Long-Term Neuropsychological Outcomes After Paediatric Liver Transplantation

Soheil Afshar

Bachelor of Psychology (Hons)

Department of Psychology

Faculty of Human Sciences

Macquarie University

Presented for the degree of

Combined Doctor of Philosophy / Master of Clinical Neuropsychology

October 2019

TABLE OF CONTENTS

SUMMARY

Paediatric recipients of liver transplant present with a complicated clinical profile and can experience poorer long-term neuropsychological outcomes than their same-aged peers. However, there is a lack of evidence regarding their specific neuropsychological profile, and the extent to which any deficits relate to medical and transplant-related factors. Furthermore, this population is highly heterogenous. This thesis aimed to better understand the long-term neuropsychological outcomes of paediatric liver transplant recipients. It was hypothesised that the sample would demonstrate poorer outcomes compared to the normative population, but that this would differ according to primary diagnosis, medical and transplant-related factors. A sample of 41 children who had undergone transplantation for chronic liver disease completed neuropsychological testing and a series of self-, parent- and teacher-report questionnaires on psychosocial functioning and quality of life. Eight children participated in an additional neuroimaging study to identify the presence of any brain pathology in a medically stable sample, as well as take measures of brain volumetrics to consider whether these were associated with medical and transplant-related factors and/or neuropsychological outcomes. Furthermore, a systematic review and meta-analysis was conducted across all studies reporting on intellectual and academic outcomes of children post-liver transplant (for either chronic disease, acute liver failure, metabolic diseases or a mix of the above). The sample demonstrated poorer neuropsychological outcomes compared to normative data across intellectual and academic outcomes, day-to-day functioning, and quality of life. Medical factors at time of transplant predicted long term neuropsychological outcomes. In particularly, longer time spent on waitlist predicted poorer long-term verbal intellect, working memory, reading ability and mathematical ability in children with biliary atresia. When a measure of disease severity was considered, the effect of waiting time was more pronounced in children with poorer liver function at transplantation. Two medically stable children demonstrated overt brain pathology on neuroimaging. Exploratory analysis of brain volumetrics showed an

association with intellectual outcomes, and were predicted by body mass index at transplant. Results from the systematic review with meta-analysis reiterated the poorer long-term intellectual and academic functioning of children with liver transplant, and demonstrated the importance of separating analyses by primary diagnosis type. It also revealed variability in methodological approaches across the literature. To conclude, paediatric liver transplant recipients are a vulnerable population requiring ongoing support. The thesis identified clinical, research and policy areas requiring review in order to give these children the best start to life.

STATEMENT OF AUTHENTICATION

This thesis is submitted to Macquarie University in partial fulfilment of the requirements for the degree: Combined Doctor of Philosophy / Master of Clinical Neuropsychology.

I declare that the research presented in this thesis is my original work. This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

All research presented in this thesis was approved by relevant Human Research Ethics Committees (Sydney Children's Hospital Network: 12SCHN45; University of New South Wales Human Research Ethics Committee: HC13358; Macquarie University Human Research Ethics Committee External Approval acknowledgement: 5201300601). Documentation of this approval is given in Appendix A.

Signed: Date: 7th October 2019

Soheil Afshar

ACKNOWLEDGEMENTS

First and foremost, I would like to thank all of the children and their families who volunteered their time to participate in the studies included in the thesis. This thesis was designed to better understand their experience and identify ways in which to improve their outcomes, as well as for those coming after them.

I would like to thank the Clinical Nurse Consultants at Children's Hospital Westmead Liver Transplant Unit, Vicky Jermyn, Janine Sawyer, and Brooke Andersen. They provided me with great support and information during recruitment and I appreciate the care and passion they bring to their patients and their work.

I would very much like to thank my supervisors, Assoc. Prof. Melanie Porter, Dr Belinda Barton and Dr Michael Stormon for guiding me through my PhD and being important role models. Thank you particularly to my principal supervisor, Assoc. Prof. Melanie Porter, who has guided me since 3rd year psychology. She has always been available to support both my PhD progress and broader clinical and professional development. I look forward to continuing to work with you in future endeavours.

Thank you to my university/PhD/Clinical Neuro friends who have watched me go through this thesis experience. Your support, humour and company have been well appreciated. Thank you to my clinical neuropsychology colleagues who have been supportive of my eventual submission. Thank you particularly to my clinical supervisor, Dr Robyn Boyle, who has always been a great source of wisdom.

To my late friend Jayne, I am sad that you are not here to see my submission. I always imagined celebrating my submission with you and to finally be able to stop you teasing me about not having submitted yet.

Thank you to my partner, Claire, for supporting me and keeping me sane through these years of this PhD. Thank you for all of your feedback, your intellectual rigor and your support in keeping me on track. I always enjoy being able to discuss and debate ideas with you and appreciate you challenging me and helping me refine my thoughts and arguments. I hope I can try to repay the favour in your process to thesis submission. I look forward to enjoying the future together without the weight of a looming PhD on our shoulders. Also, thank you for bringing our cat, Ruby, into my life, whom, whilst disruptive to any planned working-from-home sessions, was a source of great calm and comfort.

Thank you to my father and brother who have supported me in my academic pursuits and have been role models with their own academic achievements. Thanks to my families' intellectual curiosity that has meant that I would never have not thought about doing a PhD. I am very excited to be able to finally hang out with my nephews without a care in the world. I would particularly like to thank my mother, Minoo, for everything she has done for me. I would not be where I am without her support and all the sacrifices she has made for myself and our family. I want to acknowledge and show my appreciation for everything she has done.

Soheil

AUTHOR NOTE

This thesis has been prepared in the format of 'Thesis by Publication'. For the purposes of continuity, the reference style and formatting largely conformed to Chapter 2 which was published in the American Journal of Transplantation. Additionally, as Chapters 2 to 5 are prepared for submission to American scientific journals of transplantation, spelling conformed to American standards (i.e. pediatric, standardize etc.). However, the Introduction and General Discussion conform to Australian/British English spelling.

Due to the 'Thesis by Publication' format, there is some degree of repetition between the chapters. I have tried to avoid repetition as much as possible while still allowing each chapter to stand in isolation. I am the first author of all the chapters included in the thesis.

ABBREVIATIONS USED THROUGHOUT THE THESIS

A1AD: Alpha-1 Antitrypsin Deficiency

ADHD: Attention Deficit Hyperactivity Disorder

AIH: Autoimmune Hepatitis

ALF: Acute Liver Failure

BA: Biliary Atresia

BASC: Behavior Assessment System for Children

BRIEF: Behavior Rating Inventory of Executive Function

BSID: Bayley Scale of Infant Development

CBCL: Child Behavior Checklsit

CD: Conduct Disorder

CHW: The Children's Hospital at Westmead

CPS: Carbamoyl Phosphate Synthetase

DQ: Developmental Quotient

DTI: Diffusion Tensor Imaging

FRI: Fluid Reasoning Index

FSIQ: Full-Scale Intelligence Quotient

HRQOL: Health-related quality of life

IQ: Intelligence Quotient

IQR: Interquartile Range

LDLT: Living Donor Liver Transplant

LTx: Liver Transplant

LTU: Liver Transplant Unit

MMA: Methylmalonic Acidemia

MQI: Modified Quality Index

MRI: Magnetic Resonance Imaging

MRS: Magnetic Resonance Spectroscopy

OCT: Ornithine Transcarbamylase

ODD: Oppostional Defiant Disorder

PedsQL: Pediatric Quality of Life Inventory

PELD: Pediatric End-stage Liver Disease

PFIC: Progressive Familial Intrahepatic Cholestasis

PICU: Paediatric Intensive Care Unit

PIQ: Perceptual Intelligence Quotient

PPA: Propionic Acidemia

PRI: Perceptual Reasoning Index

PSI: Processing Speed Index

SB: Stanford Binet

SIQR: Semi-Interquartile Range

SWI: Susceptibility Weighted Imaging

VIQ: Verbal Intelligence Quotient

VCI: Verbal Comprehension Index

VSI: Visuospatial Index

WAIS: Wechsler Adult Intelligence Scale

WASI: Wechsler Abbreviated Scale of Intelligence

WIAT: Wechsler Individual Achievement Scale

WISC: Wechsler Intelligence Scales for Children

WJ: Woodcock Johnson

WMI: Working Memory Index

WPPSI: Wechsler Preschool & Primary Scale of Intelligence

WRAT: Wide Ranging Achievement Test

PUBLICATIONS, CONFERENCE PRESENTATIONS AND AWARDS RECEIVING DURING CANDIDATURE

Afshar, S., Porter, M.A., Barton, B., & Stormon, M. (2018). Intellectual and Academic Outcomes After Pediatric Liver Transplantation: Relationship with Transplant-Related Factors. *American Journal of Transplantation*.

Invited Speaker: Afshar, S. (2017). Long-term cognitive outcomes after pediatric liver transplantation. *9th Congress of the International Pedatric Transplant Association, Barcelona, Spain*.

Afshar, S., Porter, M.A., Barton, B., & Stormon, M. (2016). Time Spent Waiting for Liver Transplantation Predicts Long-Term Cognitive Outcomes in Children with End-Stage Liver Disease. *Presentation at Annual Meeting of the International Neuropsychological Society, Boston, USA.*

Afshar, S., Porter, M.A., Barton, B., & Stormon, M. (2015). Long-Term Cognitive Outcomes After Paediatric Liver Transplantation: Waiting time matters. *Journal of International Neuropsychological Society Conference Abstract: Joint Australasian Society for the Study of Brain Impairment and International Neuropsychological Society Mid-Year Conference, Sydney Australia. (Received Highly Commended Award for (2nd) Best Student Abstract)*

Afshar, S., Porter, M.A., Barton, B., & Stormon, M. (2015). Long-term cognitive and psychosocial outcomes of children after liver transplantation in Australia: preliminary findings. *Presentation at the College of Clinical Neuropsychologists Annual Conference, Adelaide, Australia.*

Woolgar, A., Afshar, S., Williams, M.A., & Rich, A.N. (2015). Flexible coding of task rules in frontoparietal cortex: An adaptive system for flexible cognitive control. *Journal of Cognitive Neuroscience*.

Australian Government Australian Postgraduate Award (APA) 2013-2016

AUTHORSHIP ATTRIBUTION STATEMENT

The Abstract and Introduction were written by the Candidate and edits were made based on suggestions by principal supervisor MP.

Chapter 2 is a published original article. All authors (SA, MP, BB, MS) contributed to the conception and design of the study. SA collected the data with support from MS. SA wrote the initial draft of the piece and received feedback from all authors, which was integrated into the final article.

Chapter 2-Supp. is an addendum to the above article and was conceived and written by SA. It will be submitted for publication.

Chapter 3 is an original article and will be submitted for publication. All authors contributed to the conception and design of the study. SA collected the data and wrote the manuscript. MP provided feedback for the final manuscript.

Chapter 4 is a systematic review and meta-analysis and will be submitted for publication. SA conceived of the study. SA and CM conducted the systematic review and SA completed the meta-analysis. SA wrote the initial draft of the manuscript and CM and MP gave feedback which was integrated into the final version.

Chapter 5 is a case series and will be submitted for publication. SA conceived of the study. SA recruited participants, analysed the data and wrote the manuscript. MP and BB gave feedback for the final version.

Chapter 6 serves as the general discussion and conclusion of the thesis. It was written by SA with feedback given by MP.

CHAPTER 1:

INTRODUCTION

LONG-TERM NEUROPSYCHOLOGICAL OUTCOMES AFTER PAEDIATRIC LIVER TRANSPLANTATION

1 | Origin of liver transplantation

The first liver transplant occurred in 1963, but was unsuccessful, with the paediatric patient not surviving the operation.[1] Over the next decade, surgical and technical procedures improved, leading to increasing numbers of successful transplants.[2-4] The introduction of cyclosporine in 1979 and tacrolimus in 1990 revolutionised transplantation and led to marked improvements in survival rates due to reduction in graft rejection. Liver transplant was subsequently embraced as the treatment of choice for end-stage liver disease. [5-8] The first successful liver transplant in Australia occurred in 1985 after the establishment of the Queensland Liver Transplant Service. This was soon followed by the Federal Government-funded Australian Liver Transplant Unit set up at Royal Prince Alfred Hospital in Sydney, which performed an adult and paediatric transplant in early 1986. Units were then established in Victoria (1988), South Australia (1992) and Western Australia (1994).

Since that time, a number of hepatic and metabolic disorders have been shown to be successfully treated with liver transplantation. The incidence/prevalence of a range of these disorders in the paediatric population in North America is documented in Table 1, all of which may be treated by liver transplantation, and in some instances only by liver transplantation. As can be seen, while each individual disorder may be uncommon or rare, the combined incidence of these disorders is significant. In 2017 for example, 8082 adult and 599 paediatric liver transplants were conducted in the US,[9] which had an estimated population of 326 million at the time.[10] New candidates put on the waitlist in 2017 included 11514 adult and 696 paediatric patients, with 11168 active and 2071 inactive[i] adult candidates and 373 active and

[i] An inactive listing is when an individual who has been placed on the waitlist is temporarily made ineligible for a donor organ due to an issue that needs reviewing and addressing, such as developing an infection.

177 inactive paediatric candidates remaining on the list by 31st of December 2017. Across Australia and New Zealand in 2017, with respective populations of approximately 24.5 million and 4.7 million, 269 adult and 47 paediatric transplants were conducted. Four hundred and sixteen new candidates were put on the waitlist in 2017, with 154 adult and 13 paediatric patients remaining on the list by the end of the year (1 child and 12 adults died while on the waitlist). It is clear that a substantial number of people, including children, experience liver disease and liver transplantation and, as such, there is a need to investigate and improve the experience to get optimal outcomes.

TABLE 1 Incidence/prevalence of different causes of liver disease in the paediatric population (reproduced from Cassoti and D'Antiga, Liver Disease in Paediatric Medicine: An Overview)[11]

Disease	Incidence/prevalence
Cholestatic diseases	1:2500 live birth (l.b.)
Biliary atresia	1:8000–1:21000 l.b.
Alagille syndrome	1:70000 l.b.
PFIC/BRIC	1:7000 l.b.
Caroli disease/congenital hepatic fibrosis	1:6000–1:40000
Neonatal haemochromatosis	<1:1000000 l.b.
Idiopathic neonatal hepatitis	1:4800–1:9000 l.b.
Wilson disease	1:30,000–1: 50.000 l.b.
Cystic fibrosis	1:2000 l.b.
Alpha-1-antitrypsin deficiency	1:1800 l.b.
Metabolic diseases	1:1800 l.b.
Disorders of carbohydrate metabolism	
– Fructosaemia	1:20000 l.b.
– Galactosaemia	1:63000 l.b.
– GSD I–III and IV	1:100000–1:1000000
Tyrosinemia	1:100000–1:120000 l.b.
Peroxisomal disorders	1:25000 l.b.
Urea cycle disorders	1:30000 l.b.
Organic acidosis	1:1000 l.b.
Lysosomal storage disorders	
– Gaucher disease	1:5,700 l.b.
– Niemann-Pick A/B	1:1,000,000 l.b
– Niemann-Pick C	1:130000–1:150000 l.b.
– CESD	1:300000 l.b.
– Wolman disease	1:500000 l.b.
Congenital disorders of glycosylation	1:10000–1:100000 l.b.
Mitochondrial hepatopathies	1:20000 children under 16 years of age
Tumours	1,8:1,000,000
NAFLD/NASH	Prevalence 5–17% in general paediatric population, up to 70–90% in young obese
Autoimmune liver disease	Prevalence 1:200,000
Infections	
Hepatitis A (HAV)	1.4 million cases occur annually
Hepatitis B (HBV)	Global prevalence 2–20%. Horizontal transmission responsible for 37–52%; perinatal transmission 13–26%
Hepatitis C (HCV)	Prevalence from 1:500 (age 6–11 years) to 1:250 (age 12–19 years)

PFIC: progressive familial intrahepatic cholestasis; BRIC: benign recurrent intrahepatic cholestasis; GSD: glycogen storage disease; CESD: cholesteryl ester storage disease; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; AIH: autoimmune hepatitis; ASC: autoimmune sclerosing cholangitis; PSC: primary sclerosing cholangitis.

2 | Shift from survival rates to long-term outcomes

Over the next three decades, the success rate of liver transplantation continued to improve;[12, 13] not only as a result of the effective immunosuppressants,[14] but also due to major advances in surgical techniques and medical care including split liver procedure[15, 16], living donor liver transplant (LDLT),[17] better management of nutrition during illness and post-transplant,[18-20] and emerging gene therapy.[21] Given the increase in survival rates following liver transplantation, clinicians and researchers were able to move beyond predictors of morbidity and mortality, and instead consider long-term outcomes for such survivors.[22]

The exploration of long-term outcomes has two main functions: 1) to achieve a better understanding of the long-term functioning of liver transplant recipients so that appropriate interventions or supports can be developed and implemented to meet their needs, and 2) to be able to predict long-term outcomes from disease and transplant-related factors, such as time spent on the waitlist. This would allow for future targets to be identified and modified in order to improve outcomes and give children a better start to life.[23, 24]

The function of this review is to summarise and evaluate the current state of the literature on long-term neuropsychological outcomes after paediatric liver transplantation. It identifies gaps in the field, such as the lack of studies in Australia, and considerations that need more attention, such as exploration of individual primary diagnoses when assessing long-term outcomes. It also outlines the rationale for this research including aims, scope, and intended contributions of each chapter of the thesis.

3 | Differences between adults and children

The early research investigating quality of life, cognitive and functional outcomes after liver transplantation primarily focused on the adult transplant population.[25-31]

However, there are a number of distinct clinical differences between adult and paediatric liver transplant recipients, such that conclusions about long-term outcomes for children cannot be readily drawn from adult research.[32]

3.1 | Primary diagnosis

Adults and children differ on the reason for transplantation (i.e., their primary diagnoses). While children primarily present with congenital hepatic disorders, adults have a greater rate of lifestyle-related disorders (such as alcoholic cirrhosis and non-alcoholic fatty liver disease), chronic viral hepatitis and hepatic malignancies. As of December 2017, there had been a total of 5890 liver transplants on 4514 adult and 933 paediatric patients across Australia and New Zealand over the three decades of transplantation history.[12] Amongst children, 53.7% have had biliary atresia and 14.6% have had metabolic disorders, whereas among adult recipients, these two groups represented 1% and 4.3% of those transplanted, respectively. In contrast, 28.6% of adult recipients have required a transplant due to chronic viral hepatitis, 12.7% for alcoholic cirrhosis, 11.6% for malignancies and 4% for non-alcoholic fatty liver disease, with this final group increasing in more recent years (9% in 2015-2017 period versus 0% before 1994). This increase is replicated in other developed nations including the US.[33] Only 4% of children have required a transplant for malignancies, while the other categories have not been represented in the paediatric transplant population.[12]

The differences in primary diagnoses between adults and children are relevant to research on long-term outcomes because these illnesses involve different underlying mechanisms. For example, biliary atresia, the most common paediatric hepatic illness requiring transplantation, presents at or soon after birth and is characterised by a blockage of intra- and extrahepatic bile ducts, resulting in build-up of bile that damages the liver leading to liver failure and death if left untreated (via Kasai procedure or transplant).[11] In contrast,

alcoholic liver disease is a lifestyle-based liver disorder seen almost entirely in adults and results in liver inflammation, fatty liver disease, hepatitis and cirrhosis, and the overt symptoms are often absent until complications develop.[34]

The trajectory of disease severity across disorders also varies, which then means the impact across time on an individual's health and their treatment experience differs based on the diagnosis. For example, the lifestyle disorders associated with liver transplant have a more gradual and chronic course that can be reversed or managed for a period before transplantation is necessary, whereas other disorders have a more immediate and catastrophic impact and require transplantation more urgently (such as acute liver failure or biliary atresia). It is therefore important to review and evaluate the role of primary diagnosis on long-term outcomes and to differentiate between childhood onset and adult onset diseases.

3.2 | Effects of liver disease on the brain

The impact of liver disease on the brain has long been known.[35] There are a number of mechanisms by which liver dysfunction can impact the brain, with ammonia believed to be particularly implicated.[36, 37] A healthy liver is responsible for detoxifying the blood by metabolising ammonia through the urea cycle. When this mechanism becomes impaired, as happens in liver disease, levels of ammonia increase in the body and blood (hyperammonaemia). Excess ammonia in the blood consequently raises the ammonia levels in the brain. Under normal circumstances, the ammonia levels in the brain are regulated by astrocytes. These are glial cells that fulfil a range of other roles including detoxifying cerebrospinal fluid, regulating the blood-brain barrier and neurotransmitter levels, and involved in the energy supply to neurons. However, when astrocytes are exposed to excess ammonia, they become swollen and dysfunctional and convert to pathological Alzheimer type II astrocytes. In this state, the functioning of astrocytes are disrupted and they can no longer

metabolise ammonia, leading to a dysregulation of the blood-brain barrier and an over-concentration of ammonia in the brain. The presence of the swollen, dysfunctional Alzheimer type II astrocytes increases the risk of cerebral oedemas.[36-38]

Excess ammonia and astrocyte dysfunction also lead to dysregulation of CNS glutamine and glutamate levels. [36-38] Glutamate (the principle excitatory neuron in the mammalian brain) is produced via glutaminase, with a by-product of this process being ammonia. This is normally converted to glutamine by astrocytes, but when these are impaired and this process is interrupted, glutamate remains in the synapse and continues to have a neuroexcitatory effect on the system. This excitatory effect is neurotoxic and, without treatment, can cause hepatic encephalopathy, leading to coma and ultimately, death. The excess ammonia also causes oxidative stress, energy deficits through disruption of mitochondrial processes, and neuronal death.

Because the liver plays an important role in blood coagulation, disruptions to this process can also lead to cerebrovascular incidents ranging from white matter ischaemic changes and small ischaemic events to catastrophic cerebral infarctions or haemorrhage.[38, 39] In combination with the astrocytic dysfunction discussed above, the resulting disruption to the integrity of the blood-brain barrier and dysregulation of the cerebrospinal fluid further increases the risk of cardiovascular events.[36, 37]

Another important hepatic function is regulation and excretion of heavy metals such as copper, iron and manganese.[40] A diseased liver is unable to effectively excrete these heavy metals which then accumulate within the body, and have particular affinity for deep brain nuclei of the basal ganglia, such as the globus pallidus. Furthermore, T1 hyperintensities of

the globus pallidus on brain MRI have been found to correlate with liver disease severity and blood manganese levels. [38, 41-44]

There are also a range of neurological complications that are associated with liver transplantation. These include immunosuppressant-related neurotoxicity, posterior reversible leukoencephalopathy syndrome, neuropsychiatric complications of corticosteroids, seizures, cerebrovascular complications due to coagulation disturbances or secondary to immunosuppressive therapy.[39, 45]

There are a number of other indirect impacts of liver disease upon the brain, some of which are particularly relevant to childhood development. The liver is important in the absorption of nutrients. Diseased livers can lead to malnutrition, which has a direct impact on overall development as well as neurodevelopment if not addressed.[32] Furthermore, the liver is involved in regulation of iron levels and iron has been shown to be vitally important in neurological and cognitive development, particularly in the first few years of life.[46, 47]

3.3 | Developing versus developed brains: illness during critical period of development

An important factor that differentiates the paediatric transplant experience from that of adult patients is the notion of developing versus developed brains. Children who experience end-stage liver disease often do so within the first few years of life.[11] This occurs during important periods of brain development when children are most vulnerable to the deleterious neurological impacts of liver disease.[48] This is particularly the case for children with congenital disorders who experience liver disease during the very early and critical stages of neurodevelopment. For example, it is thought that exposure to ammonia impairs axonal growth of neurons in infants.[48] Neuropsychological research has demonstrated that neurological damage in the first few years of life appears to be particularly detrimental to

cognitive development, particularly if the damage is diffuse or global, as would be the case for children with liver disease.[49] In contrast, adult brains are considered to be fully developed by the onset of their liver disease and as such, the effects of liver disease do not disrupt neurodevelopment. Figure 1 illustrates that any childhood-onset liver disease, particularly if it is congenital, occurs during the first few years of life, when critical periods of brain development are occurring such as neurogenesis and myelination. Any disease that impacts the brain during this time would disrupt these neurodevelopmental processes and would have subsequent impacts on cognition and functioning. This is in contrast to adult-onset liver disease where there is limited ongoing neurogenesis.

Another concept particularly pertinent in exploring long-term outcomes after childhood liver disease and transplantation is the idea of "emerging deficits".[49] This term describes the context where a child may show difficulties in a particular cognitive domain years after their neurological insult as a result of disruption to their developmental trajectory and failure to appropriately acquire a new skill at the expected age rather than a regression of skill due to their injury. For example, a newborn who experiences a neurological injury at birth involving regions responsible for language may not show any problems in their first year of life, but their difficulties may then become evident (or emerge) as they reach the age when language is expected to develop. Amongst children with liver disease and transplantation, the initial recovery observed after successful transplantation and the generally age-appropriate development may lead to the assumption that a child has no long-lasting deficits related to their disease experience and has, for all intents and purposes, recovered. However, deficits or vulnerabilities may appear years later due to disruption to their neurodevelopment, when higher-level skills are expected to develop but do not develop at the rate expected for their age. For example, a child who has had a liver transplant and has functioned at age-expectations for the first half of their schooling, may begin to show difficulties in the latter

years of their schooling when higher-level executive skills develop and allow for greater independent study skills including planning and prioritising.

A final important concept within paediatric neuropsychology that is relevant to the liver disease group is the idea that higher-order skills such as executive functions and attention, which are underpinned by a complex and more diffuse neural network, are at greater risk of impairment following neurological insult during childhood than foundational skills such as simple language, visual and motor skills, which are represented by more localised neural structures and show better recovery.[49] Within the liver disease population, the direct (ammonia, heavy metals, cardiovascular events) and indirect (malnutrition and impaired development) neurological impacts of the disease process have a global and diffuse impact on the brain.[39] Hence, the effects of would be assumed to be greatest on the higher-order skills, which will not show themselves until these skills are expected to develop in later childhood.

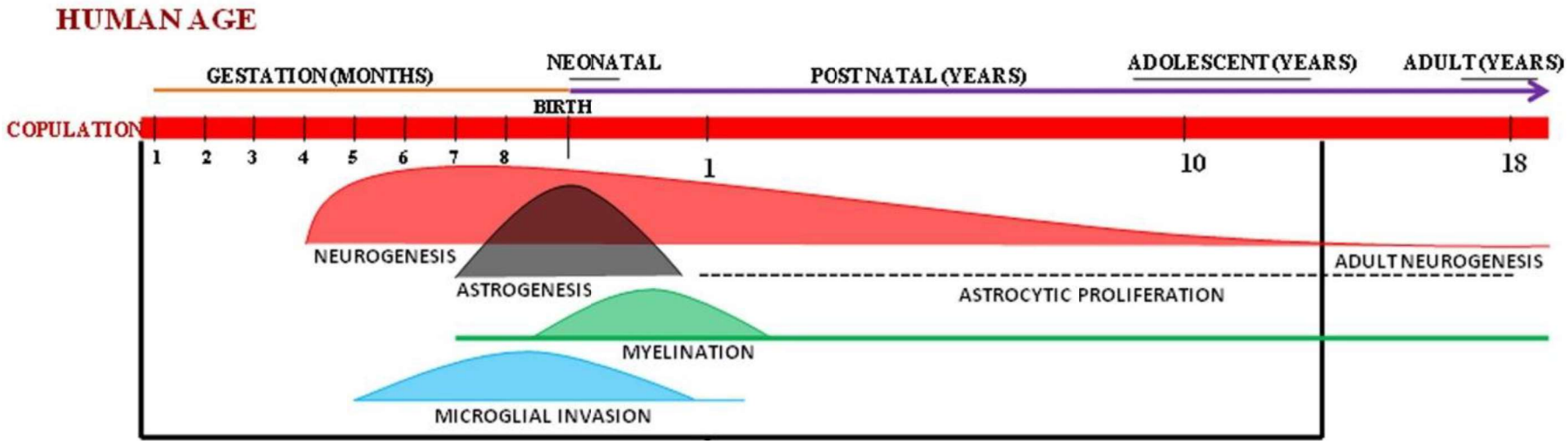


FIGURE 1 Neurological development across the lifespan. Reproduced from Sarkar (2019) Cumulative multiple early life hits- a potent threat leading to neurological disorders)[50]

Furthermore, neurological episodes are at a greater risk of being overlooked in young children and infants, particularly when they are already chronically ill, appear lethargic and occur before language acquisition. For example, hepatic encephalopathy and its precursor, minimal hepatic encephalopathy, are harder to identify in younger children and infants and hence can be left untreated for longer or missed altogether.[51-54] Similarly, smaller cerebrovascular events in young children and infants show fewer outward signs than in adults.[55, 56] In this way, subtle damage to the brain can be difficult to detect and appreciate, and as a result, slow to treat and address.

Liver disease and the transplant experience during childhood also indirectly impact on cognitive, academic and social development through missed schooling due to the illness, transplant and recovery as well as the regular follow-up requirements.[57] Furthermore, experience of significant illness in childhood has been shown to predict poorer psychosocial functioning including higher rates of anxiety.[58-60]

3.4 | Liver transplant does not fully resolve neuropsychological effects of paediatric liver disease

Together, this evidence challenges the previous expectation that once a child with liver disease received a successful liver transplant and did not experience complications, then their functioning would return to normal.[32, 61] This expectation was based on data from adults that reported full recovery following successful transplantation.[31, 62, 63] Indeed, early neuropsychological studies found evidence that this was not the case in children. The retrospective clinical findings of Zitelli et al. and the prospective investigation by Stewart et al. were the first to demonstrate that children after liver transplant had lower than expected neuropsychological functioning, and were indeed functioning lower than children with cystic fibrosis.[64, 65]

Since these seminal studies, the field has continued to demonstrate poorer neuropsychological and psychosocial functioning in children following liver transplantation compared to the general population.[66] This is despite surgical techniques and clinical management improving over time.[14, 15, 18] The field has now grown to include diverse outcomes, such as psychosocial functioning and standardised academic achievement, in addition to cognitive functioning and quality of life.[66] However, methodological quality has varied across studies.

While the field continues to grow, it is difficult to draw conclusions from existing findings due to methodological limitations. The majority of studies have been conducted in North America and Western Europe and findings may not easily generalise to other jurisdictions.[67-69] Moreover, differences in healthcare systems, donation and transplant policies, organ availability, access to specialist transplant teams and different transplant approaches, and differences in educational systems[70-72] may significantly impact the disease and transplant experience of paediatric patients.

4 | Outcomes not in formula for allocation policies

Despite this body of findings demonstrating poorer neuropsychological outcomes for children after liver transplant, transplantation policies appear to not directly address this. The Australian Government-commissioned Clinical Guidelines for Organ Transplantation from Deceased Donors accurately captures the predicament faced by decision makers. Namely, "it is necessary to strike a balance between maximising access to liver transplantation for those who would die without it and achieving the best possible outcome from each transplant."[73] Understandably, this pressure is due to the limited available donors, with current policies factoring in transplant urgency and disease severity, organ suitability (blood group match) and physical proximity.[73] However, "best possible outcome" does not explicitly include or

quantify neuropsychological outcomes or consider the factors that have been found to predict better long-term functioning. Nor does it explore or discuss the impacts of liver disease on neurodevelopment within the allocation model.[74, 75] As a whole, the current guidelines for transplantation do not include considerations for neuropsychological or quality of life outcomes beyond avoiding catastrophic complications from disease and death. While neurocognitive and quality of life outcomes are discussed in the Evaluation of the Pediatric Patient for Liver Transplantation: 2014 Practice Guideline, once again, allocation procedures do not explicitly model the impact of liver disease and transplantation on these outcome domains.[19]

5 | The Australian context

Examining the case study of Australia is helpful in highlighting these neglected factors and how they may influence outcomes for paediatric liver transplantation recipients, and hence deserve to be considered.

5.1 | Donation rates

The rates of organ donation vary markedly between international jurisdictions.[76] Within the context of the current thesis, attempts by the Australian federal government to actively increase organ donation rates through awareness campaigns in the late 2000s have meant that Australia's donation rates have increased from approximately 10 per million of population (pmp) to 23pmp in 2018. This is in comparison to Spain (48pmp) and the US (33pmp). The increase in donation rates in Australia is not as strong with regards to deceased donor livers with Australia recording approximately 7pmp in 2009 compared with 12.7pmp in 2018. One reason for this is that Australia does not utilise an opt-out system for organ donation, which reduces availability of viable organs. In addition to this, despite attempts to centralise and nationalise organ allocation process, donation and transplantation policy is still primarily managed at a state level,[73] meaning that waitlists are not fully amalgamated

nationally. In this way, higher priority cases may not automatically receive an organ if they are not in the same state as the donor organ. This is also limited by the large geographical size and low population density characteristic of Australia, with only four paediatric liver transplantation units nationwide each covering an area larger than Western Europe.[12, 73] Taken together, the result of fewer available organs invariably leads to longer waiting times for those on transplant waitlists.

5.2 | Frequency and proportion of Living Donor Liver Transplant

Another unique aspect of the Australian context is the reluctance to conduct Living Donor Liver Transplants (LDLT).[77] This means fewer LDLT are conducted when compared with other similar jurisdictions such as in the US[9, 78] or Canada.[79, 80] As of December 2017, a total of 105 LDLT (85 paediatric) have occurred across Australia and New Zealand. This accounts for 1.8% of all liver transplants and 1.9% of all patients (9% of paediatric patients). Only five LDLT occurred in 2017 (three paediatric and two adult). This was out of a total of 314 transplanted patients (1.6%), including 47 paediatric patients (6.4%). In contrast, 72 paediatric LDLT occurred in 2017 in the US, which accounted for 12% of all paediatric liver transplants.[9] Similarly, 69 living donor liver transplants (both living related and unrelated) occurred in Canada in 2018 out of a total of 515 transplants (13.4%), including 21 living donor transplants for paediatric patients out of a total of 41 (51.2%). Since 2014, approximately half of children receiving liver transplants in Canada have received a living donor organ. This high proportion is primarily driven by a policy shift in Ontario, particularly at Toronto's Hospital for Sick Kids, which actively pursues living donor transplants.[80] This policy shift also means that living donor transplants are not utilised as a last resort, as is the case in other jurisdictions like Australia,[77] but rather as a first option. This results in children spending less time waiting for a donor organ while suffering from the deleterious effects of end-stage liver disease.[80] Furthermore, there is limited research suggesting that LDLT recipients have better outcomes

than those who receive deceased donor organs.[17, 80] Reasons for better outcomes are thought to include: receiving their transplant earlier, higher quality grafts, reduced cold ischaemia times, and organs being genetically more similar when from family members which has positive ramifications of immunosuppressant regime and risk of rejection.[17, 80] It is therefore valuable to consider the Australian context in order to capture a new perspective on factors that may impact long-term neuropsychological outcomes.

5.3 | Access to universal healthcare

Australia is also different to other countries because it provides universal healthcare to its residents. This means that a lack of health insurance is not a preclusion to receiving a liver transplant, nor does it limit follow-up and rehabilitative care provided, as is the case in other countries such as the USA. For example, people on the transplant waitlist can be made inactive due to insufficient health insurance. Similarly, access to post-transplant rehabilitation services can depend on quality of health insurance.[81-83] Indeed, Australian paediatric liver transplant services are exclusively part of the public healthcare system. With about one third of studies conducted to date originating in the USA, it is important that countries with universal healthcare are better represented in the field in order to make generalisable conclusions. Insurance status may be a predictor of outcomes in jurisdictions without universal healthcare such as the USA, however it would be irrelevant in countries like Australia.[81-83] It is therefore difficult to draw conclusions without more complete data for the Australian context.

6 | Utility of subgrouping by primary diagnosis

A major and ongoing limitation in the field is the propensity to group the outcomes of all liver transplant recipients together, rather than differentiate between primary liver disease diagnoses. This assumes equivalency across disease groups, including in illness experience, underlying mechanisms, impacts on development, efficacy of treatment and long-term

outcomes. This assumption has not been adequately tested, and indeed the few studies that have separated findings by primary diagnosis have shown a difference in long-term outcomes.[84, 85] Some metabolic disorders which can be treated by liver transplantation, such as Maple Syrup Urine Disease, are not characterised by a diseased liver. They are instead a result of inability to metabolise certain amino acids which build up in the body and are toxic to the brain and organs.[86] This is in contrast to liver-specific illnesses such as biliary atresia, whose effect on overall health and development is directly linked to the functioning of the liver.[87] Despite this clear difference in underlying mechanisms, these two diagnoses are frequently combined and investigated as one homogenous group.[88-92] As discussed earlier, the chronicity of illness and disease onset are further relevant factors that require consideration.

7 | Variety of assessment techniques

A final key limitation of the field is that few studies have incorporated a range of assessment procedures and tools when seeking to ascertain the long-term outcomes after paediatric liver transplantation, beyond survival rates. Some studies only include a few measures, such as quality of life questionnaires, while others contain more comprehensive neuropsychological assessment batteries. A handful of studies utilise both performance-based standardised tools alongside informant questionnaires that measure functioning, while the majority use one or the other.[66] Amongst those studies that utilise informant measures, few incorporate multiple informants and even fewer utilise the vital perspective on a child's functioning provided by teachers. Furthermore, consistency in measurement tools within studies is problematic in retrospective designs that rely on existing clinically indicated data. For example, some studies attempt to combine developmental and intellectual measures despite each capturing different constructs.[65, 91, 93]

8 | Predicting long terms outcomes from medical and transplant-related factors

Ideally, research in this area needs to advance beyond only describing the long-term neuropsychological profile of paediatric liver transplant recipients and instead, identify which factors best predict long-term outcomes. Such predictors can then serve as targets for future research to determine whether modification of these factors can change and improve outcomes.[22, 24] The majority of studies to date do not attempt to predict long-term outcomes from medical or transplant related factors. Studies that had attempted to predict these factors often relied upon statistical methods that did not capture the complexities of the liver disease and transplantation experience, such as pairwise correlations.[64, 90, 94-96]

9 | The role of neuroimaging for understanding liver disease and transplantation

The neuropsychological literature shows reduced long-term outcomes compared to the general population in children after liver transplant.[66] In addition, liver disease is known to detrimentally impact the brain, with the developing paediatric brain particularly vulnerable.[48] Neuroimaging studies are well-placed to enrich our understanding of the deleterious effects of liver disease. Adult studies have shown neurological abnormalities on neuroimaging linked to liver disease in medically stable liver transplant recipients.[97, 98] A handful of paediatric studies have shown neuroradiological abnormalities, but these were only conducted in individuals with neurological signs such as dystonia and tremor.[42, 43, 99, 100] Hence, there is a need to explore the neuroradiological status of medically stable paediatric liver transplant recipients. This would help identify the presence of possible abnormalities or disruption to neurodevelopment, and evaluate whether the relationship between liver disease and poorer neuropsychological outcomes is associated with observable changes in the brain.[24]

10 | Thesis aims

This thesis was devised to expand our current understanding of paediatric liver transplantation outcomes, while seeking to address a number of methodological shortcomings of the field. The key goal of the thesis was to provide better information to policy makers and medical teams to facilitate informed decision making around allocation and priority listings. Without this information, decisions are being made based on an incomplete picture.

10.1 | Chapter 2, 2-supplementary and 3

Chapters 2, 2-supplementary and 3 investigate the long-term neuropsychological outcomes of Australian children with liver transplant for chronic liver disease. At the time of the study conception, no such study had been conducted in Australia. The study was designed to assist in overcoming many of the methodological shortcomings discussed above. A core strength of the studies in these chapters was the inclusion of standardised neuropsychological assessments using both performance-based tests and functional multi-informant reporting.

Chapter 2 is a published paper[101] that details the long-term intellectual and academic outcomes of 40 children who received a paediatric liver transplant at The Children's Hospital Westmead, in Sydney, Australia. The aims of Chapter 2 were not only to capture the intellectual and academic profile of these children, but also to explore the medical- and transplant-related factors that predicted long-term outcomes, with a specific focus on time spent on transplant waitlist. The third aim was to investigate whether combining different primary liver disease types, even within the overarching diagnostic group of chronic liver disease, would dilute results. The statistical analyses were devised and conducted using both a theory- and data- driven approach.

Chapter 2-supplementary re-examined the data from Chapter 2 within the Biliary Atresia subgroup. The aim of this chapter was to investigate whether the relationship between time spent on the waitlist and long-term intellectual and academic outcomes differed based on disease severity, rather than reflecting a simple linear association. It employed an interaction effect term in a series of multiple regressions.

Chapter 3 aimed to examine the everyday executive functions, attention, behaviour, academic development, psychosocial functioning, and quality of life in this sample of paediatric liver transplant recipients. By using validated standardised parent-, child-, and teacher-reports, it captured the disease experience using a multi-informant approach.

10.2 | Chapter 4

Chapter 4 was a systematic review of the literature on long-term intellectual and academic outcomes for paediatric liver transplant recipients. The aim of this chapter was to both review the quality of existing studies, and also to quantify intellectual and academic performance using a meta-analytical approach. It further attempted to differentiate results by disease subgroups to consider whether it is inappropriate to collapse across primary diagnosis type.

10.3 | Chapter 5

Chapter 5 of the current thesis explored the neuroradiological outcomes using Magnetic Resonance Imaging (MRI) for eight medically stable paediatric liver transplant recipients in order to assess whether abnormalities were present despite their medically stable status. Furthermore, through exploratory analysis, Chapter 5 was the first study of its kind to investigate whether intellectual outcomes were associated with MRI-derived brain volumetrics within a sample of paediatric liver transplant recipients. This study hoped to influence future

research; namely, that it would provide the catalyst for research into the neuroradiological outcomes of children with liver transplants for end-stage liver disease, and determine whether the poorer neuropsychological outcomes in the literature is mediated by neurological development.

10.4 | Chapter 6

Finally, Chapter 6 serves as the thesis discussion chapter. It sought to synthesise the results of the thesis, review key limitations and strengths of the thesis as a whole, and make recommendations for future research avenues. Specifically, it outlined methodological recommendations that would optimise future research and maximise their impact, making findings more reliable and representative. This would then allow researchers and clinicians to better inform policy makers and lead to better outcomes for children. It also served as interim guidelines for clinical teams to thoroughly assess and proactively and pre-emptively intervene to support children post-liver transplantation who are at risk of cognitive, academic, and psychosocial challenges.

REFERENCES

1. Starzl TE, Marchioro TL, Huntley RT, Rifkind D, Rowlands DT, Jr., Dickinson TC, et al. Experimental and clinical homotransplantation of the liver. Annals of the New York Academy of Sciences1964. p. 739-65.

2. Groth CG, Starzl TE. Liver transplantation in man. Postgraduate medicine. 1973;53(1):202-10.

3. Starzl TE, Koep LJ, Halgrimson CG, Hood J, Schroter GPJ, Porter KA, et al. Fifteen years of clinical liver transplantation. Gastroenterology. 1979;77(2):375-88.

4. Starzl TE, Koep LJ, Schroter GPJ, Halgrimson CG, Porter KA, Weil Iii R. Liver replacement for pediatric patients. Pediatrics. 1979;63(6):825-9.

5. Calne RY, Rolles K, Thiru S, McMaster P, Craddock GN, Aziz S, et al. Cyclosporin a initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. The Lancet. 1979;314(8151):1033-6.

6. Starzl TE, Klintmalm GBG, Iwatsuki S, Fernandez Bueno C. Past and Future Prospects of Orthoptic Liver Transplantation. Archives of Surgery. 1981;116(10):1342-3.

7. Todo S, Fung JJ, Starzl TE, Tzakis A, Demetris AJ, Kormos R, et al. Liver, kidney, and thoracic organ transplantation under FK 506. Annals of Surgery. 1990;212(3):295-307.

8. Baker A. Precision Medicine in Liver Transplantation. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 435-54.

9. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, et al. OPTN/SRTR 2017 Annual Data Report: Liver. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2019;19:184-283.

10. Current United States Population Estimator: United States Census Bureau, U.S. Department of Commerce; [Available from: https://www.census.gov/popclock/.

11. Casotti V, D'Antiga L. Liver Disease in Paediatric Medicine: An Overview. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 3-19.

12. Lyncyh SV, Balderson GA, editors. ANZLT Registry Report 2017. Brisbane, QLD, Australia: Australia and New Zealand Liver Transplant Registry; 2017.

13. Busuttil RW, Philip Seu MD, Micheal Millis J, Olthoff KM, Hiatt JR, Milewicz A, et al. Liver transplantation in children. Annals of Surgery. 1991;213(1):48-57.

14. McKiernan P, Mitchell E. Immunosuppression in Pediatric Liver Transplant. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 555-64.

15. Colledan M, Camagni S. Surgical Techniques. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 465-86.

16. Mogul DB, Luo X, Garonzik-Wang J, Bowring MG, Massie AB, Schwarz KB, et al. Expansion of the Liver Donor Supply Through Greater Use of Split-Liver Transplantation: Identifying Optimal Recipients. Liver Transplantation. 2019;25(1):119-27.

17. Kasahara M, Sakamoto S, Fukuda A. Pediatric Living Donor Liver Transplantation In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 487-514.

18. Lacaille F. Nutrition and Liver Disease. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 397-407.

19. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the american association for the study of liver diseases, american society of transplantation and the north american society for pediatric gastroenterology, hepatology and nutrition. Hepatology. 2014;60(1):362-98.

20. Bémeur C, Butterworth RF. Nutrition in the management of cirrhosis and its neurological complications. Journal of Clinical and Experimental Hepatology. 2014;4(2):141-50.

21. Muro AF, D'Antiga L, Mingozzi F. Gene Therapy in Pediatric Liver Disease. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 799-829.

22. Samyn M. Long-Term Outcome and Transition. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 653-64.

23. Bucuvalas JC, Alonso E, Magee JC, Talwalkar J, Hanto D, Doo E. Improving long-term outcomes after liver transplantation in children. American Journal of Transplantation. 2008;8(12):2506-13.

24. Sorensen LG. Pediatric solid organ transplantation and end stage disease: A slow journey towards understanding neurocognitive outcomes and their ramifications for clinical care. Pediatric Transplantation. 2015;19(2):136-8.

25. Taylor RM, Franck LS, Gibson F, Dhawan A. A critical review of the health-related quality of life of children and adolescents after liver transplantation. Liver Transplantation. 2005;11(1):51-60.

26. Dew MA, Switzer GE, Goycoolea JM, Allen AS, DiMartini A, Kormos RL, et al. Does transplantation produce quality of life benefits? A quantitative analysis of the literature. Transplantation. 1997;64(9):1261-73.

27. Moser JJ, Veale PM, McAllister DL, Archer DP. A systematic review and quantitative analysis of neurocognitive outcomes in children with four chronic illnesses. Paediatric Anaesthesia. 2013;23(11):1084-96.

28. Tarter RE, Switala J, Arria A, Plail J, van Thiel DH. Subclinical hepatic encephalopathy: Comparison before and after orthotopic liver transplantation. Transplantation. 1990;50(4):632-7.

29. O'Carroll RE, Couston M, Cossar J, Masterton G, Hayes PC. Psychological outcome and quality of life following liver transplantation: A prospective, national, single-center study. Liver Transplantation. 2003;9(7):712-20.

30. Tarter RE, Erb S, Biller PA, Switala J, Van Thiel DH. The quality of life following liver transplantation: A preliminary report. Gastroenterology Clinics of North America. 1988;17(1):207-17.

31. Höckerstedt K, Kajaste S, Muuronen A, Raininko R, Seppäläinen AM, Hillbom M. Encephalopathy and neuropathy in end-stage liver disease before and after liver transplantation. Journal of Hepatology. 1992;16(1-2):31-7.

32. Alonso EM. Growth and developmental considerations in pediatric liver transplantation. Liver Transplantation. 2008;14(5):585-91.

33. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 Annual Data Report: Liver. American Journal of Transplantation. 2018;18:172-253.

34. Childers RE, Ahn J. Diagnosis of Alcoholic Liver Disease: Key Foundations and New Developments. Clinics in Liver Disease. 2016;20(3):457-71.

35. K. WSA. Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of the liver. Brain. 1912;34(4):295-507.

36. Bismuth M, Funakoshi N, Cadranel JF, Blanc P. Hepatic encephalopathy: From pathophysiology to therapeutic management. European Journal of Gastroenterology and Hepatology. 2011;23(1):8-22.

37. Shawcross D, Jalan R. The pathophysiologic basis of hepatic encephalopathy: Central role for ammonia and inflammation. Cellular and Molecular Life Sciences. 2005;62(19-20):2295-304.

38. Dineen RA, Sibtain N, Karani JB, Lenthall RK. Cerebral manifestations in liver disease and transplantation. Clinical Radiology. 2008;63(5):586-99.

39. Campagna F, Biancardi A, Cillo U, Gatta A, Amodio P. Neurocognitive-neurological complications of liver transplantation: A review. Metabolic Brain Disease. 2010;25(1):115-24.

40. Butterworth RF. Metal toxicity, liver disease and neurodegeneration. Neurotoxicity research. 2010;18(1):100-5.

41. Barron TF, Devenyi AG, Mamourian AC. Symptomatic manganese neurotoxicity in a patient with chronic liver disease: Correlation of clinical symptoms with MRI findings. Pediatric Neurology. 1994;10(2):145-8.

42. Devenyi AG, Barron TF, Mamourian AC. Dystonia, hyperintense basal ganglia, and high whole blood manganese levels in Alagille's syndrome. Gastroenterology. 1994;106(4):1068-71.

43. Ikeda S, Yamaguchi Y, Sera Y, Ohshiro H, Uchino S, Yamashita Y, et al. Manganese deposition in the globus pallidus in patients with biliary atresia. Transplantation. 2000;69(11):2339-43.

44. Pujol A, Pujol J, Graus F, Rimola A, Peri J, Mercader JM, et al. Hyperintense globus pallidus on T1-weighted MRI in cirrhotic patients is associated with severity of liver failure. Neurology. 1993;43(1):65-9.

45. Ghosh PS, Hupertz V, Ghosh D. Neurological complications following pediatric liver transplant. Journal of Pediatric Gastroenterology and Nutrition. 2012;54(4):540-6.

46. Mao W, Hu Y, Lou Y, Chen Y, Zhang J. Abnormal serum iron markers in chronic hepatitis B virus infection may be because of liver injury. European Journal of Gastroenterology and Hepatology. 2015;27(2):130-6.

47. Walker SP, Wachs TD, Meeks Gardner J, Lozoff B, Wasserman GA, Pollitt E, et al. Child development: risk factors for adverse outcomes in developing countries. Lancet. 2007;369(9556):145-57.

48. Cagnon L, Braissant O. Hyperammonemia-induced toxicity for the developing central nervous system. Brain Research Reviews. 2007;56(1):183-97.

49. Anderson V, Catroppa C, Morse S, Haritou F, Rosenfeld J. Functional plasticity or vulnerability after early brain injury? Pediatrics. 2005;116(6):1374-82.

50. Sarkar T, Patro N, Patro IK. Cumulative multiple early life hits- a potent threat leading to neurological disorders. Brain research bulletin. 2019;147:58-68.

51. Foerster BR, Conklin LS, Petrou M, Barker PB, Schwarz KB. Minimal hepatic encephalopathy in children: Evaluation with proton MR spectroscopy. American Journal of Neuroradiology. 2009;30(8):1610-3.

52. Kyrana E, Dhawan A. Minimal hepatic encephalopathy in children, uncommon or unrecognised? Time to act. Journal of Hepatology. 2017;66(3):478-9.

53. Srivastava A, Chaturvedi S, Gupta RK, Malik R, Mathias A, Jagannathan NR, et al. Minimal hepatic encephalopathy in children with chronic liver disease: Prevalence, pathogenesis and magnetic resonance-based diagnosis. Journal of Hepatology. 2017;66(3):528-36.

54. Dara N, Sayyari AA, Imanzadeh F. Hepatic encephalopathy: Early diagnosis in pediatric patients with cirrhosis. Iranian Journal of Child Neurology. 2014;8(1):1-11.

55. Amlie-Lefond C. Evaluation and Acute Management of Ischemic Stroke in Infants and Children. CONTINUUM Lifelong Learning in Neurology. 2018;24(1, Child Neurology):150-70.

56. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al. Management of stroke in infants and children: A scientific statement from a special writing group of the american heart association stroke council and the council on cardiovascular disease in the young. Stroke. 2008;39(9):2644-91.

57. Gilmour S, Sorensen LG, Anand R, Yin W, Alonso EM. School outcomes in children registered in the Studies for Pediatric Liver Transplant (SPLIT) consortium. Liver Transplantation. 2010;16(9):1041-8.

58. Varni JW, Limbers CA, Burwinkle TM. Impaired health-related quality of life in children and adolescents with chronic conditions: A comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL™ 4.0 Generic Core Scales. Health and Quality of Life Outcomes. 2007;5.

59. Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: Reliability and Validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in Healthy and Patient Populations. Medical Care. 2001;39(8):800-12.

60. Martinez YJ, Ercikan K. Chronic illnesses in Canadian children: What is the effect of illness on academic achievement, and anxiety and emotional disorders? Child: Care, Health and Development. 2009;35(3):391-401.

61. Kaller T, Langguth N, Ganschow R, Nashan B, Schulz KH. Attention and executive functioning deficits in liver-transplanted children. Transplantation. 2010;90(12):1567-73.

62. Stracciari A, Guarino M, Pazzaglia P, Marchesini G, Pisi P. Acquired hepatocerebral degeneration: Full recovery after liver transplantation [7]. Journal of Neurology Neurosurgery and Psychiatry. 2001;70(1):136-7.

63. Collie A. Cognition in liver disease. Liver International. 2005;25(1):1-8.

64. Stewart SM, Hiltebeitel C, Nici J, Waller DA, Uauy R, Andrews WS. Neuropsychological outcome of pediatric liver transplantation. Pediatrics. 1991;87(3):367-76.

65. Zitelli BJ, Miller JW, Carlton Gartner Jr J, Malatack JJ, Urbach AH, Belle SH, et al. Changes in life-style after liver transplantation. Pediatrics. 1988;82(2):173-80.

66. Rodijk LH, Den Heijer AE, Hulscher JBF, Verkade HJ, De Kleine RHJ, Bruggink JLM. Neurodevelopmental outcomes in children with liver diseases: A systematic review. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(2):157-68.

67. D'Agostino D, Sanchez MC, Boldrini G. Pediatric Liver Disease in Latin America. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 687-98.

68. El-Shabrawi MHF, Kamal NM. Pediatric Liver Disease in the African Continent. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 699-742.

69. Srivastava A, Bolia R. Pediatric Liver Disease in the Asian Continent. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 743-66.

70. Perito ER, Roll G, Dodge JL, Rhee S, Roberts JP. Split Liver Transplantation and Pediatric Waitlist Mortality in the United States: Potential for Improvement. Transplantation. 2019;103(3):552-7.

71. Battula NR, Platto M, Anbarasan R, Perera MTPR, Ong E, Roll GR, et al. Intention to Split Policy: A Successful Strategy in a Combined Pediatric and Adult Liver Transplant Center. Annals of Surgery. 2017;265(5):1009-15.

72. OECD. PISA 2015 Results (Volume I)2016.

73. Clinical Guidelines for Organ Transplantation from Deceased Donors. 2019.

74. Bucuvalas J. Cognitive function, self-management and graft health in pediatric liver transplantation. American Journal of Transplantation. 2013;13(11):2790-1.

75. Ethical Guidelines for organ transplantation from deceased donors. Canberra: Australian Government National Health and Medical Research Council; 2016.

76. International registry in organ donation and transplantation: Preliminary numbers 2018. International Registry in Organ Donation and Transplantation; 2019.

77. Adult-to-Adult Living Donor Liver Transplantation (LDLT). Australian Health Minsters' Advisory Council; 2007.

78. Kim WR, Lake JR, Smith JM, Skeans MA, Schladt DP, Edwards EB, et al. OPTN/SRTR 2015 Annual Data Report: Liver. American Journal of Transplantation. 2017;17:174-251.

79. Register COR. e-Statistics report on transplant, waiting list and donor statistics. 2018 summary statistics, January 1 to December 31, 2018. Ottawa: The Society. 2019.

80. Kehar M, Parekh RS, Stunguris J, De Angelis M, Van Roestel K, Ghanekar A, et al. Superior Outcomes and Reduced Wait Times in Pediatric Recipients of Living Donor Liver Transplantation. Transplantation Direct. 2019;5(3).

81. Akateh C, Tumin D, Beal EW, Mumtaz K, Tobias JD, Hayes D, Jr., et al. Change in Health Insurance Coverage After Liver Transplantation Can Be Associated with Worse Outcomes. Digestive Diseases and Sciences. 2018;63(6):1463-72.

82. DuBay DA, MacLennan PA, Reed RD, Shelton BA, Redden DT, Fouad M, et al. Insurance Type and Solid Organ Transplantation Outcomes: A Historical Perspective on How Medicaid Expansion Might Impact Transplantation Outcomes. Journal of the American College of Surgeons. 2016;223(4):611-20.e4.

83. Arnon R, Annunziato RA, Willis A, Parbhakar M, Chu J, Kerkar N, et al. Liver transplantation for children with biliary atresia in the pediatric end-stage liver disease era: The role of insurance status. Liver Transplantation. 2013;19(5):543-50.

84. Kaller T, Langguth N, Petermann F, Ganschow R, Nashan B, Schulz KH. Cognitive performance in pediatric liver transplant recipients. American Journal of Transplantation. 2013;13(11):2956-65.

85. Robertson CMT, Dinu IA, Joffe AR, Alton GY, Yap JYK, Asthana S, et al. Neurocognitive outcomes at kindergarten entry after liver transplantation at <3 yr of age. Pediatric Transplantation. 2013;17(7):621-30.

86. Hadzic N, Vara R. Inherited Metabolic Disorders. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 271-8.

87. Betalli P, Davenport M. Biliary Atresua and Other Congenital Disorders of the Extrahepatic Biliary Tree. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 129-44.

88. Adebäck P, Nemeth A, Fischler B. Cognitive and emotional outcome after pediatric liver transplantation. Pediatric Transplantation. 2003;7(5):385-9.

89. Gritti A, Di Sarno AM, Comito M, De Vincenzo A, De Paola P, Vajro P. Psychological impact of liver transplantation on children's inner worlds. Pediatric Transplantation. 2001;5(1):37-43.

90. Haavisto A, Korkman M, Törmänen J, Holmberg C, Jalanko H, Qvist E. Visuospatial impairment in children and adolescents after liver transplantation. Pediatric Transplantation. 2011;15(2):184-92.

91. Posfay-Barbe KM, Barbe RP, Wetterwald R, Belli DC, McLin VA. Parental functioning improves the developmental quotient of pediatric liver transplant recipients. Pediatric Transplantation. 2013;17(4):355-61.

92. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Longitudinal study of cognitive and academic outcomes after pediatric liver transplantation. Journal of Pediatrics. 2014;165(1):65-72.e2.

93. Hattori H, Higuchi Y, Tsuji M, Inomata Y, Uemoto S, Asonuma K, et al. Living-related liver transplantation and neurological outcome in children with fulminant hepatic failure. Transplantation. 1998;65(5):686-92.

94. Krull KR, Fuchs C, Yurk H, Boone P, Alonso E. Neurocognitive outcome in pediatric liver transplant recipients. Pediatric Transplantation. 2003;7(2):111-8.

95. Talcott JB, Beath SV, Patel T, Griffiths G, Kelly DA. Long-term Effects of Cholestatic Liver Disease in Childhood on Neuropsychological Outcomes and Neurochemistry. J Pediatr Gastroenterol Nutr. 2019;69(2):145-51.

96. Wayman KI, Cox KL, Esquivel CO. Neurodevelopmental outcome of young children with extrahepatic biliary atresia 1 year after liver transplantation. Journal of Pediatrics. 1997;131(6):894-8.

97. Hegde AN, Mohan S, Lath N, Lim CCT. Differential Diagnosis for Bilateral Abnormalities of the Basal Ganglia and Thalamus. RadioGraphics. 2011;31(1):5-30.

98. Herynek V, Wagnerová D, Hejlová I, Dezortová M, Hájek M. Changes in the brain during long-term follow-up after liver transplantation. Journal of Magnetic Resonance Imaging. 2012;35(6):1332-7.

99. Donmez YF, Guvenc Z, Emiroglu KF, Coskun M, Haberal M. Evaluation of neurological complications in pediatric liver transplant recipients: MRI versus CT. Journal of Child Neurology. 2009;24(6):656-63.

100. Gungor S, Kilic B, Arslan M, Selimoglu MA, Karabiber H, Yilmaz S. Early and late neurological complications of liver transplantation in pediatric patients. Pediatric Transplantation. 2017;21(3).

101. Afshar S, Porter M, Barton B, Stormon M. Intellectual and academic outcomes after pediatric liver transplantation: Relationship with transplant-related factors. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2018;18(9):2229-37.

CHAPTER 2:

INTELLECTUAL AND ACADEMIC OUTCOMES AFTER PEDIATRIC LIVER TRANSPLANTATION: RELATIONSHIP WITH TRANSPLANT-RELATED FACTORS

Afshar S, Porter M, Barton B, Stormon M. Intellectual and academic outcomes after pediatric liver transplantation: Relationship with transplant-related factors. American Journal of Transplantation. 2018;18(9):2229-37.

Afshar, S., Porter, M., Barton, B., & Stormon, M. (2018). Intellectual and academic outcomes after pediatric liver transplantation: relationship with transplant-related factors. *American Journal of Transplantation*, 18(9), p. 2229-2237.

DOI: 10.1111/ajt.14924

CHAPTER 2-SUPPLEMENTARY:

THE RELATIONSHIP BETWEEN WAITING TIME AND POORER LONG-TERM OUTCOMES IS DEPENDENT ON DISEASE SEVERITY AT TRANSPLANT

Afshar S, Porter M, Barton B, & Stormon M.

1 | INTRODUCTION

We recently published a study looking at factors that predict long-term cognitive outcomes after pediatric liver transplantation.[1] The study was one of only a few studies to have attempted to predict long-term cognitive outcomes after paediatric liver transplantation,[2-13] although a number of the previous studies used non-independent samples. What is universal across all studies is the lack of exploration of interactions between factors. To date, only main effects have been considered. It is plausible, and speculated, that the role of some predictors may emerge depending on their relationship with other factors.

In the original study, we found that days on the waitlist was often a significant predictor for cognitive and academic outcomes in children with a primary diagnosis of Biliary Atresia (BA). It makes intuitive sense that the longer one is significantly ill (i.e., so ill that they have been placed on the transplant waitlist), the greater the impact will be on their functioning, including neurological and cognitive development. However, time on the transplant waitlist has not been consistently found to be a significant predictor of long-term cognitive outcomes, although it should be noted that only a limited number of studies explored the role of time on the waitlist on cognitive outcomes.[2, 8, 10, 11] This prompted the authors to question whether time on the waitlist may in fact interact with other predictors. We theorised that the role of days on waitlist may perhaps be dependent on severity of illness. More specifically, that the negative relationship between longer time waiting and poorer cognitive outcomes only emerges when children are more severely ill. In sum, we briefly present the results of additional exploratory linear multiple regression models involving the predictors of Days on Waitlist and Serum Bilirubin at Transplant (measure of liver function), along with their corresponding interaction term. We hypothesised that this model would be a significant predictor of the same intellectual and academic outcomes in children with BA explored in our

previous study, and would qualitatively account for a higher amount of variance (R^2) compared with our previous models.

2 | METHOD

2.1 | Analysis

Eight multiple linear regressions were conducted for each outcome measure of intelligence and academic achievement: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), Processing Speed Index (PSI), Word Reading, Phonological Decoding, Spelling, and Mathematics. Two predictors were included in each model, Days on Waitlist and Serum Bilirubin at Transplant (µM), along with the interaction term (Days on Waitlist x Serum Bilirubin at Transplant). The overall model was considered significant at $\alpha = 0.05$. As is convention, when the interaction term was found to be statistically significant, the statistical significance and interpretation of the component terms was ignored.[14] The R^2 for each model was qualitatively compared against the results for our original final models. Unfortunately, as the analyses in the current supplementary chapter are distinct from the original models, quantitative comparisons (such as R^2 change) could not be conducted and this is an important limitation to note. However, as the two sets of analyses involve the exact same participants, it was felt that a qualitative comparison of the magnitude of the effects via R^2 of the overall models was worthwhile and a point for future consideration. Statistical analyses were conducted on IBM SPSS version 22.[15]

3 | RESULTS

Mean Serum Bilirubin (µM) for the sample of children with BA was 271.33 (SD = 186.94, Range: 20-642; Median: 221; 1st Quartile: 104; 3rd Quartile: 386). Mean Days on Waitlist was 221.52 (SD = 288.10; Range: 1-1257; Median: 127; 1st Quartile: 34; 3rd Quartile: 211).

3.1 | Verbal comprehension index

The results from the Multiple Linear Regression revealed that VCI was predicted by the overall model ($F_{(3,23)}$ = 5.114; P = .007; R^2 = .40; $R^2_{\text{Previous Model}}$ = .27), which included Days on Waitlist (β = -.06), Bilirubin (β = .08) and the interaction term (β = -.60; P = .051). Results indicated that the influence of Days on Waitlist on VCI was dependent on the Bilirubin levels at transplant. For children with higher Serum Bilirubin, greater Days on Waitlist predicted poorer VCI scores, whereas children with low Serum Bilirubin did not show an association between Days on Waitlist and VCI.

The regression equation line for different levels of Serum Bilirubin at transplant is illustrated on Figure 1 for ease of understanding. It demonstrates that the negative relationship between Days on Waitlist and VCI is influenced by the levels of Serum Bilirubin at transplant. More specifically, VCI is more strongly associated with Days on Waitlist in children with higher bilirubin at transplant, whereas the association between VCI and Days on Waitlist is negligible in children with lower bilirubin at transplant.

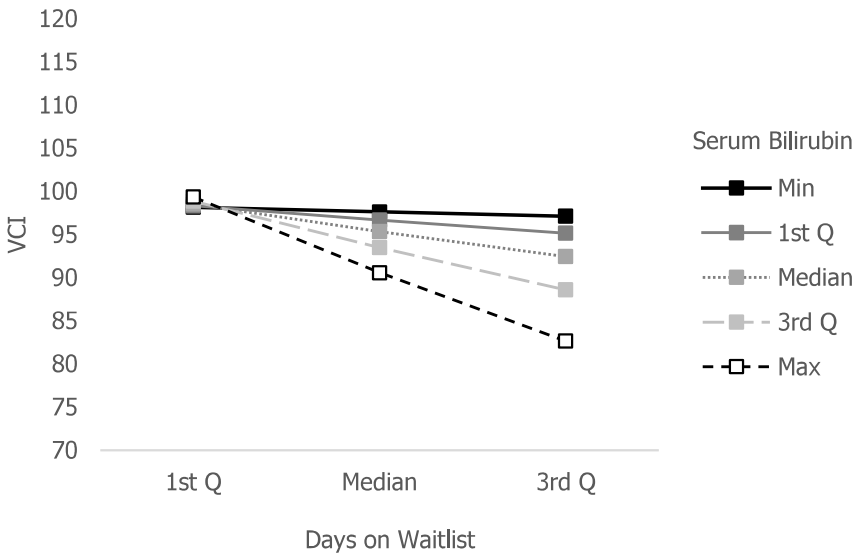


FIGURE 1 Interaction of days on waitlist and serum bilirubin in predicting VCI

VCI: verbal comprehension index; 1st Q: first quartile; 3rd Q: third quartile

3.2 | Perceptual reasoning index

The results indicated that the overall model including Days on Waitlist (β = .26), Bilirubin (β = .06) and the interaction term (β = -.81; P = .011) was also significant at predicting long-term PRI scores ($F_{(3,23)}$ = 4.962; P = .008; R^2 = .39; $R^2_{\text{Previous Model}}$ = .20). Results again demonstrated that the negative predictive power of Days on Waitlist on PRI scores was dependent on the level of Serum Bilirubin at transplant. While children with low Serum Bilirubin at transplant showed minimal variability in PRI scores across different waitlist times, children who had higher Serum Bilirubin had poorer scores the longer they spent on the transplant waitlist (Figure 2).

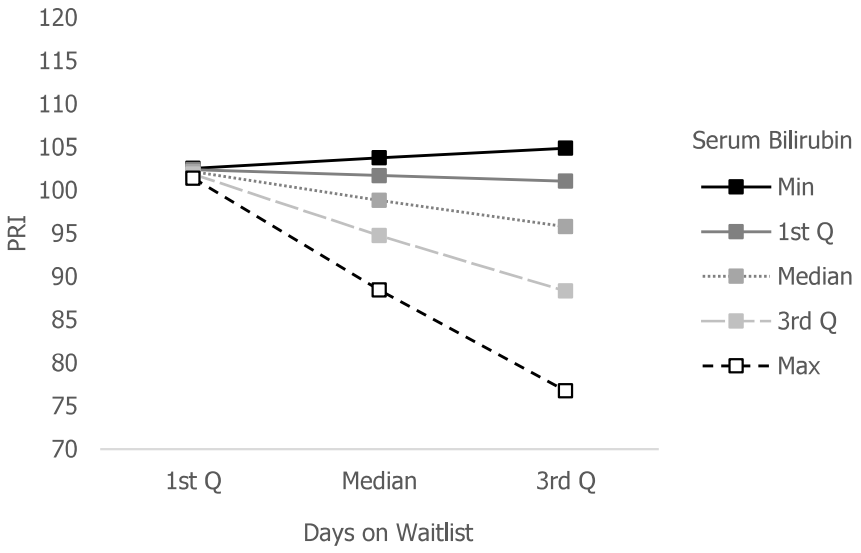


FIGURE 2 Interaction of days on waitlist and serum bilirubin in predicting PRI

PRI: perceptual reasoning index; 1st Q: first quartile; 3rd Q: third quartile

3.3 | Working memory index

The overall model was again significant ($F_{(3,23)}$ = 5.682; P = .005; R^2 = .43; $R^2_{\text{Previous Model}}$ = .16) when predicting WMI from Days on Waitlist (β = .28), Serum Bilirubin (β = .15) and the interaction term (β = -.87; P = .006). As illustrated by Figure 3, Days on Waitlist had less predictive power in children with low Serum Bilirubin at transplant, whereas there was a

negative relationship between Days on Waitlist and WMI outcomes for children with higher Serum Bilirubin.

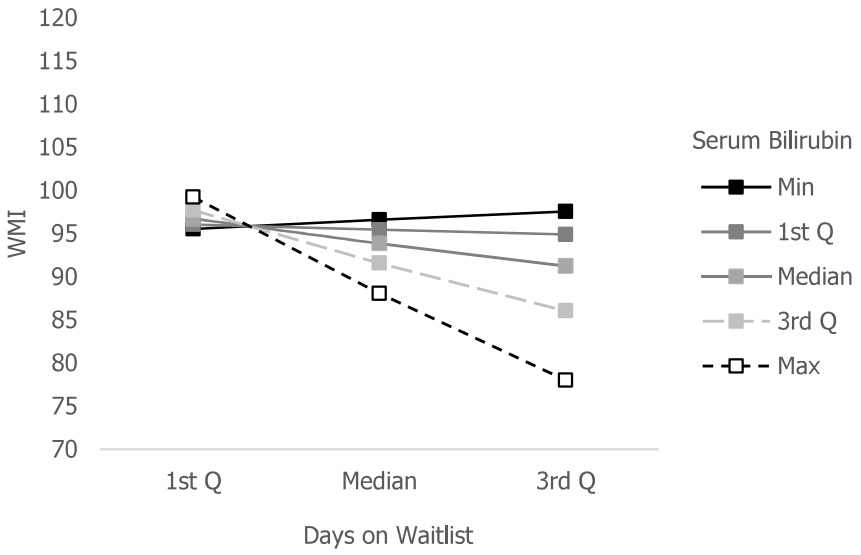


FIGURE 3 Interaction of days on waitlist and serum bilirubin in predicting WMI

WMI: working memory index; 1st Q: first quartile; 3rd Q: third quartile

3.4 | Processing speed index

The overall model was not significant in predicting long-term PSI outcomes ($F_{(3,23)}$ = 1.678; P = .199; R^2 = .18; $R^2_{\text{Previous Model}}$ = .34).

3.5 | Mathematics

The overall model showed a trend in predicting long-term mathematical ability ($F_{(3,23)}$ = 2.947; P = .054; R^2 = .28; $R^2_{\text{Previous Model}}$ = .29). However, the interaction term was not a significant predictor (β = -.40; P = .224).

3.6 | Reading

The overall model was significant ($F_{(3,23)}$ = 5.462; P = .006; R^2 = .42; $R^2_{\text{Previous Model}}$ = .17) when predicting Reading from Days on Waitlist (β = -.02), Serum Bilirubin (β = -.17) and

the interaction term (β = -.57; P = .059). As illustrated in Figure 4, the negative relationship between Days on Waitlist and Reading ability was evident amongst children with high Serum Bilirubin at transplant. However, the relationship was negligible in children with low Serum Bilirubin at transplant.

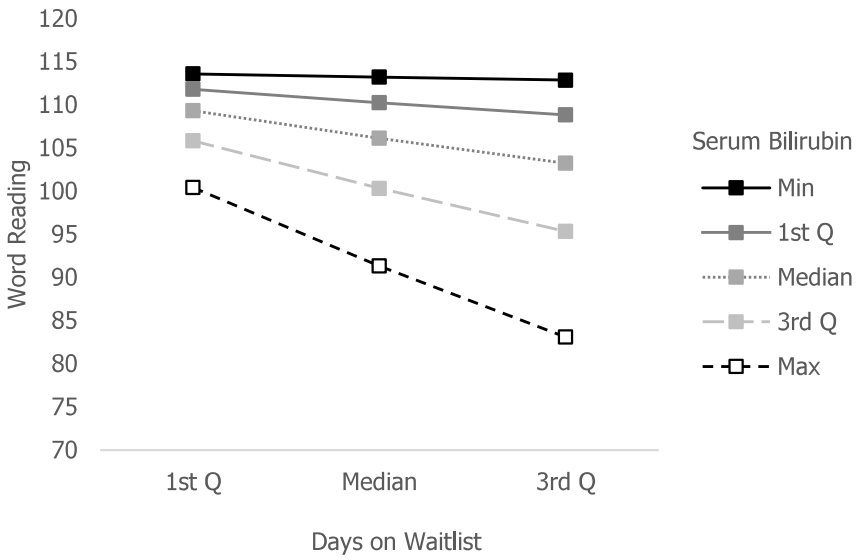


FIGURE 4 Interaction of days on waitlist and serum bilirubin in predicting Reading

1st Q: first quartile; 3rd Q: third quartile

3.7 | Phonological decoding

The overall model showed a trend (see Figure 5) in predicting phonological decoding ($F_{(3,22)}$ = 3.001; P = .052; R^2 = .29; $R^2_{\text{Previous Model}}$ = .14) from the factors of Days on Waitlist (β = .49), Bilirubin (β = -.10) and the interaction term (β = -.76; P = .024).

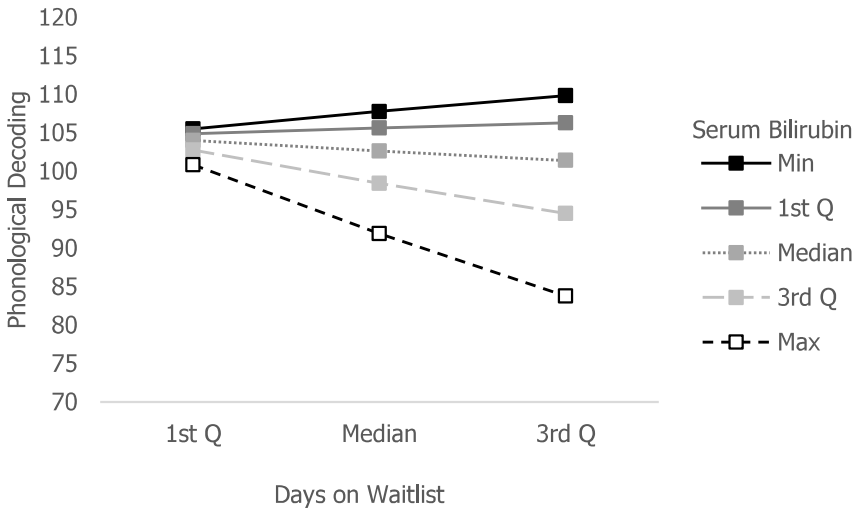


FIGURE 5 Interaction of days on waitlist and serum bilirubin in predicting Phonological Decoding

1st Q: first quartile; 3rd Q: third quartile

3.8 | Spelling

The overall model (see Figure 6) was not significant, but showed a trend in predicting Spelling ability ($F_{(3,23)}$ = 2.755; P = .066; R^2 = .26; $R^2_{\text{Previous Model}}$ = Nil significant predictors). Similarly, a trend was noted for the interaction term (β = -.54; P = .11) in the model with Days on Waitlist (β = .08) and serum Bilirubin (β = -.09).

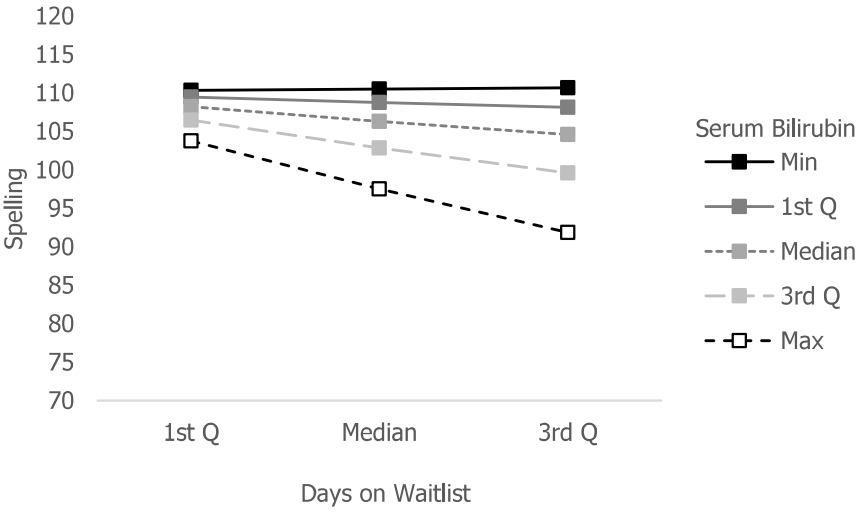


FIGURE 6 Interaction of days on waitlist and serum bilirubin in predicting Spelling

1st Q: first quartile; 3rd Q: third quartile

4 | DISCUSSION

The results of the revised analyses show that the more parsimonious model of Days on Waitlist and Serum Bilirubin along with the interaction term was frequently a better predictor of intellectual and academic outcomes than our previous model. The current model was a significant predictor of outcomes in VCI, PRI, WMI, and Word Reading. It further showed a trend in predicting Phonological Decoding and Spelling, but was not a significant predictor of PSI or Mathematics. Overall, the model was a stronger predictor of intelligence than academic outcomes. Furthermore, all of the significant models accounted for a larger proportion of the variance than the models in our previous study.

The results of the current analyses indicate that the predictive power between time spent waiting for a transplant and neurocognitive outcomes may be dependent on how ill one is while they wait (or how their liver is functioning). More specifically, in children with better-functioning livers at time of transplant, intellectual and academic outcomes were generally equivalent regardless of whether they spent a short or long time on the waitlist. In children with poorer-functioning livers at transplant however, those who spent greater days on the transplant waitlist had poorer intellectual and academic outcomes than those who spent shorter periods on the waitlist.

The current exploratory analyses included serum bilirubin at transplant. However, it could also be valuable to explore whether serum bilirubin levels at time of inclusion on the waitlist is a more worthwhile factor to investigate within this interaction. More specifically, if a patient presents with higher serum bilirubin upon entry on the transplant waitlist, they may be more sensitive to extended waiting times and hence need prioritisation. As such, this may be a more informative factor for decision makers to consider. The same can be said about highest serum bilirubin levels while on the waitlist. Whilst these were not analysed in the

current study due to issues with multiple comparisons, these are plausible avenues for further investigation and should be considered in future research.

Our current analysis is evidently exploratory and revisits previously analysed data, increasing the risk of type I error. However, we hope that researchers around the world explore whether this model has the same predictive power in their previously published and future studies, considering the simplicity of the model and strength of the results. If such a finding were to be replicated, this would have important implications for transplant procedures, insofar as they would need to prioritise shorter waiting times, especially for children with more severe presentations.

REFERENCES

1. Afshar S, Porter M, Barton B, Stormon M. Intellectual and academic outcomes after pediatric liver transplantation: Relationship with transplant-related factors. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2018;18(9):2229-37.

2. Haavisto A, Korkman M, Törmänen J, Holmberg C, Jalanko H, Qvist E. Visuospatial impairment in children and adolescents after liver transplantation. Pediatric Transplantation. 2011;15(2):184-92.

3. Gilmour S, Adkins R, Liddell GA, Jhangri G, Robertson CM. Assessment of psychoeducational outcomes after pediatric liver transplant. American Journal of Transplantation. 2009;9(2):294-300.

4. Wayman KI, Cox KL, Esquivel CO. Neurodevelopmental outcome of young children with extrahepatic biliary atresia 1 year after liver transplantation. Journal of Pediatrics. 1997;131(6):894-8.

5. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Cognitive and academic outcomes after pediatric liver transplantation: Functional outcomes group (FOG) results. American Journal of Transplantation. 2011;11(2):303-11.

6. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Longitudinal study of cognitive and academic outcomes after pediatric liver transplantation. Journal of Pediatrics. 2014;165(1):65-72.e2.

7. Stewart SM, Hiltebeitel C, Nici J, Waller DA, Uauy R, Andrews WS. Neuropsychological outcome of pediatric liver transplantation. Pediatrics. 1991;87(3):367-76.

8. Robertson CMT, Dinu IA, Joffe AR, Alton GY, Yap JYK, Asthana S, et al. Neurocognitive outcomes at kindergarten entry after liver transplantation at <3 yr of age. Pediatric Transplantation. 2013;17(7):621-30.

9. Krull KR, Fuchs C, Yurk H, Boone P, Alonso E. Neurocognitive outcome in pediatric liver transplant recipients. Pediatric Transplantation. 2003;7(2):111-8.

10. Kaller T, Langguth N, Ganschow R, Nashan B, Schulz KH. Attention and executive functioning deficits in liver-transplanted children. Transplantation. 2010;90(12):1567-73.

11. Kaller T, Langguth N, Petermann F, Ganschow R, Nashan B, Schulz KH. Cognitive performance in pediatric liver transplant recipients. American Journal of Transplantation. 2013;13(11):2956-65.

12. Kaller T, Schulz KH, Sander K, Boeck A, Rogiers X, Burdelski M. Cognitive abilities in children after liver transplantation. Transplantation. 2005;79(9):1252-6.

13. Schulz KH, Wein C, Boeck A, Rogiers X, Burdelski M. Cognitive performance of children who have undergone liver transplantation. Transplantation. 2003;75(8):1236-40.

14. Howell DC. Statistical methods for psychology: Cengage Learning; 2012.

15. IBM SPSS Statistics for Windows Version 22.0. Armonk, NY: IBM Corp; 2013.

CHAPTER 3:

LONG-TERM COGNITIVE, PSYCHOSOCIAL, AND QUALITY OF LIFE OUTCOMES OF PEDIATRIC LIVER TRANSPLANT RECIPIENTS

Afshar S, Porter M, Barton B, Stormon M.

ABSTRACT

The current cross-sectional study investigated long-term (>1 year) outcomes of 40 children (87% participation rate; aged 6–16 years) who received a liver transplant for chronic liver disease at The Children's Hospital Westmead, Sydney, Australia. It incorporated a range of validated standardized questionnaires including the Behavior Rating Inventory of Executive Functions, Conners 3, Behavior Assessment System for Children (2nd Edition), and the PedsQL™ to examine executive functions, attention, behaviour, academic development, psychosocial functioning, and quality of life. This study was the first to concurrently utilize parent-, child- and teacher-reports. Relative to normative populations, the current sample had greater difficulties with the metacognitive aspects of executive functions than self-regulatory abilities, consistent with previous literature. Greater difficulties were also noted in inattention, hyperactivity, learning problems, peer relationships, psychosocial functioning, alongside increased somatization. Defiance and withdrawal behaviours were also highlighted within the home setting. In addition, higher-than-expected ADHD symptomatology based on DSM-5 diagnostic criteria was identified. Quality of life ratings were lower than the general population but largely consistent with other chronic illness samples. Overall, findings demonstrate that childhood liver transplant recipients are at greater risk in their day-to-day functioning, and utilizing multi-informant reports is vital to better capture long-term outcomes.

1 | INTRODUCTION

Recent advances in liver transplant procedures and medical management has resulted in improved survival in pediatric recipients.[1] As a result, the focus of research has shifted from survival rates to health-related quality of life (HRQOL), and long-term cognitive, academic and psychosocial outcomes for these children.[2-5] A number of studies have utilized the cost-effective and ecologically sensitive method of informant-reports to investigate long-term outcomes.[6-8] However, research has primarily focused on parent/caregiver reports, with little attention placed upon teacher or self-reports. Additionally, studies typically incorporate a single or limited number of measures. Furthermore, investigations have almost entirely been conducted within North America and Western Europe. Research needs to be conducted in diverse jurisdictions, utilizing specific and sensitive clinical tools in addition to HRQOL of measures, as well as incorporating feedback from multiple informants in order to gain a more comprehensive and ecologically sensitive picture of the lives of children with liver transplants.

In terms of quality of life, results have consistently identified poorer HRQOL in children with liver transplants compared with healthy controls, particularly regarding psychosocial functioning but generally equivalent to those with other chronic-but-stable health conditions.[9-15] In more recent years, studies have employed specific standardized clinical tools to investigate functional outcomes in more detail, particularly cognitive, psychosocial and adaptive functioning.[3] These measures typically stratify their normative group and provide data broken down by age and sex[16-18] rather than global normative data, as is the case for most HRQOL measures.[19] This allows for more thorough assessment of a child's functioning compared to their peers and can highlight abnormality or impairment.

Studies using clinical tools have primarily utilized paper and pencil psychometric and neuropsychological tests to assess the abilities of pediatric liver transplant recipients. Overall,

findings reveal a downward shift in the distribution of the population, with pediatric liver transplant recipients as a group falling significantly below the population mean on a range of cognitive measures including intelligence, attention and mathematics.[3, 5, 6, 20, 21] While there are advantages to using performance based neuropsychological measures (such as intelligence tests), the use of these tests in isolation may be unable to unveil the day-to-day functioning of patients as they are conducted in a one-to-one, structured and distraction-free setting.[22] Standardized informant and self-report questionnaires of day-to-day functioning can offer a broader and more ecologically-sensitive picture of an individual's abilities (and impairments)[23-26] and are, therefore, worthwhile in understanding the long-term outcomes of patients, especially when data is collected from multiple informants.[27]

Findings to date have indicated that compared to the normative populations, children post-liver transplantation have significantly elevated symptoms of externalizing (aggressive and rule-breaking behavior) and internalizing (anxiety, depression and somatic problems) disorders, social and thought problems, with particular issues around attention and somatic problems,[5, 7, 8, 11, 28, 29] although this is not consistent across the literature.[30, 31] This inconsistency across studies is in part explained by the differing measurement tools used as well as the variation in how data is dissected and summarized such as reporting composite averages rather than individual subscales. Findings also suggest increased symptoms of Post-Traumatic Stress Disorder,[32] as well as poorer global adaptive functioning.[3, 28, 29, 33]

Despite their utility, only a handful of studies have used standardized questionnaires to investigate neuropsychological domains such as executive functioning.[5-7, 34, 35] Results consistently indicate greater problems with the metacognitive aspects of executive skills, sometimes referred to as "cool executive functions",[36] such as working memory, planning and organization, rather than the behavioral or self-regulatory abilities,[6, 7, 34, 37] sometimes

referred to as "hot executive functions".[36] This pattern of executive difficulties has been shown to remain stable over a two year period,[5] implying that these deficits persist beyond the acute illness period and do not simply reflect secondary issues such as adjustment. Another small study (N = 15) in Finland found executive functions and language skills to be normal on parent questionnaires, but difficulties were highlighted with other domains including perception, memory, motor skills, social functioning and emotional/behavioural problems.[38]

One key shortfall of previous studies that utilized HRQOL and standardized clinical questionnaires is that the use of teacher questionnaires has been rare, with only two studies to date incorporating teacher ratings into the study design.[5, 6, 39] Typically, only parent-report questionnaires[3, 7, 40] or parent- and child self-report questionnaires[11, 29, 30, 41] are utilized, and at times these are used in isolation.[41, 42] Teachers can provide an invaluable perspective on a child's functioning and development, as they are well-placed to see a child's academic progress and output, social interactions and relationships, and their ability to adapt and function within the school setting.[27, 43, 44] There is also a propensity in some studies to utilize or report on only one or a limited number of measures as part of the study design.[13, 28] When using more than one measure, studies are not only able to provide a broader picture of patient functioning, but this also allows for comparison of results across measures that assess overlapping domains, which in turn can provide convergent validity on findings.

The majority of studies in this field have been conducted in North America in addition to a few studies in Western Europe.[45] Only two studies to date have been conducted in Australia and both were limited by small sample sizes (N = 13 and 4 respectively),[7, 35] with the latter only including children with a specific metabolic disorder, namely ornithine transcarbamylase deficiency.[35] It is important to investigate the outcomes of children across a range of jurisdictions in order to be able to identify context-specific effects in the long-term

outcomes of children with liver transplantation.[2] If studies are restricted to one region, then the role of factors such as varying donation rates, transplant policies and procedures, and presence of universal health insurance cannot be isolated and partitioned from the findings. Therefore, studies from a broader range of jurisdictions are required to better understand the effects directly associated with the liver disease and transplantation process.

To address the current gaps and inconsistencies in the literature, the current study utilized parent-, teacher- and self-report questionnaires to investigate the long-term cognitive, psychosocial, and HRQOL outcomes of children who had received a liver transplant for chronic end-stage liver disease within Australia through a cross-sectional study. A wide range of domains were assessed including attention, executive functions, behavioural problems, psychological wellbeing, adaptive functioning, academic achievement and HRQOL. It was hypothesized that, on average, pediatric liver transplant recipients would have significantly poorer outcomes compared to published normative samples across attention, metacognitive executive functions, anxiety, somatization, adaptive skills, academic achievement and HRQOL. Furthermore, a greater number of children were predicted to have clinically significant symptoms or impairments than the general population. The current study is the first, to our knowledge, to incorporate multiple measures across a range of domains with multiple informants in order to gain a more detailed understanding of outcomes after pediatric liver transplantation, allowing for targeted pre-emptive supports and interventions to improve long-term outcomes.

2 | METHOD

2.1 | Participants

Recruitment for the current study was conducted as part of a larger study investigating long-term neuropsychological outcomes after liver transplant for chronic end-stage liver

disease.[2] Forty-six children met eligibility criteria and were invited to participate. Forty-one children (22 female) and their families agreed to participate in the current study and provided written formal consent. One family did not return any of their questionnaires. The five remaining eligible children who did not participate were aged between 6 and 16 years, and did not differ from the study sample apart from being primarily from non-metropolitan areas. Reasons for not participating included logistical difficulties for four families and one adolescent child refused to participate. The demographics of the final study sample are summarized in Table 1. The majority of children had a diagnosis of biliary atresia (BA; n = 27; 67.5%). Other diagnoses included: α-1 antitrypsin deficiency (n = 3; 7.5%); Alagille syndrome (n = 3; 7.5%); autoimmune hepatitis; progressive familial intrahepatic cholestasis; cryptogenic cirrhosis; cholestatic disease; meningococcal infection; bile acid synthesis disorder; or sub-acute hepatitis of unknown aetiology (all n = 1).

TABLE 1 Sample characteristics and demographics

	Mean	SD	N	Median	Minimum	Maximum
Age at transplant, y	2.50	3.15	40	1.11	0.40	14.49
Age at assessment, y	11.09	3.72	40	10.18	6.26	16.89
Time since transplant, y	8.60	3.83	40	7.27	1.24	16.26
Days on the waitlist	211.70	289.10	40	89	1	1257
PELD score at transplant	23.30	11.43	40	22	2	48
Days in PICU after transplant	9.05	5.84	40	8	3	39
Average Parental Education	12.73	2.23	40	12	9	17

PELD: pediatric end-stage liver disease; PICU: pediatric intensive care unit.

2.2 | Materials

The Behavior Rating Inventory of Executive Function (BRIEF),[17] the Conners 3rd Edition (Conners 3)[16] and the Behavior Assessment System for Children, Second Edition (BASC-2)[46] were utilized. There was some overlap of domains between questionnaires

allowing for qualitative comparison of results. All three questionnaires were standardized, spanned the age of participants and were psychometrically sound (see corresponding test manuals for details). T-scores were utilized with a mean of 50 and a standard deviation of 10. Higher scores indicate elevated problems/symptoms, with the exception of the adaptive scales within the BASC-2, where lower scores represent poorer functioning. The PedsQL™ Generic Core Scale, PedsQL™ Transplant Module and PedsQL™ Multidimensional Fatigue Scale were utilized to measure different aspects of HRQOL, including overall functioning, Transplant related functioning, and fatigue. Higher scores on these HRQOL measures reflected better quality of life.

2.2.1 | BRIEF

The BRIEF was used to investigate executive functioning. It is divided into nine component scales: Inhibition; Shifting; Emotional Control; Initiation; Working Memory; Planning/Organizing; Organization of Materials; and Monitoring. The first three scales together make up the broader composite index of Behavioral Regulation Index and the remaining six make up the composite index of Metacognition. The BRIEF also provides a Global Executive Composite that combines all nine scales (see manual for detailed description of each individual component).[17] Parent- and teacher-reports were provided for all participants. Self-report versions were provided for all children 11 years or older (n=19).

2.2.2 | Conners 3

The Conners 3 questionnaire is comprised of six symptomatic measures including: Inattention, Hyperactivity/Impulsivity, Learning Problems, Executive Functioning, Defiance/ Aggression, and Peer Relations. It also provides scores on diagnostic indices based on the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM–5)[47] for Attention Deficit Hyperactivity Disorder (ADHD) Inattentive presentation and Hyperactive/Impulsive

presentation, Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), as well as symptom counts for each diagnostic category. The domains of ADHD and attention are particularly relevant as studies have identified weaknesses in these areas in children post-liver transplantation.[7, 48, 49] Parent and teacher questionnaires were provided for all children and self-report versions of the questionnaires were provided to all children 8 years or older (n=27).

2.2.3 | BASC-2

The BASC-2 contains scales covering a range of domains including Externalizing problems (Hyperactivity, Aggression, and Conduct), Internalizing problems (Anxiety, Depression, Somatization), Behavioral Symptoms and School Problems (Atypicality, Withdrawal, Attention, Learning Problems), and Adaptive Functioning (Adaptability, Social Skills, Leadership, Activities of Daily Living, and Functional Communication). The child-report version includes additional factors of Attitude to School and Teachers, Sensation-Seeking, Locus of Control, Social Stress, Sense of Inadequacy, Emotional Symptoms, Relationship with Parents, Interpersonal Relationships, Self-Esteem, Self-Reliance, and Personal Adjustment. Parent-, teacher- and self-report questionnaires were provided to all participants.

2.2.4 | PedsQL™ Generic Core Scale Version 4.0

The Pediatric Quality of Life Inventory™, Version 4.0 (PedsQL™) Generic Core Scale is a brief quality of life measure developed by Varni et al.[19] that assesses physical and psychosocial functioning in children. Parent- and self-report questionnaires were provided to all participants. Results were compared against a large normative study of healthy controls including 5079 self-reports and 8714 parent-proxy reports.[50] The results were also compared with a further two published studies investigating the quality of life in a sample of solid organ transplant recipients (199 self-reports and 247 parent-reports)[14] and pediatric liver transplant recipients (363 self-report and 869 parent report).[10]

2.2.5 | PedsQL™ 3.0 Transplant Module

Complementing the PedsQL Generic Core Scale is the PedsQL™ 3.0 Transplant Module,[14] a quality of life measure that assesses transplant-specific functioning in children. The Transplant Module was provided to all families. Results were compared to the previously published sample of solid-organ transplant recipients (269 self- and 338 parent-reports).[14]

2.2.6 | PedsQL™ Multidimensional Fatigue Scale

Finally, the PedsQL™ Multidimensional Fatigue Scale is a further quality of life measure that investigates fatigue in children, and is utilized in chronic illness groups.[51-53] Parent- and self-report questionnaires were provided to all participants. Results were compared to previously published samples of healthy controls (209 self-reports and 259 parent-reports)[54] and pediatric oncology patients (220 self-reports and 337 parent-reports)[53] as well as a recently published sample of pediatric liver transplant recipients (71 self-reports and 100 parent-reports).[15]

2.3 | Procedure

Questionnaires were mailed out to consenting families with reply-paid envelopes, given at face-to-face meetings during routine follow-up clinic visits, or at the cognitive assessment appointment. Teacher questionnaires were returned directly to the first author and not to parents. Self-report questionnaires were only provided to children who were within the age range for each measure. Ethics approval was obtained from the Human Research Ethics Committee of the Sydney Children's Hospital Network (approval code: 12/SCHN/45).

2.4 | Analysis

Statistical analyses were conducted using IBM SPSS version 22.[55] One sample *t*-tests (two-tailed; $\alpha = .05$) were conducted to explore whether the sample had mean scores

significantly different to the normative population (normative mean = 50) on a range of neuropsychological, psychosocial and quality of life factors as assessed by standardized questionnaires. The rate of children falling in the borderline or clinical range (CR) for each measure, defined as more than 1.5 standard deviations (SD) above the mean, was reviewed. Due to the small sample size, Chi-square goodness-of-fit analyses could not be conducted to compare the proportion of children with symptoms in the borderline or clinical range against expected rates in the general population (7%), as expected cell counts were below five which is an underlying assumption of the analysis. Therefore, only descriptive frequencies were reported. Interrater agreement on questionnaires was assessed by examining correlations between parent-, teacher- and self-reports.

3 | RESULTS

3.1 | BRIEF

Figure 1 displays the BRIEF results. Detailed results can be viewed in Supplementary Tables 1-3. The response rate amongst informants was variable with parents the most likely to complete and return the measure. Thirty-three parent (80%), 27 teacher (66%) and 13 self-reports (68%) were returned. For parent report questionnaires, one sample *t*-tests indicated significantly higher mean scores on planning (Mean = 58.94; SD = 13.61; $t_{(32)}$ = 3.77; P =.001; CR (Clinical range) = 21%), working memory (Mean = 57.12; SD = 14.15; $t_{(32)}$ = 2.89; P = .007; CR = 21%), and monitoring (Mean = 55.79; SD = 12.35; $t_{(32)}$ = 2.69; P = .011; CR = 12%). Higher rates of children performed in the borderline or clinical range compared to the 7% expected in the normal population. For teacher-reports, one sample *t*-tests again showed significantly higher mean scores for planning (Mean = 58.74; SD =14.41; $t_{(26)}$ = 3.15; P = .004; CR = 26%), working memory (Mean = 56.37; SD = 14.42; $t_{(26)}$ = 2.30; P = .030; CR = 22%), and monitoring (Mean = 57.89; SD = 14.50; $t_{(26)}$ = 2.83; P = .009; CR = 19%). Teacher-reports additionally highlighted significantly higher mean scores for

Initiation (Mean = 57.56; SD = 13.25; $t_{(26)}$ = 2.96; P = .006; CR = 19%). Neither parent- nor teacher-reports showed significantly higher means for Inhibition, Shifting, Emotional Control, or Organisation of Material on the subdomains of the BRIEF. Overall, the results indicated that children had difficulties with the metacognitive aspects executive functions across both parent- ($Metacognition_{Parent}$ = 56.76; SD = 12.88; $t_{(32)}$ = 3.01; P = .005; CR = 21%) and teacher-reports ($Metacognition_{Teacher}$ = 57.33; SD = 14.48; $t_{(26)}$ = 2.63; P = .014; CR = 22%), but not the regulatory executive abilities (Behavioral Regulation). Child self-report questionnaires did not show significantly higher mean scores for executive functioning (all P > 0.1), although the power of the self-report results was limited by the small sample. Overall, effect sizes across all informants ranged from small to medium, with the meta-cognitive domains typically displaying larger effect sizes (see Figure 1; effect size categories were operationalized as: small = 0.2, medium = 0.5, large = 0.8 and very large = 1.3).

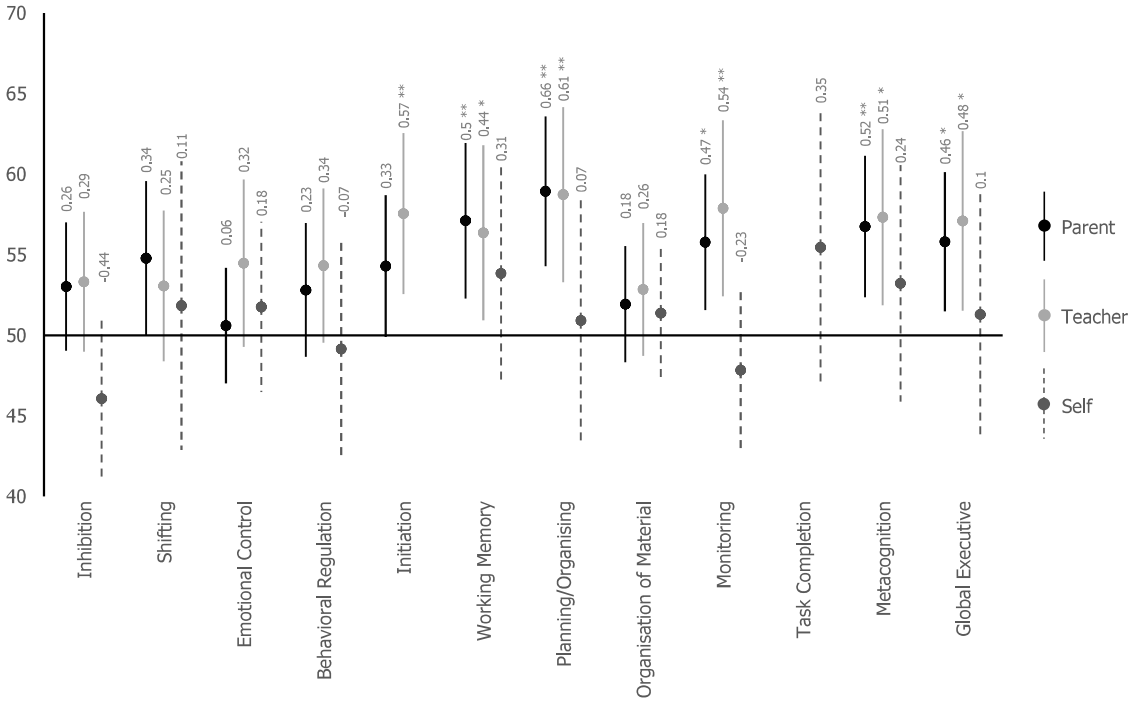


FIGURE 1 Mean scores for BRIEF parent-, teacher- and self-reports. Data labels represent effect size (small effect size = 0.2, medium = 0.5, large = 0.8 and very large = 1.3); Error bars represent 95% confidence interval; *P < .05; ** P < .01; Test statistic = 50.

3.2 | Conners 3

Figure 2 summarizes the results for parent-, teacher- and self-reports for the Conners 3. More detailed results can be viewed in Supplementary Tables 4-6. Parents and children were equally likely to complete and return their questionnaire while teachers were least likely. Thirty-two parent- (78%), 27 teacher- (66%) and 21 self-report (78%) questionnaires were returned. Parent-reports indicated significantly higher mean scores across all primary indices of the Conners 3 [Inattention (Mean = 60.25; SD = 14.60; $t_{(31)}$ = 3.97; P < .001; CR =25%); Hyperactivity/Impulsivity (Mean = 59.28; SD = 13.98; $t_{(31)}$ = 3.76; P = .001; CR = 25%); Learning Problems (Mean = 59.72; SD = 14.80; $t_{(31)}$ = 3.71; P = .001; CR = 22%); Executive Functioning (Mean = 57.91; SD = 11.62; $t_{(31)}$ = 3.85; P = .001; CR = 19%); Defiance/Aggression (Mean = 57.44; SD = 12.34; $t_{(31)}$ = 3.41; P = .002; CR = 13%)], as well as the DSM-5 based indices of: ADHD-Inattentive (Mean = 58.63; SD = 13.37; $t_{(31)}$ = 3.65; P = .001; CR = 16%); ADHD-Hyperactive (Mean = 59.38; SD = 15.05; $t_{(31)}$ = 3.52; P = .001; CR = 19%) and ODD (Mean = 57.34; SD = 12.01; $t_{(31)}$ = 3.46; P = .002; CR = 16%). Effect sizes were generally in the moderate range (see Figure 2). Further, a larger percentage of children fell in the clinical range than expected in the general population. Teacher-reports revealed significantly higher mean scores for Learning Problems (Mean = 57.11; SD = 12.03; $t_{(26)}$ = 3.07; P = .005; CR = 15%) and issues with Peer Relations (Mean = 59.33; SD = 16.30; $t_{(26)}$ = 2.98; P = .006; CR = 22%) both showing a moderate effect (see Figure 2). Trends were also evident for elevated Inattention (P = .069), Hyperactivity/Impulsivity (P = .062), and Executive Functioning (P = .058) with effect sizes in the small range. Similar to parent-reports, self-reports showed significantly higher mean scores on the domains of: Inattention (Mean = 59.48; SD = 15.91; $t_{(20)}$ = 2.73; P = .013; CR = 29%); Hyperactivity/Impulsivity (Mean = 58.52; SD = 11.16; $t_{(20)}$ = 3.50; P = .002; CR = 10% clinical range); Learning Problems (Mean = 60.81; SD = 15.40; $t_{(20)}$ = 3.22; P = .004; CR = 29%) and Defiance/Aggression (Mean = 55.95; SD = 12.92; $t_{(20)}$ = 2.11; P = .048; CR = 14%).

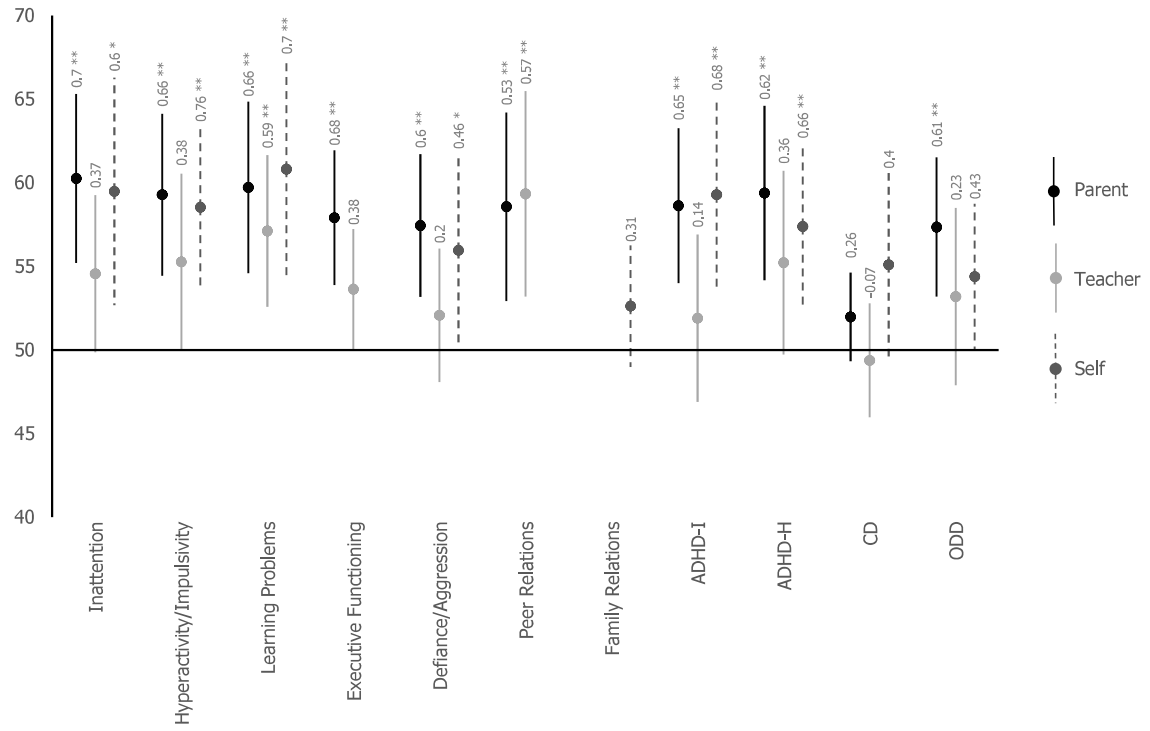


FIGURE 2 Mean scores for Conners 3 parent-, teacher- and self-reports. Data labels represent effect size (small effect size = 0.2, medium = 0.5, large = 0.8 and very large = 1.3); Error bars represent 95% confidence interval; *$P < .05$; ** $P < .01$; Test statistic = 50; ADHD-I: Attention Deficit Hyperactivity Disorder-Inattentive; ADHD-H: Attention Deficit Hyperactivity Disorder-Hyperactive/Impulsive; CD: Conduct Disorder; ODD: Oppositional Defiance Disorder.

The Conners 3 also provides a symptom count based on the DSM-5 diagnostic criteria for three specific diagnosis (ADHD; CD and ODD). The rate of probable diagnosis based on the DSM-5 by parent-, teacher- and self-report is presented in Figure 3. As can be seen, over one third of the children with a completed parent or teacher questionnaire met criteria for a probable diagnosis of ADHD, ODD and/or CD based on the responses. Self-reports highlighted a higher rate of diagnosis with half meeting criteria for a probable diagnosis of ADHD, ODD and/or CD.

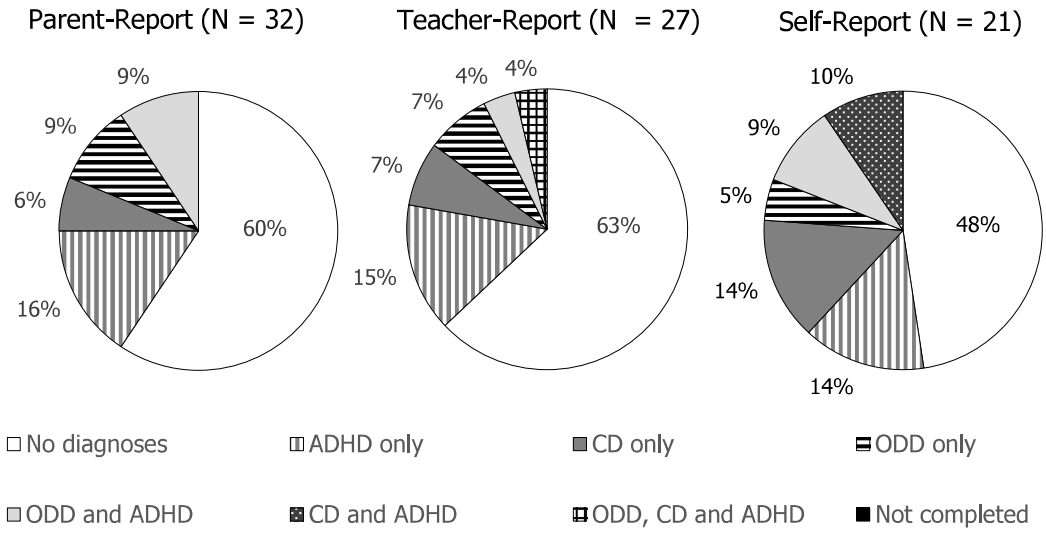


FIGURE 3 Percentage of children meeting DSM-5 diagnostic criteria based on parent-, teacher- and self-reports on the Conners 3. ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; ODD: Oppositional Defiance Disorder.

3.3 | BASC-2

Figure 4 summarizes parent- and teacher-reports, while Figure 5 represents self-reports; further details are available in Supplementary Tables 7-9. Parents were the most likely to return their questionnaire. Thirty-two parent- (78%), 24 teacher- (59%), and 28 self-report (68%) questionnaires were returned. Results indicated significant higher mean scores and moderate effect sizes for Somatization for both parent- (Mean = 59.31; SD = 13.76; $t_{(31)}$ = 3.83; P = .001; CR = 13%) and teacher-reports (Mean = 58.21; SD = 13.56; $t_{(23)}$ = 2.97; P = .007; CR = 13%). Parent-reports also showed clinically elevated symptoms of Withdrawal (Mean = 55.06; SD = 10.76; $t_{(31)}$ = 2.66; P = .012; CR = 9%) with a small to moderate effect size (see Figure 4). Self-reports revealed significantly higher mean scores for Attention Problems (Mean = 56.45; SD = 11.74; $t_{(20)}$ = 2.46; P = .024; CR = 15%) and poorer Self-Reliance (Mean = 44.50; SD = 11.32; $t_{(20)}$ = -2.17; P = .043; CR = 20%), with both showing a small to moderate effect size (see Figure 5). In contrast, significantly lower self-report scores were revealed for Depression (Mean = 47.04; SD = 7.59; $t_{(28)}$ = -2.07; P = .048; CR = 0%).

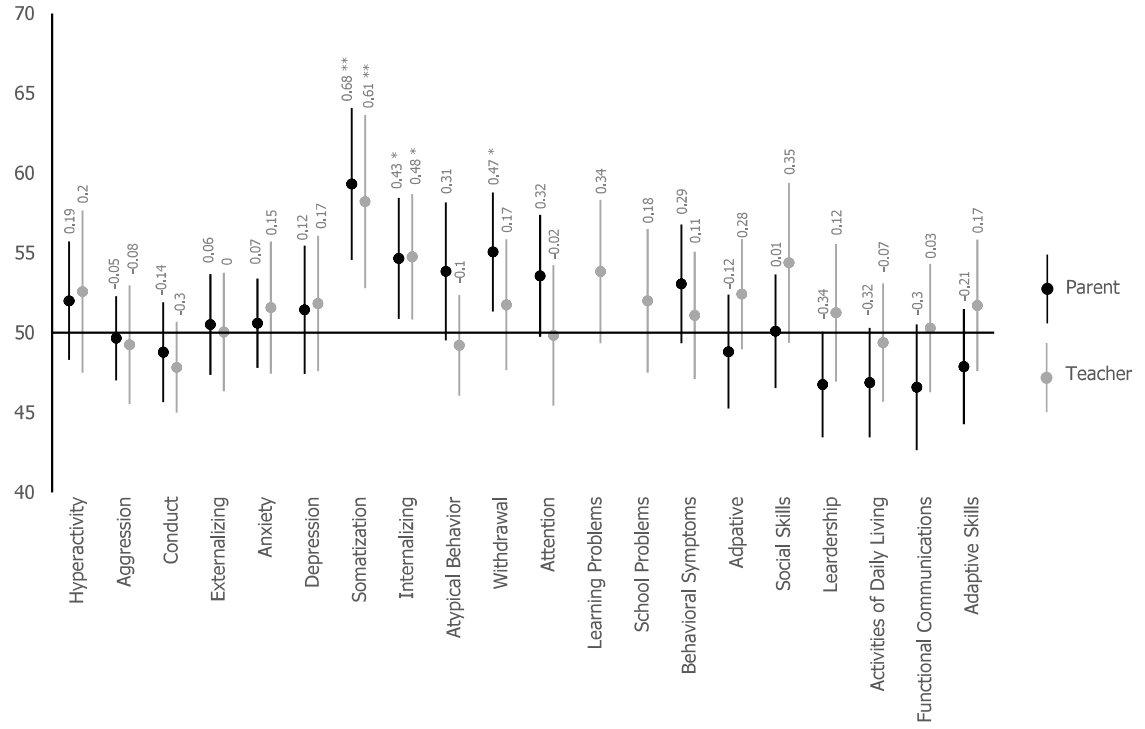


FIGURE 4 Mean scores for BASC-2 parent- and teacher-reports. Data labels represent effect size (small effect size = 0.2, medium = 0.5, large = 0.8 and very large = 1.3); Error bars represent 95% confidence interval; *P < .05; ** P < .01; Test statistic = 50.

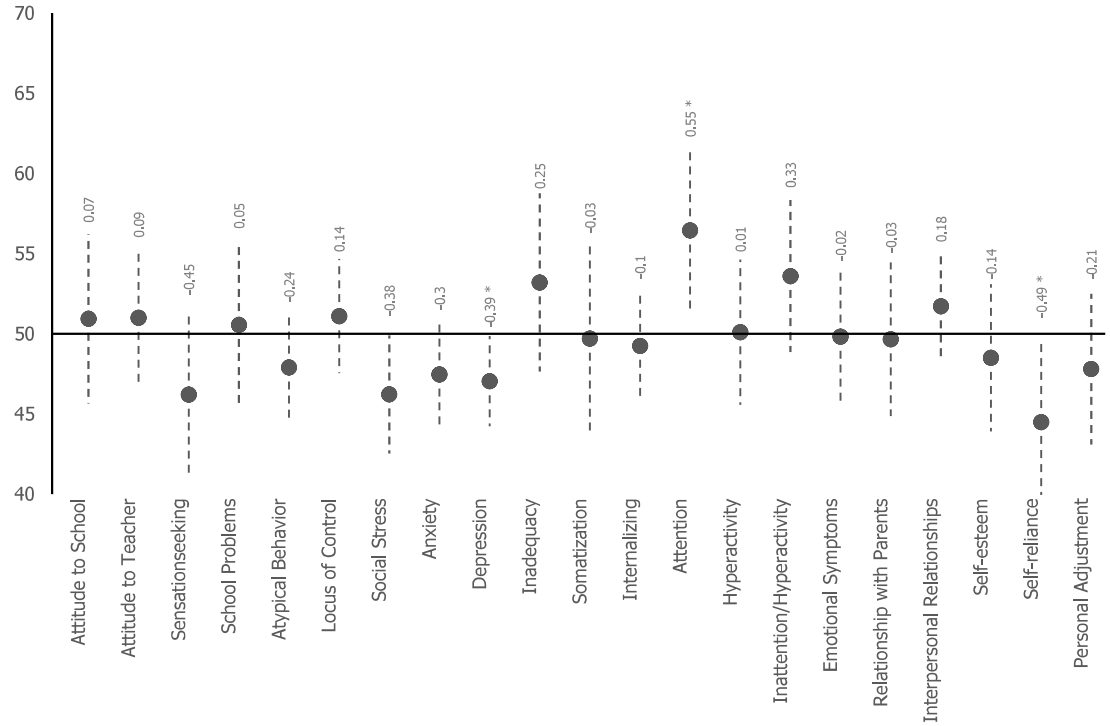


FIGURE 5 Mean scores for BASC-2 self-reports. Data labels represent effect size (small effect size = 0.2, medium = 0.5, large = 0.8 and very large = 1.3); Error bars represent 95% confidence interval; *P < .05; ** P < .01; Test statistic = 50.

3.4 | PedsQL™ Generic Core Scale Version 4.0

Thirty self- (73%) and 33 parent-reports (80%) were returned with parents again more likely to complete and return their questionnaires. As revealed in Table 2, psychosocial functioning was significantly poorer than the sample of healthy controls and this held true for both parent- and self-reports with effect sizes in the large range. While psychosocial outcomes for the current sample did not significantly differ from the solid organ transplant sample,[14] results suggested poorer functioning with a small effect size compared to the previously published liver transplant sample.[13] This finding was significant for parent-report and approaching significance for the child self-reports. Physical functioning was found to be significantly poorer than healthy controls for the child self-report only. Otherwise, physical functioning was no different to the comparison samples for parent- and self-reports. After considering effect size magnitude across all comparisons, a pattern of weaker psychosocial functioning relative to physical functioning was apparent.

TABLE 2 PedsQL Generic Core Scale™ 4.0 - Liver transplant comparison with previously published samples on healthy controls, solid organ transplant and liver transplant samples

	Liver Transplant Recipients	Healthy Controls†	Hedges' g (ES)	*t*	*P* value		Solid Organ Transplant^	Hedges' g (ES)	*t*	*P* value	Liver Transplant Sample#	Hedges' g (ES)	*t*	*P* value	
Child Self-Report															
Total (SD) N	72.83 (14.69) 30	83.91 (12.47) 5079	-0.88	4.85	< .001	**	76.09 (17.25) 199	-0.19	0.98	.327	77.21 (14.28) 363	-0.31	1.61	.108	
Physical (SD) N	80 (15.21) 30	87.77 (13.12) 5070	-0.59	3.23	.001	**	81.06 (19.67) 199	-0.06	0.28	.778	82.29 (15.62) 363	-0.15	0.77	.440	
Psychosocial (SD) N	69 (16.19) 30	81.83 (13.97) 5070	-0.92	5.01	< .001	**	73.73 (17.22) 198	-0.28	1.41	.159	74.51 (15.83) 363	-0.35	1.83	.068	
Parent-Report															
Total (SD) N	72.56 (16.83) 33	82.29 (15.55) 8713	-0.63	3.59	< .001	**	74.93 (19.40) 247	-0.12	0.67	.504	77.26 (17.58) 869	-0.27	1.51	.132	
Physical (SD) N	79.15 (20.78) 33	84.08 (19.70) 8696	-0.25	1.43	.151		79.10 (23.25) 247	0.00	0.01	.991	79.33 (22.07) 869	-0.01	0.05	.963	
Psychosocial (SD) N	68.89 (17.72) 33	81.24 (15.34) 8714	-0.80	4.61	< .001	**	72.68 (19.53) 247	-0.20	1.06	.291	75.72 (17.33) 869	-0.39	2.22	.027	*

† = healthy controls from Varni et al. (2003); ^ = solid organ transplant from Weissberg-Benchell et al. (2010); # = Liver transplant sample from Alonso et al. (2010); * = $P < .05$; ** = $P < .01$; ES = effect size (small effect size = 0.2, medium = 0.5, large = 0.8 and very large = 1.3).

3.5 | PedsQL™3.0 Transplant Module

Twenty-nine self- (71%) and 33 parent-report (80%) questionnaires were returned. The sample's total scores for the transplant specific PedsQL Transplant Module[14] were equivalent to the previously published solid organ transplant sample (see Table 3).

TABLE 3 PedsQL™ 3.0 Transplant Module - Comparison with published solid organ transplant samples

	Liver Transplant Recipients	Solid Organ Transplant^	Hedge's g (ES)	*t*	*P* value
Self-Report					
Total Mean (SD) N	78.16 (9.97) 29	79.03 (14.36) 269	-0.02	0.32	.751
Parent-Report					
Total Mean (SD) N	81.17 (12.59) 33	79.43 (14.88) 338	0.12	0.65	.517

^ solid organ transplant sample from Weissberg-Benchell et al. (2010); ES = effect size ES = effect size (small effect size = 0.2, medium = 0.5, large = 0.8 and very large = 1.3).

3.6 | PedsQL™ Multidimensional Fatigue Scale

Thirty self-report (73%) and 31 parent-report (76%) questionnaires were returned. As shown in Table 4, self- and parent-reports from the PedsQL Multidimensional Fatigue Scale indicated greater fatigue than the normative healthy control sample with large effect sizes evident. No difference was noted compared to the previously published liver transplant or pediatric oncology groups.

TABLE 4 PedsQL™ Multidimensional Fatigue Scale - Comparison with previously published samples

	Liver Transplant Recipients	Healthy Controls†	Hedges' g (ES)	*t*	*P* value		Oncology Sample^	Hedges' g (ES)	*t*	*P* value	Liver Transplant Sample#	Hedges' g (ES)	*t*	*P* value
Child Self-Report														
Total Mean (SD) N	68.01 (16.39) 30	81.80 (12.50) 209	-1.06	5.42	< .001	**	70.98 (18.20) 220	-0.17	0.85	.397	74.00 (15.29) 71	-0.38	1.76	.081
Parent-Report														
Total Mean (SD) N	74.22 (18.69) 31	88.20 (11.10) 259	-1.15	6.07	< .001	**	75.67 (17.74) 337	-0.08	0.43	.665	72.95 (15.74) 100	0.08	0.37	.709

† Healthy controls from Panepinto (2014); ^ Oncology sample from Varni et al. (2002); # Liver transplant sample from Petersen et al (2019) * $p < 0.05$; ** $p < 0.01$; ES = effect size ES = effect size (small effect size = 0.2, medium = 0.5, large = 0.8 and very large = 1.3).

3.7 | Correlations for interrater agreement

Pearson correlations between responders generally revealed consistent moderate correlations between parent- and teacher-reports on the BRIEF and Conners 3, and weaker relationships on the BASC-2 as shown in Table 5. Apart from the PedsQL Generic Core Scale, parent- and self-reports did not show strong or consistent associations. The correlations between teacher- and self-reports were moderate within the domains of executive functions, attention and hyperactivity, learning problems, and depression.

TABLE 5 Interrater Pearson correlations

	Parent-Teacher				Parent-Self				Teacher-Self			
	r	*P* value		n	*r*	*P* value		n	*r*	*P* value		n
BRIEF												
Inhibition	0.76	<.001	**	24	0.37	.242		12	0.79	.007	**	10
Shifting	0.38	.070		24	0.55	.064		12	0.49	.152		10
Emotional Control	0.53	.008	**	24	0.14	.668		12	0.34	.337		10
Behavioral Regulation Index	0.69	<.001	**	24	0.34	.274		12	0.50	.143		10
Initiate	0.68	<.001	**	24								
Working Memory	0.66	<.001	**	24	0.30	.341		12	0.69	.029	*	10
Planning/Organising	0.71	<.001	**	24	0.27	.397		12	0.77	.009	**	10
Organisation of Material	0.34	.106		24	-0.14	.670		12	0.28	.431		10
Monitoring	0.62	.001	**	24	0.00	.999		12	0.50	.143		10
Metacognition Index	0.69	<.001	**	24	0.24	.453		12	0.75	.013	*	10
Global Executive Composite	0.77	<.001	**	24	0.31	.331		12	0.62	.056		10
Conners 3												
Inattention	0.57	.003	**	24	0.20	.423		19	0.48	.059		16
Hyperactivity/ Impulsivity	0.56	.004	**	24	0.22	.375		19	0.52	.040	*	16
Learning Problems	0.69	<.001	**	24	0.46	.049	*	19	0.43	.098		16
Executive Functions	0.66	<.001	**	24								
Defiance/Aggression	0.64	.001	**	24	0.00	.997		19	-0.08	.766		16
Peer Relations	0.65	.001	**	24								
ADHD-I	0.52	.010	**	24	0.22	.368		19	0.49	.053		16
ADHD-H	0.44	.029	*	24	0.08	.753		19	0.53	.035	*	16
CD	0.43	.036	*	24	-0.01	.981		19	-0.03	.921		16
ODD	0.43	.037	*	24	0.41	.081		19	-0.13	.640		16
BASC-2												
Hyperactivity	0.37	.103		21	0.31	.199		19	0.69	.001	**	19
Aggression	0.41	.066		21								
Conduct	0.33	.151		20								
Externalizing	0.45	.047	*	20								
Anxiety	0.30	.191		21	0.01	.967		19	0.06	.816		19
Depression	0.26	.257		21	0.38	.109		19	0.42	.076		19
Somatization	0.83	<.001	**	21								
Internalizing	0.58	.006	**	21	0.41	.080		19	0.29	.232		19
Attention Problems	0.54	.012	*	21	0.43	.069		19	0.73	<.001	**	19
School Problems									0.34	.153		19
Atypicality	0.53	.012	*	21					0.36	.125		19
Withdrawal	0.55	.009	**	21								
Behavioral Symptom	0.53	.013	*	21	0.24	.314		19				
Adaptability	0.45	.041	*	21								
Social Skills	0.39	.079		21								
Leadership	0.53	.014	*	21								
Functional Communication	0.35	.128		20								
Adaptive Skills	0.52	.018	*	20								
PedsQL Generic Core												
Total					0.58	.002	**	26				
Physical					0.53	.005	**	26				
Psychosocial					0.60	.001	**	26				
Multidimensional Fatigue												
Total					0.38	.071		23				
Transplant Module												
Total					0.35	.077		26				

BRIEF: Behavior Rating Inventory of Executive Function; BASC-2: Behavior Assessment System for Children, Second Edition; ADHD-I: Attention Deficit Hyperactivity Disorder - Inattentive presentation; ADHD-H: Attention Deficit Hyperactivity Disorder - Hyperactive/Impulsive presentation; CD: Conduct Disorder; ODD: Oppositional Defiance Disorder; * $P < .05$; ** $P < .01$.

4 | DISCUSSION

The current study achieved its aim of utilizing multi-informant questionnaires to investigate the long-term cognitive, psychological, and HRQOL outcomes of pediatric liver transplant recipients within Australia. In terms of executive functioning, results found that children had greater difficulties with the metacognitive aspects of executive functioning (cool executive functions)[36] compared with the normative population, whereas their self-regulatory skills (hot executive functions)[36] were in line with age-expectations. This was consistent with predictions. Parent- and teacher-reports highlighted elevated problems with planning, working memory and self-monitoring. There was also suggestion of difficulties with initiation within the school context. These difficulties with the metacognitive executive abilities are consistent with previous findings.[5, 7, 34, 37] Weaker working memory, in particular, is consistent with previous neuropsychological results in this population.[2, 5, 37, 56] These findings are important as executive functions are a crucial higher-level skill that can explain poorer psychosocial outcomes, including academic attainment despite relatively intact intellectual abilities.[57-59]

As predicted, the results were suggestive of increased problems with attention and hyperactivity/impulsivity, including higher-than-expected ADHD symptomatology based on DSM-5 diagnostic criteria. The results also indicated that in day-to-day life, children with liver transplants have more functional difficulties with academic achievement and peer relationships, as well as increased somatization. Furthermore, issues with defiance and withdrawal were highlighted, but restricted to the home setting.

The results from the study also demonstrated that the HRQOL of children with liver transplant is significantly poorer than the general population, but is generally in line with other solid organ transplant samples. This is also the case with their day-to-day fatigue and transplant-specific HRQOL. However, the current sample showed poorer psychosocial

functioning on HRQOL measures compared with a previously published large pediatric liver transplant sample.[13] One explanation for this discordant finding may be that the previous study included children with a primary diagnosis of both chronic and acute end-stage liver disease,[60] whereas the current study focused on chronic end-stage liver disease only. This sampling decision was made because these two groups have heterogenous disease processes and their respective transplantation experiences differ markedly from one another.[61] Indeed, research has shown that the intellectual outcomes of acute and chronic diagnostic groups differ significantly.[4] Children with acute liver disease have arguably less exposure to the deleterious effects of liver disease and have shown normal development prior to illness onset. In contrast, children with chronic liver disease, many of whom have a congenital disorder, have had the illness for a prolonged period of time, particularly during the crucial early periods of development and are therefore more vulnerable to its effects. As a result, when the two groups are combined, the poorer outcomes of the chronic group may be masked by the better functioning in the acute group.

Another possible explanation for the differing results on psychosocial outcomes between the two liver transplant groups is differing organ donation rates in the two jurisdictions, as well as the prevalence of living-related donor transplantation. Australia has historically had poorer donation and living-donor rates than the USA and Canada, which would likely lead to longer wait times.[62-64] Unfortunately, the aforementioned study did not report average waitlist time to allow for comparison with the current study.[10]

Unlike previous findings in community samples,[65] the current results did not demonstrate consistent interrater agreement between parent- and self-reports. While some may dismiss child self-reports as less reliable, children might be reporting problems of which their parents are not aware, especially regarding internalizing problems.[27] Importantly, self-

reports of executive functions and attention were more strongly correlated with teacher-reports than parent-reports despite reduced power, perhaps suggesting that self-reports were indeed highlighting real areas of difficulty that may be underappreciated by parents and may be manifesting more within the school setting than at home. This emphasizes the need to consider child-reports alongside parents and teachers as informants. Furthermore, children's perception of their abilities and difficulties is also clinically relevant.

An important point of discussion is the significant level of somatization reported within the sample, which typically leads to elevated scores for internalizing disorders (such as depression and anxiety) on most clinical tools. Somatization has been frequently highlighted in previous literature.[7, 8, 11, 28, 29] However, this domain may be artificially elevated within the liver transplant context. Somatic symptoms could be attributed to the organic consequences of transplantation and the post-transplant life, including regular visits to the hospital, frequent illness, and fear of illness due to the immunosuppressant effects of medication, rather than due to a psychogenic cause. In the current study, while somatization was significantly elevated for parent- and teacher-reports (and strongly correlated), other internalizing symptoms were not endorsed. This has important implications in both clinical settings and future research. Within clinical settings, practitioners must be mindful of the role of somatization when assessing internalizing disorders through clinical tools, and be cautious in making diagnoses based solely on these tools without further clinical investigation. Similarly, researchers must be cautious when making conclusions in relation to internalizing disorders if the somatization is the main driver of any effect. Indeed, Tornqvist et al.[29] identified significant levels of internalizing disorders in a pediatric liver transplant population, but noted that the effect was greatly reduced when controlling for somatization. Consequently, it may be worthwhile developing more targeted standardized assessment tools for somatization symptoms in this and other chronic illness populations.

Results did not replicate the findings from a number of previous studies that showed significantly elevated symptoms of psychological problems including internalizing and externalizing disorders[7, 8, 11, 28, 29] excluding somatization. However, the previous studies all utilized the same questionnaire measure, the Child Behavior Checklist (CBCL),[66] whereas the current study used the BASC-2 to assess the same domains as the CBCL. It is possible that the CBCL is too sensitive a measure as the majority of studies found all or almost all domains to be significantly above the normative sample scores; and may subsequently sacrifice specificity. Conversely, it may be that the BASC-2 is not sensitive enough to identify symptoms. However, the current study assessed a range of domains using multiple informants to establish a higher degree of confidence in the findings. Hence, it is argued that the risk of false positives and false negatives is limited.

The results from the study have demonstrated that informant and self-report questionnaires are useful in illuminating the day-to-day functioning of children, and should be utilized in combination with neuropsychological testing when investigating long-term outcomes. Questionnaire data measure everyday functioning and can often dissociate from performance-based measures.[22-24] For example, neuropsychological testing alone would not have identified difficulties with peer relations and psychosocial functioning in the current study. Therefore, the utilization of questionnaire data enriches the findings greatly. Following on from this, future studies could explore social functioning in more detail including through qualitative and in vivo observational methods. The current study sought to address methodological gaps within the literature to date, and, when viewed alongside previously published results on intellectual and academic outcomes,[2-7] provides a broader understanding of long-term functioning post-transplantation. The current study is the first to incorporate teacher-informant questionnaires alongside both parent- and child self-reports in assessing long-term outcomes after pediatric liver transplantation. Furthermore, it utilized multiple

questionnaires including HRQOL measures to capture a broader picture of the long-term functional outcomes of pediatric liver transplant recipients. It was also one of only five studies to be completed outside of North America and Western Europe, offering a wider international context to the field.[7, 35, 42, 67] Additionally, the participation rate of eligible patients for the current study was particularly high compared to previously published research.[6-8, 10] Future research should continue to aim to utilize neuropsychological tests and standardized questionnaires from multiple informants to gain a comprehensive and ecologically-valid picture when investigating long-term outcomes in pediatric transplant populations.

REFERENCES

1. Lyncyh SV, Balderson GA, editors. ANZLT Registry Report 2014. Brisbane, QLD, Australia: Australia and New Zealand Liver Transplant Registry; 2014.

2. Afshar S, Porter M, Barton B, Stormon M. Intellectual and academic outcomes after pediatric liver transplantation: Relationship with transplant-related factors. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2018;18(9):2229-37.

3. Gilmour S, Adkins R, Liddell GA, Jhangri G, Robertson CM. Assessment of psychoeducational outcomes after pediatric liver transplant. American Journal of Transplantation. 2009;9(2):294-300.

4. Kaller T, Langguth N, Petermann F, Ganschow R, Nashan B, Schulz KH. Cognitive performance in pediatric liver transplant recipients. American Journal of Transplantation. 2013;13(11):2956-65.

5. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Longitudinal study of cognitive and academic outcomes after pediatric liver transplantation. Journal of Pediatrics. 2014;165(1):65-72.e2.

6. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Cognitive and academic outcomes after pediatric liver transplantation: Functional outcomes group (FOG) results. American Journal of Transplantation. 2011;11(2):303-11.

7. Ee LC, Lloyd O, Beale K, Fawcett J, Cleghorn GJ. Academic potential and cognitive functioning of long-term survivors after childhood liver transplantation. Pediatric Transplantation. 2014;18(3):272-9.

8. Kaller T, Boeck A, Sander K, Richterich A, Burdelski M, Ganschow R, et al. Cognitive abilities, behaviour and quality of life in children after liver transplantation. Pediatric Transplantation. 2010;14(4):496-503.

9. Parmar A, Vandriel SM, Ng VL. Health-related quality of life after pediatric liver transplantation: A systematic review. Liver Transplantation. 2017;23(3):361-74.

10. Alonso EM, Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, et al. Cross-Sectional Analysis of Health-Related Quality of Life in Pediatric Liver Transplant Recipients. Journal of Pediatrics. 2010;156(2):270-6.e1.

11. Fredericks EM, Lopez MJ, Magee JC, Shieck V, Opipari-Arrigan L. Psychological functioning, nonadherence and health outcomes after pediatric liver transplantation. American Journal of Transplantation. 2007;7(8):1974-83.

12. Varni JW, Limbers CA, Sorensen LG, Neighbors K, Martz K, Bucuvalas JC, et al. PedsQL™ Cognitive Functioning Scale in pediatric liver transplant recipients: Feasibility, reliability, and validity. Quality of Life Research. 2011;20(6):913-21.

13. Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, Varni JW, et al. Health-related quality of life in pediatric liver transplant recipients compared with other chronic disease groups. Pediatric Transplantation. 2011;15(3):245-53.

14. Weissberg-Benchell J, Zielinski TE, Rodgers S, Greenley RN, Askenazi D, Goldstein SL, et al. Pediatric health-related quality of life: Feasibility, reliability and validity of the PedsQL™ transplant module. American Journal of Transplantation. 2010;10(7):1677-85.

15. Petersen I, Noelle J, Buchholz A, Kroencke S, Daseking M, Grabhorn E. Fatigue in pediatric liver transplant recipients and its impact on their quality of life. Pediatric Transplantation. 2019;23(1).

16. Conners CK. Conners 3rd Edition. Toronto, Ontario, Canada: Multi-Health Systems; 2008.

17. Gioia G, Isquith P, Guy S, Kenworthy L. Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Services; 2000.

18. Wechsler D. Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV). San Antonio, TX: Pearson; 2003.

19. Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: Reliability and Validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in Healthy and Patient Populations. Medical Care. 2001;39(8):800-12.

20. Stewart SM, Hiltebeitel C, Nici J, Waller DA, Uauy R, Andrews WS. Neuropsychological outcome of pediatric liver transplantation. Pediatrics. 1991;87(3):367-76.

21. Sorensen LG. Pediatric solid organ transplantation and end stage disease: A slow journey towards understanding neurocognitive outcomes and their ramifications for clinical care. Pediatric Transplantation. 2015;19(2):136-8.

22. Chaytor N, Schmitter-Edgecombe M. The ecological validity of neuropsychological tests: A review of the literature on everyday cognitive skills. Neuropsychology Review. 2003;13(4):181-97.

23. Silver CH. Sources of data about childrens executive functioning: Review and commentary. Child Neuropsychology. 2014;20(1):1-13.

24. Barkley RA, Murphy KR. Impairment in occupational functioning and adult ADHD: The predictive utility of executive function (EF) ratings versus EF tests. Archives of Clinical Neuropsychology. 2010;25(3):157-73.

25. Ylvisaker M, Adelson PD, Braga LW, Burnett SM, Glang A, Feeney T, et al. Rehabilitation and ongoing support after pediatric TBI: Twenty years of progress. Journal of Head Trauma Rehabilitation. 2005;20(1):95-109.

26. Dewey D, Crawford SG, Kaplan BJ. Clinical importance of parent ratings of everyday cognitive abilities in children with learning and attention problems. Journal of Learning Disabilities. 2003;36(1):87-95.

27. Achenbach TM. As others see Us clinical and research implications of cross-informant correlations for psychopathology. Current Directions in Psychological Science. 2006;15(2):94-8.

28. Gritti A, Sicca F, Di Sarno AM, Di Cosmo N, Vajro S, Vajro P. Emotional and behavioral problems after pediatric liver transplantation: A quantitative assessment. Pediatric Transplantation. 2006;10(2):205-9.

29. Törnqvist J, Van Broeck N, Finkenauer C, Rosati R, Schwering KL, Hayez JY, et al. Long-term psychosocial adjustment following pediatric liver transplantation. Pediatric Transplantation. 1999;3(2):115-25.

30. Windsorová D, Stewart SM, Lovitt R, Waller DA, Andrews WS. Emotional adaptation in children after liver transplantation. The Journal of Pediatrics. 1991;119(6):880-7.

31. Adebäck P, Nemeth A, Fischler B. Cognitive and emotional outcome after pediatric liver transplantation. Pediatric Transplantation. 2003;7(5):385-9.

32. Walker AM, Harris G, Baker A, Kelly D, Houghton J. Post-traumatic stress responses following liver transplantation in older children. Journal of Child Psychology and Psychiatry and Allied Disciplines. 1999;40(3):363-74.

33. Zitelli BJ, Miller JW, Carlton Gartner Jr J, Malatack JJ, Urbach AH, Belle SH, et al. Changes in life-style after liver transplantation. Pediatrics. 1988;82(2):173-80.

34. Gutiérrez-Colina AM, Eaton CK, Lee JL, Reed-Knight B, Loiselle K, Mee LL, et al. Executive functioning, barriers to adherence, and nonadherence in adolescent and young adult transplant recipients. Journal of Pediatric Psychology. 2016;41(7):759-67.

35. Crowe L, Anderson V, Hardikar W, Boneh A. Cognitive and behavioural outcomes of paediatric liver transplantation for ornithine transcarbamylase deficiency. JIMD Reports2019. p. 19-25.

36. Zelazo PD, Carlson SM. Hot and Cool Executive Function in Childhood and Adolescence: Development and Plasticity. Child Development Perspectives. 2012;6(4):354-60.

37. Cushman GK, Stolz MG, Blount RL, Reed B. Executive Functioning in Pediatric Solid Organ Transplant Recipients: A Meta-Analytic Review. Transplantation. 2019.

38. Haavisto A, Korkman M, Törmänen J, Holmberg C, Jalanko H, Qvist E. Visuospatial impairment in children and adolescents after liver transplantation. Pediatric Transplantation. 2011;15(2):184-92.

39. Haavisto A, Korkman M, Sintonen H, Holmberg C, Jalanko H, Lipsanen J, et al. Risk factors for impaired quality of life and psychosocial adjustment after pediatric heart, kidney, and liver transplantation. Pediatric Transplantation. 2013;17(3):256-65.

40. Schwering KL, Febo-Mandl F, Finkenauer C, Rimé B, Hayez JY, Otte JB. Psychological and social adjustment after pediatric liver transplantation as a function of age at surgery and of time elapsed since transplantation. Pediatric Transplantation. 1997;1(2):138-45.

41. Gritti A, Pisano S, Salvati T, Di Cosmo N, Iorio R, Vajro P. Health-related quality of life in pediatric liver transplanted patients compared with a chronic liver disease group. Italian Journal of Pediatrics. 2013;39(1).

42. Alba A, Uribe M, Hunter B, Monzón P, Ferrada C, Heine C, et al. Health-related quality of life after pediatric liver transplant: Single-center experience in Chile. Transplantation Proceedings. 2013;45(10):3728-30.

43. Cho SC, Kim HW, Kim BN, Shin MS, Yoo HJ, Kim JW, et al. Are teacher ratings and parent ratings differently associated with children's intelligence and cognitive performance? Psychiatry Investigation. 2011;8(1):15-21.

44. Kieffer V, Longaud A, Callu D, Laroussinie F, Viguier D, Grill J, et al. Teachers' report of learning and behavioural difficulties in children treated for cerebellar tumours. Brain Injury. 2012;26(7-8):1014-20.

45. Rodijk LH, Den Heijer AE, Hulscher JBF, Verkade HJ, De Kleine RHJ, Bruggink JLM. Neurodevelopmental outcomes in children with liver diseases: A systematic review. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(2):157-68.

46. Reynolds CR, Kamphaus RW. Behavior Assessment System for Children - Second Edition. Circle Pines, MN: AGS Publishing; 2004.

47. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.

48. Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al. Outcomes of 5-year survivors of pediatric liver transplantation: Report on 461 children from a north american multicenter registry. Pediatrics. 2008;122(6):e1128-e35.

49. Kaller T, Langguth N, Ganschow R, Nashan B, Schulz KH. Attention and executive functioning deficits in liver-transplanted children. Transplantation. 2010;90(12):1567-73.

50. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL™* 4.0 as a Pediatric Population Health Measure: Feasibility, Reliability, and Validity. Ambulatory Pediatrics. 2003;3(6):329-41.

51. Varni JW, Limbers CA, Bryant WP, Wilson DP. The PedsQL™ Multidimensional Fatigue Scale in type 1 diabetes: Feasibility, reliability, and validity. Pediatric Diabetes. 2009;10(5):321-8.

52. Varni JW, Limbers CA, Bryant WP, Wilson DP. The PedsQL™ Multidimensional Fatigue Scale in pediatric obesity: Feasibility, reliability and validity. International Journal of Pediatric Obesity. 2010;5(1):34-42.

53. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL™ in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer. 2002;94(7):2090-106.

54. Panepinto JA, Torres S, Bendo CB, McCavit TL, Dinu B, Sherman-Bien S, et al. PedsQL Multidimensional Fatigue Scale in sickle cell disease: feasibility, reliability, and validity. Pediatric Blood Cancer. 2014;61(1):171-7.

55. IBM SPSS Statistics for Windows Version 22.0. Armonk, NY: IBM Corp; 2013.

56. Yssaad-Fesselier R, Lion-François L, Herbillon V, Rivet C, Brunet AS, Yantren H, et al. Intellectual and visuo-spatial assessment in long-term pediatric liver transplantation for biliary atresia. Transplantation. 2009;87(9):1427-8.

57. Biederman J, Monuteaux MC, Doyle AE, Seidman LJ, Wilens TE, Ferrero F, et al. Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. Journal of Consulting and Clinical Psychology. 2004;72(5):757-66.

58. Deotto A, Westmacott R, Fuentes A, deVeber G, Desrocher M. Does stroke impair academic achievement in children? The role of metacognition in math and spelling outcomes following pediatric stroke. Journal of Clinical and Experimental Neuropsychology. 2018.

59. Ventura LM, Grieco JA, Evans CL, Kuhlthau KA, MacDonald SM, Tarbell NJ, et al. Executive functioning, academic skills, and quality of life in pediatric patients with brain tumors post-proton radiation therapy. Journal of Neuro-Oncology. 2018;137(1):119-26.

60. Alonso EM. Growth and developmental considerations in pediatric liver transplantation. Liver Transplantation. 2008;14(5):585-91.

61. Rhee C, Narsinh K, Venick RS, Molina RA, Nga V, Engelhardt R, et al. Predictors of clinical outcome in children undergoing orthotopic liver transplantation for acute and chronic liver disease. Liver Transplantation. 2006;12(9):1347-56.

62. e-Statistics Report on Transplant, Waiting List and Donor Statistics. In: Register COR, editor. Canada: Canadian Institute for Health Information; 2016.

63. Kehar M, Parekh RS, Stunguris J, De Angelis M, Van Roestel K, Ghanekar A, et al. Superior Outcomes and Reduced Wait Times in Pediatric Recipients of Living Donor Liver Transplantation. Transplantation Direct. 2019;5(3).

64. International registry in organ donation and transplantation: Preliminary numbers 2018. International Registry in Organ Donation and Transplantation; 2019.

65. Egan KN, Cohen LA, Limbers C. Parent–child agreement on the Behavior Rating Inventory of Executive Functioning (BRIEF) in a community sample of adolescents. Applied Neuropsychology: Child. 2018:1-8.

66. Achenbach TM, Rescorla lA. Manual for the ASEBA School-Age Forms and Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families; 2001.

67. Kikuchi R, Mizuta K, Urahashi T, Sanada Y, Yamada N, Onuma E, et al. Development of the Japanese version of the Pediatric Quality of Life Inventory ™ Transplant Module. Pediatrics International. 2017;59(1):80-8.

SUPPLEMENTARY TABLE 1 One sample *t*-test results for BRIEF parent-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Inhibition	53.03	11.68	33	0.26	1.49	.146		9%
Shifting	54.79	14.04	33	0.34	1.96	.059		12%
Emotional Control	50.61	10.52	33	0.06	0.33	.743		6%
Behavioral Regulation	52.82	12.18	33	0.23	1.33	.193		12%
Initiation	54.30	12.93	33	0.33	1.91	.065		12%
Working Memory	57.12	14.15	33	0.50	2.89	.007	**	21%
Planning/Organising	58.94	13.61	33	0.66	3.77	.001	**	21%
Organisation of Material	51.94	10.55	33	0.18	1.06	.299		6%
Monitoring	55.79	12.35	33	0.47	2.69	.011	*	12%
Metacognition	56.76	12.88	33	0.52	3.01	.005	**	21%
Global Executive	55.82	12.66	33	0.46	2.64	.013	*	15%

Test statistic = 50; * *P* < .05; ** *P* < .01; Population characteristics: mean = 50, SD = 10.
Clinical range defined as > 1.5 SD above population mean (50).

SUPPLEMENTARY TABLE 2 One sample *t*-test results for BRIEF teacher-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Inhibition	53.33	11.49	27	0.29	1.51	.144		7%
Shifting	53.07	12.40	27	0.25	1.29	.209		7%
Emotional Control	54.48	13.79	27	0.32	1.69	.103		19%
Behavioral Regulation	54.33	12.68	27	0.34	1.78	.087		15%
Initiation	57.56	13.25	27	0.57	2.96	.006	**	19%
Working Memory	56.37	14.42	27	0.44	2.30	.030	*	22%
Planning/Organising	58.74	14.41	27	0.61	3.15	.004	**	26%
Organisation of Material	52.85	10.94	27	0.26	1.36	.187		7%
Monitoring	57.89	14.50	27	0.54	2.83	.009	**	19%
Metacognition	57.33	14.48	27	0.51	2.63	.014	*	22%
Global Executive	57.11	14.78	27	0.48	2.50	.019	*	22%

Test statistic = 50; * *P* < .05; ** *P* < .01; Population characteristics: mean = 50, SD = 10.
Clinical range defined as > 1.5 SD above population mean (50).

SUPPLEMENTARY TABLE 3 One sample *t*-test results for BRIEF self-reports

	Mean	SD	n	Cohen d	*t*	*P* value	% Clinical Range
Inhibition	46.08	8.94	13	-0.44	-1.58	.140	0%
Shifting	51.85	16.49	13	0.11	0.40	.694	15%
Emotional Control	51.77	9.73	13	0.18	0.66	.524	0%
Monitoring	47.85	9.47	13	-0.23	-0.82	.428	0%
Behavioral Regulation	49.15	12.23	13	-0.07	-0.25	.807	0%
Working Memory	53.85	12.46	13	0.31	1.11	.287	15%
Planning/Organising	50.92	13.74	13	0.07	0.24	.813	15%
Organisation of Material	51.38	7.52	13	0.18	0.66	.519	0%
Task Completion	55.46	15.50	13	0.35	1.27	.228	23%
Metacognition	53.23	13.52	13	0.24	0.86	.406	23%
Global Executive	51.31	13.71	13	0.10	0.34	.737	23%

Test statistic = 50; * *P* < .05; ** *P* < .01; Population characteristics: mean = 50, SD = 10.
Clinical range defined as > 1.5 SD above population mean (50).

SUPPLEMENTARY TABLE 4 One sample *t*-test results for Conners 3 parent-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Inattention	60.25	14.60	32	0.70	3.97	<.001	**	25%
Hyperactivity/Impulsivity	59.28	13.98	32	0.66	3.76	.001	**	25%
Learning Problems	59.72	14.80	32	0.66	3.71	.001	**	22%
Executive Functioning	57.91	11.62	32	0.68	3.85	.001	**	19%
Defiance/Aggression	57.44	12.34	32	0.60	3.41	.002	**	13%
Peer Relations	58.56	16.26	32	0.53	2.98	.006	**	25%
ADHD-Inattentive	58.63	13.37	32	0.65	3.65	.001	**	16%
ADHD-Hyperactive	59.38	15.05	32	0.62	3.52	.001	**	19%
CD	51.97	7.65	32	0.26	1.46	.155		6%
ODD	57.34	12.01	32	0.61	3.46	.002	**	16%

Test statistic = 50; * $P < .05$; ** $P < .01$; Population characteristics: mean = 50, SD = 10; CD: Conduct Disorder; ODD: Oppositional Defiance Disorder; Clinical range defined as > 1.5 SD above population mean (50).

SUPPLEMENTARY TABLE 5 One sample *t*-test results for Conners 3 teacher-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Inattention	54.56	12.46	27	0.37	1.90	.069		22%
Hyperactivity/Impulsivity	55.26	14.01	27	0.38	1.95	.062		19%
Learning Problems	57.11	12.03	27	0.59	3.07	.005	**	15%
Executive Functioning	53.63	9.52	27	0.38	1.98	.058		11%
Defiance/Aggression	52.07	10.58	27	0.20	1.02	.318		4%
Peer Relations	59.33	16.30	27	0.57	2.98	.006	**	22%
ADHD-Inattentive	51.89	13.27	27	0.14	0.74	.466		11%
ADHD-Hyperactive	55.22	14.56	27	0.36	1.86	.074		22%
CD	49.37	9.03	27	-0.07	-0.36	.720		4%
ODD	53.19	14.07	27	0.23	1.18	.250		15%

Test statistic = 50; * $P < .05$; ** $P < .01$; Population characteristics: mean = 50, SD = 10; CD: Conduct Disorder; ODD: Oppositional Defiance Disorder; Clinical range defined as > 1.5 SD above population mean (50).

SUPPLEMENTARY TABLE 6 One sample *t*-test results for Conners 3 self-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Inattention	59.48	15.91	21	0.60	2.73	.013	*	29%
Hyperactivity/Impulsivity	58.52	11.16	21	0.76	3.50	.002	**	10%
Learning Problems	60.81	15.40	21	0.70	3.22	.004	**	29%
Defiance/Aggression	55.95	12.92	21	0.46	2.11	.048	*	14%
Family Relations	52.62	8.51	21	0.31	1.41	.174		5%
ADHD-Inattentive	59.29	13.71	21	0.68	3.10	.006	**	29%
ADHD-Hyperactive	57.38	11.26	21	0.66	3.00	.007	**	14%
CD	55.10	12.83	21	0.40	1.82	.084		14%
ODD	54.38	10.19	21	0.43	1.97	.063		5%

Test statistic = 50; * $P < .05$; ** $P < .01$; Population characteristics: mean = 50, SD = 10; CD: Conduct Disorder; ODD: Oppositional Defiance Disorder; Clinical range defined as > 1.5 SD above population mean (50).

SUPPLEMENTARY TABLE 7 One sample *t*-test results for BASC-2 parent-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Hyperactivity	52.00	10.71	32	0.19	1.06	.299		6%
Aggression	49.66	7.61	32	-0.05	-0.26	.800		0%
Conduct	48.77	8.89	31	-0.14	-0.77	.449		0%
Externalizing	50.52	8.97	31	0.06	0.32	.751		0%
Anxiety	50.59	8.06	32	0.07	0.42	.680		6%
Depression	51.44	11.60	32	0.12	0.70	.488		9%
Somatization	59.31	13.76	32	0.68	3.83	.001	**	13%
Internalizing	54.66	10.94	32	0.43	2.41	.022	*	9%
Atypical Behavior	53.84	12.45	32	0.31	1.75	.091		13%
Withdrawal	55.06	10.76	32	0.47	2.66	.012	*	9%
Attention	53.56	11.03	32	0.32	1.83	.077		9%
Behavioral Symptoms	53.06	10.72	32	0.29	1.62	.116		6%
Adaptive	48.81	10.30	32	-0.12	-0.65	.519		3%
Social Skills	50.09	10.26	32	0.01	0.05	.959		3%
Leadership	46.75	9.53	32	-0.34	-1.93	.063		0%
Activities of Daily Living	46.88	9.88	32	-0.32	-1.79	.083		3%
Functional Communications	46.58	11.22	31	-0.30	-1.70	.100		6%
Adaptive Skills	47.87	10.26	31	-0.21	-1.16	.257		0%

Test statistic = 50; * $P < .05$; ** $P < .01$; Population characteristics: mean = 50, SD = 10.
Clinical range defined as > 1.5 SD above or below population mean (50).

SUPPLEMENTARY TABLE 8 One sample *t*-test results for BASC-2 teacher-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Hyperactivity	52.58	12.71	24	0.20	1.00	.330		13%
Aggression	49.25	9.29	24	-0.08	-0.40	.696		4%
Conduct	47.83	7.12	24	-0.30	-1.49	.150		0%
Externalizing	50.04	9.27	24	0.00	0.02	.983		4%
Anxiety	51.58	10.34	24	0.15	0.75	.461		8%
Depression	51.83	10.61	24	0.17	0.85	.406		8%
Somatization	58.21	13.56	24	0.61	2.97	.007	**	13%
Internalizing	54.75	9.81	24	0.48	2.37	.026	*	8%
Attention	49.83	10.99	24	-0.02	-0.07	.941		4%
Learning Problems	53.83	11.21	24	0.34	1.68	.107		8%
School Problems	52.00	11.24	24	0.18	0.87	.392		8%
Atypical Behaviors	49.21	7.90	24	-0.10	-0.49	.628		4%
Withdrawal	51.75	10.25	24	0.17	0.84	.411		4%
Behavioral Symptoms	51.08	9.97	24	0.11	0.53	.599		4%
Adaptive	52.42	8.64	24	0.28	1.37	.184		0%
Social Skills	54.38	12.53	24	0.35	1.71	.101		0%
Leadership	51.25	10.77	24	0.12	0.57	.575		0%
Activities of Daily Living	49.38	9.26	24	-0.07	-0.33	.744		0%
Functional Communications	50.29	10.04	24	0.03	0.14	.888		0%
Adaptive Skills	51.71	10.30	24	0.17	0.81	.425		0%

Test statistic = 50; * $P < .05$; ** $P < .01$; Population characteristics: mean = 50, SD = 10.
Clinical range defined as > 1.5 SD above or below population mean (50).

SUPPLEMENTARY TABLE 9 One sample *t*-test results for BASC-2 self-reports

	Mean	SD	n	Cohen d	*t*	*P* value		% Clinical Range
Attitude to School	50.93	14.26	28	0.07	0.34	.733		21%
Attitude to Teacher	51.00	11.69	28	0.09	0.45	.654		7%
Sensation Seeking	46.20	8.42	10	-0.45	-1.43	.187		0%
School Problems	50.55	11.22	20	0.05	0.22	.829		10%
Atypical Behavior	47.89	8.96	28	-0.24	-1.24	.224		4%
Locus of Control	51.10	8.14	20	0.14	0.60	.553		0%
Social Stress	46.21	9.96	28	-0.38	-2.01	.054		4%
Anxiety	47.46	8.59	28	-0.30	-1.56	.130		4%
Depression	47.04	7.59	28	-0.39	-2.07	.048	*	0%
Inadequacy	53.20	12.68	20	0.25	1.13	.273		15%
Somatization	49.70	9.30	10	-0.03	-0.10	.921		0%
Internalizing	49.25	7.85	20	-0.10	-0.43	.674		0%
Attention	56.45	11.74	20	0.55	2.46	.024	*	15%
Hyperactivity	50.10	10.35	20	0.01	0.04	.966		0%
Inattention/Hyperactivity	53.60	10.80	20	0.33	1.49	.153		15%
Emotional Symptoms	49.82	10.89	28	-0.02	-0.09	.932		7%
Relationship with Parents	49.65	10.94	20	-0.03	-0.14	.888		5%
Interpersonal Relationships	51.71	9.39	28	0.18	0.97	.343		4%
Self-esteem	48.50	10.49	20	-0.14	-0.64	.530		5%
Self-reliance	44.50	11.32	20	-0.49	-2.17	.043	*	20%
Personal Adjustment	47.80	10.73	20	-0.21	-0.92	.371		5%

Test statistic = 50; * $P < .05$; ** $P < .01$; Population characteristics: mean = 50, SD = 10.
Clinical range defined as > 1.5 SD above population mean (50).

CHAPTER 4:

LONG-TERM INTELLECTUAL AND ACADEMIC OUTCOMES AFTER PEDIATRIC LIVER TRANSPLANTATION: A SYSTEMATIC REVIEW WITH META-ANALYSIS

Afshar S, McAulay C, Porter M.

ABSTRACT

With liver transplantation becoming more successful for pediatric end-stage liver disease, research on long-term outcomes has shifted from survival rates to cognitive outcomes. Despite a growing number of studies on intellectual outcomes after pediatric liver transplantation, there are no comprehensive systematic reviews with meta-analysis summarising the literature. The objective of the current systematic review and meta-analysis was to identify and review studies investigating the long-term intellectual and academic outcomes of children who received liver transplantation and to explore whether differences exist between diagnostic groups. All English language publications that used standardized norm-based measures to assess the long-term (minimum 1 year) intellectual and academic outcomes of pediatric liver transplant recipients were included. A search of SCOPUS, PsycINFO and PubMed databases yielded 993 initial studies and 148 papers following title and abstract review. A total of 26 studies were retained following full-text review (interrater reliability: 100%), including 663 unique participants. Fifteen studies (426 participants) were included in the meta-analysis. Studies were of variable quality as assessed by the revised Modified Quality Index, and often omitted key descriptive and outcome statistics. Prospective studies were of better quality than retrospective studies. Children with liver transplants performed significantly below population norms on overall intelligence (FSIQ) and its sub-domains. Academic performance was significantly below population norms for mathematics and reading, but not for spelling or writing, although the latter two outcomes were limited by minimal available data. Exploratory post-hoc analyses revealed better reading and spelling in more recent studies. Comparison of performance across diagnostic groups found that the metabolic disorder group consistently performed significantly below other groups and the population mean. The Acute Liver Failure (ALF) group was equivalent to the general population. The chronic liver disease group was often significantly below the population mean, but was not significantly below the ALF group. The mixed sample diagnostic group was often similar to the mean of all studies. The current

review highlighted the vulnerabilities in cognitive and academic development in children post-liver transplant. Future research should endeavour to employ high-quality, prospective designs, and provide data for diagnostic groups separately, in order to further understand the profile of children with liver transplants and enable the development of effective screening and intervention strategies.

1 | INTRODUCTION

Liver transplantation is now the treatment of choice for end-stage liver disease.[1] As survival rates improve, the research focus has shifted to long-term intellectual and academic outcomes.[2] To date, there have been a number of cross-sectional and longitudinal, retrospective and prospective observational studies investigating the long-term cognitive outcomes of children after liver transplantation across a number of different jurisdictions, with a particular focus on intellectual and academic abilities. Results generally suggest a downward shift of intellectual and academic scores,[3-5] but a comprehensive quantitative review has not been conducted to confirm this shift. Additionally, it has been suggested that a weakness in nonverbal/perceptual abilities relative to verbal skills is seen in children post-liver transplant by a limited number of studies.[3, 6] However, this finding has not been consistently shown across all studies[7-10] and no quantitative review has definitively explored this question.

While two related reviews have been conducted recently, neither directly addressed the question of long-term intellectual and academic outcomes of pediatric liver transplant recipients. Moser et al. (2013) explored and quantitatively analysed the intellectual outcomes for pediatric end-stage liver disease as part of a broader study of neurocognitive outcomes in chronic childhood illness.[11] Five studies were identified in the review,[4, 9, 12-14] with numerous studies that met criteria for the review not identified.[6, 15-20] One study included in the review investigated the intellectual outcomes of both transplant recipients and transplant candidates awaiting transplantation, and did not differentiate the results between the two groups or perform analyses exploring the effect of transplantation, which would arguably dilute any results, as the findings capture two distinctly different populations.[12] The four remaining studies in the review exclusively explored transplanted children.[4, 9, 13, 14] The samples included in the review were heterogenous in terms of primary liver disease diagnosis and the review did not address this factor. Four studies included only children with what was classified as

chronic end-stage liver disease (biliary atresia, α_1 antitrypsin deficiency, Alagille syndrome, neonatal hepatitis, neonatal hemochromatosis, progressive familial intrahepatic cholestasis, cirrhosis of unknown aetiology, chronic active hepatitis, and sclerosing cholangitis),[4, 9, 12, 13] while the largest study was a mixed sample, which also included acute liver failure and metabolic disorders in addition to chronic liver disease in the cohort.[14] Combining different primary diagnostic groups assumes that disease mechanisms and experiences are equivalent and that the liver transplant process would have the same effect on their intellectual outcomes. However, this is not the case, as different hepatic disorders have different underlying mechanisms of disease, occur at different times during development, and consequently, would have differing impacts on neurocognitive development.[21] Indeed, variability in intellectual outcomes between the diagnoses has been demonstrated, with particular weakness amongst children with metabolic disorders.[22, 23] Nonetheless, the results indicated that the average intelligence quotient of children with end-stage liver disease, the majority of whom had received a liver transplant, was approximately half a standard deviation below the normative mean.

More recently, Ridjik et al. conducted a comprehensive systematic review without meta-analysis evaluating all studies between 2000 and 2017 that investigated neurodevelopmental outcomes of children with liver disease, with and without transplantation.[24] The review reported that most studies on children after liver transplant showed lower scores across all domains of neurodevelopment, including intelligence and academic scores (literacy and mathematics) compared with the general normative population, but mean scores remained within the normal range. The review concluded that the literature was limited by the heterogeneity of the primary diagnoses of study samples, as well as variability in both the age of sample participants and measurement outcomes used between studies. The review was the first to complete a comprehensive evaluation of the literature

across a broad range of cognitive domains, moving beyond intellectual outcomes, and allowed for simultaneous comparison between transplanted children and non-transplanted children with end-stage liver disease; however, it had a number of limitations. The review did not attempt to group outcomes into overarching diagnostic subsets despite available data,[4, 8, 9, 22, 25, 26] which would have allowed investigation into whether diagnostic groups have differing outcomes. It further did not include a study that met search criteria,[18] and included a number of studies with non-independent samples[13, 22, 27-29] which would bias any overall finding by giving additional weighting to certain samples. Finally, a quantitative analysis of the results was not conducted on common outcomes; hence, a definitive understanding of the cognitive status of children post-liver transplant was not gained.

In light of the above, the objective of the current systematic review and meta-analysis was to summarise and evaluate the literature in relation to long-term intellectual and academic outcomes of children who receive liver transplants, and to investigate whether intellectual and academic outcomes differ by primary diagnostic group. A secondary aim of the review and meta-analysis was to determine whether children post-liver transplant demonstrate a discrepancy favoring their verbal intellectual abilities over their nonverbal/perceptual intellectual abilities.

1.1 | Hypotheses

1.1.1 | Systematic Review

It was hypothesized that the quality of studies investigating intellectual and academic outcomes would be variable as suggested by previous reviews, with particular limitations around heterogeneity of diagnostic groups, age of study participants, and outcome measures used.

1.1.2 | Meta-analysis

Based on the previous reviews, it was hypothesized that the overall sample of children with liver transplantation would have significantly lower intellectual abilities compared to the normative population.[11, 24] Literacy and mathematical abilities were also predicted to be significantly below the population means.[24] Children with metabolic disorders were predicted to have the poorest intellectual and academic outcomes. The chronic illness group was expected to be better than the metabolic group, but below the general population mean, while the ALF group was predicted to be no different from the general population mean. Predictions on differences between diagnostic groups were theorised based on length of illness (chronic illness performing lower than acute illness) and the previous literature noting poorer outcomes for metabolic disorders.[22] For the secondary aim of the review, it was hypothesized that no difference would be found between verbal and nonverbal/perceptual abilities, based on the results of the majority of studies to date.

2 | METHOD

The systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines (see Supplementary Table 1).[30] The inclusion criteria were as follows:

1) English language publications
2) All studies published before September 30th, 2019
3) Study samples are independent across studies
4) Study sample received liver transplantation during childhood (less than 18 years of age)
5) Completed standardized, norm-based intellectual, and/or academic assessments (developmental assessments of cognitive skills were also included in the systematic review, but not meta-analysis, as a number of studies combined intellectual and developmental scores together)

6) Assessment conducted at least 1-year post-transplant
7) Provided descriptive results of above assessments (mean scores, standard deviations and sample size), either in-text or on request
8) Studies were published in journals that comply with the Declaration of Helsinki.[31]

Amongst studies that included non-independent samples, only the most recent study was included in the current review. Studies that combined results for transplanted and non-transplanted children were excluded if individual results could not be sought from respective authors.

2.1 | Search strategy

The search was conducted independently by two authors (SA and CM) within three databases: SCOPUS, PsycINFO and PubMed. The following search terms were used searching within *titles*, *abstract*, and *keywords* in SCOPUS: (liver AND transplant*) AND (p*ediatric OR child*) AND (neuropsych* OR neurocog* OR neurodevelopment* OR cogniti* OR academic OR intell* OR psychometric). The same search was conducted within PubMed and PsycINFO within *All Fields.* The search was commenced on 20th of April 2019, with the final search completed on 30th of September 2019. All studies conducted up until the search end date were included in the review. The reference lists of all studies retained after the full text review were screened for relevant articles. Interrater-reliability (*K*) was assessed by comparing the studies included after full text review for the systematic review by SA and CM.

2.2 | Data extraction

Data extraction was conducted by the first author (SA) onto a standard database. Half of the studies were randomly audited by the second author (CM) to assess accuracy of extraction. The primary measure collected during data extraction was the mean Full-Scale

Intelligence Quotient (FSIQ) or Developmental Quotient (DQ) after transplantation, as measured by norm-based standardized assessments, along with the sample standard deviation and sample size. Data was extracted for each study sample and/or individual diagnostic group where adequate information was provided. As the majority of studies used the Wechsler intelligence tests, additional intellectual domains that are provided by these measures were also extracted where available. These included: verbal intellect (VCI/VIQ - Verbal Comprehension Index or Verbal Intelligence Quotient); performance/perceptual abilities (PRI/PIQ - Perceptual Reasoning Index or Performance Intelligence Quotient); processing speed (PSI - Processing Speed Index); working memory (WMI - Working Memory Index); Fluid Reasoning Index (FRI) and Visuospatial Index (VSI). Results from standardized tests measuring academic achievement were also extracted including reading, spelling, writing and mathematics. Authors were contacted when mean, SD and sample size were not reported. For studies that reported outcomes at multiple time points (such as for longitudinal studies), the most recent time points were incorporated. The primary comparison for the systematic review and meta-analysis was against the standardized normative mean of 100 (SD = 15).

Other study characteristics collected during data extraction included: primary diagnosis (frequency count); participation rate; sex distribution of sample; mean/median age at assessment; country of study; single or multisite study; design of study (prospective or retrospective); year of publication and outcome measures used. Samples were categorised into four overarching primary diagnostic groups for the meta-analysis. These included: acute liver failure (ALF); chronic liver disease; metabolic disorder and a mixed diagnostic group.

2.3 | Risk of bias within individual studies

The quality of papers was reviewed by the first author using a revised version of the Modified Quality Index (MQI).[32] The revised version provided a score out of 11 assessing the

following domains: 1) *Reporting* – which included clear reporting of objectives, participant characteristics, and outcomes (out of 7); 2)*Internal Validity* – which was limited to the use of valid and reliable outcome measure/s (score out of 1); and 3) *External Validity* – which entailed the representative nature of participants and setting (score out of 3; see Supplementary Table 2 for individual items). Studies with a score above 9 were classified as *Good*, a score of 9 was categorised as *Adequate*, and a score below 9 was defined as *Low*. The quality of studies was assessed in relation to the aim of the current review, namely, investigating the long-term intellectual (and/or developmental) and academic outcomes of pediatric liver transplant recipients rather than the original aim(s) of the studies.

2.4 | Risk of bias across studies

I^2 and Cochranes test were both used as a measure of consistency to assess bias across studies.[33] Publication bias was assessed using Egger's test. Correlation analysis was utilized to assess whether the quality of studies, as measured by the revised MQI, changed linearly over time. Independent samples *t*-tests explored whether prospective and retrospective studies differed on quality.

2.5 | Analysis

Basic analysis and quantitative synthesis of results, as well as assessment of bias was completed using IBM Statistical Program for the Social Sciences, version 22[34] and Comprehensive Meta-Analysis version 3 software.[35]

2.5.1 | Meta-analysis

An estimate of the mean IQ, as well as estimates for additional intellectual and academic domains, were determined for children with liver transplantation for liver disease. Random effects models were used for all meta-analyses for the sake of uniformity regardless

of the level of between-study heterogeneity. This was because it was theorized that systematic differences would be evident across studies because of the differing sample diagnoses.

A between-subjects analysis was the only option available when comparing VCI/VIQ and PRI/PIQ results as the majority of studies did not conduct within-subjects analysis between the two indices and individual subject data was not available to calculate these ad-hoc.

2.5.2 | Meta-regression and sub-group analysis

To demonstrate the importance of limiting investigations to different liver disease groups, results were grouped across overarching primary diagnostic groups (chronic, metabolic, ALF, and mixed). Random-effects method of moments meta-regressions were conducted to assess whether intellectual and academic outcomes differed across the four groups. Where appropriate, exploratory post-hoc meta-regressions and independent samples *t*-tests were incorporated to evaluate factors that were associated with long-term outcomes.

3 | RESULTS

The full electronic search strategy is provided in Figure 1. Twenty-six studies with a final study sample of 663 unique children with liver transplantation were identified for the systematic review. No additional articles were identified through the screening of reference lists. The interrater reliability for the final inclusion for the systematic review was $K = 100\%$. A subset of 15 studies met criteria for the meta-analysis of intellectual and academic results with a total sample of 426 children with liver transplantation. Standardized academic results were always reported alongside intellectual results and were never the primary research focus.

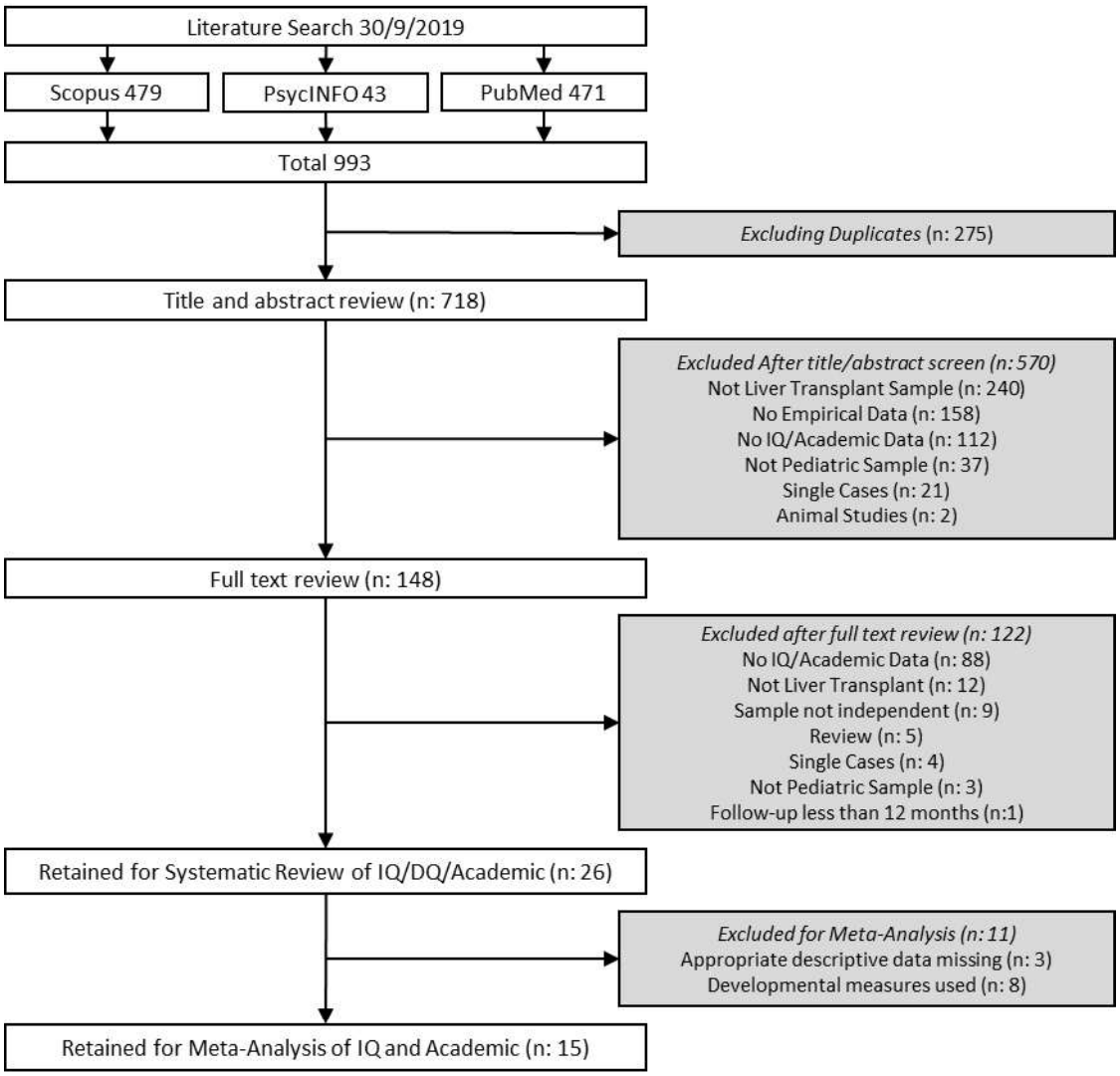


FIGURE 1 PRISMA flow diagram depicting the full electronic search and study selection

A number of studies[13, 14, 27, 29, 36-38] were excluded due to non-independent samples, one of which was the first part of a two-part longitudinal study.[14] The only exception was Robertson et al. (2013) where three participants (9%) completed the assessment of intelligence after having completed developmental assessments as part of Gilmour et al. (2009). This was justified considering that the intellectual results were the main interest in the current review and meta-analysis. One study was excluded as it included children with liver disease both with and without transplantation, but did not partition the descriptive results based on transplantation status.[39]

Attempts were made to contact the corresponding authors of studies that did not provide adequate descriptive results necessary for the meta-analysis[3, 18, 26, 40, 41] to request relevant data. One author provided appropriate data,[18] and four authors did not provide the data.[3, 26, 40, 41] Furthermore, authors of studies that did not differentiate results for separate illness groups within their samples, or where developmental and intellectual measures were combined,[3, 6, 10, 16, 17, 25, 39, 41-44] were contacted for data. No authors provided data in response to this request.

3.1 | Narrative synthesis

Table 1 summarizes all studies that were included in the systematic review. Of the 26 studies included, eleven were conducted in North America, eight in Western Europe, four in Eastern Asia, and three within Australia. The design was single-center for all but three studies, with one of the multisite studies recruiting across 20 separate medical centers in North America.[10] As has been noted previously, the age range of participants was markedly variable between and within studies (see Table 1). The mean participation rate across studies that reported participation rate was 71% (SD: 26%; Median: 78.5%; range 17 – 100%), although there was variability in the reporting of participation rate and how eligible participants were defined. Study design included 14 prospective, 10 retrospective and 2 unclear designs.

The majority of the studies utilized the Wechsler measures of intelligence (22/26 of studies in systematic review and 14/15 for studies in meta-analysis). Eleven studies utilized a range of developmental and/or intellectual measures and provided a combined overall score rather than using one measure across the sample.[3, 4, 9, 16, 17, 19, 26, 42-45] While this was unavoidable for some studies due to the age range of study participants not being compatible with the age limit of respective measures, in others it was a consequence of retrospective analysis of clinical data. Some studies also did not use the most current tools[4, 16] or did not

report the edition of the measure used.[19, 44] Eight out of 15 studies included in the meta-analysis explored academic outcomes whereas academic ability was not an outcome in any of the studies not included in the meta-analysis.

As is summarized in Table 1, 10 of the 26 studies reported on a mixed sample, with only three of these studies providing descriptive results of individual diagnostic groups.[22, 25, 26] The remaining study samples consisted of BA-only groups, chronic liver disease with and without BA, metabolic disorders, and acute/fulminant liver failure. In addition to limitations around the heterogeneity of the primary diagnoses of samples, there was inconsistency in how studies attempted to separate samples into overarching diagnostic groups. One example involves the classification of the genetic disorders of alpha-1 antitrypsin deficiency (A1AD) or Alagille Syndrome. Kaller et al. combined these two diagnoses into the broader group of genetic and metabolic disorders.[22] In contrast, other studies incorporated these diagnoses into the general chronic liver disease group.[4, 9, 23, 26] This question of classification is repeated with hepatic tumors. Three studies did not make their classification process clear.[10, 19, 43]

TABLE 1 Intellectual and academic outcomes in children after liver transplant

	Study Year	Country Single/Multi Site	Retrospective or Prospective	N (f; % participation)	Age at Assessment Mean (+/-; n) [*Median, S/IQR*]	DQ or IQ	Test(s) used IQ/DQ *Academic*	Diagnostic Group	Diagnosis (n)	Descriptive Results Mean (+/-; n) [*Median, range, S/IQR*]	Quality
Included in Meta-Analysis	Stewart 1991[15]	USA Single	Prospective	28 (14; NR)	Mean: 7.6 +/- 2.5 r: 4.6-13.4	IQ	WISC-R *WRAT*	Chronic	BA (12); A1AD (7); intrahepatic biliary hypoplasia-syndromatic type (4); chronic active hepatitis (2); progressive cirrhosis of unknown etiology (1); hepatoma (1); hamartoma (1)	VCI/VIQ: 92 (+/-16.4; n: 28) PRI/PIQ: 89.1 (+/-19.1; n: 28) Reading: 82.8 (+/-21.5; n: 28) Spelling: 80.5 (+/-22.8; n: 28) Math: 80.9 (+/-22.1; n: 28)	Adequate
	Kennard 1999[16]	USA Single	Retrospective	50 (23; 58%)	Mean: 11.1 +/- 4 r: 6-23	IQ	WISC-R (45) WAIS-R (5) *WJ-R Achievement Standard Battery*	Chronic	BA (25); A1AD (12); autoimmune hepatitis (4); Alagille syndrome (2); hepatoma (3); choledochal cyst (2); cystic fibrosis (2)	IQ: 85.72 (+/-17.38; n: 50) VCI/VIQ: 86.6 (+/-16.98; n: 50) PRI/PIQ: 87.1 (+/-17.96; n: 50) Reading: 90.78 (+/-26.16; n: 50) Spelling: 81.27 (+/-24.81; n: 50) Math: 83.65 (+/-22.98; n: 50) Writing: 82.24 (+/-27.78; n: 50)	Good
	Gritti 2001[17]	Europe Multi	Retrospective	18 (9; NR)	Mean: 6.8 +/- 1.9 r: 4.4-10.8	IQ	WPPSI WISC-R	Mixed	BA (12); Crigler Najjar (3); PFIC (3)	IQ: 91.6 (+/-10.3; n: 18)	Adequate
	Krull 2003[9]	USA Single	Unclear	15 (11; 36%)	Mean: 6.8 +/- 1.78 r: 5-10	IQ	WISC-III WPPSI-R	Chronic	BA (13); A1AD (1); PFIC (1)	IQ: 90.47 (+/-18.08; n: 15) VCI/VIQ: 86.13 (+/-19.23; n: 15) PRI/PIQ: 96 (+/-17.61; n: 15) Reading: 96.3 (+/-15.6; n: 15) Math: 93.53 (+/-23.14; n: 15) Writing: 104.9 (+/-18.96; n: 15)	Good
	Gilmour 2009[4]	Canada Single	Prospective	30 (20; 81%)	NR Approx. Mean: 5.4	IQ	WPPSI-R WISC-III *WIAT*	Chronic	BA (21); A1AD (3); neonatal hepatitis (4); Alagille Syndrome (2)	IQ: 84 (+/-15; n: 20) VCI/VIQ: 84 (+/-13; n: 20) PRI/PIQ: 86 (+/-19; n: 20) Reading: 85 (+/-18; n: 11) Spelling: 91 (+/-17; n: 11) Math: 74 (+/-13; n: 11)	Good
						DQ	BSID-II	Chronic		DQ: 75 (+/-20; n: 10)	
	Yssaad-Fesselier 2009[18]	France Single	Prospective	13 (9; NR)	Mean: 10.5 (SD NR)	IQ	WISC-IV	BA	BA (13)	IQ: 97.08 (+/-19.98; n: 13) VCI/VIQ: 104 (+/-19.9; n: 13) PRI/PIQ: 100.7 (+/-16.3; n: 13) PSI: 98.5 (+/-16.9; n: 13) WMI: 84 (+/-13.9; n: 13)	Low
	Stevenson 2010[19]	USA Single	Retrospective	21 (NR; 64%)	NR for DQ subset	DQ	BSID II (MDI)	Metabolic	NR for IQ subsample	DQ: 83 (+/-17; n: 21; r:50-110)	Low
					Approx. Mean: 10.4 Approx. +/- 2.59 Approx. r: 7.2-13.2	IQ	WPPSI WISC (editions NR)	Metabolic	Urea Cycle Disorder Only Citrullinemia (n = 3); OTC deficiency (n = 3); CPS deficiency (n = 2); arginosuccinate aciduria (n = 1)	IQ: 83.57 (+/-16.18; n: 7; r: 62-103)	
	Haavisto 2011[6]	Finland Single	Prospective	18 (11; 86%)	Mean: 11.8 +/- 3.1 r: 7.2-16.1	IQ	WISC-III (shortened)	Mixed	BA (7); Acute hepatitis of unknown etiology (3); hyperoxaluria (2); polycystic kidneys (2); hepatocellular carcinoma (1); neonatal hepatitis (1); hepatoblastoma (1); OTC deficiency (1)	IQ: 94 (+/-18.2; n: 18) VCI/VIQ: 99.6 (+/-20.6; n: 18) PRI/PIQ: 88.9 (+/-21.5; n: 18)	Good
	Shellmer 2011[20]	USA Single	Retrospective	10 (NR)	NR Approx. Mean: 7.5 Approx. +/- 3.51 Approx. r: 3.2-15.3	IQ	Abbreviated Battery SB 5	Metabolic	Maple syrup urine disease (10)	IQ: 85 (+/-16.07; n: 10)	Low

TABLE 1 Continued.

	Study Year	Country Single/Multi Site	Retrospective or Prospective	N (f; % participation)	Age at Assessment Mean (+/-; n) [*Median, S/IQR*]	DQ or IQ	Test(s) used IQ/DQ *Academic*	Diagnostic Group	Diagnosis (n)	Descriptive Results Mean (+/-; n) [*Median, range, S/IQR*]	Quality
Included in Meta-Analysis	Kaller 2013[22]	Germany Single	Prospective	64 (29; 91%)	Mean: 11.9 +/- 2.83 r: 6.3-16.9	IQ	WISC-IV	Mixed	BA (34) Cholestatic disease (8) Genetic/Metabolic Disorders (10) Acute/Other (12)	IQ: 93.08 (+/-16.25; n: 64) VCI/VIQ: 95.16 (+/-14.54; n: 64) PRI/PIQ: 94.94 (+/-15.49; n: 64) PSI: 94.13 (+/-15.56; n: 64) WMI: 94.52 (+/-18.17; n: 64)	Good
						IQ	WISC-IV	BA Subset	BA (34)	IQ: 94.38 (+/-14.69; n: 34) VCI/VIQ: 96.15 (+/-13.66; n: 34) PRI/PIQ: 96.41 (+/-13.64; n: 34) PSI: 95.97 (+/-15.04; n: 34) WMI: 94.91 (+/-18.35; n: 34)	
						IQ	WISC-IV	Chronic Not BA Subset	*Cholestatic disease (8)* PFIC (4); neonatal hepatitis (2); congenital hepatic fibrosis (1); primary sclerosing cholangitis (1)	IQ: 98.5 (+/-12.68; n: 8) VCI/VIQ: 94.5 (+/-13.42; n: 8) PRI/PIQ: 102.5 (+/-13.86; n: 8) PSI: 97.38 (+/-10.08; n: 8) WMI: 101.63 (+/-10.45; n: 8)	
						IQ	WISC-IV	Metabolic Subset	*Genetic/Metabolic Disorders (10)* A1AD (1); Wilson's (1); hyperoxaluria (1); Alagille Syndrome (1); Cigler-Najjar (2); OTC deficiency (1); citrullinemia (1); argininosuccinic aciduria (1)	IQ: 78.4 (+/-17.85; n: 10) VCI/VIQ: 84.7 (+/-16.36; n: 10) PRI/PIQ: 81.9 (+/-19.68; n: 10) PSI: 80.7 (+/-10.7; n: 10) WMI: 83.8 (+/-20.4; n: 10)	
						IQ	WISC-IV	Acute	*Acute/Other (12)* liver tumour (2); ALF (3); hepatic failure of unknown etiology (7)	IQ: 98 (+/-15.87; n: 12) VCI/VIQ: 101.5 (+/-13.08; n: 12) PRI/PIQ: 96.58 (+/-13.06; n: 12) PSI: 97.92 (+/-18.93; n: 12) WMI: 97.68 (+/-17.81; n: 12)	
	Robertson 2013[25]	Canada Single	Prospective	33 (17; 89%)	Mean: 4.6 +/- 0.7	IQ	WPPSI-III	Mixed	BA (21) Chronic cholestatic liver disease (7) ALF (5)	IQ: 93.9 (+/-17.1; n: 33) VCI/VIQ: 95.3 (+/-16.5; n: 33) PRI/PIQ: 94.3 (+/-18.1; n: 33)	Good
						IQ	WPPSI-III	BA Subset	BA (21)	IQ: 94.6 (+/-12.9; n: 21) VCI/VIQ: 97 (+/-13.4; n: 21) PRI/PIQ: 95.5 (+/-12.4; n: 21)	
						IQ	WPPSI-III	Chronic Not BA Subset	Chronic cholestatic liver disease (7)	IQ: 93.1 (+/-22.7; n: 7) VCI/VIQ: 90.9 (+/-18.5; n: 7) PRI/PIQ: 95 (+/-24.6; n: 7)	
						IQ	WPPSI-III	Acute	ALF (5)	IQ: 92 (+/-26.8; n: 5) VCI/VIQ: 94.4 (+/-27.1; n: 5) PRI/PIQ: 88.3 (+/-29.8; n: 5)	
	Ee 2014[8]	Australia Single	Prospective	13 (7; 45%)	[*Median: 13.1*] r: 6.5-17.0	IQ	WISC-IV *WIAT II*	Chronic	BA (8); Alagille syndrome (3); A1AD (1); PFIC (1)	IQ: 97.38 (+/-11.59; n: 13) VCI/VIQ: 97.31 (+/-10.79; n: 13) PRI/PIQ: 100.77 (+/-16.19; n: 13) PSI: 95.92 (+/-11.32; n: 13) WMI: 97.08 (+/-9.38; n: 13) Reading: 96 (+/-14.79; n: 13) Spelling: 98.15 (+/-13.26; n: 13) Math: 86.15 (+/-12.92; n: 13)	Good
	Sorensen 2014[10]	USA & Canada Multi	Prospective	93 (49; 20%)	[*Median: 8.5*] r: 7-9.9	IQ	WISC-IV *WRAT 4*	Mixed	BA (56); ALF (8); other cholestatic (13); metabolic (8); Other (8)	IQ: 92.1 (+/-14.9; n: 91) VCI/VIQ: 91.7 (+/-14.5; n: 91) PRI/PIQ: 95.9 (+/-15.4; n: 92) PSI: 95.1 (+/-15; n: 92) WMI: 90.7 (+/-14.6; n: 92) Reading: 98.2 (+/-14; n: 93) Math: 90.1 (+/-15.9; n: 93)	Good

TABLE 1 Continued.

	Study Year	Country Single/Multi Site	Retrospective or Prospective	N (f; % participation)	Age at Assessment Mean (+/-; n) [*Median, S/IQR*]	DQ or IQ	Test(s) used IQ/DQ *Academic*	Diagnostic Group	Diagnosis (n)	Descriptive Results Mean (+/-; n) [*Median, range, S/IQR*]	Quality
Included in Meta-Analysis	Afshar 2018[23]	Australia Single	Prospective	40 (22; 87%)	Mean: 11.2 +/- 3.64 r: 6.3-16.9	IQ	WISC-IV *WIAT-II*	Chronic	BA (27); chronic Not BA (13)	IQ: 93.15 (+/-17.25; n: 40) VCI/VIQ: 92.53 (+/-16.38; n: 40) PRI/PIQ: 94.25 (+/-18.56; n: 40) PSI: 99.55 (+/-15.74; n: 40) WMI: 92.2 (+/-14.52; n: 40) Reading: 100.48 (+/-18.37; n: 40) Spelling: 101.23 (+/-16.07; n: 40) Math: 92.33 (+/-18.77; n: 40)	Good
				27	Mean: 10.4 +/- 3.56 r: 6.3-16.9	IQ	WISC-IV *WIAT-II*	BA Subset	BA (27)	IQ: 93.7 (+/-19.17; n: 27) VCI/VIQ: 92.15 (+/-15.82; n: 27) PRI/PIQ: 95.26 (+/-20.21; n: 27) PSI: 101.52 (+/-16.29; n: 27) WMI: 91.19 (+/-16.16; n: 27) Reading: 101.78 (+/-17.7; n: 27) Spelling: 103.78 (+/-13.95; n: 27) Math: 92.81 (+/-19.69; n: 27)	
				13	Mean: 12.9 +/- 3.28 r: 6.3-16.5	IQ	WISC-IV *WIAT-II*	Chronic Not BA Subset	A1AD (3); Alagille Syndrome (3); PFIC (1); cryptogenic cirrhosis (1); cholestatic disease (1); autoimmune hepatitis (1); meningococcal infection (1); bile acid synthesis disorder (1); subacute hepatitis of unknown etiology (1)	IQ: 92 (+/-12.99; n: 13) VCI/VIQ: 93.31 (+/-18.15; n: 13) PRI/PIQ: 92.15 (+/-15.08; n: 13) PSI: 94.31 (+/-10.59; n: 13) WMI: 94.31 (+/-10.59; n: 13) Reading: 97.77 (+/-20.15; n: 13) Spelling: 95.92 (+/-19.31; n: 13) Math: 91.31 (+/-17.39; n: 13)	
	Crowe 2019[46]	Australia Single	Prospective	4 (3; 100%)	Mean: 6.69 +/- 1.13 5.75 - 8.33	IQ	WISC-IV *WRAT-4*	Metabolic	OTC deficiency (4)	FSIQ: 66.25 (+/- 11.87; n: 4) VCI: 70.00 (+/- 4.16; n: 4) PRI: 75.25 (+/- 19.00; n: 4) PSI: 77.00 (+/-12.03; n: 4) WMI: 72.25 (+/-11.93; n: 4) Word Reading: 93.67 (+/- 7.37; n: 3) Spelling 97.00 (+/- 16.82; n: 3) Math 78.67 (+/- 10.02 ; n: 3)	Adequate
Incomplete IQ/Acad. Data for Meta-Analysis	Adeback 2003[3]	Sweden Single	Unclear	21 (9; 91%)	[*Median: 9.6*] r: 1-9	IQ	WISC-III WPPSI-R	Mixed	BA (8); ALF (3); Glycogen storage type A (1); Tyrosinemia (1); PFIC (1); A1AD (1); Hepatoblastoma (1); Congenital fibrosis (1); Primary oxaluria (1); Progressive familial metabolic liver disorder of unknown etiology (1)	IQ: 86.6 (+/-NR; n: 23) VCI/VIQ: 90.6 (+/-NR; n: 23) PRI/PIQ: 84.5 (+/-NR; n: 23)	Adequate
	Gold 2017[40]	Canada Single	Prospective	13 (8; 50%)	[*Median: 4.7*] r: 3.03-6.97	IQ	WPPSI-IV	BA	BA (13)	[*IQ: 98 (IQR: 17; n: 11)*] [*VCI/VIQ: 96 (IQR: 15 ; n: 11)*] [*PSI: 100 (IQR: 17; n: 7)*] [*WMI: 106 (IQR: 22; n: 11)*] [*VSI: 90 (IQR: 24; n: 12)*] [*FRI: 97 (IQR: 27; n: 7)*]	Low
	Lee 2017[41]	South Korea Single	Prospective	28 (13; 17%)	[*Median: 12.9*] r: 3.4-16.6	IQ	WPPSI-III	Mixed	BA (19); neonatal hepatitis (2); glycogen storage disorder (2); Wilson (1); autoimmune hepatitis (1); fulminant hepatitis (2); cryptogenic cirrhosis (1)	[*IQ: 99 (range: 50-132; n: 28)*] [*VCI/VIQ: 102 (range: 61-146; n: 28)*] [*PRI/PIQ: 106 (range: 14-132; n: 28)*]	Low
	Talcott 2019[26]	United Kingdom Single	Prospective	20 (10; NR for transplanted subgroup)		IQ	WISC-IV WASI	Mixed		Group Total NR	Low
				12	[*Median: 13.4*] [*SIQR: 1.8*]	IQ	WISC-IV WASI (NR, assumed)	Chronic	BA (9); PFIC (2); A1AD (1)	[*IQ: 86.5 (SIQR: 13.0; n: 12)*] [*VCI/VIQ: 86.0 (SIQR: 14.0; n: 12)*] [*PRI/PIQ: 87.0 (SIQR: 20.0; n: 12)*] [*PSI: 89.5 (SIQR: 12.0; n: 12)*]	
				8	[*Median: 15.6*] [*SIQR: 2.7*]	IQ	WISC-IV WASI (NR, assumed)	Acute	Seronegative hepatitis (5); autoimmune hepatitis (2); hepatitis A (1)	[*IQ: 100.5 (SIQR: 10.0; n: 8)*] [*VCI/VIQ: 105.0 (SIQR: 13.5 14; n: 8)*] [*PRI/PIQ: 101.0 (SIQR: 11.5; n: 8)*] [*PSI: 104.0 (SIQR: 9.0; n: 8)*]	

TABLE 1 Continued.

	Study Year	Country Single/Multi Site	Retrospective or Prospective	N (f; % participation)	Age at Assessment Mean (+/-; n) [*Median, S/IQR*]	DQ or IQ	Test(s) used IQ/DQ *Academic*	Diagnostic Group	Diagnosis (n)	Descriptive Results Mean (+/-; n) [*Median, range, S/IQR*]	Quality
Combined DQ/IQ	Zitelli 1988[43]	USA Single	Retrospective	29 (NR for IQ)	NR	Mixed	BSID - MD; Merrill-Palmer Scale; Stanford-Binet Form L-M; WPPSI; WISC-R	Mixed	NR for IQ/DQ Subset	Mixed DQ/IQ: 93.3 (+/-3.01; n: 29)	Low
	Hattori 1998[45]	Japan Single	Retrospective	8 (4; 100%)	Mean: 6.9 +/- 4.83 r: 1.5-16.6	Mixed	WISC-R; Tanaka-Binet Scale; Tsumori-Inage Scale; Kyoto Scale of Psychological Development	Acute	ALF (8)	Mixed DQ/IQ: 97 (+/-9.09; n: 8)	Adequate
	Posfay-Barbe 2013[42]	Switzerland Single	Retrospective	21 (11; 91%)	NR [*Approx. Median: 3*] Approx. r: 2.4-6.7	Mixed	Brunet-Lezin Revised (<3yrs); BSID-II; TM Test; WPPSI-R; WISC-III	Mixed	BA (11); metabolic (2); fulminant hepatitis (1); cryptogenic cirrhosis (2); cholestatic liver disease of unknown etiology (1); Caroli syndrome (1); veno-occlusive disease (1); Alagille's syndrome (1); PFIC (1)	Mixed DQ/IQ: 86.29 (+/-17.8; n: 21)	Low
	Chu 2019[44]	Taiwan Multi	Retrospective	14 (NR; 70%)	Mean: 7.0 +/- 3.6	Mixed	Bayley III WPPSI (?) WISC-IV	Metabolic	Methylmalonic acidemia (12); propionic acidemia (2)	Mixed DQ/IQ: 59.9 (+/-16.8; n: 14)	Adequate
DQ Only	Wayman 1997[47]	USA Single	Prospective	40 (25; 70%)	Mean: 1.8 r: 1.4-2.7	DQ	BSID - MD	BA	BA (40)	DQ: 93.16 (+/-14.1; n: 40)	Low
	van Mourik 2000[48]	England Single	Retrospective	16 (NR for DQ subset; 76%)	NR for DQ subset	DQ	Griffiths Mental Ability Scale (unrevised)	Chronic	NR for DQ subsample	DQ: 108.8 (+/-3.3; n: 16)	Low
	Morioka 2007[49]	Japan Single	Retrospective	6 (3; 100%)	NR r: 0.3-1.8	DQ	McCarthy General Cognitive Index*	Metabolic	Methylmalonic acidemia (6)	DQ: 91.56 (+/-2.96; n: 6)	Low

IQR = interquartile range; NR = not reported; r = range; SIQR = semi-interquartile range.
DQ = developmental quotient; FRI = fluid reasoning index; IQ = intelligence quotient; PIQ = performance intelligence quotient; PRI = perceptual reasoning index; PSI = processing speed index; VCI = verbal comprehension index; VIQ = verbal intelligence quotient; WMI = working memory index.
A1AD = alpha-1 antitrypsin deficiency; ALF = acute liver failure; BA = biliary atresia; CPS = carbamoyl phosphate synthetase; OTC = ornithine transcarbamylase; PFIC = progressive familial intrahepatic cholestasis.
BSID = Bayley Scale of Infant Development; MD = mental development; SB = Stanford Binet; TM = Shortened Stanford Binet; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Intelligence Scale; WIAT = Wechsler Individual Achievement Test; WISC = Wechsler Intelligence Scale for Children; WJ-R = Woodcock Johnson Revised; WPPSI = Wechsler Preschool & Primary Scale of Intelligence; WRAT = Wide Ranging Achievement Test.

Seven studies utilized a comparison control group within the respective design; these varied, including: siblings;[8] other chronic illness groups[9, 15, 16] including stable liver disease without transplant[26] and healthy controls previously collected as part of normative sample for standardized tests.[6, 22] As a result of this variability, control group data was not incorporated in the current review and meta-analysis.

The overall quality of the studies within the field was variable, as can be seen in Table 1. Study objectives and results were generally reported appropriately. Reporting of sample characteristics was inconsistent across studies. This was particularly evident amongst studies with multiple research aims. These studies failed to adequately describe the sample characteristics for the subset of participants who underwent standardized intellectual/academic testing. Other areas requiring improvement included description of the participation rate compared to eligible participants and the adequate reporting of statistical results. The utilization of current, valid and reliable outcomes measures was also noted to be a weakness. However, this was almost entirely a limitation in retrospective studies and was not problematic in prospective studies. The majority of lower quality studies were characterised by mixed diagnostic samples that were not differentiated as well as those which combined developmental and intellectual results into one combined score. Detailed evaluation for each study against the revised MQI can be seen in Supplementary Table 3.

3.2 | Quality Scores

Prospective studies had significantly higher mean revised MQI scores than retrospective studies for all studies included in the systematic review ($Mean_{Prospective}$ = 9.36; SD = 1.77; n = 14; $Mean_{Retrospective}$ = 7.8; SD = 1.40; n = 10; $Mean_{Difference}$ = 1.56, Standard $Error_{Difference}$ = 0.650; n = 24; $t_{(22)}$ = 2.321; P = .030) and meta-analysis ($Mean_{Prospective}$ = 10.20; SD = 1.25; n = 10; $Mean_{Retrospective}$ = 7.75; SD = 1.92; n = 4; $Mean_{Difference}$ = 2.45,

Standard Error$_{Difference}$ = 1.038; $t_{(12)}$ = 2.863; P = .014). The quality of studies included in the meta-analysis were significantly higher than for studies not included in the meta-analysis (Mean$_{Included}$ = 9.53; SD = 1.92; n = 15; Mean$_{Not\ Included}$ = 7.73; SD = 0.96; n = 11; Mean$_{Difference}$ = 1.81; Standard Error$_{Difference}$ = 0.544; $t_{(24)}$ = 3.089; P = .006). No relationship between study quality and year of publication was evident either for all studies included in the systematic review (r = .08; n = 26; P = .698) or for studies just in the meta-analysis (r = .15; n = 15; P = .594).

3.3 | Meta-analysis

Fifteen studies provided adequate descriptive results to be included in the meta-analysis. This resulted in 12 samples of transplanted children with a primary diagnosis of chronic liver disease (including BA), 4 samples of metabolic disorder, 2 samples of ALF and 3 samples of the mixed diagnostic group.

3.3.1 | Meta-analysis of overall intelligence (FSIQ)

Twenty subgroup samples (N = 396) from 14 studies were identified that reported independent and adequate data on overall intellectual results (2 samples for ALF, 11 samples for chronic liver disease, 4 metabolic and 3 mixed diagnostic groups). All but one study utilized Wechsler intellectual measures. Evaluations of overall consistency revealed heterogeneity across studies (I^2 = 61.84%; $Q_{(19)}$ = 49.75; P < .001) indicating possible systematic differences between studies. Egger's test did not suggest the presence of publication bias (B_0 = -0.78; $t_{(18)}$ = 0.903; P = .378; 95% CI = -2.60 to 1.03; see Supplementary Figure 1 for corresponding Funnel Plot).

Results from the random effects model indicated that the mean FSIQ across all diagnostic groups was significantly below the population mean of 100 (Mean$_{Total}$ = 91.82;

Standard Error$_{Pooled}$ = 0.927; n$_{samples}$ = 20; n$_{participants}$ = 396; P < .001; 95% CI = 90.00 to 93.63), as illustrated in Table 2 and Figure 2. In children with ALF, FSIQ did not significantly differ from the general population mean of 100 (Mean$_{ALF}$ = 97.24; Standard Error$_{Pooled}$ = 4.279; n$_{samples}$ = 2; n$_{participants}$ = 17; P = .518; 95% CI = 88.84 to 105.62). FSIQ was significantly below the general population mean of 100 for children with a primary diagnosis of a Chronic liver disease (Mean$_{Chronic}$ = 92.44; Standard Error$_{Pooled}$ = 1.545; n$_{samples}$ = 11; n$_{participants}$ = 221; P < .001; 95% CI = 89.41 to 95.46), Metabolic disorders (Mean$_{Metabolic}$ = 78.51; Standard Error$_{Pooled}$ = 4.202; n$_{samples}$ = 4; n$_{participants}$ = 31; P < .001; 95% CI = 70.27 to 86.74) and for children in studies with Mixed primary diagnoses (Mean$_{Mixed}$ = 92.13; Standard Error$_{Pooled}$ = 1.256; n$_{samples}$ = 3; n$_{participants}$ = 127; P < .001; 95% CI = 89.67 to 94.59).

Results from the random-effects meta-regression revealed that the FSIQ differed by diagnostic group (Overall Model $Q_{(3)}$ = 17.49; P < .001; Variance explained by model = 0.54). The Goodness of fit test indicated heterogeneity across studies within subgroups (τ^2 = 9.02; I^2 = 41.32%; $Q_{(16)}$ = 27.26; P = .039). Pairwise comparisons revealed that the FSIQ for the Metabolic group was significantly below the other three diagnostic groups of ALF (Z = 3.09; P = .002); Chronic (Z = 3.91; P < .001); and Mixed (Z = 3.46; P < .001). The FSIQ of the other 3 groups did not significantly differ from each other (all Ps > .35; see Supplementary Table 4 for full details).

TABLE 2 Results of meta-analysis for full-scale intelligence quotient (FSIQ) - random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
ALF	Kaller 2013	ALF	98.00	4.581	20.988	89.02	106.98	-0.437	.662	87.25	0.468
ALF	Robertson 2013	ALF	92.00	11.985	143.648	68.51	115.49	-0.667	.504	12.75	-0.468
ALF			**97.24**	**4.279**	**18.312**	**88.85**	**105.62**	**-0.646**	**.518**		
Chronic	Kennard 1999	Chronic	85.72	2.458	6.041	80.90	90.54	-5.810	< .001	12.93	-1.675
Chronic	Krull 2003	Chronic	90.47	4.668	21.792	81.32	99.62	-2.041	.041	6.97	-0.348
Chronic	Gilmore 2009	Chronic	84.00	3.354	11.250	77.43	90.57	-4.770	< .001	10.08	-1.829
Chronic	Yssaad-Fesserlier 2009	BA	97.08	4.987	24.868	87.31	106.85	-0.586	.558	6.40	0.786
Chronic	Kaller 2013	BA	94.38	2.519	6.347	89.44	99.32	-2.231	.026	12.72	0.481
Chronic	Kaller 2013	Chronic (Not BA)	98.50	4.483	20.098	89.71	107.29	-0.335	.738	7.34	1.105
Chronic	Robertson 2013	BA	94.60	2.815	7.924	89.08	100.12	-1.918	.055	11.73	0.511
Chronic	Robertson 2013	Chronic (Not BA)	93.10	8.580	73.613	76.28	109.92	-0.804	.421	2.77	0.073
Chronic	Ee 2014	Chronic	97.38	3.214	10.333	91.08	103.68	-0.815	.415	2.77	1.096
Chronic	Afshar 2018	BA	93.70	3.689	13.611	86.47	100.93	-1.708	.088	2.77	0.260
Chronic	Afshar 2018	Chronic (Not BA)	92.00	3.603	12.980	84.94	99.06	-2.221	.026	2.77	-0.091
Chronic			**92.44**	**1.545**	**2.386**	**89.41**	**95.46**	**-4.898**	**< .001**		
Metabolic	Stevenson 2010	Metabolic	83.57	6.115	37.399	71.58	95.56	-2.687	.007	23.32	0.665
Metabolic	Shellmer 2011	Metabolic	85.00	5.082	25.824	75.04	94.96	-2.952	.003	27.52	0.953
Metabolic	Kaller 2013	Metabolic	78.40	5.645	31.862	67.34	89.46	-3.827	< .001	25.16	-0.015
Metabolic	Crowe 2018	Metabolic	66.25	5.935	35.224	54.62	77.88	-5.687	< .001	24.01	-1.639
Metabolic			**78.51**	**4.202**	**17.654**	**70.27**	**86.74**	**-5.116**	**< .001**		
Mixed	Gritti 2001	Mixed	91.60	2.428	5.894	86.84	96.36	-3.460	.001	26.77	-0.255
Mixed	Haavisto 2011	Mixed	94.00	4.290	18.402	85.59	102.41	-1.399	.162	8.57	0.456
Mixed	Sorensen 2014	Mixed	92.10	1.562	2.440	89.04	95.16	-5.058	< .001	64.66	-0.031
Mixed			**92.13**	**1.256**	**1.578**	**89.67**	**94.59**	**-6.267**	**< .001**		
Overall			**91.82**	**0.927**	**0.859**	**90.00**	**93.63**	**-8.831**	**< .001**		

Note: ALF = acute liver failure; BA = biliary atresia

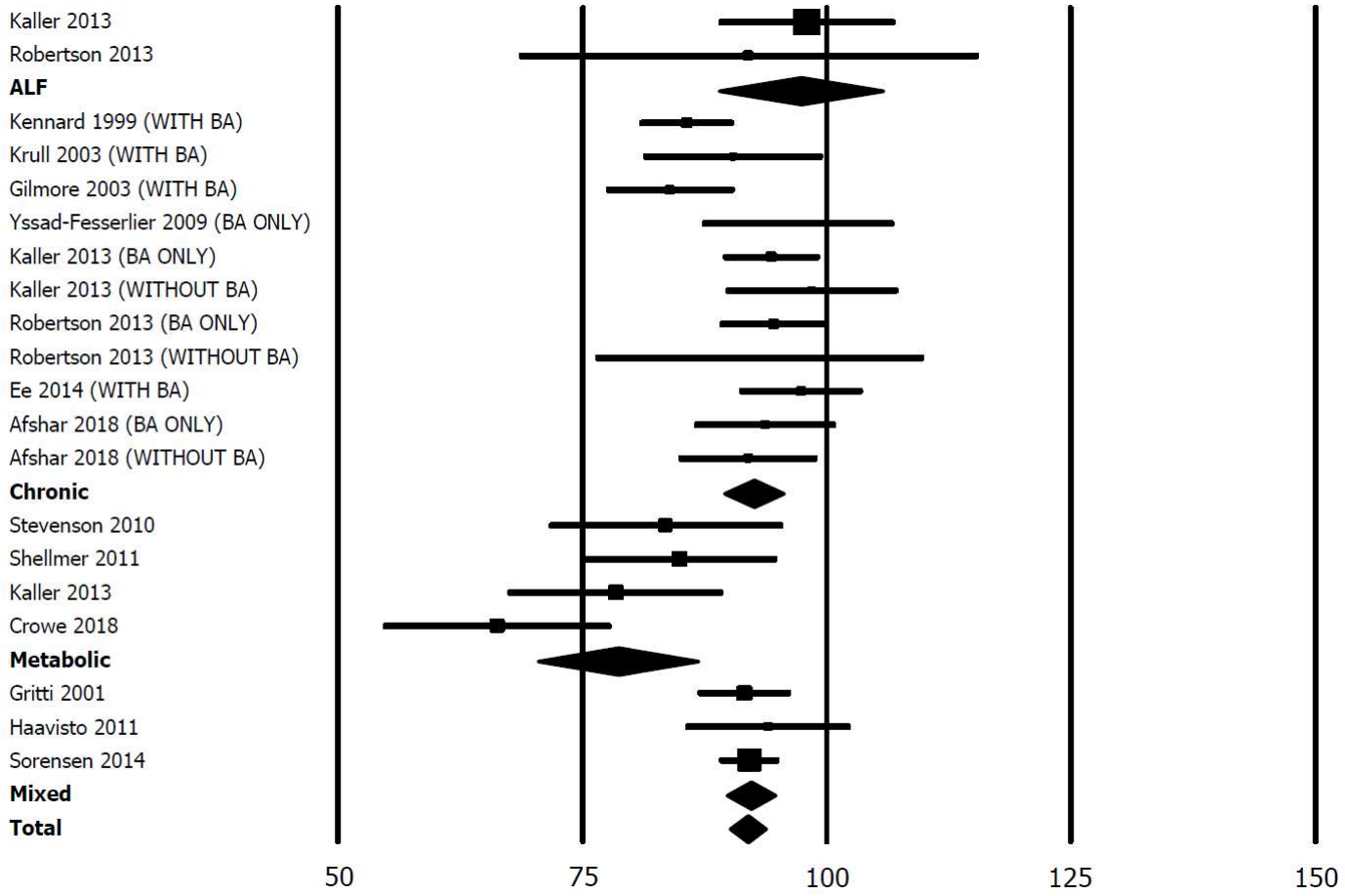


FIGURE 2 Forest plot of meta-analysis for full-scale intelligence quotient (FSIQ) - random effects model

Note: ALF = acute liver failure; BA = biliary atresia

3.3.2 | Verbal Comprehension Index/Verbal Intelligence Quotient (VCI/VIQ)

Eighteen samples from 12 studies ($N = 389$) were identified that reported independent and adequate data on Wechsler based VCI/VIQ (2 samples for ALF, 12 samples for chronic liver disease, 2 metabolic and 2 mixed diagnostic groups). Evaluations of overall consistency revealed heterogeneity across studies ($I^2 = 88.75\%$; $Q_{(17)} = 142.21$; $P < .001$). Egger's test did not indicate the presence of publication bias ($B_0 = 1.74$; $t_{(16)} = 0.994$; $P = .336$; 95% CI = -1.99 to 5.46; see Supplementary Figure 2 for corresponding Funnel Plot).

Results from the random effects model indicated that the overall VCI/VIQ across all diagnostic groups was significantly below the population mean of 100 ($Mean_{Total} = 91.68$; $Standard\ Error_{Pooled} = 2.249$; $n_{samples} = 18$; $n_{participants} = 389$; $P < .001$; 95% CI = 87.27 to 96.09) as shown in Table 3 and Figure 3. The verbal intellectual abilities of children with ALF did not significantly differ from the general population mean of 100 ($Mean_{ALF} = 100.87$; $Standard\ Error_{Pooled} = 3.605$; $n_{samples} = 2$; $n_{participants} = 17$; $P = .809$; 95% CI = 93.81 to 107.94). Similarly, VCI/VIQ of children in studies with Mixed primary diagnoses also did not differ from the normative population mean ($Mean_{Mixed} = 94.30$; $Standard\ Error_{Pooled} = 3.714$; $n_{samples} = 2$; $n_{participants} = 109$; $P = .125$; 95% CI = 87.03 to 101.58). VCI/VIQ was significantly below the general population mean for children with a primary diagnosis of a Chronic liver disease ($Mean_{Chronic} = 92.59$; $Standard\ Error_{Pooled} = 1.621$; $n_{samples} = 12$; $n_{participants} = 249$; $P < .001$; 95% CI = 89.41 to 95.77) and Metabolic disorders ($Mean_{Metabolic} = 76.59$; $Standard\ Error_{Pooled} = 7.310$; $n_{samples} = 2$; $n_{participants} = 14$; $P = .001$; 95% CI = 62.26 to 90.91).

Results from the random-effects meta-regression revealed that VCI/VIQ differed by diagnostic group (Overall Model $Q_{(3)} = 19.67$; $P < .001$; Variance explained by model = 0.71). The Goodness of fit test indicated heterogeneity across studies within subgroups ($\tau^2 = 21.24$; $I^2 = 63.05\%$; $Q_{(14)} = 37.89$; $P < .001$). Pairwise comparisons revealed that the VCI/VIQ for

the Metabolic group was significantly below the other diagnostic groups; ALF group ($Z = 3.71$; $P < .001$); Chronic group ($Z = 3.95$; $P < .001$); and Mixed group ($Z = 3.41$; $P < .001$). The VCI/VIQ of the other 3 groups did not significantly differ from each other (all Ps $> .18$; see Supplementary Table 5 for full details).

TABLE 3 Results of meta-analysis for verbal comprehension index/verbal intelligence quotient (VCI/VIQ)- random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	Std. error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	Std Residual
ALF	Kaller 2013	ALF	101.50	3.776	14.257	94.10	108.90	0.397	.691	91.15	0.559
ALF	Robertson 2013	ALF	94.40	12.119	146.882	70.65	118.15	-0.462	.644	8.85	-0.559
ALF			**100.87**	**3.605**	**12.996**	**93.81**	**107.94**	**0.242**	**.809**		
Chronic	Stewart 1991	Chronic	92.00	3.099	9.606	85.93	98.07	-2.581	.010	9.62	-0.119
Chronic	Kennard 1999	Chronic	86.60	2.401	5.766	81.89	91.31	-5.580	< .001	11.19	-1.311
Chronic	Krull 2003	Chronic	86.13	4.965	24.653	76.40	95.86	-2.793	.005	6.20	-1.025
Chronic	Gilmour 2009	Chronic	84.00	2.907	8.450	78.30	89.70	-5.504	< .001	10.04	-1.770
Chronic	Yssaad-Fesserlier 2009	BA	104.00	5.519	30.462	93.18	114.82	0.725	.469	5.46	1.690
Chronic	Kaller 2013	BA	96.15	2.343	5.488	91.56	100.74	-1.643	.100	11.32	0.784
Chronic	Kaller 2013	Chronic (Not BA)	94.50	4.745	22.512	85.20	103.80	-1.159	.246	6.53	0.311
Chronic	Robertson 2013	BA	97.00	2.924	8.550	91.27	102.73	-1.026	.305	10.00	0.907
Chronic	Robertson 2013	Chronic (Not BA)	90.90	6.992	48.893	77.20	104.60	-1.301	.193	3.95	-0.211
Chronic	Ee 2014	Chronic	97.31	2.993	8.956	91.44	103.18	-0.899	.369	9.85	0.962
Chronic	Afshar 2018	BA	92.15	3.045	9.269	86.18	98.12	-2.578	.010	9.74	-0.089
Chronic	Afshar 2018	Chronic (Not BA)	93.31	5.034	25.340	83.44	103.18	-1.329	.184	6.10	0.113
Chronic			**92.59**	**1.621**	**2.629**	**89.41**	**95.77**	**-4.570**	**< .001**		
Metabolic	Kaller 2013	Metabolic	84.70	5.173	26.765	74.56	94.84	-2.957	.003	44.81	1.000
Metabolic	Crowe 2018	Metabolic	70.00	2.080	4.326	65.92	74.08	-14.423	< .001	55.19	-1.000
Metabolic			**76.59**	**7.310**	**53.440**	**62.26**	**90.91**	**-3.203**	**.001**		
Mixed	Haavisto 2011	Mixed	99.60	4.855	23.576	90.08	109.12	-0.082	.934	32.96	1.000
Mixed	Sorenson 2014	Mixed	91.70	1.520	2.310	88.72	94.68	-5.460	< .001	67.04	-1.000
Mixed			**94.30**	**3.714**	**13.791**	**87.03**	**101.58**	**-1.534**	**.125**		
Overall			**93.43**	**1.350**	**1.823**	**90.79**	**96.08**	**-4.864**	**< .001**		

Note: ALF = acute liver failure; BA = biliary atresia

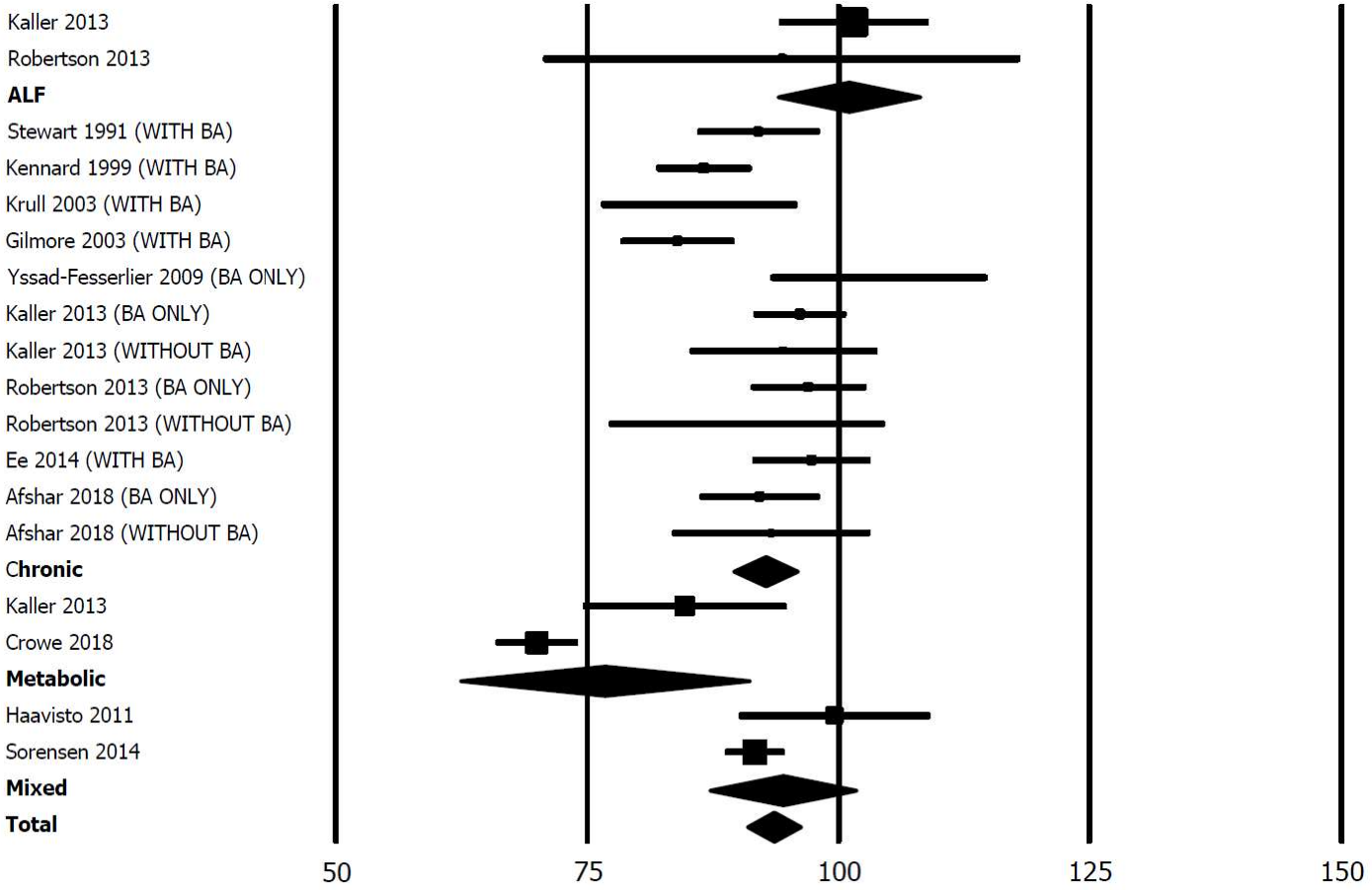


FIGURE 3 Forest plot of meta-analysis for verbal comprehension index/verbal intelligence quotient (VCI/VIQ) - random effects model

Note: ALF = acute liver failure; BA = biliary atresia

3.3.3 | Perceptual Reasoning Index/Performance Intelligence Quotient (PRI/PIQ)

Again, 18 samples were identified from 12 studies (N = 390) that reported independent and adequate data on PRI/PIQ results based on the Wechsler measures of intelligence (2 ALF, 12 chronic liver disease, 2 metabolic, and 2 mixed samples). Evaluations of overall consistency revealed heterogeneity across studies (I^2 = 48.27%; $Q_{(17)}$ = 32.861; P = .012). Egger's test did not indicate the presence of publication bias (B_0 = -0.77; $t_{(16)}$ = 1.062; P = .304; 95% CI = -2.33 to 0.77; see Supplementary Figure 3 for corresponding Funnel Plot).

Results from the random effects model indicated that the overall PRI/PIQ across all diagnostic samples was significantly below the population mean of 100 ($Mean_{Total}$ = 93.57; $Standard\ Error_{Pooled}$ = 1.260; $n_{samples}$ = 18; $n_{participants}$ = 390; P < .001; 95% CI = 91.10 to 96.04), as seen in Table 4 and Figure 4. The PRI/PIQ of children with ALF was not significantly below the population mean of 100 ($Mean_{ALF}$ = 95.97; $Standard\ Error_{Pooled}$ = 3.628; $n_{samples}$ = 2; $n_{participants}$ = 17; P = .266; 95% CI = 88.86 to 103.08). The mean PRI/PIQ was significantly lower than the general population mean of 100 for children with Chronic liver disease ($Mean_{Chronic}$ = 94.23; $Standard\ Error_{Pooled}$ = 1.558; $n_{samples}$ = 12; $n_{participants}$ = 249; P < .001; 95% CI = 91.17 to 97.28), Metabolic disorders ($Mean_{Metabolic}$ = 79.90; $Standard\ Error_{Pooled}$ = 5.206; $n_{samples}$ = 2; $n_{participants}$ = 14; P < .001; 95% CI = 69.700 to 90.106), and trending for children in studies with Mixed primary diagnoses ($Mean_{Mixed}$ = 94.05; $Standard\ Error_{Pooled}$ = 3.087; $n_{samples}$ = 2; $n_{participants}$ = 110; P = .054; 95% CI = 88.00 to 100.10).

Results from the random-effects meta-regression revealed a trend across diagnostic groups in PRI/PIQ outcomes (Overall Model $Q_{(3)}$ = 6.09; P = .107; Variance explained by model = 0.06). The Goodness of fit test indicated heterogeneity across studies within subgroups (T^2 = 11.49; I^2 = 42.94%; $Q_{(14)}$ = 24.53; P = .040). Pairwise comparisons revealed that the PRI/PIQ for the Metabolic group was significantly below the other diagnostic groups;

ALF ($Z = 2.12$; $P = .034$); Chronic ($Z = 2.42$; $P = .016$); and Mixed ($Z = 2.16$; $P = .031$). The PRI/PIQ of the other 3 groups did not significantly differ from each other (all Ps $> .77$; see Supplementary Table 6 for full details).

TABLE 4 Results of meta-analysis for perceptual reasoning index/performance intelligence quotient (PRI/PIQ)- random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
ALF	Kaller 2013	ALF	96.58	3.770	14.214	89.19	103.97	-0.907	.364	92.59	0.598
ALF	Robertson 2013	ALF	88.30	13.327	177.608	62.18	114.42	-0.878	.380	7.41	-0.598
ALF			**95.97**	**3.628**	**13.160**	**88.86**	**103.08**	**-1.112**	**.266**		
Chronic	Stewart 1991	Chronic	89.10	3.610	13.029	82.03	96.17	-3.020	.003	9.14	-1.043
Chronic	Kennard 1999	Chronic	87.10	2.540	6.451	82.12	92.08	-5.079	< .001	12.15	-1.701
Chronic	Krull 2003	Chronic	96.00	4.547	20.674	87.09	104.91	-0.880	.379	7.09	0.315
Chronic	Gilmour 2009	Chronic	86.00	4.249	18.050	77.67	94.33	-3.295	.001	7.68	-1.523
Chronic	Yssaad-Fesserlier 2009	BA	100.70	4.521	20.438	91.84	109.56	0.155	.877	7.14	1.153
Chronic	Kaller 2013	BA	96.41	2.339	5.472	91.83	100.99	-1.535	.125	12.77	0.537
Chronic	Kaller 2013	Chronic (Not BA)	102.50	4.900	24.012	92.90	112.10	0.510	.610	6.46	1.396
Chronic	Robertson 2013	BA	95.50	2.706	7.322	90.20	100.80	-1.663	.096	11.64	0.297
Chronic	Robertson 2013	Chronic (Not BA)	95.00	9.298	86.451	76.78	113.22	-0.538	.591	2.43	0.078
Chronic	Ee 2014	Chronic	100.77	4.490	20.163	91.97	109.57	0.171	.864	7.20	1.170
Chronic	Afshar 2018	BA	95.26	3.889	15.128	87.64	102.88	-1.219	.223	8.47	0.202
Chronic	Afshar 2018	Chronic (Not BA)	92.15	4.182	17.493	83.95	100.35	-1.877	.061	7.82	-0.388
Chronic			**94.23**	**1.558**	**2.427**	**91.17**	**97.28**	**-3.707**	**< .001**		
Metabolic	Kaller 2013	Metabolic	81.90	6.223	38.730	69.70	94.10	-2.908	.004	69.97	0.586
Metabolic	Crowe 2018	Metabolic	75.25	9.500	90.250	56.63	93.87	-2.605	.009	30.03	-0.586
Metabolic			**79.90**	**5.206**	**27.100**	**69.70**	**90.11**	**-3.860**	**< .001**		
Mixed	Haavisto 2011	Mixed	88.90	5.068	25.681	78.97	98.83	-2.190	.028	26.43	-1.000
Mixed	Sorenson 2014	Mixed	95.90	1.606	2.578	92.75	99.05	-2.554	.011	73.57	1.000
Mixed			**94.05**	**3.087**	**9.527**	**88.00**	**100.10**	**-1.928**	**.054**		
Overall			**93.57**	**1.260**	**1.587**	**91.10**	**96.04**	**-5.105**	**< .001**		

Note: ALF = acute liver failure; BA = biliary atresia

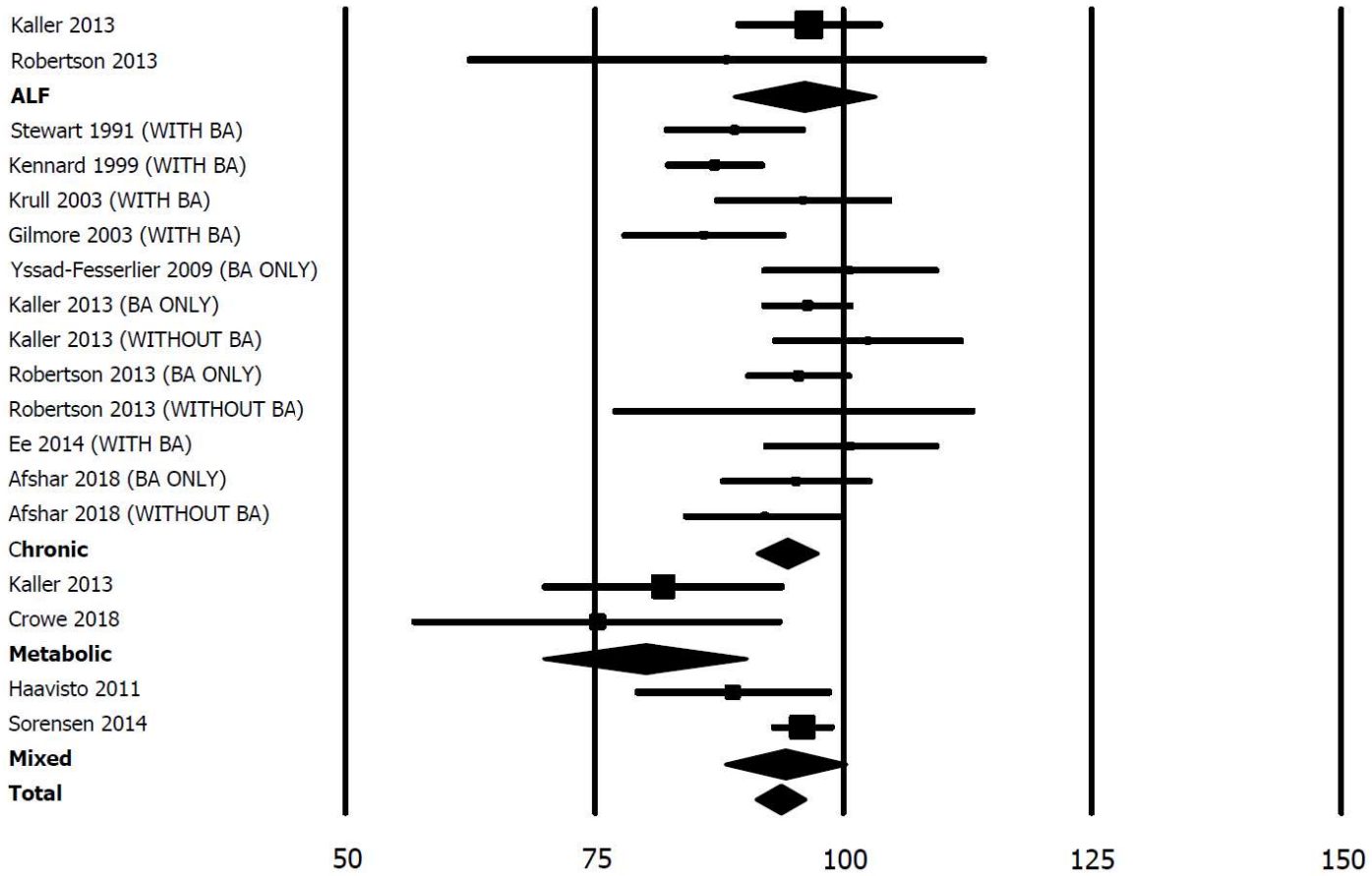


FIGURE 4 Forest plot of meta-analysis for perceptual reasoning index/performance intelligence quotient (PRI/PIQ) - random effects model

Note: ALF = acute liver failure; BA = biliary atresia

3.3.4 | Processing Speed Index (PSI)

Ten samples from six studies (N = 226) were identified with appropriate data on Wechsler based processing speed results (1 ALF, 6 chronic liver disease, 2 metabolic, and 1 mixed). Assessment of the overall consistency of the samples showed significant heterogeneity (I^2 = 72.35%; $Q_{(9)}$ = 32.55; P < .001). No evidence of publication bias was evident as evaluated by the Egger's test (B_0 = -1.06; $t_{(8)}$ = 0.639; P = .541; 95% CI = -4.87 to 2.76; see Supplementary Figure 4 for corresponding Funnel Plot).

Results from the random effects model indicated that the overall PSI across all diagnostic samples was significantly below the population mean of 100 ($Mean_{Total}$ = 94.62; $Standard\ Error_{Pooled}$ = 0.932; $n_{samples}$ = 10; $n_{participants}$ = 226; P < .001; 95% CI = 92.79 to 96.45) as seen in Table 5 and Figure 5. The PSI of children with ALF was not significantly different to the population average of 100 ($Mean_{ALF}$ = 97.92; $Standard\ Error_{Pooled}$ = 5.465; $n_{samples}$ = 1; $n_{participants}$ = 12; P = .703; 95% CI = 87.21 to 108.63). The PSI was significantly below the population average of 100 for children with Chronic liver disease ($Mean_{Chronic}$ = 96.97; $Standard\ Error_{Pooled}$ = 1.298; $n_{samples}$ = 6; $n_{participants}$ = 108; P = .020; 95% CI = 94.43 to 99.51), Metabolic disorders ($Mean_{Metabolic}$ = 79.81; $Standard\ Error_{Pooled}$ = 2.949; $n_{samples}$ = 2; $n_{participants}$ = 14; P < .001; 95% CI = 74.03 to 85.59), and for children in studies with Mixed primary diagnoses ($Mean_{Mixed}$ = 95.10; $Standard\ Error_{Pooled}$ = 1.564; $n_{samples}$ = 1; $n_{participants}$ = 92; P = .002; 95% CI = 92.03 to 98.17).

Results from the random-effects meta-regression revealed that PSI differed by diagnostic group (Overall Model $Q_{(3)}$ = 28.95; P < .001; Variance explained by model = 1.00). The Goodness of fit test did not show significant heterogeneity across studies within subgroups (T^2 = 0; I^2 = 0%; $Q_{(6)}$ = 3.60; P = .731). Pairwise comparisons revealed that the PSI for the Metabolic group was significantly below the other diagnostic groups; ALF (Z =

2.92; $P = .003$); Chronic ($Z = 5.33$; $P < .001$); and Mixed ($Z = 4.58$; $P < .001$). The PSI of the other 3 groups did not significantly differ from each other (all Ps > .36; see Supplementary Table 7 for full details).

TABLE 5 Results of meta-analysis for processing speed index (PSI) - random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
ALF	Kaller 2013	ALF	97.92	5.465	29.862	87.21	108.63	-0.381	.703	100.00	
ALF			**97.92**	**5.465**	**29.862**	**87.21**	**108.63**	**-0.381**	**.703**		
Chronic	Yssaad-Fesserlier 2009	BA	98.50	4.687	21.970	89.31	107.69	-0.320	.749	7.67	0.340
Chronic	Kaller 2013	BA	95.97	2.579	6.653	90.91	101.03	-1.562	.118	25.32	-0.448
Chronic	Kaller 2013	Chronic (Not BA)	97.38	3.564	12.701	90.40	104.36	-0.735	.462	13.26	0.124
Chronic	Ee 2014	Chronic	95.92	3.140	9.857	89.77	102.07	-1.300	.194	17.09	-0.367
Chronic	Afshar 2018	BA	101.52	3.135	9.828	95.38	107.66	0.485	.628	17.14	1.595
Chronic	Afshar 2018	Chronic (Not BA)	94.31	2.937	8.627	88.55	100.07	-1.937	.053	19.53	-1.009
Chronic			**96.97**	**1.298**	**1.684**	**94.43**	**99.51**	**-2.335**	**.020**		
Metabolic	Kaller 2013	Metabolic	80.70	3.384	11.449	74.07	87.33	-5.704	< .001	75.96	0.536
Metabolic	Crowe 2019	Metabolic	77.00	6.015	36.180	65.21	88.79	-3.824	< .001	24.04	-0.536
Metabolic			**79.81**	**2.949**	**8.697**	**74.03**	**85.59**	**-6.846**	**< .001**		
Mixed	Sorenson 2014	Mixed	95.10	1.564	2.446	92.03	98.17	-3.133	.002	100.00	
Mixed			**95.10**	**1.564**	**2.446**	**92.03**	**98.17**	**-3.133**	**.002**		
Overall			**94.62**	**0.932**	**0.869**	**92.79**	**96.45**	**-5.773**	**< .001**		

Note: ALF = acute liver failure; BA = biliary atresia

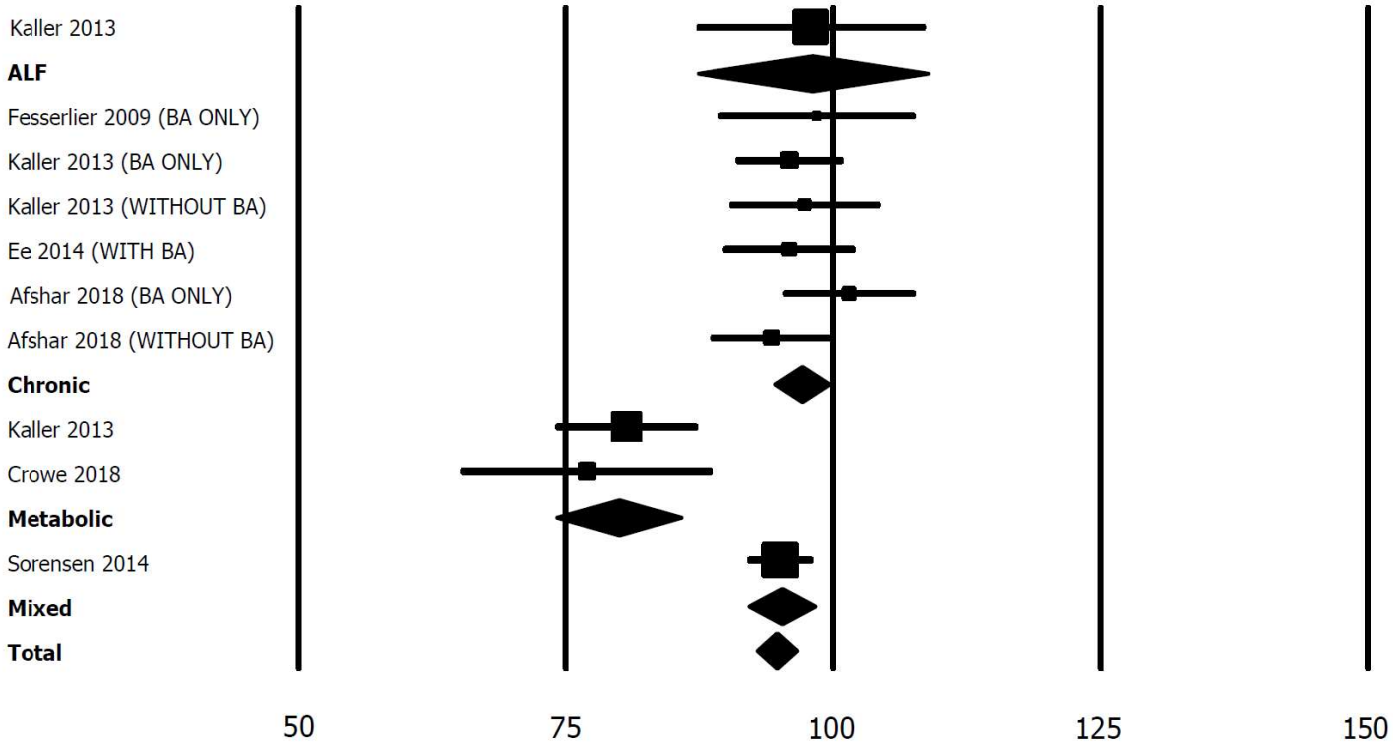


FIGURE 5 Forest plot of meta-analysis for processing speed index (PSI) - random effects model

Note: ALF = acute liver failure; BA = biliary atresia

3.3.5 | Working Memory Index (WMI)

Ten samples from six studies (N = 226) were identified with appropriate data on working memory results (1 ALF, 6 chronic liver disease, 2 metabolic, and 1 mixed). Measures of between-study consistency revealed significant heterogeneity (I^2 = 70.88%; $Q_{(9)}$ = 30.90; P < .001). Egger's test did not indicate the presence of publication bias (B_0 = -0.72; $t_{(8)}$ = 0.481; P = .643; 95% CI = -4.18 to 2.74; see Supplementary Figure 5 for corresponding Funnel Plot).

Results from the random effects model indicated that the WMI across all diagnostic samples was significantly below the population mean of 100 ($Mean_{Total}$ = 91.56; Standard $Error_{Pooled}$ = 1.176; $n_{samples}$ = 10; $n_{participants}$ = 226; P < .001; 95% CI = 89.25 to 93.86) as illustrated in Table 6 and Figure 6. The WMI of children with ALF was not significantly different to the population mean of 100 ($Mean_{ALF}$ = 97.68; Standard $Error_{Pooled}$ = 5.141; $n_{samples}$ = 1; $n_{participants}$ = 12; P = .652; 95% CI = 89.88 to 98.17). The WMI was significantly below the normative population mean of 100 for children with Chronic liver disease ($Mean_{Chronic}$ = 94.03; Standard $Error_{Pooled}$ = 2.114; $n_{samples}$ = 6; $n_{participants}$ = 108; P = .005; 95% CI = 89.88 to 98.17), Metabolic disorders ($Mean_{Metabolic}$ = 77.76; Standard $Error_{Pooled}$ = 5.769; $n_{samples}$ = 2; $n_{participants}$ = 14; P < .001; 95% CI = 66.46 to 89.07), and for children in studies with Mixed primary diagnoses ($Mean_{Mixed}$ = 90.70; Standard $Error_{Pooled}$ = 1.522; $n_{samples}$ = 1; $n_{participants}$ = 92; P < .001; 95% CI = 87.72 to 93.68).

Results from the random-effects meta-regression revealed that WMI differed by diagnostic group (Overall Model $Q_{(3)}$ = 9.08; P = .028; Variance explained by model = 0.29). The Goodness of fit test indicated heterogeneity across studies within subgroups ($\hat{\tau}^2$ = 17.08; I^2 = 59.95%; $Q_{(6)}$ = 14.98; P = .020). Pairwise comparisons revealed that the WMI for the Metabolic group was significantly below the ALF (Z = 2.37; P = .018) and Chronic (Z = 2.87;

P = .004) groups, and a trend was evident with the Mixed sample group (*Z* = 1.89; *P* = .059). The WMI of the other 3 groups did not significantly differ from each other (all *P*s > .37; see Supplementary Table 8 for full details).

TABLE 6 Results of meta-analysis for working memory index (WMI) - random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
ALF	Kaller 2013	ALF	97.68	5.141	26.433	87.60	107.76	-0.451	.652	100.00	
ALF			**97.68**	**5.141**	**26.433**	**87.60**	**107.76**	**-0.451**	**.652**		
Chronic	Yssaad-Fesserlier 2009	BA	84.00	3.855	14.862	76.44	91.56	-4.150	< .001	14.24	-1.933
Chronic	Kaller 2013	BA	94.91	3.147	9.904	88.74	101.08	-1.617	.106	16.91	0.189
Chronic	Kaller 2013	Chronic (Not BA)	101.63	3.695	13.650	94.39	108.87	0.441	.659	14.81	1.500
Chronic	Ee 2014	Chronic	97.08	2.602	6.768	91.98	102.18	-1.122	.262	19.19	0.704
Chronic	Afshar 2018	BA	91.19	3.110	9.672	85.09	97.29	-2.833	.005	17.06	-0.609
Chronic	Afshar 2018	Chronic (Not BA)	94.31	2.937	8.627	88.55	100.07	-1.937	.053	17.77	0.062
Chronic			**94.03**	**2.114**	**4.467**	**89.88**	**98.17**	**-2.826**	**.005**		
Metabolic	Kaller 2013	Metabolic	83.80	6.451	41.616	71.16	96.44	-2.511	.012	47.74	1.000
Metabolic	Crowe 2018	Metabolic	72.25	5.965	35.581	60.56	83.94	-4.652	< .001	52.26	-1.000
Metabolic			**77.76**	**5.769**	**33.282**	**66.46**	**89.07**	**-3.854**	**< .001**		
Mixed	Sorenson 2014	Mixed	90.70	1.522	2.317	87.72	93.68	-6.110	< .001	100.00	
Mixed			**90.70**	**1.522**	**2.317**	**87.72**	**93.68**	**-6.110**	**< .001**		
Overall			**91.56**	**1.176**	**1.382**	**89.25**	**93.86**	**-7.180**	**< .001**		

Note: ALF = acute liver failure; BA = biliary atresia

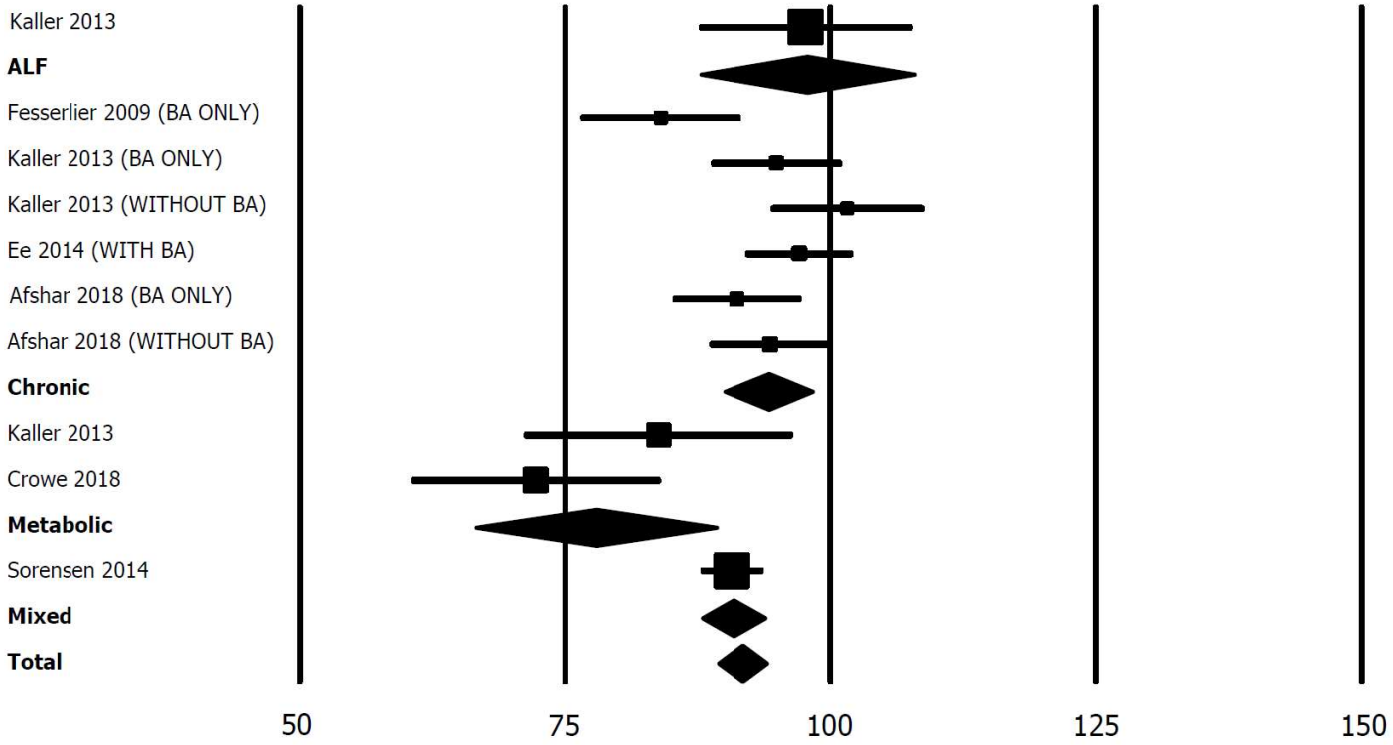


FIGURE 6 Forest plot of meta-analysis for working memory index (WMI) - random effects model

Note: ALF = acute liver failure; BA = biliary atresia

3.3.6 | Reading

Nine samples from eight studies (N = 253) were identified with appropriate data on Reading abilities (7 chronic liver disease, 1 metabolic and 1 mixed). Measures of between-study consistency revealed significant heterogeneity (I^2 = 64.01%; $Q_{(8)}$ = 22.23; P = .005). Egger's test did not indicate the presence of publication bias (B_0 = -1.87; $t_{(7)}$ = 1.692; P = .134; 95% CI = -4.49 to 0.74; see Supplementary Figure 6 for corresponding Funnel Plot).

Results from the random effects model indicated that the mean Reading ability across all diagnostic samples was significantly below the population mean of 100 ($Mean_{Total}$ = 96.78; $Standard\ Error_{Pooled}$ = 1.225; $n_{samples}$ = 9; $n_{participants}$ = 253; P = .009; 95% CI = 94.38 to 99.19), as shown in Table 7 and Figure 7. The Reading ability of children with Chronic liver disease was significantly below the mean of the general population of 100 ($Mean_{Chronic}$ = 93.12; $Standard\ Error_{Pooled}$ = 2.708; $n_{samples}$ = 7; $n_{participants}$ = 157; P = .011; 95% CI = 87.82 to 98.43). Reading ability was not significantly below the general population mean of 100 for children with a Metabolic disorder ($Mean_{Metabolic}$ = 93.67; $Standard\ Error_{Pooled}$ = 4.255; $n_{samples}$ = 1; $n_{participants}$ = 4; P = .137; 95% CI = 85.33 to 102.01) or for children in a sample of Mixed primary diagnoses ($Mean_{Mixed}$ = 98.20; $Standard\ Error_{Pooled}$ = 1.452; $n_{samples}$ = 1; $n_{participants}$ = 93; P = .215; 95% CI = 95.35 to 101.05). No data on reading abilities exclusively in children with ALF was available.

Results from the random-effects meta-regression revealed that Reading ability did not differ by diagnostic group (Overall Model $Q_{(2)}$ = 0.61; P = .737; Variance explained by model = 0.00). The Goodness of fit test indicated heterogeneity across studies within subgroups (T^2 = 32.86; I^2 = 65.26%; $Q_{(6)}$ = 17.27; P = .008).

An additional post-hoc random effects meta-regression analysis revealed a significant effect of study year (B = 0.513; P < .001), with more recent studies displaying better reading abilities (Overall Model $Q_{(1)}$ = 11.98; P < .001; Variance explained by model = 0.92). The Goodness of fit test did not reveal heterogeneity across studies within subgroups ($\hat{\tau}^2$ = 1.63; I^2 = 11.77%; $Q_{(7)}$ = 7.93; P = .338).

TABLE 7 Results of meta-analysis for Reading - random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
Chronic	Stewart 1991	Chronic	82.80	4.063	16.509	74.84	90.76	-4.233	< .001	14.85	-1.592
Chronic	Kennard 1999	Chronic	90.78	3.700	13.687	83.53	98.03	-2.492	.013	15.75	-0.374
Chronic	Krull 2003	Chronic	96.30	4.028	16.224	88.41	104.19	-0.919	.358	14.94	0.492
Chronic	Gilmour 2009	Chronic	85.00	5.427	29.455	74.36	95.64	-2.764	.006	11.77	-1.096
Chronic	Ee 2014	Chronic	96.00	4.102	16.826	87.96	104.04	-0.975	.329	14.76	0.442
Chronic	Afshar 2018	BA	101.78	3.406	11.603	95.10	108.46	0.523	.601	16.49	1.421
Chronic	Afshar 2018	Chronic (Not BA)	97.77	5.589	31.233	86.82	108.72	-0.399	.690	11.44	0.617
Chronic			**93.12**	**2.708**	**7.332**	**87.82**	**98.43**	**-2.540**	**.011**		
Metabolic	Crowe 2018	Metabolic	93.67	4.255	18.106	85.33	102.01	-1.488	.137	100.00	
Metabolic			**93.67**	**4.255**	**18.106**	**85.33**	**102.01**	**-1.488**	**.137**		
Mixed	Sorenson 2014	Mixed	98.20	1.452	2.108	95.35	101.05	-1.240	.215	100.00	
Mixed			**98.20**	**1.452**	**2.108**	**95.35**	**101.05**	**-1.240**	**.215**		
Overall			**96.78**	**1.225**	**1.501**	**94.38**	**99.19**	**-2.624**	**.009**		

Note: BA = biliary atresia

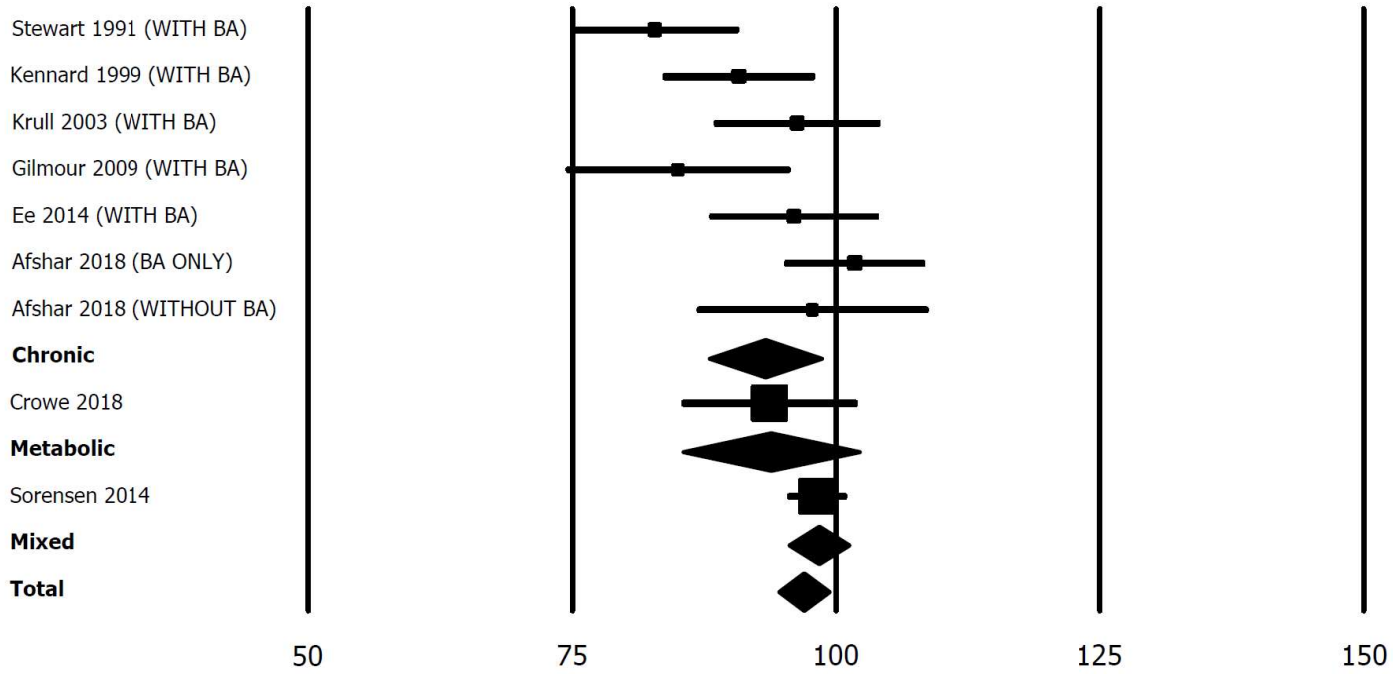


FIGURE 7 Forest plot of meta-analysis for Reading - random effects model

Note: BA = biliary atresia

3.3.7 | Spelling

Seven samples from six studies (N = 185) were identified with appropriate data on Spelling abilities (6 chronic and 1 metabolic sample). Measures of between-study consistency revealed significant heterogeneity (I^2 = 84.23%; $Q_{(6)}$ = 38.05; P < .001). Egger's test did not indicate the presence of publication bias (B_0 = -2.07; $t_{(5)}$ = 0.662; P = .537; 95% CI = -10.10 to 5.96; see Supplementary Figure 7 for corresponding Funnel Plot).

Results from the random effects model indicated that the mean Spelling ability across all diagnostic samples did not significantly differ from the population mean of 100, although a trend was evident ($Mean_{Total}$ = 92.74; Standard $Error_{Pooled}$ = 4.008; $n_{samples}$ = 7; $n_{participants}$ = 185; P = .070; 95% CI = 84.89 to 100.60), as demonstrated in Table 8 and Figure 8. The mean Spelling ability of children with Chronic liver disease was not significantly different to the mean of the general population of 100, although again a trend of lower mean scores was evident ($Mean_{Chronic}$ = 91.87; Standard $Error_{Pooled}$ = 4.400; $n_{samples}$ = 6; $n_{participants}$ = 182; P = .065; 95% CI = 83.25 to 100.49). The Spelling ability of children with Metabolic disorders, based on the small single study sample of 3 participants, was not significantly different to the population mean of 100 ($Mean_{Metabolic}$ = 97.00; Standard $Error_{Pooled}$ = 9.711; $n_{samples}$ = 1; $n_{participants}$ = 3; P = .757; 95% CI = 77.97 to 116.03).

Results from the random-effects meta-regression revealed that Spelling ability did not differ between the Chronic and Metabolic diagnostic groups (Overall Model $Q_{(1)}$ = 0.12; P = .725; Variance explained by model = 0.00). The Goodness of fit test indicated heterogeneity across studies within subgroups (T^2 = 98.88; I^2 = 86.82%; $Q_{(5)}$ = 37.93; P < .001).

An additional post-hoc random effects meta-regression revealed a significant effect of study year (B = 0.903; P < .001), with more recent studies displaying better Spelling (Overall

model: $Q_{(1)} = 34.39$; $P < .001$; Variance explained by model = 1.00). The Goodness of fit test did not reveal heterogeneity across studies within subgroups ($\tau^2 = 0$; $I^2 = 0\%$; $Q_{(5)} = 3.65$; $P = .601$).

TABLE 8 Results of meta-analysis for Spelling - random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
Chronic	Stewart 1991	Chronic	80.50	4.309	18.566	72.05	88.95	-4.526	< .001	16.48	-1.148
Chronic	Kennard 1999	Chronic	81.27	3.509	12.311	74.39	88.15	-5.338	< .001	17.41	-1.106
Chronic	Gilmour 2009	Chronic	91.00	5.126	26.273	80.95	101.05	-1.756	.079	15.47	-0.085
Chronic	Ee 2014	Chronic	98.15	3.678	13.525	90.94	105.36	-0.503	.615	17.22	0.651
Chronic	Afshar 2018	BA	103.78	2.685	7.208	98.52	109.04	1.408	.159	18.25	1.279
Chronic	Afshar 2018	Chronic (Not BA)	95.82	5.356	28.683	85.32	106.32	-0.780	.435	15.17	0.380
Chronic			**91.87**	**4.400**	**19.357**	**83.25**	**100.49**	**-1.848**	**.065**		
Metabolic	Crowe 2018	Metabolic	97.00	9.711	94.304	77.97	116.03	-0.309	.757	100.00	
Metabolic			**97.00**	**9.711**	**94.304**	**77.97**	**116.03**	**-0.309**	**.757**		
Overall			**92.74**	**4.008**	**16.060**	**84.89**	**100.60**	**-1.811**	**.070**		

Note: ALF = acute liver failure; BA = biliary atresia

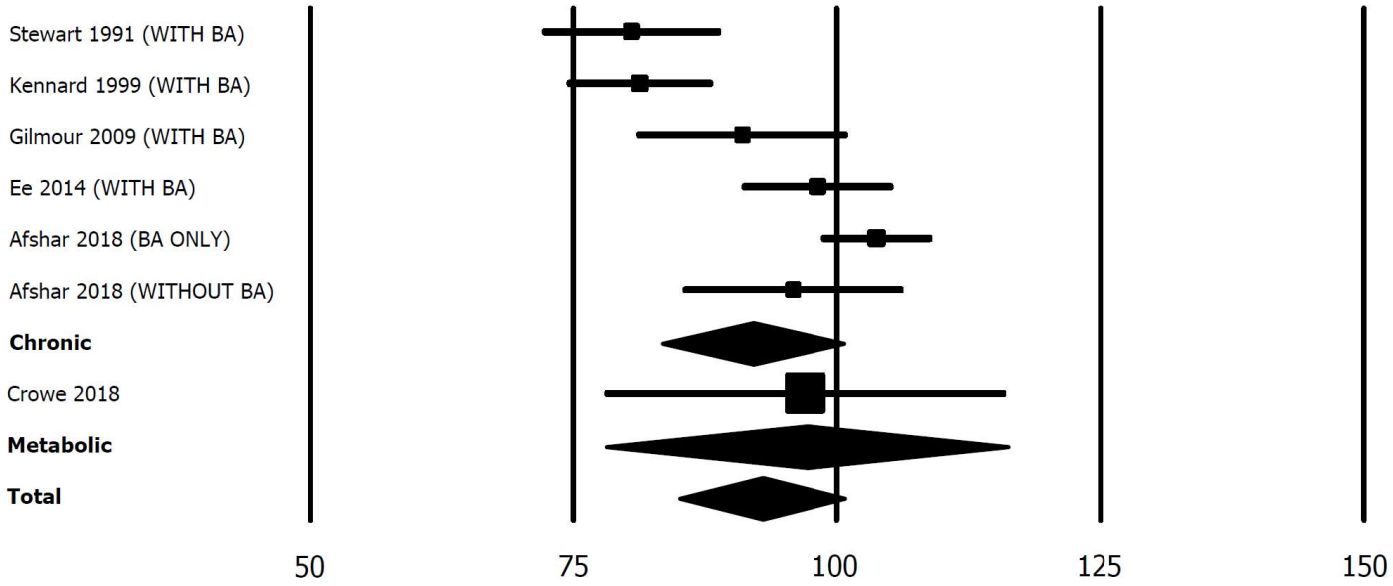


FIGURE 8 Forest plot of meta-analysis for Spelling - random effects model

Note: BA = biliary atresia

3.3.8 | Writing

Only two samples from two studies (N = 65) were identified with appropriate data on Writing skills, both of which consisted of a Chronic liver disease group. Measures of between-study consistency revealed significant heterogeneity (I^2 = 92.33%; $Q_{(1)}$ = 13.03; P < .001). Assessment of publication bias was not possible, as only two studies were identified for the analysis.

Results from the random effects model indicated that the Writing ability of children with Chronic liver disease was not significantly different to the general population of 100 ($Mean_{Chronic}$ = 93.38; $Standard\ Error_{Pooled}$ = 11.33; $n_{samples}$ = 2; $n_{participants}$ = 65; P = .004; 95% CI = 75.18 to 115.59; see Supplementary Table 9). Post-hoc analysis revealed that the more recent study had significantly higher writing skills than the former study (Difference = 22.66; $t_{(63)}$ = 2.9515; P = .004).

3.3.9 | Mathematics

Nine samples from eight studies (N = 253) were identified with appropriate data on mathematical abilities (7 chronic liver disease, 1 metabolic and 1 mixed). Measures of between-study consistency revealed significant heterogeneity (I^2 = 66.89%; $Q_{(8)}$ = 24.16; P = .002). Egger's test did not indicate the presence of publication bias (B_0 = -1.56; $t_{(7)}$ = 1.119; P = .300; 95% CI = -4.86 to 1.74; see Supplementary Figure 8 for corresponding Funnel Plot).

Results from the random effects model indicated that the mean Mathematical ability across all diagnostic groups was significantly below the normative population mean of 100 ($Mean_{Total}$ = 88.26; $Standard\ Error_{Pooled}$ = 1.354; $n_{samples}$ = 9; $n_{participants}$ = 253; P < .001; 95% CI = 85.60 to 90.91), as shown in Table 9 and Figure 9. The Mathematical ability was

significantly below the population mean for children with Chronic liver disease ($Mean_{Chronic}$ = 85.59; Standard $Error_{Pooled}$ = 2.606; $n_{samples}$ = 7; $n_{participants}$ = 157; $P < .001$; 95% CI = 80.48 to 90.70), Metabolic disorder ($Mean_{Metabolic}$ = 78.67; Standard $Error_{Pooled}$ = 5.785; $n_{samples}$ = 1; $n_{participants}$ = 3; $P < .001$; 95% CI = 67.33 to 90.01) and for children in a sample of Mixed primary diagnoses ($Mean_{Mixed}$ = 90.10; Standard $Error_{Pooled}$ = 1.649; $n_{samples}$ = 1; $n_{participants}$ = 93; $P < .001$; 95% CI = 86.87 to 93.33).

Results from the random-effects meta-regression revealed that Mathematical ability did not differ between the Chronic, Metabolic and Mixed diagnostic groups (Overall Model $Q_{(2)}$ = 1.37; $P = .505$; Variance explained by model = 0.00). The Goodness of fit test indicated heterogeneity across studies within subgroups ($\hat{\tau}^2$ = 30.14; $\hat{I}^2$ = 64.81%; $Q_{(6)}$ = 17.05; P = .009).

TABLE 9 Results of meta-analysis for Mathematics - random effects model

Diagnostic Category	Study	Diagnostic Subgroups	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
Chronic	Stewart 1991	Chronic	80.90	4.177	17.443	72.71	89.09	-4.573	< .001	14.28	-0.735
Chronic	Kennard 1999	Chronic	83.65	3.250	10.562	77.28	90.02	-5.031	< .001	16.69	-0.333
Chronic	Krull 2003	Chronic	93.53	5.975	35.697	81.82	105.24	-1.083	.279	10.32	1.033
Chronic	Gilmour 2009	Chronic	74.00	3.920	15.364	66.32	81.68	-6.633	< .001	14.93	-1.863
Chronic	Ee 2014	Chronic	86.15	3.583	12.840	79.13	93.17	-3.865	< .001	15.80	0.093
Chronic	Afshar 2018	BA	92.81	3.789	14.359	85.38	100.24	-1.897	.058	15.27	1.176
Chronic	Afshar 2018	Chronic (Not BA)	91.21	4.823	23.262	81.76	100.66	-1.822	.068	12.72	0.823
Chronic			**85.59**	**2.606**	**6.792**	**80.48**	**90.70**	**-5.529**	**< .001**		
Metabolic	Crowe 2018	Metabolic	78.67	5.785	33.467	67.33	90.01	-3.687	< .001	100.00	
Metabolic			**78.67**	**5.785**	**33.467**	**67.33**	**90.01**	**-3.687**	**< .001**		
Mixed	Sorenson 2014	Mixed	90.10	1.649	2.718	86.87	93.33	-6.005	< .001	100.00	
Mixed			**90.10**	**1.649**	**2.718**	**86.87**	**93.33**	**-6.005**	**< .001**		
Overall			**88.26**	**1.355**	**1.835**	**85.60**	**90.91**	**-8.670**	**< .001**		

Note: BA = biliary atresia

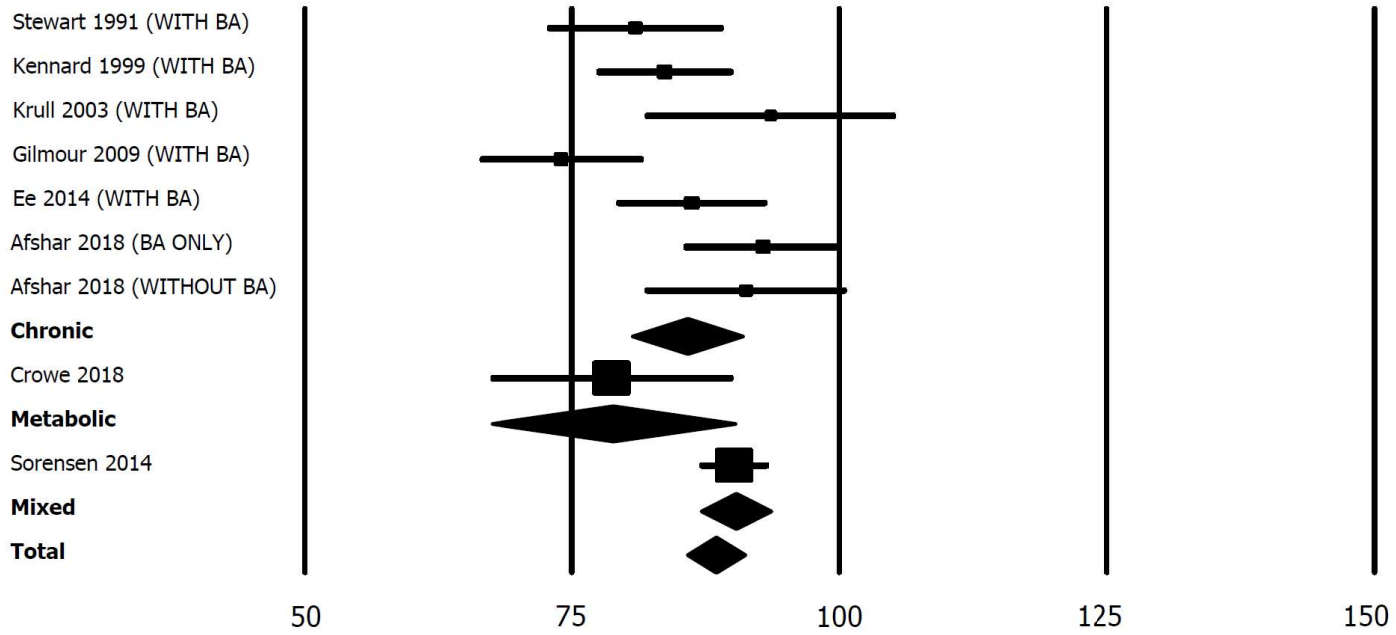


FIGURE 9 Forest plot of meta-analysis for Mathematics - random effects model

Note: BA = biliary atresia

3.3.10 | Comparison of VCI/VIQ and PRI/PIQ

The secondary meta-analysis comparing VCI/VIQ and PRI/PIQ included 18 samples from 11 studies (2 ALF, 12 chronic, 2 metabolic and 2 mixed samples; 390 participants with a VCI/VIQ score and 389 with a PRI/PIQ score). Results revealed significant heterogeneity across all studies. No heterogeneity was identified within diagnostic subgroups with the exception of the mixed group. No evidence of publication bias was present (I^2 = 0%; $Q_{(17)}$ = 11.51; P = .829). Egger's test did not indicate the presence of publication bias (B_0 = -0.46; $t_{(16)}$ = 0.918; P = .372; 95% CI = -1.53 to 0.61; see Supplementary Figure 9 for corresponding Funnel Plot).

The results of the random effects meta-analysis which utilized a between-subject approach did not show any evidence of a discrepancy between VCI/VIQ and PRI/PIQ scores in children post-liver transplant, either at the overall level or within diagnostic subgroups (see Supplementary Table 10 and Supplementary Figure 10). No pattern or trend was observable, with 8 out of 18 studies having a mean VCI/VIQ numerically greater than the mean PRI/PIQ and the remaining 10 demonstrating the reverse.

4 | DISCUSSION

The aim of the current systematic review and meta-analysis was to summarise and evaluate the literature in relation to long-term intellectual and academic outcomes of pediatric liver transplant recipients, and to investigate whether these outcomes differed by primary diagnostic group (ALF, Chronic, Metabolic, and Mixed group). The 15 studies included in the meta-analysis were primarily of good quality based on the revised MQI[32] and followed a relatively consistent design, with no evidence of publication bias. While two out of the four studies with a metabolic sample were of low quality, the results were consistent across the four samples. Together, this suggested that the findings were an accurate reflection of the

intellectual and academic outcomes of pediatric liver transplant populations, although caution is required given the small sample size of the ALF and metabolic groups.

4.1 | Intellectual outcomes

As predicted, when the findings of studies investigating pediatric liver transplantation were quantitatively amalgamated, long-term intellectual outcomes of children post-liver transplant were significantly lower than the normative population mean, consistent with the findings of two similar reviews.[11, 24] In addition, the results detected differences between diagnostic groups, which were partly consistent with predictions and previous findings.[22, 25] Metabolic participants had the lowest overall scores, whereas children with ALF did not show a significant difference in intellectual ability compared with the population mean. This result emerged despite small sample sizes in these groups. While the chronic liver disease group was significantly below the population mean and superior to the metabolic group, it was not significantly below the ALF group, potentially due to power limitations. The overall intelligence of the mixed sample group was in line with the overall intelligence of all studies, demonstrating that diagnostic group effects are masked when results are averaged across diagnoses.

A similar pattern of results was obtained for intellectual domains (VCI/VIQ, PRI/PIQ, PSI and WMI), with the poorest performance consistently found in the metabolic group, followed by the chronic disease participants, whereas ALF performance was generally commensurate with population norms. However, the issue of smaller samples in the metabolic group was particularly problematic for the intellectual subdomains. Again, the mean results for the mixed sample were similar to the results for all studies combined. These results demonstrate the importance of differentiating across diagnostic groups to better identify outcomes, and reinforce the notion that the disease experience differs across these groups.

Finally, as predicted, there was no evidence to support poorer nonverbal/perceptual (PRI/PIQ) intellectual functioning relative to verbal intellect (VCI/VIQ). Although the use of between-subject analysis unavoidably reduced the power of the analysis and risked washing out effects by averaging across individuals, it provided a better understanding of the overall pattern of results in the literature to date.

4.2 | Academic outcomes

Consistent with predictions, the average reading ability of children post-liver transplant was significantly below the population mean. However, this difference appears to be reducing over time as shown in the relevant meta-regression, with results from more recent studies not differing from normative means.[8, 10, 23, 46] One possible explanation for this gain in reading levels is the presence of cohort effects, with more recent studies conducted during a time of technical advances and better medical care,[50-53] as well as possible improvements in teaching methods and/or more effective literacy interventions. However, Sorensen et al.'s[10] longitudinal study showed that reading ability returned to normal over time in the largest sample of pediatric transplant recipients, which may be suggestive of a 'catch-up' effect after an initial vulnerability. These two explanations are not mutually exclusive; the more recent cohorts may have had more advanced medical care and better literacy interventions than previous cohorts, and were therefore more able to overcome their initial vulnerabilities in literacy development. Spelling ability appeared to follow a similar trend to reading results, with average scores improving over time across studies and results of more recent studies indicating age-expected abilities.

As predicted, mathematical ability was found to be significantly below the population mean with the chronic group performing, on average, one standard deviation below the mean. Unlike literacy skills, mathematical ability did not show a trajectory of improvement over time.

This is consistent with Sorensen et al.'s[10] longitudinal study findings. Taken together, these results support the body of literature that indicates mathematical ability is particularly vulnerable to disruption by liver disease and the associated transplant experience. This finding may be due to the specific and direct impact of the liver disease and transplant processes on brain development, as well as the disruption associated with pediatric illnesses more generally.[54, 55] Additionally, given the hierarchical approach to learning mathematics, the compounding effects of regular missed schooling may be particularly disruptive.[54]

4.3 | Reflections on methodology

Quantitative analysis revealed significant heterogeneity across studies, indicating the possible presence of systematic differences across studies both at the all-groups level and the diagnostic subgroup level. At the all-groups level, it is proposed that the systematic differences identified were primarily explained by the differing diagnostic groups. At the subgroup level, however, the significant heterogeneity is postulated to be driven to some degree by variability in study design, the varying age range of study participants, the different outcome measures used, different inclusion and exclusion criteria, and differences in how disorders were categorised into overarching diagnostic subgroups. Therefore, there is a need for consensus as well as improvements in study design to minimise heterogeneity across and within studies.

Perhaps unsurprisingly, prospective studies were found to be of higher quality compared to retrospective studies. This may be due to the deliberateness of prospective designs which aim to eliminate variability between sites, clinicians and cases, and employ hypothesis-testing rather than exploratory and retrospective data collection. Failing to adequately describe the sample characteristics for the subset of participants who underwent standardized intellectual/academic testing was common amongst retrospective studies. While word limits within manuscripts is a barrier for adequately reporting all data in text, the use of

supplementary tables is recommended to overcome this issue. Furthermore, a variety of different cognitive measures were utilized both across and within studies,[42, 43, 45] which limits the ability to synthesise the findings across the literature. In addition, the studies included in the systematic review that were not subsequently included in the meta-analysis were of a lower quality. In short, the studies reviewed were characterised by inadequate description of participant characteristics, variability in use of outcomes measures between and within studies, and limited reporting of results.

4.4 | Clinical and research implications

Findings from the current review have a number of clinical implications for children with liver transplants. Firstly, this group demonstrates vulnerabilities in intellectual and academic development relative to the general population. Children with metabolic disorders appear to confer the poorest outcomes, while children with chronic liver disease also perform below population norms but not as severely as those with metabolic disorders. Children with ALF, however, appear to function at a level commensurate with population norms following transplant and outperform children with metabolic disorders. These results demonstrate that the different diagnostic groups do not necessarily encounter equivalent illness experiences. Specific research in the underlying mechanisms affecting cognitive outcomes in each disorder is warranted. This conclusion could not have been drawn without studies separating their results by primary diagnosis.

The present systematic review demonstrates the need for continued neuropsychological monitoring and assessment of children post-liver transplant in order to identify any individual weaknesses in cognitive and/or academic functions and implement proactive, tailored interventions.[2] This is particularly crucial as difficulties can be subtle at an individual level, but are characteristic of this population. Furthermore, long-term monitoring

is needed to identify any difficulties that may emerge as academic demands increase, such as upon entering high school.

Future researchers should take heed of the following recommendations in order to maximise the impact of their projects and facilitate synthesis between sites. Study design should aim to be prospective, and utilise valid and reliable outcome measures. Studies should report sample characteristics and outcomes, both overall and by diagnostic category, to allow for subgroup analyses, even if such data must be included in supplementary material rather than the body of papers. Finally, different clinical research teams should consider the sharing of data in order to overcome the barriers of small sample sizes and the limited resources of individual sites, for example, by using collaborative online databases.

4.5 | Strengths and limitations

A major limitation of the current systematic review and meta-analysis was the inability to make definitive conclusions about outcomes for the ALF and metabolic groups due to the small sample size of available studies, particularly for the intellectual subdomains and academic outcomes. If partitioned data was available for the studies with mixed samples and mixed outcome measures, particularly the largest study to date,[10, 14] then the results of the quantitative analysis would have been more robust across the different diagnostic groups.

A further limitation was that the current systematic review and meta-analysis did not include a comparison between different solid organ transplant groups and other chronic illness groups.[2] This would have enriched the findings and helped identify which deficits were specific to the end-stage liver disease and liver transplant group rather than to the general transplant and/or chronic illness experience.[2] Unfortunately, this analysis was outside the scope of this piece, given the high number of outcome variables assessed.

The current systematic review and meta-analysis is the first to comprehensively quantify intellectual and academic outcomes of pediatric liver transplantation, as well as separating these results by disease group. This study also captured both overall intellectual outcomes, but also performed analyses of subdomains, as well as considering standardized academic outcomes. Furthermore, it was the first to systematically assess the quality of included studies using an established measure, and also explore the impact of publication date in order to estimate possible effects of improving medical care over time.

5 | CONCLUSION

The current systematic review and meta-analysis showed that pediatric liver transplant recipients experience long-term deficits in specific aspects of their intellectual and academic functioning, particularly in mathematics. The degree of these deficits, however, seems to differ according to diagnostic group, with higher risk in children with metabolic disorders. With more research that differentiates between primary diagnostic groups, the illness and transplant experiences of pediatric liver transplant recipients may become clearer. Furthermore, the field would benefit from consideration of different transplant and chronic disease populations to better distinguish between liver disease-specific effects and the impact of long-term illness in pediatric populations more broadly. Researchers would also benefit from acknowledging the differences between diagnostic subgroups. It is hoped that these recommendations promote improved research practices which may, in time, increase confidence in the results garnered. Within clinical settings, pediatric liver transplant recipients should be considered an at-risk group who require regular assessment and would likely benefit from proactive intervention.

REFERENCES

1. Kelly DA, Bucuvalas JC, Alonso EM, Karpen SJ, Allen U, Green M, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American association for the study of liver diseases and the American society of transplantation. Liver Transplantation. 2013;19(8):798-825.

2. Sorensen LG. Pediatric solid organ transplantation and end stage disease: A slow journey towards understanding neurocognitive outcomes and their ramifications for clinical care. Pediatric Transplantation. 2015;19(2):136-8.

3. Adebäck P, Nemeth A, Fischler B. Cognitive and emotional outcome after pediatric liver transplantation. Pediatric Transplantation. 2003;7(5):385-9.

4. Gilmour S, Adkins R, Liddell GA, Jhangri G, Robertson CM. Assessment of psychoeducational outcomes after pediatric liver transplant. American Journal of Transplantation. 2009;9(2):294-300.

5. Sorensen LG, Neighbors K, Zhang S, Limbers CA, Varni JW, Ng VL, et al. Neuropsychological functioning and health-related quality of life: Pediatric acute liver failure study group results. Journal of Pediatric Gastroenterology and Nutrition. 2015;60(1):75-83.

6. Haavisto A, Korkman M, Törmänen J, Holmberg C, Jalanko H, Qvist E. Visuospatial impairment in children and adolescents after liver transplantation. Pediatric Transplantation. 2011;15(2):184-92.

7. Afshar S, Porter M, Barton B, Stormon M. Intellectual and academic outcomes after pediatric liver transplantation: Relationship with transplant-related factors. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2018;18(9):2229-37.

8. Ee LC, Lloyd O, Beale K, Fawcett J, Cleghorn GJ. Academic potential and cognitive functioning of long-term survivors after childhood liver transplantation. Pediatric Transplantation. 2014;18(3):272-9.

9. Krull KR, Fuchs C, Yurk H, Boone P, Alonso E. Neurocognitive outcome in pediatric liver transplant recipients. Pediatric Transplantation. 2003;7(2):111-8.

10. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Longitudinal study of cognitive and academic outcomes after pediatric liver transplantation. Journal of Pediatrics. 2014;165(1):65-72.e2.

11. Moser JJ, Veale PM, McAllister DL, Archer DP. A systematic review and quantitative analysis of neurocognitive outcomes in children with four chronic illnesses. Paediatric Anaesthesia. 2013;23(11):1084-96.

12. Stewart SM, Uauy R, Kennard BD, Waller DA, Benser M, Andrews WS. Mental development and growth in children with chronic liver disease of early and late onset. Pediatrics. 1988;82(2):167-72.

13. Schulz KH, Wein C, Boeck A, Rogiers X, Burdelski M. Cognitive performance of children who have undergone liver transplantation. Transplantation. 2003;75(8):1236-40.

14. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Cognitive and academic outcomes after pediatric liver transplantation: Functional outcomes group (FOG) results. American Journal of Transplantation. 2011;11(2):303-11.

15. Stewart SM, Hiltebeitel C, Nici J, Waller DA, Uauy R, Andrews WS. Neuropsychological outcome of pediatric liver transplantation. Pediatrics. 1991;87(3):367-76.

16. Kennard BD, Stewart SM, Phelan-McAuliffe D, Waller DA, Bannister M, Fioravani V, et al. Academic outcome in long-term survivors of pediatric liver transplantation. Journal of Developmental and Behavioral Pediatrics. 1999;20(1):17-23.

17. Gritti A, Di Sarno AM, Comito M, De Vincenzo A, De Paola P, Vajro P. Psychological impact of liver transplantation on children's inner worlds. Pediatric Transplantation. 2001;5(1):37-43.

18. Yssaad-Fesselier R, Lion-François L, Herbillon V, Rivet C, Brunet AS, Yantren H, et al. Intellectual and visuo-spatial assessment in long-term pediatric liver transplantation for biliary atresia. Transplantation. 2009;87(9):1427-8.

19. Stevenson T, Millan MT, Wayman K, Berquist WE, Sarwal M, Johnston EE, et al. Long-term outcome following pediatric liver transplantation for metabolic disorders. Pediatric Transplantation. 2010;14(2):268-75.

20. Shellmer DA, Devito Dabbs A, Dew MA, Noll RB, Feldman H, Strauss KA, et al. Cognitive and adaptive functioning after liver transplantation for maple syrup urine disease: A case series. Pediatric Transplantation. 2011;15(1):58-64.

21. Armstrong FD. Neurodevelopment and chronic illness: Mechanisms of disease and treatment. Mental Retardation and Developmental Disabilities Research Reviews. 2006;12(3):168-73.

22. Kaller T, Langguth N, Petermann F, Ganschow R, Nashan B, Schulz KH. Cognitive performance in pediatric liver transplant recipients. American Journal of Transplantation. 2013;13(11):2956-65.

23. Afshar S, Porter M, Barton B, Stormon M. Intellectual and academic outcomes after pediatric liver transplantation: Relationship with transplant-related factors. American Journal of Transplantation. 2018;18(9):2229-37.

24. Rodijk LH, Den Heijer AE, Hulscher JBF, Verkade HJ, De Kleine RHJ, Bruggink JLM. Neurodevelopmental outcomes in children with liver diseases: A systematic review. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(2):157-68.

25. Robertson CMT, Dinu IA, Joffe AR, Alton GY, Yap JYK, Asthana S, et al. Neurocognitive outcomes at kindergarten entry after liver transplantation at <3 yr of age. Pediatric Transplantation. 2013;17(7):621-30.

26. Talcott JB, Beath SV, Patel T, Griffiths G, Kelly DA. Long-term Effects of Cholestatic Liver Disease in Childhood on Neuropsychological Outcomes and Neurochemistry. J Pediatr Gastroenterol Nutr. 2019;69(2):145-51.

27. Kaller T, Boeck A, Sander K, Richterich A, Burdelski M, Ganschow R, et al. Cognitive abilities, behaviour and quality of life in children after liver transplantation. Pediatric Transplantation. 2010;14(4):496-503.

28. Kaller T, Langguth N, Ganschow R, Nashan B, Schulz KH. Attention and executive functioning deficits in liver-transplanted children. Transplantation. 2010;90(12):1567-73.

29. Kaller T, Schulz KH, Sander K, Boeck A, Rogiers X, Burdelski M. Cognitive abilities in children after liver transplantation. Transplantation. 2005;79(9):1252-6.

30. Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D, Antes G, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Medicine. 2009;6(7).

31. General Assembly of the World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. The Journal of the American College of Dentists. 2014;81(3):14-8.

32. Ferro MA, Speechley KN. Depressive symptoms among mothers of children with epilepsy: A review of prevalence, associated factors, and impact on children. Epilepsia. 2009;50(11):2344-54.

33. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.

34. Song B, Schulze M, Goldschmidt I, Haux R, Baumann U, Marschollek M. Home monitoring and decision support for international liver transplant children. 2013. p. 268-72.

35. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-Analysis Version 3. Englewood, NJ: Biostat; 2013.

36. Mazariegos GV, Morton DH, Sindhi R, Soltys K, Nayyar N, Bond G, et al. Liver transplantation for classical maple syrup urine disease: Long-term follow-up in 37 patients and comparative united network for organ sharing experience. Journal of Pediatrics. 2012;160(1):116-21.e1.

37. Stewart SM, Silver CH, Nici J, Waller D, Campbell R, Uauy R, et al. Neuropsychological function in young children who have undergone liver transplantation. Journal of Pediatric Psychology. 1991;16(5):569-83.

38. Stewart SM, Uauy R, Waller DA, Kennard BD, Benser M, Andrews WS. Mental and motor development, social competence, and growth one year after successful pediatric liver transplantation. The Journal of Pediatrics. 1989;114(4 PART 1):574-81.

39. Sorensen LG, Neighbors K, Hardison RM, Loomes KM, Varni JW, Ng VL, et al. Health Related Quality of Life and Neurocognitive Outcomes in the First Year after Pediatric Acute Liver Failure. Journal of Pediatrics. 2018;196:129-38.e3.

40. Gold A, Rogers A, Cruchley E, Rankin S, Parmar A, Kamath BM, et al. Assessment of School Readiness in Chronic Cholestatic Liver Disease: A Pilot Study Examining Children with and without Liver Transplantation. Canadian Journal of Gastroenterology and Hepatology. 2017;2017.

41. Lee JM, Jung YK, Bae JH, Yoon SA, Kim JH, Choi YR, et al. Delayed transplantation may affect intellectual ability in children. Pediatrics International. 2017;59(10):1080-6.

42. Posfay-Barbe KM, Barbe RP, Wetterwald R, Belli DC, McLin VA. Parental functioning improves the developmental quotient of pediatric liver transplant recipients. Pediatric Transplantation. 2013;17(4):355-61.

43. Zitelli BJ, Miller JW, Carlton Gartner Jr J, Malatack JJ, Urbach AH, Belle SH, et al. Changes in life-style after liver transplantation. Pediatrics. 1988;82(2):173-80.

44. Chu TH, Chien YH, Lin HY, Liao HC, Ho HJ, Lai CJ, et al. Methylmalonic acidemia/propionic acidemia - The biochemical presentation and comparing the outcome between liver transplantation versus non-liver transplantation groups. Orphanet Journal of Rare Diseases. 2019;14(1).

45. Hattori H, Higuchi Y, Tsuji M, Inomata Y, Uemoto S, Asonuma K, et al. Living-related liver transplantation and neurological outcome in children with fulminant hepatic failure. Transplantation. 1998;65(5):686-92.

46. Crowe L, Anderson V, Hardikar W, Boneh A. Cognitive and behavioural outcomes of paediatric liver transplantation for ornithine transcarbamylase deficiency. JIMD reports2019. p. 19-25.

47. Wayman KI, Cox KL, Esquivel CO. Neurodevelopmental outcome of young children with extrahepatic biliary atresia 1 year after liver transplantation. Journal of Pediatrics. 1997;131(6):894-8.

48. Van Mourik IDM, Beath SV, Brook GA, Cash AJ, Mayer AD, Buckels JAC, et al. Long-term nutritional and neurodevelopmental outcome of liver transplantation in infants aged less than 12 months. Journal of Pediatric Gastroenterology and Nutrition. 2000;30(3):269-75.

49. Morioka D, Kasahara M, Horikawa R, Yokoyama S, Fukuda A, Nakagawa A. Efficacy of living donor liver transplantation for patients with methylmalonic acidemia. American Journal of Transplantation. 2007;7(12):2782-7.

50. Battula NR, Platto M, Anbarasan R, Perera MTPR, Ong E, Roll GR, et al. Intention to Split Policy: A Successful Strategy in a Combined Pediatric and Adult Liver Transplant Center. Annals of Surgery. 2017;265(5):1009-15.

51. Anselmo DM, Baquerizo A, Geevarghese S, Ghobrial RM, Farmer DG, Busuttil RW. Liver transplantation at Dumont-UCLA Transplant Center: an experience with over 3,000 cases. Clinical transplants. 2001:179-86.

52. Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al. Outcomes of 5-year survivors of pediatric liver transplantation: Report on 461 children from a north american multicenter registry. Pediatrics. 2008;122(6):e1128-e35.

53. Bucuvalas JC, Alonso E, Magee JC, Talwalkar J, Hanto D, Doo E. Improving long-term outcomes after liver transplantation in children. American Journal of Transplantation. 2008;8(12):2506-13.

54. Harshman LA, Johnson RJ, Matheson MB, Kogon AJ, Shinnar S, Gerson AC, et al. Academic achievement in children with chronic kidney disease: a report from the CKiD cohort. Pediatric Nephrology. 2019;34(4):689-96.

55. Martinez YJ, Ercikan K. Chronic illnesses in Canadian children: What is the effect of illness on academic achievement, and anxiety and emotional disorders? Child: Care, Health and Development. 2009;35(3):391-401.

SUPPLEMENTARY TABLES

SUPPLEMENTARY TABLE 1 PRISMA 2009 Checklist[30]

Section/topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

SUPPLEMENTARY TABLE 1 Continued

Section/topic	#	Checklist item	Page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11-12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12-18
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15-20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-52
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	20-52
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	20-52
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	20-52
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	52-56
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	57-58
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	56-58
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

SUPPLEMENTARY TABLE 2 Criteria items for the revised Modified Quality Index[30]

Reporting	1. Is the hypothesis/objective of the study clearly described?
	2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
	3. Are the characteristics of the patients included in the study clearly described?
	4. Are the main findings of the study clearly described?
	5. Does the study provide estimates of the random variability in the data for the main outcomes?
	6. Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?
	7. Is the response rate clearly described?
Internal Validity	8. Were the main outcome measures used valid and reliable?
External Validity	9. Were the patients asked to participate in the study representative of the entire population from which they were recruited?
	10. Were patients, who were prepared to participate, representative of the entire population from which they were recruited?
	11. Were the staff, places, and facilities where the patients were studied, representative of the treatment the majority of patients receive?

SUPPLEMENTARY TABLE 3 Individual scores for each criteria of the revised Modified Quality Index[30]

			Meta-Analysis																Missing Info				DQ+IQ			DQ Only			
			Stewart 1991	Kennard 1999	Gritti 2001	Krull 2003	Gilmour 2009	Yssaad-Fesselier 2009	Stevenson 2010	Haavisto 2011	Shellmer 2011	Kaller 2013	Robertson 2013	Ee 2014	Sorenson 2014	Afshar 2018	Crowe 2019	Adeback 2003	Gold 2017	Lee 2017	Talcott 2019	Zitelli 1988	Hattori 1998	Posfay-Barbe 2013	Chu 2019	Wayman 1997	Morioka 2007	van Mourik 2000	
Reporting	*Question 1*	Hypothesis or Objectives Described	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%
	Question 2	Main Outcomes Described in Introduction or Method	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	92%
	Question 3	Patient Characteristics Described?	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	0	1	0	73%
	Question 4	Main Findings Described	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	85%
	Question 5	Estimates of the Random Variability	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	1	1	1	1	85%
	Question 6	Probability Values Reported	1	0	1	0	1	0	0	1	0	1	1	1	0	1	0	0	1	1	0	0	0	0	1	0	0	0	42%
	Question 7	Response Rate Described	0	1	0	1	1	0	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	69%
		Subtotal	**6**	**6**	**6**	**6**	**7**	**4**	**3**	**7**	**5**	**7**	**7**	**7**	**6**	**7**	**6**	**5**	**5**	**4**	**4**	**5**	**6**	**4**	**6**	**5**	**4**	**4**	**78%**
Internal Validity	*Question 8*	Outcome Measures Valid and Reliable	1	**1**	**1**	**1**	**1**	1	**1**	1	1	1	1	1	1	1	1	**1**	1	1	**1**	0	0	0	0	0	0	1	77%
External Validity	*Question 9*	Patients Asked to Participate Representative of Population	0	1	0	1	1	0	0	1	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	73%
	Question 10	Patients Prepared to Participate Representative of Population	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	0	81%
	Question 11	Staff, Places, and Facilities Representative of Treatment Majority	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100%
		Subtotal	**2**	**3**	**2**	**3**	**3**	**2**	**1**	**3**	**1**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**1**	**1**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**2**	**85%**
		TOTAL	**9**	**10**	**9**	**10**	**11**	**7**	**5**	**11**	**7**	**11**	**11**	**11**	**10**	**11**	**10**	**9**	**7**	**6**	**8**	**8**	**9**	**7**	**9**	**8**	**7**	**7**	**80%**

SUPPLEMENTARY TABLE 4 P-values of comparisons between groups for FSIQ meta-regression

Diagnostic Group	Chronic		Metabolic		Mixed	
	Z value	*P* value	*Z* value	*P* value	*Z* value	*P* value
ALF vs.	-0.89	.373	-3.09	.002**	-0.86	.3907
Chronic vs.			-3.91	< .001**	-0.03	.9723
Metabolic vs.					3.46	< .001**

Note: ALF = acute liver failure; FSIQ = full scale intelligence quotient

* = *P* < .05; ** = *P* < .01

SUPPLEMENTARY TABLE 5 P-values of comparisons between groups for VCI/VIQ meta-regression

Diagnostic Group	Chronic		Metabolic		Mixed	
	Z value	*P* value	*Z* value	*P* value	*Z* value	*P* value
ALF vs.	-1.35	.178	-3.71	< .001**	-0.87	.383
Chronic vs.			-3.95	< .001**	0.42	.673
Metabolic vs.					3.41	< .001**

Note: ALF = acute liver failure; VCI = verbal comprehension index; VIQ = verbal intelligence quotient

* = *P* < .05; ** = *P* < .01

SUPPLEMENTARY TABLE 6 P-values of comparisons between groups for PRI/PIQ meta-regression

Diagnostic Group	Chronic		Metabolic		Mixed	
	Z value	*P* value	*Z* value	*P* value	*Z* value	*P* value
ALF vs.	-0.28	.779	-2.12	.034*	-0.28	.779
Chronic vs.			-2.42	.016*	-0.06	.952
Metabolic vs.					2.16	.031*

Note: ALF = acute liver failure; PRI = perceptual reasoning index; PIQ = performance intelligence quotient

* = *P* < .05; ** = *P* < .01

SUPPLEMENTARY TABLE 7 P-values of comparisons between groups for PSI meta-regression

Diagnostic Group	Chronic		Metabolic		Mixed	
	Z value	*P* value	*Z* value	*P* value	*Z* value	*P* value
ALF vs.	-0.17	.866	-2.92	.004**	-0.50	.620
Chronic vs.			-5.33	< .001**	-0.92	.358
Metabolic vs.					4.58	< .001**

Note: ALF = acute liver failure; PSI = processing speed index

* = *P* < .05; ** = *P* < .01

SUPPLEMENTARY TABLE 8 P-values of comparisons between groups for WMI meta-regression

Diagnostic Group	Chronic		Metabolic		Mixed	
	Z value	*P* value	*Z* value	*P* value	*Z* value	*P* value
ALF vs.	-0.35	.725	-2.37	.018*	-0.88	.379
Chronic vs.			-2.87	.004**	-0.68	.497
Metabolic vs.					1.89	.059

Note: ALF = acute liver failure; WMI = working memory index

* = *P* < .05; ** = *P* < .01

SUPLEMENTARY TABLE 9 Results of meta-analysis for Writing - random effects model

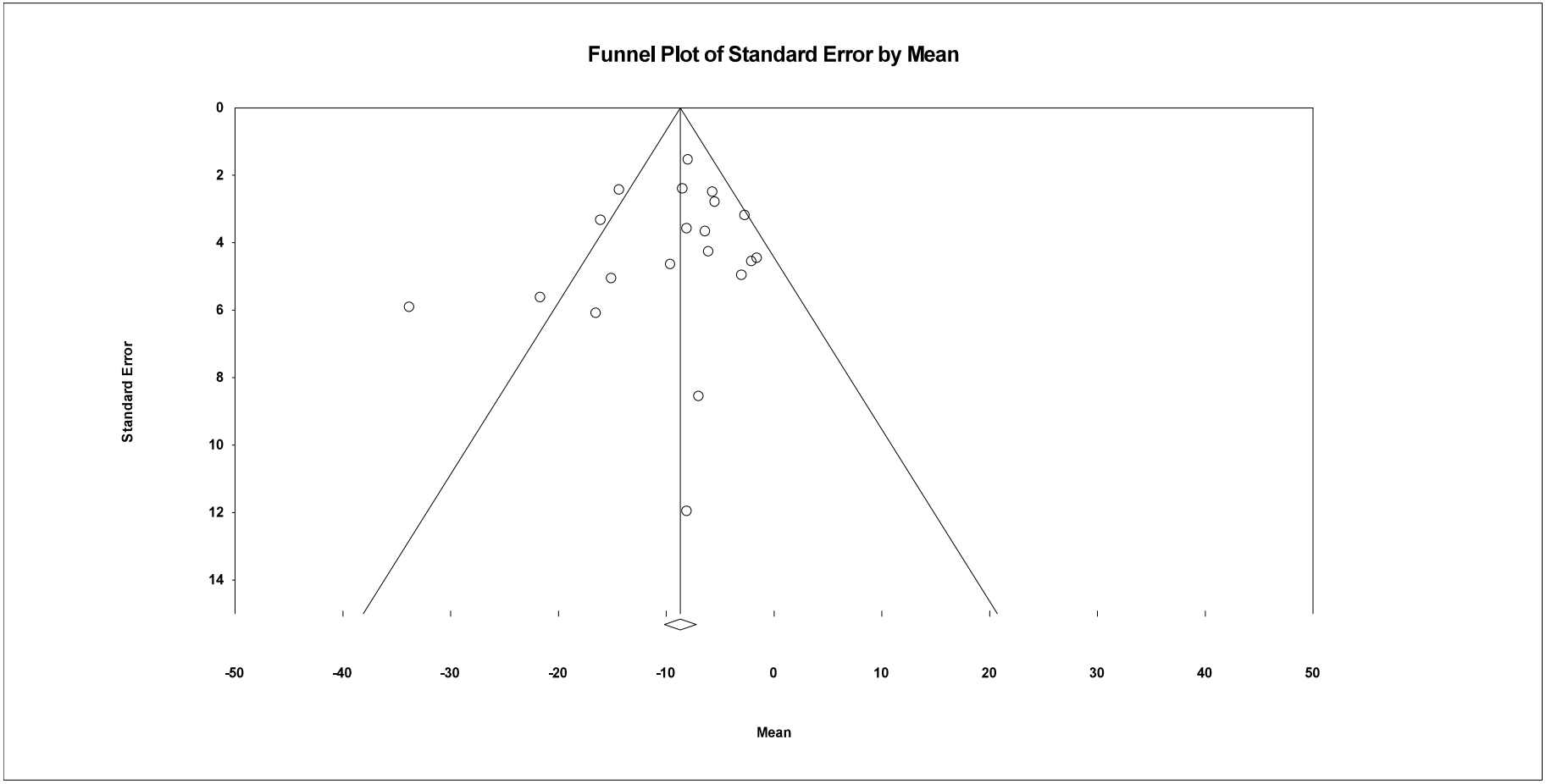
Diagnostic Category	Study	Diagnostic Subgroup	Mean	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value	Relative weight	St. Residual
Chronic	Kennard 1999	Chronic	82.24	3.929	15.435	74.54	89.94	-4.521	< .001	50.831	-1
Chronic	Krull 2003	Chronic	104.90	4.895	23.965	95.31	114.49	1.001	.317	49.169	1
Chronic			**93.38**	**11.328**	**128.333**	**71.18**	**115.59**	**-0.584**	**.559**		

SUPPLEMENTARY TABLE 10 Results of meta-analysis comparing verbal and nonverbal intellect (VCI/VIQ vs. PRI/PIQ)

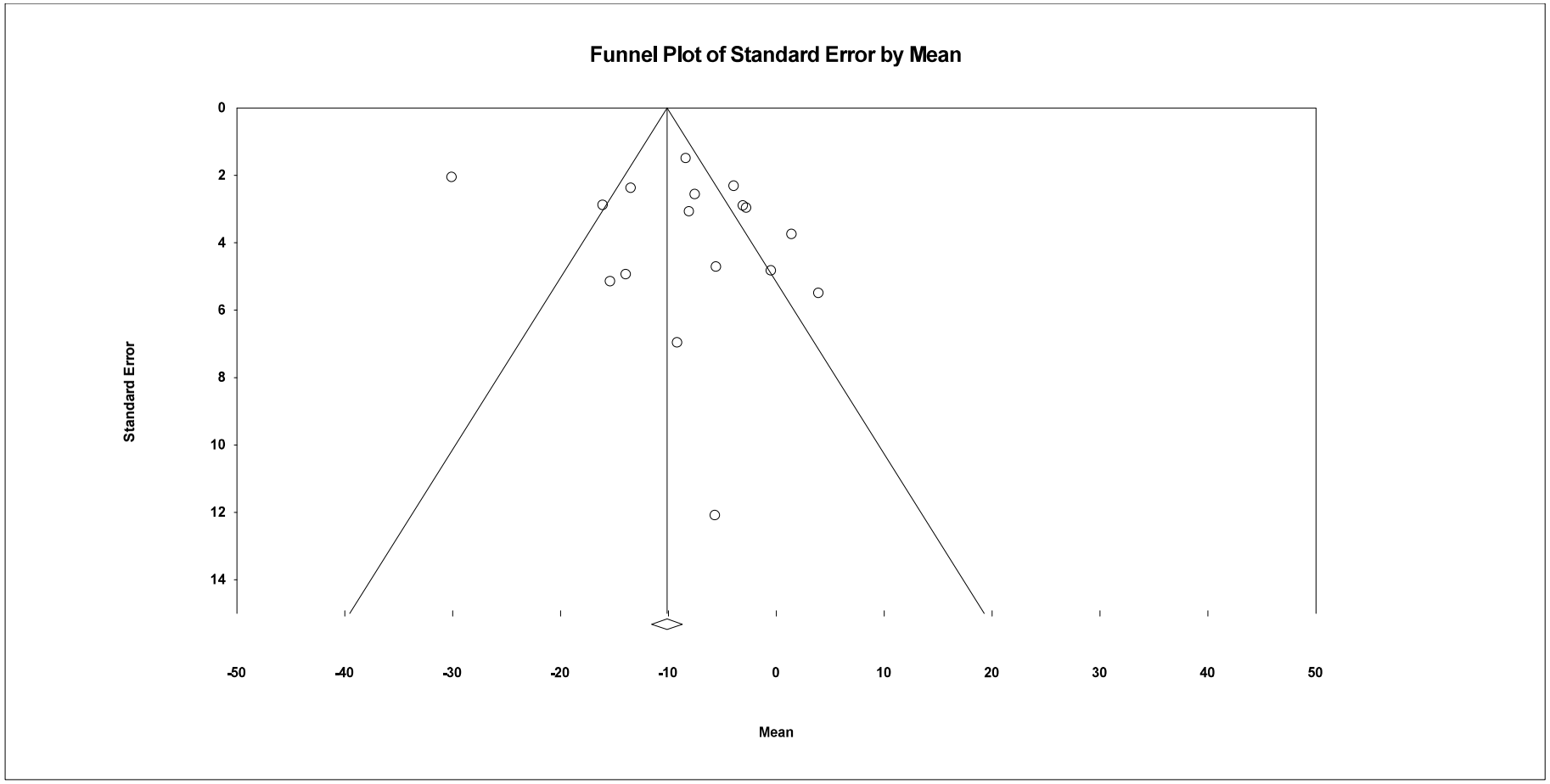
Diagnostic Category	Study	Diagnostic Subgroups	Mean Difference	St. Error	Variance	Lower limit	Upper limit	*Z* value	*P* value
ALF	Kaller 2013	ALF	-4.92	5.336	28.471	-15.38	5.54	-0.922	.356
ALF	Robertson 2013	ALF	-6.10	18.014	324.490	-41.41	29.21	-0.339	.735
ALF			**-5.02**	**5.116**	**26.174**	**-15.04**	**5.01**	**-0.980**	**.327**
Chronic	Stewart 1991	Chronic	-2.90	4.758	22.635	-12.22	6.42	-0.610	.542
Chronic	Kennard 1999	Chronic	0.50	3.495	12.218	-6.35	7.35	0.143	.886
Chronic	Krull 2003	Chronic	9.87	6.733	45.327	-3.33	23.07	1.466	.143
Chronic	Gilmour 2009	Chronic	2.00	5.148	26.500	-8.09	12.09	0.389	.698
Chronic	Yssaad-Fesserlier 2009	Chronic (BA)	-3.30	7.134	50.900	-17.28	10.68	-0.463	.644
Chronic	Kaller 2013	Chronic (BA)	0.26	3.311	10.960	-6.23	6.75	0.079	.937
Chronic	Kaller 2013	Chronic (not BA)	8.00	6.821	46.525	-5.37	21.37	1.173	.241
Chronic	Robertson 2013	Chronic (BA)	-1.50	3.984	15.872	-9.31	6.31	-0.377	.707
Chronic	Robertson 2013	Chronic (not BA)	4.10	11.634	135.344	-18.70	26.90	0.352	.725
Chronic	Ee 2014	Chronic	3.46	5.396	29.118	-7.12	14.04	0.641	.521
Chronic	Afshar 2018	Chronic (BA)	3.11	4.939	24.397	-6.57	12.79	0.630	.529
Chronic	Afshar 2018	Chronic (not BA)	-1.16	6.545	42.833	-13.99	11.67	-0.177	.859
Chronic			**1.01**	**1.433**	**2.052**	**-1.80**	**3.82**	**0.705**	**.481**
Metabolic	Kaller 2013	Metabolic	-2.80	8.093	65.495	-18.66	13.06	-0.346	.729
Metabolic	Crowe 2018	Metabolic	5.25	9.725	94.576	-13.81	24.31	0.540	.589
Metabolic			**0.49**	**6.221**	**38.697**	**-11.70**	**12.69**	**0.079**	**.937**
Mixed	Haavisto 2011	Mixed	-10.70	7.018	49.256	-24.46	3.06	-1.525	.127
Mixed	Sorenson 2014	Mixed	4.20	2.212	4.891	-0.13	8.53	1.899	.058
Mixed			**-1.76**	**7.300**	**53.286**	**-16.07**	**12.55**	**-0.241**	**.809**
Overall			**0.49**	**1.324**	**1.754**	**-2.10**	**3.09**	**0.371**	**.711**

Note: ALF = acute liver failure; BA = biliary atresia

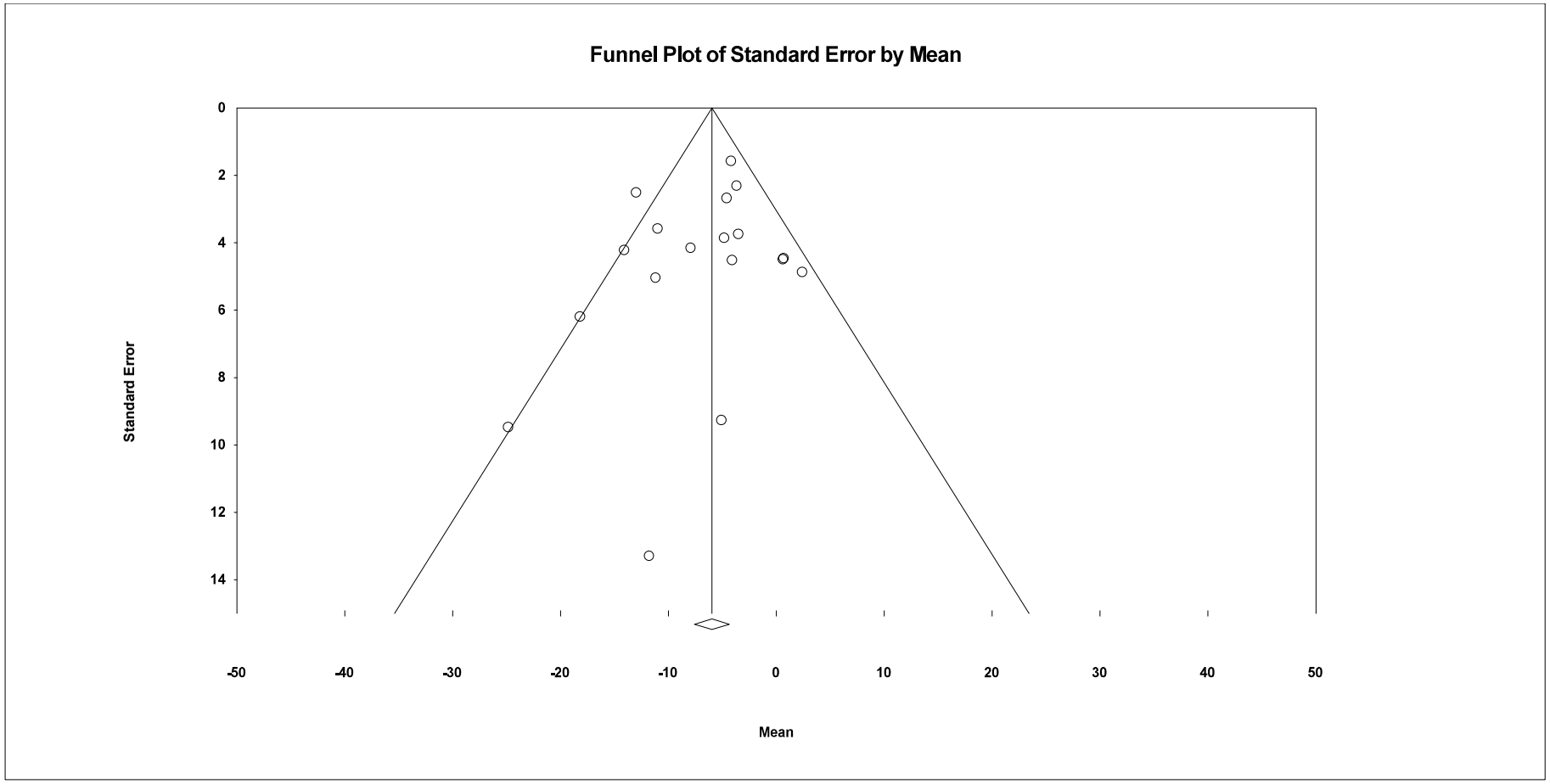
SUPPLEMENTARY FIGURES



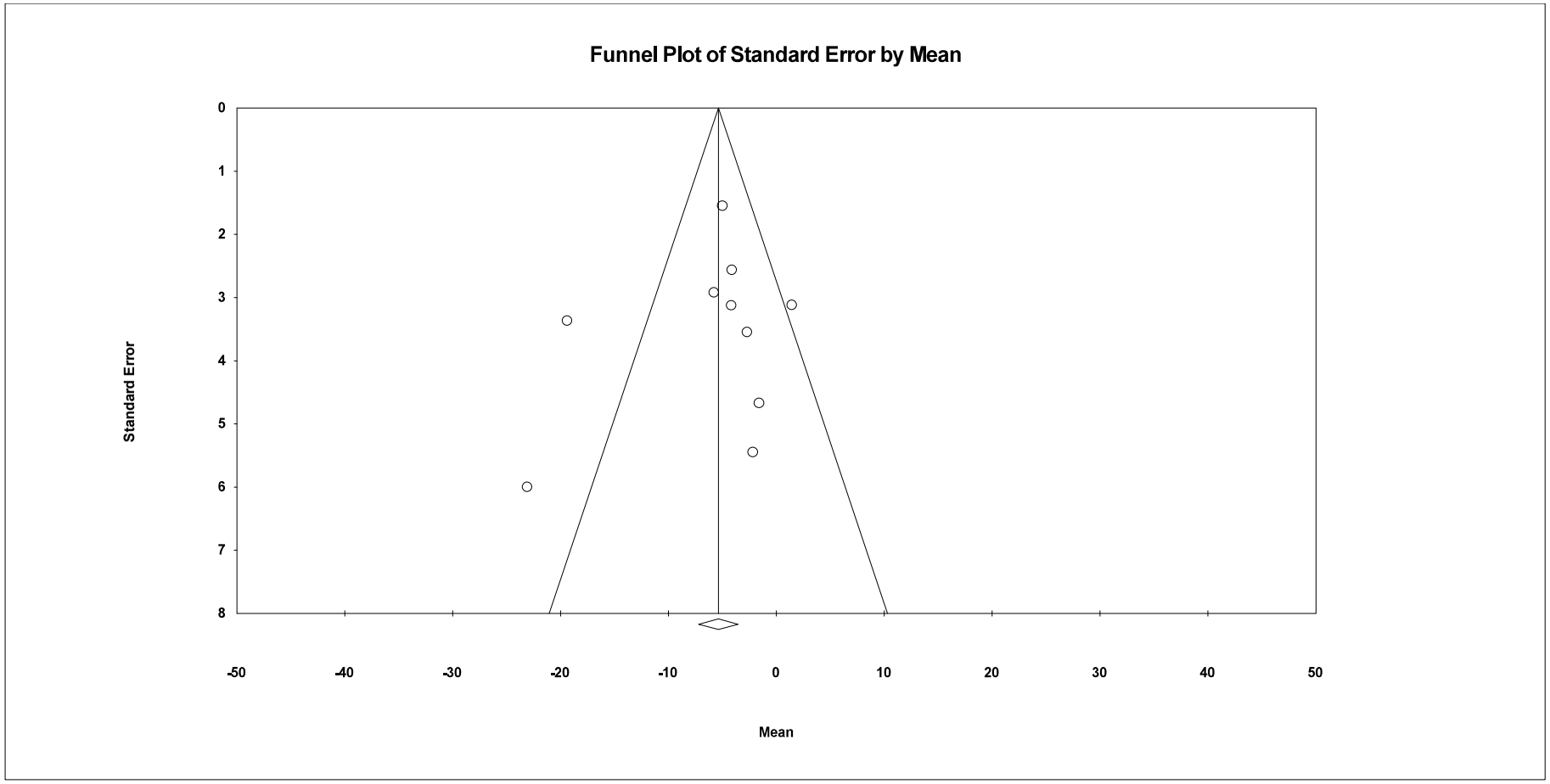
SUPPLEMENTARY FIGURE 1 Funnel plot of studies reporting Full Scale Intellectual Quotient



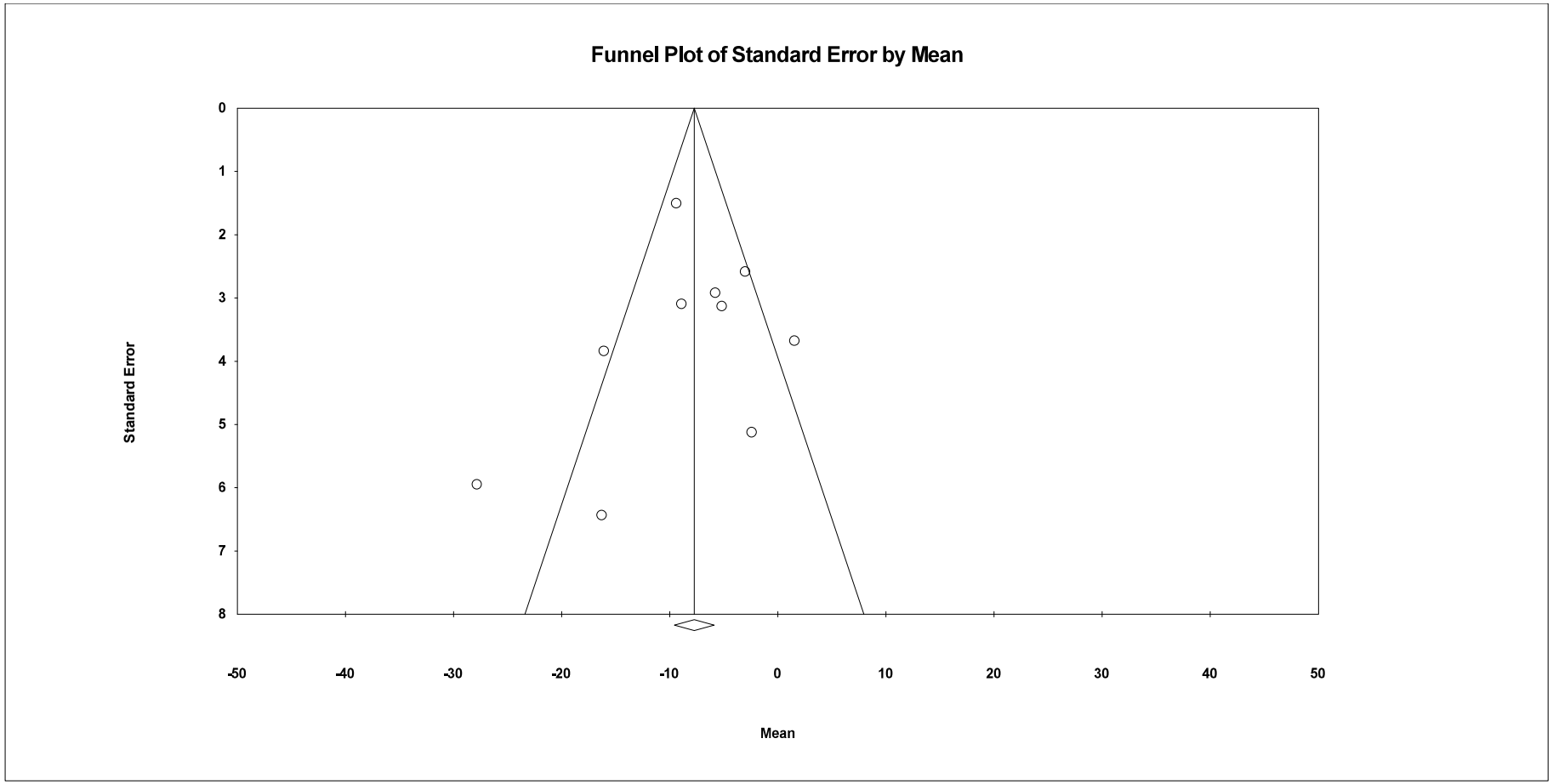
SUPPLEMENTARY FIGURE 2 Funnel plot of studies reporting Verbal Comprehension Index/Verbal Intelligence Quotient



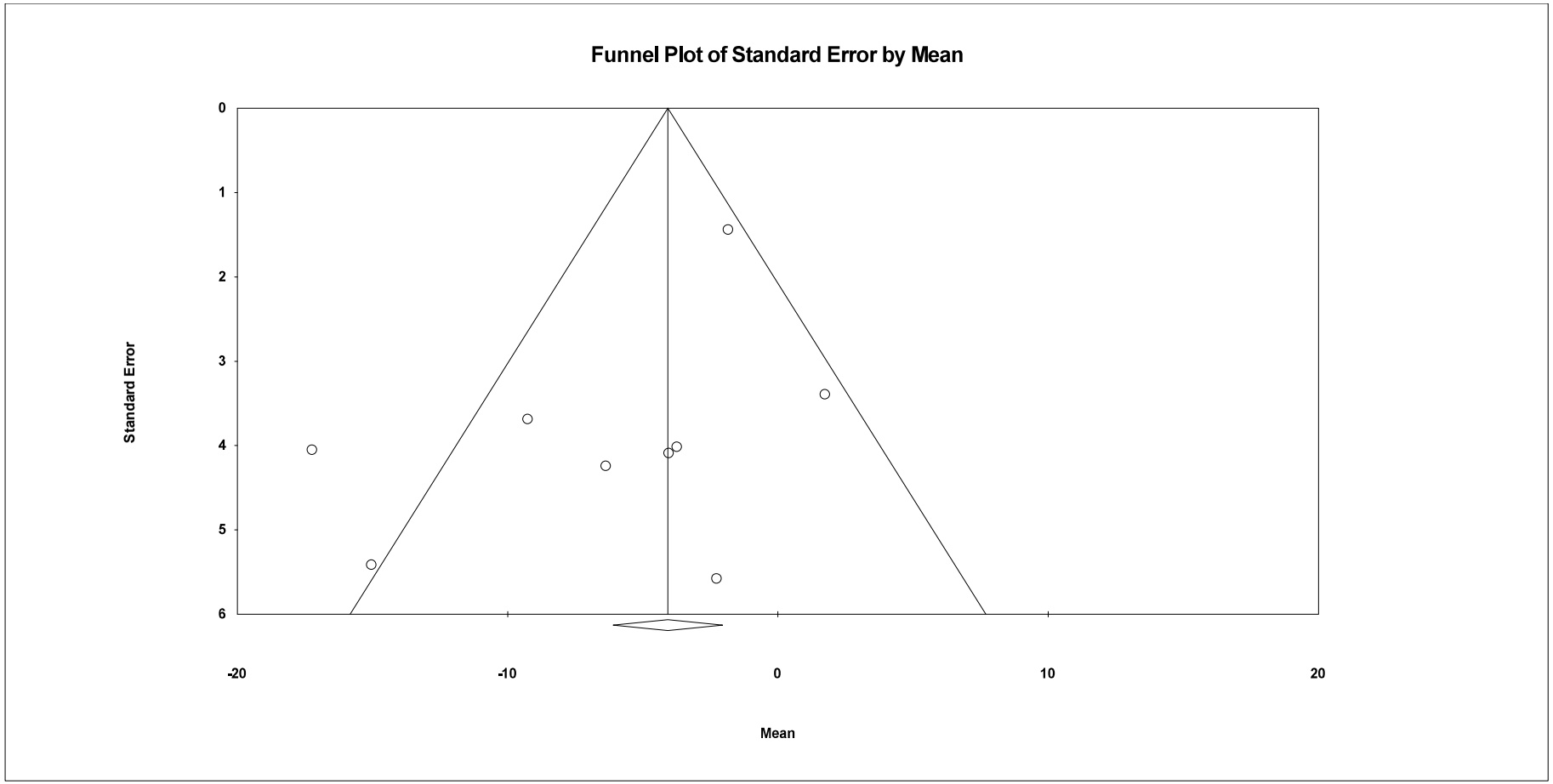
SUPPLEMENTARY FIGURE 3 Funnel plot of studies reporting Perceptual Reasoning Index/Performance Intelligence Quotient



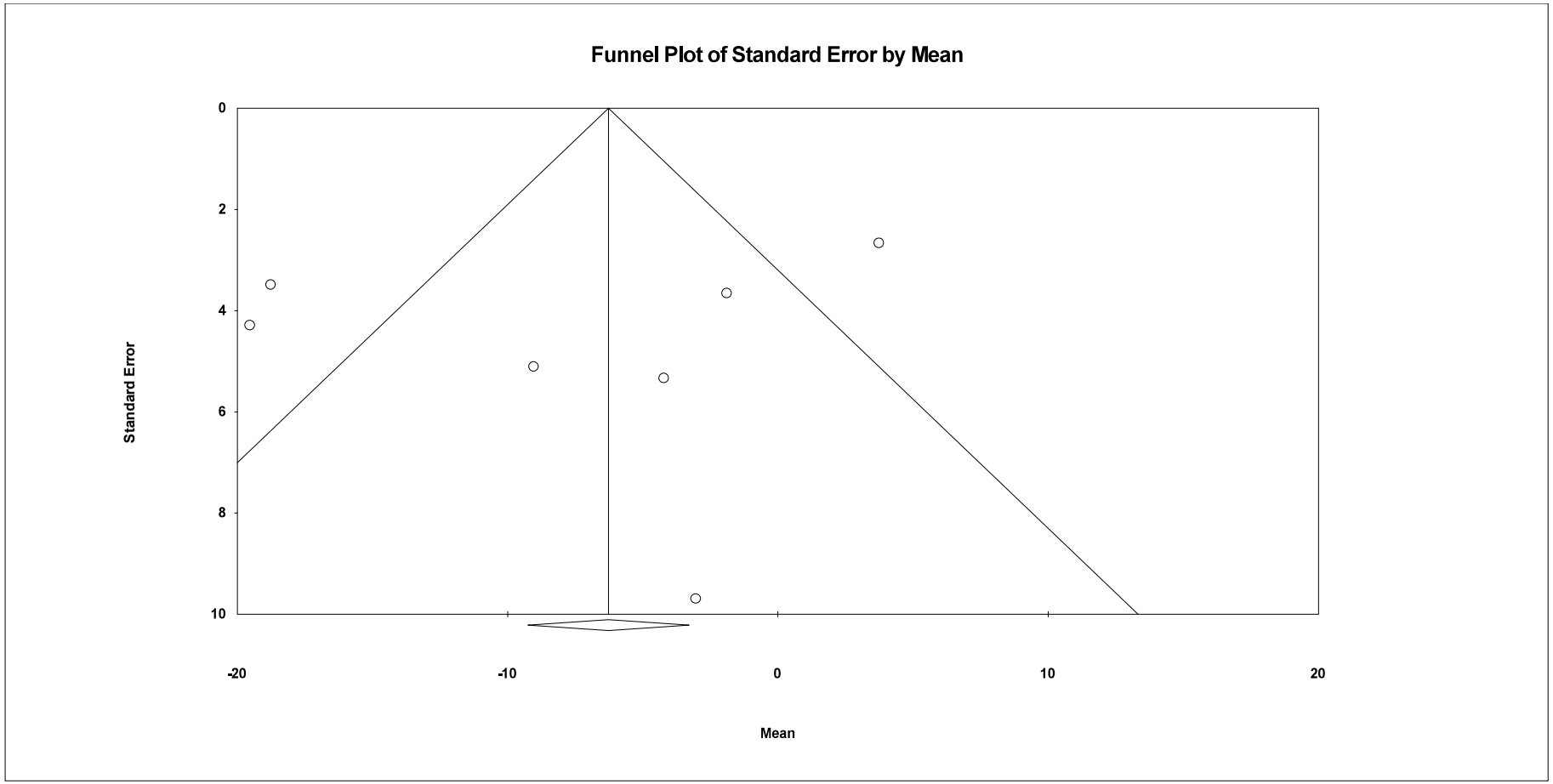
SUPPLEMENTARY FIGURE 4 Funnel plot of studies reporting Processing Speed Index



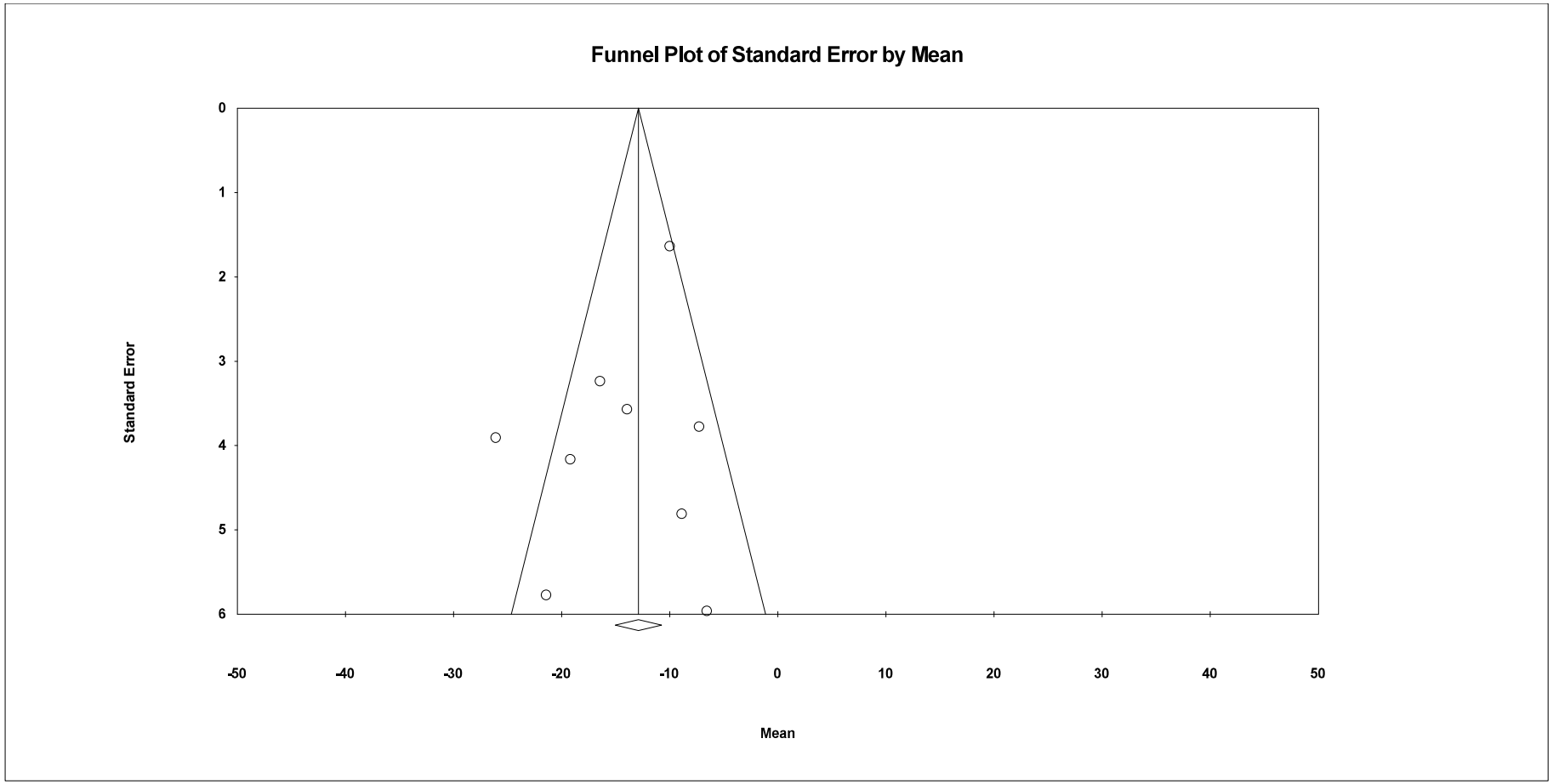
SUPPLEMENTARY FIGURE 5 Funnel plot of studies reporting Working Memery Index



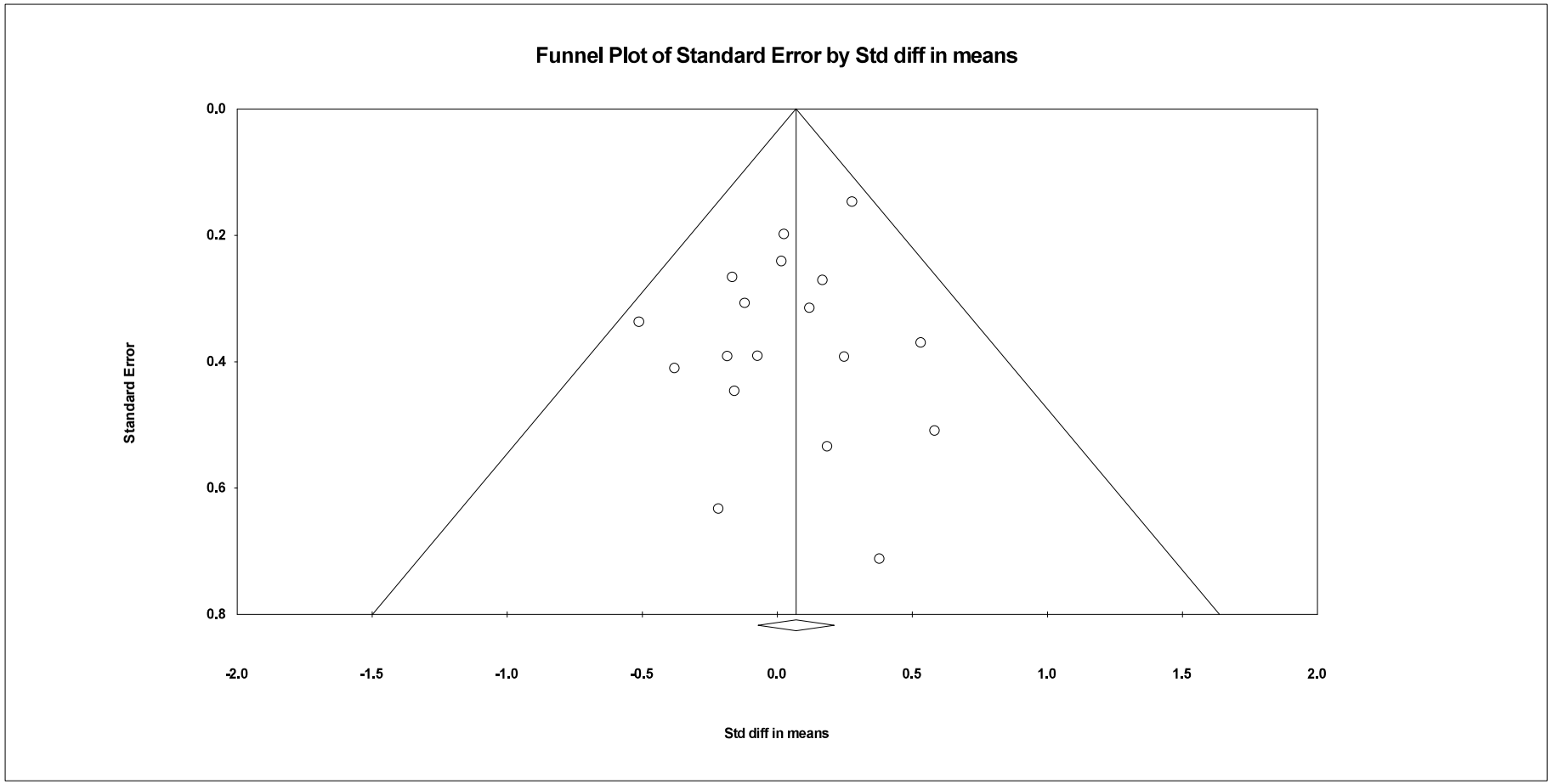
SUPPLEMENTARY FIGURE 6 Funnel plot of studies reporting Reading



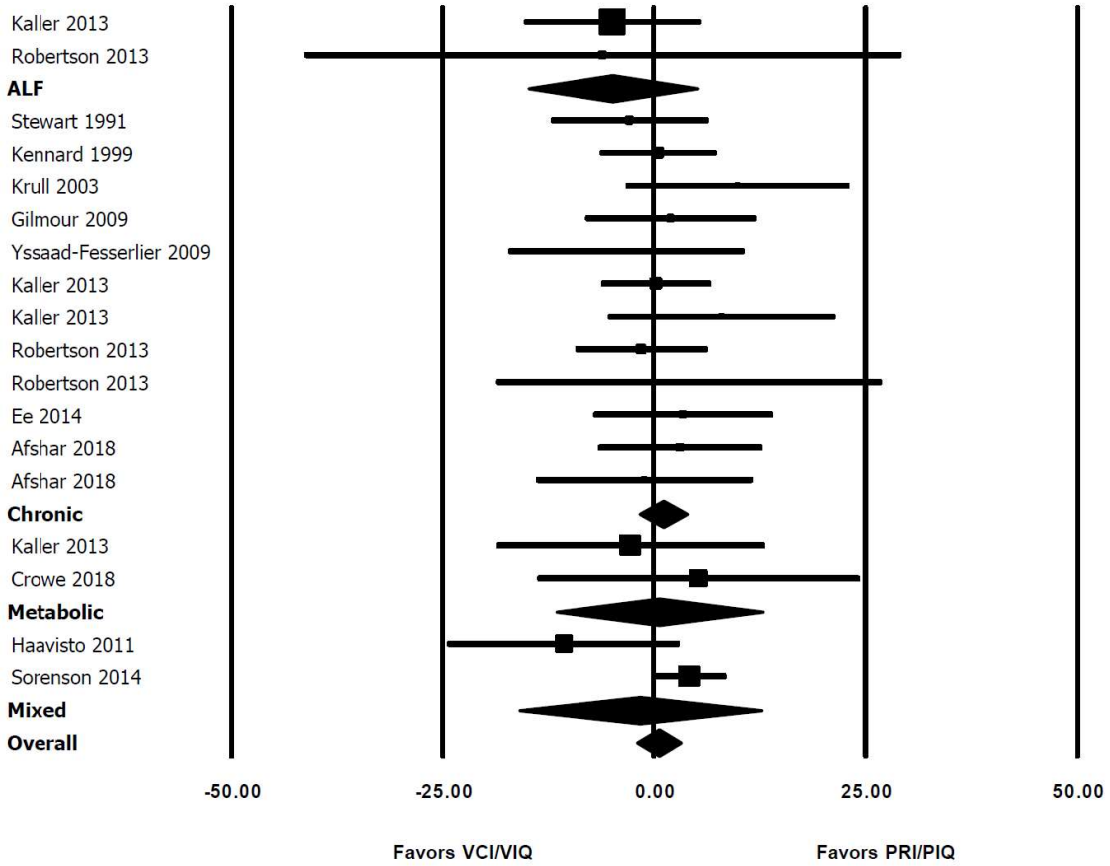
SUPPLEMENTARY FIGURE 7 Funnel plot of studies reporting Spelling



SUPPLEMENTARY FIGURE 8 Funnel plot of studies reporting Mathematics



SUPPLEMENTARY FIGURE 9 Funnel plot of studies included in the comparison of verbal and nonverbal intellectual abilities (VCI/VIQ and PRI/PIQ)



SUPPLEMENTARY FIGURE 10 Results of meta-analysis comparing verbal and nonverbal intellect (VCI/VIQ vs. PRI/PIQ)

Note: ALF = acute liver failure; BA = biliary atresia

CHAPTER 5:

MEDICALLY STABLE PEDIATRIC LIVER TRANSPLANT RECIPIENTS SHOWING BILATERAL T1 HYPERINTENSITIES IN THE BASAL GANGLIA: A CASE SERIES

Afshar S, Porter M, Barton B, Stormon M.

ABSTRACT

Few studies have investigated the long-term neurological outcomes of stable pediatric liver transplant recipients. In the current series, 8 cases of long-term (≥ 12 months) survivors of pediatric liver transplantation for chronic end-stage liver disease underwent brain magnetic resonance imaging (MRI) to assess long-term neuroradiological status in medically stable transplant recipients. Two cases displayed bilateral symmetrical T1 hyperintensities in the globus pallidus and subthalamic nuclei. Exploratory analysis of the group revealed an association between the volume of T1 white matter hypointensity (white matter abnormality) and long-term intellectual functioning. Furthermore, the volume of T1 white matter hypointensity was predicted by body mass index at transplantation. Clinical implications include consideration of neurological screening as part of routine follow-up post-transplant. Future research is required to explore the mediating role played by neurological factors in the relationship between liver disease and long-term neurocognitive outcomes.

1 | INTRODUCTION

Normal liver functioning is important for neurological status and development, and a poorly functioning liver will have numerous deleterious effects upon the brain through a number of mechanisms (see Campaigna et al.).[1-3] One of the liver's most important functions is to regulate ammonia levels in the blood, with excess ammonia being neurotoxic, leading to hepatic encephalopathy, coma and death if left untreated. The liver also processes heavy metals including copper and manganese, and when this process is interrupted, high levels of heavy metals accumulate in the deep brain nuclei of the basal ganglia, particularly the globus pallidus.[4, 5] The liver is further involved in coagulation of the blood. Abnormal coagulation can lead to cerebrovascular events, including small vessel ischemia, that may go undetected in infant patients. Additionally, nutrition relies upon healthy liver function, with malnutrition impeding physical and neurological development and growth. Other non-specific transplant-related factors that can have an effect on the brain include direct neurological side effects of immunosuppressant medications such as Posterior Reversible Encephalopathy Syndrome, seizures and opportunistic infections and diseases.

To the authors' knowledge, only one study to date has investigated the long-term neuroradiological outcomes of medically stable pediatric liver transplant recipients for chronic end-stage liver disease.[6] This study was the first to use magnetic resonance spectroscopy (MRS) to explore metabolite levels in the brains of transplanted children with a history of chronic liver disease or acute liver failure, as well as in a group of non-transplanted children with stable liver disease. Results suggested that the duration of symptomatic liver disease was associated with reduced myoinositol primarily driven by the two chronic groups. However, no association between metabolite levels and cognitive outcomes was noted. Furthermore, while measures of metabolite levels are a valuable exploration considering the known effects of liver

disease on neurochemistry,[2] the field is yet to explore the neurological development of this group through structural and neuroanatomical investigations.

Apart from this recent example, studies have otherwise been limited to pediatric recipients who have had catastrophic or overt neurological complications,[7-9] single or double case studies of clinically indicated scans in the acute period post-transplant,[10-13] and adult transplant recipients.[14-17] One study investigated the long-term neuroradiological outcomes of four pediatric liver transplant recipients with maple syrup urine disease,[18] a metabolic disorder which has a substantially different disease mechanism than chronic end-stage liver disease.[19] Hence, no study has explored the long-term neuroradiological status of medically stable pediatric liver transplant recipients for chronic end-stage liver disease.

In the few clinically indicated case studies conducted in children, bilateral T1 hyperintensities were identified in the globus pallidus pre-transplant and were found to be associated with elevated whole blood manganese levels.[10-12] The T1 hyperintensities resolved within the acute period post-transplant in all of the four cases reported.

Studies conducted within adult transplant populations suggest that neurological and neuroradiological symptoms may be reversed after transplantation although results are inconsistent. Consistent with the pediatric cases noted above, Herynek et al. reported reversal of strong hyperintense signal on T1-weighted and hypointense signal on T2-weighted bilaterally in the basal ganglia (particularly in the globus pallidus) two years after liver transplantation in adults, which was stable after 8-15 years.[15] However, bilateral abnormalities in the putamen remained 8-15 years after transplantation. Hyperintensities on T1 and T2 images were also observed in the thalamus and white matter but these were felt to be due to the permanent exposure to immunosuppressant medications. Another study

found that 18 adult patients awaiting transplantation displayed T1 hyperintensities in the basal ganglia, but 3-7 months post-transplant the signal had not resolved for 7 recipients.[17] Eight patients also showed metabolite dysregulation pre-transplantation as assessed on MRS, with normalisation evident in 5 out of 8 patients after transplantation.

Guevara et al. demonstrated that white matter and grey matter density in adult cirrhotic patients was associated with disease severity and performance on neuropsychological measures, with this persisting after transplantation.[14] Furthermore, Martinez et al. demonstrated that after liver transplantation, adult recipients showed an enlargement of ventricles compared to controls in the short- and long-term, as well as increased volume of focal T2 white matter lesions despite improvements in neuropsychological functioning.[20]

A number of neuropsychological studies to date have identified vulnerabilities in terms of neurological development in stable transplant recipients, with children showing reduced neurocognitive abilities compared to normative populations.[6, 21-24] It is therefore important to investigate whether medically stable pediatric recipients display any evidence of sub-clinical neuroradiological abnormalities.

The aim of the current case series was to examine the presence of neuroradiological abnormalities in medically stable pediatric liver transplant recipients. Exploratory investigations also sought to assess the relationship of structural volumetric measures of the brain with cognitive abilities and transplant related factors.

2 | METHOD

2.1 | Participants

Recruitment for the study was conducted as part of a larger project investigating long-term neuropsychological outcomes after liver transplantation at The Children's Hospital at Westmead in Sydney, Australia.[21] All participants who completed the cognitive study (N=40 from 46 eligible participants) were invited to take part in the neuroimaging study. Eight agreed to take part in the supplementary imaging (see Supplementary Table 1 for comparison of demographics for MRI sample with non-MRI participants). Ethics approval was received by relevant Human Ethics boards (approval codes: HC13358 and 12/SCHN/45) and all legal guardians provided written informed consent for their child to participate in the study. Medical and neuropsychological data were collected as part of the larger study.

2.2 | Materials

Brain MRI examinations were performed on a Philips Achieva 3T TX MRI. The protocol included T1 and Susceptibility Weighted Images. Images were reviewed by a pediatric neuroradiologist who was blind to participants' medical histories.

2.3 | Exploratory Analysis

Volumetric measures were obtained from T1 images using the FreeSurfer recon-all and aseg.stats commands (see previous methodological paper[25] and the FreeSurferWiki page https://surfer.nmr.mgh.harvard.edu/fswiki for details of procedure). In order to standardise volumes across participants to account for age and stature, a ratio was calculated for each child where the volume of each structure/region (in mm^3) was divided by the total intracranial space.[26] Exploratory Spearman correlation analyses between gross measures of volume and other factors of interest were conducted using IBM SPSS Version 22.[27]

3 | RESULTS

3.1 | Cases

A summary of the 8 cases is provided in Table 1. Two cases displayed similar neurological abnormalities on the research protocol, with the remaining six not showing overt pathology.

TABLE 1 Characteristics of reviewed cases

Case	Abnormal MRI	Sex	Age* (years)	Age MRI^ (years)	PELD*	BMI*	Graft	Diagnosis	Waitlist (days)	PICU (days)#	IQ	Literacy	Numeracy	Attention	Memory	FM
1	No	M	0.43	8.88	40	15.86	S	BA	21	12		-	--	-		
2	No	M	14.49	16.07	8	19.90	W	AIH	466	7	+	-	+	---		
3	No	M	2.30	14.91	3	13.47	S	ALG	49	10			--	---	+	
4	Yes†	F	1.31	8.64	18	16.62	W	BA	86	10	+	+	--	-	++	+++
5	Yes	F	1.00	13.39	27	12.78	W	PFIC	179	9	--		--	---	-	-
6	No	M	0.57	11.37	13	17.68	S	BA	21	8		+	-	--		--
7	No	M	4.31	10.87	15	13.87	S	ALG	1046	8		+	--	-		---
8	No	F	4.25	16.25	10	14.94	S	BA	1257	8	-		--	-	-	-

*At time of liver transplant #Post-transplant; ^At MRI; † retransplanted 18 months post MRI.
BMI: Body Mass Index (weight(kg)/height (m)^2); FM: fine-motor; IQ: intelligence; LTx: liver transplant; PELD: Pediatric end-stage liver disease score; PICU: pediatric intensive care unit; S: split graft; W: whole graft.
AIH: autoimmune hepatitis; ALG: Alagilles syndrome; BA: biliary atresia; PFIC: progressive familial intrahepatic cholestasis.
+: High-Average; ++: Superior; +++: Very Superior; -: Low-Average; --: Borderline-impaired; ---: Impaired; no symbol: Average.

Case 4 was an 8-year-old female who received a split liver transplantation for Biliary Atresia at 15 months. She spent 86 days on the transplant waitlist. Review of T1 gradient echo sequence as well as susceptibility weighted images revealed symmetric very subtle elevated signal in the globus pallidus and subthalamic nuclei bilaterally (see Figure 1). No evidence of calcification or haemorrhage in the susceptibility weighted sequence was identified. Neuropsychological testing revealed intact intellect, literacy and numeracy, memory and fine-motor skills, but reduced attention and impulse control. Case 4 had highly educated parents (postgraduate and doctoral level). She subsequently underwent successful retransplantation 18 months after undergoing the MRI study due to graft rejection.

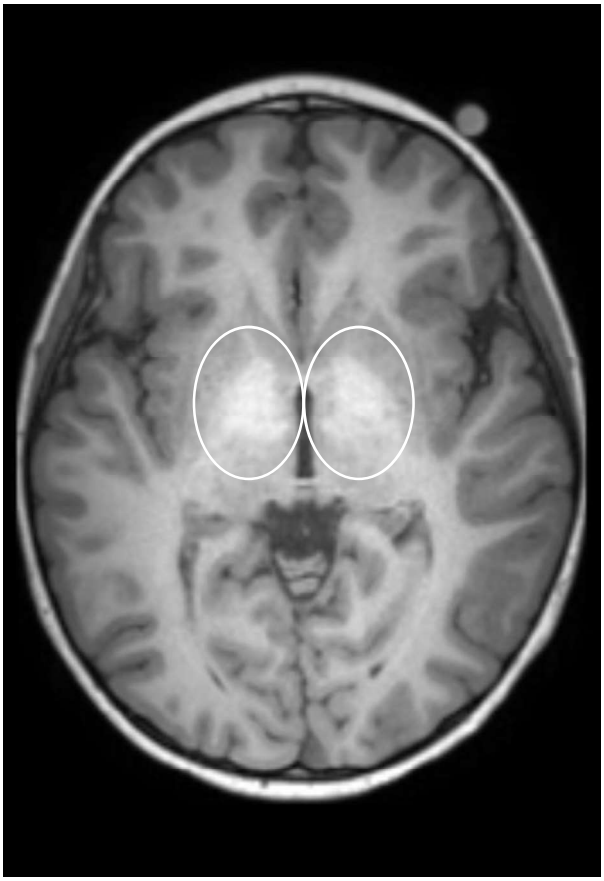


FIGURE 1 Axial T1 MR images of Case 4 highlighting bilateral hyperintensities in the globus pallidus thought to be due to elevated whole blood manganese

Case 5 was a 13-year-old female who received a whole liver transplant at 12 months due to Progressive Familial Intrahepatic Cholestatis. She spent 179 days on the transplant

waitlist. Review of images revealed symmetric mildly elevated signal in the subthalamic nuclei and globus pallidus bilaterally (see Figures 2a and 2b) very similar in distribution to Case 4, but more conspicuous. No evidence of calcification or haemorrhage in the susceptibility weighted sequence was identified. Neuropsychological testing revealed borderline-impaired intellect, academic ability, memory and fine motor skills, and impaired attention.

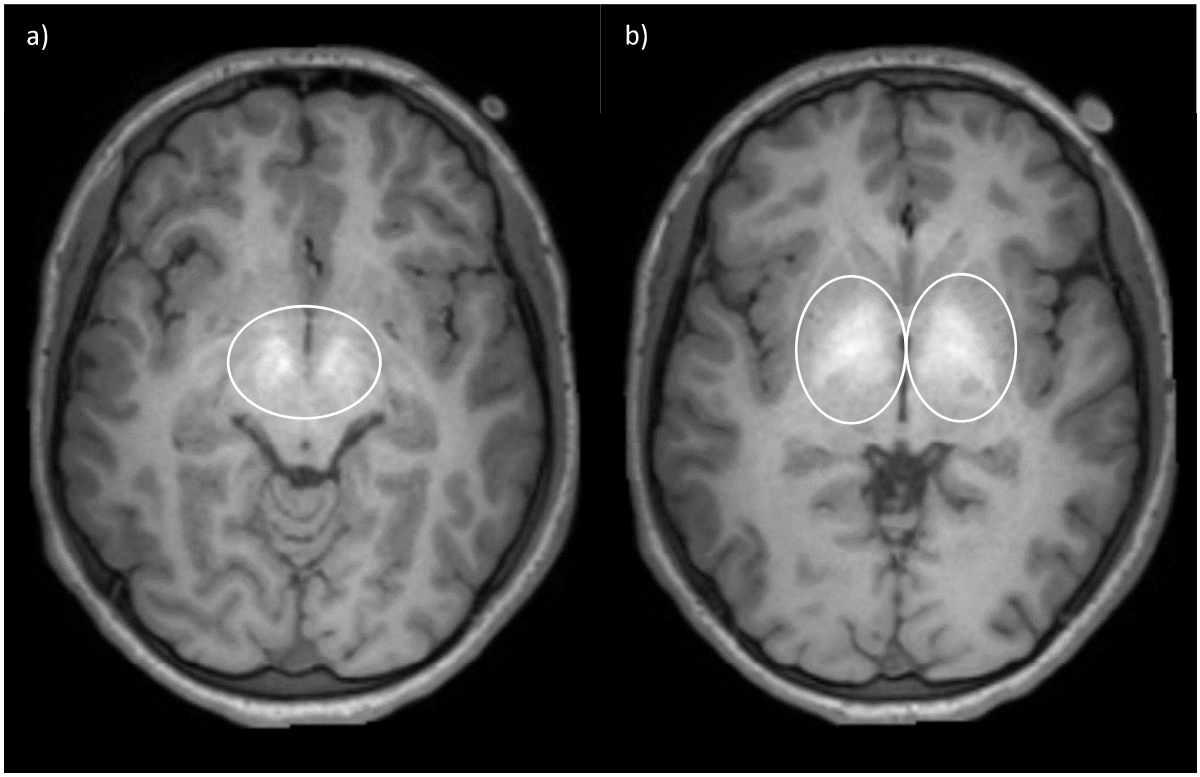


FIGURE 2 Axial T1 MR images highlighting bilateral hyperintensities in the subthalamic nuclei (a) and globus pallidus (b) of Case 5 considered due to elevated whole blood manganese levels.

3.2 | Exploratory Analysis

A number of exploratory analyses were conducted based on previous research findings. It is important to acknowledge the limited sample size and subsequent power of analyses and therefore results should be viewed with caution.

Results revealed that the volume of T1 white matter hypointesities (a measure not dissimilar to T2 hyperintensities quantifying possible white matter abnormality) was negatively

correlated with overall intelligence ($r_{Spearman}$ = -0.78; P = .023; see Figure 3). Greater volume of T1 white matter hypointensity correlated with lower overall scores on measures of intelligence.

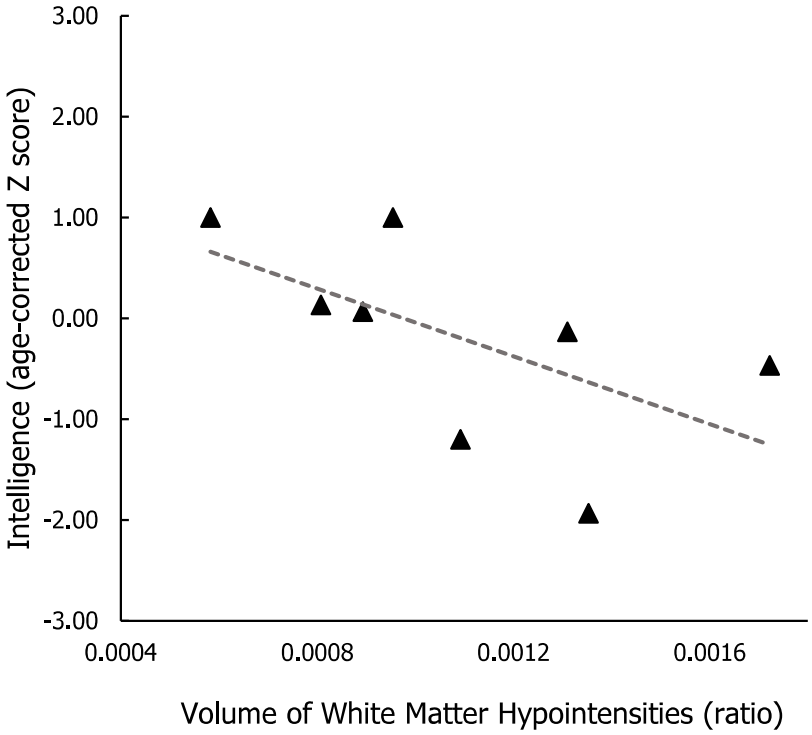


FIGURE 3 Scatterplot of total volume of white matter hypointensities (as a proportion of intracranial volume) by intelligence; $r_{Spearman}$ = -.78; P = .023.

Volume of T1 white matter hypointensity was also found to be associated with Body Mass Index (BMI) at time of transplant ($r_{Spearman}$ = -0.91; P = .002; see Figure 4). Specifically, a higher BMI at transplant was predictive of lower levels of white matter hypointensity at MRI review.

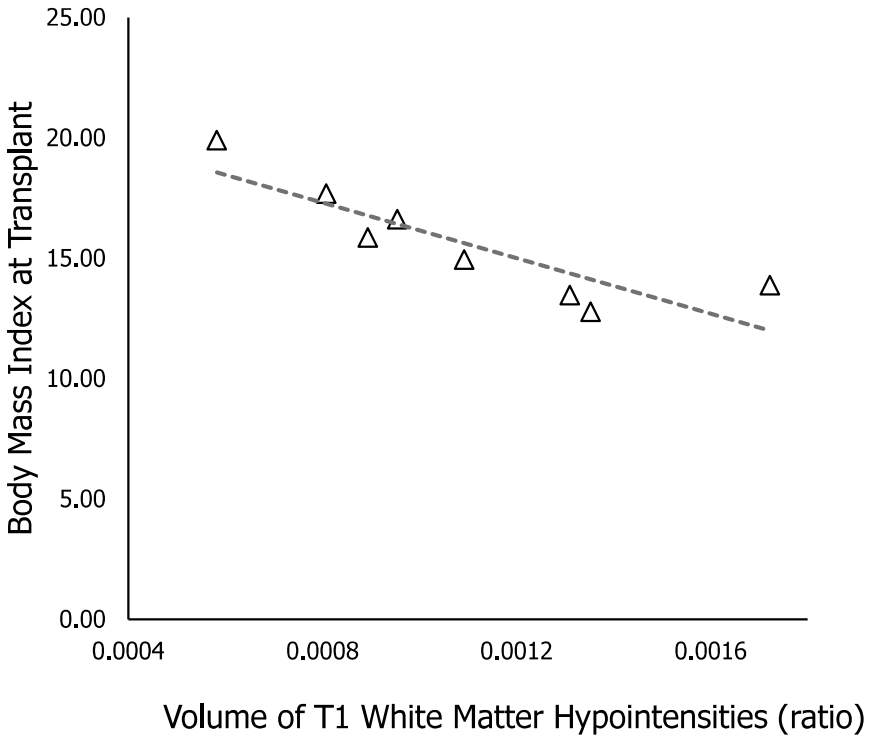


FIGURE 4 Scatterplot of total volume of white matter hypointensities (as a proportion of intracranial volume) by body mass index at transplant; $r_{Spearman}$ = -.91; P = .002.

As a validity check, the association between verbal memory and left hippocampal volume, which has been reliably shown to be negatively correlated in children,[28] was investigated. Left hippocampal volume was significantly, negatively correlated with delayed verbal memory ($r_{Spearman}$ = -.80; P = .017; Figure 5).

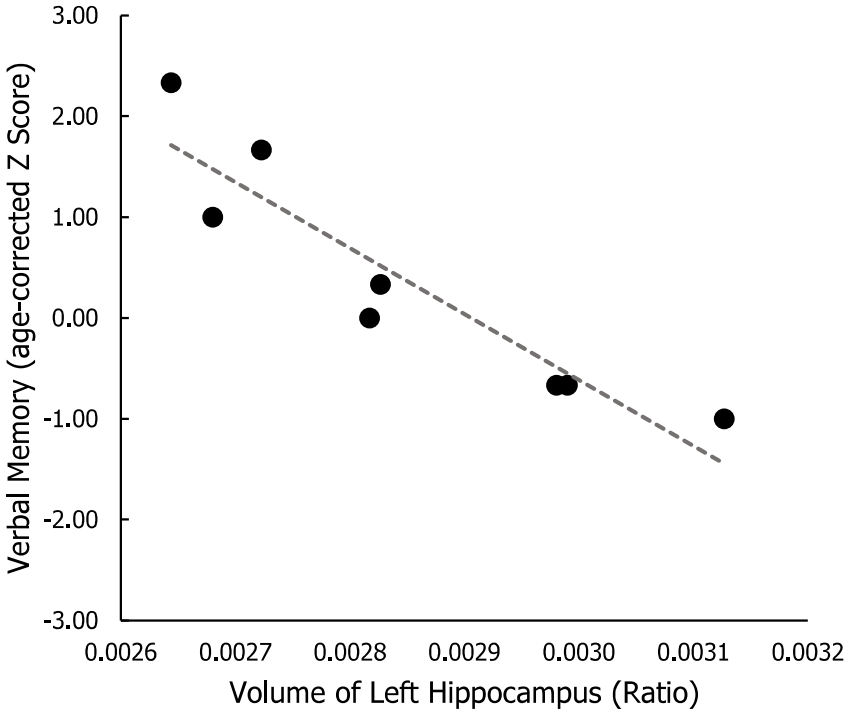


FIGURE 5 Scatterplot of total volume of left hippocampus (as a proportion of intracranial volume) by verbal memory; $r_{Spearman}$ = -.80; P = .017.

Finally, time on transplant waitlist was not associated with any measures of volume in this sample. There was a negative trend between total grey matter volume and days on waitlist ($r_{Spearman}$ = -0.68; P = .062), however, two outliers may have driven this effect.

4 | DISCUSSION

The current case series demonstrated that medically stable pediatric liver transplant recipients for chronic liver disease can present with abnormal neuroradiological findings related to liver disease and transplantation; namely, bilateral T1 hyperintensities in the globus pallidus and subthalamic nuclei considered to be due to manganese deposits.[10-12, 14, 15, 29] These findings indicate that it may not be appropriate to assume that children who appear to be medically stable will not have long term neurological abnormalities associated with their liver disease. This is consistent with the neuropsychological literature in children post-liver transplantation that has established generally reduced long-term neurocognitive functioning

compared to normative populations.[21, 24, 30-32] Furthermore, the results suggest that neuroimaging may be required as part of routine follow-up for children post-liver transplantation. A more comprehensive investigation is necessary to determine the prevalence of long-term neuroradiological abnormalities in stable pediatric liver transplant recipients as well as identifying the specific neurological abnormalities children are vulnerable to develop.

T1 hyperintensities linked to elevated manganese levels have been previously identified in the globus pallidus of adult chronic liver disease patients and pediatric case studies, but these hyperintensities are thought to generally resolve after transplantation,[10-12, 14, 15, 29] although not in all cases.[17] Based on two of the cases in the current series (25%), T1 hyperintensity in the basal ganglia may not universally resolve in all children. However, it is plausible that these hyperintensities may have developed (or redeveloped) post-transplantation due to sub-optimal functioning donor livers. This notion of suboptimal donor livers is supported by the subsequent retransplantation of one of these children due to graft rejection. Acutely, these manganese-related T1 hyperintensities primarily manifest in motor symptoms such as dystonia and tremor.[10, 11] However, long-term exposure can have more widespread neurological effects which may manifest in impaired cognitive development such as those reported in the neuropsychological literature to date.

It may be argued that these abnormalities are asymptomatic and not of clinical concern. The current case series is too limited in scope to definitively contest this. However, the presence of neuroradiological abnormalities in medically stable liver transplant recipients and reduced neurocognitive functioning identified in the neuropsychological literature together support a link between liver disease and neurological abnormalities. These may subsequently manifest as neurocognitive vulnerabilities and do not necessarily resolve upon transplantation in a pediatric population.

Furthermore, exploratory analysis in the current series revealed a possible relationship between transplant factors and neurological development. Results revealed that a higher BMI at transplantation predicted lower volumes of T1 white matter hypointensities (which was considered to be a measure of white matter abnormality). Liver disease is known to cause malnutrition.[33] Hence, a higher BMI at transplant may suggest better nutritional status and could be a proxy for disease severity and/or liver function. In addition, a higher volume of T1 white matter hypointensities was negatively associated with intelligence. Therefore, the observed relationship between BMI and white matter hypointensity may be capturing one risk factor for poorer neurological development in children with chronic liver disease. Specifically, it is hypothesised that greater disease severity may lead to poorer nutritional status which undermines neurological development. This deleterious process may subsequently manifest as poorer long-term intellectual ability. Therefore, the neuroradiological signs quantified in the current study may partly explain the association between disease severity at transplant and long-term intellectual and neurocognitive outcomes. While provisional, this finding reinforces both the need for better nutritional management during critical periods of brain development[33] and expediting pediatric transplant candidates to minimise exposure to the effects of a diseased liver.

Further studies are required to directly investigate neurological development as a likely explanatory factor for the association between medical and transplant-related factors and long-term neurocognitive outcomes.[34] These studies would benefit from comprehensive approaches that seek to fully capture the experience of transplant populations by wide-scale testing and scanning, potentially replicating and expanding upon our modest findings. Such research may be of great importance when informing future transplantation policy and long-term review procedures. Finally, larger scale research needs to be conducted that explores additional associated variables using regression models to control for confounding factors.

REFERENCES

1. Campagna F, Biancardi A, Cillo U, Gatta A, Amodio P. Neurocognitive-neurological complications of liver transplantation: A review. Metabolic Brain Disease. 2010;25(1):115-24.

2. Bismuth M, Funakoshi N, Cadranel JF, Blanc P. Hepatic encephalopathy: From pathophysiology to therapeutic management. European Journal of Gastroenterology and Hepatology. 2011;23(1):8-22.

3. Shawcross D, Jalan R. The pathophysiologic basis of hepatic encephalopathy: Central role for ammonia and inflammation. Cellular and Molecular Life Sciences. 2005;62(19-20):2295-304.

4. Malecki EA, Devenyi AG, Barron TF, Mosher TJ, Eslinger P, Flaherty- Craig CV, et al. Iron and manganese homeostasis in chronic liver disease: Relationship to pallidal T1-weighted magnetic resonance signal hyperintensity. NeuroToxicology. 1999;20(4):647-52.

5. McKinney AM, Filice RW, Teksam M, Casey S, Truwit C, Clark HB, et al. Diffusion abnormalities of the globi pallidi in manganese neurotoxicity. Neuroradiology. 2004;46(4):291-5.

6. Talcott JB, Beath SV, Patel T, Griffiths G, Kelly DA. Long-term Effects of Cholestatic Liver Disease in Childhood on Neuropsychological Outcomes and Neurochemistry. J Pediatr Gastroenterol Nutr. 2019;69(2):145-51.

7. Donmez YF, Guvenc Z, Emiroglu KF, Coskun M, Haberal M. Evaluation of neurological complications in pediatric liver transplant recipients: MRI versus CT. Journal of Child Neurology. 2009;24(6):656-63.

8. Lee YJ, Yum MS, Kim EH, Choi HW, Oh SH, Kim DY, et al. Risk factors for neurological complications and their correlation with survival following pediatric liver transplantation. Pediatric Transplantation. 2014;18(2):177-84.

9. Ghosh PS, Hupertz V, Ghosh D. Neurological complications following pediatric liver transplant. Journal of Pediatric Gastroenterology and Nutrition. 2012;54(4):540-6.

10. Barron TF, Devenyi AG, Mamourian AC. Symptomatic manganese neurotoxicity in a patient with chronic liver disease: Correlation of clinical symptoms with MRI findings. Pediatric Neurology. 1994;10(2):145-8.

11. Devenyi AG, Barron TF, Mamourian AC. Dystonia, hyperintense basal ganglia, and high whole blood manganese levels in Alagille's syndrome. Gastroenterology. 1994;106(4):1068-71.

12. Ikeda S, Yamaguchi Y, Sera Y, Ohshiro H, Uchino S, Yamashita Y, et al. Manganese deposition in the globus pallidus in patients with biliary atresia. Transplantation. 2000;69(11):2339-43.

13. Cui R, Fayek S, Rand EB, Feygin T, Khrichenko D, Shaked A. Central pontine myelinolysis: A case report and clinical-pathological review. Pediatric Transplantation. 2012;16(6):E251-E6.

14. Guevara M, Baccaro ME, Gómez-Ansón B, Frisoni G, Testa C, Torre A, et al. Cerebral magnetic resonance imaging reveals marked abnormalities of brain tissue density in patients with cirrhosis without overt hepatic encephalopathy. Journal of Hepatology. 2011;55(3):564-73.

15. Herynek V, Wagnerová D, Hejlová I, Dezortová M, Hájek M. Changes in the brain during long-term follow-up after liver transplantation. Journal of Magnetic Resonance Imaging. 2012;35(6):1332-7.

16. Martinez YJ, Ercikan K. Chronic illnesses in Canadian children: What is the effect of illness on academic achievement, and anxiety and emotional disorders? Child: Care, Health and Development. 2009;35(3):391-401.

17. Naegele T, Grodd W, Viebahn R, Seeger U, Klose U, Seitz D, et al. MR Imaging and 1H Spectroscopy of Brain Metabolites in Hepatic Encephalopathy: Time-Course of Renormalization after Liver Transplantation. Radiology. 2000;216(3):683-91.

18. Díaz VM, Camarena C, De La Vega A, Martínez-Pardo M, Díaz C, López M, et al. Liver transplantation for classical maple syrup urine disease: Long-term follow-up. Journal of Pediatric Gastroenterology and Nutrition. 2014;59(5):636-9.

19. Squires RH, Ng V, Romero R, Ekong U, Hardikar W, Emre S, et al. Evaluation of the pediatric patient for liver transplantation: 2014 practice guideline by the american association for the study of liver diseases, american society of transplantation and the north american society for pediatric gastroenterology, hepatology and nutrition. Hepatology. 2014;60(1):362-98.

20. García Martínez R, Rovira A, Alonso J, Aymerich FX, Huerga E, Jacas C, et al. A long-term study of changes in the volume of brain ventricles and white matter lesions after successful liver transplantation. Transplantation. 2010;89(5):589-94.

21. Afshar S, Porter M, Barton B, Stormon M. Intellectual and academic outcomes after pediatric liver transplantation: Relationship with transplant-related factors. American journal of transplantation :

official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2018;18(9):2229-37.

22. Crowe L, Anderson V, Hardikar W, Boneh A. Cognitive and behavioural outcomes of paediatric liver transplantation for ornithine transcarbamylase deficiency. JIMD Reports2019. p. 19-25.

23. Cushman GK, Stolz MG, Blount RL, Reed B. Executive Functioning in Pediatric Solid Organ Transplant Recipients: A Meta-Analytic Review. Transplantation. 2019.

24. Rodijk LH, Den Heijer AE, Hulscher JBF, Verkade HJ, De Kleine RHJ, Bruggink JLM. Neurodevelopmental outcomes in children with liver diseases: A systematic review. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(2):157-68.

25. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: Automated labeling of neuroanatomical structures in the human brain. Neuron. 2002;33(3):341-55.

26. Barnes J, Ridgway GR, Bartlett J, Henley SM, Lehmann M, Hobbs N, et al. Head size, age and gender adjustment in MRI studies: a necessary nuisance? NeuroImage. 2010;53(4):1244-55.

27. IBM SPSS Statistics for Windows Version 22.0. Armonk, NY: IBM Corp; 2013.

28. Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: Review and meta-analysis. Neuropsychologia. 2004;42(10):1394-413.

29. Zaitout Z, Romanowski C, Karunasaagarar K, Connolly D, Batty R. A review of pathologies associated with high T1W signal intensity in the basal ganglia on Magnetic Resonance Imaging. Polish Journal of Radiology. 2014;79:126-30.

30. Gilmour S, Adkins R, Liddell GA, Jhangri G, Robertson CM. Assessment of psychoeducational outcomes after pediatric liver transplant. American Journal of Transplantation. 2009;9(2):294-300.

31. Kaller T, Langguth N, Petermann F, Ganschow R, Nashan B, Schulz KH. Cognitive performance in pediatric liver transplant recipients. American Journal of Transplantation. 2013;13(11):2956-65.

32. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Longitudinal study of cognitive and academic outcomes after pediatric liver transplantation. Journal of Pediatrics. 2014;165(1):65-72.e2.

33. Lacaille F. Nutrition and Liver Disease. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 397-407.

34. Sorensen LG. Pediatric solid organ transplantation and end stage disease: A slow journey towards understanding neurocognitive outcomes and their ramifications for clinical care. Pediatric Transplantation. 2015;19(2):136-8.

SUPPLEMENTARY TABLE 1. Comparison of MRI participants and non-participants

			Participated in MRI (N=8; 3f)		Did not Participate (n=32; 19f)		
			Mean	*SD*	Mean	*SD*	*P*
Medical and Demographic Factors		Age at Assessment (yrs)	12.16	*3.20*	10.96	*3.75*	0.379
		Age at Transplant (yrs)	3.58	*4.67*	2.23	*2.68*	0.452
		Years Since Transplant	8.59	*3.87*	8.75	*3.87*	0.918
		Average parental Education	13.44	*2.46*	12.55	*2.18*	0.371
		PELD Score at Transplant	16.75	*11.80*	25.16	*10.87*	0.097
		Weight (age-based Z score)	-1.65	*1.30*	-1.49	*1.92*	0.788
		Height (age-based Z score)	-1.62	*1.23*	-2.57	*2.68*	0.154
		BMI At Transplant	15.64	*2.38*	17.46	*4.58*	0.133
		Days on Waitlist	390.63	*494.73*	167.59	*198.41*	0.248
		Days in PICU	9.00	*1.60*	9.63	*7.24*	0.658
		BMI at Assessment	15.87	*2.34*	16.18	*1.77*	0.815
Intelligence (WISC-IV)		FSIQ	97.13	*15.15*	92.16	*17.82*	0.439
		VCI	93.38	*18.65*	92.31	*16.09*	0.885
		PRI	102.88	*13.34*	92.09	*19.21*	0.083
		WMI	93.38	*9.68*	91.91	*15.61*	0.742
		PSI	100.38	*12.72*	99.34	*16.58*	0.850
Academics (WIAT-II)		Word Reading	97.88	*14.74*	101.13	*19.32*	0.610
		Decoding	97.38	*16.47*	100.45	*17.08*	0.649
		Mathematics	91.88	*14.24*	92.44	*19.93*	0.928
		Spelling	96.63	*13.88*	102.38	*16.57*	0.333
Attention (TEA-Ch)		Selective	9.88	*1.64*	8.87	*2.57*	0.193
		Sustained	6.50	*2.20*	7.73	*2.84*	0.209
		Shifting	6.57	*0.98*	8.64	*3.32*	0.011 *
		Divided	5.38	*3.11*	7.17	*3.71*	0.189
		Inhibition	6.25	*2.55*	4.93	*2.63*	0.223
Memory (CMS)		Visual	11.38	*2.67*	11.50	*2.72*	0.908
		Verbal	11.13	*3.60*	11.32	*3.38*	0.891
Executive (BADS-C)		Planning	11.63	*4.24*	9.04	*3.55*	0.148
Motor (Purdue)		Pegboard	-0.67	*1.36*	-0.95	*1.08*	0.605
PedsQL	PR	Total	68.32	*21.35*	74.20	*12.31*	0.509
	SR	Total	72.01	*20.67*	72.74	*15.91*	0.929
Executive (BRIEF)	PR	Behavioral Regulation	57.00	*13.93*	51.48	*11.55*	0.334
		Metacognition	60.38	*8.78*	55.60	*13.90*	0.266
		Global Executive Index	60.00	*11.43*	54.48	*12.96*	0.270
	TR	Behavioral Regulation	54.50	*13.88*	53.89	*12.80*	0.917
		Metacognition	57.38	*17.55*	56.39	*13.29*	0.890
		Global Executive Index	57.13	*17.47*	56.39	*14.08*	0.918
	SR	Behavioral Regulation	57.00	*14.45*	45.67	*10.09*	0.222
		Metacognition	59.00	*17.22*	50.67	*11.78*	0.425
		Global Executive Index	58.50	*17.06*	48.11	*11.65*	0.326
Attention (Conners 3)	PR	Inattention	64.75	*16.02*	58.75	*14.13*	0.366
		Hyperactivity/Impulsivity	68.63	*17.12*	56.17	*11.56*	0.087
	TR	Inattention	53.38	*12.22*	54.06	*12.45*	0.898
		Hyperactivity/Impulsivity	54.38	*13.29*	54.67	*14.43*	0.961
	SR	Inattention	66.67	*17.12*	56.60	*15.03*	0.242
		Hyperactivity/Impulsivity	61.00	*8.22*	57.53	*12.25*	0.465
Psychosocial and Adaptive Functioning (BASC-2)	PR	Externalizing	56.13	*8.98*	48.57	*8.29*	0.060
		Internalizing	58.63	*17.86*	53.33	*7.55*	0.439
		Behavioral Symptoms	57.25	*14.12*	51.67	*9.27*	0.323
		Adaptive Skills	42.75	*9.44*	49.65	*10.12*	0.104
	TR	Externalizing	48.00	*6.27*	50.13	*10.14*	0.548
		Internalizing	52.86	*12.20*	55.00	*8.97*	0.686
		School Problems	52.43	*7.89*	50.81	*12.25*	0.710
		Behavioral Symptoms	49.71	*6.97*	50.81	*10.91*	0.775
		Adaptive Skills	50.00	*6.88*	53.13	*11.51*	0.431
	SR	School Problems	48.83	*11.74*	51.29	*11.36*	0.675
		Internalizing	51.33	*9.24*	48.36	*7.37*	0.505
		Personal Adjustment	46.83	*9.45*	48.21	*11.54*	0.785

PELD: Pediatric End-stage Liver Disease; BMI: Body Mass Index; PICU: Pediatric Intensive Care Unit; FSIQ: Full Scale Inelligence Quotient; VCI: Verbal Comprehensive Index; PRI: Perceptual Reasoning Index; WMI: Working Memory Index; PSI: Processing Speed Index; WISC-IV: Wechsler Intelligence Scale for Children 4th Edition; WIAT-II: Wechsler Individual Achievement Test 2nd Edition; TEA-Ch: Test of Everyday Attention for Children; CMS: Children's Memory Scale; BADS-C: Behavior Assessment of the Dysexecutive Syndrome in Children; BRIEF: Behavior Rating Inventory of Executive Function; BASC-2: Behavior Assessment System for Children 2nd Edition; PR: Parent-Report; TR: Teacher-Report; SR: Self-Report; * = $P < 0.05$; ** = $P < 0.01$.

CHAPTER 6:

GENERAL DISCUSSION

GENERAL DISCUSSION

1 | Aim of the thesis

The aim of the current thesis was to investigate the neuropsychological outcomes of paediatric liver transplantation for chronic liver disease within a novel jurisdiction, whilst also seeking to address a number of methodological shortcomings of the field.

With this overarching aim in view, Chapter 1 (the thesis introduction) provided an overview of liver transplantation and impacts of liver disease on the brain. Specifically, it set the scene for why paediatric cases need to be analysed separate to adult studies; why the field needs data from new jurisdictions such as Australia; and why researchers need to start identifying disease-modifiable factors, in order to give these children a better life.

Chapter 2 is a published, empirical paper that investigated the long-term intellectual and academic outcomes of Australian children who received a liver transplant for chronic liver disease. This study aimed to predict long-term outcomes from medical and transplant-related factors. It also hoped to demonstrate the utility of running analyses on more homogenous samples in order to more accurately predict long-term outcomes.

Chapter 2-supplementary re-analysed the data from Chapter 2 using an exploratory model based on a novel idea that the relationship between long-term outcomes and medical and transplant-related factors may not be linear, and hence, interaction effects may need to be considered.

Chapter 3 examined multi-informant reports of long-term day-to-day functioning across a range of neuropsychological and quality of life domains for children post-liver

transplant for chronic liver disease. It utilised multiple measures to achieve convergent validity on findings.

Chapter 4 was a systematic review with meta-analysis that aimed to summarise the long-term intellectual and academic outcomes of children post-liver transplant. It hoped to demonstrate the importance of separating analyses and results by diagnostic groups.

Chapter 5 reviewed a series of eight children who received a liver transplant for chronic liver disease. They underwent MRI to investigate the presence of any brain pathology in otherwise medically stable children. It explored measures of neurological development, namely, measures of brain volumetrics, to consider whether these results were associated with long-term neuropsychological outcomes and/or medical and transplant-related factors.

2 | Key findings of the thesis

Three core findings arose from the present thesis: 1) children who received a liver transplant for chronic liver disease had poorer long-term neuropsychological outcomes than the general population with particular cognitive areas of vulnerability; 2) greater time spent waiting for a donor organ was predictive of poorer neuropsychological outcomes; and 3) averaging long-term neuropsychological outcomes across primary diagnostic groups masks important effects. Each key finding is detailed further below.

2.1 | Paediatric liver transplant recipients had poorer outcomes

Results from the current thesis revealed that, as a whole, children who received a liver transplant for chronic liver disease had poorer intellectual and academic outcomes than the general population, particularly in working memory, verbal intellect, perceptual/nonverbal ability and mathematics (Chapters 2 and 4). A downward shift of the distribution was observed

(as illustrated in Figure 1), consisted with previous studies.[1-5] Speed of information processing and literacy skills, however, were no different to age-expectations. Findings from the thesis (Chapters 2 and 4), which captured all available data on intellectual outcomes in children with liver transplant, did not support the results of two previous studies that claimed that these children have poorer nonverbal/visuospatial skills compared with verbal abilities.[1, 6]

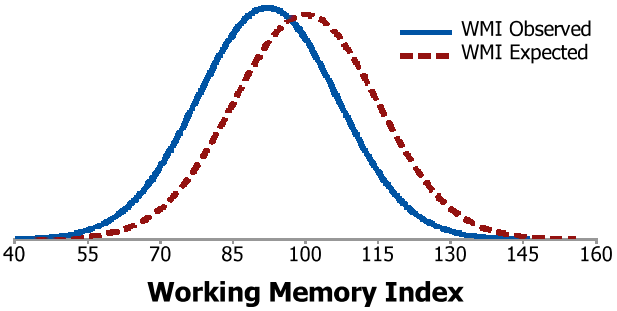


FIGURE 1 Example of downward shift of distribution as demonstrated by observed and expected working memory index scores

Results from Chapter 3 revealed that children who received a liver transplant for chronic liver disease had greater day-to-day functional difficulties relative to the normative population, based on parent-, teacher- and child self-reports using standardised questionnaire measures. These measures identified attention as a particular area of vulnerability, with results indicating higher-than-expected rates of clinical issues (including a higher risk of ADHD). Executive functioning was a further area of concern. However, this was limited to the metacognitive aspects of executive functions (working memory, planning and organising, self-monitoring and initiation) rather than the behavioural and emotional regulation domains. These findings supported other studies that have shown higher-than-expected problems in day-to-day attention and the metacognitive aspects of executive functions.[7-10] This has also been demonstrated in a recent systematic review and meta-analysis which synthesised both informant- and performance-based results into attention and executive functions. It found that following paediatric transplantation, children exhibited problems with attentional control and the metacognitive aspects of executive function, but behavioural regulation was found to be equivalent to the normative population.[7]

Paediatric liver transplant recipients in the current thesis also showed significantly poorer psychosocial quality of life and problems with fatigue when compared with healthy controls (Chapter 3). Fatigue, as well as psychosocial and transplant-related quality of life, were generally in line with results from other solid organ transplant samples.[11-13] However, psychosocial quality of life appeared poorer than a large North American paediatric liver transplant population.[11] This contrasting result was thought to be a consequence of differences in the sampling across the two studies; namely that the previously published study included children with a primary diagnosis of acute liver failure alongside children with a primary diagnosis of end-stage chronic liver disease whereas the current thesis only included the chronic group. This is pertinent because transplanted children with a primary diagnosis of acute liver failure appear to have more favourable outcomes compared to the chronic illness group.[5] Jurisdictional characteristics may have also played a role in explaining these differences, such as variability in donations rates and transplant policies (see Chapter 1).

In contrast to findings on psychosocial functioning, parent-reports on physical quality of life were found to be no different from healthy controls or other paediatric transplant samples. This suggests that psychosocial quality of life may be a more pressing clinical consideration than physical quality of life for this group. However, child self-reports highlighted significantly poorer perceived physical functioning compared to the healthy control normative group. This discrepancy between parent- and child-reports around physical wellbeing may be reflecting a difference in perspective; while parents may be comparing their children to their former ill state or "what could have been", children may be comparing themselves to their same age peers and being more sensitive to subtle differences (such as in activities they are allowed to engage in[14, 15] or physical capacity).

In Chapter 5 of the current thesis, neuroradiological exploration revealed bilateral pathology in the globus pallidus and subthalamic nuclei of two out of the eight medically stable transplant recipients, one of whom underwent retransplantation within 18 months. This pathology was thought to reflect elevated levels of whole blood manganese.[16-18] However, it was unclear whether this was due to historical liver disease or reflecting recent decline in the functioning of each child's respective donor liver. Indeed, one of the children subsequently underwent retransplantation which may suggest that brain MRI could be a useful tool in identifying early signs of declining liver function.

Additional exploratory analyses revealed a possible association between brain volumetrics (including volume of white matter abnormality), neurocognitive outcomes (overall intelligence and verbal memory) and transplant-related factors (body mass index at transplant). The findings from Chapter 5 provided preliminary support that neuroimaging studies may help to explain the neurological mechanisms that underly the cognitive and functional deficits seen on neuropsychological evaluation. Further neuroradiological research with larger samples and broader imaging techniques in medically stable children after liver transplant is warranted to replicate and expand these findings.

Taken together, the findings from the current thesis demonstrate that childhood liver transplant recipients are at significant risk of poorer outcomes than their same-age healthy peers across a range of neuropsychological, neurological and psychosocial domains.

2.2 | Greater time on transplant waitlist predicted poorer long-term outcomes in biliary atresia

Another major finding of the present thesis was that time on the transplant waitlist predicted long-term intellectual and academic outcomes. Chapter 2 found that children with

biliary atresia who waited longer on the transplant waitlist had poorer long-term intellectual and academic outcomes. Namely, verbal intellectual ability, working memory, mathematics and reading ability. With the exception of reading, these intellectual and academic domains were the areas in which children showed the poorest performance compared to the normative population. Furthermore, additional exploratory analyses in Chapter 2-supplementary indicated that the deleterious effect of time spent on the waitlist was most pronounced amongst children who had the poorest functioning liver at transplant (as measured by serum bilirubin level). Additionally, findings from Chapter 2 indicated that younger age at transplant predicted better processing speed, which may again suggest that earlier transplantation is associated with better outcomes. These results are consistent with findings from previous studies that have shown long-term outcomes to be predicted by a related factor, namely disease duration.[6, 9, 19, 20] As was argued in Chapter 2, time spent on waitlist is associated with disease duration and arguably a better estimate of how long a child was unwell with severe liver disease. This is because a child is required to reach a specific threshold of disease severity to be eligible for the transplant waitlist. Chapters 2 and 2-supplementary, however, join only four existing studies to have directly explored the role of time on transplant waitlist as a predictor,[5, 6, 9, 21] but only one of these found this factor to uniquely predict long-term neuropsychological outcomes in paediatric liver transplant recipients.[5]

Overall, findings from the current thesis reinforced the urgency of reducing waitlist times for paediatric liver transplant candidates with biliary atresia, as it is a promising and tangible disease-modifying target. This is particularly important for those with greater disease severity. When viewed within the framework of critical periods of development that are vulnerable to disruption due to disease processes that impact the brain, it makes sense that extended illness duration would have a greater impact on neurodevelopment and its

manifestation in day-to-day life and functioning. Future higher quality studies may also clarify whether this also applies to other liver disease groups.

2.3 | Averaging across primary diagnoses masks long-term outcomes

The final key finding of the present thesis was that long-term intellectual and academic outcomes varied depending on the primary cause of liver disease, such as chronic liver disease, acute liver failure or metabolic disorder. Results of the systematic review and meta-analysis in Chapter 4 indicated that children with metabolic disorders who received a liver transplant had poorer intellectual and academic outcomes than other diagnostic groups. In contrast, paediatric liver transplant recipients who had acute liver failure performed in line with the normative population. Children who received a liver transplant for chronic liver disease performed below the normal population, but above children with metabolic disorders. The chronic group appeared to be below the acute liver failure group, although this difference was not statistically significant. This non-significant finding is believed to be due to underpowered analyses, which was a consequence of limited acute liver failure samples.

With the exception of three studies[5, 20, 21], the majority of studies prior to the present thesis did not investigate the impact of primary diagnosis on a range of long-term outcomes including intelligence, academic functioning, executive functions, psychosocial development, motor skills, and health-related quality of life.[1, 6-10, 12, 19, 22-35] As a result, there is a risk of masking important effects as outcomes are typically averaged across these heterogenous diagnostic groups.

Some studies have attempted to partition out effects of primary diagnosis through statistical methods such as linear or logistical regression.[9, 10] However, there are multiple issues with this approach. Firstly, by not providing the initial univariate descriptive results of

each disease category, the wider research and clinical community is unable to appreciate the profile of each diagnostic group for different domains (such as neuropsychological or quality of life outcomes). It also limits the capacity of quantitative reviews to explore group effects across studies. Second, statistical analyses cannot accurately differentiate effects between groups when some of the diagnostic groups have very low frequencies. A number of analyses have underlying assumptions that need to be met for these analyses to be valid. These assumptions may include categorical groups having generally equal numbers of observations or the requirement that a group has a minimum number of observations.[36] For example, when a regression model explores the role of diagnostic group on a particular outcome in a sample of 100 individuals, but one group accounts for 60 observations and the remaining four groups account for 10, then the underlying assumptions of the regression model are at risk of violation. Furthermore, this approach would typically be underpowered from small subgroup sample sizes, meaning that the effect of diagnostic group would be unclear. Third, as discussed in Chapter 4, a consensus has not been reached regarding how to categorise individual and uncommon diagnoses into overarching diagnostic groups. As a result, different studies tend to categorise the more uncommon disorders in differing groups.[2, 5, 19, 20] This often occurs for alpha-1 antitrypsin deficiency, Alagille syndrome and hepatic cancers, which have been observed to fall in the chronic, genetic-metabolic, and "other" categories.

This masking was further illustrated in the meta-analysis in Chapter 4. When the results were averaged across all studies, they were near-identical to the overall weighted mean of all studies that contained mixed diagnostic samples. This held true for both intellectual and academic results. In this way, Chapter 4 demonstrated the importance of dividing results by primary diagnosis in order to parse out the differential effects of disparate diagnoses rather than relying on an overall average.

In a similar vein, chronic liver disorders, particularly biliary atresia, are the most common reason for paediatric liver transplantation.[37, 38] As such, when analyses were conducted across all diagnostic groups as a whole, the chronic liver disease sample had the greatest weighting on findings compared to the less frequently occurring disorders such as acute liver failure, metabolic, or hepatic cancer groups. As such, the effects of biliary atresia may wash out effects relevant to these smaller groups.

Additionally, results from Chapter 2 revealed that this masking effect may be observed even *within* broader diagnostic groups such as the chronic illness group. Results showed that time on the transplant waitlist was not a predictor of long-term intellectual or academic outcomes in the broader chronic illness group. However, the predictive role of time on waitlist emerged when the analysis was restricted to the more homogenous group of children with a primary diagnosis of biliary atresia. As discussed throughout the current thesis, collapsing across groups assumes equivalent disease and transplant experiences, as well as underlying mechanisms between different diagnoses. Intuitively, differing underlying disease mechanisms as outlined in Chapter 1, and the empirical results from Chapter 2 and 4 suggest that this is not the case. As such, primary diagnoses should be differentiated within the research and clinical settings.

3 | Strengths and limitations of the current thesis and suggested future directions

This final section of the general discussion serves to review the core strengths and limitations of the thesis as a whole. It also identifies the key clinical and research implications of the thesis, as well as recommendations for furthering the field. It concludes with a concise summary for researchers, clinicians and policy makers who share the goal of improving outcomes for paediatric liver transplant recipients.

3.1 | Significance of waiting time

The current thesis was one of only a few studies to explore the effect of time on the transplant waitlist on neuropsychological outcomes.[5, 6, 9, 21] To date, investigations into this factor have been scarce, despite this being a feasible modifiable factor that could achieve better long-term outcomes. While other factors such as disease severity or access to dialysis-like processes for the liver cannot be changed, increased prioritisation of paediatric transplant candidates is one practical solution to reduce waiting times.[39] Hence, this finding could help in advocating for new policies to increase organ donation in Australia and beyond. This could mirror previous successful efforts, such as changes made in the world leading jurisdiction of Spain to improve organisational systems and to promote public support for organ donation.[40] Shifting to an opt-out policy of organ donation could also improve outcomes as it has been associated with higher rates of donation across the world.[40-42] Similarly, changing policies to promote living donor transplantations or pushing for increased use of split liver transplantation, as has been done in other jurisdictions, are also achievable modifications that can assist further in reducing the time spent on the transplant waitlist.[43-47] Unfortunately, existing research does not always attempt to predict long-term outcomes from medical and transplant-related factors, and it is recommended that this become standard practice so that other modifiable factors can be identified.

Based on the findings of the thesis, policy makers should consider explicitly including the risk to cognitive outcomes in future organ allocation models. For example, the pediatric end-stage liver disease (PELD) scoring system which is used for prioritisation of candidates could be modified to include factors that predict poorer outcomes such as longer waiting times in children with biliary atresia.

3.2 | The Australian context

A major strength of the current thesis was the novelty of the jurisdiction in which it was conducted. When this research was being devised, it was to be the first study within Australia exploring the long-term neuropsychological outcomes in children after liver transplantation. This was an important feature of the study, as the majority of studies to date have occurred in North America and Western Europe. These jurisdictions are characterised by significant differences in donation rates and organ availability, transplant policies, and organisational and systemic structures (such as availability of universal healthcare, nationalised transplant services or general educational outcomes).[40, 48-51] Therefore, data from less researched jurisdictions was clearly needed to achieve a richer understanding of the impacts of liver disease and transplantation, and to delineate the role that jurisdiction plays in determining outcomes. For example, data from developing nations, jurisdictions with varying donation rates or jurisdictions with proactive living-donor liver transplant programs would help better elucidate the post-transplant experience. The current thesis contributed data from a developed jurisdiction with lower donation rates and a reluctance towards using living donor liver transplants.

3.3 | A call for proactive neuropsychological assessments and interventions

Taken together, the three decades of research and the current thesis demonstrate the clinical utility of neuropsychological assessment in evaluating long-term outcomes. This thesis has demonstrated that children who have received a liver transplant are a vulnerable population whose neurocognitive development requires regular monitoring through neuropsychological assessments including multi-informant measures of functioning. These assessments would allow for identification of areas of weakness so that targeted and proactive interventions can be devised and implemented.[52] It is, therefore, suggested that neurocognitive assessments be established as part of usual follow-up care, as is characteristic

in other clinical populations such children with traumatic brain injury.[53-55] It is further suggested that a consensus be reached regarding a brief standardised battery to be used in these follow-up neuropsychological assessments (clinicians can then add additional measures based on individual presentation and hypotheses).[56] It is recommended that these minimum batteries be broader than a simple screening measure in order to allow for early identification of subtle vulnerabilities that may become more visible later in life when they are typically expected to develop or emerge. Using screeners that are invariably less sensitive than formal measures may overlook important symptoms particularly for the meta-cognitive aspects of executive functions and mathematics, which are known to be areas of weakness in this population.[4] These steps would achieve better clinical and follow-up care. In addition, this approach would contribute high quality research data thorough higher participation rates, more representative data, reduction in missing data and consistent neuropsychological measures across settings.

A limited number of studies to date have explored neuropsychological outcomes beyond intellectual and academic ability including attention, executive functions, memory, and language skills.[4] This approach needs to be adopted universally, as often children with chronic illness will show more specific neuropsychological deficits while demonstrating relatively intact intellectual ability.[52, 57, 58] A better understanding of the nature and degree of difficulties in these more specific neuropsychological domains will help guide future screening and intervention practices. Interventions could include cognitive remediation programs, targeted academic programs in numeracy, special educational settings, medical intervention for disorders such as ADHD, and/or parent training/support for psychosocial functioning.

The current thesis was the first to collect data from multiple sources, incorporating both performance-based standardised neuropsychological testing, as well as seeking feedback

from parents, children and teachers on each child's day-to-day functioning. By evaluating functioning from various perspectives, the thesis assessed the validity of the results by exploring whether the overarching findings were convergent. It concluded that children have particular functional difficulties in areas of attention, the metacognitive aspects of executive functions and psychosocial quality of life. Similar studies typically utilised either standalone informant questionnaires or combined a single-informant questionnaire (usually parent-report) with performance-based measures. Only one previous study had sought feedback from teachers, despite teachers having a particularly ecologically valid perspective of a child's day-to-day functioning.[10, 59-61] It is hoped that future studies incorporate this multi-informant, multi-modal collection of data to better encapsulate the long-term outcomes of children post-liver transplant. A more comprehensive assessment such as that proposed above could, in turn, be used to more accurately inform policy makers and allocation models.

Chapter 4 provided the first comprehensive systematic review and meta-analysis of intellectual and academic outcomes of paediatric liver transplant recipients. The findings were particularly noteworthy in that they strongly supported dividing analyses by primary diagnosis, due to the demonstrated heterogeneity inherent in the paediatric liver transplant population.

The systematic review and meta-analysis demonstrated that prospective designs with clear aims and hypotheses produced studies of stronger clarity. Utilising standardised neurocognitive batteries as part of usual follow-up care would fulfil the requirements of prospective study design alongside ensuring high quality long-term clinical care. For example, assessing the mathematical ability of children post-liver transplant as part of standard follow-up care would: 1) allow for early identification of children at risk of learning difficulties around mathematics and hence allow them to receive early intervention and support;[52] 2) allow the field to track mathematical ability in the population and determine if outcomes are changing;

3) identify possible disease-modifying factors that can be targeted; and 4) allow for evaluation of the efficacy of interventions applied to this population. The consistent finding of mathematical vulnerabilities in children following liver transplant suggests that clinicians should proactively employ interventions for mathematics for these children rather than responding to deficits once they emerge. The domains of attention and the metacognitive aspects of executive function are also vulnerable and require universal screening.[8-10, 29]

3.4 | Value of theory-driven research

Another strength of the thesis was that the regression analyses employed in Chapters 2 and 2-supplementary were grounded in theoretical models, rather than utilising entirely data-driven approaches. While early exploratory studies had invariably used data-driven approaches, the current state of the research meant that theory-driven approaches were indicated to prevent type I error and to test hypotheses surrounding the underlying mechanisms and disease-modifiable factors of paediatric chronic liver disease. For example, days on waitlist was tested as a predictor, as it seemed a plausible concept that the longer a child is ill with end-stage liver disease, the poorer their outcomes. Additionally, having this hypothesis supported would provide a practical factor to target so as to improve long-term outcomes. Attempts were not made to predict other outcomes from medical and transplant-related factors so as to limit the risk of type I error due to the unavoidably small sample size.

This theory-driven approach also led to the consideration of a potential interaction effect. The thesis highlighted, albeit in an exploratory context, that the deleterious effect of time on waitlist was most pronounced in children with biliary atresia who had the poorest functioning livers. The presence of an interaction effect appears logical, considering that the disease and transplant experience is not a straightforward affair and the complexity inherent in the process may be better accounted for by an interaction effect. It is hoped that this

finding prompts other researchers to explore this interaction effect in both previously published and future studies. Furthermore, it may be worthwhile to consider other possible interactions relevant for long-term outcomes, such as whether the relationship between disease severity and cognitive outcomes varies as a function of age at transplant.

3.5 | Neuroradiological exploration in a novel population

The most novel aspect of the current thesis was the neuroradiological evaluation of children post-liver transplant whom, despite being considered medically stable, showed brain pathology. This pathology is thought to be indicative of higher blood manganese levels and may suggest screening for this as part of follow-up care. The thesis was also the first to introduce volumetric analyses to link neurological development with both transplant-related factors and long-term outcomes. Greater participation was anticipated for this component of the thesis. However, only a limited number of families volunteered and these children represented a wide range of chronic liver disorders, which restricted the ability to make firm conclusions about this more heterogenous group.

The intention behind incorporating neuroradiological investigations was twofold. First, to explore whether medically stable children showed any evidence of brain pathology following liver transplantation. Second, it was hypothesised that the associations that have been found between medical/transplant factors and long-term outcomes are explained by neurological changes. For example, the reason that days on waitlist predicts cognitive outcomes may be because the longer a child waits on the waitlist, the longer they are exposed to the neurotoxic effects of liver disease which then has a deleterious impact on their neurodevelopment. It is proposed that if this deleterious impact could be quantified, such as by measuring brain volume, cortical thickness or white matter integrity, then these measurements would predict the long-term cognitive outcomes.

It is hoped that these early, promising results will act as a catalyst in the field and prompt other research teams to explore this avenue. Future prospective studies could explore neuroradiological outcomes in medically stable paediatric liver transplant recipients and include age-matched healthy controls, other paediatric solid organ transplant recipients and children with chronic disease, if resources permit. This would highlight changes that are specific to liver disease and associated transplantation, as opposed to changes that may be attributable to the general transplant process or the chronic disease experience.

Additional neuroradiological methods would be recommended for future investigations. A proposed method, which was unsuccessful in the current thesis due to technical issues, is the exploration of connectivity and white matter integrity through Diffusion Tensor Imaging (DTI). This technique provides data beyond what is captured by T1 MRI methods which is limited to measuring volumetrics and more overt pathology. DTI would allow for examination of the hypothesis that the vulnerabilities observed in the paediatric liver transplant population, particularly in regards to working memory, attention, executive functions and mathematics, may be a consequence of the liver disease process impacting the brain more globally through disruption of white matter development and integrity. This disruption may only be observable at the group level rather than individual level, and hence larger sample sizes would be required. The link between white matter and these neurocognitive abilities has been demonstrated in other clinical groups.[62-67] It is plausible that the global effects of liver disease would have direct impacts on white matter, particularly in the vulnerable developing brain. Indeed, results from the MRI case series in the current thesis was suggestive of lower intellectual abilities in children with greater volume of T1 white matter hypointensity.

Similarly, continued use of Susceptibility Weighted Imaging (SWI) may be helpful in identifying evidence of possible white matter changes or disease in paediatric liver transplant

recipients. This is an important area of exploration as liver disease is a risk for cerebrovascular events. These cerebrovascular events or changes (which could be subtle) could be occurring in very young and ill infants who may not show any outward clinical symptoms at the time and could be missed by clinicians.[68-71] As such, quantifying the presence of any white matter changes may provide another disease variable that could more directly predict and explain long-term neurocognitive outcomes.

3.6 | Capturing heterogeneity through big data: overcoming sampling challenges

The current thesis was particularly successful in achieving a high rate of participation from eligible children which allowed for greater certainty in the representativeness of the results. However, despite this success in recruitment, the sample size and size of specific diagnostic categories within chronic liver disorders was small. This is inherent to all research exploring rare or uncommon disorders.[72-75] A key recommendation of the thesis is the establishment of multi-centre collaboration such as the Studies of Pediatric Liver Transplantation (SPLIT) registry based across Canada and the US. This approach is recommended so as to increase both the total sample size of studies and reduce the confounding impact of site-specific factors on long-term outcomes.[52] In particular, international collaborations are recommended as these would also reduce the impact of jurisdiction on outcomes.

As a further suggestion, the research community could benefit from the establishment of an online database where anonymous data on paediatric liver transplant recipients can be uploaded, and then accessed by registered users to explore a range of research questions. This would allow for large scale analyses including more complex models, not encumbered by risk of type II error and would follow the rare diseases model of collaboration.[72-75] Procuring larger samples through online databases and/or multi-centre methods would also overcome

the challenges of meeting the underlying assumptions of statistical models (such as normality or homoscedasticity) and mitigate the influence of outliers which is common in small samples such as the present thesis and the majority of research in the field.

Multi-centre and/or online databases may also be more effective at capturing the impact of specific predictors of the transplant experience; for example, the role of time since transplant. Currently, the majority of empirical studies, including the current thesis, combine all children who are considered medically stable including children who are 12 months post-transplant and those who are greater than 10 years. It can be argued that these children represent distinct groups and study designs and/or analyses should stratify based on this variable.

Attempts to partition the effect through statistical analysis have limited validity due to issues of low power and small sample sizes endemic to the research area. This is a significant limitation, including in the current thesis. Online databases would not only allow for discrete investigations of children in a restricted period in their transplant journey, such as has been achieved by the SPLIT studies where participants were aged between 6 and 7, but would also allow for robust statistical analyses.

A further limitation of the current thesis, and indeed the general field of research that would be overcome by the use of multi-centre studies and/or online databases is the practice of conducting statistical analyses within one sample without correcting for multiple comparisons. However, it is also important to note that due to the small sample sizes inherent to the research within rare or uncommon disorders, corrections for multiple comparisons may constitute conservative data management and risk inflation of type II error. As such, the current thesis attempted to address this by two main approaches. First, the data for all

analyses were provided uncorrected, including for non-significant findings. This enabled the reader to evaluate the results for themselves and apply their own corrections if deemed necessary. It would also allow for future meta-analyses to include both significant and non-significant findings. Second, effect sizes (including Z value, Cohen's d, Hedge's g, Pearson's r, Spearman's r, standardised ß and unstandardised B, and R^2) were consistently provided throughout the thesis, regardless of whether findings were significant or not. Arguably, interpretation of effect sizes is more appropriate rather than an overemphasis on statistical significance, given the small sample sizes. In addition, the thesis included measures of clinical significance; for example, by reporting the proportion of participants scoring in the clinical range on a number of outcomes such as the percentage in the range for intellectual disability, or the number of children who met criteria for specific neurodevelopmental disorders such as ADHD.

The utilisation of an online database would also remove the need for synthesis of published works through meta-analyses and allow for more nuanced analyses, as researchers would have access to all data collected across jurisdictions and sites. An online database approach would make the inclusion and evaluation of the rarer conditions requiring liver transplantation (such as cryptogenic cirrhosis, autoimmune hepatitis or some of the metabolic disorders) more practical.[38] Currently, most studies that include different diagnoses are forced to combine and analyse the diagnoses together.

Indeed, it would be ideal for studies like the current thesis to include additional diagnostic categories such as acute liver failure and metabolic disorder alongside the chronic liver disease group. However, these diagnoses are not typically highly represented in single-centre liver transplant units. This would limit the ability to conduct comparisons across diagnostic groups or to explore primary diagnosis as a predictive factor in regression models.

As such, it was decided to not include these additional disorders in the current thesis. Furthermore, in light of the time-limited nature of the thesis, it was felt that attempting to recruit from other diagnostic categories would mean less resources and focus would be put on achieving the high participation rate that was achieved for the chronic liver group.

Continuing on a similar theme, studies would benefit from comparing the paediatric liver transplant population against other solid organ transplant populations, as has been argued for by Sorensen et al.[52] This would allow for delineation of liver specific impacts from general transplant effects. Furthermore, liver disease is unique as it does not have a dialysis-like maintenance strategy. Preferably, any online database would also include other transplant groups. Additional inclusion and comparison with other chronic illness groups, such as children with cystic fibrosis or epilepsy, could further discriminate between the impacts of chronic illness from the more specific effects of liver disease and transplantation.[76, 77] Comparison to other transplant or chronic illness groups could also include a healthy control group.

Longitudinal study designs are a necessary next step for fully understanding the disease and transplant experience.[10, 52] This would also be made more feasible from the establishment of an online database. Longitudinal studies would allow for tracking of the developmental trajectory and to better highlight areas of vulnerability. Longitudinal studies can also better determine the presence of cohort effects or ascertain whether differences in outcomes may be attributable to intervention strategies implemented between phases. For example, Sorensen et al., who conducted the only post-liver transplant longitudinal study to date, demonstrated that while children showed lower reading abilities compared to the general population when aged between 5-7 years, their reading abilities improved to fall in line with the general population at their 2 year follow-up review.[10]

Longitudinal studies utilising a pre-post design face a significant barrier. The majority of childhood liver transplant recipients have a congenital liver disorder that requires transplantation within the first few years of life. This means that reliable standardised testing is not practical due to their young age, and this is exacerbated by the fact that many of them are severely ill and cannot effectively engage in testing process relative to their same-age peers. Only a minority of liver disorders allow for children to be transplanted in later childhood (such as acute liver failure, autoimmune hepatitis, metabolic disorders or in cases where a semi-successful Kasai procedure allowed a child to grow older before needing a transplant). Therefore, circumstances mean that it is difficult to recruit enough transplant candidates within a single centre who are old enough to satisfactorily participate in any pre-post study design. However, the online database solution once again would overcome this barrier enabling enough older candidates to be collected worldwide to allow for meaningful and robust pre-post analyses to be conducted. To date, the only pre-post liver transplant studies were conducted in earlier periods where transplantation was less common and children waited longer or were older when they underwent their transplant.[78, 79]

4 | Recommendations for future directions

The final recommendations stemming from the thesis can be seen in Figure 2.

Clinical Recommendations

- Adopt regular neuropsychological follow-up as part of usual care utilising a minimum standardised battery which assesses beyond IQ and academic outcomes
- Proactively implement interventions for known areas of vulnerability including mathematics, attention, working memory, metacognitive aspects of executive functions, and psychosocial quality of life
- Explore brain MRI as part of routine follow-up care as well as measuring blood manganese levels

Research Recommendations

- Establish an online database across jurisdictions
- Pursue prospective design
- Explore longitudinal analyses
- Utilise data from standardised neuropsychological follow-up in the clinical setting for research
- Explore predictive models using theory driven analyses
- Differentiate by primary diagnosis in either study design or analyses
- Compare outcomes against other organ transplant and chronic illness groups
- Further explore link between neurological development and medical/transplant factors and cognitive outcomes

Policy Recommendations

- Include factors that predict better cognitive outcomes in allocation models such as time on waitlist
- Further prioritise paediatric candidates in allocation models
- Actively promote living related liver transplant and split liver transplant
- Adopt existing policies from international jurisdictions that have been shown to increase organ donation such as opt-out donation policies, improve organisational systems and promote public support for organ donation

FIGURE 2 Summary of clinical, research and policy recommendations.

5 | Conclusion

Children with chronic liver disease who undergo paediatric transplantation need ongoing support to promote their neurocognitive development, educational attainment, psychosocial functioning, and quality of life. Findings from the current thesis support further development of tailored, proactive care that includes comprehensive long-term neuropsychological follow up as a standard protocol; the implementation of early interventions when indicated, including preventative interventions for known vulnerabilities such as mathematics or working memory; and consideration of neuroradiological investigations in long-term follow-up.

The research findings of the thesis suggest that transplantation policies need to be reviewed to improve the long-term neuropsychological outcomes of children following liver transplantation for chronic liver disease. Specifically, the finding that longer waiting time predicts poorer neuropsychological outcomes in children with biliary atresia has significant real-world implications. Policy makers should consider including predictive factors, such as time on waitlist, in organ allocation models to improve the long-term outcomes of these children. Furthermore, policy makers need to reduce the time that children spend on the waitlist for a liver transplant. Ultimately, improving outcomes in this group must involve policy changes that prioritise paediatric candidates further; reconsider the utility of living related liver transplant and split liver procedures; promote organ donation within the community; and consider larger-scale changes to the infrastructure around organ donation and transplantation more broadly.

Research in this area should consider common methodological challenges, including difficulties achieving appropriate sample size as is inherent in uncommon disorders; collapsing across diagnostic groups; atheoretical analyses; and underrepresentation of the illness

experience of children outside North America and Western Europe. To overcome the research field's shortcomings, there is a need for increased collaboration across jurisdictions (including the use of online databases). Furthermore, there is a need for comparison with other transplant and chronic illness groups to tease apart liver and transplant specific effects from broader chronic illness processes. Researchers should additionally remember that paediatric liver disease and transplantation experience is heterogeneous, and it is crucial to explore diagnostic groups separately. Longitudinal, prospective designs are also best-placed to capture the experience of these patients and the field should move more towards theory-driven analyses with predictive models. Prospective designs may also facilitate larger samples. Finally, it is recommended that further neuroimaging studies are conducted so as to explore the link between liver disease, the developing brain, and associated impacts on long-term neuropsychological outcomes. Together, these approaches will continue to inform policy with the goal of improving long-term outcomes for children following liver transplantation.

REFERENCES

1. Adebäck P, Nemeth A, Fischler B. Cognitive and emotional outcome after pediatric liver transplantation. Pediatric Transplantation. 2003;7(5):385-9.

2. Gilmour S, Adkins R, Liddell GA, Jhangri G, Robertson CM. Assessment of psychoeducational outcomes after pediatric liver transplant. American Journal of Transplantation. 2009;9(2):294-300.

3. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Cognitive and academic outcomes after pediatric liver transplantation: Functional outcomes group (FOG) results. American Journal of Transplantation. 2011;11(2):303-11.

4. Rodijk LH, Den Heijer AE, Hulscher JBF, Verkade HJ, De Kleine RHJ, Bruggink JLM. Neurodevelopmental outcomes in children with liver diseases: A systematic review. Journal of Pediatric Gastroenterology and Nutrition. 2018;67(2):157-68.

5. Kaller T, Langguth N, Petermann F, Ganschow R, Nashan B, Schulz KH. Cognitive performance in pediatric liver transplant recipients. American Journal of Transplantation. 2013;13(11):2956-65.

6. Haavisto A, Korkman M, Törmänen J, Holmberg C, Jalanko H, Qvist E. Visuospatial impairment in children and adolescents after liver transplantation. Pediatric Transplantation. 2011;15(2):184-92.

7. Cushman GK, Stolz MG, Blount RL, Reed B. Executive Functioning in Pediatric Solid Organ Transplant Recipients: A Meta-Analytic Review. Transplantation. 2019.

8. Gutiérrez-Colina AM, Eaton CK, Lee JL, Reed-Knight B, Loiselle K, Mee LL, et al. Executive functioning, barriers to adherence, and nonadherence in adolescent and young adult transplant recipients. Journal of Pediatric Psychology. 2016;41(7):759-67.

9. Kaller T, Langguth N, Ganschow R, Nashan B, Schulz KH. Attention and executive functioning deficits in liver-transplanted children. Transplantation. 2010;90(12):1567-73.

10. Sorensen LG, Neighbors K, Martz K, Zelko F, Bucuvalas JC, Alonso EM. Longitudinal study of cognitive and academic outcomes after pediatric liver transplantation. Journal of Pediatrics. 2014;165(1):65-72.e2.

11. Alonso EM, Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, et al. Cross-Sectional Analysis of Health-Related Quality of Life in Pediatric Liver Transplant Recipients. Journal of Pediatrics. 2010;156(2):270-6.e1.

12. Petersen I, Noelle J, Buchholz A, Kroencke S, Daseking M, Grabhorn E. Fatigue in pediatric liver transplant recipients and its impact on their quality of life. Pediatric Transplantation. 2019;23(1).

13. Weissberg-Benchell J, Zielinski TE, Rodgers S, Greenley RN, Askenazi D, Goldstein SL, et al. Pediatric health-related quality of life: Feasibility, reliability and validity of the PedsQL™ transplant module. American Journal of Transplantation. 2010;10(7):1677-85.

14. Maurice-Stam H, Nijhof SL, Monninkhof AS, Heymans HSA, Grootenhuis MA. Review about the impact of growing up with a chronic disease showed delays achieving psychosocial milestones. Acta Paediatrica, International Journal of Paediatrics. 2019.

15. Miserachs M, Parmar A, Bakula A, Hierro L, D'Antiga L, Goldschmidt I, et al. Health-related quality of life in pre-adolescent liver transplant recipients with biliary atresia: A cross-sectional study. Clinics and Research in Hepatology and Gastroenterology. 2019;43(4):427-35.

16. Barron TF, Devenyi AG, Mamourian AC. Symptomatic manganese neurotoxicity in a patient with chronic liver disease: Correlation of clinical symptoms with MRI findings. Pediatric Neurology. 1994;10(2):145-8.

17. Devenyi AG, Barron TF, Mamourian AC. Dystonia, hyperintense basal ganglia, and high whole blood manganese levels in Alagille's syndrome. Gastroenterology. 1994;106(4):1068-71.

18. Ikeda S, Yamaguchi Y, Sera Y, Ohshiro H, Uchino S, Yamashita Y, et al. Manganese deposition in the globus pallidus in patients with biliary atresia. Transplantation. 2000;69(11):2339-43.

19. Kaller T, Boeck A, Sander K, Richterich A, Burdelski M, Ganschow R, et al. Cognitive abilities, behaviour and quality of life in children after liver transplantation. Pediatric Transplantation. 2010;14(4):496-503.

20. Talcott JB, Beath SV, Patel T, Griffiths G, Kelly DA. Long-term Effects of Cholestatic Liver Disease in Childhood on Neuropsychological Outcomes and Neurochemistry. J Pediatr Gastroenterol Nutr. 2019;69(2):145-51.

21. Robertson CMT, Dinu IA, Joffe AR, Alton GY, Yap JYK, Asthana S, et al. Neurocognitive outcomes at kindergarten entry after liver transplantation at <3 yr of age. Pediatric Transplantation. 2013;17(7):621-30.

22. Almaas R, Jensen U, Loennecken MC, Tveter AT, Sanengen T, Scholz T, et al. Impaired motor competence in children with transplanted liver. Journal of Pediatric Gastroenterology and Nutrition. 2015;60(6):723-8.

23. Alonso EM, Martz K, Wang D, Yi MS, Neighbors K, Varni JW, et al. Factors predicting health-related quality of life in pediatric liver transplant recipients in the functional outcomes group. Pediatric Transplantation. 2013;17(7):605-11.

24. Gilmour S, Sorensen LG, Anand R, Yin W, Alonso EM. School outcomes in children registered in the Studies for Pediatric Liver Transplant (SPLIT) consortium. Liver Transplantation. 2010;16(9):1041-8.

25. Goldschmidt I, van Dick R, Jacobi C, Junge N, Pfister E, Richter N, et al. Impact of Immunosuppression on Executive Functioning After Pediatric Liver Transplantation: An Observational Cohort Study. Journal of pediatric gastroenterology and nutrition. 2019;68(4):480-7.

26. Gritti A, Di Sarno AM, Comito M, De Vincenzo A, De Paola P, Vajro P. Psychological impact of liver transplantation on children's inner worlds. Pediatric Transplantation. 2001;5(1):37-43.

27. Limbers CA, Neighbors K, Martz K, Bucuvalas JC, Webb T, Varni JW, et al. Health-related quality of life in pediatric liver transplant recipients compared with other chronic disease groups. Pediatric Transplantation. 2011;15(3):245-53.

28. Lee YJ, Yum MS, Kim EH, Choi HW, Oh SH, Kim DY, et al. Risk factors for neurological complications and their correlation with survival following pediatric liver transplantation. Pediatric Transplantation. 2014;18(2):177-84.

29. Ng VL, Fecteau A, Shepherd R, Magee J, Bucuvalas J, Alonso E, et al. Outcomes of 5-year survivors of pediatric liver transplantation: Report on 461 children from a north american multicenter registry. Pediatrics. 2008;122(6):e1128-e35.

30. Posfay-Barbe KM, Barbe RP, Wetterwald R, Belli DC, McLin VA. Parental functioning improves the developmental quotient of pediatric liver transplant recipients. Pediatric Transplantation. 2013;17(4):355-61.

31. Törnqvist J, Van Broeck N, Finkenauer C, Rosati R, Schwering KL, Hayez JY, et al. Long-term psychosocial adjustment following pediatric liver transplantation. Pediatric Transplantation. 1999;3(2):115-25.

32. Zitelli BJ, Miller JW, Carlton Gartner Jr J, Malatack JJ, Urbach AH, Belle SH, et al. Changes in life-style after liver transplantation. Pediatrics. 1988;82(2):173-80.

33. Parmar A, Vandriel SM, Ng VL. Health-related quality of life after pediatric liver transplantation: A systematic review. Liver Transplantation. 2017;23(3):361-74.

34. Schulz KH, Wein C, Boeck A, Rogiers X, Burdelski M. Cognitive performance of children who have undergone liver transplantation. Transplantation. 2003;75(8):1236-40.

35. Kaller T, Schulz KH, Sander K, Boeck A, Rogiers X, Burdelski M. Cognitive abilities in children after liver transplantation. Transplantation. 2005;79(9):1252-6.

36. Howell DC. Statistical methods for psychology: Cengage Learning; 2012.

37. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, et al. OPTN/SRTR 2017 Annual Data Report: Liver. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2019;19:184-283.

38. Lyncyh SV, Balderson GA, editors. ANZLT Registry Report 2017. Brisbane, QLD, Australia: Australia and New Zealand Liver Transplant Registry; 2017.

39. Squires JE, Mazariegos GV. Liver Allograft Donor Selection and Allocation. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 455-63.

40. Matesanz R, Domínguez-Gil B, Coll E, Mahíllo B, Marazuela R. How Spain Reached 40 Deceased Organ Donors per Million Population. American Journal of Transplantation. 2017;17(6):1447-54.

41. Shepherd L, O'Carroll RE, Ferguson E. An international comparison of deceased and living organ donation/transplant rates in opt-in and opt-out systems: A panel study. BMC Medicine. 2014;12(1).

42. Witjes M, Jansen NE, Van Der Hoeven JG, Abdo WF. Interventions aimed at healthcare professionals to increase the number of organ donors: A systematic review. Critical Care. 2019;23(1).

43. Busuttil AA, Goss JA, Seu P, Dulkanchainun TS, Yanni GS, McDiarmid SV, et al. The role of orthotopic liver transplantation in the treatment of ornithine transcarbamylase deficiency. Liver Transplantation and Surgery. 1998;4(5):350-4.

44. Colledan M, Camagni S. Surgical Techniques. In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 465-86.

45. Kasahara M, Sakamoto S, Fukuda A. Pediatric Living Donor Liver Transplantation In: D'Antiga L, editor. Pediatric Hepatology and Liver Transplantation. Cham: Springer International Publishing; 2019. p. 487-514.

46. Kehar M, Parekh RS, Stunguris J, De Angelis M, Van Roestel K, Ghanekar A, et al. Superior Outcomes and Reduced Wait Times in Pediatric Recipients of Living Donor Liver Transplantation. Transplantation Direct. 2019;5(3).

47. Perito ER, Roll G, Dodge JL, Rhee S, Roberts JP. Split Liver Transplantation and Pediatric Waitlist Mortality in the United States: Potential for Improvement. Transplantation. 2019;103(3):552-7.

48. OECD. PISA 2015 Results (Volume I)2016.

49. DuBay DA, MacLennan PA, Reed RD, Shelton BA, Redden DT, Fouad M, et al. Insurance Type and Solid Organ Transplantation Outcomes: A Historical Perspective on How Medicaid Expansion Might Impact Transplantation Outcomes. Journal of the American College of Surgeons. 2016;223(4):611-20.e4.

50. International registry in organ donation and transplantation: Preliminary numbers 2018. International Registry in Organ Donation and Transplantation; 2019.

51. Clinical Guidelines for Organ Transplantation from Deceased Donors. 2019.

52. Sorensen LG. Pediatric solid organ transplantation and end stage disease: A slow journey towards understanding neurocognitive outcomes and their ramifications for clinical care. Pediatric Transplantation. 2015;19(2):136-8.

53. Ylvisaker M, Adelson PD, Braga LW, Burnett SM, Glang A, Feeney T, et al. Rehabilitation and ongoing support after pediatric TBI: Twenty years of progress. Journal of Head Trauma Rehabilitation. 2005;20(1):95-109.

54. Ross GS, Zelko F, Klein-Gitelman M, Levy DM, Muscal E, Schanberg LE, et al. A proposed framework to standardize the neurocognitive assessment of patients with pediatric systemic lupus erythematosus. Arthritis Care and Research. 2010;62(7):1029-33.

55. Babikian T, Merkley T, Savage RC, Giza CC, Levin H. Chronic Aspects of Pediatric Traumatic Brain Injury: Review of the Literature. Journal of neurotrauma. 2015;32(23):1849-60.

56. Thomas S, Reynolds D, Morrall MCHJ, Limond J, Chevignard M, Calaminus G, et al. The European Society of Paediatric Oncology Ependymoma-II program Core-Plus model: Development and initial implementation of a cognitive test protocol for an international brain tumour trial. European Journal of Paediatric Neurology. 2019;23(4):560-70.

57. Araujo GC, Antonini TN, Anderson V, Vannatta KA, Salley CG, Bigler ED, et al. Profiles of Executive Function Across Children with Distinct Brain Disorders: Traumatic Brain Injury, Stroke, and Brain Tumor. Journal of the International Neuropsychological Society. 2017;23(7):529-38.

58. Van Der Plas E, Erdman L, Nieman BJ, Weksberg R, Butcher DT, O'connor DL, et al. Characterizing neurocognitive late effects in childhood leukemia survivors using a combination of neuropsychological and cognitive neuroscience measures. Child Neuropsychology. 2018;24(8):999-1014.

59. Achenbach TM. As others see Us clinical and research implications of cross-informant correlations for psychopathology. Current Directions in Psychological Science. 2006;15(2):94-8.

60. Cho SC, Kim HW, Kim BN, Shin MS, Yoo HJ, Kim JW, et al. Are teacher ratings and parent ratings differently associated with children's intelligence and cognitive performance? Psychiatry Investigation. 2011;8(1):15-21.

61. Kieffer V, Longaud A, Callu D, Laroussinie F, Viguier D, Grill J, et al. Teachers' report of learning and behavioural difficulties in children treated for cerebellar tumours. Brain Injury. 2012;26(7-8):1014-20.

62. Gropman AL, Gertz B, Shattuck K, Kahn IL, Seltzer R, Krivitsky L, et al. Diffusion tensor imaging detects areas of abnormal white matter microstructure in patients with partial ornithine transcarbamylase deficiency. American Journal of Neuroradiology. 2010;31(9):1719-23.

63. Klingberg T, Vaidya CJ, Gabrieli JDE, Moseley ME, Hedehus M. Myelination and organization of the frontal white matter in children: A diffusion tensor MRI study. NeuroReport. 1999;10(13):2817-21.

64. Krogsrud SK, Fjell AM, Tamnes CK, Grydeland H, Due-Tønnessen P, Bjørnerud A, et al. Development of white matter microstructure in relation to verbal and visuospatial working memory—A longitudinal study. PLoS ONE. 2018;13(4).

65. Van Beek L, Vanderauwera J, Ghesquière P, Lagae L, De Smedt B. Longitudinal changes in mathematical abilities and white matter following paediatric mild traumatic brain injury. Brain Injury. 2015;29(13-14):1701-10.

66. Wilde EA, Newsome MR, Bigler ED, Pertab J, Merkley TL, Hanten G, et al. Brain imaging correlates of verbal working memory in children following traumatic brain injury. International Journal of Psychophysiology. 2011;82(1):86-96.

67. Wozniak JR, Krach L, Ward E, Mueller BA, Muetzel R, Schnoebelen S, et al. Neurocognitive and neuroimaging correlates of pediatric traumatic brain injury: A diffusion tensor imaging (DTI) study. Archives of Clinical Neuropsychology. 2007;22(5):555-68.

68. Amlie-Lefond C. Evaluation and Acute Management of Ischemic Stroke in Infants and Children. CONTINUUM Lifelong Learning in Neurology. 2018;24(1, Child Neurology):150-70.

69. Foerster BR, Conklin LS, Petrou M, Barker PB, Schwarz KB. Minimal hepatic encephalopathy in children: Evaluation with proton MR spectroscopy. American Journal of Neuroradiology. 2009;30(8):1610-3.

70. Kyrana E, Dhawan A. Minimal hepatic encephalopathy in children, uncommon or unrecognised? Time to act. Journal of Hepatology. 2017;66(3):478-9.

71. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al. Management of stroke in infants and children: A scientific statement from a special writing group of the american heart association stroke council and the council on cardiovascular disease in the young. Stroke. 2008;39(9):2644-91.

72. Feenstra I, Fang J, Koolen DA, Siezen A, Evans C, Winter RM, et al. European Cytogeneticists Association Register of Unbalanced Chromosome Aberrations (ECARUCA); an online database for rare chromosome abnormalities. European Journal of Medical Genetics. 2006;49(4):279-91.

73. Douglas I, Evans S, Rawlins MD, Smeeth L, Tabrizi SJ, Wexler NS. Juvenile Huntington's disease: A population-based study using the General Practice Research Database. BMJ Open. 2013;3(4).

74. Eades-Perner AM, Gathmann B, Knerr V, Guzman D, Veit D, Kindle G, et al. The European internet-based patient and research database for primary immunodeficiencies: Results 2004-06. Clinical and Experimental Immunology. 2007;147(2):306-12.

75. Akinsolu FT, Balczár E, Kovács N, Gáll T, Harangi M, Varga O. Developing a database for Rett syndrome research performed in the European Union: A resource for researchers and stakeholders. Child: Care, Health and Development. 2018;44(5):794-800.

76. Stewart SM, Hiltebeitel C, Nici J, Waller DA, Uauy R, Andrews WS. Neuropsychological outcome of pediatric liver transplantation. Pediatrics. 1991;87(3):367-76.

77. Krull KR, Fuchs C, Yurk H, Boone P, Alonso E. Neurocognitive outcome in pediatric liver transplant recipients. Pediatric Transplantation. 2003;7(2):111-8.

78. Kennard BD, Stewart SM, Phelan-McAuliffe D, Waller DA, Bannister M, Fioravani V, et al. Academic outcome in long-term survivors of pediatric liver transplantation. Journal of Developmental and Behavioral Pediatrics. 1999;20(1):17-23.

79. Stewart SM, Uauy R, Waller DA, Kennard BD, Benser M, Andrews WS. Mental and motor development, social competence, and growth one year after successful pediatric liver transplantation. The Journal of Pediatrics. 1989;114(4 PART 1):574-81.

APPENDICES

SUPPLEMENTARY TABLE 1 Multicollinearity analysis between predictive factors for cognitive outcomes

		Time Since Transplant		Average Parental Education		PELD Score at Transplant		Serum Bilirubin at Transplant		Days on Waitlist		PICU Length of Stay
Age at Transplant	$r_{Pearson}$	-.466		.015		-.486		-.368		.341		-.251
	P	.002	**	.928		.001	**	.019	*	.031	*	.118
Time Since Transplant	$r_{Pearson}$			-.230		.149		.337		-.122		.028
	P			.154		.358		.034	*	.455		.862
Average Parental Education	$r_{Pearson}$					-.022		.006		-.299		.083
	P					.893		.973		.061		.610
PELD Score at Transplant	$r_{Pearson}$							.600		-.302		.097
	P							<.001	**	.058		.551
Serum Bilirubin at Transplant	$r_{Pearson}$									-.198		.013
	P									.221		.934
Days on Waitlist	$r_{Pearson}$											-.140
	P											.389

PELD, Pediatric end-stage liver disease; PICU, pediatric intensive care unit.
N = 40.
*P < .05.
**P < .01.

Appendix B of this thesis has been removed as it may contain sensitive/confidential content

APPENDIX C

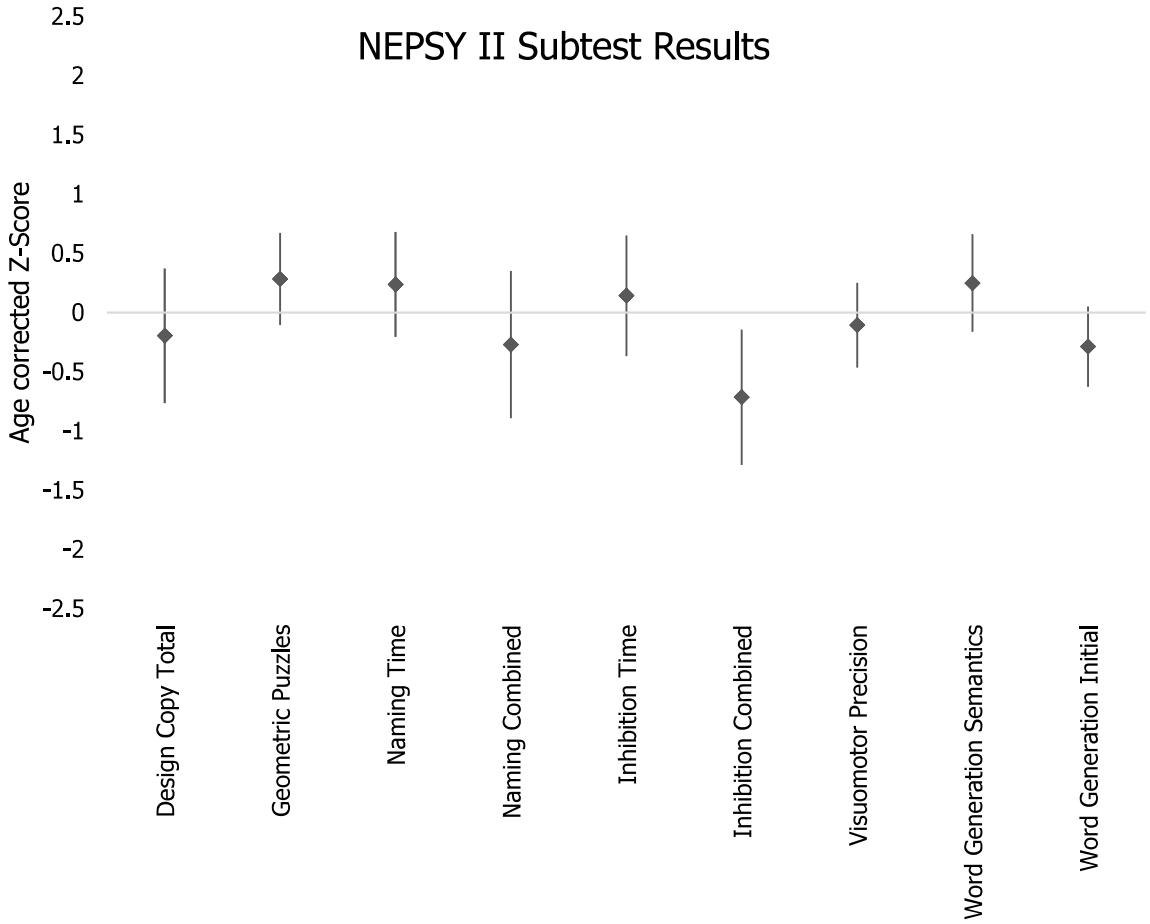


FIGURE 1 Descriptive results on the NEPSY II

Error bars represent 95% confidence interval

APPENDIX C

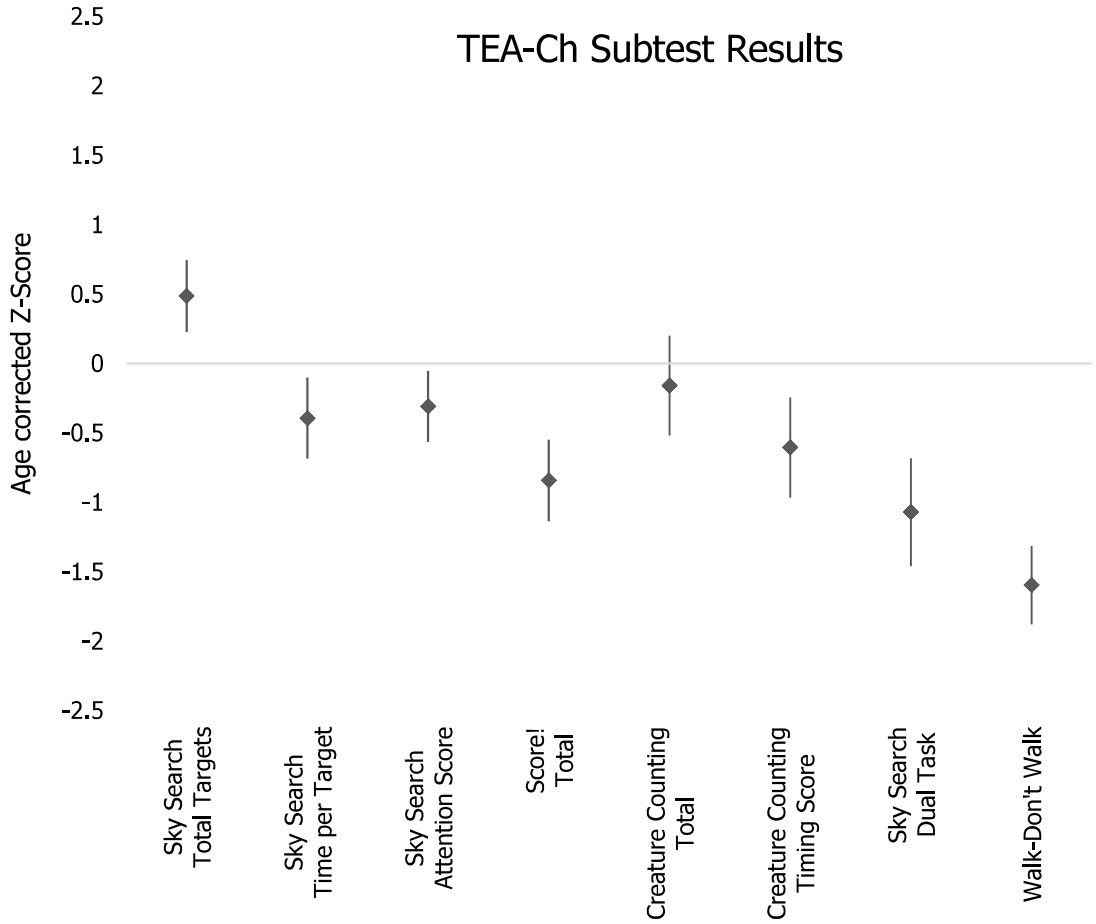


FIGURE 2 Descriptive results on the Test of Everyday Attention for Children (TEA-Ch)

Error bars represent 95% confidence interval

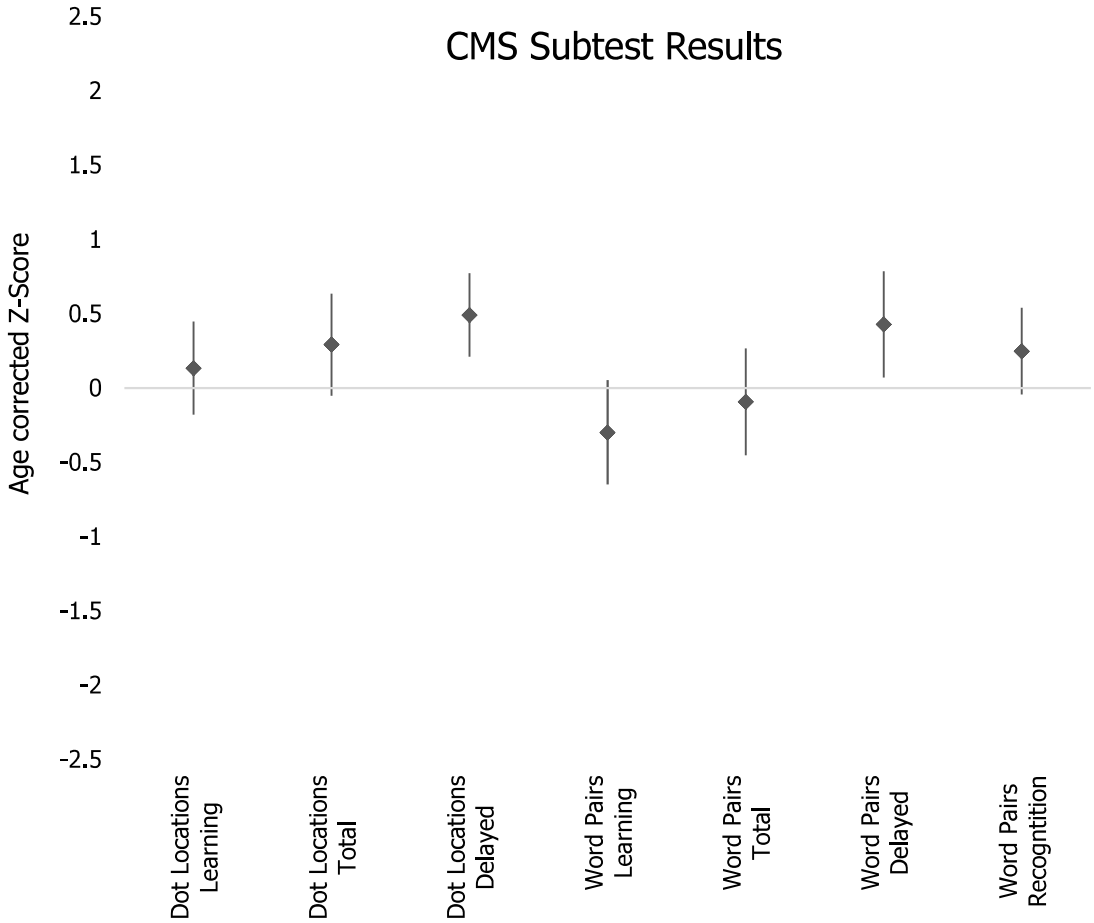


FIGURE 3 Descriptive results on the Children's Memory Scale (CMS)

Error bars represent 95% confidence interval

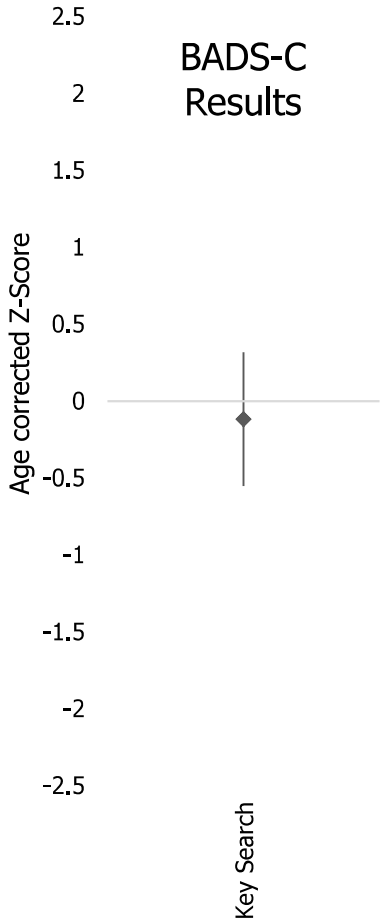


FIGURE 4 Descriptive results on the Behavioural Assessment of the Dysexecutive Syndrome in Children (BADS-C)

Error bars represent 95% confidence interval

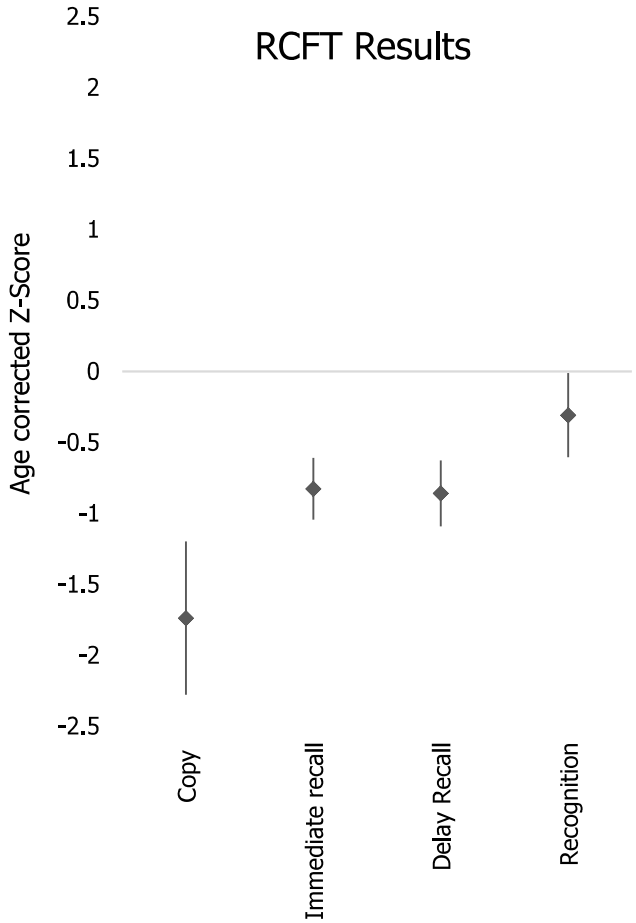


FIGURE 5 Descriptive results on the Rey Complex Figure (RCFT)

Error bars represent 95% confidence interval

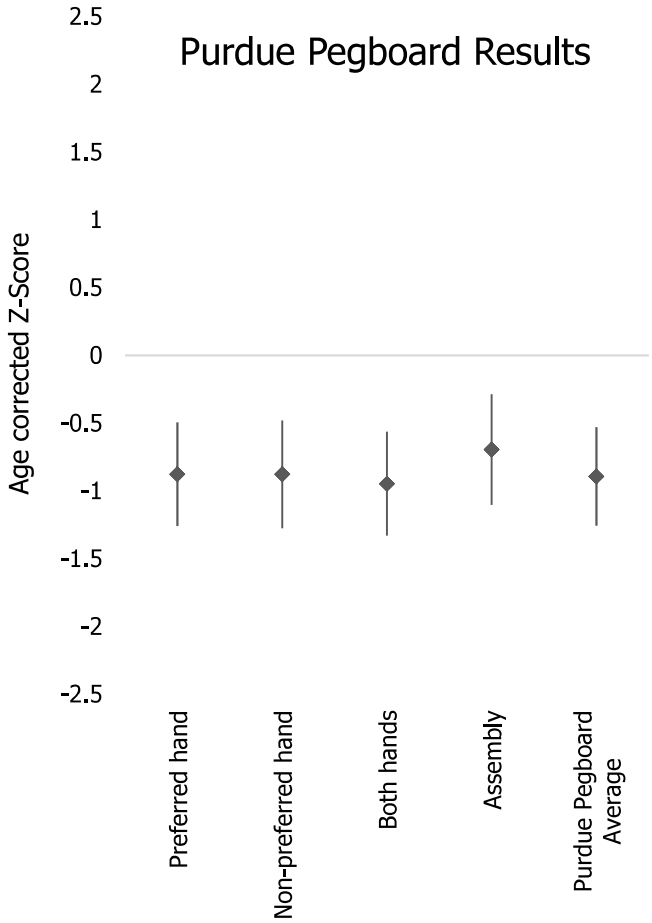


FIGURE 6 Descriptive results on the Purdue Pegboard

Error bars represent 95% confidence interval

APPENDIX C

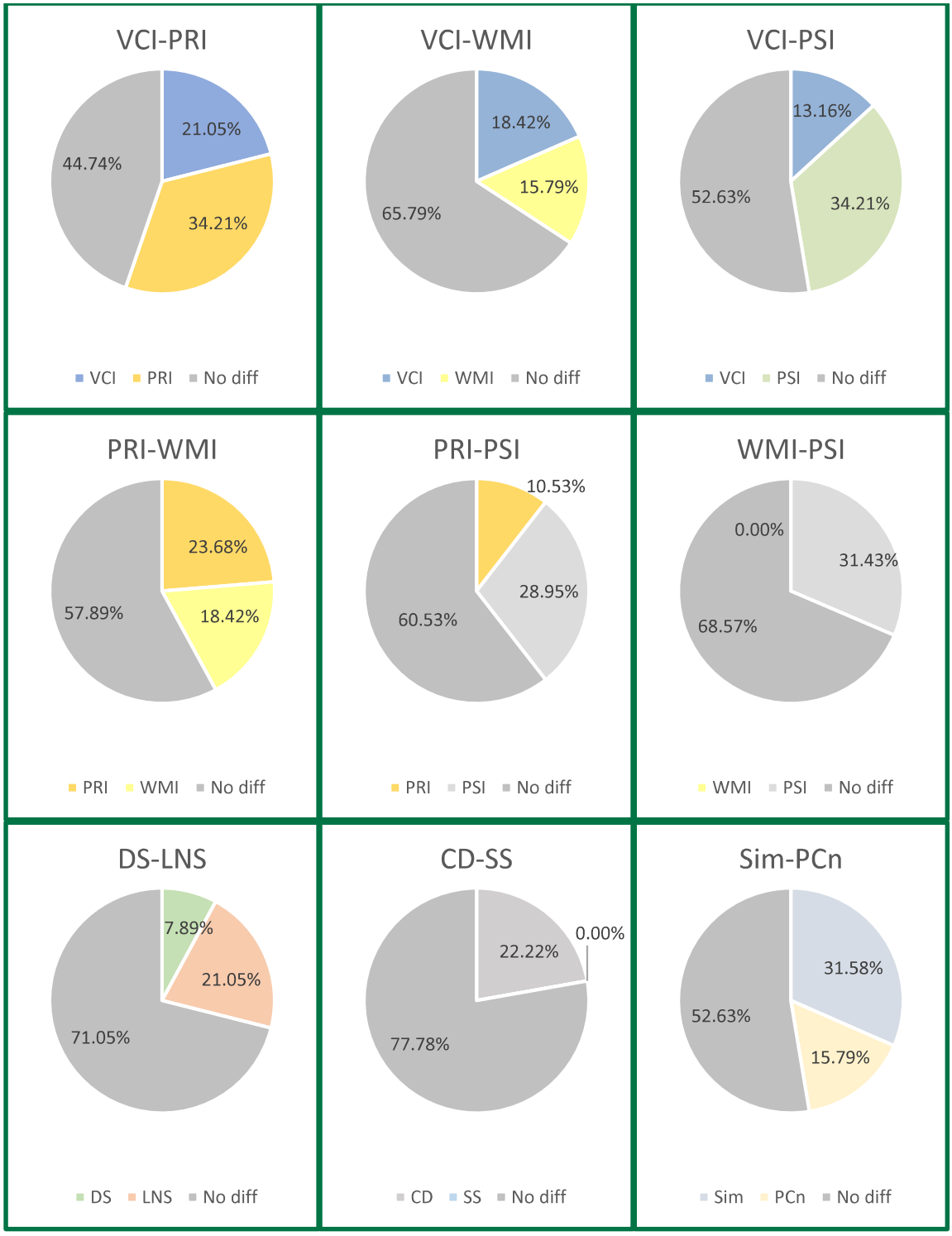


FIGURE 7 Frequency of significant difference between Indices and Subtests using the Index and Subtest level discrepancy analysis

Alpha set at $P = .05$

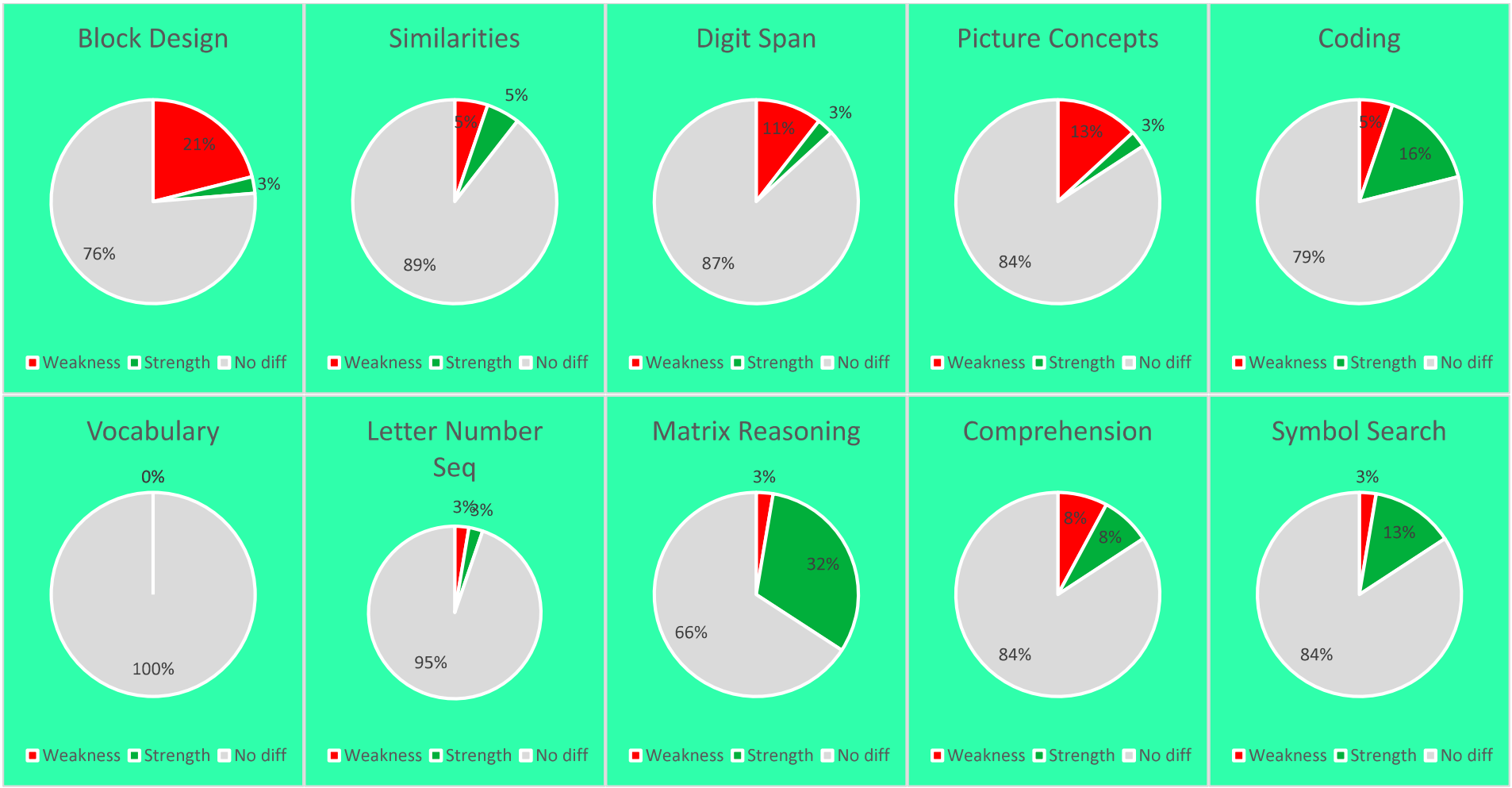


FIGURE 8 Descriptive results of rate with which a subtest was a relative strength or weakness

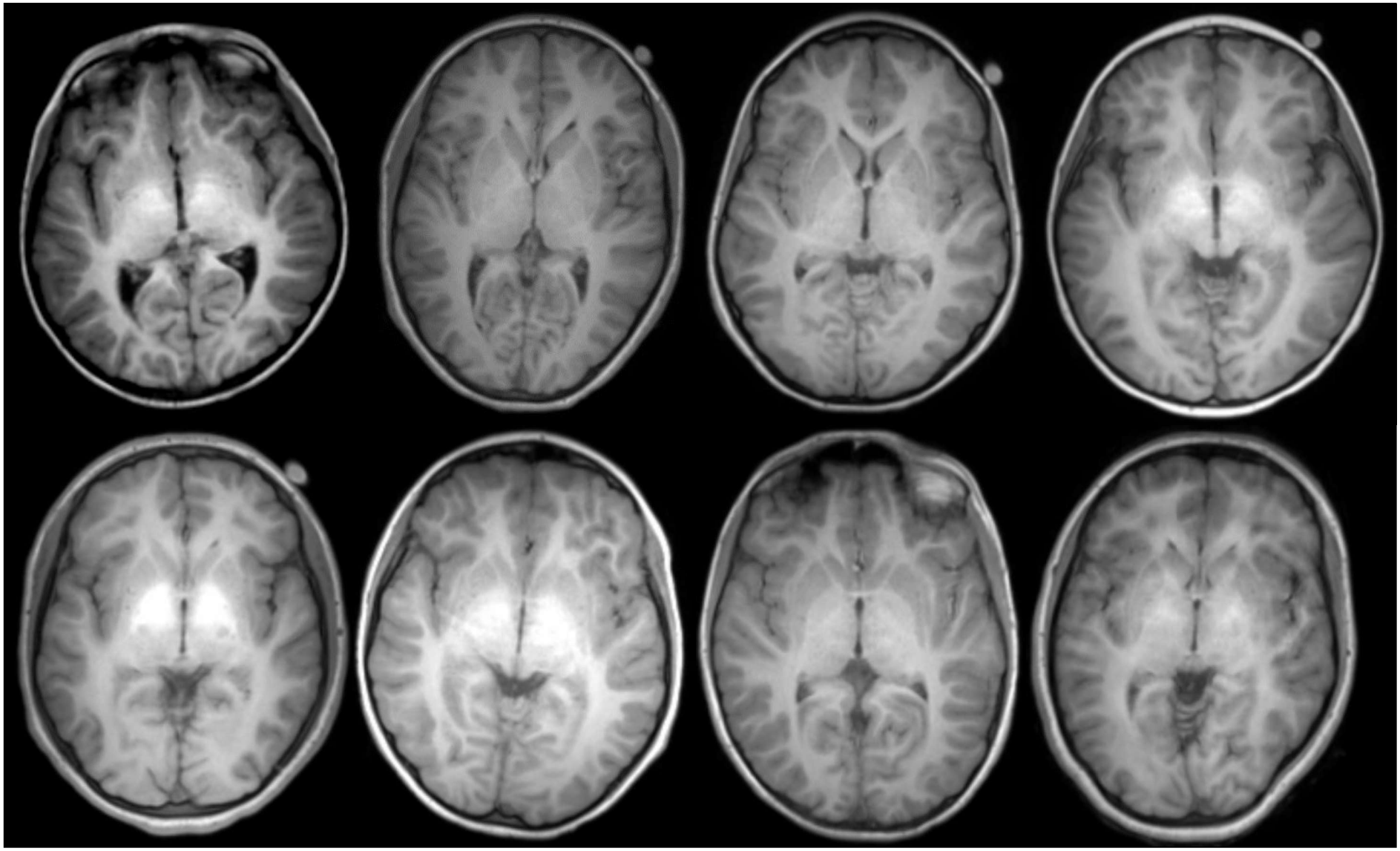


FIGURE 9 Axial T1 image of each of the 8 cases