1.35 (1.01–1.80)	1.38 (1.03–1.84)
Polyhydramnios	58	15,350	34.0 (25.4–42.6)	14.9 (14.7–15.1)	2.27 (1.76–2.93)	2.34 (1.82–3.02)
Infection or sepsis	122	49,849	71.6 (59.3–83.8)	48.4 (48.0–48.8)	1.47 (1.24–1.75)	1.48 (1.25–1.76)
Antepartum hemorrhage	92	30,088	54.0 (43.2–64.7)	29.2 (28.9–29.6)	1.83 (1.49–2.24)	1.88 (1.54–2.30)
Postpartum hemorrhage	122	73,785	71.6 (59.3–83.8)	71.7 (71.2–72.2)	0.97 (0.82–1.15)	0.98 (0.83–1.17)
Severe maternal morbidity	81	24,533	47.5 (37.4–57.6)	23.8 (23.5–24.1)	1.94 (1.56–2.40)	1.86 (1.50–2.31)
Intensive care unit	17	4057	10.0 (5.3–14.7)	3.9 (3.8–4.1)	2.44 (1.51–3.95)	2.35 (1.46–3.79)

[a]Risk ratio for inborn error of metabolism vs. no error of metabolism, adjusted for maternal age, parity, child sex, multiple births, socioeconomic deprivation, place of residence, and time period.
[b]Excludes 284 children missing gestational age.
[c]Excludes 2 children missing birth weight.
[d]Excludes 995 children without small- and large-for-gestational age birth data.

Table 3. Congenital anomalies among children with inborn errors of metabolism.

	No. of children with outcome		Prevalence per 1000 children (95% confidence interval)		Risk ratio (95% confidence interval)	
	Inborn error of metabolism	No error of metabolism	Inborn error of metabolism	No error of metabolism	Unadjusted	Adjusted[a]
Any congenital anomaly	297	66,975	171.4 (153.6–189.1)	64.8 (64.3–65.3)	2.63 (2.37–2.92)	2.62 (2.36–2.90)
Central nervous system	34	2428	19.6 (13.1–26.1)	2.3 (2.3–2.4)	8.31 (5.88–11.75)	8.34 (5.91–11.79)
Microcephaly	13	680	7.5 (3.4–11.6)	0.7 (0.6–0.7)	11.41 (6.62–19.67)	12.58 (7.29–21.71)
Eye, ear, and nose	31	7288	17.9 (11.6–24.1)	7.1 (6.9–7.2)	2.53 (1.79–3.60)	2.57 (1.81–3.65)
Orofacial clefts	9	1206	5.2 (1.8–8.6)	1.2 (1.1–1.2)	4.38 (2.26–8.48)	4.29 (2.22–8.31)
Heart	120	13,190	69.2 (57.3–81.2)	12.8 (12.5–13.0)	5.37 (4.50–6.40)	5.28 (4.44–6.28)
Critical	12	1178	6.9 (3.0–10.8)	1.1 (1.1–1.2)	6.07 (3.45–10.70)	5.98 (3.39–10.54)
Noncritical	115	12,709	66.4 (54.6–78.1)	12.3 (12.1–12.5)	5.34 (4.46–6.39)	5.26 (4.40–6.27)
Respiratory	10	1317	5.8 (2.2–9.3)	1.3 (1.2–1.3)	4.52 (2.43–8.42)	4.58 (2.46–8.53)
Digestive system	27	2871	15.6 (9.7–21.4)	2.8 (2.7–2.9)	5.60 (3.85–8.16)	5.63 (3.87–8.19)
Biliary or intestinal atresia	13	768	7.5 (3.4–11.6)	0.7 (0.7–0.8)	10.10 (5.85–17.43)	9.84 (5.70–16.97)
Abdominal wall	17	1145	9.8 (5.2–14.4)	1.1 (1.0–1.2)	8.86 (5.50–14.27)	8.35 (5.18–13.44)
Gastroschisis	12	357	6.9 (3.0–10.8)	0.3 (0.3–0.4)	20.05 (11.30–35.57)	17.61 (9.90–31.34)
Urinary	42	10,733	24.2 (17.0–31.5)	10.4 (10.2–10.6)	2.30 (1.70–3.11)	2.30 (1.70–3.11)
Genital	14	6137	8.1 (3.9–12.3)	5.9 (5.8–6.1)	1.35 (0.80–2.29)	1.27 (0.75–2.14)
Musculoskeletal	74	23,102	42.7 (33.2–52.2)	22.3 (22.1–22.6)	1.91 (1.53–2.39)	1.93 (1.54–2.41)
Congenital hip dislocation	12	4555	6.9 (3.0–10.8)	4.4 (4.3–4.5)	1.58 (0.90–2.76)	1.67 (0.95–2.92)
Clubfoot	27	10,443	15.6 (9.7–21.4)	10.1 (9.9–10.3)	1.53 (1.05–2.23)	1.51 (1.04–2.21)
Polydactyly, syndactyly	15	2838	8.7 (4.3–13.0)	2.7 (2.6–2.8)	3.21 (1.96–5.28)	3.17 (1.93–5.21)
Chromosomal	23	1883	13.3 (7.9–18.7)	1.8 (1.7–1.9)	7.23 (4.79–10.90)	7.48 (4.95–11.28)
Down syndrome	9	828	5.2 (1.8–8.6)	0.8 (0.7–0.9)	6.49 (3.37–12.49)	6.81 (3.54–13.11)

[a]Risk ratio for inborn error of metabolism vs. no error of metabolism, adjusted for maternal age, parity, child sex, multiple births, socioeconomic deprivation, place of residence, and time period.

frequent in boys and among multiple births. Newborns with errors of metabolism more often had mothers under the age of 25, who were socioeconomically deprived, and in rural areas.

Inborn errors of metabolism were associated with several adverse birth outcomes (Table 2). Compared with unaffected children, children with inborn errors of metabolism had a high risk of preterm birth (RR 2.51; 95% CI 2.27–2.77), low birth weight (RR 3.08; 95% CI 2.77–3.42), and small-for-gestational age birth (RR 1.70; 95% CI 1.52–1.90). In addition, affected children had 9.42 times the risk of severe preterm morbidity (95% CI 7.76–11.43), 13.22 times the risk of blood transfusion (95% CI 10.89–16.04), and 3.34 times the risk of admission to a neonatal intensive care unit (95% CI 3.02–3.69). Mothers of children with errors of metabolism were also at risk of adverse outcomes, including preeclampsia (RR 1.53; 95% CI 1.27–1.83) and cesarean delivery (RR 1.18; 95% CI 1.11–1.25). There was no association with gestational diabetes.

Inborn errors of metabolism were associated with most types of congenital anomalies (Table 3). Children with errors of metabolism had 2.62 times the risk of any anomaly (95% CI 2.36–2.90), 8.34 times the risk of central nervous system defects (95% CI 5.91–11.79), and 8.35 times the risk of abdominal wall defects (95% CI 5.18–13.44). Inborn errors of metabolism were strongly associated with microcephaly (RR 12.58; 95% CI 7.29–21.71), gastroschisis (RR 17.61; 95% CI 9.90–31.34), and biliary or intestinal atresia (RR 9.84; 95% CI 5.70–16.97).

Among children with errors of metabolism, disorders of lipoprotein (19.6%), porphyrin and bilirubin (17.1%), other amino acid (17.0%), and carbohydrate metabolism (11.6%) were most frequent (Table 4). Disorders of urea cycle metabolism (9.5%), pure hyperglyceridemia (9.3%), and albinism (6.3%) were prevalent.

Most types of inborn errors of metabolism were associated with adverse birth outcomes (Table 5). Disorders of mineral metabolism were strongly associated with the risk of preterm birth (RR 3.74; 95% CI 2.41–5.80), whereas disorders of lipoprotein metabolism were strongly associated with the risk of low birth weight (RR 3.96; 95% CI 3.26–4.81). All errors of metabolism were associated with an elevated risk of congenital anomalies, except for disorders of glycosaminoglycan metabolism. Disorders of porphyrin and bilirubin, aromatic amino acid, glycoprotein, and lipoprotein metabolism were associated with a higher risk of preeclampsia. Disorders of glycoprotein, purine and pyrimidine, aromatic amino acid, branched-chain amino acid and fatty acid, and lipoprotein metabolism were associated with an increased risk of cesarean delivery.

In sensitivity analysis, restricting the data to children who were diagnosed with inborn errors of metabolism after the birth hospitalization did not affect the associations (Supplementary Table S2). Inborn errors of metabolism diagnosed before 1 year of age or between 1 and 14 years of age were both associated with adverse birth outcomes. In models additionally adjusted for preterm birth, inborn errors of metabolism remained associated with adverse birth outcomes (Supplementary Table S3). Stratifying by sex and restricting to singleton births did not alter the association between inborn errors of metabolism and birth outcomes.

Table 4. Distribution of inborn errors of metabolism by type.

Type of inborn error of metabolism	No. of children (%)
Disorder of aromatic amino acid metabolism	187 (10.8)
Phenylketonuria and other hyperphenylalaninemia	35 (2.0)
Disorder of tyrosine metabolism	41 (2.4)
Albinism	109 (6.3)
Disorder of branched-chain amino acid and fatty acid metabolism	134 (7.7)
Maple syrup urine disease, other disorder of branched-chain amino acid and fatty acid metabolism	54 (3.1)
Disorder of fatty acid metabolism	80 (4.6)
Other disorder of amino acid metabolism	295 (17.0)
Disorder of amino acid transport	63 (3.6)
Disorder of sulfur-bearing amino acid metabolism	26 (1.5)
Disorder of urea cycle metabolism	165 (9.5)
Disorder of lysine and hydroxylysine metabolism	18 (1.0)
Disorder of ornithine metabolism	11 (0.6)
Disorder of glycine metabolism	7 (0.4)
Disorder of carbohydrate metabolism	201 (11.6)
Glycogen storage disease	90 (5.2)
Disorder of fructose metabolism	8 (0.5)
Disorder of galactose metabolism	27 (1.6)
Other disorder of intestinal carbohydrate absorption	46 (2.7)
Disorder of pyruvate metabolism and gluconeogenesis	22 (1.3)
Disorder of sphingolipid metabolism and other lipid storage disorder	101 (5.8)
GM2 and other gangliosidosis	9 (0.5)
Other sphingolipidosis	81 (4.7)
Disorder of glycosaminoglycan metabolism	37 (2.1)
Mucopolysaccharidosis, types I and II	18 (1.0)
Other mucopolysaccharidosis	22 (1.3)
Disorder of glycoprotein metabolism	155 (8.9)
Defect in post-translational modification of lysosomal enzymes	8 (0.5)
Defect in glycoprotein degradation and other disorder of glycoprotein metabolism	147 (8.5)
Disorder of lipoprotein metabolism and other lipidemia	339 (19.6)
Pure hypercholesterolemia	90 (5.2)
Pure hyperglyceridemia	161 (9.3)
Hyperchylomicronemia, other hyperlipidemia	45 (2.6)
Lipoprotein deficiency	25 (1.4)
Disorder of purine and pyrimidine metabolism	49 (2.8)
Hyperuricemia without inflammatory arthritis and tophaceous disease	45 (2.6)
Disorder of porphyrin and bilirubin metabolism	297 (17.1)
Gilbert's syndrome	41 (2.4)
Crigler–Najjar syndrome	8 (0.5)
Porphyria, defect in catalase and peroxidase, other disorder of bilirubin metabolism	253 (14.6)
Disorder of mineral metabolism	59 (3.4)
Disorder of copper metabolism	10 (0.6)
Hemochromatosis	15 (0.9)
Other disorder of iron and mineral metabolism	27 (1.6)
Disorder of zinc metabolism	8 (0.5)

DISCUSSION

This study of 1 million children born in Canada between 2006 and 2019 found that inborn errors of metabolism were associated with preterm birth, congenital anomalies, preeclampsia, and other adverse birth outcomes. Relative to unaffected children, children with inborn errors of metabolism had more than 2.5 times the risk of preterm birth and low birth weight, and more than 1.5 times the risk of small-for-gestational age birth. Inborn errors of metabolism were associated with most types of congenital anomaly, as well as with adverse maternal outcomes including preeclampsia and cesarean delivery. Disorders of mineral, lipoprotein, and carbohydrate metabolism were associated with the greatest risk of adverse birth outcomes. The findings suggest that inborn errors of metabolism have a considerable impact on fetal development even though most are undetected at birth and only diagnosed during childhood.

While Quebec has a voluntary newborn screening program,[25] many inborn errors of metabolism are not included. Quebec's screening panel can detect 14 errors of metabolism, such as phenylketonuria, tyrosinemia type I, and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency through blood or urine analysis.[25] The panel excludes some inherited metabolic disorders with higher prevalence in the Saguenay-Lac-Saint-Jean region of Quebec, including hyperlipoproteinemia type III, cystinosis, and mucolipidosis type II.[21] As neonatal screening panels are incomplete in many countries,[1] most inborn errors of metabolism are diagnosed later in life rather than at birth. The birth outcomes of these children are therefore rarely studied. Our findings suggest that children later diagnosed with inborn errors of metabolism are likely to have had adverse birth outcomes.

Very few studies have examined the birth outcomes of children with inborn errors of metabolism. Reports have mainly focused on low birth weight, preterm birth, and small-for-gestational age birth.[7,8,13] A Saudi Arabian study of 313 children from a single hospital reported that children with inborn errors of metabolism had an increased risk of low birth weight, but not preterm birth.[7] A Finnish case series found that children with long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency were more often preterm and small-for-gestational age than unaffected children.[13] Some studies suggest that children with inborn errors of metabolism frequently require mechanical ventilation.[9–11] A Czech newborn screening program found that low birth weight was a risk factor for LCHAD deficiency but not other errors of metabolism.[8] In our cohort, most errors of metabolism were associated with an elevated risk of low birth weight. Furthermore, children with inborn errors of metabolism had elevated risks of preterm birth, small-for-gestational age birth, and intubation.

Children with inborn errors of metabolism were also at risk of neonatal jaundice. Neonatal jaundice is a result of insufficient bilirubin conjugation and increased amounts of unconjugated bilirubin circulating in the bloodstream.[26] Bilirubin is a product of heme degradation that is neurotoxic.[26] Bilirubin is normally conjugated with glucuronic acid in the liver for excretion,[26] but may lead to neonatal jaundice if inborn errors of metabolism

Table 5. Birth outcomes of children with specific inborn errors of metabolism.

	Risk ratio (95% confidence interval)[a]					
	Preterm birth	Low birth weight	Neonatal jaundice	Congenital anomaly	Preeclampsia	Cesarean delivery
Disorder of aromatic amino acid metabolism	1.73 (1.17–2.55)	2.28 (1.49–3.49)	1.33 (0.99–1.77)	1.82 (1.24–2.69)	1.93 (1.16–3.20)	1.27 (1.08–1.51)
Disorder of branched-chain amino acid and fatty acid metabolism	2.18 (1.56–3.04)	3.70 (2.64–5.19)	1.38 (0.98–1.96)	2.19 (1.48–3.23)	1.13 (0.50–2.54)	1.26 (1.00–1.58)
Other disorder of amino acid metabolism	1.96 (1.51–2.55)	2.67 (2.04–3.50)	1.24 (0.98–1.58)	2.69 (2.10–3.44)	1.37 (0.85–2.20)	1.06 (0.91–1.24)
Disorder of carbohydrate metabolism	2.81 (2.14–3.70)	3.60 (2.69–4.81)	2.10 (1.70–2.59)	3.87 (3.05–4.92)	0.68 (0.31–1.47)	1.12 (0.95–1.33)
Disorder of sphingolipid metabolism and other lipid storage disorder	1.21 (0.65–2.27)	1.50 (0.77–2.94)	1.14 (0.74–1.74)	2.23 (1.40–3.56)	1.08 (0.46–2.55)	1.11 (0.87–1.41)
Disorder of glycosaminoglycan metabolism	1.91 (0.82–4.47)	1.97 (0.74–5.26)	1.57 (0.84–2.92)	1.65 (0.64–4.22)	–	1.11 (0.83–1.48)
Disorder of glycoprotein metabolism	2.94 (2.15–4.03)	3.50 (2.56–4.78)	1.44 (1.08–1.93)	2.58 (1.82–3.65)	1.88 (1.14–3.10)	1.31 (1.13–1.53)
Disorders of lipoprotein metabolism and other lipidemia	2.97 (2.45–3.61)	3.96 (3.26–4.81)	2.00 (1.71–2.35)	3.29 (2.68–4.04)	1.62 (1.09–2.42)	1.22 (1.07–1.39)
Disorder of purine and pyrimidine metabolism	2.11 (0.99–4.50)	3.29 (1.64–6.63)	0.79 (0.34–1.84)	2.93 (1.65–5.23)	–	1.29 (1.00–1.67)
Disorder of porphyrin and bilirubin metabolism	2.91 (2.32–3.66)	3.03 (2.33–3.94)	2.03 (1.70–2.42)	1.78 (1.30–2.43)	2.14 (1.49–3.09)	1.12 (0.96–1.30)
Disorder of mineral metabolism	3.74 (2.41–5.80)	3.77 (2.20–6.45)	2.09 (1.41–3.08)	3.59 (2.26–5.70)	1.76 (0.80–3.84)	1.24 (0.87–1.77)

[a]Risk ratio for inborn error of metabolism vs. no error of metabolism, adjusted for maternal age, parity, child sex, multiple births, socioeconomic deprivation, place of residence, and time period.

affect liver function, such as with Crigler–Najjar syndrome, galactosemia, tyrosinemia, hemochromatosis, and methylmalonic acidemia.[4,27] However, disorders of glycoprotein and lipoprotein metabolism were also associated with neonatal jaundice in our data.

Inborn errors of metabolism are known to cluster with some birth defects. Central nervous system defects such as corpus collosum agenesis are frequently reported in children with pyruvate dehydrogenase deficiency, nonketotic hyperglycinemia, peroxisomal disorders, and organic acidurias.[28–30] Microcephaly is common in children with pyruvate dehydrogenase deficiency.[30] Eye defects including corneal opacity are a feature of Hurler's syndrome and mucolipidosis type II or III.[29] Cataracts are associated with galactosemia and Fabry's disease.[29] Fetuses with peroxisomal and fatty acid oxidation disorders are at risk of renal anomalies.[31] In our population, however, inborn errors of metabolism were associated with a range of other anomalies, suggesting that previous studies may underestimate the risk of birth defects.

It is known that certain inborn errors of metabolism affect fetal development.[30] Metabolic enzymes responsible for energy biosynthesis are essential for normal fetal development.[30] Metabolic disorders that impede the normal activity of mitochondrial enzymes involved in fatty acid oxidation or the citric acid cycle, such as pyruvate dehydrogenase deficiency, could therefore lead to congenital malformations.[30] Complex molecules that are not metabolized by the fetus and do not readily cross the placental barrier may also accumulate and lead to anomalies.[30]

The association between inborn errors of metabolism and maternal outcomes receives less attention in the literature. Two studies found that mothers of children with LCHAD deficiency have a higher risk of preeclampsia and HELLP syndrome.[13,32] Case reports have noted the presence of HELLP syndrome in women with severe preeclampsia carrying MCAD and short-chain acyl-CoA dehydrogenase deficient fetuses.[33,34] Researchers have proposed that preeclampsia may be triggered by the diminished activity of enzymes involved in fatty acid oxidation and oxidative phosphorylation in the placenta.[35] In our cohort, only disorders of porphyrin and bilirubin, lipoprotein, glycoprotein, and aromatic amino acid metabolism were associated with an elevated risk of preeclampsia.

We acknowledge that this study has limitations. We used hospital data and cannot rule out misclassification of exposures and outcomes due to coding errors. We used the International Classification of Diseases to identify errors of metabolism, and therefore could not study specific disorders that were grouped in broad categories. We could not identify children with inborn errors of metabolism managed out of the hospital and did not have enough statistical power to examine rare birth defects. We lacked information on potential confounders such as ethnicity, nutrition, and stress. Hence, we cannot exclude the possibility of residual confounding. Finally, our cohort reflects the population of Quebec which has a higher frequency of select errors of metabolism common in the Saguenay-Lac-Saint-Jean region.[21] It is unclear whether we can extrapolate the findings to other provinces or countries.

In this retrospective study encompassing over 1 million children, children with inborn errors of metabolism had increased risks of preterm birth, low birth weight, neonatal jaundice, and congenital anomalies. Mothers of children with inborn errors of metabolism were more likely to experience preeclampsia and cesarean delivery. Inborn errors of metabolism are often serious and affect quality of life during childhood, but this study suggests that there may also be an impact on an array of birth outcomes that have not been previously documented. As children with inborn errors of metabolism may be more likely to experience adverse perinatal outcomes, screening for these genetic conditions may be merited at birth.

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AUTHOR CONTRIBUTIONS

N.A., M.B.-B., and É.B. conceived and designed the study. M.B.-B. and É.B. analyzed the data and N.A., C.N., and L.A. helped interpret the results. N.A., M.B.-B., and É.B. drafted the manuscript, and C.N. and L.A. revised it critically for important intellectual content. All authors approved the version to be published.

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COMPETING INTERESTS

The authors declare no competing interests.

CONSENT STATEMENT

Patient consent was not required.

ADDITIONAL INFORMATION

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