NEW RESEARCH

Maternal Migration, Prenatal Stress and Child Autistic Traits: Insights From a Population-Based Cohort Study

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Objective: There is emerging evidence for an increased prevalence of autism in children of mothers with a migration background. To date, the mechanisms underlying this relationship are poorly understood. We investigated whether prenatal stress exposure mediates the association between maternal migration and child autistic traits, assessing first- and second-generation migrant mothers in the Netherlands and their children.

Method: The study was embedded in the prospective population-based Generation R cohort. Of the 4,727 participants, 1,773 mothers (38%) had a migration background. Prenatal stress was assessed using questionnaires related to stressful life events, family functioning, self-esteem, long-lasting difficulties, symptoms of psychopathology, social support, and perceived discrimination. Autistic traits were measured at age 6 years with the parent-reported Social Responsiveness Scale exclusively. Longitudinal multiple mediation analyses were performed. Analyses were stratified by migration origin (Europe and outside Europe) because of differences in migration characteristics.

Results: Maternal migration background was associated with more experienced stress and with higher child autistic trait scores (Europe: mean = 0.42, SD = 0.25; outside Europe: mean = 0.50, SD = 0.24) compared to no migration background (Netherlands: mean = 0.38, SD = 0.23; both $p < .01$). Prenatal stress, especially perceived discrimination and maternal psychopathology, accounted for up to half of the total effect of maternal migration, which remained after adjusting for sociodemographic factors ($B_{indirect} = 0.035$, 95% CI = 0.027, 0.043, $B_{total} = 0.074$).

Conclusion: Stress during pregnancy mediated the association between maternal migration status and child autistic traits. Future research should focus on early interventions to assess whether reducing prenatal stress exposure among women with a migration background can result in lower offspring autistic traits.

Diversity & Inclusion Statement: We worked to ensure that the study questionnaires were prepared in an inclusive way. We worked to ensure sex and gender balance in the recruitment of human participants. We worked to ensure race, ethnic, and/or other types of diversity in the recruitment of human participants. We actively worked to promote sex and gender balance in our author group. The author list of this paper includes contributors from the location and/or community where the research was conducted who participated in the data collection, design, analysis, and/or interpretation of the work.

Key words: autism spectrum disorder; migrant; ethnic minority; discrimination; prenatal stress

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The number of migrants worldwide is higher than ever before; yet this group remains more prone to health-related issues than host populations.[1-3] Only recently, the World Health Organization advocated addressing the health needs among migrants, defining a migrant as "a person who moves from one place to another."[2] In addition, the Lancet Commission on Migration and Health reported evidence for an increased autism prevalence in children of migrants.[3] Autism (or autism spectrum disorder) reflects a diverse group of conditions, characterized by unique challenges and strengths in social communication and interaction, and characteristic patterns of sensory–motor behaviors.[4] Given the impact of autism on individuals' daily life, it is important to gain a full understanding of its possible preventable underlying pathways.[5] Established global literature has shown that the risk of autism among children of migrant parents is 2-sided: the risk is increased in narrowly defined autism and reduced in high-functioning autism.[6,7] A study in the Netherlands suggested that this reduced risk of high-functioning autism in children of migrant parents may be due to racial or ascertainment bias.[8] In general, a potential measurement bias due to cross-cultural challenges in the identification, help-seeking, and diagnostic process of autism must not be ignored.[9] However, despite this potential role of bias, evidence suggests true differences exist in the prevalence of

autism among children of migrant parents.[10,11] To date, the mechanisms underlying this relationship are poorly understood.[7]

The Lancet Commission on Migration and Health refers to the so-called "migration theory of autism,"[12] which suggests that the increased autism risk among children of migrant parents may be mediated by parents' reactions to stress, as, even in the best circumstances, migration is stressful.[3] This potential underlying mechanism of stress may particularly play a role in utero,[6,7,12,13] as exposure to intrauterine stress is a risk factor for a wide array of developmental disorders.[14,15] These findings are grounded in the concept of "fetal programming," which states that environmental exposures during pregnancy can influence the later developmental trajectory of the child.[16] In the field of autism research, there is a substantial body of evidence suggesting a link of psychosocial stress in utero with an increased risk of autism and autistic traits in the general population.[14,17-21] For instance, a population-based study including more than 2 million Swedish participants found that the loss of a first-degree relative, especially in the third trimester, was associated with an increased risk of autism in the offspring.[17] Similar results were found for other stressful prenatal life events such as the experience of a hurricane[18] or exposure to partner abuse.[20] However, most studies focused on one (or a few) of these specific prenatal stressful life events, whereas studies examining a range of possible long-term stressors, such as difficulties in work or family life, are lacking.

The high stress levels that mothers with a migration background often experience may reflect an accumulative effect of social disadvantage in the periods before, during, and after migration.[22] The exposure to traumas such as armed conflicts, severe poverty, food insecurity, or violence, let alone the lack of opportunities for development and education, may cause migrants to flee.[23] The act of migration frequently entails life-threatening experiences.[22] When having arrived in a host country, migrants may again face stressors related to the asylum procedure, such as structural racism, acculturation difficulties, financial hardship, ongoing family separation, social isolation, and discrimination.[22] Stressors in each of these periods are associated with poorer mental health outcomes of migrants and their offspring, as compared to the host population.[2,3,22,23]

This prospective, population-based cohort study is, to our knowledge, the first that aims to examine the potential mediating role of a wide range of prenatal maternal stressors in the association between maternal migration status and child autistic traits. The questions addressed in this paper are as follows: what is the association between maternal migration and offspring autistic traits in a population-based sample, and to what extent do prenatal maternal stress indicators mediate this possible association? The term "migrant" in this paper refers to the "international migrant," defined as "any person who changes his or her country of usual residence."[2] The "mothers with a migration background" in our study cohort were pregnant with their participating child while living in the Netherlands, and either had moved to the Netherlands earlier in life (first-generation migrant) or their parents did (second-generation migrant). To enable a longitudinal prospective examination of the link between a wide range of stressors in a sample of mothers with a migration background and later autistic traits in the offspring, a population-based approach was used. This approach also decreases the risk of an ascertainment bias due to possible barriers in seeking or receiving clinical help. Consequently, we focused on a continuum of autistic traits in the general population, rather than on a diagnosis of autism in a clinical sample. We assessed a spectrum of autistic traits related to social cognition, social communication, and stereotypic mannerisms. In line with the "migration theory of autism," we hypothesized a mediating role of prenatal stressors in the association between maternal migration and child autistic traits. Such information offers directions for future (clinical) research, policy, and practice in the autism field.

METHOD

Study Design and Participants

Data from the Generation R Study were used. This is a multi-ethnic, population-based cohort in Rotterdam, the Netherlands. Women with a delivery date between April 2002 and January 2006 were recruited in early pregnancy (gestational age <18 weeks), and their children were followed from fetal life onward. A total of 8,976 mothers were included in pregnancy. Of these, 7,258 mothers and children participated in follow-up at mid-childhood. Participants with missing data on child autistic traits (n = 2,531) were excluded, yielding a sample size of 4,727 mother–child dyads for the present study (flowchart in Figure S1). All questionnaires were available in Dutch, English, and Turkish. If participants were unable to read these languages, research assistants speaking Arabic, Berber, English, French, Portuguese, or Turkish helped with filling out the questionnaires. The study protocol was approved by the Medical Ethics Committee. Parents and children provided written informed consent and assent, respectively. More details about the Generation R Study, the procedure of enrollment, and follow up assessments are described elsewhere.[24]

Exposure

Information on maternal migration background was obtained by a self-report questionnaire at enrollment in the study in early pregnancy. A mother was classified as having a country of origin outside the Netherlands (ie, migration background) if she or at least one of her parents was born abroad, following the definition of Statistics Netherlands.[25] Migration background was divided into originating from a European country (n = 383) or from outside Europe (n = 1,390), because of differences in migration characteritics. European countries[25,26] mostly included surrounding countries of the Netherlands (ie, Belgium, France, Germany, Great Britain). The main countries of origin outside Europe were Cape Verde (n = 135), Dutch Antilles (n = 80), Indonesia (n = 161), Morocco (n = 173), Suriname (n = 284), Turkey (n = 311), and other countries (n = 246), which represent the general distribution in the Rotterdam study area.[24] In the main analyses of this study, the subdivisions "the Netherlands," "Europe," and "outside Europe" were used.

Outcome

Child autistic traits were assessed using the parent-reported Social Responsiveness Scale (SRS) at 6 years of age.[27] By this age, both clinical and more subtle autistic traits would have been noticed. The SRS is a reliable quantitative questionnaire measuring autistic symptomatology and severity in the general population.[27] The questionnaire has been translated into more than 20 languages and has been validated in various countries, supporting the cross-cultural use of the questionnaire.[7] To minimize subject burden, an 18-item short version of the scale was used (Table S1, available online). It has been developed within Generation R, in consultation with the original SRS test developer, as described by Román *et al.*[28]

This version has been shown to correlate highly with the full SRS scale (Table S1, available online).[29,30] We analyzed the continuous score of the SRS because no cut-off score of the SRS short form is available. Nonetheless, the SRS gains a good impression of autistic traits and is routinely used for screening in clinical practice in the Netherlands. The SRS consists of 3 subscales, assessing Social Cognition (5 items), Social Communication (8 items), and Mannerisms (5 items). All items are scored on a 4-point Likert scale, from "never true" (0) to "almost always true" (3), assessing parental observations (mostly mothers, 91%) of child behavior in the past 6 months. Higher scores indicate more autistic traits.

Mediators

To measure different domains of stress exposure, 7 questionnaires were used (Table 1[27,31-36]). These self-report questionnaires are related to maternal symptoms of psychopathology, self-esteem, stressful life events, family functioning, long-lasting difficulties, social support and perceived discrimination, as described below.

Life Events. Life events were assessed making use of the List of Threatening Experiences, short version (10 items).[31] This is a modified version of the Social Readjustment Rating Scale,[37] which evaluates the extent of impactful life events in the past year. Answering options were dichotomous (yes/no). Every item was connected to an impact score (Life Changing Unit), ranging from 0 (no event) to 123 (event with highest impact).[37] The impact scores were added up per participant, resulting in a sum score. A higher sum score indicated more impactful life events. Examples of questions are, "Has one of your children died?" and "Did you divorce or break off the relationship with your partner?"

Long-Lasting Difficulties. The Long Lasting Difficulties Inventory is a validated questionnaire intended to measure chronic stressors in the longer term.[31] The 12 items assess chronic stressors in life, related to housing, work and free time. The questionnaire contains questions such as, "Have you had problems with or at your work?" and "Have there been difficulties between you and your partner?" It is measured on a 3-point scale, from not stressful (0) to very stressful (2). A higher average sum score indicates more stressful long-lasting difficulties.

Family Functioning. To assess family functioning, the Family Assessment Device—General Functioning (FAD-GF) subscale was used.[36] The FAD is a valid self-report instrument that provides an impression of overall family health and pathology.[36] The questions contain 12 statements about the current family functioning, with responses ranging from totally disagree (0) to fully agree (4). Examples of statements are "We trust each other" and "People in our family accept each other as they are." Higher average sum scores indicate poorer family functioning.

Self-Esteem. A modified version of the Rosenberg Self-Esteem Scale was administered.[32] The Rosenberg Self-Esteem Scale is a reliable self-report questionnaire used in up to 53 nations.[32] This instrument consisted of statements such as "In most areas, my life is ideal" and "I sometimes think I am worthless" (reverse coded), with responses ranging from totally disagree (0) to fully agree (4). Higher average sum scores indicate higher self–esteem.

Psychopathology. Maternal symptoms of psychopathology were assessed using the Brief Symptom Inventory

TABLE 1 Overview of Variables Included in the Study

	Time point	Questionnaire[a]	Details
Exposure (self-report)			
Maternal country of origin	First trimester	Multiple choice question specifying different countries and an "other" category	Based on country of birth, as defined by Statistics Netherlands[25]
Mediators (self-report)			
Life events	Second trimester	List Threatening Experiences[31]	Presence of stressful life events, such as loss of a child
Long-lasting difficulties	Second trimester	Long Lasting Difficulties Inventory[31]	Presence of long-lasting stressors such as difficulties at work
Family functioning	Second trimester	Family Assessment Device[36]	Statements about family functioning, such as being able to express feelings toward each other
Self-esteem	Third trimester	Rosenberg Self-Esteem Scale[32]	Statements about the way one thinks about oneself
Psychopathology	Second trimester	Brief Symptom Inventory[33]	Presence of physical or emotional problems in the past week
Social Support	6 Months postpartum	Social Support List[34]	Questions related to received everyday support, support in problem situations, and esteem support
Perceived discrimination	Third trimester	Perceived Discrimination Scale[35]	Statements related to individual discrimination, such as being teased or insulted because of one's ethnicity
Outcome (parent report)			
Child autistic traits	Age 6 y	Social Responsiveness Scale (SRS-short)[27]	18-Item questionnaire, measuring autistic symptomatology and severity in the general population
Covariates (self -and parent-report)			
Child: gestational age	At birth	Medical record	In months
Child: weight	At birth	Medical record	In grams
Child: sex	At birth	Medical record	Defined as male/female
Mother: education level	First trimester	Multiple choice question	Self-reported, subdivided in primary/secondary/higher

Note: [a]*All questionnaires are available upon request.*

(BSI).[33] The BSI is a validated questionnaire with 53 self-appraisal statements about the past 7 days related to somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. All questions can be answered on a 5-point Likert scale, from not at all (0) to continually (4). Items are summed to create the overall Global Severity Index score. A higher score represents more distress.

Social Support. To assess social support, the Social Support List–Interaction was used.[34] The original 53-item version has been adapted into a validated shorter version with 12 items.[34] The items focus on received everyday support, support in problem situations, and support in improving self-esteem. Examples of questions are as follows: "Do others sometimes offer to help to look after the children?" "Do others sometimes invite you to join them for a party or meal?" "Do others pay you compliments?" Questions were

answered on a 4-point scale, from seldom/never (1) to often (4). A higher sum score indicates more social support.

Perceived Discrimination. The degree of perceived discrimination was assessed based on a scale developed by the International Comparative Study of Ethnocultural Youth, a large study on the acculturation of migrant adolescents in different countries including the Netherlands.[35] The scale has a good to excellent reliability.[35,38] Four statements related to individual discrimination were assessed: "I feel Dutch people have something against me"; "I have been teased or insulted because of my ethnic background"; 'I have been threatened or attacked because of my ethnic background"; and "I do not feel accepted by Dutch people." Item responses are given on a 5-point Likert scale, ranging from totally disagree (1) to fully agree (5). Higher average sum scores indicate more perceived discrimination.

Covariates. Considered child-related covariates are gestational age at birth, birth weight, and sex (male/female), which were obtained from medical records completed by obstetricians and community midwives. Maternal education, based on self-report questions during the first trimester of pregnancy, was also included as a covariate. The highest obtained education level was classified into 3 categories, based on the classification of Statistics Netherlands[39]: lower (primary school or lower vocational training), medium (lower and intermediate vocational training), and higher (higher vocational training and university).

Statistical Analyses

Descriptive statistics and correlations between study variables were calculated. Parallel mediation analyses were executed with regression-based path analyses, using the PROCESS approach model 4 (test of multiple mediation) provided by Hayes.[40] The mediation analyses were performed twice, both with Dutch country of origin as reference. The first set included migration backgrounds from outside Europe, and the second set included migration backgrounds from within Europe. In all analyses, the SRS sum score was included as the dependent variable, and 7 prenatal stress indicators were included as the potential mediating variables. To approach normal distributions, the SRS and all potential mediators except for social support were square root transformed in the regression models. Missing values in mediators and covariates were handled using Multivariate Imputation by Chained Equations (MICE).[41] We created 20 imputed datasets. The number of bootstrap samples for bias-corrected bootstrap confidence intervals in all analyses was 10,000, setting the seed parameter on 500,000. As the PROCESS approach does not integrate with multiple imputation procedures, the parallel mediation analyses were conducted 20 times, in each imputed dataset separately. Results are presented for one imputed dataset, including a reflection on results in the other 19 imputed datasets. We focus on unstandardized effect sizes (B), because partially standardized effect sizes (β) of a dichotomous exposure variable should be considered with caution, as they can be influenced by group mean differences as well as by the distribution of cases within the 2 groups.[40] As a sensitivity analysis, the imputed datasets were also analyzed using the multiple single causal mediation approach with the Mediation package in R.[42] In this way, pooled estimates were calculated, which could be done only for single mediators. All mediation analyses were adjusted for covariates. The statistical analyses were carried out using R version 3.2.3.[43]

Nonresponse Analyses

The characteristics of the 4,727 mother–child dyads included in the present analyses were compared with those of the 2,531 dyads who had missing data on the SRS (Figure S1, available online). Mothers with missing data were, on average, younger (28.2 vs 31.1, $p < .001$) and had lower education (lower education: 19.0% vs 6.4%, medium education: 55.9% vs 39.2%, higher education: 25.1% vs 53.3%, $p < .001$). Their children had a slightly lower gestational age at birth (median 40.0 vs 40.14 weeks $p < .001$) and a lower mean birth weight (3,353.7 vs 3,432.6 g, $p < .001$). No differences were found in sex of the child.

RESULTS

Descriptive Analyses

Sample characteristics of participating mothers and children are shown in Table 2, separately for maternal country of origin: the Netherlands (n = 2,954), Europe (n = 383), or outside Europe (n = 1,390). Mothers with a European country of origin migrated more often for labor reasons and less often for family reasons than did mothers from outside Europe ($p < .001$). They also had an older age at migration ($p < .001$) and their mean stay in the Netherlands was shorter (Europe: mean = 9.03, SD = 8.93; outside Europe: mean = 14.18, SD = 9.64, $p < .001$). Mothers with a migration background scored higher on almost all stress-related assessments compared to mothers with a Dutch background (all $p < .01$, except for self-esteem), with mothers originating from outside Europe generally scoring highest.

TABLE 2 Sample Characteristics by Maternal Country of Origin

	Netherlands	Europe		Outside Europe			Missing total,
	n = 2,954	n = 383	p^a	n = 1,390	p^a	p^b	n (%)
Maternal characteristics							
Maternal age at intake, y, mean (SD)	31.84 (4.09)	31.43 (4.27)	.074	29.57 (5.41)	<.001	<.001	0 (0.00)
Education level, %							138 (2.92)
Lower education	1.55	4.03	.002	17.99	<.001	<.001	
Medium education	34.32	30.38		52.76			
Higher education	64.14	65.59		29.25			
Maternal migration characteristics							
Generation status[c]							69 (3.89)
Born outside the Netherlands (First generation, %)		62.83		66.17		.256	
Parents born outside the Netherlands (second generation, %)		37.17		33.83			
Age at migration, y (%)[d]							158 (14.17)
0-15		16.04		42.68		<.001	
>15		83.96		57.32			
Time in the Netherlands, y, mean (SD)[p]		9.03 (8.93)		14.18 (9.64)		<.001	158 (14.17%)
Migration reason, %							
Family		61.72		73.87		<.001	814 (45.91%)
Labor		20.57		6.40			
Education		7.18		10.40			
Asylum		5.26		4.53			
Other		5.26		4.80			
Child characteristics							
Sex, % male	50.14	46.21	.165	50.43	.881	.160	0 (0.00%)
Age at SRS, mo, mean (SD)	73.58 (5.27)	73.92 (5.32)	.231	75.59 (7.08)	<.001	<.001	0 (0.00%)
Gestational age at birth, wk, median (IQR)	40.29 (1.86)	40.14 (1.86)	.520	40.00 (1.86)	<.001	.010	0 (0.00%)
Birth weight, g, mean (SD)	3,475.52 (567.91)	3,409.97 (576.31)	.037	3,347.60 (569.75)	<.001	.061	2 (0.04%)
Mediators							
Life events, median (IQR)	0.00 (55.00)	0.00 (68.00)	<.001	36.00 (96.00)	<.001	.002	627 (13.26%)
Long-lasting difficulties, median (IQR)	0.08 (0.25)	0.13 (0.33)	<.001	0.17 (0.42)	<.001	.001	637 (13.48%)
Family functioning, median (IQR)	1.33 (0.58)	1.42 (0.60)	.005	1.67 (0.75)	<.001	.001	709 (15.00%)
Self-esteem, median (IQR)	4.50 (0.70)	4.50 (0.78)	.894	4.50 (0.90)	.077	.247	754 (15.95%)
Psychopathology, median (IQR)	0.12 (0.17)	0.17 (0.23)	<.001	0.23 (0.38)	<.001	<.001	678 (14.34%)
Social support, mean (SD)	34.36 (6.20)	32.25 (7.03)	<.001	32.81 (7.46)	<.001	.296	1,854 (39.22%)
Perceived discrimination, median (IQR)	1.00 (0.00)	1.00 (0.50)	<.001	1.25 (1.25)	<.001	<.001	1,673 (35.39%)

Note: Continuous variables are presented as mean/median with SD or interquartile range (IQR). Categorical variables are presented as percentages. p Values are derived from analyses of variance for parametric continuous variables, Kruskal–Wallis tests for non-parametric continuous variables, and χ^2 *tests for categorical variables. SRS = Social Responsiveness Scale.*

[a]*Reference group is "the Netherlands."*

[b]*Reference group is "Europe."*

[c]*Only participants with migration background (n = 1,773)*

[d]*Only participants born outside the Netherlands (first generation, n = 1,115).*

TABLE 3 Child Autistic Traits by Maternal Country of Origin

	Participants	Score on SRS					Missing	
	n	Mean	SD	Score range	p^a	p^b	n	%
Maternal country of origin								
The Netherlands	2,954	0.38	0.23	0-1.63			34	1.15
Europe	383	0.42	0.25	0-1.68	.008		4	1.04
Outside Europe	1,390	0.50	0.24	0-1.63	<.001	<.001	54	3.88
Cape Verde	135	0.55	0.27	0-1.39	<.001	<.001	10	7.41
Dutch Antilles	80	0.50	0.20	0-0.97	<.001	.002	4	5.00
Indonesia	161	0.38	0.25	0-1.63	.971	.138	2	1.24
Morocco	173	0.54	0.22	0-1.16	<.001	<.001	9	5.20
Suriname	284	0.49	0.25	0-1.58	<.001	<.001	8	2.82
Turkey	311	0.53	0.22	0-1.13	<.001	<.001	10	3.22
Other	246	0.48	0.26	0-1.20	<.001	.004	11	4.47

Note: Variables are presented as mean (SD). p Values are derived from analyses of variance for parametric continuous variables. SRS = Social Responsiveness Scale.
[a]*Reference group is "the Netherlands."*
[b]*Reference group is "Europe."*

Table 3 presents mean SRS scores by country of origin. Children of mothers with a migration background had higher mean SRS scores, indicating more autistic traits, compared to no migration background (Europe: mean = 0.42, SD = 0.25; outside Europe: mean = 0.50, SD = 0.24; the Netherlands: mean = 0.38, SD = 0.23; all $p <$ .01). Analysis of the SRS subscales (Table S2, available online) indicate a similar pattern, with higher scores on Social Cognition and Social Communication among children of mothers with a migration background (eg, for Social Cognition: the Netherlands: mean = 0.44, SD = 0.35; Europe: mean = 0.49, SD = 0.38; outside Europe: mean = 0.66, SD = 0.37; $p <$ .01). For Mannerisms, only children of mothers with a migration background from outside Europe had a higher mean score.

Relatively modest but significant correlations were found between the SRS and almost all mother and child variables, except for age at migration (Table S3, available online). Among the prenatal stress assessments, the highest correlations were found with family functioning, psychopathology, and perceived discrimination (r = 0.23, 0.23, and 0.22 respectively; all $p <$ .001), indicating small but significant positive associations between prenatal stress exposure and later child autistic traits.

Mediation Analyses

The results of the mediation analysis comparing no migration background vs a migration background from outside Europe are shown in Table 4 and Figure 1. These results reveal that prenatal stress indicators mediated the association between maternal migration and child autistic traits, accounting for up to nearly half (47%) of the total effect of maternal migration ($B_{indirect}$ = 0.035, 95% CI = 0.027, 0.043; B_{total} = 0.074, B_{direct} = 0.039). The prenatal stress indicator with the highest mediating effect was perceived individual discrimination, accounting for 17% of the mediating effect ($B_{indirect}$ = 0.013, 95% CI = 0.007, 0.018). Other significant mediating prenatal stress indicators were psychopathology ($B_{indirect}$ = 0.012, 95% CI = 0.006, 0.017), family functioning ($B_{indirect}$ = 0.009, 95% CI = 0.005, 0.013), and social support ($B_{indirect}$ = 0.003, 95% CI = 0.001, 0.005). Similar results of the mediation analysis were found in all imputed datasets. In addition, results of the sensitivity analysis using the single causal mediation approach showed a similar trend, with perceived discrimination being the most important mediator (Table S4, available online).

Table S5 and Figure S2, available online, show the results of the mediation analysis comparing no migration background with a migration background from European countries. More than half (59%) of the association between maternal migration within Europe and reported child autistic traits was mediated by prenatal stress indicators ($B_{indirect}$ = 0.022, 95% CI = 0.014, 0.030; B_{total} = 0.038, B_{direct} = 0.015). The most important stress indicator was psychopathology, followed by social support, perceived discrimination, and family functioning. Similar results were found in the other imputed datasets, as well as in the sensitivity analysis with the single causal mediation approach (Table S6, available online).

TABLE 4 Association of Maternal Migration Background (No Migration Background vs Originating From Outside Europe) With Child Autistic Traits and Indirect Effects via Maternal Stress

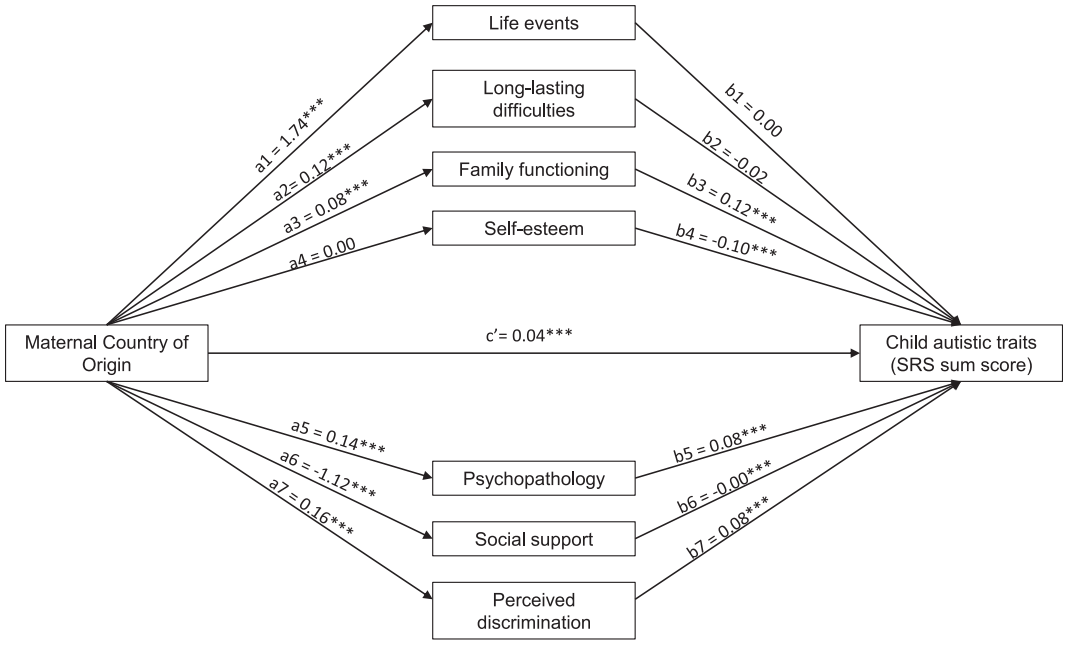
	B for SRS	SE	CI lower	CI upper	β	% of Total effect
Total effect***	0.074	9.008	0.058	0.090	0.305	100.00
Direct effect***	0.039	0.009	0.022	0.056	0.161	52.84
Indirect effect						
Total[a]	0.035	0.004	0.027	0.043	0.144	47.16
Life events	0.002	0.001	−0.001	0.005	0.007	2.30
Long-lasting difficulties	−0.002	0.002	−0.006	0.002	−0.009	−2.97
Family functioning[a]	0.009	0.002	0.005	0.013	0.036	12.03
Self-esteem	0.000	0.001	−0.002	0.001	−0.002	−0.54
Psychopathology[a]	0.012	0.003	0.006	0.017	0.048	15.68
Social support[a]	0.003	0.001	0.001	0.005	0.012	3.92
Perceived discrimination[a]	0.013	0.003	0.007	0.018	0.052	16.89

Note: Models are adjusted for gestational age at birth, weight at birth and sex of the child, and education level of the mother. Results are based on a parallel mediation analysis in one imputed dataset. B = unstandardized effect; β = partially standardized effect (as the independent variable is dichotomous); CI = 95% confidence interval, for the indirect effects these are bootstrapped; SE = standard error; SRS = Social Responsiveness Scale.
[a]*Significant mediating effect, based on CI that does not include zero as lower or upper bound.*
****p* < .001.

DISCUSSION

In this population-based sample following women and their children from early pregnancy to middle childhood, maternal migration background was associated with more autistic traits in their children. Prenatal stress was an important mediator in this association, accounting for up to half of the total effect of maternal migration. Stress indicators with the largest

FIGURE 1 Association of Maternal Migration Background (No Migration Background vs Originating From Outside Europe) With Child Autistic Traits and Indirect Effects via Maternal Stress Indicators



Note: Results are based on parallel multiple mediation analysis (PROCESS) in one imputed dataset. Models are adjusted for gestational age at birth, weight at birth, and sex of the child, and education level of the mother. Effects are shown as unstandardized regression coefficients. c' = Direct effect (exposure variable on outcome variable); SRS = Social Responsiveness Scale.
****p* < .001.

mediating effect were perceived discrimination and maternal psychopathology.

The higher level of autistic traits among children of mothers with a migration background is in line with previous studies globally, showing an overall higher risk of autism in children of migrant parents.[6,12,13] Specifically, this risk is often found to be increased in narrowly defined autism but decreased for so-called high-functioning autism.[6-8] Studies hypothesize that this reduced risk for high-functioning autism in migrant children might be caused by a low detection rate.[6-8] Our study underscores this idea of an underrepresentation of ethnic minorities in child psychiatric services, as we found higher levels of autistic traits in a nonclinical, population-based sample. A conceptual framework mapping the factors that may affect the process of help seeking and diagnosis in autism identified several factors that might act as barriers, including the role of stigma, cultural norms of typical behavior, cultural beliefs and attitudes, affordability and availability of care, and language difficulties.[9] Also, the clinician's role in a potential referral or diagnostic bias[44] should not be overlooked, in addition to the use of culturally appropriate diagnostic instruments.[9]

Whereas previous studies have examined maternal migration in relation to a clinical diagnosis of autism,[6,12,13] this study offers an examination of autistic traits on a continuum in the general population, showing more reported autistic traits on all core domains (ie, social cognition, social communication, and mannerisms) among children of mothers with a migration background. This scope helps to gain information on autistic traits across a wide spectrum, not only on the diversity of traits but also on the range from low to (sub)clinical levels. In addition, we obtained detailed information on a broad range of potential risk factors in pregnancy. Therefore, this approach helps to better understand associations at the interface of migration and autism, pointing into specific directions for research and potential interventions targeting the broad spectrum of autistic traits in the general population as well as in clinical settings.

Results of this study emphasize previous findings in which increased stress levels were found among mothers with a migration background,[14,17-20,45-47] as well as an increased risk of autism among mothers with higher prenatal stress levels.[2,3,22,23,48,49] Nevertheless, to our knowledge, this is the first study to have examined the mediating role of maternal prenatal stress in the association between maternal migration background and child autistic traits. In addition, this study provides novel insights into perceived discrimination among minorities in relation to traits of autism in the next generation. Associations between perceived discrimination in migrants and mental health diagnoses such as psychosis[49] and depression[50] have been established before. This study extends these findings by showing an association between perceived discrimination among ethnic minorities and early-life neurodevelopmental risk in offspring, with implications that may reach across future generations. Possible explanations for this association may be 2-fold. First, it is hypothesized that because of perceived discrimination, mothers are less likely to receive optimal prenatal care, resulting in a higher risk of pregnancy complications and possible neurodevelopmental complications.[7] Second, in line with the "fetal programming" concept,[16] it is hypothesized that the sociocultural stress caused by discrimination during pregnancy has a direct effect on the fetus, affecting the prevalence of autism in children of mothers with a migration background.[12] In both cases, future prevention programs should focus on decreasing exposure to ethnic discrimination in pregnant women (eg, by giving it media attention), as well as paving the road to adequate, culturally appropriate health care during and after pregnancy (eg, by making medical information available in various languages). Nevertheless, prenatal stress might not be the only underlying pathway in the association between maternal migration status and child autistic traits. Other suggested possible explanations for the increased prevalence of autism and autistic traits in ethnic minorities are the influence of biological factors, such as the exposure to environmental pollutants (eg, air pollution, pesticides), differences in vitamin D status, nutrition, birth complications, and lead levels, as well as the influence of genetic effects such as consanguinity and the paternal and maternal heritability of autism.[6,7]

The present study has several strengths, including the large number of participating mothers and children from various countries of origin and the study's population-based prospective design. In addition, the study provided a broad scale of information on stressors in different aspects of life. Nonetheless, current findings should be interpreted in light of several limitations. First, autistic traits and stress indicators were assessed using parental (mostly maternal) reports on questionnaires. Albeit cross-culturally validated, there might also be slight differences in how caregivers with divergent cultural backgrounds report on autistic traits of their children, as well as on their own stress levels.[7,9] Additional potential pitfalls of this type of data collection are single-informant and same-rater bias. Furthermore, in a few cases, research assistants were needed to help fill out the questionnaires of participants because of illiteracy, which might result in socially desirable answers. In addition, the non-response analyses indicated that mothers in the group lost to follow-up had a lower socioeconomic background, poorer birth outcomes, and more reported behavioral

problems, pointing to a selective attrition bias. Finally, the focus of this study was on prenatal stress indicators and autistic traits at age 6 years. Analyzing the influence of factors that might affect child development during infancy, such as family relationships, postnatal maternal stress, and school functioning, as well as possible overlap with traits of other mental health conditions such as anxiety, depression, and attention-deficit/hyperactivity disorder, would be of additive value in future research, both in population-based research as well as (intervention) research in a clinical sample. Similarly, information on both fathers' and mothers' autistic traits or autism diagnosis or a social communication disorder would have been a valuable addition in our study analyses, given the heritability of autism.

A research topic of future interest would be to further explore the migration motive, as well as the timing of migration and of experienced stress levels in relation to autism. In our study sample, stress questionnaires were administered during different trimesters in pregnancy. Yet, the timing of experienced prenatal stress was not further identified, as we lacked repeated measures at multiple time points during pregnancy. A previous population-based study has shown that exposure to high stress levels, especially in the third trimester of pregnancy, was decisive in the risk of autism.[17] Likewise, in our study sample, the majority of the women migrated when they were more than 15 years of age. Earlier studies reported that the risk on low-functioning autism increased when maternal migration took place in the year before[10] or around[11] the birth of the child. These results underscore the hypothesis that prenatal factors such as migration stress may be a core explanation in the association of maternal migration and autism prevalence, rather than ethnicity or an ascertainment bias.

To summarize, this study suggests that children of mothers with a migration background have a higher risk of autistic traits, in part because of mothers' higher experienced stress levels during pregnancy due to perceived discrimination and maternal mental health problems, among other factors. Insights into these mediating pathways open a window of opportunity, as prenatal stress factors are environmental factors with a possible preventable character. A first step is to acknowledge the higher levels of stress and perceived discrimination among mothers with a migration background, and to raise awareness of its association with childhood autism in policy and practice. To illustrate, the recently published World Health Organization publication "World Report on the Health of Refugees and Migrants" uses the slogan "health for all."[2] Migrant parents and their children with autism should not be overlooked in this claim. Building stronger research capacity at the interface of migration and autism is of vital importance in strengthening these calls and ensuring this policy impact "for all." Prevention programs and early intervention in clinical practice such as obstetric, mental health, and migrant care should prioritize reducing the exposure to prenatal stress (eg, by addressing it during consultation) and treating existing mental health problems, especially among mothers with a migration background. We recommend evaluation of such programs to determine whether they contribute to laying a healthy foundation with lifetime benefits.

CRediT authorship contribution statement

Anne E. de Leeuw: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Wietske A. Ester:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Koen Bolhuis:** Writing – review & editing, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hans W. Hoek:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Pauline W. Jansen:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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