Measuring Core Outcomes from Metabolic Chart-Abstracted Data for Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

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A thesis submitted to the University of Ottawa
in partial fulfillment of the requirements for the
Master of Science degree in Epidemiology

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Preface

Approvals

Chapters 2 and 3 involved a secondary analysis of an existing dataset from an established cohort study, for which permission to access and use the data was obtained. The original cohort study (Emerging Team in Rare Diseases: Long-Term Follow-up of Children with Inborn Errors of Metabolism (IEM) in Canada – Phase I: CIMDRN Participant Enrollment and Clinical Data Collection) obtained ethics approvals from the Children's Hospital of Eastern Ontario Research Ethics Board (#13/23E) and the Ottawa Health Science Network Research Ethics Board (#20140436-01H), as well as each participating metabolic centre. Therefore, this study did not require alternative ethics review.

Author Contributions

The student, Ryan Iverson (RI), was the primary author on both manuscripts in this thesis, which were also co-authored by his supervisor, Dr. Beth K Potter (BKP), co-supervisor, Dr. Monica Taljaard (MT), thesis advisory committee member, Dr. Pranesh Chakraborty (PC), and Dr. Michael T Geraghty (MTG). The student (RI) was responsible for planning the methodology, conducting analyses, interpreting findings, and drafting the manuscripts. Each of these processes was done with guidance and in collaboration with BKP, PC, and MT. The additional co-author, MTG, provided content expertise and assisted with the interpretation of data for both studies.

Abstract

Background: Generating evidence to inform care for pediatric medium-chain acyl-CoA dehydrogenase (MCAD) deficiency requires sustainable and integrated measurement of priority outcomes.

Methods: From an existing Canadian cohort study, we evaluated the quality of metabolic clinic chart-abstracted data for measuring core outcomes for pediatric MCAD deficiency. We then modelled variation in emergency department (ED) use, in association with disease severity, child age, and distance to care.

Results: Children with MCAD deficiency visit the metabolic clinic at least annually on average but we identified data quality challenges related to inconsistent definitions of core outcomes and missing information in patient charts. Rates of ED use were highest among children aged 6 to 12 months, with more severe disease, and living closest to care.

Conclusion: While measuring core outcomes through the metabolic clinic for children with MCAD deficiency is feasible, harmonized data collection is needed to evaluate care and further understand ED use.

(149/150 words)

Acknowledgements

I'd like to thank my supervisor, Dr. Beth Potter, for her incredible mentorship and unwavering support throughout my degree and in the completion of this project. Your continued encouragement and guidance are truly a testament to your dedication to student learning and success. I am so grateful for the many lessons learned under your supervision that I will carry through my academic endeavors and professional career.

Thank you to my co-supervisor and thesis advisory committee member, Dr. Monica Taljaard and Dr. Pranesh Chakraborty, for expertly guiding me through this process and generously offering their time and meaningful contributions. This thesis benefitted immensely from our conversations. As well, thank you to Dr. Michael Geraghty for his valuable insight and for helping me to navigate the clinical aspects of this disease.

I would also like to acknowledge my colleagues: Andrea Chow, Kylie Tingley, Michael Pugliese, Monica Lamoureux, and other members of the Canadian Inherited Metabolic Diseases Research Network central team. Thank you for sharing your wealth of experience and knowledge, for challenging me to be a better researcher, and for taking the time to create so many learning opportunities throughout this process.

Finally, I thank my family, my partner, and my friends, whose continued support, unconditional love, and patience have been invaluable throughout this degree. This work would not have been possible without your encouragement and I share this accomplishment with all of you.

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Abbreviations

aIRR	Adjusted incidence rate ratio
CoA	Coenzyme A
CIMDRN	Canadian Inherited Metabolic Diseases Research Network
COMET	Core Outcome Measures in Effectiveness Trials
COS	Core outcome sets
C6	Hexanoylcarnitine
C8	Octanoylcarnitine
C10	Decenoylcarnitine
ED	Emergency department
FAOD	Fatty acid oxidation disorders
FCS	Fully conditional specification
FSA	Forward sortation area
GEE	Generalized estimating equation
GIS	Geographic information system
IMD	Inherited metabolic diseases
IQR	Interquartile range
MCAD	Medium-chain acyl-CoA dehydrogenase
MS/MS	Tandem mass spectrometry
NBS	Newborn screening
PKU	Phenylketonuria
REDCap	Research Electronic Data Capture
SEPH	School of Epidemiology and Public Health

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Chapter 1 – Introduction

Rare inherited metabolic diseases

It is estimated that approximately 1 in 12 Canadians, equivalent to over 3 million people, have one of the at least 7000 known rare diseases, the large majority of which are of genetic etiology and are diagnosed in children.[1,2] Despite recent efforts toward understanding genetic diagnoses and improving clinical management, largely prompted by multi-stakeholder research groups, patients with rare diseases and their families continue to report shared experiences that reflect important obstacles in navigating their disease and the health care system. Specifically, there are challenges in the receipt of timely and accurate diagnoses, the availability of effective and coordinated treatment, and the provision of adequate support appropriate for individual needs.[3,4]

Inherited metabolic diseases (IMD) represent a collection of more than 1000 substantiated, monogenic disorders typically identified in early life that are individually rare but collectively (by virtue of the large number of such diseases) affect a relatively large number of children.[5,6] Although the estimated birth prevalence can vary widely based on the specific population and individual IMD, together they affect approximately 1 in 2000 children at birth globally, and are responsible for an estimated 0.4% of all-cause mortality in children.[7–9] The majority of IMD are caused by autosomal recessive mutations in specific genes that result in erroneous protein (i.e., enzyme) folding, impair the function of that protein in a particular intermediate metabolic pathway, and lead to certain defects in energy synthesis, or an excess, a lack of, and/or a change in function of metabolic precursors or products.[5,10] These intermediates can further activate or competitively inhibit additional metabolic processes.[11]

Although various approaches to the nosology of IMD have been proposed, they can be generally classified according to the substrate involved such as, for example, disorders affecting carbohydrates, amino acids, mitochondria, lipids, vitamins, metals, neurotransmitters, nucleic acids, and other organelles.[12] IMD can be further grouped according to their anticipated clinical trajectories, ranging from acute episodes prompted by non-specific illnesses throughout the neonatal period and beyond, to chronic organ and/or organ system sequelae (e.g., neurological disorders, delayed cognitive development, cardiac diseases, and hepatic abnormalities), although the symptoms expected for each disease can vary widely across categories of diseases and within individual diseases and frequently depend on the characteristics of the individual patient.[13]

Similarly, considerations for treatment modalities may depend on numerous factors, such as the biochemical and clinical features of the IMD, the unique characteristics of the patient, and the age at which the child experienced an onset of symptoms. Strategies can involve administering supplements (e.g., vitamins, co-factors), drugs (i.e., binding to accumulated toxins, enhancing energy production), alternative diets and restrictive guidelines (e.g., formulas without specific amino acids, avoidance of prolonged fasting), and other therapies during emergency care (e.g., intravenous fluids, respiratory support).[14,15] These strategies are frequently accompanied by close monitoring from a variety of medical specialists and sub-specialists. Thus, similar to other children with special health care needs, and particularly those with medical complexities,[16,17] children with IMD typically may experience disproportionately high health care needs depending on the nature of their illness. Consequently, children with IMD, their families/caregivers, and patients groups have identified significant challenges in navigating the health care system, managing the IMD, and obtaining high-quality care outside of disease-specific clinics directly involved in treating the IMD.[18,19]

Newborn screening

For those IMD that are amenable to treatment, early detection is often necessary to prevent early metabolic crises and subsequent, long-term manifestations.[20,21] In addition to their rarity, broad phenotypic heterogeneity, and resource limitations, diagnostic complexity for IMD is further complicated by the need for advanced ascertainment techniques after initial laboratory tests, including biochemical and molecular genetic testing.[11,22] Therefore, population-based newborn screening is routinely employed as part of standard post-natal care to prompt early ascertainment and treatment initiation for some IMD and other rare treatable diseases.[23] The goal is to identify screened conditions prior to the onset of clinical manifestations for those diseases where earlier treatment initiation is associated with improved outcomes. Evidence has shown a reduction in early infant mortality, as well as improved long-term outcomes in association with newborn screening for a number of IMD.[23–27] The current process involves an analysis of dried blood spot samples from cord blood or heel prick samples in asymptomatic newborns; heel prick samples are most commonly used.[28,29] Although other analytic technologies can be considered, tandem mass spectrometry (MS/MS) is the technology used by most newborn screening programs to identify the majority of screened IMD. It has the ability to detect abnormalities in metabolite markers indicative of the screened IMD, including many amino acid disorders, urea cycle disorders, fatty acid oxidation disorders, and organic acidemias.[30,31] Upon receipt of an abnormal result, disease-specific diagnostic tests, such as organic acids from urine, amino acids from plasma, or ammonia from blood, can be used to establish or rule out specific IMD diagnoses based on detected metabolites.[30] For many screened conditions, including many IMD, newborn screening has led to an expansion of the clinical spectrum of disease, with screening identifying a higher proportion of milder cases of disease than detection based on clinical presentation alone.[32]

Fatty acid oxidation disorders

The largest group of IMD commonly identified by population-wide newborn screening are mitochondrial fatty acid oxidation disorders (FAOD).[33] They include more than 20 known, clinically heterogeneous and autosomal recessive disorders characterized by impaired enzymatic reactions, notably those responsible for releasing fatty acids from adipose tissue and beta-oxidation in the mitochondrial matrix; only a subset of these conditions are included as targets of newborn screening programs.[34,35] During extended periods of fasting or in the presence of other catabolic stresses, which deplete glycogen stores and stop glycogenolysis, the mobilization of fatty acids and subsequent oxidation into acetyl-coenzyme A (CoA) is essential to maintain energy production (i.e., through hepatic ketogenesis), which in turn, fuel peripheral tissues.[34,36]

FAOD can be categorized according to the loss of function caused by the deficient enzyme, such as disorders that affect the passage of molecules (e.g., carnitine, long-chain fatty acids) across the plasma membrane, disorders that impede the transport of fatty acids across the mitochondrial membrane, and disorders that prevent the breakdown of small-, medium-, long-, and very long-chain fatty acids.[34] The resulting spectrum of possible clinical manifestations depends widely on the unique FAOD, but can include hypoglycemia, hepatic dysfunction, cardiomyopathy, skeletal myopathy, and rhabdomyolysis.[37,38] In general, however, a defining feature of FAOD is that most children are at risk of experiencing acute and potentially life-threatening episodes of hypoglycemic illness during periods of catabolic stress,[39] particularly in the neonatal period due to limited stores of liver glycogen, metabolic stress throughout labour and delivery, and inadequate calorie intake (e.g., feeding difficulties if breastfeeding).[40–42]

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

Epidemiology

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency represents the most common FAOD and one of the most common IMD.[43] The addition of MCAD deficiency to newborn screening panels in many jurisdictions around the world has identified a larger proportion of children with MCAD deficiency relative to the pre-screening era. The birth prevalence is estimated to be between 1 in 14,000 and 1 in 12,000 for screened populations in Canada,[44,45] and the highest estimates are observed in European populations, for example, with 1 in 4,900 births affected in northern Germany.[46]

Pathophysiology

The MCAD enzyme is involved in the initial dehydrogenation of medium-chain fatty acids, which span from 6 to 12 carbon atoms in length, during beta-oxidation in the mitochondrial matrix.[47,48] Once glycogen stores become used in response to, for example, high energy activities exacerbating catabolism, intercurrent acute illness with vomiting/febrile illness (i.e., reduced caloric intake), and/or fasting for periods exceeding safe intervals, beta-oxidation catalyzes hepatic ketogenesis to generate alternative forms of usable energy and to sustain energy metabolism.[48] A loss of MCAD enzyme function impairs the first step in the beta-oxidation process for medium-chain fatty acids, and leads to an inability to cleave them into acetyl-CoA in the mitochondrial matrix.[49] This can give rise to a pattern of symptoms (including risk of acute metabolic decompensation during catabolic stress) that may depend commensurately on the level of residual enzyme activity from various genotypes, and the extent to which concentrations of the by-product, octanoylcarnitine (C8), formed by acyl-CoA and carnitine, are elevated in the blood.[50–52]

Genetics

MCAD deficiency is caused by pathogenic variants found on the *ACADM* gene, located on chromosome 1p31, and has an autosomal recessive inheritance.[53] After a differential diagnosis of MCAD deficiency is made, following newborn screening and confirmatory diagnostic testing, children typically undergo single-gene molecular genetic testing to identify biallelic variants. The implementation of newborn screening has revealed a larger spectrum of *ACADM* mutations;[54] however, the majority of children with MCAD deficiency in screened cohorts have a homozygous form (i.e., have two copies) of the mutation, c.985A>G.[42,55,56] This particular mutation is a severe, missense mutation replacing a lysine for a glutamate during protein formation, sometimes resulting in extremely elevated C8 levels and a higher risk for acute episodes of metabolic decompensation relative to other genotypes.[54] The missense mutation, c.199T>C, replacing a tyrosine for a histidine, is also common but is associated with relatively higher residual enzyme activity and milder phenotypes under usual circumstances.[57] To date, there are 161 *ACADM* mutations registered in the Human Gene Mutation Database, 73% of which are missense mutations, although splicing mutations, deletions, and insertions have been identifed.[58]

Clinical features and presentation

The prognosis for children with MCAD deficiency identified by newborn screening is generally favourable; catabolic stress, however, can increase the risk of hypoketotic hypoglycemia and lead to serious complications if left untreated, including metabolic decompensation, seizures, liver dysfunction, coma, sudden death, and other neurological sequelae.[48,59] Other signs and symptoms of episodic illness in MCAD deficiency include lethargy and encephalopathy. Newborn screening has substantially altered the natural history of this disease, effectively reducing

morbidity and mortality by alerting parents and health care providers of the potential risk and taking steps to both prevent catabolic stress and respond quickly when it occurs.[60] In fact, before MCAD deficiency was added to most newborn screening programs, it was estimated that approximately 20% of children with clinically identified MCAD deficiency experienced sudden infant death.[61] The exact relationship between genotype, biochemical phenotype, and the severity of clinical symptoms have not been well-elucidated, and may depend partly on environmental stressors contributing to the clinical course of the individual patient.[50]

Ascertainment and diagnosis

The ascertainment of MCAD deficiency is currently achieved through newborn screening, and primarily involves an analysis of acylcarnitines obtained from blood plasma, collected via a heel prick, and measured using tandem mass spectrometry.[62] As mentioned, the disease pathophysiology results in an inadequate breakdown of medium-chain fatty acids and a subsequent accumulation of C8 species in the blood. Newborn-screened C8 concentrations of 0.30 μmol/L or higher in plasma is sometimes, but not always, sufficient to impart a suspicion high enough to report a positive screening result.[63,64] Secondary components of the complete acylcarnitine profile can be considered in combination with elevated C8 levels, such as hexanoylcarnitine (C6) and decenoylcarnitine (C10) peaks and other ratios (C10:C1, C8:C2, C8:C10).[65] In addition to molecular genetic testing, other laboratory tests can be used to confirm a fatty acid oxidation defect among infants with positive newborn screening results, such as additional plasma acylcarnitine analysis and/or measuring urine acylglycines and medium-chain dicarboxylic organic acids.[38]

Treatment

The primary goal of medical care for children with MCAD deficiency involves appropriately responding to the risk for metabolic decompensation by preventing catabolic stress where possible and rapidly responding to such stress when it occurs. Therefore, the mainstay of treatment typically includes avoiding fasting (i.e., frequent feedings) to maintain energy production, coupled with the consumption of complex carbohydrates (e.g., cornstarch) to prevent risk associated with unavoidable stress periods such as overnight fasting or intense exercise.[66,67] During illness or early signs of potential catabolic stress, to prevent mortality and severe morbidity, these strategies can be delivered concomitantly with the administration of intravenous glucose and close medical monitoring.[68] Routine L-carnitine supplementation has been proposed as a long-term measure to offset free carnitine deficiency and reduce the severity of episodes, although evidence pertaining to its effectiveness is lacking.[69–72] In order to prevent symptoms throughout childhood, children with MCAD deficiency have substantially higher rates of interactions with the health care system, such as encounters with physicians, emergency department visits, and hospital admissions, as compared to healthy children.[73] While the success of these preventive strategies for modulating disease-specific outcomes have justified newborn screening for MCAD deficiency, improving long-term outcomes among children with this disease requires identifying which interventions work best, informed by consistent measurement of clinically meaningful and patient-centred outcomes.

Challenges in rare disease research

In addition to population health and health system impact, the overall experience of individual patients in health care, as described by Berwick and colleagues (2008), is a fundamental

component of health care systems operating at a high standard.[74] Thus, appropriately applying resources or treatment to a population must support the key dimensions of the "quality chasm", namely safety, effectiveness, timeliness, efficiency, equitability, and patient-centredness.[75]

Evidence regarding the effectiveness of interventions for pediatric MCAD deficiency is fragmented. Improving patient experience in the context of IMD, and rare diseases in general, however, requires generating evidence to support the safety and effectiveness of current and novel treatment for those IMD, while also considering impacts and costs to the health care system.[76] Responding to research questions in this area and selecting appropriate clinical trial or other study designs is challenging and can be complicated by a variety of factors. For example, there is a lack of knowledge regarding clinical expression and disease progression between diseases and within the same disease (i.e., influenced by clinical heterogeneity). Moreover, the limited number of children available poses challenges for recruitment and ability to achieve adequate statistical power when using traditional trial designs.[76–78]

One possible means of overcoming drawbacks to rare disease research are disease registries, which seek to establish a comprehensive database to: connect patients with other patients, their families and health care professionals; establish a platform of patients to plan and launch registry-based randomized trials assessing the effectiveness of therapies for a particular disease; and, generate pragmatic evidence to better understand the natural history and underlying components of those diseases.[79] Registry-based randomized trials have been launched in Canada for rare diseases using an established registry; the Canadian Neuromuscular Disease Registry is one such example.[80] They reflect a promising study design to address expressed gaps in rare disease research, but require a high-quality registry platform that incorporates rigorous, standardized measurement of meaningful, patient-oriented endpoints, as well as explicit

collaboration and interoperability between patient communities, researchers, stakeholders, and health systems.[81,82]

Quality of medical records data for research

The secondary use of medical records for research can offer many advantages, particularly with respect to convenience, cost-effectiveness, and the large breadth of clinical information often collected passively as part of standard care.[83] Medical records as a data source can facilitate retrospective reviews to investigate research questions that, for example, preclude randomization or that involve rare endpoints.[84]

The quality of these data, however, may be limited by a number of factors inherent to their collection as part of the medical chart as well as challenges associated with manual abstraction for research purposes. First, they are subject to various errors with regards to interpretation and documentation processes by clinicians, information reported by patients and families, and measurements generated by laboratory equipment.[85] In fact, the validity of administrative data has been found to be dependent on the quality of documentation by clinicians.[86] Second, the accuracy of chart-abstracted data is related to the complexity and consequent level of content expertise and derivation required for interpretating clinical information, the format of individual data items, and the characteristics of the abstractor(s).[87] Finally, missing or incomplete data can be methodologically challenging and can contribute to bias,[88] yet this phenomenon is relatively common in medical records and in chart-abstract databases, the level of which may be influenced by the degree of consistency and standardization in data abstraction procedures.[87]

Minimizing the aforementioned challenges associated with employing medical records for research requires comprehensive data quality assurances and controls. Strategies might involve

extensive training of those involved in interpreting and abstracting the medical chart to ensure maximum adherence to the protocol, designing high-quality data collection tools outlining clear definitions and requisite data items, and periodic analyses of aggregate data or audits to identify systematic data quality issues.[89] Procedures might also involve measuring reliability between abstractors or the validity of abstracted information (for example, by comparing unique fields to a standardized care report form developed by experts).[87]

Core outcome sets

Outcomes measured across research studies for rare diseases such as MCAD deficiency may be relatively disparate in the absence of a recommended standard; and yet, combining results across studies is essential for understanding treatment effectiveness, particularly given small patient populations and differences in clinical presentation.[77] Core outcome sets (COS) are increasingly used in evaluative research to encourage a harmonious reporting of a standard group of modifiable endpoints for research conducted in a population with a specific health condition.[90–92] The Core Outcome Measures in Effectiveness Trials (COMET) initiative describes best practices with respect to methods for developing core outcome sets, which include a comprehensive literature review to identify the complete breadth of outcomes previously measured in a particular health area, followed by a multi-step consensus process, for example, using a Delphi method and a conference to narrow priority outcomes.[93,94]

In particular for rare diseases, establishing and implementing well-defined COS can facilitate comparisons between studies to generate robust evidence regarding possible interventions for a specific disease, support the development of multi-centre studies through standardized outcome data collection across different clinical settings, and overcome

aforementioned challenges in rare disease research.[78,95] Prior studies have developed COS for other chronic and rare pediatric conditions, applying them to research in those contexts to support comparable outcome measurement.[96–98] The development of a COS is planned for another IMD, mucopolysaccharidosis type II.[99]

The Canadian Inherited Metabolic Diseases Research Network

The Canadian Inherited Metabolic Diseases Research Network (CIMDRN) is a pan-Canadian group of investigators collaborating on research that aims to measure outcomes, understand experiences, and develop interventions for children with IMD and their families, including MCAD deficiency. The CIMDRN has established a cohort of approximately 800 children who were diagnosed with one of 31 IMD, born from 2006 to 2015, and received care from one of 13 participating tertiary care pediatric hospitals from birth until March 31, 2017. A comprehensive database, assembled through retrospective chart review and abstraction, collected detailed information on patient characteristics, ascertainment, and disease-specific treatment and outcomes at each clinical visit.[100]

In response to a need to identify patient-oriented outcomes, and following the COMET initiative guidelines,[78,90] the CIMDRN developed core outcome sets for two of the most common IMD: phenylketonuria (PKU) and MCAD deficiency.[90] They conducted a systematic review of outcomes for each disease,[101] a multi-stakeholder Delphi survey, and hosted a final consensus workshop to identify the final outcomes for each set. The core outcome set for MCAD deficiency includes the following eight outcomes across the domains of death, growth and development, life impact, pathophysiological manifestations, and resource use: (i) death, (ii) overall child development, (iii) fasting, (iv) child quality of life, (v) parental experiences with illness care and

prevention, (vi) metabolic decompensation, (vii) access to care, and (viii) emergency department use.[102] Once a COS for a particular condition has been described, it is important to identify the method by which these outcomes will be measured.[92] As part of this process, the CIMDRN also developed operational definitions and recommended outcome measurement instrument(s) for each core outcome.[102]

Rationale for the thesis project

As described, MCAD deficiency is the most common disorder of fatty acid oxidation, posing significant challenges for children and their caregivers. The effectiveness of current and novel treatments for MCAD deficiency with respect to long-term, patient-centred outcomes remains unclear,[103] and registry-based randomized trials are a promising strategy to address these evidence gaps.[82] The CIMDRN is a pan-Canadian network that has enrolled a large cohort of children with MCAD deficiency, with potential to be developed into a registry to launch such trials.

A COS has been developed toward this aim, and in order to take the registry platform forward, there was a need to determine the sustainability and value of measuring these outcomes, over a long-term and on a regular basis, in clinical settings for children with MCAD deficiency. The longitudinal clinical data that have already been assembled by the CIMDRN, through chart reviews, provided an opportunity conduct this research. In addition to evaluating the potential to measure core outcomes for children with MCAD deficiency using information that is routinely available from patient charts, there was a need to better understand the longitudinal health of children with MCAD deficiency, by describing their trajectory according to one or more priority

outcomes and the characteristics of children associated with such outcomes. Collectively, this work contributed to improving evidence generation to inform care for pediatric MCAD deficiency.

Objectives

The first objective of this thesis (Chapter 2) was to assess the feasibility of prospectively measuring clinically reported core outcomes during routine metabolic clinic visits for children with MCAD deficiency. To accomplish this, leveraging an existing Canadian cohort of children with MCAD deficiency followed for up to 11 years, the quality of metabolic chart-abstracted data pertaining to four core outcomes (emergency department use, fasting, metabolic decompensation, and death) was evaluated. We applied a data quality framework assessing the following criteria: i) completeness of each data component contributing to the ascertainment of the outcome as reflected in the chart, ii) extent to which reported data conformed to expected measurement restrictions and ranges to foster comparability and synthesis, and iii) plausibility of summary data with respect to expected norms for children with this disease at different ages.

The second objective of this thesis (Chapter 3) was to develop a robust working definition of MCAD deficiency disease severity, and to describe and identify variation in one core outcome of interest, emergency department use, according to characteristics of Canadian children diagnosed with MCAD deficiency. To do so, we classified each child with MCAD deficiency participating in the aforementioned cohort as having severe, intermediate, or mild disease severity by merging two commonly measured proxy indicators independently associated with more severe presentation: i) biallelic mutations contributing to severe, intermediate, or mild phenotypes from previous literature, and ii) quartiles of newborn-screened C8 concentration in blood spots obtained from this sample. Next, we used multivariable regression modelling to explore possible

independent predictors (i.e., age, disease severity, distance to travel to the metabolic clinic) associated with a single high-priority core outcome, emergency department use. The analysis accounted for the longitudinal nature of the data, which provided multiple measurements for each participating child over the study follow-up period.

Organization of the thesis

This thesis has four chapters and is written using a thesis by article(s) format in accordance with guidelines provided by the University of Ottawa's School of Epidemiology and Public Health (SEPH). Chapter 1 has described the extant literature on the topic and other key concepts, as well as the rationale and objectives for the thesis. In accordance with the first objective, Chapter 2 describes the feasibility of measuring core outcomes for reporting by clinicians from a recently developed core outcome set for MCAD deficiency using routinely collected information previously recorded in metabolic charts. Chapter 3 describes the methods and results related to the second objective, which involves developing a working definition for disease severity and analyzing variation in one core outcome of interest, emergency department use, according to clinical characteristics of children with this disease. Finally, chapter 4 presents an integrated discussion summarizing the main findings of previous chapters and their implications for future research.

INTERFACE

The following article, titled "*Assessing the value of metabolic chart data for capturing core outcomes for pediatric medium-chain acyl-CoA dehydrogenase (MCAD) deficiency*", presents a secondary data analysis that addresses objective 1 of this thesis, exploring the degree to which metabolic chart data from an established cohort of children with MCAD deficiency could be considered for prospectively and routinely measuring core outcomes. This involved investigating the frequency of opportunity to measure core outcomes based on the rate of visits to the metabolic clinic throughout early childhood, and an analysis of the quality of chart data items commonly recorded in the metabolic chart that may contribute to ascertaining emergency department use, fasting, metabolic decompensation, and death. Ethics approval was received for the original cohort study upon which this study was established, namely from the Children's Hospital of Eastern Ontario Research Ethics Board, from the Ottawa Health Science Network Research Ethics Board, and from each participating metabolic centre. This article is formatted for submission to the *Orphanet Journal of Rare Diseases*.

Author contributions: RI and BKP conceived of the study idea. RI, BKP, PC, and MT planned the methodology. RI conducted data analyses and drafted the manuscript. All authors assisted with the interpretation of data and results, and provided feedback and made major revisions to the final manuscript.

Chapter 2 – Assessing the value of metabolic chart data for capturing core outcomes for pediatric medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

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Abstract

Background: Generating rigorous evidence to inform care for rare diseases requires reliable, sustainable, and longitudinal measurement of priority outcomes. We have developed a core outcome set for children with the rare inherited metabolic disease, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. To assess the feasibility of future measurement of the core outcomes prospectively during routine metabolic clinic visits, we used existing cohort data to investigate the frequency of clinic visits and quality of metabolic chart data for selected outcomes.

Methods: We used longitudinal data abstracted from the metabolic charts of 124 newborn screened children diagnosed with MCAD deficiency who participated in a Canadian retrospective cohort study collecting data from birth to a maximum of 11 years of age. We described the frequency of opportunities to record outcomes from the clinical chart based on the rate of visits to the metabolic clinic, overall and by treatment centre and child age. We applied a data quality framework to evaluate chart data based on completeness, conformance, and plausibility for three core outcomes: emergency department use, recommended fasting tolerance, and episodes of metabolic decompensation.

Results: The frequency of metabolic clinic visits decreased with increasing age, from a rate of 2.8 visits per child per year (95% confidence interval, 2.3-3.3) among infants < 6 months, to 1.0 visit per child per year (95% confidence interval, 0.9-1.2) among those ≥ 5 years of age. Rates of emergency department visits were lower than expected but followed anticipated trends by child age. Supplemental findings suggested that some emergency visits occurring outside of the treatment centre from which routine metabolic care was received were likely not recorded. Recommended fasting times were updated relatively infrequently in patients' charts. Episodes of metabolic decompensations were identifiable but required an operational definition based on acute manifestations most commonly reported in the clinic chart.

Conclusions: Based on visit frequency, opportunities to record core outcomes at the metabolic clinic occur at least annually for children with MCAD deficiency. Methods to identify emergency services received at outside institutions may be needed. Improved reporting standards are required to promote consistent documentation of recommended fasting and metabolic decompensations.

Keywords (maximum 10): inherited metabolic diseases; MCAD deficiency; data quality; core outcome set

(348 words/350 words)

Background

Inherited metabolic diseases (IMD) are a group of over 1000 disorders characterized by a disturbance to an intermediate metabolic pathway, typically with onset during early childhood.[1,2] IMD are individually rare but collectively relatively common, with a global prevalence of approximately 1 in 2000 live births.[3] Particularly when left untreated, IMD can precipitate a diverse range of clinical features that can include a risk of acute life-threatening episodes of illness and/or chronic manifestations, which depend on the specific IMD and occasionally on the characteristics of the individual patient.[4,5] IMD often require specialized care, alternative diets, and ongoing medical interventions which pose challenges to patients, families, and health care systems.[6–8] In common with other rare diseases, evidence regarding the comparative effectiveness of treatments for IMD is often lacking and is challenging to generate due to small patient populations, high levels of phenotypic heterogeneity, and uncertainty regarding natural history in screened and unscreened populations.[9–12]

The mitochondrial fatty acid oxidation disorder, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, is one of the most common IMD,[13] with an estimated birth prevalence as high as 1 in 12,000 in Canada.[14,15] The MCAD enzyme is involved in the breakdown of medium-chain fatty acids, which is required for sustaining metabolic function after the depletion of glycogen stores, for example, during high energy activities, when fasting for periods exceeding recommended intervals, or when unwell with fever or vomiting.[16,17] Insufficient activity of this enzyme markedly increases the risk of episodes of life-threatening manifestations during such periods of catabolic stress, including metabolic decompensation characterized by hypoketotic hypoglycemia, lethargy, or seizures.[18,19] Particularly among children with MCAD deficiency, appropriately responding to the risk of metabolic decompensation is essential for mitigating an

acute crisis and for preventing the possibility of long-term sequelae. This response typically involves avoidance of prolonged fasting, medical monitoring during periods of illness, and provision of rapidly available carbohydrates, such as intravenous dextrose, as appropriate.[20] Longer-term preventive interventions, such as carnitine supplementation, are used in some children with MCAD deficiency but evidence regarding benefits and harms is insufficient.[21–23]

To improve care and long-term outcomes for children with MCAD deficiency, rigorous approaches to evaluation of treatments are needed, informed by reliable, sustainable, and longitudinal measurement of clinically meaningful and patient-centred outcomes.[24] A core outcome set (COS) is a small group of priority outcomes agreed upon by stakeholders interested in a specific health condition with the goal of encouraging the standardized measurement and reporting of endpoints measured during clinical trials for that condition.[25–27] The development and implementation of COSs can support the synthesis of evidence and the comparison of findings across clinical trials where appropriate. COSs can also be collected as part of a high-quality disease registry to provide robust observational data on outcomes over time and to facilitate registry-based randomized trials, where a trial is launched from a registry platform that incorporates rigorous outcome measurement.[28] There is a particular need for multi-centre and international collaboration in rare disease settings, given the small number of patients in any single centre. The development of COSs can help to overcome limitations in rare disease research by promoting the generation of robust, pooled evidence for long-term outcomes and treatment effectiveness in small populations.

We previously developed a COS for children with MCAD deficiency as part of the Core Outcome Measures in Effectiveness Trials (COMET) initiative,[25,29] using: (i) a systematic review of prior studies of MCAD deficiency to derive a potential list of relevant outcomes; and (ii) a multi-stakeholder consensus approach (Delphi survey and workshop) involving patients and

families, clinicians, and policymakers.[29,30] The final COS includes eight core outcomes for children up to age 12 diagnosed with MCAD deficiency, within the core areas of death, growth and development, life impact, pathophysiological manifestations, and resource use (Box 1).[30]

Box 1. Core outcomes and their definitions according to core areas for MCAD deficiency

1. **Core area: Growth and development**
   A. Overall child development:

      Measures related to the attainment of developmental milestones throughout childhood, such as cognition, speech and language skills, motor skills, and socialization.
2. **Core area: Life impact**
   A. Fasting:

      Recommended maximum amount of time without food or drink.
   B. Child quality of life:

      Physical, emotional, and social aspects of child health and well-being.
   C. Parental experiences with illness care and prevention:

      Perceptions related to caring for a child with MCAD deficiency, such as barriers and facilitators involved in preventing acute crises.
3. **Core area: Pathophysiological manifestations**
   A. Metabolic decompensation:

      Acute episode characterized by profound hypoglycemia or encephalopathy and the accumulation of biomarker(s) indicating the alteration of a usual physiological state.

4. Core area: Resource use

A. Access to care:

The extent to which a child receives adequate health care services required to meet their individual need.

B. Emergency department use:

Frequency and reasons prompting emergency care at the hospital.

5. Core area: Death

A. Death:

The end of a child's life.

While several of these core outcomes are patient or parent-reported by nature (e.g. child health-related quality of life), others require clinical evaluation and/or laboratory assessment. To facilitate prospective collection of these clinical outcomes and thereby support observational registries and clinical trials for children with MCAD deficiency, there is a need to establish the sustainability and value of measuring these outcomes in routine clinical settings on a long-term and regular basis.[31] In this study, we used existing cohort data to investigate the frequency of clinic visits and quality of metabolic chart data for selected outcomes to assess the feasibility of future measurement of core outcomes prospectively during metabolic clinic visits.

Materials and methods

Data source, design, and eligibility

The Canadian Inherited Metabolic Diseases Research Network (CIMDRN) established a consent-based cohort of nearly 800 children across Canada diagnosed with one of 31 IMD, including MCAD deficiency.[33] This cohort study involved the detailed retrospective collection of longitudinal clinical data from metabolic charts for enrolled children, from birth to a maximum of 11 years of age, and achieved a participation rate of approximately 74%. This presented an opportunity to evaluate the feasibility of using data from routine clinic visits to measure core outcomes.

Thus, for the present study, we conducted a secondary analysis of the CIMDRN cohort database, specifically relying on previously abstracted metabolic chart data from children with MCAD deficiency enrolled in the cohort.[33] Participants were children born between January 1, 2006 and December 31, 2015 who received at least some care for a confirmed MCAD deficiency diagnosis at one of the 13 participating treatment centres between birth and March 31, 2017. For data collection in the CIMDRN cohort, data coordinators at participating centres retrospectively abstracted data from electronic and/or paper charts (depending on the type of chart in use at the participating centre at the time of each visit). At baseline, abstracted data pertained to participant and family characteristics, medical history and ascertainment, and diagnostic tests received. For each visit to the metabolic clinic post-diagnosis, the results of follow-up tests, disease-specific outcomes, interventions and treatment, and acute and chronic diagnoses were abstracted. All data were entered as open- and closed-ended responses in a series of standard, study-specific, web-based data collection forms developed with extensive input from metabolic physicians across

Canada. The data collection forms were submitted to and stored on a central study database in Research Electronic Data Capture (REDCap),[32] a secure platform hosted at the Children's Hospital of Eastern Ontario Research Institute. In addition to the careful design of intuitive data collection tools and regular communication with treatment centre staff, in order to maintain data quality, the data were subject to a detailed verification process by staff at the central site, including a review of each participant's full dataset and periodic monitoring of summary measures.[33] A unique, study-specific patient identifier was assigned to each participant in lieu of names and other identifying information to uphold patient confidentiality. Ethics approval for the cohort enrollment and data collection and analysis was received from the Children's Hospital of Eastern Ontario Research Ethics Board and the Ottawa Health Science Network Research Ethics Board. The cohort study was also approved by the research ethics board at each participating centre.

For the present study, we excluded children enrolled in the cohort for whom there were no recorded clinic visits after initial enrollment, for example, due to complete absence of data entry or death prior to their initial clinic visit. All children were followed until the study end date of March 31, 2017, unless they were deceased or discharged from a participating metabolic clinic during the follow-up period (e.g. due to relocation to a clinic not participating in the cohort study). Since data were entered chronologically, all available data during the follow-up period were used for participants with incomplete data. For the calculation of follow-up time and age-specific rates, however, these children were considered to be lost to follow-up at the end of the oldest age group to which they were known to contribute a complete period of follow-up. Children who moved to a participating centre from a non-participating centre partway through the study were followed from the date of their first recorded clinic visit with the current centre.

Core outcomes potentially measurable from the clinical chart

Certain core outcomes require the implementation of alternative data collection procedures including, for example, patient- or parent-reported surveys; however, four of the core outcomes were considered candidate outcomes for collection as part of routine clinical care from a child's medical chart and identified as of primary interest for the present study: emergency department use, fasting, metabolic decompensation, and death.[30]

Analysis of the feasibility of measuring core outcomes in clinic

We described the demographic characteristics (e.g., year of birth, sex, consenting treatment centre) and baseline clinical characteristics (e.g., ascertainment method and neonatal complications) of children with MCAD deficiency in the sample using frequencies and percentages. We calculated confidence intervals for incidence rates using the exact Poisson distribution or the normal approximation to the Poisson distribution as appropriate. Confidence intervals for means are expressed using the standard normal distribution. All cell counts representing fewer than five children were suppressed as "<5" to reduce the risk of inadvertently identifying participants, as per the cohort study's REB-approved protocol. SAS software® version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) was used for all statistical analyses.

Data collection intervals among participants varied, depending on each child's schedule of visits to the metabolic clinic. We considered the frequency of visits as an indicator of the frequency of opportunity for outcome measurement. To determine the potential future feasibility of collecting core outcomes prospectively by relying on existing clinical encounters, we reported the frequency of visits to the metabolic clinic and telehealth encounters over time, expressed as rates per child per year, and calculated by summing the number of visits as the numerator and the accumulated

person-time of follow-up as the denominator. Results are presented by child age using 6-month intervals in the first year of life and 2-year intervals thereafter. We also explored variation in the frequency of clinic visits across participating centres treating five or more children by presenting results separately for each centre.

To evaluate the quality of data for each of the outcomes of interest, we were guided by Kahn et al.'s framework,[34] which focuses on data quality pertaining to the secondary use of electronic health data, and applies well to chart-abstracted data. Specifically, the four core outcomes of interest and their components were explored using the following data quality concepts: completeness, conformance, and plausibility. To address completeness, we examined the extent to which each component of a particular outcome was routinely captured in the chart for children in each age group, and the frequency of measurement of outcomes and their individual components. To address conformance, we measured the extent to which data were consistently entered in the proposed format and whether there existed variation in how outcomes were measured, abstracted, or reported across sites. To address plausibility, we examined whether values reflect a reasonable measurement or health trajectory over time for a child with MCAD deficiency, expressed as rates or summary measures of priority outcomes across age groups as appropriate. For one of the core outcomes of interest, metabolic decompensation, there is no widely accepted clinical definition. Thus, to ascertain whether chart abstracted data may be used to measure this outcome for children with MCAD deficiency, we first identified possible decompensations from chart data capturing the clinical manifestations of decompensation (e.g., hypoglycemia, seizures). Next, two metabolic physicians (PC, MTG) made independent inferences about whether each possible decompensation event identified by abstracted data constituted a true metabolic decompensation, judging each event as a yes (decompensation) or no (not a

decompensation). The physicians relied solely on the abstracted data items to make this judgement. We measured agreement between the two raters using Cohen's kappa coefficient.

Results

Cohort description

There were 132 children with a confirmed diagnosis of MCAD deficiency enrolled in the CIMDRN cohort. Eight children were excluded from further analyses since they were either deceased within the neonatal period, lost-to-follow-up prior to their first clinic visit, or data had not been abstracted from their metabolic chart. Children were distributed across the eligible years of birth, with the highest proportion born in 2014-2015 (Table 1). Slightly less than half (43.5%) of children were female. Proportions of children recruited from different metabolic clinics generally reflect the population catchment associated with each clinic, with the largest number (24.2%) enrolled through The Hospital for Sick Children. Ascertainment was almost exclusively achieved through newborn screening, occasionally in combination with other methods such as family history/cascade testing or symptomatic presentation. The most commonly reported neonatal complications were hypoglycemia (10.5%), requirement for intravenous fluids (6.5%), respiratory distress (6.5%), need for antibiotics (6.5%), and jaundice (5.6%). The median follow-up time was 5.2 years (IQR=3.0-8.4) among participating children, with 113 children (91%) followed from birth until the end of the data collection period. Eleven children had less than complete follow-up due to late enrollment (e.g. moving from a non-participating centre) or were lost to follow-up prior to the completion of the study (e.g., discharge, incomplete data entry).

Table 1. Demographic and clinical characteristics for children with MCAD deficiency eligible for longitudinal follow-up

Characteristic	**Frequency (%)**
Year of birth (n=124)	
2006-2007	20 (16.1)
2008-2009	27 (21.8)
2010-2011	18 (14.5)
2012-2013	28 (22.6)
2014-2015	31 (25.0)
Sex (female) (n=124)	54 (43.5)
Participating treatment centre (n=124)	
BC Children's Hospital - Vancouver, BC	29 (23.4)
Alberta Children's Hospital - Calgary, AB	10 (8.1)
London Health Sciences Centre - London, ON	10 (8.1)
Hamilton Health Sciences Centre - Hamilton, ON	15 (12.1)
Hospital for Sick Children - Toronto, ON	30 (24.2)
Kingston General Hospital - Kingston, ON	5 (4.0)
Children's Hospital of Eastern Ontario - Ottawa, ON	8 (6.5)
Other participating centre*	17 (13.7)
Ascertainment (n=124)	
Newborn screening method only	107 (86.3)
Newborn screening and other method(s)	>10
Other method(s) only	<5
Neonatal complications (yes) (n=104)	32 (30.8)

* Other participating centres (each with fewer than 5 enrolled children with MCAD deficiency) include Stollery Children's Hospital, Winnipeg Health Sciences Centre, Montreal Children's Hospital, CHU Sherbrooke, Izaak Walton Killam Health Centre and Janeway Children's Health Centre

† Cells representing less than 5 children are suppressed as "<5" based on CIMDRN's privacy policy

‡ Valid percentages are presented (the sum of cells for each characteristic may not represent all 124 eligible participants due to missing or unknown data)

Visits to establish diagnosis and rate of follow-up visits to the metabolic clinic

Overall, there were 202 recorded visits to the metabolic clinic that were considered to be part of the diagnostic period (this was pre-defined in the database) among eligible children. This represented an average of 1.7 (95% confidence interval, 1.5-1.9) diagnostic visits per child during which they underwent biochemical testing and molecular genetic testing related to establishing a diagnosis of MCAD deficiency. We defined follow-up visits as those visits to the metabolic clinic occurring after the first two months of age, to emphasize visits occurring after a complete diagnosis is typically established, and when core outcome measurement may be most relevant.

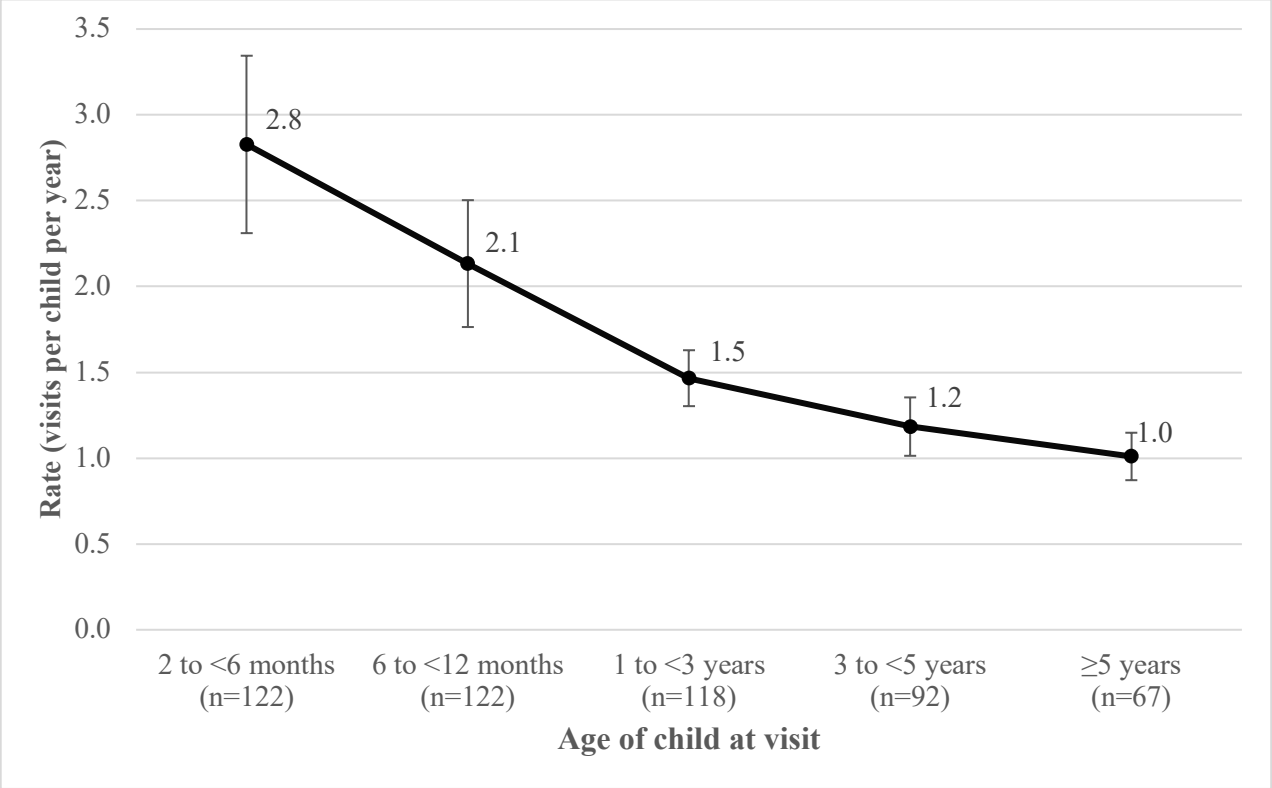

Figure 1. Rates of follow-up visits to the metabolic clinic according to the age at the visit

* Error bars representing 95% confidence intervals using the normal approximation to the Poisson distribution
* One child may contribute to multiple age groups due to longitudinal follow-up

After two months of age, there were a total of 945 follow-up visits to the metabolic clinic among eligible children in the sample. The frequency of visits to the metabolic clinic over time was highest among children aged 2 months up to 6 months of age (2.8 visits per child per year), with a gradual, but sustained decline thereafter (2.1 visits per child per year from 6 months up to 1 year, 1.5 from 1 year up to 3 years, 1.2 from 3 years up to 5 years, and 1.0 from 5 years of age and older) (Figure 1). After stratifying by participating treatment centre, among centres treating five or more children with MCAD deficiency, the centre-specific trends in visit rates by child age were mostly consistent with the overall trend (see Additional file 1). There was, however, considerable variation in the magnitude of the rates, likely due to random variation, but possibly reflecting differences in centre- and physician-specific management practices.

Data quality relating to core outcomes measurable from the metabolic chart

Table 2. Highlighted findings for core outcomes according to each data quality concept

Emergency department (ED) use	1. **Completeness:** Presence or absence and number of ED visits since the last clinic visit was reported at 95% of clinic visits. 2. **Conformance:** Exact dates of ED visits were not always reported, but the age at the visit could often be inferred if it occurred between two clinic visits at known ages. 3. **Plausibility:** Although exhibiting similar trends by age, observed rates are underestimated when compared to a previously published study using health care administrative data among a similar sample in Ontario. Only 42% of expected visits were recorded in the chart when compared to that previous Ontario-based study.

Fasting	1. **Completeness:** Recommended fasting times were updated during approximately 39% of visits. Use of clinic-specific standard age-based recommendations, and consequent lack of patient-specific reporting in the chart, were common. 2. **Conformance:** Reporting using fasting ranges, fasting times with or without intervention, and fasting times during the day/overnight required rules to define exact measures. 3. **Plausibility:** The infrequency of updates to maximum fasting times would result in lower than expected fasting times at older ages if we carried earlier recorded times forward. Median fasting times that were explicitly recorded in this sample, however, followed published recommendations by age.
Metabolic decompensation	1. **Completeness:** Temporal association of events was challenging, notably when biochemical tests were expected to be ordered but results were unavailable in the chart. 2. **Conformance:** Decompensations were rarely reported in an explicit manner. The exact date of episodes could not always be ascertained. 3. **Plausibility:** Median age at decompensation roughly followed known ages during which children with MCAD deficiency commonly exhibit symptoms.
Death	Although death is a critical core outcome for clinical measurement and reporting, it was fortunately extremely rare in this cohort. Data quality with

	respect to metabolic chart data could therefore not be evaluated and this outcome was excluded from further analyses.

Emergency department visits

Emergency department visits were measured at each metabolic clinic visit, based on the number of trips to the emergency department that had occurred since the most recent previous clinic visit and the reasons prompting the visits. This information was based on what was recorded in the child's metabolic chart, either by clinician report based on the interaction with the family during the clinic visit or through emergency department records embedded in the metabolic clinic chart.

Completeness

The number of times that the child had visited the emergency department since their last clinic visit was reported at approximately 95% of metabolic clinic visits but this varied widely between centres and among individual participants. Among 389 recorded emergency department visits for the 124 participants, 94 visits (24.2%) were missing the exact calendar date of the visit and five visits (1.3%) were missing the reason for which the child had received emergency care (the latter included unintelligible entries).

Conformance

The majority of emergency department visits were recorded clearly using validated date fields with accompanying text fields for the reason prompting the visit. However, among the 94 visits without an exact date, 22 emergency department visits had a partial time period entered in a

separate open-ended comment (e.g., the month, season within a particular year). For all visits missing the calendar date or with a partial date, it was possible to infer at least the approximate age of the child at the time of the visit since it occurred temporally between two clinic visits at known ages for 59 visits (62.8% of visits with missing information).

Plausibility

There were no duplicates for data values identifying unique emergency department visits and all emergency department visits were reported as occurring after the participant's date of birth. Approximately 25 children had no recorded emergency visits during their follow-up over an average period of 4.6 years. Based on a previously published study using health care administrative data for 40 children with MCAD deficiency in Ontario,[35] approximately 924 emergency department visits were expected in the present study cohort. However, among 124 eligible participants, there were only 389 emergency department visits reported, representing 42% of expected visits.

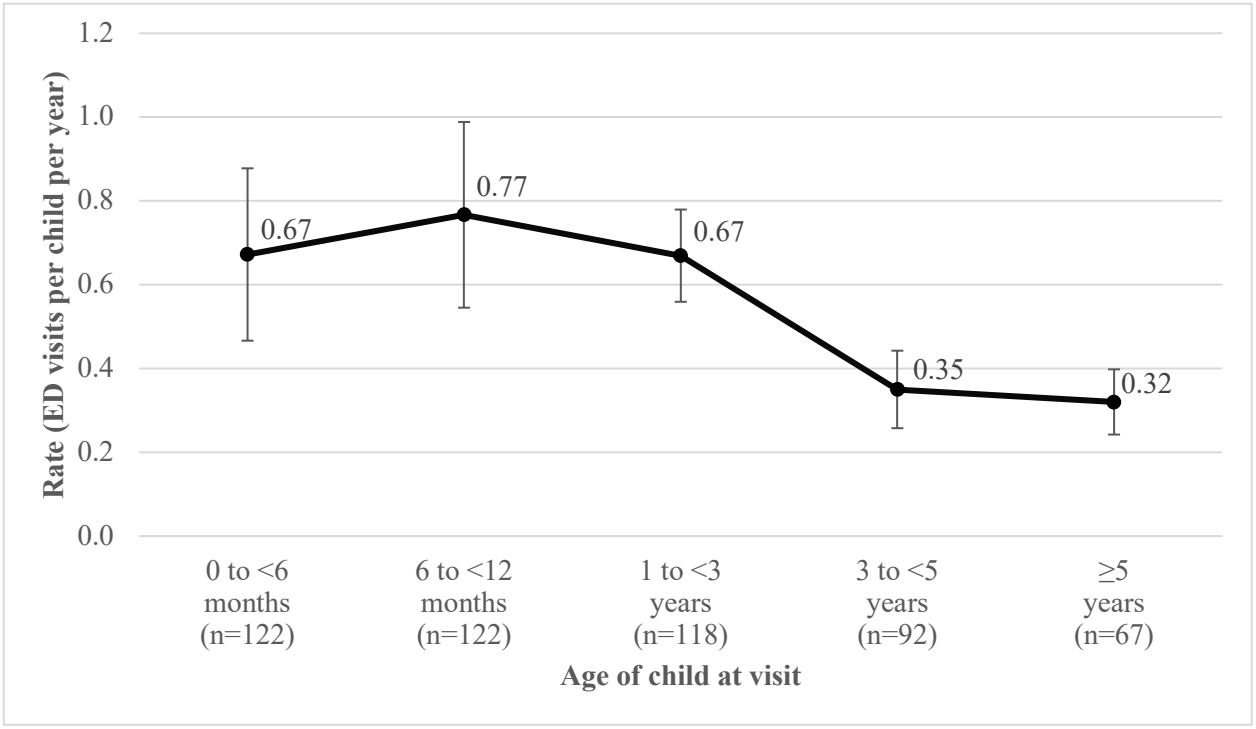

Figure 2. Rates of visits to the emergency department according to the age at the visit

* Error bars representing 95% confidence intervals using the normal approximation to the Poisson distribution
* One child may contribute to multiple age groups due to longitudinal follow-up

Rates of visits to the emergency department were lower than expected within all age groups based on comparison to the previously published study (Figure 2).[35] For example, on average, children with MCAD deficiency in the previous Ontario study visited the emergency department 3 times within the first 6 months of age and 5 times between 6 months and 1 year of age. For children in the present study cohort, however, there were 1.2 and 1.5 chart-recorded emergency department visits on average during the same time periods, respectively. Interestingly, the general trend across age groups was similar across the two studies, and the highest observed frequency of emergency department use occurred between 6 and 12 months of age. The most common reasons for seeking emergency care were largely identical between our cohort and the previous Ontario study as well: nausea/vomiting (131 visits), upper respiratory tract infections with or without

cough (86 visits), and fever (66 visits). Conversely, the frequency of inpatient hospitalizations over time aligned more closely with previously published health care administrative data (see Additional file 2),[35] with 68% (190/281) of expected hospital admissions captured.

Fasting

Fasting refers to a prescribed maximum period without food or drink as tolerated during usual circumstances or during intercurrent illness to prevent acute manifestations of MCAD deficiency. An increased fasting tolerance may be reflective of, or change in response to, improved clinical health of the patient.[36]

Completeness

Eighty-one children (65.3%) were prescribed an initial treatment pertaining to fasting avoidance with 67 prescriptions providing specific details regarding the maximum number of hours recommended without a feeding. Beyond the initial treatment, four treatment centres (n=18 children) did not report prescribed maximum fasting times and an additional eight children from other centres were missing fasting values at every metabolic clinic visit. Upon further investigation, we learned that at some centres, a clinic-specific protocol was provided to families of children with MCAD deficiency which described maximum fasting times according to specific age periods. In such cases, only exceptions to this algorithm may be recorded in the medical chart. For all visits to metabolic clinic for children with MCAD deficiency, there was an update to the prescribed diet (e.g., energy, fat, carbohydrates, protein, etc.) and composition (e.g. medical foods, supplements, etc.) during approximately 52.4% of the visits. It was unknown whether an update occurred during 24 (2.3%) of the visits. For the 556 metabolic clinic visits during which there was an update to the overall diet, the prescribed fasting time was recorded approximately 73.6% of the

time. When fasting time was not recorded, it may have been missing, unknown, or unchanged from the previous visit.

Conformance

When an acceptable fasting range was provided instead of a specific amount of time (e.g. a prescribed maximum fasting range of 8 to 10 hours), we considered the median value of the range to define the fasting time. Some children, however, were prescribed different fasting times for daytime versus overnight. In this case, we defined the child's fasting time as the largest value (maximum amount of time). Secondly, there were some cases when a child's fasting time was defined based on whether there was the presence of an additional source of carbohydrates (e.g., fasting with or without cornstarch). We defined these fasting times as those without extraneous intervention (the lower values) since they represented the maximum tolerated fasting in a natural physiological state.

Plausibility

For a number of children, there were no updates to the prescribed diet for long periods of time. As a result, if a lack of update in a chart were to be considered equivalent to an unchanged prescribed maximum tolerated fasting time (i.e., if we were to carry forward the last explicitly recorded fasting time), the recommended duration of fasting would appear much lower than expected at older ages.

Table 3. Comparison of reported fasting times in the CIMDRN cohort and published recommendations

Age Group	**No. children with at least one measurement***	**Recommendations in CIMDRN cohort** Median (IQR)	**Recommendations based on literature**[36]
< 6 months	99	3.5 hours (3.3-4.0)	N/A
6 to < 12 months	67	6.0 hours (5.0-8.0)	8.0 hours
1 to < 2 years	59	10.0 hours (8.5-12.0)	10.0 hours
≥ 2 years	55	12.0 hours (10.0-12.0)	12.0 hours

* Median values were calculated for children with more than one fasting prescription reported within a single age group, and only for those prescriptions with exact values provided (for example, excluding prescriptions stating only "avoidance of fasting" or "frequent feedings")

However, when considering only explicitly reported values, the median prescribed fasting time was 3.5 hours (IQR=3.3-4.0 hours) for children under 6 months of age, 6.0 hours (IQR=5.0-8.0 hours) for those aged 6 months up to 12 months, 10.0 hours (IQR=8.5-12.0 hours) for those aged 1 year up to 2 years, and 12.0 hours (IQR=10.0-12.0 hours) for those aged 2 years and older (Table 3). These lengths of time were in approximate agreement with published fasting recommendations for children with MCAD deficiency,[36] with a lower median time identified from 6 up to 12 months of age corresponding to the age period with the highest rate of emergency department use in this cohort. There was no evidence to suggest that the frequency of fasting prescriptions changed over calendar time within age categories (data not shown).

Metabolic decompensation

The core outcome set defined metabolic decompensation as an acute episode characterized by one or both of the following cardinal features: 1) hypoglycemia and 2) encephalopathy (e.g., lethargy, seizure). Additional supportive evidence based on the results of biochemical tests could include at least one documented abnormal level of substances in the blood indicative of an altered physiological state (e.g., depleted blood glucose, elevated liver aminotransferases).[30]

Completeness

The components required to ascertain a decompensation were routinely available within the medical chart (e.g., the results of biochemical tests, reasons for seeking emergency care, acute manifestations). However, identifying a positive event required clinical judgement influenced by a variety of factors and circumstances, which rendered its derivation complicated. Temporal association of laboratory findings or biomarkers with diagnoses or symptoms was not always possible, particularly when no tests were recorded during known emergency department visits or hospital admissions. To this end, there existed large variation among treatment centres in the level of detail abstracted and/or available in the metabolic chart. The ascertainment of metabolic decompensations also depended upon the completeness of reporting of emergency department visits and hospital admissions.

Conformance

Research coordinators rarely used the data collection forms to specify a metabolic decompensation as a direct disease-specific outcome even when it was otherwise apparent that an episode had occurred based on other reported clinical measures. Rather, we relied on associated

complications as noted in the chart based on the language used by the health care team to describe a metabolic decompensation. Furthermore, acute manifestations indicative of a metabolic decompensation were not always associated with a specific date so that multiple manifestations could not always be considered as mutually exclusive events. On a case-by-case basis and to avoid duplicating events, we considered multiple data items possibly contributing to a metabolic decompensation to be related to a single episode if they were reported within the same general time period (e.g., during a single hospital admission) and could not be reliably separated.

Plausibility

We identified 99 unique events among eligible participants comprised of individual clinical indicators (e.g., reasons for emergency department visits and hospital admission, acute/chronic diagnoses and manifestations, and biochemical measurements) potentially contributing to a single metabolic decompensation. This included one of or any combination of the following: i) direct reference to metabolic decompensation (reported during 13 events); ii) laboratory-confirmed blood (<3.5mmol/L) or physician-reported hypoglycemia (reported during 34 events); or iii) emergency department visits, hospital admissions or findings reported outside of routine metabolic clinic visits for indications of preventative IV glucose use and/or monitoring for hypoglycemia (reported during 32 events), elevated aspartate and alanine aminotransferases (reported during 18 events), lethargy (reported during 14 events), seizures (reported during nine events), or direct reference to possible encephalopathy (reported during two events).

Two pediatric metabolic physicians independently assessed abstracted data items for the 99 possible events. Inter-rater agreement yielded a Cohen's kappa statistic of 0.61, indicating

moderate to substantial agreement.[37] The physicians reached consensus on 35 episodes of metabolic decompensation. An additional 20 events were identified as metabolic decompensations by one of two raters only; 19 of these were classified as episodes of decompensation by physician 1 and not by physician 2. The remaining events were not considered decompensations by either physician. Unless there was documented hypoglycemia warranting intervention, raters agreed that reports of isolated intravenous glucose administration (or elevated blood glucose levels during hospital admission) were likely to be precautionary measures taken to avoid fatty acid oxidation and insufficient to ascertain the incidence of a metabolic decompensation. In fact, in all cases agreed upon by both assessors, there was a direct report of a metabolic decompensation and/or evidence for hypoglycemia.

During infancy (prior to 12 months of age), on average, there were approximately 13-18 episodes of metabolic decompensation per 100 children per year depending on the number of raters establishing that one had occurred (Table 4). Among children 12 months of age or older, on average, there were approximately 3 to 6 episodes of metabolic decompensation per 100 children per year. Overall, the median age of metabolic decompensation was approximately 12 to 15 months depending on the number of raters identifying episodes that could be ascribed an exact age (i.e., with exact dates available). This is consistent with the typical ages for clinical presentation for children with MCAD deficiency, which commonly occurs between 3 months and 3 years of age, averaging 12 months.[38,39] Metabolic decompensations are most common between 6 months and 18 months of age.[40] Similar to our results, in a previous study, among a sample of 114 children with MCAD deficiency who had previously experienced an acute crisis, the median age at first manifestation was approximately 18 months.[41]

Table 4. Rates of metabolic decompensation according to age and based on the number of raters identifying the event

Age Group	Number of potential events considered	Number of events labelled as decompensations	Rate per 100 children per year (95% CI)
Overall			
Both raters	99	35	5.0 (3.6-6.9)
At least one rater		55	7.9 (6.0-10.2)
<12 months			
Both raters	38	16	13.0 (7.8-21.0)
At least one rater		22	18.0 (11.7-27.1)
≥ 12 months			
Both raters	61	19	3.3 (2.1-5.1)
At least one rater		33	5.7 (4.0-8.0)

* 95% confidence intervals calculated using the exact Poisson distribution
* One child may contribute to both age groups due to longitudinal follow-up

Death

Since children in this cohort were almost exclusively ascertained by newborn screening, as expected from early identification and initiation of treatment,[14] the core outcome of death was fortunately very rare (n < 5), occurring only in few neonates exhibiting highly adverse clinical features prior to diagnosis. Therefore, in response to the low incidence of this event, the feasibility of measuring this outcome in clinic could not be evaluated. It should be noted, however, that children who died prior to a positive newborn screening result and referral, and thus without a confirmed diagnosis of MCAD deficiency prior to death, may not be identifiable using metabolic chart data.

Discussion

This study sought to evaluate the quality of existing metabolic chart data and its future suitability for measuring select core outcomes from a COS for MCAD deficiency: emergency department use, fasting, metabolic decompensation, and death. We found a decreasing rate of follow-up visits to the metabolic clinic by age, consistent with evidence suggesting that the highest risk periods for developing complications occur in younger age groups.[41] Based on the frequency of follow-up visits to the metabolic clinic, we found that an opportunity exists to measure core outcomes in the metabolic clinic setting at least once per year regardless of patient age. Although other COS studies have defined specific time points for measurement of core outcomes according to disease-specific milestones and timelines,[42] there is an absence of a published benchmark for the frequency of collection of core outcomes. For MCAD deficiency, the minimum frequency of visits required to capture variation in an outcome may depend on the outcome itself, its responsiveness to change, and, in a study evaluating care, the specific treatment being evaluated (i.e. the length of time expected to detect variation in outcomes). Strategies to collect core outcomes from children who visit the metabolic clinic less frequently may be required.

Rates of emergency department visits were underestimated when relying on chart data alone, but followed anticipated trends by age. We found the highest rate of emergency department visits between 6 and 12 months of age, which is consistent with previous literature and corresponds with the highest risk period for experiencing metabolic decompensations.[43] It is known that the accuracy of medical records data depend on the type of data collected; demographic, outcome, and discharge information collected as part of standardized sections of the chart have been found to have the highest accuracy.[44] Data quality may be further maximized when relying on outcomes,

such as emergency department visits, that rely in large part on a binary response, such as the presence or absence of an event. However, following consultation with data coordinators at each participating centre, it was discovered that information captured within the metabolic chart pertaining to emergency department visits often corresponded to visits that had occurred at same institution's emergency department. Emergency department visits occurring at other centres, such as at local community hospitals, may not have been captured unless the information had been parent-reported, forwarded by the emergency care team, or otherwise requested by the metabolic team. There was an improved comparability of rates of inpatient hospitalizations with gold standard measures relative to rates of emergency department visits.[35] This suggests that emergency department visits warranting more critical and longer-term care may be more rigorously documented in the metabolic chart. Collectively then, when relying on metabolic chart data, we hypothesize that whether an emergency department visit that occurs is captured depends on the nature and severity of the visit and its relevance to a child's disease as well as whether the visit occurred at the same institution (which in turn seems likely to vary according to both disease severity and geographic proximity of the child's residence to the clinic hospital). The fact that visits occurring at community hospitals may be missing from charts and that these may be different in nature from those that are captured suggests a need for additional measures to supplement metabolic chart data and systematically capture emergency care, such as patient- or parent-reported forms or linkable comprehensive health care administrative data.

Measuring prescribed maximum fasting times from chart data that had been recorded for clinical rather than research purposes was problematic. Although similar to emergency department visits in that the quality of reporting of this outcome relies on the presence of absence of a fasting

prescription recorded in the medical chart,[44] it is possible that updates are often the product of informal discussions between a clinician and a patient or their family member/caregiver and may not be documented in the chart; and at some centres, parents were provided with standard recommended fasting times by age. Consequently, recommended fasting times were updated highly infrequently in patients' charts, particularly at certain centres. Therefore, consistent reporting of fasting times for prospective research will require the use of clinic report forms completed at each metabolic clinic visit to appropriately capture variation in prescribed diets based on the child's age and improved health status, possibly in response to treatment.

Consistent reporting of metabolic decompensation requires an operational definition based on acute manifestations most commonly reported in the clinic chart. In this study, the agreement among metabolic physicians was moderate to substantial in terms of characterizing abstracted data items as episodes of metabolic decompensation. The nature of the disagreements in classification between the two observers suggested that each had a differential threshold for considering an event to be a decompensation. Thus, not only is there a need to measure the components of metabolic decompensation more systematically, but there is also a need for a consensus definition of this outcome. For example, hypoglycemia was a common clinical characteristic among all events identified by both raters, but invariably reflects a late manifestation of metabolic decompensation.[43] This is challenging because emergency care for MCAD deficiency is often focused on mitigating risk and thus it can be difficult to distinguish a "near miss" (i.e., decompensation avoided due to care) from a full decompensation. It was also difficult to temporally associate clinical manifestations contributing to a single event based on chart data. For example, certain features occurring alone may not always constitute a true decompensation and

may require clinical expertise and judgement (e.g., based on the age of child, the perceived severity of disease, temporal association with other indicators, "susceptibility" from prior events, and other comorbidities). A complicating factor for abstraction and reporting of this outcome is that it is rarely reported in language that would make it clear to abstractors unfamiliar with this condition that a metabolic decompensation had occurred, and requires a considerable amount of interpretation and derivation of a number of components. In general, diagnostic information has been found to have lower accuracy compared to other data, which can introduce systematic errors in the absence of standardized definitions and non-adherence to those definitions.[44] Thus, consistent measurement of this outcome requires explicit reporting of specific indicators/components, informed by a clear consensus definition meaningful to a large number of clinicians treating children with MCAD deficiency.

Metabolic centres with both paper-based charts and electronic health records participated in the initial cohort study, with some having referenced both formats of the chart concurrently and others having transitioned to their electronic system during the latter period of the clinic visit eligibility. It was not possible to formally examine whether the quality of chart data differed based on the format of the chart. Anecdotally, however, we anticipate that differences between centres in the quality of data and reporting were not dependent on the format of the chart due to the way that clinical data are currently captured. In order for electronic health records to resolve and/or improve upon the data quality issues identified relative to paper-based methods, platforms would need to be integrated across the health care system and incorporate standardized fields.

Limitations

We capitalized on the availability of existing cohort data abstracted from clinical charts to evaluate reporting of core outcomes for pediatric MCAD deficiency. However, because the cohort study was not specifically designed to collect our core outcome set, it is possible that we underestimated the extent to which the information required to document core outcomes was present in patients' original charts (as compared to the cohort database variables that were extracted from those charts). Therefore, a health event or variable that was indicative of a particular outcome may be inadequate or unavailable in the longitudinal database simply because the definitions and measurement criteria for that outcome were selected *a posteriori* relative to the cohort data collection. A further limitation to our study is the limited data available for older children. Data on older age groups were populated mainly by children with longer follow-up and born in earlier years by nature of the data collection period relative to the years of birth included in this study. Finally, clinicians relied solely on abstracted data items to evaluate the incidence of metabolic decompensations, and did not have access to the child's medical history, which may have influenced their clinical judgement and their ability to identify incident episodes.

Conclusions

Based on visit frequency, opportunities to record core outcomes at the metabolic clinic occur at least annually for children with MCAD deficiency. Our findings suggest that methods to comprehensively identify all emergency department visits are needed, particularly for services occurring at institutions other than the institution where the specialist metabolic clinic is located. Improved reporting standards are needed to promote consistent documentation of recommended fasting duration at each visit, which is required to capture important variation in response to interventions. The clinical criteria used to identify an episode of metabolic decompensation should

be explicitly defined such that they can be operationalized to reduce substantial heterogeneity across treatment centres. Understanding issues pertaining to the quality of data available in metabolic charts and their suitability for the future measurement of core outcomes can inform steps required to improve and enhance the methods used to collect them as outcomes in future observational studies and clinical trials. Addressing the identified issues by enhancing clinical data for research purposes or employing alternative data collection procedures to yield sustainable and reliable data, collected longitudinally as part of a high-quality disease registry, could mitigate challenges in generating sound evidence to inform care for children with MCAD deficiency.

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Supplementary Information

Additional file 1. Rates of follow-up visits to the metabolic clinic stratified by treatment centres

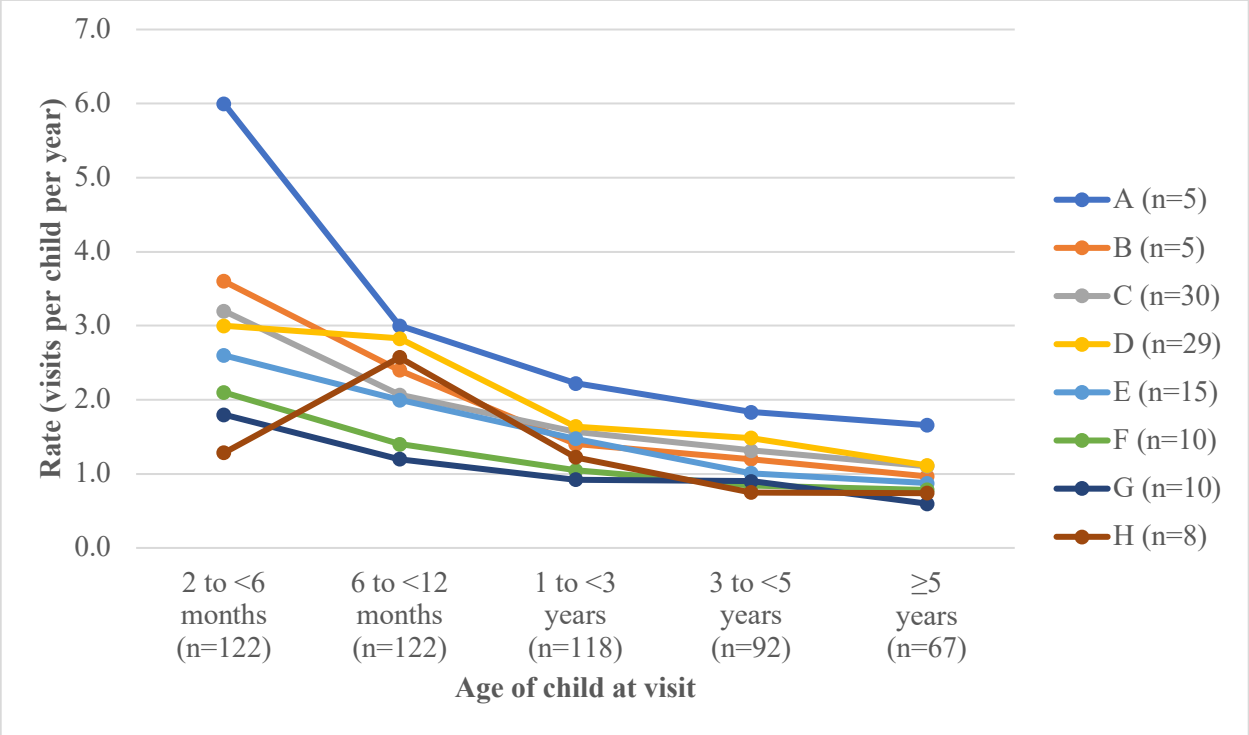

Figure S1. Rates of follow-up visits to the metabolic clinic stratified by treatment centres (A-H)

* One child may contribute to multiple age groups due to longitudinal follow-up
* Only includes centres treating 5 or more children

Additional file 2. Rates of follow-up visits to the metabolic clinic stratified by treatment centres

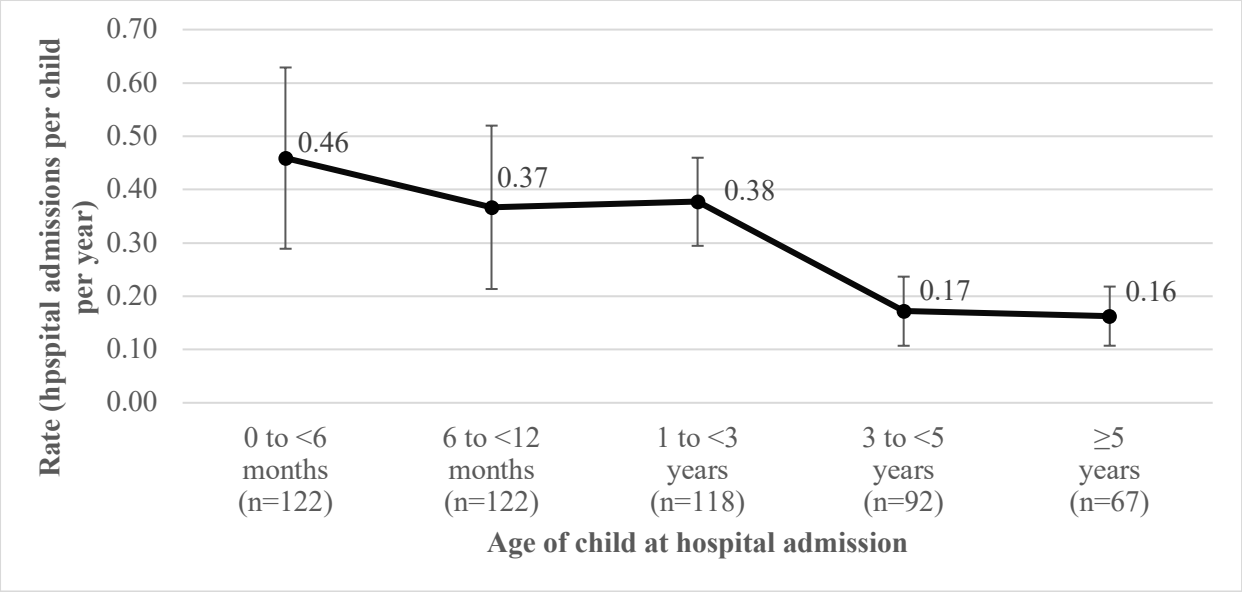

Figure S2. Rates of inpatient hospitalizations according to the age at the visit

* Error bars representing 95% confidence intervals using the normal approximation to the Poisson distribution
* One child may contribute to multiple age groups due to longitudinal follow-up

INTERFACE

The following article, titled "*Disease severity, age, and distance to care in association with emergency department use among children with pediatric medium-chain acyl-CoA dehydrogenase (MCAD) deficiency*", presents a secondary data analysis for objective 2 of this thesis, which sought to explore how one core outcome of interest, emergency department use, varies according to characteristics of children with MCAD deficiency: age, disease severity, and travel time to the primary metabolic centre's emergency department. We first established a study-specific definition of disease severity based on two commonly measured proxy indicators in the neonatal period and implemented this definition in the model of emergency department use. The existing cohort's data collection was approved by the Children's Hospital of Eastern Ontario Research Ethics Board and the Ottawa Health Science Network Research Ethics Board. It also received approval from each metabolic centre from which children in this sample seek care. This article is formatted for submission to the *Journal of Inherited Metabolic Disease*, with additional details provided in the methods section for this version which exceeds the word limit imposed by the journal.

Author contributions: RI and BKP conceived of the study idea. RI, BKP, PC, and MT planned the methodology. RI conducted data analyses and drafted the manuscript. All authors assisted with the interpretation of data and results, and provided feedback and made major revisions to the final manuscript.

Chapter 3 – Disease severity, age, and distance to care in association with emergency department use among children with pediatric medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

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Abstract

Background: Children with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency are at risk for metabolic decompensation precipitated by catabolic stress. Identifying factors associated with emergency department (ED) use in this population may clarify characteristics of children at highest risk. We explored variation in ED use according to the age of the child, the severity of the disease, and the travel time to the primary metabolic clinic's ED.

Methods: We developed a definition of disease severity using molecular genotype and newborn screening octanoylcarnitine (C8) concentration for 124 children with MCAD deficiency in a Canadian retrospective cohort study. We described age-specific ED visit rates stratified by disease severity and travel time to the metabolic clinic. We investigated associations between these characteristics and ED visits using negative binomial regression.

Results: Sixty-five children (59.6%) had severe, 16 (14.7%) had intermediate, and 28 (25.7%) had mild MCAD deficiency, respectively. The highest rates of ED use were found in children aged 6 to 12 months (adjusted incidence rate ratio [aIRR]=2.64 (1.64-4.25) compared to ≥5 years), with severe disease (aIRR=1.75 (1.19-2.56) compared to mild disease), and with the shortest travel time to the primary metabolic clinic's ED (aIRR=1.76 (1.25-2.46) compared to the longest time).

Conclusion: Children with MCAD deficiency were at highest risk to present for urgent care for intercurrent illnesses from 6 to 12 months of age. Children with severe genotypes, especially when accompanied by relatively elevated newborn screening C8 levels, required closest monitoring. Possible barriers to accessing ED care for children in rural areas should be explored.

(250/250 words)

Take-home message: Rates of emergency department use in children with MCAD deficiency were associated with patient age, disease severity defined by merging two proxy indicators, and the distance required to travel to the primary metabolic centre's emergency department.

Keywords: MCAD deficiency; severity; emergency department use

Introduction

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency has a birth prevalence of approximately 1 in 12,000 in Canada,[1] and causes impaired beta-oxidation of fatty acids for ketone body production. Individuals with MCAD deficiency are therefore at risk of metabolic decompensation and life-threatening complications during periods of catabolic stress (e.g., due to prolonged fasting, especially in the context of febrile illness or sustained high energy demands), particularly during infancy.[2,3] Treatment focused on avoidance of fasting and maintenance of euglycemia during intercurrent illnesses or unavoidable fasting has led to favourable long-term outcomes. This, along with the recognition that the initial symptomatic presentation is associated with a high risk of mortality or significant morbidity, underscores the importance of early detection.[4] In fact, the widespread implementation of population-wide newborn screening (NBS) has prevented the majority of fatal crises, but has also revealed a wider spectrum of underlying pathogenic mutations and a larger proportion of children at lower risk of metabolic decompensation.[4–7]

The *ACADM* gene codes the MCAD enzyme.[8] Homozygosity of the predominant missense mutation, c.985A>G, is found in approximately half of children in screened cohorts,[4,9,10] and leads to extremely low residual enzyme activity.[11] The incomplete oxidation of medium-chain fatty acids in patients with MCAD deficiency causes an accumulation of acylcarnitines species, particularly octanoylcarnitine (C8), reflected in blood.[8,12,13] The extent to which newborn screening C8 concentrations are elevated may in turn reflect the level of metabolic dysfunction, with increased rates of disease-related symptoms observed throughout childhood among neonates with relatively high levels.[14,15] There is an imperfect relationship between genotype, biochemical phenotype, and the overall clinical trajectory in MCAD deficiency; acute manifestations have been observed

regardless of predicted severity.[14] Genotypes associated with higher predicted severity and markedly elevated C8 concentrations have been independently associated with symptoms in the neonatal period and may highlight heightened vulnerability.[14,15]

Given that children with MCAD deficiency who experience metabolic decompensation or are at acute risk of a decompensation are typically managed initially in the emergency department (ED), ED use is a high priority outcome in this population, further evidenced by its inclusion in a recently developed core outcome set for MCAD deficiency.[16,17] It is known that children with MCAD deficiency and other fatty acid oxidation disorders are more frequent users of the ED compared to the general population,[18] and relative to children with other inherited metabolic diseases.[19,20] To our knowledge, no studies have investigated an association between characteristics of children with MCAD deficiency and the frequency of ED visits. Identifying factors associated with ED use within this population can provide insight into those at most risk or at highest perceived risk for developing adverse outcomes.

The objectives of this study were two-fold. First, we sought to develop and implement a proxy definition of disease severity for MCAD deficiency using a combination of molecular genotype and NBS C8 concentration. Second, we aimed to describe and to identify variation in ED use for Canadian children diagnosed with MCAD deficiency based on their age, severity of their disease, and travel distance to the ED.

Methods

Data source

This study involved a secondary analysis of longitudinal data from an established retrospective multi-centre cohort study of children diagnosed with MCAD deficiency who were born between January 1, 2006 and December 31, 2015, and followed by one of 13 participating Canadian pediatric metabolic treatment centres between birth and the study end date of March 31, 2017.[21] The cohort study achieved a participation rate of 74% based on eligible children diagnosed with one of 31 inherited metabolic diseases. Briefly, beginning in 2014, clinical information was retrospectively abstracted from medical charts of all cohort participants with parental consent for all clinic visits from birth (or the earliest age of available data) until the study end date (or earlier if the participant was lost to follow-up), and stored in a central database in Research Electronic Data Capture (REDCap), a web-based, secure platform.[21,22] Baseline data included child demographics, household characteristics, ascertainment methods and diagnostic tests, and preliminary treatment. The results of follow-up tests, disease-specific outcomes, treatments, co-morbidities, and other clinical descriptors were collected longitudinally from chart entries for each metabolic clinic visit. Each participant's full dataset was verified by a central research team.[21] Ethics approval for the cohort study was obtained from the CHEO Research Institute, the Ottawa Health Science Network Research Ethics Board, and all participating metabolic centres.

Eligibility for secondary analysis

Follow-up intervals among participants in the original cohort study corresponded to the dates of metabolic clinic visits, which were associated with medical chart entries. The analytic sample for this study excluded children without any reported clinic visits after initial enrollment.

The follow-up period began at birth (or upon joining a participating clinic during the study period) and ended at the study end date (or earlier if lost to follow-up). Children were considered lost to follow-up if they moved from a participating centre, refused additional follow-up, or were deceased during follow-up. Additionally, children with incomplete data entry at the time of analysis were followed until the end of the oldest age group to which they were known to be followed for a complete period.

Key variables

ED visits

The primary outcome for this study was ED use, defined as the number of, and reasons prompting, ED visits at the hospital over time.[17] Details about ED visits, including the number of new ED visits since the last metabolic clinic visit as well as their dates and reasons, were recorded at each metabolic clinic visit.

Age

For children with MCAD deficiency, the higher risk periods for disease manifestations may depend on age-related biological and environmental factors. Therefore, we described ED use according to 6-month age intervals within the first year of life, followed by bi-annual intervals thereafter. The exact age of the child was calculated from the date of the visit and the child's birth date. For visits with an unknown date, we approximated an age range since the ED visit occurred between two metabolic clinic visits at known ages.

MCAD deficiency disease severity: molecular genotype and NBS C8 concentration

For participants with molecular genetic testing results, we adapted a classification scheme proposed by Bentler et al. (2016), and individual allele variants were categorized into four groups (A-D) based on the severity described by published literature of mutations (Box 1).[15] These classifications were used to describe the complete allelic pair (severe, mild, or unknown). If the results of molecular genetic testing were missing for a member of a sibling group, that child was assigned the same confirmed genotype as their full sibling.

Box 1. MCAD deficiency genotype severity classifications based on both alleles

Individual variants:

- *Type A* (c.985A>G)
- *Type B* (has been associated with severe acylcarnitine profile, clinical presentation or impairment of MCAD enzyme activity; *ACADM* deletions)
- *Type C* (has been associated with mild acylcarnitine profile, clinical presentation or impairment MCAD enzyme activity)
- *Type D* (insufficient evidence to classify into former categories; unidentified mutations)

Severe genotype:

- *Group AA* (homozygous for c.985A>G)
- *Group AB* (compound heterozygous for c.985A>G and a second severe mutation)
- *Group BB* (two severe mutations other than c.985A>G)

Mild genotype:

- *Group AC* (compound heterozygous for c.985A>G and a second mild mutation)

- *Group BC* (one severe mutation other than c.985A>G and a second mild mutation)
- *Group CC* (two mild mutations)

Genotype of unknown severity:

- *Group AD* (c.985A>G and a second mutation of unknown severity)
- *Group BD* (one severe mutation other than c.985A>G and a second unknown mutation)
- *Group DD* (two unknown mutations)

Second, we complemented this severity classification with an additional proxy indicator of severity based on biochemical phenotype, operationalized as quartiles of NBS C8 levels within the sample. If not reported, we used the first confirmatory diagnostic C8 value measured within the neonatal period (defined as the first 21 days of life). From this, disease severity was assigned based on a combination of both indicators (Table 1).

Table 1. Summary of MCAD deficiency severity classifications based on the combination of proxy indicators

<table>
<tr><th rowspan="2">C8 Quartile
(μmol/L)</th><th colspan="3">Genotype Severity</th></tr>
<tr><th>Mild
(AC)</th><th>Unknown
(AD, BD, DD)</th><th>Severe
(AA, AB, BB)</th></tr>
<tr><td>Mild (lowest 25%)
<2.42</td><td rowspan="2">Mild</td><td>Mild</td><td>Intermediate</td></tr>
<tr><td>Intermediate (IQR)
2.42-15.28</td><td>Intermediate</td><td rowspan="2">Severe</td></tr>
<tr><td>Severe (highest 25%)
≥15.29</td><td>Intermediate</td><td>Severe</td></tr>
</table>

† Quartiles of C8 concentrations are based on NBS results from the CIMDRN sample of eligible participants

Travel time to primary metabolic care centre

Our previous study found that ED visits occurring at community hospitals (hospitals other than the one where the metabolic clinic is located) may not be captured in the metabolic clinic chart (see Chapter 2). In addition, it is possible that travel time or distance to care may influence decision-making of families regarding whether to seek emergency care, particularly when a child is ill but there is uncertainty about need for ED interventions; or may influence families' abilities to access ED care. Therefore, we hypothesized that ED visits in this sample may be influenced by the travel time to the metabolic centre, either due to data artefact (missing ED visits from other hospitals) or differences in actual ED use (care-seeking or access to care).

We estimated the time required to travel by vehicle in minutes from the geometric centroid of a child's forward sortation area (FSA, as reflected in the first three digits of the postal code of the participant's mailing address) to the primary metabolic centre, using the geographic information system (GIS) software, ArcGIS. Children were classified into one of three categories based on the travel times from their area of primary residence to the metabolic clinic: less than 30 minutes, 30 minutes up to 60 minutes, or 60 or more minutes. We assumed that children requiring alternative modes of travel (e.g., flight) resided outside of catchment areas at each time cut point (i.e., 60 or more minutes from the metabolic clinic). We validated our findings using self-reported data from a survey conducted as part of the initial cohort study, which directly asked families of a subset of cohort participants to report travel time to care.

Data analysis

We described the distributions of participants across demographic and clinical characteristics using frequencies and percentages. To explore how the frequency of ED visits

varied according to factors of interest, we expressed observed age-specific rates per child per year with 95% confidence intervals using the exact Poisson distribution, overall and stratified by predicted severity of MCAD deficiency and travel distance to the metabolic clinic. We also described the most common reasons reported for seeking emergency care, organized according to similar diagnostic categories and their potential applicability to MCAD deficiency.

To examine the independent associations of child age, disease severity, and travel time to the metabolic clinic in association with rates of ED visits over time for children with MCAD deficiency, we used a multivariable generalized estimating equation (GEE) model with a negative binomial distribution and log link function. The model was used to obtain adjusted incidence rate ratios (aIRR) with 95% confidence intervals. We used an unstructured working correlation to accommodate correlations in repeated measures. Since disease severity and distance to care were missing for 12.1% and 2.4% of eligible participants, respectively, we used multiple imputation to create 15 completed datasets for analysis. We used the method of fully conditional specification (FCS) and specified a cumulative logit model to impute the two ordered categorical variables. The imputation model included all of the variables of interest in the analysis including the dependent variable, and the interaction term for the sensitivity analysis. SAS 9.4 (SAS Institute, Cary, North Carolina, USA) software was used for all statistical analyses, with statistical significance defined as $\alpha < 0.05$.

Sensitivity analysis

First, we conducted a complete case analysis. Second, we restricted ED visits to only those with reasons deemed relevant to MCAD deficiency, either by nature of the reasons in relation to the disease itself or because the visit reasons were of particular concern based on the child having

this disease. This judgement was made by a pediatric metabolic physician (PC) prior to conducting the primary regression analysis. This restricted analysis was conducted since ED visits for disease-specific manifestations were deemed most likely to be captured by the metabolic chart data regardless of where the visit occurred. Third, disease severity could not be measured for children without a C8 level recorded in the first 21 days of life. As a result, we alternatively defined disease severity using only molecular genotype in order to explore whether its derivation using only one proxy indicator yielded similar results with respect to the association with ED visits. Fourth, we investigated the possibility of a statistical interaction between the age of the child at the visit and disease severity in association with rates of ED use. For this analysis, we collapsed the oldest three age groups due to sample size limitations; children with intermediate MCAD deficiency represented a small and highly heterogeneous group with few events during older age groups, and our model with five age groups could not support this interaction analysis.

Results

Study population

The median follow-up time was 5.2 years (IQR=3.0-8.4 years) among 124 eligible children with at least one follow-up visit recorded, with 91% followed for the entirety of their eligibility period. All eligible birth years were represented, with the highest proportion of children born towards the end of this period (25% 2014-2015, Table 2). The majority of participants were male (56.5%). Each participating centre reported following at least one eligible child diagnosed with MCAD deficiency, but children from BC Children's Hospital (23.4%) and the Hospital for Sick Children (24.2%) made up nearly half of the sample. Almost every child was identified primarily by NBS, although sometimes combined with other methods (Table 2).

Table 2. Demographic and clinical characteristics (n=124)

Demographic characteristics	**Frequency (%)**
Year of birth	
2006-2007	20 (16.1)
2008-2009	27 (21.8)
2010-2011	18 (14.5)
2012-2013	28 (22.6)
2014-2015	31 (25.0)
Sex (female)	54 (43.5)
Sibling with MCAD deficiency participating in this cohort (yes)	19 (15.3)
Participating treatment centre	
BC Children's Hospital - Vancouver, BC	29 (23.4)
Alberta Children's Hospital - Calgary, AB	10 (8.1)
London Health Sciences Centre - London, ON	10 (8.1)
Hamilton Health Sciences Centre - Hamilton, ON	15 (12.1)
Hospital for Sick Children - Toronto, ON	30 (24.2)
Kingston General Hospital - Kingston, ON	5 (4.0)
Children's Hospital of Eastern Ontario - Ottawa, ON	8 (6.5)
Other participating centre[b]	17 (13.7)
Travel time to the participating treatment centre (n=121)	
< 30 minutes	25 (20.7)
30 to < 60 minutes	23 (19.0)
≥ 60 minutes	73 (60.3)
Clinical characteristics	**Frequency (%)**
Neonatal complications (yes) (n=104)	32 (30.8)

Ascertainment[c]	
NBS method only	107 (86.3)
NBS method and other method(s)	>10
Other method(s) only	<5
Genotype (n=113)	
Homozygous c.985A>G (c.985A>G / c.985A>G)	52 (46.0)
Compound heterozygous c.985A>G (c.985A>G / non-c.985A>G)	46 (40.7)
Other (non-c.985A>G / non-c.985A>G)	15 (13.3)
Newborn screening C8 concentration (n=111)	**Median (range)**
Quartile 1 (< 2.4 μmol/L)	1.1 (0.5-2.3)
Quartile 2 (2.4 to < 9.8 μmol/L)	5.1 (2.4-9.1)
Quartile 3 (9.8 to < 15.3 μmol/L)	13.4 (9.8-15.2)
Quartile 4 (≥ 15.3 μmol/L)	23.3 (15.3-39.7)
Disease severity (n=109)	
Severe	65 (59.6)
Intermediate	16 (14.7)
Mild	28 (25.7)

[a] Represents members of one of nine sibling groups in this cohort
[b] Other participating centres (each with fewer than 5 enrolled children) include Stollery Children's Hospital, Winnipeg Health Sciences Centre, Montreal Children's Hospital, CHU Sherbrooke, Izaak Walton Killam Health Centre and Janeway Children's Health Centre.
† Measures representing fewer than five children are not presented to avoid identifying participants
‡ Valid percentages are presented

For 113 children with molecular genetic testing (inferred for 6 siblings), the most common variant type was a point mutation and the most common mutations were c.985A>G followed by c.199T>C, representing allelic frequencies of 67.6% and 3.6% of all reported alleles, respectively. Sixty-nine children had a known severe genotype (75% of which were homozygous for

c.985A>G), 15 children had a known mild genotype (53% of which were compound heterozygous for c.985A>G accompanied by a c.199T>C mutation), and 29 children had a genotype for which the severity could not be determined based on published literature ("unknown severity"). Individual mutations and their respective severity classifications for children with MCAD deficiency in the cohort are presented in Appendix S1.

The median NBS C8 concentration was 9.8 μmol/L (IQR=2.4-15.3 μmol/L). For children with molecular genetic testing, the median C8 level was highest for those with a severe genotype (13.7 μmol/L), followed by those with a genotype of unknown severity (2.7 μmol/L), and lowest for those with a mild genotype (1.8 μmol/L) (Appendix S2). There were 109 children with complete data on both proxy indicators of disease severity. Of this group, the majority were children with severe MCAD deficiency (n=65, 59.6%). Disease severity could not be ascertained for 15 children because they were missing at least one of the two indicators (i.e., the results of molecular genetic testing, and/or a C8 level measured within the first 21 days of life).

Based on the approximated GIS measure for travel time estimated for 121 children, the median travel time to care was 67 minutes (IQR=21-147 minutes). One centre treating fewer than 5 children did not provide geographic information for participants. For 44 children with MCAD deficiency whose families previously reported their travel time (in categories) to the metabolic clinic as part of a survey, a validation demonstrated close correspondence between our estimated measure and the survey, with mostly slight underestimation in a few cases compared to parent-reported measures (Appendix S3).

Observed rates of ED use

There were a total of 389 ED visits recorded during the study period. For 32 visits reported without dates, the exact age group during which they occurred could not be determined and these visits were excluded for the purpose of calculating age-specific rates.

On average, there were 0.55 visits per child per year (95% CI 0.50-0.61) overall. The highest rate of ED use was among children between 6 and 12 months of age (0.77 visits per child per year, 95% CI 0.57-1.02), followed by children below 6 months of age (0.67 visits per child per year, 95% CI 0.49-0.91) and between 1 and 3 years of age (0.67 visits per child per year, 95% CI 0.67-0.79), with a decreasing trend thereafter among children aged 3 to 5 years (0.35 visits per child per year, 95% CI 0.27-0.46) and children 5 years and older (0.32 visits per child per year, 95% CI 0.25-0.41). Approximately one-third of all ED visits among children with MCAD deficiency had documented reasons related to vomiting, nausea, or abdominal pain. Other commonly reported reasons for emergency visits were related to respiratory tract infections and their associated symptoms (86 visits, 22.1%), fever (66 visits, 17.0%), viral illnesses and gastroenteritis (66 visits, 17.0%), poor feeding (57 visits, 14.7%), and diarrhea or constipation (39 visits, 10.0%) (Table 3).

Table 3. Number of ED visits reporting specific reasons prompting the visit, according to whether or not they were relevant to an MCAD deficiency diagnosis

Reason deemed relevant to MCAD deficiency[a]	**Number of visits (%)**
Emesis, nausea, and/or abdominal pain	131 (33.6)
Respiratory infection and associated symptoms (colds, runny nose)	86 (22.1)
Febrile illness	66 (17.0)
Viral illness and gastroenteritis	66 (17.0)
Poor feeding and oral intake (including dehydration)	57 (14.7)

Diarrhea, constipation	39 (10.0)
Ear or eye infection	15 (3.9)
Hypoglycemia or related issues (e.g., IV fluids, +NBS result)	15 (3.9)
Lethargy or hypoactivity	14 (3.6)
Myoclonic movement, seizures	6 (1.5)
Urinary tract infection	6 (1.5)
Reasons deemed likely unrelated to MCAD deficiency	**Number of visits (%)**
Physical injury or insult	11 (2.8)
Asthma or respiratory distress	6 (1.5)
Dermatological conditions	<5 (<1.3)
Allergy	<5 (<1.3)
Chest pain	<5 (<1.3)
Miscellaneous or unknown	7 (1.8)

† The sum of the total number of visits does not equal 389 since a single visit can be prompted by multiple reasons
‡ Measures representing fewer than five children are not presented to avoid identifying participants
[a] Reason for visit was deemed relevant to MCAD deficiency if the reason was directly related to the disease or was concerning based on the child's diagnosis of the disease

Observed rates of ED use within subgroups of interest

MCAD deficiency disease severity

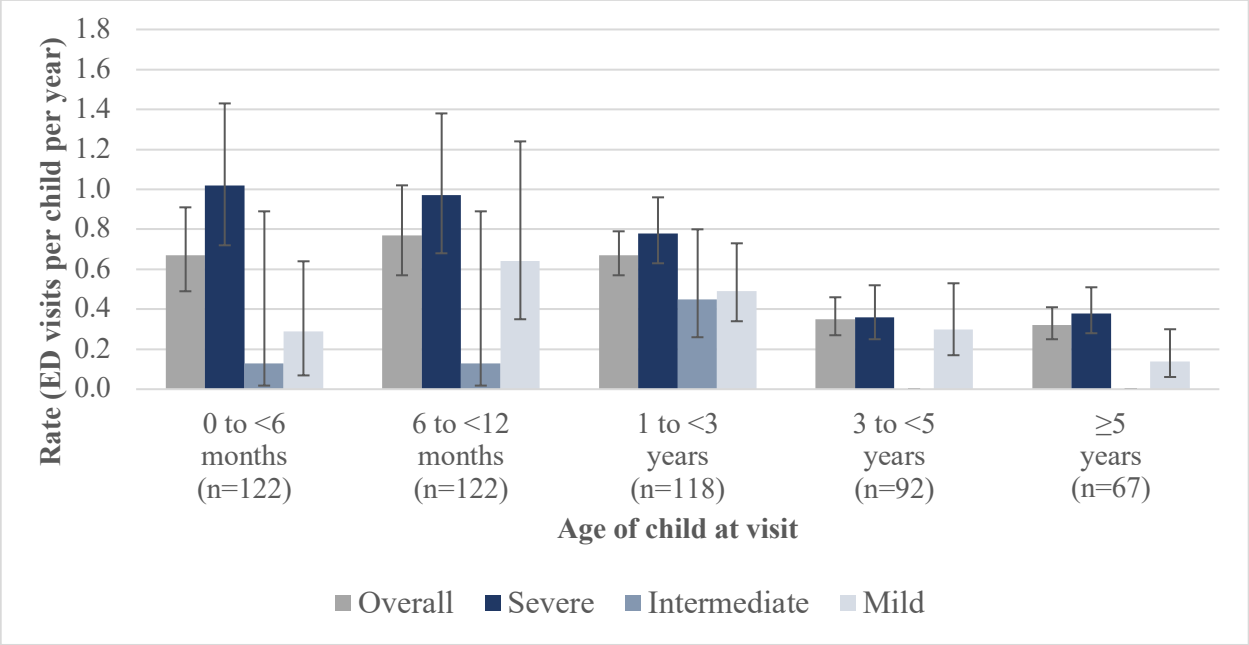

Figure 1. Observed rates of ED visits according to age overall (n=124), and stratified by severe (n=65), intermediate (n=16), and mild (n=28) disease severity

* Error bars represent 95% confidence intervals using the exact Poisson distribution
* One child may contribute to multiple age groups due to longitudinal follow-up
* The sum of the participants contributing to each stratified category does not add to 124 participants overall due to missing data and differential lengths of follow-up

On average, children with severe MCAD deficiency had the highest observed frequency of ED use during all age groups relative to children with disease of intermediate and mild severity (Figure 1). The largest differences in rates by disease severity were apparent during the youngest age groups, with a pattern of increasing convergence between severity groups with increasing age. Less intuitively, children with intermediate MCAD deficiency had lower rates of ED use than those with mild disease, with 0.13 visits per child per year (95% CI 0.02-0.89) in the first year of life and 0.45 visits per child per year (95% CI 0.26-0.80) from 1 year up to 3 years. There were no

events among children with intermediate disease severity after 3 years of age, but this group was comprised of only 16 children overall, and only 10 of these children contributed data after 3 years of age.

Travel time to primary metabolic care centre

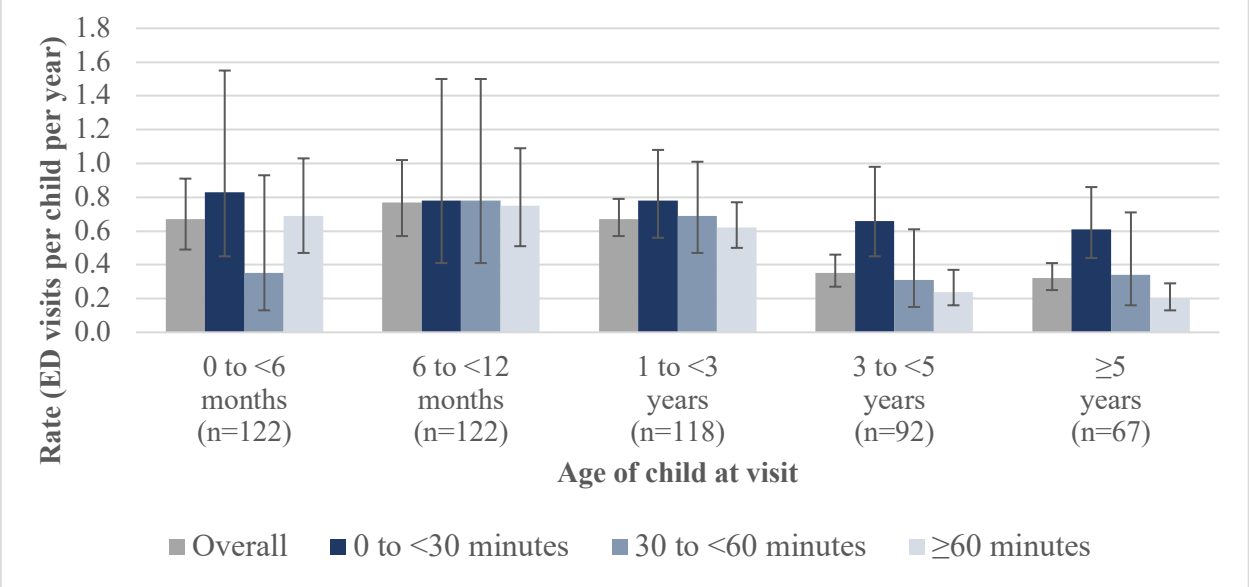

Figure 2. Observed rates of ED visits according to age overall (n=124), and stratified by 0 to <30 minutes (n=25), 30 to <60 minutes (n=23), and ≥60 minutes (n=73) driving distance to the metabolic centre

* Error bars represent 95% confidence intervals using the exact Poisson distribution
* One child may contribute to multiple age groups due to longitudinal follow-up
* The sum of the participants contributing to each stratified category does not add to 124 participants overall due to missing data and differential lengths of follow-up

With respect to rates of ED use stratified by driving time to care, the highest rates in all age groups, except 6 to 12 months of age, were observed among children who lived fewer than 30 minutes from their primary metabolic centre and associated ED (Figure 2). However, the trend toward longer driving time being associated with lower rates of ED use was not consistent across all age groups and distances. For example, before 6 months of age, children who lived from 30

minutes up to 60 minutes from the clinic experienced a lower rate of emergency care compared with children who lived 60 or more minutes away (0.35 visits per child per year [95% CI 0.13-0.93] vs. 0.69 visits per child per year [95% CI 0.47-1.03]).

Multivariable regression analysis of factors associated with ED use

Table 4. Unadjusted and adjusted incidence rate ratios of ED visits according to child characteristics (n=124)

Characteristic	Unadjusted incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)[a]
Age at visit		
0 to < 6 months	**2.09 (1.28-3.39)**	**2.23 (1.37-3.62)**
6 to < 12 months	**2.38 (1.48-3.83)**	**2.64 (1.64-4.25)**
1 to < 3 years	**2.04 (1.35-3.10)**	**2.35 (1.56-3.54)**
3 to < 5 years	1.08 (0.67-1.73)	1.15 (0.72-1.83)
≥ 5 years	Reference	Reference
Disease severity		
Severe	**1.66 (1.10-2.51)**	**1.75 (1.19-2.56)**
Intermediate	0.61 (0.27-1.37)	0.62 (0.29-1.32)
Mild	Reference	Reference
Distance to care		
0 to < 30 minutes	**1.53 (1.09-2.16)**	**1.76 (1.25-2.46)**
30 to < 60 minutes	1.13 (0.75-1.69)	1.19 (0.80-1.77)
≥ 60 minutes	Reference	Reference

***** 349 ED visits included in this analysis

***** Unadjusted and adjusted measures estimated using GEE specifying a negative binomial distribution and the multiple imputation completed dataset

[a] Adjusted for age at visit, disease severity, and distance to care

The adjusted incidence rate ratios (aIRR) were mostly consistent with unadjusted measures (Table 4). Relative to children 5 years of age and older, the rate of ED use was significantly higher among children under 3 years of age: 0 to <6 months (aIRR: 2.23, 95% CI 1.37-3.62), 6 to <12 months (aIRR: 2.64, 95% CI 1.64-4.25), and 1 to <3 years (aIRR: 2.35, 95% CI 1.56-3.54). Children aged 3 up to 5 years of age did not have a significantly higher rate of use relative to children 5 years of age and older (aIRR: 1.15, 95% CI 0.72-1.83). For children with severe MCAD deficiency, as defined by their genotype and NBS C8 concentration, rates of ED use were 75% higher (aIRR: 1.75, 95% CI 1.19-2.56) on average compared to children with mild MCAD deficiency, regardless of age, equating to approximately 0.25 additional visits per child per year on an absolute scale. There was not a significant difference in ED visit rates between children with intermediate MCAD deficiency and those with mild MCAD deficiency (aIRR: 0.62, 95% CI 0.29-1.32). Children who lived fewer than 30 minutes from their participating metabolic centre had a significantly higher rate of visits compared to those living 60 or more minutes away (aIRR: 1.76, 95% CI 1.25-2.46), experiencing approximately 0.21 additional visits per child per year. Those living 30 minutes up to 60 minutes away did not experience a statistically significant difference in visits rates relative to those living more than 60 minutes away (aIRR: 1.19, 95% CI 0.80-1.77).

Sensitivity analysis

First, a complete case analysis is presented in Appendix S4. The only substantive difference in findings was that in the complete case analysis, children who lived fewer than 30 minutes from their participating metabolic centre did not have a significantly higher rate of ED visits compared to those living 60 or more minutes away, with an aIRR that was attenuated although in the same direction (aIRR: 1.43, 95% CI 0.98-2.07). Second, 24 ED visits were excluded from the initial model which were deemed to be likely unrelated to MCAD deficiency; these visits were prompted

by one or more of a physical injury or insult, asthma or respiratory distress, a dermatological condition, allergy, chest pain, or miscellaneous and unknown (Table 3). The changes in point estimates with removal of these visits were small and the conclusions from the main analyses remain unchanged (Appendix S5). Third, disease severity was defined using only molecular genotype (Box 1). Severe genotype alone was not associated with statistically significantly higher rates of ED visits relative to children with mild genotypes; however, those with unknown genotypes had significantly lower rates of ED visits compared to those with mild genotypes (Appendix S6). Fourth, the last three age groups (1 to <3 years, 3 to <5 years, and ≥5 years) were collapsed into one age category to support the inclusion of an interaction term between age and disease severity. Although some convergence across severity categories in rates was observed descriptively with increasing age, the difference in rates between severity groups was not significantly different across the re-categorized age variable (p=0.089) (Appendix S7). Before 6 months of age, children with severe MCAD deficiency had visit rates 4.79 (95% CI 1.40-16.39) times higher, on average, compared to children with mild MCAD deficiency. These measures had high degrees of uncertainty, and as a result, all other age-specific incidence rate ratios examining differences on a relative scale between severity groups were not statistically significant.

Discussion

According to our study-specific definition of disease severity based on molecular genotype and newborn screening C8 concentration, the majority of children in this cohort had severe MCAD deficiency, followed by intermediate and mild MCAD deficiency, respectively. We found that children aged 6 to 12 months, with severe disease, and with the shortest travel time to the primary metabolic clinic's ED had higher ED visits, potentially indicating that these characteristics were associated with a higher risk of developing illness requiring emergency care.

Following other screened cohorts of children with MCAD deficiency identified mainly by NBS,[5,9,10,23,24] we identified a lower proportion of children homozygous for the common c.985A>G pathogenic variant (46% of our sample) relative to non-screened cohorts and a relatively larger spectrum of children with both c.985A>G compound heterozygous genotypes and other combinations of disease-causing mutations.[25] We found a median C8 level of 9.8 μmol/L in our sample, but children with a severe genotype had the highest median C8 levels and the majority of this group were homozygous for c.985A>G. Lower median C8 levels were found for children with genotypes of unknown severity and mild genotypes, respectively. These findings are consistent with evidence suggesting children who are homozygous for c.985A>G have higher C8 blood concentrations relative to other children.[9,15,26,27]

Previous studies have predicted disease severity for children diagnosed with MCAD deficiency based on existing literature or based on primary data collection (e.g., enzyme assay analysis) as an initial step toward risk stratifying individual patients.[15,28,29] Ideally, a gold standard measure of MCAD deficiency disease severity would predict the risk of adverse outcomes such as metabolic decompensation, but actual decompensations are fortunately rare in individuals with MCAD deficiency who receive preventive interventions. From our definition of combined disease severity based on independently assessing molecular genotype and biochemical phenotype, we found that 59.6% of children in our cohort had severe MCAD deficiency, 14.7% of children had intermediate MCAD deficiency, and 25.7% had mild MCAD deficiency.

Significantly higher rates of ED visits were found among children before 3 years of age relative to children 5 years of age and older, with the highest rate of use observed for children aged 6 months up to 12 months. These findings support previous evidence examining age-specific health services use among children with MCAD deficiency,[18] with older infancy known to be a

high risk period for acute metabolic crises for children with this disease and for children with other fatty acid oxidation disorders,[30] perhaps because it coincides with many infants discontinuing exclusive breastfeeding or when recommended maximum fasting times are typically lengthened.

Children with severe MCAD deficiency were significantly more frequent users of the ED when compared to children with intermediate and mild MCAD deficiency. As expected, children with a severe form of the disease present with a higher rate of clinical symptoms that require urgent care. The observed association, however, could be influenced by the metabolic team's prior knowledge of potential indicators contributing to risk. This may influence the recommendations provided to caregivers and their subsequent decision-making when considering whether illnesses require care. Children assigned in our study to the category of intermediate MCAD disease severity experienced the lowest rates of ED visits compared to children with severe and mild MCAD deficiency. This was a relatively small group was composed almost entirely of children with at least one apparently novel *ACADM* mutation (not previously described in published literature) or unidentifiable mutation (possibly the result of single-gene testing). As a result, for the majority children with this classification, the initial NBS C8 level influenced the severity classification used. Therefore, this finding may be explained in part by the implementation of NBS, which prompted the diagnosis in children with underlying disease who may have remained asymptomatic and thus undiagnosed in the absence of screening.[9]

Children who resided closest to the metabolic centre had the highest rates of ED visits relative to children who lived at least one hour away by road travel. The exact relationship between distance to care and ED use is complicated. Since ED visits for MCAD deficiency are often preventive (to receive interventions that have the potential to prevent metabolic decompensations during at-risk periods), lower rates may reflect challenges in accessing the ED (e.g., related to

distance to care), but could be influenced by individual care-seeking behaviours, and treatment centre-specific recommendations and preferences (e.g., availability of telemedicine support). In fact, other studies have identified differences in care-seeking behaviours and pediatric ED utilization based on the proximity to the ED.[31,32] Furthermore, in addition to the possibility of a higher threshold for seeking emergency care based on the perceived barrier to accessing that care, it is known from previous analyses within this same cohort that metabolic clinic chart data may underestimate ED visits occurring at outside hospitals (assumed to be frequented most often by children who live the furthest distance from their metabolic centre's ED). Therefore, our findings may reflect the ease of accessing the metabolic clinic's ED, as well as the quality of metabolic chart data in capturing ED visits.

This study relied on comprehensive chart data assembled using high-quality collection tools designed in collaboration with clinicians involved in the management of children with MCAD deficiency. The initial cohort study accomplished a high participation rate, and employed a multi-centered approach that targeted almost all pediatric metabolic treatment centres from which the population of children with MCAD deficiency receive care in Canada.[21] However, since a large metabolic centre in Quebec did not participate in the initial cohort, it is important to acknowledge the possible under-representation of eligible children relative to the catchment area in this region and the possible implications with respect to external validity of these findings. Thus, this study would need to be replicated in the Quebec population to determine whether the findings generalize to the full population of children with MCAD deficiency in that jurisdiction. Our sample, although small, was large relative to studies in the same rare disease area. Some limitations, however, should be considered. First, in the absence of a gold standard method to classify disease severity, the criteria used by other studies varied greatly (e.g., studies measuring

residual enzyme activity, relative extent of observed clinical symptoms). Our definition, however, using the interrelation of genotype and biochemical phenotype, is corroborated by our findings and the fact children with more severe disease are expected to require heightened levels of care. Second, metabolic chart-abstracted data may not reflect all ED visits occurring at institutions outside of the primary metabolic clinic's ED; an overall underestimation of the number of visits recorded in this sample was identified by referring to age-specific rates in a similar population of children with MCAD deficiency (see Chapter 2). This phenomenon affects our ability to fully interpret some findings. For example, children living closer to the metabolic clinic may be more likely to have emergency visits recorded in the chart if those visits took place at the same institution where the metabolic clinic resides. Adjusted absolute risk differences quantifying the number of additional ED visits expected based on these characteristics were likely underestimated due to missing outcome data. Third, we considered our measure of distance to care as a time-fixed variable in our analyses. In the event that families re-located during follow-up, we computed the distance to care from the most current postal code since these data were updated throughout the duration of the initial cohort study. Any distances prior to re-location, if substantially different than present, were not considered. Finally, to our knowledge, there is an absence of literature examining the influence of possible exogenous or endogenous factors on newborn screening C8 levels beyond the actual inherited deficiency of the MCAD enzyme within the population of children with MCAD deficiency (for example, birth characteristics, type of feeding, timing of the newborn screening sample relative to newborn feeding). Although these factors could be considered and incorporated to refine the C8 measure as a predictor of true severity in future research, validation of these approaches are not yet possible since it requires a comparison to a gold standard definition of disease severity.

Identifying characteristics of children with MCAD deficiency who experience higher rates of intercurrent illness requiring emergency care, possibly placing them at higher risk or perceived risk for metabolic decompensation, is important to prevent long-term and adverse outcomes. Children with MCAD deficiency require close medical monitoring and ongoing treatment regardless of unique characteristics, but children between 6 and 12 months of age, and those with a known severe genotype coupled with a moderate to extremely elevated NBS C8 level typically require the highest level of emergency care throughout childhood. In particular, these proxy indicators of disease severity are measurable shortly after birth, making them important targets for consideration in the future development of clinical guidelines and care recommendations for patients with MCAD deficiency and their families. The role of the distance required to travel to the ED and subsequent rates of use among children with acute illnesses should be further explored and corroborated using healthcare administrative data. If children living furthest from the metabolic clinic, such as in rural areas, experience poor access to ED care and other centralized services evidenced by a lower frequency of interactions than expected, mitigating strategies should ensure that symptoms can managed remotely to avoid metabolic decompensation. Increasing our understanding of the natural history of MCAD deficiency should involve studies that closely investigate the role of novel, disease-causing mutations in the impairment of MCAD enzyme formation, the extent to which residual enzyme activity is affected, and their impact on relevant outcomes.

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Supporting information

Appendix S1

Table 5. Classification of severity assigned to individual *ACADM* alleles in the CIMDRN cohort

Severity Classification	Alleles
A	c.985A>G[120,132,133]
B	c.85C>T[120] c.157C>T[134] c.250C>T[120,134] c.347G>A[135] c.362C>T[136] c.616C>T[120] c.734C>T[136] c.799G>A[120,133] c.928G>A[136] c.1010A>C[120] c.424-426delAAG c.984delG
C	c.199T>C[57,120] c.127G>A[120,134] c.558T>A[137] c.600-18G>A[134,138] c.797A>G[134] c.820A>G[139,140]
D	c.1A>G c.134A>G c.142T>C c.216+2T>C

	c.233T>G
	c.234T>G
	c.250T>C
	c.277G>A
	c.287G>T
	c.388-5G>A
	c.395C>G
	c.433T>C
	c.443G>A
	c.503A>C
	c.551T>C
	c.604T>C
	c.617G>A
	c.622C>T
	c.688G
	c.826G>C
	c.839C>T
	c.850-2A>G
	c.860G>A
	c.883G>C
	c.890A>G
	c.1010A>G
	c.1073A>T
	c.1117G>A
	IVS8-13A>G

* These 49 unique alleles collectively make up 47 unique genotypes

Appendix S2

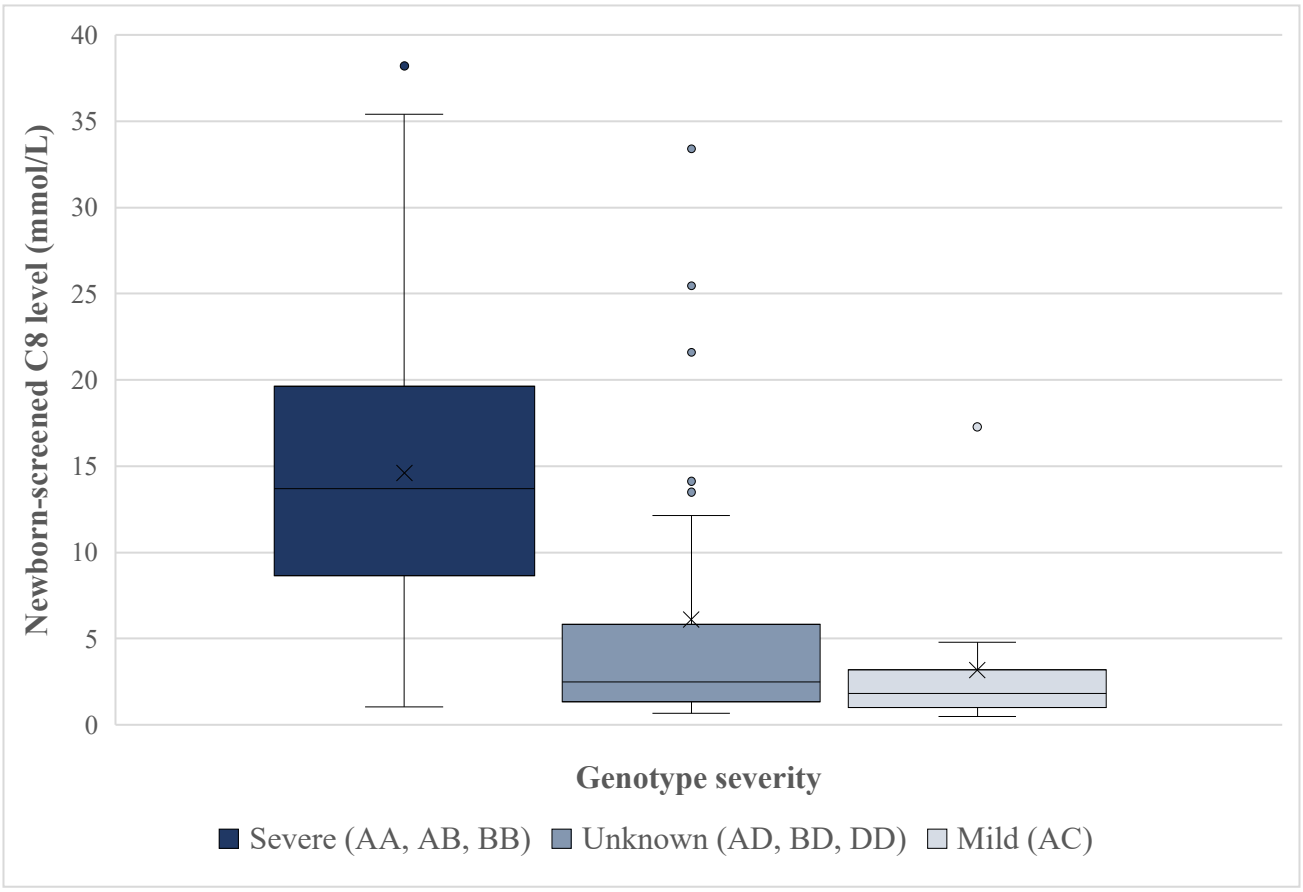

Figure 3. Newborn screening C8 level (μmol/L) according to severe (n=62), unknown (n=29), and mild (n=14) genotype severity

* Children missing results for molecular genetic testing and/or newborn screening C8 level are excluded

Appendix S3

Table 6. Validation of distances obtained from GIS based on a clinic survey of family-reported ranges of travel times to the metabolic clinic (and associated ED)

Family-reported range of time to travel to the metabolic clinic	**GIS measure (minutes)** Median (IQR)
Less than 30 minutes (n=15)	16 (9-24)
30 minutes up to 60 minutes (n=5)	36 (33-45)
60 minutes up to 120 minutes (n=14)	74 (67-82)
More than 120 minutes (n=10)	254 (214-373)

* Five GIS measures were outside of the range of family-reported travel distances, representing an average of 9 minutes per measure

Appendix S4

Table 7. Unadjusted and adjusted incidence rate ratios of ED visits according to child characteristics, using a complete case analysis (n=108)

Characteristic	Unadjusted incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)[a]
Age at visit		
0 to < 6 months	**2.19 (1.37-3.51)**	**2.54 (1.54-4.19)**
6 to < 12 months	**2.50 (1.60-3.90)**	**2.90 (1.77-4.76)**
1 to < 3 years	**2.14 (1.44-3.20)**	**2.54 (1.63-3.98)**
3 to < 5 years	1.10 (0.72-1.69)	1.12 (0.70-1.78)
≥ 5 years	Reference	Reference
Disease severity		
Severe	**1.77 (1.17-2.69)**	**1.78 (1.22-2.60)**
Intermediate	0.61 (0.32-1.17)	0.57 (0.32-1.04)
Mild	Reference	Reference
Distance to care		
0 to < 30 minutes	**1.57 (1.09-2.26)**	1.43 (0.98-2.07)
30 to < 60 minutes	1.11 (0.64-1.93)	1.07 (0.64-1.79)
≥ 60 minutes	Reference	Reference

* 349 ED visits included in this analysis
* Unadjusted and adjusted measures estimated using GEE specifying a negative binomial distribution and using casewise deletion
[a] Adjusted for age at visit, disease severity, and distance to care

Appendix S5

Table 8. Unadjusted and adjusted incidence rate ratios of ED visits according to child characteristics, with reasons only related to MCAD deficiency (n=124)

Characteristic	Unadjusted incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)[a]
Age at visit		
0 to < 6 months	**2.18 (1.33-3.56)**	**2.30 (1.40-3.77)**
6 to < 12 months	**2.50 (1.54-4.04)**	**2.76 (1.70-4.46)**
1 to < 3 years	**2.08 (1.37-3.17)**	**2.39 (1.57-3.63)**
3 to < 5 years	1.10 (0.68-1.77)	1.17 (0.73-1.87)
≥ 5 years	Reference	Reference
Disease severity		
Severe	**1.66 (1.13-2.45)**	**1.73 (1.20-2.49)**
Intermediate	0.54 (0.24-1.21)	0.55 (0.27-1.20)
Mild	Reference	Reference
Distance to care		
0 to < 30 minutes	**1.43 (1.00-2.02)**	**1.64 (1.16-2.30)**
30 to < 60 minutes	1.12 (0.74-1.68)	1.17 (0.78-1.74)
≥ 60 minutes	Reference	Reference

***** 325 ED visits included in this analysis

***** Unadjusted and adjusted measures estimated using GEE specifying a negative binomial distribution and the multiple imputation completed dataset

[a] Adjusted for age at visit, disease severity, and distance to care

Appendix S6

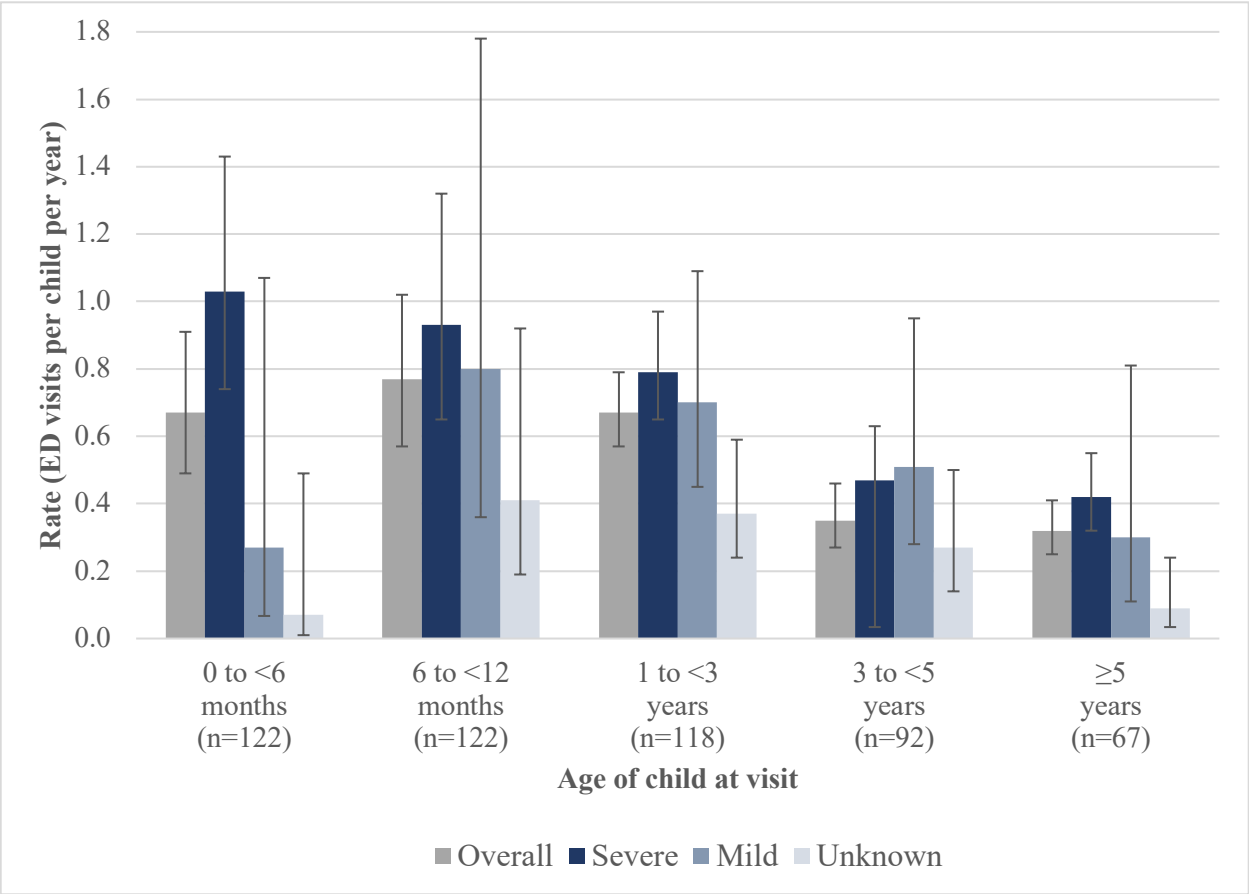

Figure 4. Rates of ED visits according to age overall (n=124), and stratified by severe (n=69), mild (n=15), and unknown (n=29) genotype severity

* Error bars represent 95% confidence intervals using the exact Poisson distribution
* One child may contribute to multiple age groups due to longitudinal follow-up
* The sum of the participants contributing to each stratified category does not add to 124 participants overall due to missing data

Table 9. Unadjusted and adjusted incidence rate ratios of ED visits according to child characteristics, using MCAD genotype severity as a proxy for overall disease severity (n=124)

Characteristic	Unadjusted incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)[a]
Age at visit		
0 to < 6 months	**2.09 (1.28-3.39)**	**2.20 (1.38-3.52)**
6 to < 12 months	**2.38 (1.48-3.83)**	**2.62 (1.66-4.12)**
1 to < 3 years	**2.04 (1.35-3.10)**	**2.31 (1.56-3.42)**
3 to < 5 years	1.08 (0.67-1.73)	1.13 (0.72-1.75)
≥ 5 years	Reference	Reference
Genotype severity		
Severe	1.22 (0.79-1.87)	1.33 (0.90-1.96)
Unknown	0.38 (0.22-0.67)	0.41 (0.24-0.70)
Mild	Reference	Reference
Distance to care		
0 to < 30 minutes	**1.53 (1.08-2.15)**	**1.62 (1.18-2.24)**
30 to < 60 minutes	1.12 (0.75-1.69)	1.38 (0.95-2.02)
≥ 60 minutes	Reference	Reference

* 349 ED visits included in this analysis
* Unadjusted and adjusted measures estimated using GEE specifying a negative binomial distribution and the multiple imputation completed dataset
[a] Adjusted for age at visit, disease severity, and distance to care

Appendix S7

Table 10. Age-stratified unadjusted and adjusted incidence rate ratios of ED visits according to MCAD disease severity (n=124)

Characteristic	Unadjusted incidence rate ratio (95% CI)	Adjusted incidence rate ratio (95% CI)[a]
Age at visit		
0 to < 6 months		
Severe	**4.55 (1.31-15.80)**	**4.79 (1.40-16.39)**
Intermediate	0.72 (0.27-1.91)	0.76 (0.30-1.92)
Mild	Reference	Reference
6 to < 12 months		
Severe	1.52 (0.74-3.13)	1.58 (0.76-3.27)
Intermediate	0.22 (0.02-2.28)	0.23 (0.02-2.36)
Mild	Reference	Reference
≥ 1 year		
Severe	1.39 (0.83-2.32)	1.45 (0.89-2.36)
Intermediate	0.65 (0.28-1.52)	0.70 (0.32-1.50)
Mild	Reference	Reference

***** 349 ED visits included in this analysis

***** Unadjusted and adjusted measures estimated using GEE specifying a negative binomial distribution and the multiple imputation completed dataset

[a] Adjusted for age at visit, disease severity, and distance to care

Chapter 4 – Integrated Discussion

This thesis aimed to examine clinical outcomes from a recently developed core outcome set for the rare pediatric fatty acid oxidation disorder, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Specifically, we sought to 1) evaluate the potential to measure core outcomes at the metabolic clinic setting by using chart data collected as part of routine clinical care for children with this disease, and 2) apply these abstracted chart data to a more detailed investigation of one core outcome of interest, emergency department use.

We conducted two secondary analyses that relied on an established Canadian retrospective cohort of children diagnosed with MCAD deficiency and born from 2006 to 2015, which had previously compiled comprehensive metabolic chart information pertaining to a wide range of disease-specific diagnostic procedures, treatments, and clinical outcomes collected at metabolic visits up to March 31, 2017. First, we assessed the feasibility of using this data source to reliably capture components of core outcomes measurable in the metabolic clinic. This included investigating the frequency of opportunities to measure outcomes based on age-specific rates of visits to the metabolic clinic; and then applying a data quality evaluation framework to investigate chart data for four specific core outcomes (emergency department use, fasting, metabolic decompensation, and death). Second, we examined one core outcome, emergency department use, in more detail. Specifically, we described rates of emergency department visits longitudinally and investigated characteristics of children that were associated with higher visit rates. This was done to demonstrate how the core outcome set may be used in research, but also to inform clinical practice by clarifying which children with MCAD deficiency are the highest users of emergency care and who thus may be at higher risk and/or highest perceived risk for metabolic decompensation. For this emergency department-focused analysis, we developed a study-specific

definition of severity of MCAD deficiency, with input from metabolic physicians, using a combination of two indirect, albeit commonly measured, diagnostic measures. In addition to disease severity, the other characteristics we investigated were child age and distance to travel to the metabolic clinic's emergency department. Together, the goal of this research was to evaluate the readiness of metabolic chart data for conducting high-quality clinical trials and other observational studies, to identify possible challenges with relying solely on data that are not primarily collected for research purposes, and to put this core outcome set into practice with the aim of improving clinical care for children with MCAD deficiency.

Summary of findings: Feasibility of metabolic chart data for capturing core outcomes

From the core outcome set, four core outcomes (overall child development, child quality of life, parental experiences with illness care and prevention, and access to care) require patient or parent report using validated tools.[102] Four remaining core outcomes (emergency department use, fasting, metabolic decompensation, and death) could reasonably be captured in the child's metabolic chart as part of their routine clinical care (as recorded by a clinician, dietitian, or other health care professional). Death could also be reported in the metabolic chart, but this outcome was not evaluated since it was fortunately extremely rare in this cohort, and rare in general among fatty acid oxidation disorders since the implementation of newborn screening.[60]

We used the frequency of children's visits to the metabolic clinic as an indicator of the interval of clinical entries in the metabolic chart, and thus as the frequency of possible opportunities to measure core outcomes prospectively in future studies. Among 124 children with MCAD deficiency participating in the initial cohort study, we found the highest rate of visits to the metabolic clinic immediately following diagnosis (from 2 months up to 6 months of age). The

rate of visits to the metabolic clinic progressively declined with increasing age, but always exceeded at least one visit per child per year, on average, in all age groups, with an identical trend observed between metabolic centres but some variability in the extent to which children were monitored.

Each clinical core outcome was assessed using an established data quality framework for electronic health data by Kahn et al.,[104] modified for chart-abstracted data, with domains covering *completeness* (the frequency of measurement of core outcomes and their components), *conformance* (the extent to which data components adhered to data field constraints and variation in measurement practices across centres), and *plausibility* (the extent to which core outcomes' summary measures reflect sensible values for children with MCAD deficiency).

Emergency department use

For completeness, the presence or absence of emergency department visits were generally known; however, among reported visits, we mainly identified issues with missingness. Approximately one-quarter of visits were not associated with an exact date during which the visit had occurred. In fact, for conformance, we identified that many visits' dates were entered into the database in a way that did not conform to pre-defined data fields, and some were accompanied by estimated ranges or general times of the calendar year. Interestingly, for plausibility, the primary reasons cited for seeking emergency care (nausea/vomiting, upper respiratory tract infections, and fever) and the respective trend of rates of emergency department visits according to age (highest from 6 to 12 months of age and lowest after 3 years of age) were almost identical to a health administrative data sample of children diagnosed with MCAD deficiency, but underestimated at all ages.[73]

Fasting

For completeness, updates to the prescribed safe fasting time were reported during approximately 39% of metabolic clinic follow-up visits. For conformance, many children were provided a range of safe fasting times, or individual fasting times that varied based on the time of day or in the presence of other preventive treatment. For plausibility, the overall median age-specific fasting times for this sample corresponded to best practice recommendations outlined in the literature,[66] with slightly lower actual times recorded for children aged 6 to 12 months, which also corresponded to the highest risk period for emergency department visits in this cohort.

Metabolic decompensation

For completeness, since no gold standard definition or measure exists, the extent to which chart-abstracted data items corresponded to possible indicators of an event varied greatly between participating metabolic centres and the specific dates during which symptoms possibly contributing to a decompensation were not always reported. For conformance, this outcome was almost exclusively described using associated symptoms rather than labelled as a "metabolic decompensation" in the chart. For plausibility, the median age for experiencing a metabolic decompensation in this cohort was between 12 and 15 months, based on events confirmed either by consensus of two independent metabolic physician raters, or at least one of the raters. This corresponded to the highest risk period for disease-specific symptoms and decompensation based on previous literature.[68,105–107]

Summary of findings: Emergency department use in association with disease severity, age, and distance to care

Disease severity

Our study-specific definition of disease severity used existing literature documenting the severity of mutations on the *ACADM* gene to classify the severity of unique genotypes, to which we added biochemical phenotype (newborn screening levels of octanoylcarnitine, C8) to create a more comprehensive measure. We found that the majority of children in this sample had a severe form of MCAD deficiency (65/109, 59.6%). That is, these children had a known severe genotype and a newborn-screened C8 level in the highest 75th percentile, or an unknown genotype and a C8 level in the highest 25th percentile. The rest of the sample consisted of children with intermediate (16/109, 14.7%) and mild (28/109, 25.7%) MCAD deficiency. Similar to previous evidence,[42,51,108,109] we identified a pattern whereby higher newborn screened C8 concentrations corresponded to more severe genotype classifications.

Factors associated with emergency department use

To our knowledge, this was the first study to examine the independent associations of characteristics of children with MCAD deficiency with rates of emergency department use. We noted that children from birth up to 3 years of age had significantly higher rates of emergency department visits, with at least two-fold increased visits relative to children 5 years of age and older (aIRR=2.23 [95 CI 1.37-3.62] from birth up to 6 months of age, 2.64 [95% CI 1.64-4.25] from 6 months up to 12 months of age, and 2.35 [95% CI 1.56-3.54] from 1 year up to 3 years of age. These findings supported previous evidence identifying that younger children with MCAD deficiency or other fatty acid oxidation disorders have the highest rates of emergency department

use and are at the highest risk for metabolic decompensation.[73,106] We found that disease severity was also significantly and independently associated with emergency department use: children with severe disease, as classified by the aforementioned proxy indicators of disease severity, had approximately 75% increased emergency department visits compared to children with mild disease, after adjusting for age and distance to care (aIRR=1.75 [95% CI 1.19-2.56]). In addition to being a reflection of actual risk for acute crises, we speculated that this relationship may also be influenced by providers' prior knowledge of risk associated with indicators of disease severity, which could prompt them to advise families more to visit the emergency department at a lower threshold of symptoms. Unexpectedly, children classified as having an intermediate level of disease severity had the lowest observed rates of emergency department visits, but this group was made up of a small number of children expected to have largely heterogeneous clinical presentation and in fact, their visit rates were not statistically different from those classified with mild disease. Children who lived closest to the metabolic clinic (< 30 minutes driving time) had a higher documented rate of visits to the emergency department compared to children who lived furthest away (≥ 60 minutes driving time) based on a GIS measure from the first three digits of the child's postal code (forward sortation area), adjusted for age and disease severity (aIRR=1.76 [95% CI 1.25-2.46]). The results of the complete case analysis were largely consistent with the primary analysis using multiple imputation to handle missing data.

Integration of findings

With respect to the feasibility of measuring core outcomes using the metabolic chart, our finding that routine measurement of these outcomes is possible, as evidenced by at least one visit per child per year throughout early childhood, suggests that important variation in those outcomes possibly amenable to various treatment strategies would be captured. For children who may not

visit the metabolic clinic as frequently within particular age groups, measurement of certain outcomes could be supplemented by alternative methods such as patient-report (e.g., through an application, diary, or tool which specifically asks the patient or caregiver about disease-related outcomes). We hypothesize that children who require less frequent monitoring may exhibit a milder disease relative to children whose outcomes may fluctuate more readily in response to catabolic stress and who require more intensive treatment regimens. Regardless, the most important variation in outcomes may be expected at younger ages based on the known clinical trajectory of this disease and the common ages for the development of symptoms,[68] and frequent visits during these periods (at least 2 visits per child per year prior to 1 year of age and 1.5 visits per child per year from 1 year of age up to 3 years of age) may reflect an appropriate interval of collection for these outcomes.

The challenges identified with the quality of metabolic chart data pertaining to core outcomes directly impacted our operationalization of these outcomes in describing the clinical progression of children with MCAD deficiency. For example, with respect to emergency department use, if we assume that the children in our Canadian cohort are similar to the children with MCAD deficiency identified by newborn screening in a previous Ontario study,[73] metabolic chart data for the Canadian cohort underestimated emergency care, capturing only 42% of expected visits. In fact, at all ages, emergency department visit rates in the present study were approximately 1.5 to 3.5 times lower in magnitude than expected, and more similar to children without diagnosed MCAD deficiency in the Ontario-based administrative data cohort.[73] Secondary findings suggested that in many centres, only visits to the emergency department co-located at the same tertiary care centre as the metabolic clinic are recorded unless information had been provided by the patient, the family, or the emergency department where the visit had occurred. It may be

further suspected that if a visit occurred at an emergency department outside of the same hospital as the metabolic clinic, whether or not the visit was relevant to the diagnosis of MCAD deficiency (i.e., of concern due to the risk of metabolic stress) would affect the likelihood that the visit would be captured by metabolic clinic. This may explain: 1) our finding that a higher proportion of inpatient hospital admissions were recorded as compared to emergency department visits,[73] which may be elicited more commonly from reasons related to the disease, 2) our finding that visits were not always well-described in exact detail, possibly as a result of parent-reported emergency care receive at outside institutions which could have been subjected to recall bias, and 3) our finding that children living furthest from the metabolic clinic (≥ 60 minutes driving time) had lower rates of emergency department use relative to children living closest (< 30 minutes driving time), which in addition to actual differences in care needs, could influence the proportion of visits that would be missed by metabolic chart data. Therefore, metabolic chart data may be used to measure this outcome, but should be complemented by patient- or parent-reported measures of care, or administrative records, to ensure capture of data regarding visits to emergency departments not affiliated with the metabolic centre.

With respect to fasting, the most challenging feature of these data were related to the infrequent updates of this information in patient charts. We found that clinic-specific algorithms outlining standard, age-specific fasting guidelines were provided to families at some centres. In such cases, only deviations from these recommendations would be recorded in the chart. Other changes to appropriate feeding intervals may also result from less formal conversations with families in response to the child's needs and thus remain unrecorded in the chart. In order to identify changes in fasting tolerance, possibly as an indicator of an altered health status of the patient,[66] this outcome should be included as part of a clinical case report form such that any

variation (or lack thereof) of this outcome in response to treatment, age, or illness may be identified.

Similarly, in the absence of an agreed upon definition of metabolic decompensation, the clinical information reported in the metabolic chart is not currently recorded in a manner that would allow reliable measurement of this outcome. Thus, it is possible that the metabolic chart is most suitable tool to collect specific details about a metabolic decompensation, but a supporting field would be required on a case report form completed by a health care professional. Since numerous indicators may signify that a metabolic decompensation had occurred, a case report form should include standardized reporting options that accommodate practice variation between clinicians (i.e., different combinations of clinical presentation and/or biomarkers that may be considered to ascertain the incidence of acute episodes).

Implications for future research

Measuring a recommended, harmonized set of agreed upon outcomes in a high-quality and consistent manner, by employing standardized measurement instruments, can facilitate the synthesis of findings across observational and experimental studies and thus strengthen the evidence base regarding disease natural history and response to therapy.[93,94] Collecting these outcomes prospectively as part of a larger, centralized registry with multi-centre collaboration could facilitate the design and implementation of registry-based prospective trials. Such registry-based trials can facilitate the conduct of more pragmatic trials testing the comparative effectiveness of interventions and generate stronger, more generalizable evidence for children with this disease.[77] Registry-based designs may also simplify research ethics requirements, accelerate trial recruitment, and lower costs relative to traditional randomized controlled trials.[110] The ability to leverage a core outcome set to support clinical trials or other studies depends on the quality of data

collection tools and their reliability in measuring endpoints.[111] The appeal of using metabolic chart data as a data source for outcome measurement reflects its "real-world" application and relationship to decision-making in the context of common clinical practice, and the fact that many of these outcomes and their components are at least in part collected passively for routine care.[112] These findings can be applied to health care settings with the goal of informing clinical practice and improving the outcomes most relevant to patients, parents/caregivers, policy makers, and health care professionals involved in their care.

Our findings highlighting important limitations of metabolic chart data for capturing these outcomes proposes that future intervention research should consider further standardizing the collection of these outcomes prospectively since these data may be subject to fragmented or inconsistent data collection methods, reporting, and workflows within and between centres. Future implementation of this core outcome set as part of a registry or other study design should also ensure proper training of research staff to manage and interpret data components and to properly report on the occurrence of outcomes. Additionally, our findings that observed rates of emergency department use among children with MCAD deficiency, as measured from chart data, varied according to age, disease severity, and distance to care suggest that future research should seek to disentangle the potential influence of these characteristics on health care needs, access to care, care-seeking behaviour, and data capture for children with MCAD deficiency. This will help to better understand their relationship with actual risk of acute health crises in this population. The evidence base should also further explore the role of novel and/or rare *ACADM* mutations in the development of clinical symptoms or in response to treatment among children with such mutations relative to other children with MCAD deficiency. From a clinical practice perspective, although children with MCAD deficiency require ongoing evaluation throughout childhood and beyond,

our findings suggest that children before 3 years of age and children with known severe mutations coupled with relatively high newborn screened C8 levels are particularly at risk of requiring emergency care. Clinical guidelines focusing on emergency and acute care should reflect this possible vulnerability to decompensation, for example, in the emergency protocols provided to parents. In addition, as suggested by our finding that children living furthest from the metabolic clinic have the lower rates of emergency care relative to children living closest, future studies should explore whether possible barriers in accessing the emergency care elicit any adverse health outcomes.

Limitations

For our evaluation of the quality of chart data that reported on core outcomes, we were limited by the fact that the core outcome set, the subsequent definitions of the components contributing to each core outcome, and the recommended core outcome measurement instruments were developed after the initial cohort study's data abstraction had been completed. It is possible that our findings pertaining to the quality of chart data are partially an artefact of the data collection process for the initial cohort study since these data were not necessarily collected to satisfy the requirements of the core outcome set. This would most likely have affected our evaluation of the quality of chart data measuring metabolic decompensations since the components required to measure this outcome were not necessarily collected cohesively in the absence of an accepted definition. The initial cohort study, however, developed extensive data collection tools that covered a wide range of diagnostic and follow-up measures that would be expected in the metabolic chart.[100] The judgement on whether a decompensation occurred was made without knowledge of the medical history of individual children in our study, which may not fully reflect

"real-world" judgements by clinicians who are familiar with a child's complete clinical characteristics and history.

With respect to both secondary analyses, our sample based on the retrospective cohort was small and data were limited among older age groups in particular, which limited some of our analyses and interpretations. For example, we were unable to examine possible statistical interactions between characteristics of interest without collapsing categories of characteristics. Missing data were common, particularly for children who moved from non-participating centres partway through the eligibility period or for children receiving care from metabolic centres who did not collect or report of certain items of interest. Also due to sample size, we were unable to explore the relationship between the metabolic centre from which children seek care and emergency department use, which would give more insight into variation in practice with respect to emergency care recommendations and regimens. However, we conducted several sensitivity analyses that confirmed the findings from our main analysis, with few exceptions.

Conclusions

This thesis evaluated metabolic chart data as a potential data collection tool to capture information related to clinical core outcomes for MCAD deficiency, identifying several limitations with this method specifically for capturing emergency department use, fasting and metabolic decompensation. We recommended ways to improve the quality of these data for their future use in observational studies and clinical trials, mainly by exploring ways to overcome heterogeneity in definitions and reporting. We applied the core outcome set to a Canadian cohort of children with MCAD deficiency to investigate emergency department use. We found that children at the youngest ages and with the most severe disease had the highest rates of emergency department use, possibly indicating that they are at higher risk or higher perceived risk of metabolic

decompensation throughout childhood. Children living furthest from care may experience challenges accessing these services. Future research with this core outcome set should ideally evaluate the impact of various care strategies, guidelines, and treatment on the severity of these outcomes, and explore whether children who may not be able to readily access the emergency department, based on the geographic proximity to the metabolic clinic, have worse health outcomes. It is imperative that clinical guidelines consider how best to manage the care of children with MCAD deficiency who may be most at risk for metabolic decompensation based on their age and disease severity.

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