BMJ Open

Protecting against brain damage by improving treatment in neonates with hypoglycaemia: ProBrain-D—a study protocol of a prospective longitudinal study

Henrike Hoermann [ID] , Marcia Roeper, Roschan Salimi Dafsari, Felix Koestner, Dominik Schneble, Dunja von Zezschwitz, Ertan Mayatepek, Sebastian Kummer, Thomas Meissner

Department of General Paediatrics, Neonatology and Paediatric Cardiology, Medical Faculty, University Hospital Düsseldorf, Heinrich-Heine-University, Düsseldorf, Germany

Correspondence to
Professor Thomas Meissner;
thomas.meissner@med.uni-duesseldorf.de

ABSTRACT

Introduction Although neonatal hypoglycaemia is the most common metabolic problem in neonates, there is no standard guideline for screening. Additionally, treatment of neonatal hypoglycaemia and glucose administration thresholds are discussed controversially. Severe hypoglycaemia can lead to brain damage, but data on the effects of mild hypoglycaemia on neurological development are limited. To our knowledge, this is the first prospective longitudinal cohort study to analyse if the implementation of a new diagnosis and treatment standard for neonatal hypoglycaemia may improve the outcome of neonates at risk for hypoglycaemia, especially concerning neurodevelopment. Furthermore, the acceptance and feasibility of the standard among different professional groups and parents are analysed.

Methods and analysis After implementation of a structured standard operating procedure (SOP), detailing preventive measures, blood glucose screening and neonatal hypoglycaemia treatment in a tertiary care hospital, 678 neonates ≥35+0 weeks of gestation will be recruited in a monocentric prospective cohort study. For comparison, 139 children born before the implementation of this new SOP, who had risk factors for neonatal hypoglycaemia or qualified for blood glucose measurements are recruited (retrospective cohort). For the primary end point, comparative analyses between and within the prospective and retrospective cohorts will be performed regarding the neurological outcome at 2–2.5 years of age in Bayley Scales of Infant Development. Furthermore, comprehensive clinical data and data on nutrition and developmental milestones are assessed at different time points (6 weeks, 6, 12, 18 and 24 months) in the prospective cohort. Acceptance and feasibility of the new standard are assessed using questionnaires.

Ethics and dissemination The study has been approved by the Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (20201162). The results of this study will be disseminated through peer-reviewed journals and presented at international conferences.

Trial registration number DRKS00024086.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective longitudinal cohort study analysing how the implementation of a new diagnosis and treatment standard improves the outcome of neonates at risk for hypoglycaemia.

⇒ The study analyses a large cohort, comprising a total of 817 children.

⇒ The longitudinal approach with regular assessments of developmental milestones and the standardised neurodevelopmental testing at the age of 2–2.5 years with Bayley Scales of Infant Development improve the informative value of the study.

⇒ A limitation of the study may be that sometimes mild neurodevelopmental delays can manifest at a later age and may not yet be detected at 2–2.5 years of age. However, this can be addressed by following the cohort longer into the future and re-examining at an older age.

INTRODUCTION

Neonatal hypoglycaemia is a common metabolic condition, affecting up to 15% of all newborns.[1] Several risk factors for neonatal hypoglycaemia are known, including small for gestational age (SGA), large for gestational age (LGA), maternal diabetes/gestational diabetes mellitus (GDM), prematurity, perinatal stress, etc.[1–3] Profound hypoglycaemia as commonly seen in children with persistent or transient congenital hyperinsulinism can lead to irreversible brain damage with severe developmental delay and epilepsy.[4–6] The extent to which mild hypoglycaemia affects neurodevelopment has been poorly studied and understood. Thus, a uniform treatment threshold and a standard for management of neonatal hypoglycaemia do not exist.[7]

van Kempen et al, who compared treatment thresholds of 36 mg/dL and 47 mg/

dL (2.0 mmol/L and 2.6 mmol/L) in neonatal hypoglycaemia, showed that psychomotor development at the age of 18 months did not differ between both groups.[8] McKinlay *et al* found no association between hypoglycaemia and adverse neurologic outcome in children aged 2 years;[9] however, they found an association of neonatal hypoglycaemia with an increased risk for poorer executive and visual motor function in children aged 4.5 years.[10] When the same cohort was re-examined at 9–10 years of age, the groups did not differ regarding the neurodevelopmental outcome. However, both groups showed concerningly high rates of poor performance across different measures.[11] Conversely, Kaiser *et al* showed an association of early transient neonatal hypoglycaemia and poorer academic performance at the age of 10 years.[12] It, therefore, remains to be clarified to what extent neonatal hypoglycaemia alone and risk factors such as, for example, maternal gestational diabetes, SGA and LGA themselves lead to developmental delay. Large population studies and meta-analyses have found that children of mothers with diabetes during pregnancy presented with lower school performance results[13] and children experiencing intrauterine growth restriction had worse cognitive outcomes.[14] However, these studies did not address abnormal development or cognitive impairment associated with hypoglycaemia that may have occurred.

There is no consistent international guideline for screening and management of neonatal hypoglycaemia.[15] However, there exist several national guidelines that have in common that they recommend a blood glucose screening for neonates with risk factors for hypoglycaemia or clinical signs of hypoglycaemia.[3 16 17] In Germany, there is only one published guideline that exclusively applies to infants born to diabetic mothers.[18] The lack of a consistent guideline leads to heterogeneity in treatment thresholds and management of neonatal hypoglycaemia,[19] potentially harming the child due to delayed or inadequate treatment.

Research hypotheses and aims

In March 2020, a new standard operating procedure (SOP) for diagnosis and treatment of neonatal hypoglycaemia was established at the University Children's Hospital Düsseldorf, Germany (figure 1). Before implementation of this new SOP, only neonates of mothers with diabetes/GDM received a blood glucose screening during the first hours of life. In neonates with other risk factors for hypoglycaemia, blood glucose was only measured on individual physician's order.

The overall goal is the development of a validated guideline for the management of neonatal hypoglycaemia that has been shown to balance the prevention of hypoglycaemia-related, even mild brain damage, with a minimum burden on neonates.

A critical aspect is to place the interventional threshold sensitive enough to avoid severe hypoglycaemia. Emphasis was placed on preventive measures such as keeping the neonate warm, early and supplemental feeding and the use of dextrose gel. If profound hypoglycaemia occurs, it should be treated fast and intense, meaning that the duration of the profound hypoglycaemic phase should be kept as short as possible to prevent brain damage. On the other hand, the burden of measures such as blood glucose monitoring or interventions to stabilise blood glucose levels should be kept as low as reasonably possible. Transfer to the neonatal unit and the separation of mother and child should be minimised.

After a comparative analysis of the previously published guidelines, the new SOP for neonatal hypoglycaemia was drafted and clinically tested for its feasibility for several months. During this process, a multiprofessional team of nurses, midwives, neonatologists, paediatric endocrinologists and obstetricians revised and improved it several times. The SOP is adapted from Figure 3 of the 'Swedish national guideline for prevention and treatment of neonatal hypoglycaemia in newborn infants with gestational age ≥35 weeks', Wackernagel *et al* Acta Paediatrica, 2019[16]; with the kind permission of John Wiley & Sons (2019 Foundation Acta Pædiatrica. Published by John Wiley & Sons). The SOP is structured as a flowchart and includes preventive measures, risk stratification and therapeutic measures. The treatment and escalation steps in the SOP intend to standardise and simplify physician orders. Deviations from this are possible on an individual basis depending on the severity of the disease and comorbidities of the child.

We decided to include dextrose gel to the preventive as well as the therapeutic measures of our SOP even though the use of dextrose gel especially as a preventive measure is controversial. Several studies have shown that dextrose gel reduces the need for intravenous dextrose, intravenous fluids, admission to neonatal intensive care unit and increases breast feeding.[20–22] Edwards *et al* recently stated that 'oral dextrose gel is probably an effective and safe first-line treatment for infants with neonatal hypoglycaemia in high-income settings'.[23] However, the use of 'prophylactic oral dextrose gel at 1 hour of age compared with placebo showed no significant difference in the risk of neurosensory impairment at 2 years' corrected age'.[24] Further long-term follow-up studies are required to evaluate the effect of preventive dextrose gel for infants with risk factors for neonatal hypoglycaemia on neurodevelopmental outcome. In our clinical setting, early breast feeding and supplemental feeding in neonates at risks are the preferred preventive measures and dextrose gel is mainly used in case of hypoglycaemia or if the child is not drinking well.

Our SOP includes the off-label use of continuous subcutaneous glucagon infusion for hypoglycaemia treatment. Continuous glucagon therapy is frequently used for the treatment of persistent hypoglycaemia in children with congenital hyperinsulinism and may reduce the need of high volumes of dextrose infusion.[25] However, a recently published meta-analysis by Walsh *et al* who included studies with intravenous administered glucagon showed that the efficiency and safety of glucagon for the treatment

Diagnosis and Treatment Standard for Neonatal Hypoglycaemia (≥35+0 weeks of gestation)
University Children's Hospital Düsseldorf

For all neonates within the first 30 minutes of life

Prevention + **Risk assessment** + **Symptom assessment**

Prevention
- Keep neonate warm (≥36.5 °C)
- Safe skin-to-skin care
- Breastfeed neonate postnatally (then every 2-3 h, watch for signs of hunger)
- Formula feeding in case of breastfeeding problems or separation of mother and child: if possible, with cup or spoon. If mother is not aiming to breastfeed: bottle feeding.

Neonates at-risk
- Prematurity (<37+0 weeks)
- SGA or LGA (see weight table)
- Infants of diabetic mothers
- Infants of mothers with GDM
- According to a physician's order in case of perinatal stress (e.g. vacuum/forceps delivery, secondary caesarean section, pathological CTG, respiratory distress, APGAR <5 etc.)

Symptoms
- Trembling
- Hypotonia/lethargy
- Insufficient feeding
- Shrill crying
- Hypothermia (<36.5 °C)
- Cyanosis/paleness
- Apnoea/tachypnoea
- Irritability
- Bradycardia/tachycardia
- Seizures

Supplemental feeding* for neonates at risk after breastfeeding.
Except for:
- LGA without maternal diabetes/GDM
- Adequate birth weight and diet-controlled maternal diabetes/GDM
- Preterm infants (36+0 – 36+6 weeks of gestation)

*Suppl. feeding: First day of life: 10-20 ml formula-nutrition every 2-3h; stepwise increase afterwards

Prevention
Early breastfeeding and suppl. feeds* or dextrose gel within 1 h

Blood glucose measurement
Before the 2nd feed (at the latest in the 3rd hour of life)

Immediate blood glucose measurement

Blood glucose (BG) measurements

<30 mg/dl (<1.7 mmol/l) or <45 mg/dl (<2.5 mmol/l) and severe symptoms like apnea, seizures, unconsciousness etc.	**30 - 45 mg/dl** (1.7-2.5 mmol/l)	**46 - 54 mg/dl** (2.6-3.0 mmol/l)	**≥55 mg/dl** (≥3.1 mmol/l)
1. Dextrose gel 2. Inform pediatrician immediately 3. IV-line and glucose bolus 4. IV-glucose: Step I 5. Suppl. feed* 6. Continue breastfeeding *Caution: If IV-line is not possible, a glucagon bolus of 250 µg SC should be considered.*	1. Dextrose gel 2. Intensify breastfeeding/suppl. feeds* **Exception: 3 x BG ≤45 mg/dl (≤2.5 mmol/l)** within 24 h → Inform pediatrician → IV-glucose: Step I	1. Feed at least every 2-3 h 2. In case of insufficient feeding, give dextrose gel afterwards	1. Feed at least every 2-3 h
BG after 30 min	**BG after 1 h**	**BG before next feed**	**BG before every feed (SGA every 2nd)**

--- Escalate 1 step if BG is 1x red/orange or 2x consecutive yellow ---

Treatment	Bolus	Step I	Step II	Step III	Step IV	Step V	Step VI
				Additional:	**Glucagon SC**	*Central line!*	*Central line!*
Medication Dose Infusion rate	G10% 2 ml/kg	G10% 5 mg/kg/min =3 ml/kg/h *(Caution: electrolytes)*	G10% 6.7 mg/kg/min =4 ml/kg/h *(Caution: electrolytes)*	**Glucagon SC** 1 mg ad 25 ml NaCl 0.9% 1.0 ml/h	Increase by 0.2-0.4 ml/h up to a maximum infusion rate of 2 ml/h	Continue **Glucagon** **+ G20%** 10 mg/kg/min = 3 ml/kg/h	Stepwise increase glucose infusion until stabilization of BG values.
De-escalation: if BG is ≥55 mg/dl (≥3.1 mmol/l) in 2 consecutive measurements prior to feeding (age <72 h) or 2 x ≥65 mg/dl (≥3.6 mmol/l) (age >72 h). Stepwise reduction of glucose infusion rate by 1-3 ml/h or glucagon infusion rate by 0.2 ml/h.							

Dextrose Gel
Conc.: 400 mg/mL
Dose: 0.5 mL/kg

Dry the inside of the baby's cheek. Massage the gel in the buccal mucosa.

Dose
- 2.0 kg → 1.0 ml
- 2.5 kg → 1.25 ml
- 3.0 kg → 1.5 ml
- 3.5 kg → 1.75 ml
- 4.0 kg → 2.0 ml
- 4.5 kg → 2.25 ml
- 5.0 kg → 2.5 ml

Infusion management
age <48h: G10%
age ≥48h: G10% + electrolytes (NaCl, KCl) both: ~ 2-3 mmol/kg/d
≈ 5 ml NaCl 20%/500 ml
≈ 10 ml KCl 7.45%/500 ml

Check electrolytes every 1-2 days.

Caution: hyperhydration, limited diuresis.

SGA / LGA ** weight table**

weeks	SGA (♂/♀)	LGA (♂/♀)
37+	< 2530 / 2420g	> 3670 / 3540g
38+	< 2750 / 2630g	> 3870 / 3720g
39+	< 2930 / 2810g	> 4040 / 3878g
40+	< 3060 / 2930g	> 4190 / 4010g
41+	< 3160 / 3030g	> 4310 / 4130g

** SGA (birth weight <10th percentile)
LGA (birth weight >90th percentile)
Caution: only approximate values are displayed.

End of BG measurements:
1. Neonates at-risk without BG ≤45 mg/dl (≤2.5 mmol/l):
- LGA, infants of diabetic mothers: after 12 h
- SGA, preterm infants: after 36 h
  only if: feeding is successful + BG before last feed ≥55 mg/dl (≥3.1 mmol/l)
2. BG ≤45 mg/dl (≤2.5 mmol/l) at least once
- 2 consecutive BG in range (age <72 h: ≥55 mg/dl (≥3.1 mmol/l); age >72 h: ≥65mg/dl (≥3.6 mmol/l))
3. Therapy was ≥ step III or ≥ step I for >48 h: 'safety fast' (at least for 6 h) prior to discharge
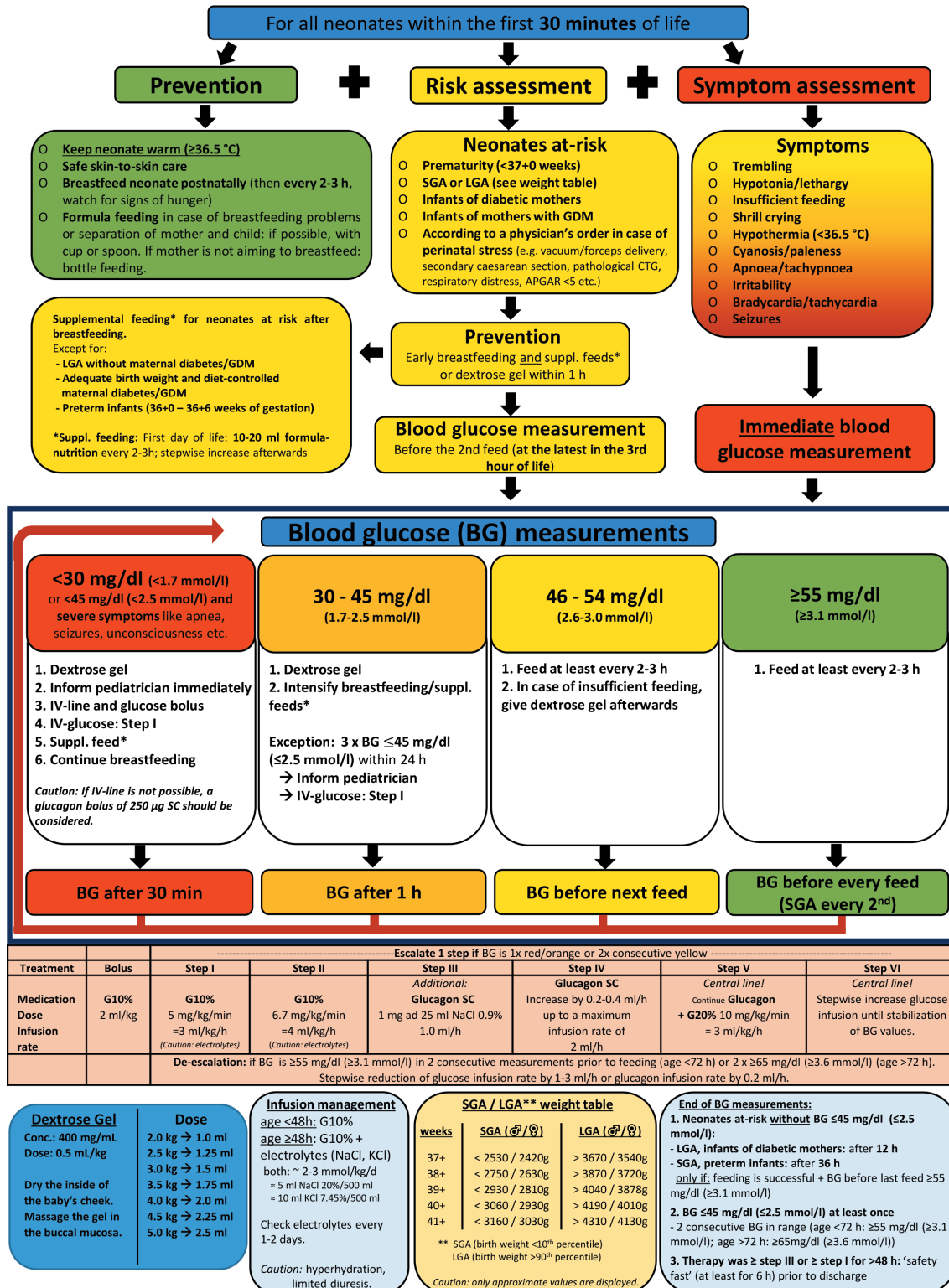
Figure 1 Diagnosis and treatment standard for neonatal hypoglycaemia (≥35+0 weeks of gestation). BG, blood glucose; CTG, cardiotocography; G10%, Glucose 10%; G20%, Glucose 20%; GDM, gestational diabetes mellitus; IV, intravenous; KCl, potassium chloride; LGA, large for gestational age; NaCl, sodium chloride; SC, subcutaneous; SGA, small for gestational age. This figure is adapted from Figure 3 of the 'Swedish national guideline for prevention and treatment of neonatal hypoglycaemia in newborn infants with gestational age ≥35 weeks', Wackernagel D, Gustafsson A, Edstedt Bonamy AK, et al. Acta Paediatrica, 2019[16]; with the kind permission of John Wiley & Sons Ltd. (©2019 Foundation Acta Pædiatrica. Published by John Wiley & Sons Ltd.).

of neonatal hypoglycaemia are still not fully elucidated as high-quality randomised studies are lacking.[26] Still, to avoid fluid overload and the need for a central line, we have decided to use continuous subcutaneous glucagon early in the treatment of persistent hypoglycaemia based on our extensive clinical experience in the treatment of children with congenital hyperinsulinism.

The duration of the blood glucose measurements depends on the respective risk factors and are described in detail on the flowchart.

We hypothesise that neonates with hypoglycaemia/risk factors for hypoglycaemia who are screened and treated according to the new SOP will perform better in neurodevelopmental tests at 2 years of age, compared with infants with neonatal hypoglycaemia/risk factors for hypoglycaemia who were not screened or treated according to the new SOP (superiority). Furthermore, we hypothesise that within our prospective study cohort, neonates who suffer from hypoglycaemia but are treated according to the new SOP have no impairments in long-term neurological development compared with neonates without hypoglycaemia (non-inferiority).

In addition, several exploratory secondary end points will be evaluated, including comprehensive analyses of the occurrence and duration of neonatal hypoglycaemia in relation to nutritional intake as well as alternative energy sources such as β-hydroxybutyrate. Management of hypoglycaemia is analysed in detail, including the rate and duration of transfer to the neonatal unit due to hypoglycaemia. Furthermore, the acceptance and feasibility of the new standard are evaluated by anonymous questionnaires for parents and healthcare employees.

METHODS AND ANALYSIS
Study design
The ProBrain-D study is a monocentric prospective longitudinal clinical cohort study. Enrolment of study participants commenced on 18 March 2021. The last follow-up at 2 years of age is scheduled for 31 July 2024.

Inclusion and exclusion criteria
Neonates screened and treated according to the new SOP (prospective cohort): neonates with at least one risk factor for neonatal hypoglycaemia (maternal diabetes, maternal GDM, SGA or LGA (birth weight <10th or >90th percentile, calculated according to Voigt *et al*[27]), perinatal stress (diagnosed by the responsible physician, eg, in case of vacuum extraction, forceps delivery or pathological cardiotocography), 5 min Apgar-score <5, secondary caesarean section, respiratory distress, 35+0 to 36+6 weeks gestational age) are recruited prenatally or postnatally. Written informed consent is obtained from both parents. Neonates without known risk factors for hypoglycaemia but who had blood glucose measurements, for example, because of clinical signs of hypoglycaemia during the first days of life, are recruited postnatally.

Neonates born before the implementation of the SOP (retrospective cohort): children who are 2–2.5 years old at the time of recruitment, and either had one or more risk factors for neonatal hypoglycaemia (see list of risk factors above) or had at least one plasma glucose level ≤45 mg/dL (≤2.5 mmol/L) during the first days of life. Whether a child meets the inclusion criteria is assessed by retrospective medical chart review. Parents are informed of the study by telephone, e-mail, or letter. Written informed consent is obtained before inclusion.

Exclusion criteria (prospective and retrospective cohort) are lack of written parental consent and birth before 35+0 weeks of gestation. For the analysis of the primary endpoint, all children are excluded who have any known cause of developmental delay unrelated to blood glucose values.

Study size
Sample sizes were calculated using G*Power.[28] To assess whether the management in the prospective cohort improves the neurological outcome compared with the retrospective cohort, we calculated that with 139 children in each group the study has 80% power to show superiority (Bayley Scales of Infant and Toddler Development-Third Edition; BAYLEY-III scores cross the prespecified limit of 5 points (=1/3 of the SD of 15 of the normative value (100±15))), at a one-sided alpha level of 0.05.

To prove non-inferiority (BAYLEY-III scores do not cross the prespecified limit of −5 points (=minus 1/3 of the SD of 15 of the normative value (100±15))) of neonates with and without hypoglycaemia regarding neurological development within the prospective cohort, we calculated that with 242 children in each group the study will have 95% power at a one-sided alpha level of 0.05. With an expected drop-out rate of 25% in the prospective cohort, a total sample size of 678 children was calculated.

No sample size calculation was performed for the exploratory assessment of acceptability and feasibility of the new standard. The aim is to obtain 25 questionnaires from each professional group (midwives, nurses, physicians) and a total of 100 questionnaires from parents.

Data sources and measurements
Figure 2 shows an overview of data collection for the prospective and retrospective cohort at designated time points.

Prospective cohort
The prospective cohort receives a blood glucose screening and if applicable treatment measures according to the new SOP. Blood glucose is measured using a StatStrip Glucose Meter (Nova Biomedical, Waltham, Massachusetts) as this is the standard point-of-care device in the clinical routine in our hospital. Clinical data are obtained from the medical files, including blood glucose values, blood glucose in arterial cord blood, treatment measures, etc. β-hydroxybutyrate is intended to be determined at each blood glucose measurement using a StatStrip
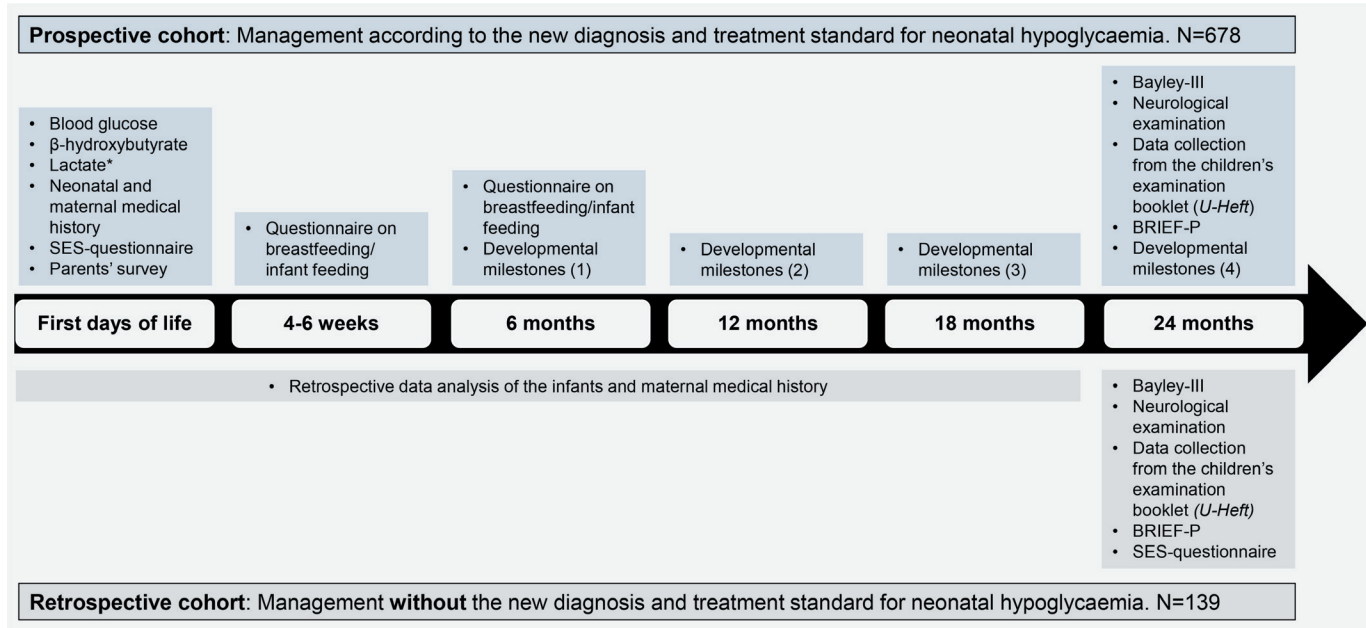
Figure 2 Overview of data collection at defined time points for the prospective and retrospective study cohort. BRIEF-P, Behaviour Rating Inventory of Executive Function-Preschool Version; N, number; SES, socioeconomic status. *Only in case of blood gas analysis in clinical routine.

Ketone Meter (Nova Biomedical, Waltham, Massachusetts). If a blood gas analysis is performed based on a clinical indication, the lactate level is also analysed. In case of prenatal inclusion of the participants in the study, insulin is determined in arterial cord blood after cord clamping.

During the postpartum inpatient stay, parents fill out an anonymous questionnaire regarding their perspective on the management concept (online supplemental figure 1).

Data on breastfeeding or formula feeding are obtained from parents at 4–6 weeks and 6 months of age by telephone survey (online supplemental figure 2). Furthermore, developmental milestones are assessed by telephone interview at 6, 12, 18 and 24 months of age (online supplemental figure 3).

Prospective and retrospective cohort

At 2–2.5 years of age, the German version of the Bayley-III (NCS Pearson, 2014) is used to assess developmental functioning.[29 30] The Bayley-III is conducted by trained members of the study team who are blinded to the child's medical history. Furthermore, an evaluative neurological examination is performed blinded by a study physician, and information on any neurological or developmental abnormalities, current medical history, number of siblings, languages spoken with the child and daily care are surveyed. Any abnormalities documented in the children's examination booklet (German *U-Heft*) are collected. The Behaviour Rating Inventory of Executive Function-Preschool questionnaire[31] is filled out by the parents to assess executive functioning. Parental socio-economic status (SES) is measured according to Lampert *et al* and is based on information about education, occupational status and income.[32]

The acceptance and feasibility of the standard among healthcare professionals are evaluated using anonymous questionnaires completed by nurses, midwives and physicians (online supplemental figures 4 and 5)

Primary endpoint

Neurological outcome in Bayley Scales of Infant Development[29 30] at 2–2.5 years of age.

Secondary endpoints

1. Blood glucose
   – Number of measurements.
   – Number and timing of hypoglycaemic episodes.
   – Duration of hypoglycaemia (from time of detection to blood glucose value in target range).
   – Number of severe hypoglycaemia <30 mg/dL (<1.7 mmol/L) despite treatment.
   – Number of rebound hypoglycaemia (hypoglycaemia within 6 hours after initial correction).
   – Age at last routine blood glucose measurement.
2. Hypoglycaemia therapy/nutrition
   – Number/duration of different treatment interventions (dextrose gel, glucagon, intravenous glucose, nutrition) according to the treatment standard.
   – Average duration of therapy.
   – Average increase in blood glucose after intervention according to the standard of care until next measurement.
   – Percentage of fully breastfed infants (at discharge, after 4–6 weeks, at 6 months of age).
   – Nutritional intake in the first days of life (volume and frequency of administration of breast milk, formula, intravenous glucose, dextrose gel).

- Correlation of β-hydroxybutyrate/lactate concentration and form plus quantity of nutrition (breast milk vs formula).
- Transfer rate to neonatal unit due to hypoglycaemia treatment and duration.
3. Incidences of risk factors for neonatal hypoglycaemia.
4. Correlation between maternal haemoglobin A1c level (if known) and incidence of neonatal hypoglycaemia.
5. Correlation and postnatal course of blood glucose levels, β-hydroxybutyrate and lactate concentrations.
6. Number of patients with suspected transient hyperinsulinism.
7. Neurological development
   - Correlation of number, duration and severity of hypoglycaemia and delayed achievement of developmental milestones.
   - Occurrence of seizures.
   - Correlation of blood glucose, β-hydroxybutyrate and lactate concentration with the occurrence of seizures, abnormalities in magnetic resonance imaging or electroencephalography visual disturbances at the age of 2 years, hearing disorders at the age of 2 years, cerebral palsy at the age of 2 years, developmental delay at the age of 2 years, disorder of executive function at the age of 2 years, behavioural problems/disorders at the age of 2 years.
8. Acceptance and feasibility of the new diagnosis and treatment standard for hypoglycaemia.
9. Parents' opinion about the procedures carried out within the standard—feeling of safety vs additional worries.

Statistical analysis plan
IBM SPSS Statistics V.25.0 (IBM, Armonk, New York) will be used for statistical analyses. For group analyses, data will be tested for normal distribution and depending on the results appropriate tests such as student's t test, ANOVA (analysis of variance), Mann-Whitney U test or Kruskal-Wallis test will be applied with post hoc correction, if necessary. For the comparison of categorical data, χ^2 test and Fisher's exact test will be used. For comparison of continuous variables, Spearman or Pearson correlation or regression analysis will be performed when applicable. For comparison of the retrospective and prospective cohort, matching of groups by SES, sex, risk factor for neonatal hypoglycaemia, if any, and presence of older siblings will be conducted.

Quality assurance of data collection, storage and management
Data collection is based on specified variables in a database created for the study with FileMaker Pro V.19 (Claris, Santa Clara, California). It is stored pseudonymised on a password-protected file on a secure server at the University Hospital Düsseldorf. Only authorised members of the study group have access to the data.

Patient and public involvement
Patients/parents and public were not involved in the design of the study.

Ethics and dissemination
The study protocol was approved by the Ethics Committee of the Medical Faculty of the Heinrich-Heine-University Düsseldorf (20201162) according to the Declaration of Helsinki. The study is registered in the German Clinical Trials Register; date of registration: 15 January 2021. Results will be published in peer-reviewed journals and presented at conferences. Anonymised raw data may be shared after completion of the study on reasonable request.

Summary
Even though neonatal hypoglycaemia is a common metabolic condition, treatment thresholds and screening recommendations are inconsistent across guidelines. Furthermore, only limited reliable evidence is available concerning the neurodevelopmental outcome after neonatal hypoglycaemia. This is the first prospective longitudinal cohort study to systematically evaluate a diagnostic and treatment standard for neonatal hypoglycaemia with a focus on neurodevelopmental outcome. This study extends our knowledge of the effects of neonatal hypoglycaemia on brain function. It also provides a guideline that is not only based on expert opinion but has also been evaluated for its feasibility and potential to balance risk and benefit to standardise and improve the care of neonates with hypoglycaemia in the future.

of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iD
Henrike Hoermann http://orcid.org/0000-0001-6596-0633

REFERENCES

1 Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. *J Pediatr* 2012;161:787–91.
2 Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. *Pediatrics* 1971;47:831–8.
3 Narvey MR, Marks SD. The screening and management of newborns at risk for low blood glucose. *Paediatr Child Health* 2019;24:536–54.
4 Avatapalle HB, Banerjee I, Shah S, *et al*. Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism. *Front Endocrinol* 2013;4:60.
5 Roeper M, Salimi Dafsari R, Hoermann H, *et al*. Risk factors for adverse neurodevelopment in transient or persistent congenital hyperinsulinism. *Front Endocrinol* 2020;11:580642.
6 Helleskov A, Melikyan M, Globa E, *et al*. Both low blood glucose and insufficient treatment confer risk of neurodevelopmental impairment in congenital hyperinsulinism: a multinational cohort study. *Front Endocrinol* 2017;8:156.
7 Shah R, Harding J, Brown J, *et al*. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. *Neonatology* 2019;115:116–26.
8 van Kempen AAMW, Eskes PF, Nuytemans DHGM, *et al*. Lower versus traditional treatment threshold for neonatal hypoglycemia. *N Engl J Med* 2020;382:534–44.
9 McKinlay CJD, Alsweiler JM, Ansell JM, *et al*. Neonatal glycemia and neurodevelopmental outcomes at 2 years. *N Engl J Med* 2015;373:1507–18.
10 McKinlay CJD, Alsweiler JM, Anstice NS, *et al*. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. *JAMA Pediatr* 2017;171:972–83.
11 Shah R, Dai DWT, Alsweiler JM, *et al*. Association of neonatal hypoglycemia with academic performance in Mid-Childhood. *JAMA* 2022;327:1158–70.
12 Kaiser JR, Bai S, Gibson N, *et al*. Association between transient newborn hypoglycemia and Fourth-Grade achievement test proficiency: a population-based study. *JAMA Pediatr* 2015;169:913–21.
13 Dahlquist G, Källén B. School marks for Swedish children whose mothers had diabetes during pregnancy: a population-based study. *Diabetologia* 2007;50:1826–31.
14 Sacchi C, Marino C, Nosarti C, *et al*. Association of intrauterine growth restriction and small for gestational age status with childhood cognitive outcomes: a systematic review and meta-analysis. *JAMA Pediatr* 2020;174:772–81.
15 Casertano A, Rossi A, Fecarotta S, *et al*. An overview of hypoglycemia in children including a comprehensive practical diagnostic flowchart for clinical use. *Front Endocrinol* 2021;12:684011.
16 Wackernagel D, Gustafsson A, Edstedt Bonamy A-K, *et al*. Swedish national guideline for prevention and treatment of neonatal hypoglycaemia in newborn infants with gestational age ≥35 weeks. *Acta Paediatr* 2020;109:31–44.
17 Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics* 2011;127:575–9.
18 Segerer H, Bührer C, Kapellen T. Betreuung von Neugeborenen diabetischer Mütter. Leitlinie Der GNPI, DGPM, DDG, DGHWi, dem DHV, Der DGKJ und DGGG. *Z Geburtshilfe Neonatol* 2018;222:107–14.
19 Roeper M, Salimi Dafsari R, Hoermann H, *et al*. Clinical management and knowledge of neonatal hypoglycaemia in Germany: a national survey of midwives and nurses. *J Paediatr Child Health* 2021;57:854-859.
20 Gupta K, Amboiram P, Balakrishnan U, *et al*. Dextrose gel for neonates at risk with asymptomatic hypoglycemia: a randomized clinical trial. *Pediatrics* 2022;149. doi:10.1542/peds.2021-050733. [Epub ahead of print: 01 06 2022].
21 Rawat M, Chandrasekharan P, Turkovich S, *et al*. Oral dextrose gel reduces the need for intravenous dextrose therapy in neonatal hypoglycemia. *Biomed Hub* 2016;1:1–9.
22 Harris DL, Weston PJ, Signal M, *et al*. Dextrose gel for neonatal hypoglycaemia (the sugar babies study): a randomised, double-blind, placebo-controlled trial. *Lancet* 2013;382:2077–83.
23 Edwards T, Liu G, Battin M, *et al*. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. *Cochrane Database Syst Rev* 2022;3:Cd011027.
24 Edwards T, Alsweiler JM, Crowther CA, *et al*. Prophylactic oral dextrose gel and neurosensory impairment at 2-year follow-up of participants in the hPOD randomized trial. *JAMA* 2022;327:1149–57.
25 Salomon-Estebanez M, Yau D, Dunne MJ, *et al*. Efficacy of dose-titrated glucagon infusions in the management of congenital hyperinsulinism: a case series. *Front Endocrinol* 2020;11:441.
26 Walsh EPG, Alsweiler JM, Ardern J, *et al*. Glucagon for neonatal hypoglycaemia: systematic review and meta-analysis. *Neonatology* 2022;119:285–94.
27 Voigt M, Fusch C, Olbertz D. Analysis of the neonatal collective in the federal Republic of Germany12th report: presentation of detailed Percentiles for the body Measurementof newborns. *Geburtshilfe Frauenheilkd* 2006;66:956–70.
28 Faul F, Erdfelder E, Lang A-G, *et al*. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods* 2007;39:175–91.
29 Bayley N. *The Bayley scales of infant and toddler development*. 3rd ed. San Antonio: TX: Harcourt Assessment, Inc, 2006.
30 Reuner G, Rosenkranz J. *Deutschsprachige Version des Bayley Scales of Infant and Toddler Developemt*. 3rd ed. von Nancy Bayley NCS Pearson, Inc, 2014.
31 Daseking M, Petermann F. *Verhaltensinventar zur Beurteilung exekutiver Funktionen für das Kindergartenalter (BRIEF-P). Deutschsprachige Adaptation des Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P) von Gerard A. Gioia, Kimberly Andrews Espy und Peter K. Isquith*. Bern: Verlag Hans Huber, 2013.
32 Lampert T, Hoebel J, Kuntz B. *Messung des sozioökonomischen status und des subjektiven sozialen status in KiGGS Welle 2: Robert Koch-Institut, Epidemiologie und Gesundheitsberichterstattung*, 2018.