The relationship between maternal migration and an increased risk of childhood autism

A systematic review

Anne Roos van der Ende*, Merel Stegenga*, Mila Ivanova*
*Medical student, Erasmus MC University Medical Center Rotterdam, the Netherlands
Intended to be submitted to British Journal of Psychiatry

Abstract
Objective: To conduct a systematic review of recent literature in order to assess the relationship between maternal migration and the risk of autism in children.

Methods: The PubMed/MEDLINE database was searched for articles published in the English language between January 1, 2000 and January 16, 2015. Only primary investigations examining the correlation between autism risk and immigration of the mother were included. The remaining studies were systematically reviewed by all authors independently and after screening of references articles that matched the inclusion criteria were added.

Results: Six articles were included, five of which showed a significantly higher risk of autism in children born to immigrant mothers. Only the results of the retrospective cohort study of 943,664 children have showed no significantly increased risk of autism (RR 1.4, 95% [CI] 0.9-2.4).

Conclusions: Children of immigrant mothers have an increased risk of autism. This knowledge is important for an early diagnosis of autism because maternal migration could be considered as a risk factor.

Introduction

Autism
Autism is a neurodevelopmental disorder characterized by impaired social interaction, abnormalities in social communication, and stereotyped patterns of behavior (1). Because of an incidence of 1/1,000 births which is still rising (2), autism is largely considered to be one of the most common severe neurodevelopmental conditions. Despite extensive research, the etiology of the condition remains unclear. In the past, only environmental factors were thought to cause autism. More recently, genetic predisposition as well as de novo mutations are considered to contribute to the manifestation of the condition. Although the genetic basis of Systematic review the disease is well-studied, the individual phenotype still cannot be explained using this model alone (3). Therefore the cause of autism is considered multifactorial and the exact pathogenesis remains unknown.

Environmental factors
Six major environmental factors associated with a higher risk of childhood autism were identified and explored in a comprehensive meta-analysis by Gardener et al. (4). An increased risk of autism was related to 50 factors in total, either in combination or alone, which influence the risk of autism. The variation could be explained by six major factors. These six major environmental factors identified in the study, were advanced parental age at birth, maternal prenatal medication use, bleeding during pregnancy, gestational diabetes, being firstborn versus third or later born, and, important in the light of our present review, having a mother born abroad (4).

Maternal immigration
In light of the increasing number of first, second and third generation immigrants in Western countries, maternal immigration could be considered an increasingly important risk factor for autism. Autism is underdiagnosed in children from ethnic minorities (5). Early diagnosis, however, is of great importance for treatment of this disorder. The epidemiology of many diseases among immigrants is not well-studied yet and could be considered a new research area. Studies published before April 2007 were previously reviewed by Gardener et al. Besides, numerous perinatal and neonatal factors were analyzed in the meta-analysis. As this new research area has shown rapid progress, more studies published recently focused on the association between autism and maternal immigration. The purpose of this study is to provide a systematic review of recent literature on the association between autism and maternal immigration, offering the first summary of the latest articles exploring this environmental factor.

Methods
Literature search
The search was performed using the specific controlled vocabulary of this database (Medical Subject Heading terms). The search included the key words ‘autistic disorder’ in combination with ‘emigrants and immigrants’ or ‘emigration and immigration’ or ‘human migration’ or ‘second generation’ or ‘maternal immigration’ or ‘emigration and immigration’ or ‘immigration/statistics and numerical data’ as major topic.
Systematic Review

Inclusion
The PubMed/MEDLINE database was searched for articles published from January 1, 2000 through August 31, 2015. Articles published in the English language and available on PubMed were used.

Results
Thirty-five articles were identified using this search strategy (Figure 1). After screening of abstracts and titles 27 articles were excluded. Full text of the remaining eight articles was reviewed and three more studies focusing on the diagnostic process and challenges among immigrants and behavioral problems as a whole, were excluded. After screening of references, one more study was identified that met all inclusion criteria and it was therefore included. In total, six articles examining the risk of autism in children of immigrants were identified and reviewed systematically.

The studies were clustered per study type in order to facilitate the comparison and analysis of the results. We will discuss all included studies in turn. In the case-control study of Lehti et al.(6) (Table 1) children from second-generation immigrants (n=1132) in Finland, born by the year 2007, were compared with children who have two Finnish parents (n=4515). Information of the autistic children, parents and control group was collected from the Finnish Hospital Discharge Register, the Finnish Medical Birth Register and the Finnish Central Population Register. Matching of controls and cases was performed by the child’s date of birth (+/- 30 days), sex, region of birth, and residence in Finland. The risk of childhood autism was increased for those with two immigrant parents (OR 1.8, 95% [CI] 1.2-2.7) and for those with only an immigrant mother (OR 1.8, 95% [CI] 1.2-2.7). Children with parents born in several areas (Vietnam, former Soviet Union and former Yugoslavia) 4 were associated with the highest risk, respectively aOR 7.0, 95% [CI] 2.3-21.2, aOR 1.7, 95% [CI] 1.05-2.9 and aOR 1.8, 95% [CI] 1.2-2.9).

The second study, a retrospective case-note analysis of Keen et al. (7) (Table 2) included children diagnosed with autism-spectrum disorder presenting to the child development services in Lambeth or Wandsworth in the United Kingdom (n=428).

Table 1 - Study characteristics of case control studies, analysing the autism risk in children born to immigrant mothers.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Cases</th>
<th>Control</th>
<th>Risk factors</th>
<th>OR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haglund et al. (2011)</td>
<td>Sweden</td>
<td>157</td>
<td>68964</td>
<td>Maternal age at delivery, maternal country of birth, maternal parity at delivery, maternal smoking in early pregnancy, background and features child.</td>
<td>2.7, 2.0-3.7</td>
</tr>
<tr>
<td>Hultman et al. (2002)</td>
<td>Sweden</td>
<td>408</td>
<td>2040</td>
<td>Maternal characteristics, pregnancy and delivery complications, infant characteristics.</td>
<td>3.0, 1.7-5.2*</td>
</tr>
<tr>
<td>Lehti et al. (2013)</td>
<td>Finland</td>
<td>1132</td>
<td>4515</td>
<td>Parental immigration status, parental region and country of birth</td>
<td>1.8, 1.2-2.7*</td>
</tr>
</tbody>
</table>

*adjusted for confounders, such as parental age, parity, gestational age, birth weight, birth length.

Table 2 - Study characteristics of retrospective case note analysis, analysing the autism risk in children born to immigrant mothers.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Sample size</th>
<th>Setting</th>
<th>Variables</th>
<th>aRR*, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keen et al. (2010)</td>
<td>UK</td>
<td>428</td>
<td>Examination of the hypotheses that maternal ethnicity and/or immigration are linked to childhood ASD in the second generation.</td>
<td>Demographic characteristics, region of birth and ethnic group of mother</td>
<td>3.97, 2.01-7.84d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.01, 5.53-18.1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.92, 5.39-11.6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.01, 5.53-18.1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.97, 2.01-7.84d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.01, 5.53-18.1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.92, 5.39-11.6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.01, 5.53-18.1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.97, 2.01-7.84d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.01, 5.53-18.1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.92, 5.39-11.6b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.01, 5.53-18.1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.97, 2.01-7.84d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.01, 5.53-18.1c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.92, 5.39-11.6b</td>
</tr>
</tbody>
</table>

Although the child development teams in these two boroughs in London were different, they used the same diagnostic method and provided the same services. All children diagnosed between 1 September 1999 and 31 August 2005 participated in the study, if they were resident and born in the United Kingdom. Mothers born outside Europe had a significant higher risk of having a child with an autism-spectrum disorder compared with those born in the United Kingdom, with the highest risk observed.

Examination of the hypotheses that maternal ethnicity and/or immigration are linked to childhood ASD in the second generation Demographic characteristics, region of birth and ethnic group of mother Lambeth 7.92, 5.39-11.6b 10.01, 5.53-18.1c 3.97, 2.01-7.84d for the Caribbean group (Lambeth: RR 10.01, 95% [CI] 5.39-18.1/ Wands-worth: (RR 8.89, 95% [CI] 5.08-15.5). Children with an African mother had the second highest risk (Lambeth: RR 7.92, 95% [CI] 5.39-11.6/ Wands-worth: RR 3.27, 95% [CI] 2.36-4.53)and children with Asian parents had the third highest risk (Lambeth: RR 3.97, 95% [CI] 2.01-7.84/Wands-worth: RR 2.08, 95% [CI] 1.33-3.25). Also Black mothers born in the United Kingdom had a significant higher risk compared with white mothers (RR 3.85, 95% [CI] 2.12-6.99). The risk of autism was not increased in children born to immigrants from Western countries. In the case-control study of Hultman et al. (8) (Table 1) all Swedish children born between 1974 and 1993 and registered in the Swedish Birth Register were included. A total of 408 cases of children who were diagnosed with infantile autism were compared with 2040 matched controls. Controls were matched to cases by age, year and hospital of birth. Maternal immigration was not the only risk factor 5 analyzed in this study. Hultman et al. found that the risk of autism was associated with maternal birth outside Europe and North America (OR 3.0, 95% [CI] 1.7-5.2). No further analysis of the ethnicity of the mother was performed. In the prospective cohort of Lauritsen et al. (9) (Table 3) a total of 943,664 children born in Denmark and younger than ten ears were followed from 1994 through 2001 and various risk factors were assessed at baseline, such as maternal immigration. Children were followed from their first birthday or January 1994, until onset of autism, their tenth birthday, death, emigration or 2001. Of all children 81 8 developed autism. The risk of autism increased if the mother was born outside Europe (RR 1.42, 95% [CI] 1.10-1.83). The risk was not higher if the mother was born in Europe (RR 1.02, 95% [CI] 0.75-1.39). It was increased if the parents were not born in the same country (RR 1.36, 95% [CI] 1.08-1.76).

In the case-control study of Haglund et al.(10) (Table 1) 250 children participated who were born in Malmö, Sweden and were diagnosed with autism or Asperger syndrome. All children were born during 1980-2005 and they enrolled at the local Child and Youth Habilitation Center. The researchers found that maternal birth outside the Nordic countries (Scandinavia) was positively associated with autism (OR 2.2, 95% [CI] 1.6-3.1). The highest risk estimated for autism was found among children to women who were born in Sub-Saharan Africa (OR 7.3, 95% [CI] 1.6-3.1). This risk was significantly higher than the risk in children born to mothers from other regions (p=0.007). The aim of the retrospective cohort of Van der Ven et al.(11) (Table 3) was to estimate the risk of developing autism-spectrum disease in children born to immigrants as compared with children of Dutch-born parents. A total of 150 children diagnosed with autism-spectrum disorder were included. Loss to follow-up occurred mainly because of emigration 6 and 13.8% of the participants did not finish the study. Van der Ven et al. found that children with migrant parents appeared to have an increased risk, but there was no significant difference between the risk in children born to Dutch-born parents and children born to immigrants (RR 1.4, 95% [CI] 0.9-2.4). The authors state that the study may have lacked the power to reveal significant differences in the incidence of autistic disorders as a function of parental migrant status. The restricted number of cases (n=150) also prevented in-depth analysis.

Discussion
This systematic review aimed to provide a summary of recent literature on the relationship between autism and maternal immigration. Overall, this systematic literature review found consistent evidence that…. there is an association between maternal immigration and the increased risk of having a child with autism. Five out of six studies positively associated maternal birth outside Europe with autism. One found an increased but non-significant risk if the mother was born in developing countries (e.g. Turkey, Morocco, Suriname and Dutch Antilles).

Possible explanations
There are several theories which explain The association between maternal migration and a higher risk of autism. In 1996, Gillberg and Gillberg (1996) (12) suggested that children with mothers born outside Sweden had an increased vulnerability to intra-uterine infections because their mothers were non-immunized migrants. However, there is not enough evidence to confirm or reject this hypothesis. Besides, the role of the immune system in autism has been supported by earlier studies. Secondly, it is assumed that autistic men tend to travel abroad to seek a female partner due to the observation that their lack of social skills would be less obvious in foreign countries. Haglund et al. (2011) (10) did not find support for the two theories above as well as Lauritsen et al. (2005) (9). Also, there might be an

Table 3 - Characteristics of cohort studies, analyzing the autism risk in children born to immigrant mothers.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Study type</th>
<th>Cases</th>
<th>Setting</th>
<th>Variables</th>
<th>RR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauritsen et al. (2005)</td>
<td>Denmark</td>
<td>Prospective</td>
<td>818</td>
<td>Family history of psychiatric disorder, age of parents, paternal identity</td>
<td>1.4, 1.10-1.83</td>
<td></td>
</tr>
<tr>
<td>Van der Ven et al. (2013)</td>
<td>Netherlands</td>
<td>Retrospective</td>
<td>150</td>
<td>Paternal and maternal age at birth, parental country of birth</td>
<td>1.4, 0.9-2.4</td>
<td></td>
</tr>
</tbody>
</table>

Note: OR, Odds Ratio; CI, Confidence Interval.
association between vitamin D deficiency and autism(13), which could explain the association found in this review. Vitamin D deficiency in dark skinned immigrants is caused by a reduced exposure to sun in Northern countries and prenatal exposure to vitamin D deficiency might increase the risk of having an infant with autism.

However, there is no convincing evidence that vitamin D deficiency is the main cause of the increased risk for autism in children of black women and only one of the studies examined in this systematic review could provide evidence for this hypothesis, so additional research is required. Exposure to environmental hazards in country of origin might support this relationship as well. Lehti et al. (2013), who focused on former Yugoslavia, former Soviet Union and Vietnam, mentions these factors since these countries had been in war during their research period. One of those environmental hazards is Agent Orange, a very toxic herbicide used during the Vietnam War. Polychlorinated biphenyls (PCBs) and depleted uranium are environmental toxics used in the Balkan wars. Even though there is no evidence to support the hypothesis that exposure to these materials cause neurodevelopmental problems in the long term, this should be considered as a possible explanation. Further investigation is needed. Another possible explanation could be intrauterine Toxoplasmosis. Toxoplasma gondii is associated with a higher risk of schizophrenia and schizophrenia is associated with an elevated risk of autism. This risk factor has been discovered recently and may be this is the reason it was not included in any of the reviewed articles for they examined other potential hazards during pregnancy and birth.

It could also be possible that the prevalence of autism is higher in non-Western countries. This could explain why children of non-Western mothers are more likely to be diagnosed with autism. However, the prevalence rates of autism in non-Western countries seem lower than the incidence rates in Western countries so the origin of the mothers could not explain the findings in this research.

Psychosocial stress during migration is also mentioned to be a cause of this association. It has been suggested that this stress, accompanied by high maternal adrenal androgen concentrations, is a risk factor for autism. (14) The studies examined in this review did not specifically measure the psychosocial stress and testosterone concentrations in migrants. However, this could be investigated and in order to do so the prenatal testosterone exposure should be estimated by measuring and analyzing the finger length ratio. A lower finger length ratio is associated with exposure to higher levels of androgens during the second trimester and a higher sensitivity for testosterone (15), which offers the opportunity for retrospective investigation of these levels. Children diagnosed with autism had lower finger length ratios than children without the diagnosis (16). The finger length ratio was not measured in any of the studies included in this systematic review. Therefore, no conclusions could be made about this explanation, based on our research.

Strengths and limitations
One of the strengths of this systematic review is the inclusion of all available studies published in the English language over the past fifteen years. Only articles from the pubmed/MEDLINE database were used for this review which implies that some other studies could have been missed. The limitations of the reviewed studies define most of the limitations of our study. The investigation of Lauritsen et al. is not prone to recall bias because the diagnoses were made independently for this study by clinicians. Another strength of this study is that the risks were adjusted for confounders such as age, gender, time of diagnosis of the disorder, parental age and place of birth, except for the confounder socioeconomic status. In contrast, the outcomes in the study of Keen et al. were not adjusted for a number of variables known to be risk factors for autism. These confounders could potentially have differed between the groups of interest in the study. The risk of misclassification of the diagnosis of childhood autism in the Danish Psychiatric Central Register is believed to be very low, the possibility that some individuals with autism were missed cannot be excluded. In most studies misclassification is known to be a problem. It is more likely to occur if a child has a different cultural background than the clinician. In most studies it was unknown if the parent immigrated as a child or as an adult. Also, the reason for immigration is unknown in most studies. It could be possible that the age of the parent at the moment of migration and the reason for leaving the country of origin could affect the autism risk.

Another important limitation of some of the reviewed studies was not taking all variables into account that could influence the results. Not all of the studies examined risk factors for autism such as prenatal exposure to alcohol, smoking and drugs.

Implications and future research
One of the implications of these findings could be screening of children born to immigrant mothers. Physicians should be aware of the higher risk of autism in these children and consider a screening test in case they notice any atypical behavior. A routine screening test could be another option in order to diagnose patients as soon as possible.

The impact of the six major factors Gardener et al.(4) mentions needs further investigation. However, maternal migrations is one of the most robust and well-studied of them. (17) Future research on the importance of this and other perinatal factors is recommended in order to identify risk groups. Studies of the etiology of autism are crucial in order to understand the underlyind pathophysiology as the cause of autism remains unclear.

Conclusions
Children with autistic disorder typically have more social, communication and cognitive delays than children with other autism-spectrum disorders(18). Therefore it is crucial to identify children with autism as soon as possible. This will have a lot of benefits such as earlier access to intervention programs and an early diagnosis. Also the parents will feel relieved when a diagnosis is made, as it gives them a better understanding of their child’s behavior (18). There is strong evidence that the causes of autism are multifactorial: genetic and environmental. (14) We studied one of these factors: the association between immigration of the mother and a higher risk of having a child.
with autism. In this review we described the increased risk for immigrated mothers on having a child with autism. Even though this is concluded, more research is required to define to what extent immigration causes autism, since it is clear that the disease is multifactorial.

References