Extended Risk of Mortality in Children with Inborn Errors of Metabolism: A Longitudinal Cohort Study

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Objectives To determine the long-term risk of mortality among children with inborn errors of metabolism.

Study design We conducted a retrospective cohort study of 1750 children with inborn errors of metabolism (excluding mitochondrial disorders) and 1 036 668 children without errors of metabolism who were born in Quebec, Canada, between 2006 and 2019. Main outcome measures included all-cause and cause-specific mortality between birth and 14 years of age. We used adjusted survival regression models to estimate HRs and 95% CIs for the association between inborn errors of metabolism and mortality over time.

Results Mortality rates were greater for children with errors of metabolism than for unaffected children (69.1 vs 3.2 deaths per 10 000 person-years). During 7 702 179 person-years of follow-up, inborn errors of metabolism were associated with 21.2 times the risk of mortality compared with no error of metabolism (95% CI 17.23-26.11). Disorders of mineral metabolism were associated with greater mortality the first 28 days of life (HR 60.62, 95% CI 10.04-365.98), and disorders of sphingolipid metabolism were associated with greater mortality by 1 year (HR 284.73, 95% CI 139.20-582.44) and 14 years (HR 1066.00, 95% CI 298.91-3801.63). Errors of metabolism were disproportionately associated with death from hepatic/digestive (HR 208.21, 95% CI 90.28-480.22), respiratory (HR 116.57, 95% CI 71.06-191.23), and infectious causes (HR 119.83, 95% CI 40.56-354.04).

Conclusions Children with errors of metabolism have a considerably elevated risk of mortality before 14 years, including death from hepatic/digestive, respiratory, and infectious causes. Targeting these causes of death may help improve long-term survival. *(J Pediatr 2023;252:16-21)*.

It is estimated that 0.4% of childhood deaths are linked to inborn errors of metabolism,[1] or genetic disorders that disrupt enzyme activity in essential metabolic pathways.[2,3] Most deaths in children with inborn errors in the neonatal period are due to disorders of energy or intermediary metabolism, such as pyruvate dehydrogenase deficiency and organic acidurias.[4] After the first year of life, disorders of energy metabolism and lysosomal storage tend to account for a greater proportion of deaths.[4] However, mortality rates in childhood have yet to be quantified. What is currently known stems from cross-sectional assessments of pediatric death records that provide no estimate of the long-term risk of mortality.[4]

A number of studies have examined mortality for children with inborn errors of metabolism in the context of newborn screening programs.[5-9] Although the age and cause of death were not documented systematically, most deaths occurred in children with organic acidurias or fatty acid oxidation disorders.[5-9] Short length of follow-up was, however, a limitation of this work.[5-9] In the only report with sufficient follow-up, more than one quarter of children with inborn errors of metabolism did not survive to adulthood.[10] The majority of deaths occurred in the 1980s and 1990s, when survival was likely lower.[10] A compounding problem is that mortality rates of children with inborn errors of metabolism have not been contrasted against a general pediatric population.[5-10] Owing to the paucity of data, we investigated the association between inborn errors of metabolism and risk of mortality before 14 years of age in a large cohort of children from Canada.

Methods

We designed a retrospective cohort study 1 038 418 children born in Quebec between April 1, 2006, and March 31, 2019, using the Maintenance and Exploitation of Data for the Study of Hospital Clientele repository.[11] We followed the children over time until March 2020 using unique patient identifiers to capture in-hospital mortality. In Quebec, the majority of child deaths are included in hospital data.

Follow-up started on the child's birth date and finished on the date of death or March 31, 2020, the last day that data were available. As the study started in 2006, the oldest child was 14 years of age by the end of the study. We excluded children who did not have valid patient identifiers, as they could not be followed over time.

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Inborn Errors of Metabolism

The main exposure measure was any inborn error of metabolism, defined by the 10th Revision of the *International Classification of Diseases* in effect in Quebec since 2006. We considered the following inborn errors of metabolism: disorders of aromatic amino acid; branched-chain amino acid and fatty acid; other amino acid; carbohydrate; sphingolipid; glycosaminoglycan; glycoprotein; lipoprotein; purine and pyrimidine; porphyrin and bilirubin; and mineral metabolism (**Table I**; available at www.jpeds.com). We only included codes for metabolic disorders in the *International Classification of Diseases*, *10th Revision*, that are confirmed inborn errors of metabolism, not codes for electrolyte imbalance or conditions that may have other causes. We did not include mitochondrial disorders, amyloidosis, or cystic fibrosis.

We included children who were diagnosed with inborn errors at birth or during subsequent hospitalizations. The comparison group consisted of children in the general population without inborn errors of metabolism.

Mortality

The main outcome measure was in-hospital mortality between birth and 14 years of age. The data are representative of the population, although deaths caused by rare circumstances that prevented transportation to the hospital may be excluded.

We assessed the following immediate causes of death, identified through diagnostic codes of the *International Classification of Diseases*, *10th Revision*: infection (A00-B99), cancer (C00-D48), nervous system (G00-G99), circulatory (I00-I99), respiratory (J00-J99), hepatic/digestive (K00-K93), perinatal (P00-P96.3, P96.5-P96.9), congenital anomaly (Q00-Q99), shock and related conditions (R00-R99), and other remaining causes. We also included a category for errors of metabolism, as the cause of death may be classified as the inborn error in a proportion of children.

Covariates

We included the following birth characteristics as covariates: maternal age (<25, 25-34, ≥35 years), parity (0, 1, ≥2 previous deliveries), child sex (male, female), multiple birth (yes, no), socioeconomic disadvantage (yes, no, unknown), residence (urban, rural, unknown), and time period (2006-2010, 2011-2019). We defined socioeconomic disadvantage as the lowest quintile of material deprivation, measured as a composite index of education, income, and employment at the neighborhood level.[12]

Statistical Analyses

We calculated mortality rates per 10 000 person-years and cumulative mortality at age 14 years. In primary analyses, we evaluated the association of inborn errors of metabolism with all-cause and cause-specific mortality using HR and 95% CIs from Cox proportional hazard models adjusted for study covariates. We used robust error estimators to account for outcomes that may be clustered within siblings. The time axis was specified as the number of days between birth and death or the study end. We censored children who survived at the end of the study. In a subsequent set of models, we examined the risk of mortality using parametric survival models to obtain age-specific HRs on a continuous scale.[13]

In secondary analyses of other chronic disorders, we investigated children who were born preterm or with birth defects. Preterm birth and birth defects are leading causes of child mortality that could influence the risk of death in children with inborn errors of metabolism.[14,15] To assess the role of these factors, we created a joint variable capturing children with inborn errors of metabolism who were born preterm, at term, preterm but without an error of metabolism, or with neither exposure. Similarly, we created a joint variable capturing children with inborn errors of metabolism and birth defects. We defined preterm birth as less than 37 weeks of gestational age, and identified birth defects using the *International Classification of Diseases*, *10th Revision*, and Canadian Classification of Health Interventions.[16]

We conducted all analyses in SAS, version 9.4 (SAS Institute Inc), and received an ethics waiver from the University of Montreal Hospital Centre's institutional review board, as we used only deidentified data in this study.

Results

In this cohort of 1 038 418 children followed for a total of 7 702 179 person-years, 1750 children had inborn errors of metabolism (**Table II**; available at www.jpeds.com). Among children with errors of metabolism, a greater proportion were male, socioeconomically disadvantaged, from rural areas, and had mothers younger than 25 years at time of birth.

Among 2525 deaths between 0 and 14 years of age, 93 (3.7%) occurred in children with inborn errors of metabolism (**Table III**). The mortality rate for inborn errors of metabolism was 69.1 per 10 000 person-years (95% CI 56.4-84.7), compared with 3.2 per 10 000 persons-years (95% CI 3.0-3.3) for no error of metabolism. Children with errors of metabolism had more than 21.2 times the risk of death before 14 years compared with unaffected children (95% CI 17.23-26.11). Risk of death was elevated for all types of inborn errors, especially disorders of sphingolipid (HR 69.89, 95% CI 47.01-103.90), mineral (HR 36.72, 95% CI 16.30-82.75), and other amino acid metabolism (HR 31.75, 95% CI 21.12-47.73).

At 14 years of age, cumulative mortality rates were greatest for disorders of sphingolipid metabolism at 225.1 deaths per 1000, mineral metabolism at 107.8 deaths per 1000, glycoprotein metabolism at 94.2 deaths per 1000, branched-chain amino acid and fatty acid metabolism at 61.2 deaths per 1000, and other amino acid metabolism at 89.1 deaths per 1000 (**Figure 1**; available at www.jpeds.com). Children with no error of metabolism had the lowest cumulative mortality, with 2.5 deaths per 1000 at 14 years.

Table III. Association between inborn errors of metabolism and all-cause mortality

Types of inborn error of metabolism	No. children (no. deaths)	Mortality rate per 10 000 person-years (95% CI)	HR (95% CI)	
			Unadjusted	Adjusted*
Any	1750 (93)	69.1 (56.4-84.7)	22.64 (18.44-27.80)	21.21 (17.23-26.11)
Aromatic amino acid	187 (0)	0	–	–
Branched-chain amino acid and fatty acid	134 (8)	100.6 (50.3-201.2)	26.29 (13.33-51.86)	22.58 (11.01-46.33)
Other amino acid	301 (23)	104.2 (69.3-156.8)	32.76 (21.97-48.84)	31.75 (21.12-47.73)
Carbohydrate	205 (11)	68.9 (38.1-124.4)	22.88 (12.78-40.93)	21.57 (11.91-39.07)
Sphingolipid	101 (18)	262.0 (165.1-415.8)	76.53 (49.07-119.38)	69.89 (47.01-103.90)
Glycosaminoglycan	37 (<5)	38.3 (5.4-271.6)	11.59 (1.68-80.20)	12.30 (1.75-86.70)
Glycoprotein	156 (12)	91.3 (51.9-160.8)	32.53 (18.77-56.36)	28.13 (15.82-50.02)
Lipoprotein metabolism and other lipidemia	345 (13)	43.4 (25.2-74.7)	15.90 (9.30-27.16)	14.23 (8.22-24.61)
Purine and pyrimidine	49 (<5)	23.6 (3.3-167.9)	8.57 (1.23-59.65)	10.04 (1.47-68.50)
Porphyrin and bilirubin	297 (8)	36.2 (18.1-72.4)	11.50 (5.80-22.77)	11.06 (5.54-22.07)
Mineral	60 (6)	134.8 (60.6-300.1)	43.23 (20.19-92.56)	36.72 (16.30-82.75)
No error of metabolism	1 036 668 (2432)	3.2 (3.0-3.3)	Reference	Reference

*HR for inborn errors vs no error of metabolism, adjusted for maternal age, parity, child sex, multiple birth, socioeconomic disadvantage, residence, and time period.

Risk of mortality for children with inborn errors of metabolism increased with age (Figure 2). Inborn errors of metabolism were associated with 3.1 times the risk of death the day of birth (95% CI 0.81-12.19), 27.4 times the risk by 28 days (95% CI 18.07-41.49), 67.2 times the risk by 1 year (95% CI 52.65-85.77), and 180.9 times the risk by 14 years of age (95% CI 114.41-286.13). On the first day of life, disorders of mineral metabolism (HR 46.90, 95% CI 4.41-498.85) and branched-chain amino acid and fatty acid metabolism (HR 11.31, 95% CI 1.51-84.41) displayed the greatest risk of mortality. Disorders of mineral (HR 60.62, 95% CI 10.04-365.98), other amino acid (HR 54.61, 95% CI 26.59-112.15), and carbohydrate metabolism (HR 53.69, 95% CI 20.66-139.54) were most strongly associated with mortality the first month of life. By 1 year, disorders of sphingolipid (HR 284.73, 95% CI 139.20-582.44), other amino acid (HR 105.81, 95% CI 67.21-166.58), and glycoprotein metabolism (HR 95.41, 95% CI 48.53-187.56) were strongly associated with mortality. By 14 years, the long-term risk of mortality was greatest for disorders of sphingolipid (HR 1066.00, 95% CI 298.91-3801.63), porphyrin and bilirubin (HR 296.17, 95% CI 73.43-1194.63), and glycoprotein metabolism (HR 279.47, 95% CI 92.37-845.56).

Inborn errors of metabolism were associated with mortality despite preterm birth or birth defects (Table IV). However, risk of death was particularly elevated among children with inborn errors who were born preterm (HR 140.38, 95% CI 96.88-203.42) or had birth defects (HR 58.79, 95% CI 40.63-85.08). Children with inborn errors of metabolism who were born at term also had an elevated risk of mortality (HR 65.64, 95% CI 50.30-85.65), relative to no inborn error at term. The risk was not as elevated for preterm birth alone (HR 40.96, 95% CI 37.29-44.98). Nevertheless, among children with errors of metabolism, risk of mortality was greatest for birth at <28 weeks (HR 1.92, 95% CI 0.60-6.09) and 28-31 weeks (HR 1.92, 95% CI 0.53-7.03), followed by 32-36 weeks (HR 1.84, 95% CI 0.99-3.41), compared with term. Children with errors of metabolism but no birth defect had an elevated risk of mortality (HR 27.35, 95% CI 21.09-35.46), relative to no inborn error or birth defect. The risk was not as elevated for birth defects alone (HR 10.71, 95% CI 9.83-11.65).

Respiratory causes accounted for the largest fraction of deaths among children with inborn errors of metabolism (19 of 93 deaths; 20.4%) (Table V). Children with inborn errors were 116.6 times more likely to die from respiratory (95% CI 71.06-191.23), 208.2 times more likely to die from hepatic/digestive (95% CI 90.28-480.22), and 119.8 times more likely to die from infectious causes (95% CI 40.56-354.04), compared with unaffected children. Risk of death from cancer (HR 73.60, 95% CI 35.16-154.06), circulatory (HR 38.38, 95% CI 18.72-78.67), and nervous system disorders (HR 47.35, 95% CI 22.95-97.67) was also elevated. The cause of death was specified as an inborn error of metabolism for only 14 deaths (15.1%).

Discussion

In this cohort of more than 1 million children followed until 14 years of age, inborn errors of metabolism were strongly associated with mortality in childhood and adolescence. Inborn errors of metabolism were associated with 21 times the risk of death relative to no error of metabolism. For disorders of mineral metabolism, risk of death was most prominent before 28 days of life. For disorders of sphingolipid metabolism, risk of mortality strengthened after 1 year of age. Inborn errors of metabolism were associated with mortality regardless of preterm birth or the presence of birth defects. Only 15% of deaths in affected children were attributed to the inborn error of metabolism at the time of mortality. Children with errors of metabolism were most at risk of death from hepatic/digestive, respiratory, and infectious causes.

Few studies have evaluated the risk of mortality in children with inborn errors of metabolism. This oversight may stem from a past focus on evaluating screening programs aimed at detecting inborn errors at birth.[5-9] Children with errors of metabolism detected through newborn screening are less at risk of death than children diagnosed later in life.[5,7] Other studies have assessed the number of deaths in newborns who

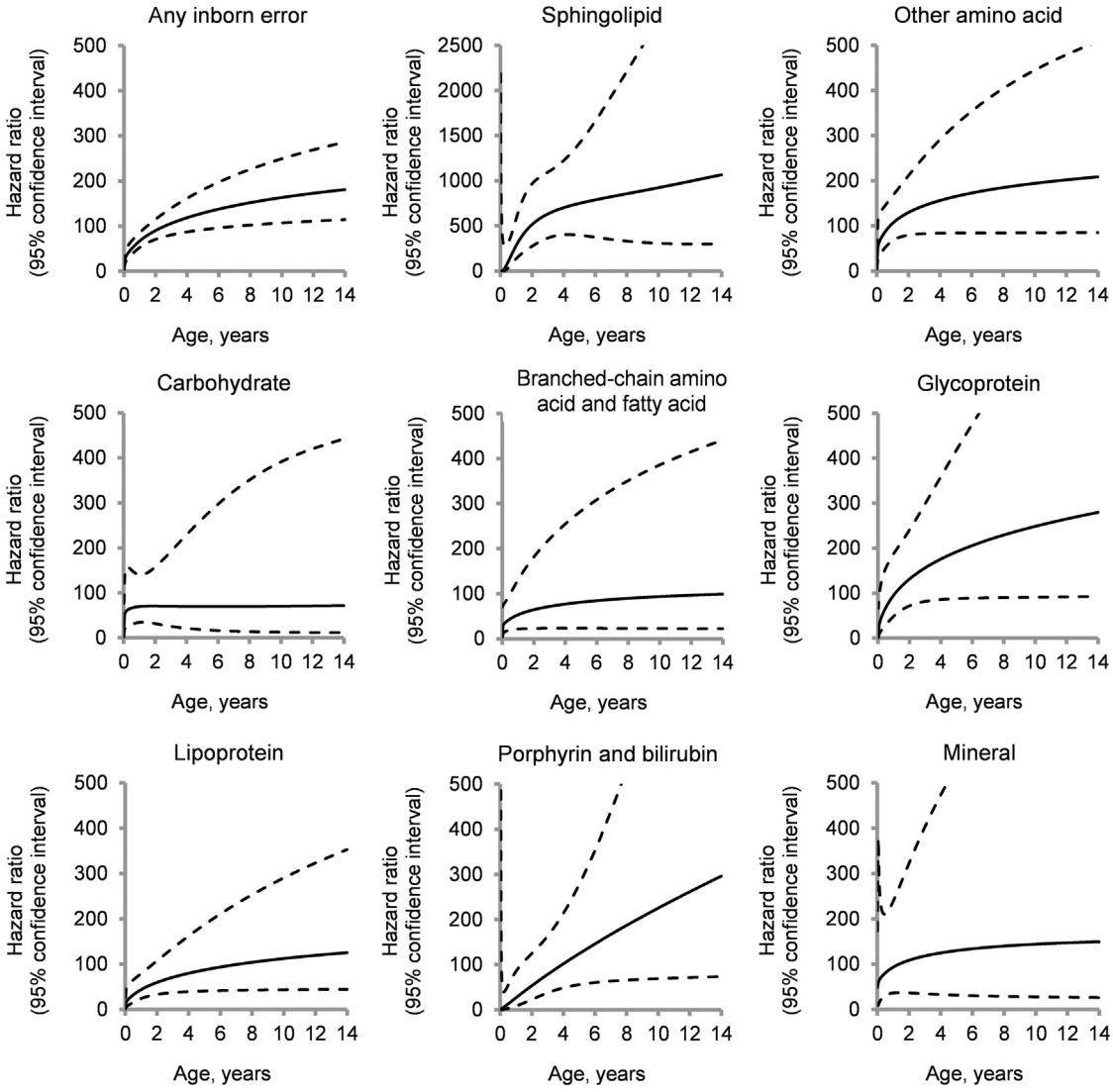

Figure 2. Age-specific association between inborn errors of metabolism and all-cause mortality before 14 years. HR (*solid line*) and 95% CI (*dashed line*) for inborn errors vs no error of metabolism, adjusted for maternal age, parity, child sex, multiple birth, socioeconomic disadvantage, residence, and time period.

were screened for inborn errors.[6,8,9] In the few reports that did not focus on screening, around 3% of pediatric mortality was attributed to inborn errors of metabolism, and 25% of affected children did not survive.[4,10] As these studies only included children with inborn errors of metabolism,[4-10] there are no estimates of the risk of death relative to other pediatric populations. When we compared children with inborn errors with a general population of unaffected children, errors of metabolism were associated with 21 times the risk of death in childhood.

Little is known on the causes of death in patients with inborn errors of metabolism. In the only study that considered causes, researchers identified only 4 deaths in children with medium-chain acyl-CoA dehydrogenase deficiency and methylmalonic and propionic acidurias.[6] All 4 deaths were caused by acute infections.[6] Others have shown that lower airway infections are prevalent in patients with lysosomal storage disorders, Farber disease, and glycogen storage disease.[17] In our cohort, inborn errors of metabolism were strongly associated with mortality due to infectious causes. Respiratory illnesses also accounted for a large fraction of deaths. Respiratory disorders including interstitial lung disease and upper airway obstruction frequently cluster with inborn errors of metabolism such as lysosomal storage disorders and mucopolysaccharidoses.[17] Certain errors of metabolism, such as organic acidurias, increase the risk of chronic pulmonary aspiration.[17] Respiratory conditions may therefore be an important target for mortality reduction.

Inborn errors of metabolism also were strongly associated with mortality from hepatic/digestive causes and cancer in our data. Liver dysfunction may be caused by toxic accumulation of metabolites such as copper in Wilsons disease, or

Table IV. Association between inborn errors of metabolism and mortality according to preterm birth and the presence of birth defects

	No. children (no. deaths)	Mortality rate per 10 000 person-years (95% CI)	HR (95% CI)	
			Unadjusted	Adjusted*
Inborn error of metabolism and preterm birth				
Inborn error only	1412 (61)	55.2 (43.0-71.0)	66.96 (51.45-87.16)	65.64 (50.30-85.65)
Preterm birth only	70 041 (1814)	36.4 (34.8-38.1)	41.21 (37.59-45.18)	40.96 (37.29-44.98)
Both	338 (32)	133.0 (94.1-188.1)	153.22 (107.62-218.16)	140.38 (96.88-203.42)
Neither	966 627 (618)	0.9 (0.8-0.9)	Reference	Reference
Inborn error of metabolism and birth defect				
Inborn error only	1448 (60)	53.5 (41.5-68.8)	29.32 (22.72-37.83)	27.35 (21.09-35.46)
Birth defect only	67 217 (1066)	22.0 (20.7-23.4)	11.35 (10.46-12.32)	10.71 (9.83-11.65)
Both	302 (33)	148.3 (105.4-208.6)	78.21 (56.09-109.06)	58.79 (40.63-85.08)
Neither	969 451 (1366)	1.9 (1.8-2.0)	Reference	Reference

*HR for inborn errors vs no error of metabolism, adjusted for maternal age, parity, child sex, multiple birth, socioeconomic disadvantage, residence, and time period.

decreased activity of hepatic enzymes as in Crigler–Najjar syndrome.[18,19] Hepatocellular carcinoma may also be prevalent in patients with Wilson disease, glycogen storage disease, and tyrosinemia type I.[18,20] Other types of cancer have been reported, including renal cell carcinoma in Fabry disease and bone cancer in Gaucher disease.[20] Researchers have proposed that accumulation of toxic metabolites in tissues could promote carcinogenesis.[20]

Some errors of metabolism may be associated with a greater risk of death. An Australian cross-sectional study of death records from 120 children with inborn errors found that disorders of intermediary and energy metabolism were principal causes of neonatal death, and most deaths between 1 and 14 years were due to lysosomal storage and energy metabolism disorders.[4] An Italian investigation of 1935 children noted that most deaths before 18 years were due to primary lactic acidemias and peroxisomal or lysosomal disorders, although the specific age of death was not reported.[10] In our cohort, disorders of mineral metabolism exhibited the greatest risk of mortality within 28 days of life, whereas disorders of sphingolipid metabolism were associated with the greatest risk between age 1 and 14 years. Treatment availability and the underlying etiology of different errors of metabolism may contribute to some of the differences in the long-term risk of death.

Inborn errors of metabolism tend to be associated with low mortality in utero, as the mother's metabolism frequently compensates.[21] Water-soluble molecules originating from the fetus can cross the placenta to be metabolized by the mother, preventing toxic accumulation.[21] Acute metabolic decompensation may however follow after birth for certain inborn errors, such as urea cycle disorders.[21] Other errors of metabolism, especially lysosomal storage disorders, require longer periods for metabolites to accumulate before generating toxicity.[21] Some of these differences may account for the variation in age-specific risks of death between errors of metabolism. Although treatments such as phenylalanine-restricted diets are available for phenylketonuria,[22] there is no effective treatment for mucolipidoses,[23] and therapies for diseases such as Tay–Sachs have yet to yield promising results in clinical trials.[22] It remains to be seen if emerging therapies can improve long-term outcomes of children with errors of metabolism in the coming years.[22]

In our data, children with isolated inborn errors had greater mortality than children affected solely by preterm birth or birth defects. Previous studies have not considered the effect of preterm birth or birth defects,[4-10] even though these conditions are

Table V. Association between inborn errors of metabolism and cause-specific mortality

Causes of death	No. deaths		HR (95% CI)	
	Inborn error of metabolism	No error of metabolism	Unadjusted	Adjusted*
All causes	93	2432	22.64 (18.44-27.80)	21.21 (17.23-26.11)
Inborn error of metabolism	14	0	–	–
Congenital anomaly	<5	198	6.03 (1.50-24.20)	5.66 (1.41-22.79)
Infection	<5	19	123.87 (42.14-364.15)	119.83 (40.56-354.04)
Cancer	8	62	74.33 (35.59-155.23)	73.60 (35.16-154.06)
Nervous system	8	94	49.91 (24.25-102.74)	47.35 (22.95-97.67)
Circulatory	8	119	40.03 (19.57-81.87)	38.38 (18.72-78.67)
Respiratory	19	96	116.15 (71.00-190.02)	116.57 (71.06-191.23)
Hepatic/digestive	8	19	249.95 (109.43-570.92)	208.21 (90.28-480.22)
Perinatal	8	1154	4.11 (2.05-8.25)	3.66 (1.83-7.34)
Shock and related conditions	7	89	46.63 (21.60-100.65)	44.90 (20.75-97.15)
Other	7	582	7.13 (3.39-15.02)	7.18 (3.41-15.13)

*HR for inborn errors vs no error of metabolism, adjusted for maternal age, parity, child sex, multiple birth, socioeconomic disadvantage, residence, and time period.

risk factors for chronic morbidity and mortality,[14,15] and are common in children with inborn errors.[21,24-26] Nevertheless, our results suggest that preterm birth and congenital anomalies do not make a major contribution to mortality beyond the effect of inborn errors of metabolism.

This study has limitations. We used hospital discharge data and could not account for a small fraction of children who died outside of hospital due to rare causes. We also could not include inborn errors of metabolism diagnosed in an outpatient setting that never required hospitalization. Coding errors may have entailed misclassification of the exposure or other covariates. As we used the *International Classification of Diseases, 10th Revision*, we were unable to investigate errors of metabolism that were combined with congenital anomalies or classified under larger categories. We could not identify mitochondrial disorders. The low number of children affected by errors of metabolism limited the statistical power of the study and resulted in broad CIs. Finally, the external validity of our findings remains uncertain, as detection and treatment of inborn errors of metabolism may vary worldwide.

Although inborn errors of metabolism play a significant role in pediatric morbidity,[1] the long-term risk of mortality has been understudied. This study demonstrates that children with inborn errors of metabolism have a considerably elevated risk of mortality compared with unaffected children. Mortality is greatest for disorders of mineral metabolism within the first month of life and disorders of sphingolipid metabolism after 1 year of age. As children with inborn errors were more likely to die from hepatic, respiratory, and infectious causes, targeted studies to determine underlying contributors and potential prevention strategies in these areas may be indicated. ■

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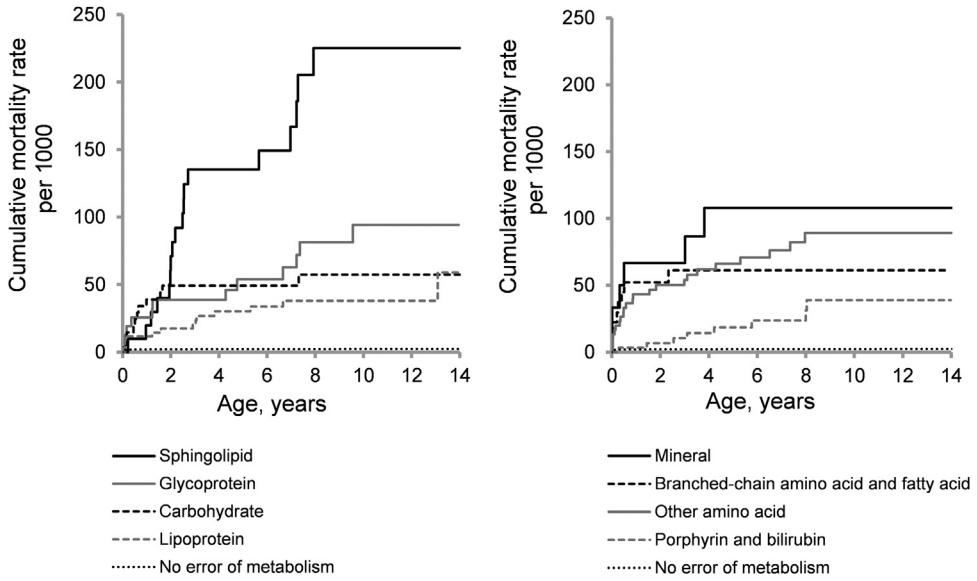

Figure 1. Cumulative mortality rate in children with inborn errors of metabolism.

Table I. Diagnostic codes for inborn errors of metabolism*

Metabolic disorders	*International Classification of Diseases, 10th Revision*
Disorder of aromatic amino acid metabolism	E70
Disorder of branched-chain amino acid and fatty acid metabolism	E71
Other disorder of amino acid metabolism	E72
Disorder of carbohydrate metabolism	E74
Disorder of sphingolipid metabolism	E75
Disorder of glycosaminoglycan metabolism	E76
Disorder of glycoprotein metabolism	E77
Disorder of lipoprotein metabolism	E78
Disorder of purine and pyrimidine metabolism	E79
Disorder of porphyrin and bilirubin metabolism	E80
Disorder of mineral metabolism	E83.0-E83.2, E83.8-E83.9

*The following errors of metabolism were detected by newborn screening: phenylketonuria (E70.0, E70.1), propionic acidemia (E71.1), methylmalonic acidemia (E71.1), 3-methylcrotonylglycinuria (E71.1), medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (E71.3), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (E71.3), very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (E71.3), tyrosinemia type I (E70.2), triple H syndrome (E72.4), citrullinemia type I (E72.2), citrullinemia type II (E72.2), argininemia (E72.2), glutaric acidemia type 1 (E72.3), and argininosuccinic aciduria (E72.2).

Table II. Characteristics of children with and without inborn errors of metabolism

Characteristics	Inborn error of metabolism		No error of metabolism	
	No. children	% (95% CI)	No. children	% (95% CI)
Maternal age, y				
<25	366	20.9 (19.0-22.8)	158 426	15.3 (15.2-15.4)
25-34	1118	63.9 (61.6-66.1)	690 807	66.6 (66.5-66.7)
≥35	266	15.2 (13.5-16.9)	187 435	18.1 (18.0-18.2)
Parity				
0	893	51.0 (48.7-53.4)	508 708	49.1 (49.0-49.2)
1	550	31.4 (29.3-33.6)	359 685	34.7 (34.6-34.8)
≥2	307	17.5 (15.8-19.3)	168 275	16.2 (16.2-16.3)
Child sex				
Male	992	56.7 (54.4-59.0)	531 905	51.3 (51.2-51.4)
Female	758	43.3 (41.0-45.6)	504 763	48.7 (48.6-48.8)
Multiple birth				
Yes	53	3.0 (2.2-3.8)	20 533	2.0 (2.0-2.0)
No	1697	97.0 (96.2-97.8)	1 016 135	98.0 (98.0-98.0)
Socioeconomic disadvantage				
Yes	455	26.0 (23.9-28.1)	207 896	20.1 (20.0-20.1)
No	1221	69.8 (67.6-71.9)	787 182	75.9 (75.9-76.0)
Residence				
Rural	378	21.6 (19.7-23.5)	189 346	18.3 (18.2-18.3)
Urban	1346	76.9 (74.9-78.9)	829 814	80.0 (80.0-80.1)
Time period				
2006-2010	727	41.5 (39.2-43.9)	369 755	35.7 (35.6-35.8)
2011-2019	1023	58.5 (56.1-60.8)	666 913	64.3 (64.2-64.4)
Total	1750	100	1 036 668	100