PEDIATRICS ON THE MOVE:

THE FUTURE IS NOW

ABSTRACT BOOK AKS

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DELAMAR THEATER

AMSTERDAM
KINDER SYMPOSIUM

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Preface Hans van Goudoever

Time to celebrate! An anniversary! For the tenth year, a group of young researchers organizes the Amsterdam Kindersymposium. Actually it is the 11th year as we organized last year a digital AKS. We decided to name that one the first digital one, while hoping for a big party this year. A big party is still not yet possible, but we are so glad we will have a live AKS this year!

Pediatrics on the move: The future is now. The title says it all. AKS, a teaching course in itself, as it is the second largest conference of the Netherlands with famous guest speakers, plenary sessions, parallel sessions, prize winning competitions, a masterclass, acquisition of sponsors, organizing the logistics of the venue, putting together the abstract portal and many other things. This has been the tradition from the beginning, as it is the tradition that all Amsterdam research groups, but also important researchers from regional hospitals and other academic hospitals, present their latest findings.

The meeting expands, as we see an increase in abstracts submitted by researchers from other regions and many more pediatricians attending the meeting. The message that is broadcasted by this increasing success is simple: Scientific research is key for progress in medicine. Through research we will continue to improve our treatment of the children, through research we will understand the mechanism behind a disturbance in functional outcome, through research we will know what treatment is best for both the patient as well as the family surrounding him or her.

Again, the meeting is held in the New DeLaMar theatre, originally built as a school, so the setting could not fit better. Where in the late 1800s, predominantly young children went to school here, after the Second World War, the school was rebuilt into a theater. So teaching and performing on this site, like we will do on February 6th, has its historical roots.
The SLAM presentations are the backbone of the symposium, while the plenary sessions will be held in the view of “Pediatrics on the move”. The Committee has invited very interesting speakers, and has selected almost 70 abstracts to be presented, which makes this day a very special one for many.

I wish you all a beautiful day in the DeLaMar Theater at our Amsterdam Kindersymposium 2022.

Hans van Goudoever
Former Chair, Emma Children’s Hospital – Amsterdam UMC
At present Dean of the University of Amsterdam, vice chair executive board Amsterdam UMC

Preface symposium committee

After a long period of digital congresses and working online, we are extremely happy to invite you to this eleventh edition of the Amsterdam Kindersymposium (AKS) in the DeLaMar Theatre in Amsterdam.

This year's theme is 'Pediatrics on the move – the future is now'. Research in pediatrics is a highly dynamic and constantly evolving field and to keep up, 'movement' in all forms possible is an absolute necessity. In addition, we have all experienced the impact of being limited in our movements during the COVID restriction. Inspired by this year's theme we have selected several honorable speakers to present their work on topics in and adjacent to the field of pediatrics.

Nutricia will kick -off the day with their breakfast session that will focus on movement in research techniques. Nowadays, we move more and more away from animal research and towards the rapidly evolving field of organs-on-a -chip. Then, we welcome prof. dr. Marcel Levi, who will elaborate on leadership by both professionals and patients in current healthcare. Next, we will put our best foot forward, when wrapping up the first session with Dr. Marije Smits. We will dive further into physical movement with prof. dr. Annemieke Buizer to explore patient centered treatment options that aim to improve the mobility of children with a movement disorder. We will end the morning program with former PhD student Annike Bekius who will present her research on impaired walking development in children with cerebral palsy.

In the afternoon, Ms Vanessa Liem will provide a peek into the other side of the patient-doctor perspective. Last, we will move through time with prof. dr. Hugo Heymans and wrap up the day with a topic that brings us all together: the Amsterdam Kindersymposium.

Grateful for this inspiring and exciting day, we would like to thank all that have contributed to the AKS 2022 and whose efforts will hopefully make the AKS 2022 to a great success.

The Amsterdam Kindersymposium Committee 2022

Rosalie Linssen, Michelle Romijn, Britt van Keulen, Tamara den Harink, Charlotte Verburgt, Thomas Dierikx, Puck Peltenburg, Jasmijn Jagt, Thijs Lilien, Lorynn Teela and Ella Metry

AKS committee 2022











Program Amsterdam Kinder Symposium 2022
February 3rd, 2022 - Live @ DeLaMar theater

7:30 - 8:45	**Registration, coffee & tea**
8:00 - 8:30	**Nutricia breakfast session** (registration required)
8:45- 9:00	**Opening *Amsterdam Kindersymposium 2022*** *Prof. dr. Hans van Goudoever & moderators*
9:00 - 9:45	**Hugo Heymans lecture "Professionals and patients in the lead"** *Prof. dr. Marcel Levi*, President Executive Board at Dutch Research Council (NWO), professor of Medicine at University of Amsterdam & University College London
9:45 - 10.10	**Motivational lecture "Putting my best foot forward"** *Dr. Marije Smits*, pediatric resident (UMC Utrecht), former Paralympic athle
10:10 - 10:40	***Coffee break***
10:45 - 12:00	**SLAM session I**
12:00 - 12:40	**Keynote lecture "Moving forward: targeted treatment to improve mobility in childhood movement disorders"** *Prof. dr. Annemieke Buizer*, professor of Pediatric Rehabilitation medicine at University of Amsterdam
12:40 - 13:00	**PhD in the spotlight: "A small step towards understanding impaired walking development in children with cerebral palsy"** *Dr. Annike Bekius*
13:00 - 13:45	***Lunch***
13:10 – 13:30	**ELGAN Lunch symposium**
13:45 - 15:10	**SLAM session II**
15:10 – 15:30	***Coffee break***
15:30 – 16:00	**Motivational lecture "From another perspective"** *Ms. Vanessa Liem*, Partner at Van Doorne N.V., cofounder 'Wij zien je wel' & '2CU'
16:00 - 16:20	**SLAM Battle & Prize Ceremony**
16:20 - 16:40	**Lustrum lecture "History of the Amsterdam Kinder Symposium"** *Prof.dr. Hugo Heymans*
16:40 – 17:00	**Closing word** *Prof.dr. Hans van Goudoever & moderators*

Program SLAM Sessions

SLAM Session 1A – LOCATION Wim Sonneveld zaal (1st floor) 10:45-12:00

Moderators: Brigitte de Bie & Ilan Koppen

Presentations

Program	First name	Surname	Title
1	Caroline/ Lydian	Vuong/ de Ligt	Long Term Follow Up - Morbidity and mortality of pediatric patients with Sickle Cell Disease
2	Esmee	Kooijmans	Hypertension in long-term childhood cancer survivors after treatment with potentially nephrotoxic therapy; DCCSS-LATER 2: RENA
3	Inés	García-Rodríguez	Parechovirus: an infection of the intestinal epithelium: differences between genotypes A1 and A3
4	Irene	van Beelen, MD	Age and sex distribution in patients in a registry for Vanishing White Matter
5	Jiska	van Schaik	Dextroamphetamine treatment in children with hypothalamic obesity
6	Josjan	Zijlmans	Mental health problems during the COVID-19 pandemic in Dutch children and adolescents with and without pre-existing mental health problems
7	Sarah-May	The	Appendicitis and its associated mortality and morbidity in infants up to three months of age: A systematic review of 40 years of literature
8	Soumaya	Laabar	The identification of predictive risk factors of recurrent venous thromboembolism in pediatric patients

SLAM Session 1B – LOCATION Mary Dresselhuys zaal 10:45-12:00

Moderators: Frans Plötz & Bas Vaarwerk

Presentations

Program	First name	Surname	Title
1	Annemieke	De Lange	Moving forward in the transitional care research for children with medical complexity
2	Fabienne	Kloosterman	The clinical phenotype of patients with non-severe hemophilia A and B
3	Jodie	Man	Cortical pathology in Vanishing White Matter
4	Laura	Tseng	Timing of therapy and neurodevelopmental outcomes in pyridoxine-dependent epilepsy
5	Lisa	Deesker	Improved outcome of infantile oxalosis in Europe
6	Martijn	Brands	“Nearly picture perfect”: a mixed-methods study on experiences with hemophilia care in the Netherlands
7	Quinty	Bisseling	The role of MLC1, volume-regulated ion channels and the cytoskeleton in astrocyte dysfunction in the white matter disease Megalencephalic Leukoencephalopathy with subcortical Cysts
8	Stejara	Netea	Anti-cytokine autoantibodies in Kawasaki disease and SARS-CoV-2 related Multisystem Inflammatory Syndrome in Children

SLAM Session 1C – LOCATION Diner Foyer (2nd Floor) 10:45-12:00

Moderators: Mariet Felderhof & Trix Katz

Presentations

Program	First name	Surname	Title
1	Cor-Jan	van der Perk	Ready for discharge? Prognostic factors on parental empowerment.
2	Liz	van de Riet	Long stayers and frequent flyers on the Dutch Pediatric Intensive Care Units
3	Lorynn	Teela	The use of paediatric PROMIS® item banks in Dutch boys with haemophilia
4	Maud	van Muilekom	Health-related quality of life in infants, toddlers, and young children with sickle cell disease
5	Merel	Hermans	Multi-omics in classical galactosemia: phosphate depletion as pathophysiological mechanism?
6	Michiel	Luijten	Internalizing problems before and during the COVID-19 pandemic in Dutch children and adolescents from the general population
7	Nancy	Deianova	Association between duration of empiric antibiotics and late-onset sepsis and necrotizing enterocolitis in preterm infants: a multicenter cohort study
8	Pamela	Capendale	Cerebral organoids as a model to study genotype dependent potential of Parechovirus A to cause Central Nervous System related illnesses in infants
9	Sahinde	Sari	Identification of predictive markers for the development of post thrombotic syndrome in pediatric patients after a Deep Vein Thrombosis

SLAM Session 1D – LOCATION Rode Foyer (–1st floor) 10:45-12:00

Moderators: Dasja Pajkrt & Rosalie Linssen

Presentations

Program	First name	Surname	Title
1	Bibiche	den Hollander	NANS-CDG: Novel insights into phenotype, prognostic biomarkers, and treatment
2	Ebony	Janssen	Transition readiness among adolescents and young adults with hemophilia in the Netherlands
3	Kirsten	van Ham	The reliability of the Sexual Knowledge Picture Instrument, a diagnostic instrument for sexual abuse in young children.
4	Lieke	Barten	Oral immunotherapy in young children with food allergy: sustained unresponsiveness after 1 year of treatment.
5	Lotte	de Boer	Lipoprotein(a) levels in children with and without familial hypercholesterolemia
6	Renate	Verbeek	The Guanabenz Trial: Treatment of patients with early-childhood onset Vanishing White Matter
7	Roxanne	Assies	Prevalence, aetiology and outcome of paediatric shock in Malawi - a prospective study
8	Shanice	Beerepoot	Acute-onset paralytic strabismus in toddlers is important to consider as a potential early sign of late-infantile Metachromatic Leukodystrophy

SLAM Session 2A – LOCATION Wim Sonneveld zaal (1st floor) 13:45-15:10

Moderators: Jeroen Hol & Mirjam van de Velde

Presentations

Program	First name	Surname	Title
1	Anne	Hillen	CRISPR/Cas9-based gene therapy for Vanishing White Matter
2	Debbie	Stavleu	An evidence-based guideline for social restrictions in children with cancer
3	Eva	van der Leest	Improving hospital to home transition for children with medical complexity and their families by understanding parental needs: A systematic review of qualitative studies following a meta-aggregative approach
4	Floor	Veltkamp	Incidence and relapse of idiopathic nephrotic syndrome: meta-analysis
5	Joyce	van Assem	A health care evaluation on the use of dextrose gel incorporated in the new national guideline for hypoglycemia in neonates
6	Lisanne	Heeger	Survey of Transfusion practices in European Preterm Infants (STEP)
7	Roxanne	Assies	Identifying critically ill children at risk of dying during hospital admission in Malawi: Prognostic accuracy of a modified qSOFA score for low resource settings
8	Yoni	van Dijk	Analysis of metabolites in exhaled breath for the phenotyping of eosinophilic asthma in children

SLAM Session 2B – LOCATION Mary Dresselhuys zaal 13:45-15:10

Moderators: Moniek op de Coul & Annemarie van de Geer

Presentations

Program	First name	Surname	Title
1	Barbara	Geven	Early mobilization in the Pediatric Intensive Care Unit: the views of healthcare professionals
2	Chantal	Olij	Effective interventions to support self-management for parents of children with a chronic condition: a systematic review.
3	Constance	Pieters	Stick figure videos contain sufficient information to assess dyskinesia
4	Esmee	Kooijmans	Tubular dysfunction and treatment-related risk factors in long-term childhood cancer survivors; DCCSS-LATER 2: RENA
5	Ilja	Oomen	Genetic and non-genetic determinants of the outcome of immune tolerance induction in patients with hemophilia A and inhibitors –a systematic review
6	Menno	Stellingwerff	Natural MRI history in Vanishing White Matter
7	Piet	Leroy	Design research for procedural comfort in children
8	Sebastian	Bon	Parents' experiences with whole-exome sequencing in pediatric renal cancer
9	Thijs	Lilien	Association of arterial hyperoxia with outcomes in critically ill children: A Systematic Review and Meta-Analysis

SLAM Session 2C – LOCATION Diner Foyer (2nd floor) 13:45-15:10

Moderators: Marieke Merelle & Noor Mutsaerts

Presentations

Program	First name	Surname	Title
1	Anne-Fleur	Zwagemaker	Joint status of patients with non-severe hemophilia A
2	Julie	van der Post	A longitudinal assessment of circulating neurofilament light in pediatric HIV infected patients: investigating the relation between neuronal injury and cognitive outcome
3	Marinka	de Groot	Needs and wishes of general practitioners in Pediatric Palliative Care
4	Mark	Bosch	Retrospective cohort study on morbidities in moderate and late preterm infants in the first 5 years of life
5	Michelle	Romijn	Bronchopulmonary dysplasia and neurofilament light chain biomarker in preterm infants
6	Murtadha	Al-Saady	Neurodegenerative disease after haematopoietic stem cell transplantation in metachromatic leukodystrophy
7	Nancy	Deianova	Neonatal antibiotics duration in preterm infants is associated with need for bronchodilatation in early childhood
8	Renée	Hovenier	The use of personalized masks to optimize non-invasive ventilation in children admitted to the Paediatric Intensive Care Unit

SLAM Session 2D – LOCATION Rode Foyer (–1st floor) 13:45-15:10

Moderators: Annemieke Buizer & Ella Metry

Presentations

Program	First name	Surname	Title
1	Amal	Abdi	Genetic and clinical determinants of the outcome of immune tolerance induction in severe hemophilia A – preliminary results
2	Amrita	Biharie	Comorbidities, clinical characteristics and outcomes of COVID-19 in pediatric patientis in a tertiary medical center in the Netherlands.
3	Anouk	Scholten	Feasibility of wireless cardiorespiratory monitoring with dry electrodes incorporated in a belt in preterm infants
4	Caroline	Vuong	Long Term Follow Up of Dutch patients with Sickle Cell Disease diagnosed by neonatal screening
5	Corien	de Groot - Eckhardt	Fly me to the Moon: Virtual reality to reduce anxiety and pain during acute pain episodes in children with Sickle Cell Disease
6	Maya	Keuning	Saliva SARS-CoV-2 antibody prevalence in children after 1 year pandemic
7	Thiara	Guerra	Cardiovascular risk of cART treated perinatally HIV infected children compared to healthy children based on lipid profile and biomarker alterations: a narrative review
8	Trixie	Katz	Severity of bronchopulmonary dysplasia and neurodevelopmental outcome at two and five years corrected age

Plenary sessions

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Moderators of the day

Dr. Bart Cortjens

Which study/studies did you do (incl. time period in years)?
Medicine 2005-2012.

At which university did you study?
UVA

When did you obtain your PhD and what was the title of your thesis?
2017, Neutrophils in respiratory syncytial virus disease: untangling the NET.

Since when are you working at your current institution?
2018

Which publication or grant are you most proud of?
My paper regarding the detection of NETs in human RSV disease. It was my first paper during my PhD, which makes it really special for me.

Which aspects of your work do you like most?
As a pediatrician, the diverse landscape of diseases combined with the endlessly diverse landscape of social interaction with patients/parents.

What is an important innovation in the field you are working in?
Big innovations in our field is our growing knowledge of the human immune response during viral infections and with that our ability to utilize these tools (e.g. highly specific anti-RSV monoclonal antibodies) to prevent disease in young children.

What do you like to do after work hours?
I like to cycle, both indoors and outdoors. And during the summer I like to hike in the mountains and attempt some alpine ascents.

What are your future plans?
My goals are to start with a fellowship pediatric intensive care medicine and combine this with research towards further insights in the respiratory immune response during infections.

What are you most excited about of this symposium?
I am really excited to hear what everyone (all other researchers/PhD's are) is doing, and to feel all that positive energy and enthusiasm.

What music album did you play most?
My all-time favorite would be Berlin Calling from Paul Kalkbrenner.

What is your favorite food?
I am a big fan of Italian food, nothing beats a fresh pizza or simple pasta dish in my opinion!

Dr. Charlotte Nusman

Which study/studies did you do (incl. time period in years)?
2007-2009 Sport radiology, 2011-2015 imaging in juvenile idiopathic arthritis, from 2017 several research projects mainly on infection in neonates/infants.

At which university did you study?
University of Amsterdam.

When did you obtain your PhD and what was the title of your thesis?
Oct 2015 Innovating imaging in juvenile idiopathic arthritis – an ongoing quest.

Since when are you working at your current institution?
Since I started my study Medicine in 2007.

Which publication or grant are you most proud of?
'Wetenschapssubsidie' van Noordwest Academie – first grant as project leader.

Which aspects of your work do you like most?
Making a difference in communication, teamwork and critically ill patients.

What is an important innovation in the field you are working in?
Family-centered care.

What do you like to do after work hours?
Live in the moment with friends & family, dance, indoor soccer.

What are your future plans?
I hope to continue to live by the day and follow the butterflies in my belly.

What are you most excited about of this symposium?
Inspirational talks that make you think outside of the box.

What music album did you play most?
Sophie Straat – 't is niet mijn schuld.

Keynote speaker – prof. dr. M. Levi

Prof. dr. Marcel Levi is president of the Dutch Research Council. He is also Professor of Medicine at Amsterdam University Medical Center/University of Amsterdam and at University College London and a specialist in Internal Medicine and Haematology. Earlier he worked at the University of Perugia (Italy), in Oxford (UK) and the Center for Transgene Technology and Genetherapy of the University of Leuven, Belgium. He is currently chairman or board member of several national and international research organisations and charities. He is a member of the Royal Netherlands Academy of Science.

Motivational Speaker – dr. Marije Smits

Dr. Marije Smits is currently a pediatric resident at UMC Utrecht. She studied medicine at the University of Amsterdam and graduated in 2014. During her study she was a professional Paralympic athlete because of above knee amputation. She received the 2nd place on the world championships in 2011 on the longjump, of which she is and can be rely proud of!

During and after her medicine study, she had the opportunity to do a PhD in pediatric gastro-enterology, which she finished in 2015 with Prof. Dr. Benninga as her promotor. The biggest challenge in her career is to live up to her own expectations. With her talk about 'Putting my best foot forward' she will tell us her inspiring story about how she went from losing her leg as a teenager to gaining a whole lot! That doesn't mean everything is easy or 'nothing is impossible', but she experienced that with the right help, you can come a long way. Like Johan Cruijff said 'elk nadeel heb z'n voordeel'.

Keynote Speaker – prof. dr. Annemieke Buizer

Prof. dr. Annemieke Buizer is the first Professor of Pediatric Rehabilitation Medicine at the Amsterdam UMC. Her clinical work and research focus on children with a disability or chronic disease which is associated with a disorder of movement, and therefore she collaborates with a lot of disciplines, including a team of rehabilitation professionals, pediatricians, child neurologists, clinical geneticists, neurosurgeons, neurophysiologists, orthopedic surgeons, radiologists, physicists and movement scientists. Her main research focus is on interventions to improve motor function and mobility in children with cerebral palsy and children with other movement disorders.

One of the great achievements of which she is really proud of is starting a national registry aimed at improving care for children with cerebral palsy in the Netherlands of which she is the chair. This registry has been built in collaboration with many disciplines throughout the country, and with people with cerebral palsy and their families. The biggest ongoing challenge in her career is to find enough hours in a day to combine clinical care and research. But this also brings the biggest rewards, since she is in a position where she can translate clinical questions into research, and translate study results into improvement of clinical care. With her lecture titled ‘Moving forward: targeted treatment to improve mobility in childhood movement disorders’, she will give us a look inside her world of pediatric rehabilitation medicine and will show us how to develop personalized interventions by analyzing movement in movement disorders and using new technology.

Motivational speaker – Ms. Vanessa Liem

Vanessa Liem, 42 years old, mother and parental expert, co-founder of Complex Care United foundation, chair of the advisory board Jeroen Pit Huis and lawyer at Van Doorne. Her two children Thijmen and Olivia are the big inspiration and motivation for her work. During her motivational talk she will try to give you a glimpse of her families journey the past 9 years and life with a severely PIMD child. A view from a different perspective.

PhD in the spotlight – Dr. Annike Bekius

Dr. Annike Bekius is a Psychobiology teacher at the University of Amsterdam. She recently defended her thesis in November 2021 at the VU University. Her research focuses on characterizing the underlying mechanisms of walking development in children with cerebral palsy and typically developing children, through the combined measurement of electromyography (EMG) and electroencephalography (EEG). Within this project, she has collaborated with the department of Human Movement Sciences and Rehabilitation medicine. The biggest challenge in her carreer has been performing recordings with very young children (a few months up to 5 years old), measuring activity of a large number of muscles plus EEG. Completing recordings with useful data and most importantly a smile on the face of these children is her main goal in her daily research activities. During her PhD thesis, she focused on impaired walking development in children with cerebral palsy using EMG. With her talk “A small step towards understanding impaired walking development in children with cerebral palsy” she will take us along in her PhD research project.

Abstracts selected for the masterclass

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Nguyen, T.M. (1), Vijverberg, S.J.H (1,2), Hashimoto, S (1,2), Maitland-van der Zee, A.H. (1,2)

(1) Department of Respiratory Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands (2) Department of Pediatric Pulmonology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

ADRB2 Arg16Gly polymorphisms are associated with nocturnal asthma symptoms in asthmatic children using LABA*

Rationale
ADRB2 encodes for the beta-2-adrenergic-receptor. Previous studies have linked polymorphisms in ADRB2 to an increased risk of exacerbations despite the use of long-acting beta-2 agonists (LABA) in asthmatic children and to an increased risk of nocturnal asthma symptoms. In this study we investigate whether polymorphisms in ADRB2 also increase the risk of mild-to-severe nocturnal asthma symptoms despite LABA use in asthmatic children.

Methods
Asthmatic children (4-12 years) were recruited via community pharmacies. ADRB2 Arg16Gly (rs1042713) and Gln27Glu (rs1042714) polymorphisms were genotyped. Nocturnal asthma (NA) symptoms and LABA use were assessed using questionnaires. Mild-to-severe NA was defined as being awakened by asthma symptoms multiple times a week and/or mild-to-severe asthmatic symptoms in the early morning. An additive genetic model was assumed. The association between the polymorphisms and mild-to-severe NA was assessed using multivariate logistic regression models, adjusted for sex and age.

Results
Data were available for 543 children, of which 28% reported LABA use. In children using LABA, the prevalence of mild-to-severe nocturnal asthma symptoms was 29%. ADRB2 Arg16Gly increased the risk of mild-to-severe nocturnal asthma symptoms in children using LABA (adjOR per increase in G-allele: 1.93, 95CI%:1.09-3.42, p=0.02), but not in the total population (adjOR per increase in G-allele: 0.80, 95%CI: 0.60-1.06, p=0.12). In contrast, ADRB2 Gln27Glu was not associated with mild-to-severe nocturnal asthma symptoms in the total population, nor in the subset of children using LABA.

Discussion
Genetic variation in ADRB2 Arg16Gly is a risk factor for mild-to-severe nocturnal asthma symptoms despite LABA use in children. These children might benefit from an alternative treatment to control nocturnal asthma symptoms.

* See Appendix for additional Table and/ or Figure

Mank, E. (1), Sáenz de Pipaón, M. (2), Lapillonne, A. (3), Carnielli, V.P. (4), Senterre, T. (5), Shamir, R. (6), van Toledo, L. (1), van Goudoever, J.B. (1), on behalf of the FIT-04 study group

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Efficacy and Safety of Enteral Recombinant Human Insulin in Preterm Infants: A Randomized, Double-Blind, Placebo-Controlled Trial

Rationale
Feeding intolerance is a common condition among preterm infants due to immaturity of the gastrointestinal tract. Enteral insulin appears to promote intestinal maturation. Insulin is absent in formula and the natural insulin concentration in human milk declines rapidly postpartum. The objective of this study was to assess the efficacy and safety of two different dosages of recombinant human insulin (rh-insulin) as a supplement to both formula and human milk. The primary endpoint was time to achieve full enteral feeding (FEF; ≥150 mL/kg/day for three consecutive days).

Methods
This multicenter, double-blind, placebo-controlled trial was conducted at 46 neonatal intensive care units throughout Europe, Israel, and the United States. Preterm infants (gestational age (GA) of 26–32 weeks and birth weight (BW) ≥500 grams) were randomly assigned to receive either low-dose (LD) rh-insulin (400 µIU/mL milk), high-dose (HD) rh-insulin (2000 µIU/mL milk), or placebo for 28 days.

Results
The intention-to-treat analysis included 303 infants. Median (IQR) GA was 29.0 (27.7–30.4) weeks and BW was 1210 (1000–1435) grams. Time to FEF was 10.0 (7.0–21.8) days in the LD group, 10.0 (6.0–15.0) days in the HD group, and 14.0 (8.0–28.0) days in the placebo group. Compared to placebo, time to FEF was significantly shorter in the LD group (P=0.033) and HD group (P=0.001). Weight gain rates did not differ significantly between groups. Necrotizing enterocolitis (Bell stage 2 or 3) occurred in 7 (6%) infants in the LD group, 4 (5%) infants in the HD group, and 10 (10%) infants in the placebo group. None of the infants developed serum insulin antibodies.

Discussion
Enteral administration of two different rh-insulin dosages is safe, and, compared to placebo, significantly reduces time to FEF in preterm infants with a GA of 26–32 weeks. These findings support the use of rh-insulin as a supplement to formula and human milk for preterm infants.

Kloosterman, F.R. (1), Zwagemaker, A. (1), Gouw, S.C. (1,2), Bagot, C.N. (3), Beckers, E.A.M. (4), Boyce, S. (5), Brons, P. (6), Cnossen, M.H. (7), Eikenboom, J. (8), Leebeek, F.W.G. (9), Male, C. (10), Meijer, K. (11), Nieuwenhuizen, L. (12), Coppens, M. (13), Van der Bom, J.G. (2,14) Castaman, G. (15), Fijnvandraat, K. (1,16).

(1) Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Hematology, Amsterdam, The Netherlands (2) Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands (3) Department of Haematology, Glasgow Royal Infirmary, Glasgow, UK. (4) Department of Hematology, Maastricht University Medical Centre, Maastricht, the Netherlands (5) Department of Haematology, University Hospital Southampton, Southampton, United Kingdom (6) Department of Pediatric Hemato-Oncology, Radboud University Medical Center, Nijmegen, The Netherlands. (7) Department of Pediatric Hematology, Erasmus University Medical Center – Sophia Children's Hospital, Rotterdam, the Netherlands (8) Department of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden (9) Department of Hematology, Erasmus University Medical Center, Rotterdam, the Netherlands (10) Department of Pediatrics, Medical University of Vienna, Vienna, Austria (11) Department of Hematology, University Medical Center Groningen, Groningen, the Netherlands (12) Department of Hematology, Maxima Medical Center Eindhoven, Eindhoven, The Netherlands. (13) Department of Vascular Medicine, Amsterdam University Medical Centres, Amsterdam, the Netherlands (14) Center for Clinical Transfusion Research, Sanquin-Leiden University Medical Center, Leiden (15) Department of Oncology, Center for Bleeding Disorders, Careggi University Hospital, Florence, Italy (16) Department of Molecular Cellular Hemostasis, Sanquin Research and Landsteiner Laboratory, Amsterdam, the Netherlands

The clinical phenotype of patients with non-severe hemophilia A and B*

Rationale
Patients with hemophilia have an increased bleeding tendency and those with non-severe hemophilia have a milder clinical phenotype compared to severe cases. Nonetheless, patients with non-severe hemophilia may still experience serious bleeding events. Detailed information on the frequency and severity of bleeding in non-severe hemophilia is currently limited. We aim to provide insight into the clinical phenotype of patients with non-severe hemophilia.

Methods
In the international multicenter DYNAMO cohort study, patients with non-severe (FVIII/FIX 2-35 IU/dL) hemophilia A and B aged 12-55 years were included. Data on the first (joint) bleed and all treated bleeding episodes in the last 10 years were collected from medical files. The treated annual bleeding rate (ABR) and annual joint bleeding rate (AJBR) were calculated.

Results
In total, 304 patients were included (70 moderate and 234 mild hemophilia). Median age was 38 years (IQR 25-49) and the median baseline factor activity level was 12 IU/dL (IQR 5-21). In their lifetime, 81% had experienced at least one bleed and 51% had experienced at least one joint bleed that required treatment with factor concentrate. The median age at first bleed and first joint bleed was 8 (IQR 3-17) and 10 (IQR 6-19) years. Patients with moderate hemophilia experienced their first bleed and first joint bleed at a younger age than patients with mild hemophilia (Figure. 1). Median ABR was 0.6 (IQR 0.2-1.4) in patients with moderate hemophilia and 0.2 (IQR 0-0.4) in mild cases. Median AJBR was 0.2 (IQR 0-0.4) and 0.0 (IQR 0.0-0.1) in patients with moderate and mild hemophilia, respectively. The majority of joint bleeds occurred in the ankles (38%) and knees (29%), where 15% occurred spontaneously and 59% was activity/trauma related.

Discussion
Despite a low bleeding rate, half of the patients with non-severe hemophilia suffered a joint bleed. This further highlights the need for patient education and adequate monitoring.

* See Appendix for additional table and/ or figure

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Association between duration of empiric antibiotics and late-onset sepsis and necrotizing enterocolitis in preterm infants: a multicenter cohort study

Rationale
Antibiotics are routinely administered in preterm infants. The effects of antibiotic exposure on the risk of necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) are still debated. Aim of this study was to investigate the duration of early empirical antibiotic exposure (EEAE) in relation to the risk of NEC and LOS in preterm infants.

Methods
In this multi-center cohort study, conducted in nine neonatal intensive care units in the Netherlands and Belgium, infants born at <30 weeks' gestation were included between October 2014 and July 2019. Association between empirical antibiotic exposure, and development of NEC (modified Bell's stage ≥ 2a) and culture-proven LOS was analyzed by multivariate logistic regression.

Results
A total of 1259 infants born before 30 weeks of gestation were included. Overall, NEC and LOS incidence was 8% and 33%, respectively. Infants with a short course (≤72h) of antibiotics had a lower incidence of NEC when compared to both infants without initial antibiotic exposure (adjusted odds ratio (aOR) 0.39; 95% confidence interval (CI) 0.19 – 0.80; p=0.01) and with prolonged (>72h) antibiotic exposure (aOR 0.58; 95% CI 0.35 – 0.96; p=0.03). With every additional day of antibiotic exposure, LOS incidence decreased (OR 0.90; 95% CI 0.85-0.97; p=0.003).

Discussion
NEC and LOS incidence altered based on the duration of empirical antibiotics after birth. The role of antibiotics, and potentially induced dysbiosis, in development of NEC and LOS should further be explored both in longitudinal microbiota sequence studies and RCTs.

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CRISPR/Cas9-based gene therapy for Vanishing White Matter

Rationale
Vanishing White Matter (VWM) is a leukodystrophy resulting in neurological decline and premature death. It is caused by mutations in the genes encoding eukaryotic Translation Initiation Factor 2B (eIF2B). The well-defined genetic loci of VWM-causing variants make VWM a good candidate for gene therapy. Recent advances in gene editing technology have greatly stimulated the development of such a gene therapy.

Methods
We used CRISPR/Cas9 technology to correct the pathogenic R191H variant in the Eif2b5 gene in a VWM mouse model. The CRIPSR/Cas9 complex was directly targeted to the mutated sequence, and delivered using a dual AAV approach. One construct encoded the guideRNA and a DNA template with the wild-type variant of the relevant Eif2b5 sequence. The other AAV coded for the Cas9 nuclease. Neonatal mice of the experimental group were injected with both viruses whereas animals in the control group only received Cas9.

Results
We found that treatment with CRISPR/Cas9 induced very severe detrimental effects that were not observed in the Cas9-only control group. Sequencing of the type of edits made by our CRISPR/Cas9 approach indicated that the rate of correction of the variant was low, while editing-induced additional mutations of Eif2b5 were comparatively high.

Discussion
The finding of additional mutations being generated by CRISPR/Cas9 is well-described. However, the rate at which this occurs versus the rate of correction using the DNA template, has not been studied before for the Eif2b5 locus targeted here. These extra mutations are likely cause of the severe decline in health observed in CRISPR/Cas9-treated animals. This argues against gene therapy for VWM based on nucleases, such as CRISPR/Cas9.

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Lipoprotein(a) levels in children with and without familial hypercholesterolemia*

Rationale
Children with familial hypercholesterolemia (FH) are at risk of premature atherosclerosis if left untreated. FH is preferably diagnosed by DNA-analysis, however, in many children, no mutation can be found and they are diagnosed as having clinical FH. Several studies have shown that high lipoprotein(a) [lp(a)], a risk factor for cardiovascular disease (CVD), may underlie this clinical diagnosis in a considerable group of patients. However, most studies are done in adults. Hence, we evaluated Lp(a) levels in a large cohort of children with and without FH.

Methods
Children that visited the lipid clinic of the Amsterdam UMC between 1989 and 2019 were eligible. Children were included if Lp(a) was measured at first visit and if DNA-analysis was performed. We divided the cohort into four groups: children with molecular proven non-FH (mutation of parent was not found)(mol-non-FH); molecular proven FH (mutation of parent was found)(heFH); clinical non-FH (no mutation was found yet + LDL-C<4 mmol/l or LDL-C 4-5 mmol/l and no family history of CVD)(clin-non-FH) and clinical FH (no mutation was found yet + LDL-C>5 mmol/l or LDL-C>4 mmol/l and a family history of CVD)(clin-FH).

Results
We included 2,721 children (mean age: 10.3 years); 291 children with mol-non-FH; 1,953 with heFH; 112 with clin-non-FH and 365 with clin-FH. Mean (95% CI) Lp(a) of children in the groups is displayed in figure 1. Lp(a) of children with clin-FH was significantly higher than in heFH ($p<0.001$). Lp(a) was elevated in 10%, 10%, 18% and 30% of children with mol-non-FH, heFH, clin-non-FH and clin-FH, respectively.

Discussion
High Lp(a) may play a role in children with clinical FH in whom no mutation is found. We believe that these children make up a separate group and cannot be classified as having (clinical) FH. To distinguish between FH and high Lp(a), we recommend performing DNA-analysis as well as measuring Lp(a) as these children may benefit from different treatment strategies.

* See Appendix for additional table and/ or figure

Abstracts selected for the Speech Republic workshop

AMSTERDAM KINDER SYMPOSIUM

van der Post, J. (1), van Genderen, J.G. (1), Pajkrt, D. (1)

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A longitudinal assessment of circulating neurofilament light in pediatric HIV infected patients: investigating the relation between neuronal injury and cognitive outcome

Rationale
Despite combination antiretroviral therapy (cART), perinatally Human Immunodeficiency Virus (PHIV)-infected adolescents exhibit cerebral injury and cognitive impairment. The pathophysiologic mechanisms contributing to these complications are not fully understood. Serum neurofilament light (sNfL), a marker released following axonal injury, has been identified as a promising marker reflecting neuronal injury or degeneration. To investigate whether cerebral injury in PHIV-infected adolescents is ongoing, we longitudinally and cross-sectionally assessed sNfL levels and its association with brain structure and cognitive function.

Methods
We included 21 PHIV-infected adolescents and 23 controls matched for age, sex, ethnic origin and socio-economic status twice with a mean follow-up time of 4.6 years. The cross-sectional assessment included 35 PHIV-infected adolescents and 38 controls. We measured sNfL of all participants using Single Molecule Array (Simoa) immunoassay. We compared sNfL levels between groups and also assessed associations between sNfL levels and brain structure, cognitive function and HIV-related characteristics using linear mixed models and linear regression models for the longitudinal and cross-sectional study, respectively.

Results
We found similar concentrations of sNfL in PHIV+ and HIV- children in both longitudinal (beta coefficient; -0.19, 95%CI -0.50 to 0.12, p>0.05) and cross-sectional assessment (beta coefficient; -0.09, 95%CI -0.39 to 0.18, p>0.05). We found no significant associations between sNfL and HIV or cART related variables, imaging outcomes or cognitive performance.

Conclusions
Our results suggest that neuronal injury in PHIV-infected adolescents is not an ongoing process. We hypothesize that the neuronal injury largely occurred in the past.

Halbmeijer, N.M. (1), Onland, W. (1), Cools, F. (2), Swarte, R. (3), van der Heide-Jalving, M. (4), Dijk, P.H. (5), Mulder-de Tollenaer, S. (6), Tan, R. (7), Mohns, T. (8), Bruneel, E. (9), van Heijst, A. F. (10), Kramer, B. W. (11), Debeer, A. (12), van Weissenbruch, M. (13), Marechal, Y. (14), Blom, H. (15), Plaskie, K. (16), Offringa, M. (1,17), Leemhuis, A.G. (1), van Kaam, A. H. (1), Aarnoudse-Moens, C. S. H. (1,18), for the SToP-BPD study group*.

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The Effect of Systemic Hydrocortisone in Ventilated Preterm Infants on Behavioural outcomes at 2 years' Corrected Age: follow-up of a randomized clinical trial*

Rationale
Dexamethasone is effective in reducing the incidence of bronchopulmonary dysplasia, but is associated with adverse neurodevelopmental outcomes, including behavioural problems. Hydrocortisone is increasingly studied as an alternative for dexamethasone but evidence on long-term safety of hydrocortisone initiated after the first week of life is lacking. In this study, we report behavioural outcomes at 2 years' corrected age (CA) assessed by the Child Behaviour Checklist 1.5 to 5 years (CBCL) of infants included in the SToP-BPD study.

Methods
In this double-blind, placebo-controlled, randomised trial mechanically ventilated very preterm infants were randomly assigned to a 22-day course of systemic hydrocortisone (cumulative dose 72.5 mg/kg; n=182) or placebo (n=190). Prior to the 2-year follow-up visit, parents completed the CBCL to assess the child's behaviour problems.

Results
183 parents completed the CBCL (96 in the hydrocortisone group; 87 in the placebo group). Multiple imputation was used to account for missing data. Clinically abnormal T-scores for total, internalising and externalising problems were found in 22.9%, 19.1% and 29.4% of infants, respectively. The total, internalising and externalising problems T-scores were not significantly different between hydrocortisone and placebo group (mean difference -1.52 [95% CI -4.00, 0.96], -2.40 [95% CI -4.99, 0.20] and -0.81 [95% CI -3.40, 1.77], respectively). In addition, the subscales were not significantly different between both groups, except for a significantly lower T-score for anxiety problems in the hydrocortisone group (mean difference, -1.26 [95% CI -2.41, -0.12]).

Discussion
This randomised placebo controlled clinical trial comparing systemic hydrocortisone initiated between 7 to 14 days after birth in ventilated preterm infants to placebo treatment, did find high

rates of behaviour problems at 2 years' CA following preterm birth, however these were not associated with hydrocortisone treatment.
* See Appendix for additional Table and/ or Figure

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The identification of predictive risk factors of recurrent venous thromboembolism in pediatric patients

Rationale
A serious long term complication following venous thromboembolism (VTE) is recurrent thrombosis. Prolongation of the initial anticoagulant therapy is effective in reducing recurrent VTE, but associated with bleeding complications. Therefore, identification of the patients at risk of recurrent VTE is crucial to target prolonged anticoagulation in this specific group. The primary aim of this study was to determine these risk factors and the secondary aim was to determine the incidence of recurrent VTE and recurrent-free survival.

Methods
For this retrospective cohort study all children (0-18 years) with a VTE between 2000 and 2021 treated at Emma Children's Hospital, Amsterdam UMC were eligible. The following determinants were studied: age, comorbidity, CVC, thrombus resolution, thrombophilic mutation, inflammatory status and thromboprophylaxis.

Results
During the observation period 703 patients were eligible and 637 (91%) were included in the current analysis. Recurrent VTE occurred in 134/637 patients (21%). Median age was comparable in the recurrence (4.5± 7.0 years) and non-recurrence group (4± 7.2 years). Most frequent comorbidity in recurrent VTE was total parenteral nutrition (TPN) (22.4%) and active malignancy (20.9%) compared to infection (21.9%) and active malignancy (20.3%) in patients without recurrence. The median time to recurrence was 182 days after the initial VTE. Risk factors significantly associated with recurrent VTE were lack of thrombus resolution (p=0.026, OR=4.6), TPN dependency (p=0.002, OR=59.7), active inflammation at time of VTE (p=0.011, OR=5.0) and the presence of a thrombophilic mutation (p=0.007, OR=0.2).

Discussion
This study demonstrated a high recurrence rate that was associated with the following determinants: lack of thrombus resolution, TPN dependency, active inflammation at time of VTE and the presence of thrombophilic mutation. These findings may aid in targeting personalized treatment strategies in the future.

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Anti-cytokine autoantibodies in Kawasaki disease and SARS-CoV-2 related Multisystem Inflammatory Syndrome in Children*

Rationale
Kawasaki disease (KD) is a paediatric vasculitis predominantly affecting coronary arteries. Although its etiology is uncertain, it is likely triggered by infectious agents causing cytokine-induced hyperinflammation. Multisystem Inflammatory Syndrome in Children (MIS-C), developing after COVID-19 infection, highly resembles KD, raising the question of a possibly shared etiology as well. Therefore, we aimed to elucidate immunological pathways and over-time signatures characteristic for KD and MIS-C.

Methods
Clinical data and blood samples of KD (n=45) and MIS-C (n=25) cases were collected during the (sub)acute and convalescent phase for our long-standing longitudinal Kawasaki disease cohort study. Over-time trends of inflammatory proteins and anti-cytokine autoantibodies (ACAA) were determined using Luminex and/or ELISA assays, compared between KD and MIS-C patients and linked to clinical characteristics.

Results
Our findings indicated hyperinflammation with transiently increased T helper 1 (i.e., IL-18, IFN-□, CXCL-10) and T helper 17 (i.e., IL-6, IL-17) related cytokine levels. Increased levels of IFN-□ related proteins, LBP, ST2, CD163 and sIL2R differentiated MIS-C from KD in the acute phase. Transient ACAA (e.g., anti-IFN-□, anti-IL-17F) were present in both patient groups, peaking in the subacute phase. The anti-IFN-□ autoantibodies were partially neutralizing in a functional read-out.

Discussion
KD and MIS-C present with overlapping immune cascades, including the novel finding of ACAA in both. Although the value of ACAA and other blood parameters need further investigation, ACAA may play a more general role in the physiological regulation of cytokines. Ultimately, they may guide patient-tailored diagnostic and treatment decisions concerning KD, MIS-C and other severe inflammatory disorders.

* See Appendix for additional table and/or figure

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Neonatal antibiotics duration in preterm infants is associated with need for bronchodilatation in early childhood

Rationale
Preterm neonates are at particular high risk of developing small airway obstruction (SAO) in childhood as a result of immaturity of the lungs at birth. Research has indicated a correlation between gut microbiota imbalance and development of inflammatory lung diseases in infancy (gut-lung-axis). Antibiotics are known to impact microbial colonization, resulting in gut dysbiosis. We explored the association between duration of antibiotics administration in preterm neonates and the risk of SAO beyond the 1000th day of life.

Methods
In this Dutch multi-center (7 NICUs) cohort study in ex-preterm children born before 30 weeks' gestation, daily antibiotic use (type and dose) was registered in the first month of life. Beyond the 1000th day of life, parents were surveyed on, i.a., bronchodilator use as therapy for SAO. Odds ratio's (OR) were calculated by logistic regression analysis and adjusted for ventilation type at NICU, parents'/siblings' atopy, age, gestational age and delivery mode.

Results
Of 121 children, aged 2.5-6 years, 31% were using short acting bronchodilators. Every additional day of antibiotics in the first 14 days of life was associated with a higher odds for short acting bronchodilatator use in childhood (adjusted OR (aOR)=1.2 [1.0-1.4], p-value 0.02). There was no association between length of antibiotics therapy between the 14th and 28th day of life and SAO therapy.

Discussion
Extended duration of antibiotics therapy during the first two postnatal weeks after preterm birth were associated with increased odds of bronchodilatator use in childhood. It remains to be elucidated whether there is a causal relation between antibiotics therapy and lung development via the gut-lung axis. Future studies should include antibiotics' influence on microbiota and metabolomics to identify potential pathways influencing lung development in this specific population and to stimulate
early, targeted microbiota-based interventions aimed at prevention of SAO.
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Identifying critically ill children at risk of dying during hospital admission in Malawi: Prognostic accuracy of a modified qSOFA score for low resource settings

Rationale
In low resource settings there is a lack of a reliable bedside identification score to identify children at risk of dying, but could help focus limited resources and improve survival. The rapid bedside Liverpool qSOFA (LqSOFA) score may be suitable and performed well in the UK, however has not been validated in a resource-limited setting.

Methods
In a cohort of critically ill children in Malawi, we calculated the LqSOFA score using age-adjusted heart rate (HR) and respiratory rate (RR), capillary refill time (CRT) and Blantyre Coma Scale (BCS) and evaluated its prognostic performance for mortality. An adjusted score, the Blantyre qSOFA (BqSOFA) score was developed (omitting HR, adjusting cut-off values for RR, adding pallor), validated in a second cohort of Malawian children and compared with the similar but more complex nine parameter FEAST PET score. Evaluation of prognostic performance for mortality included area under the receiving operating characteristic curve (AUC).

Results
Mortality was 15.4% in the study (n=493) and 22.0% in the validation cohort (n=377). In the study cohort, discriminative ability of the LqSOFA score predicting mortality was 0.68 (AUC, 95% CI: 0.60-0.76). The BqSOFA score yielded an AUC of 0.84 (95% CI: 0.79-0.89) in the study cohort and 0.74 (95% CI 0.68-0.79) in the validation cohort. The FEAST PET score revealed an AUC of 0.83 (95% CI: 0.77-0.89) and 0.76 (95% CI: 0.70-0.82) in the study and validation cohort respectively.

Discussion
The LqSOFA score showed a moderate prognostic performance in a resource-limited setting, but the four parameter BqSOFA score performed well in both the study and validation cohort. It further was non-inferior to the more complex FEAST PET score. The BqSOFA score might be used as a simple bedside tool to identify critically ill children at risk of dying in resource-limited settings and prioritize care to improve outcome.

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Cardiovascular risk of cART treated perinatally HIV infected children compared to healthy children based on lipid profile and biomarker alterations: a narrative review

Rationale
In adults, an HIV infection is an independent and established risk factor for cardiovascular disease (CVD). Effectively treated perinatally HIV-infected (PHIV) children have a near normal life expectancy. Potentially, PHIV children have a greater CVD risk later in life compared to HIV-negative peers. To assess a potential higher CVD risk in combination antiretroviral therapy (cART) treated PHIV children, we narratively reviewed the literature on plasma lipid and biomarker concentrations.

Methods
We conducted an electronic search through PubMed. We assessed the following plasma lipids and biomarkers: total cholesterol Total cholesterol (TC), High-density lipoprotein-cholesterol (HDL-C), Low-density lipoprotein-cholesterol (LDL-C), Triglycerides (TG), Lipoprotein(a) (Lp(a)), Highly sensitive C-reactive protein (hsCRP), Interleukin-6, Interleukin-18 (IL-18) and soluble vascular cell adhesion molecule (sVCAM). We compared plasma lipid and hsCRP concentrations of PHIV children and HIV-negative peers to the reference values of the National Heart, Lung, and Blood Institute and to the hsCRP cut-off value, respectively. We also assessed lipid profile and biomarker differences between PHIV children and the control group.

Results
We included one longitudinal study and eleven cross-sectional studies. Higher concentrations of TC, LDL-C, Lp(a) and TG were seen in PHIV children compared to the reference values and HIV-negative peers. PHIV children had lower HDL-C concentrations than the reference values. All plasma lipid concentrations of the HIV-negative peers were within the reference values. PHIV children had higher concentrations of hsCRP, sVCAM and IL-18 compared to HIV-negative peers.

Discussion
Evidence suggests a higher CVD risk in cART treated PHIV children compared to healthy HIV-negative children. Due to mostly cross-sectional data, considerable heterogeneity and small study populations, conclusions concerning future CVD risk cannot be drawn.

den Hollander, B. (1,2,3,22), Rasing, A. (2), Post, M.A. (3,4,5), Klein, W.M. (6), Oud, M.M. (7), Brands, M.M. (1,3,22), de Boer, L. (2), Engelke, U.F.H. (5), van Essen, P. (8), Fuchs, S.A. (3,9), Haaxma, C.A. (10), Jensson, B.O. (11), Kluijtmans, L.A.J. (3,5), Lengyel, A. (12), Lichtenbelt, K.D. (13), Østergaard, E. (14,15), Peters, G. (16), Salvarinova, R. (17,18), Simon, M.E.H. (13), Stefansson, K. (11,19), Thorarensen, O. (20), Ulmen, U. (21), Coene, K.L.M. (5), Willemsen, M.A. (3,10), Lefeber, D.J. (3,4,5) and van Karnebeek, C.D.M. (1,2,3,17,18,22)

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NANS-CDG: Novel insights into phenotype, prognostic biomarkers, and treatment

Rationale
NANS-CDG is a recently described congenital disorder of glycosylation caused by biallelic genetic variants in NANS, encoding an essential enzyme in de novo sialic acid synthesis. Sialic acid at the end of glycoconjugates plays a key role in biological processes such as brain/skeletal development. This observational cohort study aims to delineate the genetic, biochemical, clinical phenotype and assess possible correlations.

Methods
Medical records were reviewed with retrospective extraction and analysis of genetic, biochemical, clinical data (2016–2020).

Results
Nine patients were included, phenotyping confirmed hallmark features: intellectual developmental disorder (IDD), facial dysmorphisms, neurologic impairment in 100%; short stature, skeletal dysplasia, short limbs in 89%. Newly identified features include ophthalmological abnormalities and abnormal septum pellucidum in 67%, (progressive) cerebral atrophy, gastrointestinal dysfunction, thrombocytopenia in 56%, hypo–LDL cholesterol in 44%. Elevated urinary N-acetylmannosamine (ManNAc) is pathognomonic, concentrations showing a significant correlation with clinical severity. Eight novel NANS variants were identified. Three severely affected patients harbored identical compound heterozygous pathogenic variants; one was experimentally treated with pre/postnatal sialic acid, showing markedly better psychomotor development than the other two genotypically identical males.

Discussion
ManNAc screening should be considered in all patients with IDD, short stature, short limbs, facial dysmorphisms, neurologic impairment, abnormal septum pellucidum +/– degenerative lesions on MRI. Personalized management includes genetic counseling, access to supports, tailored care for GI-symptoms, thrombocytopenia, epilepsy, and rehabilitation services for cognitive/physical impairments. Motivated by short-term positive effects of oral sialic acid, we have initiated this intervention with protocolized follow-up in 4 patients.

Lilien, T.A. (1), Groeneveld N.S. (1), Etten van-Jamaludin, F. (2), Peters, M.J. (3), Buysse C.M.P. (4), Ralston, S.L. (5), van Woensel, J.B.M. (1), Bos, L.D.J. (6), Bem, R.A. (1)

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Association of arterial hyperoxia with outcomes in critically ill children: A Systematic Review and Meta-Analysis*

Rationale
Oxygen therapy is a cornerstone treatment in the pediatric intensive care unit (PICU). Accumulating evidence suggests that overzealous use of oxygen, leading to hyperoxia, is associated with worse outcome. We aimed to describe the definitions of hyperoxia and to evaluate its association with clinical outcome in critically ill children.

Methods
We performed a systematic search of EMBASE, MEDLINE, Cochrane and Clinicaltrials from inception to February 2021. Studies of children admitted to the PICU that examined hyperoxia, by any definition, and described at least one outcome of interest were included. No language restrictions were applied. The review process was performed independently by two reviewers following the MOOSE-guideline. Data were pooled with a random-effects model. The primary outcome was 28-day mortality. This was converted to mortality at longest follow-up due to insufficient studies reporting the initial primary outcome. Secondary outcomes included length of stay, ventilator related outcomes, organ support and functional performance.

Results
In this review, 16 studies (27,555 patients) were included. All, but one pilot clinical trial, were observational studies. Definitions and assessment of hyperoxia differed greatly among studies. PaO2 was most frequently used to define hyperoxia. Meta-analysis included 11 studies (23,204 patients). Hyperoxia showed an OR of 1.59 (95% CI 1.05-2.38 after HK-adjustment) for mortality with substantial between-study heterogeneity (I2 92%). This association was maintained in less heterogeneous subsets and was stronger at higher thresholds of PaO2 when grouped by definition of hyperoxia. Secondary outcomes were inadequate for meta-analysis.

Discussion
Despite methodological limitations, a positive association exists between hyperoxia and mortality. This underlines the further need for prospective observational studies and importance to address the clinical implications of hyperoxia in critically ill children.

* See Appendix for additional table and/ or figure

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Age and sex distribution in patients in a registry for Vanishing White Matter*

Rationale
Vanishing White Matter (VWM) is a leukodystrophy, characterized by chronic neurologic deterioration and stress-provoked episodic decline. The age of onset (AoO) ranges from infancy to adulthood. Early onset is associated with mostly motor dysfunction, severe disease course and early demise, whereas adult onset is associated with mostly cognitive problems, slow decline and long survival. We set up a registry to study the natural clinical course of VWM in more detail.

Methods
Genetically confirmed VWM patients were included in a registry. We collected information with customized and standardized questionnaires. Patients were stratified based on the AoO: group 1 (<1 year), 2 (1-<2 y), 3 (2-<4 y), 4 (4-<8 y), 5 (8-<18 y), and 6 (≥18 y). Descriptive statistics were used to present demographic data.

Results
A total of 378 patients (47% male (M)) were included, and divided in group 1 (12%, 60% M), 2 (16%, 53% M), 3 (28%, 43% M), 4 (20%, 53% M), 5 (10%, 47% M), and 6 (13%, 27% M). AoO varied from 0 to 55 years. 129 patients were deceased, in group 1 83%, 2 44%, 3 36%, 4 11%, 5 16%, 6 20% (Figure 1). 81% had an AoO <4 years. Of the remaining 249 patients, the median current ages for each group were: 12.4 y (75% M), 15.2 y (49% M), 17.3 y (41% M), 22.7 y (55% M), 31.1 y (50% M), 54.8 y (28% M). Overall, 64% of living patients are currently 18 years or older (42% M).

Discussion
Our data confirm the wide age distribution in VWM. Of the patients who were deceased, a large proportion had an AoO below 4 years. As onset in childhood is most common, VWM is generally considered a pediatric disorder. However, a large proportion of the patients reaches adulthood and most surviving patients are adult. Patients with adult onset are more commonly female. These data underscore the need to consider adult VWM patients for therapeutic trials. The VWM Registry can aid in making informed decisions when designing trials and for preselecting eligible patients.

* See Appendix for additional table and/ or figure

Man, J.H.K. (1,2), van Gelder, C.A.G.H. (3,4), Breur, M. (1,2), Okkes, D.Y. (1,2), Molenaar, D. (5), van der Sluis, S. (6), Wolf, N.I. (1,2), Altelaar, M. (3,4), van der Knaap, M.S. (1,2,7), Bugiani, M. (2,8)

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Cortical pathology in Vanishing White Matter

Rationale
Vanishing white matter (VWM) is a prevalent childhood white matter disorder resulting from mutations in any of the five genes encoding the subunits of eukaryotic translation initiation factor 2B. This is a ubiquitously expressed enzyme crucial for protein translation. Brain white matter is allegedly selectively affected with astrocytes as primary drivers in the pathogenesis, secondary to defects in oligodendrocytes and axons. This categorizes VWM under the astrocytopathies. Although VWM is known as a leukodystrophy, MRI documents progressive thinning of the cortex in long surviving patients. Postmortem routine analyses, however, have never pointed to any involvement of the cortical gray matter so far. This prompted us to explore the cortex in VWM.

Methods
We first aimed at assessing a possible astrocyte pathology in the VWM cortex and second, to gain insight into molecular disease mechanisms using high-resolution mass spectrometry-based proteomics.

Results
We showed that VWM cortical astrocytes exhibit morphological changes and are less complex in structure. They are also immature. Overall, we detected 267 differentially expressed proteins in VWM cortical gray matter compared to controls. We found increased expression of proteins associated with dense body and interstitial matrix. In contrast, we observed decreased expression of proteins associated with mitochondrial function and extracellular matrix. Importantly, some of these proteins were also altered in the cortex of other leukodystrophies, indicating common disease mechanisms.

Discussion
Taken together, we show that the cortex, rather than being spared, is indeed affected in VWM. This has probably been long overlooked because of the rapidly progressing leukodystrophy, which causes patients to die before cortical pathology becomes obvious. Cortical gray matter pathology therefore has to be taken into account when developing therapeutic strategies.

Beerepoot, S. (1), Wolf, N.I. (1), Wehner, K. (2), Bender, B. (3), Van der Knaap, M.S. (1), Krägeloh-Mann, I. (2), Groeschel, S. (2)

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Acute-onset paralytic strabismus in toddlers is important to consider as a potential early sign of late-infantile Metachromatic Leukodystrophy

Rationale
Metachromatic leukodystrophy (MLD) is a fatal lysosomal storage disease characterized by progressive demyelination within the central and peripheral nervous system. Rapid diagnosis is crucial in view of evolving therapeutic options. Strabismus has anecdotally been described as a feature in children with MLD. Our first aim was to examine the prevalence of strabismus as an early or even presenting sign of MLD in two nationwide cohorts. Second, we aimed to investigate the temporal relation between the onset of strabismus and gross motor deterioration, other early onset eye movement disorders and brain white matter abnormalities.

Methods
Clinical records of 204 MLD patients at the University Children's Hospital Tubingen and Amsterdam University Medical Center were reviewed on the presence of strabismus and other eye movement disorders. Gross motor deterioration and white matter abnormalities on brain MRI were evaluated by using the Gross Motor Function Classification in MLD and MLD LOES score, respectively.

Results
We identified strabismus as an early sign in MLD patients with the late-infantile form only, with a prevalence of 22% (N = 14). The onset of strabismus preceded gross motor symptoms and brain white matter abnormalities in 79% and 50% respectively of the cases. Important characteristics were an acute-onset paralytic esotropia, partly accompanied by other eye movement abnormalities, and gadolinium enhancement of the cranial nerves.

Discussion
Acute-onset paralytic strabismus in toddlers should be considered a potential early sign of late-infantile MLD and might result from early cranial nerve involvement. Brain MRI with gadolinium contrast may facilitate early diagnosis.

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Incidence and relapse of idiopathic nephrotic syndrome: meta-analysis

Rationale
Idiopathic nephrotic syndrome (INS) in children is a disease with considerable morbidity, yet the incidence and risk for relapse have not been systematically reviewed. To estimate the overall pooled weighted incidence and risk for relapse of INS in children we conducted a systematic review of literature and performed a meta-analysis.

Methods
MEDLINE and Embase were searched until December 2020 using a comprehensice search strategy. All studies reporting incidence (per 100,000 children/year) and/or risk for relapse (proportion of total patients who experience ≥1 relapse) of INS in children (age <18 years) were eligible. After quality assessment, the following data were extracted: study (design, localisation, sample size) and patient (age, sex, steroid response, ethnicity) characteristics, incidence, and risk for relapse.

Results
After screening, 73 studies were included for analysis (27 incidence, 54 relapse). The overall pooled weighted estimate and corresponding prediction interval (PI) of the incidence was 2.92 (95% PI 0.00-6.51) per 100,000 children/year. Higher incidences were found in non-Western countries (p<0.001). Incidence tended to be lower in white children, but this was not significant. The overall pooled weighted estimate of the risk for relapse was 71.9% (95% PI 38.8-95.5). Between 1945 and 2011, incidence did not change (p=0.39), yet the risk for relapse decreased significantly (p=0.024) from 87.4% to 66.2%.

Discussion
INS has a low incidence with ethnic variation but a high risk for relapse. Although corticosteroids have significantly reduced the risk for relapse, it remains unacceptably high, underscoring the need for alternative treatment strategies.

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Stick figure videos contain sufficient information to assess dyskinesia

Rationale
Dystonia and choreoathetosis in dyskinetic cerebral palsy (CP) are currently assessed by clinical scales such as the Dyskinesia Impairment Scale (DIS). Most of these scales use video recordings for scoring. However, these methods are rater-dependent and therefore can be subjective. Furthermore, they are time-consuming. Clinicians and researchers seek for more objective and less time-consuming possibilities. A machine learning approach to automatically classify dyskinetic movement patterns, using stick figure videos extracted by markerless motion tracking from real videos, might be an option. As a first step, this study aimed to assess if relevant information is preserved within stick figures videos.

Methods
Videos of 34 children with dyskinetic CP (mean age 14y2m (4.0), 26 male) were available. Stick figure videos were created using markerless motion tracking and were scored following the DIS. DIS scores on real videos were previously assessed. To assess the concurrent validity, correlations between DIS (sub)scores of real videos and stick figure videos were calculated.

Results
A moderate correlation between total DIS scores of stick figure videos and total DIS scores of real videos ($r=0.537$, $p<0.000$) was found. There was a significant correlation between stick figures and real videos within the DIS dyskinesia subscores of the proximal arms ($r=0.559$, $p<0.000$) and the proximal legs ($r=0.456$, $p<0.000$).

Discussion
Scoring of dyskinesia with the DIS using stick figure videos appears to be a valid method to assess the severity of dyskinesia compared to using real videos. Therefore, using stick figures within a machine learning approach to classify dyskinesia should be further explored. The added value of using stick figure data is also that it does not contain privacy sensitive information and can be openly shared and combined towards big datasets needed for training of models for automatic detection.

Zwagemaker, A. (1), Kloosterman F.R. (1), Hemke, R. (2), Gouw, S.C. (1,3), Coppens, M. (4), Romano, L.G.R. (5), Kruip, M.J.H.A. (5), Cnossen, M.H. (6), Leebeek, F.W.G. (5), Hutten, B.A. (7), Maas, M. (2), Fijnvandraat, K. (1,8)

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Joint status of patients with non-severe hemophilia A*

Rationale
Hemophilia A is an inherited coagulation disorder in which joint bleeding is the hallmark of disease. In severe hemophilia, recurrent spontaneous joint bleeding may lead to irreversible joint damage. In non-severe hemophilia, joint bleeds are less common and occur mainly after trauma. It is currently not well known to what extent joint damage is present in this population. Therefore, we investigated the joint status of patients with non-severe hemophilia A.

Methods
In the cross-sectional DYNAMO study, patients with non-severe hemophilia A (FVIII 2-35 IU/dL) aged 24-55 year treated in the hemophilia treatment centers of the Amsterdam UMC and Erasmus MC were included. Joint status was assessed by magnetic resonance imaging (MRI) of elbows, knees and ankles and hemophilia-specific MRI IPSG (International Prophylaxis Study Group) scores were calculated. Lifetime joint bleeding data was collected from medical charts.

Results
The study population comprised 51 male patients, including 19 (37%) patients with moderate and 32 (63%) patients with mild hemophilia. The median age was 43 years (IQR 32-50), the median FVIII level 10 IU/dL (IQR 4-16) and the median annual joint bleeding rate 0.0 (IQR 0.0-0.2). MRI revealed soft tissue changes (IPSG sub-score >0) in the elbows, knees and ankles in 19%, 71% and 71% of patients, respectively. Additionally, osteochondral changes (IPSG sub-score >0) in the elbows, knees and ankles were detected in 0%, 20% and 35% of patients, respectively. Hemosiderin depositions were observed in 14% of joints with a negative lifetime joint bleed history.

Discussion
We found joint changes in a substantial proportion of this study population, despite a low frequency of joint bleeding. Importantly, hemosiderin was detected in joints without overt joint bleeding in the past which may suggest the occurrence of subclinical bleeding. These findings call for more awareness of joint health in patients with non-severe hemophilia.

* See Appendix for additional table and/ or figure

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Long Term Follow Up - Morbidity and mortality of pediatric patients with Sickle Cell Disease

Rationale
Sickle cell disease (SCD) is the most common inherited hemoglobinopathy with increased morbidity and mortality compared to the general population. Due to the severity of SCD, newborn screening for SCD has been introduced in January 2007 in the Netherlands. The objective of this study is to assess the effectiveness of this neonatal screening for SCD by describing the residual risks of death and major disease-related events during the first 14 years of life in children diagnosed with SCD at birth in the Netherlands.

Methods
Data were retrospectively collected from medical files of all children born after 1 January 2007, diagnosed with SCD identified through neonatal screening in the Amsterdam UMC. Descriptive data on sex, SCD genotype, survival state, first event of major SCD related complications, penicillin prophylaxis, vaccination coverage and TCD/MRI results were collected. Assessment of overall survival and survival without specific SCD-related complications will be generated by the time to first event. Residual risk of death and major disease-related events will be calculated. The major disease-related events include vaso-occlusive crisis and dactylitis with admission, acute chest syndrome, severe infections and neurological complications.

Results
Currently, 94 (54.5% HbSS or HbS/beta0-thalassemia and 42.4% HbSC or HbS/beta+-thalassemia) out of 174 eligible subjects have been included with a median age of 9.2 (IQR 5.0, 11.5). Overall probability of survival by fourteen years was 99.0%, with 1 death by pneumococcal septicemia related to SCD. A total of 5 patients (5.3%) had a severe infection, either meningitis, septicemia or osteomyelitis. Five patients had an abnormal TCD during the follow-up, but fortunately none of these patients experienced a stroke.

Discussion
In this cohort of neonatally screened SCD patients, the SCD-related mortality and morbidity is impressive with 1% mortality and 5 severe infections in the age group up to 14 years.

Lange de, A. (1), Alsem, M.W. (2), Karnebeek van, C (1), Woensel van, J.B.W. (2), Etten – Jamaludin, F.S. (3), Maaskant, J.M. (1,4)

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Moving forward in the transitional care research for children with medical complexity

Rationale
Research in the field of transitional care for Children with Medical Complexity (CMC) is hampered by the heterogeneity of outcomes. One method to overcome this problem is the development of a Core Outcome Set (COS). A COS is an agreed minimum set of outcomes that should be reported in all clinical trials. The development of a COS consists of three parts: a systematic review, a Delphi study and focus group discussions. Here we report the results of the systematic review on the used outcomes in studies that investigated the efficacy of transitional care interventions.

Methods
A systematic search of quantitative studies was conducted in Medline, EMBASE, Cochrane library, CINAHL, PsychInfo and Web of Science. Studies that describe any type of transitional care intervention that supports (parents of) CMC between 0-18 years were included. Two reviewers executed the selection and data extraction independently. The outcomes were categorized in five areas: mortality and survival, physical health, life impact, resource use, and adverse events.

Results
We identified 171 outcomes in 52 studies. Our research group identified the outcomes with similar wording or meaning, resulting in a final list of 25 outcomes. Physical health was operationalized as well controlled disease of CMC after hospital admission. The impact on life was evaluated by 13 different outcomes, e.g. quality of life, compliance, satisfaction, and self-efficacy. Resource use was covered by 9 different outcomes, of which hospital (re)admission was the most frequently reported. Adverse events were reported as the number of unsafe events concerning the child at home.

Discussion
We identified and categorized 25 outcomes that are reported in publications on transitional care for children. This list will be presented to an expert group (healthcare professionals and parents of CMC) in the next steps of the development of a COS: the Delphi study and focus group discussions.

van de Riet, L (1,2,3)*, Otten, M.H.(1*), van Woensel, J.B.M. (1,3), PICE registry (4)

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(4) Multicentre national PICU registry, the Dutch paediatric intensive care evaluation (https://www.pice.nl)

Long stayers and frequent flyers on the Dutch Pediatric Intensive Care Units

Rationale
Medical advancements have resulted in a growing population of children with chronic underlying diseases who often require prolonged Pediatric Intensive Care Unit (PICU) admissions and frequent readmissions. To emphasize this change in the PICU population, we describe time trends and the burden of long duration admissions and frequent readmissions on the Dutch PICU capacity over the course of 15 years.

Methods
All patients aged 0-17 years admitted to a Dutch PICU between 2003 and 2017 were included. The year 2018 was used as a follow-up year. Data were retrospectively extracted from the PICE registry, a national database in which data of all patients admitted to the PICU are continuously registered. Long stay was defined as an admission of ≥30 days, frequent flyers as ≥3 readmissions within the first year after discharge.

Results
A total of 47,424 critically ill children were admitted on 68,812 occasions and accounted for 386,525 cumulative admission days. Mortality decreased from 5.5% (2003) to 2.9% (2017). Long stayers (2.7% of the admissions) accounted for 33% of PICU bed occupancy days. Long stayers were younger (median 5 months) compared to the overall population (median 27 months) at admission. Frequent flyers (2.1% of unique patients) accounted for 13% of PICU bed occupancy days. No time trends were observed between 2003 and 2017 for number of long stayers and frequent flyers nor for accounted PICU occupancy days.

Discussion
Although a very small proportion of the total PICU population, both long stayers and frequent flyers comprise up to 33% of PICU bed occupancy days, creating substantial burden on healthcare systems. Between 2003 and 2017 mortality decreased, but number of long stayers, frequent flyers and their burden on PICU capacity remained constant.

Abstracts accepted for the Slam sessions

AMSTERDAM KINDER SYMPOSIUM

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An evidence-based guideline for social restrictions in children with cancer

Rationale
In current clinical practice, recommendations regarding social restrictions for children with cancer are often not evidence-based. Critically reviewing the evidence and recommendations is therefore of great importance as these social restrictions (e.g. swimming, school attendance, sports) can impair the quality of life of these children severely. Therefore, a clinical practice guideline (CPG) was developed to establish an overview of the available evidence and provide recommendations for both clinicians and children and their parents.

Methods
A systematic literature review was performed, including dual appraisal of all citations. The GRADE methodology was used to assess, extract and summarize the evidence. A comprehensive multidisciplinary panel was assembled, comprising 24 professionals and patient representatives. Multiple in-person meetings were held to rank outcomes, discuss evidence, complete evidence-to-decision frameworks and formulate recommendations. Final recommendations were unanimously supported by all panel members.

Results
Nine studies (including more than 1400 children) with various study designs formed the evidence base for the recommendations. Considering the limited amount of studies in children with cancer, additional evidence was extracted from adult guidelines. Our experts assessed all evidence and translated it, transparently, into recommendations. Eventually, more than 20 recommendations were formulated for specific clinical questions on social restrictions in children with cancer.

Discussion
In this clinical practice guideline, we provide both evidence-based recommendations and best practice statements regarding social restrictions in children with cancer. With these recommendations we provide guidance for both clinicians and children and their parents and contribute to improving quality of life for children with cancer.

Stellingwerff, M.D. (1), Al-Saady, M.L. (1), Van de Brug, T. (2), Barkhof, F. (3,4), Pouwels, P.J.W. (3), van der Knaap, M. S. (1,5)

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Natural MRI history in Vanishing White Matter

Rationale
Vanishing white matter (VWM) is a leukodystrophy, characterized by chronic neurological decline and stress-provoked episodes of rapid, partially transient decline. Earlier onset is associated with faster progression. Radiological hallmarks are rarefaction and cystic decay of the cerebral white matter (WM). Information on clinical-radiological correlation is lacking.

Methods
We retrospectively scored MRI scans of genetically confirmed VWM patients. Information on age at onset and episodic decline was collected. The ventricle-to-skull ratio was measured to estimate brain atrophy. Cerebral WM was visually scored on FLAIR images as normal, hyperintense, rarefied or cystic in percentage of the total volume and converted into a WM decay score. Cerebral WM was also segmented into normal-appearing, FLAIR-hyperintense (abnormal but present), and FLAIR-hypointense (rarefied or cystic) WM. Cerebellum, brainstem, thalamus and basal ganglia were scored as normal or T2-hyperintense.

Results
485 scans of 277 patients were scored. Cerebral WM was always abnormal. Earlier onset was related to higher rarefied or cystic WM volume [$F(5)=13.3$; $P<.001$], higher WM decay score [$F(5)=4.68$; $P<.001$], and faster progression of the WM decay score [$b=-1.6$, $t(109)=-3.9$; $P<.001$]. Later onset was associated with more cerebral atrophy [$F(5)=8.42$; $P< .001$]. Cerebral WM never improved.
Patients with acute episodes more often had diffuse T2-hyperintensities in the brainstem, thalamus and/or basal ganglia. These appeared with acute decline and mostly resolved over time.

Discussion
Cerebral WM abnormalities never improve and likely reflect the chronic aspect of VWM. Signal abnormalities in brainstem, thalamus and basal ganglia appear with rapid decline and mostly resolve; they likely reflect the acute episodes. These insights are essential for proper interpretation of MRI findings. Insight in the natural MRI history is crucial in upcoming trials.

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Retrospective cohort study on morbidities in moderate and late preterm infants in the first 5 years of life

Rationale
Most of all preterm births are moderate and late preterm infants (MLPT, gestational age 32 to 35+6 weeks, 80%). Surprisingly, their middle and long term outcomes have scarcely been reported in literature and their follow-up time after hospital discharge is usually short. To better detect the morbidities they suffer from in the first 5 years of their life, this retrospective study has been performed.

Methods
Patients born in or transferred to the Noord-West Ziekenhuisgroep between January 2014 and April 2016 were included. After reaching the age of five, data of all morbidities during the neonatal follow-up period and those leading to a referral to the hospital were analysed. Patients transferred to and followed-up in other hospitals were excluded.

Results
A total of 200 patient files were analysed, from which 192 were included. MLPT patients were found to have a 37.5% chance of hospital admission. The main reasons for hospital admission were the RS virus (3.6%), viral wheezing (4.7%) and other infections (14.6%). The risk of undergoing an operation was 31.3%, which was mainly due to adenotomies, tympan paracenteses, tonsillectomies (18.2%) and inguinal hernia surgery (5.7%). Other frequently seen morbidities were feeding difficulties (36.5%), gastroesophageal reflux disease (17.2%) and eczema (9.9% topical steroid use). Less frequently occurring but notable abnormalities were delays in motor development (12%), speech and language development (8.9%) and pyramidal symptoms (2.1%).

Discussion
This study provides a clear indication that MLPT patients suffer from many morbidities in early life, which should be followed-up throughout their childhood. A limitation is that this study has no cohort of patients born at term. A case control study should be performed to further analyse this data.

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Appendicitis and its associated mortality and morbidity in infants up to three months of age: A systematic review of 40 years of literature

Rationale
We recently encountered two cases of appendicitis in young infants in our tertiary paediatric surgical referral centre. Due to a low incidence of appendicitis in this age group and non-specific symptoms, appendicitis is often not primarily considered. Therefore, a systematic review was performed to enhance insights into appendicitis in this vulnerable patient group and to evaluate the associated mortality and morbidity.

Methods
A systematic review was performed (according to the PRISMA Statement) including articles on infants up to three months of age with appendicitis. Our primary outcome was the associated mortality and morbidity rate.

Results
In total, 98 articles, comprising 127 unique cases, were included after a search in PubMed and Embase (2128 articles). Our own two cases were encompassed for final review. Overall, 72% (93/129) of the patients had intra-abdominal manifestations of appendicitis while the remaining patients had an Amyand's hernia or umbilical hernia containing an inflamed appendix. The majority (75%) of patients was neonatal (0-28 days), with an even distribution of term compared to preterm. The overall perforation rate was 70% (90/129). We found a mortality and/or morbidity rate in 30% of the patients: a mortality rate of 14% (18/129) and morbidity rate of 16% (21/129). Importantly, the perforation rate was comparable between fatal and surviving cases. However, all fatal cases concerned patients with intra-abdominal manifestations. In addition, among these fatal cases a higher percentage was found of neonatal, female, and term patients and patients with presence of comorbidity. Furthermore, we will provide insights in the clinical presentation of appendicitis in this young population, its diagnostic work-up and potential treatment strategies.

Discussion
Awareness of the diagnosis of appendicitis remains critical in the vulnerable population of infants up to three months due to its associated high mortality and morbidity rates.

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Timing of therapy and neurodevelopmental outcomes in pyridoxine-dependent epilepsy

Rationale
Pyridoxine-dependent epilepsy (PDE-ALDH7A1) is a neurometabolic disorder of lysine degradation, which typically presents with intractable neonatal seizures. Pyridoxine treatment results in adequate seizure control, but 75% of patients suffer intellectual developmental disorders. Adjunct lysine reduction therapies (LRT) were developed to overcome this and are associated with improved cognitive outcomes. Not all patients have had normal outcomes, possibly due to timing of treatment. The aim of this study was to determine whether patients treated early with pyridoxine monotherapy and adjunct LRT have an improved neurodevelopmental outcome compared to their late treated siblings.

Methods
Patients with confirmed PDE-ALDH7A1 with at least one affected sibling and a difference in age at treatment initiation were eligible. Subjective clinical neurodevelopmental outcomes were assessed over 7 domains, including overall neurodevelopment assessed as normal (similar to a FSIQ>86), borderline (FSIQ 71-85), mild (FSIQ 51-70), moderate (FSIQ 36-50), or severe (FSIQ <35) and speech/language, cognition, fine motor, gross motor, and activities of daily living, were similarly assessed. Behavioral/psychiatric abnormalities were scored per finding.

Results
37 patients from 18 sibling pairs were included. Treatment regimen was pyridoxine monotherapy in 9 families and pyridoxine with adjunct LRT in 9 sibling pairs. There was no apparent difference between the siblings on pyridoxine monotherapy. For adjunct LRT, the early treated sibling performed better on the domains of overall neurodevelopment, cognition, fine motor and behavior/psychiatry. 14% of the total cohort was assessed as normal on all domains.

Discussion
Early treatment with adjunct LRT seems beneficial for neurodevelopmental outcome. Extensive neurodevelopmental assessment shows that almost no patient with PDE-ALDH7A1 is unaffected, and that the impairment rate of 75% stated in literature may be in fact higher.

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Cerebral organoids as a model to study genotype dependent potential of Parechovirus A to cause Central Nervous System related illnesses in infants

Rationale
Parechovirus A (PeV-A) from the Picornaviridae family is among the most prevalent human viruses worldwide. The most prevalent genotype PeV-A1 usually causes respiratory and gastrointestinal infections in infants. The second most prevalent genotype PeV-A3 causes severe (central nervous system-CNS) diseases such as encephalitis and meningitis. The cause for differential outcomes for these genotypes is poorly understood. Here, we investigate the viral dynamics and tropism of genotype PeV-A1 and PeV-A3 in the CNS by using iPSC (induced pluripotent stem cell)- derived human cerebral organoids.

Methods
Cerebral organoids were cultured for 67 days before inoculation with PeV-A1 and PeV-A3. Echovirus 11 (Echo11) was included as a positive control. Production of viral particles and their infectivity were quantified using reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) and median tissue culture infectious dose (TCID50) assay respectively. Changes in cytokine expression upon infection were quantified by RT-qPCR.

Results
RT-qPCR and TCID50 data shows replication of PeV-A1, PeV-A3, and Echo11 and the production of infectious particles in the cerebral organoids over 10 days. Upregulation of cytokine expression was observed upon infection with PeV-A3 and Echo11 for pro-inflammatory cytokines TNF- α, IFN-γ and IFN- α2. Notably, even though PeV-A1 genotype also productively infected cerebral organoids, no significant cytokine upregulation was observed upon PeV-A1 infection.

Discussion
For the first time, we demonstrate in vitro infection of PeV-A using iPSC-derived human brain organoids. Difference in CNS related pathology between the two genotypes of PeV-A is not due to inability of PeV-A1 to infect the CNS, as both PeV-A1 and PeV-A3 were shown to productively generate (infectious) particles. Upregulation of pro-inflammatory cytokines upon PeV-A3 infection indicates that PeV-A3 related CNS illness could be related to an increased pro-inflammatory response in the host.

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Prevalence, aetiology and outcome of paediatric shock in Malawi - a prospective study

Rationale
Shock is associated with high mortality. Limited prospective data is available on the prevalence, aetiology and outcome of shock in children in low resource settings. This constrains effective treatment strategies and contributes to mortality. The aim of this study was to assess prevalence, characteristics, outcome and potential risk factors of shock in children admitted to a large tertiary hospital in Blantyre, Malawi.

Methods
We collected demographic, clinical, laboratory and outcome data for paediatric patients aged 2 months – 16 years admitted with shock between February 2019 – January 2020. Shock was defined using modified FEAST criteria. We calculated descriptive statistics and performed uni- and multivariate analysis to determine the association between clinical diagnosis and outcome. To assess the role of shock definition, a secondary analysis using alternative definitions was performed.

Results
Prevalence of shock was 679/12840 (5.3%) using modified FEAST criteria, 3.2% using FEAST criteria excluding viral/reactive airway disease and 0.1% using WHO criteria. Main diagnoses were viral/reactive airway diseases (44.9%), pneumonia (18.8%), gastroenteritis (13.6%) and presumed sepsis (12.0%). Mortality was 79/679 (11.6%), and the main diagnoses in those who died were presumed sepsis (44.7%) and gastroenteritis (27.6%). Both diagnoses were more likely in children who died compared to those discharged (AOR 9.9, 95%CI: 4.1–23.8 for presumed sepsis) and (AOR 3.7, 95%CI: 1.8-7.4 for gastroenteritis). Mortality was 26% for FEAST criteria excluding viral/reactive airway disease and 60% for WHO criteria.

Discussion
In this prospective study assessing paediatric shock in a LMIC, 5.3% of admissions qualified as shock. Mortality was high at 11.6%, with presumed sepsis and gastroenteritis being common and associated with a poor outcome. Prevalence and mortality numbers were affected by the definition of shock used.

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Design research for procedural comfort in children*

Rationale
Negative emotions during medical procedures often have a major impact on children and their parents. Due to the limited implementation of proven effective strategies for minimizing fear and pain, procedural distress remains an ongoing problem. We aimed to design a child-centered solution for comfortable blood sampling in outpatient children (> 6 yrs). The underlying research question was how to develop a design solution integrating optimal preparation, correct use of topical anesthesia (EMLA®) and easily applicable distraction and engagement.

Methods
User-centered design process including 4 phases: interdisciplinary problem analysis, synthesis of relevant perspectives, integrated design of a product solution and its validation. A rational, evidence-based view was combined with an intuitive, hands-on design approach. Sketches and models were created and iteratively adapted by active participation of both healthcare professionals and experienced children.

Results
An interactive toolkit was developed as a self-to-explore printed paper box, guiding child and parents through an individualized preparation. Anatomically designed tattoo-like stickers indicating correct EMLA® application and a self-to-build distraction tool were enclosed. The final prototype 'OkidoKit' (Fig 1; https://www.youtube.com/watch?v=NtXuzMkdWkM) was positively evaluated by 10 children, showing they adequately interacted with the toolkit and enjoyed using it. In addition, 12 experts positively evaluated the design on various child-friendly values.

Discussion
Design research may be a powerful tool to bridge the current gap between evidence-based strategies for procedural comfort and their successful implementation. The OkidoKit effectively engaged school age children into a multimodal preparation for blood sampling. A similar strategy might yield practical solutions for different ages and procedures. Controlled studies are needed to test their effectiveness in realistic conditions.

* See Appendix for additional table and/ or figure

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Neurodegenerative disease after haematopoietic stem cell transplantation in metachromatic leukodystrophy

Rationale
Metachromatic leukodystrophy (MLD) is an inherited white matter (WM) disease with progressive demyelination of both the central and peripheral nervous system, caused by deficient arylsulfatase A (ASA). Hematopoietic stem cell transplantation (HSCT) has been shown to stabilize and even improve WM damage, yet some patients still deteriorate after successful transplantation. We hypothesized that clinical deterioration after treatment might be caused by the grey matter (GM) component of MLD.

Methods
We analysed deep grey matter (DGM) in three treated MLD patients who clinically deteriorated after HSCT, despite unchanged WM on brain MRI. Longitudinal volumetric MRI was used. Histopathological analyses with staining for ASA and sulfatides on brain tissue of three (other) treated and six untreated MLD patients were also performed.

Results
Volumetric MRI performed on patients who showed clinical deterioration with stable WM abnormalities identified progressive atrophy of DGM, specifically of the thalamus. Histopathology data showed neuronal sulfatide accumulation in untreated patients, most notably in the thalamus. ASA expression in thalamic neurons was not higher in transplanted than in untransplanted patients. Cortical GM of patients treated with HSCT contained substantially less ASA than the WM. Additionally, ASA-expressing donor macrophages were clearly present in the WM while nearly absent in the cortical GM of transplanted patients.

Discussion
Our findings confirm the GM involvement previously reported in MLD. The current study shows that this involvement may progress alongside stable WM pathology after seemingly successful HSCT treatment, and that this might be caused by a limited effect of HSCT on the GM component of MLD. The clinical deterioration of the analyzed patients illustrates the potential clinical relevance of the GM involvement for MLD.

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Dextroamphetamine treatment in children with hypothalamic obesity

Rationale
Hypothalamic obesity (HO) may have devastating consequences for the child and its family. Currently, no effective treatment is available for HO. Amphetamines, commonly used in children with attention deficit/hyperactivity disorder, are known for their stimulant side effect on resting energy expenditure (REE) and suppressing appetite, resulting in weight loss. We here present our experiences of dextro-amphetamine treatment in children with HO.

Methods
A retrospective cohort evaluation was performed of patients with HO treated with dextroamphetamine at two academic endocrine pediatric clinics. Off-label use of dextroamphetamine was initiated in patients with progressive, therapy-resistant acquired, genetic, or congenital HO. Anthropometrics, REE, subjectively reported (hyperphagic) behavior and energy level, and side effects were assessed at start and during treatment.

Results
Nineteen patients with a mean age of 12.3 ± 4.0 years were treated. ΔBMI SDS could be evaluated in 17 patients. Fourteen patients (n = 10 acquired HO, n = 3 genetic HO, n = 1 congenital HO) responded by weight loss or BMI stabilization (mean ΔBMI SDS of -0.6 ± 0.8, mean treatment duration 25.7 ± 13.1 months). In three patients, BMI SDS increased (mean ΔBMI SDS of +0.5 ± 0.1, mean treatment duration 14.2 ± 3.9 months). In 11 responders, who had REE measurements before and during treatment, mean REE increased with +164 kcal/day (+8.9% of predicted). Thirteen patients (68.4%) reported decreased hyperphagia and improvement of energy level and/or behavior. Two patients developed hypertension during treatment, which resulted in one patient to adjustment of the dosage and in the other patient to stop of treatment. Twelve children continued treatment at last moment of follow-up.

Discussion
In addition to supportive lifestyle interventions, dextroamphetamine treatment may lower or stabilize BMI and reduce hyperphagia in children with HO. Future studies are needed to support these results.

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The Guanabenz Trial: Treatment of patients with early-childhood onset Vanishing White Matter

Rationale
Vanishing White Matter (VWM) is a rare, devastating leukodystrophy (genetic brain white matter disorder) caused by recessive mutations in the genes EIF2B1-5. VWM primarily affects the brain white matter leading to chronic and progressive dysfunction characterized by ataxia, spasticity and cognitive decline. Additionally, there are episodes of subacute major neurological decline, provoked by stresses like febrile infections and minor head trauma. These episodes can lead to coma and death. Earlier disease onset correlates with more severe and faster disease. In VWM, the so-called integrated stress response (ISR), a protective response activated by physical stresses, is continuously abnormally activated. Guanabenz, an old α2-adrenergic antihypertensive drug, decreases ISR activation. In a mutant VWM mouse model, beneficial effects of Guanabenz were observed on motor function, brain white matter integrity and ISR activation. We currently conduct an open-label clinical trial with a historical control group using Guanabenz in children with early onset VWM.

Methods
Children with genetically proven VWM with clinical onset <6 years of age and brain MRI compatible with VWM, who are still be able to walk ≥10 steps, will be included in the trial. We will evaluate (1) safety and tolerability of Guanabenz, (2) pharmacokinetic profile, (3) efficacy as measured by clinical outcome and quantitative brain MRI parameters, and (4) potential biomarkers for future studies. We expect that in 2 years 30-40 patients can be included. The total trial duration will be 4 years.

Results
The first patient was included on May 31, 2021. By November 1, 6 patients were treated with Guanabenz. Until now, none of the patients deteriorated. Common side-effects were drowsiness, fatigue, nausea and nightmares. In all patients, tolerance was observed.

Discussion
Preliminary results suggest that Guanabenz is tolerated by VWM patients. Longer follow-up is needed to evaluate efficacy.

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Mother milk inhibits enveloped virus infection, including SARS-CoV-2, in a human gut organoids model

Rationale
Viral transmission from mother to child through infected mother milk is well established for viral infections such as human immunodeficiency virus (HIV) and cytomegalovirus (CMV) known to cause perinatal disease. Similarly, in the case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), it has been suggested that breastfeeding could potentially be a mechanism for transmission during the acute phase of disease.

Methods
The 3D human fetal intestinal organoids are an "inside out" representation of human physiology with the basal side on the outside facing the environment and the apical side facing the inwards. During culture, the organoids are "opened up" and cultured as a monolayer on transwell inserts to evaluated the protective ability of breastmilk against SARS-CoV-2. The monolayers were apically exposed to SARS-CoV-2 and mother milk mix. Samples were collected on different time point for different analysis.

Results
In the current study, we evaluated the protective ability of mother milk against SARS-CoV-2 infection in a human fetal primary intestinal organoids model. We find that human mother milk blocks SARS-CoV-2 replication, irrespective of the presence of SARS-CoV-2 specific antibodies, in this model. Furthermore, complete inhibition of both enveloped Middle East Respiratory Syndrome Coronavirus and Respiratory Syncytial Virus infections while no inhibition of non-enveloped Enterovirus A71 infection was observed.

Discussion
Our data indicate that mother milk has potent antiviral activity against some enveloped viruses and identification of the potential mechanism will be of value in antiviral treatment.

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Identification of predictive markers for the development of post thrombotic syndrome in pediatric patients after a Deep Vein Thrombosis

Rationale
Post thrombotic syndrome (PTS) is a severe chronic condition following thrombosis (DVT), caused by venous insufficiency of the collaterals and associated with pain, swelling and restricted use of the affected limb. Although there is no curative treatment available for PTS, it is important to identify patients at increased risk of this complication, to evaluate the efficacy of preventive measures.

Method
This retrospective study included all children (0-18 years) treated for a DVT at Emma Children's Hospital between March 2001 and January 2021. The determinants studied were: provoked/unprovoked DVT, >1 vessel involved, >1 comorbidity, CVC related DVT, oral contraceptives, physical activity, lack of thrombus resolution, recurrent DVT, use of compression stockings and inflammatory status. The outcome was PTS development. Associations were analysed by multivariate analysis with backward variable selection.

Results
This cohort/analysis consists of 342 patients out of a total of 703 eligible patients (35% (n=241) neonates and 64% (n=462) children ≥1 year). 115 Children developed PTS (23% of the neonates and 40% of the children ≥1 year).
In neonates >1 vessel involved during the DVT was the only determinant associated with PTS development (OR: 3.3; 95%CI 1.5-9.5).
In children ≥ 1 year, an unprovoked DVT (OR: 9.2; 95%CI 1.8-30.6), age ≥11 years (OR: 5.4; 95%CI 1.2-26.3), oral contraceptives (OR: 5.4; 95%CI 1.2-36.3) and > 1 vessel involved (OR: 5.7; 95%CI 2.6-13.9) were associated with PTS development. On the contrary, physical activity decreased the risk for PTS (OR: 0.2; 95%CI 0.08-0.7).

Discussion
In neonates >1 involved vessels contributed to PTS. In children ≥1 year unprovoked DVT, age ≥11 years, oral contraceptives and an >1 vessel involved were associated with PTS. Physical activity decreases PTS risk. These data can be helpful to identify patients at risk for PTS development and target individualized prevention and therapy in the future.

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A health care evaluation on the use of dextrose gel incorporated in the new national guideline for hypoglycemia in neonates

Rationale
Hypoglycemia is a common problem, especially in neonates with predisposing risk factors. Persistent hypoglycemia can cause brain damage and therefore it is important to screen neonates at risk. The protocol for screening at the Noordwest Ziekenhuisgroep Alkmaar was changed according to the new national guideline. The main adjustments were the implementation of oral dextrose gel and lowering the intervention threshold of serum glucose to 1.6 mmol/L for the first 2 hours after birth and 2.0 mmol/L for 2 to 48 hours. This healthcare evaluation aims to compare the new protocol with the old protocol in the need for intravenous glucose administration.

Methods
A retrospective data analysis was performed from September 1, 2020 to March 31, 2021, and April 26, 2021 to June 6, 2021. The primary outcome was the need for intravenous administration of glucose. The secondary outcome measures were the incidence of hypoglycemia, duration of glucose controls, length of hospital stay, need for supplemental feeding during hospitalization, admission to the neonatal ward for hypoglycemia, and type of feeding at discharge.

Results
A total of 408 neonates were included, 342 were treated with the old protocol and 66 with the new protocol. The incidence of hypoglycemia was equal, respectively 59,9% and 60,6%. To treat hypoglycemia, 49 neonates (23,9%) versus 6 neonates (15.0%) needed intravenous glucose administration. Significantly fewer neonates received supplemental feeding during hospitalization (63,5% versus 37,9%) and more neonates were fed with breast milk at discharge (36,5% versus 59,1%).

Discussion
After implementation of the new protocol and oral dextrose gel, fewer neonates needed intravenous glucose administration to treat hypoglycaemia. Also, more neonates were fed with breast milk at discharge. However, the incidence of hypoglycemia remained the same. We will evaluate after 6 months whether these results remain significant.

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Genetic and clinical determinants of the outcome of immune tolerance induction in severe hemophilia A – preliminary results*

Rationale
Eradicating inhibitors to restore factor VIII (FVIII) efficacy is a desirable treatment goal for patients with severe hemophilia A (SHA), as this enables treatment of bleeding episodes with FVIII concentrates. However, since immune tolerance induction (ITI) is a burdensome and costly treatment, it is important to identify determinants for ITI success to decide if worth undertaking. We aim to identify genetic and clinical determinants for ITI success in SHA.

Methods
Dutch and Canadian patients with SHA who underwent ITI between 2015 and 2019 were included. Clinical successful ITI was defined by (1) a negative inhibitor titer and (2) an adequate clinical response to standard FVIII doses. We analyzed the following genetic determinants: FCGR2A (p.His166Arg, p.Gln62Trp, c.777+1G>A), FCGR2B (p.Ile232Thr, promotor haplotypes 2B.1/2B.4), FCGR2C (p.Gln57Ter, promotor haplotypes 2B.1/2B.2),
FCGR3A (p.Val176Phe), FCGR3B (haplotypes NA1/NA2), CTLA-4 (rs5742909 -318C/T), TNF (rs1800629 -308G/A) and IL10.G CA repeat microsatellites. Clinical determinants included patient, treatment and inhibitor characteristics. Crude relative risks (RR) were calculated for ITI success with 95% confidence intervals [CI].

Results
76 patients were included. Baseline characteristics are shown in Table 1. Historical peak titer ≥200 BU/ml was associated with ITI failure (RR 0.48 [0.28-0.80]) compared to <200 BU/ml. Moreover, patients with pre-ITI titers >5 BU had lower changes for ITI success compared to those with titers ≤5 BU (RR 0.80 [0.66-0.98]). No clear associations were found between ethnicity, F8 genotype and genetic variation in FCGR, CTLA-4 and TNF and ITI success. The role for IL10.G CA microsatellite repeats on ITI outcome needs further investigation.

Discussion
Our preliminary results suggest that historical peak titer <200 BU/ml and pre-ITI titer ≤5 BU/ml are predictors for ITI success. Multivariate analyses will be available at the time of the AKS 2022.

* See Appendix for additional table and/or figure

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The reliability of the Sexual Knowledge Picture Instrument, a diagnostic instrument for sexual abuse in young children

Rationale
Aim is to determine the intra- and inter-rater reliability of the Sexual Knowledge Picture Instrument (SKPI), a potential diagnostic instrument for young suspected victims of sexual abuse.

Methods
A group of 78 children aged three to nine years, of whom 39 with and 39 without suspicions of a history of sexual abuse was recruited and interviewed with the SKPI. The child-interviews were video recorded, and then observed and scored by two trained, independent raters by using three standardized scoring forms on verbal responses, non-verbal reactions and red flags. Intra and inter-rater reliability of the scoring data was assessed by Cohen's kappa and percentage of agreement (POA).

Results
The overall intra-rater agreement was almost perfect in both groups on all three forms (Cohen's kappa's >0.90, and POA >95), except for a moderate agreement on the red flag form in the suspected group (Cohen's kappa 0.538, POA 87.2).
The overall inter-rater agreement was almost perfect on the verbal scoring form in the suspected and control group (both Cohen's kappa 1.000, POA 100), fair on the non-verbal form (Cohen's kappa 0.373 and 0.473, POA 97.4 and 100 respectively), and moderate on the red flag form (Cohen's kappa 0.371 and 0.422 , POA 73.7 and 76.9 respectively).

Discussion
The reliability of the SKPI was sufficient, allowing further validation of the instrument. The verbal scoring form needs no further adjustments. The reliability of the non-verbal and red flag form may be improved, for example by adjusting the rater training, or removing the unreliable scoring items.

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Point-of-care ultrasound provides useful information in children with Crohn's Disease visiting the outpatient clinic

Rationale
Point-of-care ultrasound (POCUS) is increasingly used in clinical practice as disease monitoring tool for children with Crohn's Disease (CD). However, it's additional value next to conventional markers of disease activity, such as faecal calprotectin (FC) has not been studied. This study aimed to assess the clinical added value of POCUS in children with CD.

Methods
Children aged 3-17 years with CD visiting the outpatient clinic underwent POCUS in addition to FC test and mucosal inflammation non-invasive index for paediatric Crohn's disease (MINI-index). Both tests were categorized into normal, uncertain and abnormal. Paediatric gastroenterologists decided on clinical management before and after POCUS disclosure. The predictive value of POCUS for clinical flares within 4 months was assessed. Outcomes were the proportion (95% CI) of patients where the POCUS result was discordant from FC and MINI-index, proportion of patients where POCUS changed clinical management, and predictive values of POCUS for clinical disease flares.

Results
We included 76 CD patients (median age: 16 years, 34 (45%) female, median disease duration: 2 years). In 7 (9% (4-18%)), and 2 (3% (0-9%)) patients, the POCUS resulted in a less severe classification and in 43 (57% (45-70%)), and 44 (58% (46-69%)), in a more severe classification of disease severity than FC and MINI-index, respectively. Clinical management changed in 46 (58%) cases after POCUS result disclosure. The positive and negative predictive value for clinical flares within four months of an abnormal POCUS were 71 (57-82)% and 74 (64-83)%, respectively.

Discussion
This study shows that the routine use of POCUS in outpatient care provides additional information on CD activity, impacts clinical decision making in an important portion of children with CD, and predicts clinical flares. In all, our results support the uptake of routine POCUS in the clinical management children with CD.

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Oral immunotherapy in young children with food allergy: sustained unresponsiveness after 1 year of treatment.

Rationale
Most food allergies start in childhood, frequently with lifelong dietary and psychosocial impact. Oral immunotherapy started early in life (e-OIT), is a very promising food allergy treatment, changing the lifelong implications of a food allergy. In peanut-allergic infants, this therapy has shown to be very effective in achieving long-term tolerance due to its immunomodulatory effect. In our study, we investigate safety, feasibility and effectiveness of low-dose e-OIT in infants with a broad range of food allergies.

Methods
In this prospective intervention study, children aged 9-24 months with a proven food allergy based on sensitization and a positive oral food challenge (OFC) are included. Participants receive a maintenance dose of 300 mg/day allergenic protein during 1 year after a build-up phase. The endpoints are safety, feasibility and sustained unresponsiveness at 4 weeks after stopping e-OIT, as assessed by an exit OFC.

Results
Until now, 34 children (median age 14, range 9-23 months) finished e-OIT for peanut, tree nuts or egg. Median allergen-specific IgE at inclusion was 6.1 kU/l (IQR 2-15.5 kU/l). The median baseline threshold level determined by an OFC was 1000 mg (range 10-3000 mg) allergenic protein. Most parents assessed e-OIT as feasible. The majority of side effects were mild allergic symptoms. Thirty-two children achieved sustained unresponsiveness, consuming 4.4 grams of allergenic protein without allergic reaction during the exit OFC and continued dietary allergen consumption at home. Median allergen-specific IgE levels declined to 2.5 kU/l (IQR 0.42-5.6 kU/l, $p<0,001$). The two patients with persistent allergy had high baseline allergen-specific IgE levels (33 and 24 kU/l) and low threshold levels (100 and 300 mg).

Discussion
E-OIT is a safe and feasible treatment in young food allergic children and was highly effective in achieving sustained unresponsiveness. These unique results suggest that e-OIT is a very promising treatment.

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Bronchopulmonary dysplasia and neurofilament light chain biomarker in preterm infants*

Rationale
A common complication after preterm birth is bronchopulmonary dysplasia (BPD), a multifactorial chronic lung disease that is strongly associated with poor neurodevelopmental outcome. Neurofilament light chain (NfL) has been identified as a biomarker for neuroaxonal injury, in adult as a well as preterm populations. We hypothesize that NfL predicts neurodevelopmental outcome associated with BPD and studied NfL serum levels during the first month of life in preterm infants with and without BPD.

Methods
This was a prospective cohort study, PRIDICT-BPD study, which studied the feasibility of various assays for the prediction of BPD in infants born <30 weeks of gestational age (GA), admitted to the Neonatal Intensive Care Units (NICUs) of the Amsterdam University Medical Center (Amsterdam UMC), between October 2019 and March 2021. We obtained cord and venous blood at postnatal days 3, 7, 14 and 28 from 70 infants and determined Serum NfL levels using Simoa assay and compared between infants with BPD (BPD group) and infants without BPD (no BPD group).

Results
Of the 70 included infants (37 (52.9%) males) in our study, 22 (31.4%) infants were included in the BPD group and 48 (68.6%) in the no BPD group. Infants in the BPD group were born at a lower GA and were more often small for gestational age (SGA) compared to infants in the no BPD group.
In the whole group NfL concentrations increased during the first week of life, and declined thereafter (figure 1). Analyses regarding the differences in NfL levels of infants in the BPD group compared to infants in the no BPD group are in progress.

Discussion
With this study, we showed that NfL serum levels increased during the first week of life and declined afterwards in preterm born infants below 30 weeks of gestational age. This is in line with observations from previous studies. The differences between NfL serum levels of infants with and without BPD are being analyzed.

* See Appendix for additional table and/ or figure

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Tubular dysfunction and treatment-related risk factors in long-term childhood cancer survivors; DCCSS-LATER 2: RENA

Rationale
The aim of this nationwide cross-sectional cohort study was to determine the prevalence of and risk factors for tubular dysfunction in childhood cancer survivors (CCS).

Methods
In the DCCSS-LATER 2 RENA study on renal toxicity, 1,024 CCS (≥5 years after diagnosis), aged ≥18 years at study visit, treated between 1963 and 2001 with potentially nephrotoxic therapy (i.e. nephrectomy, abdominal radiotherapy, total body irradiation, cisplatin, carboplatin, ifosfamide, high-dose cyclophosphamide (≥1g/m2 per course or ≥10 g/m2 in total), or hematopoietic stem cell transplantation participated and 500 age- and sex matched controls from Lifelines. Tubular electrolyte loss was defined as low serum levels (respectively magnesium <0.7, phosphate <0.7 and potassium <3.6 mmol/L) in combination with increased renal excretion, or receiving electrolyte supplementation. α1-microglobulin:creatinine ratio >1.7 mg/mmol was considered as low-molecular weight proteinuria (LMWP). Chi-square analyses and multivariable logistic regression analyses were performed.

Results
Median age at diagnosis was 4.7 years (interquartile range [IQR] 2.4-9.2), at study 32.5 years (IQR 27.7-38.0), and follow-up time 25.5 years (IQR 21.4-30.3). Overall prevalence of electrolyte losses in CCS (magnesium 5.6%, potassium 4.5%, phosphate 5.5%) was not higher compared to controls, while LMWP was significantly more prevalent (CCS 20.1% versus controls 0.4%). Ifosfamide exposure was a risk factor for potassium loss, phosphate loss (when cumulative dose >42 g/m2) and LMWP. Cisplatin treatment increased the odds for magnesium loss and cumulative dose > 500 mg/m2 for potassium and phosphate loss. Carboplatin cumulative dose > 2800 mg/m2 was associated with potassium loss.

Discussion
After a median follow-up of 25 years 20% of CCS had LMWP, but tubular electrolyte loss was infrequent. Yet, ifosfamide, cisplatin and carboplatin were associated with tubular toxicity.

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The use of personalized masks to optimize non-invasive ventilation in children admitted to the Paediatric Intensive Care Unit*

Rationale
The use of non-invasive ventilation (NIV) in the Paediatric Intensive Care Unit (PICU), as an alternative to invasive ventilation, has increased substantially over the past two decades. However, paediatric NIV also presents a major challenge: finding a properly fitting ventilation mask. Improper fit of the mask results in patient discomfort, air leakage, and skin pressure sores, which lead to treatment failure. The aim of this study is to design and validate a tailor-made NIV mask for critically ill children in the PICU.

Methods
A modular ventilation mask was designed that is custom-made by semi-automated 3D scanning and printing techniques. This concept was further developed, including material specifications and process design. Additionally, a pilot study was set up to investigate the effectiveness of this 3D printed mask in comparison to two commercial alternatives, with the focus on air leakage and skin pressure. This was tested in a laboratory setting using a 3D printed test head model connected to a mechanical ventilator and lung simulator.

Results
The different parts of the personalized mask were designed and developed, and could be assembled together into a firm, usable, and airtight ventilation mask. Preliminary results of the conducted pilot study showed that the mask can be used for NIV, and has the potential to surpass the commercially available masks in performance.

Discussion
The personalized ventilation mask seems to be a good concept with a feasible prototype. Optimization of the mask might even improve the results and hence treatment with NIV, but validation in vivo is needed to confirm these findings. Our ultimate goal is to make it possible to provide an individual NIV mask for all children within 24 hours after admission to the PICU.

* See Appendix for additional table and/or figure

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Mental health problems during the COVID-19 pandemic in Dutch children and adolescents with and without pre-existing mental health problems*

Rationale
Previous research has shown that psychological problems in children and adolescents have increased due to the COVID-19 pandemic. However, less is known about changes in mental and social health throughout the COVID-19 pandemic and whether changes in children with pre-existing mental health problems are similar to those in children from the general population.

Methods
We included children (8–18 years) who receive psychiatric care (NT1=275; NT2=508) and children from the general population (NT1=832; NT2=746). We assessed measures during the first lockdown (April-May 2020) and before the second lockdown (November 2020) in the Netherlands. Main outcome measures were Patient-Reported Outcomes Measurement Information System (PROMIS®) domains: Global Health, Peer Relationships, Anxiety, Depressive Symptoms, Anger, and Sleep-Related Impairment, as reported by children. We differentiated between boys and girls, and between ages 8 to 11 and 12 to 18.

Results
At the first time point, the psychiatric sample reported significantly more problems than the general population sample on all measures except for Anxiety and Peer Relationships. From the first to the second time point, the psychiatric sample deteriorated on all measures expect Peer Relationships, whereas the general population sample remained stable. Within the psychiatric sample, increases in mental health problems were largest for girls aged 12-18 (see Figure 1).

Discussion
This study shows that throughout the COVID-19 pandemic, the mental health of children in psychiatry is deteriorating, particularly in adolescent girls. Our findings indicate that specific groups of children are more vulnerable to negative mental health effects during the pandemic and suggests they may require comparatively more care in the long term.

* See Appendix for additional table and/or figure

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Improved outcome of infantile oxalosis in Europe

Rationale
Infantile oxalosis is the most severe form of primary hyperoxaluria (PH), with onset of end-stage kidney disease (ESKD) during infancy. We aimed to analyze the outcome of these patients as our current understanding is limited due to a paucity of reports.

Methods
A retrospective registry study was conducted using data from the OxalEurope registry. All PH1 patients with ESKD onset at age <1 year were analyzed.

Results
We identified 95 patients born between 1980 and 2018 with infantile oxalosis. Median (IQR) age at ESKD was 0.4 (0.3 – 0.5) years. Four patients diagnosed by family screening developed ESKD despite early diagnosis. Eleven patients had a genotype associated with vitamin B6 responsiveness. Twenty-seven of 89 patients (30%) died at a median age of 1.4 (0.6 – 2.0) years (five-year patient survival of 69%). Systemic oxalosis was described in 96% (n=54 of 56) of screened patients. The first transplantation procedure was performed at a median age of 1.7 (1.3 – 2.9) years. In 42 cases this procedure was combined liver-kidney transplantation, and in 23 cases liver transplantation was part of a sequential technique. Survival rates of both strategies were similar. Patient survival was significantly higher in patients born after 2000. Intra-familial phenotypic variability was present in 14 families of patients with infantile oxalosis.

Discussion
Nearly all screened infantile oxalosis patients developed systemic disease. Patient survival is low but has significantly improved over time and might further improve under new RNA interfering therapies. The high intra-familial phenotypic variability warrants further investigation.

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Severity of bronchopulmonary dysplasia and neurodevelopmental outcome at two and five years corrected age

Rationale
Bronchopulmonary dysplasia (BPD) is associated with neurodevelopmental impairment (NDI), but it remains unclear whether this association is dependent on the severity of BPD at five years corrected age (CA), and whether NDI and its association with BPD severity changes over time between two- and five years CA.

Methods
Patients with a gestational age < 30 weeks surviving to discharge were included in this single center retrospective cohort study, dividing them into groups according to BPD severity. NDI was defined as having cognitive or motor abilities below -1 standard deviation, cerebral palsy, or a hearing or a visual impairment. The association between BPD severity, and NDI at two- and five years CA was assessed using a multivariate logistic regression model analysis, adjusting for known confounders for NDI, and mixed model analysis.

Results
Of the 790 surviving infants in this cohort (15% diagnosed with mild, 9% with moderate and 10% with severe BPD), 88% and 82% were longitudinal assessed at two- and five years CA, respectively. Analysis showed a statistically significant increase in NDI in all levels of BPD severity compared to the infants with no BPD (OR 2.01, 95% confidence (CI) 1.12, 3.59, p = 0.028; OR 2.12, 95% CI 1.08, 4.13, p =0.019, and 3.28, 95% CI 1.74, 6.19, p<0.001 for mild, moderate and severe BPD, respectively). Compared to the infants without the diagnosis BPD, a fivefold increased risk in NDI rate was seen from two to five years CA in all degrees of BPD severity (OR 5.36, 95% CI 3.82, 7.53, p<0.001). The strength of the association between NDI and BPD severity did not change over time.

Discussion
Increasing BPD severity is associated with an increasing risk of NDI at both two- and five years CA. The absolute incidences of NDI significantly increased from two to five years CA in all BPD severity categories, but the increasing risk between these categories was similar at both time points.

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Ready for discharge? Prognostic factors on parental empowerment.

Rationale
The number of children requiring complex care during hospital stay is growing. Because this care often has to be continued at home, transition from hospital to home requires careful preparation and parental training. However, many parents do not feel empowered in their role as caregiver for their child, and it is unclear how to tailor the hospital-to-home interventions. Therefore, we designed a study to explore prognostic factors associated with parental empowerment after discharge of hospitalized children aged 0-18 years.

Methods
A literature search was executed on prognostic factors influencing parental empowerment. Subsequently, a cross-sectional study was conducted among parents of admitted children in January-March 2021. Two weeks following discharge, data were collected on potential prognostic factors and parents filled in the Family Empowerment Scale (FES). The FES is a validated questionnaire; higher scores meaning more empowerment. Univariable and multivariable linear regression analyses were performed to establish the associations between the prognostic factors and the FES.

Results
Data from 228 patients and their parents were analysed. Three factors were significantly associated with parental empowerment. The older the child the higher the FES score (β=0.01, p=0.00). Parents of a child with medical complexity (CMC) have higher FES scores compared to parents without a CMC (β=0.20, p=0.00). Also, employed couples feel more empowered compared to unemployed couples (β=0.30, p=0.00). These three variables explained 11% of variance in the FES scores.

Discussion
We found that parental empowerment is associated with the child's age and medical complexity, and parental employment status. Attention should be paid to the discharge preparation of parents of children without or with less medical complexity. Healthcare professionals should be aware of other risk factors for less parent empowerment, such as age of the child and parental employment status.

van de Riet, L.(1,2); Alsem, M.W. (3); van der Leest, E.C. (4); van Etten – Jamaludin, F.S.(5); Maaskant, J.M. (6,7); van Woensel, J.B.M. (1); van Karnebeek, C.D. (6,8)

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Improving hospital to home transition for children with medical complexity and their families by understanding parental needs: A systematic review of qualitative studies following a meta-aggregative approach*

Rationale
Families of Children with Medical Complexity (CMC) have particular needs that extend well beyond the hospital grounds. The gap between a protective hospital environment and home is large, making the transition from one to the other a major challenge. Understanding these needs will help us create more personalized interventions to improve this process of transition in the future. The aim of this review is to systematically identify, appraise and synthesise all existing qualitative evidence regarding the needs and experiences of parents of CMC during transition from hospital towards home.

Methods
An extensive search in Medline, PsychINFO and CINAHL yielded 1515 papers of which 22 proved eligible for final inclusion. All articles were assessed for methodological quality for which we used the JBI Critical Appraisal Checklist for Qualitative Research.[ref JBI] Data was extracted and pooled using MaxQDA software. We performed a meta-aggregation method to aggregate our study findings into categories and formulate overarching synthesised findings, which were rated according to their level of credibility, following the CONQual approach. [ref JBI]

Results
Meta-aggregation resulted into (3) synthesised findings [figure 1]. Empowerment, Engagement and Enablement. A total of (346) study findings were extracted from the included 22 articles and were subsequently aggregated into 46 subcategories and 10 main categories. These categories are all incapsulated by these 3 synthesized findings described earlier by Fumagali et al. (2014).

Discussion
While CMC families face various and particular transition needs and obstacles, certain overarching themes arise. Identifying them is the first step to creating interventions that are both personalized and flexible and that stimulate interdisciplinary collaboration to ensure a safe and sustainable transition home.

* See Appendix for additional table and/ or figure

Oomen, I. (1,2), Camelo, R.M. (3), Rezende, S.M. (3), Voorberg, J. (2), Mancuso, M.E. (4), Oldenburg, J. (5), Carcao, M. (6), Matino, D. (7), Lillicrap, D. (8), Fischer, K. (9), Fijnvandraat, C.J. (1,2), Gouw, S.C. (1,10), on behalf of the International GO-ITI study group

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Genetic and non-genetic determinants of the outcome of immune tolerance induction in patients with hemophilia A and inhibitors –a systematic review*

Rationale
Immune tolerance induction (ITI) is the only therapy to eradicate anti-factor VIII antibodies (inhibitors) in patients with hemophilia A. However, this burdensome and costly treatment fails in 10-40%. In order to determine whether to attempt ITI, it is important to identify predictors of ITI success. This systematic review aims to assess association between genetic and non-genetic factors and ITI success in patients with hemophilia A.

Methods
A comprehensive literature search was conducted on February 17 2021, in the MEDLINE and Embase databases using the following search terms; hemophilia and immune tolerance. Studies reporting on predictors for ITI outcome in patients with congenital hemophilia A who underwent ITI therapy were eligible for inclusion. Data were extracted on study, patient, treatment and determinant characteristics. Two independent reviewers performed the study selection, data extraction and methodological quality assignment using an adapted checklist of the Joanna Briggs Institute. If heterogeneity is limited, pooled effect estimates of individual determinants will be assessed.

Results
The literature search yielded 1021 unique papers. Article selection is depicted in Figure 1. Preliminary results showed that the majority of studies (≥5 studies) reported as determinants for ITI success included lower pre-ITI titer, lower historical peak titer and lower peak titer on ITI. Factors associated with ITI failure in the majority of studies (≥5 studies) were younger age at inhibitor development and longer interval between inhibitor detection and ITI initiation. The final results of this systematic review will be available at the time of the AKS 2022.

Discussion
The results of the systematic review summarizes the current evidence on factors associated with ITI outcome. Further research is required on predictors of ITI outcome. Our future aim is to create a prediction model in order to tailor treatment on the basis of predicted ITI outcome.

* See Appendix for additional table and/or figure

Snoek L. (1), van Kassel M.N. (1), Krommenhoek J.F. (1), Achten N.B. (2,3), Plötz F.B. (2,3), van Sorge M.N. (4,5), Brouwer M.C. (1), van de Beek D. (1), Bijlsma M.W. (1,3)

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Neonatal early-onset infections: comparing the sensitivity of the neonatal early-onset sepsis calculator to the Dutch and the updated NICE guideline in an observational cohort of culture-positive cases

Rationale
Neonatal early-onset sepsis and meningitis (early-onset disease; EOD) are rare, but potentially devastating diseases. Many healthy infants with risk factors for EOD are treated with antibiotics. The early-onset sepsis calculator (EOSC) is a tool to identify EOD cases and reduce unnecessary antibiotic treatment. However, its performance in identifying EOD cases is unclear. We compared the sensitivity of the EOSC to the current Dutch and NICE guidelines when applied to a cohort of newborns with culture-positive early-onset sepsis and meningitis.

Methods
Culture-positive Streptococcus agalactiae (GBS) and Escherichia coli (E. coli) sepsis and meningitis patients ≤3 days old with a gestational age ≥34 weeks from a prospective nationwide cohort study were included. Primary outcome was the proportion of patients that would have been treated according to the EOSC, the Dutch and the NICE EOD prevention guidelines. Differences between proportions were analysed using McNemar's test.

Results
We included 88 infants with culture-positive EOD, 81 were caused by GBS and 7 by E. coli. At 4 hours after birth, the EOSC would have recommended antibiotic treatment in 32 (36%) patients, compared to 44 (50%) by the Dutch guideline ($p<0.01$) and 48 (55%) by the NICE guideline ($p<0.01$). At 24 hours after birth, the EOSC would have recommended antibiotic treatment in 54 (61%) infants, compared to 64 (73%) by the Dutch guideline ($p=0.02$) and 63 (72%) by the NICE guideline ($p=0.06$).

Discussion
The sensitivity of the EOSC is lower compared to both Dutch and NICE guidelines, especially in the first hours after birth. The EOSC relies more on clinical symptoms and results in less overtreatment of healthy newborns at the cost of delayed antibiotic treatment in initially well-appearing EOD patients. Better EOD risk stratification methods are needed.

Draijer, L. (1), Voorhoeve, M. (1), Kusters, D. (1), de Groot, E. (2), Troelstra, M. (3), Beuers, U. (4), Nederveen, A. (3), Benninga, M. (1), Koot, B. (1)

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The natural history of non-alcoholic fatty liver disease: a 10-year follow-up study

Rationale
The long term hepatic outcome of pediatric Non-alcoholic Fatty Liver Disease (NAFLD) remains unclear due to the lack of robust longitudinal data on the natural history of pediatric onset NAFLD into adulthood. The aim of this follow-up study is to determine the 10-year natural history of pediatric onset NAFLD.

Methods
Between 2008-2012, an unselected cohort of 133 children with severe obesity was screened for NAFLD. All participants were invited to participate in the present study. Change in steatosis and fibrosis was measured using Proton Magnetic Resonance Spectroscopy (1H-MRS) and the Enhanced Liver Fibrosis Test (ELF test), respectively. Steatosis was defined as 1H-MRS > 1.8%, which was validated to correspond with > 5% steatosis at histology.

Results
In total, 51 of the 133 subjects from the original cohort participated in the present study (38%). At follow-up, 65% was female, mean BMI was 40.06 kg/m2 and median ALT was 21 IU/L. The median 1H-MRS and proportion of subjects with steatosis did not change significantly: 1.72% (IQR 0.83-4.51) vs 1.67% (IQR 0.96-4.34) and 24/50 (46%) vs 24/50 (46%) at baseline and follow-up, respectively (Table 1). In those with NAFLD at baseline, nine subjects had a change in 1H-MRS of > 5%. The ELF test did not significantly change: 8.81 ± 0.66 at baseline versus 8.52 ± 0.72 at follow-up (p=0.118). At univariate linear regression, change in steatosis was significantly associated with change in BMI z-score, triglycerides and ALT within those with NAFLD at baseline.

Discussion
This 10-year follow-up study suggests that progression of steatosis and fibrosis is uncommon in young adults with childhood onset obesity and NAFLD. The established metabolic risk factors for steatosis were also longitudinally associated with change in steatosis. These data support that it is justified to screen for NAFLD and monitor for progression of fibrosis at a low frequency, unless metabolic risk factors worsen.

García-Rodríguez, I. (1,2), van Eijk, H. (1), Koen, G. (1), Sridhar, A. (1,2), Wolthers, K.C. (1), Pajkrt, D. (2)

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Parechovirus: an infection of the intestinal epithelium: differences between genotypes A1 and A3

Rationale
Human parechoviruses (PeV-As) are viruses within the Picornaviridae family with the most often detected genotypes being PeV-A1 and PeV-A3. PeV-A1 is mainly associated with gastroenteritis in children, while PeV-A3 is linked to severe disease with neurological symptoms in infants. One of the entry sites for PeV-As is speculated to be the gastrointestinal tract. In this study viral entry is characterized using enteroid technology. Enteroids are 3D structures composed of intestinal epithelial cells that closely resemble the human gut. Fetal derived enteroids resemble the neonatal intestine in vivo and are therefore useful to study PeV-As infection.

Methods
To allow viral infection enteroids were broken and seeded into Transwell® inserts where cells differentiate into the different intestinal cell types. This system was infected with PeV-A1 and PeV-A3, both lab-adapted and clinical strains. After infection analysis of the replication kinetics using quantitative PCR and viral titration was performed. Infected monolayers were imaged using confocal microscopy to determine the cell tropism.

Results
Infection with both genotypes was established in human fetal derived enteroids. PeV-A3 replication was only observed for the clinical isolates and the kinetics were slower compared to PeV-A1 for which both the lab-adapted and the clinical strains showed replication. Infection of both genotypes was preferentially from the basolateral side and virions were primarily released on the apical side. The cell target was different for the two genotypes with PeV-A1 infecting both enterocytes and Paneth cells, while PeV-A3 infected mainly goblet cells.

Discussion
These results show that both PeV-A1 and PeV-A3 can infect the intestinal epithelium preferentially from the basolateral side of the human fetal derived enteroids and they target different cell types. This difference in cell tropism may explain the difference in replication kinetics and associated disease in humans.

Brands, M.R. (1), Haverman, L. (2), Muis, J.J. (2), Driessens, M.H.E. (3), van der Meer, F.J.M. (4,5), Goedhart, G. (4,5), Meijer, S. (3), de Jong, M. (6), Bellinck, F. (7), van der Bom, J.G. (8), Cnossen, M.H. (9), Fijnvandraat, C.J. (1,10), Gouw, S.C. (1,8) and for the SYMPHONY consortium

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"Nearly picture perfect": a mixed-methods study on experiences with hemophilia care in the Netherlands

Rationale
Hemophilia care has improved greatly in past decades through treatment advances and establishing comprehensive care centers. However, in-depth insight in patients' perspectives on their care is still lacking. Moreover, it is unknown which care improvements are considered most required by patients and healthcare professionals. Therefore, aims for this study are: (1) to assess patient satisfaction with hemophilia care and (2) to explore determinants of satisfaction and identify potential improvements, among others using remote healthcare tools.

Methods
This mixed-methods study consists of two parts. First, data from a nationwide, cross-sectional questionnaire among 867 adult and pediatric Dutch patients with hemophilia A or B were analyzed. Validated questionnaires on patient satisfaction (Hemo-SAT) and quality of life (CHO-KLAT) were used, as well as open questions.
Second, based on responses, semi-structured interview topics were determined. Interviews were conducted with 19 adult and pediatric patients with hemophilia and their caretakers, and 18 professionals, including (pediatric) hematologists, nurses and physiotherapists.

Results
In the survey, 96.5% of patients indicated to be (very) satisfied with their care, particularly with patient-professional relationships. However, in surveys and interviews, patients advised to improve information provision and coordination of care, especially interprofessional collaborations. This aligned with the 3 determinants of satisfaction identified in interviews: (1) patient-professional interactions, (2) availability of care and (3) coordination of care. Both patients and professionals suggested remote healthcare could aid in improving this, although accessibility and inclusiveness should be taken into account.

Discussion
Treatment satisfaction is high among hemophilia patients, although coordination of care and information provision could be improved. Remote healthcare tools might contribute in achieving this.

Houwing, M.E. (1)*, Muntendam, M.J. (1)*, van Muilekom, M.M. (2), Teela, L. (2), Fijnvandraat, K. (3), de Pagter, A.P.J. (1), Heijboer, H. (3), van Oers, H.A. (2), Cnossen, M.H. (1)*, Haverman, L. (2)*

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* Houwing ME & Muntendam MJ contributed equally to the study as first authors. Cnossen MH & Haverman L contributed equally to the study as last authors.

Health-related quality of life in infants, toddlers, and young children with sickle cell disease

Rationale
Little is known about health-related quality of life (HRQoL) in young children with sickle cell disease living in a European country.

Methods
A retrospective cross-sectional evaluation of TNO-AZL Preschool Children Quality of Life questionnaire (TAPQOL, 0–1 year) and Pediatric Quality of Life Inventory (PedsQL, 2–7 years) data was conducted. Study participants included caregivers of children with sickle cell disease aged 0–7 years attending the sickle cell centre at the Erasmus Medical Center or the Amsterdam University Medical Centers between April 2012 and October 2020. Comparisons were made with normative data on HRQoL in the general paediatric population.

Results
The study enrolled 136 caregivers of 136 children. In children aged 0–5 years, no significant differences emerged between children with sickle cell disease and the general population. However, in children aged 5–7 years, children with sickle cell disease scored significantly lower on all subscales except for emotional functioning. Multiple regression models showed a negative association between age and HRQoL. No association was found between HRQoL and disease severity or sociodemographic characteristics.

Discussion
This study demonstrates that HRQoL is negatively correlated with age in young children with sickle cell disease with a significantly lower HRQoL in 5- to 7-year-olds when compared to the general population. Our study underlines the importance of measuring HRQoL in young children to identify patients with impaired HRQoL early in life in order to be able to intervene accordingly. Future research should focus on deepening the knowledge of factors influencing HRQoL in children with sickle cell disease.

van Leenen, G. (1), Oomen, I. (1,2), Fijnvandraat, C.J. (1,2), Gouw, S.C. (1,3)

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Genetic determinants of inhibitor development in patients with severe hemophilia A*

Rationale
The major complication of hemophilia A treatment is the formation of neutralizing anti-FVIII antibodies, called inhibitors. This complication occurs in about 20-30% of patients. It is important to identify predictors for inhibitors development to be able to tailor therapy. We aim to systematically review the association between genetic determinants and inhibitor development in patients with severe hemophilia A.

Methods
A literature search was performed on September 14th 2021, in the MEDLINE database using the following search terms: 'hemophilia A', 'genetic determinant' and 'inhibitors'. Studies reporting on genetic determinants of inhibitor development in patients with severe hemophilia A, published after 2011, were eligible for inclusion. Data were extracted on study, patient, inhibitor and genetic characteristics. Methodological quality was assessed using an adapted checklist of the Joanna Briggs Institute.

Results
The literature search yielded 239 articles. Article selection is depicted in Figure 1. This study includes 26 studies with 5792 patients, of whom 2226 have developed inhibitors. In total 20 genes and 41 mutations were reported by more than one study. Determinants associated with inhibitor development were F8 intron 22 inversion, intron 1 inversion, nonsense mutations, large deletions, CTLA-4 +49 A/G rs231775, IL-10 -1082 G/A rs1800896, CSF1R rs17725712, DOCK2 rs1863993, MAPK9 rs4147385 and HLA DRB1*01. Mutations protective for inhibitor development were F8 missense mutation, F13A1 rs13206518 and HLA DRB1*11.

Discussion
The result of this systematic review summarizes the literature of the last ten years on genetic determinants associated with inhibitor development in patients with severe hemophilia A.

* See Appendix for additional table and/or figure

Scrivens, A. (1), Reibel, N.J. (2), Heeger, L.E. (3), Stanworth, S. (1,4), Lopriore, E. (5), New, H. (6), Dame, C. (2), Fijnvandraat, C.J. (7), Deschmann, E. (8), van der Bom, J.G. (5), Aguar Carrascosa, M. (9), Brække, K. (10), Cardona, F. (11), Cools, F. (12), Farrugia, R. (13), Ghirardello, S. (14), Lozar Krivec, J. (15), Matasova, K. (16), Mühlbacher, T. (17), Sankilampi, U. (18), Soares, H. (19), Szabó, M. (20), Szczapa, T. (21), Zaharie, G. (22), Roehr, C.C. (1,23) and Fustolo-Gunnink, S.F. (3,7), on behalf of the Neonatal Transfusion Network.

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Survey of Transfusion practices in European Preterm Infants (STEP)

Rationale
Infants born below 32 weeks' gestation often receive blood transfusions. Although several RCT's on thresholds for RBC and platelet transfusions have been published, international consensus is lacking. As an NTN initiative, a survey on transfusion practice was performed across NICUs in 18 European countries.

Methods
The survey was distributed amongst units in 18 European countries between October and December 2020, regarding transfusion thresholds, indications, volumes and rates of transfusion for infants.

Results
The analysis included responses from 343 NICUs across 18 European countries. The median response rate was 57% (range: 21 - 100%). RBC transfusion thresholds varied. They were higher in younger infants and those requiring a higher level of respiratory support. In 53% of NICUs, clinically stable neonates without signs of bleeding were received a transfusion at a platelet threshold higher than 25x10^9/L, despite results of the PLANET2 study. Substantial variation between NICUs in platelet thresholds was seen, with higher thresholds in infants undergoing procedures, or active bleeding. Plasma is routinely given to infants with coagulopathy and active bleeding in 93% of NICUs, coagulopathy in 30%, active bleeding in 45%, in case of sepsis in 26% and volume replacement in 26% of NICUs. The median volumes of RBC, platelets and plasma given per transfusion were 15ml/kg. The rates of transfusion varied significantly with interquartile ranges: RBC: 3.75-5 ml/kg/hr, platelets: 7.5-20ml/kg/hr, plasma 5-15 ml/kg/hr.

Discussion
Blood transfusion thresholds, indications, volumes and rates vary considerably across European NICUs. There is a rationale for assimilation of the existing evidence into guidelines. These findings may motivate quality improvement projects to bridge the evidence-practice gap and further investigate optimal rates and volumes for blood component transfusion in infants born preterm. Our survey provides a starting point for this work.

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Effective interventions to support self-management for parents of children with a chronic condition: a systematic review

Rationale
Parents of children with a chronic condition report that raising their child, whilst trying to maintain the quality of life for the whole family, is challenging. An overview of prior research, regardless of the children's diagnosis, is lacking. Therefore, this systematic review provides an overview of the scientific literature that describes interventions to support self-management for parents of children with a chronic condition.

Methods
A systematic search of Randomised Controlled Trials (RCTs) was conducted in CENTRAL, CINAHL, EMBASE, MEDLINE and PsychInfo. Studies that describe any type of self-management intervention or a combination of self-management interventions that support parents of children with a chronic condition between 0-18 years were included. Two reviewers executed the selection, data extraction and quality assessment independently. The interventions were categorized in four areas: medical management, adjustment of lifestyle, shared decision-making and managing the consequences of a chronic condition.

Results
We included 23 RCTs. The studied interventions and outcome measurements were heterogeneous. For example, the interventions consisted of booklets, telephone sessions, group trainings, shared medical appointments, home visits, or stress management. The outcome measurements were self-efficacy, quality of life, anxiety and/or depression. Twenty studies showed statistically significant effects in favour of the self-management intervention on at least one of the outcomes. Disease management, (parent) group training, psycho-education and the Positive Parental Program (Triple P) showed favourable results in more than one study. 11 studies showed high risk of bias.

Discussion
Despite the moderate quality of the studies, the favourable results of disease management, (parent) group training, psycho-education and the Positive Parental Program (Triple P) indicate these interventions support parents of children with a chronic condition.

Scholten, A. J. W. (1,3), van Leuteren, R. W. (1,3), de Waal, C. G. (1), de Jongh, F. H. (1,4), van Kaam, A. H. (1,2), Hutten, J. (1,2)

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Feasibility of wireless cardiorespiratory monitoring with dry electrodes incorporated in a belt in preterm infants*

Rationale
Monitoring heart rate (HR) and respiration is essential in preterm infants. Currently, ECG and chest impedance (CI) measure these parameters, but CI can be unreliable and the wired adhesive electrodes can cause skin damage and hinder parent-infant interaction. We assessed the feasibility of a newly designed wireless belt with incorporated dry electrodes to measure transcutaneous electromyography of the diaphragm (dEMG), and thereby ECG and respiration (sponsor: De Louise Vehmeijer Stichting).

Methods
In this prospective observational study, infants were monitored with the belt (Bambi Medical B.V., Eindhoven, The Netherlands) for 72 hours max. Feasibility of the belt was expressed by skin-friendliness of the belt (skin score), the ability to retrieve a respiratory waveform from dEMG, determining the percentage of time with stable respiration data without signal errors ('lead-off' and Bluetooth Loss Error(BLE)), and by exploring the ability to monitor trends in HR and respiratory rate (RR).

Results
In all 19 included infants (median gestational age 27.3 weeks, median measurement length 27.8 hours) no adverse skin effects were observed and a respiratory waveform was obtained. The amount of signal errors provided by the belt was low (lead-off 0.5%(0.1-1.6), BLE 0.3%(0.1-0.9)) and 73.3%(71.0-77.7) of the respiration measurement was stable. A similar HR and RR trend between the belt and ECG/CI was observed (Fig. 1).

Discussion
This was the first study showing feasibility of recording diaphragm activity in preterm infants with dry electrodes incorporated in a belt. The belt provided a trend in HR and RR similar to ECG/CI. Study limitations are using CI as a RR reference and including clinically stable infants. However, CI is currently the standard monitor. Future non-inferiority studies are required to investigate if the belt could safely replace ECG/CI and thus if the wireless belt could be a skin-friendly alternative and improve parent-infant interaction.

* See Appendix for additional table and/ or figure

Fischer, K. (1, 2), Tieskens, J.M. (3), Luijten, M.A.J. (2, 4, 5), Zijlmans, J. (2, 6), van Oers, H.A. (2, 4), de Groot, R. (2, 7), van der Doelen, D. (8), van Ewijk, H. (3), Klip, H. (8), van der Lans, R.M. (3), De Meyer, R. (9), van der Mheen, M. (10, 11), van Muilekom, M.M. (2, 4), Hyun Ruisch, I. (12), Teela, L. (2,4), van den Berg, G. (13), Bruining, H. (6), van der Rijken, R. (9), Buitelaar, J. (8, 14), Hoekstra, P.J. (12), Lindauer, R. (10, 11), Oostrom, K.J. (2, 4), Staal, W. (8), Vermeiren, R. (3), Cornet, R. (2, 7), Haverman, L. (2, 4), Bartels, M. (1, 2), Polderman, T.J.C. (2, 3, 6, 8, 12), Popma, A. (2, 6, 10)

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Internalizing problems before and during the COVID-19 pandemic in Dutch children and adolescents from the general population

Rationale
In May/April 2020 the COVID-19 pandemic swept the nation, which resulted in an intelligent lockdown. Both the pandemic outbreak and the restrictions had consequences for children and adolescents. In this study we assessed the presence of internalizing problems (anxiety/depression) of children during the COVID-19 pandemic and compared it to pre-COVID 19 reference data.

Methods
Two general population samples were approached in April 2020/November 2020. A representative sample of Dutch children (KLIK; N=832/746) and a population sample of the Netherlands Twin Register (NTR, N=3524/1168). The KLIK sample collected self-reported data whereas the NTR collected parent-reported data, both with instruments that assess internalizing problems in children for which pre-COVID reference data was available (KLIK, N=1319 & NTR, N=34038).

Results
For both parent- and self-report we found increased average levels and amount of children with (at least mild) internalizing problems. In self-reports of children (KLIK) almost twice as many children displayed mild or severe internalizing problems when compared to a pre-COVID19 reference sample. In the parent-reports (NTR) we were able to compare the current data to the past 20 years of data collection and since the outbreak of the pandemic the amount of children with worrying internalizing problems has remained substantially higher than in all previous years.

Discussion
This study showed that the pandemic outbreak and governmental regulations regarding lockdown have resulted in an increased amount of children with internalizing problems in the general population through both self- and parent-report that has no yet returned to baseline. This should be brought to the forefront of political decision making and mental health care policy, intervention and

prevention. Further research is required to see if the presence of internalizing problems in children is subsiding or if the pandemic outbreak has had long-term consequences.

Bisseling, Q. (1,2), Passchier, E.M.J. (1,2), Antonovaite, N. (4), van der Knaap, M.S. (1,3), Mansvelder, H.D. (2) & Min, R. (1,2)

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The role of MLC1, volume-regulated ion channels and the cytoskeleton in astrocyte dysfunction in the white matter disease Megalencephalic Leukoencephalopathy with subcortical Cysts

Rationale
Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare white matter disease characterized by infantile-onset white matter edema and slow neurological deterioration. There is no treatment. In most patients MLC is caused by mutations in the gene encoding MLC1. This protein indirectly influences opening of volume-regulated ion channels in astrocytes, and its dysfunction in MLC leads to impaired recovery of astrocytes from swelling. How MLC1 interacts with ion channels is not understood. The cytoskeleton is an important modulator of volume-regulated ion channels, and previous studies uncovered interactions between MLC1 and the cytoskeleton. We hypothesize that cytoskeletal alterations underlie ion channel dysfunction in MLC. Testing this hypothesis will uncover if the cytoskeleton is a potential druggable target in MLC.

Methods
We studied mechanical properties of astrocytes isolated from wildtype or Mlc1-null mice using an indentation technique. Additional assessment of cytoskeletal organization will be done with immunostainings. To assess volume-regulated ion channel function, whole-cell patch clamp recordings will be made from cultured astrocytes.

Results
Indentation measurements of astrocytes show that Mlc1-null astrocytes are softer than wildtype astrocytes. In addition, modulating the cytoskeleton with an actin polymerization inhibitor induces softening in wildtype, but not in Mlc1-null astrocytes. Stainings to investigate differences in density and organization of the actin cytoskeleton and patch clamp experiments to investigate ion channel activation in wildtype and Mlc1-null astrocytes are ongoing.

Discussion
Mlc1-null astrocytes are softer than wildtype astrocytes, suggesting altered cytoskeletal organization. Stainings and patch clamp experiments will further elucidate how cytoskeletal alterations in MLC relate to dysfunction of volume-regulated ion channels.

van den Brink, D.A. (1), de Vries, I (1), Datema, M (1), Perot, L (1), Sommers, R (1), Daams, J (3), Calis, J (1,2,4), Brals, D (1,2), and Voskuijl, W (1,2,4)

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The first signs of change: predicting clinical deterioration and mortality across a child's hospital journey. A meta-analysis assessing risk prediction scores in children hospitalized in Low-and Middle Income Countries (LMICs).

Rationale
5.2 million children under 5 years die annually, predominantly in LMICs. Early identification of children most at risk for clinical deterioration is a major challenge. Many pediatric triage tools are based on clinical signs. We systematically searched the literature on risk prediction tools that were used throughout the hospital 'journey' (emergency department (ED), pediatric ward (PW), and pediatric Intensive Care Unit (PICU)) and performed analysis to determine which tools best predicted clinical deterioration.

Methods
Embase and Medline were systematically searched (PRISMA guidelines). Inclusion criteria: developed or validated studies with a risk prediction tool, children 0-18 years, presenting to ED, PW, or PICU of a hospital in LMICs. Relevant results on performance of tools were extracted and analyzed. The Prediction Model Risk of Bias Assessment Tool (PROBAST) was used to assess risk of bias. Meta-analysis was performed with R to determine overall performance of tools used in multiple studies; specifically using random effect model and calculating I2 for statistical heterogeneity.

Results
A total of 127 results from 53 individual tools were assessed across 58 articles. There was a high risk of bias in all studies, predominantly in analysis sections. The primary outcome was mortality (86%). There were 19 tools performing outstanding (AUROC of 0.9 or above). Best performing tools were PEWS (PW), SICK (ED), and p-SOFA (PICU). Meta-analysis of tools used in multiple studies highlighted PELOD, p-SOFA, and PRISM III as tools that performed outstanding, although the PELOD and p-SOFA were exclusively used in the PICU.

Discussion
There was a large heterogeneity in population sizes and settings. Few studies were conducted in the emergency department or at admission. A large scale validation using multiple tools in a multi country cohort, throughout the hospital journey, would be beneficial to assess which tools can best predict clinical deterioration.

van Dijk, Y.E. (1) Dieker, F.W.M. (2) Abdel-Aziz, M.I. (2) Brinkman, P. (2) Neerincx, A.H. (2) Vijverberg, S.J.H. (1) Hashimoto, S. (2) Gorenjak, M. (3) Toncheva, A.A.(4) Harner, S. (4) Brandstetter, S. (5) Wolff, C. (5) Hedman, A.M. (6) Almqvist, C. (6) Corcuera Elosegui, P. (7) Korta Murua, J. (7) Pino-Yanes, M. (8) Potočnik, U. (3) Kabesch, M. (4) Kraneveld, A.D. (9) Maitland-van der Zee, A.H. (2) and on behalf of the SysPharmPediA consortium

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Analysis of metabolites in exhaled breath for the phenotyping of eosinophilic asthma in children

Rationale
Asthma phenotyping according to airway inflammation allows the identification of patients more likely to respond to anti-inflammatory treatment. We hypothesized that the analysis of exhaled volatile organic compounds (VOCs) by gas chromatography-mass spectrometry (GC-MS) allows discrimination between EA and non-eosinophilic asthma (NEA) in pediatric asthmatics.

Methods
Patients were recruited as part of SysPharmPediA cohort. Participants were classified as EA/NEA using two absolute eosinophilic blood cell counts thresholds, selected based on the definition of pediatric EA in the literature, 300 cells/µl (AEC300) and the median of the participants, 400 cells/µl (AEC400). Through univariate Mann-Whitney U testing, we selected VOC fragments that differed significantly ($p<0.05$) between EA and NEA. Subsequently, we performed partial least square – discriminant analyses (PLS-DA) and calculated the area under the receiver operating characteristic curves (AUROCCs). Putative identification of identified VOCs was carried out using NIST libraries. With the retaining compounds, we repeated PLS-DA and calculated AUROCCs in a training (75%) and validation (25%) set.

Results
Complete data were available of 100 patients (11.7±3.6 year, 61% male, FEV1PB 101.5%), of which 69 (AEC300) and 52 (AEC400) were classified as EA. Univariate testing showed 31 (AEC300) and 70 (AEC400) significantly different VOC fragments between EA/NEA. Nine of these fragments were found at both thresholds and therefore selected for identification. Of the identified compounds, benzaldehyde and 1-methylenepropylbenzene retained after removal of potential contaminants. Final PLS-DA models resulted in AUROCCs of 0.67 (95%CI 0.53-0.81) for the training set and 0.68 (95%CI 0.39-0.97) for the validation set..

Discussion
In this explorative study, we identified benzaldehyde and 1-methylenepropylbenzene as candidate biomarkers for discrimination between EA and NEA in pediatric asthmatics.

Mussies, C.M. (1), Veltkamp, F. (2), Bouts, A.H.M. (3)

Lower incidence of Idiopathic Nephrotic Syndrome in children during the Covid-19 pandemic

Rationale
Idiopathic nephrotic syndrome (INS) is the most common glomerular disease in children. To date, the exact pathogenesis of INS remains largely unidentified. It is hypothesized that a viral trigger may induce histopathological changes occurring in the kidney leading to proteinuria, hypoalbuminemia and edema. Over the years, the incidence of INS has remained stable. However, during the Covid-19 pandemic, fewer presentations were observed in by LEARNS study. We hypothesized that there was a lower incidence during the Covid-19 pandemic compared to the previous cohort.

Methods
A retrospective, cross-sectional study was conducted by the means of an online survey among pediatricians in the Netherlands and Belgium. They were asked to report any new case of INS in the period between the 1st of March, 2020 and the 31st of May, 2021. All children aged 1-18 with a first episode of INS were eligible for inclusion. These data were compared to a 2017-2019 cohort. True estimates were simulated using a Monte Carlo simulation. The incidence and corresponding intervals were calculated. Incidences were compared using the proportion Z-test.

Results
A total of 47 cases were reported. This corresponded with an estimated incidence of 1.17 (95% CI 0.78-1.61) in the Netherlands and 1.78 (0.73-3.30) in Flanders. The incidences between countries did not differ (p=0.10), nor between the previous cohorts in both the Netherlands (vs. 1.21, p=0.81) and Flanders (vs. 1.18, p=0.10). Incidence during school and sport closure was lower in the Netherlands (0.66 vs. 1.45, p=0.033), but not in Belgium (2.40 vs. 1.57, p=0.38).

Discussion
During the Covid-19 pandemic, the incidence was comparable to 2017-2019. However, when looking up closely, a significant lower incidence of INS was observed during school closure in the Netherlands. More interestingly, we observed a marked increase after the schools reopened.

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Comorbidities, clinical characteristics and outcomes of COVID-19 in pediatric patientis in a tertiary medical center in the Netherlands

Rationale
Currently available evidence on the association between comorbidities and severity of pediatric COVID-19 is limited. Most studies describe the severity of disease based on ICU admission as opposed to a detailed description of clinical characteristics. Thus, this study aimed to assess the association between comorbidities, clinical characteristics and outcomes in pediatric patients with SARS-CoV-2 infections in the tertiary medical center Amsterdam UMC.

Methods
This retrospective observational cohort study describes data of patients aged 18 years or younger with a PCR or serum antibody confirmed SARS-CoV-2 infection between March 2020 and April 2021. Data were retrieved from medical records to classify acute COVID-19 and MIS-C into predefined categories describing disease severity. Subsequently, statistical analyses were performed to assess associations between comorbidities and severity.

Results
Eighty-three patients were included in this study. Out of 58 patients with acute COVID-19, 38 (65.5%) had pre-existing comorbidities. Most patients had mild disease (69.0%), while eight had severe or critical disease. Having comorbidities was found to be associated with disease severity of acute COVID-19 (p=0.041, OR 11.43, 95% CI 0.62 – 209.03) and ICU admission (p=0.032, OR =11.72, 95% CI: 0.64 – 215.29). Twenty- eight patients met the criteria for MIS-C, seven (25%) of which had pre-existing comorbidities. Twelve patients developed critical disease (42.9%). No differences in severity of MIS-C were found between those with comorbidities and those without comorbidities (p=0.854).

Discussion
The results of this study implicate that children with comorbidities are at risk for more severe acute COVID-19. However, absolute numbers of severe pediatric COVID-19 are low. More prospective large-scale data on the susceptibility of children with comorbidities for COVID-19 is needed to establish adequate management strategies in specific groups of pediatric patients.

Janssen, E.A.M. (1), Brands, M.R. (1) Hassan, S. (2), van Balen, E.C. (2), Rosendaal, F.R. (2), Smit, C. (2), van Vulpen, L.F.D. (3), Valk, P.R. (3), Eikenboom, H.C.J. (4), Beckers, E.A.M. (5), Hooimeijer, L (6), Ypma, P.F. (7), Nieuwenhuizen, L. (8), Coppens, M. (9), Schols, S. (10,11), Laros, B.A.P. (10,11), Leebeek F.W.G. (12), Driessens, M.H.E. (13), Cnossen, M.H. (14), van der Bom, J.G. (2,15), Fijnvandraat, C.J. (1,16), Gouw, S.C. (1,2)

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Transition readiness among adolescents and young adults with hemophilia in the Netherlands

Rationale
Care for patients with a chronic disease is transferred from pediatric to adult care around the age of 18 years. Transition programs have been developed to help guide patients in a structured, holistic way. The first transition program in the Netherlands was implemented in hemophilia care. This study aims to assess self-reported transition readiness in Dutch adolescents and young adults with hemophilia, and determine which factors are associated with transition readiness.

Methods
Data from a national, cross-sectional questionnaire among Dutch people with hemophilia were analyzed. Adolescents aged 12-17 years and young adults aged 18-25 years completed age-specific questionnaires on, among others, their transition readiness and transition preparation. Validated questionnaires were used to assess quality of life (CHO-KLAT), adherence to treatment (VERITAS-Pro) and self-efficacy (HSES).

Results
A total of 45 adolescents and 84 young adults (46.5% (n=60) with severe hemophilia, 49.6% (n=64) using prophylaxis) were included. Self-reported readiness improved with increasing age, from 38.5% (n=10) aged 12-14 years to 63.2% (n=12) aged 15-17 years. Only 1 young adult (1.2%) reflected to have not been ready to transition. Still, 13 young adults (15.5%) would have liked to be better prepared for which professionals they would encounter in adult care, and 10 (11.9%) on costs. Family history, prophylaxis and joint bleeds were not associated with transition readiness. Neither were quality of life, self-efficacy and treatment adherence, although positive trends were identified. A more optimal score on the treatment adherence domain 'Planning' was independently associated with improved readiness.

Discussion

Self-reported transition readiness is high among adolescents and young adults with hemophilia. Data suggests that improved executive functions, such as planning, are associated with improved transition readiness, although further research is needed to support this.

Kooijmans, E.C. (1,2), van der Pal, H.J.H. (2), Pluijm, S. (2), Bresters, D. (2,3), van Dulmen-den Broeder, E. (1), van der Heiden-van der Loo, M. (2,4), van den Heuvel-Eibrink, M. (2,5), Kremer, L.C.M. (2), Loonen, J.J. (6), Louwerens, M. (7), Neggers, S. (8), Pilon, M. (1), Ronckers, C. (2), Tissing, W.J.E. (2,9), de Vries, A.C.H. (2,5), Kaspers, G.J.L. (1,2), Bökenkamp, A. (10), Veening, M.A. (1,2), on behalf of the Dutch LATER study group

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Hypertension in long-term childhood cancer survivors after treatment with potentially nephrotoxic therapy; DCCSS-LATER 2: RENA

Rationale
We evaluated the prevalence of and risk factors for hypertension in childhood cancer survivors (CCS). Furthermore, a 24-hour ambulatory blood pressure monitoring (ABPM) pilot study was performed.

Methods
In the DCCSS-LATER 2 RENA study, 1,024 CCS ≥5 years after diagnosis, aged ≥18 years at study participation, treated between 1963-2001 with nephrectomy, abdominal radiotherapy (RT), total body irradiation (TBI), cisplatin, carboplatin, ifosfamide, high-dose cyclophosphamide (≥1g/m2 per course or ≥10g/m2 total) or hematopoietic stem cell transplantation participated and 500 age- and sex matched controls from Lifelines. Hypertension was defined as blood pressure (BP) (mmHg) systolic ≥140 and/or diastolic ≥90 or receiving antihypertensive medication for diagnosed hypertension. Multivariable regression analyses were used.
The ABPM-pilot study was performed in 77 CCS. Hypertension was defined as BP daytime: systolic ≥135 and/or diastolic ≥85, nighttime: systolic ≥120 and/or diastolic ≥70, 24-hour: systolic ≥130 and/or diastolic ≥80. Outcomes were masked hypertension (MH), white coat hypertension (WCH) and abnormal nocturnal dipping (aND).

Results
Median age at diagnosis was 4.7 years (IQR 2.4-9.2), at study 32.5 years (IQR 27.7-38.0), and follow-up time 25.5 years (IQR 21.4-30.3). The prevalence of hypertension was comparable in CCS (16.3%) and controls (18.2%). A decrease in glomerular filtration rate (GFR) per 10 ml/min/1.73m2 was associated with hypertension in CCS (OR 1.2, 95%CI 1.1-1.3), but not in controls. Risk factors were abdominal RT ≥20 Gy and TBI. The ABPM-pilot study showed 7.8% MH, 2.6% WCH, and 20.8% aND.

Discussion
Although CCS with median 25 year follow-up have a prevalence of hypertension comparable to matched controls, hypertension is already associated with a decrease in GFR in survivors. Risk factors for hypertension include abdominal RT and TBI. ABPM has added value by identifying masked hypertension and abnormal nocturnal dipping.

Teela, L. (1), Kuijlaars, I.A.R. (2), Luijten, M.A.J. (1), Van Hoorn, E.S. (3), Gouw, S.C. (4), Fijnvandraat, K. (4), Fischer, K. (2), Cnossen, M.H. (3), Liem. C. (5). Jansen-Zijlstra, M.E. (6), Peters, M. (4), Haverman, L. (1)

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The use of paediatric PROMIS® item banks in Dutch boys with haemophilia*

Rationale
Legacy haemophilia-specific Patient Reported Outcome Measures (PROMs) can be experienced as a burden due to their length, sometimes irrelevant questions, and poor methodologic quality. Patient Reported Outcomes Measurement Information System (PROMIS®) item banks, including short forms (SF) and Computerized Adaptive Testing (CAT), could solve this problem. The objective of this study is therefore to assess the psychometric properties of eight PROMIS item banks within boys with haemophilia.

Methods
All boys with haemophilia (8-17 years) from five Dutch Haemophilia Treatment Centres are eligible. Reliability of the PROMIS item banks will be expressed as the proportion of reliable scores (standard error ≤4.5). The number of completed items will be reported to determine feasibility. Convergent validity will be assessed by comparing PROMIS T-scores with (subscales of) the Haemophilia Quality of Life Questionnaire for Children (HaemoQoL) and the Paediatric Haemophilia Activities List (PedHAL) by using Pearson's r (for hypothesis see Table 1).

Results (preliminary)
To date, 47 (of the 162) invited boys responded (mean age 13.5 years, SD=3.0). The reliability of the PROMIS item banks was good with 90% of the standard errors ≤4.5, except for Mobility. Mean number of completed items per CAT varied from 9-12. Convergent validity is not assessed yet and will be presented at the symposium.

Discussion
Preliminary results show that most PROMIS item banks are reliable with a limited number of items. Further analyses are needed to determine the construct validity of the instruments. If the paediatric PROMIS item banks prove to be a good alternative to the legacy instruments, they will be implemented in daily clinical care for boys with haemophilia in order to reduce the burden of completing PROMs.

* See Appendix for additional table and/ or figure

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Early mobilization in the Pediatric Intensive Care Unit: the views of healthcare professionals

Rationale
There is increased interest for early mobilization in critically ill children, following the experiences and evidence that show better outcomes in critically ill adults. However, the opinions and concerns of Dutch PICU professionals directly involved in mobilizing critically ill children are unknown. Therefore, in this study we explored the opinions, concerns, and barriers and facilitators of healthcare professionals regarding early mobilization in critically ill children.

Methods
In this cross-sectional study, a survey was disseminated to all PICU healthcare professionals in the Netherlands.

Results
Of the 641 healthcare professionals who were invited for participation, 215 (33.5%) responded, of whom 159 (75%) were nurses, 40 (19%) physicians, and 14 (6%) physical therapists. Early mobilization was believed to be a useful intervention by all respondents, and considered as beneficial for shorter duration of mechanical ventilation, improved sleep/wake rhythm and shorter length of stay in the PICU. Nearly all respondents (98%) believed it is safe to mobilize critically ill children on non-invasive mechanical ventilation, and 80% believed it is safe in invasive mechanically ventilated children. However, respondents showed reluctance to mobilize patients on ECMO (63%) and patients with traumatic brain injury (49%). Perceived barriers for mobilization were instability of the patient (60%), the risk of dislocation of lines/tubes (59%), and the level of sedation of the patient (33%). Only 43% of the respondents believed there is enough support from physical therapists and 28% have adequate equipment.

Discussion
All respondents considered mobilization as being useful and potentially beneficial in improving outcomes. However, the respondents are reluctant in certain patient groups. Perceived barriers for mobilization are the risk of dislocation of lines and tubes, physiological instability and the sedation level of the patient.

Bon, S.B.B. (1), Wouters, R.H.P (1), Hol, J.A. (1), Jongmans, M.C.J. (1,2), van den Heuvel-Eibrink, M.M. (1), Grootenhuis, M.A. (1)

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Parents' experiences with whole-exome sequencing in pediatric renal cancer

Rationale
In pediatric cancer, germline whole-exome sequencing (WES) contributes to the identification of predisposing factors, which in turn can facilitate surveillance and family counseling. However, studies on the impact of sequencing studies on families are scarce in pediatric cancer. Our qualitative study explores families' experiences to improve counseling and support.

Methods
33 interviews were conducted with parents after recruitment for a germline WES study in children with renal tumors, comprising a renal cancer predisposition gene panel analysis and optional exome-wide trio-analysis. The interviews were analyzed using an inductive thematic approach.

Results
Parents were positive about participating in genetic sequencing and reported both individual and altruistic motives. Altruistic motives e.g., helping future patients, seemed to be relatively more important after the child's treatment had finished compared to families recruited during treatment. Families recruited shortly after diagnosis felt overwhelmed. Parents often preferred exome-wide (trio-)analysis over cancer panel analysis, although afterwards many had difficulties distinguishing these two. Families in which a predisposition was not identified felt relieved, but some worried about yet undiscovered genes or felt disappointed. In most families with a predisposition no significant distress was observed, although in some the predisposition added up to the already existing psychosocial burden.

Discussion
Families are positive about participating in the genetic study; however, we identified several challenges pertaining to timing, consent, and post-test support. We suggest counseling families during a relatively stable phase in their child's treatment trajectory. Separating consent for panel and exome-wide analysis could possibly help parents to make a more deliberate decision. Attention is necessary for families who receive negative test results and for those who already have a high burden.

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Long term follow up of Dutch patients with Sickle Cell Disease diagnosed by neonatal screening

Rationale
An estimated number of 3,000 patients with SCD are living in the Netherlands, and annually 40 new patients are born. Although SCD is caused by a single mutation, the clinical phenotype in these patients is highly heterogeneous. The ability to identify the severe phenotype of a patient with SCD would allow a reliable prognosis and could guide therapeutic decision making. The aim of this study is to create a descriptive overview of the pediatric patients with SCD, diagnosed by neonatal screening and identify determinants that are associated with a clinically severe phenotype.

Methods
The study is a retrospective, observational, cohort study with children diagnosed with SCD through neonatal screening and treated at the Sickle Cell Comprehensive Care Center of Amsterdam UMC between 2007 and 2021. With descriptive analyses, an overview of the pediatric SCD population is presented. A clinically severe phenotype was defined by one or more of the following events: 2 painful crises/year, occurrence of acute chest syndrome and acute spleen sequestration. The association between determinants and the severe phenotype is established by regression analyses.

Results
A number of 93 out of 173 eligible patients has been included up to now, with a mean age of 7.9 years (SD, 3.9). The genotype of 51% (n=47) patients was HbSS/HbSβ0-thalassemia and in 42% (n=39) it was HbSC/HbSβ+-thalassemia. Half of our patients had been admitted at least once. Of these patients, 42% (n=20) had their first admission before the age of 2 years. Acute chest syndrome occurred in 4.3% (n=4) of the patients, and acute spleen sequestration in 3.2% (n=3). Due to the lack of power, determinants of a severe phenotype could not yet be established.

Discussion
Expansion of the neonatal screening with SCD has allowed health care providers to identify patients with SCD shortly after birth, and improve timely patient care from Sickle Cell Comprehensive Care Centers in the Netherlands.

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Multi-omics in classical galactosemia: phosphate depletion as pathophysiological mechanism?

Rationale
Classical Galactosemia (CG) is one of the more frequent inborn errors of metabolism. Patient care is hampered by a lack of valid prognostic biomarkers. Despite a life-saving diet, patients develop highly variable long-term complications including low intelligence and movement disorders. The pathophysiology of these complications is still poorly understood. Multi-omics approaches might discover new biomarkers and improve patient prognostication. In CG, only one metabolomics study was published demonstrating the involvement of multiple metabolic pathways in plasma. As galactose metabolism takes place in cells, we expect erythrocytes to be a more reliable matrix for metabolomics and lipidomics.

Methods
Two-phase extraction was used in the erythrocyte samples of 40 patients with both classical and variant phenotypes, and 39 healthy controls to perform untargeted mass-spectrometry based metabolomics and lipidomics in a single sample.

Results
Between patients and controls, 115 discriminatory metabolites were detected. Using PLS-DA analysis, 38 important metabolites were identified involved in multiple metabolic pathways. The pentose phosphate pathway, glycolysis, and purine and creatine metabolism were affected. The majority of metabolites with altered levels are phosphorylated metabolites, including a lowered ATP. There was no consistent relation between identified metabolites and galactose-1-phosphate, IQ and movement disorders. Lipidomics did not show any significant changes or deficiencies.

Discussion
Our results demonstrate significant differences in a number of metabolites in erythrocytes of CG-patients, representing several metabolic pathways. The decrease in multiple phosphorylated metabolites, such as ATP, may confirm the long-existing theory that phosphate depletion resulting from galactose-1-phosphate accumulation is a major pathophysiological mechanism. New therapeutical options for CG could be aimed at optimizing intracellular phosphate homeostasis.

de Groot - Eckhardt, C.L. (1), Heijboer H. (1), Beijlevelt - van der Zande, M. (1), Nieland, L. (2), Sieswerda - Hoogendoorn, T. (2), Fijnvandraat, K. (1)

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Fly me to the Moon: Virtual reality to reduce anxiety and pain during acute pain episodes in children with Sickle Cell Disease

Rationale
Sickle Cell Disease (SCD) is caused by a mutation in the hemoglobin gene that results in transformation of red blood cells into a sickle-like shape under certain conditions. This leads to severe lifelong complications such as anemia, recurrent painful vaso-occlusive crises (VOC), organ failure and premature death.
Pain management in SCD is extremely difficult due to its complex nature. Pharmacological interventions are limited by not addressing all aspects of the condition and can have serious side effects. Virtual Reality (VR) is an innovative technology that has proven to be an effective method in pain management. New modalities enable the use of VR devices for an expanding range of purposes, including biofeedback, cognitive therapy, hypnosis and education.
This project is the first to investigate efficacy of VR to reduce perceived pain and complications in children with SCD admitted for VOC, to address the urgent need to improve pain management in these children.

Methods
In this proof of concept study we will investigate efficacy and safety of VR in reducing pain in SCD patients by performing a randomized clinical trial in 40 children admitted for VOC. The intervention group will receive a customized VR module during 30 minutes three times daily and the control group will receive a tablet to play games instead. We will assess the efficacy and safety of VR by length of hospitalization, anxiety and pain assessed by validated measures, total opioid use and complications.

Results
In 2021 a pilot study has started in the Emma Children's hospital to assess feasibility and safety of VR in hospitalized children with VOC. The first 3 included children with SCD (9, 13, 16 years) admitted to the hospital for the treatment of VOC received one or more VR sessions. They reported no side effects and desired VR again when in pain.

Discussion
The preliminary results of this pilot study show that VR seems safe and feasible in hospitalized children with VOC.

van den Brink, D.A. (1), Mponda, K (2), Thompson, D (3), van Hees, C (4), Ngong'a, F (5), Segula, E (5), M Bale, E.M (5), Boele van Hensbroek, M (1), Bandsma, R (7,8), Berkley, J (7,9), Voskuijl, W (1,5,9)

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Dermatological changes not as prevalent as previously thought in children with severe malnutrition: a prospective cohort characterizing skin changes in a population of hospitalized Malawian children

Rationale
In 1935, Dr. Cicely Williams first documented skin changes in malnourished children. Over the decades, the skin and hair changes in severely malnourished children were described using multiple terms with discrepancies in reported prevalence. There is a need to determine prevalence of skin changes in malnourished children. The primary objective: describe skin conditions in children admitted to Queen Elizabeth Central Hospital, Blantyre, Malawi, with an acute illness. A secondary objective: validate a newly developed skin assessment tool.

Methods
Children between 1 month and 23 months of age were enrolled. Upon recruitment, children had photos taken to document the skin according to standardized practices. 3 Dermatologists with experience in LMICs assessed skin changes and scored each child according to SCORDOK tool.

Results
In total 103 children were enrolled, and 92% of children were severely malnourished. Pigmentary changes were observed in 33% of the children, with telogenic effluvium and bullae-erosion-desquamation being the second most prevalent skin changes seen. Severe skin changes like flaky paint dermatosis were hardly seen. Most skin changes were unrelated to malnutrition. The study had an overall mortality rate of 19.41% but this was primarily seen in the group of children with Kwashiorkor (26%). Only 47% of children that died had skin changes, with pigmentary changes most prevalent. Inter-rater variability calculations showed only fair agreement, while inter-rater variability had fair-moderate agreement, illustrating difficulties with SKORDOK.

Discussion
This was a well documented cohort able to clearly report on the prevalence of skin changes in a largely malnourished hospitalized pediatric population. There was a low prevalence of skin changes that could be attributed to malnutrition and no link between mortality and skin changes. Skin changes may not be as prevalent as previously thought and this calls into question the need for a tool.

Baaleman, D.F. (1,2), Vriesman, M. H. (1,2), Benninga, M.A. (2), Bali , N (1), Vaz, K.H.(1), Yacob, D (1), Di Lorenzo, C(1), Lu, P. L (1), Koppen, I.J.N.(1,2)

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A pilot study on the use of three-dimensional anorectal manometry in children with functional constipation; comparing outcomes and experiences with high-resolution anorectal manometry*

Rationale
In children with constipation refractory to conventional treatment, anorectal manometry (ARM) can be used to asses neuromuscular function of the anorectal canal. It is used as a screening tool for Hirschsprung's disease by investigating the presence of the recto-anal inhibitory reflex (RAIR). ARM is usually performed with water-perfused, or high-resolution solid-state catheters (HR-ARM) containing up to 8 sensors. Recently, a new catheter has been introduced, which contains 256 solid-state radially oriented microtransducers which utilizes high-definition (or "3D") high-resolution (3D-ARM) technology, see Figure 1. However, its clinical usefulness and tolerability in children are unknown. With this pilot study we intended to examine the agreement between findings on HR-ARM and 3D-ARM, and we wanted to evaluate patient and provider experience.

Methods
A prospective cohort was conducted including children (8-18 years of age) with constipation scheduled for ARM. Children underwent HR-ARM and 3D-ARM consecutively. We compared manometry results of both procedures and collected data on patient and provider experience.

Results
Data of ten subjects were analyzed (60% female, median age 14.9 years), in the majority of subjects (n=8, 80%) ARMs were performed awake. Anal sphincter resting pressures were higher during 3D-ARM compared to HR-ARM (median 77 mmHg [IQR 59-94] vs. 69 mmHg [IQR 51-91], respectively, P=0.037). In two patients (20%) the RAIR was only visualized during HR-ARM. No significant anatomical or muscular abnormalities were visualized during the 3D-ARM. The majority of children found the 3D-ARM the most unpleasant procedure (n=5, 71%) and most painful procedure (n=6, 86%) and therefore preferred the HR-ARM (n=4, 57%).

Discussion
Data of this pilot study indicate that in our patient sample the use of the 3D-ARM may cause more discomfort without providing more useful information, and may even result in a more difficult visualization of the RAIR.

* See Appendix for additional table and/ or figure

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Saliva SARS-CoV-2 antibody prevalence in children after 1 year pandemic*

Rationale
In adult COVID-19 patients, SARS-CoV-2 specific antibodies have been detected in serum and saliva up to 8 months after infection. In children, saliva SARS-CoV-2 specific antibodies are scarcely described. Following our earlier findings of heterogeneity in serum and saliva SARS-CoV-2 antibodies in the beginning of the pandemic, we now describe antibody prevalence in serum and saliva of children attending medical services in the Netherlands one year after the beginning of the pandemic and explore associations.

Methods
We assessed SARS-CoV-2 antibody prevalence in paired serum and saliva of 220 children attending medical services in the Netherlands (irrespective of COVID-19 exposure) from May to October 2021. The cohort included both vaccinated and unvaccinated children. We explored prevalence of SARS-CoV-2 spike (S), receptor binding domain (RBD) and nucleocapsid (N) specific IgG in serum and saliva with a Luminex assay.

Results
The antibody prevalence in serum was 33% (95% CI 24 – 42) for S specific antibodies, 30% (95% CI 22 – 39) for RBD specific antibodies and 17% (95% CI 11 – 25) for N specific antibodies. In saliva S, RBD and N specific antibodies were present in 22% (95% CI 15 – 31), 18% (95% CI 12 – 26) and 11% (95% CI 6 – 18) respectively. The prevalence was similar when assessing only unvaccinated children, with lower N specific antibodies compared to S and RBD ($P < 0.001$). When comparing serum and saliva, most children with serum IgG antibodies also showed saliva IgG. Age, sex and comorbidity is not associated with the presence of saliva antibodies.

Discussion
SARS-CoV-2 antibody prevalence in children attending medical services in the Netherlands increased in serum and saliva. One year after the beginning of the pandemic, antibody prevalence is lower in saliva compared to serum, and in both serum and saliva N specific IgG is less prevalent compared to S and RBD specific IgG antibodies which should be taken into account when selecting an assay.

* See Appendix for additional table and/or figure

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Needs and wishes of general practitioners in Pediatric Palliative Care

Rationale
General practitioners (GPs) are rarely confronted with pediatric palliative care (PPC) in contrast with palliative care in adults. Most GPs are not familiar with PPC and the work of the PPC-teams (PPCT) in the seven university hospitals. GPs mostly do not realize that PPCTs can support them and play an active role in PPC, even when the child is at home. It has never been investigated what GPs need and wish for support.
This study focuses on identifying needs and wishes of GPs in PPC and how a PPCT can contribute to this.

Method
A qualitative study through semi-structured interviews was conducted among 10 GPs who were involved PPC together with Emma's PPCT between January 2019 and December 2020. The data were analyzed thematically.

Results
Five themes were identified. GPs want to be involved earlier in the process of PPC and want to be kept informed of medical policy and end-of-life decisions. GPs need a central point of contact and clear coordination of care. GPs need a careplan drawn up by the medical specialist for PPC, including dosages of medication. GPs want to be involved and kept informed about psychosocial care by specialized care providers and sometimes GPs need support in providing aftercare. GPs want an active role in aftercare for the families and an evaluation with the PPCT after the death of the child to share experiences and improve care.

Discussion
Our studies emphasizes that GPs want to be actively involved in PPC. As was shown in previous studies joint home visits, involvement in end-of-life decisions, a careplan provided by the PPCT, adequate information about psychosocial care and a joint evaluation after the death of the child are valuable ways to involve and support the GPs.
The PPCT should involve the GPs in an early phase of PPC.
Future studies can focus on the difference in the needs of GPs in PPC with short trajectories and long trajectories, and how to improve involvement of GPs in psychosocial and spiritual care.

Abstracts accepted for publication in the abstract book

AMSTERDAM KINDER SYMPOSIUM

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Mapping Neonatal Transfusion in Europe: an International Neonatal tranSfusion PoInt pREvalence (INSPIRE) study

Rationale
Premature neonates are a highly transfused patient group, though robust evidence supporting neonatal transfusion practice is scarce. Two randomized trials indicated no benefit in long-term outcomes of liberal compared to restrictive thresholds for red blood cell (RBC) transfusions. Another randomized trial, comparing a high and low platelet transfusion threshold, even reported evidence that transfusions can cause harm. No neonatal transfusion guidelines have been implemented by Europe as a whole, resulting in significant variation in transfusion practice. Detailed contemporary data on neonatal transfusion practice in Europe is lacking.

Methods
In this international, multicenter, prospective, observational point prevalence study, we will include neonates with a gestational age at birth <32 weeks admitted to a participating tertiary level neonatal intensive care unit (NICU). This study will be performed by the Neonatal Transfusion Network (NTN), an international, interdisciplinary, neonatal transfusion research network. We will recruit at least 61 NICUs to reach the calculated sample size. A total of 19 European countries have confirmed their participation. Data will be collected over a one-year period, in which each NICU will collect data during six weeks. The primary outcome of this study is the prevalence of RBC, platelet, and plasma transfusions. Secondary outcomes are variations in prevalence, indications for transfusion, adverse effects and component specifications, evidence-baseness of practice and guideline use.

Results
The INSPIRE-study will provide high-quality multinational epidemiologic data, which can be used to identify current neonatal transfusion practices that can be improved and areas with substantial clinical variation which can be targeted in future clinical trials.

Discussion
The resulting data may help reduce unnecessary transfusions through increased awareness of the proper use of transfusions in this vulnerable patient group.

Balfoort, B.M. (1), Buijs, M.J.N. (2), Ten Asbroek, A.L.M.A. (2), Bergen, A.A.B. (2,3), Boon, C.J.F. (3,4), Ferreira, E.A. (1), Houtkooper, R.H. (5), Wagenmakers, M.A.E.M. (6), Wanders, R.J.A. (5), Waterham, H.R. (5), Timmer, C. (7), Van Karnebeek, C.D. (1,8), Brands, M.M. (1)

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A review of treatment modalities in gyrate atrophy of the choroid and retina (GACR)

Rationale
Gyrate atrophy of the choroid and retina (GACR) is a rare inborn error of amino acid metabolism caused by bi-allelic pathogenic variations in OAT. It is characterized by its ophthalmic phenotype, with chorioretinal degeneration ultimately progressing to severe visual impairment. There is no curative treatment for GACR, although several therapeutic modalities aim to slow progression of the disease by targeting different steps within the ornithine pathway. We systematically collected all international literature on therapeutic interventions in GACR to provide an overview of published treatment effects.

Methods
Following PRISMA guidelines, a systematic review of English literature was performed. It covered literature on therapeutic interventions in GACR patients until December 22nd 2020.

Results
33 studies (n=107 patients) met the inclusion criteria. Most studies were designed as case reports (n=27) or case series (n=4). No randomized controlled trials were found. Treatments applied were a protein-restricted diet, pyridoxine, and supplementation of creatine, creatine precursors, L-lysine, and proline. A protein-restricted diet lowered ornithine levels with 16.0-91.2%. Pyridoxine responsiveness was reported in 30% of included variations. L-lysine supplementation lowered ornithine with 21-34%.

Discussion
Based on primarily case reports, it can be concluded that a protein-restricted diet lowers plasma ornithine. Pyridoxine (variation-dependent) and lysine also lower plasma ornithine. The lack of pre-defined clinical outcome measures and structural follow-up in all included studies impeded conclusions on clinical effectiveness. To harmonize treatments based on available knowledge, we developed a national care pathway. Future research should be aimed at 1) unraveling the OAT biochemical pathway to identify other possible pathologic metabolites, 2) pre-defining GACR-specific clinical outcome measures, and 3) establishing an international historical cohort.

Winkel, A.M.A.M (1), Noij, L.C.E. (1), Lap, C.R. (1), Hashimoto, S (1), Brackel-Kosterink, C.L.H. (1), Teela, L (2), Haverman, L (2), Buddingh, E.P. (3), Haverkort , M (4), van Houten, M (5), Terheggen-Lagro, S. (1)

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Pediatric long-COVID: the long-term impact of SARS-CoV-2 infection in previously hospitalized children*

Rationale
Children are less severely affected by SARS-CoV-2 than adults. Nevertheless, there are studies showing that children can also suffer from long-COVID. However, occurrence and characteristics of long-COVID in children remain poorly characterized, as well as the consequences on heath related quality of life (HRQoL). The pandemic lockdown measures seriously impacted daily activities and quality of life in children. In order to take these effects into account, we assessed occurrence and characteristics of long-COVID and HRQoL in children previously hospitalized with COVID-19 and in children tested negative for SARS-CoV-2 in the same period and lockdown measures.

Methods
This is a prospective case-control study. Children admitted to any Dutch hospital with COVID-19 formed the cases. Children tested negative for SARS-CoV-2 at public health service formed the control group. Online questionnaires assessed symptoms at baseline (directly after hospital admission or in the week of PCR-test) and at follow-up (6 to 12 weeks after baseline). Long-COVID was defined as persistent or new symptoms present for more than 4 weeks after SARS-CoV-2 infection that were not pre-existing. HRQoL was also evaluated at the follow-up questionnaires.

Results
At follow up, 43.9% of cases reported to have symptoms, which were not present prior to SARS-CoV-2 infection. HRQoL-scores were significantly lower in children with symptoms compared to children without symptoms (Figure 1). Higher age was significantly associated with persistent symptoms (OR 1.07, 95% C 1.02-1.14, p=0.04).

Discussion
Nearly half of children experienced symptoms 6-12 weeks after hospitalization with acute COVID-19, leading to impairment in HRQoL. Older age was associated with increased risk of persistent symptoms at follow-up. Our findings highlight the need for of awareness about pediatric long-COVID, to perform prospective follow-up and intervention studies, and to create multidisciplinary, evidence-based guidelines for diagnosis and treatment.

* See Appendix for additional table and/ or figure

van 't Westende, C. (1), Geraedts, V.J. (2), van Ramesdonk, T. (1), Dudink, J. (3), Schoonmade, L.J. (4), van der Knaap, M.S. (1, 5), Stam, C.J. (6), van de Pol, L.A. (1)

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Neonatal quantitative electroencephalography measures and long-term outcome: a systematic review*

Rationale
To evaluate qEEG measures as predictors of long-term neurodevelopmental outcome in infants with a postconceptional age below 46 weeks, including healthy full-term born infants, infants with heterogeneous underlying pathologies, and prematurely born infants.

Methods
A comprehensive search was performed using PubMed, Embase and Web of Science from inception up to January 8th, 2021. Studies that examined associations between neonatal qEEG measures, based on conventional EEG (cEEG) as well as amplitude-integrated EEG (aEEG), and standardized neurodevelopmental outcomes at two years of age or older were reviewed. Significant associations between neonatal qEEG and long-term outcome measures were grouped into one or more of the following outcome categories: cognitive outcome, motor outcome, composite scores, and other standardized outcome assessments.

Results
Twenty-four out of 1740 studies were included. Multiple studies showed that cEEG based absolute power in the delta, theta, alpha and beta frequency band and cEEG and aEEG related amplitudes seem to be positively associated with favourable long-term outcome across several domains, including cognition and motor performance. Furthermore, a lower amount of discontinuous background pattern was also associated with favourable outcomes. However, the interpretation of the results is limited by the heterogeneity in study populations and study designs.

Discussion
Neonatal qEEG measures may be used as prognostic biomarkers to identify those infants who will develop long-term difficulties and who might benefit from early interventions.

* See Appendix for additional Table and/ or Figure

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Human stem cell-derived cell transplantations in Vanishing White Matter mice

Rationale
Vanishing White Matter (VWM) is a leukodystrophy resulting in neurological decline and premature death. The brain shows degeneration of the white matter. Glial cells of the brain, astrocytes and oligodendrocytes, remain immature. Astrocytes in particular are implicated in the pathophysiology of VWM. Transplantation of mouse healthy glial progenitors into a VWM mouse model has shown a potential of cell replacement therapy for VWM. Here, we investigate whether this is also true when transplanting human cells.

Methods
We generated a variety of stem cell-derived glial populations, ranging from matured astrocytes to young progenitor populations. Cells were injected into the white matter of neonatal VWM mice. In adulthood, animals were tested on various phenotypic assays including motor tests and VWM brain pathology. A regression analysis was used to determine based on these phenotypic assays whether animals had improved in terms of disease severity. Transplanted cells were analyzed using immunohistochemistry.

Results
We found that transplantation of human glial progenitors could improve the VWM phenotype. Regression analysis showed that improved VWM mice more closely resembled healthy control animals than saline-injected VWM animals. In addition, analysis of the brain tissue showed that that the host brain microenvironment exerted an influence on the cellular behavior of the transplanted cells in vivo.

Discussion
We show that transplantation of human glial cells has therapeutic potential for treating VWM, indicating that cell replacement therapy can be of benefit for VWM patients. This confirms an earlier proof-of-principle study and shows the translational potential of cell replacement therapy for VWM. Importantly, the modulating effects of the host microenvironment should be considered in further therapeutic treatment strategies.

Cristian, G. (1,2), Juarez-Martinez, E. L. (3,4), Sprengers, J. J. (4), Linkenkaer-Hansen, K. (3), Bruining, H. (1,4).

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EEG-based predictions of repetitive behavioral improvement in a randomized controlled trial testing bumetanide in autism spectrum disorder

Rationale
The heterogeneous manifestation of autism spectrum disorder and mixed findings on group treatment effectiveness prompt the identification of biomarkers of clinical response. Bumetanide, a chloride-acting drug shown to impact electroencephalographic (EEG) signals, also showed promise in improving repetitive behavior, as previously demonstrated by a recently conducted randomized controlled trial. We investigate if repetitive behavioral improvement is associated with bumetanide-induced EEG change at (sub)group level. Using machine learning, we devise EEG-based predictions of improvement.

Methods
The correlation significance level was adjusted to account for multiple tests. Using machine learning, using 5 clinical and 315 EEG features we predicted clinical improvement of 34 bumetanide subjects above or below the thresholds RBS-R: 7- and 16- pt. 100 random data partitions were created for training (80% ± 5% of the data) and 100 for out-of-sample validation (20% ± 5% of the data). For each training partition we identified the feature subsets which most strongly discriminate subjects below or above the response thresholds. A random forest classifier was trained on each of the 100 training partitions using the selected feature sub-sets. The resulting predictions, being situated above or below the improvement thresholds, were validated on the 100 validation partitions.

Results
Brain activity changes were correlated with repetitive behavioral improvement in subsets exceeding a 7-pt. improvement. Using machine learning, we predicted, based on EEG measures and baseline clinical severity, moderate and strong repetitive behavior improvement with an 80% and 92% accuracy respectively. EEG features of absolute power and excitation-inhibition ratio in the central-parietal region and baseline clinical severity were most predictive of improvement.

Discussion
EEG biomarkers and clinical measures may have predictive value in assessing ASD symptom improvement.

Stavleu, D.C.(1,2), Mulder, R.L.(1), Kruimer, D.M.(1), Kremer, L.C.M.(1), Tissing, W.J.E.(1,2), Loeffen, E.A.H.(1,2)

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An evidence-based guideline for platelet transfusions in children with cancer

Rationale
Children with cancer often suffer from thrombocytopenia. Platelet transfusions are important for both prevention and treatment of bleeding in thrombocytopenic children with cancer. In current clinical practice, recommendations regarding thresholds for administering platelet transfusions are often not evidence-based. This is problematic, given the important balance between the overuse of platelet transfusions versus risk of bleeding. Therefore we developed a clinical practice guideline (CPG) to establish an overview of evidence and provide recommendations for clinicians.

Methods
A systematic literature review was performed, including dual appraisal of all citations. The GRADE methodology was used to assess, extract and summarize the evidence. A comprehensive multidisciplinary panel was assembled, comprising 20 professionals and patients representatives. Multiple in-person meetings were held to discuss evidence, complete evidence-to-decision frameworks and formulate recommendations. Final recommendations were unanimously supported by all panel members.

Results
Five studies (including more than 1600 children) with various study designs formed the evidence base for the recommendations. Considering the limited amount of studies in children with cancer, additional evidence was extracted from adult guidelines and children with other diseases prone to thrombocytopenia. Our experts assessed all evidence and translated it, transparently, into recommendations. Eventually, more than 15 recommendations were made regarding platelet transfusions in children with cancer.

Discussion
In this clinical practice guideline, we provide both evidence-based recommendations and best practice statements regarding platelet transfusions in children with cancer. With these recommendations we aim to provide guidance for clinicians and contribute to improving outcomes for children with cancer.

Orriëns, L.B. (1), van Hulst, K. (2), van den Hoogen, F.J.A. (3), van der Burg, J.J.W. (4,5), Erasmus, C.E. (6)

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Parent-reported impact of glycopyrronium for the treatment of drooling: towards individualised outcome measurement in children with neurodevelopmental disabilities

Rationale
The importance of involving parents when evaluating treatment effectiveness is increasingly recognised in paediatric care, but standardised outcome measures continue to be used often. It is time to take a step forward and focus on what is relevant to the child and its parents, instead. Glycopyrronium, an anticholinergic drug used to treat drooling in children with neurodevelopmental disabilities, was proven to be effective in multiple RCTs, but its true impact has scarcely been studied.

Methods
We determined whether glycopyrronium diminishes the negative impact of drooling in daily life, and assessed whether a patient-centred outcome measure would be suitable in this patient population. A pragmatic retrospective cohort study and prospective pilot study were conducted. Parents of 61 children who used glycopyrronium in 2011-2021 were interviewed and provided data on the impact of treatment. A patient-centred outcome measure was used to evaluate treatment impact in 11 children newly prescribed glycopyrronium by our multidisciplinary saliva control team.

Results
Glycopyrronium caused an improvement in practical, social, and emotional aspects of daily life impacted by drooling in 55%, 31%, and 24% of the included children, respectively. For several children, however, not all of these aspects were relevant, hindering the establishment of a meaningful change in impact. When using a patient-centred outcome measure, parents reported specific and personal situations impacted by drooling, which nevertheless related to recognizable themes (i.e. (social) participation, physical interaction, discomfort).

Discussion
Our results highlight the importance of implementing individualised outcome measures in the evaluation of children treated for drooling. A patient-centred outcome measure enabled parents to focus solely on situations of importance to the child and themselves. This could aid problem definition and facilitate individualised follow-up of treatment effect, also in other interventions for drooling.

Kooper, C.C. (1), Oosterlaan, J. (2), Bruining, H. (3), Engelen, M. (4), Pouwels, P.J.W. (5), Popma, A. (6), van Woensel, J.B.M. (7), Buis, D.R. (8), Steenweg, M.E. (9), Hunfeld, M. (10) & Königs, M. (11)

Towards PErsonalized PRognosis for Children with Traumatic Brain Injury: The PEPR Study Protocol*

Rationale
Children with traumatic brain injury (TBI) are at risk of poor outcome in crucial functional domains, including motor, neurocognitive and behavioral functioning. However, outcome varies strongly between patients and is determined by complex interplay between demographic factors, pre-morbid functioning and (sub)acute clinical characteristics. Current clinical prediction methods to understand let alone predict outcome are lacking, which contributes to unnecessary follow-up as well as undetected impairment in children. This study aims to develop prognostic models for the individual outcome of children with TBI in a range of important developmental domains. In addition, we will assess the potential added value of advanced neuroimaging and the use of machine learning algorithms in the development of prognostic models.

Methods
210 children (4-18 years) diagnosed with mild to severe TBI will be prospectively recruited via Dutch hospitals. They will be matched 2:1 to a control group of neurologically healthy children (n = 105). Predictors in the model will include demographic, premorbid and clinical variables prospectively registered from hospital admission onwards. Comprehensive magnetic resonance imaging is performed at one month post-injury. Outcome will be assessed at six months post-injury.

Results
Prognostic models will be developed to identify high-risk children with impairments in a range of crucial domains of daily life functioning; motor functioning, intelligence, behavioral functioning, and school performance. In addition to conventional linear regression, we will determine the added value of support vector machines and regression trees for prediction performance.

Discussion
The findings of our multicenter study may contribute to better planning of early rehabilitation and follow-up, prevent unnecessary care for children in whom good recovery is expected, and facilitate adequate monitoring and treatment of children with a high-risk of adverse outcome.

* See Appendix for additional table and/or figure

Roskam MJ (1), Hulsmann S (1), Dierikx T (1), Leijdekkers V (2), Garssen F (3), Dunker M (4), Van der Bilt J (5), Bakx R (1) and De Meij TGJ (1) (order of co-authors to be determined).

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Risk of Crohn's disease in children presenting with perianal abscess and fistula increases with age: a retrospective cohort study

Rationale
Perianal abscesses (PA) and fistulas-in-ano (FIA) are frequently diagnosed in children and have been associated with Crohn's disease (CD). The risk for children presenting with PA and FIA to develop CD and the correlation between CD and age in this population is largely unknown. Therefore, the aim of this study is to investigate the association between PA and FIA in children and the risk for development of CD, stratified by age.

Methods
A retrospective, multi-center cohort study was performed. Children between 2-17 years who initially presented between January 2000 and December 2018 with a PA or FIA at the department of (pediatric) surgery, were eligible to participate.

Results
151 patients with PA/FIA were included in the study, of whom twenty-eight (18.5%) developed CD. The median interval between presentation with PA/FIA and CD diagnosis was 6 months. Children aged 2-6 years old were at lower risk for CD compared to children aged 6-12 and 12-18 years old (3.6%, 14.8% and 27.5% respectively; p=0.02). Furthermore, elevated fecal calprotectin (FCAP), having a first-grade family member with IBD and recurrence(s) of PA/FIA were all significantly associated with development of CD.

Discussion
In this cohort, we observed that the risk of CD in children presenting with PA and FIA was increased in children aged ≥6 years. Since the median interval between presentation with PA/FIA and CD diagnosis was 6 months, we recommend close monitoring children presenting with PA/FIA for development of CD in the years following initial presentation.

van den Berg, R.B. (1), Laarman, A.R.C. (2), Dijkstra, J.A. (1), Veldkamp, A.I. (1), Swart, E.L. (1), van Weissenbruch, M.M. (2)

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The relation between serum trough concentration paracetamol and pain reduction in preterm and term neonates: a retrospective observational study*

Rationale
Measuring the concentration of paracetamol could be a strategy to optimize the treatment of pain in preterm and a term neonates. A target concentration in the effect compartment of 10 mg/L in neonates was defined after one loading dose. However, this target concentration was reached several hours before the trough concentration. Low trough concentration could result in inadequate pain relief, like end-of-dose pain. The aim of this study was to determine if the serum trough concentration paracetamol at steady state conditions could predict a decrease in pain scores in preterm and term neonates.

Methods
In this retrospective observational study a hospital database was used to select neonates who were treated with at least 48 hours of paracetamol intravenously or rectally. Linear regression was performed to determine if serum trough concentration paracetamol at steady state conditions was a predictor for pain reduction. Pain reduction was defined as the difference between COMFORTneo scores before administration and after the fifth administration of paracetamol.

Results
21 neonates were included for determining the association between serum trough concentration paracetamol. The median (IQR) of the trough concentration paracetamol after the fifth gift was 4.5 mg/L (2.7 – 8.5 mg/L). At steady state conditions the serum trough concentration paracetamol was no significant predictor of pain reduction in preterm and term neonates ($p = 0.79$ for preterm neonates and $p = 0.49$ for term neonates).

Discussion
No association was found between the serum trough concentration paracetamol at steady state conditions and pain reduction in preterm and term neonates. The absence of a significant association between the trough concentration paracetamol and pain reduction could be due to inadequate trough concentrations paracetamol. Further research is needed to investigate the association between trough concentration paracetamol of ≥ 10 mg/L and pain reduction.

* See Appendix for additional table and/ or figure

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Exploring the 'Shared' in Shared Decision Making in Child Health: What are the roles of parents and professionals?

Rationale
In family-centered care for children with a chronic condition and/or disability, families are regarded as crucial partners in all phases of planning, delivery and evaluation of healthcare. Studies over the past two decades have provided important knowledge on how the family-centered approach can be successfully implemented in the healthcare process. As a result, there is a growing body of literature that recognises the importance of shared decision making (SDM). However, few studies elaborate on the respective roles of parents and professionals. Role definitions may support both partners in the process of SDM.

Methods
A scoping review was performed to investigate the available knowledge on the interpretation and variability of different roles of parents and professionals in medical child care systems. A scoping review of English literature was conducted using databases APA Psycinfo, CINAHL, Web of Science, and MEDLINE. In total, 41 articles were included.

Results
The results show that two overarching roles can be identified: leading and initiating.
These overarching roles can be filled in and/or activated by six sub-roles: informing, advocating, supporting, facilitating, coordinating and interacting. Within the definition of the roles, a difference can be made between parents as leading and initiating, and professionals as leading and initiating.

Discussion
The literature provides a first definition of the various roles parents and professionals may take during SDM. A next step is to study whether these roles can be observed during SDM in clinical practice, and whether these roles are stable or variable over time.

Revers, I.M. (1, 2), Böck, D. (3), Hillen, A.E.J. (1, 2), Bomhof, A.S.J. (1, 2), Van der Knaap, M.S. (1, 2), Schwank, G. (3), Van Til, N.P. (1, 2).

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Development of gene therapy for the leukodystrophy vanishing white matter

Rationale
Vanishing white matter (VWM) is an autosomal recessive neurologic disorder, characterized by central nervous system (CNS) white matter degeneration, causing slowly progressive ataxia, spasticity and cognitive decline. There are additional stress-provoked episodes of rapid and major deterioration. The onset of the disease is predominantly in early childhood. VWM leads to progressive handicap and early death. No curative therapy is available for VWM. VWM is caused by bi-allelic mutations in any of the five genes (EIF2B1-5) encoding the subunits of eukaryotic translation initiation factor 2B (eIF2B). A mutation that causes severe VWM in humans is EIF2B5 R195H. A VWM mouse disease model with a homozygous R191H mutation (Eif2b5R191H/R191H) recapitulates the neurological phenotype including abnormal white matter and progressive gait ataxia.
We aim to employ gene therapy with state-of-the-art base-editing technology to correct mutations and phenotype in the CNS in VWM mice.

Methods
Neurotropic adeno-associated vectors (AAV) containing CRISPR–Cas-associated base editors were administered via intracerebroventricular (ICV) injection at postnatal day 0 (P0) in VWM mice (n = 22); saline was injected in control VWM mice (n = 13). Brain and spinal cord were harvested one month post-AAV injection to assess EIf2b5 gene correction.

Results
Quantification of molecular correction will be performed by next generation sequencing in different brain regions. Additionally, cellular correction and white matter rescue are assessed by histological stainings.

Discussion
We postulate that molecular correction on one allele will be sufficient to provide cellular correction and rescue the white matter pathology and clinical phenotype. Based on the pilot study results a proof-of-concept study in Eifb5R191H/R191H mice will be initiated to show long-term efficacy and safety.

Peersmann, S.H.M. (1, 2), Grootenhuis, M. A. (1,3), van Straten, A. (4), Tissing, W. J. E. (1,5), Abbink, F. (2), de Vries, A. C. H. (1,6), Loonen, J. (7), Kremer, L. C. M. (1), Kaspers, G. J. L. (1,2), van Litsenburg, R. R. L. (1,2)

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Insomnia, a sleeping problem in adolescents and young adults within pediatric oncology: who is at risk?

Rationale
Insomnia entails difficulty with initiating or maintaining sleep which considerably impacts daily functioning. It is associated with negative health outcomes and impaired quality of life, which poses a health risk for adolescents and young adults who had cancer. Knowing who is at risk enables targeted treatment. This study's aim is to determine the prevalence of insomnia in adolescents and young adults across all cancer diagnoses and associated risk factors.

Methods
Patients (12-30 years old) who were at least 6 months after treatment for diverse childhood cancer types and within 10 years after diagnosis were invited to fill out questionnaires including: the Insomnia Severity Index (ISI-score 0-28) and sociodemographic/medical questions. A backward stepwise regression model was used to evaluate risk factors.

Results
576 patients participated (response 55.8%): 49.5% females, mean age 17.0 years, 44.4% hemato-oncology, 31.9% solid tumors, 23.6% neuro-oncology. Overall, 179 (31.1%) reported insomnia symptoms, which varied in severity: 20.0% subthreshold (ISI-score 8-14), 9.7% moderate-severe (ISI score 15-21) and 1.4% severe (ISI-score 22-28). Risk factors for insomnia entailed: being female (β = .13, $p<.01$), having co-morbid health problems (β = .19, $p<.001$), sleeping together (β = .08, $p<.05$), needing someone else to fall asleep (β = .26, $p<.001$), bedtime consistency (β = .10, $p<.05$) and wake time consistency (β = -.16, $p<.001$). No association ($p>.05$) was found with age group, bedtime routine, bedtime technology use and cancer diagnosis or treatment type and age or time at diagnosis.

Discussion
Insomnia is common after treatment for childhood cancer, independent from cancer diagnosis or treatment type. Several risk factors were determined. Targeted interventions for these risk groups aimed at improving sleep could potentially improve the health of adolescents and young adults who had childhood cancer.

de Sonnaville, E.S.V. (1), Königs, M. (1), Aarnoudse-Moens, C.S.H. (1), van Woensel, J.B.M. (2), Oosterlaan, J. (1), Knoester, H. (2)

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Long-term follow-up of daily life functioning after Pediatric Intensive Care Unit admission

Rationale
Long-term morbidity after Pediatric Intensive Care Unit (PICU) admission is a growing concern. Currently long-term daily life functioning of children after PICU admission remains largely unknown. This study aims to investigate long-term daily life functioning of children after PICU admission and to investigate the role of neurocognitive functioning on daily life functioning.

Methods
This study compared 65 children aged 6-12 years, previously (age <1 year) admitted to our PICU for bronchiolitis (patient group) with 76 normally developing peers (control group). Assessed daily life outcome domains were academic performance (assessed by the Dutch pupil monitoring system), behavioral functioning, health-related quality of life (QoL) and perceived neurocognitive functioning (assessed by validated questionnaires). Objective neurocognitive functioning was assessed by validated neurocognitive tests. The relationship between daily life functioning and objective neurocognitive functioning was assessed by regression analysis and mediation analysis.

Results
The patient group and control group did not differ on behavioral functioning. The patient group performed poorer than the control group on academic performance; school-related QoL and perceived neurocognitive functioning (ps<.04, d=-0.48 to -0.26). Within the patient group, lower FSIQ was associated with poorer academic performance, school-related QoL and perceived neurocognitive functioning (ps<.008). Poorer verbal memory was associated with poorer spelling performance (p=.002). FSIQ mediated the observed effects of PICU admission on reading comprehension and arithmetic performance.

Discussion
Children with a history of PICU admission for bronchiolitis are at risk of long-term impairments in daily life functioning with respect to academic performance, school-related QoL and perceived neurocognitive functioning. Intelligence mediates the relationship between PICU admission and academic underachievement.

Oomen, I. (1,2), Miranda, M. (2), Voorberg, J. (2), Kaijen, P. (2), Allacher, P. (3), Schweiger, H. (3), Schols, S. (4), Gouw, S.C. (1,5)

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Explaining the prevalence and characteristics of non-neutralizing antibodies (XPlain) - preliminary results*

Rationale
Recently, non-neutralizing antibodies (NNAs) have been identified that bind non-functional sites on the FVIII-molecule in patients with hemophilia A (HA). NNAs appeared to increase the clearance of administrated clotting factor concentrate, limiting hemostatic efficacy of administered concentrates. We hypothesize that FVIII-binding antibodies form a spectrum from low titer, low affinity NNAs and high affinity antibodies with or without inhibitory potential, to inhibitory antibodies detectable with the widely used Bethesda assay, depicted in Figure 1. We hypothesize that a subset of NNAs are in fact low-titer inhibitory antibodies with titers below the detection limit (0.6 BU) of the Bethesda assay. We aim to assess the prevalence and characteristics of FVIII-specific NNAs among patients with HA, in order to address the negative effects of this complication.

Methods
In total, 514 HA patients were included from an unselected cohort. Inclusion criteria were (1) pediatric HA patients with FVIII activity levels <0.40 IU/ml; (2) participation in Hemophilia in the Netherlands-6 study; (3) available plasma sample. The NNA prevalence will be explored by using a highly sensitive and fully validated ELISA. We will investigate the antibody isotypes including IgA, IgM and IgG subclasses. Samples with confirmed specificity for FVIII will be assessed for apparent affinity with a competition-based ELISA approach.

Results
Preliminary results will be available at the time of the AKS 2022.

Discussion
This study will be the first to describe the full spectrum of anti-FVIII antibodies in an unselected population of patients with all types of hemophilia. Improved knowledge of the prevalence and characteristics of NNAs will eventually contribute to understanding of differences in pharmacokinetics. If this will be confirmed, screening for NNAs may lead to earlier identification of a shorter half-life and providing personalized dosing regimens.

* See Appendix for additional table and/or figure

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Preclinical therapy development for PDE and GA1 using patient-derived cellular models

Rationale
Pyridoxine-dependent epilepsy (PDE-ALDH7A1) and glutaric aciduria type-1 (GA1) are two rare neurometabolic disorders of lysine metabolism, caused by pathogenic variants in ALDH7A1 and GCDH, respectively. Deficiency of the encoded enzymes results in accumulation of neurotoxic metabolites causing debilitating neurological sequelae in patients. Currently, only dietary treatment strategies are available which do not eliminate, but at best mitigates neurologic impairments. Therefore, we aim to develop preclinical therapies for PDE-ALDH7A1 and GA1 based on inhibition of AASS, the first enzyme of the lysine catabolic pathway working upstream of ALDH7A1 and GCDH.

Methods
Since no PDE and GA1 human model is available, patient-derived iPSCs and isogenic knock-out lines are used to generate human neuronal cultures that will allow us to further understand the disease and test therapeutics. Antisense oligonucleotides (AONs) are used to downregulate AASS expression. To assess the effect of AON mediated AASS downregulation, electrophysiological studies are performed using micro-electrode arrays. In addition, medium of fibroblasts and neurons is collected for subsequent metabolomic analysis.

Results
ALDH7A1 and GCDH knock-out lines have been generated and subsequently characterized at molecular, electrophysiological and metabolomic levels. Electrophysiological and metabolomic studies are currently being performed for both models. Additionally, patient-derived ALDH7A1 fibroblasts have shown to reproduce the altered metabolomic profile described in patients. Optimization of AON transfection in fibroblasts and reprogramming of patient derived fibroblasts to iPSCs is currently ongoing.

Discussion
By using AONs to downregulate expression of AASS, and testing these in neuronal iPSCs, brain organoids, and zebrafish/mouse models, we aim to prevent the accumulation of neurotoxic metabolites and potentially their neurological consequences in both PDE-ALDH7A1 and GA1 patients.

Pigeaud, L.E.M. (1), de Veld, L. (2), Van Hoof, J.J. (3), Van der Lely, N. (4)

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Acute alcohol intoxication in Dutch adolescents before, during, and after the first COVID-19 lockdown

Rationale
The association between acute alcohol intoxication among adolescents and the COVID-19 lockdown has been studied previously in Trieste, Italy. They recommended that emergency services should be prepared for a potential peak of alcohol intoxication-related emergencies among adolescents as a result of the COVID-19 lockdown. Therefore, this study investigated the influence of the COVID-19 pandemic on the prevalence of acute alcohol intoxication among adolescents in the Netherlands.

Methods
To determine both the prevalence and characteristics of adolescents admitted for acute alcohol intoxication in 2019-2020, a retrospective cohort study was conducted. All adolescents <18 years of age admitted for acute alcohol intoxication in the 12 participating hospitals in the Netherlands in 2019-2020 were included. Adolescents were divided in periods before, during, and subsequent to the first COVID-19 lockdown and the beginning of the second lockdown, in comparison with the same periods in 2019.

Results
The prevalence of acute alcohol intoxication among adolescents decreased by 70% during the first lockdown (March 16-May 31, 2020) compared with the period before lockdown (January 1-March 15, 2020). Between the first lockdown phase and the reopening period (June 1-October 14, 2020), the prevalence significantly increased.

Discussion
This study demonstrates that COVID-19 lockdown led to a decrease in acute alcohol intoxication among adolescents. This decrease is multifactorial, including the closure of bars/restaurants, sport clubs, schools and increased parental supervision due to obligatory working from home of parents. Based on the findings, this specific population requires close monitoring, especially in the reopening phases.

Veenvliet, A. (1,2,3,4), den Hollander, B. (1,2,3), Lindenschot, M. (5,6), Peters, G. (5), Brands, M.M. (1,2,3), Jacobs, B.A.W. (7,8), van Karnebeek, C.D. (1,2,3,9).

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Evidence for effect of L-serine, a novel therapy for GRIN2B-related neurodevelopmental disorder

Rationale
Loss-of-function (LoF) mutations in GRIN2B result in a neurodevelopmental disorder (NDD) due to N-methyl-D-aspartate receptor (NMDAR) dysfunction. In vitro experiments showed that the co-agonist D-serine restores function in GluN2B LoF mutation-containing NMDARs. In a 5-year old patient with a GRIN2B LoF mutation, notable improvements in motor/cognitive performance and communication were observed after L-serine supplementation. Thus, L-serine offers a potential treatment for these patients, previously considered untreatable.

Methods
3 female patients (13 months, 4.5 years, 13 years) with confirmed LoF mutations and a heterogeneous clinical phenotype were treated with oral L-serine (500mg/kg/day in 3 doses) for 12 months. Primary outcome measures are cognitive and behavioural testing (evaluated by the PRPP-assessment; a standardized, performance-based tool), neurologic testing, irritability, sleep, and stools.

Results
All patients tolerated L-serine well. In 2 patients in whom PRPP-assessment was performed, significant improvement in performance mastery and cognitive strategy use was observed. In one patient, L-serine was stopped for 1 day and irritability relapsed to the pre-treatment level, and improved on the restart of supplementation. All 3 patients were reported by caregivers as more alert with better communication. In the most severely affected patient, PRPP was refused by parents and no other major changes in outcomes were observed.

Discussion
Our study showed that L-serine exerts a positive effect on cognitive performance, i.e. the execution of every-day activities in 2 out of 3 patients (evidence level 4). We showed that for heterogeneous patient groups, the PRPP is a useful client-centered tool to assess the application of information processing strategies. To generate stronger evidence for effect of L-serine in Grin2B-NDD, we will perform placebo-controlled n-of-1 trials. Meta-analysis of individual n-of-1 trials will yield evidence level 1.

Müller, A.R. (1,2), Brands, M.M.M.G. (1), Cornel, M.C. (3), Van Karnebeek, C.D.M. (1,4), Den Hollander, B. (1), Wijburg, F.A. (1), Boot, E. (2,5,6), Van Eeghen, A.M. (1,2)

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N-of-1 studies in children with rare genetic neurodevelopmental disorders: A study protocol and systematic review of the literature*

Rationale
Millions of children worldwide are affected by a rare genetic neurodevelopmental disorder (RGND), often characterized by psychiatric comorbidity. However, interventional research is challenging due to vulnerable, small and heterogeneous patient populations. To study the effectiveness of cannabidiol (CBD) on behavioural problems in RGNDs, and to illustrate how challenges can be overcome, we designed an N-of-1 trial protocol. N-of-1 studies are randomized, controlled, multiple crossover trials within a single patient. In addition, we systematically reviewed the literature and formulated recommendations for future studies to improve and implement N-of-1 studies in RGNDs.

Methods
An N-of-1 trial protocol was designed to study the effectiveness of CBD in children and adults with Tuberous Sclerosis Complex, Fragile X syndrome and Sanfilippo disease (see Figure). EMBASE and MEDLINE were searched for N-of-1 studies in RGNDs. Information was recorded on types of interventions, outcome measures, validity, strengths and limitations.

Results
In the systematic review, twelve N-of-1 studies were identified for drug as well as non-drug interventions. Main strengths were the use of personalized and clinically relevant outcome measures. Limitations included lack of power analyses and the use of ancillary statistical analyses. Generalizability was compromised due to limited use of validated and generalizable outcome measures.

Discussion
Properly executed N-of-1 studies may provide a powerful, patient-centred alternative to conventional RCTs and a much-needed bridge between practice and science. Beside the suitability at an individual level, these should pursue the generalization to a population level. Recommendations are provided for future N-of-1 studies, ultimately optimizing evidence-based and personalized care.

* See Appendix for additional table and/or figure

Heeger, L.E. (1,2), Prins, S. (3), Cassel, F. (4), d'Haens. E. (5), van Westering-Kroon, E. (6), de Kort, E. (7), Vrancken, S.L. (8), Hulzebos, C.V. (9), Vijlbrief, D.C. (10), van der Bom, J.G. (1,2), Fijnvandraat, C.J. (1,3), Lopriore, E. (2), and Fustolo-Gunnink, S.F. (1)

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Blood Management in Neonates (BlooMIN)

Rationale
Patient Blood Management (PBM) programs are bundles of care. Their overarching aim is to prevent anemia and to reduce unnecessary transfusions. This is achieved through a range of interventions, such as small volume diagnostic assays, reducing iatrogenic blood loss and adherence to transfusion guidelines. In various adult populations, PBM has successfully reduced the number of transfusions and improved patient outcomes. As neonates have a different physiology and different comorbidities compared to adults, an adapted PBM program is necessary. Literature on neonatal blood management programs is scarce, but existing studies suggest implementation of a total of 20 PBM elements. It is unknown to what extent these elements apply to or have been implemented into clinical practice in the Netherlands. In this study, we will evaluate to what extent 20 previously identified neonatal PBM program elements are currently implemented into clinical care for preterm neonates in the Netherlands.

Methods
This national retrospective observational cohort study will include a random selection of 400 preterm neonates born with a gestational age (GA) below 28+0 weeks, plus a random selection of 400 neonates born with a GA between 28+0 and 31+6 weeks, admitted to level III Neonatal Intensive Care Units (NICU's) in the Netherlands between January 1st 2020 and January 1st 2021.

Results
For all 20 neonatal PBM elements, we will calculate the percentage of eligible neonates in which it was applied, corrected for case-mix variation. We will estimate the prevalence for each element per center and an overall prevalence in the Netherlands.

Discussion
The use of neonatal PBM elements will likely vary between the Dutch NICUs. By describing the prevalence of each element, we will identify possible room for improvement, establish current areas of national consensus, and provide a starting point for a Dutch neonatal PBM.

van Karnebeek, C.D. (1,2,4), van Eeghen, A.M. (1,4), Houtkooper, R.H. (3,4), Bergen, A.A (2,4), van Haelst M.H. (2,4)

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Emma Personalized Medicine Center: bridging the gap for children with genetic disorders*

Rationale
More than 30% of children in an academic hospital are estimated to suffer a genetic disorder. Sadly, diagnosis is often missed or delayed, care fragmented, therapeutic intervention hampered by logistic and policy issues.

Methods
To address this medical gap, our multidisciplinary team synergizes Amsterdam UMC strengths –large patient groups, centers of expertise for rare diseases, cutting edge laboratories, (para-)medical / psychosocial expertise- by establishing the Emma Personalized Medicine Center.

Results
In Q1 of 2022, with patients as partners, we open our doors to deliver P4-medicine: 1) Precision Diagnostics: rapid identification of the underlying disease, discovery of novel disease genes via multi-omics & artificial intelligence, accurate counseling (eg CIAO1 defects causing iron sulphur cluster disruption and neurologic phenotype) 2) Therapy & Evidence: To go 'beyond a diagnosis' disease mechanisms are unraveled via experiments in iPSCs cells/organoids. We develop or repurpose drugs, diets, transplants, enzyme, stem cell, RNA/gene therapy (eg Gyrate Atrophy). Therapies are evaluated and made accessible to the patient as quickly and personalized as possible. Small numbers and heterogeneity require a solid clinical trial unit infrastructure, alternative trial methodology, patient registries and collaboration with policy makers to address access and reimbursement issues. Examples: L-serine for GRIN2B, sialic acid for NANS-CDG, glibenclamide for Cantu s, cannabidiol for San Filippo and TSC, RNA Tx for PDE 3) Customized Care: To deliver the right care at the right location, we implement network medicine and transmural innovations (eg Jeroen Pit Huis) with multidisciplinary care pathways coordinated by a nurse specialist.

Discussion
Training of the next generation, digitalization, knowledge dissemination to the professional/general public are essential for success… and so are you! We invite all colleagues to join and strengthen our center.

* See Appendix for additional table and/ or figure

Oudejans, E. (1), Witkamp, D. (1), Hu-A-Ng, G. (1), Hoogterp, L. (1), Van Leeuwen, G. (1), Kruijff, I.D. (1), Lalaoui El Mouttalibi, Z. (1), Schonewille, P. (1), Van der Knaap, M.S. (1), Abbink, T.E.M. (1)

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ISR modulating compounds as treatment for Vanishing White Matter

Rationale
Vanishing White Matter (VWM) is a fatal leukodystrophy that mainly affects children and is currently without a cure. The disease is characterized by chronic neurological deterioration and episodic stress-sensitive acute decline. VWM is caused by hypomorphic mutations in eIF2B, which regulates the integrated stress response (ISR), an adaptive response aimed to alleviate cellular stress and restore homeostasis. In VWM, eIF2B activity is reduced causing continuous ISR activation in brain astrocytes. ISR inhibition targeted at or downstream of eIF2B ameliorates VWM in representative mouse models. The current study aims to target and modulate the ISR upstream of eIF2B in VWM mice with two well-characterized and FDA approved compounds: 4-PBA and TUDCA.

Methods
The compounds 4-PBA, TUDCA or vehicle (placebo) were administered daily to 8-week-old presymptomatic VWM and wild type (WT) mice for a period of 9-10 weeks. Dosage regimens were based on available pharmacological data. Neurological deterioration was scored weekly. Gait and coordination were assessed on the balance beam and Catwalk. Post mortem tissue was collected for neuropathological examination.

Results
The data are currently being collected and analysed for disease-modifying and ISR-modulating effects.

Discussion
The clinical and molecular effects of 4-PBA and TUDCA in VWM mice will increase insight into the mechanisms underlying VWM pathogenesis and open up potential treatment targets for the disease.

Moussa, I. (1), Vuong, C. (1), van Muilekom, M. (2), de Groot-Eckhardt, C.L. (1), Haverman, L. (2), Fijnvandraat, K. (1)

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The impact of pain on the health-related quality of life in pediatric patients with Sickle Cell Disease

Rationale
Sickle cell disease (SCD) is an inherited autosomal recessive multisystem disorder, that currently affects 3,000 people in the Netherlands. Patients with SCD are mainly affected by chronic hemolysis and occlusion of small blood vessels. The occlusion of small blood vessels manifests itself as severe pain, also called the vaso-occlusive crisis (VOC). Pain in general has a major impact on patient's perceived quality of life. In pediatric patients with SCD, previous research has shown that VOCs affect the quality of life substantially. However, there is limited evidence about whether and how this effect changes over time. The aim of this study is to identify the impact of VOCs on Health Related Quality of Life (HRQOL) in pediatric patients with SCD over time. Identifying the impact of hospital admission(s) for VOC on HRQOL over time allows health care providers to intervene and to restore HRQOL in pediatric sickle cell patients.

Methods
In this retrospective cohort study, children between the age of 8 and 18 years who were diagnosed with any type of SCD were included. The Pediatric Quality of Life Inventory (PedsQL) was used to measure the main outcome HRQOL every year between 2012 and 2021. The determinant was hospital admission(s) for a VOC. A linear mixed model is used to analyze the impact of hospital admission(s) for a VOC on the HRQOL over time, and adjusted for the variables: age, gender, genotype and socio-demographic factors.

Results
A total of 51 patients are included in the study. Further descriptive data and analysis are being conducted. We expect to present the results in the Spring of 2022.

Vuong, C. (1), Heijboer, H. (1), Brinkman, P (2), van Stuyvenberg-Neerincx, A.H. (2), Terheggen-Lagro S.W.J. (3), Maitland-van der Zee (2), Fijnvandraat, K. (1), de Groot-Eckhardt C.L. (1)

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Giving Relieve in Pain (iGRIP) in Sickle Cell Disease

Rationale
Sickle cell disease (SCD) is a hereditary disorder of hemoglobin, characterized by hemolytic anemia and vascular occlusion. Patients with SCD experience frequent, unpredictable, extremely painful crises that are elicited by physical or emotional stress, infections or cold temperatures. Although the frequency and severity of crises are variable among patients, all families with a child with SCD experience regular stressful disruption of daily life. Once a pain crisis has started, it has a self-reinforcing effect that makes the pain more and more intense. The sooner we can intervene in this process, the more effective it will be at preventing damage and reducing pain. Unfortunately, we presently lack adequate markers that predict that a painful crisis is bound to occur. This project is focusing on a promising novel technique that has potential as an early marker for the pain crisis: the breathprint – exhaled air analysis. These “breathprints” may be used as noninvasive biomarkers for disease activity, as they reflect inflammation. This project aims to investigate the use of breathprints to predict painful crises in SCD. As a first step, we will determine whether breathprints do actually discriminate between steady state and a painful crisis in patients with SCD.

Methods
Breathprints– exhaled air analyses will be measured by the electronic nose (eNose) and gas chromatograph-mass spectrometer (GCMS). Exhaled air from 25 hospitalized patients will be collected during hospital admission for a painful crisis at the first day of (T= 0) and the third day of admission (T = 3). After discharge, in these patients breathprints will be measured twice in steady state at the outpatient clinic: after 6 weeks and after 3 months.

Results
From November 2021 onwards the first patients will be included. I expect to present the first results in February 2022.

Van den Berg E. (1), Verbeek R.J. (1), Diepenhorst-Kristanto S. (1), Voermans M.M. (1), van der Knaap M.S. (1)
Amsterdam University Medical Centers, Amsterdam, The Netherlands

Antisense Suppression of Glial Fibrillary Acidic Protein as a treatment for Alexander Disease

Rationale
Alexander disease is a rare, usually fatal, neurologic disease that can affect both children and adults and is characterized by bulbar symptoms, pyramidal signs, ataxia and cognitive impairment. Currently no specific treatment is available and treatment is only supportive. Accumulation of abnormal Glial fibrillary acidic protein (GFAP) in astrocytes, in complexes termed Rosenthal fibers, is important in the disease mechanism, and leads to astrocyte dysfunction and subsequent white matter abnormality and loss. Suppression of GFAP using an antisense oligonucleotide (ASO) has been associated with resolution of Rosenthal fibers and improvement of motor coordination and strength in a rat model of Alexander disease. The aim of this study is to test the effect of ION373 (ASO against GFAP) in improving or stabilizing gross motor function in humans with Alexander disease.

Methods
In this international phase 1-3 double-blind placebo-controlled study sponsored by Ionis Pharmaceuticals, humans aged 2-65 years with manifest Alexander disease, who are still ambulant, receive ION373 or placebo intrathecally every three months in a 2:1 randomization ratio, for a 60 week double blind treatment period, followed by a 60 week open-label treatment period. At least two dose cohorts will be evaluated (i.e. low dose for cohort A and higher dose for cohort B). The primary outcome is the percent change from baseline in the 10-meter walking test.

Results
All patients for cohort A have been enrolled, including one child with Alexander disease from the Amsterdam UMC. Currently the ION373 concentration and safety data is being reviewed before enrollment of cohort B will start.

Discussion
Antisense suppression of GFAP has shown to improve motor coordination and strength in animal models of Alexander disease. This is the first time antisense suppression of GFAP is evaluated in humans. Hopefully this will lead to new treatment options for patients with Alexander disease.

Witkamp, D. (1). Oudejans, E. (1), Krzywanska, A.M. (1), van Leeuwen (1), G.M. (1), Hu-a-ng, G. (1), Hoogterp, L. (1), van der Knaap, M.S. (1), Abbink, T.E.M. (1).

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The role of CHOP in vanishing white matter

Rationale
Vanishing white matter (VWM) is a stress-sensitive fatal leukodystrophy mainly presenting in young children. VWM shows extensive variability in disease course. Without curative treatment, patients exhibit neurological deterioration and develop severe ataxia. Bi-allelic mutations in the genes encoding the eukaryotic initiation factor 2B (eIF2B) diminish its activity. eIF2B is essential for translation initiation and plays an important part in the integrated stress response (ISR) to proteotoxicity. ISR activation in healthy circumstances encompasses eIF2 phosphorylation and eIF2B inhibition, which in turn upregulates transcription factors ATF4 and CHOP. CHOP is part of a negative feedback loop important for eIF2 dephosphorylation. The ISR is deregulated in VWM: ATF4 and CHOP activities are increased, despite reduced levels of eIF2 phosphorylation. Studies have shown that ISR deregulation is a suitable treatment target. How ATF4 and CHOP contribute to VWM is investigated in representative VWM models. As bi-allelic genetic deletion of ATF4 has a severe negative impact on health, this study focuses on the role of CHOP.

Methods
VWM mouse models with mutations in eIF2B replicate the human spectrum of VWM. VWM mice with a mild or moderate phenotype were crossbred with CHOP-/- mice to generate CHOP-deficient VWM mice. These mice were characterized for VWM hallmarks including ataxia and ISR deregulation and dysfunctional astrocytes in brain.

Results
CHOP deletion strikingly altered the VWM clinical phenotype. CHOP-independent ISR markers remained unaffected, while CHOP-regulated markers were changed in expression.

Discussion
The mechanism underlying CHOP's effects are currently studied to increase insight into VWM disease mechanisms.

Van der Staaij, H. (1), Lopriore, E. (2), Fijnvandraat, K. (3), Onland, W. (4), Putter, H. (5), Van der Bom, J.G. (1, 6), Fustolo-Gunnink, S. F. (1)

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Dynamic prediction of bleeding and mortality risks in thrombocytopenic preterm neonates: a model validation study

Rationale
Thrombocytopenic neonates routinely receive prophylactic platelet transfusions with the aim to prevent bleeding. As most neonates with severe thrombocytopenia never develop bleeding, platelet count alone is likely not a good indicator for platelet transfusion decisions. A recent randomized controlled trial comparing high and low platelet transfusion thresholds in preterm neonates indicated harm with higher transfusion thresholds, highlighting the need for an individualized approach to assess bleeding risk. We have successfully developed a dynamic model to predict major bleeding in thrombocytopenic preterm neonates using a set of clinical variables in addition to platelet count. As validation on new patients is required before implementation in clinical practice, we aim to validate the model in all NICUs of the Netherlands.

Methods
We will validate the model in a multicenter, retrospective cohort of preterm neonates <34 weeks with a platelet count <50.000/µL. The main endpoints are major bleeding or death within the coming 3 days. If the model performs worse in the validation dataset, model updating strategies will be performed to improve its predictive accuracy.

Results
After validation, the dynamic prediction model allows clinicians to quantify the risk of bleeding and mortality and adjust it as the clinical situation of the neonate changes. Risks can be predicted at any timepoint during the first two weeks after the onset of severe thrombocytopenia.

Discussion
The validated dynamic prediction model can be used to identify which thrombocytopenic neonates are at high risk for bleeding or mortality. As a second step, we will assess whether platelet transfusions modify this risk and design a clinical impact study to assess the benefit of model-based platelet transfusion decisions compared to the current approach of platelet count-based transfusion decisions with the ultimate goal to develop individualized platelet transfusion guidelines.

Buijtendijk, M.F.J. (1), Peltenburg, P.J. (2), Hoetjes, N.J. (1), Van der Hulst, A.E. (2), Clur, S.A.B. (2)
Blom, N.A. (2), Van den Hoff, M.J.B. (1)

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3D fetal heart models to enhance prenatal screening for congenital heart defects*

Rationale
Ultrasound imaging is the primary screening modality used to diagnose congenital heart defects (CHD) before birth. However, current prenatal CHD detection is suboptimal. The heart is a complex three-dimensional (3D) structure, making prenatal cardiac assessment based on ultrasound imaging extremely challenging. The objective of this study is to create a novel educational resource that will increase the ability to understand the three-dimensional (3D) heart based on 2D ultrasound imaging.

Methods
The hospital database is retrospectively screened for stored four-dimensional (4D) cardiac ultrasound volumes of healthy fetuses and fetuses with CHD with a known postnatal or pregnancy outcome. The open source software 3D Slicer (https://www.slicer.org/) is used for image processing and creation of 3D digital models of the fetal heart and major vessels based on the ultrasound volumes. The created models are combined with an interactive ultrasound interface, allowing the user to examine cardiac morphology through the interrogating ultrasound images and correlate this to the 3D model.

Results
A total of 188 patients with stored 4D volumes have been identified. Segmentation and 3D reconstruction is ongoing. So far, 16 models have been created and validated, including four healthy cases and 12 cases with CHD. In all cases, the morphology of the cardiac chambers, atrial and ventricular septa, atrioventricular valves, and the pulmonary and systemic arterial and venous connections have been successfully reconstructed.

Discussion
Our results show that reconstructing the heart and major vessels based on ultrasound data is feasible. The next step will be integrating the created models with the interactive ultrasound interface. This novel approach to presenting ultrasound imaging of the fetal heart for educational purposes provides an exciting opportunity to increase and spread knowledge of fetal cardiac assessment, an important step towards improving prenatal diagnosis of CHD.

* See Appendix for additional table and/ or figure

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Cystic Fibrosis: Correlation of lung function, peripheral muscle strength and body mass in children with Cystic Fibrosis

Rationale
Cystic Fibrosis (CF) is an autosomal recessive genetic condition known by its multi-system effects and life threatening prognosis. According to 2021 data from the European CF Society Patient Registry (ECFSPR), median survival age for these patients is 51.7 years (95% C.I. 50.0–53.4) in Europe. Patients with CF have impaired chloride and sodium transport across secretory epithelia which results in thickened, viscous secretions in the bronchi, biliary tract, pancreas, intestines, and reproductive system. Progessive lung disease is the major cause of morbidity and mortality for them. In light of the many facets of CF, a number of routine tests are proposed to these patients, this study looks at them investigating the relationship between lung (mal)function, peripheral muscle strength and body composition.

Methods
The present single center retrospective study analyses routine exams (DEXA, Spirometry and CPET) from 64 patients followed by the Wilhelmina Kinderziekenhuis (WKZ) CF clinic.

Results
Strong correlation between FEV1 and appendicular (Pearson`s r=0,72) and total (r=0,68) lean body mass index (LMI) was found. Maximal inspiratory and expiratory pressure (Pimax and Pemax) were also reasonably correlated with aLMI and tLMI (r=0,59; 055; 0,45; 0,43). Peak Expiratory flow and Oxygen uptake also expressed strong correlations with the LMI (r=0,65;r=0,63;r=0,76;r=0,69). Gender and age differences are already accounted for in CPET and lung function results.

Discussion
A considerable limitation is the fact it is a single-center study. Furthermore, the genetic factor could not be entirely accounted for because only 23 patients had their CF genotype available. Nevertheless, the correlations between exercise capacity, respiratory function and LMI in our sample are significant and corroborate previous hypotheses on peripheral muscle development and improved ventilatory and respiratory functions, as well as a better exercise capacity.

Tieskens, J.M. (1), Zijlmans, J. (2,3), De Meyer, R. (4), van der Rijken, R. (4), DREAMS consortium, Popma, A. (2,3,5), Bartels, M. (2,6), Polderman, T.C.J. (1,2,3,7,8)

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Differences in mental health problems before and during the COVID-19 pandemic in Dutch children and adolescents referred to (psychiatric) youth care

Rationale
There is increasing empirical evidence for the impact of the pandemic on mental health of youth worldwide. This might result in aggravated pressure on youth mental health care institutions. To provide adequate treatment, it is important to obtain a clear image of those who are referred to youth care in times of the pandemic. We will investigate whether the age, gender, type and severity of problems, of those referred to youth care during the pandemic differ compared to before the pandemic.

Methods
We include participants (8–18 years) who are referred to (psychiatric) youth care institutions. We will compare participants that enrolled treatment before the pandemic (1 year: Oct 2018 – Mar 2020) with participants that enrolled treatment during the pandemic (1 year: Apr 2020 - Oct 2021). Main outcomes are self- and parent reports on different domains of psychiatric problems assessed with respectively Youth Self Report and Child Behaviour Checklist.

Results
In our previous study (Fischer et al., 2021) we showed that children from a psychiatric sample showed increases in mental health problems over the course of the pandemic. Based on these findings, we expect to find that mental health problems, especially internalizing problems, are higher in the group of children that enrolled treatment during the pandemic. Also, in our previous study it was shown that girls between age 12—18 are most affected by the pandemic compared to boys and younger children. In the present study we will investigate differences between gender and age groups where we expect to find most severe increases in mental health problems in adolescent girls.

Discussion
Empirical evidence indicates that careful follow up of mental health of youth during the pandemic is important. Specifically, it is key to identify specific groups of children that are more vulnerable to negative mental health effects during the pandemic to properly anticipate on the demand for youth care in the future.

Hermans, M.E. (1), Van Oers, H.A. (2), Geurtsen, G.J. (3), Haverman, L. (2), Hollak, C.E.M. (4), Rubio-Gozalbo, M.E. (5), Bosch, A.M. (1)

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Health-related quality of life in patients with classical galactosemia

Rationale
Classical galactosemia (CG) is an inborn error of metabolism with an estimated incidence of 1:53.000 in the Netherlands. The only available treatment is a galactose-restricted diet which resolves critical symptoms in affected newborns but does not prevent long-term complications including cognitive impairment, movement disorders and primary ovarian insufficiency. Health-related quality of life (HRQoL) represents the effect of a disease from the perspective of the patient. The last Dutch HRQoL-studies in CG were published almost two decades ago, and demonstrated a lower HRQoL in both children and adults with CG in motor- cognitive-, and/or social function. In recent years, new published international guidelines resulted in the implementation of a more relaxed diet, emphasis on support of social difficulties and regular neurological and cognitive evaluations. Moreover, the spectrum of CG-patients has been expanded since the start of the newborn screening (NBS) in 2007, detecting variant patients with milder phenotypes. Therefore, it is important to investigate effects of interventions and any remaining unmet needs by assessing the HRQoL of CG-patients.

Methods
All adult and pediatric patients visiting the galactosemia expertise outpatient clinics Amsterdam UMC and Maastricht UMC were invited. Disease-specific questionnaires within the Patient Reported Outcomes Measurement Information System (PROMIS) addressing mental health, social function, cognition, fatigue, and upper extremity function are being completed online by both patients and/or the parents of minor patients. In addition, a generic HRQoL questionnaire (TNO) is completed.

Results
At present, the data collection is still running with already a response rate of 40%. Results will be presented at the symposium and describe the HRQoL of the entire patient group, the difference between classical patients and NBS-detected variant patients, and the relation with biochemical parameters and outcome measures.

Reijman, M.D. (1), Kusters, D.M. (1), Wiegman, A. (1)

(1) Department of Pediatrics, Amsterdam University Medical Center, Amsterdam, Netherlands

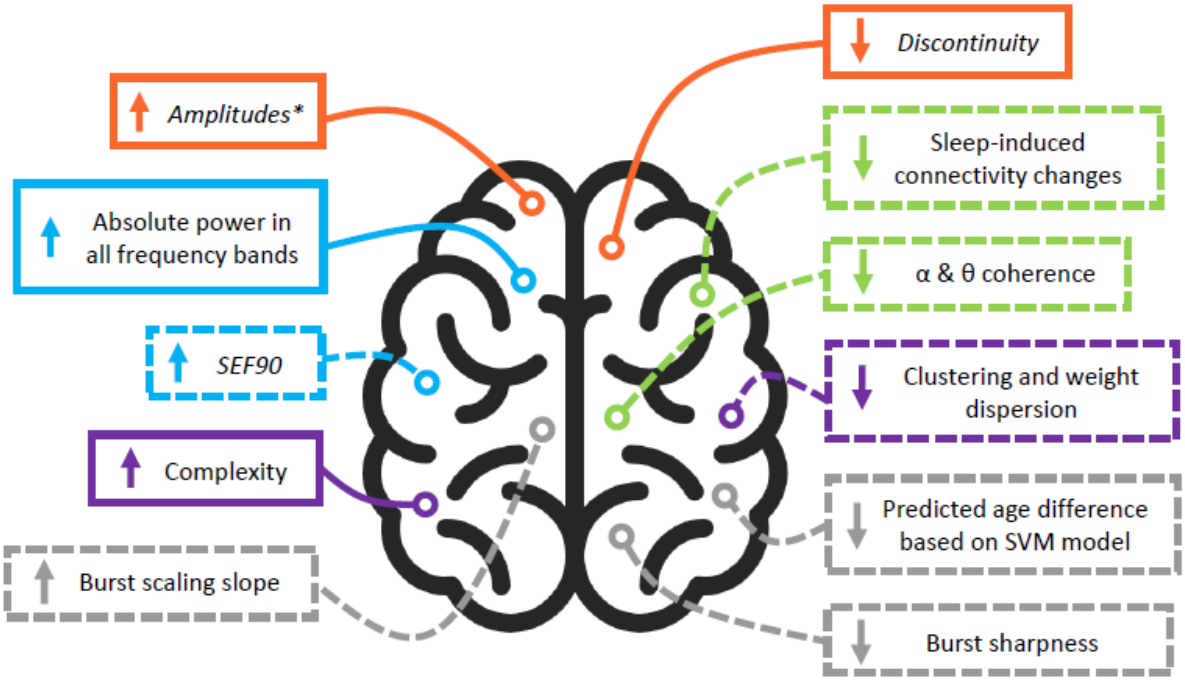
Advances in familial hypercholesterolaemia in children

Familial hypercholesterolaemia is a common, dominantly inherited disease that results in high concentrations of low-density lipoprotein cholesterol and in premature cardiovascular disease. To prevent cardiovascular disease and premature mortality, patients with the condition need to be identified and to start treatment early in life.
In this Review, we discuss the treatment of heterozygous and homozygous familial hypercholesterolaemia in children, including lifestyle modifications, current pharmacological treatment options, and promising novel lipid-lowering treatments. In particular, these new therapies are expected to improve outcomes for patients with severe heterozygous familial hypercholesterolaemia or statin intolerance.
For patients with homozygous familial hypercholesterolaemia, lipoprotein apheresis is currently the most valuable therapy available, but new approaches might reduce the need for this effective yet invasive, time-consuming, and expensive treatment.

Appendix: Figures and Tables of Abstract

AMSTERDAM KINDER SYMPOSIUM

Neonatal quantitative electroencephalography measures and long-term outcome: a systematic review



Measures related to:
- aEEG amplitudes and discontinuous background pattern
- Power spectrum
- Connectivity
- Network analysis

- findings based on one study
- findings based on multiple studies

*Text in *italics* identifies quantitative EEG measures that are based on amplitude-integrated EEG data

- positive association with favourable outcome
- negative association with favourable outcome

PROMIS item bank	items (n)	Legacy	items (n)	Hypothesized *r*
		HaemoQoL Physical		
Pain Interference	5 to 12	Health	7	0,7 - 0.9
Depressive Symptoms	5 to 12	HaemoQoL Feelings	7	0.5 - 0.7
Anxiety	5 to 12	HaemoQoL Feelings	7	0.5 - 0.7
Anger	9	HaemoQoL Feelings	7	0.5 - 0.7
Fatigue	5 to 12	HaemoQoL Feelings	7	0.5 - 0.7
		HaemoQoL Other		
Peer Relationships	5 to 12	Persons	6	0,7 - 0.9
Mobility	5 to 12	PedHAL	55	0,7 - 0.9
Global Health	9	HaemoQoL total score	81	0,7 - 0.9

The use of paediatric PROMIS® item banks in Dutch boys with haemophilia

Table 1: Hypothesized correlations between PROMIS item bank domains and the corresponding legacy domains.

The Effect of Systemic Hydrocortisone in Ventilated Preterm Infants on Behavioural outcomes at 2 years' Corrected Age: follow-up of a randomized clinical trial.

	Multiple imputation analysis		
	Hydrocortisone	Placebo	Mean difference (95% CI)[a]
CBCL			
Total problems	46.8 (10.4)	48.3 (10.5)	-1.52 (-4.00, 0.96)
Internalising problems	45.1 (11.0)	47.5 (10.8)	-2.40 (-4.99, 0.20)
Externalising problems	49.2 (10.4)	50.0 (11.5)	-0.81 (-3.40, 1.77)
CBCL syndrome scales			
Emotionally reactive	52.3 (5.1)	53.0 (6.2)	-0.72 (-2.01, 0.57)
Anxious/Depressive	50.8 (2.6)	51.0 (2.8)	-0.24 (-0.83, 0.35)
Somatic complaints	54.5 (7.7)	55.3 (8.1)	-0.83 (-2.72, 1.07)
Withdrawn behaviour	53.8 (6.0)	54.3 (6.4)	-0.52 (-1.99, 0.95)
Sleep problems	52.3 (5.7)	53.4 (7.3)	-0.64 (-2.19, 0.90)
Attention problems	56.0 (8.7)	56.3 (8.6)	-0.25 (-2.28, 1.77)
Aggressive behaviour	52.9 (5.5)	53.6 (7.2)	-0.71 (-2.23, 0.80)
CBCL DSM-IV-oriented subscales			
Affective problems	53.9 (6.1)	53.9 (5.3)	0.04 (-1.29, 1.37)
Anxiety problems	51.3 (3.8)	52.6 (5.8)	-1.26 (-2.41, -0.12)*
Pervasive developmental	53.8 (7.0)	54.7 (7.3)	-0.92 (-2.59, 0.75)
Oppositional defiant problems,	53.6 (6.0)	54.0 (6.7)	-0.34 (-1.75, 1.07)
Attention deficit/hyperactivity problems	54.1 (6.6)	54.3 (6.9)	-0.24 (-1.83, 1.36)

Table 1. Behavioural outcomes assessed by CBCL 1.5-5 year at 2 years' corrected age.

Data are mean (SD). CI=confidence interval.
[a] Mean difference with 95% CI was calculated using a t-test.
*significant mean difference

ADRB2 Arg16Gly polymorphisms are associated with nocturnal asthma symptoms in asthmatic children using LABA

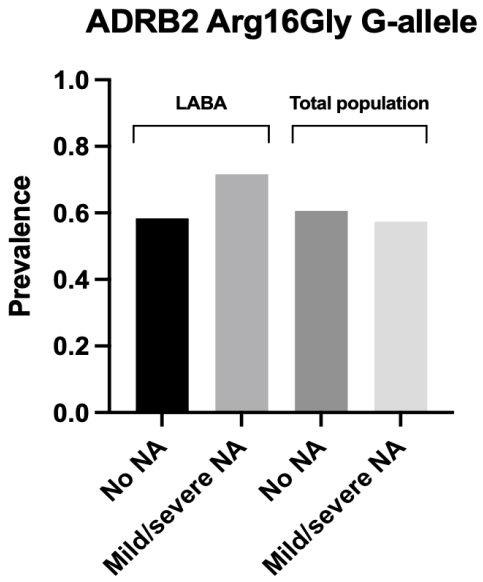


Figure 1. Increased prevalence of the *ADRB2* Arg16Gly G-allele in asthmatic children with nocturnal asthma (NA) despite LABA use compared to children without nocturnal asthma symptoms.

The relation between serum trough concentration paracetamol and pain reduction in preterm and term neonates: a retrospective observational study

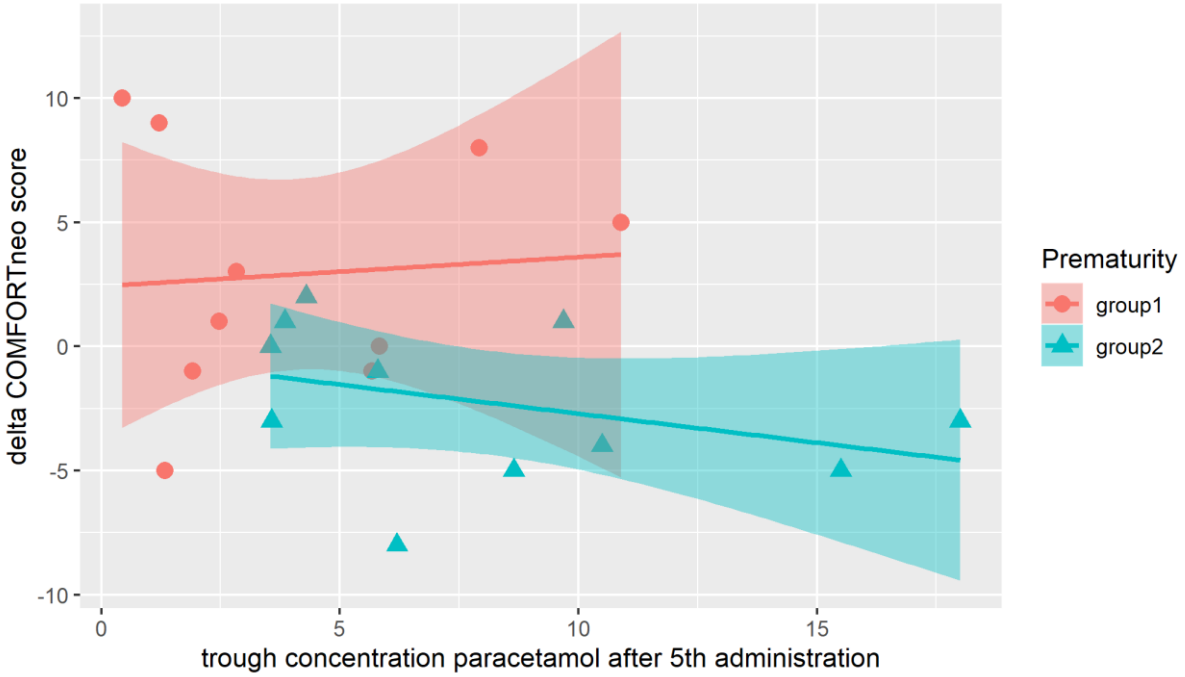


Figure 1: Linear regression between trough concentration paracetamol after the fifth administration and pain reduction calculated as the difference in COMFORTneo score before start and after the fifth dose of paracetamol. Linear regression is y = 2.43 + 0.12 * x for group 1 (premature neonates) and y = -0.37 – 0.234 * x for group 2 (term neonates).

Feasibility of wireless cardiorespiratory monitoring with dry electrodes incorporated in a belt in preterm infants

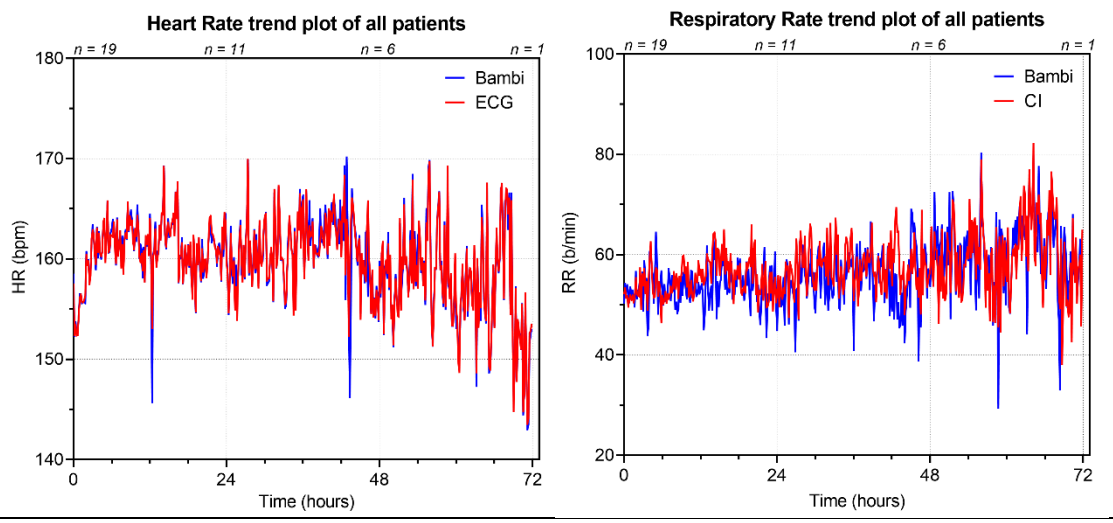
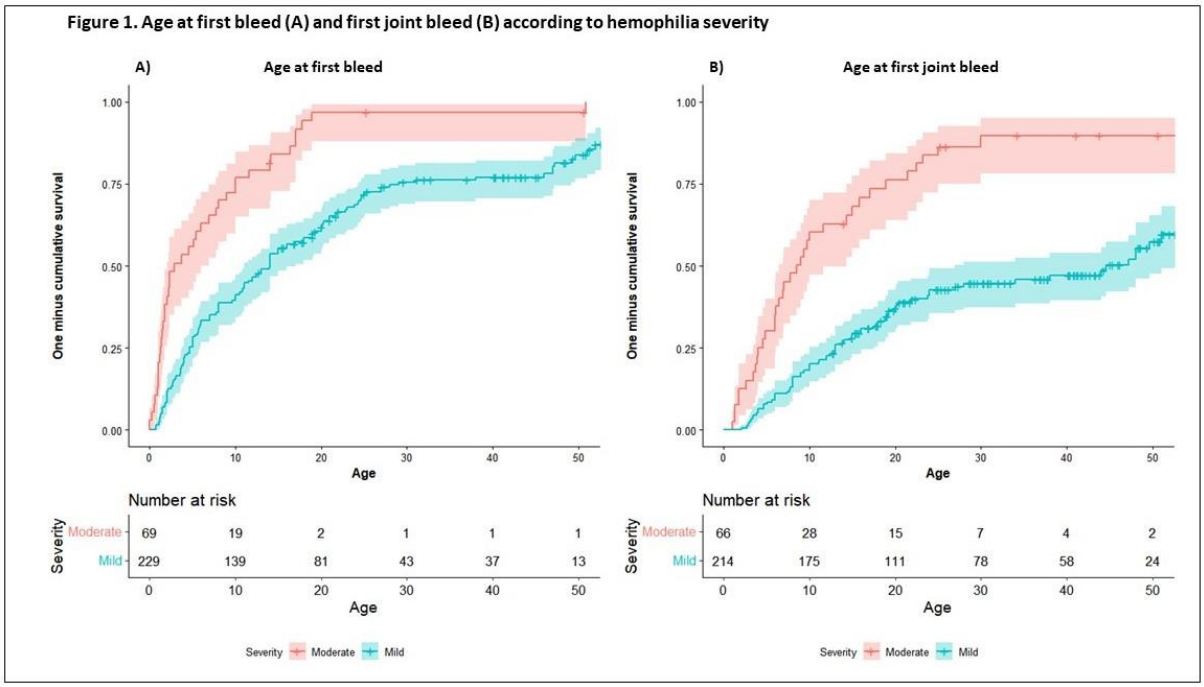


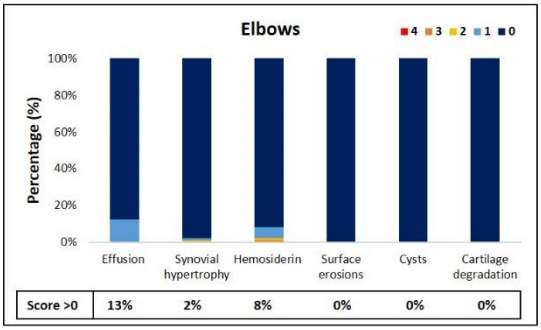
Fig. 1 – *The trend in heart rate (HR, left) and respiratory rate (RR, right) measured with the Bambi belt in blue and ECG/Chest Impedance (CI) in red. Each trend consists of the mean HR or RR value at 10-min intervals of all measured subjects. The amount of subjects (n) on each measurement day is presented above the graphs.*
Note: As errors and large signal artefacts are removed in the data, the patients included per timepoint could vary.

The clinical phenotype of patients with non-severe hemophilia A and B

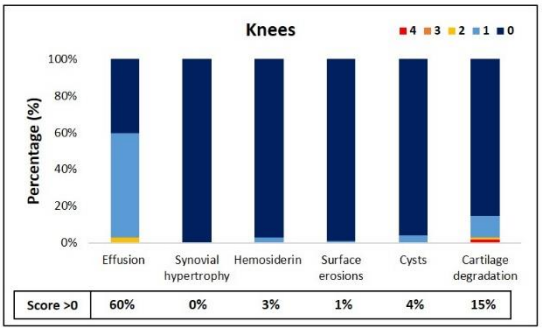


Joint status of patients with non-severe hemophilia A

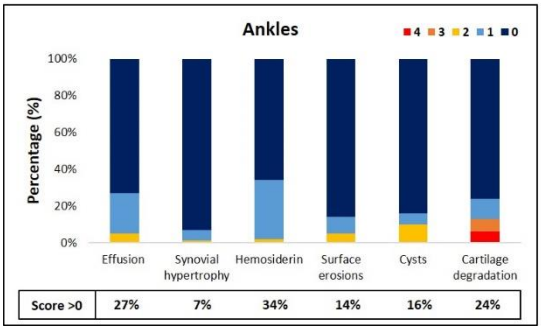
Figure 1. IPSG-scores per item for evaluated elbows (n=96), knees (n=102) and ankles (n=101).



Score >0	13%	2%	8%	0%	0%	0%



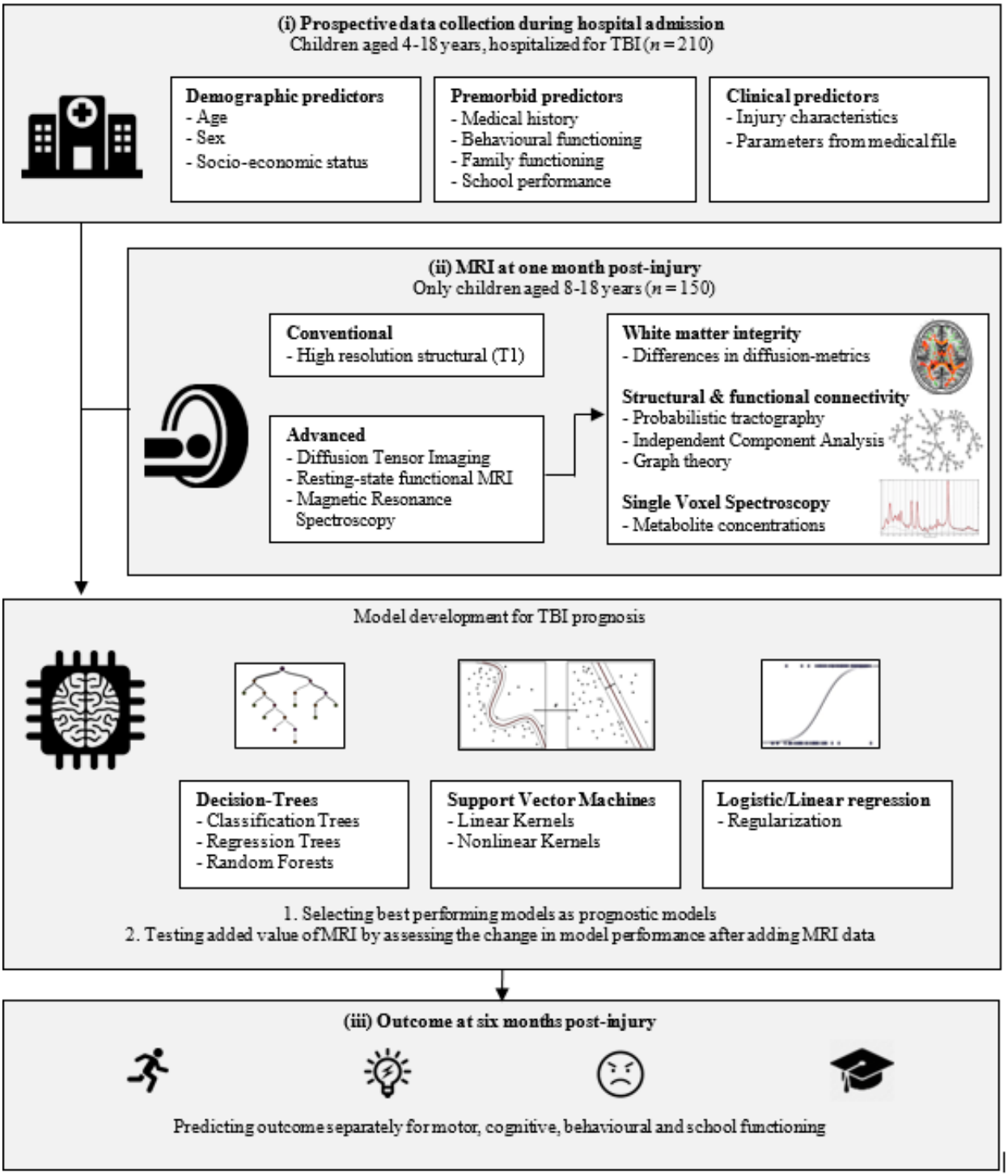
Score >0	60%	0%	3%	1%	4%	15%



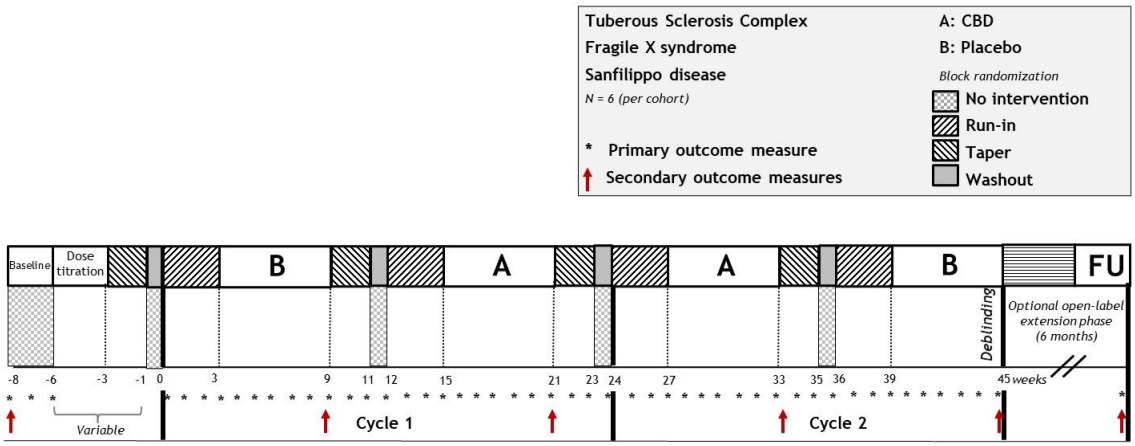
Score >0	27%	7%	34%	14%	16%	24%

Item	Score range
Effusion	0-3
Hemosiderin depositions	0-3
Synovial hypertrophy	0-3
Surface erosions	0-2
Subchondral cysts	0-2
Cartilage degradation	0-4
Total per joint	0-17

Towards PErsonalized PRognosis for Children with Traumatic Brain Injury: The PEPR Study Protocol



N-of-1 studies in children with rare genetic neurodevelopmental disorders: A study protocol and systematic review of the literature



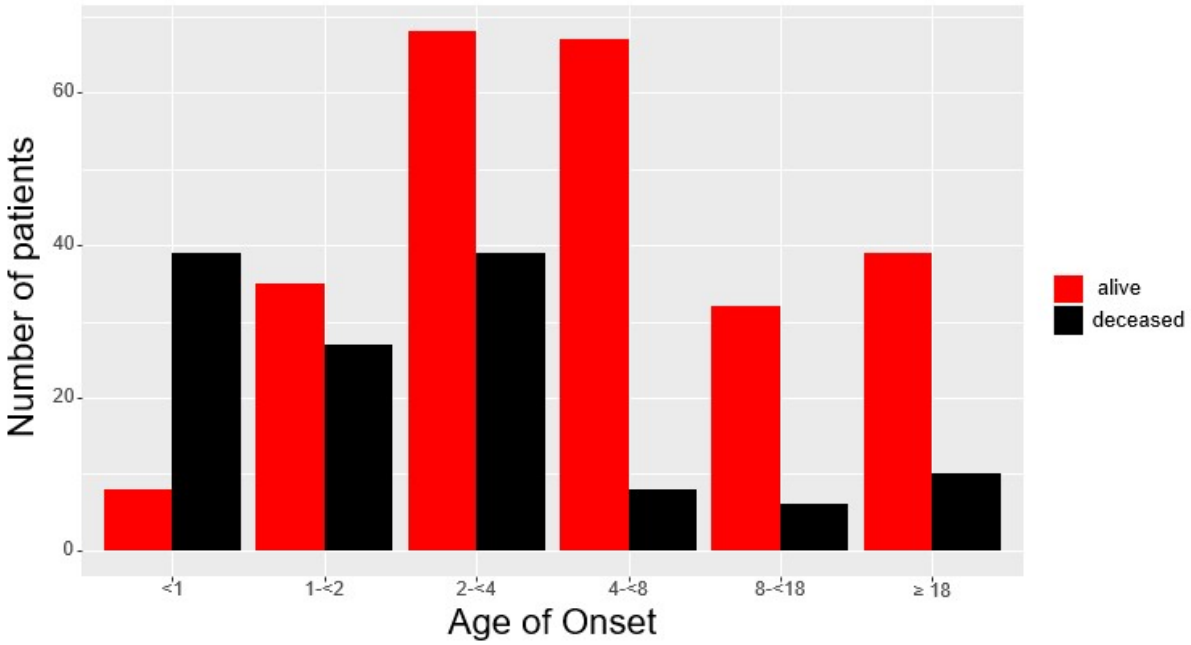
Improving hospital to home transition for children with medical complexity and their families by understanding parental needs: A systematic review of qualitative studies following a meta-aggregative approach

Synthesized findings	Enablement								Engagement				Empowerment		
Categories	Coordination of care		Practical preparation for discharge		(Access to) resources and support system	Training skills and knowledge	Communication		Emotional preparation for discharge		Emotional issues: Uncertainty and Anxiety	Parent-Professional relationship	Changing perspective: finding (new) routines		Parental Empowerment and taking responsibility	Total
Aasen 2018	1	2	0	0	2	0	2	0	1	1	0	5	5	1	2	17
Berman 2018	2	0	3	0	7	3	3	2	1	1	0	2	1	2	1	21
Brenner 2015	1	0	3	0	3	1	0	0	0	0	0	2	0	2	2	11
Callans 2016	1	1	2	0	2	0	0	0	0	0	5	2	3	0	7	21
Coelho Ramos 2015	0	0	3	0	4	0	0	0	0	0	1	0	0	0	1	9
Cohen 2015	0	0	2	0	2	0	0	0	0	0	2	0	1	0	2	9
Desai 2015	2	0	3	0	4	2	0	8	1	0	3	1	1	0	3	28
Gaskin 2018	0	0	0	0	7	0	0	0	0	0	3	0	6	0	3	19
Lakshmanan 2019	2	0	0	0	4	1	0	1	1	0	6	1	0	11	0	16
Lerret 2017	0	0	0	0	0	0	0	0	0	0	5	1	1	4	0	17
Leyenaar 2017	1	0	3	0	0	2	0	1	1	0	1	4	4	1	2	19
Manhas 2012	0	0	3	0	3	0	0	0	1	1	4	2	2	1	2	13
Margolan 2004	1	0	2	0	10	0	0	0	0	0	0	3	3	3	0	19
Murdoch 2011	0	0	0	0	1	4	0	0	1	0	4	0	0	4	5	19
Okido 2012	0	0	0	0	5	0	0	0	0	0	1	0	0	3	1	10
Okido 2015	0	0	0	0	7	0	0	0	0	0	1	4	4	1	2	15
Silva-Rodrigues 2019	2	0	0	0	2	7	0	2	1	0	6	3	8	1	1	32
Simeone 2018	0	0	0	0	0	0	0	0	0	0	2	1	2	0	0	5
Zanello 2015	2	0	0	0	0	2	0	4	0	0	1	4	1	7	0	14
Barone 2020	0	0	0	0	3	0	0	0	0	0	2	1	7	2	0	13
Gaskin 2021	0	0	1	0	3	0	0	0	0	0	4	0	2	1	0	10
Leary 2020	1	0	3	0	3	0	1	0	0	0	0	2	1	1	0	9
Total	16	12	26	71	3	0	22	1	8	0	53	38	2	65	35	346

Figure 1 Total number of original findings per included paper that were used to determine the categories and synthesized findings.

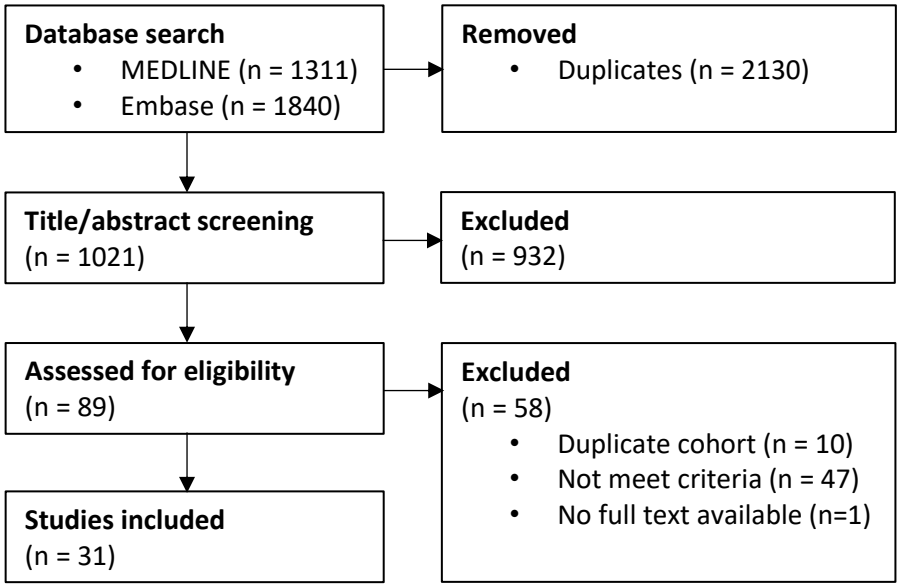
Age and sex distribution in patients in a registry for Vanishing White Matter

Figure 1. Age of onset in VWM patients



Genetic and non-genetic determinants of the outcome of immune tolerance induction in patients with hemophilia A and inhibitors –a systematic review

Figure 1. Flow chart article inclusion



Explaining the prevalence and characteristics of non-neutralizing antibodies (XPlain) – preliminary results

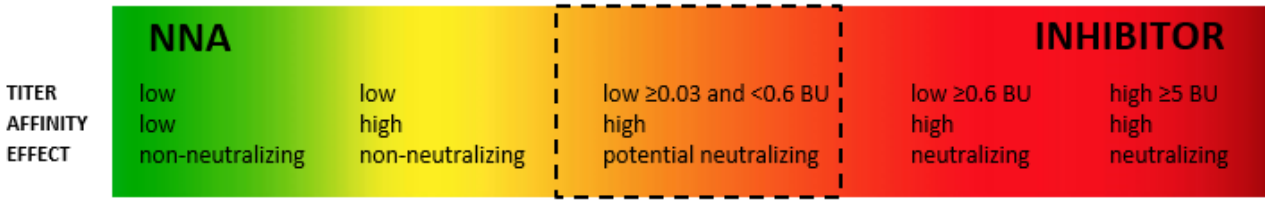
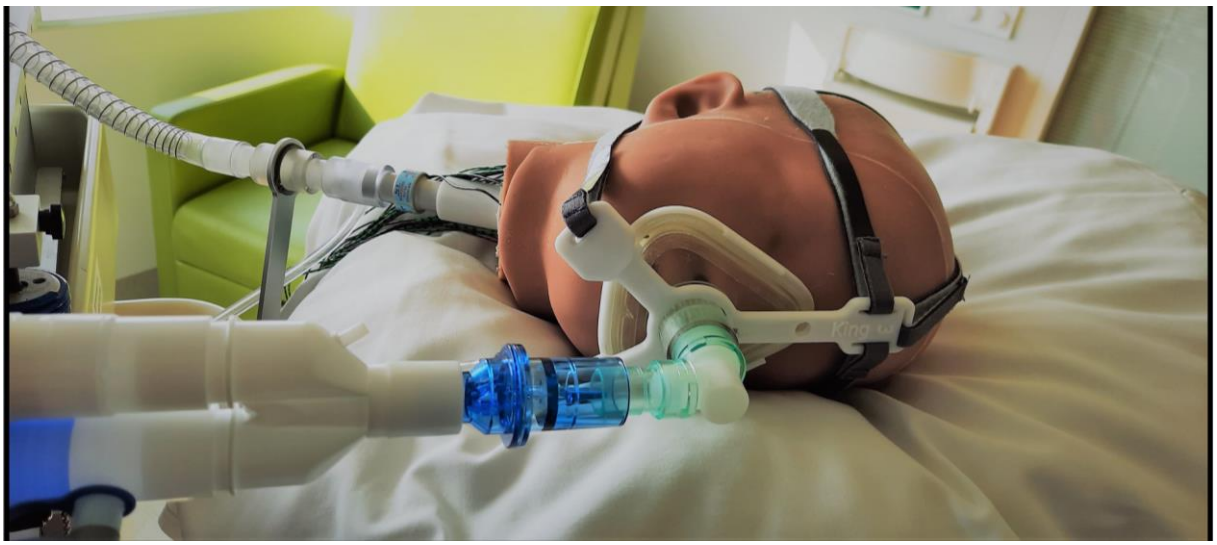
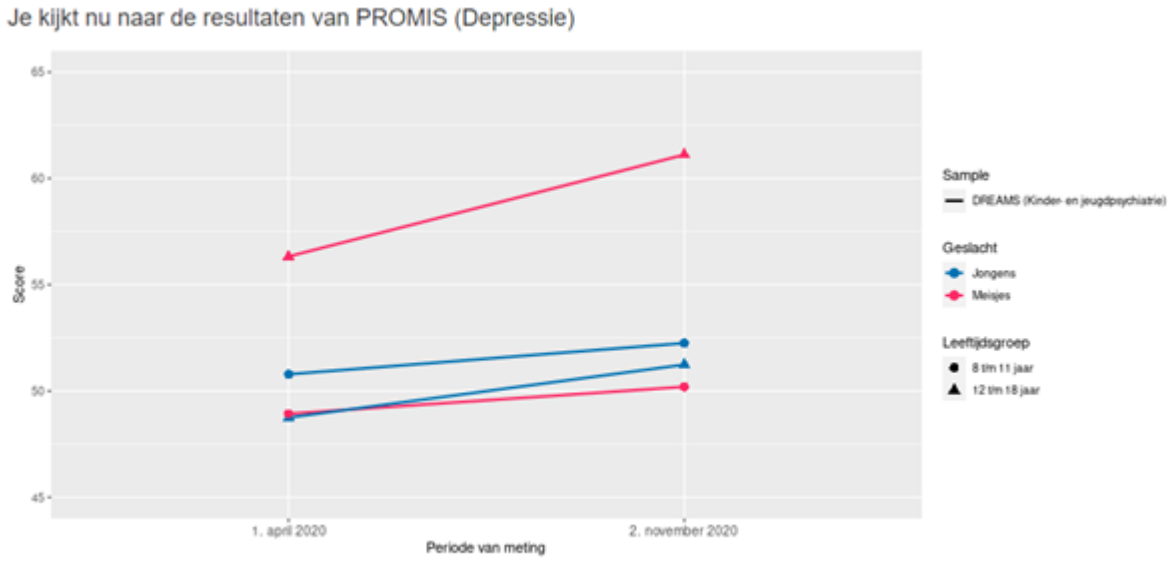


Figure 1. The hypothesized spectrum of anti-FVIII/FIX antibodies. The subset in the middle, indicated by the dashed square, represents our hypothesis. We hypothesize that a subset of NNAs are in fact low-titer inhibitors with titers <0.6 BU (lower detection limit of the Bethesda assay). *BU = Bethesda Unit.*

The use of personalized masks to optimize non-invasive ventilation in children admitted to the Paediatric Intensive Care Unit



Mental health problems during the COVID-19 pandemic in Dutch children and adolescents with and without pre-existing mental health problems



Genetic determinants of inhibitor development in patients with severe hemophilia A.

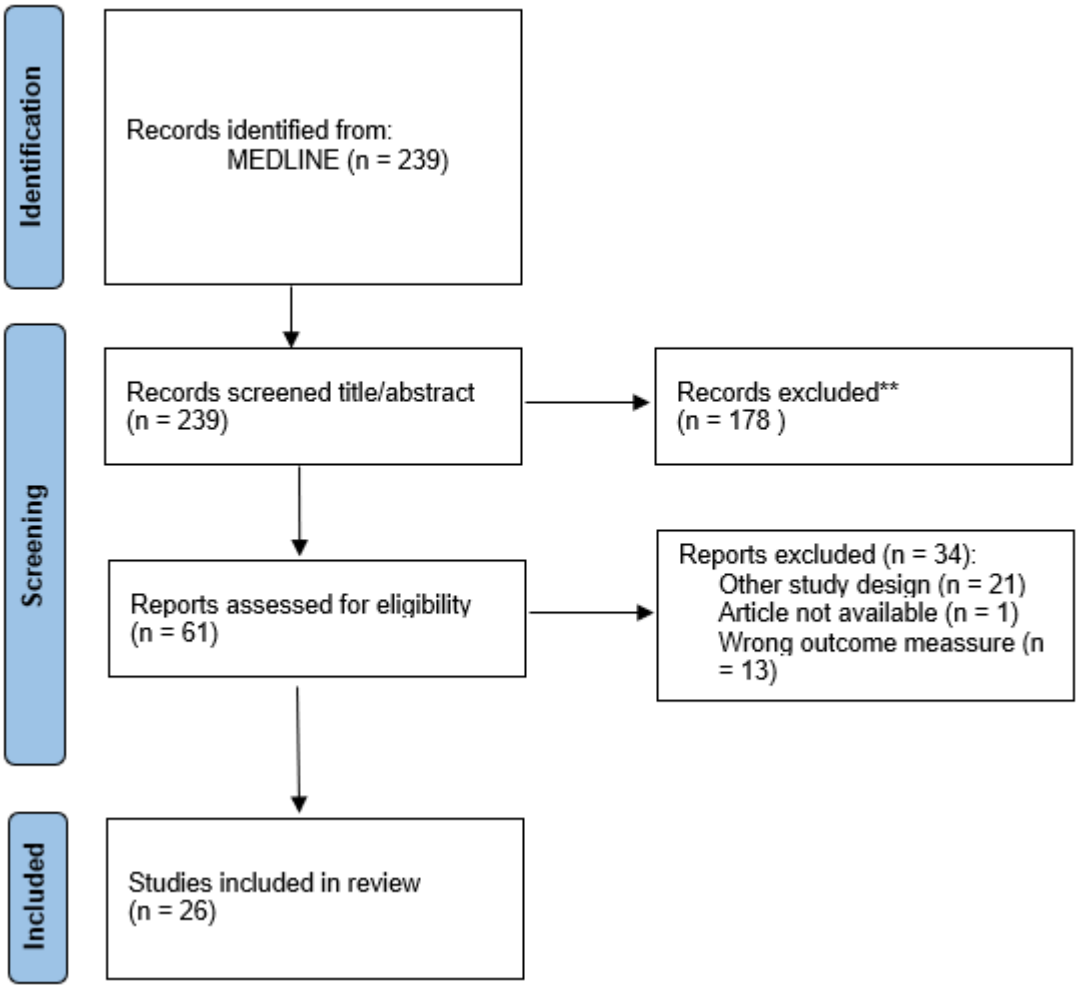


Figure 1. Flow chart of study selection

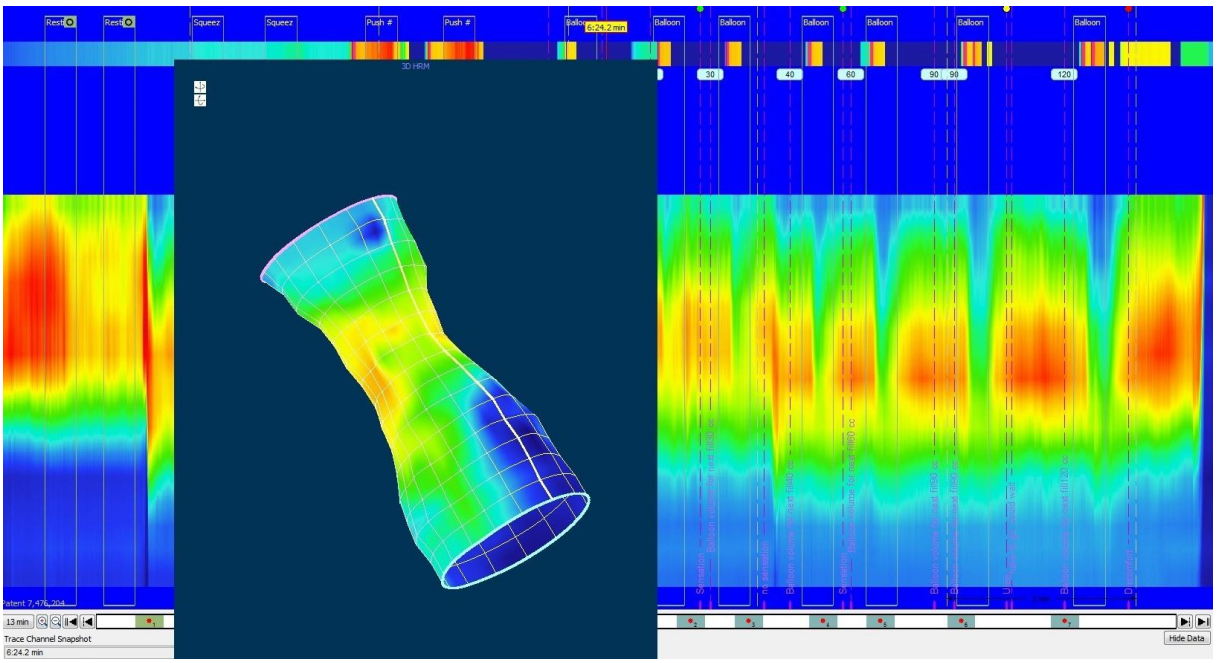
Genetic and clinical determinants of the outcome of immune tolerance induction in severe hemophilia A – preliminary results

Characteristics		**Total cohort (n=76)**
F8 genotype, n(%)	Intron 22 inversion	46 (61)
Ethnicity, n(%)	Caucasian	52 (68)
	Asian	5 (7)
	African	6 (8)
	Other	12 (16)
FVIII product at start ITI, n(%)	Recombinant	65 (86)
	Plasma-derived	11 (14)
Interval inhibitor detection and start ITI, weeks (IQR)		8.1 (1.0 – 28.5)
Age at start ITI, years (IQR)		2 (1 – 4)
Inhibitor titer, BU/ml (IQR)	At first detection	4.7 (1.3 – 14.9)
	Pre-ITI	5.8 (2.6 – 20.0)
	Peak	25.3 (4.7 – 194.3)

Table 1. Baseline characteristics

Design research for procedural comfort in children

A pilot study on the use of three-dimensional anorectal manometry in children with functional constipation; comparing outcomes and experiences with high-resolution anorectal manometry



Bronchopulmonary dysplasia and neurofilament light chain biomarker in preterm infants

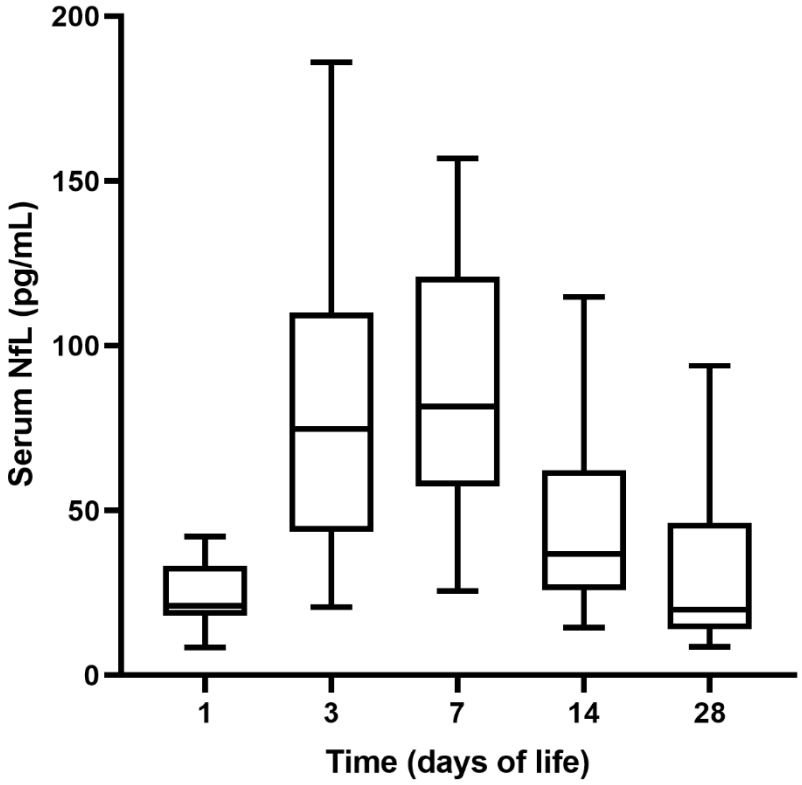
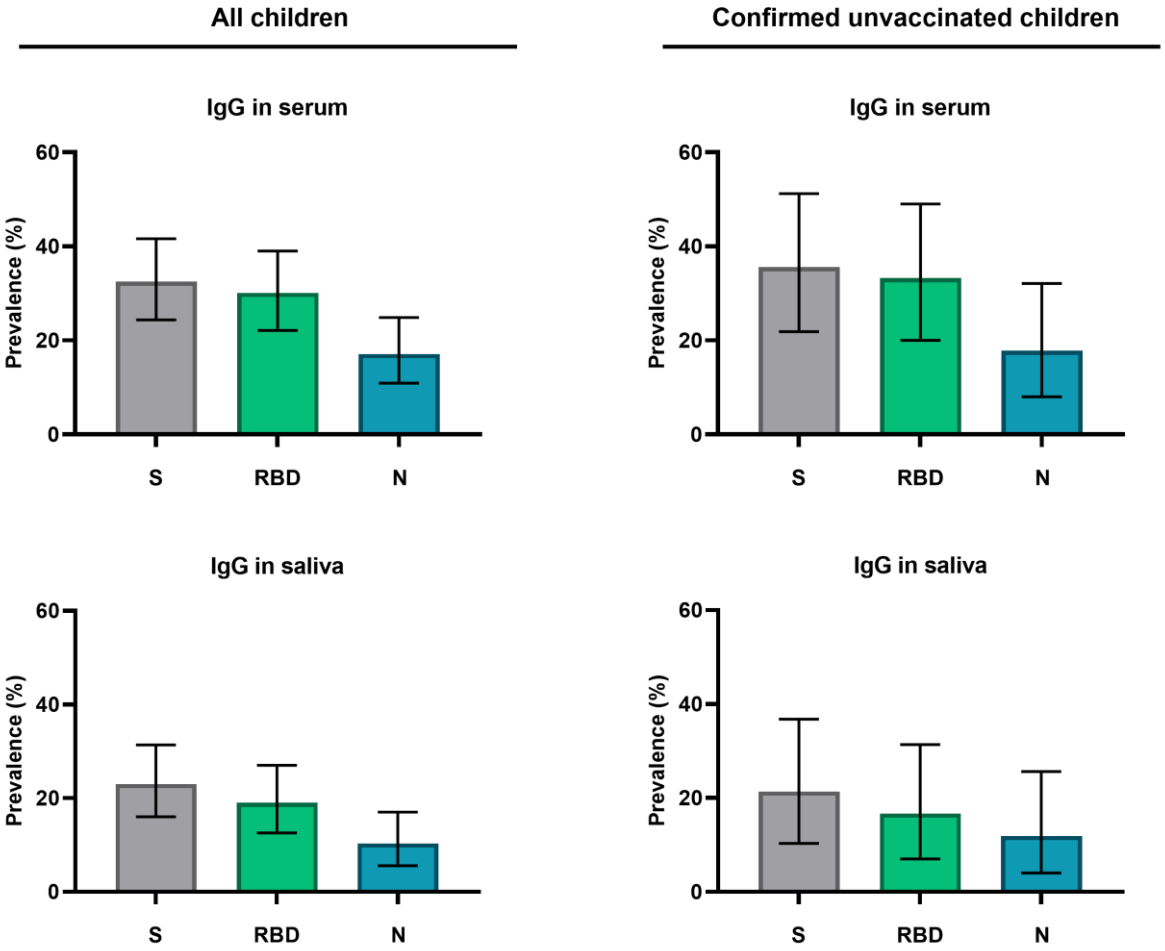


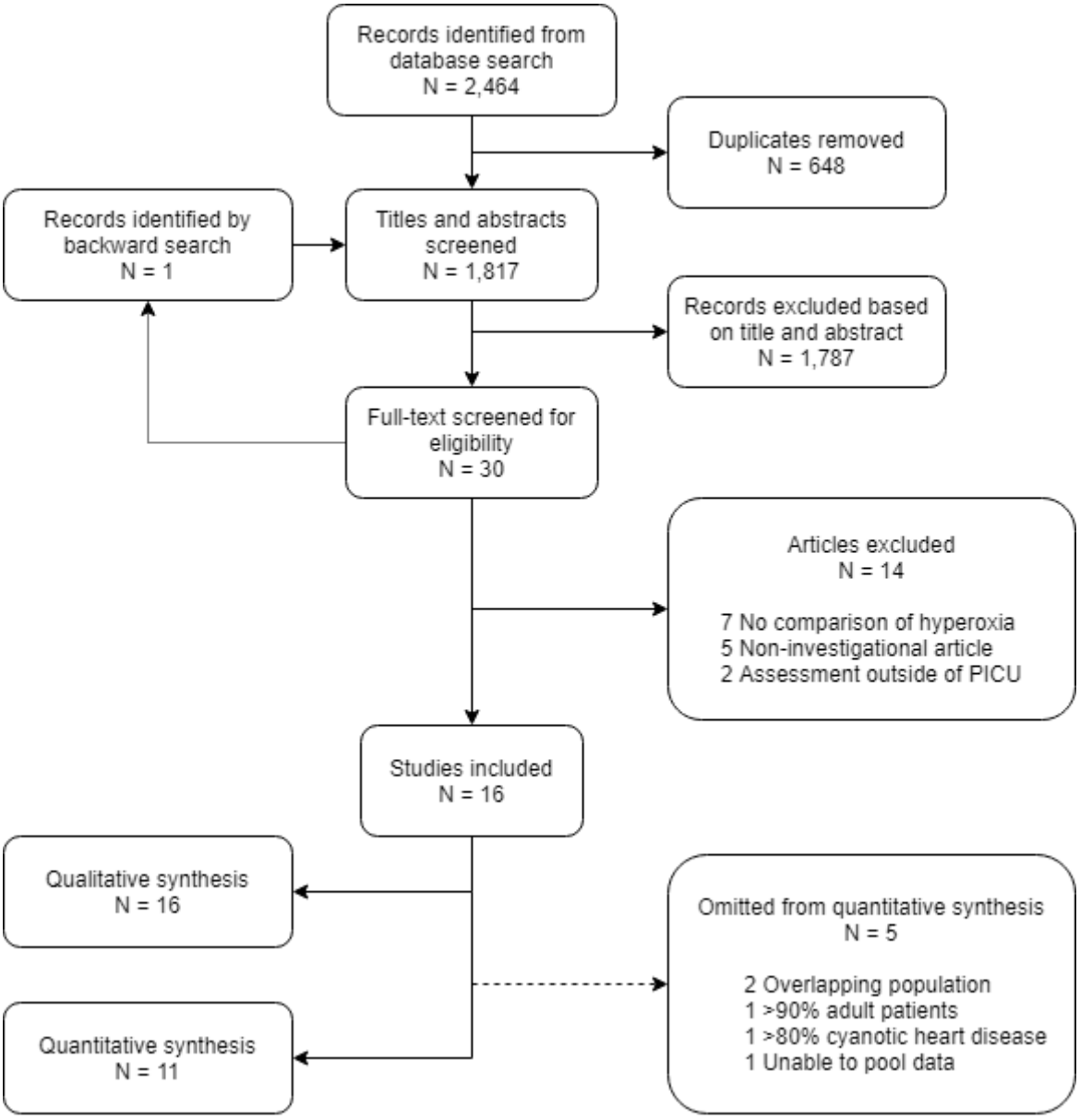
Figure 1. Serum NfL levels during the first month of life in preterm born infants <30 weeks gestational age.

Saliva SARS-CoV-2 antibody prevalence in children after 1 year pandemic

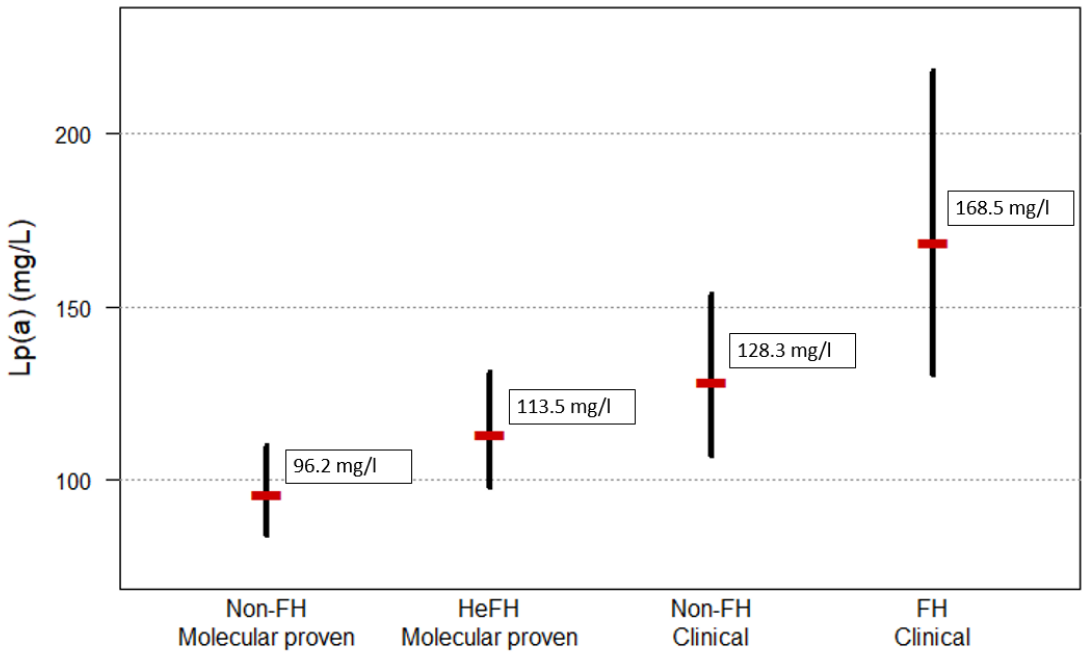


Emma Personalized Medicine Center: bridging the gap for children with genetic disorders

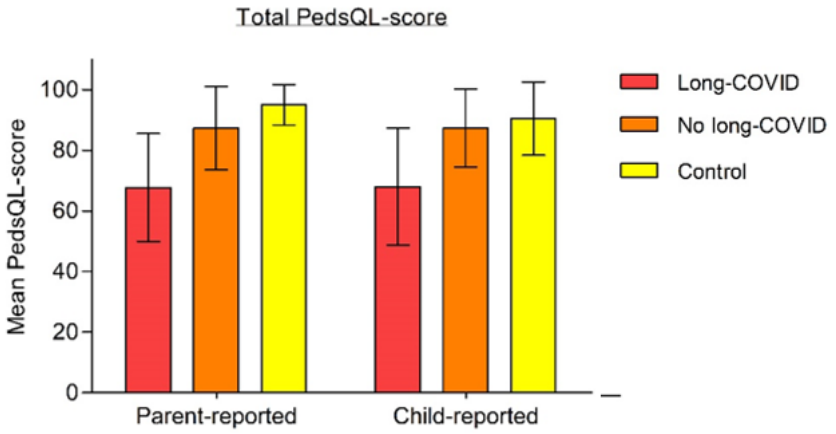
Association of arterial hyperoxia with outcomes in critically ill children: A Systematic Review and Meta-Analysis



Lipoprotein(a) levels in children with and without familial hypercholesterolemia

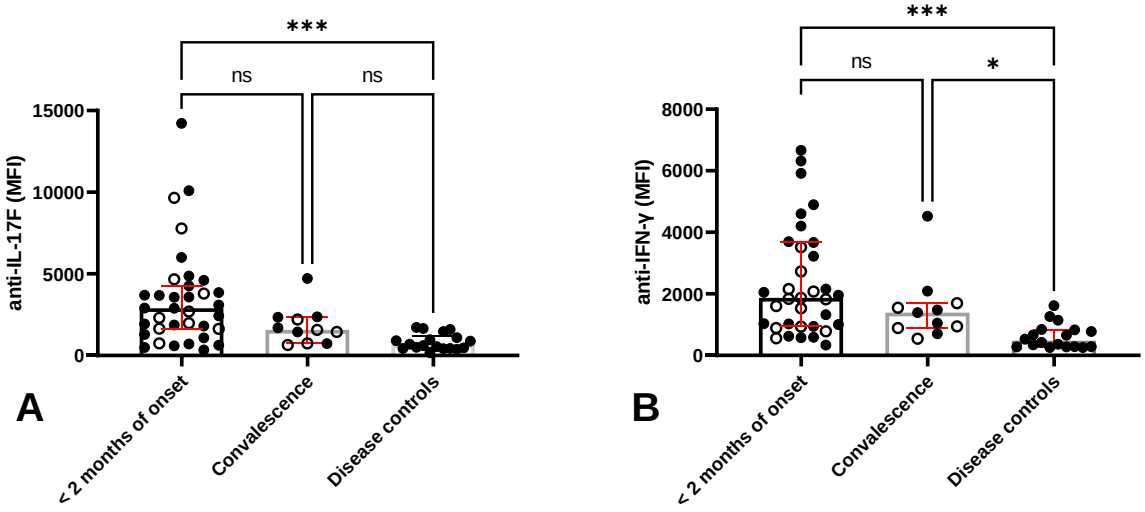


Pediatric long-COVID: the long-term impact of SARS-CoV-2 infection in previously hospitalized children

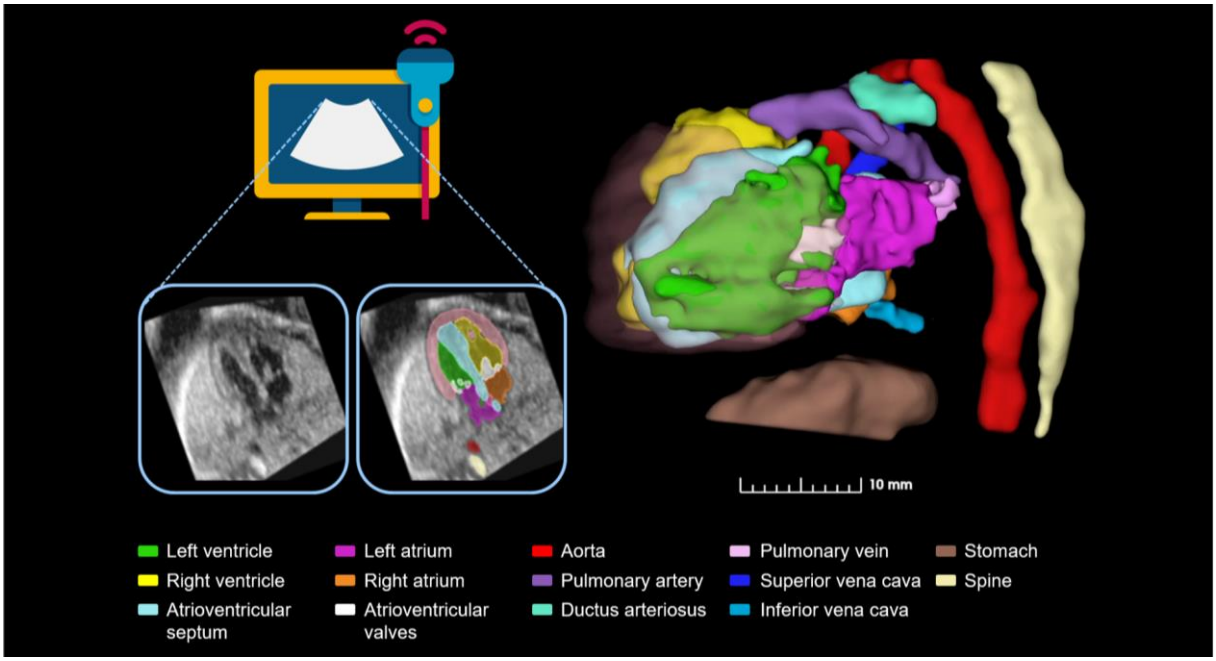


Error Bars: ±1 SD. Psychosocial health score: combined score of the emotional, social, and school functioning subscales. Total score: combined score of the emotional, social, school, and psychical subscales. Higher scores indicate better quality of life.

Anti-cytokine autoantibodies in Kawasaki disease and SARS-CoV-2 related Multisystem Inflammatory Syndrome in Children



3D fetal heart models to enhance prenatal screening for congenital heart defects



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Platinum partner
- Breakfast session: Nutricia

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- DrFalk
- MeadJohnson

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- Stotterfonds
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- Crisp
- Dr C.J. Vaillantfonds
- Proefschriftmaken
- Speech republic
- Gildeprint
- Touch training & coaching

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- Dr. Annike Bekius
- Ms. Vanessa Liem

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- Dr. Charlotte Nusman en Dr. Bart Cortjens

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