Prospective Longitudinal Study of High-Risk Infants and Early Identification of Autism Spectrum Disorder

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Abstract

Early identification of Autism Spectrum Disorder (ASD) facilitates the implementation of early diagnosis and early intervention, which is crucial for improving developmental outcomes in children with ASD. High-risk prospective longitudinal studies, which take high-risk infants (younger siblings of children with ASD, enrolled at less than 12 months of age) as the primary research subjects, provide important evidence for early identification of ASD by delineating early developmental trajectories and identifying early manifestations of core symptoms in high-risk infants later diagnosed with ASD (high-risk infants diagnosed with ASD between 24 and 36 months). Future research could increase sample sizes, extend observation periods with denser time points, focus on comorbid conditions, comprehensively consider the influences of genetic, environmental, and cultural factors, and conduct in-depth exploration in conjunction with early intervention studies. Conducting related research in China in the future holds significant scientific value and clinical importance.

Full Text

Prospective Longitudinal Studies of High-Risk Infants and Early Identification of Autism Spectrum Disorder

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Abstract: Early identification of autism spectrum disorder (ASD) facilitates timely diagnosis and intervention, which is crucial for improving developmental outcomes in children with ASD. Prospective longitudinal studies of high-risk infants—defined as younger siblings of children with ASD enrolled before 12 months of age—have provided critical evidence for early identification by mapping developmental trajectories and identifying early manifestations of core symptoms in infants later diagnosed with ASD between 24 and 36 months. Future research should expand sample sizes, extend observation periods with denser time points, examine comorbid conditions, and comprehensively consider genetic, environmental, and cultural factors while integrating early intervention studies. Conducting such research in China holds significant scientific and clinical value.

Keywords: autism spectrum disorder; early identification; prospective longitudinal studies; high-risk infants; developmental trajectory
Classification: R395

1 Introduction

Autism spectrum disorder (ASD), also known as autism, is a neurodevelopmental disorder characterized by impairments in social communication and interaction, alongside restricted interests and repetitive behaviors (American Psychiatric Association, 2013). According to the Centers for Disease Control and Prevention (CDC), ASD prevalence has reached 1.68% (Baio et al., 2018). While China lacks nationwide epidemiological data, analytical reports indicate a prevalence of 3.48‰ among children aged 0–6 years (Dai et al., 2017). Individuals with ASD frequently present with comorbid conditions including developmental delay, intellectual disability, language and motor impairments, and attention deficit hyperactivity disorder (ADHD) (Lord, Elsabbagh, Baird, & Veenstra-Vanderweele, 2018). Currently, no effective pharmacological treatments exist for core ASD symptoms (Ji & Findling, 2015), and most individuals require lifelong support, imposing substantial burdens on families and society (Lord et al., 2018).

Early identification of ASD has long been a research priority. Parents typically notice atypical behaviors in their children before 18–24 months (Shattuck & Grosse, 2007), yet often delay seeking professional help by approximately one year, with diagnosis taking an additional 3.5 years (Lord et al., 2018). Early identification thus addresses parental concerns while enabling timely intervention. Young children, particularly those under 24 months, exhibit strong neural plasticity, and early intensive intervention can substantially improve language, cognitive, and adaptive functioning (Hadders-Algra, 2011; Kretch, Franchak, & Adolph, 2014; Schreibman et al., 2015). Consequently, early identification is essential for implementing early diagnosis and intervention to improve developmental outcomes (Schreibman et al., 2015).

Early behavioral abnormalities in ASD include the "Five No' s" : reduced look-

ing, responding, pointing, speaking, and appropriate behavior (中华医学会儿科学分会发育行为学组, 中国医师协会儿科分会儿童保健专业委员会, 儿童孤独症诊断与防治技术和标准研究项目专家组, 2017). These primarily involve atypical eye contact, lack of appropriate gestures, language delays, and unusual object use with associated sensory-perceptual abnormalities. Current understanding of early ASD manifestations derives largely from parent reports (De Giacomo & Fombonne, 1998), case studies (Dawson, Osterling, Meltzoff, & Kuhl, 2000), and home video analysis (Mars, Mauk, & Dowrick, 1998). However, these methods have significant limitations. While home video analysis offers objective behavioral data, videos are not randomly recorded but rather captured by parents for specific reasons in particular contexts, failing to provide comprehensive, objective representation of early development. This has motivated researchers to develop improved early identification methods. Prospective longitudinal studies beginning at birth can collect objective data on early social communication, motor development, vocalization, and sensory responses, providing crucial evidence for early identification. However, ASD' s low prevalence in the general population (Merrick, Kandel, & Morad, 2004) makes large-scale, long-term follow-up studies inefficient.

Researchers subsequently identified younger siblings of children with ASD as ideal participants for prospective longitudinal studies. Given strong genetic contributions to ASD (Tick, Bolton, Happe, Rutter, & Rijsdijk, 2016), early familial studies revealed that siblings of ASD children have dozens of times higher risk than the general population (Micali, Chakrabarti, & Fombonne, 2004). This led to the establishment of the Baby Siblings Research Consortium (BSRC) (Yirmiya & Ozonoff, 2007). This approach—prospective longitudinal studies of high-risk infants—utilizes standardized paradigms from developmental science to enable comparative analysis of data collected at different time points, gaining increasing application in ASD early identification research.

Prospective longitudinal studies of high-risk infants (here referring to studies of infants at familial high risk for ASD) have become a critical research paradigm. "High risk" specifically denotes familial high risk: younger siblings of children with ASD, known as high-risk infants (HR infants), who face elevated genetic risk with incidence rates reaching 18.7% or even 30%, significantly higher than the general population (Miller et al., 2019; Ozonoff et al., 2011). These studies enroll HR infants (typically under 12 months at enrollment) and low-risk infants (LR infants; younger siblings of typically developing children) as controls, tracking participants from 6 months of age or earlier through 24–36 months when ASD symptoms stabilize and reliable diagnosis becomes possible. HR infants are then classified as ASD high-risk (HR-ASD) or non-ASD high-risk (HR-non-ASD), with some studies further subdividing HR-non-ASD into high-risk infants with typical development (HR-Typical) and those with atypical development (HR-Atypical). By comparing early manifestations across these groups, researchers investigate ASD' s early development (see Figure 1 [Figure 1: see original paper]).

This paradigm validates findings from case reports, parent reports, and home

video analyses while enabling integration with advanced neuroimaging and deep learning technologies for deeper investigation (Jones, Gliga, Bedford, Charman, & Johnson, 2014).

Figure 1 Paradigm of Prospective Longitudinal Studies of High-Risk Infants
Note: 1. High-risk infants (HR infants): younger siblings of children with ASD; 2. Low-risk infants (LR infants): younger siblings of typically developing children; 3. ASD high-risk infants (HR-ASD): high-risk infants diagnosed with ASD; 4. Non-ASD high-risk infants (HR-non-ASD): high-risk infants not diagnosed with ASD; 5. High-risk infants with typical development (HR-Typical): typically developing high-risk infants; 6. High-risk infants with atypical development (HR-Atypical): high-risk infants with atypical development not meeting ASD diagnostic criteria.

This paper reviews recent advances from high-risk prospective longitudinal studies on early ASD identification, discusses their strengths and limitations, and explores future directions to inform new research initiatives in China.

2.1 Visual Attention

Social attention refers to orientation toward socially relevant stimuli such as human faces and eyes (Klein, Shepherd, & Platt, 2009), providing crucial cues about others'emotional states and influencing successful social engagement (Itier & Batty, 2009). Typically developing infants show responsiveness to social interaction within hours of birth, demonstrating a preference for faces (Bushnell, 2001). Individuals with ASD exhibit deficits in social attention, with early impairments reducing engagement with social stimuli (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012). Karen Pierce and colleagues' series of studies revealed that toddlers with autism show a preference for geometric patterns that correlates with symptom severity, with geometric patterns significantly interfering with face-looking time (Kwon, Moore, Barnes, Cha, & Pierce, 2019; Moore et al., 2018; Pierce, Conant, Hazin, Stoner, & Desmond, 2011; Pierce et al., 2015). Gliga et al. (2015) found that stronger visual search abilities at 9 months in high-risk infants predicted greater ASD severity at 15 and 24 months. Jones and Klin (2013) demonstrated through prospective longitudinal research that eye-gaze ability in HR-ASD infants declined progressively between 2 and 6 months. Another study of 43 HR and 45 LR infants examined visual attention (habituation) and brain function (event-related potentials to faces and objects) at 6 and 12 months (Jones et al., 2016). Results showed that HR-ASD infants had shorter visual attention durations at 6 months, faster but briefer neural activation to faces, and delayed sensitization responses (increased face-finding time). These findings suggest that early social attention deficits, particularly declining eye-gaze ability, may serve as early markers, though larger samples and integration of eye-tracking and visual ERP methods are needed to establish validity and sensitivity.

Joint attention (JA) involves sharing attention to objects and plays a vital

role in early learning and social interaction. Infants begin showing responding to joint attention (RJA) by following others' gaze and pointing at 3–4 months (Perra & Gattis, 2010), and initiate joint attention (IJA) to guide others at 8–13 months (Beuker, Rommelse, Donders, & Buitelaar, 2013). Children with ASD show reduced engagement and initiation of joint attention. Parent-reported JA behaviors at 8 months have been shown to predict diagnostic status 7 years later (Veness, Prior, Eadie, Bavin, & Reilly, 2014). Thorup et al. (2018) found that in a study of 67 HR and 16 LR infants, HR-ASD infants showed reduced alternating gaze during adult interaction at 10 months, with the degree of reduction correlating with ASD symptom severity. Ibanez, Grantz, and Messinger (2013) demonstrated through prospective longitudinal research that both RJA and IJA levels at 8 months predicted ASD diagnosis at 30 months. Future research should further clarify early developmental trajectories of RJA and IJA to enhance early identification.

2.2 Social Emotion

Crying represents an early communication method between infants and caregivers, yet infants with ASD cannot express needs through crying like typically developing children. Sheinkopf et al. (2012) observed crying behavior in 17 HR and 11 LR infants at 6 months, finding that HR-ASD infants showed higher crying frequency but fewer vocalized cries for both pain-induced and non-pain-induced crying compared to non-ASD HR and LR infants. Esposito et al. (2014) and Unwin et al. (2017) similarly found shorter crying durations in HR-ASD infants at 12 months.

Social smiling emerges between 2–3 months in typical development, becoming one of the most common social behaviors in the first 6 months (Yale, Messinger, Cobo-Lewis, & Delgado, 2003), and grows increasingly purposeful, directed, and communicative between 6–12 months (Venezia, Messinger, Thorp, & Mundy, 2004). Social smiling involves temporal integration of non-social smiling (positive emotional facial expressions) and social attention (eye contact), both of which are impaired in children with ASD (Swettenham et al., 1998). Nichols et al. (2014) found that HR-ASD infants showed lower average social smiling at 15 months, with reduced eye contact and non-social smiling. Filliter et al. (2015) demonstrated that HR-ASD infants had lower social smiling rates at 12 months compared to non-ASD HR and LR infants. Researchers propose that reduced social smiling at 12 months may serve as an early risk marker for ASD.

2.3 Temperament

Temperament refers to relatively stable individual differences in activity, emotion, attention, and self-regulation, shaped by complex interactions among genetic, biological, and environmental factors (Hertzig, 2012). Early temperamental characteristics may serve as potential risk markers for psychiatric conditions (Pérez-Edgar & Fox, 2005). Zwaigenbaum et al. (2005) identified characteristic

temperamental features in HR infants: increased passivity and decreased activity levels at 6 months, increased attention to specific objects at 12 months, and reduced positive affect expression. Garon et al. (2016) also found that temperamental affective components at 12 months predicted effortful control at 24 months in HR infants. Del Rosario et al. (2014) observed declining adaptive capacity and approach behaviors over time in HR-ASD infants. Recently, Pijl et al. (2019) examined temperament as a potential early risk marker, assessing 170 HR and 70 LR infants at 8, 14, and 24 months with diagnostic evaluation at 36 months. Results showed HR-ASD infants differed from non-ASD HR and LR infants in distress, negative affect, and effortful control. However, machine learning analysis could identify non-ASD HR infants but not accurately classify HR-ASD infants based on temperament alone. Thus, temperament' s utility for early ASD identification requires further large-scale investigation.

2.4 Response to Name

Infants begin responding to their own names at 4–6 months, selectively turning their heads when hearing their names, indicating comprehension that their name signals a greeting (Imafuku, Hakuno, Uchida-Ota, Yamamoto, & Minagawa, 2014). Retrospective home video analyses show diminished response to name in children with ASD as early as 12 months (Werner, Dawson, Osterling, & Dinno, 2000). A prospective longitudinal study tested response to name in 156 HR and LR infants at 6, 9, 12, 15, 18, and 24 months to differentiate ASD from typical development (Miller et al., 2017). Results showed HR-ASD infants lacked response to name at 9 months, persisting through 24 months. Half of HR-ASD infants failed the response-to-name task two or more times between 9–24 months, showing lower language levels and earlier ASD diagnosis compared to those failing once or less. Researchers conclude that consistent failure to respond to one' s name during the second year of life indicates high ASD risk.

2.5 Language and Motor Skills

Typically developing infants recognize meanings of highly familiar words at 6–9 months (Bergelson & Swingley, 2012) and produce single words around 12 months. Language deficits are hallmark early features of ASD. Ozonoff et al. (2014) compared receptive (language comprehension) and expressive (communication through speech, writing, or gesture) language in 294 HR and 116 LR infants at 6, 12, 18, 24, and 36 months, finding lower levels in both domains for HR-ASD infants at 12 months. This finding was confirmed in subsequent larger-scale research (Ozonoff et al., 2015). Levin et al. (2017) examined correlations between EEG abnormalities and language development, finding that reduced frontal alpha waves at 3 months in HR-ASD infants significantly predicted weaker expressive language at 12 months.

Between 3–6 months, improved grasping enables toy-mediated interaction with caregivers; crawling at 6–9 months increases opportunities for social engagement;

and independent walking around 12 months significantly enhances mother-infant interaction quality (Kretch et al., 2014) and correlates with receptive and expressive language levels (Libertus & Violi, 2016). Bradshaw et al. (2018) examined links between motor and social communication skills in 86 HR and 113 LR infants at 12 months, suggesting independent walking may promote social communication development in HR infants. A recent prospective longitudinal study comparing gross and fine motor skills in 6-month-old HR and LR infants found that fine motor scores at 6 months predicted ADOS scores at 36 months but could not fully predict ASD diagnosis, as infants with elevated ADOS scores without ASD also showed fine motor abnormalities (Iverson et al., 2019). This indicates that motor features require further investigation for early identification, with future research needing to examine motor subdomains while considering individual differences and variations in early educational methods.

3.1 Stereotyped and Repetitive Behaviors

Stereotyped and repetitive behaviors constitute a core ASD symptom domain and serve as reliable diagnostic features in children over 2 years (Richler, Bishop, Kleinke, & Lord, 2007). Elison et al. (2014) examined earlier development of these behaviors, assessing repetitive movements and stereotyped patterns in 12-month-old HR and LR infants, later diagnosing ASD at 24 months and classifying participants into three groups: 30 HR-ASD, 75 non-ASD HR, and 53 LR infants. Results showed HR-ASD infants displayed more stereotyped behaviors at 12 months, with both HR groups scoring higher than LR infants on repetitive movements. Wolff et al. (2014) analyzed repetitive behavior data from 190 HR infants (41 later diagnosed with ASD) and 60 LR infants between 12–24 months, similarly finding significant differences at 12 months between HR-ASD infants and both non-ASD HR and LR infants. Targeted assessment of repetitive behaviors in infancy may thus facilitate early ASD identification (Wolff et al., 2017).

3.2 Sensory Perception

Atypical sensory responses were newly included as diagnostic criteria in DSM-5, referring to hyper- or hypo-reactivity to sensory input or unusual interest in environmental stimuli (American Psychiatric Association, 2013). Researchers have used prospective longitudinal studies to investigate early atypical responses to various sensory stimuli.

The pupillary light reflex (PLR) regulates retinal light exposure through pupil constriction and dilation. Previous studies showed attenuated PLR in individuals with ASD, correlating with sensory abnormalities (Daluwatte, Miles, Sun, & Yao, 2015). However, Nystrom et al. (2015) found that 10-month-old HR-ASD infants showed faster, stronger PLR—opposite to findings in older children and adults with ASD—suggesting PLR may be developmentally trajectory-related. Further research revealed that HR-ASD infants at 9–10 months showed greater

relative pupillary constriction than non-ASD HR infants, with constriction magnitude correlating with ASD symptom severity (Nystrom et al., 2018). These findings indicate a unique PLR developmental trajectory in ASD, with enhanced relative constriction potentially serving as an early identification marker.

ASD commonly involves auditory processing deficits, with hypersensitivity or hyposensitivity to environmental and speech sounds (Filipe, Watson, Vicente, & Frota, 2018; Lucker & Doman, 2015). Event-related potentials (ERPs) measure electrophysiological responses to repeated auditory stimuli, widely used in auditory and language processing research. Auditory ERP studies show atypical latencies and amplitudes across components including cortical slow responses (P1-N1-P2), mismatch negativity (MMN), and P3a in ASD, indicating deficits in primary auditory processing, pre-attentive processing, and higher-order auditory cognition (Vlaskamp et al., 2017). Riva et al. (2018) used ERPs to study auditory processing deficits in HR infants, testing at 12 months using an oddball paradigm and assessing auditory processing and ASD symptoms at 20 months. Results showed larger P3 amplitudes in HR-ASD infants compared to controls, with ERP results correlating with subsequent expressive language and autism assessment outcomes. Additionally, functional MRI studies of 4–7-month-old HR infants have identified atypical cortical responses to human voices (Blasi et al., 2015). Understanding and assessing auditory response characteristics is thus important for early identification and pathophysiological understanding of ASD.

Multisensory integration—the ability to effectively integrate information from different sensory modalities—is essential for perceiving diverse environments. Typically developing children prioritize multisensory information (Bahrick, Lickliter, & Flom, 2004), while this ability is impaired in ASD (Brandwein et al., 2013). Falck-Ytter et al. (2018) used prospective longitudinal methods to examine the role of impaired multisensory integration in early ASD development, specifically investigating audiovisual synchrony in visual attention as a potential early marker. Using eye-tracking tasks to assess audiovisual synchrony during biological motion observation in 10-month-old HR infants, they found that HR-ASD infants failed to attend to audiovisual synchrony, suggesting that reduced audiovisual synchrony detection in biological motion represents an early ASD symptom and that impaired multisensory integration may serve as an early marker.

Wolff et al. (2019) recently conducted a prospective longitudinal study using the Sensory Experiences Questionnaire (SEQ) in 331 HR infants (74 later diagnosed with ASD) and 135 LR infants, analyzing sensory and repetitive behaviors. Results showed that SEQ scores in HR-ASD infants began increasing at 12 months, with differences from LR infants becoming more pronounced between 12-24 months. At both 12 and 24 months, SEQ scores significantly correlated with all subtypes of restricted repetitive behaviors. This indicates that sensory abnormalities are present in the first year and become more pronounced in the second year in children with ASD.

4.1 Brain Volume

Brain overgrowth represents a major ASD developmental theory (Courchesne et al., 2007), with numerous studies showing significantly increased total brain volume in young children with ASD (Mosconi & Sweeney, 2015). Accelerated proliferation, migration, and differentiation of brain cells due to genetic predisposition and environmental insults result in abnormally enlarged brain volume during the first two years of life, followed by growth stagnation. Brain volume in adolescents and adults with ASD shows no significant differences from typical populations (Haar, Berman, Behrmann, & Dinstein, 2016).

Given early brain overgrowth and the fact that head circumference (HC) indirectly reflects brain volume and is easily measured, some researchers have proposed HC during early childhood as an early identification marker (Bartholomeusz, Courchesne, & Karns, 2002; Courchesne, Carper, & Akshoomoff, 2003; Dawson et al., 2007). However, others argue that overall developmental status affects brain growth interpretation (Campbell, Chang, & Chawarska, 2014), with some studies finding no HC differences between ASD and control groups (Suren et al., 2013). A large-scale multi-site prospective longitudinal study of 442 HR and 253 LR infants measured HC and developmental information from 6 months to 3 years, with ASD diagnosis at 36 months (Zwaigenbaum et al., 2014). Results showed no significant HC or height differences between HR-ASD and non-ASD HR infants or between HR and LR infants, leading researchers to conclude that HC cannot serve as an early identification marker. Other studies similarly do not support enlarged HC as an early ASD marker (Dinstein, Haar, Atsmon, & Schtaerman, 2017).

Magnetic resonance imaging (MRI) enables quantitative observation of early brain development in ASD. A prospective longitudinal study using high-resolution MRI found cortical surface area overgrowth between 6–12 months in HR-ASD infants, with deep learning algorithms using cortical surface area achieving 81% positive predictive value and 88% sensitivity for predicting ASD diagnosis at 24 months (Hazlett et al., 2017). The UC Davis research team conducted a series of prospective longitudinal MRI studies, first scanning 55 infants (33 HR, 22 LR) at three time points (6–9, 12–15, and 18–24 months), finding significantly increased total brain volume in HR-ASD infants at 12–15 and 18–24 months (Shen et al., 2013). Notably, they also found significantly increased extra-axial cerebrospinal fluid (EA-CSF) in HR-ASD infants as early as 6–9 months, persisting at 12–15 and 18–24 months. Subsequent larger-scale research confirmed EA-CSF volume increases at 6 months with persistent elevation at 12 and 24 months, correlating significantly with ASD symptom severity (Shen et al., 2017). These findings suggest that total brain volume and EA-CSF volume measured by MRI may serve as biological markers for early ASD identification.

4.2 Brain Connectivity

Brain connectivity refers to structural or functional connections between brain regions forming networks that support various functions and tasks. Atypical brain connectivity in ASD often precedes behavioral symptoms, holding significant importance for early identification (Belmonte et al., 2004).

Prospective longitudinal studies have demonstrated functional connectivity abnormalities in HR infants between 6–12 months (Jones et al., 2016; Vissers, Cohen, & Geurts, 2012). Jin et al. (2015) found significant white matter tract reductions in HR-ASD infants at 6 months, preceding symptom onset. Lewis and colleagues conducted a series of prospective longitudinal studies on early white matter connectivity abnormalities, first identifying reduced connectivity efficiency in temporal, parietal, occipital, and Broca's regions in HR-ASD infants diagnosed at 24 months (Lewis et al., 2014), then examining earlier effective connectivity (Lewis et al., 2017). They found connectivity deficits in low-level processing regions (temporal and occipital lobes) at 6 months in HR-ASD infants, affecting brain functional integration, cognition, and social behavior, and correlating with ASD symptom severity at 24 months.

5 Summary and Outlook

Prospective longitudinal studies of high-risk infants have enabled systematic scientific observation of early developmental processes in ASD, significantly advancing understanding of early emergence and progression while informing early identification and intervention (Soto, Giserman, & Carter, 2016).

5.1 Advantages of High-Risk Prospective Longitudinal Studies for Early ASD Identification

Unlike isolated observations at single time points, high-risk prospective longitudinal studies track infants across multiple time points, enabling clearer mapping of ASD developmental trajectories. Compared to retrospective studies, this paradigm provides more scientific understanding of early symptom manifestations and individual differences (Ozonoff et al., 2015). Advantages include prospective design, young enrollment age, long observation periods, direct assessment, standardized diagnostic procedures, and integration with neuroimaging technologies including EEG, ERPs, eye-tracking, functional near-infrared spectroscopy (fNIRS), MRI, functional MRI (fMRI), and diffusion tensor imaging (DTI) to obtain longitudinal neurobehavioral, neuroanatomical, and physiological data (Jones et al., 2014). Additionally, this approach has advanced development of early screening tools. While most existing tools target children aged 16–30 months, prospective longitudinal research has shown that the Autism Parent Screen for Infants (APSI) can differentiate ASD from non-ASD infants as early as 6 months (Sacrey et al., 2018). Further prospective longitudinal studies could extend screening tool application to infants under 18 months, even below 12 months.

5.2 Limitations of High-Risk Prospective Longitudinal Studies for Early ASD Identification

This paradigm has several limitations. First, HR infants carry substantial genetic risk, raising questions about generalizability to the general population (Szatmari et al., 2016). Second, like most longitudinal studies, intensive follow-ups every 3–6 months may affect the natural course of development and potentially influence developmental trajectories (Szatmari et al., 2016). Third, given ASD' s substantial heterogeneity in age of onset (Ozonoff et al., 2015) and symptom presentation (Kim, Macari, Koller, & Chawarska, 2016), will early markers identified in HR studies apply to other individuals (Pijl et al., 2019)? These issues warrant careful consideration in future research.

5.3 Future Directions for High-Risk Prospective Longitudinal Studies in Early ASD Identification

Future research should address several key areas. First, existing studies typically include only dozens of HR infants, with some enrolling fewer than 20 participants. Most studies also have limited time points, rarely exceeding six. Studies with more than six time points tend to have smaller samples, while those with over 100 participants have sparser time points. As this paradigm becomes more widely adopted, future studies should recruit larger samples—ideally over 30 participants, with over 100 providing greater reliability—while observing behaviors across more time points over longer durations and conducting cross-task consistency checks. Second, current research primarily focuses on ASD identification itself. However, HR infants exhibit developmental disorders beyond ASD, including epilepsy, motor disorders, language impairments, intellectual disability, sleep disorders, and ADHD (Varcin & Jeste, 2016). Future studies should validate the specificity and sensitivity of early behavioral and neurobiological markers while examining comorbid conditions to provide more comprehensive data. Third, naturalistic prospective longitudinal studies should be integrated with early intervention research (Varcin & Jeste, 2016) to identify precise intervention targets based on atypical developmental trajectories and develop early intervention strategies for HR infants. Fourth, ASD is a highly heterogeneous neurodevelopmental disorder influenced by genetic, environmental, cultural, and social factors. Chinese and Caucasian populations show different ASD genetic variants (Liang et al., 2014), with large-scale Chinese sequencing studies identifying 29 ASD high-risk genes in Chinese populations (Wang et al., 2016). Recent research indicates complex genetic underpinnings, with siblings of ASD patients sometimes carrying different ASD-related genes (Yuen et al., 2015). Environmental factors including prenatal lifestyle, infections, medication, and pollution also contribute significantly. Additionally, parental knowledge about child development, parental cognition and attitudes, and social awareness and support vary across countries and regions, affecting diagnosis and intervention (Lord et al., 2018; Norbury & Sparks, 2013). Given the absence of high-risk prospective longitudinal studies in China, the unique influences of Chinese genetic, environ-

mental, social, and cultural factors warrant thorough investigation. Conducting longitudinal studies of high-risk ASD children in China to identify behavioral and objective markers for early identification and diagnosis holds major scientific and social significance.

In summary, high-risk prospective longitudinal studies facilitate discovery of early ASD markers, mapping of developmental trajectories, multidimensional consideration of ASD manifestations, and clarification of relationships among early screening, identification, and intervention (Landa, 2018; Zhang et al., 2018). This research paradigm will see increasing application in future ASD research.

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