Why are immigrants at increased risk for psychosis? Vitamin D insufficiency, epigenetic mechanisms, or both?

M.J. Dealberto *

Department of Psychiatry, Ottawa Hospital and University of Ottawa, General Campus, 501 Smyth Road, Ottawa, Ont., Canada K1H 8L6
Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ont., Canada

Received 18 July 2006; accepted 26 July 2006

Summary European researchers have observed that schizophrenia is 3 times more frequent in immigrants than in native-born subjects. This increased risk is even higher in dark-skinned immigrants, and the second generation is more affected than the first one. Immigrant status is an important environmental risk factor not only for schizophrenia but also for other psychoses. The explanations proposed to date have been mainly related to epidemiological biases and psychological reasons, such as racism or social defeat, but no biological hypotheses have been tested so far.

This article proposes two biological hypotheses related to changes in sun exposure, changes in diet, and stress associated with immigration, which would explain the increased risk for psychosis associated with immigrant status. (1) Vitamin D insufficiency has been proposed as a risk factor for schizophrenia. The main source of vitamin D is through photosynthesis by sun exposure, and dark skins need more sun exposure to maintain adequate blood levels. Vitamin D insufficiency in adulthood could explain why dark-skinned immigrants develop psychosis when moving to high latitude countries, and its insufficiency during pregnancy could explain why the observed risk is higher in the second generation. (2) The second hypothesis is that of epigenetics, with psychosis resulting from modifications in gene expression caused by changes in diet and/or stress related to immigration. The role of homocysteine and the vitamin B-complex, especially folic acid, in these changes in DNA transcription would vary according to the polymorphism of the methylenetetrahydrofolate reductase gene.

The vitamin D insufficiency and epigenetics hypotheses are consistent with yet unexplained findings well known in the epidemiology of schizophrenia, such as the increased risk in the urban environment, the excess of winter births, the excess of schizophrenia births after maternal famine, and the shorter interbirth period before a schizophrenia birth.

In order to test these hypotheses, epidemiological studies of psychosis and immigration should include objective measures of skin color, which is predicted to be a more important risk factor than ethnicity. They should measure vitamin D, homocysteine and vitamin B-complex status and assess the polymorphisms of the vitamin D receptors and the methylenetetrahydrofolate reductase gene.

* Tel.: +1 613 737 8054; fax: +1 613 739 9980.
E-mail address: dealbert@uottawa.ca.
If confirmed, these hypotheses would lead to effective and inexpensive preventive measures which would markedly decrease the rates of psychosis and schizophrenia, as well as the burden and stigma of these diseases, and greatly improve the mental health of immigrants.

© 2006 Elsevier Ltd. All rights reserved.

The epidemiological evidence: increased risk for psychosis associated with immigrant status

Increased risk for psychosis associated with immigrant status

Since Ödegaaard [70] noted in 1932 an increased prevalence of psychosis in Swedish immigrants to the US and the pioneering work of Malzberg in the US and in Canada [53–55], many studies, mainly European, have confirmed the increased incidence of schizophrenia in immigrants. This increase is especially high in African-Caribbeans in the UK (see reviews: [78,8,39,35,21]).

A recent meta-analysis of 18 carefully selected studies by Cantor-Graae & Selten [12] calculated that, overall, immigrants were 2.9 (95% CI: 2.5–3.4) times more at risk for schizophrenia than the host population (the population who receives the immigrants). The increase in risk was similar in both genders. The risk differed according to skin colour and was higher in black than in both white and nonwhite/nonblack immigrants (respectively 4.8, 2.3 and 2.2). Skin colour was a more important factor than the level of economic development of the country of birth (relative risk 3.3 for developing countries, 2.3 for developed countries). Interestingly, all but one of the studies selected in this meta-analysis were conducted in Northern Europe: UK, Netherlands, Sweden, Denmark.

When the meta-analysis considered separately the first and second generations of immigration, the risk was still higher in the second one. The risk for schizophrenia associated with immigration was estimated at 2.7 (95% CI 2.3–3.2) for the first generation compared to the host population, and 4.5 (95% CI 1.5–13.1) for the second one. Two earlier studies in the UK [82,36] had observed a higher risk for schizophrenia in siblings of second-generation black immigrants compared to their white counterparts. This increase in risk for schizophrenia in the second generation suggests an interaction between genes and environment. Whatever the risk factor for which immigration is a proxy, the second generation is more exposed than the first one, or is exposed at a more vulnerable time, possibly during critical times in brain development.

The increased risk associated with immigration is not restricted to young adults as it is also observed for very late-onset (>60 years) schizophrenia-like psychosis. In London, the rate was more than 10 times higher in African-born and Caribbean-born compared to British-born elders [73], and another study in the same city confirmed an increased risk for all immigrant communities except Bangladeshi [64].

The increased risk for psychosis has also been observed for psychoses other than schizophrenia. Epidemiological studies of mania and of bipolar disorders are much less common than those of schizophrenia. Most of those that recorded immigration status have reported an increased risk for bipolar disorders and manic episodes in immigrants [47,72,45,49]. Discrete psychotic symptoms have also been associated with immigrant status. In a large community survey, hallucinations were reported 2.5 times more frequently in the African-Caribbean immigrants than in the white sample [44]. In children and adolescents aged 6–18 years, migration was associated with a two-fold higher risk for psychotic symptoms [71].

Several authors have searched for differences in clinical presentation between immigrants and non-immigrants. The younger age consistently observed at the onset of psychosis in immigrants is probably related to the younger age of the immigrant population as a whole. Immigrant patients with schizophrenia present more affective symptoms, manic and mixed, along with catatonic symptoms [37], Dealberto: personal observation]. Van Os et al. [91] reported an intermediate syndrome, schizomania, between manic episodes and schizophrenia. Violence is frequently observed, and involuntary admissions are more frequent in immigrants, particularly dark-skinned immigrants [19,85,18,84,43,65].

Since the first tentative explanation of selective migration advanced by Ödegaaard [70], many authors have tried to explain the increased risk for psychosis associated with the immigration experience.

Classic risk factors do not explain the excess of psychosis in immigrants

No systematic biases explain the increased risk for psychosis in immigrants. No excess of psychosis has been observed in dark-skinned populations living in
the Caribbean. Three studies conducted in Jamaica, Trinidad, and Barbados found rates comparable to those observed in the white population in the UK [31,6,51]. It is noteworthy that the populations in these Caribbean islands are mainly constituted by descendants of immigrants several generations ago.

Immigrants have a lower risk than the native-born for other psychiatric diagnoses including personality disorders, alcohol and drug use [5]. The rate of depression is lower in recent immigrants and increases to the level of the native-born population only after several years in the host country.

Classic risk factors associated with schizophrenia do not explain the excess risk observed in immigrants, particularly in dark-skinned persons. Drug use is a recognised factor precipitating and aggravating psychoses, but is less frequent in immigrant populations [92]. Similarly, obstetrical complications are not observed more frequently in immigrants compared to the native-born [38]. Immigrants have a lower prevalence of pre-morbid neurological illness [62]. Only one factor, urban living, could explain partly the increased rates of psychosis in immigrants, as immigrants are attracted by major cities, and the urban factor (urban birth and urban living) is associated with an increase in risk for schizophrenia estimated between 1.5 and 2 [8]. This urban risk factor cannot, however, explain fully the magnitude of the immigration effect and could be partly due to selective migration, as suggested by Jablensky [39]. Ethnic density in fact has been reported to be a protective factor: in South London, the incidence of schizophrenia decreased significantly as the proportion of such minorities in the local population rose [9].

Immigration status is associated with ethnicity and skin colour. The major epidemiologic studies in the United States, the Epidemiologic Catchment Area studies and the national comorbidity surveys found few differences in the prevalence of psychoses across US ethnic groups. However, other studies observed large differences across these groups, specifically African American patients having more diagnoses in the schizophrenia spectrum [23,63], and more severe psychotic symptoms [3].

Social defeat [77], social adversity, psychological difficulties related to the migration process and racism have been advanced to explain the excess risk for schizophrenia associated with immigration. Indicators of social adversity are more frequent in immigrant patients with a first episode of psychosis: unemployment [52], single adult household, adults receiving social welfare, parental unemployment, poor housing and low socio-economic status [32]. Other psychological difficulties observed relate to separation from parents in childhood [52] and family dysfunction [71]. Finally, the influence of post traumatic stress disorder on psychosis [76] has not been systematically studied in immigrants. Stressful events have been associated with a 1.5 increase in risk for schizophrenia [39] and the social and psychological difficulties do not explain the magnitude and the consistency of the observed effect of migration on psychosis.

Two biological hypotheses for the increased risk for psychosis in immigrants

The vitamin D insufficiency hypothesis

Recent data have attracted interest in the neuroprotective role of vitamin D [26]. A possible protective effect for multiple sclerosis is being considered [14]. McGrath has been the first to suggest a role of vitamin D in schizophrenia [57,58,60]. The increased risk associated with immigration, particularly in dark-skinned persons, has been consistently observed in Northern Europe but studies in Israel and Australia are not conclusive.

It is proposed that vitamin D insufficiency during pregnancy is a risk factor for schizophrenia and psychosis in the offspring, and that this insufficiency during adulthood is associated with psychotic episodes. The clinical characteristics of these psychotic episodes associated with vitamin D insufficiency are violent behaviour with a mixed or manic affective component and catatonic symptoms. These episodes are more frequently observed in dark-skinned persons living in high latitudes. Proneness to catatonia could explain why Black patients are more at risk for neuroleptic malignant syndrome, considered as a type of malignant catatonia [22, pp. 194–195].

Vitamin D3 (calciferol) is a fat-soluble vitamin [93,33] with a large number of effects which acts through vitamin D receptors widely distributed, particularly in the developing and adult brain. Its most active metabolite, 1,25-dihydroxy-vitamin D (1,25(OH)2D: calcitriol) is a hormone with multiple roles, in particular for genomic stability. Vitamin D is mainly synthesized in the skin by the ultra-violet component of sunlight and partly obtained in food, particularly fatty fish (salmon, eel, cod) and fortified milk or margarine. Subjects of African ancestry are often lactose intolerant and therefore do not benefit from vitamin D supplementation in milk. Blood levels of vitamin D vary with skin pigmentation, exposure to sunlight and seasons; this seasonal variation is more marked in high latitudes.
Skin colour varies greatly within ethnic groups and therefore should not be used to determine ethnicity [40]. Human skin derives most of its colour from two types of melanin: the brownish black eumelanin, and the reddish yellow pheomelanin. Higher concentrations of eumelanin characterize darker skin phenotypes. Individuals with deeply pigmented skin require a much longer sun exposure than their light skinned counterparts [34,56].

Although 1,25(OH)2D is the most active metabolite, 25 hydroxy-vitamin D (25(OH)D; calcidiol) is the main circulating form and the functional indicator of vitamin D stores. Severe vitamin D deficiency, defined as a level of 25(OH)D < 12.5 nmol/L, is associated with rickets in children and osteomalacia in adults [50]. Insufficiency, with a level below 50 nmol/L, is frequent, especially in African American women in northern latitudes, where sun exposure is sufficient for an adequate supply of vitamin D only during summer months. As shown in Table 1, the mean level of African American women in 80 counties in the US and in Boston all year round is within the insufficiency range, while white women maintain adequate levels except in Boston during the winter. Lamberg-Allard et al. [46] recently suggested the threshold of 80 nmol/L is required to prevent physiological changes associated with vitamin D insufficiency. This is the level below which parathyroid hormone secretion begins to rise. Similarly, according to Vieth [94], the current recommendation of 15 mcg of cholecalciferol daily do not meet the desirable serum level of 70 nmol/L of 25(OH)D.

There is growing evidence that low prenatal levels of 1,25(OH)2D can influence critical components of early brain development [20]. Transient prenatal vitamin D deficiency in rats is associated with subtle learning and memory dysfunctions [4]. Supplementation with vitamin D in the first year of life was associated with a greatly diminished risk for schizophrenia in males: the risk ratio was equal to 0.08 for irregular, and 0.12 for regular supplementation [61]. An earlier study of the same group showed an absence of difference in serum levels of mothers of subjects with schizophrenia versus controls, but the trend in the small group of black subjects was in the expected direction [59]. Not surprisingly, black mothers had significantly lower levels of 25(OH)D than did white mothers. The magnitude of the protective effect of vitamin D (risk 8–12 times lower) is comparable to that observed for the excess risk of psychosis in black immigrants (5 times higher). Serum levels of 25(OH)D in dark skinned patients hospitalised for psychosis are in the deficiency or insufficiency range (Dealberto: personal observation). There are anecdotal accounts among Inuits of "Piblotko" or manic excitement linked to vitamin D deficiency [13].

The vitamin D insufficiency hypothesis could answer some puzzling issues in the epidemiology of schizophrenia, including:

1. The 5–8% excess of schizophrenic births in winter/spring [39], which is significantly larger in high latitudes [17],
2. The sharp increase in schizophrenia in cohorts exposed to famine in early gestation during the Dutch Hunger Winter of 1944–45 [83], confirmed by a recent publication on the effects of famine in China during years 1959–61 [81],
3. The association between short birth interval and schizophrenia in the offspring [80], which has been related to folic acid deficiency but could also be related to vitamin D insufficiency,
4. The excess of schizophrenia in urban centres and the excess of urban schizophrenia births [39,8], as blood levels of vitamin D are lower in urban than rural environment [67], possibly related to a lower sun exposure,
5. The excess of schizophrenia in dark-skinned immigrants in northern European countries [12],

### Table 1

Variation of serum 25 hydroxy-vitamin D levels with season, latitude, and skin color

<table>
<thead>
<tr>
<th>Location</th>
<th>Latitude</th>
<th>n, skin color, gender, age</th>
<th>Summer/fall (nmol/L)</th>
<th>Winter/spring (nmol/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td></td>
<td>1546, African American, women, 15–49 yr</td>
<td>43.3/49.6</td>
<td>43.7/38.8</td>
<td>[67]</td>
</tr>
<tr>
<td>(81 counties)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>1426, Caucasian, women, 15–49 yr</td>
<td>82.9/90.9</td>
<td>78.8/66.0</td>
<td>[67]</td>
</tr>
<tr>
<td>(81 counties)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston, MA</td>
<td>42°N</td>
<td>51, African American, women, 20–40 yr</td>
<td>41.0</td>
<td>30.2</td>
<td>[28]</td>
</tr>
<tr>
<td>Boston, MA</td>
<td>42°N</td>
<td>39, Caucasian, women, 20–40 yr</td>
<td>85.4</td>
<td>60.0</td>
<td>[28]</td>
</tr>
<tr>
<td>Toronto, ON</td>
<td>43°N</td>
<td>47/35, nonwhite nonblack, women, 18–35 yr</td>
<td>68</td>
<td>51</td>
<td>[95]</td>
</tr>
<tr>
<td>Toronto, ON</td>
<td>43°N</td>
<td>380/322, white, women, 18–35 yr</td>
<td>76</td>
<td>58</td>
<td>[95]</td>
</tr>
<tr>
<td>Calgary, AB</td>
<td>51°N</td>
<td>188, (185 white), men and women, 27–89 yr</td>
<td>71.6/52.9</td>
<td>57.3/62.9</td>
<td>[74]</td>
</tr>
</tbody>
</table>
Why are immigrants at increased risk for psychosis? Vitamin D insufficiency, epigenetic mechanisms

(6) the protective factor of ethnic density for ethnic minorities [8] which could be explained by easier availability of ethnic food in these areas, (7) the north–south gradient in prevalence rates of schizophrenia suggested by Torrey [86] with this latitude effect confirmed for prevalence and incidence in a recent metaanalysis [75], (8) the less severe course of illness observed for schizophrenia in the developing countries [11], which could be attributed to the fact that these developing countries are in general located in lower latitudes.

The epigenetic mechanisms hypothesis: stress and/or changes in diet influence DNA methylation

The observed increased rate of psychosis in immigrants is found not only in dark-skinned immigrants, but also in white and light-skinned immigrants, for whom the increase is risk estimated at 2.3 and 2.2, respectively [12]. Another interesting finding is that of Cantor-Graae et al. [11] in Denmark, who observed an increased risk of 1.6 in Danes with a history of foreign residence. The magnitude of the risk in these persons is comparable to the risk associated with stressful events, estimated at 1.5 [39]. The fact that stress can trigger a psychotic episode is well known [68,69]; but the mechanisms remain poorly understood. It is proposed that DNA methylation may play a role.

After decades of genetic research, it is clear that schizophrenia and other psychoses are complex disorders that do not follow the classic Mendelian model. A promising hypothesis is that of DNA methylation [1] in which stress or nutritional factors would modify DNA transcription [79]. Epigenetic differences are a possible explanation for the discordance between monozygotic twins [24]. Analyses of monozygotic twins discordant for schizophrenia have shown discrepancies in the methylation pattern of certain gene promoters [89].

By definition, epigenetics refer to modifications in gene expression controlled by heritable but potentially reversible changes in DNA methylation and/or chromatin structure [29]. Two molecular mechanisms mediate epigenetic phenomena, DNA methylation and histone deacetylation, and they are interrelated. DNA methylation is an essential epigenetic mechanism that modulates gene expression and genomic integrity during cellular differentiation [7]. Methylation is also essential for the expression of imprinted genes [90]. DNA hypomethylation could cause chromosome instability and aberrant gene expression. Interestingly, epigenetic modifications can be affected by diet and drug therapy [87]. Valproate is being extensively studied for its properties as a mild histone deacetylation inhibitor, as it could prevent the downregulation of genes involved in schizophrenia, for example reelin and glutamate decarboxylase 67 [88].

In humans, DNA methylation involves mainly the addition of a methyl group to the 5′ position of cytosine within Cytosine-phosphodiester-Guanine (CpG) dinucleotides [1]. Of particular interest is the methylation status of CpG islands, which are groups of CpGs located close to the regulatory region of genes [41]. The methyl groups of 5′methyl cytosine are either supplied from the diet (choline, methionine, vitamin B12, and folic acid) or synthesized from one-carbon metabolism. Any excess or deficiency in choline, methionine, folic acid, vitamin B6 or B12, or zinc may alter the methyl supply [42,79].

Evidence of one-carbon impaired metabolism in schizophrenia was reported in the 1970s. Many studies observed the exacerbation of symptoms in response to a large oral dose of methionine in about 40% of patients with chronic schizophrenia [2,15,16]. Increased levels of homocysteine are associated with schizophrenia. In a recent meta-analysis of 8 studies, Muntjewerff et al. [66] observed that a 5 μmol/L increase in serum homocysteine level was associated with a 1.70 higher risk of schizophrenia. Folate deficiency has been reported in patients with schizophrenia [30,27, Dealberto: personal observation].

An important enzyme is methylenetetrahydrofolate reductase (MTHFR). It converts 5,10 methylenetetrahydrofolate into 5-methyltetrahydrofolate, producing the methyl donor for remethylation of homocysteine to methionine. One of the known polymorphisms of the MTHFR gene, C677T, influences DNA methylation status through an interaction with folate level [25]. Homozygotes with the ther- molabile variant (TT) had a decreased DNA methyla- tion compared to homozygotes with the wild type (CC); but when the analysis was performed according to folate level, only TT homozygotes with low folate level had impaired DNA methylation. In the meta-analysis previously cited [66] involving 9 published studies of the polymorphism of MTHFR on the risk of schizophrenia, the TT genotype had a 1.36 higher risk compared to the CC genotype. Another meta-analysis [48] found similar results, with an odds ratio equal to 1.48 for the TT compared to the CC genotype.
The few studies on MTHFR and schizophrenia which have reported the ethnicity of their subjects observed that the thermolabile variant of MTHFR was not frequent in subjects of African ancestry. No studies on folate or homocysteine and schizophrenia have reported ethnicity. The moderate risk for psychosis associated with the thermolabile variant of MTHFR and the higher levels of homocysteine is consistent with the 1.5 increase in risk associated with stressful events [39] and the 2.3 and 2.2 increase in risk observed in white and non-white/nonblack immigrants.

Testing the hypotheses

Epidemiological surveys with objective measure of skin color, vitamin D and vitamin-B complex status, homocysteine level with MTHFR polymorphism

The best suited study to test the proposed hypotheses would be an epidemiological survey of first contacts for psychosis, measuring vitamin D and vitamin B-complex status, homocysteine level with MTHFR polymorphism, and objective assessment of skin colour. In order to maximise differences between light and dark skinned persons, it would be conducted in a country in the high latitudes with a large group of immigrants of diverse origins.

All types of psychoses would be included. Along with DSM-IV criteria, clinical scales and diagnosis interviews would be chosen in order to maximise the clinical differences in affective and catatonic symptoms observed by previous studies between native-born subjects and dark-skinned immigrants. Skin colour would be objectively measured by reflectance spectrophotometry on the inner surface of the upper arm, a part of the body not exposed to the sun which has long been the standard for measuring skin color. Ethnicity and immigration status would be defined by place of birth of patient, parents, and grandparents, and by the patient.

It is predicted that the risk for psychosis and for schizophrenia associated with immigrant status and ethnicity will be in large part mediated by skin colour and vitamin D status.

Hospital studies of clinical symptoms according to skin colour

Hospital studies are more feasible than epidemiological studies but their biases are well known. They can provide results upon which to base an epidemiological survey.

Epidemiological studies of rates of psychosis according to skin colour in the same country at different sites differing in latitude and sun exposure

Epidemiological studies of the rate of psychosis according to skin colour can be performed in the same country extending over a broad range of latitudes and sun exposure.

Family studies in different ethnic groups

Case control studies can replicate previous results of higher rates of schizophrenia in siblings of dark-skinned patients compared to white ones, taking into account skin colour and vitamin D status in patients and relatives. Pregnancy and birth history should be documented, along with vitamin D maternal supplementation during pregnancy or early childhood supplementation, as well as diet during pregnancy and in childhood.

Studies of hospital admissions according to diagnosis, month and skin colour

According to the vitamin D insufficiency hypothesis, in high but not in low latitudes, dark-skinned persons will be more often admitted for psychosis in winter and spring months.

Cohort studies to observe the protective effect of vitamin D supplementation during pregnancy on cognitive function in the offspring

Because of the length of observation required, a prospective cohort study to observe the expected decrease in rate of schizophrenia and psychosis in the offspring with supplementation of vitamin D during pregnancy would not provide results before at least 3 decades. Given the effect of vitamin D deficiency during pregnancy on the cognitive function of the offspring in rats, a randomized controlled trial of vitamin D supplementation during pregnancy in women with vitamin D insufficiency is warranted to correlate its effect on the cognitive function in the offspring.

Cohort studies to monitor changes in schizophrenia and psychosis rates with systematic folic acid supplementation during pregnancy

Folic acid supplementation is recommended for pregnant women to prevent neural tube defects.
It would be interesting to monitor changes rate of schizophrenia and psychosis in the years to come.

Conclusions and relevance for public health

Psychoses, and in particular schizophrenia, are devastating for patients and for families. Their financial cost is enormous, when totalling admissions to hospital, cost of medications, inability to work with loss of income and loss of productivity. Immigrants going to a foreign country face many difficulties in adapting to a new culture, another language, and a different work environment. The psychotic episodes observed more frequently in these persons further increase their difficulties and prevent some of them from adapting to the new country.

The vitamin D insufficiency and the epigenetics hypotheses, if confirmed, could lead to preventive measures for dark-skinned persons, new immigrants and particularly pregnant women. If vitamin D insufficiency is confirmed to be a major risk factor for psychosis in dark-skinned persons, it could lead to inexpensive measures of supplementation during pregnancy, early childhood or later in life. These measures would be more important in high latitudes and in countries with high rates of immigrants from low latitudes. They would be particularly important for women who cover their bodies for cultural or religious reasons. The epigenetics hypothesis could lead to measures to decrease blood levels of homocysteine and improve vitamin B complex status, especially folic acid.

If confirmed, these hypotheses will ease the burden of the psychotic disorders and lead to promising avenues for new research.

Acknowledgement

This work is supported by a grant from the Canadian Institutes of Health Research (grant number HDD 77945).

References


