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## ORIGINAL ARTICLE

# Screening preterm-born infants for autistic traits may help to identify social communication difficulties at five years of age

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**Abstract**

**Aim:** This study compared neurodevelopmental screening questionnaires completed when preterm-born children reached 2 years of corrected age with social communication skills at 5.5 years of age.

**Methods:** Eligible subjects were born in 2011 at 24–34 weeks of gestation, participated in a French population-based epidemiological study and were free of motor and sensory impairment at 2 years of corrected age. The Ages and Stages Questionnaire (ASQ) and the Modified Checklist for Autism in Toddlers (M-CHAT) were used at 2 years and the Social Communication Questionnaire (SCQ) at 5.5 years of age.

**Results:** We focused on 2119 children. At 2 years of corrected age, the M-CHAT showed autistic traits in 20.7%, 18.5% and 18.2% of the children born at 24–26, 27–31 and 32–34 weeks of gestation, respectively ( $p=0.7$ ). At 5.5 years of age, 12.6%, 12.7% and 9.6% risked social communication difficulties, with an SCQ score  $\geq 90$ th percentile ( $p=0.2$ ). A positive M-CHAT score at 2 years was associated with higher risks of social communication difficulties at 5.5 years of age (odds ratio 3.46, 95% confidence interval 2.04–5.86,  $p<0.001$ ). Stratifying ASQ scores produced similar results.

**Conclusion:** Using parental neurodevelopmental screening questionnaires for preterm-born children helped to identify the risk of later social communication difficulties.

**KEYWORDS**

autism checklist, early screening, neurodevelopmental trajectories, preterm birth, social communication skills

**Abbreviations:** ASD, autism spectrum disorder; ASQ, Ages and Stages Questionnaire; CI, confidence interval; EPIPAGE-2, Epidemiological Study on Small Gestational Ages-2; M-CHAT, Modified Checklist for Autism in Toddlers; M-CHAT-R/F, M-CHAT Revised with Follow up; OR, odds ratio; SCQ, Social Communication Questionnaire; SD, standard deviation.

For affiliations refer to page 8.

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## 1 | INTRODUCTION

Children born preterm face an increased risk of developmental disabilities, including motor, sensory, cognitive and learning difficulties and emotional and behavioural dysregulation.<sup>1</sup> Deficits in social skills have also been reported, including a prevalence of autism spectrum disorder (ASD) of approximately 7%.<sup>2,3</sup> However, subclinical difficulties with social skills are more common. A preterm behavioural phenotype has been described, characterised by an increased risk of inattention, anxiety and social difficulties.<sup>4</sup> This can extend into adulthood. Approximately 31% of young adults who were born extremely preterm have been reported to have subclinical difficulties that meet the broader autism phenotype.<sup>5</sup> Screening for autistic traits in infancy may help identify individuals at risk of later social difficulties who may benefit from early interventions.

Parental questionnaires are increasingly used to improve the early identification of neurodevelopmental problems and engage families as collaborative partners in follow-up treatment.<sup>6</sup> One of the most commonly used questionnaires is the Ages and Stages Questionnaire (ASQ), which covers several dimensions of neurodevelopment.<sup>7</sup> It identifies children at risk of cognitive impairment<sup>8</sup> or later educational difficulties,<sup>9</sup> especially if they are born preterm.<sup>10</sup> The Modified Checklist for Autism in Toddlers (M-CHAT) is a screening tool for ASD in children aged 16–30 months. The M-CHAT has been shown to have good screening properties in the general population.<sup>11</sup> However, screening properties in preterm infants are limited by the high rate of motor or sensory impairments identified by the M-CHAT that are not part of ASD.<sup>12</sup> Therefore, the M-CHAT is not routinely used in the high-risk population of children born preterm. Both communication and personal-social skills are explored with the ASQ and the M-CHAT, but the M-CHAT includes questions that are more specifically related to social communication with autistic traits. We do not know whether early development screening, using a combination of the M-CHAT and the ASQ, would help to identify preterm-born children who risk social communication difficulties at school age.

The aim of this study was to investigate any associations between neurodevelopmental screening, carried out using parental questionnaires at 2 years of corrected age, and social communication skills at 5.5 years of actual age. The children included in the study were part of the French Epidemiological Study on Small Gestational Ages (EPIPAGE-2) cohort.<sup>13</sup> We hypothesised that combining the M-CHAT and ASQ at 2 years of corrected age could help identify children with social communication difficulties at 5.5 actual years of age.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

The EPIPAGE-2 study covered 25 of the 26 French regions, comprising 21 metropolitan regions and four overseas regions.<sup>13</sup> All births that took place at 22–34 weeks from 28 March to 31 December

### Key notes

- This study compared neurodevelopmental screening questionnaires, completed when 1493 preterm-born children reached 2 years of corrected age, with social communication skills at 5.5 years of age.
- At 2 years of corrected age, autistic traits were found in 20.7%, 18.5% and 18.2% of the children born at 24–26, 27–31 and 32–34 weeks of gestation, respectively.
- At 5.5 years of age, 12.6%, 12.7% and 9.6% of the children born at these gestational ages risked social communication difficulties.

2011 were eligible for inclusion in the cohort. The only region that did not participate accounted for 2.2% of all births in 2011 in France. We recruited infants born at 22–26 weeks of gestation during an eight-month period, those born at 27–31 weeks during a 6-month period and those born at 32–34 weeks during a 5-week period. The sample size was calculated to obtain a sufficient number of children at each week of gestation. After discharge, the children were enrolled in a follow-up study, with assessments at 2 years of corrected age<sup>14</sup> and at 5.5 years of actual age.<sup>15</sup> There was only one child born at 22–23 weeks of gestation who survived to discharge, but was lost to follow up at 5.5 years of age. Therefore, this age group was not included in the study.

### 2.2 | Population

Children eligible for this study were born at 24–34 weeks of gestation and were free of motor or sensory impairments at 2 years of corrected age, including congenital brain malformation, cerebral palsy, deafness or blindness. We excluded children with uninterpretable M-CHAT or ASQ questionnaires due to incomplete data, an unknown date of completion or completion outside the expected range of 22–26 months of corrected age.

### 2.3 | Follow-up evaluations

At 2 years of corrected age, parents completed the first version of the M-CHAT questionnaire and the second version of the 24-month ASQ. Both questionnaires have been validated in France.<sup>16,17</sup> One study reported that the M-CHAT was considered positive if the children failed three or more of the 23 items, indicating an increased risk of autistic traits.<sup>11</sup> It was also considered positive if they failed two or more of the six critical items.<sup>11</sup> The ASQ measures development in five dimensions: communication, gross motor, fine motor, problem solving and personal-social abilities. Parents completed the second edition of the ASQ, which was the version available in France during the study period. However, the differences between

the second and third editions are small, and we used the third edition references to analyse the results.<sup>14</sup> This meant that children were reported to be at high risk of developmental delay if any of the five ASQ domains scored below two standard deviations (SD) from the mean.<sup>7</sup> At 5.5 years of age, parents completed the lifetime version of the Social Communication Questionnaire (SCQ), which has been validated in France.<sup>18</sup> The SCQ is a 40-item screening measure that focuses on social communication skills and ASD-related behaviours, including reciprocal social interaction, communication and repetitive and stereotypical behaviours. The reference data for the SCQ were derived from contemporary term-born children assessed with the EPIPAGE-2 follow-up protocol.<sup>15</sup> In this reference group, 10% of the assessed children had a total SCQ score of  $\geq 11$ .

## 2.4 | Outcome measures

The main outcome measure was a total SCQ score  $\geq 90$ th percentile of the reference population ( $\geq 11$ ), with higher scores indicating an increased likelihood of formally diagnosed social communication difficulties. Mean SCQ scores and scores  $\geq 15$ , which are established cut-offs for ASD risk, were also considered.<sup>19</sup>

## 2.5 | Data management and statistics

First, children with and without SCQ data available at 5.5 years of age were compared using a range of maternal, pregnancy, neonatal and environmental characteristics. The same comparisons were made for children included and excluded at 2 years of corrected age. The SCQ, M-CHAT and ASQ results were reported by gestational age group at birth, namely 24–26, 27–31 and 32–34 weeks, according to the recruitment periods. We tested the statistical interaction between the M-CHAT screening scores and gestational age group in relation to the SCQ scores. The association between the M-CHAT at 2 years of corrected age and the SCQ at 5.5 years of age was tested by logistic regression for binary outcomes and linear regression for continuous outcomes. This analysis was performed in the whole population, then for both groups of children at high or low risk of developmental delay, according to the ASQ results. All the tests used generalised estimating equation models to account for the non-independence of outcomes related to multiple births. Finally, a sensitivity analysis was performed that only included singletons and children who were raised alone. The latter referred to children who were part of multiple pregnancies but lost their siblings before 2 years of corrected age.

Percentages are given with exact 95% binomial confidence intervals (95% CI), and means with SDs. The data were weighted to account for the study design with different recruitment periods. We present results for complete cases and, after multiple imputations to account for selective dropouts and missing information at 5.5 years of age. Variables in the imputation model included those that potentially predicted non-responses or outcomes (Table S1). Missing

data were imputed by chained equations with the SAS Multiple Imputation procedure (SAS Institute Inc., North Carolina, USA).<sup>20</sup> Predictive mean matching was used for continuous variables, logistic regression for binary variable and multinomial regression for categorical variables. We generated 50 independent imputed data sets, each with 30 iterations. Estimates were pooled according to Rubin's rules.<sup>21</sup>

## 2.6 | Ethics

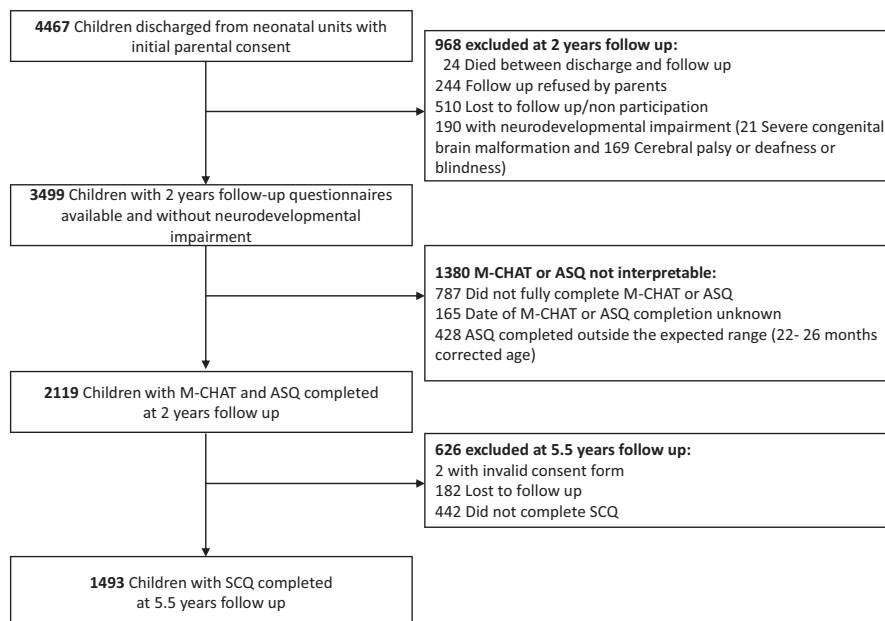
The parents provided written, informed consent and the study was approved by the National Data Protection Authority (DR-2016-290). Agreements were also obtained from the Consultative Committee on the Treatment of Data on Personal Health for Research Purposes (N 16.263) and from the Committee for the Protection of People Participating in Biomedical Research (2016-A00333-48).

## 3 | RESULTS

The study comprised 2119 of the 4467 infants who were eligible for follow-up after their hospital discharge, as their parents had completed the M-CHAT and ASQ questionnaires at 22–26 months of corrected age. Of those, 1493 had a complete SCQ at 5.5 years of age (Figure 1). The mothers of children included in the analysis at 5.5 years of age were younger, more likely to be primiparous, born in France and lived with their partner. They also had more social insurance coverage, which is an indirect measure of wealth in France, and a higher level of education than the mothers of the excluded children (Table S2). There was no difference in gestational age and other neonatal characteristics. At 2 years of corrected age, the children who were included in the study were more likely to live with both parents in a French-speaking environment and less likely to have a positive M-CHAT than the excluded children (Table S2).

At 5.5 years of age, 12.6% of children born at 24–26 weeks of gestation had SCQ scores of  $\geq 90$ th percentile. It was 12.7% for children born at 27–31 weeks and 9.6% for those born at 32–34 weeks ( $p=0.2$ ) (Table 1). The various SCQ measures did not differ significantly between the gestational age groups. Figure S1 indicates how the SCQ scores were divided across the analysed population.

At 2 years of corrected age, 20.7%, 18.5% and 18.2% of the children born at 24–26, 27–31 and 32–34 weeks of gestation had a positive M-CHAT score with no significant differences across gestational age groups (Table 1). These rates were lower when the critical M-CHAT items were analysed. Moreover, they decreased with increasing gestational age, ranging from 4.5% among children born at 24–26 weeks of gestation to 1.2% among children born at 32–34 weeks ( $p=0.01$ ). The proportions of children at risk of developmental delay, according to the ASQ, decreased significantly with increasing gestational age, ranging from 49.1% among children born at 24–26 weeks of gestation to 36.7% of children born at 32–34 weeks ( $p=0.01$ ).

**FIGURE 1** Flow chart of the study population.

The distribution of different combinations of ASQ and M-CHAT results differed significantly between the gestational age groups (Figure 2).

Children with a positive M-CHAT at 2 years of corrected age were more likely to have social communication difficulties at 5.5 years of age. Of the children with a positive M-CHAT score, 21.5% (95% CI 15.0–28.0) had SCQ scores of  $\geq 90$ th percentile at 5.5 years, compared to 7.3% (95% CI 5.4–9.2) of children with a negative M-CHAT. The odds ratio (OR) was 3.46 (95% CI 2.04–5.86,  $p < 0.0001$ ). There were no significant interactions between the M-CHAT scores and the gestational age groups.

Significant associations between positive M-CHAT scores and social communication difficulties at 5.5 years of age were found. These referred to both children with a high and low risk of developmental delay, according to the ASQ at 2 years of corrected age: OR 2.76 (95% CI 1.53–4.99) and OR 3.90, (95% CI 1.78–8.53) respectively (Table 2). All the SCQ domains showed the same trend, but the associations were not statistically significant for the communication domain in children at high risk. When only the critical items of the M-CHAT were considered, the associations were similar in the high-risk group (Table S3). In the low-risk group, a positive critical M-CHAT was associated with a significant increase in the SCQ scores at 5.5 years of age. Sensitivity analyses of children raised as singletons showed the same trends (Table S4).

## 4 | DISCUSSION

This study focused on a large cohort of children who were born preterm and were free of motor and sensory impairments at 2 years of corrected age. When they were followed up at 5.5 years of actual age, their risk of social communication difficulties were 12.6%, 12.7% and 9.6% when they were born at 24–26, 27–31 and 32–34 weeks of gestation, respectively. The risks of autistic

traits at 2 years of corrected age were 20.7%, 18.5% and 18.2%, respectively. These rates were assessed by parental questionnaires and were similar across gestational age groups. An increased risk of having autistic traits at 2 years of corrected age was associated with an increased risk of social communication difficulties at 5.5 years of age, regardless of the ASQ scores.

We used standardised parental questionnaires, which have been shown to have satisfactory screening properties for developmental delay, autistic traits and social communication difficulties. However, they are not diagnostic instruments. The lack of formal assessments meant that we were unable to estimate the prevalence of ASD in our population. Parents completed the second edition of the ASQ, which was the version available in France during the study period. However, the differences between the second and third editions are small, and we used the third edition references to analyse the results, as it had better psychometric properties to evaluate social communication. Its use has been validated in extremely preterm populations.<sup>4</sup> Several cut-off points have been discussed in the literature:  $\geq 15$  allows the user to screen for ASD, but  $\geq 14$  has been reported to have optimal diagnostic use in extremely preterm populations.<sup>4</sup> A liberal cut-off of  $\geq 9$  was used in a regional cohort of children born at  $< 2000$ g.<sup>22</sup> This study focused on social communication difficulties that fell outside the diagnostic threshold of ASD, as larger proportions of children born preterm are affected by subclinical difficulties.<sup>4,5</sup> We therefore defined the risk of social communication difficulties as an SCQ score of  $\geq 90$ th percentile of our reference sample of contemporary term-born children examined with the same protocol.<sup>15</sup> In our population, the proportions of children born preterm with an SCQ score of  $\geq 90$ th percentile were close to the reference sample of term-born children, which is reassuring for parents and professionals. However, two important points should be considered when interpreting these results. First, we only analysed children who did not have motor and sensory impairments, and social communication difficulties are likely to be more frequent in children with such impairments. Second, we have previously shown

**TABLE 1** Screening for autistic traits and developmental delay with the Modified Checklist for Autism in Toddlers (M-CHAT) and the Ages and Stages Questionnaire (ASQ) at 2 years of corrected age and scores for the Social Communication Questionnaire (SCQ) at 5.5 years of age.

	Gestational age			p value <sup>e</sup>
	24–26 weeks	27–31 weeks	32–34 weeks	
<b>At 2 years of corrected age (N = 2119)</b>	N = 246	N = 1328	N = 545	
High risk of autistic traits (M-CHAT)				
Positive M-CHAT <sup>a</sup> , n	51	246	99	
% (95% CI)	20.7 (15.7–25.8)	18.5 (16.4–20.6)	18.2 (14.9–21.4)	0.7
Positive Critical M-CHAT <sup>b</sup> , n	11	43	7	
% (95% CI)	4.5 (1.9–7.0)	3.2 (2.3–4.2)	1.2 (0.3–2.2)	0.01
High risk of developmental delay (ASQ) <sup>c</sup>				
n	121	531	200	
% (95% CI)	49.1 (42.9–55.4)	39.9 (37.3–42.6)	36.7 (32.6–40.7)	0.01
<b>At 5.5 years of age (N = 1493)</b>	N = 172	N = 943	N = 378	
High risk of social communication difficulties				
SCQ score ≥ 90th percentile <sup>d</sup> , n	19	112	32	
% (95% CI), CC	11.0 (6.3–15.7)	11.9 (9.8–13.9)	8.5 (5.6–11.3)	0.2
% (95% CI), MI	12.6 (7.8–17.4)	12.7 (10.7–14.7)	9.6 (6.8–12.4)	0.2
SCQ score, mean (95% CI), CC	5.3 (5.0–6.3)	5.52 (5.3–5.8)	5.1 (4.7–5.4)	0.1
SCQ score, mean (95% CI), MI	5.9 (5.3–6.5)	5.74 (5.5–6.0)	5.3 (5.00–5.7)	0.1
SCQ score ≥ 15, n	4	24	1	
% (95% CI), CC	2.3 (0.1–4.6)	2.5 (1.5–3.6)	0.3 (0.0–0.8)	0.2
% (95% CI), MI	3.2 (0.6–5.7)	3.0 (2.0–4.0)	1.3 (0.1–2.5)	0.1

Note: Percentages are weighted considering the study design.

Abbreviations: 95% CI, 95% confidence interval; ASQ, Ages and Stages Questionnaire; CC, complete case; M-CHAT, Modified Checklist for Autism in Toddlers; MI, multiple imputation; SCQ, Social Communication Questionnaire.

<sup>a</sup>Positive M-CHAT is defined by at least 3 of the 23 items failed.

<sup>b</sup>Positive critical M-CHAT is defined by at least 2 of 6 critical items failed.

<sup>c</sup>High risk of developmental delay is defined by an ASQ score < -2 SDs from the mean in any of the five ASQ domains.

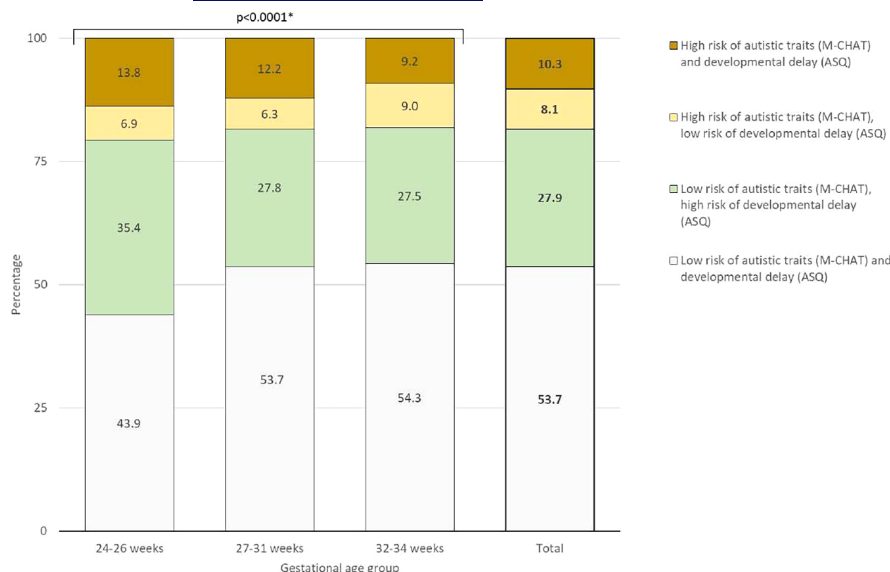
<sup>d</sup>SCQ score ≥ 90th percentile of the reference group of term-born children corresponds to SCQ score ≥ 11.

<sup>e</sup>p value comparing gestational groups. Tests based on generalised estimated equation to account for non-independence between children related to multiple birth.

that the children in our reference sample had slightly more behavioural difficulties, as reported by their parents, than in the general population.<sup>15</sup> This may have helped to underestimate the SCQ scores ≥ 90th percentile in the preterm population. The mean SCQ score of 5.3 in our extremely preterm population was lower than the mean score of 8.0 reported in the UK EPICure cohort,<sup>5</sup> but that study evaluated children at 11 years of age, when social communication difficulties may have been more apparent. Screening in middle childhood has greater discriminative validity for social communication difficulties, due to the emergence of social and behavioural competencies.<sup>4</sup> Rates of positive M-CHAT in the EPIPAGE-2 cohort were similar to those observed in other cohorts or large databases of children born preterm after children with motor and sensory impairment were excluded. These were 16.5% in the EPICure-2 study in the United Kingdom and Ireland,<sup>4</sup> 14.5% in a UK regional cohort of children born at 32–36 weeks<sup>23</sup> and 16% in the Extremely Low Gestational Age Newborn cohort in the United States.<sup>24</sup> Interestingly, the rates of positive M-CHAT in our

study were not statistically different among gestational age groups. However, differences were observed when only critical items were used to interpret the M-CHAT, with higher rates of positive critical M-CHAT with decreasing gestational age. Another M-CHAT screening study that only used critical items was more predictive of a later diagnosis of ASD than failing three items overall.<sup>11</sup> This may suggest that autistic traits are more severe in children born extremely preterm. The M-CHAT was updated in 2014, 1 year after our data collection, by the M-CHAT-R/F.<sup>25</sup> Using the M-CHAT-R/F may have reduced the initial screen-positive rate described in the general population. The predictive value of the M-CHAT-R/F for ASD is better when a follow-up interview is performed. Nevertheless, as we focused on the preterm behavioural phenotype rather than on ASD per se, it is unlikely that using the M-CHAT-R/F would have changed the associations between the M-CHAT and the SCQ at 5.5 years of age.

Children with a positive M-CHAT had higher risks of social communication difficulties at 5.5 years of age. This was verified in



**FIGURE 2** Screening with the Modified Checklist for Autism in Toddlers (M-CHAT) and the Ages and Stages Questionnaire (ASQ) at 2 years of corrected age by gestational age groups at birth.

children with a high or low risk of developmental delay at 2 years of corrected age. All SCQ domains were failed, suggesting a global vulnerability in social communication that should be considered by organisations following children up. These days, pathways to psychopathology following preterm birth are usually described as a complex interplay between structural and functional alterations in the brain areas involved in processing emotions and social stimuli, biological vulnerability and parenting strategies.<sup>26</sup> This vulnerability may only clinically manifest itself when social demands become more complex.<sup>26</sup> In the EPICure cohort, children born extremely preterm were more likely to have an ASD diagnosis at 11 years of age if they displayed withdrawn behaviour at 2.5 years of age and cognitive impairment and peer relationship problems at 6 years of age.<sup>27</sup> Another study found that SCQ scores at 11 years were significantly correlated with scores for the broader autism phenotype questionnaire at 19 years of age.<sup>5</sup> This indicated a moderate association between autistic traits in childhood and early adulthood that was not found in the control group.<sup>5</sup> Identifying children at risk of later social difficulties at an early age may mean they are offered social skills training, which is effective in populations with ASD.<sup>28</sup>

The M-CHAT and ASQ questionnaires have complementary approaches. For example, they both explore motor skills. The ASQ is designed to recognise whether a specific development step has been reached, whereas the M-CHAT is more focused on how the task is carried out. In addition, the M-CHAT includes questions that are specifically focused on social communication, such as the ability to point with one finger to ask for something or to display joint attention. Responding to both questionnaires at the same time could be seen as unnecessary and time-consuming by parents and limit the validity of the answers. The ASQ-Social-Emotional questionnaire was not available during the EPIPAGE-2 data collection. It is designed to specifically screen for social and emotional development.<sup>29</sup> Including this questionnaire in the developmental screening of preterm-born children at 2 years of corrected age could be an

alternative to using both the ASQ and M-CHAT, especially in children without motor or sensory impairments.

#### 4.1 | Strengths and limitations

The strengths of this study include the national population-based cohort design, which prospectively enrolled a large number of infants born extremely, very and moderately preterm. Routine screening of autistic traits in preterm children is discussed because of high false-positive screenings due to motor or sensory impairments.<sup>12</sup> The large size of the cohort allowed us to exclude children with brain malformations, cerebral palsy or sensory impairments. This adds information on using M-CHAT screening for autistic traits in infants born preterm. However, the selection bias inherent in long-term follow-up studies was a limitation. Loss of follow-up was particularly prevalent in families with low socioeconomic status and young mothers, but also in children with a positive M-CHAT at 2 years of corrected age. This could have contributed to underestimating the prevalence of children with high SCQ scores. We used multiple imputation to account for missing data at 5.5 years. This resulted in higher rates of SCQ scores  $\geq 90$ th percentile at all gestational ages, which was consistent with the characteristics of the children excluded from the analysis.

#### 5 | CONCLUSION

This study suggests that rates of social communication difficulties in children born preterm, without motor or sensory impairments, were close to those of the general population. However, the risk was three times higher for children with autistic traits in infancy, irrespective of the risk of developmental delay. Early screening for autistic traits in infancy may add useful information to neurodevelopmental screening. Identifying risks at an early age

**TABLE 2** Social Communication Questionnaire (SCQ) scores at 5.5 years of age according to screenings with the Ages and Stages Questionnaire (ASQ) and the Modified Checklist for Autism in Toddlers (M-CHAT) at two years of corrected age.

	High risk of developmental delay (ASQ) <sup>a</sup>						Low risk of developmental delay (ASQ) <sup>a</sup>					
	Negative M-CHAT <sup>b</sup>			Positive M-CHAT <sup>b</sup>			Negative M-CHAT <sup>b</sup>			Positive M-CHAT <sup>b</sup>		
	n/N	% or mean (95% CI)	p value <sup>e</sup>	n/N	% or mean (95% CI)	p value <sup>e</sup>	n/N	% or mean (95% CI)	p value <sup>e</sup>	n/N	% or mean (95% CI)	p value <sup>e</sup>
SCQ scores ≥ 90th percentile <sup>c</sup> , %	CC 50/430	12.0 (7.8–16.2)	44/161	22.4 (14.1–30.8)	2.08 (1.08; 4.00)	0.02	48/800	4.8 (3.0–6.7)	21/102	20.3 (9.9–30.6)	5.14 (2.16; 12.19)	<0.01
	MI	11.9 (8.1–15.7)		27.4 (18.7–36.1)	2.76 (1.53; 4.99)	<0.001		5.6 (3.7–7.6)		18.4 (9.0–27.8)	3.90 (1.78; 8.53)	<0.01
Total SCQ score, mean	CC 430	5.6 (5.2–6.1)	161	7.5 (6.9–8.2)	1.87 (1.04; 2.70)	<0.001	800	4.4 (4.2–4.7)	102	6.8 (5.8–7.7)	2.32 (1.24; 3.41)	<0.001
	MI	5.8 (5.3–6.2)		8.2 (7.3–9.0)	2.40 (1.42; 3.38)	<0.001		4.7 (4.4–5.0)		6.7 (5.8–7.6)	2.07 (1.08; 3.05)	<0.001
Reciprocal social interactions, mean	CC 436	1.2 (1.0–1.4)	166	2.0 (1.7–2.3)	0.79 (0.39; 1.18)	<0.001	823	0.8 (0.7–0.9)	103	1.4 (1.1–1.8)	0.67 (0.29; 1.05)	<0.001
	MI	1.2 (1.0–1.4)		2.1 (1.8–2.5)	0.94 (0.51; 1.38)	<0.001		0.8 (0.7–0.9)		1.4 (1.0–1.7)	0.57 (0.21; 0.92)	<0.01
Communication, mean	CC 430	2.6 (2.4–2.9)	164	2.9 (2.4–3.3)	0.27 (–0.27; 0.82)	0.3	806	2.0 (1.8–2.1)	103	2.9 (2.4–3.4)	0.87 (0.31; 1.42)	<0.01
	MI	2.6 (2.4–2.8)		3.0 (2.6–3.4)	0.38 (–0.11; 0.88)	0.1		2.1 (1.9–2.2)		2.7 (2.3–3.2)	0.69 (0.20; 1.17)	<0.01
Repetitive and stereotyped behaviours, mean	CC 436	1.5 (1.3–1.7)	168	2.5 (2.1–2.9)	0.97 (0.36; 1.58)	<0.01	819	1.4 (1.3–1.6)	104	2.1 (1.6–2.6)	0.68 (0.08; 1.28)	0.03
	MI	1.6 (1.4–1.8)		2.5 (2.1–3.0)	0.89 (0.36; 1.43)	0.001		1.5 (1.4–1.7)		2.2 (1.6–2.7)	0.69 (0.11; 1.26)	0.02

Note: Percentages are weighted considering the study design.

Abbreviations: 95% CI, 95% confidence interval; ASQ, Ages and Stages Questionnaire; CC, complete case; M-CHAT, Modified Checklist for Autism in Toddlers; MI, multiple imputation; OR, odds ratio; SCQ, Social Communication Questionnaire; SD, standard deviation.

<sup>a</sup>Risk of developmental delay defined as high (ASQ score < –2 SDs from the mean on any of the 5 ASQ domains) or low (ASQ score ≥ –2 SDs from the mean on any of the 5 ASQ domains).

<sup>b</sup>Positive M-CHAT if ≥3 of any 23 total items failed, negative M-CHAT if <3 of any 23 items failed.

<sup>c</sup>SCQ score ≥ 11, 90th percentile of the reference group of term-born children.

<sup>d</sup>OR for SCQ ≥ 90th percentile, β coefficients for all other variables.

<sup>e</sup>p value for comparison across gestational groups. Tests based on generalised estimated equation to account for non-independence between children related to multiple births.



and engaging parents in behaviours that support the development of social communication may help reduce the risk of later mental health disorders.

## AUTHOR CONTRIBUTIONS

**Héloïse Torchin:** Conceptualization; writing – original draft; supervision; methodology. **Muriel Tafflet:** Data curation; formal analysis; writing – original draft; methodology. **Marie-Laure Charkaluk:** Investigation; writing – review and editing; validation. **Mathilde Letouzey:** Writing – review and editing; validation. **Sabrina Twillhaar:** Writing – review and editing; validation. **Gildas Kana:** Methodology; data curation; formal analysis. **Valérie Benhammou:** Funding acquisition; resources; project administration; investigation. **Stéphane Marret:** Conceptualization; methodology; investigation; writing – review and editing. **Eliane Basson:** Writing – review and editing; validation; investigation. **Gilles Cambonie:** Writing – review and editing; validation; investigation. **Valérie Datin-Dorrière:** Writing – review and editing; validation; investigation. **Isabelle Guellec:** Writing – review and editing; validation; investigation. **Cécile Lebeaux:** Project administration; investigation; funding acquisition. **Jean-Baptiste Muller:** Writing – review and editing; validation; investigation. **Alexandra Nuytten:** Investigation; writing – review and editing; validation. **Monique Kaminski:** Methodology; supervision; writing – review and editing. **Pierre-Yves Ancel:** Methodology; supervision; project administration; resources; funding acquisition; validation. **Véronique Pierrat:** Conceptualization; formal analysis; writing – original draft; methodology; investigation; funding acquisition; resources.

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## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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## DATA AVAILABILITY STATEMENT

The EPIPAGE studies are subject to a data sharing policy. The datasets analysed during the current study are available on reasonable request.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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