Cardiology in the Young

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A scoping review: urinary markers of metabolic maturation in infants with CHD and the relationship to growth

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Abstract

Background: Growth failure in infants born with CHD is a persistent problem, even in those provided with adequate nutrition. *Objective:* To summarise the published data describing the change in urinary metabolites during metabolic maturation in infants with CHD and identify pathways amenable to therapeutic intervention *Design:* Scoping review. *Eligibility criteria:* Studies using qualitative or quantitative methods to describe urinary metabolites pre- and post-cardiac surgery and the relationship with growth in infants with CHD. *Sources of evidence:* NICE Healthcare Databases website was used as a tool for multiple searches. *Results:* 347 records were identified, of which 37 were duplicates. Following the removal of duplicate records, 310 record abstracts and titles were screened for inclusion. The full texts of eight articles were reviewed for eligibility, of which only two related to infants with CHD. The studies included in the scoping review described urinary metabolites in 42 infants. A content analysis identified two overarching themes of metabolic variation predictive of neurodevelopmental abnormalities associated with anaerobic metabolism and metabolic signature associated with the impact on gut microbiota, inflammation, energy, and lipid digestion. *Conclusion:* The results of this scoping review suggest that there are considerable gaps in our knowledge relating to metabolic maturation of infants with CHD, especially with respect to growth. Surgery is a key early life feature for CHD infants and has an impact on the developing biochemical phenotype with implications for metabolic pathways involved in immunomodulation, energy, gut microbial, and lipid metabolism. These early life fingerprints may predict those individuals at risk for neurodevelopmental abnormalities.

Original Article

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What we know

- Good growth in infants born with CHD is associated with improved surgical outcomes.
- Growth failure in infants born with CHD is a persistent problem, even in those provided with adequate nutrition.
- Aberrant growth during the first 2 years of life may be associated with poorer metabolic outcomes later in life.

What this study adds

- There are considerable gaps in our knowledge relating to how metabolic maturation occurs in infants with CHD, specifically:
- What factors are associated with metabolic instability and developmental delay.

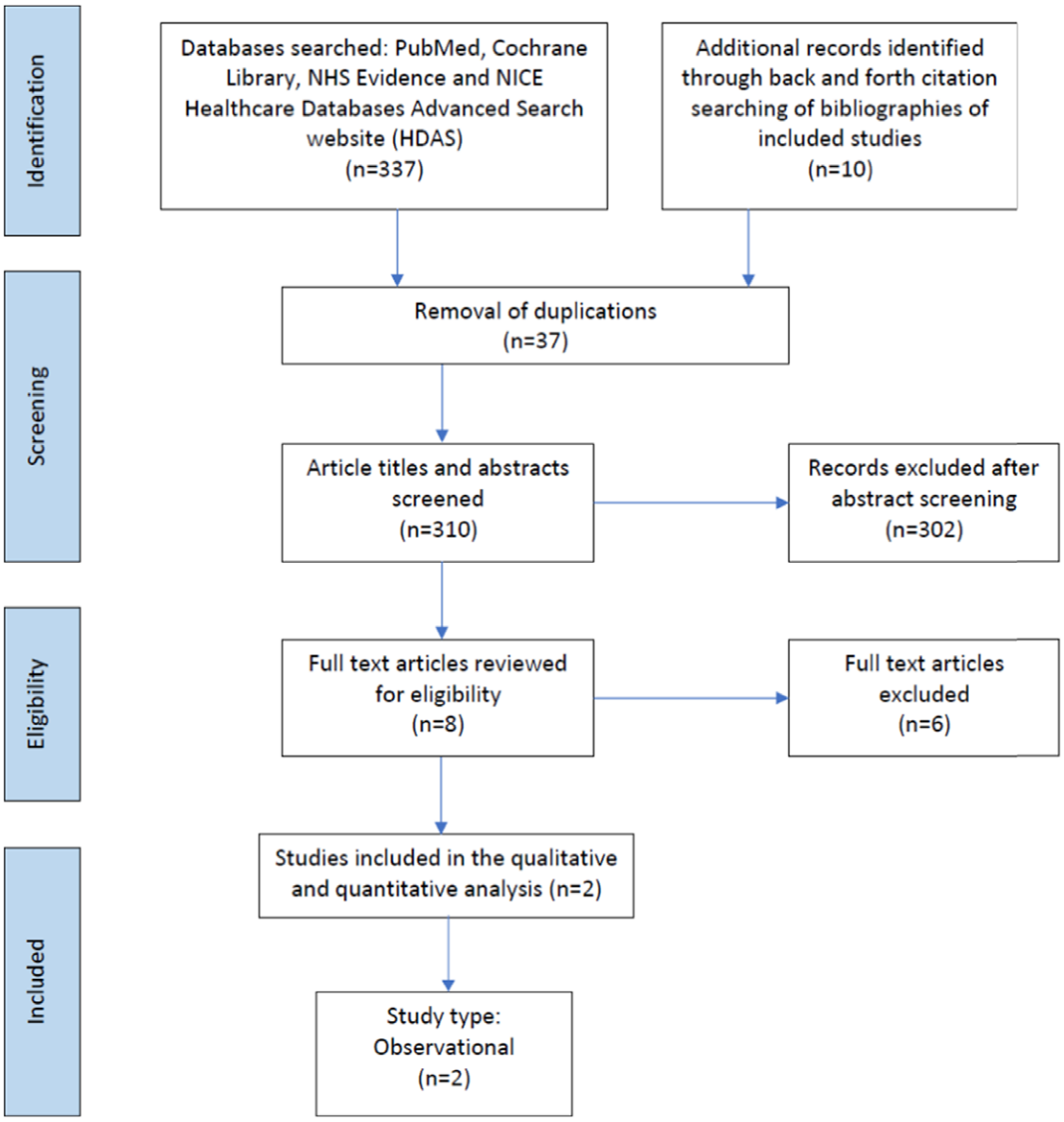

Figure 1. Prisma flow chart of studies included in the scoping review. Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR) checklist.

- Which metabolites are useful to monitor with regards to haemodynamic stability and growth outcomes, and how do these change over time in infants with CHD.
- In the small number of cases studied, there is an accumulation of metabolites associated with the tricarboxylic acid cycle, with a potential downstream effect on the availability of ketone bodies necessary for the developing brain and growth.

CHD represents one-third of all major congenital anomalies, with a reported prevalence of 9 per 1000 live births [95%CI:8.1–9.3].[1] During the past 50 years, there have been significant improvements in the medical and surgical management of CHD, with more children now reaching adulthood.[1] Improved survival, especially of infants with complex CHD lesions, is associated with increased risk of neurodevelopmenal delay.[2] Brain maturation and altered cerebral blood flow have been described in infants with CHD *in utero* and following birth. Those infants requiring medical, surgical, or catheter-based procedures especially in the first few weeks of life may be impacted by inadequate cerebral blood flow, hypoxaemia, and cerebral embolism.[3] Other factors impacting neurodevelopment delay include mechanical support provided during surgery, including cardiopulmonary bypass and haemodilution, hypothermia, glucose management, poor cardiac output, and hypotension post-operatively.[2] Work is ongoing to identify modifiable risk factors to improve long-term neurodevelopmental outcomes.[2,3]

Infants with CHD represent a heterogenous group.[4] Pre-operative malnutrition is a persistent problem with the prevalence of underweight for age reported as 27.4% (95% CI, 21.7–34.0), 24.4% (95% CI, 19.5–30.0) for stunting, and 24.8% (95% CI, 19.3–31.3) for wasting.[4–9] Infants with CHD who have persistent malnutrition at the time of surgery have poorer post-operative clinical outcomes irrespective of their cardiac lesion or complexity of surgical intervention.[10,11] These

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Table 1. Studies describing urinary metabolites in infants with CHD.[27,28]

Title	Author, year	Methodology	Number of participants	Cardiac Lesion	Patient Characteristics	Inclusion criteria	Exclusion criteria	Study Aim/method	Main findings
Urinary metabolomics reveals kynurenine pathway perturbation in newborns with transposition of great arteries (TGA) after surgical repair	Simonato et al. 2019, Metabolomics	Observational cohort, single centre	14	TGA with intact ventricular septum	Age: <3 weeks – (mean 9 days, range 3–15 days, weight 3.2 kg (± 0.4), pre-operative oxygen saturation 86% (± 7), all received breast milk as minimal enteral feeding, mean CPB time 142 min (± 28)	TGA, intact ventricular septum, undergoing arterial switch procedure with the use of cardio-pulmonary bypass (CPB), age <3 weeks	Age >3 weeks, corrected GA <37 weeks, previous cardiac surgery, hemodynamic instability, respiratory failure, factor V <0%, creatinine clearance <30%, confirmed or suspected errors of metabolism, chromosomal abnormality, major neurological abnormalities prior to surgery	To detect early changes in the metabolic profile of infants with CHD following neonatal cardiac surgery. Untargeted UHPLC-mass spectrometry was used to compare the pre-operative/ post-operative metabolic profiles	The urinary metabolic profile of TGA patients changes post-surgery. 2. Metabolites with the greatest fold-change were involved in the tryptophan-kynurenine pathway. Urinary tryptophan, trans-3-indole-acrylic acid and indole-3-carboxaldehyde increase post-surgery whereas 5-hydroxy-l-tryptophan, kynurenine, 3-hydroxy-kynurenine, and kynurenic acid decrease. 3. Other metabolic pathways altered following surgery were, phenylalanine metabolism, glucocorticoid biosynthesis, bile acid biosynthesis and omega-3 biosynthesis. However, within the study it is difficult to distinguish metabolic changes related to surgery and resolutions/ alterations of metabolites related to TGA.
Pre-surgery urine metabolomics may predict late neurodevelopmental outcome in children with congenital heart disease	Vedovelli et al. 2019, Heliyon	Observational, single centre	28	Tetralogy of Fallot (n = 11) Septal defects (ventricular septum defect or atrial septal defect *n* = 3) TGA (n = 6)	Age at cardiac surgery 3.0 (0.4–6.5) months, weight 4.8 (3.4–6.6) kg. Weight-to-age z score of −1.4 (−2.5, −0.5) pre-operative oxygen	Children age <5 years; Complex CHD requiring cardiopulmonary bypass during surgery; elective cardiac surgery (patient on spontaneous	Age >5 years, liver damage defined as coagulation factor V <20%, kidney failure with creatinine clearance <30%, and pre-operative diagnosis of	To examine pre-operative urinary metabolic profiles that may be able to predict post-operative neurodevelopmental outcomes. Urinary metabolic profiles	1. ^{1}H NMR spectra classification can predict infants' neurodevelopment outcomes with higher accuracy than using either anatomical or clinical

(*Continued*)

Table 1. (*Continued*)

Title	Author, year	Methodology	Number of participants	Cardiac Lesion	Patient Characteristics	Inclusion criteria	Exclusion criteria	Study Aim/method	Main findings
				Univentricular circulations (n = 8)	saturations 88 (88–95) (Median, (interquartile range))	breathing before surgery), stable hemodynamic conditions (constant inotropic support if needed, no volume load at admission or during the hospital stay prior to surgery)	chromosomal abnormality	were examined using H NMR spectroscopy and principal component analysis.	classifications. 2. Metabolites identified to be positively correlated with poor neurodevelopmental outcomes were citric acid cycle intermediates and glucose.

include an increased risk of cardiac arrest, infection,[12] prolonged ICU stay,[7] total length of hospital stay,[6,9] and increased risk of mortality at both 3 and 12 months of age. Even if catch up growth is achieved later in childhood, if this occurs after 2 years of age, it is associated with an increased risk of metabolic disease.[13,14] In addition, poor growth and feeding difficulties amongst infants with CHD cause parents significant distress and worry.[15,16]

Even in children treated with a structured nutrition pathway, designed to provide intensive nutrition from birth to the time of surgical intervention, 20% remain underweight and 14% remain stunted at the time of surgery.[8] Giallouri et al. have previously shown that malnourished children in resource-constrained environments show time-dependent changes in metabolites derived from nutrient–gut microbial–host metabolic interactions, and muscle-associated molecules (energy- and choline-related metabolites).[17,18] Using this approach, age-specific reference curves for urinary metabolites associated with growth in malnourished children were obtained and phenome-for-age z-scores for each child (a measure of biochemical maturity) were calculated. This work suggested that nutritional interventions could be targeted using metabolic rather than chronological age.[18]

Using advanced analytics, complex metabolic signatures (metabolomes) can be characterised and integrated with conventional anthropometric and biological data to identify novel nutritional phenotypes. This systems biology approach can increase the molecular and temporal resolution at which the biochemical status of these individual children can be studied. Such metabolic phenotypes can highlight the dynamic nutritional demands of the child, providing detailed information against which personalised nutritional support can be tailored.[17] ^{1}H nuclear magnetic resonance (^{1}H NMR) spectroscopy and mass spectrometry are high-resolution analytical chemistry techniques that can be used to comprehensively profile biofluid (urine, blood, saliva) and tissue metabolomes.[18] Such analyses, particularly in non-invasive samples such as urine, can provide a clinical tool to better understand the maturing metabolism of children with CHD, its relationship to growth,[17,18] response to nutrition interventions as well as identifying target for nutritional supplementation. This may provide an opportunity to refine nutritional recommendations and consider targeted supplementary interventions to ensure improved growth outcomes.[18–21]

The aim of this scoping review is to review the evidence describing associations between urinary metabolomics, nutrition, and growth in infants with CHD and characterise metabolites that could be used to develop phenome-for-age z scores.

Methods

A scoping review was conducted to assess the evidence available relating to urinary metabolites and growth in infants with CHD. The scoping review framework facilitates the analysis of a broad range of evidence in an emerging field and the identification of gaps in knowledge to direct future research priorities.[22] The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)[23] was used to report the evidence examined in this review.

Protocol development

The PRISMA-ScR checklist[23] was used to develop a protocol.[24] The protocol described the research question, the information sources to be searched, a description of the full electronic search strategy,

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study inclusion and exclusion criteria, data extraction and charting, data collection, analysis, and critical appraisal to answer the research questions posed.

1. *The research questions*
   a. Do infants with CHD have abnormal metabolic maturation?
   b. Are there specific metabolic signatures associated with appropriate growth in infants with CHD?
2. *Data Sources Searched*

The databases searched were PubMed, the Cochrane Library, NHS Evidence, and the NICE Healthcare Databases Advanced Search website (HDAS) (https://hdas.nice.org.uk/). HDAS was used to allow searches within multiple databases, including, PsycInfo, Cumulative Index to Nursing and Allied Health Literature, and Medline.

3. *The Search Strategy*

A search strategy, using key words from articles relating to infants born with CHD (Supplementary File: Table 1), was devised with the assistance of a library information specialist. Search terms included infants or neonates; CHD; urinary metabolomics or urinary metabolites; growth or weight gain; metabolic maturation or metabolic maturity. Searches were adapted for the additional electronic databases. Forward and backward citation searching was completed until February 2022.

4. *Study Selection*

Studies were eligible for inclusion if they were published before February 2022 in the English language, based on human subjects, and used a qualitative or quantitative design to describe urinary markers of metabolic maturation or growth in infants with CHD. Opinion pieces, editorials, and congress abstracts were excluded as per the scoping methodology advocated by Aksey and O'Malley.[25] Article titles and abstracts were screened, duplicates deleted, and then full-text articles reviewed for eligibility (SP, LVM, JJA, CW). Where multiple articles described the same cohort of children, these were only counted once. Bibliographies of included studies were hand searched for additional studies which may fulfil the inclusion criteria. Exclusion criteria included preterm infants with patent ductus arteriosus.

Data extraction and charting

A two-stage process was completed as part of data extraction. A data extraction template (Microsoft 2010, Redmond, WA) was used to capture the study design, results, and conclusions, followed by a content analysis.

5. *Collating, summarising, and reporting results*

Content analysis was chosen for reporting subjects common to the data sets.[25,26] Descriptive aspects about the population studied, methodology, outcomes, and any key findings were coded. Initial themes, identified from the key findings, were grouped into subcategories, and then into overarching themes. The overarching themes and sub-categories from this process were used to develop a conceptual framework.

Results

Study characteristics

347 records were identified, of which 37 were duplicates. Following the removal of duplicate records, 310 abstracts and titles were screened for inclusion. The full texts of eight articles were reviewed for eligibility, of which two related to infants with CHD (Table 1). The studies included in the scoping review described urinary metabolites in 42 infants.[27,28] The studies identified infants with CHD who had poorer neurodevelopment outcomes post-surgery excreted greater amounts of certain metabolites pre-surgery. This included metabolites associated with energy metabolism (glucose, sucrose, succinate, 2-oxoglutarate, lactate), gut microbial metabolism (acetate, formate), creatine, and urea. Surgery was also found to disrupt gut microbial metabolism in infants with CHD altering the excretion of the gut microbial-host co-metabolite, phenylacetylglutamine, as well as the primary conjugated bile acid, glycocholic acid, and the indolic compounds, indole-3-aldehyde, and indoleacrylic acid. The greatest impact of surgery involving cardiopulmonary bypass was related to inflammation and modulation of the tryptophan-kynurenine pathway, with tryptophan, kynurenine, 3-OH-kynurenine, and kynurenic acid excretion altered post-surgery.[27,28]

Content analysis: conceptual framework and overarching themes

Content analysis identified two overarching themes relating to metabolic variation predictive of neurodevelopmental abnormalities associated with anaerobic metabolism and metabolic signature associated with the impact on gut microbiota, inflammation, energy, and lipid digestion (Table 2).

Category 1: Metabolic variation

Both studies characterised cross-sectional patterns of urinary metabolites in infants with CHD. Vedovelli et al. describe changes in metabolites before and after surgery, and a shift to anaerobic metabolism with dysregulated ketone body production was more likely to occur in infants with neurodevelopmental impairment.[28] The metabolite clusters indicating a shift to anaerobic metabolism were not associated with age, cardiac lesion, or presence or absence of cyanotic heart disease, suggesting that other undescribed factors may be responsible for the observed alteration of the urinary metabolome. Simonato et al. described shifts in metabolites associated with energy production (glycolysis), protein synthesis (phenylalanine and tryptophan (kynurenine) pathways), and fat metabolism following surgery involving cardiopulmonary bypass.[27]

Category 2: Metabolic signatures

Both studies characterised cross-sectional patterns of urinary metabolites in infants with CHD. Vedovelli et al.[28] described decreases in metabolites post-cardiac surgery. They identified metabolic variation associated with neurodevelopmental abnormalities post-surgery. Such predictive markers included metabolites related to the energy generation such as succinate, lactate, glucose, and sucrose. In infants following surgery using cardiopulmonary bypass, Simonato et al.[27] described alterations in the excretion of tryptophan, kynurenine, quinolinic acid, and metabolites related to fatty acid oxidation, inflammation, and oxidative stress.

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Table 2. Metabolites associated with the two overarching themes.[27,28]

Theme	Comparison	Findings	Comments
Metabolic variation	Infants with CHD and infants with CHD with poorer neuro-developmental outcomes	Anaerobic metabolism with accumulation of intermediates of tricarboxylic acid (TCA) (sucrose, acetate, lactate, succinate, 2-oxoglutarate, creatine), and glucose.[28]	• Although ketone bodies were not reported in the selected papers, they are associated with anaerobic metabolism. Ketone bodies are an important source of energy, and their metabolism is a tightly regulated process. When there are lower glucose availability fatty acids are made available to the liver for oxidation, leading to the consequent production of energy-rich molecules, most notably acetyl-CoA. Acetyl-CoA can either enter the citric acid cycle in the liver or be used for the synthesis of ketone bodies. However, aberrance in fatty acid pathways may lead to an accumulation of TCA cycle metabolites and reduced availability of ketone bodies to be used by the developing brain.[29]
Metabolic signature	Pre- and post-surgery	Metabolites were distributed into five different pathways; phenylalanine metabolism (*N*-phenylacetylglutamine); glucocorticoid biosynthesis (cortisol); tryptophan metabolism (indole-3-carboxaldehyde, indoleacrylic acid, kynurenic acid, tryptophan, 5-hdroxyl-L-tryptophan); gut microbiota related bile acid biosynthesis (glycocholic acid)[27]	• Glucocorticoid biosynthesis and release of cortisol may occur in infant's post-cardiac surgery due to the use of extracorporeal circuits which lead to systemic inflammatory response.[30] • Phenylalanine is a building block for protein and histidine is an essential amino acid in infants up to 6 months of age, inadequate consumption results in growth failure, and increased loss of nitrogen.[31] • Bile acids deconjugate glycocholic acid to cholic acid. Animal studies describe the importance of the bile acid as host factors that shape the postnatal intestinal microbiota composition and develops with age.32 Differences metabolites in bile acid pathway could indicate a more immature pathway. • Tryptophan metabolism, includes brain pathways such as methoxy indole and kynurenine, with melatonin-associated neuroprotective abilities against convulsion.[33] • Indole-3-carboxaldehyde and indole acrylic acid modulating acute and chronic inflammatory response.[27]. • Tryptophan is an essential precursor of the kynurenine pathway of which 3% is metabolised into serotonin/melatonin pathway. Tryptophan is metabolised along the kynurenine pathway. Kynurenine and tryptophan can be transported across the blood brain barrier and metabolised into kynurenic acid (KYNA) by astrocytes or into quinolinic acid (QUIN) by microglia KYNA has anti-inflammatory, immunosuppressive, and antioxidant functions. QUIN can lead to neuronal dysfunction and/or death compared to picolinic to quinolinic acid is neuroprotective. Picolinic acid is an essential component of glycolysis and may be associated with dysregulation of interconnect components of metabolism of substrate transport and utilisation, mitochondrial phosphorylate, and energy production and ATP transport.[34].

Discussion

This scoping review has outlined the current understanding of metabolic signatures and their maturation associated with CHD. Due to the paucity of data, it was not possible to draw any conclusions about the relationship between urinary metabolites and growth. Indeed, only two studies were identified describing urinary metabolites in 42 infants with CHD and were included in this scoping review. The findings of these studies characterised changes in the urinary metabolome of infants with CHD before[28] and following cardiac surgery.[27] Prior to surgery, urinary metabolic profiles were predictive of alterations in energy metabolism (TCA cycle), and the accumulation of intermediaries such as succinate, lactate, and glucose suggested a switch towards anaerobic metabolism. These changes were not associated with age or the presence or absence of cyanosis but were associated with poorer neurodevelopmental outcomes. This suggests that other undescribed factors may influence the observed changes in the urinary metabolome.[28] Following cardiac surgery, there were marked alterations in the kynurenine pathway of peripheral tryptophan metabolism. This pathway plays a crucial role in the immune response to inflammation, and can either be neuroprotective, neurotoxic or neuro- immunomodulatory, and can also impact on the serotonin pathway with implications for behaviour.[35] The association of the observed changes in urinary metabolic profiles with neurodevelopmental delay is unclear. Neurodevelopmental abnormalities are common in children born with transposition of the great arteries and other cyanotic lesions, and their aetiology is multifactorial.[36] Factors thought to be involved include ischaemia reperfusion injury,[37] intrauterine cerebral oxygen delivery, or a lack of ketone bodies for the developing brain.[28]

Following surgery involving cardiopulmonary bypass, Simonato et al. identified discriminant metabolites spanning five different pathways including nicotinamide metabolism (including tryptophan, kynurenine) and glycolysis.[27] Correira et al.[38] analysed serum metabolites during and after cardiac surgery and found that ketone bodies appeared to be associated with improved survival, and observed an association between eight other metabolites (intermediaries of the TCA cycle, muscle metabolism (creatine, creatinine) and fatty acid and ketone body metabolites (acetone, acetoacetate, 3-hydroxybutyrate), and surgical and disease severity. These metabolic derangements may also be affected by other factors such as iron deficiency anaemia, which is common in infants and more so in infants with cyanotic CHD, who are at risk of secondary erythrocytosis.[39] Iron deficiency is known to impact on the TCA cycle as it includes two enzymes that contain Fe-S clusters, aconitase, and succinate dehydrogenase.[40] In addition, iron deficiency leads to impaired ketogenosis, decreased citrate synthase and succinate dehydrogenase activity, and thus reduced availability of free fatty acids. Given the important role of free fatty acids and ketone bodies for CNS metabolism, this may have a direct effect on brain development and function.[41]

Importantly neither of the studies included in this scoping review described the impact of these metabolic changes on growth. There are therefore significant gaps in knowledge especially relating to the relationship between an altered urinary metabolome and metabolic maturation, overall and organ-specific growth and neurodevelopmental outcomes, longitudinal changes in the urinary metabolome and energy, protein, and fat metabolism, and metabolic maturation and associations with weight and length gain in infants with complex disease such as CHD compared to a control group of healthy infants.

Evidence that metabolic developmental delay may affect organ growth and maturation is derived from studies of energy expenditure and body composition abnormalities in infants with CHD.[42] It has been shown that there is no difference in resting or total energy expenditure in infants with CHD who had surgery within the first 30 days of life at 3 months and 12 months of age, compared to healthy controls.[43,44] However, infants with lower total percentage body fat were more likely to experience growth failure.[42,43] Infants with CHD have been shown to have a diminished capacity to metabolise free fatty acids, with higher serum levels of lactate and alanine,[45] reduced production of ketone bodies,[46] and abnormal fatty acid oxidation and lipid metabolism. These abnormalities may be central to growth retardation;[45] however, further work will be required to explore the relationship of these metabolites and growth.

Limitations

This is a scoping review designed to present the current range of evidence specific to urinary metabolites in infants with CHD. It highlights the paucity of longitudinal data describing metabolic maturation. Given this, it was not possible to synthesise results or reliably identify the metabolites associated with growth failure commonly seen amongst infants with CHD despite adequate nutrition support.

Future research priorities

There are considerable gaps in our knowledge relating to how metabolic maturation occurs in infants with CHD, specifically, which factors are associated with metabolic instability and developmental delay. Phenotypes relative to metabolic maturation could be used to inform the development of longitudinal normal phenome-for-age z scores of metabolites of interest to identify metabolic aberrance in infants with CHD with heterogenous disease

Whether future studies targeting metabolites associated with metabolic instability will improve nutrition and growth outcomes in infants with CHD is unknown. Future research is required to describe and define the normal range for urinary metabolites in healthy infants and those with complex disease and of different gestational age to allow the development of phenome age z score charts for metabolites of interest. This might allow the design and testing of age and disease-specific nutritional interventions. In addition, these data may guide refinement of nutrient-energy dense feeds or supplements required for infants with alterations in metabolic maturation to support ideal growth during the first 6 months of life.[17,18,47]

Developing a better understanding of this relationship[17,18] will help refine our understanding of phenotypic and metabolic responses in infants with CHD and define age-related reference ranges for specific metabolites particularly with regards to developmental delay in the first 6 months of life in order to improve growth outcomes.[18–21]

Conclusion

The results of this scoping suggest that there are considerable gaps in our knowledge relating to metabolic maturation of infants with CHD. Some infants with CHD appear to have aberrant metabolic signatures with an accumulation of TCA intermediaries, with a subsequent downstream effect on lower amounts of ketone bodies available for the developing brain and growth.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951122003262

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Appendix

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	4
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	5
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	6
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	6
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	7
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	7
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	7
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7

(*Continued*)

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(*Continued*)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	7
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	7
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	7
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	8
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	9
Limitations	20	Discuss the limitations of the scoping review process.	13
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	14
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	15

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
*Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
†A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

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