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Early biomarkers of neurodevelopmental disorders in preterm infants: protocol for a longitudinal cohort study

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ABSTRACT

Introduction Preterm (PT) infants are at high likelihood for poor neurodevelopmental outcomes, including autism spectrum disorder (ASD), attention-deficit hyperactivity disorder (ADHD) and other neurodevelopmental disorders (NDDs), which could considerably impair the individuals' functions throughout their whole life. The current cohort study aims to investigate adverse outcomes, especially NDDs, in PT children, and the related early aberrant brain developmental biomarkers.

Methods and analysis This is a prospective cohort study in Beijing, China. We plan to recruit 400 PT infants born at <37 weeks of gestational age (GA), and 200 full-term (FT) controls during the neonatal period (40 weeks corrected GA), then follow them up until they reach 6 years of age. This cohort is designed to assess neuropsychological functions, brain development, related environmental risk factors and the incidence of NDDs by using the following measures: (1) social, emotional, cognitive and sensorimotor functions; (2) MRI, electroencephalogram and functional near-infrared spectroscopy; (3) social economic status, maternal mental health and DNA methylation; and (4) symptoms and diagnosis of NDDs. Main data analyses will include comparing the neurodevelopment outcomes and brain developmental trajectories between PT and FT children using linear or logistic regressions and mixed-effects models. Regression analyses and machine learning will be used to identify early biological predictors and environmental risk or protective factors for later NDDs outcomes.

Ethics and dissemination Ethical approval has been obtained from the research ethics committee of Peking University Third Hospital (M2021087). This study is under review in the Chinese Clinical Trial Register. The study results from the current cohort will be disseminated and popularised through social media to participating parents, as well as parents who are giving care to PT children.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Four hundred preterm (PT) infants and 200 full-term infants are being intensively followed for the first 6 years.
⇒ The current cohort evaluates diagnoses and symptom levels of all neurodevelopmental disorders defined by the Diagnostic Statistical Manual Fifth Edition since the very early life stages leveraging gold standard psychiatric interviews and widely accepted questionnaires.
⇒ The current cohort studies the developmental trajectories of PT children in multiple dimensions, including behavioural phenotypic information, biological manifestations and environmental factors.
⇒ Participants will be recruited and followed at only one site located in a metropolis, which might cause bias in terms of demographic characteristics.
⇒ Most assessments require offline participation, which might be inconvenient and could result in dropouts and missing data.

INTRODUCTION

Newborns with a gestational age (GA) of less than 37 weeks are considered as preterm (PT). According to the WHO, the PT birth rate has reached 10% worldwide, with nearly 15 million PT babies are born each year worldwide, and this number is still rising.[1] Currently, although modern medicine has enabled more PT infants to survive at low GA and weight, long-term neurodevelopmental outcomes of PT infants still have not improved, with PT birth remaining a strong risk factor for neurodevelopmental disorders (NDDs).[2–6]

NDDs are a group of early-onset disorders with high prevalence and usually long courses, including attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), intellectual disability, communication disorder, specific learning disorder and motor disorder.[7] PT children have an elevated likelihood for NDDs. The likelihood of developing ASD and ADHD was much higher in PT than in FT children, with prevalence of 6% versus 1% and 12.7% versus 5.9%, respectively.[8–11] This likelihood tends to increase with the GA decrease. PT individuals also present worse cognitive performance than their FT counterparts, including poorer attention and lower IQ, from childhood to adulthood.[12 13]

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As has been demonstrated, early exposure to the extrauterine environment significantly affects the early neurodevelopment process, which might be the biological substrates and indicators for later poor neurodevelopmental outcomes and could aid in early diagnosis.[3 14–18] On the other hand, individuals with NDDs often present biological abnormalities since the fetal stage, including abnormalities in the proliferation of neural progenitor cells, neuron generation and synapse formation, which have been found to be interrupted in PT infants and could ultimately lead to brain morphological and functional aberrations, such as the imbalance between excitatory and inhibitory functions.[19] Previous studies have reported that vulnerabilities associated with the stage of brain development in PT children might be the neural substrate of poor neurodevelopmental outcomes, mainly caused by disrupted synaptogenesis and myelination.[20 21]

Currently, longitudinal cohorts focusing on brain development in PT children have been established, including the LaPrem,[22] the Theirworld Edinburgh birth cohort,[23] the PREBO cohort,[24] the ePrime cohort and so on. On the other hand, researchers established prospective birth cohorts among infants with a family history of ASD including the autism Baby Siblings Research Consortium (BSRC),[25] Genome, Environment, Microbiome and Metabolome in Autism (GEMMA) study,[26] European autism interventions–a multicentre study for developing new medications (EU-AIMS)[27] and additional examples.

Despite the progress made by these cohorts, most of them are enrolled in Western countries and few have focused on the outcomes of NDDs in PT children.

Currently, the absence of early diagnostic tools for infants makes early intervention challenging. Establishing a longitudinal follow-up cohort to further delineate the trajectory of PT development, explore the relationships between aberrant brain development and NDDs and identify early modifiable risk factors would not only be beneficial in understanding the biological process underlying NDDs, but also shedding light on early diagnosis and intervention.

Therefore, the aims of this study are fourfold: (1) to provide a comprehensive and overall picture of early life development in PT children by comparing the developmental trajectories of neuropsychological functions (including social, emotional, cognitive and sensorimotor functions) and brain development (using MRI, electroencephalogram (EEG) and functional near-infrared spectroscopy (fNIRS)) from birth to 6 years old between PT and FT children; (2) to evaluate the outcomes of NDDs from 18 months to 6 years old, examine the differences between FT and PT children; (3) to explore the relationships between NDDs and early neuropsychological functions, brain development to identify early biomarkers for NDDs; and (4) to identify the patterns in which early life environmental factors affect neurodevelopment, including parental mental health, social economic status and breast feeding.

METHODS AND ANALYSES

Study design and setting

This study is a prospective longitudinal cohort study that examines the neuropsychological and brain development in PT children from birth to 6 years old. The current work was designed following the guidelines of STROBE.[28]

The current study was conducted at the Peking University Third Hospital and the Peking University Sixth hospital. Both sites locate in Beijing, China. The Children's Healthcare Center at the Third Hospital serves over 10 000 children per annum, with more than 8000 children currently under follow-up.

All the procedures, including participants recruitment, follow-up and the assessments will take place at the Children's Healthcare Center at the Peking University Third Hospital. The assessments of NDDs diagnosis will be carried out by professional licensed psychiatric doctors from the Peking University Sixth Hospital. Recruitment begun in August 2021 and is expected to be completed in December 2025. Follow-up visits will continue until December 2031.

Study participants

Inclusion criteria

The current study aims to recruit 400 PT infants (GA <37 weeks) and 200 full-term (FT) infants (GA >37 weeks).

Exclusion criteria

1. Congenital anomalies: (a) cerebral haemorrhage, periventricular leukomalacia, hypoxic ischaemic encephalopathy and brain structural defects; (b) pulmonary disease or bronchopulmonary dysplasia; (c) ventricular haemorrhage; (d) congenital malformations; (e) chromosomal abnormalities; (f) pia or ventricular surface abnormalities; (g) necrotising enterocolitis and complex feeding/nutritional disorders; (h) hearing or visual impairment; and (i) epilepsy.
2. Infants with contraindications to MRI.
3. FT control infants are additionally required to have no history and no first-degree relative with a diagnosis of NDDs.

Sample size

To ensure adequate statistical power, we estimated the sample size according to previous relevant studies. Sample estimation was completed by PASS 2021, with an alpha of 0.05, (1-beta of 0.90 and a follow-up rate of 80%.

1. The primary outcome is the different occurrences of NDDs between PT and FT infants. Previous studies have shown that the prevalence of ASD and ADHD was about 6% and 12.7% in PT infants, compared with 1.5% and 5.9% in the general population.[8 9 11 29] To observe a significant difference in incidence between the two groups, a minimum sample size of 59:30 and 89:45 would be required.
2. The secondary outcome is the development of neuropsychological functions among PT children. Previous findings have demonstrated neurodevelopmental de-

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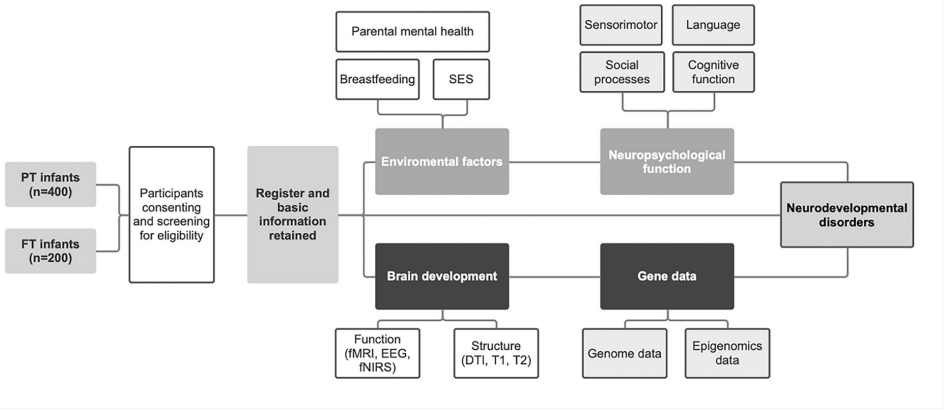

Figure 1 Flow chart of recruitment and follow-up procedure. EEG, electroencephalogram; fNIRS, functional near-infrared spectroscopy; FT, full term; PT, preterm; SES, social economic status.

lay in PT children. According to the results reported by Olsen *et al* 2022, a sufficient sample size would be 126:32, 74:38 and 42:22 in social–emotional, cognitive and language development, respectively.[30]

3. The development trajectories of the brain are also a main focus of the study. According to total brain volume changes during the first year of life in ASD and non-ASD children reported by Hazlett *et al* 2017, a minimum of 20 subjects with ASD are needed to obtain statistically significant results.[31] The required number of premature infants was ASD cases (20)/incidence (7%)/insurance factor (0.8)=357.
4. As the current study is a multidimensional cohort study that investigates the outcomes at multiple time points, it is challenging to estimate an accurate sample size for building diagnostic models as well as examining complex non-linear relationships between multidimensional data.[23] Therefore, we enlarged the sample size to 600, including 400 PT infants and 200 FT infants, in hope to provide sufficient data for multimodal integrative analysis.

Sample recruitment and procedure

The details of recruitment and study process are shown in figure 1. Participants recruitment take place in Peking University Third Hospital, using two methods: (1) mothers who deliver in the Department of Obstetrics will be enrolled after or before birth; and (2) PT and FT infants who visit the Healthcare Center at 40 weeks (±2 weeks) will be recruited as well. Research coordinators will provide eligible parents with a pamphlet containing all necessary information about the study, and will introduce the cohort to them face-to-face. All participants will be recruited only after fully informed and written consents retained.

The Children's Healthcare Center of Peking University Third Hospital provides primary care on a regular schedule, which was formulated in accordance with the Chinese follow-up guidelines for PT infants (http://www.nhc.gov.cn/fys/mrgzdt/). According to the schedule, infants receive check-ups once a month before the age of 3 months, once every 2 months from 3 to 12 months old, once every 6 months after 1 year old and ends around the age of 3.

Time points of our cohort mainly overlapped with the regular visit before the age of 3, which provide convenience to participating families. Additionally, we will perform extra assessments at specific time points (details are shown in table 1 and figure 2), and keep following up at 4 and 6 years old (further details have been shown in the online supplemental materials).

Study retention

After enrolment, we will stay in contact with all participants through WeChat and messages. Coordinators will send out schedules before each time-point, and an official account will post popular science articles about caring for infants, especially PT infants, and address any healthcare issues raised by caregivers, which are supposed to increase the follow-up rate of the cohort. We will provide the results of the assessments to the parents, and a clinician will give them comprehensive clinical advice at the visit centre. Meanwhile, the families will have the option to receive an electronic explanation instead of visiting the care centre.

During the COVID-19 pandemic, if a family undergoes restrictions and could not finish the off-line assessment, questionnaires will be collected online under telephone instructions. If the restriction finished within 2 weeks, other assessments will be conducted after that. If not, this time-point will be marked as uncompleted.

Data collection

Table 1 and figure 2 summarise the assessment schedule, data collection methods, sample type/domain and the test or task. Data from cases and controls are collected using the same data collection instruments.

General information

Maternal and infant clinical information will be collected at baseline through hospital information system. Demographic information, including social economic status

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Table 1 Details of the assessments in the cohort study

Time points	Data type	Assessments tools/data content
40 weeks	Clinical record and demographic information	HIS system and questionnaire
	MRI, EEG, fNIRS	fMRI, T1, T2, dMRI, EEG, fNIRS
	Neuropsychology	Bayley-III, ASQ-3, CNBS-R2016, ASQ-SE:2, face-to-face still face
	Maternal mental health & Breastfeeding	EPDS, BDI, BAI; feed-type and BSES-SF
	Gene and epigenetics	Saliva sample, faecal sample
6 months	MRI, EEG, fNIRS	fMRI, T1, T2, dMRI, EEG, fNIRS
	Neuropsychology and language	Bayley-III, ASQ-3, CNBS-R2016, ASQ-SE:2, CSBC, cup task and planning test; CSBC
	Maternal mental health & Breastfeeding	EPDS, BDI, BAI; feed-type and BSES-SF
12 months	MRI, EEG, fNIRS	fMRI, T1, T2, dMRI, EEG, fNIRS
	Neuropsychology and language	Bayley-III, ASQ-3, CNBS-R2016, ASQ-SE:2, IBQ-R, face-to-face still face, Cup task and Planning test, VABS-III; CSBC
	Maternal mental health and breast feeding	EPDS, BDI, BAI; feed-type and BSES-SF
18 months	Neuropsychology and language	Bayley-III, ASQ-3, CNBS-R2016, ASQ-SE:2, LUI, cup task and planning test; LUI
	Maternal mental health and breast feeding	EPDS, BDI, BAI; feed-type and BSES-SF
	ASD symptoms	ABC, M-CHAT, Q-CHAT
2 years	MRI, EEG, fNIRS	fMRI, T1, T2, dMRI, EEG, fNIRS
	Neuropsychology and language	Bayley-III, ASQ-3, CNBS-R2016, ASQ-SE:2, VABS-III, LUI, ECBQ, A-not-B task; LUI, CSBC
	Maternal mental health	EPDS, BDI, BAI
	Symptoms of ASD and ADHD and other NDDs	ABC, M-CHAT, CARS; CBCL, SDQ; YGTSS
	NDDs diagnosis	Clinical interview, DIPA
3 years	Neuropsychology	Bayley-III, ASQ-3, CNBS-R2016, ASQ-SE:2, VABS-III, Simon says task
	Maternal mental health	EPDS, BDI, BAI
	Symptoms of ASD and ADHD and other NDDs	ABC, CARS; CBCL, SDQ; YGTSS
	NDDs diagnosis	Clinical interview, DIPA
4 years	Neuropsychology	Bayley-III, ASQ-3, CNBS-R2016, ASQ-SE:2, VABS-III, Simon says task
	Maternal mental health	EPDS, BDI, BAI
	Symptoms of ASD and ADHD and other NDDs	ABC, CARS; CBCL, SDQ, DIPA; YGTSS
	NDDs diagnosis	Clinical interview, DIPA, CRAT
6 years	Neuropsychology	CNBS-R2016, WSIC-IV, VABS-III, Stroop color-word test, TMT A and B, RCFT, DAP:IQ
	Maternal mental health	EPDS, BDI, BAI
	Symptoms of ASD and ADHD and other NDDs	ABC, CARS; CBCL, SDQ, DIPA, ADHD rating scale
	NDDs diagnosis	Clinical interview, KSADS-PL, CRAT

ABC, autism behaviour checklist; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ASQ-3, age and stages questionnaire-third edition; ASQ-SE:2, ages and stages questionnaire-social and emotion: second edition; BAI, Beck anxiety inventory; BDI, Beck depression inventory; BSES-SF, breastfeeding self-efficacy scale-short form; CARS, childhood autism rating scale; CBCL, child behaviour checklist; CNBS-R2016, children neuropsychological and behavioural scale revision 2016; CRAT, Chinese reading ability test; CSBC, communication and symbolic behaviour scale; DAP:IQ, draw-a-person intellectual ability test; DIPA, diagnostic infant and preschool assessment; ECBQ, early childhood behaviour questionnaire; EPDS, Edinburgh postnatal depression scale; fNIRS, functional near-infrared spectroscopy; HIS, hospital information system; IBQ, infant behaviour questionnaire; KSADS-PL, schedule for affective disorders and schizophrenia for school-age children-present and lifetime version; LUI, language use inventory; M-CHAT, modified-checklist for autism in toddlers; NDDs, neurodevelopmental disorders; RCFT, Rey complex figure test and recognition trial; SDQ, strengths and difficulties questionnaire; SES, social economic status; TMT, trail making test; VABS-III, Vineland adaptive behaviour scale-III; WSIC-IV, Wechsler intelligence scale for children, fourth edition; YGTSS, Yale global tic severity scale.

(SES) and family history will be collected using questionnaires (for details see online supplemental materials).

Neurodevelopment

In the current study, neuropsychological functions will be assessed following the guidelines of research domain criteria (RDoC): social process, sensorimotor and cognitive system. In addition, language and communication abilities will also be assessed. Assessment tools have been selected according to age stages, the details are shown in table 1 and figure 2.

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Domain of measurement	Data type	Assessment/Test	40w	6m	12m	18m	2y	3y	4y	6y
Basic information	Demographic information	/	√							
	Clinical record	/	√							
Neuropsychological function	Standard assessments	Bayley-III	√	√	√	√	√	√	√	√
		ASQ-3	√	√	√	√	√	√	√	√
		CNBS-R2016	√	√	√	√	√	√	√	√
	Social-emotional function	ASQ-SE:2	√	√	√	√	√	√	√	√
		IBQ			√					
		ECBQ					√			
		Face-still-face paradigm	√		√					
	General cognitive ability	WSIC-IV								√
		DAP:IQ								√
	Language	CSBC		√	√		√			
		LUI				√	√			
	Executive function	Cup task and Planning test		√	√	√				
		A-not-B					√			
		Simon says							√	
		Stroop color-word test, TMT A and B, RCFT								√
	Adaptive function	VABS-III			√	√	√	√	√	√
Neuroimaging	Brain structure	T1, T2, dMRI	√	√	√		√			√
	Brain function	rsMRI, EEG, fNIRS	√	√	√		√			√
Environmental risk factors	Breastfeeding	/	√	√	√	√				
	Maternal mental health	/	√	√	√	√	√	√	√	√
	Air pollution	/	√							
	SES	/	√							
Gene	DNA	/	√							
	DNA methylation	/	√							
ASD	Symptoms	/				√	√	√	√	√
	Diagnosis	/				√	√	√	√	√
ADHD	Symptoms	/					√	√	√	√
	Diagnosis	/							√	√
Other NDDs	Symptoms	/						√	√	√
	Diagnosis	/							√	√

Figure 2 Overall schedule of follow-up assessments. ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ASQ-3; age and stages questionnaire-third edition; ASQ-SE:2, ages and stages questionnaire-social and emotion: second edition; CNBS-R2016, children neuropsychological and behavioural scale revision 2016; CSBC; communication and symbolic behaviour scale; DAP-IQ, draw-a-person intellectual ability test; ECBQ, early childhood behaviour questionnaire; EEG, electroencephalogram; IBQ, infant behaviour questionnaire; LUI, language use inventory; NDDs, neurodevelopmental disorders; RCFT, Rey complex figure test and recognition trial; SES, social economic status; TMT, trail making test; VABS, Vineland Adaptive Behaviour Scale-III; WSIC-IV, Wechsler intelligence scale for children, fourth edition.

1. Standardised overall developmental assessments: several standardised tools will be used to assess the development in infancy, including the Bayley scales of infant and toddler development, third edition (Bayley-III), the ages and stages questionnaire-third edition (ASQ-3) and the children neuropsychological and behavioural scale, revision 2016 (CNBS-R2016). Both Bayley-III and ASQ-3 were widely used assessment tools worldwide.[32 33] Both have been introduced and widely adopted in China, with Chinese norms have been built and the reliability and validity tested.[34 35] The CNBS-R2016 is an indigenous development assessment tool, developed by the Capital Institute of Pediatrics of China.[36 37] The CNBS-R2016 is the mostly used developmental assessment scale in China, which includes 294 items in five domains: gross motor, personal social, language, fine motor and adaptive behaviour. Previous studies reported the high reliability and validity of CNBS-R2016 and indicated an important role in the early screening of NDDs.[37–39]
2. General cognitive ability: (a) the Chinese version of the Wechsler intelligence scale for children, fourth

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edition (WSICS-IV) will be used at the age of 6.[40 41] (b) A simple and easy completing test, the draw-a-person intellectual ability test (DAP:IQ),[42–44] which has been accepted worldwide, will also be incorporated to further ensure successful and accurate assessing among children with delay (6 years).

3. Language and social communication assessments: previous studies have demonstrated the importance and validity of early screening for predicting later communication disorder, specific learning disorder and other NDDs.[45 46] In the current cohort, we will comprehensively assess language ability and communication behaviour using the parent questionnaire of communication and symbolic behaviour scale (CSBC) (6 months, 12 months, 24 months) and language use inventory (LUI) (18 months, 24 months). The CSBS consists of 24 items, including three subscales: social, speech and symbolic composite.[47] The LUI provides an assessment for pragmatic development, that is, the ability to use language in social situations.[48]
4. Social–emotional function and temperature: (a) ages and stages questionnaire-social and emotion: second edition (ASQ-SE:2) will be used at 6 months, 12 months, 18 months and 24 months. ASQ-SE:2 is a brief caregivers-reported instrument for children aged 6–60 months;[49] (b) infant behaviour questionnaire-revised (IBQ-R) very short form (12 months) and early childhood behaviour questionnaire (ECBQ) very short form (24 months) will be used to examine the temperature and early emotional competencies,[50 51] which contain 37 and 36 items in three subscales (surgency, negative affect and effortful control), respectively; and (c) infants' affective states will be coded during face-to-face still-face paradigm (40 weeks and 12 months).[52 53]
5. Executive function: age-appropriate tasks were chosen to measure various executive processes, including working memory, inhibition and planning ability: (a) Cup task and Planning test (6, 12 and 18 months);[54] (b) A-not-B with invisible displacement (24 months); (c) Simon says (36 and 48 months);[55] (d) Stroop color-word test, Trail Making Test (TMT) A and B, and Rey complex figure test and recognition trial (RCFT) (6 years)[56–59] (details of the tasks are shown in the online supplemental materials).
6. Adaptive function: Vineland Adaptive Behaviour Scale-III (VABS-III) will be used at 12 months, 18 months, 24 months, 3 years, 4 years and 6 years to assess the adaptive functions in five domains—communication, daily living skills, socialisation, motor skills and maladaptive behaviour.[60]

Brain development

The key aim of the current cohort is to depict brain developmental trajectories in PT infants during early life stage, and to explore the relationship between early brain development and later diagnosis of NDDs. To fulfil this aim, we plan to evaluate brain development both functionally and structurally using MRI, EEG and fNIRS technologies at five time points (table 1 and figure 2).

1. Brain MRI: MRI will be performed with a 3T MRI machine (Magnetom Tim Trio; Siemens, Erlangen, Germany), multimodal data will be acquired (T1w, T2w, resting-state fMRI (rsMRI) and diffusion-weighted MRI (dMRI)). The detailed imaging protocols are shown in table 2.

   For infants, sleep scan will be tried for several times, if failed, sedation will be used before scan. At the time

Table 2 Neuroimaging protocol

Modality	Protocols	Time
T1-weighted 3D BRAVO scan	sagittal scan, TR=8.2 ms, TE=3.2 ms, FOV=256 × 256 mm^2, turning Angle=9°, frequency width=31.25 Hz/pixel, plane resolution=1 ×1 mm^2, layer thickness=1 mm, 192 layers in total	5 min and 4 s
T2-weighted dual-echo fast spin-echo scan	Axial scanning, TR=3000 ms, TE1=36 ms, TE2=162 ms, FOV=256 × 256 mm^2, rotation Angle=90°, Plane resolution=1 × 1 mm^2, layer thickness=1 mm, 192 layers in total	8 min and 24 s
rs-MRI	Axial scan with BOLD sensitive GRE-EPI sequence, TR=2000 ms, TE=20 ms, FOV=256 × 256 mm^2, turning Angle=90°, plane resolution=2 × 2 mm^2, layer thickness=3 mm, layer spacing=0.6 mm, 41 layers, including 240 time points	8 min
Diffusion MRI	Axial scan, gradient echo EPI sequence, TR=9000 ms, TE=89.4 ms, FOV=256 × 256 mm^2, layer thickness=2 mm, Matrix=128 × 128, plane resolution=2 × 2 mm^2, 75 layers, B=1000 s/mm^2, 64 gradient weighted directions of spherical distribution, 32 B=1000 s/mm^2, 32 B=3000 s/mm^2, 12 B0 images	10 min and 48 s

FOV, field-of-view; TE, echo time; TR, repetition time.

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point of 6 years, awake scan will be scheduled, if necessary, a training session will be performed.
MRI data will be visually checked during scan for excessive motion, insufficient coverage and ghosting. If the data are poor-quality, several tries will be made.
T1w, T2w and dMRI images will be transferred to a DICOM workstation and examined by at least one trained radiologist, parents could obtain the reports conveniently through self-service printing in the hospital. If there were any brain anomalies reported, another outpatient visit will be assigned to give further clinical advice to the family.

2. EEG and fNRIS: EEG and fNRIS data will be acquired in (a) resting state and (b) during emotional face task, details are shown in online supplemental materials.

Genes and epigenetics

The current cohort plans to collect saliva samples at baseline (corrected GA of 40W). Saliva DNA extraction kits will be used for DNA extraction. DNA samples will be stored at −80°C and quality controlled before genotyping. The quality control (QC) standards include the main band of the sample being clear and more than 10 kb, no obvious degradation, a total amount of more than 1 µg and the standard A260/A280 being in the range of 1.7–2.1. DNA methylation (DNAm) will be measured by HumanMethylation450 Bead Chip.

Environmental risk factors

1. Breast feeding: breast feeding is an important early life environmental factor;[61–63] recent umbrella review and meta-analysis have suggested that breastfed infants tend to show better intelligence performance and lower ASD prevalence than those who are formula fed.[64–66]
   In the cohort study, we assessed feed type and BF self-efficacy using the following methods: (i) according to the proportion of breast milk in total infant food intake, feeding type was divided into six categories—exclusive BF (=100%), almost exclusive BF (≈100%), high proportion BF (≥80%), medium proportion BF (≥20%), low proportion BF (>0%, <20%) and token BF (≈0%);[67 68] (ii) the Chinese version of the breastfeeding self-efficacy scale-short form (BSES-SF).[69]
2. Paternal mental health: the importance of maternal mental health for parent–infant attachment and child development has been widely noticed.[70 71] Moreover, mothers experiencing a PT birth or nursing a PT infant are at high risk for mental health issues.[72] In the cohort study, the following self-report questionnaires will be used at each time-point to assess symptoms of anxiety and depression among mothers—Edinburgh postnatal depression scale (EPDS), Beck depression inventory (BDI) and Beck anxiety inventory (BAI). If any score reaches the cut-off line, the coordinators will inform and communicate with the participants, if necessary, an outpatient visit to a psychiatrist will be assigned.

Outcomes of NDDs

1. ASD symptoms:
   a. Autism behaviour checklist (ABC) is a widely used questionnaire that consist of 57 items in five subscales: sensory, relating, motor, language and self-help (18 months, 24 months, 3 years, 4 years and 6 years).[73]
   b. Modified-checklist for Autism in toddlers (M-CHAT) will be used at 18 months and 24 months. M-CHAT was developed for early screening, and showed good sensitivity and specificity (0.96 and 0.60).[74]
   c. Childhood autism rating scale (CARS) will be used at 24 months, 3 years, 4 years and 6 years. CARS is one of the most widely used questionnaires for assessing ASD symptoms. The CARS consists of 15 items on a four-point Likert scale. A total score of 30 or above indicates ASD diagnosis.[75 76]
2. ADHD symptoms:
   a. Two versions of the Child behaviour checklist (CBCL) will be used to assess ADHD symptoms and emotional-behavioural problems at 2 years and 3 years (CBCL for ages 2–3), 4 years and 6 years (CBCL). CBCL 2–3 is a questionnaire consisting of 99 items in six subscales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, attention problems, aggressive behaviour and sleep problems.[77] CBCL contains 118 items in nine empirically based syndromes: withdrawn, somatic complaints, anxious/depressed, social difficulties, thought difficulties, attention difficulties, sex difficulties, delinquent behaviour and aggressive behaviour.[78]
   b. Strengths and difficulties questionnaire (SDQ) will be used at 24 months, 3 years, 4 years and 6 years.[79] SDQ is a screening tool for ADHD and emotional-behavioural problems well utilised worldwide, which consists of 25 items including four difficulty subscales (emotional symptoms, behavioural problems, hyperactive-attention deficit, peer relationship problems) and a strengths scale (prosocial behaviour).
   c. ADHD rating scale (6 years old), a norm-referenced checklist that measures ADHD symptoms, which includes 18 items in two subscales: inattention and impulsivity/hyperactivity.[80 81]
3. Motor disorder: Yale Global Tic Severity Scale (YGTSS) will be used to assess the severity of tic symptoms in five domains—total motor tic score, total verbal tic score, total tic score (motor+verbal), overall impairment rating, and global severity score.[82 83]
4. Diagnosis: Based on the results of the aforementioned NDDs questionnaires, families of children who surpass the diagnostic cut-off of one of the questionnaires will be arranged a psychiatric interview. Clinical diagnosis of ASD (24 months and later), ADHD (48 months and later) and other NDDs will be made by a licensed paediatric psychiatrist after interviewing the

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parent/caregiver and the child according to Diagnostic Statistical Manual Fifth Edition (DSM-5).

In this study, the diagnosis of NDDs will be verified using the semistructured interview of DIPA (after 2 years and before 6 years) or KSADS-PL (schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version) (6 years).[84] The Diagnostic infant and preschool assessment (DIPA) is a semistructured interview tool for caregivers for children from 9 months to 6 years old. It covers symptoms in 13 diagnostic categories, including ADHD, post-traumatic stress disorder, separation anxiety disorder and other mental disorders.[85] DIPA has been translated into Chinese and verified the validity and reliability;[86] Autism Diagnostic Observation Schedule-Second Edition (ADOS-2) will be used to aid in ASD diagnosis, which is the most widely accepted standard for identifying children with ASD.[87 88] Children who meet the criterion of specific learning disorder in DSM-5 will also undergo a set of comprehensive assessments using the Chinese reading ability test (CRAT).[89]

Data management

Data management system

Data management will be conducted through an electronic system called h6 world (https://www.h6world.cn/). The system enables both participants and doctors/researchers to access the data, which benefits participant retention and real-time monitoring. The procedures of data management are as follows: (1) after enrolment, participants will be assigned a unique research ID code and an electronic CRF (eCRF) will be created using this code. The eCRF will contain all items of questionnaires and results of assessments in the entire follow-up schedule, and the location of storage for neuroimaging data and biosamples, which will also be registered in the eCRF; (2) at each time-point, questionnaires will be collected through eCRF, after finished, a report for each questionnaire will be generated automatically; (3) results of neuropsychological assessments will be entered into the eCRF by the coordinators; and (4) neuroimaging data will be stored and backed-up in a secure data storage facility using the ID code. Biological samples (saliva) will be frozen at −80°C. Neuroimaging data and biosamples will be registered in the h6 world system after collection and storage.

Data monitoring and quality assurance

Before undergoing assessments, coordinators will communicate with the parents about instructions for each assessment and questionnaire, and inform them of the use methods of electronic methods. After completion, each questionnaire will be evaluated by at least two coordinators/doctors for the completeness and reliability. If a questionnaire is of low quality, a telephone or face-to-face interview will be performed to complete and revise the questionnaire. QC methods for neuroimaging data are described in the Statistical analysis section. In addition, monitors will choose a random sample of the collected data and check the quality per month.

Statistical analysis

General statistical analysis methods

Neuropsychological functions, outcomes of NDDs and brain development profiles at each time point will be compared between PT and FT children, and between children with and without NDDs, using linear or logistic regression. The statistical significance level was set as $p<0.05$. To test early risk factors and signs, multivariate logistic regression will be used to select important risk factors including both biological and environmental determinants for later NDDs diagnosis or poor neurodevelopmental outcomes (online supplemental table S1), (online supplemental figure S1) (further details are shown in the online supplemental materials).

Developmental trajectory analysis

Generalised Linear Mixed Model will be used to compare the differences in developmental trajectories, including neuropsychological functions and neuroimaging between PT and FT infants, and between children with and without NDDs.

As previous studies have indicated, the developmental trajectories of infants are heterogeneous, several subgroups might exist.[12] We intend to use the group-based trajectory modelling method in Proc TraJ, SAS V.9.1 software to classify the subjects according to the trajectories. Bayesian Information Criterion (BIC) and mean post-test grouping probability (AvePP) will be used to test the model fit.

Neuroimaging data analysis

Details of analytic methods during preprocessing the MRI, EEG and fNIRS data are shown in the online supplemental materials.

Genetic and epigenetic data analysis

Details of analytic methods are shown in the online supplemental materials.

Patient and public involvement

The design of the current study did not involve participants or parents directly. However, the research coordinators will maintain contact with parents/caregivers through email, telephone or social media, and we will collect feedback during study procedure. Messages with necessary information, including appointment time and location will be sent before each follow-up visit.

Generally, PT children require special attention from their parents in daily life, which could be difficult and cause significant pressure to parents. The current cohort hopes to provide comprehensive healthcare not only for the children, but also for their parents, especially in terms of mental health. The cohort will screen and monitor parental mental health and provides further clinical consultants to all participating parents.

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ETHICS AND DISSEMINATION

Ethical approval has been obtained from the Peking University Third Hospital medical science research ethics committee (M2021087). The ethical approval was obtained from one site only because all the procedures will be conducted at the Third Hospital. Although psychiatric interviews will be conducted by doctors from the Sixth Hospital, they will also take place at the Third Hospital.

The study results from the current cohort will be disseminated and popularised through social media to participating parents, as well as parents who are giving care to PT children.

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Contributors YZ designed the study and drafted the manuscript. LY and YH conceived the study, read and revised the manuscript and gave the final approval for the version to be published. XT gave necessary advice about the study plan and further supervised the manuscript, YL conceived and designed the study and contributed to the concept and management of the research. DW, XG, RX and NW contributed to planning the study. All authors read and approved the final version of the manuscript.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

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