AMSTERDAM KINDER SYMPOSIUM

ABSTRACTBOOK

Sustainable Pediatrics

here to stay

3 februari 2023

Content

Program Amsterdam Kindersymposium

7:30 - 8:45	Registration, coffee & tea
8.00 – 8.45	Nutricia breakfast session (Diner Foyer)
8:45- 9:00	Opening Amsterdam Kindersymposium 2023 (Mary Dresselhuyszaal) *Prof. dr. Willem de Vries & chairmans of the day*
9:00 - 9:40	Green team Emma kinderziekenhuis (Mary Dresselhuyszaal) *Berber Kapitein & Wouter Hehenkamp*
9:40 - 10.05	PhD in the spotlight (Mary Dresselhuyszaal) *Charlotte Bekker*
10:05 - 10:30	Coffee break
10:30 - 11:45	SLAM session I
11:45 - 12:30	Hugo Heymans lecture by Tessa Roseboom (Mary Dresselhuyszaal) *Tessa Roseboom*
12:30 - 13:10	Lunch and Elgan lunch symposium (Diner Foyer)
13:10 - 14:25	SLAM session II
14:25 – 15:10	Micro plastics and toxicity (Mary Dresselhuyszaal) *Gavin Ten Tusscher*
15:10 – 15:35	Coffee break
15:35 - 16:20	Luscii app (Mary Dresselhuyszaal) *Daan Dohmen*
16:20 - 16:45	SLAM Battle & Prize Ceremony (Mary Dresselhuyszaal) *Brigitte de Bie & Floor Postema*
16:45 – 17:00	Closing word (Mary Dresselhuyszaal) *Prof.dr. Willem de Vries & chairmans of the day*
17:00 – 20:00	AKS after drinks at Café Lux

Preface prof. dr. Willem de Vries

For the twelfth time, a group of young researchers organizes the Amsterdam Kinder- symposium. A teaching course in itself, with 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 children, through research we will understand the mechanism behind disturbance in functional outcome, through research we will know what treatment is best for the patient as well as the family surrounding him or her.

Again, as in former years, 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 3th, has its historical roots. The SLAM presentations are the backbone of the symposium, while the plenary sessions will be held in the view of the leading topic of the symposium “Sustainable Pediatrics: Here to Stay”. In which we set our sights on the future of pediatrics organized by our young researchers, who are part of that future. The Committee has invited very interesting speakers, and has selected 60 abstracts to be presented, which makes this a very special day for many.

I wish you all a beautiful day in the DeLaMar Theater at our Amsterdam Kindersymposium 2023.

Willem de Vries
Chair Emma Children’s Hospital at Amsterdam UMC

Preface symposium committee

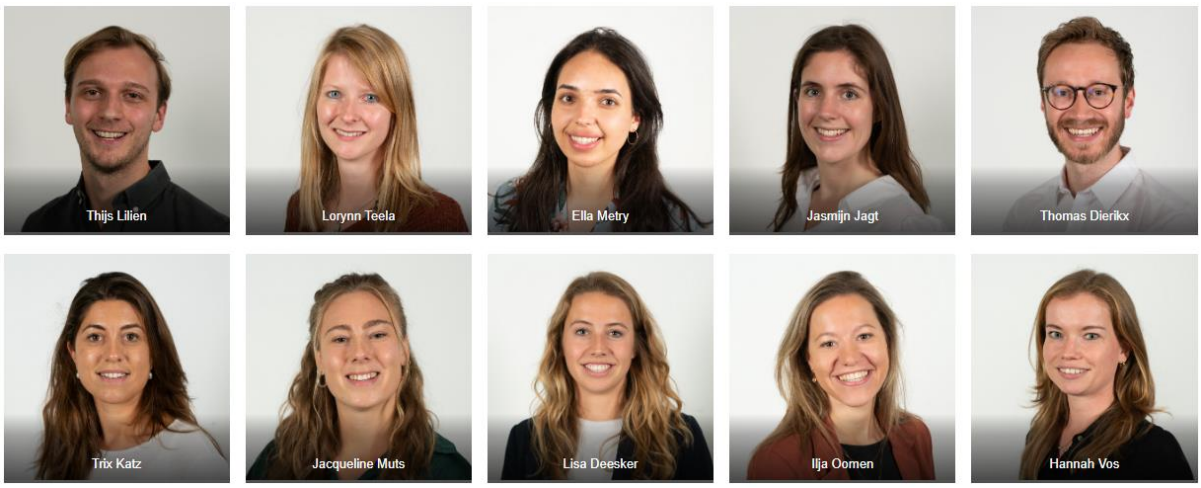
With excitement, we invite you to the 12th edition of the Amsterdam Kindersymposium (AKS) in the DeLaMar Theatre in Amsterdam. This year's theme is **'Sustainable Pediatrics: here to stay'** and with this inspiration we have selected several honorable speakers to present their work on topics in and adjacent to the field of pediatrics and sustainable healthcare. Sustainable healthcare is now more urgent than ever, and as caregivers and researchers in the field of pediatrics we want to contribute to a green(er) future to take care of health for children, now and in the future!

Nutricia powers the annual **breakfast session**, where you can enjoy a delicious breakfast while you wake up with inspiring talks about research in the field of pediatric gastroenterology and nutrition. Then, we welcome the green team of the Amsterdam UMC with **Berber Kapitein and Wouter Hehenkamp**. This year's PhD in the spotlight is **Charlotte Bekker** a young and promising post-doc. Furthermore, **Tessa Roseboom** will provide us with her view on a good fair start for children. During the lunch ELGAN brings us a refreshing **lunch symposium**. Subsequently, **Gavin Ten Tusscher** will learn us about micro plastics and toxicity in pediatrics and **Daan Dohmen** will provide his view on sustainable healthcare by using e-health applications.

We are looking forward to an inspiring day and hope that you will enjoy the AKS 2023. We would like to thank all that have contributed to making the AKS a great success and we hope to continue and expand this endeavor in the future.

The Amsterdam Kindersymposium Committee 2022–2023,

Thijs Lilien, Lorynn Teela, Ella Metry, Jasmijn Jagt, Thomas Dierikx,
Trix Katz, Jacqueline Muts, Lisa Deesker, Ilja Oomen & Hannah Vos



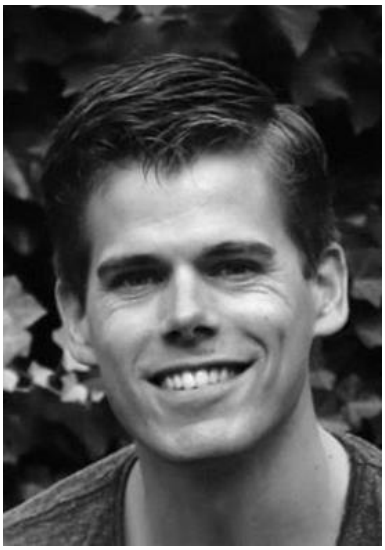
Introduction moderators of the day

Annemarie van de Geer

Dr. Annemarie van de Geer has a degree in both Medicine and Law. She obtained a PhD on Neutrophil defects and deficiencies. After finishing her PhD, she obtained a WAR grant, her first big step in becoming a Postdoc and pursuing a scientific career besides a clinical career. She likes spending her spare time with family, in restaurants and on sandy beaches.

"Green, greener, greenest!"

Bart Cortjens



After obtaining his master degree in medicine, Bart finished his PhD on Neutrophils in respiratory syncytial virus disease. His first publication, regarding the detection of NETs in human RSV disease, is extra special to him. As a pediatrician in spe, his favorite aspect is the diverse landscape of diseases combined with the endlessly diverse landscape of social interaction with patients and parents. In the future he aspires to become a neonatologist. In his time off, you can find him on a bike, in the mountains or enjoying some good Italian food.

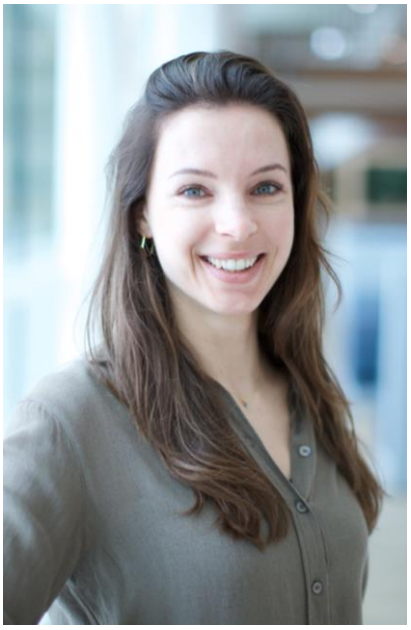
"I am really excited to hear what everyone (all other researchers/PhD's) is doing, and to feel all that positive energy and enthusiasm during the AKS"

Introduction Invited Speakers

Berber Kapitein (1976) is a paediatric intensivist and medical biologist at the Amsterdam UMC. She did her PhD on immunomodulation in atopic children. Her current focus in research is immunologic endotyping of severe acute asthma and the influence of disparities on PICU outcomes. After giving birth to her second son she became increasingly aware of the importance to take action against the climate change for the future generation. In 2020 she founded the PICU Green team and soon found out there were a lot of enthusiastic people with great idea's how to make not only the PICU environment, but also the Emma children's hospital a greener and healthier place. This year she received an Innovation impulse to start a so called "burgerberaad" at the AMC to work together towards more sustainable commuting to the AMC. She lives with her partner and their two sons in a 400 year old farmhouse in Abcoude. In her spare time, she writes, skates and tries to make the farmhouse more sustainable.

Wouter Hehenkamp (1976) has been a gynecologist since 2011. He did his PhD in 2007 on two treatments for the very common uterine fibroids. His main focus in his current research is appropriate care in uterine abnormalities and sustainability in healthcare. The latter gained his interest around 2019 after the birth of his youngest son and the realization of the future perspectives of this newborn in this world, tormented by climate change. He is the chair of the national green gynecologists alliance (Gynae Goes Green) and founded the green gynecologists network with an ambassador in every hospital in the Netherlands. Also he is one of the board members of the research department of Amsterdam UMC Centre for Sustainable Healthcare. His sustainability research focuses on quantifying healthcare-pathways by Life-Cycle-Assessment methodology, investigating climate literacy among patients and healthcare workers and ethics in sustainable health care.

Charlotte Bekker



Dr. Charlotte Bekker is a biomedical scientist and obtained her PhD at Utrecht University in 2018. Currently she works as an assistant professor at Radboudumc, department of Pharmacy. She is passionate to combat societal challenges and her research interest revolves around establishing sustainable medication use. For example, Charlotte investigates novel strategies aiming to reduce medication waste, to tailor drug dosages to individual patients through shared decision making, and to implement medication adherence interventions. In her work, Charlotte collaborates with many different stakeholders from the pharmaceutical supply chain such as policy makers, health insurers, pharmaceutical industry, healthcare providers and patients. With her talk about "**Feasibility of redispensing medications unused by patients"** she will show us the advances on circularity for drug treatments.

Tessa Roseboom

Tessa Roseboom (www.tessaroseboom.nl) is Professor of Early Development and Health at the University of Amsterdam. She works at the Amsterdam UMC where she is also director of the Amsterdam Reproduction & Development research institute. Her research focuses on how the environment during early human development affects its later growth, development and health. She is a passionate advocate for the importance of a good start, and wrote several books about the topic The first 1000 days (De Tijdstroom, 2018, 2023) and Gelijk goed beginnen (De Tijdstroom, 2022). She is an ambassador for the national program Promising Start, and chair of the council that advises RIVM on the monitoring of the Promising Start program. In addition, she advises international organisations on the translation of scientific insights into policy and practice. The ultimate goal of her work is to contribute to a healthier fairer future by investing in a good start for every child.

Gavin Ten Tusscher

Gavin ten Tusscher is paediatrician at the Dijklander Hospital, location Hoorn, and member of staff of the General Practitioner Training AUMC, location VU. In 2002 he defended his thesis “Later childhood effects of perinatal dioxin exposure”. The last twenty years he has continued with research on background exposures to environmental chemicals and their effects on health and development in children. The last years his research has been focused on foetal and childhood exposure to nanoplastics. He helped reduce PVC and endocrine chemical exposures on the neonatology and paediatric wards of Dijklander Hospital. Gavin has had various advisory functions on a national and European level. He strives for healthcare with a reduced environmental footprint and free of endocrine disrupting chemicals.

Daan Dohmen

Prof. dr. Ir. Daan Dohmen started out as a carer for the elderly and envisioned the power of technology after his PhD on digital health. Today, he is professor of Digital transformation in healthcare, entrepreneur, best-seller author of the book Green on and advisor to the Dutch government. With over 25 million registrations in 11 countries in Europa and Africa, his company Luscii is one of the fastest growing remote monitoring platforms.

The digital platform supports doctors and nurses to offer care at home, helping their patients get more control over their own health whilst staying connected with their care team. It is used in over 70 disease areas, includes special attention for digital inclusion for vulnerable patients and is validated in more than 30 scientific publications.

Based on his experience and research, Daan Dohmen will take us through the three most important trends in the field of digital transformation in healthcare for the next two to three years. Digital transformation is a magic word, but what does it mean in day to day healthcare for patients and professionals? During his talk Daan Dohmen will reflect on the most important trends in digital health as well as how healthcare organizations can organize themselves for this transformation. He recently started a new initiative, eLearnity, to help talents learn faster and he will present to all the visitors of the conference a revolutionary program on this platform to become leaders of the future themselves!

Program Nutricia breakfast session Diner Foyer 08:00 – 09:45

Program	Presenters' Name	Title
1	Deianova	Health outcome after preterm birth: a microbiota-inspired longitudinal cohort study
2	Hilde Krom	Avoidant restrictive food intake disorder (ARFID)

Program SLAM session I Mary Dresselhuyszaal 10:30 – 11:45

Moderators: Douwe Visser & Charlotte Nusman

Program	Presenters' Name	Title	Abstract number
1	Haspels	A Core Outcome Set for transitional care in Children with Medical Complexity	02
2	De Sonnaville	Long-term Follow-up of Daily Life Functioning after Pediatric Intensive Care Unit Admission	09
3	Bisseling	Unraveling astrocyte dysfunction in the white matter disease MLC: linking the cytoskeleton to volume-regulated ion channels	38
4	Kooper	Prediction Models for Neurocognitive Outcome of Mild Traumatic Brain Injury in Children: a Systematic Review	49
5	Van de Heisteeg	Exploring roles of parents and healthcare professionals in paediatric rehabilitation from a parent's perspective: a qualitative study	55
6	Anand	Analyses of Resting state EEG biomarkers in a Subject-Specific Bumetanide Treatment of Neurodevelopmental Disorders using The Neurophysiological Biomarker Toolbox	56
7	Marfo	Evaluation of the risk factors inventory questionnaire: social risk factors in children with sickle cell disease	62
8	Stellingwerff	Two clinically feasible myelin water imaging methods (MCR-DIMWI and METRICS) can differentiate patients with a leukodystrophy from controls	64
9	Van der Perk	Parents' opinions and insights on their children's sleep quality during hospitalization	12
10	Winkel	Persistent Symptoms after SARS-CoV-2 infection in the Dutch Paediatric Population	76

Program SLAM session I Glazen Foyer 10:30 – 11:45

Moderators: Mariet Felderhof & Sofia El Manouni

Program	Presenters' Name	Title	Abstract number
1	Romijn	Exhaled volatile organic compounds for early prediction of bronchopulmonary dysplasia in preterm infants	04
2	Revers	In vivo genome base editing in a murine model of vanishing white matter modulates the phenotype through multiple mechanisms	27
3	Van Silfhout	PROM4RARE: Giving a voice to individuals with a rare genetic disorder associated with intellectual disability (GD-ID)	33
4	Van der Mheen	Prevalence and comorbidity patterns of psychiatric classifications in a large child and adolescent psychiatric sample (N=71,119)	48
5	Geertjens	Towards mechanism-based treatment options in neurodevelopmental disorders: preliminary results of the multiple n-of-1 BUDDI trial	58
6	Louman	Short-term air pollution exposure and pediatric wheeze in the Netherlands: new insights	65
7	Van den Brink	The first signs of change: predicting clinical deterioration and mortality at different stages during hospital admission. A systematic review of risk prediction models in children in Low-and Middle-Income countries	66
8	Reijman	Lipoprotein(a) levels in children with homozygous familial hypercholesterolaemia	70
9	Fourie	High Detection Rate of Viral Pathogens in Nasal Discharge in Children Aged 0 till 5 Years	74
10	Verhoeven	Immunodeficiency, autoimmunity, and increased risk of B cell malignancy in humans with TRAF3 mutations	77

Program SLAM session I Diner Foyer 10:30 – 11:45

Moderators: Jeroen Hol & Hilde Krom

Program	Presenters' Name	Title	Abstract number
1	Koenis	Child participation during outpatient consultations: a mixed methods study	03
2	Plug	Human post-mortem organotypic brain slices to study leukodystrophies	13
3	Van Boven	Machine learning prediction models for neurodevelopmental outcome after preterm birth: A scoping review and new machine learning evaluation framework	06
4	Brands	Development of a nationwide, digital personal health record for patient empowerment and personalization of care	10
5	Pigmans	Developing a test setup for exploring personalized non-invasive ventilation masks for children with facial dysmorphic features	43
6	De Proost	"If they had followed the guideline, I wouldn't be alive": adults born at the limit of viability on guidelines and personalization	07
7	Pijpers	The incidence of associated anomalies in children with congenital duodenal obstruction – a retrospective cohort study of 112 patients	47
8	Galestin	The safety of rapid versus standard infliximab infusions in children with inflammatory bowel disease: a multi-center retrospective cohort study	50
9	Hoeben	Collaborating to improve neonatal care: ParentAI paRticipation on The NEonatal waRd – the neoPARTNER study	60
10	Langeslag	Multiple organ dysfunction as a predictor of outcome in infants with perinatal asphyxia after therapeutic hypothermia	69

Program ELGAN lunch symposium Diner Foyer 12:30 – 13:10

Program	Title
1	Premature GI-tract and long term outcomes

Program SLAM session II Mary Dresselhuyszaal 13:10 – 14:25

Moderators: Jasper Jopsis & Dana Yumani

Program	Presenters' Name	Title	Abstract number
1	Vermeijden	The use of pictograms in the evaluation of functional abdominal pain disorders in children: an international survey study	08
2	Romijn	Glucocorticoid signature of preterm infants developing bronchopulmonary dysplasia	05
3	Vuong	Use of consumer wearables to predict pain in sickle cell disease	11
4	Flierman	The development of the e-TOP information app for parents of very and moderate preterm-born infants	24
5	De Ridder	The association between the implementation of HFNC on lung growth in preterm infants	29
6	Müller	Can we make personalized care for children with an intellectual disability happen? Insights from a large intellectual disability registry	34
7	Groen	Potential of Molecular Culture in Early-onset Neonatal Sepsis Diagnosis: a Proof of Principle Study	53
8	Van Oers	The effects of COVID-19 on child mental and social health: biannual assessments up to April 2022 in a clinical and two general population samples	67
9	Hieltjes	A national translational research agenda for inherited metabolic disorders	71
10	Fourie	Biomarkers for the diagnosis of early onset neonatal sepsis: a systematic review and meta-analysis	63

Program SLAM session II Glazen Foyer 13:10 – 14:25

Moderators: Marlies van Houten & Fien van Dongen

Program	Presenters' Name	Title	Abstract number
1	Orriëns	Predicting nonresponse to intraglandular botulinum toxin injections: working towards an individualised treatment approach for drooling in children with neurodevelopmental disabilities	01
2	Van Leuteren	Triggering the ventilator based on transcutaneous electromyography of the diaphragm: a proof-of-concept study	17
3	Den Hollander	Efficacy and safety of volanesorsen in Lipoprotein lipase (LPL) deficiency : a pediatric case study	18
4	De Ligt	Screening for cerebrovascular disease in children with sickle cell disease using Transcranial Doppler and MRA to prevent stroke: the Amsterdam cohort	21
5	IJdo	Objective Neurocognitive assessment of young children with Sickle cell disease by Eye-Tracking - ONSET study	79
6	Groeneveld	Diagnostic prediction rules for pediatric bacterial meningitis: a systematic review and validation study in children with suspected CNS infection	41
7	Netea	Speckle tracking echocardiography in patients with Multisystem Inflammatory Syndrome in Children (MIS-C): a cohort study	45
8	Van den Berg	Predicting theophylline escalation in severe acute asthma at the paediatric intensive care unit	57
9	Muts	Growth and body composition of moderate and late preterm infants up to 6 months corrected age, a randomized controlled trial on nutrition after discharge	72
10	Buijs	Generation of an in vitro stem cell based model for researching gyrate atrophy of the choroid and retina	73

Program SLAM session II Diner Foyer 13:10 – 14:25

Moderators: Frans Plötz & Roy Zuurbier

Program	Presenters' Name	Title	Abstract number
1	Van der Leest	Clinical characteristics, treatment, and prognosis of children with early onset (neonatal) Marfan syndrome	20
2	Schoenmakers	Recognizing early MRI signs (or their absence) is crucial in diagnosing metachromatic leukodystrophy	23
3	Van Gastel	Female adolescents and young adults with bleeding disorders and their experiences in daily life functioning in the Netherlands - A qualitative study	26
4	Hermans	Health-related quality of life in pediatric and adult patients with classical galactosemia	31
5	Bachiri	Management and outcome of high-risk neuroendocrine tumors of the appendix in children: a systematic review	35
6	Vermeer	Methotrexate in Paediatric Inflammatory Bowel Disease: A Pharmacokinetic Study	51
7	Al-Saady	"In vivo histology" using MRI in two distinct leukodystrophies; MLD and VWM	54
8	Van den Brink	Low prevalence of dermatological changes in children with severe malnutrition: A prospective cohort characterizing skin changes in a population of hospitalized acutely ill Malawian children	68
9	Van den Bosch	The association between statin adherence and pulse wave velocity in patients with familial hypercholesterolemia	61
10	Bout	Menke-Hennekam syndrome – delineation of domain-specific subtypes using genome-wide methylation episignatures and 3D protein structure modelling	81

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Appendix

Abstract 01

Predicting nonresponse to intraglandular botulinum toxin injections: working towards an individualised treatment approach for drooling in children with neurodevelopmental disabilities

Orriëns, L.B. (1), van Hulst, K. (2), Erasmus, C.E. (1)

(1) Radboudumc, Amalia Children's Hospital, Department of Paediatrics and Paediatric Neurology, Nijmegen, the Netherlands; (2) Radboudumc, Amalia Children's Hospital, Department of Rehabilitation, Nijmegen, the Netherlands.

Rationale

Botulinum neurotoxin type-A (BoNT-A) injections are commonly used to diminish drooling in children with neurodevelopmental disabilities. Nevertheless, there is no consensus on which salivary glands should be injected to sufficiently diminish drooling. An individualised treatment approach, based on the child's risk of nonresponse, would be preferable. We aimed to develop multivariable prediction models for nonresponse to 1) submandibular BoNT-A injections and 2) concurrent submandibular and parotid (four-gland) BoNT-A injections.

Methods

A retrospective cohort study was conducted, using prospectively collected data from 262 children (aged 4-18 years) treated with submandibular BoNT-A injections and 74 children treated with four-gland BoNT-A injections after initial submandibular injections. Multivariable logistic regression analyses were used to estimate associations between biologically plausible candidate predictors and nonresponse (i.e. <50% reduction in drooling) at 8 weeks post-injection.

Results

Ninety-six children (37%) were classified as nonresponders to submandibular injections, for which developmental age <6 years was the strongest predictor (multivariable odds ratio [OR] 2.08; 95% CI 1.00-4.31). Other identified predictors were the child's diagnosis, sex, and head position. Nonresponse to four-gland injections occurred in 34 children (46%), for which tongue protrusion (OR 3.10; 95% CI 1.14-8.43) and a single preceding submandibular injection (OR 2.94; 95% CI 0.85-10.0) were most predictive. Nevertheless, predictors were unstable across different definitions of nonresponse and both models seemed to have insufficient discriminative ability.

Discussion

Although significant predictors of nonresponse to BoNT-A injections were identified, the developed prediction models appeared inadequate for the guidance of treatment decisions. Future studies may focus on less generic predictors and aim for consensus on a comprehensive definition of nonresponse.

Abstract 02
A Core Outcome Set for transitional care in Children with Medical Complexity

Haspels, H.N. (1,2) Lange de, A. (3), Alsem, M.W. (3,4), Sandbergen, B. (5), Dulfer, K. (2), Hoog de, M. (2), Joosten, K.F.M. (2), Karnebeek van, C.D. (6), Woensel van, J.B.M. (1), Maaskant, J.M. (3,7)

(1) Amsterdam UMC location University of Amsterdam, Emma Children's Hospital, Department of Pediatric Intensive Care Unit, Amsterdam Reproduction and Development, Meibergdreef 9, Amsterdam, The Netherlands; (2) Erasmus Medical Centre, Sophia Children's Hospital, Department of Pediatric Intensive Care Unit, 3015 CN Rotterdam, The Netherlands; (3) Amsterdam UMC location University of Amsterdam, Emma Children's Hospital, Department of Pediatrics, Meibergdreef 9, Amsterdam, The Netherlands; (4) Amsterdam UMC location University of Amsterdam, Department of Rehabilitation, Amsterdam Movement Sciences, Meibergdreef 9, Amsterdam, The Netherlands; (5) Expert by experience; (6) Amsterdam UMC location University of Amsterdam, Emma Children's Hospital, Department of Pediatrics and Human Genetics, Emma Center for Personalized Medicine, Amsterdam Reproduction and Development, Meibergdreef 9, Amsterdam, The Netherlands; (7) Amsterdam UMC location University of Amsterdam, Department of Data Science and Epidemiology, Meibergdreef 9, Amsterdam, The Netherlands.

Rationale
Research in the field of transitional care from hospital to home (H2H) for Children with Medical Complexity (CMC) is hampered by the heterogeneity of outcomes. Our objective was to develop a Core Outcome Set (COS), that can be used to assess clinical trials evaluating the transitional care for CMC.

Methods
The development process consisted of three phases: (1) a systematic review identifying all reported outcomes, (2) a modified three-round Delphi study in which different professionals rated outcome domains from the previous executed systematic review for inclusion in the COS and (3) focus groups with parents of CMC to validate the results of the Delphi study.

Results
The systematic review identified 24 outcome domains for the Delphi survey. Forty-five (67%) professionals participated in the Delphi study, overall response rates were 55%, 57%, and 58% for each round. In the first round 12 additional outcomes were suggested by the professionals. The COS development process resulted in 20 important outcome domains and a final set of four core outcome domains: (1) Children with well-controlled disease management, (2) Children's Quality of Life, (3) Impact on the life of families, and (4) Self-efficacy of parents.

Discussion
An evidence-informed COS based on international consensus, including healthcare professionals and parents has been developed. This COS is recommended for future studies evaluating the hospital to home (H2H) transition of CMC in order to facilitate comparison between trials, data synthesis and meta-analyses.

Abstract 03
Child participation during outpatient consultations: a mixed methods study

Koenis, M.M. (1), v Woerden, C. (1), Vroman, H. (1)

(1) Department of pediatrics, Bravis Ziekenhuis, Bergen op Zoom, the Netherlands.

Rationale
Violation of the children's right to participate in their medical encounter is a worldwide problem and has been acknowledged for over four decades. Most importantly, children wish to be more included in their healthcare, as reported by the Dutch Child Ombudsman. Despite adaptation of a more patient-centered medical consultation style, data on the current state of child participation are missing. We aim to measure actual child participation in a Dutch pediatric clinic.

Methods
Children aged 4-18 years visiting an outpatient clinic for consultation after general practitioner's referral were included. Sixteen consultations of six pediatricians were recorded and transcribed verbatim. Quantitative measurement included word count and speech turn; conversation analysis with qualitative appraisal provided data on participatory behavior.

Results
Quantitative child participation equals parent participation in turns (28% vs 29%), but remains rather limited in words (11%). Children are mostly involved during social history, introduction and physical examination but do not actively speak during the decision-making segment. Children take an active role by instigating talks and presenting the problem. Qualitative facilitators include appropriate language and verbal or non-verbal child allocated turns. Adults involved children by asking them questions, cracking jokes and verifying their opinions or plans with the child. All pediatricians involved children in a part of the explanation, however children are not actively involved in decision-making.

Discussion
Based on an equal speech turn between child and parent, child participation has markedly improved over 20 years. Although children more actively presented the problem or instigated talks without having been allocated a turn, their contribution in words remains limited, especially during decision-making processes. Facilitators and barriers for child participation may guide improvement of clinical practice.

Abstract 04

Exhaled volatile organic compounds for early prediction of bronchopulmonary dysplasia in preterm infants

Romijn, M. (1,2,3), Van Kaam, A.H. (1,2), Fenn, D. (4,5), Bos, L.D. (4,5), Van den Akker, C.H.P. (1,2), Finken, M.J.J. (2,3), Rotteveel, J. (2,3), Cerullo, J. (6), Brinkman, P. (4)*, Onland, W. (1,2)*

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Rationale

Early identification of preterm infants at high-risk of developing bronchopulmonary dysplasia (BPD) is challenging. Volatile organic compounds (VOCs) in exhaled breath are promising prognostic biomarkers in several respiratory diseases in both adults and children. The aim of this study is to investigate the discriminating accuracy of a prediction model based on VOCs in exhaled breath of preterm infants for predicting BPD in the first week of life. And secondary, we aim to evaluate the predictive power of adding VOCs to an existing clinical prediction model for BPD.

Methods

Exhaled breath was collected from infants born <30 weeks' gestation at days 3 and 7 of life. Ion-fragments detected by Gas-Chromatography–Mass-Spectrometry analysis were used to derive and internally validate a VOC prediction model for moderate or severe BPD at 36 weeks postmenstrual age. We tested the predictive performance of the National Institute of Child Health and Human Development (NICHD) clinical BPD prediction model with and without VOCs.

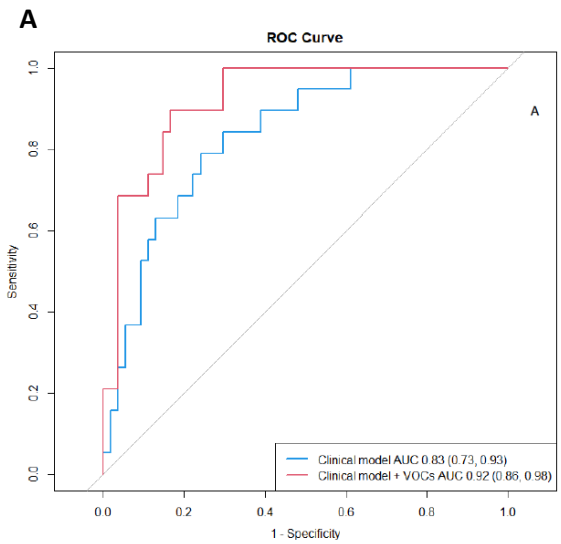
Results

Breath samples were collected from 117 infants (mean gestation 26.8 (±1.5) weeks). Thirty-three percent of the infants developed moderate or severe BPD. The VOC model showed a c-statistic of 0.89 (95% confidence interval (CI) 0.80-0.97) and 0.92 (95% CI 0.84-0.99)) for the prediction of BPD at days 3 and 7, respectively. Adding the VOCs to the clinical prediction model in non-invasive supported infants resulted in significant improvement in discriminative power on both days (day 3: c-statistic 0.83 versus 0.92, p-value 0.04; day 7: c-statistic 0.82 versus 0.94, p-value 0.03).

Discussion

This study showed that VOC profiles in exhaled breath of preterm infants on non-invasive support in the first week of life differ between those developing and not developing BPD. Adding VOCs to a clinical prediction model significantly improved its discriminative performance.

Figure 1. Receiver operating characteristic (ROC) curves of prediction model including clinical predictors with or without volatile organic compounds (VOCs) at day 3 (A) and 7 (B) with solely non-invasive samples.

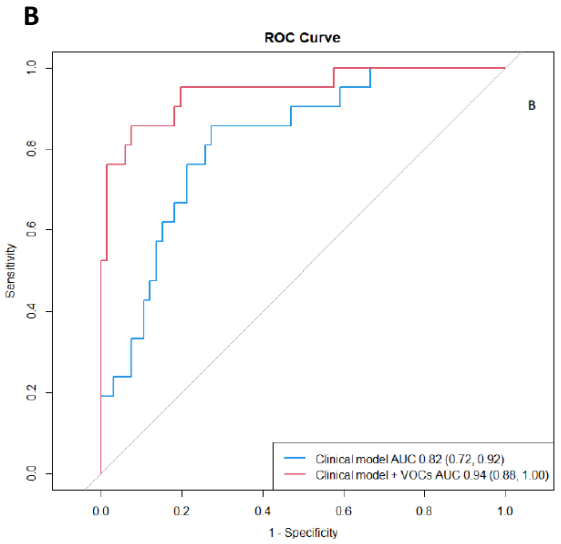


Regression formula of NICHD BPD prediction model alone:

y=-8.6811+ Birth weight *-0.3648 + GA*-0.1935 + FiO_2 at day 3*0.2401 + Sex*0.7229

Regression formula of combined NICHD BPD prediction model and VOCs:

y= 11.5898+ Birth weight *-0.3648 + GA*-0.1935 + FiO_2 at day 3*0.2401 + Sex*0.7229 + PredProbVOC1*0.8718 + PredProbVOC2*15.1332



Regression formula of NICHD BPD prediction model alone:

y= -4.5949 + Birthweight*-0.3321 + GA*-0.0226 + FiO_2 at day 7*0.5762 + Sex*0.7067

Regression formula of combined NICHD BPD prediction model and VOCs:

Y= 8.7094+ Birthweight*-0.3321 + GA*-0.0226 + FiO_2 at day 7*0.5762 + Sex*0.7067 + PredProbVOC1*-2.3086 + PredProbVOC2*4.6764

ROC: Receiver operating characteristic. VOC: volatile organic compounds. AUC: area under the curve. CI: confidence interval.

NICHD: National Institute of Child Health and Human Development.

Abstract 05
Glucocorticoid signature of preterm infants developing bronchopulmonary dysplasia

Romijn, M. (1,2,3), Onland, W. (2,3), van Keulen, B.J. (1,3), Heijboer, A.C. (3,4,5), Rotteveel, J. (1,3), van Kaam, A.H. (2,3), Finken, M.J.J. (1,3)

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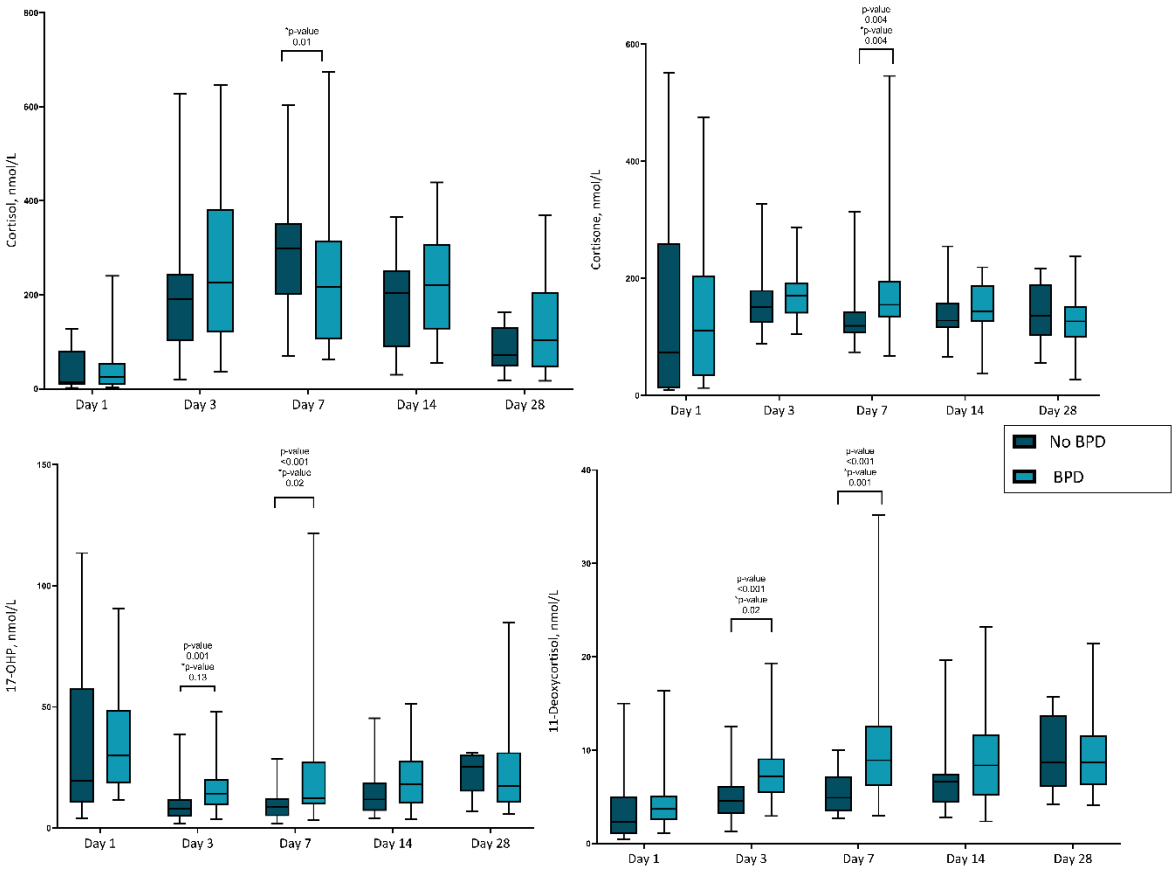
Rationale
Bronchopulmonary dysplasia (BPD) is a major complication of preterm birth, and systemic inflammation plays a key role in its development. Cortisol is known for its anti-inflammatory effect. However, many preterm infants experience relative adrenal insufficiency early in life, resulting in insufficient cortisol levels for the degree of inflammation, and a relative abundancy of cortisol precursors. This study aimed to investigate whether this glucocorticoid pattern could contribute to the development of BPD.

Methods
Preterm infants born <30 weeks of gestation were eligible for this prospective observational study. Using liquid chromatography-tandem mass spectrometry cortisol, cortisone, 17-OH progesterone (17-OHP) and 11-deoxycortisol were measured in serum obtained at postnatal days 1, 3, 7, 14 and 28. Linear regression analysis was used to compare hormone levels between infants with and those without BPD at 36 weeks postmenstrual age.

Results
Sixty-five infants (gestational age 27±1.3 weeks, 52% males) were included for analysis, of whom 32 (49%) developed mild, moderate or severe BPD. Preterm infants developing BPD, as compared to those without BPD, had higher levels of 17-OH progesterone, 11-deoxycortisol and cortisone relative to cortisol in their first week of life, but not at birth or beyond day 7.

Discussion
Preterm infants developing BPD had higher levels of cortisone and cortisol precursors relative to cortisol in the first week of life compared to infants without BPD. These findings suggest that BPD is preceded by an activated hypothalamus-pituitary-adrenal axis that could not meet the high cortisol demands in tissues, which may predispose to inflammation and BPD.


Cortisol, nmol/L
*p-value
0.01
Day 1
Day 3
Day 7
Day 14
Day 28
Cortisone, nmol/L
p-value
0.004
*p-value
0.004
No BPD
BPD
17-OHP, nmol/L
p-value
<0.001
*p-value
0.02
p-value
0.001
*p-value
0.13
11-Deoxycortisol, nmol/L
p-value
<0.001
*p-value
0.02
p-value
<0.001
*p-value
0.001

Abstract 06

Machine learning prediction models for neurodevelopmental outcome after preterm birth: A scoping review and new machine learning evaluation framework

Van Boven, M.R. (1,2), Henke, C.E. (2,3), Leemhuis, A.G. (1,2), Hoogendoorn, M. (4), Van Kaam, A.H. (1,2), Königs, M. (2), Oosterlaan, J. (2)

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Rationale

Outcome prediction of preterm birth is important for neonatal care, yet prediction performance remains insufficient using conventional statistical models. Machine learning has high potential for complex outcome prediction.This scoping review provides an overview of the current applications of machine learning models in the prediction of neurodevelomental outcome in preterm infants, assesses the quality of the developed models, and provides guidance for future application of machine learning models to predict neurodevelopmental outcome of preterm infants.

Methods

A systematic search was performed in PubMed.Studies were included if they reported neurodevelopmental outcome prediction in preterm infants, using predictors from the neonatal period and applying machine learning techniques. Data extraction and quality assessment was independently performed by two reviewers.

Results

Fourteen studies were included, focusing mainly on very or extreme preterm infants, predicting neurodevelopmental outcome before the age of 3 years, mostly assessed with the Bayley Scales of Infant development. Predictors were most often based on MRI. The most prevalent machine learning techniques included linear regression and neural networks. None of the studies met all newly developed quality assessment criteria. Studies least prone to inflated performance showed promising results, with area under the curves up to 0.86 for classification, and R2 values up to 91% in continuous prediction.

Discussion

Only one data source was used for the literature search.Studies least prone to inflated prediction results show promising results. The provided evaluation framework may contribute to improved quality of future machine learning models.

Abstract 07

“If they had followed the guideline, I wouldn’t be alive”: adults born at the limit of viability on guidelines and personalization

De Proost, L. (1,2), de Boer, A. (2,3), Geurtzen, R. (3), Verweij, E.J. (2)

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Rationale
This qualitative study aimed to describe perspectives of adults who were born extremely premature on periviability guidelines, and personalization. Three types of guidelines were discussed: gestational age(GA)-based, GA-based-plus (that also consider other factors), and prognosis-based guidelines.

Methods
Four 2-hour focus groups were organized in January 2022 in the Netherlands, with 23 participants in total. Participants were all born at the (then) limit of viability, now aged between 19 and 56. Self-reported outcomes of premature birth highly varied between participants.

Results
Participants agreed that a periviability guideline is necessary, primarily to avoid arbitrariness in providing treatment, and counter physician bias. None preferred a GA-based guideline – as is the current Dutch guideline. Discussion arose about GA-based-plus and prognosis-based guidelines because of the heterogeneity of value judgments about outcomes, and the possibility of estimated prognoses at birth turning out different. In general, most preferred GA-based-plus guidelines; they found it to be a good mix between professional judgment and parental values. It was stressed, however, that whatever the type of guideline, there must be room for deviation. Participants associated personalization mainly with information-provision, decision-making, and relationships. Participants defined personalization as ‘looking at the human being instead of the numbers’.

Discussion
To our knowledge, this is the first qualitative study with extreme prematurely born adults on this topic. This is an understudied – yet highly valuable – perspective for guideline development. Participants recommend a guideline that considers multiple factors and leaves room for parental involvement, and deviation. An important additional finding of this study is the lack of aftercare for the infants/adults and their families; the consequences of experiencing an extreme preterm birth must not be underestimated.

Abstract 08

The use of pictograms in the evaluation of functional abdominal pain disorders in children: an international survey study

De Bruijn, C.M.A. (1), Rexwinkel, R. (1), Vermeijden, N.K. (1), Hoffman, I. (1) Tack, J. (1), Benninga, M.A. (1)

(1) Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

Rationale
To evaluate whether the use of pictograms improves symptom evaluation for children with functional abdominal pain disorders (FAPDs).

Methods
This international survey study in two academic centers included patients (8 - 18 years) visiting the outpatient clinic for FAPD-symptom evaluation. Patients were randomized to fill out the questionnaire without or with accompanying pictograms to assess gastrointestinal symptoms. Afterwards, patients underwent clinical health assessment by the health care professional (HCP). Subsequently, the HCP filled out the same questionnaire without pictograms, whilst blinded to the questionnaire completed by the patient. Primary outcome was the level of agreement between identified symptoms as assessed by patients and HCP.

Results
144 children were included (questionnaire without (n= 82) and with accompanying pictograms (n=62)). Overall agreements rates were not significantly different (without pictograms median (M) 70%, vs. with pictograms M 70%). Accompanying pictograms did not significantly improve assessment of abdominal pain symptoms. Accompanying pictograms were beneficial for concordance rates for nausea and vomiting symptoms (without pictograms M 67% vs. with pictograms M 100%, P = .047). Subgroup analyses for children aged 8-12 years revealed similar results (concordance on the presence of nausea and vomiting without pictograms M 67% vs. with pictograms M 100%, P=.015). Subgroup analyses for children aged 12-18 years showed no significant differences in concordance rates.

Discussion
The use of pictograms improves the evaluation of nausea and vomiting, especially for children 8 to 12 years. Therefore, we advise HCP to use pictograms in this setting during consultations.

Abstract 09
Long-term Follow-up of Daily Life Functioning after Pediatric Intensive Care Unit Admission

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

(1) Amsterdam UMC, University of Amsterdam, Emma Children's Hospital, Department of Pediatric Intensive Care, Amsterdam Reproduction and Development Research Institute, Meibergdreef 9, Amsterdam, The Netherlands; (2) Amsterdam UMC, University of Amsterdam, Emma Children's Hospital, Department of Pediatrics, Emma Children's Hospital Amsterdam UMC Follow Me program & Emma Neuroscience Group, Amsterdam Reproduction and Development Research Institute, Meibergdreef 9, Amsterdam, The Netherlands.

Rationale
Long-term morbidity after Pediatric Intensive Care Unit (PICU) admission is a growing concern. This study aims to investigate the long-term impact of PICU admission on daily life functioning, while exploring the potential mediating role of neurocognitive outcome.

Methods
This cross-sectional observational study compared children aged 6-12 years with previous PICU admission (age </= 1 year) for bronchiolitis requiring mechanical ventilation ("patient group", n = 65) to demographically comparable healthy peers ("control group", n = 76). The patient group was selected because bronchiolitis is not expected to affect neurocognitive functioning in itself. Assessed daily life outcome domains were behavioral and emotional functioning, academic performance and health-related quality of life. The role of neurocognitive outcomes in the relationship between PICU admission and daily life functioning was assessed by mediation analysis.

Results
The patient group did not differ from control group regarding behavioral and emotional functioning and health-related quality of life, but performed poorer on academic performance with respect to spelling (p = .015, d = -0.48), reading comprehension (p =.015, d = -0.41), and arithmetic performance (p = .04, d = -0.26). Within the patient group, lower full-scale IQ (FSIQ) was associated with poorer academic performance (ps </= .02). 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 admitted to the PICU are at risk of long-term adverse daily life outcome in terms of academic performance. The findings suggest that adverse intelligence outcome may contribute to academic difficulties after PICU admission. Findings underline the importance of monitoring daily life and neurocognitive functioning after PICU admission.

Abstract 10

Development of a nationwide, digital personal health record for patient empowerment and personalization of care

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

(1) Department of Pediatric Hematology, Emma Children's Hospital, Amsterdam UMC location AMC, Amsterdam, the Netherlands; (2) Psychosocial Department, Emma Children's Hospital, Amsterdam UMC location AMC, Amsterdam, the Netherlands; (3) Netherlands Haemophilia Patient Society (NVHP), Nijkerk, the Netherlands; (4) HemoNED Foundation, Leiden University Medical Center, Leiden, the Netherlands; (5) Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands; (6) Independent patient representative, Utrecht, the Netherlands; (7) Independent patient representative, The Hague, the Netherlands; (8) Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands; (9) Department of Pediatric Hematology, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands; (10) Department of Molecular Cellular Hemostasis, Sanquin Research and Landsteiner Laboratory, Amsterdam, the Netherlands.

Rationale

Dutch people with a chronic disease, such as a congenital bleeding disorder, use a variety of digital tools to view their medical data, manage care, and communicate patient-reported outcomes. Especially for people with many healthcare providers, fragmented data hampers integrated care. A digital personal health record would enable patients to manage all relevant health information in a single environment and support empowerment. Our aim is to describe the primary phase of the development of a national personal health record for people with chronic disorders, thereby focusing on people with a congenital bleeding disorder and their caretakers. We describe the selection, prioritization and development of a set of functionalities.

Methods

A formal qualitative interview study was performed among persons with a congenital bleeding disorder, their caretakers and healthcare providers. Furthermore, based on Agile principles, a wide range of stakeholders was interviewed for the identification and prioritization of requirements in other chronic disorders.

Results

Prioritized functionalities include: a summary of health information, an up-to-date medication list, an appointment overview and appointment making, integrated teleconsulting, and collection of all relevant patient-reported outcomes in one app. It is feasible to include all these functionalities. For the development of a semi-standardized, customizable solution for the collection of patient-reported outcomes, congenital bleeding disorders will be used as a use case. Several challenges related to data transfer and implementation in practice are still to be overcome.

Discussion

Congenital bleeding disorders as a use case to pioneer the development of an integrated application for health data and patient-reported outcomes, suitable for all chronic disease, is not only promising, but seems feasible. We hope to implement an open-source, white-label, national personal health record in the coming year.

Abstract 11
Use of consumer wearables to predict pain in sickle cell disease

Vuong, C. (1,2), Utkarsh, K. (2), Stojancic, R. (2), Fernandez, O. (2), Mallikarjunan, A. (2), Fijnvandraat, K. (1), Shah, N. (2)

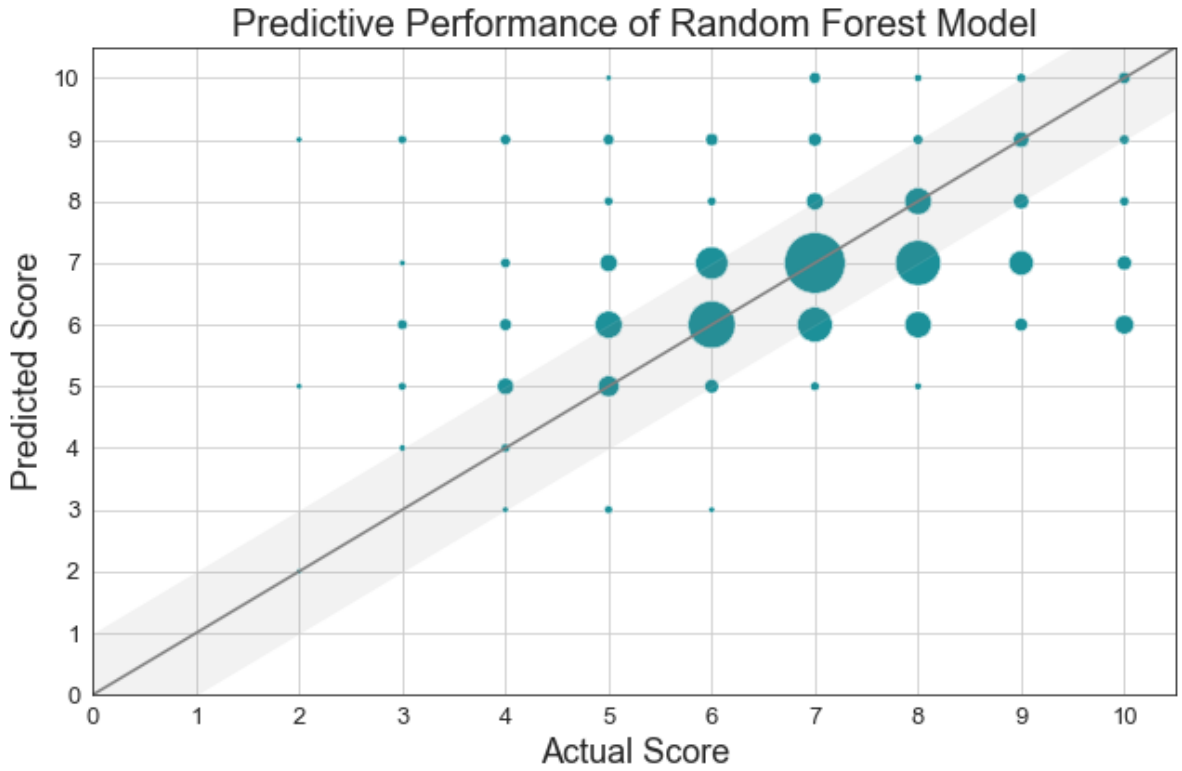
(1) Department of Pediatric Hematology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; (2) Department of Medicine, Division of Hematoloy - Duke Sickle Cell Comprehensive Care Unit, Duke University Hospital, Durham, North Carolina, United States; (3) Department of Engineering Sciences and Applied Mathematics, Northwestern University, Evanston, Illinois, United States.

Rationale
In sickle cell disease (SCD), episodes of acute and severe pain known as vaso-occlusive crises (VOC) are the most common cause for hospital admission. In our previous work, we were able to accurately predict pain scores using machine learning (ML) models in patients who were admitted for a VOC at the SCD Day Hospital. This study aims to evaluate the feasibility of extended monitoring for 30 days post-discharge and to refine the ML models to predict pain scores in patients with SCD.

Methods
Patients with SCD aged 18 and above who were admitted for a VOC to Duke University Hospital were eligible for this study. Patients were provided: 1) a mobile app; 2) Apple Watch. Patients were instructed to report their pain scores at least once daily within the app and to continuously wear the Apple Watch for 30 days following discharge. Data collected by the Apple Watch included heart rate, heart rate variability, calories and step count. These data were associated with pain scores to fit 5 different ML classification models.

Results
Nineteen patients were included in this study from April through June 2022. The median age at time of inclusion was 30 years (IQR:22-34). The majority of the patients had genotype HbSS (68%). This preliminary dataset consisted of 1480 data points. The metrics of the best performing ML model, the random forest model, were: micro-averaged accuracy: 0.89, micro-averaged F1-score: 0.50, RMSE: 1.52, AUC: 0.83.

Discussion
The high accuracy along with the low F1-score in our model reflects the high degree of class imbalance and lack of data probably due to inconsistent pain reporting after discharge. Future efforts will focus on larger numbers of patients and monitoring patients for longer periods of time to provide a larger dataset, to further improve the accuracy of pain prediction. Nonetheless, the consumer wearable Apple Watch was a feasible method to collect physiologic data and provided accuracy in prediction of higher pain scores.


Predictive Performance of Random Forest Model
Predicted Score
Actual Score
0
1
2
3
4
5
6
7
8
9
10

Abstract 12
Parents' opinions and insights on their children's sleep quality during hospitalization

Van der Perk, C.J. (1), Burger, P. (1), Gemke, R.J.B.J. (1), Maaskant, J.M. (1,2)

(1) Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; (2) Amsterdam UMC, University of Amsterdam, Science and Epidemiology, Amsterdam, The Netherlands.

Rationale
Sleep is an essential daily requirement for the development and maintenance of physical and psychological health. Also for children it is important that the natural biological rhythm of the child is guaranteed. Hospitalized children are at risk for sleep disturbances caused by environmental, psychological and social factors. Few studies have researched the sleep quality in hospitalized children. To expand the scope of different views of sleep during hospitalization, it is vital to also include the opinions and insights of parents on the quality of sleep of their children.

Methods
We performed a descriptive explorative qualitative design with semi-structured interviews. Twelve parents of eleven children admitted on a general pediatric ward, participated in the study. We conducted eleven interviews between October 2021 and April 2022. The interviews were audio recorded and transcribed verbatim.

Results
Parents reported a difference in their child's sleep quality during hospital compared to home. Children generally go to bed later, sleep less hours and their sleep is often interrupted during the night. In addition, there is less time to take a daytime nap. Four themes emerged from the data: being informed, keeping informed(1), coordination of care can make a difference(2), parents as main advocates for their child's sleep(3), environmental disturbers (4).

Discussion
The sleep quality of children admitted in hospital is substantially worse compared to home due to the child's physiological or mental state, care related activities, and ambient factors. Inadequate communication and coordination of care compromises the quality of sleep of the children. Parents have an important role in facilitating their child's sleep during admission.

Abstract 13
Human post-mortem organotypic brain slices to study leukodystrophies

Plug, B.C. (1), Breur, M. (1), Hamberg, D. (1), Wagendorp, J. (1), Nutma, E. (2), Amor, S. (2,3), Van der Knaap, M.S. (1,4) & Bugiani, M. (1,2)

(1) Department of Paediatrics/Child Neurology, Emma Children's Hospital, Amsterdam UMC, Amsterdam Neuroscience, Amsterdam, The Netherlands; (2) Department of Pathology, Amsterdam UMC, Amsterdam Neuroscience, Amsterdam, The Netherlands; (3) Center for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, UK; (4) Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, VU University, Amsterdam Neuroscience, Amsterdam, The Netherlands.

Rationale
Leukodystrophies are inherited disorders characterized by the predominant involvement of the central nervous system white matter. Due to the complex mechanisms driving the pathogenesis of these disorders, there is urgent need to develop models in which one can assess the molecular and cellular interplay between multiple cell types. We aimed at developing an ex vivo organotypic brain slice culture (OSC) method using post-mortem human brain tissue to study leukodystrophy disease mechanisms. We evaluated whether OSCs recapitulate the known neuropathological characteristics and if they are able to survive several weeks ex vivo. Additionally, we assessed whether addition of human cerebrospinal fluid (hCSF) increases tissue viability.

Methods
Post-mortem brain tissue and hCSF was obtained at autopsy from six leukodystrophy patients and five unrelated control subjects. Slices of 300 µm-thick were cut using a vibratome and cultured onto semi-porous membrane inserts up to six weeks. Slices were either cultured in normal culture medium or culture medium with addition of hCSF. (Immuno-)Histochemical staining and a cytotoxicity assay were employed to assess disease-specific neuropathological characteristics and tissue viability.

Results
Human OSCs remain viable up to at least six weeks ex vivo. The tissue structure remains well preserved and the different neural cell types are present. Addition of hCSF to the cultures can improve tissue recovery following slicing. Importantly, leukodystrophy patient-derived OSCs demonstrate disease-specific changes throughout the culture period that correspond to known neuropathological disease hallmarks.

Discussion
Human post-mortem OSCs represent an ex vivo model suitable for studying leukodystrophy disease mechanisms. Using this model, we aim to screen for treatment molecules and assess effects of cell replacement and/or gene therapies.

Abstract 14
Towards PErsonalized PRognosis for Children with Traumatic Brain Injury: The PEPR Study Protocol

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

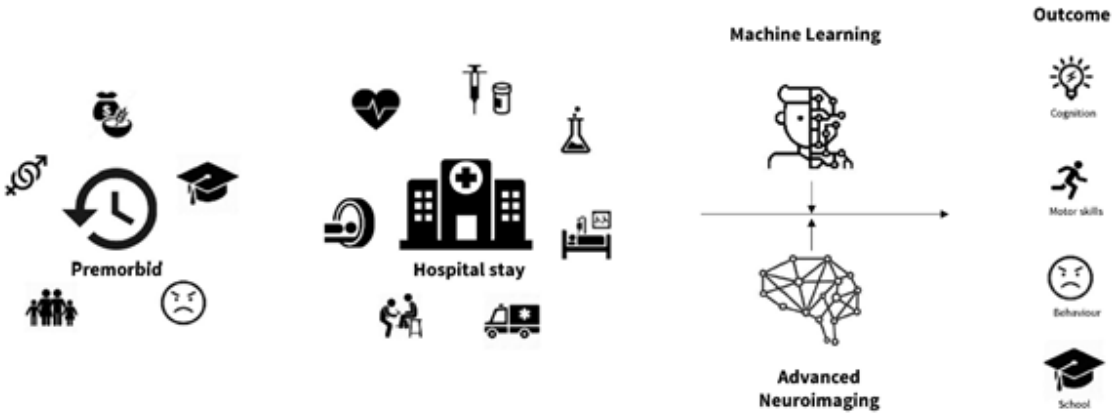
(1) Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; (2) Child and Youth Psychiatry, Amsterdam UMC, Vrije Universiteit Amsterdam, Emma Children's Hospital, Levvel, Amsterdam, the Netherlands; (3) Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands; (4) Department of Pediatrics, Onze Lieve Vrouw Gasthuis (OLVG), Amsterdam, The Netherlands; (5) Department of Pediatric Neurology, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands.

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.



PErsonalizing the PRognosis of Children with Traumatic Brain Injury

Abstract 15
Diaphragm activity measured with standard cardiorespiratory monitoring electrodes

Scholten, A.W.J. (1,2), Van Leuteren, R.W. (1,2), De Jongh, F.H. (1,3), Van Kaam, A.H. (1,2), Hutten, G.J. (1,2)

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Rationale
Current cardiorespiratory monitoring in neonates with ECG and chest impedance (CI) has important limitations. Adding transcutaneous electromyography of the diaphragm (dEMG) may provide better cardiorespiratory monitoring, but requires three additional electrodes at a different location. We aimed to measure dEMG and ECG/CI simultaneously using only three electrodes positioned at the dEMG location.

Methods
Fifteen stable infants (median post-menstrual age 30.1 weeks) on nasal CPAP were included. ECG and CI were measured for ±30 minutes at the standard location. Then, the electrodes were repositioned to the dEMG location and data was recorded for 30 min per ECG-lead (Figure 1). Breathing related changes in airway pressure were measured as reference for respiratory rate (RR). Main outcomes were: agreement in RR based on dEMG per lead and airway pressure, the discrepancy in measured RR between airway pressure and CI at the two electrode locations, and the ability to measure ECG at the dEMG location.

Results
The mean RR difference and limits of agreement for lead I, II and III were 0.80 [-9.0 to 10.6], 0.44 [-10.0 to 10.9] and -0.19 [-9.51 to 9.13] breaths/min, respectively. These limits corresponded to intraclass correlation coefficients of 0.85 (0.81-0.89), 0.83 (0.78-0.87) and 0.85 (0.79-0.89), respectively. No significant RR discrepancy at the two locations was observed (p=0.20) and the ECG could be measured at the alternative position.

Discussion
This study shows that measuring dEMG with standard monitoring electrodes on the diaphragm is feasible in infants, while still reliably measuring ECG/CI.

Abstract 16
Modulating the ISR with FDA-approved compounds as treatment for vanishing white matter

Oudejans, E. (1), Witkamp, D. (1), Hu-A-Ng, G. (1), Hoogterp, L. (1), Van Rooijen, 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)

(1) Child Neurology, Emma Children's Hospital, Amsterdam University Medical Centers, Vrije Universiteit and Amsterdam Neuroscience, Amsterdam, The Netherlands.

Rationale
Vanishing white matter (VWM) is a leukodystrophy that mainly presents in children and is currently without a cure. The disease is characterized by chronic neurological deterioration and episodic stress-provoked acute decline. Motor problems are the most common signs in VWM patients. VWM is caused by hypomorphic pathogenic variants 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 ameliorates VWM clinical and neuropathological hallmarks in representative preclinical models and one of these drugs is currently assessed in the first clinical trial for VWM. The current study aims to identify additional treatments with FDA-approved compounds that target and modulate the ISR.

Methods
The FDA-approved compounds were assessed in a preclinical model for VWM. Dosage regimens were based on available pharmacological data. Neurological deterioration was scored weekly with a new method. Gait and coordination were assessed on a narrow balance beam and Catwalk. Tissues were collected for neuropathological examination.

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

Discussion
The outcomes of this preclinical study will increase insight into the mechanisms underlying VWM pathogenesis and open up potential treatment targets for the disease.

Abstract 17

Triggering the ventilator based on transcutaneous electromyography of the diaphragm: a proof-of-concept study

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Rationale

Preterm infants often require respiratory support, with clinicians wanting to avoid invasive mechanical ventilation due to its detrimental long-term effects. Nasal intermittent positive pressure ventilation (nIPPV) is the most supportive non-invasive modality, but synchronization with the infant's own breathing effort is often hampered by air leakage or alternative methods are unavailable. The aim of this study was to develop and test a new triggering modality, based on electrical activity of the diaphragm, measured with transcutaneous electromyography (dEMG).

Methods

A software algorithm was developed in Simulink to process dEMG data in real-time. The algorithm removed cardiac interference and detected the inspiratory effort. Every detected breath generated a trigger. After simulations, a bench was designed in which the raw dEMG data was inserted, breaths were detected and subsequently a ventilator was triggered, resulting in the inflation of a test lung. Main outcome measure was the trigger time delay between start inspiration and start inflation.

Results

Pre-recorded dEMG measurements of 15 patients were used as pilot data. Segments of 2 minutes were played back to the developed software algorithm, which was able to detect 93.4% (IQR 71.2 – 96.7) of all inspiratory efforts. The resulting triggers were send successfully to the ventilator. Although most inspiratory efforts were detected, their detection was relatively late. Compared to offline detected inspirations, the detection delay had a median of 341 ms (IQR 315.2 – 374), increasing the overall trigger delay to approximately 400 ms.

Discussion

The preliminary data of this ongoing study indicate that it is technically feasible to trigger a ventilator, based on transcutaneous measured diaphragm activity. However, the signal processing delay is currently too large for clinical use. The next step is to optimize the algorithm and reduce the trigger delay, before testing it in various settings.

Abstract 18
Efficacy and safety of volanesorsen in Lipoprotein lipase (LPL) deficiency : a pediatric case study

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Rationale
Lipoprotein lipase (LPL) deficiency is an inherited metabolic disorder, due to LPL variants, presenting with lipid abnormalities and medical complications, including high triglyceride (TG) levels, recurrent episodes of abdominal pain, pancreatitis, and hepatomegaly. A lifelong severe fat restricted diet, that is very hard to comply with, is the only therapy. Volanesorsen, a 2nd-generation 2'-MOE chimeric antisense therapeutic oligonucleotide (ASO) that reduces plasma TG levels, is approved by the EMA in adult patients. In this study, for the first time we explore the benefit-risk profile and effect of the disease-modifying treatment volanesorsen in a pediatric patient.

Methods
In this prospective, open label, experimental trial, a 13-year old girl with confirmed homozygous LPL deletions was treated with weekly subcutaneous injections volanesorsen for 12 months. Her medical history included 52 hospital admissions (including 4 IC admissions with life-threatening pancreatitis). The primary endpoint was change in fasting TG levels. Secondary endpoints included safety and tolerability, thrombocyte counts, acute pancreatitis rate, hospital admittance rate, change in hepatosplenomegaly, and quality of life (QoL) (PedsQL and parents'/patient's reports).

Results
Volanesorsen was well tolerated and decreased TG levels from an average 20-25 mmol/L to 5-10 mmol/L (reference: <2 mmol/L). There were no episodes of pancreatitis, abdominal pain, hospital admissions, thrombocytopenia; the dietary restrictions could be loosened to a near normal fat intake. Both parents and patient reported an improved QoL.

Discussion
Patients with severe LPL deficiency suffer very high morbidity and limited treatment options. Our study in the first pediatric patient shows that also at this age volanesorsen as an ASO lowers TG levels to near normal, and prevents the life threatening complications. This RNA therapy should be made available to other children with severe LPL deficiency.

Abstract 19
Prevalence and characteristics of FVIII-specific antibodies in persons with hemophilia A

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Rationale
Inhibitor development is a major complication of hemophilia therapy, which neutralizes FVIII-activity and therewith renders replacement therapy ineffective and increases bleeding complications. Recently, non-neutralizing FVIII-specific antibodies (NNA) have been identified that increase clearance of exogenous clotting factors and limit its hemostatic efficacy. Therefore, we hypothesize that a subset of NNA are in fact low-titer inhibitors with titers below the detection limit of the Nijmegen Bethesda assay (NBA). We aim to assess the prevalence and characteristics of FVIII-specific antibodies in persons with hemophilia A (PwHA), including whether these antibodies have neutralizing potential.

Methods
The cross-sectional nationwide Hemophilia in the Netherlands-6 cohort recruited a substantial group of Dutch PwHA. In this study, all PwHA with an available plasma sample were included. Presence of FVIII-binding antibodies, IgG subclasses and corresponding titer levels were assessed using direct-binding ELISAs. FVIII-specificity was assessed using a competition-based ELISA approach. The neutralizing potential was assessed using the Nijmegen ultra-sensitive Bethesda Assay (NusBA), and if positive the Nijmegen Bethesda Assay was assessed.

Results
788 PwHA were included (Table 1). A total of 174 FVIII-specific binding antibodies were detected in 141 PwHA (57 mild, 27 moderate, 57 severe). IgG1 was most abundant, and was positive in 95 PwHA. Highest titer levels were found for IgG1 and IgG4 (1:5120 and 1:40960, respectively). Nine out of 19 NusBA positive patients, had negative ELISA results.

Discussion
In a hemophilia A population of all severities, 13.1% had NNA, 0.3% had low-titer inhibitors and 0.6% had inhibitors. IgG1 was the most abundant antibody. Highest titer levels were found for IgG1 and IgG4. Interestingly, 9 out of 19 NusBA positive PwHA, had negative ELISA results. Further studies need to clarify if these results have clinical significance.

Table 1. Prevalence and characteristics NNA, low-titer inhibitors and inhibitors

	N (%)	No Ab. (%)	NNA (%)	LTI (%)	INH (%)	*Missing*
Prevalence						
All types of hemophilia A	788	647 (82.1)	103 (13.1)	2 (0.3)	5 (0.6)	*31 (3.9)*
Mild	336	279	48	0	1	*8*
Moderate	123	96	11	0	3	*13*
Severe	329	272	44	2	1	*10*
Characteristics						
Positive for 1 subclass of IgG	114 (80.9)		90 (78.9)	1 (0.9)	1 (0.9)	*22 (19.3)*
IgG1	68		56	1	0	*11*
IgG2	0		0	0	0	*0*
IgG3	40		30	0	0	*10*
IgG4	6		4	0	1	*1*
Positive for 2 subclasses of IgG	22 (15.6)		10 (45.5)	1 (4.5)	3 (13.6)	*8 (36.4)*
IgG1 + IgG3	5		4	0	0	*1*
IgG1 + IgG4	17		6	1	3	*7*
Positive for 3 subclasses of IgG	4 (2.8)		3 (75)	0 (0)	1 (25)	*0 (0)*
IgG1 + IgG2 + IgG3	1		1	0	0	*0*
IgG1 + IgG3 + IgG4	3		2	0	1	*0*
Positive for all subclasses of IgG	1 (0.7)		0 (0)	0 (0)	0 (0)	*1 (100)*

Abbreviations N = number of persons, No Ab. = no antibodies detected with ELISA, NNA = non- neutralizing antibodies, LTI = low titer inhibitors, INH = inhibitor.

Abstract 20

Clinical characteristics, treatment, and prognosis of children with early onset (neonatal) Marfan syndrome

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Rationale

Neonatal Marfan syndrome (nMFS) is a rare form of Marfan syndrome that is caused by variants of the FBN1 gene. FBN1 codes for an extracellular matrix protein, therefore variants cause defects in connective tissues. Most studies describing nMFS mention severe atrioventricular valve insufficiency before the age of 1 year, which is almost always the cause of death. The median age of death is 16.3 months. But, there are cases described of children who get a lot older, suggesting early surgical intervention increases the life expectancy. The aim of this study was to evaluate which factors influence survival based on 10 new cases and the existing literature.

Methods

Children with nMFS were identified via our academic network, Genesis, and the social network of a nMFS patient's mother. In addition, nMFS individuals described in the literature presenting with atrioventricular valve insufficiency before the age of 1 year, were included. Data was gathered retrospectively. All individuals were divided into two groups, deceased before 16 months and still alive at 16 months, to analyze factors that may influence survival.

Results

We identified 41 children that fit our criteria to include in our study: 9 newly enrolled individuals, and 32 individuals from previously published work. Of these children, 64% were deceased at last follow up. The median age of death was 1 month. More individuals in the group "alive at age 16 months" did undergo cardiac surgery [77% vs. 8,3%; p= 0.000] at an older age [13 vs. 2 months; p= 0.001]. Most deceased children already passed away by the time the other children obtained their first cardiac surgery.

Discussion

While in the group "alive at 16 months" there is a window for surgical intervention, understanding why the group "deceased before 16 months" has so little chance of survival should provide insight into how these children with nMFS may be treated in the future.

Abstract 21

Screening for cerebrovascular disease in children with sickle cell disease using Transcranial Doppler and MRA to prevent stroke: the Amsterdam cohort

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Rationale

To identify Sickle Cell Disease (SCD) patients at risk of a first cerebrovascular accident (CVA), the American Society of Hematology (ASH) 2020 guideline recommends annual transcranial Doppler ultrasonography (TCD) screening for children aged 2-16 years with HbSS or HbSβ0 thalassemia. When abnormal TCD velocities are detected, chronic transfusion therapy is advised for at least a year. Since 2000 we have implemented a different management protocol in the Amsterdam UMC that only prescribes transfusion therapy for children with both abnormal TCD and MRA results. This protocol reduces exposure to blood transfusions but we need to investigate the safety.

Methods

In this longitudinal single center cohort study, all patients managed according to the Amsterdam Protocol between January 2000 and September 2022 were included and their TCD/MRA results and outcomes were evaluated.

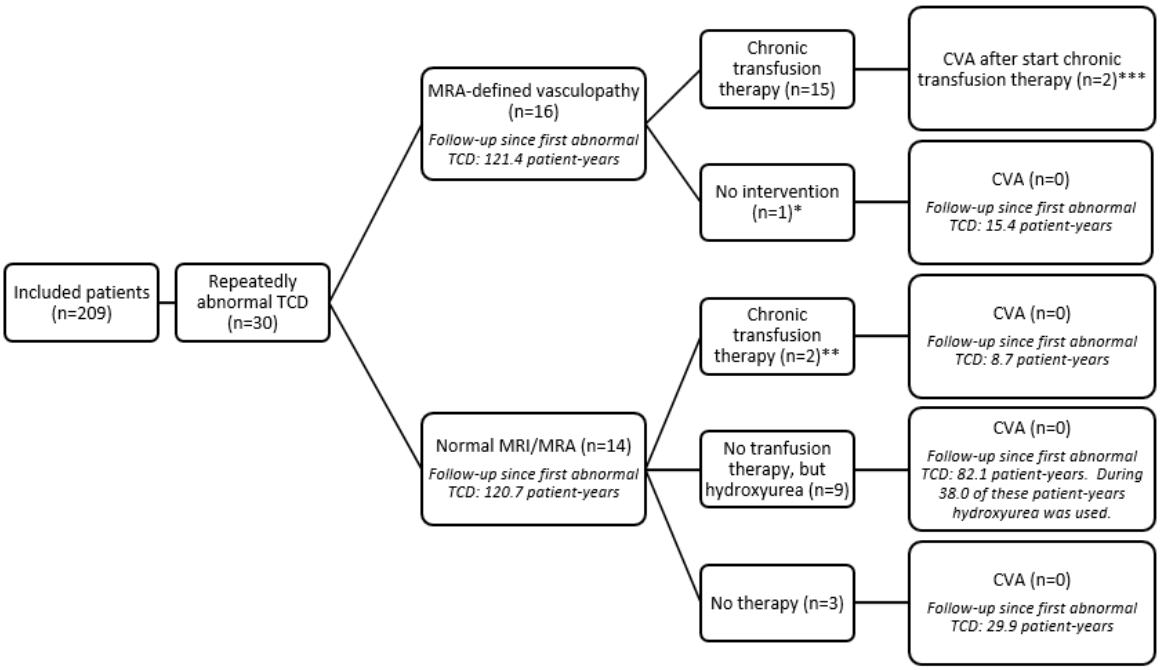
Results

209 SCD patients were included, cumulative 2321 patient-years of follow-up. The median age of these patients at the start of the follow-up was 4.43 (IQR: 2.3, 8.2) years. In this cohort, 30 patients had abnormal TCD results at 2 separate assessments. In all of these patients MRA was performed, which showed abnormal results in 16 cases. In the other 14 patients MRA was normal. Two of these 14 patients were treated with transfusion therapy for other indications. None of the 12 patients with abnormal TCD and normal MRA results who did not receive transfusion therapy developed a CVA. These 12 patients had a median follow-up of 7.5 years (IQR: 6.0, 11.9) after the first abnormal TCD.

Discussion

These data suggest that treatment according to the Amsterdam Protocol is a safe and efficient way to prevent primary CVA in children with SCD and to reduce exposure of these patients to chronic transfusion therapy. We believe the results of this study are reassuring, since none of the patients with abnormal TCD and normal MRA developed a CVA during a cumulative follow-up of 112 patient-years.

Figure 1. Flow Chart



** patient refused therapy*

*** In one patient chronic transfusion therapy was started because of recurrent ACS, 6.1 years after the first abnormal TCD. In the other patient chronic transfusion therapy was started because of repeatedly abnormal TCD results (despite normal MRA results).*

**** Patient 1: First MRI/MRA already showed severe cerebral vascular abnormalities, including multiple stenoses. The CVA occurred 14.9 years after the initiation of chronic transfusion therapy. During these years the patient had developed severe iron overload as a result of the frequent blood transfusions and non-compliance to iron chelation therapy. Compliance to transfusion therapy was moderate to good. Patient 2: Development of Moyamoya disease, despite chronic transfusion therapy. The CVA occurred 7.7 years after start of chronic transfusion therapy. During these years the patient had developed severe iron overload as a result of the frequent blood transfusions and non-compliance to iron chelation therapy. Compliance to transfusion therapy was moderate to good.*

Abstract 22
GUIDELINES4RARE: An ERN ITHACA project to improve care for individuals with rare genetic disorders and intellectual disability

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Rationale
Patients with rare genetic disorders associated with intellectual disability are often affected by complex multiorgan comorbidity, requiring lifelong care. In order to optimize care for this population, effective (international) sharing and application of knowledge are indispensable. Clinical practice guidelines (CPGs) are central to evidence-based medicine as they bridge the gap between scientific evidence and clinical practice. Yet, CPGs for rare genetic intellectual disability remain scarce and their methodology and quality are variable. Challenges include limited scientific evidence; a lack of grading criteria for atypical experimental designs; the need to retrieve experiential knowledge from clinical experts, patients, and their relatives; and international collaboration across varying social and healthcare contexts.

Methods
The objective of the Ph.D. trajectory is to establish a methodological framework for clinical guideline development on a European level through ERN ITHACA, a European network aimed at improving care for rare genetic neurodevelopmental disorders. In line with the suggestions for the development of methodological frameworks of McMeekin et al. (2020), the following project phases are proposed: (1) identifying evidence through purposeful literature review, qualitative research among stakeholders, and collaboration and consultation with experts, (2) developing the methodological framework, and (3) evaluating and refining the framework through pilot projects within ERN ITHACA guideline groups and Delphi panels among experts.

Results
Not yet available.

Discussion
A methodologically sound and widely accepted framework for CPG development is needed to provide evidence-based medicine and improve health outcomes for patients with genetic neurodevelopmental disorders. By providing a blueprint of good care, guidelines may contribute to health equity across national boundaries.

Abstract 23

Recognizing early MRI signs (or their absence) is crucial in diagnosing metachromatic leukodystrophy

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Rationale

Metachromatic leukodystrophy (MLD) is a fatal lysosomal storage disorder leading to neurological deterioration. Hematopoietic stem cell transplantation or gene therapy can be used in pre- and early symptomatic patients. When the disease is too advanced, only supportive care is possible. MLD has characteristic white matter (WM) changes on brain MRI, which often trigger biochemical and genetic confirmation of the diagnosis. In early or pre-symptomatic disease stages, these typical MRI changes might be absent, hampering early diagnosis. This study aims to describe the characteristics of MRI WM abnormalities at diagnosis, related to clinical presentation.

Methods

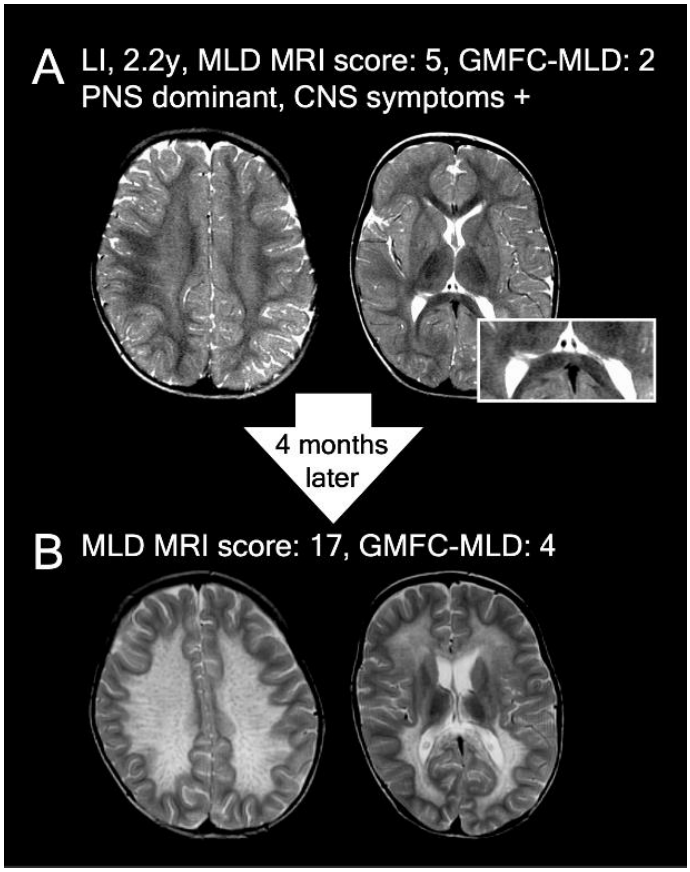
We retrospectively reviewed brain MRIs of MLD patients followed in 2 centers at the time of diagnosis regarding MLD MRI score and presence of tigroid pattern. In addition, MLD subtype, symptom status, CNS/PNS phenotype, motor/cognitive/mixed phenotype, and the presence of CNS symptoms were evaluated.

Results

We included 104 brain MRIs from patients with late-infantile (n = 43), early-juvenile (n = 24), late-juvenile (n = 20) and adult (n = 17) onset. Involvement of the corpus callosum was a characteristic early MRI sign and was present in 71% of the symptomatic late-infantile patients, 94% of the symptomatic early-juvenile patients and 100% of the symptomatic late-juvenile and adult patients. Symptomatic early-juvenile, late-juvenile and adult patients generally had WM abnormalities on MRI suggestive of MLD. By contrast, 47% of the early-symptomatic lateinfantile patients had no or only mild WM abnormalities on MRI, even in the presence of CNS symptoms including pyramidal signs.

Discussion

Patients with late-infantile MLD may have no or only mild, nonspecific abnormalities at brain MRI, partly suggestive of 'delayed myelination', even with clear clinical symptoms. This may lead to significant diagnostic delay. Knowledge of these early MRI signs (or their absence) is important for fast diagnosis.


A LI, 2.2y, MLD MRI score: 5, GMFC-MLD: 2
PNS dominant, CNS symptoms +
4 months later
B MLD MRI score: 17, GMFC-MLD: 4

Abstract 24

The development of the e-TOP information app for parents of very and moderate preterm-born infants

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Rationale

Being home after the hospital discharge, parents of preterm born infants identify struggles to feel confident in their capacity to parent. They seek accessible information about the consequences and impact of the premature birth. The aim of this study is to develop an information module (e-TOP app) in co-creation with parents, TOP pediatric physical therapists and experts.

Methods

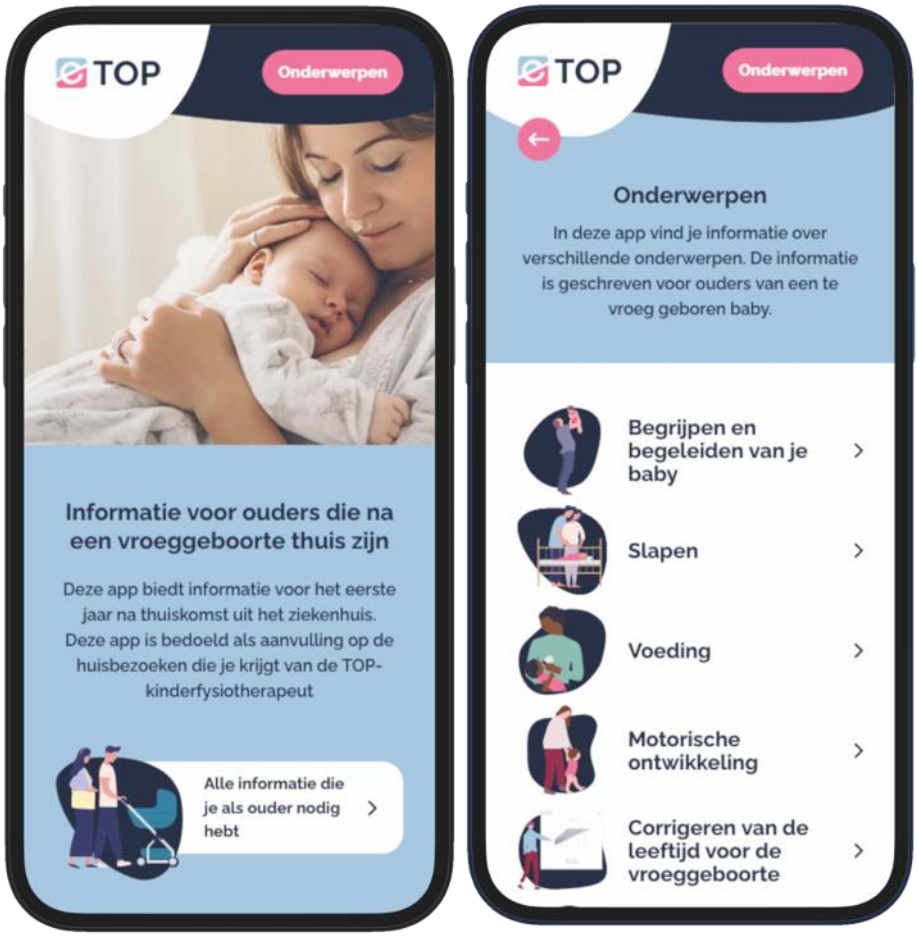
The e-TOP app was developed in an iterative, co-creation process. To obtain insight in the information needs and usability needs, interviews and co-creation sessions were conducted with mothers and fathers of VPT and MPT infants, with both high and low health literacy skills, and TOP interventionists. Experts were asked to generate content for the main topics. Weekly sprints were held to develop the first prototype. The research team reviewed and adapted the content for accessibility. The e-TOP app will be used for 6 months by 40 families of VPT infants receiving the TOP program and by 40 families of MPT infants that will receive the adapted TOP program.

Results

Interviews were conducted with parents (n=10), three online co-creation sessions were held with parents with high and low health literacy skills (n=14) and TOP interventionists (N=8). Based on parent and expert input, ten relevant topics, including motor development, feeding, sleeping, long-term outcomes were included in the e-TOP app. In co-creation with parents, the prototypes of the e-TOP app were designed. Parents preferred information that reassured them to gain confidence, written in a style of a friendly professional. Together, this lead to the final version of the e-TOP app.

Discussion

The e-TOP mobile app provides an accessible source of parent- and expert-generated content for discharged NICU parents. November 2022, the feasibility study with a pre-posttest design started. Usability, parental satisfaction and potential effectiveness will be assessed.


TOP
Onderwerpen
Informatie voor ouders die na een vroeggeboorte thuis zijn
Deze app biedt informatie voor het eerste jaar na thuiskomst uit het ziekenhuis. Deze app is bedoeld als aanvulling op de huisbezoeken die je krijgt van de TOP-kinderfysiotherapeut
Alle informatie die je als ouder nodig hebt
TOP
Onderwerpen
Onderwerpen
In deze app vind je informatie over verschillende onderwerpen. De informatie is geschreven voor ouders van een te vroeg geboren baby.
Begrijpen en begeleiden van je baby
Slapen
Voeding
Motorische ontwikkeling
Corrigeren van de leeftijd voor de vroeggeboorte

Abstract 25

Don’t forget about me: Dementia in rare genetic neurodevelopmental disorders, a systematic review

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Rationale

While the developmental course of children with rare genetic neurodevelopmental disorders (RGNDs) is increasingly known, cognitive trajectories throughout adulthood are understudied. Early onset of decline in functioning is often seen clinically. This may be caused by dementia, which has been studied rather extensively in Down Syndrome but barely in other genetic neurodevelopmental disorders. The aim of this systematic review was to study associations between RGNDs and dementia in order to improve dementia recognition and care in this population.

Methods

A search was conducted in several databases. Search terms were related to dementia and genetic neurodevelopmental disorders in adults, the latter including generic search terms for neurodevelopmental disorders as well as an extensive list of rare genetic syndromes from the National Institute of Health. As studies on dementia were expected to be scarce, broader search terms on cognitive and adaptive decline were also included. This search yielded a total of 11,917 articles to be screened. Title, abstract and reference screening reduced this to 199 full-text articles. This led to a total inclusion of 36 articles in 17 different syndromes in 4,985 adult patients, from which data was extracted.

Results

Results will be presented on epidemiology, pathology, and clinical manifestations of dementia and cognitive decline in rare genetic neurodevelopmental disorders. Validity of diagnostic methods, strengths and limitations of the studies are reported. Qualitative and descriptive analyses were performed.

Discussion

Findings shall be discussed, providing recommendations to optimize screening and diagnosis of dementia and care for adults with neurodevelopmental disorders. A neuropsychological test battery is proposed. Converging pathways between genetic neurodevelopmental disorders and dementia are explored.

Abstract 26

Female adolescents and young adults with bleeding disorders and their experiences in daily life functioning in the Netherlands - A qualitative study

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Rationale

Sexual functioning, social functioning and participation in work/education can be impaired in female adolescents and young adults (AYA's) with bleeding disorders. The aim of this study is to get insight in the experiences of female AYA's with bleeding disorders with respect to these aspects.

Methods

Eligible female AYA's (aged 18-30 years) diagnosed with a bleeding disorder, responded to an announcement by the Dutch Haemophilia Society and are known at one of the Haemophilia Treatment Centres (HTC). Data collection started May 2022 and will continue until data saturation is reached. Focus groups or semi-structured interviews were conducted in person or online. A focus group- and interview guide was developed including 4 themes: sexual functioning, social functioning, work/education and healthcare needs. All sessions were recorded and transcribed. Coding and analysing was done by two independent researchers.

Results

So far, 13 women with bleeding disorders (mean age = 25.6, range 19-30 years) participated. Regarding sexual functioning, women reported that heavy menstruation, bleeding as a result of penetration and an overly concerned partner influenced their sexual functioning. With respect to social functioning, women experienced in general support from friends and family. However, some women mentioned they are reluctant to talk about their diagnosis with people other than friends and family. Some women reported not to join social activities due to heavy menstruation, fear of period leaks and tiredness (shortage of iron). Regarding work, differences were found between women about disclosure to managers and colleagues. A reported reason to disclose at work was the need to know how to handle in case of emergency.

Discussion

Awareness for the experiences of female AYA's with a bleeding disorder is important. This study contributes to this knowledge. A next step will focus on how we can better meet their care needs in the future.

Abstract 27

In vivo genome base editing in a murine model of vanishing white matter modulates the phenotype through multiple mechanisms

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Rationale

Vanishing white matter (VWM) is an autosomal recessive neurologic disorder with a disease onset predominantly in early childhood. It is characterized by central nervous system (CNS) white matter degeneration, causing slowly progressive ataxia, spasticity and cognitive decline with stress-provoked episodes of rapid and major deterioration. VWM leads to progressive handicap and early death. There is no curative therapy available. VWM is caused by bi-allelic mutations in any of the five genes (EIF2B1-5) encoding the subunits of eukaryotic translation initiation factor 2B. We aim to employ gene therapy with state-of-the-art base-editing technology to directly correct the mutation in the CNS to prevent disease symptoms in a well-characterized VWM murine model (Eif2b5R191H/R191H).

Methods

AAV vectors with neurotropic capsid expressing adenine base editors were administered via intracerebroventricular (ICV) injection at postnatal day 0 in VWM mice. Base editing efficiency was measured by next generation sequencing and phenotype assessment of bodyweight and motor function.

Results

Molecular analysis showed correct conversion of the pathogenic mutation (A to G resulting in H191R) in multiple brain regions (up to ~45%), and low percentage of insertions/deletions or bystander edits. The approach improved bodyweight and grip strength, however, composite neuroscores were mildly exacerbated in both VWM mice and healthy controls.

Discussion

We achieved successful in vivo base editing of a pathogenic variant in the CNS of VWM mice, depending on the region investigated, but lower levels of off-targeting edits were also observed. This data shows the potential of base editors, but it simultaneously demonstrates that off-target effects could potentially exacerbate certain phenotypic traits. Implementation of base-editors with higher specificity or improving biodistribution may enhance phenotype correction, which requires further investigation.

Abstract 28

The Role of Biomarkers in Predicting Mortality in Children Admitted to the Hospital in Sub-Saharan Africa: A Systematic Review

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Rationale
Children below five years have the highest mortality rates in sub-Saharan Africa. Early recognition and timely and effective care are needed to end preventable deaths of children under five years old. In settings with limited resources prioritization is essential to facilitate timely care, the models to assist the clinician seem limited. Besides clinical predictors, biomarkers are commonly used in high income settings. The prognostic use of biomarkers has not previously been summarized for children in sub-Saharan Africa.

Methods
In order to find articles on biomarkers to predict mortality in children in sub-Saharan Africa PubMed and Embase were searched using search terms related to child, sub-Saharan Africa, biomarker, mortality and prognostic. After screening eligibility according to preset inclusion and exclusion criteria a critical appraisal was performed. The data extracted included article characteristics, p-values and odds ratios predicting death, sensitivity, specificity and the area under the receiving operator curve.

Results
The search resulted in 2448 articles of which 12 articles were included in this review, studying a total of 24 biomarkers for prognostic use in 8141 sub-Saharan African children. The biomarkers angiopoietin-2, lactate, soluble triggering receptor ex-pressed on myeloid cells-1 (sTREM-1), chitinase-3 like-protein-1 (CHI3L1), soluble tumor necrosis factor receptor-1 (sTNFR-1), soluble fms-like tyrosine kinase-1 (sFlt-1), interleukin-8, interleukin-6 and soluble T cell immunoglobulin and mucin-domain containing protein 3 (sTIM-3) showed a significant association between the concentration and death and were accurate in predicting death.

Discussion
Limited data were found on biomarkers predicting death in children presenting to the hospital in sub-Saharan Africa. The results suggest that angiopoietin-2, lactate and several newer biomarkers may be of use to aid prognostic screening in children in sub-Saharan Africa.

Abstract 29
The association between the implementation of HFNC on lung growth in preterm infants

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Rationale
Noninvasive respiratory support is essential for neonatal care in preterm infants born <32 weeks. Continuous Positive Airway Pressure (CPAP) is a form of noninvasive respiratory support which can deliver continuous positive end-expiratory pressure (PEEP). This respiratory modality differs from High Flow Nasal Cannula (HFNC) which delivers variable PEEP. No studies have been performed investigating the effect of variable versus continuous PEEP on lung growth in preterm infants. The aim was to compare two periods of different noninvasive respiratory strategies, CPAP and HFNC, on the difference in lung growth at six months corrected age (CA) in preterm infants born <30 weeks.

Methods
This study is a retrospective single-center cohort study. Preterm infants born <30 weeks during the period with CPAP (2009-2012) or during the period with CPAP followed by HFNC (2015-2018) were included. Death before six months CA led to exclusion. Bodyweight at six months CA was used as proxy for lung growth. Differences in outcomes were obtained using the linear or logistic regression model analysis.

Results
271 infants (86.6%) in the CPAP cohort and 239 (83.5%) infants in the HFNC cohort were included. No differences in body weight were found between the HFNC cohort compared to the CPAP cohort (mean difference 0.03 kilograms, 95% confidence interval (CI) -0.15–0.20, p=0.77). Significant secondary outcomes were prolonged duration of PEEP support (19.8 versus 31.1 days, estimate=1.24 days, 95% CI 1.14–1.42, p<0.01) and increased risk of severe BPD (8.5% versus 18.9%, odds ratio=2.07, 95% CI 1.17–3.69, p=0.01)

Discussion
The implementation of HFNC is non inferior to only CPAP on lung growth in preterm infants <30 weeks at six months CA. Nevertheless, the addition of HFNC led to a significant prolonged duration of PEEP support and higher risk of severe BPD. Further research is necessary to investigate the effect of HNFC on lung growth at two and five years follow-up.

Abstract 30
Attitudes of patients towards sex-specific newborn screening for X-linked adrenoleukodystrophy

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Rationale
X-linked adrenoleukodystrophy (ALD) is a potentially life-threatening disease in boys and men, which can be treated by hormone suppletion and stem cell transplantation. The default phenotype is a slowly progressive myelopathy, which presents at an older age in both men and women and for which there is no cure. Newborn screening (NBS) for ALD has in the past decade received increasing attention and has become part of screening programs in 30 US states. A number of states and European countries is currently considering its addition. The difference in disease manifestations between sexes, however, raises the question whether NBS for ALD should only be performed in boys. We will investigate the attitudes of ALD patients and their relatives towards sex-specific screening for ALD.

Methods
We have constructed a survey with questions related to the addition of ALD to NBS. Respondents will be asked who in their opinion should be screened: boys only, both boys and girls, or neither. The survey will be sent to all patients in the Dutch ALD cohort (n=95). Patients will be asked to forward the questionnaire to 2 family members.

Results
The results of this study will be obtained in the upcoming months. The most important motives for respondents to be in favor of either sex-specific screening or screening boys only will be compared. Regression analysis will be performed to analyze the influence of sociodemographic factors and disease severity on responses. The results will also be compared to a previous study that investigated attitudes towards the addition of ALD to NBS in a general population.

Discussion
This study will be the first to investigate the attitude of patients and their family members towards sex-specific NBS for ALD. These results should be taken into account by countries and US states that are considering the addition of ALD to their screening programs.

Abstract 31
Health-related quality of life in pediatric and adult patients with classical galactosemia

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Rationale
Classical Galactosemia (CG) is an inborn error of galactose metabolism. Despite a galactose-restricted diet, many patients with CG develop long-term complications including cognitive impairment and movement disorders. In 2004, we found that having CG negatively affects the mental-, physical-, and social Health Related Quality of Life (HRQoL) of both pediatric and adult patients. Since 2004, the diet has been relaxed, newborn screening was implemented in the Netherlands and new international guidelines resulted in major changes in follow-up. The aim of this study was to assess the HRQoL of the patients and to detect HRQoL-domains in need of additional care.

Methods
All patients visiting the galactosemia expertise outpatient clinics Amsterdam UMC and Maastricht UMC were invited. HRQoL-questionnaires focused on the complications of CG (i.e. anxiety, depression, cognition, fatigue, social- and upper extremity function) within the Patient-Reported Outcomes Measurement Information System (PROMIS®) and generic HRQoL-questionnaires (TAPQOL, TACQOL, TAAQOL) were completed online by either self-report (≥ 8 years) and/or proxy-report (1-18 years). Scores were compared to available Dutch or US reference populations by one-sample t-tests or non-parametric equivalents.

Results
Data of 61 patients (aged 1 – 52 years) were included in the study. Adult patients reported on PROMIS-measures lower cognitive functioning ($p = 0.030$), higher anxiety ($p = 0.004$) and more fatigue ($p = 0.026$), which became more apparent in the older age groups. Children reported more fatigue ($p = 0.044$). Parents of pediatric patients reported social difficulties ($p < 0.001$). The generic HRQoL-questionnaires showed cognitive difficulties for all age groups, and physical- social and sleeping difficulties for adults.

Discussion
CG remains to have a negative impact on HRQoL especially on cognition, anxiety and fatigue. Clinicians should be aware of more difficulties in the older group of CG-patients.

Abstract 32
The Role of Biomarkers in the Detection of Bacterial Sepsis in Children in sub-Saharan Africa: A Systematic Review

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Rationale
The U5MR is globally the highest in sub-Saharan Africa. Sepsis is an important contributor to this mortality and largely preventable if treated promptly. The diagnostic capacity is limited in low-income countries, which contributes to the high sepsis related mortality. Biomarkers may be useful as bedside tests to avoid the limited blood culture capacity, but little is known about their performance in sub-Saharan Africa. We therefore summarized data on the ability of biomarkers to detect bacterial sepsis in children under 5 years of age in sub-Saharan Africa.

Methods
A literature search was performed using PubMed/MEDLINE and Embase. Articles were selected using predefined inclusion and exclusion criteria. Studies were included into the analysis if they reported on accuracy. We extracted AUC-ROC and Youden's J statistic (Jmax) to assess the discriminative value.

Results
Ten studies were included in our analysis, representing 1101 patients. Twenty biomarkers were reported on, CRP and PCT were used most often. Three out of eighteen cut-off values (26.92 ug/l, 20 mg/l, 120 mg/l) showed a good Jmax for CRP. The AUC-ROC ranged from 0.60-0.81. For PCT, two out of ten cut-off values (0.64 ng/ml, 0.83 ng/ml) showed a good Jmax. The AUC-ROC ranged from 0.63-0.86. CRP and PCT showed excellent discriminative value. Five out of eighteen biomarkers that could not be grouped showed a good Jmax. Seven out of eighteen biomarkers showed an AUC-ROC between 0.5-0.7. Nine out of eighteen biomarkers showed an AUC-ROC higher than 0.7. These biomarkers showed a promising discriminative value.

Discussion
CRP and PCT showed a good discriminative value for sepsis, and multiple cut-off values showed high sensitivity and specificity. These biomarkers can be clinically used as bedside biomarker tests for the diagnosis of sepsis. There were several other biomarkers that showed promising results. These biomarkers should be studied further before potential use in the clinic.

Abstract 33

PROM4RARE: Giving a voice to individuals with a rare genetic disorder associated with intellectual disability (GD-ID)

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Rationale

In order to improve quality of care for individuals with a rare genetic disorder associated with intellectual disability (GD-ID), it is essential to measure patient reported outcomes (PROs). PROs represent patient perspective on their health status and can be measured with patient reported outcome measures (PROMs). PROMs can be used in the consultation room to monitor and discuss symptoms and physical and psychosocial functioning. Unfortunately, the use of PROMs in clinical care for individuals with GD-ID is scarce, due to the unsuitable and time-consuming questionnaires. The objectives of this study are to (1) develop a core outcome set (COS) of PROs (CoPROs) for GD-ID, (2) select suitable generic PROMs with the best psychometric properties and add specific questions for GD-ID, (3) validate the core PROM set (CoPROMs) for GD-ID, and (4) implement the CoPROMs in daily clinical care for individuals with GD-ID.

Methods

We will use a mixed method design; (1) CoPROs: Identifying common PROs measured in clinical trials (review) and perform a qualitative study on the relevant PROs for individuals with GD-ID and their caregivers (focus groups). Eventually, reaching consensus on the most important PROs for GD-ID (Delphi method). (2) CoPROMs: Identifying and selecting PROMs, which measure the CoPROs (review). (3) Subsequently, validate the CoPROMs for the GD-ID population. (4) Implementation of CoPROMs at the Emma Children's Hospital, Amsterdam UMC and at 's Heerenloo, a large care organization for individuals with ID.

Results

This research project will result in the development en implementation of the CoPROMs for individuals with GD-ID.

Discussion

With the identification of relevant PROs, the development of a CoPROMs, and implementation of the CoPROMs, we hope to maximize the value of personalized care and science for the complex and vulnerable patient population with GD-ID.

Abstract 34

Can we make personalized care for children with an intellectual disability happen? Insights from a large intellectual disability registry

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Rationale

Intellectual disability (ID) is estimated to affect 1-3% of the population, with far-reaching consequences for the child's function in daily life. Technological advances have contributed to the rapid progress in identifying genetic causes of ID, which can contribute to ID care with regard to understanding, preventing and treating physical and mental health manifestations. The aim of this study was to investigate to what extent information on the genetic etiology was actually part of multidisciplinary ID care, and to identify factors that were associated with integration of the genetic diagnosis in ID care to increase disorder-specific care.

Methods

The client database of 's Heeren Loo (care organization for people with ID) was used to obtain a random sample of the ID population, consisting of 374 (2.5%) out of 14,549 clients of all ages. Data on genetic diagnosis, clinical and demographic characteristics and types of support were collected from medical records and files used by behavioral scientists, psychologists, and professional caregivers.

Results

Genetic test results were available in 40%, with a diagnosis of a (genetic) syndrome in 54% of these individuals, as reported by the caregiver. Information on genetic etiology was documented in medical files (93%), psychologists/behavioral therapists files (29%), and files of professional caregivers (68%) when involved. Level of ID, age and the legal representative's relationship to the patient contributed most to the predictive model for factors associated with presence of information on the genetic etiology.

Discussion

Information on genetic etiology has often not been documented by various types of health care providers. We identified factors associated with presence of information on genetic etiology. Education on the importance of knowledge on genetic etiology for all types of health care professionals may increase empowerment of the child, family members and care providers, and improve quality of multidisciplinary personalized care.

Abstract 35

Management and outcome of high-risk neuroendocrine tumors of the appendix in children; a systematic review

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Rationale

This study systematically reviewed the literature to investigate the value of secondary surgery for children with a high-risk neuroendocrine tumor (NET) of the appendix.

Methods

A systematic search was performed in PubMed, Embase and Web of Science. All randomized controlled trials, cohort studies, and case series reporting on the management and outcomes of patients (<20 years) with a histopathologically proven NET of the appendix were eligible for inclusion. Two authors independently selected eligible articles, assessed risk of bias, and extracted data. The outcomes of patients with a high-risk NET treated with secondary surgery were compared to those treated without secondary surgery. Primary outcomes were recurrence rate and disease-free survival.

Results

The literature search yielded 667 articles, of which 29 were included. These studies reported on 1112 patients, of whom 145 (13%) had high-risk NET. Heterogeneity between studies was large and risk of bias was serious in 26 and moderate in three studies. Secondary surgery after primary appendectomy was performed in 64 of 145 patients (44%). Length of follow-up ranged between 0-612 months. In both treatment groups no recurrences were reported, and thus disease-free survival was 100%.

Discussion

Based on current literature, the value of secondary surgery for pediatric high-risk NET of the appendix may be questioned. However, evidence is scarce, of low-quality, and heterogeneity between studies is large. Large international studies with adequate follow-up are needed to generate high-quality evidence on this topic.

Abstract 36
fAMily Integrated CAre in the neonatal ward: 5-year follow up - the AMICA-5 study

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Rationale
Parents are often appointed a passive role during the admission of their preterm or ill newborn. Multiple studies have demonstrated that information, communication and participation are crucial for families of intensive care patients. However, common practice in neonatal wards regarding daily rounds is that the medical rounds are only attended by the physician and nurse without the presence and participation of the parents. Family Integrated Care (FICare) consists of bringing parents, medical and nursing staff together and involving parents as equal partners, minimising separation, and supporting parent-infant closeness. FICare has a collaborative program of psychological, educational, communication, and environmental strategies to support parents to cope with the neonatal environment and to prepare them to be able to emotionally, cognitively, and physically care for their infant. In this study we want to evaluate the long term effects of FICare. Study design: This is a follow up study of the AMICA study (NL Trial Register 6175). The original AMICA study was a prospective observational cohort study with 1 FICare centre and 2 standard care centres.

Methods
In the AMICA-5 study we will include the participants of the original AMICA study at the child's age of 5.5 years with the aim to include 319 children and 663 parents between Otctober 2022 and April 2026. The primary outcome for the children is cognitive development at 5.5 years of age as defined by the total score on the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV). The primary outcome for the parents is parenting stress defined by the total score on the Parenting Stress Questionnaire (PSQ). Secondary outcomes include additional children developmental outcomes and additional parental mental health outcomes.

Abstract 37

Integrating families at neonatal intensive care units for empowering them as primary caregivers: the impact of the programme - RISEinFAMILY study

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Rationale

Infants admitted to the neonatology ward are at risk of developing short-term and long-term health problems. This can also lead to anxiety and stress for parents. To minimise the negative effects of the admission on parents and child, a new care model has been developed, the Family Integrated Care (FICare) model, in which parents are involved as primary caregivers at the neonatal ward. FICare has a collaborative program of psychological, educational, communication, and environmental strategies to support parents to cope with the neonatal environment and to prepare them to be able to emotionally, cognitively, and physically care for their infant. The aim of the RISEinFAMILY project is to develop a FICare model adapted to different culture, architecture and social-economic settings as the new international standard for neonatal care. Study design: International, multi-centre, pluri-cultural, stepped wedge cluster randomised controlled trial is conducted on 7 neonatal wards.The clinical sites are located in Spain, Netherlands, United Kingdom, Canada, Romania, Turkey and Zambia. Timing of start of intervention is randomised between sites.

Methods

All (parents of) infants admitted to the neonatal ward with gestational age below 34 weeks and a minimum admission duration of 7 days are eligible for participation, with the aim to include 630 participants between January 2023 and November 2024. The neonatal growth pattern is considered the main outcome and will be defined according to Patel’s method. Secondary outcomes include parental-, neonatal-, professional- and organisational outcomes.

Abstract 38

Unraveling astrocyte dysfunction in the white matter disease MLC: linking the cytoskeleton to volume-regulated ion channels

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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 these 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 were made from cultured primary 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.

Abstract 39

Intrauterine growth compared to growth and developmental outcomes in the first 2 years of life in moderate and late premature infants.

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Rationale
10% of all newborns are born preterm. Of these preterm born babies 80% is born moderate to late preterm (MLPTI). In recent years, it has been increasingly thought that MLPTI have a greater risk of abnormal development and behavioral problems. This contrasts with earlier insights, namely that the MLPTI group was a healthy group of children without neurodevelopmental problems. Until now, there is no research at all regarding the relationship between intrauterine growth and extra-uterine growth (and development) in the first two years of life in MLPTI.

3 sub-questions:
1. Is there an association between intrauterine growth and growth in the first two years of life in MLPTI?
2. Is there an association between intrauterine growth and neurodevelopmental outcomes in the first two years of life in MLPTI?
3. Is there an association between maternal risk factors during pregnancy and abnormal neurodevelopmental outcomes in the first two years of life in MLPTI?

Methods
Infants born at 32 0/7 till 356/7 weeks of gestation and who were born in the NWZ were included. Infants with congenital abnormalities of the gastrointestinal tract, metabolic diseases, cardiac abnormalities, chromosomal syndromes and chronic diseases that influence growth and infants with necrotic enterocolitis in the past were excluded. Approximately 100 MLPTI are included in this study. Included patients were extracted from a database. This database consists of data concerning growth and neurodevelopmental outcomes (BSID-III). Data of the second trimester anomaly scan, third trimester serial fetal growth scan and multiple measurements in the first two years of life is available. Regarding maternal risk factors, we can include for example: smoking, preeclampsia spectrum disorders, premature ruptured membranes and gestational diabetes.

Results
Study is still ongoing and results are not yet known. Results section will follow.

Discussion
Study is still ongoing. Discussion will follow.

Abstract 40

Diagnosing, Discarding or De-VUSsing: a practical guide to (un)targeted metabolomics as variant-transcending functional tests

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Rationale

For patients with inherited metabolic disorders (IMDs), any diagnostic delay should be avoided because early initiation of personalized treatment could prevent irreversible health damage. While whole exome/genome sequencing (WES/WGS) has revolutionized the diagnostic trajectory for IMD and other rare genetic disorders, many patients are still left without a genetic diagnosis. Functional tests are often considered in the context of testing the effect of a specific genetic variant of unknown significance (VUS), however it can be time-consuming to customize assays for every new variant that is encountered in genomic data. While for IMD, such tests are readily available in biochemical assays, also known under the term 'metabolomics' which covers both targeted and untargeted methods. We have developed a practical guide that features variant-transcending gene function tests for nearly 2000 genes associated with human metabolism.

Methods

Using information from a diagnostic IMD exome panel, Kyoto Encyclopedia of Genes and Genomes, and Inborn Errors of Metabolism Knowledgebase, we compiled a guide for metabolomics-based gene function tests. From our practical experience with this guide, we retrospectively selected illustrative cases for whom combined metabolomic/genomic testing improved diagnostic success and evaluated the effect hereof on clinical management.

Results

The guide contains 2047 metabolism-associated genes for which a validated or putative variant-transcending gene function test is available. We present 16 patients for whom metabolomic testing either confirmed or ruled out the presence of a second pathogenic variant, validated or ruled out pathogenicity of variants of uncertain significance, or identified a diagnosis initially missed by genetic analysis.

Discussion

Metabolomics-based gene function tests provide additional value in the diagnostic trajectory of IMD-suspected patients, by enhancing and accelerating diagnostic success.

Abstract 41

Diagnostic prediction rules for pediatric bacterial meningitis: a systematic review and validation study in children with suspected CNS infection

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Rationale

Bacterial meningitis is a severe disease requiring immediate medical treatment. Diagnostic prediction models have been developed to assess the probability of bacterial meningitis in pediatric patients. External validation of such models in children suspected of CNS infections is essential to determine the diagnostic accuracy of these models.

Methods

We performed a systematic review of literature to identify diagnostic models for bacterial meningitis in children and subsequently validated them in a prospective cohort of children aged 0-18 years old with a suspected CNS infection. We performed a subgroup analysis in neonates (<1 month old). We calculated sensitivity, specificity, predictive values and area under the curve (AUC).

Results

We identified 7724 publications including 36 publications on 26 prediction models for bacterial meningitis. For validation we included 461 patients with a suspected CNS infection (including 40% aged <1 month) from 2012 to 2015. In 75 patients (17%) the final diagnosis was a CNS infection including 31 with bacterial meningitis (7%). Sensitivity of the 26 models ranged from 13-99% overall and 15%-100% for neonates. The model of Oostenbrink showed the highest sensitivity overall (99%, 95%CI 99-100%), the model of Freedman for neonates (100%, 95% C.I. n.a.). Negative predictive value (NPV) was ≥99% in 6 of 26 models overall. Specificity ranged from 6-99% (7-99% in neonates). The model of Huang reached the highest AUC of 0.92 (95%CI 0.87-0.96) overall and AUC of 0.89 (95%CI 0.80-0.99) for neonates.

Discussion

Prediction models show good to excellent test characteristics for diagnosing bacterial meningitis in children, however, it remains unclear whether use of these models in clinical practice is superior to routine clinical care.

Abstract 42

Mapping differences in perceptions of complexity between professionals and their preferences for more sustainable interprofessional care planning in complex pediatric care

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Rationale

Children with medical complexities (CMC) experience severe chronic multiple system conditions, various functional limitations and high family needs (Cohen et al., 2018). Shared mental models of these complexities between professionals, patients and their families are not only essential to provide truly integrated care planning, but can also result in more sustainable care teams in which all members are valued. To integrate perspectives, Kraus de Camargo et al. (2019) propose using the International Classification of Functioning (ICF; WHO, 2001) as framework for interprofessional collaboration (IPC) in CMC-care. IPC-outcomes can be linked to the quintuple aims (IHI, 2022), especially to better quality of patient-centered care, more sustainable IP-care teams and higher health equity.

Methods

This cross-sectional study examines differences between professionals' perceived complexity and IPC-preferences in CMC-care. We created patient cases, and modelled their complexity along the five ICF-axes (functions, activities, participation, external & personal factors). For each case 50 doctors, 50 nurses and 50 paramedics from the Emma Children's Hospital score their perceived degree of case-complexity, anticipated importance of integrated care planning and preferred IP-team composition, including the ideally weighted input of respective IP-team members.

Results

To estimate the effects of ICF-axes on and differences between professionals' perceived complexity and IPC-preferences multivariate linear models with main and interaction effects for ICF-axes and professions will be used. Data are currently collected, and results will be presented during the symposium.

Discussion

Better understanding of differences in perceptions of patient complexities, and varying needs and expectations for IPC within and between health professions may not only lead to better patient care in the CMC-population, but also to more inclusive and therefore more sustainable IP-teams.

Abstract 43

Developing a test setup for exploring personalized non-invasive ventilation masks for children with facial dysmorphic features

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Rationale

Non-invasive ventilation (NIV) is increasingly used in the pediatric intensive care unit to support children with respiratory insufficiency. However, one of the major issues in pediatric NIV is improper fitting of the face mask, in particular in young children and those with abnormal facial features. This leads to air leakage with less efficient ventilation and painful pressure sores, resulting in treatment failure. The main objective of this study is to develop a model based on young children with abnormal facial features to test the performance of personalized 3D-printed masks.

Methods

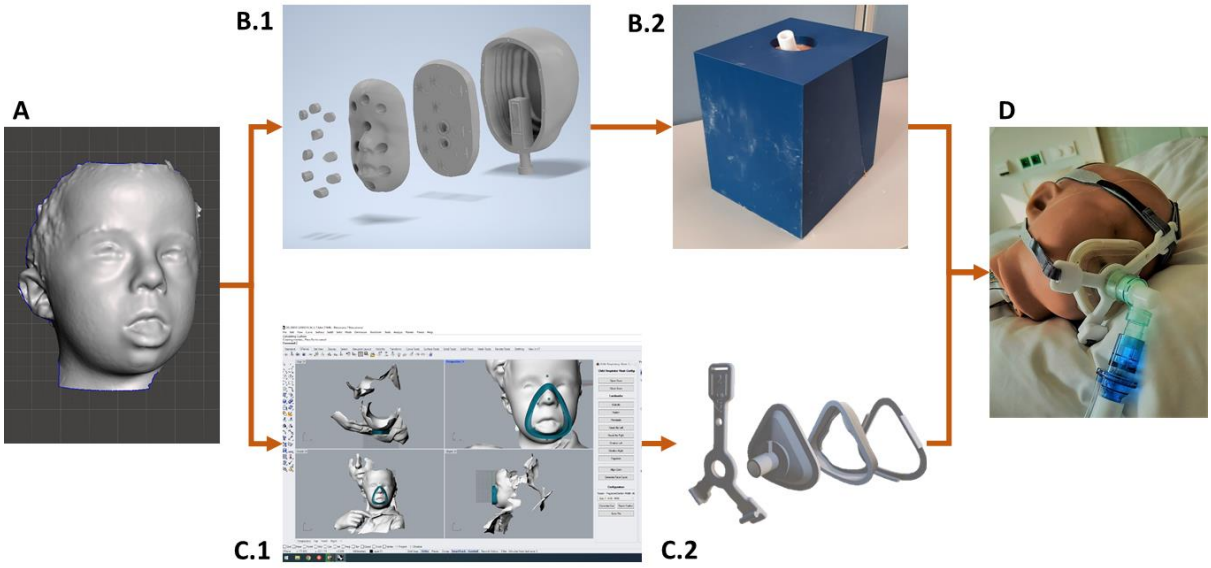
Pediatric head models were developed in Autodesk Inventor (Autodesk, San Rafael, CA, USA) based on 3D anthropometric data of patients with syndromes. The inner head model and outer silicone layer were produced as described before (Hovenier et al., 2022). In addition, pressure sensors (Singletact, PSS UK Limited, Glasgow, UK) were installed in the inner head model to measure surface pressure during NIV. For the modeling of personalized masks the Children's Respiratory Mask Configurator (Rhinoceros 7.23, manual plugin) was designed. Personalized masks were 3D printed using a silicone 3D printer (Spectroplast AG, Schlieren, Switzerland) and assembled with pre-sized holders.

Results

Three head models were successfully produced based on a male with Trisomy 21 (3 years old (y/o)), a female with VCF syndrome (3 y/o) and a male with CFC syndrome (4 y/o). In total 12 personalized NIV face mask prototypes were obtained, all models had 2 sizes in 2 shores (20 and 35). Together with the connection to a lung simulator and ventilator, this resulted in a complete test setup (Figure 1).

Discussion

In this study, we were able to successfully produce a test setup for personalized NIV mask performance in young children with dysmorphic facial features. Further studies should reveal whether personalized 3D-printed NIV masks reduce air leak and pressure compared to conventional NIV masks.


A
B.1
B.2
C.1
C.2
D

Abstract 44

Teenagers' and Parental Individual Needs for Side Effects Information and the Influence of Nocebo Effect Education

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Rationale

When developing a policy on how information about medication and its side effects (SE) should be provided in pediatrics, it is crucial to know individual needs. Therefore, the primary aim of this study was to investigate teenagers' and parental attitudes on information on SE, before and after education on the nocebo effect (NE).

Methods

This multicenter survey study included 226 teenagers (12–18 years) and 525 parents of patients (0–18 years). Questions assessed demographics, clinical characteristics and attitudes towards the amount of SE information before and after the explanation of NE.

Results

Before NE education, 679 (93%) participants preferred to receive SE information: 337 (45%) about all possible SE and 360 (48%) desired specific information (i.e., severe, common, visible, or long-term SE). After NE explanation, significantly more participants (58%) wished to receive information about all possible SE ($p < .001$). When explaining SE, teenagers preferred positive framing more than parents (64% vs. 54%, $p = .043$).

Discussion

This study showed that teenagers and parents generally wish to receive extensive information about SE, even after explaining the concept of the nocebo effect, but preferences may vary. Therefore, healthcare professionals should use tailor-made communication strategies during consultation, and ask patients and their parents up front to what extent they want to be informed on SE.

Abstract 45

Speckle tracking echocardiography in patients with Multisystem Inflammatory Syndrome in Children (MIS-C): a cohort study

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Rationale

Multisystem Inflammatory Syndrome in Children (MIS-C) is a SARS-CoV-2 related hyperinflammatory syndrome with a risk of acute cardiac dysfunction in about half of the cases. We aimed to investigate the short- and long-term cardiac outcomes in MIS-C in combination with laboratory outcomes to guide future studies and clinical recommendations.

Methods

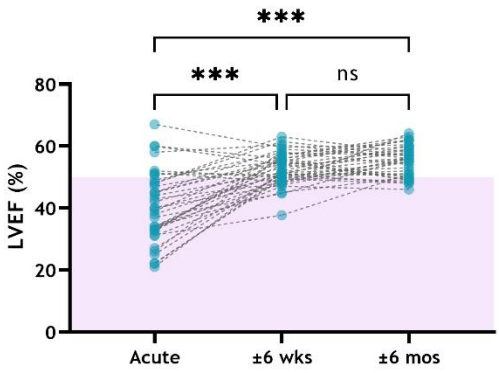
We conducted a cohort study including children diagnosed with MIS-C admitted in the Amsterdam UMC. Data concerning clinical characteristics, conventional echocardiography (i.e., left ventricle ejection fraction [LVEF], shortening fraction [SF]) and speckle tracking parameters (e.g., global longitudinal strain [GLS]) were collected during the acute (nadir value during admission), early convalescent (±6 weeks) and late convalescence (±6 months). Multiple statistical tests were performed to assess over-time patterns and identify predictors for late speckle tracking impairment (i.e., Friedman test, Spearman correlation, multivariate logistic regression).

Results

We included 48 MIS-C patients (median age 11.9 years, 58.3% male). In 83.0% acute cardiac dysfunction was present, based on LVEF <50% and/or FS <28%. A minority (8.5%) had a preserved LVEF and FS, while the GLS was elevated (>[-17]%). In the longitudinal analysis, LVEF and FS levels plateaued within the first six weeks of follow-up, while the GLS continued to decrease from the acute (-13.1%) to early convalescent phase (-16.4% , P=0.02 [vs. acute]) into the late convalescent phase (-18.2%, P=0.005 [vs. acute]). In a multivariate analysis, soluble troponin (>62.0 ng/L) was associated with GLS dysfunction (>[-17]%) during late convalescence (OR=8.2 [95% CI 1.1-60.4]).

Discussion

Speckle tracking more sensitively detects subclinical myocardial impairment than conventional echocardiography. GLS in combination with other markers, such as troponin, may be useful in predicting delayed cardiac recovery.


***
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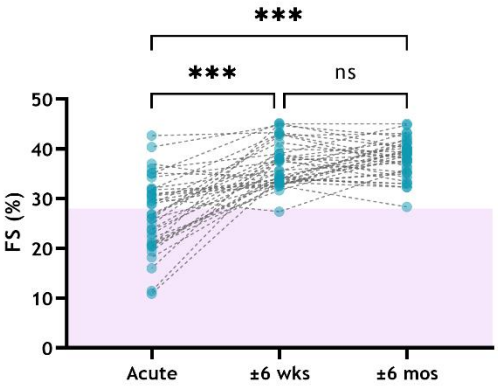
ns
LVEF (%)
80
60
40
20
0
Acute
±6 wks
±6 mos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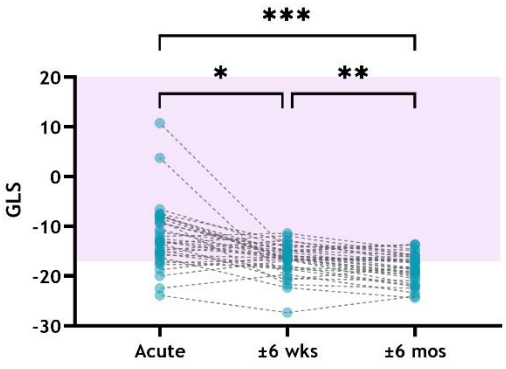
ns
FS (%)
50
40
30
20
10
0
Acute
±6 wks
±6 mos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*
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GLS
20
10
0
-10
-20
-30
Acute
±6 wks
±6 mos

Abstract 46

Arg86 and Ile181 ARSA variants lead to metachromatic leukodystrophy with prominent cognitive decline and sparing of motor function

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Rationale

Patients with metachromatic leukodystrophy (MLD) suffer from motor and cognitive decline with premature death. There is great clinical variability. Previous studies suggest that disease-causing missense ARSA variants affecting p.Arg86 (c.256C>T or c.257G>A) and p.Ile181 (c.542T>G) are associated with predominantly cognitive decline. We aimed to compare phenotypes of patients harboring these variants.

Methods

We performed a multinational study including patients with at least one missense ARSA variant affecting p.Arg86 or p.Ile181 and analysed MLD onset type, presenting symptoms, cognitive function, gross motor function, central motor tract involvement on brain MRI, MRI severity score, peripheral neuropathy, and survival.

Results

47 patients (3 homozygous for c.256C>T and 5, 12 and 27 compound heterozygous for c.256C>T, c.257G>A and c.542T>G, respectively) were included. Phenotype was characterized by a late-juvenile (46.8%) or adult (44.7%) MLD onset of prominent cognitive decline (n=40/41 symptomatic patients). Preserved independent walking, sparing of the central motor tracts, and absence of demyelinating neuropathy were observed in most untreated patients at diagnosis (97.2%, 87.5% and 95.5%, respectively) and follow-up (73.3%, 71.4% and 64.7%, respectively) up to 24 years after symptom onset. An early-juvenile MLD onset and rapid motor decline were only observed in patients compound heterozygous for c.256C>T and a severe second ARSA variant, all showing central motor tract involvement already at diagnosis. Only 2 of the 47 patients died due to disease progression (both compound heterozygous for c.256C>T).

Discussion

Phenotype of MLD patients who are compound heterozygous for c.257G>A or c.542T>G is characterized by a late-juvenile or adult onset of prominent cognitive decline and long-term preservation of motor function associated with sparing of the central motor tracts. Phenotype of patients harboring c.256C>T depends on the second ARSA variant.

Abstract 47

The incidence of associated anomalies in children with congenital duodenal obstruction – a retrospective cohort study of 112 patients

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Rationale

Duodenal obstruction (DO) is a congenital anomaly, caused by duodenal atresia (DA), membrane or annular pancreas and is highly associated with other anomalies. Cardiac anomalies and trisomy 21 are most frequently described. However, a complete overview of anomalies is lacking, as well as potential risk factors for cardiac anomalies in patients with DO. A potential link between DO and VACTERL-spectrum (vertebral, anorectal, cardiac, trachea-esophageal, renal and limb anomalies) remains unknown. Therefore, we aim to determine the incidence of cardiac anomalies and other anomalies in patients treated for DO, to determine a VACTERL-spectrum association and find patient specific risk factors for having cardiac anomalies.

Methods

Patients treated for DO in Amsterdam University Medical Centers between 1996-2021 are retrospectively included. Potential risk factors for cardiac anomalies are analyzed using multivariate logistic regression and included trisomy 21, prematurity and multiple birth.

Results

Of 112 neonates with DO, 47% (N=53/112) have an associated anomaly and 38% (N=20/53) has multiple anomalies. Cardiac anomalies (N=35/112) and Trisomy 21 (N=35/112) are present in 31% of the patients. In 4% (N=4/112) of the patients, VACTERL is discovered, and all of them have a cardiac anomaly. Multivariate logistic regression shows that trisomy 21 (OR: 6.5; CI-95% 2.6-16.1) is a significant risk factor for a congenital cardiac anomaly in DO, whilst prematurity and multiple birth are not.

Discussion

An associated anomaly is present in half of patients with DO, of which the majority are cardiac anomalies and trisomy 21. VACTERL-spectrum is diagnosed in 4% and every one of them has a cardiac anomaly. Trisomy 21 is found to be a significant risk factor for cardiac anomalies. Therefore, we recommend that all patients with DO receive a preoperative echocardiogram. In case a cardiac anomaly is found in patients without trisomy 21, VACTERL screening should be performed.

Abstract 48

Prevalence and comorbidity patterns of psychiatric classifications in a large child and adolescent psychiatric sample (N=71,119)

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Rationale

Psychiatric comorbidity has potential implications for prognosis, clinical presentation, and type of treatment. However, representative overviews of psychiatric comorbidity patterns in children and adolescents are lacking. Therefore, we aimed to provide a systematic overview of psychiatric comorbidities in a large sample of youths who received psychiatric care.

Methods

Data were derived from medical records covering five years (2015-2019) of child and adolescent psychiatric care at one of four academic centers for child and adolescent psychiatry (DREAMS). Psychiatric classifications were assigned according to DSM-5 criteria following diagnostic procedures performed in clinical practice. Prevalence was defined as the proportion of youths who received care for a specific primary psychiatric classification. Comorbidity was defined as all psychiatric classifications for which an individual received care between 2015-2019.

Results

In total, 71,119 youths (mean age at admission 10.8 years [SD = 4.2], range 0-23, 62% male) received care between 2015-2019. Psychiatric classifications of 53,043 youths were available. The most prevalent psychiatric classifications were autism spectrum disorders (ASD; 32%), attention deficit/hyperactivity disorder (ADHD; 23%), and trauma and stressor-related disorders (9%). 71% of youths had at least one comorbid psychiatric classification and 41% had at least two. The most common comorbidity was a primary classification of a schizophrenia spectrum disorder with a comorbid intellectual disorder (30%), followed by a primary classification of a substance-related disorder with a comorbid disruptive disorder (28%).

Discussion

In this large sample, neurodevelopmental disorders were the most prevalent. The majority of youths had at least one comorbid psychiatric classification. This underlines the importance of taking comorbidity into account regarding diagnosis, treatment and outcome predictions in child and adolescent psychiatric care.

Abstract 49

Prediction Models for Neurocognitive Outcome of Mild Traumatic Brain Injury in Children: a Systematic Review

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Rationale

Mild traumatic brain injury (mTBI) is highly prevalent in children. Recent literature suggests that children with mTBI are at considerable risk of persisting neurocognitive deficits, threatening post-injury child development. Nevertheless, clinical tools for early identification of children at risk are currently not available. This systematic review aims to describe the available literature on neurocognitive outcome prediction models in children with mTBI.

Methods

The electronic literature search was conducted in PubMed, EMBASE, CINAHL, Cochrane, PsychINFO and Web of Science. We included all studies with multivariate models for neurocognitive outcome based on original data from only children (< 18 years) with mTBI. Following PRISMA guidelines, two authors independently performed data extraction and risk of bias analysis.

Results

We identified 8 original studies reporting prediction models for neurocognitive outcome, representing a total of 1,033 children diagnosed with mTBI (mean age at injury = 10.5 years, 37.6% girls). Outcome assessment took place between 1 month and 7 years post-injury. Model performance varied greatly between weak and substantial, R2 = 10.0% - 54.7%. The best performing model was based on demographic and premorbid risk factors in conjunction with a subacute neurocognitive screening to predict general neurocognitive deficits 1 year post-injury. None of the models performed external validation.

Discussion

This systematic review reflects the absence of robust prediction models for neurocognitive outcome of children with mTBI. Based on the available evidence, evaluation of demographic and premorbid risk factors with a subacute neurocognitive screening may have the best potential to predict neurocognitive outcome for children with mTBI. The findings underline the importance of future research contributing to early identification of children at risk of persisting neurocognitive deficits.

Abstract 50

The safety of rapid versus standard infliximab infusions in children with inflammatory bowel disease: a multi-center retrospective cohort study

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Rationale

Rapid infliximab (IFX) infusions have shown to be safe in adults with inflammatory bowel disease (IBD), but data on its safety in pediatric IBD is limited. This study aimed to assess the frequency and timing of infusion reactions (IR) in children with IBD who received rapid (1-h) vs. standard (2-h) IFX infusions.

Methods

This retrospective cohort study included IBD patients 4-18 years old, treated with IFX between January 2006 - November 2021 at two tertiary centers (AMC and VUmc) in Amsterdam, the Netherlands. The AMC protocol was adjusted from standard to rapid infusions with a 1-h post-infusion observation period in July 2019, whereas in VUmc only standard infusions were administered without a post-infusion observation period. After merging both departments in 2022, VUmc patients were allocated from standard to rapid infusions. The primary outcome was the frequency of acute IR amongst rapid vs. standard infusions. Secondary outcomes were the timing, severity and management of IR.

Results

Totally, 297 (150 VUmc, 147 AMC) patients (221 Crohn's disease; 65 ulcerative colitis; 11 IBD-unclassified) were included, with a total of 7500 maintenance IFX-infusions. No differences were found in the frequency of IR between the patients receiving standard infusions (16/115, 13.9% of patients), rapid infusions (1/31, 3.2%) and both infusion rates (11/151, 7.3%) (p= 0.105). No difference in the frequency of IR was found between standard infusions (26/4383, 0.6% of infusions) and rapid infusions (9/3117, 0.3%) (p= 0.083). Twenty-six of 35 IR (74.3%) occurred during infusion, while nine occurred post-infusion (25.7%). All post-infusion IR were mild, requiring no intervention or oral medication.

Discussion

Rapid IFX infusions did not result in an increased frequency of IR compared to standard infusions. Post-infusion IR were mild. Our data have resulted in adjustment of the protocol to rapid infusion without a post-infusion observation period for all IFX patients.

Table 1. Characteristics infusion reactions

	Standard infusion (n= 4383)	Rapid infusion (n= 3117)	p-value
Acute infusion reaction, n (%)	26 (0.6)	9 (0.3)	0.083 [a]
Severity, n (%)			
Grade 1	6 (0.1)	5 (0.2)	0.771 [b]
Grade 2	8 (0.2)	3 (0.1)	0.380 [b]
Grade 3	11 (0.3)	1 (0.03)	**0.019** [b]
Grade 4	1 (0.02)	0	1.000 [b]
Timing of reaction, n (%)			
During infusion	20 (0.5)	6 (0.2)	0.071 [b]
After infusion	6 (0.1)	3 (0.1)	0.744 [b]
Timing infusion reaction* in minutes, mean (SD)	20.6 (11.2)	31 (22.5)	0.373 [c]
Infusion number**, median (IQR)	7 (6-17)	21 (12-32)	**0.009** [d]
Symptom, n (%)			
Dyspnea	14 (0.3)	1 (0.03)	**0.007** [b]
Flushing	10 (0.2)	1 (0.03)	**0.032** [b]
Nausea and/or vomiting	6 (0.1)	0	**0.045** [b]
Rash	6 (0.1)	3 (0.1)	0.744 [b]
Headache	6 (0.1)	0	**0.045** [b]
Dizziness	6 (0.1)	4 (0.1)	1.000 [b]
Angioedema	5 (0.1)	0	0.081 [b]
Chest pain	2 (0.05)	2 (0.06)	1.000 [b]
Pruritus	1 (0.02)	1 (0.03)	1.000 [b]
Hypotension	3 (0.07)	1 (0.03)	0.646 [b]
Hypertension	0	1 (0.03)	0.416 [b]
Myalgia	1 (0.02)	0	1.000 [b]

[a] Chi-square test: http://vassarstats.net/
[b] Fisher's exact test: https://www.socscistatistics.com/tests/fisher/default2.aspx
[c] Unpaired t-test: http://vassarstats.net/
[d] Mann-Whitney U test
* Time until infusion reaction occurs, in minutes after starting infusion
** Infusion sequence number at which the first acute infusion reaction took place.

Abstract 51
Methotrexate in Paediatric Inflammatory Bowel Disease: A Pharmacokinetic Study

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Rationale
Methotrexate (MTX) is increasingly prescribed in paediatric Inflammatory Bowel Disease (IBD), but therapeutic drug monitoring (TDM) is currently not feasible. This is a limiting factor when optimising individualised MTX dosages and minimising the risk of adverse events. A novel technique of erythrocyte MTX polyglutamate (PG) analysis could serve for TDM, but data in paediatric IBD are lacking. We aimed to identify the potential of erythrocyte MTX-PG analysis to measure MTX levels and to identify factors influencing outcome in paediatric IBD.

Methods
In this observational cross-sectional study, we determined MTX-PG concentrations in erythrocytes retrieved from blood samples of paediatric IBD patients on MTX maintenance therapy. Furthermore, we identified how sex, age, diagnosis, route of administration and MTX dose influence MTX-PG concentrations. MTX-PG concentrations were determined by stable-isotope dilution LC-MS/MS.

Results
Seventeen paediatric IBD patients on MTX maintenance therapy were included. The predominant subspecies was MTX-PG3 (mean 42.9 nmol/L, SD ± 22.5) and the mean MTX PGtotal concentration was 121.3 nmol/L (SD ± 64.8). A higher dose was associated with significantly higher MTX-PG3 (ρ=0.739), MTX-PG4 (ρ=0.789), MTX-PG5 (ρ=0.737) and MTX-PGtotal (ρ=0.639) levels. When adjusted for body surface area, MTX dose was also associated with significantly higher MTX-PG3 (ρ=0.716), MTX-PG4 (ρ=0.713), MTX-PG5 (ρ=0.559) and MTX-PGtotal (ρ=0.652) concentrations.

Discussion
Higher dosages are associated with higher MTX-PG concentrations. No correlation was found for sex, age, route of administration and duration of treatment. This is the first pharmacokinetic study of erythrocyte MTX-PG concentrations in paediatric IBD. To assess if MTX is suitable for TDM, more research should be conducted. Future studies should explore the correlation between MTX-PG concentrations and efficacy, and the association of these concentrations with adverse events.

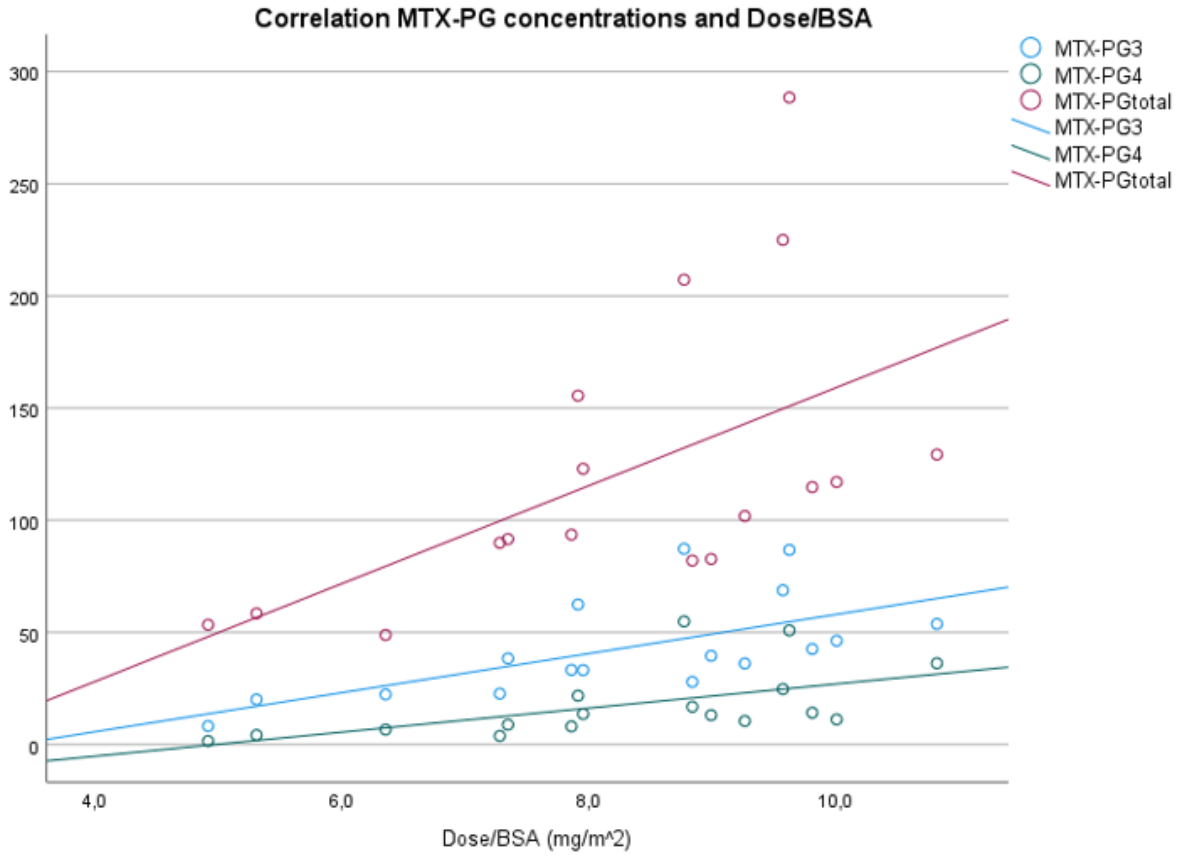

Figure 1 *Correlations of MTX-PG concentrations and MTX-dose per body surface area (BSA).*

Abstract 52
The association of neonatal antibiotic exposure with growth and constipation after preterm birth

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Rationale
Preterm born neonates are often exposed to antibiotics, which can alter the development of the microbiota. Little is known about neonatal antibiotic exposure (NABE) and the subsequent development of childhood gastrointestinal symptoms and growth. We aimed at investigating the association of NABE with childhood constipation and growth impairment.

Methods
Children born <30 weeks of gestation were followed from birth into childhood in an ongoing multicenter study, primarily investigating biomarkers for neonatal disease. A cross-sectional survey was performed when children were 2-6 years old. Parents were asked to complete a health questionnaire and collect a fecal sample of their child. Three groups of NABE were defined: (1) <5days NABE; (2) >5days NABE without confirmed infectious diagnosis; (3) >5days NABE with confirmed neonatal NEC, sepsis or meningitis. We analyzed the association of NABE with constipation and growth. Constipation was assessed by means of the ROME IV criteria asked via the questionnaire. Weight and height at the corrected age of 2 years were extracted from the patients' record.

Results
Of 1237 cross-sectionally approached subjects, 27% completed the questionnaire and collected a fecal sample: 99, 142 and 89 in group 1, 2 and 3, resp. Median postnatal age was 56-57 months in all groups. Childhood constipation and growth were comparable in all NABE groups (p= 0.91 and 0.16, resp.). Mean weight and height z-score were close to 0 in all groups. Food intake, including fruit and vegetable intake, and the need for high caloric (tube) feeding, did not differ between groups.

Discussion
In conclusion, constipation and growth were not associated with NABE. Microbiota analysis is currently performed to investigate whether childhood health outcomes, including constipation, atopy, growth and psychomotor impairment are related to dysbiosis.

Abstract 53
Potential of Molecular Culture in Early-onset Neonatal Sepsis Diagnosis: a Proof of Principle Study

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Rationale
Results of a conventional blood culture (BC), the gold standard for diagnosis of early onset neonatal sepsis (EOS), are only available 36-72 hours after sampling. Consequently, 5% of all newborns and over 85% of very preterm infants are exposed to antibiotics empirically under suspicion of EOS awaiting results of the BC, while the incidence of EOS is only 1%. This overuse of antibiotics leads to gut dysbiosis and subsequent poor health outcome. We aimed to evaluate the potential for EOS diagnosis of an advanced molecular diagnostic technique called Molecular Culture (MC), able to generate results within 4 hours following sampling, in order to reduce redundant antibiotic use in neonates.

Methods
In this prospective cohort study, all participants receiving antibiotics under suspicion of EOS were consecutively included. At initial presentation, a blood sample was collected for MC and BC. Results of MC were compared to BC results for infants with culture-proven EOS, clinical EOS and uninfected infants.

Results
A total of 38 infants suspected of EOS were included of whom 17 fulfilled criteria of clinical EOS. All BC were negative after 72 hours and MC was positive in one clinical EOS case (Enterococcus faecalis), which was missed by BC, and in two uninfected infants (Streptococcus mitis and multiple species), referred to as contamination. The remaining MC outcomes were identical to the BC outcomes.

Discussion
In this proof of principle study, the vast majority of MC and BC outcomes were comparable. Since MC generates outcomes within 4 hours after sampling, compared to 36-72 hours in BC, MC seems to have potential to replace conventional culture in the current EOS guidelines and may guide clinicians to discontinue antibiotics already several hours after birth in case of a negative MC test. Future, larger prospective studies are needed in cohorts also including culture-positive EOS cases to evaluate the accuracy of MC for EOS diagnosis in clinical practice.

Abstract 54

"In vivo histology" using MRI in two distinct leukodystrophies; MLD and VWM

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Rationale

Imaging biomarkers are needed for studying leukodystrophies, which are inherited white matter (WM) diseases. Myelin water imaging (MWI) is a quantitative MRI method that estimates myelin content, and is promising for use in leukodystrophies. We aimed to test the applicability of two novel MWI techniques, MCR-DIMWI and METRICS, for use in the context of white matter disease.

Methods

9 patients with several different leukodystrophies (median age (in years) 9.2; range 0.4-62.4) and 15 control subjects (23.5; 2.3-61.3) were included. MCR-DIMWI and METRICS myelin water fractions (MWFs), relaxation times, and quality control parameters were extracted per region of interest (ROI) and analyzed using RStudio.

Results

Good quality myelin water fractions (MWF) maps were obtained for all patients and controls (see figure 1). MWFs from both techniques correlated well. In leukodystrophy patients, MWF was decreased. For both techniques region-specific MWFs and relaxation metrics could differentiate patients from controls.

Discussion

Both MCR-DIMWI and METRICS provide whole brain MWF-maps and are able to distinguish leukodystrophy patients from controls. A relatively low spatial resolution ensured short acquisition times, which is important in a clinical setting, and is sufficient for globally affected WM disorders. Future studies incorporating clinical measures from leukodystrophy patients can further explore the potential use of these MWI techniques in monitoring disease progression, as well as treatment effects.

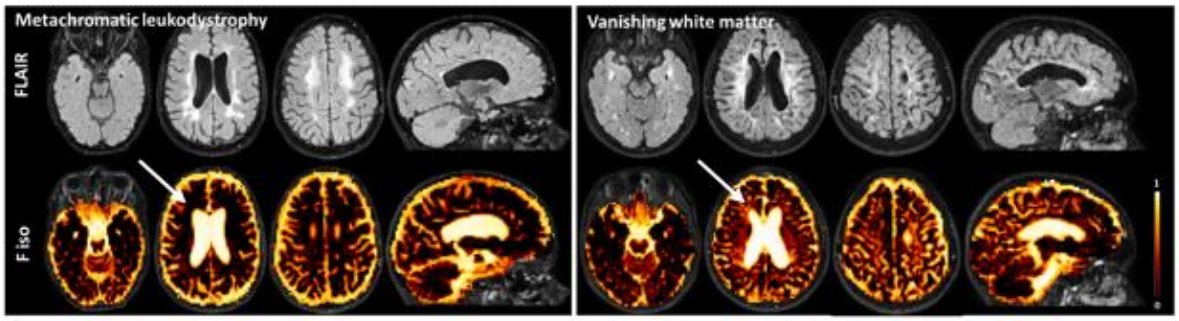

Figure 1: MRI scans of a 14-year old patient with MLD, and a 15-year old patient with VWM. On the FLAIR-images, a hyperintense (white) signal is seen in the MLD and the VWM patient, indicating pathologically affected white matter. On the F_{iso} images (volume fraction of isometric diffusion=free water), an increase of the fraction of free water is only seen in the VWM patient (see white arrows).

Abstract 55

Exploring roles of parents and healthcare professionals in paediatric rehabilitation from a parent's perspective: a qualitative study

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Rationale

Paediatric rehabilitation is often a long-term care process in which cooperation between parents and professionals is important. To achieve optimal care, a collaborative and family-centred care approach, in which both professionals and parents fulfil multiple roles, is required. Since role division often takes place 'intuitively' by professionals, it does not always match the wishes of parents. Making roles explicit will help parents understand what roles are available and can assist professionals in collaborating the most suitable way. However, little is known about the roles, especially with regard to parents. This research aimed to gain more insight in the possible roles parents and professionals can take in a paediatric rehabilitation process, focussing on parent's perspectives.

Methods

In this qualitative study, a phenomenological approach was used. Ten semi-structured interviews were conducted with parents of children under consultation at the paediatric rehabilitation department of Amsterdam UMC.

Results

Eleven roles were identified: expert, representative, collaborator, coordinator, gatherer, informant, adviser, sparring partner, decider, implementer and supporter. These roles can be played by both parent and professional. Three roles form the basis of the collaboration: expert, representative, collaborator. Parents expect these roles from both themselves and the professional as they continue to work together. The other eight roles alternate during the care process depending on the demands of the situation. Although all roles have different features, in general parents find mutual respect, equality, good communication, involvement and fulfilling agreements of both themselves and professionals essential.

Discussion

The findings of this study contributed to knowledge regarding the role division between parents and professionals in paediatric rehabilitation process. It raises awareness to available roles and their variability in the care process.

Abstract 56

Analyses of Resting state EEG biomarkers in a Subject-Specific Bumetanide Treatment of Neurodevelopmental Disorders using The Neurophysiological Biomarker Toolbox

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Rationale
A pathophysiological hallmark of NDDs (neurodevelopmental disorders) are bidirectional imbalances in the Excitation-Inhibition (EI) ratio in local and global networks in the brain. With novel resting state EEG techniques, we can track whole brain disturbances in EI balances (functional E/I (fE/I)) during treatment with mechanism based drugs like Bumetanide. The Bumetanide for Developmental Disorders (BUDDI) is an N-of-1 design at the N=You Precision center, in which we aim to assess individualized treatment effect measurements, including EEG biomarkers of E/I balance.

Methods
Resting state EEG (eyes closed) was recorded from patients (N=25) with NDDs undergoing bumetanide treatment at multiple time points from baseline to completion. Whole brain average of resting state EEG biomarkers such as absolute and relative power and fEI were computed using a unique software called Neurophysiological Biomarker Toolbox (NBT). An fEI value of 1 indicates a balanced fEI and a value lesser or greater than 1 indicates an inhibition dominated or excitation dominated network, respectively.

Results
First analyses of the BUDDI results at baseline show that this novel suite of EEG biomarkers dissects the heterogeneity in cognitive symptoms and clinical manifestations children diagnosed with NDDs.

Discussion
BUDDI is a subject specific Nof1 design to study treatment effects of Bumetanide in children with NDDs. NBT is a unique toolbox that allows for the computation of resting state EEG biomarkers of EI balance and preliminary results suggest that this toolbox has promise to support precision therapy application in NDDs.

Abstract 57
Predicting theophylline escalation in severe acute asthma at the paediatric intensive care unit

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Rationale
Severe acute asthma (SAA) is a highly heterogeneous disease with a variable response to conventional treatment of systemic corticosteroids and beta-2 receptor agonists at the paediatric intensive care unit (PICU). It is therefore desirable to aim for more personalised treatment. In the Netherlands, if a child deteriorates despite maximal therapy, treatment can be escalated by administering theophylline. The main objectives of this study were to identify predictors of theophylline escalation in children with SAA and to describe their clinical characteristics.

Methods
In this retrospective nested case-control study, we analysed medical records of all children (2-18 years of age) admitted for SAA to a tertiary PICU in Amsterdam between 2014 and 2021. Cases were selected based on theophylline administration during PICU admittance, controls (1:1) were matched on age, season and year of admission. Social and disease severity indicators were assessed in a classical machine learning model based on multiple binary logistic regression.

Results
A total of 45 out of 388 children (11.6%) were treated with theophylline. Six main predictors were identified, demonstrating that a non-Caucasian ethnicity, being male, having divorced parents, being raised by a single parent, having a presenting pH<7.2 or asthma score>12 could predict a patient's chance of receiving theophylline with an accuracy of 0.75 and a cross-validation error rate of 0.25. The cases had a significantly higher percentage of intubation (35.6% vs. 2.2%) and longer length of stay (4 vs. 2 days).

Discussion
Children with SAA admitted to the PICU that end up receiving theophylline show a higher severity of admission. With our prediction model, the more severe cases that end up receiving theophylline may be selected at the start of the admission. Consequently, treatment escalation may be started more promptly diminishing the risk for intubation or prolonged admission; however, this requires further validation.

Abstract 58

Towards mechanism-based treatment options in neurodevelopmental disorders: preliminary results of the multiple n-of-1 BUDDI trial

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Rationale

Bumetanide is an example of a potential mechanism-based treatment option for neurodevelopmental disorders. This NKCC1 chloride importer antagonist is hypothesized to affect an imbalance between excitation and inhibition. In contrast to symptom suppressing agents these compounds are expected to only be effective in subpopulations given the heterogeneity in underlying mechanisms. We previously performed three trials using varying strategies to identify children responsive to bumetanide [1,2,3]. The completed trials indicated effectiveness on repetitive and irritable behavior in a subset of participants. We developed a strategy to identify responsive individuals using a combination of EEG and behavioral measures [4]. To validate and improve predictions we are performing a series of single-case experimental designs (SCEDs).

Methods

In the N=You neurodevelopmental precision center, we performed a series of SCEDs in which participants receive 6 months bumetanide treatment. Treatment effect is evaluated on multiple domains using patient and parent interviews, a set of patient reported outcome measures, conventional questionnaires, resting state EEG and cognitive measurements.

Results

In the first series of 40 completed SCEDs 82% of participants experienced a subjective positive change during the treatment period accompanied by either behavioral, physiological or cognitive outcomes improvement. In total, 30 participants showed a positive change in behavioral outcomes, with 25 also showing a favorable change in EEG or cognition. In reverse, 90% of participants with a significant change on EEG and/or cognition measures experienced positive clinical improvement.

Discussion

In this preliminary evaluation of treatment effects of bumetanide using n-of-1 trials we replicate previously found effects on core symptom behavior. In addition, favorable clinical effects in the majority of case were accompanied by a change in physiological or cognitive measurements.

Abstract 60
Collaborating to improve neonatal care: ParentAl paRticipation on The NEonatal waRd – the neoPARTNER study

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Rationale
Infants born premature or ill often spend a considerable amount of time in hospital, which is often for parents. Although multiple studies have shown information and communication to be crucial for families of intensive care patients, parents are often appointed a passive role during the hospitalization of their baby. Common practice in neonatal wards is that the medical rounds are held by the physician and nurse, without parental presence. Parents are usually updated by the nurse afterwards. In Family Centred Rounds (FCR) parents are included in the rounds (digital or physical presence), providing them the opportunity to hear their infant's condition first-hand, to provide information on their child's wellbeing, to ask questions and participate in shared decision making. Family Integrated Care (FICare) is a concept of neonatal care based on psychological, educational, communication and environmental strategies and comprises a framework for the implementation of FCR. FICare aims to support parents to cope with neonatal environment and to prepare them to be able to emotionally, cognitively and physically care for their infant. In the NICU setting, FICare has shown to be effective in reducing parental stress and improving neonatal outcomes. However, information on the effect on level 2 neonatal wards is missing.

Methods
A multicenter stepped wedge cluster randomized trial is currently being conducted on 10 Dutch level 2 neonatal wards. Timing of start of intervention is randomized between sites. All (parents of) infants admitted to the neonatal ward for a minimum of 7 days are eligible for participation, with the aim to include 720 participants between March 2022 and November 2023. Parental stress at discharge is the primary outcome, and will be defined by the total score on the Parental Stress Scale (PSS:NICU) questionnaire. Secondary outcomes include parental, neonatal, healthcare professional and organizational outcomes.

Abstract 61
The association between statin adherence and pulse wave velocity in patients with familial hypercholesterolemia

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Rationale
Familial hypercholesterolemia (FH) leads to severely elevated levels of LDL-c and increased risk for premature atherosclerosis. Statin therapy, preferably started in childhood, slows progression of atherosclerosis. There are surrogate markers to assess the effect of statins on atherosclerosis, such as pulse wave velocity (PWV), as parameter for arterial stiffness. The aim of this study is to evaluate the association between PWV and adherence to statin therapy in patients with FH.

Methods
For this cross-sectional study, 214 patients with FH, originally participated in a double-blind, placebo-controlled trial on the efficacy and safety of pravastatin in children, were eligible. After twenty years of follow-up, PWV measurements of the carotid arteries using 4D Flow MRI were made. Statin adherence was assessed using the Medication Adherence Self-Report Inventory: use of ≥80% of their prescribed statins over the last month was defined as 'adherent'.

Results
We included 108 patients (mean [SD] age: 32.1 [3.3] years, 52 (48.1%) males). Of these, 74 (69%) were adherent. Adherent patients had lower mean (SD) PWV than patients who were not adherent (4.02 [1.42] m/s vs. 4.31 [1.15] m/s; p=0.290). After adjustment for confounders, this association remained not significant (p=0.217). Similar results were observed when different definitions of adherence were used (Table).

Discussion
We found a trend of lower PWV in patients with FH that were adherent compared with non-adherent patients, but not significant. Possible explanations for being non-significant may be technical aspects of 4D flow MRI measurements (variable coverage of carotid arteries, poor temporal resolution). Also, self-reporting of adherence could lead to an overestimation of the PWV in statin adherent categories resulting in an underestimation of the association. Further follow-up and improvement of techniques is needed to determine the possible changes of PWV in these FH patients in the coming years.

Table Mean difference in PWV between adherent and non-adherent patients according to the different definitions for adherence

Adherence		Mean PWV[a,b]	95% CI[c]		Difference [a]	p-value[d]
			lower	*upper*		
≥80% last month		4.02	3.69	4.35	-0.29	0.290
<80% last month		4.31	3.91	4.72		
≥80% last year		4.05	3.70	4.41	-0.15	0.561
<80% last year		4.20	3.84	4.57		
≥90% last month		4.03	3.68	4.38	-0.22	0.410
<90% last month		4.25	3.88	4.61		
≥90% last year		4.00	3.58	4.40	-0.21	0.393
<90% last year		4.21	3.89	4.54		

[a] = in meters per second (m/s), [b] PWV = pulse wave velocity, [c] CI = confidence interval
[d] = unadjusted

Abstract 62

Evaluation of the risk factors inventory questionnaire: social risk factors in children with sickle cell disease

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Rationale

Sickle cell disease (SCD) is associated with adverse health outcomes including frequent pain, organ damage, and mortality. Social factors can negatively contribute to these adverse health outcomes. Yet, knowledge about social risk factors in Dutch children with SCD is limited. The aim of this study was to describe social risk factors of children with SCD.

Methods

We conducted a retrospective observational cohort study that included patients with SCD (0-17 years) from the Emma Children's hospital, Amsterdam UMC. Their parents completed between August 2020-October 2022 the self-developed risk inventory questionnaire (RIV), measuring social risk factors in two categories: socio-demographics and perceived stress factors. Descriptive analyses were performed for all outcomes. The number of perceived stress factors was divided into categories: 0, 1-2 and ≥3 factors. The socio-demographic risk factors were shown for each category.

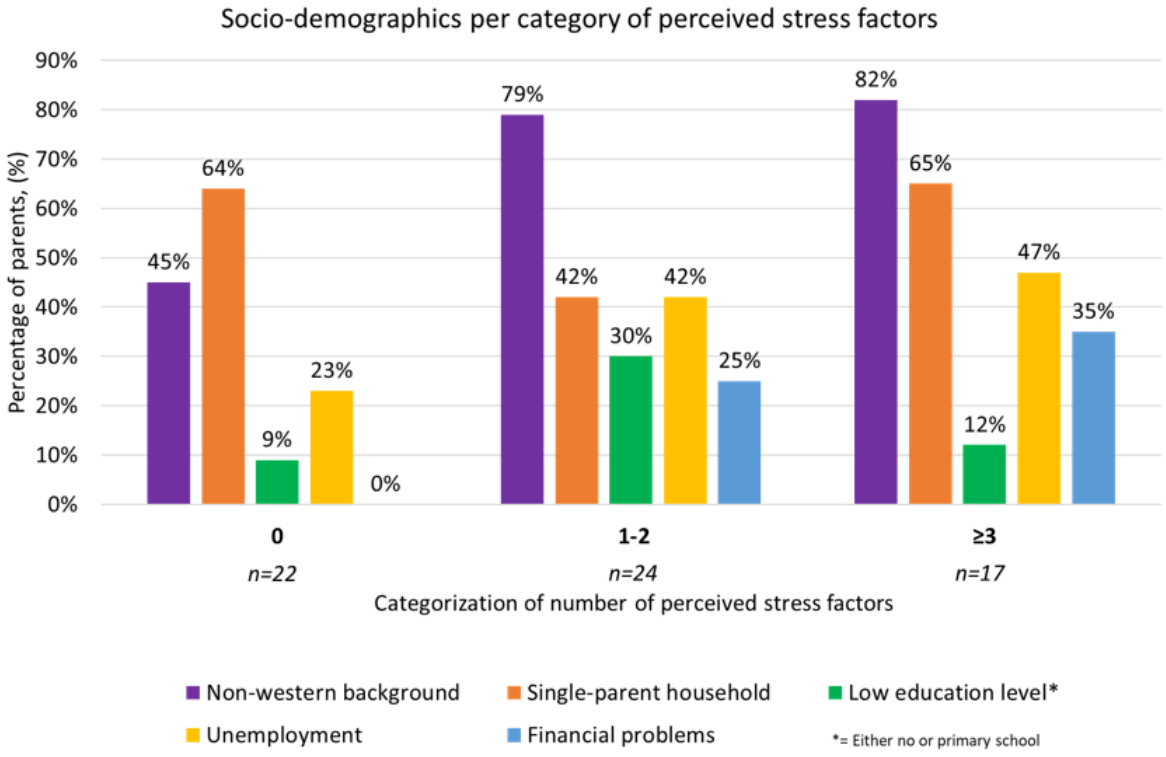
Results

Parents of 63 children aged 7 IQR (3-11) were included in this study. The most reported socio-demographic risk factors were non-western background (68%), single-parent households (54%), unemployment (37%), financial problems (19%), and a low education level (17%). Excessive worries and medical illness of family member were the most often mentioned stress factors. Twenty-two parents did not perceive stress factors, while 24, and 17 perceived respectively 1-2 and ≥3 stress factors. When ≥3 stress factors were perceived, highest percentages of sociodemographic risk factors were found for non-western background (82%), single-parent household (65%), unemployment (47%), and financial problems (35%) (Figure 1).

Discussion

Further research is needed to identify the effect of the reported social risk factors on health outcomes in Dutch children with SCD. However, these results do emphasize the importance of using screening tools as the RIV in clinical practice, so that clinicians can provide psychosocial help at an early stage.

Figure 1. Socio-demographics per category of perceived stress factors



Abstract 63

Biomarkers for the diagnosis of early onset neonatal sepsis: a systematic review and meta-analysis

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Rationale

Early onset sepsis (EOS), an invasive bacterial infection in the first days of life, may result in severe morbidity and mortality for which prompt start of antibiotics is essential. Subtle symptoms at onset complicate an accurate clinical diagnosis, resulting in significant antibiotic overtreatment. A biomarker discriminating between infected and non-infected newborns could improve the diagnosis of EOS. We aim to provide a complete overview of the diagnostic values of tested biomarkers in the prediction of EOS in maternal samples, umbilical cord blood and neonatal serum.

Methods

We searched PubMed-Medline, EMBASE, The Cochrane Library and Web of Science until June 16, 2022. Articles describing the role of at least one biomarker in the detection of EOS up to one week after birth, independent of gestational age, were included and evaluated with Rayyan. The QUADAS-2 tool was used to assess study quality. A meta-analysis, using a random-effects model, was performed with all manuscripts describing diagnostic accuracy (i.e. sensitivity/specificity). Heterogeneity was assessed using I2 statistics.

Results

Of the 2221 identified articles, 307 unique reports were included in the systematic review and 63 reports in the meta-analysis. Potentially interesting markers are PCT and IL-6 in umbilical cord blood, but diagnostic accuracy is not sufficient for use as single predicting marker. Presepsin and serum amyloid A in neonatal serum show a high diagnostic accuracy and could be of potential use in clinical practice. A promising approach in the diagnosis of EOS would be the combination of biomarkers, however study results on this topic were limited, not enabling us to draw any conclusion.

Discussion

Biomarker stand-alone test are currently not reliable to direct antibiotic stewardship in newborns, although presepsin and serum amyloid A show promising initial results. However, further research into biomarker combinations could lead to an improved EOS diagnosis and reduce antibiotic overtreatment.

Abstract 64

Two clinically feasible myelin water imaging methods (MCR-DIMWI and METRICS) can differentiate patients with a leukodystrophy from controls

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Rationale

Imaging biomarkers are needed for studying leukodystrophies, which are inherited white matter (WM) diseases. Myelin water imaging (MWI) is a quantitative MRI method that estimates myelin content, and is promising for use in leukodystrophies. We aimed to test the applicability of two novel MWI techniques, MCR-DIMWI and METRICS, for use in the context of white matter disease.

Methods

9 patients with several different leukodystrophies (median age (in years) 9.2; range 0.4-62.4) and 15 control subjects (23.5; 2.3-61.3) were included. MCR-DIMWI and METRICS myelin water fractions (MWFs), relaxation times, and quality control parameters were extracted per region of interest (ROI) and analyzed using RStudio.

Results

Good quality myelin water fractions (MWF) maps were obtained for all patients and controls (see figure 1). MWFs from both techniques correlated well. In leukodystrophy patients, MWF was decreased. For both techniques region-specific MWFs and relaxation metrics could differentiate patients from controls.

Discussion

Both MCR-DIMWI and METRICS provide whole brain MWF-maps and are able to distinguish leukodystrophy patients from controls. A relatively low spatial resolution ensured short acquisition times, which is important in a clinical setting, and is sufficient for globally affected WM disorders. Future studies incorporating clinical measures from leukodystrophy patients can further explore the potential use of these MWI techniques in monitoring disease progression, as well as treatment effects.

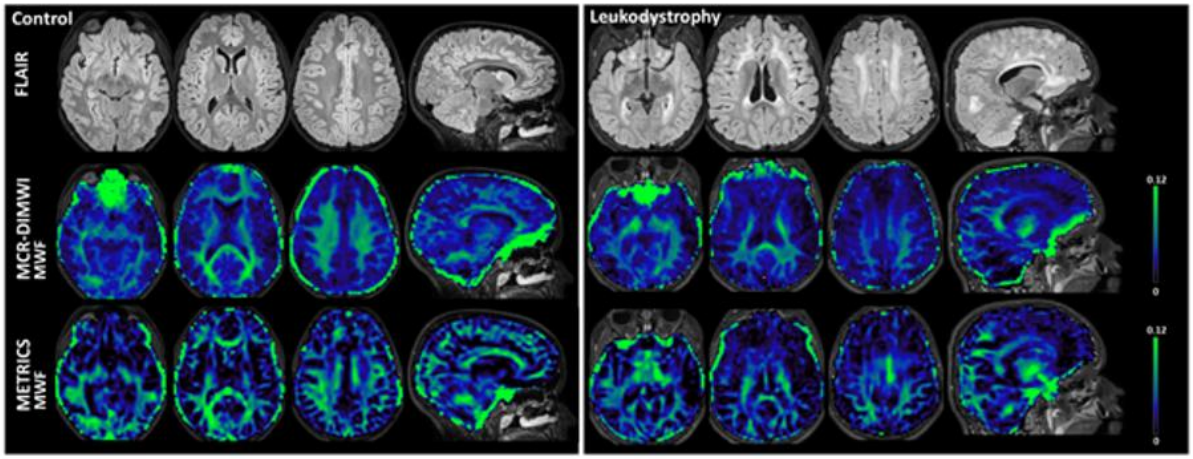

Figure 1: FLAIR and maps of myelin water fraction (MWF) in a control subject (aged 11 years) and a patient with a leukodystrophy (aged 12 years). Patient FLAIR shows white matter hyperintensities mainly in the frontal WM, illustrating pathological lesions. Both MWI techniques show lower MWF in the corresponding areas. Both techniques also contain some hyperintense (bright green) artefacts mainly at the orbitofrontal rim of the brain.

Abstract 65
Short-term air pollution exposure and pediatric wheeze in the Netherlands: new insights

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Rationale
Seasonal trends in air pollution are very similar to viral seasonality. This makes it difficult to study short-term air pollution effects on wheeze associated disorders in children. The shifting viral seasons during the COVID pandemic provide a unique opportunity to correct for viral exposure and investigate the effect of viral seasons on the association between air pollution and wheeze associated disorders.

Methods
Data from four Dutch general hospitals on children aged 2-18 years presenting to emergency departments with wheezing during the years 2016-2021 were combined with data on daily air pollution, viral prevalence and weather factors. A time-series analysis using negative binomial regression with correction for time-trends was performed.

Results
A total of 3962 emergency department visits for wheeze associated disorders were recorded. Overall, daily NO2 levels were independently associated with more visits (OR 1.05; 95% CI 1.003 – 1.090; p = 0.03). When analyzing the years during the COVID pandemic, in which viral seasons shifted, the effects of NO2 were non-significant and an effect of ozone was found. In all models the daily number of rhinovirus positives was significantly associated with the number of visits and appeared to be a stronger predictor than other respiratory viruses (OR 1.055; 95%CI 1.036 to 1.073; p < 0.001).

Discussion
NO2 and ozone showed associations with daily pediatric wheeze associated visits but this was highly sensitive to changes during the COVID period. Residual confounding should be strongly considered in similar studies and causality can only be established if residual confounding is addressed. Exposure to rhinovirus is an essential confounder in these studies and should be corrected for in future studies.

Abstract 66

The first signs of change: predicting clinical deterioration and mortality at different stages during hospital admission. A systematic review of risk prediction models in children in Low-and Middle-Income countries

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Rationale

There is little consensus on which risk-prediction model best predicts clinical deterioration in children, at different stages of hospital admission, in low-middle-income countries (LMICs). We set out to determine which risk prediction model best predicted clinical deterioration according to the hospital setting.

Methods

PRISMA guidelines were used and Embase and Medline databases were searched. The key search terms used were "development or validation study with risk-prediction model" AND "deterioration or mortality" AND "age 0-18 years" AND "hospital-setting: emergency department (ED), pediatric ward (PW), or pediatric intensive care unit (PICU)" AND "low-and middle income countries". Study characteristics, risk prediction model score, and hospital setting were extracted. The Prediction Model Risk of Bias Assessment Tool was used by two authors. Forest plots were used to plot AUC according to hospital setting. Risk prediction models used in two or more of studies included were included in a meta-analysis.

Results

We screened 9684 articles, selected 78 publications, including 67 unique predictive models comprising over 1.5 million children. Twenty six results of risk prediction models performed outstanding (AUC of 0.9 or above). The best performing models (per setting) individually were SICK (ED), PEWS-RL (PW), as well as PIM3 and p-SOFA (PICU). Best performing models after meta-analysis were SICK (ED), p-SOFA and PEDIA-immediate score (PW), and PELOD (PICU). There was a high risk of bias in all studies.

Discussion

This is the largest systematic review of risk prediction models in LMIC and first to look at risk prediction models across all stages of hospitalization. We identified risk-prediction models that best predict deterioration allowing clinicians to select the appropriate model according to hospital setting. Future studies should focus on large scale external validation with strict methodological criteria of multiple risk prediction models.

Abstract 67

The effects of COVID-19 on child mental and social health: biannual assessments up to April 2022 in a clinical and two general population samples

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Rationale

The COVID-19 pandemic has had an acute impact on child mental and social health, but long-term effects are unclear. We examined how child mental health has developed since the start of the COVID-19 pandemic up to 2 years into the pandemic (April 2022).

Methods

We included children (age 8-18) from two general population samples (N=222-1333 per measurement and N=2401-13362 for pre-covid data) and one clinical sample receiving psychiatric care (N=334-748). Behavioral questionnaire data were assessed five times from April 2020 till April 2022. Pre-pandemic data were available for both general population samples. We collected parent-reported data on internalizing and externalizing problems with the Brief Problem Monitor and self-reported data on Anxiety, Depressive symptoms, Sleep-related impairments, Anger, Global health, and Peer relations with the Patient-Reported Outcomes Measurement Information System (PROMIS).

Results

In all samples, parents reported overall increased internalizing problems, but no increases in externalizing problems, in their children. Children from the general population self-reported increased mental health problems from before to during the pandemic on all six PROMIS domains, with generally worst scores in April 2021, and scores improving towards April 2022 but not to pre-pandemic norms. Children from the clinical sample reported increased mental health problems throughout the pandemic, with generally worst scores in April 2021 or April 2022 and no improvement. We found evidence of minor age effects and no sex effects.

Discussion

Child mental health in the general population has deteriorated during the first phase of the COVID-19 pandemic, has improved since April 2021, but has not yet returned to pre-pandemic levels. Children in psychiatric care show worsening of mental health problems during the pandemic, which has not improved since. Changes in child mental health should be monitored comprehensively to inform healthcare and policy.

Abstract 68

Low prevalence of dermatological changes in children with severe malnutrition: A prospective cohort characterizing skin changes in a population of hospitalized acutely ill Malawian children

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Rationale

Since first documentation of skin changes in malnutrition in the early 18th century, various hair and skin changes have been reported in severely malnourished children globally. We aimed to describe skin conditions in children across a spectrum of nutritional status admitted with acute illness to Queen Elizabeth Central Hospital, Blantyre, Malawi. We also sought to validate an existing skin assessment tool.

Methods

Children with acute illness between one week and 23 months of age were systematically enrolled and stratified by anthropometry. Standardized photographs were taken and three dermatologists assessed skin changes and scored each child according to the SCORDoK tool.

Results

Among 103 children, median age was 12 months, 31 (30%) had severe wasting, 11 (11%) had kwashiorkor (nutritional edema) and 18 (17%) had a positive HIV antibody test. Six (5.8%) of the included patients died. Fifty-one (50%) of children presented with at least one skin change. Pigmentary changes commonest, observed in 35 (34%), with hair loss and bullae, erosions and desquamation the second most prevalent skin condition. Common diagnoses were congenital dermal melanocytosis, diaper dermatitis, eczema, and post-inflammatory hyperpigmentation. Severe skin changes like flaky paint dermatosis were rarely observed. Inter-rater variability calculations showed only fair agreement (overall Fleiss Kappa 0.25), while intra-rater variability had fair-moderate agreement (Cohen's Kappa score of 0.47-0.58).

Discussion

In a small but well-documented cohort of hospitalized children we report the prevalence of dermatological pathology. The low prevalence of skin changes in this study does not support the use or further development of a tool to characterize skin changes that are specific to severe malnutrition. The disagreement rates in scoring also highlights difficulties with interpretive dermatological diagnostic tools.

Abstract 69

Multiple organ dysfunction as a predictor of outcome in infants with perinatal asphyxia after therapeutic hypothermia

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Rationale

Multiple Organ Dysfunction (MOD) is a severe complication of perinatal asphyxia. The presence and severity of MOD is often included in prognostication of the individual patient, but solid evidence of discriminating accuracy is lacking. The aim of this study was to assess if MOD in asphyxiated infants during therapeutical hypothermia (TH) predicts mortality or adverse outcome at 24 months and which peripartum variables are associated with the onset of MOD.

Methods

A retrospective analysis of a prospectively collected cohort of asphyxiated infants undergoing TH (the PharmaCool study). MOD was defined as a dysfunction of the brain combined with two or more organ systems. Long-term neurodevelopmental outcome was routinely assessed by standardized assessments at the age of 24 months. The predictive accuracy of MOD on the combined outcome and its separate components (death and adverse) was expressed as areas under the ROC curves (AUCs). The associations of peripartum variables and the development of MOD were expressed as odds ratios and their confidence intervals. A sensitivity analysis using a stricter definition for MOD was performed.

Results

189 infants were included. The incidence of MOD was 47%. The prediction of the combined long-term outcome and its separate components by the development of MOD showed an AUC <0.70. Associations were found between MOD and Thompson score, first ph, first lactate, first base excess and meconium sustained fluid.

Discussion

MOD has shown to be an unreliable predictor of the outcome at 24 months and therefore should not be used as a predictor in multi-disciplinary discussion. The Thompson score, first pH, first lactate, first base excess and meconium sustained fluid are associated with MOD with the current definition.

Abstract 70
Lipoprotein(a) levels in children with homozygous familial hypercholesterolaemia

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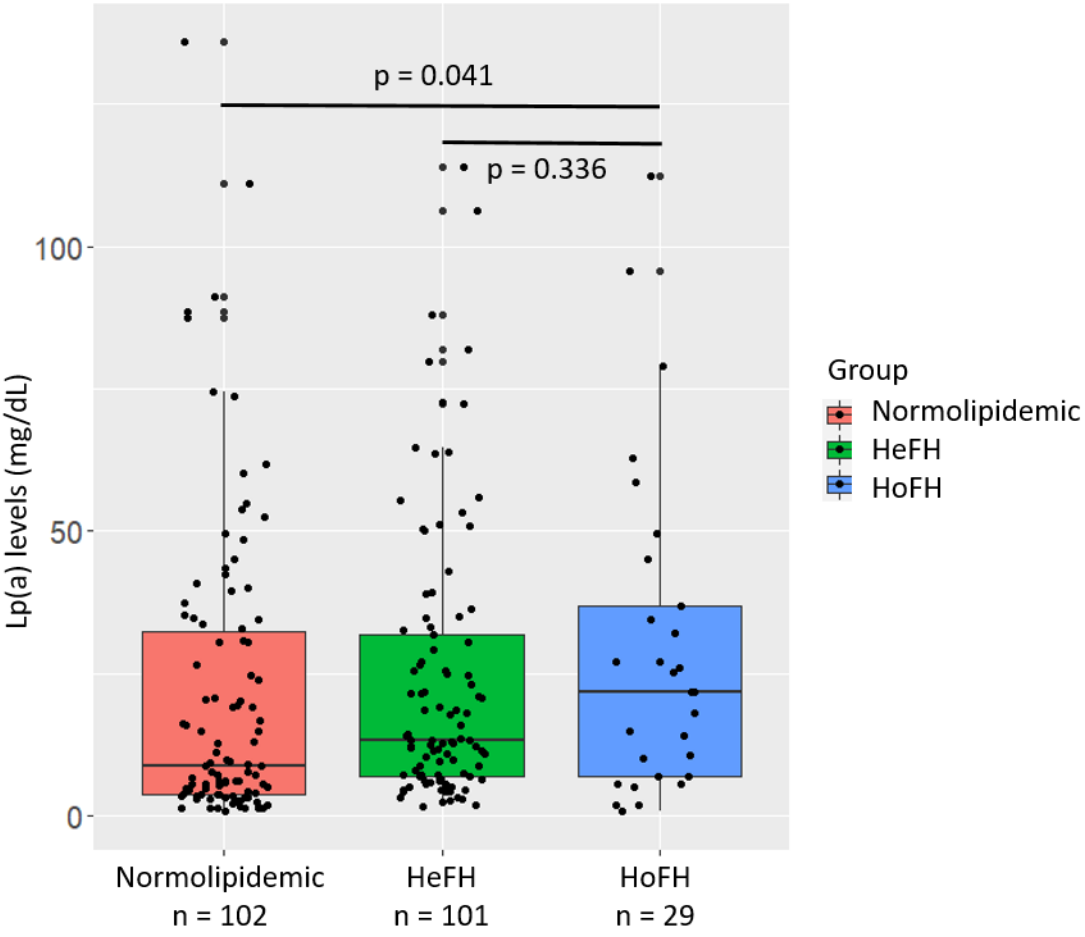
Rationale
Homozygous familial hypercholesterolemia (HoFH) is a life-threatening disorder characterized by extremely elevated LDL-C levels. If treated insufficiently, severe atherosclerotic cardiovascular disease (ASCVD) may already occur in childhood. Next to the conventional risk factors, another important, and likely causal, risk factor for ASCVD is elevated lipoprotein(a) [Lp(a)]. Elevated Lp(a) is independently associated with ASCVD in the general population as well as in children with heterozygous FH (HeFH). It is very common in the general paediatric population and is assumed to be even more prevalent in children with HeFH. However, data on Lp(a) levels in children with HoFH are scarce. Therefore, the aim of this study is to evaluate Lp(a) levels in children with HoFH and compare these to Lp(a) levels of children with HeFH and of normolipidemic controls.

Methods
We performed a cross-sectional study in children with HoFH that visited the paediatric lipid clinic of the Amsterdam UMC. Children with HoFH were matched with HeFH children as well as normolipidemic controls. Children were eligible if Lp(a) was measured ≤18 years of age.

Results
In total, we included 29 patients with HoFH, 101 controls with HeFH and 102 normolipidemic controls. Mean (SD) LDL-C levels in the three groups were 11.0 (4.5), 5.3 (1.3) and 2.6 (0.7) mmol/L, respectively ($p<0.001$). Median (IQR) Lp(a) levels of children with HoFH, HeFH and normolipidemic controls were 21.7 (7.0-36.9), 13.2 (7.0-31.8), and 8.8 (3.7-32.3) mg/dL, respectively (Figure 1). The median Lp(a) levels were significantly higher in children with HoFH compared to the normolipidemic controls.

Discussion
Lp(a) levels were higher in children with HoFH compared to HeFH and normolipidemic controls. We recommend measuring Lp(a) levels in children with HoFH to identify children with an extra ASCVD risk factor. Knowing a child's Lp(a) level may influence the choice of lipid-lowering treatment in the future.


p = 0.041
p = 0.336
100
50
0
Lp(a) levels (mg/dL)
Normolipidemic
n = 102
HeFH
n = 101
HoFH
n = 29
Group
Normolipidemic
HeFH
HoFH

Abstract 71
A national translational research agenda for inherited metabolic disorders

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Rationale
Inherited metabolic disorders (IMD) are rare diseases, often with enormous impact on patients' lives. There are many knowledge gaps and unmet medical needs. United for Metabolic Diseases, a Dutch consortium involving 6 metabolic centers and patient organizations, initiated a national translational research agenda to prioritize research activities and enhance funding possibilities.

Methods
The methodology of the Knowledge Institute of the Dutch Association of Medical Specialists was used. All relevant stakeholders, including medical specialists (pediatricians, neurologists, internists), researchers, laboratory specialists, patient representatives, nurses and dietitians were invited and participated in the process. Research questions were collected from an earlier survey, from vision documents and by an online questionnaire sent to all potential stakeholders by snowballing. Duplicates were removed, and two steering group members independently assessed all remaining items; items which were not consistent with pre-set inclusion criteria were excluded. The residual research questions were presented to representatives of all stakeholder groups invited for a prioritization meeting. The prioritization consisted of two discussion rounds in which the number of items was reduced based on explicit criteria, and a final voting round.

Results
158 stakeholders responded to the online survey which resulted in 462 items being submitted. After excluding duplicates and items inconsistent with the inclusion criteria 178 research questions were prioritized by 24 attendees at the prioritization meeting, which resulted in a selection of 23 research questions ordered according to the votes of the participants.

Discussion
This transparent procedure resulted in a consensus agenda prioritizing areas of IMD research and translation into improved care. Unique aspects include translational research focus, prospective versus retrospective nature, involvement of >30 patient organizations, and multitude of disorders covered.

Abstract 72

Growth and body composition of moderate and late preterm infants up to 6 months corrected age, a randomized controlled trial on nutrition after discharge

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Rationale

In preterms, optimal nutrition is pivotal for growth, body composition and potential cardiometabolic consequences. In moderate-to-late preterm (MLP) infants (i.e., gestational age (GA) 32-36 weeks), we aimed to test the effects of protein- and mineral-enriched postdischarge formula (PDF) versus standard term formula (STF), compared to human milk (HM), on growth and body composition between term equivalent age (TEA) and 6 months corrected age (CA).

Methods

MLP infants were included at birth and fed PDF and/or fortified HM, depending on parental preference. At TEA, exclusively PDF-fed infants were randomized to receive either PDF (n=47) or STF (n=50); unfortified HM-fed infants (n=60) served as controls. At TEA and 6 months CA, we assessed anthropometry and dual-energy x-ray absorptiometry estimated lean mass (LM), fat mass (FM), and bone mineral content (BMC).

Results

All groups had similar GA (median(P25;P75): 34.3(33.5-35.1) weeks), birthweight (mean±SD: 2175±412 g), anthropometry, and body composition at TEA, except for lower %FM at TEA in PDF- than HM-fed infants (17.4±6.2 versus 19.8±6.6%, P=0.02). At 6 months CA, PDF-fed infants had similar weight and FM but higher head circumference and LM than STF-fed infants (head circumference: 43.9±1.3 versus 43.4±1.5 cm; LM: 4772±675 versus 4502±741 g; P<0.05). Also, PDF-fed infants had higher length and BMC than STF- and HM-fed infants (length: 67.7±2.5, 66.9±2.6 and 67.0±2.5 cm; BMC: 140.1±20.3, 130.8±22.6 and 128.2±19.7 g; P<0.05).

Discussion

MLP infants fed PDF, compared to STF, from TEA to 6 months CA demonstrated modest improvements in LM, BMC, length, and head circumference, potentially beneficial for future health.

Abstract 73

Generation of an in vitro stem cell based model for researching gyrate atrophy of the choroid and retina

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Rationale

Gyrate atrophy of the choroid and retina (GACR) is a rare autosomal recessive metabolic eye disorder. Starting from a very young age, GACR patients suffer from progressive vision loss, which progresses to complete blindness by the age of 50. Mutations in the gene encoding for ornithine amino transferase (OAT) impair the function of the encoded enzyme to convert ornithine. It is currently unknown by which mechanism OAT deficiency results in deterioration in vision. In this study we developed GACR in vitro models which can be used to gain a better understanding of the disease mechanism responsible for inducing cell death in GACR.

Methods

Skin biopts and blood was collected from 2 clinically well characterized GACR patients with OAT mutations. From this 2 2 induced pluripotent stem cell lines (iPSCs) were generated. We performed RNA analysis, western blot and immunostainings to determine the presence of OAT in the iPSCs. Both patient and healthy control iPSCs were exposed to a range of ornithine and arginine concentrations and subsequently assayed for cell viability using a MTT assay.

Results

We have been able to determine the presence of OAT gene products in our healthy control cell lines. Interestingly, 1 of the patients cell lines showed almost no loss of OAT activity. In contrast, the other patient cell line showed only residual expression of OAT protein. Cell viability assays demonstrated an increased sensitivity towards ornithine and arginine in our patient iPSCs compared to the healthy controls.

Discussion

We have demonstrated that our patient derived iPSC model displays key characteristic of GACR. Our first functional results are promising and encourages further use of the iPSC model to further identify the disease mechanism responsible for ornithine induced toxicity. We are currently differentiating our iPSCs to iRPE cells yielding more specifically relevant information about the effect of OAT deficiency in the eye.

Abstract 74
High Detection Rate of Viral Pathogens in Nasal Discharge in Children Aged 0 till 5 Years

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Rationale
Respiratory tract infections (RTI) in children remain a cause of disease burden worldwide. Nasopharyngeal (NP) & oropharyngeal (OP) swabs are used for respiratory pathogen detection, but hold disadvantages particularly for children, highlighting the importance and preference for a child friendly detection method. We aim to evaluate the performance and tolerability of a rhinorrhea swab in detecting viral pathogens when compared to a combined OP(/NP) or mid-turbinate (MT) nasal swab.

Methods
This study was conducted between September 2021 - July 2022 in the Netherlands. Children aged 0-5 years, with an upper respiratory tract infection and nasal discharge, were included and received a combined swab and a rhinorrhea swab. Multiplex polymerase chain reaction (PCR) and SARS-CoV-2 PCR were used for viral pathogen detection. Tolerability was evaluated with a questionnaire and visual analogue scale (VAS) scores.

Results
During a period of 11 months 88 children were included, with a median age of 1,00 year (IQR 0,00-3,00). In total 122 viral pathogens were detected in 81 children (92%) and in 7 children no virus was detected in either sample. Sensitivity and specificity of the rhinorrhea swab compared to a combined swab were respectively 97% [95% CI 91%-100%] and 78% [95% CI 45%-94%]. In 24 (27%) of the cases a co-infection was found with two pathogens, 7 (8%) cases revealed three viral pathogens and 1 (1%) case had 4 pathogens. Rhinorrhea samples detected more pathogens than the (combined) nasal samples, 112 vs 108 respectively. Median VAS scores were significantly lower for the rhinorrhea swab in both children (2 vs. 6) and their parents (0 vs. 5).

Discussion
In conclusion, a rhinorrhea swab is just as effective and reliable as the combined swab in detecting viral pathogens in young children and additionally is better tolerated by both children and their parents/caregivers. Therefore the future implementation of this method of testing would be highly advised and easily achievable.

Abstract 75

The association between nutritional intake in the first 6 months of life, growth from birth until two years of age and neurodevelopment at two years of age in moderate and late preterm infants

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Rationale
Moderate and late preterm infants (MLPTI), infants born between a gestational age of 32 and 35 6/7 weeks, may be at risk for poor growth and poor weight gain in the first few years of life. And poor growth has been associated with impaired neurodevelopment. But data on longitudinal growth in MLPTI is lacking. The aim of this study was to determine the association between nutritional intake in the first months of life, growth from birth until two years of age and neurodevelopment at two years of corrected age for prematurity in MLPTI.

Methods
In this prospective cohort study, daily actual nutritional intake form 100 MLPTI was collected during hospital admission from birth until discharge. After discharge nutritional intake was collected at the out-patient clinic. Growth was collected during hospital admission and during several visits at the outpatient clinic. At two years, children underwent a cognitive, language and motor assessment using the Bayley Scales of Infant and Toddler Development (BSID-III-NL). To determine the association between nutritional intake, growth and scores on the BSID-III-NL) we used multivariable linear regression analyses.

Results
This study is currently still carried out. Results will follow soon.

Discussion
This study is currently still carried out. Discussion will follow soon.

Abstract 76
Persistent Symptoms after SARS-CoV-2 infection in the Dutch Paediatric Population

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Rationale
Paediatric post-COVID is much rarer than its adult counterpart1, yet can take a heavy toll, affecting school attendance, social abilities, and physical activity, health, and family. Post-viral persistent complaints (PCs) aren't unique to SARS-CoV-2, so to understand the scope of the problem, and separate it from “post-lockdown syndrome”, we compared the incidence with a negative control group.

Methods
Through an ongoing longitudinal observational population survey study in the Netherlands, children at national testing centres, regardless of test outcome, filled out questionnaires on the day of inclusion, at 4 and 12 weeks, and 6 and 12 months after their test.

Results
Since April 2021, 1175 children have been included at the first timepoint (t0), 780 at 4 weeks (t1), 574 at 12 weeks (t2), 418 at 6 months (t3), and 129 at 12 months (t4). (Table 1). We used the WHO's definition2 for post-COVID2. At t2 a significantly higher proportion of SARS-CoV-2 positive children at t0¬ reported PCs compared to the negative control group (15% vs. 2.3%; p:< 0.001). Prevalence at t2 rises from 11% at 0-6 years old, to 25% in children 13-18 years old. Prevalence at t3 drops to 5.9% vs 1.6% in the negative group. At t2 fatigue is the most common PC (9.6% positive group vs. 1.9% negative group; p < 0.001), dropping to 4.9% vs 0.5% at t3¬ (positive vs. negative group; p: 0.002). Of the positive tested children at t2 with PCs (n=39), 15.4% experience moderate to severe social limitations, vs 0% in the negative group (n=6). 23.1% experience moderate to severe limitations in physical functioning (<50% of functioning) vs 17% in the negative group.

Discussion
After a SARS-CoV-2 infection, significantly more children develop persistent complaints compared to a control group. This prevalence drops over time. Daily social and physical limitations differ significantly between groups. This cohort helps understand the prevalence and burden of post-COVID complaints in children.

Table 1: Post COVID complaints			
	Negative	Positive	p*
Persistent Complaints (12 weeks)			
n	257	260	
Yes	6 (2.3%)	39 (15%)	< 0.001
Fatigue	5 (1.9%)	25 (9.6%)	< 0.001
Headache	1 (0.4%)	15 (5.8%)	< 0.001
Coughing	2 (0.8%)	11 (4.2%)	0.006
Stomach ache	0 (0%)	11 (4.2%)	< 0.001
Concentration difficulties	1 (0.4%)	9 (3.5%)	0.007
Persistent Complaints (6 months)			
n	192	185	
Yes	3 (1.6%)	11 (5.9%)	0.013
Fatigue	1 (0.5%)	9 (4.9%)	0.002
Concentration difficulties	0 (0%)	3 (1.6%)	0.084
Coughing	1 (0.5%)	3 (1.6%)	0.233
Shortness of breath	1 (0.5%)	2 (1.1%)	0.719
Headache	1 (0.5%)	2 (1.1%)	0.009
Persistent Complaints (12 months)			
n	94	21	
Yes	5 (5.3%)	0 (0%)	0.497
Daily limitations with †:			
School	**Negative† *(n = 6)***	**Positive† *(n = 39)***	
None	3 (50%)	21 (54%)	
Mild: 1-2 days of absence per month	0 (0%)	11 (28%)	
Moderate: 1-2 days of absence per week	1 (17%)	4 (10%)	
Severe: 3-5 days of absence per week	0 (0%)	1 (2.6%)	
Does not go to school	2 (33%)	2 (5.1%)	
Social			
None	3 (50%)	23 (59%)	
Mild: 1-2 days per month not capable	1 (17%)	10 (26%)	
Moderate: 1-2 days per week not capable	0 (0%)	5 (13%)	
Severe: no social contact possible	0 (0%)	1 (2.6%)	
NA	2 (33%)	0 (0%)	
(Physical) Functioning			
None	0 (0%)	16 (41%)	
Mild: 80% of functioning possible	3 (50%)	12 (31%)	
Moderate: 50% of functioning possible	1 (17%)	6 (15%)	
Severe: no physical functioning	0 (0%)	3 (7.7%)	
NA	2 (33%)	2 (5.1%)	

** Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test*
† Participants who reported PCs at 12 weeks

Abstract 77

Immunodeficiency, autoimmunity, and increased risk of B cell malignancy in humans with TRAF3 mutations

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Rationale

Tumour necrosis factor receptor-associated factor 3 (TRAF3) is a central regulator of immunity. TRAF3 is often somatically mutated in B cell malignancies, but its role in human immunity is not defined.

Methods

Here, in five unrelated families, we describe an immune dysregulation syndrome of recurrent bacterial infections, autoimmunity, systemic inflammation, B cell lymphoproliferation and hypergammaglobulinaemia. Affected individuals each had monoallelic mutations in TRAF3 that reduced TRAF3 expression.

Results

Immunophenotyping showed patients' B cells were dysregulated, exhibiting increased NF-kB2 activation, mitochondrial respiration, and heightened inflammatory responses. Patients had mild CD4+ T cell lymphopenia, with reduced naïve T cell proportions but increased regulatory T cells and circulating T follicular helper cells. Guided by this clinical phenotype, targeted analyses demonstrated that common genetic variants, which also reduce TRAF3 expression, are associated with risk of B cell malignancies, systemic lupus erythematosus, higher immunoglobulin levels, and bacterial infections in the wider population. Reduced TRAF3 conveys disease risks by driving B cell hyperactivity via intrinsic activation of multiple intracellular pro-inflammatory pathways and increased mitochondrial respiration, with a likely contribution from dysregulated T cell help.

Discussion

Thus, we define monogenic TRAF3 haploinsufficiency syndrome, and demonstrate how common TRAF3 variants impact upon a range of human diseases.

Abstract 78

Intra-familial phenotypic variability in primary hyperoxaluria type 1: data from the OxalEurope registry

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Rationale
Clinical variability in primary hyperoxaluria type 1(PH1) is reported within families with identical genotypes. In this study, we aimed to analyze the disease course of families with PH1 to determine whether and to what extent intra-familial heterogeneity is present, based on a clear definition of intra-familial heterogeneity in PH1. Furthermore, we aimed to analyze the impact of family screening on the prognosis of siblings.

Methods
We retrospectively analyzed data from the OxalEurope registry. All families with PH1 were identified and analyzed. A six-point PH1 clinical outcome scoring system was developed to calculate the heterogeneity score within a family. We considered a score ≥2 as significant intra-familial heterogeneity.

Results
We identified 101 families with PH1 in the OxalEurope registry. In total, 88 families were included in this study, including a total of 193 patients with PH1. The median (interquartile range [IQR]) follow-up time was 7.8(1.9-17) years. Family screening was conducted in most families,(n=64;77%). There were 38(43%) families with intra-familial heterogeneity. Moreover, in 23 families with extended follow-up of more than 15 years, intra-familial heterogeneity was present in 11 families(48%). A (partly) B6-sensitive mutation showed no significant difference in heterogeneity score of families compared to a vitamin B6 unresponsive mutation($p = 0.82$). Finally, Kaplan-Meier analyses revealed that index cases reach kidney failure at an earlier age and earlier in follow-up compared to siblings(Logrank,$P<0.0001$).

Discussion
Intra-familial heterogeneity is found in nearly half of families with PH1. Although the exact cause of heterogeneity in PH1 is still unknown, family screening is essential and strongly recommended since it improves the kidney failure-free survival of siblings.

Abstract 79

Objective Neurocognitive assessment of young children with Sickle cell disease by Eye-Tracking - ONSET study

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Rationale

Children with sickle cell disease (SCD) are at risk of derailed neurodevelopmental outcome through cerebral infarctions, anemia and inflammation. Neurocognitive functioning is an important determinant of daily life functioning, and is influenced by the course of SCD and the often suboptimal environment in which these children grow up. This study aims to investigate early neurocognitive functioning in very young children with SCD, exploring early determinants and the relation to adaptive functioning.

Methods

This is a prospective observational study with an accelerated longitudinal design. Children with SCD between the ages of 4–22 months will be recruited from Amsterdam UMC & Erasmus MC and will be matched with healthy developing children, based on demographic variables. Early neurocognitive functioning will be measured using eye-tracking, measuring aspects of oculomotor control, information processing, attention, learning and memory using gap-overlap and habituation paradigms. Blood samples of children with SCD will be taken to identify biomarkers by proteomics and methylation analyses. At the age of 22 months additional assessment of adaptive functioning will be conducted (TaPsQoL, CBCL, BSID). Statistical analyses will be performed using generalized estimation equations. The impact of SCD on early neurocognitive functioning will be investigated by comparing study groups and the interaction between groups over time. Predictors of poor neurocognitive outcome will be investigated by developing multivariate prediction models using demographic characteristics, clinical parameters and the biomarkers. Likewise, the relation between early neurocognitive functioning and adaptive daily life functioning will be investigated.

Results & Discussion

Early identification of children at the risk of neurocognitive impairment would facilitate the possibility to deploy early interventions aimed at dampening of the detrimental effects of SCD on the developing brain.

Abstract 80

Correlations between capillary density and degree of skin pigmentation in healthy children analysed by nailfold video capillaroscopy

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Rationale

Nailfold Video Capillaroscopy (NVC) is a simple, non-invasive diagnostic tool but studies with normal values for capillary density in healthy children are rare. Ethnic background seems to play a role in capillary density; however, this is not well substantiated yet. In this work, we set out to evaluate influence of ethnic background/skin pigmentation and age on capillary density reading in healthy children. Secondary aim was to investigate whether there is a significant difference in density between different fingers within the same patient.

Methods

Capillaroscopic images from healthy children were obtained in a one-time visit videocapillaroscopy (x200 magnification) addressing the capillary density (i.e. number of capillaries per linear millimeter in the distal row). This parameter was compared to age, sex, ethnicity, skin pigment grade (I-III) and between eight different fingers, excluding the thumbs.

Results

We investigated 145 healthy children with mean age of 11.03 years (SD 3.51). The range of capillary density was 4-11 capillaries per millimetre. We observed a lower capillary density in the 'grade II' (6.4 ± 0.5cap/mm, $p<0.001$) and 'grade III' (5.9 ± 0.8 cap/mm, $p<0.0001$) pigmented-classified groups compared to the 'grade I' group (7.0 ± 0.7 cap/mm). We did not find a significant correlation between age and density in the overall group. The fifth fingers on both sides had a significantly lower density compared to the other fingers.

Discussion

Healthy children <18 years with higher degree of skin pigmentation show a significantly lower nailfold capillary density. No correlation was found between age and capillary density. The fifth fingers on both hands displayed lower capillary density compared to the other fingers. This needs to be taken into account when describing lower density in pediatric patients with connective tissue diseases.

Abstract 81

Menke-Hennekam syndrome – delineation of domain-specific subtypes using genome-wide methylation episignatures and 3D protein structure modelling

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Rationale

Cyclic AMP response element-binding protein (CREB)-binding protein (CBP, encoded by CREBBP) and its paralog E1A-associated protein p300 (encoded by EP300) are involved in histone acetylation and transcriptional regulation. Variants that produce a null allele or disrupt the proteins' catalytic domains cause Rubinstein-Taybi syndrome, while in-frame pathogenic variants in parts of exons 30 and 31 cause phenotypes recently described as Menke-Hennekam syndrome (MKHK). In this study, we aimed to further delineate subtypes of MKHK.

Methods

To distinguish MKHK subtypes and define their characteristics, molecular and extensive clinical data on 82 individuals (54 unpublished) with variants in CBP(n=71) or p300(n=11) (NCBI reference sequence NP_004371.2 residues 1705-1875, and NP_001420.2 1668-1833, respectively); were systematically gathered. Additionally, genome-wide DNA methylation profiles (episignatures) were assessed in DNA extracted from whole peripheral blood from 53 individuals.

Results

Most variants clustered closely around the Zinc binding residues of two Zinc finger domains (ZZ and TAZ2) and within the first α-helix of the fourth intrinsically disordered linker (ID4) of CBP/p300. A domain-specific episignature was discerned for the ZZ domain in CBP/p300 (found in 9/10 tested individuals) and TAZ2 domain in CBP (in 16/20) and was further refined for ID4 in CBP/p300 (in 21/21). Phenotypes included intellectual disability of varying degree and distinct physical features for each of the regions were identified, with variants in the first α-helix of ID4 causing a clearly recognizable phenotype.

Discussion

We conclude that MKHK consists of at least three domain-specific, rather than CREBBP/EP300 gene-specific subtypes (MKHK-ZZ, MKHK-TAZ2, and MKHK-ID4), based on distinct phenotypes and domain-specific episignatures. Our data furthermore show that DNA methylation episignatures provide a powerful tool to discern and differentiate between disease entities within a gene or across paralogous genes.

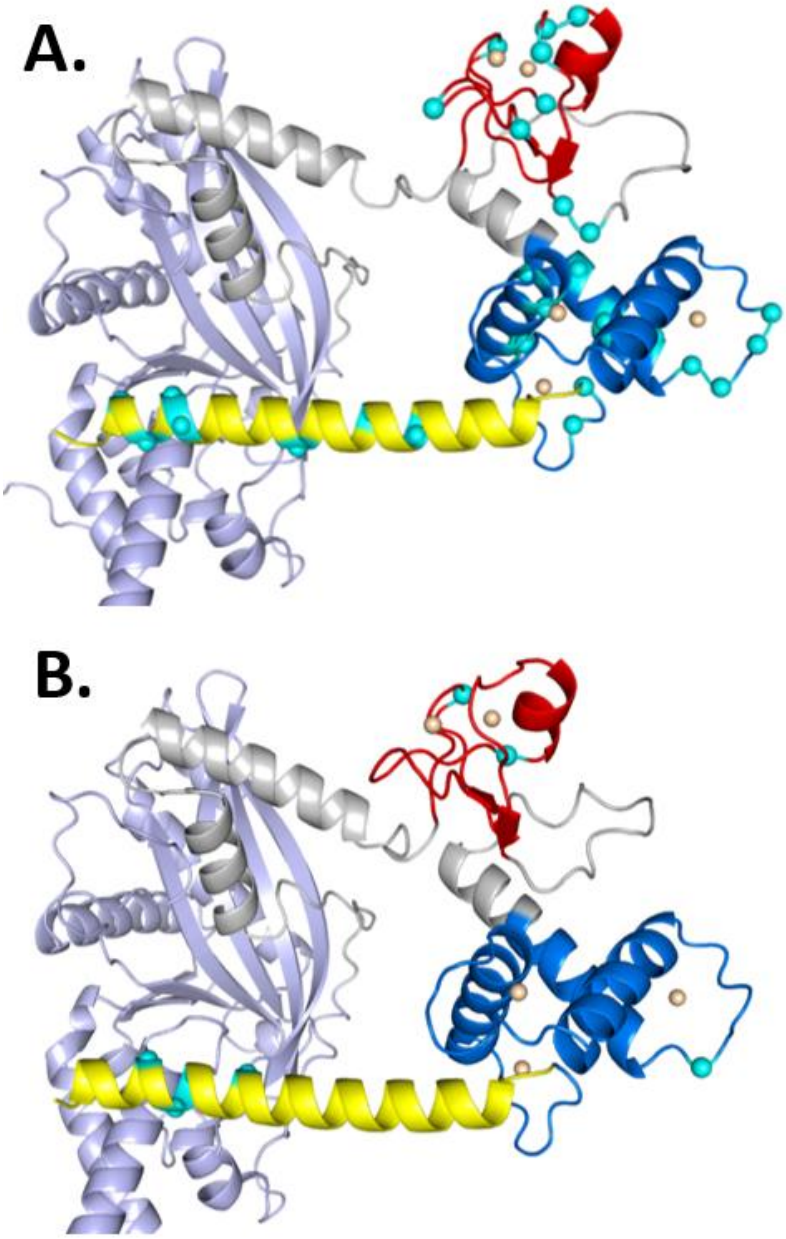

Figure 1. 3D predicted protein structures **A.** CBP, including HAT-domain (1342-1649; in purple), ZZ-domain (1705-1745; in red), TAZ2-domain (1772-1840; in blue) and first α-helix of ID4 (1842-1875; in yellow). Gray structures are not part of functional domain according to NCBI consensus. Cyan spheres represent residue variants, duplications and deletions not included. Orange spheres represent zinc ions. **B.** p300, including HAT-domain (1306-1612), ZZ-domain (1668-1708), TAZ2-domain (1735-1803) and first α-helix of ID4 (1806-1832).