The Risk for Schizophrenia and Related Disorders among First- and Second-Generation Migrants: a Systematic Review and Meta-Analysis

by

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Abstract

Background: Migration is known as a risk factor for schizophrenia and related disorders, but the magnitude of the risk in second-generation migrants is unclear. This study aims at determining the risk of psychosis in first- and second-generation migrants and exploring sources of variation.

Methods: A systematic review of population-based incidence studies of psychosis among first- and second-generation migrants was conducted. Descriptive and meta-analytic syntheses of identified studies were performed and sources of heterogeneity were examined.

Results: Nearly all migrant groups were at increased risk for psychotic disorders. The magnitude of the risk was similar in first- and second-generation migrants, but varied considerably according to ethno-racial status, social contexts and methodological variables.

Discussion: The risk clearly persists into the second generation, indicating that post-migration factors are more important than pre-migration factors or migration per se. The observed variability suggests that socio-environmental determinants contribute to the onset of psychotic disorders.

Résumé

Contexte: L'immigration est associée à un risque accrû de troubles psychotiques, mais le doute persiste quant au risque chez les immigrants de deuxième génération demeure. Cette étude vise à évaluer le risque de psychoses des immigrants de première et deuxième génération et à en explorer la variabilité.

Méthode: Une revue systématique des études d'incidence de psychoses chez les immigrants de première et deuxième génération a été menée. Des synthèses descriptives et méta-analytiques des études ont été complétées. Les sources d'hétérogénéité ont été examinées.

Résultats : Presque tous les groupes d'immigrants ont un risque accrû de développer des troubles psychotiques. Le risque est comparable pour les deux générations, mais son ampleur varie considérablement selon le statut ethno-racial, le contexte social et la méthodologie.

Discussion : La persistance du risque dans la deuxième génération indique que les facteurs post-migratoires sont plus influents que les facteurs pré-migratoires ou la migration. La variabilité observée suggère que l'environnement social contribue au développement des psychoses.

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CHAPTER 1: BACKGROUND

Epidemiology of Schizophrenia: Review of the Literature

"Schizophrenia is *the* defining problem for psychiatry" states Kleinman in prefacing a seminal work on schizophrenia and culture (Jenkis & Barrett, 2004). Indeed, psychotic disorders – such as schizophrenia – are arguably the most serious conditions encountered in psychiatry (Tandon, Keshavan, & Nasrallah, 2008). With recent lifetime prevalence estimates of about 1% for schizophrenia and 3% for all psychoses, psychotic disorders result in considerable burden to sufferers, their family and society (Perala et al., 2007). According to the World Health Report 2001 of the World Health Organization, schizophrenia represents the 5th leading cause of non-fatal burden globally, accounting for 2.8% of Years Lost to Disabilities (YLDs) in 2000 (Mathers et al., 2002). While schizophrenia is primarily regarded as a genetically determined disorder, its exact causes are unknown. Despite intensive research efforts over the last decades, the etiology of schizophrenia remains unclear, and hence, preventive efforts have been marginal. In addition, while undoubtedly helpful in alleviating symptoms, therapeutic advances in the field have not yet altered significantly the course of the illness nor have they enabled sufferers to regain their prior levels of functioning in the majority of cases (Tandon et al., 2008).

A long-held axiom about schizophrenia is that its incidence was uniform across the world countries and societies. The World Health Organization 10-country study, which is one of the largest investigation of the incidence of schizophrenia in different cultures across the world, was very influential in this respect (Jablensky, Sartorius, & Ernberg, 1992). Using a uniform and rigorous methodology at all sites, this landmark study provided incidence data from eight sites across the world. Incidence rates ranged from 14 to 42 per 100 000 when a broad definition of schizophrenia was applied using the criteria of the International Classification of Diseases, 9th version (ICD-9). When a narrower definition was used, based on diagnostic criteria of the computer-based CATEGO program derived from the Present State Examination (PSE), the incidence then ranged from 7 to 14 per 100

000. While a two-fold variation across the sites was still evident with this stricter definition, the authors emphasized the homogeneity of incidence rates across cultures. They concluded that, '*schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures and have clinical features that are more remarkable by their similarity across cultures than by the difference.*' On the basis of these findings, other prominent schizophrenia researchers have further highlighted the universality of schizophrenia and the implications for its aetiology (Crow, 1994):

> *The evidence points to the singular conclusion that, contrary to almost any other common condition, the incidence of schizophrenia is independent of the environment and a characteristic of human populations.* (p.119)

This assumption of universality of schizophrenia – despite the contrary evidence – largely contributed to the dominant paradigm of schizophrenia as a biologically determined disorder, with limited contribution from social or environmental factors (Jablensky, 1999). However, this assumption has been recently challenged, namely on the basis of findings from migrant studies in Europe (Fearon & Morgan, 2006). The most striking and consistent findings are probably those from the African-Caribbean migrant population in the United Kingdom, with incidence rates as high as 10 times that of the host population (Fearon et al., 2006). An extensive systematic review of incidence studies of schizophrenia has challenged many tenets on schizophrenia in highlighting geographical variability of incidence rates and demonstrating significant variations as a result of migration status, urbanicity and gender (McGrath et al., 2004). Interest for migration and schizophrenia has accelerated over the past decade, and along with it, increasing consideration has been given to the putative role of social factors in the onset of schizophrenia and related disorders (Cantor-Graae, 2007). While the important contribution of genetic determinants in the aetiology of schizophrenia is clearly established, the concordance rates for schizophrenia among monozygotic twins – who share 100% of their genetic material – is between 40% and 50%, suggesting that environmental factors may play a significant causal role in the development of schizophrenia

(Tandon, Keshavan, & Nasrallah, 2008). The notion that social factors contribute to the causation of schizophrenia is still controversial; however, social causation mechanisms are being increasingly considered as potential determinants of schizophrenia and related disorders. Studies of migration and schizophrenia have been invaluable in this respect (Cantor-Graae, 2007; Fearon & Morgan, 2006).

Migration and Schizophrenia: a Historical Perspective

The study of migration and schizophrenia is not a new field of interest. Remarkably, North American pioneers had produced a rich body of literature on the relationship between schizophrenia and immigration. For instance, in his classical study, Ödegaard demonstrated that the admission rates for schizophrenia among Norwegian immigrants to the United States were twice as high as that of native-born Americans and Norwegians in Norway (Odegaard, 1932). Ödegaard attributed his findings to a selection hypothesis, according to which those predisposed to schizophrenia were more likely to migrate. Around the same time, the seminal *Chicago Study* revealed that blacks in Chicago had higher psychiatric hospital admissions, but not in parts of the city where they represented the majority group (Faris & Dunham, 1939). In fact, in these areas, whites were found to have unusually high admission rates and blacks, unusually low rates. The authors postulated that social factors contributed to the onset of psychiatric disorders, possibly in relation to the strain of living in a minority status. In Canada, Malzberg observed similar findings of elevated rates of schizophrenia among ethnic groups, when these groups constituted the minority in a given area (Cantor-Graae, 2007).

The issue of migration and schizophrenia was largely ignored thereafter, and the search for social causes of psychosis lagged behind the inexorable neuroscientific and genetic advances, especially in the North American context (Jarvis, 2007). In contrast, interest for the topic has been rekindled among European psychiatrists in recent decades, namely after findings of strikingly high incidence rates of schizophrenia among persons of Afro-Caribbean background living in the UK (Fearon et al., 2006). The UK has been the recipient of large waves of migration in

the post Second World War context, in particular from the Caribbean islands. Since then, a number of studies have reported a significantly higher incidence of schizophrenia among the Afro-Caribbean migrant group, with rates between 2 and 14 times greater than for whites in the UK. While earlier studies focused on first-generation migrants, later studies have also reported elevated rates for second-generation migrants (Harrison, 1990; Harrison, Owens, Holton, Neilson, & Boot, 1988; McGovern & Cope, 1991). These findings have been received with much scepticism namely because of methodological shortcomings of earlier studies, such as unreliability of census data for ethnic minority groups or concerns about the extensiveness of case ascertainment (Fearon et al., 2006).

Investigations of the incidence of schizophrenia have lately extended to a number of different migrant groups in other European countries. A number of Dutch studies have reported increased incidence rates among migrants from Morocco, Surinam and Dutch Antilles (Selten & Sijben, 1994; Selten, Slaets, & Kahn, 1997). A more recent larger scale study has reported increased risks among all non-Western immigrants, with strikingly high rates among second-generation Moroccans who presented a seven-fold risk increase compared to the native Dutch populations (Veling et al., 2006). The relationship between migration, ethnicity and schizophrenia has also been studied in Scandinavian countries, namely Denmark and Sweden, where elevated risks were reported among both first- and second-generation migrants (Cantor-Graae & Pedersen, 2007; Cantor-Graae, Pedersen, McNeil, & Mortensen, 2003; Leao et al., 2006). Therefore, it appears from these findings that the increased risk for schizophrenia affects not only persons who migrate, but also their children born in the host society context.

Schizophrenia and Migration: Evidence from a Meta-Analytic Review

In a meta-analytic review of 18 population-based migrant studies – which were conducted almost exclusively in Europe – Cantor-Graae and Selten concluded that almost all immigrant groups had higher incidence rates of schizophrenia compared to native-born groups, with an overall approximately threefold risk elevation

associated with a personal or family history of migration (Cantor-Graae & Selten, 2005). A significant finding was that greater effect sizes were associated with black skin colour, thus suggesting the potential contribution of factors such as discrimination to explain this risk. Furthermore, the authors have observed elevated risks of schizophrenia not only among first-generation immigrants, but also among second generation immigrants (native-born with one or two foreign-born parents). A meta-analysis was performed separately for both generations of migrants, which yielded mean-weighted relative risks of 2.7 (95% CI 2.3-3.2) among first-generation migrants, and of 4.5 (95% CI 1.5-13.1) among second-generation immigrants. Such a risk elevation is considerable and cannot be disregarded in our attempts to understand the causation of psychotic disorders in general. An important limitation of this review is that the relative risk estimate for second-generation immigrants was computed from only 7 effect sizes and very small sample sizes, hence the very wide confidence interval.

While migration is now increasingly recognized as a risk factor for schizophrenia, there remains considerable doubt with regards to the persistence and the magnitude of the risk in the second generation. Also, the reasons for this relation between migration and schizophrenia remain a conundrum. So far, biological factors – such as cannabis use or obstetrical complications – have failed to account for the risk of schizophrenia among migrant groups (Fearon & Morgan, 2006). Also, socio-environmental factors – such as urban density, discrimination or socio-economic deprivation – are increasingly looked upon as potential determinants for psychotic disorders that may explain the risk for schizophrenia observed among immigrants (Cantor-Graae, 2007). Generational differences in the risk for psychotic disorders may provide valuable clues in this regard.

Schizophrenia versus Psychosis: *What is Being Studied?*

Schizophrenia is a clinical syndrome characterized by psychotic or positive symptoms, negative symptoms and cognitive impairments, which becomes apparent in adolescence or early adulthood, with severe and long-lasting effects on physical

and mental health and on psychosocial functioning (McGurk & Mueser, 2004; Murray & Jones, 2003). While psychosis – or the presence of delusions or hallucinations along with impaired thought processes and reality testing – is an inherent characteristic of the schizophrenia syndrome, it can also occur in a variety of related schizophrenia spectrum disorders, affective disorders and brief psychotic states.

While schizophrenia remains the focus of significant research efforts, there has been increasing debate over the validity and usefulness of its current diagnostic construct in recent decades (Morgan, McKenzie, & Fearon, 2008). Despite the overlap between diagnostic categories for psychotic disorders, the diagnosis of schizophrenia as defined by DSM-IV TR criteria is generally regarded as a reliable one. However, there is increasing concern about whether the illness represents a discrete entity or whether it lies at the end of a continuum from normal experience (van Os, 2000). In addition, over the last decade, clinicians and researchers have become increasingly focused on the early manifestations of schizophrenia and related disorders, as illustrated by the evolving field of early intervention for psychoses in a broad sense. Most migrant studies in recent decades have been concerned with schizophrenia (Cantor-Graae & Selten, 2005). In contrast, a number of more recent investigations have focused on the first episode of psychosis in a broader sense (Coid et al., 2008; Fearon et al., 2006; Veling et al., 2006). Similarly, recent scholarly works on the topic are increasingly concerned with psychosis in general, rather than schizophrenia (Morgan, McKenzie et al., 2008). In light of this ongoing debate and recent trends, this thesis is concerned not only with schizophrenia, but with psychosis in a broad sense, although much of the literature focuses on schizophrenia.

Concepts of Migration, Generation Status, Ethnicity and Race

Migration

Migration is defined as the process of moving from one country, place or locality to another ("Merriam-Webster Online Dictionary,"). It is a universal phenomenon that

has characterized human nations at all times. Bhugra has further described migration as *a process of social change whereby an individual, alone or with others, moves from one cultural setting to another for the purposes of settling either permanently or for a prolonged period* (Bhugra, 2000). This shift may be motivated by a variety of reasons, including 'push' factors (e.g., fleeing political persecution) and 'pull' factors (e.g., seeking economic betterment). As Bhugra argues, migration is a highly heterogeneous process determined by a variety of factors, such as the underlying motives, the groups or families involved, the timing (permanent versus temporary) or the geo-political context of the source and destination environments (Bhugra, Still, Furnham, & Bochner, 2004). The migration process has been divided into three stages, each of which may be accompanied by a number of stressors that could potentially contribute to distress and mental illness (Bhugra & Becker, 2005; Bhugra & Jones, 2001):

- Pre-migration: the individuals decide to migrate and plan the move;
- Migration: the process itself and the physical transition from one place to another, with the associated psychological and social steps;
- Post-migration: dealing with the new social and cultural frameworks of the host society, and adjusting to new roles.

The term 'migrant' is the generic term used to designate an individual who leaves a place to go to another, without reference to direction or duration. On the hand, the terms 'emigrant' and 'immigrant' are used to designate respectively a person who moves out of a place in another, and a person who moves into a place, usually permanently as opposed to the temporary situation of migrant workers. The term 'migrant' is most frequently used in the literature on migration and schizophrenia in reference to immigrant groups in the host society context. For simplification purposes, the term 'migrant' will be used henceforth in reference to its meaning of 'immigrant'.

Generation or Migration Status

Most investigations on migration and schizophrenia have focused on foreign-born immigrants. However, as migrants have had children in their host society context, these have increasingly become the focus of attention in recent decades. The children of migrant parents, who were born in the host society context, are usually referred to as second-generation immigrants although they have no personal history of migration. The migration process should therefore be differentiated from the migration or generational status, and to consider generational differences with regards to mental health (Bhugra et al., 2004). As children of migrant parents have not migrated themselves, they were most likely not exposed to pre-migration factors or to migration stresses; however, they share the post-migration stage and may plausibly be exposed to the same post-migration stressors as their parents. While there is some variation in the definition of migrant generations in the literature, it is generally accepted that first-generation migrants refer to those with a personal history of migration, and second-generation migrants, to those born in the host society to one migrant parent or both.

Race

Race and ethnicity are two related concepts, which have evolved significantly over time and which have been used to subdivide and classify populations (Bhopal, 2007). As Bhopal describes, there is no consensus on the definitions of these concepts, nor on their appropriate use in epidemiological research; also they have often been used interchangeably. The issue of race has been a particularly contentious one. The *Merriam-Webster* defines "race" as a category of humankind that shares certain distinctive physical traits *(Merriam-Webster Online Dictionary)*. This definition is in line with the traditional idea of race as a biological concept, which has a long history in human societies, with a legacy of misuse and injustice (Bhopal & Rankin, 1999). This notion of race as a biological concept therefore became increasingly contested and challenged, especially after its scientific validity became undermined by modern genetic findings (Jones, 1981). Increasingly, scholars conceptualize the notion of 'race' as a social construct used for classifying

humans on the basis of social perceptions (Bhopal, 2007; Satzewich & Liodakis, 2007). As a result, recent scientific literature has largely replaced the use of race classifications by that of ethnicity (Morgan, McKenzie et al., 2008).

Despite its lack of biological basis and contested use, the concept of race may nonetheless be a relevant variable in reference to its related social perceptions (Lin & Kelsey, 2000). Racism may represent an example of such a social perception of race, and it has been shown to negatively influence a number of health outcome. The visible minority status, such as used officially by the Canadian government, may be used as alternate variable to inform about social perceptions on the basis of skin color (Statistics Canada, 2008).

Ethnicity

The concept of ethnicity is another complex and evolving one in its use to classify people (Bhopal, 2007). This term is derived from the Greek work *ethnos*, which means 'people'. There are multiple definitions of ethnicity, but most emphasize the notion of belonging to a social group. A dictionary of epidemiology defines an 'ethnic group' as follows (Porta & Last, 2008):

> A social group characterized by a distinctive social and cultural tradition, maintained within the group from generation to generation, a common history and origin, and a sense of identification with the group. (p.85)

Bhopal highlights that this sense of belonging and identification according to ethnicity results from a variety of factors, such as language, diet, religion, ancestry, and physical features associated with race (Bhopal, 2007). From this perspective, ethnicity is clearly a complex and multifaceted concept, which is in part determined by aspects of culture – as a set of shared social practices, customs and behaviors – ancestry, and race. Various authors have highlighted the fluid nature of ethnicity, which may change over time and space in relation to the social context (Bhopal, 2007; Morgan, McKenzie et al., 2008).

Migration, Race and Ethnicity in Epidemiological Research

Although their definitions and use in health research remain contested, studies on issues of migration, ethnicity, race and health have generated invaluable contributions in the arenas of etiological research, public health, healthcare services and clinical practice (Lin & Kelsey, 2000). However, these related concepts are inevitably complex and pose significant challenges when considering the variables to be measured (Bhopal, 2007; Morgan, McKenzie et al., 2008). While migration is clearly a complex variable, it is also perhaps easier to measure in its simplest meaning – having a personal or parental history of migration or not. This distinction is provided by most population-based migrant studies on the incidence of schizophrenia (Cantor-Graae & Selten, 2005). Classifications on the basis of ethnicity or race are contested, challenging and evolving depending on a given social context. However, the determination of migration status is straightforward on the basis of personal and parental place of birth. Nonetheless, in evaluating incidence rates according to migration status, we should be reminded that the outcome of interest (e.g., schizophrenia) may be determined not only by the migratory process itself, but also by aspects of race, culture and ethnicity. This is particularly relevant when focusing on second generation migrants, who have no history of migration themselves.

Generational Differences in the Risk for Psychotic Disorders

Migration is now clearly established as a risk factor for schizophrenia (Selten, Cantor-Graae, & Kahn, 2007). However, it is uncertain whether second-generation immigrants have a similar or even a higher risk than first-generation immigrants. If that were the case, this would remove the focus away from pre-migration factors and the migratory process and suggest to further consider the role of post-migration factors, such as acculturation or the social experience of migrants in the context of their host society. In addition, if second-generation migrants were found to be at higher risk for psychosis, this would further highlight the potential contribution of social causation mechanisms in the onset of the illness. Indeed, a risk elevation that persists or increases in the second generation could hardly be explained strictly by

biological or genetic factors. Generational differences in the risk for psychotic disorders thus have the potential to yield significant insight into the causes of schizophrenia and related disorders.

It is worth mentioning that migrant studies have generated significant advances in epidemiological research in areas other than schizophrenia (Lin & Kelsey, 2000). For instance, breast cancer incidence rates were three times higher in Japanese women in the United States than their counterpart in Japan. In addition, higher rates were observed among Asian American women born in US than in their foreign-born counterpart. In addition, the longer these women lived in the US, the higher were their rates. These findings were instrumental in uncovering the role of environmental factors – such as diet and lifestyle – in the causation of breast cancer. Similarly, migrants in Western countries were found to be at higher risk for multiple sclerosis than native-born residents in the host society or in their source country (Ramagopalan, Dyment, & Ebers, 2008). The risk magnitude was found to vary according to both the migrant's country of origin and of destination (Dean & Elian, 1997). Whether in the case of breast cancer or multiple sclerosis, investigations of incidence rates of first- and second-generation migrant groups in various geographical areas have provided significant advances in the etiological research of either field. If such investigations would have focused strictly on the ethnicity variable, they would have missed significant insights from the exploration of generational differences in the risk for the disease.

Why a Systematic Review and Meta-Analysis?

McGrath argues that, *gaining traction on the epidemiological landscape of schizophrenia* may help us identify risk-modifying factors for schizophrenia, and that we need to do so urgently in light of the burden associated with the illness (McGrath, 2003). The evidence on the increased risk of schizophrenia associated with migrant status indicates that potential risk factors operate between the time of migration and the onset of the illness. There exists already a wealth of data reporting an association between migration and the risk for schizophrenia and related

disorders. However, in order to generate viable hypotheses about the causation mechanisms in schizophrenia, it is important to take stock of the existing knowledge by systematically evaluating the available literature and assessing the existing data in a rigorous and transparent way. In recent decades, there has been an increasing appreciation for the role of the systematic review methodology to synthesize the available evidence, in contrast with the traditional narrative reviews (Borenstein, Hedges, Higgins, & Rothstein, 2009).

Systematic reviews can provide detailed and critically appraised information in a descriptive format and/or as a meta-analysis. Systematic reviews enable us to take stock of the existing knowledge, to address its limitations and to propose avenues for future research. A meta-analysis, a statistical synthesis of quantitative data, provides an objective and transparent framework to synthesize the data in addition to the substantive appraisal of the results. The goal of a meta-analysis has often been restricted to the statistical pooling of data from different studies to estimate a common or mean effect size. However, meta-analysis may also consider the dispersion of results along with the mean effect, or even focus exclusively on the sources of variation in the available data. By its nature, a meta-analysis usually widens the base of studies by addressing broader questions than individual studies and exploring the pattern of available answers. A common criticism of meta-analysis has been that researchers *mix apples and oranges* in the same analysis, thus ignoring possibly important differences across studies. Borenstein answers to this criticism as follows: *a meta-analysis may be thought of as asking a question about fruit, for which both apples and oranges contribute valuable information* (Borenstein et al., 2009). The current review is primarily concerned by further examining migration status as a risk factor for psychotic disorders. It is nonetheless acknowledged that multiple methodological and substantive variables may account to differences within and across studies. A systematic review and meta-analysis provides a rigorous framework to explore these considerations.

Research Questions and Objectives of this Study

Migration is clearly is now clearly established as a risk factor for schizophrenia. However, it is uncertain whether second-generation immigrants have a similar or even a higher risk than first-generation immigrants. Such knowledge is necessary to explain the mechanisms underlying the increased risk of psychotic disorders among migrants. Also, understanding generational differences in the risk for schizophrenia may shed further light into the causes of psychotic disorders.

Research Questions:

1. *What is the magnitude of the risk for schizophrenia and related disorders among first- and second-generation migrants relative to the reference population?*
2. *Are there generational differences in the risk for psychotic disorders?*
3. *What are the sources of variation in the risk for psychotic disorders among first- and second-generation migrants?*

This systematic review and meta-analysis will synthesize findings of population-based studies of the incidence of schizophrenia and related disorders among immigrants. Its aims are threefold:

a) to determine the magnitude of risk of developing schizophrenia and related disorders among first- and second-generation migrants in comparison with reference groups (non-migrants);
b) to examine generational differences in the risk for psychotic disorders among migrants;
c) to explore variations and potential moderators underlying the risk for psychotic disorders among first- and second-generation migrants.

CHAPTER 2: METHODOLOGY

The methodology for this systematic review and meta-analysis was based on the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000).

Search Strategy

Prior to developing a search strategy for studies to be included, a search through the Cochrane Database of Systematic Reviews was completed to verify whether there was any published or registered systematic review related to the review questions since the implementation of the database in 1988. No systematic review was identified through this search. A broad search string was developed to systematically search MEDLINE, PsycINFO and EMBASE for potentially relevant articles published between January 1977 and December 2008. Each database was searched using the appropriate medical subject headings for "migration", "psychosis" and "schizophrenia" concepts and special features (e.g., explosion) as indicated. In this way, the search was based not only on these keywords, but also on the specific terms used in each database to refer to these concepts. This computerized search strategy was developed with the assistance of a medical librarian with expertise in systematic reviews. Here are listed the specific search strategy and terms for each database:

- MEDLINE: ((‘emigration and immigration’ OR ‘emigrants and immigrants’) AND (‘psychotic disorders’ OR exp ‘schizophrenia’))
- PsycINFO: ((exp ‘human migration’ OR ‘immigration’) AND (exp ‘schizophrenia’ OR ‘psychosis’))
- EMBASE: ((exp ‘migration’ OR ‘immigrant’) AND (‘psychosis’ OR exp ‘schizophrenia’))

In addition to these 3 searches, a search string based on the following keywords was applied the three databases: (migrat* OR migrant* OR immigra* OR emigra* OR foreign*) AND (‘psychosis’ OR ‘psychoses’ OR ‘psychotic’ OR ‘schizophrenia’).

Reference lists of significant articles and previous reviews on the topic were screened manually to locate additional articles. The database of a previous extensive review of schizophrenia incidence studies was screened carefully (McGrath et al., 2004). We tracked forward and backward citations of articles included, using Web of Science (Bakkalbasi, Bauer, Glover, & Wang, 2006). We also contacted experts in the field of migration of migration and psychosis (EJ and JPS) to review our list of studies and verify whether any studies had been missed. Potentially relevant citations from all sources were imported in a reference manager software.

Study Selection: Identification of Eligible Studies

Inclusion criteria were established a priori. Based on our background review of the literature on migration and psychosis, 1977 was selected as the earliest publication time limit for inclusion in our study, as previously done by Cantor-Graae and Selten (2005). First, there were more methodological concerns in earlier migrant studies (most of which were conducted in the UK) especially with regards to the reliability of denominator data and to demographic differences (e.g., age and sex) between migrant and non-migrant populations. Cochrane's study of first admissions among migrants and non-migrants is the first that has systematically attempted to use reliable numerator and denominator data and to standardize for potential age and sex differences in populations involved (Cochrane, 1977). In addition, a primary aim of our review was to examine the risk of psychotic disorders among second-generation migrants. We only found studies of second-generation migrants in the two recent decades. Also, it appeared highly unlikely that studies conducted prior to the 1980's would include any second-generation migrant groups, given the relatively recent history of any significant migration to Europe. We therefore considered 1977 as a conservative lower time limit for inclusion in our review.

All retrieved citations were screened independently by two reviewers in a 3-fold process (FB and AM for the first and second screening, and FB and EV for the third screening). The screening process was completed sequentially as follows:

- The first screen was based on citations, including titles and abstracts if available, and using the following broad inclusion criteria: published in a peer-reviewed journal in 1977 or after, relevant to both psychotic disorders and migration or ethnicity. No language restrictions were applied at this initial stage. In case of doubt, citations were kept for a second screen.
- A second screen was completed based on the abstracts of all identified citations using strict inclusion criteria. Citations were excluded if it was clear that they did not meet one of the inclusion criteria, including the language criteria. Conference abstracts, editorials, case reports, letters or comments were excluded at this stage. In case of doubt, citations were kept for a third screen on the basis of full-text articles.
- The third and final screening was based on the full-text articles of each study kept at the end of the second screen. A piloted study selection grid (see Appendix I) was completed for each study at this stage and a log of excluded studies was kept.

The studies were included in the review if they met all of the following inclusion criteria:

1) The study was published in a peer-reviewed journal after 1977;
2) The study was written in either English, French, Spanish, Dutch or German language;
3) The study is a population-based incidence study - either first admission or first contact;
4) Diagnoses used included schizophrenia, first-episode psychosis or psychotic disorders in general;
5) Incidence rates for these diagnoses were provided for at least one migrant group and a reference group from a defined catchment; alternately incidence rate ratios were provided or numerators and denominators that enabled to compute incidence rate ratios;
6) The study investigated a general adult population or was not restricted to children or to elderly population;

7) The study differentiates first-generation from second-generation migrants, the former referring to migrants born in a foreign country and the latter, to native-born persons with one or both parents born abroad;
8) The study provided results corrected for age differences between migrant and reference groups or data that enable such calculations.

The selection of studies at the end of each step was determined by consensus between the two reviewers. A third independent party was available for consultation in case of disagreement, but consensus was reached at each stage. At the end of the selection process, we found that some eligible studies reported findings from the same population or from populations that overlapped in time and location. When this occurred, we selected the most informative version of the study. For instance, we would select the study with the largest sample size or with the longest observation period. A log of all studies was kept (available upon request), along with the reasons for exclusions in the second and third screening stages.

Data Extraction and Quality Assessment of Eligible Studies

Once we agreed on the final list of studies to be included in the review, data were extracted independently by two reviewers (FB and EV) on pre-piloted forms (see Appendix II). This data extraction and quality assessment form was used to assess various aspects of the internal validity (quality) of selected studies: selection bias, information bias and confounding. Detailed information on study features (e.g., authors, years of publication, setting) and methodological characteristics (e.g., case ascertainment method, diagnostic criteria, etc.) were obtained for all included studies. Studies were assigned an overall quality score on the basis of both study design features and comprehensiveness of reporting, using the same scoring scale as McGrath et al. in their comprehensive review of schizophrenia incidence studies (McGrath et al., 2004). Since there is currently no agreement on the validity of quality scoring in meta-analyses of observational studies (Stroup et al., 2000), we also completed an overall quality appraisal that reflected our assessment of the internal validity of all studies. Studies were classified within higher, average or

lower quality ranges. Quality scores and appraisals were then reviewed independently by a 3rd independent reviewer (AM) who rated each study into three tertiles: higher quality, average quality and lower quality. Full details of the quality assessment in this review are available from the author. These quality assessments were used in the descriptive synthesis and in the meta-analysis by stratifying the studies by quality to determine the impact of quality on summary effect sizes (Pai et al., 2004).

On a second data extraction form, detailed quantitative results were extracted for each study, including numerator and denominator data and incidence rates for both migrant and reference groups. Most studies presented figures for more than one migrant group. Some studies reported results on various first-generation and/or second-generation migrant groups. Data were extracted for each migrant group identified and, as per our review objectives, reported separately for each generation. Most studies reported results for schizophrenia, but some reported results for schizophrenia combined with other psychoses or for all first episodes of psychosis. When available, the results for schizophrenia only were selected. Other studies reported separate results for non-affective and affective psychoses. The results of the former were then selected.

Incidence rate ratios (RR) were selected as a measure of the effect size to evaluate the risk associated with migrant status for all migrant groups. For each study, age-adjusted RRs were extracted or computed for one or more migrant groups by dividing the incidence rates of each migrant group by that of the reference (non-migrant) group of the study. When required, age adjustments were performed by direct or indirect standardization, depending on the available data. Gender-specific RRs were extracted when available, and a gender-adjusted RR was obtained through direct standardization or through a Mantel-Haenszel procedure. All data extraction and computations were performed independently by two investigators (FB and EV). Discrepancies were resolved by consensus. If required, authors were contacted to provide clarifications or additional information. Prior to initiating meta-analysis, we

completed a descriptive synthesis of the selected studies by tabulation of study characteristics, adjusted RRs for each migrant groups, quality scores and overall appraisal, and comments on the main findings and limitations of individual studies.

Descriptive Synthesis

At the end of the study selection, data extraction and quality assessment processes, we completed a descriptive synthesis of selected studies prior to initiating a meta-analysis synthesis. The sample in our study consisted of the primary studies identified and included in the review. The main features of our study sample were then described, namely their settings, observation periods, study populations and methodological features. We tabulated the main features and quality appraisals of each reviewed study. A narrative table with more detailed information about the methods and results of individual studies was also completed. It has been argued that much can be learned about the distribution of epidemiological data by evaluating quantiles (e.g., 10% to 90% range) around measures of central tendency (e.g., mean or median) rather than relying exclusively on the pooling of data (Saha, Chant, & McGrath, 2008). We have therefore computed central tendency and dispersion measures from the effect sizes for both first- and second-generation migrants. We examined and described the variability in the key findings of primary studies. Potential confounders and risk moderators reported in primary studies were also described.

Meta-Analytic Methods

There were large differences in the reporting of numerators, denominators and other quantitative data between studies. The combination of findings from these various studies requires the information contributed by each study be comparable. Therefore, in the first stage of meta-analyses, a summary statistic or effect size is computed for each study or independent group to reflect the magnitude of the risk associated with the exposure variable (Borenstein et al., 2009; Egger, Smith, & Altman, 2001). Since most studies reported findings on more than one migrant group (e.g., Black Africans and Caribbeans), each reported migrant group was

considered as a subgroup that contributes independent information about the magnitude of the risk associated with migration status in that ethnic group. Hence, migrant groups had to be considered as mutually exclusive so that subjects could not be included in two different groups. Therefore, separate effect sizes were estimated for each available migrant groups as done previously by Cantor-Graae and Selten (Cantor-Graae & Selten, 2005). When individual studies reported data for overlapping categories (e.g., *all first-generation migrants* and *first-generation Caribbean migrants*), we ensured that data included in the analyses were based on specific and independent migrant categories.

Rate ratios were preferred as an effect size measure, partly because their meaning is more intuitive as a measure of the effect of a risk factor, and also because they are less sensitive to baseline differences in estimation of risk and more robust in relation to heterogeneity (Cooper & Hedges, 2009). The performance of a meta-analysis also requires that a comparable variance be estimated for each effect size. To ensure the comparability of effect sizes across studies, we estimated the variance for each study group using the same formula as follows (Borenstein, 2009):

$$V = 1/N_m + 1/N_n$$

where N_m is the number of migrant cases and N_n is the number of cases in the reference (non-migrant) group. The variance estimates will determine the weight assigned to each study group, more precise studies generally being assigned more weight (Borenstein et al., 2009).

From the individual group effect sizes, a log RR measure was computed to carry out the analyses given its optimal statistical properties and to avoid the skewed distribution associated with RR measures (Borenstein et al., 2009; Cooper & Hedges, 2009). Meta-analysis was used to obtain a pooled estimate (or mean-weighted effect size) of the risk for schizophrenia associated with both first-generation and second-generation migrant status. Analyses were conducted on two main data sets:

- A comprehensive dataset (dataset 1) that included all available effect sizes for first- and second-generation migrants.
- A more restricted dataset (dataset 2) that included only the effect sizes from studies that reported data on *both first- and second-generation migrants*. This analysis was justified in order to better highlight generational differences by comparing effect sizes for related migrant groups in the same social contexts and also as an attempt to reduce heterogeneity across studies.

Our primary analyses consisted of separate meta-analyses of effect sizes for the first and the second generation migrant groups, in both the comprehensive and restrictive datasets. These analyses enabled us to obtain a mean-weighted effect size of the magnitude of the risk for schizophrenia in first- and second-generation migrants.

Analyses were conducted under the random-effects model. Unlike the fixed-effect model, which starts with the assumption that the true effect is the same in all studies, the random-effects model assumes that different effect sizes underlie different studies as a result of variations in methodology or study populations (Borenstein et al., 2009). Under this model, it is usually assumed that the true effects are randomly distributed around a mean effect size. When attempting to estimate a summary effect, we need to consider two sources of variance: first, the within-study error – which results from error in estimating the true effect size of the study – and second, the between-studies variance, which results from the variance of the true effect sizes for each study. Both these sources of variance will be estimated to determine the weight assigned to each unit of analysis (independent subgroup), as the weight is the inverse of that subgroup's variance. Since the selected studies are based on migrant groups of diverse ethnic backgrounds and in various settings, it appeared unlikely that the methods and study populations could be considered as equivalent across all sites. We could not assume that these studies would share a same true effect; therefore, the random-effects model is more easily justified a priori, before assessing heterogeneity across studies.

In systematic reviews, it is important to consider the potential for publication bias that may result from the non-publication of studies with negative or non-significant findings, as studies with higher effect sizes may be more likely to published (Borenstein et al., 2009). According to the model generally used to assess publication bias, small studies are at greatest risk for being unreported, with only the largest effects being published, as opposed to large studies which are likely to be published regardless of statistical significance. As a result, it is expected that the bias would increase as the sample size goes down. The funnel plot is a mechanism that allows us to display the relationship between study size and effect size. We have devised funnel plots of effect sizes for both first- and second-generation in the comprehensive dataset to verify whether there was any evidence for publication bias.

Assessing and Exploring Heterogeneity

In a meta-analysis, the variation across the reported effect sizes might reflect partly true variations in effect sizes and partly random variation that results from sampling error. The term *heterogeneity* is used to refer to the former, i.e., the differences in the true effects only (Borenstein et al., 2009). A Cochran Q statistics can be used to assess the level of heterogeneity across studies. First, a Q_W – for Q within – homogeneity statistic was calculated for each analysis to determine whether the subgroups studied could be assumed to share a common population effect size (Cooper & Hedges, 2009). A significant p-value for Q_W indicates significant heterogeneity across the individual effect sizes, indicating that effect sizes cannot be assumed to estimate the same population. The Q_B statistic – or a between-category homogeneity statistic – was also used to test whether differences between various groups were statistically different (e.g., first- versus second-generation migrants). The I^2 index was also computed to assess the level of heterogeneity in various analyses (Borenstein et al., 2009). This statistic represents the ratio of true heterogeneity to total variance across the observed effect estimates. This ratio is usually expressed on a percent scale. As opposed to the Q statistic, I^2 is not directly

affected by the number of studies in the analysis and it reflects the amount of variance on a relative scale.

In a meta-analysis, the assessment of heterogeneity will often influence the later stages of the analyses and the interpretation of the results. When the observed effect sizes are highly homogeneous, more emphasis may be placed on the precise determination of the summary effect. On the other hand, in cases of significant variations across effect sizes, the focus may shift to the assessment of the dispersion in addition to the determination of a mean effect (Borenstein et al., 2009). In fact, consideration of possible sources of heterogeneity may often provide more insights than the overall measure of effect per se Some means may be used to reduce the observed heterogeneity when encountered, such as changing the measures of associations used or excluding outliers. Sensitivity analyses may also be used by excluding studies with a certain number of shared features. However, it can also be highly informative to explore the sources of variability across studies. A number of methods for exploring heterogeneity are available (Song, Sheldon, Sutton, Abrams, & Jones, 2001):

- Graphical methods, such as forest plots of point estimates and confidence intervals;
- Subgroup analyses according to certain study-level variables or moderators (e.g., patient characteristics, study features) that may contribute to the observed heterogeneity.
- Meta-regression: a regression analysis that correlates study effect sizes (dependent variable) in function of one or more study-level variables (independent variables or predictors).

In this meta-analysis, subgroup analyses were used as the primary mode of investigating heterogeneity as they have the potential to generate relevant categories or effect moderators and to evaluate heterogeneity within subgroups. A first step in investigating heterogeneity in meta-analysis is to identify study-level variables that may be associated with the results of studies, thus acting moderator variables or

effect modifiers (Song et al., 2001). Such study descriptors may include substantive variables (e.g., characteristics of study participants and settings), method variables (study design features) and extrinsic variables (e.g., characteristics of the researchers or study sponsors). There are no agreed guidelines on the identification of moderator variables to be tested in a meta-analysis. Their selection will therefore be based on pre-existing knowledge and on the descriptive synthesis of the available studies. Substantive issues will first be considered as potential variables of interest, followed by method variables.

Exploring Heterogeneity: Substantive Variables

In their meta-analysis on this topic, Cantor-Graae and Selten had reported a significantly higher risk of psychosis for migrants from countries where the majority of the population is black (relative risk = 4.8, 95% CI= 3.7-6.2) versus those from countries where the population was classified as white or neither black nor white (Cantor-Graae & Selten, 2005). We have therefore decided to determine the effect of ethno-racial or visible minority status on developing psychosis. Two main classifications were used:

- A classification of ethno-racial status was used based on the following categories: White, Black (African and Afro-Caribbean), Asian, Middle Eastern. This classification was developed on the basis of the recent UK official ethnicity data classification (National Statistics, 2003) and adapted to encompass the majority of the migrant groups identified by the review.
- A second broader classification was developed to determine the effect of the visible minority status variable, such as used in the official Statistics Canada censuses (Statistics Canada, 2008). The visible minority categories were collapsed in two main categories: black and non-white non-black. Including the reference category white, the following categories were used: ‘black’, ‘non-black non-white’, and ‘white’. The category ‘white’ does not refer to visible minority; however, it does still refer to migrant or ethnic minority groups, and not to the native-born populations. These categories were devised in reference with the visible minority classification used in Canadian

censuses. Migrant groups from various areas were classified on the basis of skin color of the majority population in their areas of origin. Thus, migrants from Europe, North America and Australia were classified as white (non-visible minority); migrants from the Caribbean and sub-Saharan Africa, as black; migrants from Asia, South America, North Africa, Turkey and Greenland, as neither black nor white.

In both classifications, a mixed / other category was also used for groups that did not belong to any pre-defined category or that combined migrants from diverse birthplace, for example, the groups described as other Western and other non-Western in the study by Veling et al (Veling et al., 2006). These groups were excluded from analysis. Each migrant group identified was categorized independently by the main author and an expert in trans-cultural psychiatry. Discrepancies were resolved by consensus. The analyses for ethno-racial status and visible minority status were based on the comprehensive set of migrant studies (dataset 1). A first analysis combined first- and second-generation migrant groups to examine the ethno-racial variable only; then, the effects were examined for each generation separately.

The analyses described above aimed at identifying potential moderators of the association between migration and psychosis. In addition to these, a number of exploratory analyses were added to investigate further sources of variation in the risk for psychotic disorders among migrants:

- Multiple studies reported separate findings for males and females. Therefore, we performed analyses using all gender-specific data available to explore possible gender effects. This analysis examined gender effects in the risk for both first- and second-generation migrants.
- Analyses were also conducted to examine the potential effects of the socio-environmental contexts, by comparing the risk estimates in various study settings (host countries).

- A few studies have reported second-generation migrant findings separately for those born to one or both migrant parents. An analysis was conducted on the available effect sizes to determine whether having one non-migrant had any protective role in the risk observed in the second generation.
- An additional analysis for generational differences was conducted exclusively for Caribbean migrants in the UK. This analysis was justified because this migrant population is the most studied group and generates the most data, but it also enabled us to examine generational differences in the context of a specific ethnic group in the same social context.

Exploring Heterogeneity: Methodological Variables

Method variables will largely differ according to the design of studies included. Also, the methodological features of studies are significant determinants of the study quality or internal validity. We have therefore selected to evaluate the impact of our quality assessments on our findings. A sensitivity analysis is a method that enables to test the robustness of findings according to a number of factors, such as quality or methodological features (Egger et al., 2001). Therefore, we have first completed an analysis including only higher quality studies in the comprehensive dataset to determine whether this impacted the summary effect sizes. Using this same dataset, we have also completed a meta-regression of the effect size as a function of the quality score. We have also completed sensitivity analyses according to two potentially salient quality features in migrant studies: the case ascertainment method and the diagnostic classification used. The former may contribute to selection bias, and the latter to information bias. Using the comprehensive dataset, we first analyzed separately the studies in which ascertainment was based on all first contact and the studies based on first admissions only. Secondly, we analyzed separately the studies that used operationalized DSM-IV criteria for schizophrenia and those that used ICD-8, 9 or 10 criteria.

All analyses were carried out using the Comprehensive Meta-Analysis (King et al.) statistical software, version 2.2 (Borenstein, Hedges, & Higgins, 2005). Here is a summary of the main and subgroup analyses conducted:

- Meta-analysis based on all first- and second-generation migrants effect sizes (dataset 1).
- Meta-analysis based on the restricted subset of studies with both first- and second-generation migrants (dataset 2).
- Subgroup analyses for the following substantive variables:
    - Gender
    - Visible minority status
    - Ethno-racial category
    - Host countries
    - Urbanization of study setting
- Subgroup analyses for the following methodological variables:
    - Diagnostic classification system
    - Case ascertainment type (first-admission versus first-contact)
    - Quality range

CHAPTER 3: RESULTS

Descriptive Synthesis

Search Results

The computerized search strategy yielded an initial set of 1671 potentially relevant citations. 19 additional potential studies were located from manual searches and contacts with experts and added to this initial set. Of the 1690 citations identified for a first screen, 1379 were rejected upon reviewing the titles and abstracts as they were not related to human migration and/or to schizophrenia and related disorders or because they were published prior to 1977. From the remaining 311 citations and abstracts reviewed through a second screen, 185 potential studies were excluded because they clearly did not meet criteria for inclusion in the review. These included abstracts, commentaries, reviews or publications in other languages. At the end of this second screen, there remained 112 publications for a detailed full-text review using a study selection form (Appendix I). In this final screen, 86 studies were excluded because they did not meet one of the inclusion criteria. 6 additional studies were excluded because they overlapped in time and location with other studies. In such cases, the most informative study was kept for inclusion in the review (i.e., the study which reported data on a wider area or over a longer observation period). A log of excluded studies along with reasons for exclusion was kept. At the end of this three-fold screening process, 20 population-based migrant studies were identified that met our criteria for inclusion in the systematic review and meta-analysis. The study selection process is illustrated in a flowchart (figure 1).

Study Characteristics

Among the 20 studies identified, 9 provided data for both first- and second-generation migrants (Cantor-Graae et al., 2003; Cantor-Graae, Zolkowska, & McNeil, 2005; Castle, Wessely, Dean & Murray, 1991; Coid et al., 2008; Harrison et al., 1988; Leao et al., 2006; Thomas, Stone, Osborn, Thomas, & Fisher, 1993; W. Veling et al., 2006; Weiser et al., 2008), 9 provided data for first-generation migrants only (Cochrane & Bal, 1987; Dean, Walsh, Downing, & Shelley, 1981;

Hitch & Clegg, 1980; Krupinski & Cochrane, 1980; Rwegellera, 1977; Selten & Sijben, 1994; Selten et al., 1997; Smith et al., 2006; Zolkowska, Cantor-Graae, & McNeil, 2001) and 2 studies concerned only second-generation migrants (Cantor-Graae & Pedersen, 2007; Corcoran et al., 2008). After extracting data separately for each migrant group identified, this set of studies yielded 59 effect sizes for first-generation migrants and 28 effect sizes for second-generation migrants. In total, these effect sizes contributed information based on 5204 first-generation migrant cases and 4422 second-generation migrant cases.

The retrieved studies were conducted in the following countries:

- 8 studies from the United Kingdom (Castle et al., 1991; Cochrane & Bal, 1987; Coid et al., 2008; Dean et al., 1981; Harrison et al., 1988; Hitch & Clegg, 1980; Rwegellera, 1977; Thomas et al., 1993)
- 3 studies from the Netherlands (Selten & Sijben, 1994; Selten et al., 1997; Veling et al., 2006)
- 3 studies from Sweden (Cantor-Graae et al., 2005; Leao et al., 2006; Zolkowska et al., 2001)
- 2 studies from Israel (Corcoran et al., 2008; Weiser et al., 2008)
- 2 studies from Denmark (Cantor-Graae & Pedersen, 2007; Cantor-Graae et al., 2003; Corcoran et al., 2008; Weiser et al., 2008)
- 1 study from Australia (Krupinski & Cochrane, 1980)
- 1 study from Canada (Smith et al., 2006)

Apart from one study conducted in Australia (Krupinski & Cochrane, 1980), one in Canada (Smith et al., 2006) and two recent Israel-based studies (Corcoran, Perrin et al. 2008; Weiser, Werbeloff et al. 2008), all remaining studies were conducted in Western Europe. The single study based on data from the North American continent was conducted recently, but based on hospital-data from the early 20th century (Smith et al., 2006) . Although the data used in this study were temporally much further from the other studies, it nonetheless met all inclusion criteria. It used a rigorous methodology comparable to that of other contemporary migrant studies

based on data from recent decades. Diagnoses were assigned according to current diagnostic categories based on detailed case notes and using DSM-IV TR criteria. In addition, our review examined migration status as a risk factor for psychotic disorders without assuming that the phenomenon was a different one across decades. In light of these considerations, we chose not to exclude this study from our review and meta-analysis.

Some studies reported effect sizes strictly for first-generation or for second-generation migrants irrespective of their ethnicity or place of origin (Cantor-Graae & Pedersen, 2007; Cantor-Graae et al., 2003; Cantor-Graae et al., 2005; Corcoran et al., 2008; Hitch & Clegg, 1980; Zolkowska et al., 2001). This included 3 of the 4 Scandinavian studies. The remaining studies specified the ethnicity or the country of origin of the studied migrant groups. The regions of birth and ethnicity of these migrant groups differed across different settings. British studies reported incidence rates mainly for Caribbean, Black African, Asian and Irish migrant population. In contrast, the main migrant groups in the Netherlands were from Surinam, Turkey, Morocco and the Dutch Antilles. Migrants from the United Kingdom and other European countries were studied in both the Canadian and the Australian studies. The migrant groups included in the Israel and Scandinavian studies were of very diverse geographic origin, but some important groups were Ethiopian and former Soviet Union migrants in Israel and Finns in Sweden. Overall, the Caribbean population in the United Kingdom was the most frequently studied migrant group, with such data being reported in 7 out the 8 British studies.

All 20 studies were population-based incidence studies, but they differed in their case ascertainment procedures: 9 studies were based on first-contacts for psychotic disorders (ascertaining both in-patients and out-patients) (Cantor-Graae & Pedersen, 2007; Cantor-Graae et al., 2003; Cantor-Graae et al., 2005; Castle et al., 1991; Coid et al., 2008; Harrison et al., 1988; Rwegellera, 1977; Veling et al., 2006; Zolkowska et al., 2001) and 11 were hospital-based first-admissions studies (Cochrane & Bal, 1987; Corcoran et al., 2008; Dean et al., 1981; Hitch & Clegg, 1980; Krupinski &

Cochrane, 1980; Leao et al., 2006; Selten & Sijben, 1994; Selten et al., 1997; Smith et al., 2006; Thomas et al., 1993; Weiser et al., 2008). Among the latter, 5 studies were based on national registers (Cantor-Graae, Pedersen et al. 2003; Leao, Sundquist et al. 2006; Cantor-Graae and Pedersen 2007; Corcoran, Perrin et al. 2008; Weiser, Werbeloff et al. 2008). Cases were ascertained prospectively in 4 studies (Cantor-Graae et al., 2005; Coid et al., 2008; Harrison et al., 1988; Veling et al., 2006); all the others used a retrospective design. Most studies have used either ICD-8 to 10 or DSM-IV standardized diagnostic criteria; non-standardized diagnostic criteria were used in 6 studies.

Studies varied widely in terms of their quality. Quality scores ranged from 4 to 15 out of a maximal score of 16. In terms of their overall quality appraisals, 10 studies were considered as having fair or average quality, 5 were classified in the lower quality range, and 5 in the higher quality range. Those studies considered as having higher methodological quality were all conducted within the last decade. In contrast, studies considered as having lower methodological quality were mostly among the early studies conducted in the UK. These studies shared some similar methodological shortcomings, such as uncertainty about the reliability of census data used in the denominators of incidence rates. The characteristics of these studies are summarized in table 1, along with the quality score and appraisal for each individual study. Table 3 provides a more in-depth narrative synthesis of all retrieved studies.

Main Findings from Migrant Studies

From those 20 studies, we extracted 59 effect sizes – or rate ratio (RR) estimates - for first-generation migrant groups and 28 effect sizes for second-generation migrant groups as some studies reported data on multiple migrant groups. Almost all of the computed effect sizes indicated higher risks for schizophrenia and related disorders among migrants than among non-migrants. This held for both first- and second-generation migrants. Although the risk was consistently elevated among migrant

groups in almost all studies, the magnitude of the risk varied widely across settings and migrant groups.

As proposed by McGrath and Saha, we have summarized the retrieved risk estimates with quantiles around measures of central tendency (McGrath et al., 2004; Saha et al., 2008). The measures of central tendency and dispersion of rate ratios for first- and second-generation migrants are reported in table 2.

The rate ratio estimates for first-generation migrants ranged from 0.6 to 24.5 with a rate ratio median (10%-90% quantile) of 2.1 (1.2 – 4.7). For second-generation migrants, the retrieved rate ratios ranged from 0.9 to 18.0 with a median (10%-90% quantile) of 2.0 (1.0-4.7). Despite significant variations across various ethnic groups, the median and dispersion of rate ratios is remarkably similar for both first- and second-generation migrant groups. As per our study inclusion criteria, all included effect sizes – or RR estimates – were adjusted to control for age differences between migrant groups and host populations.

Variations in the Risk Magnitude

Ethnicity and Host Country

The risk for schizophrenia and related disorders was almost consistently elevated in all migrant groups in comparison with reference groups. The only notable exception is the Israel-based incidence study of the Jerusalem perinatal cohort of second-generation migrants, which did not find any risk elevation associated with migrant status (Corcoran et al., 2008). This study reported a relative risk for schizophrenia of 0.9 (95% CI = 0.8-1.1) among children born to both migrant parents, after adjustments for parental age, maternal education, paternal social class, sex and birth order. The authors commented that their results contrast from the risk observed among second-generation migrants in Europe and this may result from the differential nature of the immigration experience in Israel. In contrast, another Israel study reported increased incidence rates of schizophrenia for both first- and second-generation migrants, with a highest risk among migrants from Ethiopia (HR 3.0,

95% CI = 1.9-4.7). The authors concluded that the migrants groups at increased risk for schizophrenia are *those who differ the most in culture and appearance from the host population* (Weiser et al., 2008).

The highest effect sizes were extracted for Caribbean migrants in the United Kingdom with an extreme RR estimate of 18.0 in the second generation (Harrison et al., 1988). In contrast, the lowest RR estimate among Caribbean migrants concerned the first generation with a RR = 0.6 (Thomas et al., 1993); however, this estimate concerned a group with only 2 migrant cases. If we exclude these outlying values, then the RR estimates range between 2.3 and 6.7 for first-generation migrants, and between 4.5 and 9.1 in the second generation. Overall, these estimates imply some of the highest risks for schizophrenia and related disorders in both first- and second-generation migrants, with a trend for a further risk increase in the second generation. Black Africans also represent a group at high risk in the United Kingdom, ranging from a lower outlying RR estimate of 0.6 in one study to an extreme RR estimate of 24.5 in another one (Rwegellera, 1977; Thomas et al., 1993). Effect sizes concerning Asian migrants in the United Kingdom also suggested a risk increase for psychotic disorders, but of a much smaller magnitude with RRs ranging from 1.2 to 3.1 in the first generation, and from 1.0 to 1.3 in the second generation.

Although Caribbean migrants have also been studied in the Netherlands, the magnitude of their risk appeared lower than in the United Kingdom. The Moroccans appear to present the highest risk in the Netherlands, with a magnitude between 3.3 and 4.0 for the first generation, and of 5.8 in the second generation. Migrants from Surinam also presented significantly elevated risks with RRs ranging between 2.6 and 3.8 in the first generation and RR = 2.9 in the second generation. A recent Dutch study (Veling et al., 2006) confirmed significant risk elevation for migrants from Turkey, Surinam, Morocco and other non-Western countries, with particularly high rates in the second generation.

Visible Minority Status

All the migrant groups discussed above can be considered as visible ethnic minorities. However, an increased risk for psychotic disorders is also observed in multiple other migrant groups that cannot be considered as visible ethnic minorities, such as white European migrants. Hence, migrants from Britain or Continental Europe to Canada in the early 20th century were at increased risk for schizophrenia (RR = 1.5, 95% CI = 1.3 – 1.8) (Smith et al., 2006). This contrasts with the situation in Australia in the early 1970's where British migrants were not found to be at increased risk for schizophrenia. However, this Australian study found an increased incidence of schizophrenia among migrants from Italy, Germany and, in particular, those from Poland (RR = 4.2) (Krupinski & Cochrane, 1980). White migrants – including the Irish – to the United Kingdom were also found to be at higher risk for psychotic disorders, though not to the same extent as Caribbeans or Black Africans (Coid et al., 2008; Dean et al., 1981). In a Swedish study, Finn migrants actually presented the highest incidence rates of psychotic disorders, with risk estimates higher than those of labour immigrant and refugee groups (Leao et al., 2006).

Upon examination of the risk estimates across various migrant groups, there appears to be some variation according to the visible minority status of the groups. The migrant groups that can be classified as black visible minority status seem to share the highest relative risk of psychotic disorders in comparison with the reference groups. A few studies have specifically sought to examine this variable. In a first-contact study of immigrants in Malmö, the relative risks for developing psychotic disorders among first-generation migrants from countries where the majority of the population is 'white', 'neither black nor white', and 'black' were respectively 2.9 (95% CI 2.0-4.2), 2.6 (95% CI 1.6-4.2) and 5.8 (95% CI 2.8-13.4).

Potential confounding or moderating variables addressed in the studies

Most studies reported incidence data adjusted for both age and gender. As specified in the methods section, studies had to provide age-adjusted incidence rates or risk estimates or data that enable such computations in order to be included. Therefore,

all the reported effect sizes have been adjusted for a potential age effect that could result from differences in the age composition of migrant and non-migrant populations. Regarding gender, most studies have also reported either incidence rates adjusted for gender or incidence data that combined both males and females, but some studies have reported gender-specific incidence data.

Gender

Gender-specific effect sizes could be extracted for a subset of studies (Cochrane & Bal, 1987; Dean et al., 1981; Hitch & Clegg, 1980; Krupinski & Cochrane, 1980; Leao et al., 2006; Selten & Sijben, 1994; Selten et al., 1997; Veling et al., 2006). When gender-specific rate ratios were examined, the risk estimates for males and females were in general of similar magnitude. A notable exception concerned the Moroccan group in the Netherlands, as first- and second-generation Moroccan males presented very high RRs, while the rates for Moroccan females were not significantly elevated (Veling et al., 2006). Another significant gender difference was reported in the recent East London First Episode Psychosis study (Coid et al., 2008). While both male and female first-generation Asian migrants were at increased risk for psychotic disorders, only females remained at increased risk in the second generation. The authors attributed this situation to the differential social experience of Asian men and women in the British context.

Urbanization

The retrieved migrant studies were conducted either in urban settings (Cantor-Graae et al., 2005; Coid et al., 2008; Corcoran et al., 2008; Harrison et al., 1988; Rwegellera, 1977; Thomas et al., 1993; Veling et al., 2006; Zolkowska et al., 2001) or in mixed urban and rural settings, such as in the case of nation-based cohorts (Cantor-Graae & Pedersen, 2007; Cantor-Graae et al., 2003; Cochrane & Bal, 1987; Dean et al., 1981; Hitch & Clegg, 1980; Krupinski & Cochrane, 1980; Leao et al., 2006; Selten & Sijben, 1994; Selten et al., 1997; Smith et al., 2006; Weiser et al., 2008). No obvious trends emerge upon comparing the risk of migrant groups from urban settings with those from mixed urban and rural settings. The Danish cohort

study of second-generation migrants (Cantor-Graae & Pedersen, 2007) investigated the association between the degree of urbanization and the risk of schizophrenia among second-generation migrants. Among second-generation migrants by one parent, the greater the degree of urbanization at birth, the greater was the risk of schizophrenia associated with urban birth with a RR = 1.52 (95% CI 1.26-1.84). However, there was no dose-response association observed among second-generation migrants by both parents. In contrast, native-born Danes presented a greater association between the degree of urbanization at birth and the risk of schizophrenia with RR = 1.98 (95% CI 1.88-2.09). When adjusting the relative risk estimates for the role of urbanization and parental characteristics, this study reported that the magnitude of the risk among second-generation migrants was only slightly reduced and not accounted for by urbanization at birth nor mental illness in the family.

Socio-economic status

A few recent studies have reported risk estimates adjusted for socio-economic status or income as a potential confounding factor (Corcoran et al., 2008; Leao et al., 2006; Weiser et al., 2008). In all these studies, the adjustments for socio-economic status did not change significantly the reported risk estimates for migrant groups. The Swedish National Cohort Study (Leao et al., 2006) reported that low individual socio-economic status, measured as individual income, was associated with an increased risk for psychotic disorders, but there was no interaction between socio-economic status and migration status in the risk for psychosis. Although the East London First Episode Psychosis Study did not adjust for the potential role of socio-economic status (Coid et al., 2008), the effects of socio-economic status on the incidence rates among migrants were examined in a related article (Kirkbride et al., 2008). The authors demonstrated that although the socio-economic status did contribute to the increased rates of psychosis among migrants, the association between migration status and the risk for psychosis was unlikely confounded by individual-level social class.

Parental migrant status

A few studies have attempted to determine whether the risk for second-generation migrants differed depending on whether the mother, the father or both parents had migrated. Findings from the reviewed studies were inconsistent. While one Israel study reported an increased risk for second-generation migrants (Weiser et al., 2008) and the other did not (Corcoran et al., 2008), in neither study did the risk differ depending on whether one or both parents were foreign-born. A large study based on the Swedish Psychiatric Registry reported findings according to the parental migrant status (Leao et al., 2006). The authors concluded that having one parent born in Sweden had no protective effect for second-generation migrants. On the other hand, another large study based on the Danish Psychiatric Register found that the risk in the second generation was further increased when both parents had migrated (RR 3.0 versus 1.9 when one parent was non-migrant) (Cantor-Graae & Pedersen, 2007).

Trends in Time

Most of the earlier studies were conducted in the United Kingdom and based on cases ascertained from 1965 until the late 1980's. In contrast, studies from the last two decades were conducted in various countries in Western Europe, as well as Israel and Canada. Most studies with data on second-generation migrants were conducted in the last decade, which is consistent with the patterns of migration in Europe, since the earlier cohorts of first-generation migrants have migrated in the mid-20th century in the post-World War II context (Fearon & Morgan, 2006). The North American study provided information on the risk of schizophrenia associated with migration at a much earlier time period, with its observation period in the early 20th century (Smith et al., 2006). At any of the observation periods in this review, an elevated incidence of schizophrenia and related disorders was observed among migrant groups compared with non-migrant population.

In their extensive register-based study of a second-generation migrants in Denmark from 1970 until 2001, Cantor-Graae and Pedersen reported that the magnitude of the risk for schizophrenia was not associated with the calendar year of birth, thus

suggesting that the risk remained constant over the 3 decades of observation (Cantor-Graae & Pedersen, 2007). The Canadian study of European migrants also examined the evolution of the risk estimates over its 12 year observation period (Smith et al., 2006). The authors report that the incidence of schizophrenia increased over time in migrants but not in the native-born population, with incidence rate ratios for migrants increasing from 1.20 (95% CI 0.95 – 1.50) in period 1902-1905 to 1.94 (95% CI 1.73-2.15) in period 1910-1914. The authors comment that this risk elevation coincided with a period of social change characterized by increasing economic recession, unemployment and intolerance of immigrants.

Descriptive Synthesis Summary

Further details on findings from individual studies can be viewed in table 3. Overall, the key findings from these studies can be summarized as follows:

- An increased incidence of schizophrenia and related disorders has been observed in nearly all migrant groups studied.
- Both first- and second-generation migrants are at increased risk for schizophrenia and related disorders.
- These increased risks are not accounted entirely for by age, gender, urbanization, socio-economic status or parental migration status.
- There appears to be considerable variation in the magnitude of the risk depending on the ethnic background of migrant groups and on the settings of the study. Visible minority status may contribute to the elevated risk among some groups.

Quantitative Synthesis

Main Meta-Analyses

The results of the main meta-analyses are presented in table 4. Overall, our meta-analyses based on all retrieved effect sizes yielded mean-weighted rate ratio estimates of 2.33 (95%CI 2.04-2.66) for first-generation migrants and 2.09 (95%CI 1.78-2.46) for second-generation migrants. These analyses were computed from 59 effect sizes for first generation migrant groups and 28 effect sizes for the second generation. The confidence intervals for both pooled estimates include our rate ratio medians of 2.1 for the first generation, and 2.0 for the second. In addition, they suggest that the magnitude of the risk does not differ significantly between the first and the second generation, as also indicated by the non-significant Q_B statistic for between-group differences. Both analyses based on this comprehensive dataset were statistically significant for heterogeneity within subgroups, which suggest that the various migrant groups should not be regarded as coming from a homogeneous population sharing a common effect size. The I^2 statistics – 94.0% for the first generation and 91.1% for the second – indicate that a high proportion of the variation observed in both groups can be attributed to real differences between the effect sizes for the various migrant groups rather than to random error only.

A second analysis was conducted based on the subset of 9 studies that reported data for both first- and second-generation migrant groups (Coid et al., 2008; Veling et al., 2006; Weiser et al., 2008) (Cantor-Graae et al., 2003; Cantor-Graae et al., 2005; Castle et al., 1991; Coid et al., 2008; Harrison et al., 1988; Leao et al., 2006; Thomas et al., 1993; Veling et al., 2006; Weiser et al., 2008). This restricted dataset included 36 effect sizes for the first generation, and 24 for the second generation. Analyses from this dataset yielded a mean-weighted rate ratio of 2.12 (95% CI 1.84-2.43) for the first generation and 2.42 (95% CI 2.04-2.87) for the second generation. As opposed to the analysis based on the comprehensive dataset, this analysis suggests a somewhat higher risk magnitude for the second generation than for the first, although not at a statistically significant level. The Q_W homogeneity statistic

was quite reduced in absolute value, compared with the comprehensive dataset analysis, but remained statistically significant for heterogeneity within both groups.

Exploration of Heterogeneity: Subgroup Analyses

In the context of statistically significant heterogeneity for both first- and second-generation migrant groups in both the comprehensive and restricted datasets, it was important to carefully explore potential sources of heterogeneity by examining a number of potential moderators of the estimated risks for psychotic disorders among migrants. A number of categorical subgroup analyses were therefore conducted for both substantive variables (gender, visible minority status, ethno-racial category, countries of origin and urbanization of study setting) and study-level methodological variables (diagnostic system, incidence study type and quality assessments). All subgroup analyses were conducted from the comprehensive dataset, with the exception of the analysis for gender differences that was based on a subset of studies that reported gender-specific information (Cochrane & Bal, 1987; Coid et al., 2008; Dean et al., 1981; Hitch & Clegg, 1980; Krupinski & Cochrane, 1980; Leao et al., 2006; Selten & Sijben, 1994; Selten et al., 1997; Veling et al., 2006). The results for all these subgroup analyses are reported in table 5.

No significant differences were observed when the effect sizes for male migrants were compared to those for female migrants. However, significant between-group differences emerged when migrant groups were categorized according the skin color of the majority of population in their countries of origin. The mean weighted rate ratio for first-generation migrants from areas where most of the population is black was 3.89 (95% CI 3.33-4.55) versus 1.85 (95%CI 1.57-2.17) for groups classified as 'white' and 1.99 (95% CI 1.58-2.52) for groups classified as 'other' (neither black nor white). The rate ratio for migrant groups classified in the 'black' visible minority category was even higher for the second generation, with a mean weighted rate ratio of 5.37 (95% CI 3.27-8.80) versus 1.87 (95% CI 1.18-2.95) for the 'white' category and 1.98 (0.97-4.03) for the non-black / non-white category. Although heterogeneity levels within subgroups were substantially reduced, as indicated by the Q_W and I^2

statistics, heterogeneity remained statistically significant within each subgroup, suggesting that still other factors contribute to variations within groups.

Significant between-group heterogeneity was also observed when migrant groups were grouped according to their host countries. For both generations, the highest mean weighted rate ratios were obtained in the United Kingdom (2.75 for the first generation and 3.69 for the second), followed by the Netherlands (2.52 for the first generation and 3.00 for the second), the Scandinavian countries (2.26 for the first generation and 1.79 for the second), and finally by Israel with the lowest rate ratios (1.52 for the first generation and 1.09 for the second).

No significant between-group differences were observed when effect sizes were grouped according to the urbanization status of the study setting. However, there was a trend towards higher risk estimates in urban settings (2.69 for the first generation and 2.55 for the second) than in mixed urban/rural settings (2.20 for the first generation and 1.73 for the second generation). The differences according to urbanization status were more important in the second generation, though still not significant ($Q_B = 3.0$, $p=0.08$). No migrant studies were conducted in exclusively rural areas.

The results of first-admission (hospitalization) studies were compared to those of first-contact studies. For first-generation migrants, there was a trend towards a higher mean RR in first-contact studies than in first-admission studies, with respective RR of 2.88 (95% CI 2.09-3.98) and 2.17 (95% CI 1.86-2.53). The difference between both case ascertainment types was greater in the second generation, with a mean RR of 3.16 (95% CI 2.13-4.68) in first-contact studies compared with 1.56 (95% CI 1.34-1.83) in first-admission, with statistically significant between group heterogeneity ($Q_B = 10.6$, $p=0.001$).

Analyses according to diagnostic classification system did not yield significant between category differences, although the effect sizes derived from non-

standardized diagnostic classifications yielded slightly higher mean rate ratios (2.67 in the first generation, 3.71 in the second generation) than those based on DSM (1.96 and 2.42 in first and second generations) or ICD (2.22 and 1.90 in first and second generations) standardized criteria.

Finally, sensitivity analyses were conducted to determine whether robustness of findings varied according to the quality assessments of the individual studies. No significant differences emerged for the first generation, with a mean RR of 2.06 (95% CI 1.68-2.51) in higher quality studies versus 2.41 (95% CI 2.06-2.81) for the studies in the mid and lower quality ranges. A wider difference was observed in the second generation with a mean RR of 2.66 (95% CI 1.91-3.70) in higher quality studies versus 1.84 (95% CI 1.54-2.20) in mid and lower quality studies, though not at a statistically significant level for between group differences ($Q_B = 3.8$, $p=0.053$).

Funnel Plot Analyses

Funnel plots were computed separately for both generations using the effect sizes of the comprehensive dataset (see figures 2A and 2B). These plots compute the effect sizes on a log scale against the precision of these effect sizes (the inverse of the standard error). According to the model used to assess for publication bias, larger studies appear toward the top and tend to cluster near the mean effect while smaller studies would appear toward the bottom and be dispersed across a wider range around the mean effect size. In the absence of publication bias, the studies would be expected to be distributed symmetrically about the combined effect size and the plot would have the appearance of a funnel. Publication bias would be expected if smaller studies were more likely to be published when reporting larger effect sizes, thus resulting in a higher concentration of studies on one size and loss of a funnel appearance (Borenstein et al., 2009). Examination of the plot for the first generation (figure 2A) does not provide any evidence of asymmetry that would suggest publication bias. The plot of the effect sizes for the second generation (figure 2B) is still funnel-shaped though slightly less symmetrical. There is no evidence for publication bias, which could be suspected if less effect sizes were found to the left

of the mean effect towards the bottom of the graph. However, a closer examination of the plots indicates the presence of outliers, such as the migrant groups represented at the right bottom corners of both graphs.

Meta-Analysis: Summary of Findings

- The meta-analysis based on the comprehensive study dataset yielded mean-weighted rate ratios of 2.3 (95% CI 2.0 – 2.7) for first-generation migrants and 2.1 (95% CI 1.8-2.5) for second-generation migrants. The meta-analysis based on the restricted dataset yielded rate ratios of 2.1 (95% CI 1.8-2.4) for first-generation migrants and 2.4 (95% CI 2.0-2.9) for second-generation migrants. In both meta-analyses, the magnitude of the risk of psychosis is comparable for first- and second-generation migrants.
- Heterogeneity was statistically significant for the first- and second-generation migrants effect sizes in both the comprehensive and restricted datasets. Therefore, migrant groups should not be regarded as coming from a homogeneous population sharing a common effect size.
- Subgroup analyses revealed significant between-group differences for the following categorical variables: visible minority status, ethno-racial category, host countries and case ascertainment method (first-admission versus first-contact). No significant between-group differences were observed when effect sizes were grouped according to gender, diagnostic classification system or quality level
- Funnel plot analyses provided no evidence for publication bias.

Table 1: Summary of study features and quality assessments

	Author	Year	Country	Case ascertainment	Diagnostic classification	Quality score	Quality range
1	Coid	2008	UK	First contact - prospective	DSM-IV	15	High
2	Corcoran	2008	Israel	First admission - retrospective	ICD-10	8	Mid
3	Weiser	2007	Israel	First admission - retrospective	ICD-10	8	Mid
4	Cantor-Graae	2007	Denmark	First contact - retrospective	ICD-8, ICD-10	9	Mid
5	Smith	2006	Canada	First admission - retrospective	DSM-IV	12	High
6	Veling	2006	Netherlands	First contact - prospective	DSM-IV	15	High
7	Leao	2006	Sweden	First admission - retrospective	ICD-10	9	Mid
8	Cantor-Graae	2005	Sweden	First contact - prospective	DSM-IV	13	High
9	Cantor-Graae	2003	Denmark	First contact - retrospective	ICD-8, ICD-10	10	Mid
10	Zolkowska	2001	Sweden	First contact - retrospective	DSM-IV	13	High
11	Selten	1997	Netherlands	First admission - retrospective	ICD-9 or ICD-10	10	Mid
12	Selten	1994	Netherlands	First admission - retrospective	ICD-9, DSM IV	7	Low
13	Thomas	1993	UK	First admission - retrospective	Unspecified	5	Low
14	Castle	1991	UK	First contact - retrospective	ICD-9, RDC	10	Mid
15	Harrison	1988	UK	First contact - prospective	ICD-9, DSM-IV	11	Mid
16	Cochrane	1987	UK	First admission - retrospective	Unspecified	7	Mid
17	Dean	1981	UK	First admission - retrospective	Unspecified	4	Low
18	Krupinski	1980	Australia	First admission - retrospective	Unspecified	5	Low
19	Hitch	1980	UK	First admission - retrospective	Unspecified	6	Low
20	Rwegellera	1977	UK	First contact - retrospective	Other	8	Mid

Table 2: Dispersion measures of rate ratios for first and second generation migrants

Generation	No. of RRs	10%	25%	Median	75%	90%	Mean (SD)	Geometric Mean
First	59	1.2	1.3	2.1	3.3	4.7	2.95 (3.43)	2.20
Second	28	1.0	1.3	2.0	3.0	4.7	2.54 (1.89)	2.10

Table 3: Descriptive synthesis of individual migrant studies

Author Year	Setting Country Period	Study Features	Migrant Groups	RR* FGM (95% CI)	RR* SGM (95% CI)	Key findings
1 Coid 2008	London, UK 1996-1998	Prospective population-based survey of FEP during a 2-year period in 3 London boroughs First-contact study Age groups 18-64 Extensive case ascertainment; leakage study DSM-IV non-affective or affective psychosis Diagnostic interviews Urban environment	White Black Caribbean Black African Asian Other	1.6 (1.1-2.4) 2.3 (1.2-4.3) 3.2 (2.2-4.6) 1.8 (1.3-2.5) 1.3 (0.8-2.3)	2.8 (1.5-5.3) 4.9 (3.5-6.9) 3.7 (2.2-6.3) 1.3 (0.8-2.1) 1.1 (0.5-2.7)	**Raised incidence observed for all black and ethnic minority groups c/w white British for both affective and nonaffective psychoses.** Risks for both generations varied by ethnicity. Only Black Caribbeans had significantly higher risk for second than first-generation. Authors emphasize that the risk differs more by ethnicity than generation and that factors operate differentially by ethnicity. *Note: UK-born data also include a proportion of 3rd generation immigrants.*
2 Corcoran 2008	Jerusalem, Israel 1964-1976	Retrospective cohort First admission incidence Jerusalem perinatal cohort of 88829 born 1964-1976 and followed until 1998 (F/U 21-33 years) Cases ascertained by linking database to Israel National Psychiatric Registry Registry-based ICD-10 diagnosis Urban environment	Father migrant Mother migrant SGM both parents	NA	0.9 (0.8-1.1) 1.0 (0.8-1.3) 0.9(0.8-1.1)	**No risk elevation observed among 2nd generation immigrants in this cohort** , including those with only 1 immigrant parent or 2 immigrant parents (RR=0.9, 95% CI 0.7-1.2). These findings differ from other European studies and suggest that the nature of the immigration experience may be relevant to the risk.
3 Weiser 2007	Israel	Cohort of 661792 consecutive adolescents (age 16-17) screened by the Israeli Draft Board First admission incidence study Cases ascertained from Israel Psychiatric Hospitalization Case Registry Average F/U period 7.7±3.7 years Age 16 –30. Registry-based ICD-9 and 10 diagnoses of schizophrenia (sensitivity = 0.89) Mixed urban / rural environment	FGM all SGM by 1parent SGM - both parents FG subgroups: Former Soviet Union Europe Ethiopia North America South America Asia and Australia Africa	1.6 (1.2-2.2) - - 1.6 (1.1-2.1) 1.0 (0.6-1.7) 3.0 (1.9-4.5) 1.3 (0.7-2.4) 1.3 (0.6-2.7) 1.0 (0.4-2.4) 1.7 (0.7-4.3)	- 1.4 (1.0-2.0) 1.5 (1.1-2.0)	**Risk for schizophrenia was increased among both 1st and 2nd generation immigrants.** Immigrants from Ethiopia were at highest risk (RR=2.95, 95% CI 1.88-4.65). The authors conclude that immigrants who differ most in culture and appearance from the host population are at increased risk. Limitations: missing data on country of origin for 14% of cohort; no age adjustment – but narrow age group.

4 Cantor-Graae. 2007	Denmark 1970-2001	Population-based cohort of 2.0 million Danes age > 15, born 1954-1986 and followed 1970-2001 Cases ascertained from Danish Psychiatric Register, First admission only until 1995 First-contact (in- or out-patient) after 1995 Adjustment for urbanization of birthplace ICD-8 or 10 diagnosis (to verify) Mixed urban / rural	SGM by 1 parent SGM - both parents	NA	1.6 (1.5-1.7) 2.3 (2.0-2.8)	**Risk increased for 2nd generation immigrants by one parent and more so by both parents; even if accounting for urbanization, parental age, mental illness or geographic origin.** This risk remained constant over the 30 yr FU History of residence abroad is a risk factor, whether parents foreign-born or not. Risk greater if parents from developing countries. Urbanization at birth/upbringing associated with increased risk if parents born in Denmark and not for SGM by both parents.
5 Veling 2006	The Hague, Netherlands 1977-99; 2000-02	Prospective population-based cohort, aged 15-54 First-contact incidence study of schizophrenic disorders over two periods: 1997-99; 2000-02 Community-based case ascertainment DSM-IV diagnoses assigned following semi-structured diagnostic interviews Blinding for ethnicity in the second period Urban environment	All FGM All SGM Moroccans Surinameses Antilles Turks Non-Western Western	2.3 (1.7-3.0) - 4.0 (2.6-6.3) 2.6 (1.7-4.0) 1.9 (0.8-4.7) 1.4 (0.8-2.6) 2.2 (1.4-3.4) 1.2 (0.6-2.6)	- 2.5 (1.7-3.7) 5.8 (3.0-11.2) 2.9 (1.7-5.0) 1.4 (0.2-10.0) 2.3 (1.0-5.3) 3.5 91.8-6.8) 1.6 (0.7-3.7)	**Increased risk for 1st and 2nd generation immigrants from Morocco, Surinam and other non-Western countries.** **Risk significantly higher for 2nd generation compared with 1st** (RR=1.53, 95%CI 1.02-2.31). Risk very high for 1st and 2nd generation Moroccan males, but not for Moroccan females.
6 Smith 2006	BC, Canada 1902-1913	Retrospective cohort of BC residents aged 10-59 observed over 3 periods between 1902 and 1913 First-admission incidence study Cases ascertained from the provincial institution DSM-IV diagnoses or schizophrenia or related disorders assigned from chart reviews Mixed urban / rural environment	European/UK	1.5 (1.3-1.8)	NA	**Migration from Britain / Continental Europe to Canada was a risk factor for schizophrenia in early 19th century.** Increasing incidence in immigrants but not in native-born over the study period in a context of economic recession.
7 Leao 2006	Sweden 1992-1999	Cohort of >2 million adults aged 20-39 and followed 1992-1999 First-admission incidence study Cases ascertained: Swedish Psychiatric Registry ICD-9 and 10 register-based diagnoses of schizophrenia and other psychoses Mixed urban / rural environment	Finns Labour immigrants Refugees	2.2 (2.0-2.4) 1.2 (1.1-1.4) 1.4 (1.3-1.6)	2.3 (2.0-2.7) 1.2 (1.0-1.5) 1.9 (1.4-2.6)	**The increased risk of psychotic disorders among FGM persists in the next generation.** Highest incidence rates found among 1st and 2nd generation Finns. Having one parent born in Sweden has no protective effect for SGM. Low SES associated with an increased risk, but the risk of migrants persists after adjusting for SES.

8 Cantor-Graae 2005	Malmö, Sweden 1999-2001	Retrospective cohort of adults aged 18-54 followed 1999-2001 First-contact incidence study of all in- and out-patient contact with psychiatric services DSM-IV diagnoses of psychotic disorders assigned through case-notes review Urban environment	FG Immigrants SG Immigrants	4.0 (1.9-8.6) -	- 2.0 (0.7-5.9)	**Risk for schizophrenia and psychotic disorders significantly increased in 1st generation migrants, but not in 2nd generation** (RR=2.9, 95%CI 2.0-4.0 versus 2.0, 95%CI 0.7-5.9) – possible lack of power for SGM. **Immigrants with black skin colour or born in a developing country were at higher risk.**
9 Cantor-Graae 2003	Denmark 1970-1988	Cohort of 2.14 million Denmark residents born 1954-1983, living in Denmark prior to age 15 First-contact incidence (in- and out-patient) Observation period: 1970-1998 Cases with ICD-8 or 10 diagnosis of schizophrenia identified from Danish Psychiatric Central Register Mixed urban / rural environment	FG immigrants SG immigrants	2.5 (2.3-2.7) -	- 1.9 (1.7-2.1)	**Increased risk of schizophrenia among 1st and 2nd generation immigrants.** **Danes with a history of foreign residence prior to age 15 at also a higher risk** (RR=1.60, 95%CI 1.25-2.05), suggesting that migration per se may confer a risk independent of ethnicity. Migrants from Australia, Africa, Middle East and Greenland have higher risks.
10 Zokowlska 2001	Malmö Sweden 1998	Population-based cohort of adults aged 18-64 First-contact based incidence over 1 year (1998) DSM-IV diagnoses of schizophrenia and other non-affective psychoses assigned from case-notes Urban environment	FG immigrants	1.9 (1.0-3.2)	NA	**Significantly increased risk of first onset schizophrenia-like psychosis in 1st generation migrants** (RR=1.88, 95%CI 1.10-3.22). Markedly increased risk of admissions for schizophrenia in migrants from East-Africa.
11 Selten 1997	Netherlands 1983-1992	First-admission incidence Retrospective population-based cohort Age 15-39 Observation period: 1983-1992 Cases from the Dutch Psychiatric Registry Registry-based ICD-9 diagnosis of schizophrenia Mixed rural / urban environment	Surinam Antilles	3.8 (3.5-4.1) 3.9 (3.4-4.4)	NA	**Immigrants have a risk 3 to 4 times higher than Dutch-born, especially for males.** Selective migration unlikely given that the extent of the migration from Surinam (> 1/3 population).
12 Selten 1994	Netherlands 1990	Population-based cohort of persons aged 20-39 First-admission incidence in 1990 Cases ascertained from Dutch National Register Registry-based ICD-9 diagnosis of schizophrenia Mixed urban / rural environment	Turkey Morocco	0.9 (0.6-1.5) 3.3 (2.4-4.5)	NA	**Rates of schizophrenia significantly increased for immigrants from Surinam and the Antilles and for male immigrants from Morocco.** Data for Surinam and Morocco available but included in Selten 1997.

13 Thomas 1993	Manchester UK 1984-1987	First admission incidence Age 16-pensionable Retrospective incidence over 4 years (1984-87) Use of 1981 census Cases ascertained from the Central District of Manchester records of psychiatric admissions ICD-9 diagnosis Urban environment	Asians Caribbeans	1.6 (0.6-4.0) 0.6 (0.1-2.4)	1.0 (0.1-7.4) 9.1 (4.4-18.8)	**Highest rates of admissions for schizophrenia observed among 2nd generation Afro-Caribbean, especially males.** Limited reliability of census data for ethnic groups.
14 Castle 1991	Camberwell UK 1980-1984	First-contact incidence Retrospective population-based incidence study Over 4 periods 1965-1984 Registry and notes based diagnosis (reliability verified with Research Diagnostic Criteria) Age groups not specified Urban environment	West Indies	5.6 (3.4-9.2)	4.5 (2.5-8.3)	Data available for 4 different periods between 1965 and 1984. Data extracted for 1980-84 only because RR for both generations can be computed. Over the four periods, RRs have varied from 4.0 to 8.2, with a trend for decreasing rates. The comparison group included an increasing proportion of SGM over the study period, which might explain the declining ratio over the four cohorts. A comparison of Afro-Caribbean ethnicity with all other ethnic groups yielded RR = 5.9
15 Harrison 1988	Nottingham UK	First-contact incidence Prospective population-based study Extensive case ascertainment PSE, CATEGO diagnosis and ICD-9 Age group 16-29 (for which generation status is available) Urban environment	Afro-Caribbean	6.7 (2.1-22.8)	18.0 (10.2-32.9)	A plausible estimate differentiating generations is only available for Afro-Caribbean SGM in the 16-29 age group using restricted ICD-9 criteria. Authors suggest that more atypical syndromes affect the FG, while SGM have a syndrome similar to that of the host population.
16 Cochrane 1987	England 1981	First-admission incidence Retrospective population-based study Ages 16 and over Cases ascertained from hospital register Mixed urban / rural environment	Ireland Caribbean India Pakistan	1.6 (1.4-2.0) 3.2 (2.6-3.8) 1.3 (1.0-1.8) 1.3 (1.0-1.9)	NA	Crude rates show higher than expected frequency of schizophrenia observed among all groups except Pakistani women – much reduced when considering age-standardized rates.

17 Dean 1981	SE England 1976	First-admission incidence Retrospective hospital-based case ascertainment 1971 census Diagnostic system not specified All ages Mixed urban//rural environment	India Pakistan/Asia Caribbean NC Africa Ireland	3.1 (2.4-4.0) 1.2 (1.0-1.9) 5.1 (4.2-6.2) 4.2 (3.3-5.2) 2.4 (1.9-2.9)	NA	Significantly more first psychiatric admission for migrant groups, mostly schizophrenia. Overall, first admission rates for schizophrenia were 5x higher than expected for Caribbeans, 4x for NC Africa and 3x for India.
18 Krupinsky 1980	Australia 1970-1972	First admission incidence Retrospective case ascertainment from psychiatric institutions records Ages 15 and above 1971 census Mixed urban/rural environment	Britain Germany Italy Poland	1.1 (0.9-1.3) 2.8 (1.9-3.1) 1.8 (1.5-2.2) 4.2 (3.2-5.5)	NA	**Significantly higher first admission rates for schizophrenia observed among Eastern European migrants, and to a lesser extent for Germans and Italians.** Migrant rates comparatively higher for first-admissions than all admissions, suggesting that door-revolving may be more common among UK and Australian-born subjects. Note: first-admission data available only for Australia data (not the UK).
19 Hitch 1980	N England 1968-1970	First admission incidence Retrospective case ascertainment Diagnosis assigned from cases notes and contacts with clinicians Ages 16-64 Mixed urban/rural environment	NC Foreign	3.2 (2.2-4.50 4.7 (3.0-7.4)	NA	**Higher first admission rates only for schizophrenia among immigrants from New Commonwealth and other countries.** New Commonwealth migrants are mostly from India and Pakistan, while foreign migrants are mostly from Eastern European countries.
20 Rwegellera 1977	Camberwell UK 1965-1968	First-contact incidence study Retrospective case ascertainment from the Camberwell Psychiatric Case Register Case notes diagnosis Schneiderian diagnostic criteria Urban environment	West Africans West Indians	24.5 (13.0-46.1) 6.2 (3.8-10.2)	NA	Rates elevated among both West Indians and West Africans for all diagnostic categories except reactive depression and paranoid delusions. Age-adjusted rates were provided using age groups 15-24 and 25-44.

RR: Reported or computed incidence rate ratios. * all rate ratios are adjusted for age and gender.
FGM: first-generation migrants; SGM: second-generation migrants
NC: New Commonwealth

Table 4: Results of meta-analyses of the risk for schizophrenia and related disorders in first and second-generation migrants

Dataset	Generation	No. effect sizes	Rate Ratio	Lower Limit	Upper Limit	Q_W	Q_B	I^2
Comprehensive	First	59	2.33	2.04	2.66	963†		94,0
	Second	28	2.09	1.78	2.46	302†		91,1
							0,97	
Restricted	First	36	2.12	1.84	2.43	253†		86,2
	Second	24	2.42	2.04	2.87	191†		87,9
							1,454	

Abbreviations: Q_W: within-category homogeneity statistic; Q_B: between-category homogeneity statistic.

Levels of significance: † p<.01, ‡ p<.05

Table 5: Results of Subgroup Analyses for Categorical Moderators

		First Generation Migrants						Second Generation Migrants					
Variable	**Subgroups**	**n**	**RR**	**95% CI**	**I^2**	**Q_W**	**Q_B**	**n**	**RR**	**95% CI**	**I^2**	**Q_W**	**Q_B**
Gender	Female	33	2,25	1,88-2,70	87,8	263,0†		13	2,96	2,09-4,18	63,9	33,2†	
	Male	33	2,19	1,78-2,69	94,9	626,4†		13	2,46	1,79-3,38	78,8	56,7†	
							0,04						0,6
Visible	Black	17	3,89	3,33-4,55	77,8	72,2†		7	5,37	3,27-8,80	78,9	28,4†	
minority	Other	16	1,99	1,58-2,52	84,7	97,8†		5	1,98	0,97-4,03	73,8	15,3†	
category	White	18	1,85	1,57-2,17	90,2	173,8†		4	1,87	1,18-2,95	87,2	23,5†	
							47,6†						10,6†
Ethno-racial	White	16	1,93	1,65-2,27	88,3	128,22†		3	2,34	2,05-2,67	0,0	1,17†	
category	Black Caribbean	11	3,78	3,22-4,43	70,3	33,7†		7	5,77	3,53-2,44	77,2	26,3†	
	Black African	6	4,33	2,77-6,77	86,9	38,1†		1	3,70	2,16-6,33	0,0	0,0	
	Asian	8	1,61	1,21-2,15	82,7	40,4†		2	1,28	0,80-2,06	0,0	0,06†	
	Middle East	5	2,34	1,36-4,03	87,5	31,9†		2	2,34	1,36-4,03	65,8	2,93†	
							51,1†						19,9†
Host countries	Israel	7	1,52	1,11-2,08	51,9	12,5§		5	1,09	0,89-1,34	68,8	12,8‡	
	Netherlands	10	2,51	1,98-3,19	85,3	61,2†		6	3,00	2,06-4,36	30,7	7,2	
	Scandinavia	15	2,26	1,86-2,74	92,4	185,0†		8	1,79	1,58-2,03	84,8	46,0†	
	UK	22	2,75	2,15-3,53	91,6	251,0†		9	3,69	2,07-6,58	87,6	64,5†	
							9,3‡						34,1†
Urbanization	Mixed urban/rural	40	2,20	1,89-2,57	95,4	848,0†		9	1,73	1,54-1,95	83,4	48,2†	
study setting	Urban	19	2,69	1,96-3,67	83,5	109,3†		19	2,55	1,67-3,88	92,9	253,1†	
							1,2						3,0§
Incidence	First admission	42	2,17	1,86-2,53	95,2	852,1†		14	1,56	1,34-1,83	91,3	149,8†	
study type	First contact	17	2,88	2,09-3,98	84,5	103,5†		14	3,16	2,13-4,68	80,8	67,6†	
							2,4						10,6†
Diagnostic	DSM	8	1,96	1,54-2,49	65,7	20,4†		6	2,42	1,41-4,14	79,9	24,9†	
system	ICD	32	2,22	1,86-2,66	94,6	570,2†		20	1,90	1,61-2,24	91,8	230,5†	
	Non-standardized	19	2,67	2,03-3,50	94,8	348,9		2	3,71	0,44-31,22	76,07	4,18‡	
							2,8						1,1
Overall	High	14	2,06	1,68-2,51	65,4	37,6†		12	2,66	1,91-3,70	65,8	32,2†	
quality	Average and Low	45	2,41	2,06-2,81	95,2	907,9†		16	1,84	1,54-2,20	93,4	228,7†	
							1,5						3,8§

Abbreviations: n: number of effect sizes; RR: mean-weighted rate ratio; Q_W: within-category homogeneity statistic; Q_B: between-category homogeneity statistic.

Levels of significance : † p<.01, ‡ p<.05, § p<.10

Figure 1: Study selection flowchart

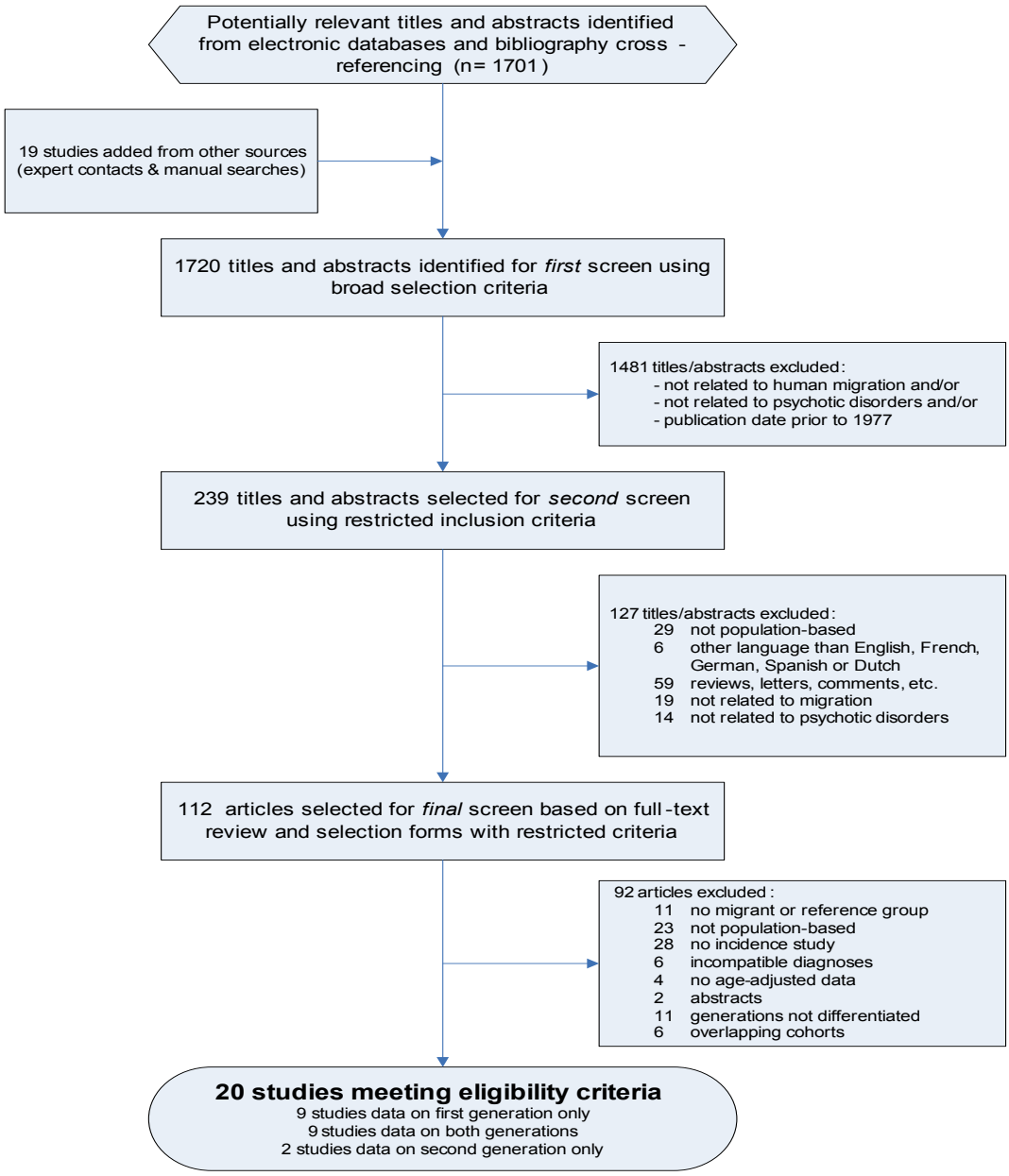


Figure 2A: Funnel Plot Analysis – First Generation

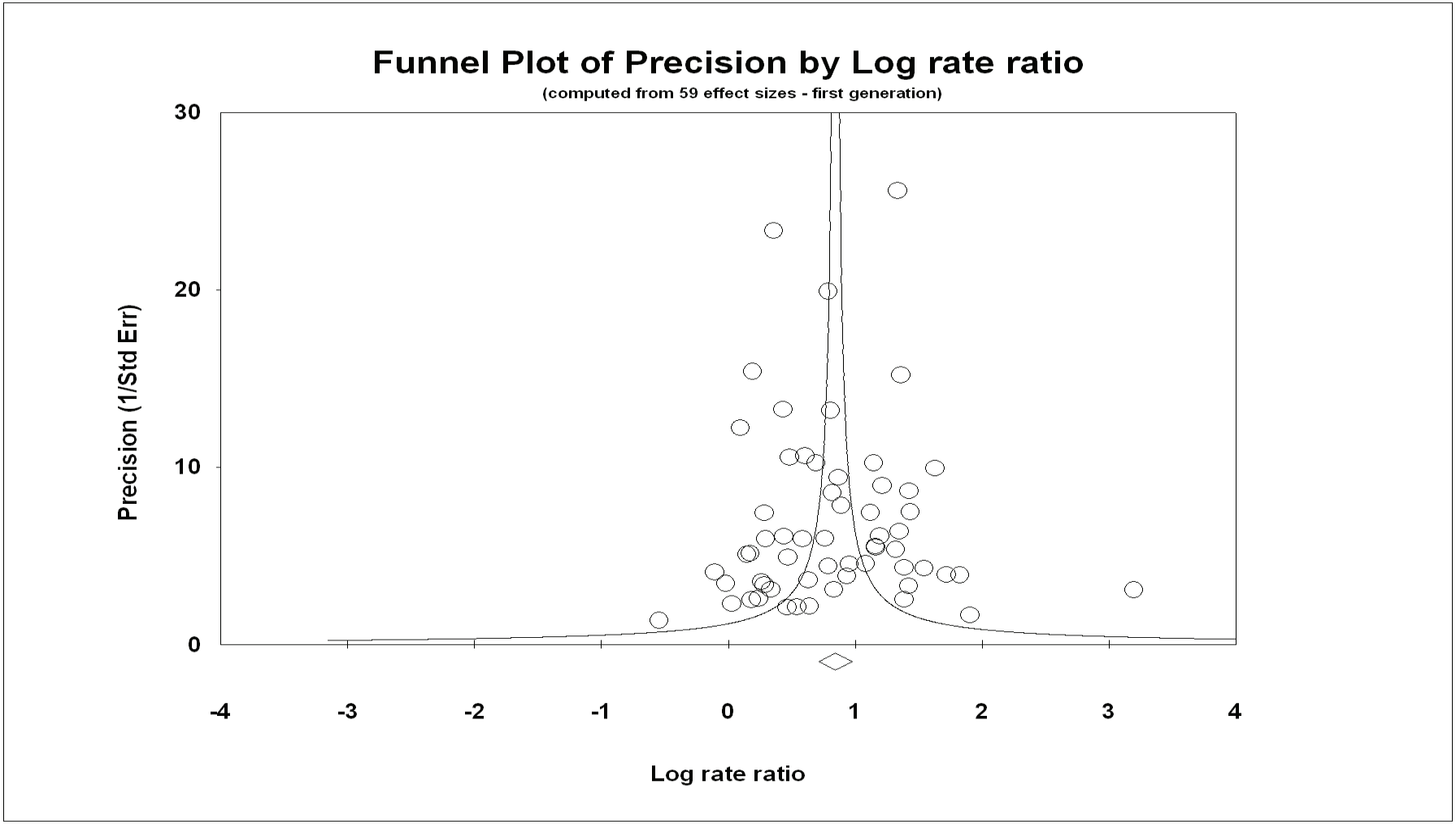
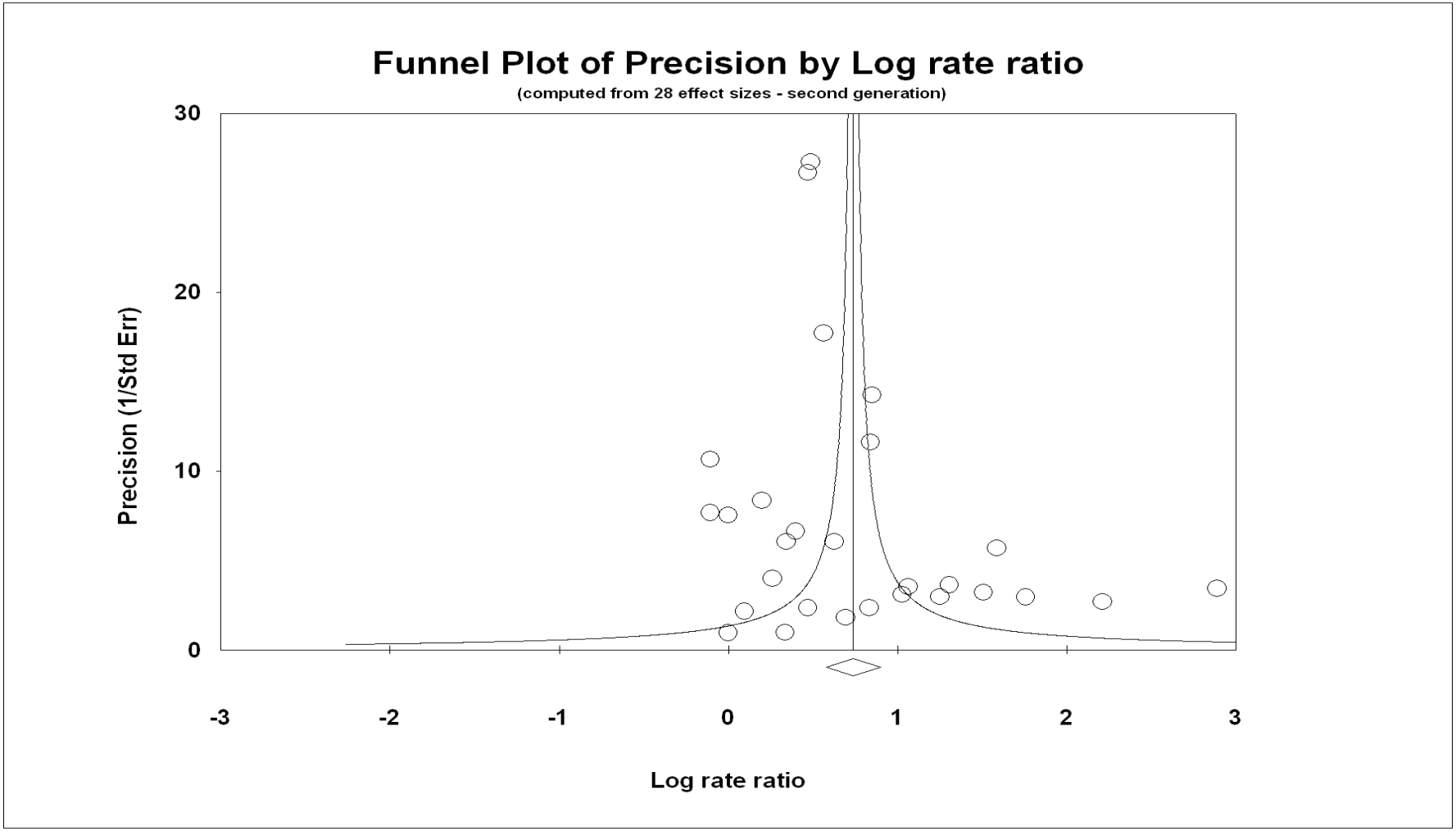


Figure 2B: Funnel Plot Analysis – Second Generation



CHAPTER 4: DISCUSSION

Main Findings

Are Second-Generation Migrants at Higher Risk for Psychotic Disorders?

Our review confirms that both first- and second-generation migrants have an increased risk for developing schizophrenia and related disorders. The descriptive synthesis of the studies revealed that almost all migrant groups were at an increased risk for schizophrenia and related disorders, and this finding held for both the first and second generations. However, there were significant variations in the magnitude of the relative risk across ethnic groups within studies and across countries in which studies were conducted. This suggests that migrant status is not sufficient to explain the risk for psychotic disorders among migrants, but that aspects such as ethnicity of a migrant group or the social context in the host environment may also be associated with the risk among immigrants. Only one study did not report a significant association between migrant status and the risk for schizophrenia: the Israel-based cohort of second-generation migrants (Corcoran et al., 2008).

What is the Magnitude of the Risk associated with Migrant Status?

The magnitude of the risk associated with migrant status was assessed through meta-analytic synthesis. The meta-analysis based on the comprehensive dataset (59 effect sizes for the first generation, 28 effect sizes for the second generation) yielded a mean-weighted rate ratio of 2.3 (95% CI 2.0-2.6) for first-generation migrants and 2.1 (95% CI 1.8-2.4) for second-generation migrants. The meta-analysis based on the restricted dataset yielded mean weighted rate ratios of 2.1 (95% CI 1.8-2.4) for the first generation and 2.4 (95% CI 2.0-2.9) for the second generation.

While the findings from both analyses are comparable, the analysis based on the restricted dataset suggests a trend towards an increased in the second generation compared with the first generation.

A potential factor contributing to this slightly higher rate in the second generation is that the negative findings from the Israel second-generation migrants cohort were

not included as the data provided concerned the second generation exclusively (Corcoran et al., 2008). Also the ethnicity of the migrant groups in this restricted subset may differ from that of the comprehensive dataset. For instance, earlier studies were primarily UK-based and focused on first-generation Caribbean and South Asian migrants. The earliest reviewed study which provided data on the second-generation was published in 1988 (Harrison et al., 1988). However, since the studies included in the restricted dataset provided data on both migrant generations using comparable methods, it may be argued that pooled estimates from this dataset may be more suitable to compare the risk between first- and second-generation migrant status.

Previous researchers in schizophrenia epidemiology had proposed that descriptive synthesis and measures of central tendencies may be preferable to data pooling by meta-analyses, given the issues of combining heterogeneous data, the variability in the data reporting and the lack of guidance about how best to assign weight to individual studies (Saha et al., 2008). Our synthesis of the distribution of rate ratios resulted in a median rate ratio (10% to 90% quantiles) of 2.1 (1.2 to 4.7) for the first generation and 2.0 (1.0 to 5.2) for the second generation. Similarly to what was observed by McGrath et al. in their systematic review of the incidence of schizophrenia (McGrath et al., 2004; Saha et al., 2008), our median values were consistent with our synthesized effect sizes for both generations. Taken together, these findings suggest not only that the risk for schizophrenia and related disorders persist in the second generation, but also that the magnitude of the risk is overall similar for both generations of migrants and at least twice as high as the risk for non-migrants.

Currently, the most important risk factor for developing schizophrenia is having a monozygotic twin with schizophrenia (concordance rate of 40-50%) or else a positive family history for the illness (Tandon et al., 2008). If we exclude the genetic liability associated with family history, some of the next major risk factors are cannabis use, urbanicity and perinatal complications, each of these factors being

associated with a relative risk for schizophrenia between 2 and 3. Our findings suggest that the magnitude of the risk associated with first- or second-generation migrant status falls within the same range globally.

It should be highlighted in both the comprehensive and the restricted study samples, significant heterogeneity was observed across studies. This indicates that, in both cases, the different migrant groups may not be regarded as samples from a homogeneous underlying population that shares a common effect size. The statistically significant heterogeneity indicates that the variation across subgroups is not only due to random sampling error but also to true variation in the effect sizes (Borenstein et al., 2009). Therefore, our findings may be interpreted as an overall estimate of the magnitude of the risk associated with first- or second-generation migrant status in general, but they should not be seen as indicator of the risk for a given migrant group in a given context. This is in fact the case for many risk factors which may be estimated at the population-level, yet may operate differentially within various subgroups in the population. In that context, it was considered necessary to investigate potential sources of heterogeneity and moderators of the risk for psychotic disorders among migrants.

How do our Findings Compare with Previous Findings?

Our review replicates the previous findings of increased risk for psychotic disorders associated with migrant status reported in two previous systematic reviews (Cantor-Graae & Selten, 2005; McGrath et al., 2004). Our review also confirms that this risk increase clearly persists among second-generation migrants. However, the magnitude of the effect size in our review is slightly less than that reported in the two previous reviews. In their systematic review of the incidence of schizophrenia, McGrath et al. have reported a median rate ratio (10% to 90% quantiles) of 4.6 (1.0 to 12.8) associated with migrant status without differentiation of migrant generation (McGrath et al., 2004). On the other hand, Cantor-Graae and Selten had reported mean weighted relative risks for 2.7 (95% CI 2.3-3.2) for first-generation migrants (40 effect sizes) and 4.5 (95% CI 1.5-13.1) for second-generation migrants (7 effect

sizes) (Cantor-Graae & Selten, 2005). Our findings, which are based on 59 effect sizes for the first generation and 28 effect sizes for the second, had the potential to generate a somewhat more precise estimate of the risk associated with migrant status. An explanation for this might result from the increasing diversity of the migrant groups and settings of study, while most early studies focused on the Afro-Caribbean migrant population in the UK. Our review observed some of the highest risk estimates for that group in comparison with other migrant groups in the UK or in other countries.

Based on evidence from a systematic review, McGrath argued that the epidemiological landscape is anything but flat, as there are considerable variations in incidence rates of schizophrenia across places and people (McGrath et al., 2004; McGrath, 2007). This notion is another key finding of this meta-analytic review, which demonstrates considerable variability in the incidence of psychotic disorders across groups according to ethnicity and social contexts. This contribution clearly adds to the growing body of evidence that the incidence of schizophrenia and related disorders is not uniform across the world, as previously assumed. As McGrath argued, such variations deserve further attention as the epidemiological landscape of schizophrenia may generate valuable insights into the causal pathways of psychotic disorders.

Exploring the Variability of the Findings

Sources of Variation from the Descriptive Synthesis

Prior to using meta-analytic tools to explore heterogeneity, a number of potential sources of variability were highlighted from the descriptive synthesis of the studies reviewed. Overall, while an increased risk for psychotic disorders was observed among most first- and second-generation migrant groups, risk estimates clearly varied in magnitude. There were significant generational differences in risk estimates among some groups, especially in Caribbean migrants in the UK (Coid et al., 2008; Harrison et al., 1988; Thomas et al., 1993) and in Moroccan migrants in the Netherlands (Veling et al., 2006). However, these generational differences were

not consistent across ethnic groups and countries. On the other hand, there appeared to be considerable variation in the magnitude of the risk according to the ethnic background or the origin of migrant groups and also according to the setting of the study (or the host environment). For instance, some of the highest risk estimates concerned the Caribbean population in the UK (Castle et al., 1991; Dean et al., 1981; Harrison et al., 1988; Hitch & Clegg, 1980; Rwegellera, 1977; Thomas et al., 1993). In contrast, some of the lowest risk estimates concerned second-generation migrants in Israel (Corcoran et al., 2008), some first-generation migrant groups in Israel (Weiser et al., 2008), and a few other groups such as British migrants in Australia (Krupinski & Cochrane, 1980). The fact that the groups at higher risk within a given study often concern Black migrants suggests that visible minority status may also represent an important source of heterogeneity across studies.

We observed significant variations in risk estimates even for migrants of the same background in the same context. For instance, one study did not report a risk increase among first-generation Caribbean migrants in the UK (Thomas et al., 1993) while another reported a RR = 6.7 in first-generation migrants and RR = 18.0 in second-generation migrants of the same ethnic group (Harrison et al., 1988). Although the descriptive synthesis of the data did not reveal any obvious variation according to study type and quality, specific methodological features – such as case ascertainment – may also contribute to large variation between studies and were further explored meta-analytically. Also, concerns about the reliability of the denominator data have been expressed regarding the early studies from the UK: these may also have contributed to generate some of the outlying risk estimates.

Meta-analytic Exploration of Heterogeneity

Upon conducting the meta-analysis, a first attempt to reduce heterogeneity was to conduct analyses from a restricted subset of studies reporting data on both generations of migrants. Although heterogeneity was reduced in both absolute and relative values, in particular for the first generation, it nonetheless remained statistically significant. Subgroup analyses were then conducted according to

categories based on substantive or methodological variables, heterogeneity levels were in most cases significantly reduced although within-subgroup heterogeneity remained significant in almost all instances.

No significant differences emerged when effect sizes were grouped according to gender. Thus, overall, the migrant effect cannot be explained by gender issues. Nonetheless, it does not rule out the relevance of gender issues in some migrant groups. For instance, there is a striking difference in the risk magnitude for males and female among Moroccan first- and second-generation migrants, males being at a much higher risk than female migrants (Selten & Sijben, 1994; Veling et al., 2006). The authors commented that this situation might result from differential social attitudes towards Moroccan men and women. On the other hand, recent findings from the East London First Episode Psychosis study suggest that among Asian migrants, the risk for psychotic disorders was higher among females, in particular for the second generation (Coid et al., 2008). The researchers proposed that the excess risk of psychoses among this group may be partly attributed to the marginal status faced by women in Indian, Pakistani and Bangladeshi communities, compared with the men from those communities who are generally more involved in the professional and economical world and who have a higher social status. Such differences suggest that gender differences in the risk for psychoses among migrants should be considered, and may reflect gender differences in the nature of social experiences in the host environment.

Visible Minority Status: an Important Risk Moderator?

Perhaps one of the most significant finding in this meta-analytic review is the significant variation associated with the skin color of the migrant groups. Visible minority status emerged as a source of significant between-group heterogeneity, with migrant groups who originally came from countries where the majority of the population is black presenting the highest risk for psychotic disorders (RR = 3.9, 95% CI=3.3-4.6 in the first generation, and RR = 5.4, 95% CI=3.3-8.8 in the second generation). This contrasts with the magnitude of the risk among migrants from

countries where the majority population is white (RR = 1.9 for both generations) and from countries where the population is neither black nor white (RR = 2.0 in both generations). The risk associated with black skin color also appears to increase from the first to the second generation (from 3.9 to 5.4). Such findings are consistent with those reported by Cantor-Graae and Selten who reported a relative risk of 4.8 (95% CI=3.7-6.2) for migrants from areas where the majority of the population is black (Cantor-Graae & Selten, 2005). However, these risk estimates were not stratified for generational status. Taken together, these findings raise questions as to what may underlie this shared risk increase among migrants from areas as diverse as Jamaica, Surinam or the Sub-Saharan Africa. Shared experiences of discrimination in host societies may plausibly contribute to this risk elevation.

When a more detailed ethno-racial classification was used to compare subgroups, the highest risk estimates were unsurprisingly observed again among Black Caribbeans and Black Africans, with respective rate ratio estimates of 3.8 and 4.3 in the first generation, and 5.8 and 3.7 in the second generation. White migrants presented an intermediate risk (RR = 1.9 in the first generation and RR = 2.3 in the second generation), while Asian migrants formed the group with the least risk increase (RR = 1.6 in the first generation and RR = 1.3 in the second generation). Such findings are consistent with those from the large 3-center AESOP investigation: rate ratios for schizophrenia of 9.1 in Afro-Caribbeans, 5.8 in Black Africans, 2.5 in white groups, and 1.4 in Asian groups (Fearon et al., 2006). It should be noted that findings from the AESOP study were not included in our review, namely because results were not stratified by generation status. Both findings from our review and from the AESOP study suggest that the migrant cannot be restricted to the visible minority status, as clearly white migrants are also at an increased risk. In addition, their risk estimates appear higher than those of Asian migrants who can be considered as visible minority groups (Statistics Canada, 2008). However, this does not negate the potential contribution of discrimination, which may operate differentially across various groups and not exclusively as a

result of visible minority status or alternatively other migrant groups may have certain unexplored protective mechanisms which modify the magnitude of such risk.

Urbanization

Urbanization of the study setting did not account for significant between group differences. Yet a trend is observed towards increased relative risks in urban settings (RR = 2.7 in the first generation and RR = 2.6 in the second-generation) in comparison with mixed urban/rural settings (RR=2.2 in the first generation and 1.7 in the second generation). It has been demonstrated that being born and raised in an urban environment was associated with higher risk for schizophrenia than those born and raised in the country (Pedersen & Mortensen, 2001). Since immigrants tend to settle primarily in urban settings in the host environment, the question remains as to whether urbanization in itself might contribute to their risk for psychotic disorders. One study in our review reported incidence rates controlled for the effect of urban density and found that the migrant risk still persisted (Cantor-Graae & Pedersen, 2007). It is suspected that social factors underlie the *urban effect* and such factors may operate on migrant populations as well; however, the relation between urbanization and the risk for psychosis remains poorly understood (Cantor-Graae, 2007).

Study Settings (Host Countries)

Significant between-group heterogeneity emerged when effect sizes were grouped according to the countries in which studies were conducted. The lowest mean effect sizes concerned Israel (RR=1.5 in the first generation and RR=1.1 in the second generation), while the highest estimates were those for the UK (RR=2.8 in the first generation and RR=3.7 in the second generation). Intermediate risk estimates were reported from Scandinavian countries (RR=2.3 in the first generation, RR=1.8 in the second generation) and the Netherlands (RR=2.5 in the first generation and RR= 3.0 in the second generation). The authors of the Jerusalem second-generation migrant cohort study highlight that Jewish migrants moving to a Jewish state frequently escaped discrimination in their homelands and migration to Israel may have relieved

that source of stress (Corcoran et al., 2008). The authors add that migrants to Israel may not be perceived as "outsiders" in the same way as migrants in other countries. They conclude that the nature of the immigration experience may be relevant to the risk for psychotic disorders among migrants. It is worth highlighting at this point that in the other Israeli cohort study, both first- and second-generation migrants present a slight but significant risk increase for schizophrenia. However, first-generation migrants from Ethiopia were at a much higher risk than other groups (RR=3.0, 95% CI=1.9-4.7) (Weiser et al., 2008). Researchers concluded that migrants who differ most in culture and appearance from the host population may present a greater risk. Our findings of significant risk variation according to ethnic background, visible minority status (or skin color) and host environment not only support these notions, but also highlight that the post-migration social experience and risk exposure may vary from a geo-political setting to another.

Methodological Variables and Heterogeneity

Although results from higher quality studies did not differ significantly from the average and lower quality studies, between-group heterogeneity was nearly significant when considering the second generation effect sizes ($Q_B = 3.8$; $p = 0.0505$). The I^2 statistic also revealed that, although still high, heterogeneity was much reduced in higher quality studies (about 65%) compared with average and lower quality studies (about 95%). While the methodological quality of individual studies clearly does not account for the variability observed across the risk estimates, these findings nonetheless suggest that lower quality (or internal validity) of studies may contribute to a significant proportion of the observed heterogeneity. In other words, it is plausible that lower quality studies would yield "a lot of noise" in addition to the real-world variations.

Case ascertainment type (first-contact versus first-admission) emerged as a significant source of between-group heterogeneity, for the second generation in particular. For both generations, studies based on first-contact for psychotic disorders yielded higher mean weighted risk estimates (2.9 for the first generation

and 3.2 for the second generation) than studies based on first-admission (2.2 for the first generation and 1.6 for the second generation). Such differences highlight that pathways to care need to be considered when attempting to determine the risk based on treated incidence estimates. Schizophrenia is a relatively rare disorder, which render impractical to use extensive community surveys in attempting to find cases of schizophrenia. Therefore, incidence rates are usually based on treated cases and may therefore differ from the true incidence in the population (McKenzie, Fearon, & Hutchinson, 2008). Authors have often presented first contact studies as more accurate in estimating the incidence, since they include not only first hospitalizations, but also first presentations with mental health services (including community resources in some studies) (McKenzie et al., 2008). It is plausible that first contact studies, which generally identify cases from multiple sources, may enable a better approximation of the 'true' population incidence. However, authors have argued that we cannot predict whether we are more likely to underestimate or overestimate the risk depending on the study type (McKenzie et al., 2008). Findings from our subgroup analyses suggest that first-admission studies may actually underestimate the risk associated with migration status. If that were the case, it may be argued that first- and second-generation migrants have a risk of first-onset psychotic disorders that is about three times higher than that of non-migrants, which is slightly higher than the estimates from our meta-analysis.

However, there are other factors may operate differentially among migrants and non-migrants and contribute to differences between first-contact and first-admission incidence rates. Also, caution is needed in attempting to explain the variability that result from the case ascertainment process, as case-finding is inevitably related to the complex issue of pathways to care, which may vary according to ethnicity (Van Os & McKenzie, 2001). For instance, it is known that Caribbean migrants are more likely to be admitted compulsorily for psychotic disorders than the white British population in the UK (Bhui et al., 2003; Craig Morgan et al., 2005). Variations in the pathways to care may result from a multitude of factors, such as discrimination, access to primary care services or attitudes towards mental illness. Nonetheless, the

clinical state or severity of the condition at presentation remains an obvious determinant of the need for an admission. Our findings suggest that the relative treated incidence of first- and second-generation migrants may be higher when we consider any first-contact with healthcare services than hospital admissions. Assuming that both migrants and non-migrants have the same odds of being admitted for comparable clinical states, it is then plausible that migrants may be more prone to psychotic states than non-migrants but in a less severe form. This notion would actually be compatible with the widely held stress-diathesis model of schizophrenia onset, if migrants were overall less vulnerable to the illness genetically, but exposed to higher stress levels (Norman & Malla, 1993; Zubin & Spring, 1977). Obviously, this would require further investigation, including a comparison of the clinical presentations of migrants and non-migrants at first contact.

There were no significant differences in the risk magnitude associated with use of ICD or DSM standardized diagnostic criteria or the use of non-standardized diagnostic criteria. It should be highlighted that subgroup analyses according to diverse categorical moderators reduced the within-group proportion of heterogeneity (as indicated by the I^2 statistics), but the Cochran Q statistics nonetheless remained statistically significant in almost all cases. It is therefore likely that other potential sources of heterogeneity remain unexplored. Also, the significant residual within-group heterogeneity may have limited our ability to unravel between-group differences. Therefore, it is still possible that given a larger number of effect sizes or a more homogeneous set of studies, other variables such as diagnostic classification would be found to generate significant differences in the risk estimates.

Meaning of the Findings

Methodological Issues: *Are these Rates truly Elevated?*

This review clearly demonstrates that the findings of increased risk for psychotic disorders among migrants are consistent and strong, although the actual magnitude of the risk may still be debated. However, before discussing the reasons for which

migrants may be at higher risk for psychotic disorders, it is appropriate to first address the following question: are these rates truly elevated or could they simply represent artefactual observations as a result of the methods of investigation? In fact, the findings of elevated incidence rates among the Caribbean population in the UK have been the matter of considerable debate (Fearon & Morgan, 2006; Ingleby & Bevelander, 2008; McKenzie et al., 2008). A number of methodological concerns about fueled the debate about the validity of early findings from migrant studies in the UK, in particular issues about the denominator data, potential for misdiagnosis and concern about the case ascertainment process.

Denominator Data

A number of studies included in this review have reported on the challenge of determining appropriate population denominators to enable the computation of incidence rates among migrant groups (Harrison et al., 1988; Rwegellera, 1977; Thomas et al., 1993). There were significant doubts expressed about the validity of census data for members of ethnic minority groups in the UK. These were arguably under-enumerated in comparison with the British native-born, partly because population statistics were based on the birthplace of head of household, such as in the 1981 UK census (Fung, Bhugra, & Jones, 2006). This was corrected in the 1991 census, which included data about the ethnicity of individuals; yet, this census had allegedly underestimated the population by about 1million people. Those absent from this census were reportedly in a large proportion young, male and from ethnic minority groups (Fung et al., 2006; McKenzie et al., 2008). In response to these issues, researchers have applied various correction factors to the denominators used in incidence data or resorted other databases (e.g., a labour force survey in Harrison's study) (Harrison et al., 1988). These uncertainties could lead to some error in estimating the risk associated with migration status. However, even large uncertainties could hardly account for five- to tenfold risk increase in migrants relative to the host population. Also, more rigorous studies have consistently reproduced the findings of elevated incidence of psychotic disorders. In contrast to

the UK, census data used in other European countries have generally been regarded as accurate (Cantor-Graae & Selten, 2005).

Diagnosis

Concerns about clinician bias or about cross-cultural diagnostic validity have often been evoked as potential explanations for the migrant risk. Various authors have argued that British psychiatrists, who are unfamiliar with the Caribbean culture, may have wrongly attributed some beliefs or phenomena to schizophrenia (Littlewood & Lipsedge, 1981; Sashidharan, 1993). A study was conducted specifically to determine whether diagnoses would differ between British psychiatrists and a Jamaican psychiatrist (Hickling, McKenzie, Mullen, & Murray, 1999). No significant differences emerged in the number of Black patients diagnosed as having schizophrenia by either the Jamaican psychiatrist or the British psychiatrists. However, these diagnoses agreed in only 55% of cases. Other studies have shown no evidence of significant diagnostic instability over time among either Caribbean or white British patients (Takei, Persaud, Woodruff, Brockington, & Murray, 1998). A more recent longitudinal Dutch study also found that incidence rates of schizophrenia increased over a two and a half year follow-up, but the relative incidence in migrants compared with Dutch nationals was stable, again suggesting that diagnoses are not less stable among migrant cases (Veen et al., 2004). In our subgroup analyses, we observed no significant differences between studies which used ICD or DSM standardized criteria and those did not.

A few recent migrant studies have actually sought to minimize the potential for clinician bias by having researchers assigning diagnoses from detailed clinical information while remaining blind to the ethnicity of patients (Coid et al., 2008; Smith et al., 2006; W. Veling et al., 2006). Similarly elevated rates for psychotic disorders were observed in those studies. On the other hand, a recent study based on a small sample of Morrocan patients in Morocco (n = 29) suggested that a commonly used diagnostic instrument, the Comprehensive Assessment of Symptoms and History (CASH), resulted in a poor agreement with the clinical

diagnosis of psychosis by Moroccan psychiatrists, unless used in its culturally-sensitive version (Zandi et al., 2008). Despite some remaining doubts about the reliability and validity of the diagnosis in ethnic minorities, there has been no convincing evidence that misdiagnosis or diagnostic bias could account for the elevated incidence rates among migrants (Cantor-Graae & Selten, 2005; Selten & Hoek, 2008). While the debate about diagnostic bias is not solved, it could unlikely explain the elevated rates among virtually all migrant groups for which data are available. In fact, it has been argued that unfounded claims of artefactual elevated rates among ethnic minorities have potentially hindered the development of appropriate responses to a major public health problem in the UK (Morgan & Hutchinson, 2009).

Case Ascertainment

The comprehensiveness of the case finding approach has often been questioned in earlier studies. The study by Harrison has a set a standard its attempt to adhere to rigorous epidemiological principles through prospective case finding within a defined catchment area, along with use of standardized assessments and diagnostic criteria (Harrison et al., 1988). This study resulted in some of the highest rates reported among both first- and second-generation Caribbean migrants, although concerns about census data were not overcome.

Since incidence rates from treated cases, the differential pathways to treatment also need to be considered. For instance, it was demonstrated that Black Caribbeans in the UK – men in particular – have more adverse pathways to care, with increased risk of compulsory admissions and referral through the justice system (Morgan et al., 2005). Such findings do not imply an elevated incidence, but suggest that first-admission and first-contact studies may yield different findings. If migrants were more likely to be admitted than non-migrants, first-admission studies could potentially overestimate their relative risk. Our findings suggest that this is not the case, since first-contact studies yield somewhat higher risk estimates.

Confounding Variables

A number of variables may potentially confound the relation between migration status and the risk for psychotic disorders. Age and gender are two obvious variables to consider, as differences in the population structures of migrant groups and reference populations could lead to artefactual findings. All effect sizes in this review were adjusted for age (as per our inclusion criteria) and gender. Urbanization could also be considered as a potential confounder, if for instance, migrants were at higher risk of psychosis simply because they are more likely to live in urban environments. As discussed earlier, a Danish cohort study reported that the association between migrant status and the risk of psychosis was not confounded by urban dwelling (Cantor-Graae & Pedersen, 2007). We did not observe significant differences when comparing migrant groups from urban environments to those of migrants from mixed urban / rural environments. Nonetheless, the risk associated with urbanization is poorly understood and there may be an underlying risk exposure common to migrants and urban populations.

Socio-economic status is another important variable that could potentially confound – or at least contribute to – the risk for psychotic disorders among migrants. Researchers from the East London First Episode Psychosis Study specifically investigated this question (Coid et al., 2008; Kirkbride et al., 2008). The authors report that their study took place in a homogeneously deprived area of London, thus providing some control for this factor. Also, individual-level socio-economic status was not found to explain the increased rates of psychoses in black and minority ethnic groups. The authors specify however that some socio-environmental factors may contribute to both socio-economic deprivation and the risk of psychosis. A recent study of the relation between ethnic density of neighbourhoods and the incidence of psychotic disorders in The Hague, Netherlands, also examined the potential confounding effect of socio-economic level of neighbourhoods (Veling et al., 2008). The authors found the incidence of psychotic disorders was most elevated among migrants living in neighbourhoods where their ethnic group comprised a small proportion of the population. This effect was not explained by confounding

from socio-economic deprivation, as determined by income, housing, employment status and education level.

Another study was conducted on a large Swedish cohort to determine whether rates of schizophrenia and other psychoses were related to a number of household socio-economic indicators (e.g., single parenthood, parental unemployment, housing status) (Hjern, Wicks, & Dalman, 2004). Both first- and second- generation migrants were at increased risk for psychotic disorders. The migrant effect remained high, but decreased considerably after rates were adjusted for socio-economic indicators, but remained elevated nonetheless. The authors concluded that social adversity, such as social exclusion poverty, probably contributes to the risk for psychotic disorders among migrants. It appears relevant to determine specifically which forms of social adversity are etiologically related to the onset of psychotic disorders and potentially modifiable. It is indeed plausible some forms of social adversity may determine both socio-economic indicators and an increased risk for psychoses.

Consistency of Findings from Migrant Studies

In spite of all methodological concerns and debates about reports of elevated incidence of psychotic disorders among migrants, the literature has been remarkably consistent in reporting an association between migration and an increased risk of psychosis. Furthermore, such findings have now been demonstrated well beyond the borders of the UK. In light of the methodological shortcomings of earlier studies and of remaining gaps in knowledge, the UK Medical Research Council has launched one of the largest and most rigorous investigations in recent years: the 3-center AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study (Fearon et al., 2006; Morgan et al., 2006). This first-contact study sought to address the shortcomings of prior studies and to clarify whether rates of psychoses other than schizophrenia were increased in Caribbean migrants and whether other ethnic minority groups were at increased risk for psychoses. Elevated incidence rates of schizophrenia – and of any psychotic disorders – were observed among all ethnic minority groups in comparison with native-born white British. Strikingly high

incidence rate ratios (IRR) were found for schizophrenia among African-Caribbeans (IRR = 9.1, 95% CI = 6.6-12.6) and black Africans (IRR = 5.8, 95% CI = 3.9-8.4) (Fearon et al., 2006). Other ethnic minority groups were also at increased risk of psychosis in comparison with the white British population, though not to the same extent.

Using more rigorous methods than prior studies, the AESOP study actually reported some of the highest risks of psychosis ever reported for black and other ethnic minorities in the UK (McKenzie et al., 2008). Although our review did not generate risk estimates as high as those of the AESOP study, our findings are nonetheless consistent with those of this large-scale investigation in various ways: a) all migrant groups appear to be at higher risk for psychosis; b) the magnitude of the risk appears to be especially high among black migrants; c) more comprehensive ascertainment methods, which include all first presentations rather than first admissions only, may unravel higher risk estimates among migrant groups.

Why are Migrants at Higher Risk for Psychotic Disorders?

Once it is accepted that both first- and second-generation migrants are at increased risk for psychotic disorders, the obvious next question is why? Again, this question has generate much speculation ever since Ödegaard's seminal work in the early 20th century (Odegaard, 1932). This review demonstrates that the risk for psychotic disorders operates not only in the first generation, but also in the second generation. Although the causes for these increased rates may differ from a generation to another, it is likely that similar underlying risk factors operate in both generations. Viable hypotheses for the causes underlying these elevated rates should therefore be plausible for both generations.

Pre-migration Factors

Selective Migration

As he attempted to explain the increased incidence of schizophrenia in Norwegian migrants, Ödegaard argued that the phenomenon resulted from the selective

migration of individuals already vulnerable to the disorder (Odegaard, 1932). His paper was quite influential and may have deterred further investigation of the question until recent decades (Selten et al., 2007). The selective migration hypothesis has been increasingly refuted by researchers on the basis of recent findings (Selten, Cantor-Graae, Slaets, & Kahn, 2002). For instance, it is difficult to explain how selective migration could account for findings of fivefold higher risk among Surinamese migrants to the Netherlands given this context in which nearly half of the Surinamese population migrated to the Netherlands. Also, selective migration could not explain the risk of psychosis in second-generation migrants, although it would not exclude the selective migration of their parents. Finally, it may be argued that prodromal features of schizophrenia-related disorders do not seem compatible with the efforts and motivation required to emigrate.

Genetic Predisposition

Since schizophrenia is considered as a highly genetically determined disorder, genetic predisposition has often been evoked to explain the incidence rates in migrant populations. This hypothesis would be plausible if incidence of schizophrenia was higher in the countries of origin. However, incidence studies conducted in Barbados, Jamaica and Surinam have all revealed schizophrenia incidence rates similar to those of the native-born population in the host countries (Hanoeman, Selten, & Kahn, 2002; Hickling & Rodgers-Johnson, 1995; Mahy, Mallett, Leff, & Bhugra, 1999).

Two studies have investigated the risk of schizophrenia in the siblings of second-generation African Caribbean migrants in comparison with that of their parents (Hutchinson et al., 1996; Sugarman & Craufurd, 1994). Sugarman and Craufurd observed that the lifetime morbid risk in the parents of white subjects was the same as that of the parents of Afro-Caribbean patients (8.9% versus 8.4%) (Sugarman & Craufurd, 1994). However, the siblings' lifetime risk of developing schizophrenia was only 2% in white British patients, 9% in first-generation Afro-Caribbeans, and 27% in second-generation Afro-Caribbeans. Such a pattern indicates that the

contribution of genetic factors is not more important in Afro-Caribbeans than in white patients; also, it is consistent with an increased exposure to environmental factors in Afro-Caribbean population. These findings do not rule out the role of genetic factors among migrants, but they strongly emphasize the putative role of environmental factors in conferring the risk for psychosis among migrants and ethnic minorities.

Migration

The stress induced by the migration process has often been evoked to explain the increased rates of schizophrenia., which would be compatible with to the current stress-diathesis model of schizophrenia (Zubin & Spring, 1977). If that were the case, we would expect a relationship between the time of migration and the onset of psychosis. There is no current evidence for such a relationship. A Danish population-based cohort study reported no association between the migrant risk and the number of years since migration (Cantor-Graae et al., 2003). A strong argument against the role of migration as the major determinant of psychoses in migrants rests in the persistence of the risk in the second generation migrants, who were born in the host society and, for the most part, never experienced the migration process. A study based on a large Danish cohort revealed that individuals with a history of foreign-residence prior to age 15 years had increased risk for developing schizophrenia (Cantor-Graae et al., 2003). These findings also held for the native-born people with a Danish background, suggesting that the migratory process should not be discounted as a potentially relevant factor.

Post-migration Factors

Biological Factors

A number of environmental biological factors have proposed as potential explanations for the relation between migration and psychosis. Similar to the infectious hypotheses for the migration patterns in the incidence of multiple sclerosis, various infections agents have been proposed as candidates for the migrant effect (Cantor-Graae & Selten, 2005). There has been no convincing evidence for

such factors so far. Pregnancy and birth complications are associated with an increased risk for schizophrenia and have been proposed to explain the risk in migrant groups. However, current evidence suggests that there are fewer obstetric complications in Afro-Caribbean patients than in white British patients with schizophrenia. (Hutchinson et al., 1997). Prenatal exposure to vitamin D deficiency is another proposed hypothesis which could affect dark-skinned migrants who live in cold climates and increase their vulnerability for schizophrenia (Dealberto, 2007; J. McGrath, 1999). This hypothesis has yet to be tested, but it appears hardly applicable to first-generation migrants who grew up in their countries of origin. Also, an increased risk is also observed among light-skinned migrants who moved from cold to warmer climates.

Drug use – cannabis in particular – is another risk factor for psychotic disorders (Fergusson, Poulton, Smith, & Boden, 2006). However, there was no evidence of increased cannabis use in Afro-Caribbean migrants in the UK, not in ethnic minority groups in the Netherlands (Pinto, Ashworth, & Jones, 2008; Veen et al., 2002). Nonetheless, it is suggested that substance use patterns be further investigated in migrant populations (Cantor-Graae, 2007; Selten & Cantor-Graae, 2009). Overall, there is very thin evidence to suggest that biological factors could explain the increased incidence of psychotic disorders associated with migrant status.

Socio-environmental Factors

Unlike biological factors, there is increasingly evidence that socio-environmental factors may contribute to the increased rates of psychosis in migrant populations. Living in an urban environment is associated with an increased risk for psychotic disorders in a dose-response fashion (Krabbendam & van Os, 2005; Pedersen & Mortensen, 2001). Commonly settled in urban environments of their host countries, migrants may be more exposed to the effects of urban density (Paul Fearon & Morgan, 2006). The urban effect is still poorly, but the social isolation that often characterizes urban life has been proposed as a potential underlying factor (McKenzie et al., 2008).

The AESOP study found that separation from – and death of – a parent before the age of 16 were associated with a two- to threefold risk for developing a psychotic disorder (Morgan & Hutchinson, 2009; Morgan et al., 2007). The strength of this association was similar for both white British and African-Caribbean subjects. However, the experience of early parental separation was much more common among African-Caribbean individuals, and might contribute to the elevated incidence in that group. A number of indicators of social disadvantage in adulthood – such as unemployment, housing instability and social isolation – were similarly associated with an increased for psychotic disorders in general, but observed more frequently in the Black Caribbean population (Morgan, Kirkbride et al., 2008).

Perhaps one of the most striking findings in the topic of migration and psychosis lies in the inverse relationship between a neighborhood ethnic density and the rates of psychosis. It has now been replicated in 3 different studies that the relative incidence of psychotic disorders among migrants increase as they form a decreasing proportion of the population (Boydell et al., 2001; Kirkbride et al., 2007; Veling et al., 2008). It has been hypothesized that living in neighborhoods with higher ethnic density may ensure better social support and potentially protect against the effects of discrimination or other forms of social adversity. Discrimination itself is increasingly recognized as a risk factor for psychotic disorders. A prospective study has shown that perceived discrimination in healthy persons actually predicted the later occurrence of psychotic symptoms, such as delusions (Janssen, Hanssen, & Bak, 2003). Based on findings from the 7-year incidence study of first-episode psychotic disorders in The Hague, Dutch researchers reported that the relative incidence of psychotic disorders in an ethnic minority group was correlated with the degree of perceived discrimination in that group. The incidence rate ratios for schizophrenia and the degree of perceived discrimination were highest for Moroccan migrants (Veling et al., 2007a).

Discrimination and Relations between Migrants and Host Societies

One of the most striking finding from our meta-analytic was that the magnitude of the risk was significantly higher among migrants groups from countries where the majority population is black compared with those from countries where the majority population is either white or neither black nor white. Among those groups, the magnitude of the risk may even be higher in the second generation than in the first. In the absence of any evidence of elevated incidence of psychotic disorders in the source countries, these findings strongly support the contributory role of the social environment and raise questions about a common exposure to adverse social experiences such as discrimination. Individuals with darker skin color – who may differ most in appearance from the majority population in the host environment – may be more often discriminated against in Western societies. The findings of differential incidence rates depending on the neighborhood ethnic composition would be compatible with this notion if black migrants living in predominantly black neighborhoods were less exposed to discrimination or other forms of social exclusion and disadvantage. The fact that the risk is at least as high and perhaps even higher the second generation is also plausible if early negative social experiences are causally associated with the later onset of psychotic disorders. Unlike their parents who may have been exposed such negative experiences or social disadvantage only after the migratory process, second-generation migrants might be exposed to factors such as discrimination at earlier stage of their life and for longer periods of time than the first generation. Alternately, they may be exposed to the same social factors, but at a more critical stage of their development. Obviously, such a notion has yet to be investigated, but it would be consistent with the neurodevelopmental model of schizophrenia.

The variations of the risk according to skin color could reflect the social experience of discrimination. In spite of our findings of higher risk associated with black visible minority status, black migrants are not necessarily those at highest risk for psychosis as indicated by findings from the Netherlands. In fact, all Dutch incidence studies

seem to indicate higher risk for psychotic disorders among first- and second-generation Moroccans than among migrants from Surinam or the Antilles (Selten & Sijben, 1994; Selten et al., 1997; Veling et al., 2006). Yet there is still evidence that that levels of discrimination are associated with the magnitude of the risk for psychotic disorders (Veling et al., 2007b). Two considerations can be derived from such findings. First, discrimination may result not only from differences in physical appearance, but also from differences in culture or religion. For instance, it has been demonstrated that of all ethnic minorities in the Netherlands, Moroccan migrants are the most disliked by the native population, as well as the most disadvantaged socio-economically and the most likely to report discrimination incidents (Schalk-Soekar, van de Vijver, & Hoogsteder, 2004; W. A. Veling, 2008) . It has been argued that that Moroccans who migrate to the Netherlands, a secular state with a majority Christian population, are mostly Muslims. This may contribute to the level of discrimination encountered by this ethnic group (Weiser et al., 2008). A second consideration that these findings highlight is that it is not only the characteristics of migrant groups that matter, but also the social contexts and the attitudes of the host societies.

Immigration occurs from a social context to another. As such, its effects cannot be understood without consideration of the characteristics of the host social context and the social experiences resulting from interactions between migrants and host societies. Our review provides ample support for the role of a dual dynamic between ethnic minority groups and host societies in relation with the risk for psychotic disorders. For example, the Canadian study, based on findings from the early 20th century, provides some results suggestive of a relationship between a changing social context and the risk associated with migrant status (Smith et al., 2006). Incidence rates were reported for both Canadian-born and European-born migrants over 3 distinct periods from 1902 to 1913. Over this observation period, the incidence rate ratios for schizophrenia among migrants increased from 1.20 (95% CI 0.95-1.50) to 1.94 (1.73-2.15). The researchers commented that this risk increase

occurred in an era of sudden recession associated with increasing unemployment and intolerance of immigrants in Western Canada.

The two Israel-based migrant studies also provide some interesting findings that contrast with those from other European studies. Based on the Jerusalem Perinatal Study cohort, one study failed to demonstrate any increased risk for schizophrenia among second-generation migrants (Corcoran et al., 2008). As the authors commented, this situation might be related to the differential nature of migration to Israel, as Jewish migrants move to a Jewish state and often escape a minority status associated with anti-semitic discrimination in their countries of origin. In such circumstances, migration to Israel might perhaps even relieved some forms of pre-migration stress. Also, children of migrants in Israel may not be considered as outsiders unlike second-generation migrants in other European countries. Yet another larger Israel-based study – covering the whole country – revealed that overall both first- and second-generation were are increased risk for schizophrenia (RR = 1.6 in the firs generation and RR = 1.5 in the second) (Weiser et al., 2008). However, when rates were obtained for ethnic groups separately, migrants from Ethiopia were clearly those at highest risk for schizophrenia (RR = 3.0). The authors concluded that different physical appearance and cultural dissimilarity may be associated with increased risk for schizophrenia. There is also a significant literature reporting on the racism and discrimination faced by Ethiopian Jews in Israel (Ben-Eliezer, 2004). Similarly to the situation in the UK, it appears that migrant groups with black skin color in Israel are also at higher risk for developing psychotic disorders, most likely as a result of social processes in the host environment. Similar patterns may plausibly underlie the increased incidence rates reported among migrants from Greenland in Denmark (Cantor-Graae & Pedersen, 2007) or among Eastern European migrants in Australia (Krupinski & Cochrane, 1980). Taken together, all these findings point in one direction: if it is accepted that social factors likely contribute to the onset of psychotic disorders among migrants, then patterns of relations between migrant groups and host societies should also be considered in

attempting to unravel the mechanisms underlying those increased risks for schizophrenia and related disorders.

A Potential Unifying Model: the S*ocial Defeat* Hypothesis

The accumulating evidence from migrant studies, which has so far defied any definitive explanation, has stimulated interest for the role of social causation mechanisms in the onset of psychotic disorders. Among the few hypotheses proposed to explain this excess risk among ethnic minorities, the *social defeat* hypothesis is currently one of the most influent (Selten & Cantor-Graae, 2005, 2007). The experience of social defeat is defined as one of subordinate position or 'outsider status' in a given environment. The social defeat hypothesis is actually derived from the resident-intruder animal model, whereby a male rat – the intruder – is put into the cage of another male – the resident. The resident animal then forces the intruder into a submissive position. When such an experiment is repeated, the defeated animal eventually displays an abnormally sensitive brain dopamine system – the neurotransmitter which is thought to be predominant in the pathogenesis of psychotic disorders in humans. According to the social defeat hypothesis, the chronic experience of social defeat may lead to sensitization of the mesolimbic dopamine system, thus resulting in an elevated baseline risk for schizophrenia (Cantor-Graae, 2007). Cantor-Graae and Selten suggest that this hypothesis is a plausible unifying explanation for the elevated rates of schizophrenia not only among migrants, but also among other individuals at higher risk of being socially disadvantaged, such as residents of densely populated areas or people with lower intelligence.

The social defeat hypothesis also provides a plausible explanation for the elevated incidence of psychotic disorders among those who report high levels of perceived discrimination or those who live in neighborhoods where their ethnic group represents a small proportion of the local population. As Selten and Cantor-Graae argue, such a phenomenon may be compatible with the findings of elevated risk of psychosis among second-generation migrants, since their experience of an 'outsider

status' may result in even higher social stress levels given the entitlement conferred by their birthright (2007). The social defeat hypothesis has yet to be demonstrated in human population, which may pose significant challenges. Nonetheless, it deserves serious consideration as it provides a socially and biologically plausible framework to link societal context and serious psychopathology.

Strengths and Limitations

To our knowledge, this contribution represents the most extensive systematic review of the risk for psychotic disorders among migrants, in particular for second-generation migrants. We have extracted 59 effect sizes for the first generation and 28 for the second generation, which enabled us to estimate the risk of psychosis in first- and second-generation migrants and to explore the variability of the risk in a variety of groups and contexts. In developing our methods, we closely adhered to the current guidelines for systematic reviews of observational studies in epidemiology (Stroup et al., 2000). These guidelines provided us a rigorous framework for identifying studies, extracting data and generating transparent information. In particular, we conducted detailed quality assessments of identified studies and addressed the methodological shortcomings of the literature in the field. In addition to the primary author, two independent reviewers were involved at various stages of the review process. Also, we went beyond statistical data pooling by completing a detailed descriptive review, providing measures of central tendency and dispersion and finally, by carefully exploring the variability of the data.

Nonetheless, there are a number of potential limitations that need to be taken in consideration when appraising the results of this review. First, it should be noted that systematic reviews are secondary research. In the current context, the objects of analyses are the population-based studies on migration and psychotic disorders and their reported findings, not the primary incidence data. Therefore, the validity of the review is inevitably contingent on the methodological quality of the underlying studies, as well as on the accuracy and completeness of their reporting. We have attempted to control for this important issue by completing an extensive quality

assessment of each individual studies and examining whether quality levels were associated with differences in the magnitude of the effect sizes. Also, when necessary, we have contacted primary authors to obtain clarifications or additional data. Obviously, the methodological issues discussed earlier about findings from migrant studies – such as concerns about misdiagnosis in ethnic minorities, unreliable denominator data, incomplete case ascertainment or the potential for confounding from factors such as socio-economic status – are not only limitations for primary studies, but also for secondary research based on those studies. On the other hand, this systematic review enabled us to highlight the consistency and plausibility of all these findings from primary studies.

As in all systematic reviews, studies may have been missed despite efforts to conduct a comprehensive and sensitive search. We have attempted to minimize this by developing a rigorous search strategy with the assistance of an expert librarian. We have also sent of retrieved studies to experts in the field to advise us about any potentially missed studies. Some authors advocate that efforts should be made to also search for additional sources such as conference proceedings and ongoing studies or unpublished material, often referred to as the "grey literature", as this is thought to reduce the potential for publication bias (Borenstein et al., 2009). Other authors rather emphasize that selecting studies in peer-reviewed journals may serve as a step in quality control. We have selected a priori to exclude such literature in our inclusion criteria, mainly for quality considerations, but also for practical reasons as it appeared highly unlikely that we would locate unpublished population-based migrant studies that met all our inclusion criteria. This approach is consistent with that of prior systematic reviews on the incidence of schizophrenia (Aleman, Kahn, & Selten, 2003; Cantor-Graae & Selten, 2005; McGrath et al., 2004). Publication bias nonetheless remains possible although funnel plot analyses did not suggest that this was present.

Although this study was extensive and generated some relatively precise estimates of the risk associated with migration status, it should be reminded that for some

studies, risk estimates were based on very small sample sizes for a few migrant groups. Thus some studies may have lacked the power to demonstrate significant risk increase in migrant populations, in particular for second-generation migrants. Since the most significant migration waves to UK and other European countries were initiated in the post-war decades, it is also likely that many second-generation migrants have not yet gone their period at risk, unlike a significant proportion of first-generation migrants. Similarly, our subgroup analyses – which were based on smaller subset of studies – may have lacked the power to demonstrate significant between-group differences or to provide more precise risk estimates.

Finally, another important limitation of the meta-analytic process lies in the significant heterogeneity of findings from primary studies regarding the risk of psychosis associated with both first- and second-generation migrant status. Therefore, all migrant groups cannot be assumed to come from a homogeneous underlying population, and caution is needed in interpreting the risk estimates derived from these effect sizes. While we were able to provide an estimate of the weighted average risk associated with first- or second-generation migrant status in general, we have focused on the exploration of some factors underlying the considerable variability of risk estimates across studies, ethnic groups and social contexts.

CHAPTER 5: CONCLUSION

Migration is now recognized as a risk factor for schizophrenia and related disorders (Tandon et al., 2008). Our systematic review and meta-analysis confirms that this increased risk of psychosis affects not only first-generation migrants – with a personal history of migration – but also second-generation migrants who were born to one or two migrant parents in the host country. Overall, first-generation migrants appear to present a similar relative risk (RR = 2.3, 95% CI 2.0-2.6) to that of second-generation migrants (RR = 2.1, 95% CI 1.8 –2.4). A few analyses indicated a trend towards a higher risk for second-generation migrants than for first-generation migrants, namely the meta-analysis of the restricted dataset (including data, the subgroup analysis for black visible minority status and that of first-contact studies. Clearly, studies on migration and the incidence of psychotic disorders should also consider the second generation and examine potential generational differences. Also, future hypotheses to explain the relation between migration and the onset of psychotic disorders should ideally be applicable to both generations of migrants, although the underlying factors may operate differentially in each generation.

Our findings strongly argue against the selective migration of predisposed individuals to explain the relation between migration and psychosis. Misdiagnosis is unlikely to account for the elevated incidence of psychosis in migrants and ethnic minorities, though diagnostic considerations are still a matter of debate and should not be ignored. Current evidence does not suggest that genetic and biological factors – such as infections or cannabis use – contribute to the risk of psychosis among migrants. The persistence of elevated incidence rates among second-generation migrants clearly indicates that the primary risk-contributing factors do not operate in the pre-migration period nor around the migratory process, but rather in the post-migration context. The relation between migration and psychosis has yet to be explained, but socio-environmental factors are increasingly suspected. Indeed, there is increasing evidence that social determinants, such as discrimination or neighbourhood ethnic density, are associated with the risk of psychosis. Our review

also highlights that the magnitude of the risk varies according to both ethnicity and the social context, thus suggesting that the dynamic relationship between migrant groups and host societies may moderate the risk of psychosis associated with migrant status.

Findings from this systematic review and meta-analysis have some major implications. First, it is crucial from a public health perspective to recognize that both first- and second-generation migrants are generally at higher risk for schizophrenia and related disorders. This indicates that improved efforts are needed to prevent and recognize psychotic disorders in migrants, and importantly, to further develop accessible and culturally-sensitive early intervention services. Second, these findings add weight to the increasingly recognized notion that the incidence of psychotic disorders is heterogeneous across socio-cultural contexts. This knowledge is important to advance our understanding of the causes of schizophrenia and related disorders not only among migrants, but also in the general population. Finally, our findings are profound implications from a societal perspective. Indeed, if it is suspected that the social world and some patterns of relations migrants / host societies can contribute to burdensome health outcomes such as psychotic disorders in some social groups, it may then be important to consider interventions at the societal and socio-political level. Such considerations would be clearly relevant to ethnically diverse Canadian population, in a country that prides itself for its multicultural policies and efforts to integrate immigrants (Jarvis, 2007; Satzewich & Liodakis, 2007).

Future Avenues

The knowledge generated by migrant studies has been invaluable in better understanding schizophrenia and other psychotic disorders, especially with regards to the role of environmental factors (Fearon & Morgan, 2006). Our findings support this conclusion, but also call for further concerted research efforts on the topic. Importantly, future studies should consider limitations from prior studies and attempt to overcome methodological concerns with regards to the accuracy of

census data, cross-cultural diagnostic validity and comprehensiveness of case ascertainment. In spite of the usefulness of first-admission studies, epidemiological studies based on first-contact for psychotic disorders may yield more accurate information on the true incidence of illness and on the actual magnitude of the risk in various groups. Migrant studies would yield valuable information if they were designed to better explore the differential pathways to mental health care across migrant groups and reference populations.

Multiple migrant groups in our review were comprised of a small number of cases, especially among second-generation migrants. Also, unlike first-generation migrants, a significant proportion of second-generation migrants in Europe may not have gone through their period at risk, since the most important migration waves occurred between the 1950's and the 1970's. Future studies of second-generation migrants with larger sample sizes are therefore warranted. Generational differences in the risk for psychotic disorders may help us to disentangle the respective role of migration status and ethnicity and shed further light into social causation mechanisms. The distribution of the illness according to age and time since migration may inform us about the period at risk for each migrant generation. It may be relevant to replicate migrant studies at different points in time, as the composition of populations and the social contexts change over time (e.g., as a result of changes in government and social policies).

Ethnic identity and acculturation are widely discussed in the field of social psychology with regards to mental health (Berry, 2001). However, these topics are still virtually absent from the literature and current debates on migration and psychotic disorders. Such issues should not be ignored and may be of particular relevance to second-generation migrants, who often have to negotiate two cultures – potentially conflicting at times – throughout their development.

Finally, much could be learned by further exploring why some ethnic groups appear to be at lower risk than others or why the risk of migrants may be lower in some

countries than in others. Studying potential risk and protective factors across social groups and contexts may provide some clues in understanding the relation between migration, ethnicity and the onset of psychotic disorders. We would argue that a valuable avenue would be to compare the incidence of psychotic disorders among various ethnic minority groups across different social contexts using a similar and rigorous methodology. Also, future research in social psychiatry would certainly benefit from integrating the methods and knowledge of neurosciences and social sciences in order to better understand how the social world contributes to psychopathology (Morgan, McKenzie et al., 2008). In a country comprised of a diverse multicultural population at various generational stages, Canadian psychiatry is undoubtedly well-poised for a significant contribution in this respect.

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Appendix I: Review Study Selection Form

STUDY IDENTIFICATION

Title	
Authors	
Journal, Year	

STUDY SELECTION CRITERIA GRID

Selection Criteria	Y	N	?	Comments
1. Is this study published in a **peer-reviewed journal**?				
2. Was this study published in **1977 or after**?				
3. Is this study in **English, French, Spanish, Dutch or German**?				
4. Is this study **population-based** in a defined **catchment area**?				
5. Are the **diagnoses used** schizophrenia, first episode psychosis or psychotic disorders in general?				
6. Are **incidence rate ratios or incidence rates or numerator / denominator data** provided for **at least a migrant group and a reference group**?				
7. Does the study differentiate **first- from second-generation** migrants?				
8. Does the study provide **corrected results** for age / sex differences between comparison groups or data that enable such corrections?				

SUMMARY

Are further data needed to determine eligibility? N ☐ Y ☐ specify:	Need for contacting author(s): ☐ No ☐ Yes - date: ☐ Responded - date: Email:
Is this study included in the final set for data extraction and quality assessment? Y ☐ N ☐	Assign study ID number for included studies: ☐☐☐

Appendix II: Data Extraction and Quality Assessment Form

Form completed by: ☐ FB ☐ EV

Form reviewed by: ☐ FB ☐ EV ☐ AK

Data Extraction Process Summary (to be completed by independent reviewer):	
Was there consensus on data extraction?	☐ Yes ☐ No – specify:
Are further information needed from authors?	☐ No ☐ Yes – specify:
Was there consensus on quality rating?	☐ Yes ☐ No
What is the overall quality rating for this study? (determined by consensus or by independent reviewer in case of disagreement)	☐ Good ☐ Fair ☐ Poor
What is the final status of this study?	☐ Included ☐ Incomplete ☐ Excluded

Section I: STUDY IDENTIFICATION	
Article Title:	
First Author:	Second Author:
Journal:	Country of study:
Year of publication:	Language of publication: ☐ English ☐ Other:
Need to contact author (s)? ☐ No ☐ Yes Email:	Information / Clarification needed from authors:
Notes:	

Section II: STUDY CHARACTERISTICS

Type of Publication:
- ☐ peer-reviewed paper
- ☐ other _____

Study design: ☐ cohort: prospective
- ☐ cohort: retrospective
- ☐ cross-sectional
- ☐ case-control
- ☐ other – describe:

Specify / describe catchment area (s):

Urbanicity: ☐ Urban area
- ☐ Rural area
- ☐ Mixed urban / rural

Observation period (s) :

Number of years:

Study population – Gender:
☐ M/F ☐ M ☐ F

Study population - age range:
- ☐ General adult population
- ☐ Children and adolescents (18 or less)
- ☐ Elderly (65 and above)

Age grouping - list:

Age adjustments provided? Yes ☐ No ☐

Case ascertainment:
- ☐ First admission (hospital inpatient)-
- ☐ First contact:
  - ☐ inpatients and outpatients
  - ☐ outpatients only
  - ☐ community resources / clinics
- ☐ Case registers

Describe method:

Diagnoses used:

Classification system: ☐ DSM-IV
- ☐ ICD-9 or ICD-10
- ☐ Other:

Diagnosis assignment method:
- ☐ Diagnostic interview
- ☐ Charts or case notes review
- ☐ Registry
- ☐ Unspecified
- ☐ Other:

Migrant Generations:
☐ 1st generation only ☐ 1st and 2nd generation
☐ 2nd generation only ☐

Additional grouping?
☐ Regions of birth ☐ Race / skin color
☐ Ethnic affiliation ☐ Religion

Definitions of ethnicity / migrant status in this study:
1st generation migrant:
2nd generation migrant:

How was ethnicity / migrant status ascertained?

Were there changes in the case ascertainment, diagnostic or classification methods over time?
Yes ☐ No ☐
If so, describe:

Section III: QUALITY ASSESSMENT CHECKLIST AND SCALE	
What is this study design?	☐ Cohort ☐ prospective ☐ retrospective ☐ Cross-sectional ☐ Case-control
SELECTION / CASE ASCERTAINMENT (Numerator Data)	
**How were cases ascertained?*	(2) ☐ Community survey or multiple type of institutions (1) ☐ Hospital inpatients & outpatients or ☐ Hospital admissions only or ☐ Case registers (0) ☐ Not specified
Were the cases newly diagnosed, incident cases?	☐ Yes ☐ No ☐ Unable to tell
Was there an effort to locate additional or potentially missed cases (e.g. use of community resources, multiple institutions, registers, etc.)?	☐ Yes ☐ No ☐ Unable to tell
Are the cases derived from a clearly described catchment area?	☐ Yes ☐ No ☐ Unable to tell
Were migrants/ethnic minority groups and reference groups drawn from the same community or catchment area?	☐ Yes ☐ No ☐ Unable to tell
Help-seeking bias: *From the information provided, do migrant and control cases appear as likely to present to health care services?*	☐ Yes ☐ No ☐ Unable to tell
Are the inclusion /eligibility criteria provided for both migrant/minority cases and cases from the reference group?	☐ Yes ☐ No
POPULATION AT RISK (Denominator Data)	
Is the population at risk clearly defined?	☐ Yes ☐ No ☐ Unable to tell
Is any information provided about the attrition rates or losses to follow-up of the study population? If so, specify:	☐ Yes ☐ No
** Was a **leakage study** conducted?* *Or else, was there any information provided about potential leakage from the study catchment area?*	(1) ☐ Yes (0) ☐ No (0) ☐ Unable to tell

INFORMATION / MEASUREMENT BIAS	
Diagnosis **How were Schizophrenia / Psychotic Disorders diagnosed?* *(not only classification in registry)*	(2) ☐ Diagnostic system reported (e.g., CATEGO, DSM, ICD) (1) ☐ Clearly described, validated criteria (0) ☐ Own system / symptoms description (0) ☐ No system or not specified
Was there extensive use of collateral history?	☐ Yes ☐ No ☐ Unable to tell
Method of diagnostic assignment **What was the method of diagnostic assignment?*	(3) ☐ Diagnostic Interview (2) ☐ Case note review – standardized (1) ☐ Clinical diagnosis in notes or registries (0) ☐ Unspecified
Was ethnicity / migration status assignment independent of diagnostic assignment?	☐ Yes ☐ No ☐ Unable to tell
Were measures taken to reduce the potential for misdiagnosis?	☐ Yes ☐ No ☐ Unable to tell
Inter-rater reliability **Was there information about inter-rater reliability?*	(1) ☐ Yes (0) ☐ No
Data reporting: Information on rates **Is the following information provided on rates?*	(1) ☐ Raw data numerator (1) ☐ Raw data denominator (1) ☐ Age ± sex standardized (1) ☐ If standardized, method provided (1) ☐ Confidence intervals (1) ☐ Num/den match - time (1) ☐ Num/den match – space
CONFOUNDING	
List the major confounders (age, gender, SES, etc.) and specify whether they were adjusted in analysis/ design.	

OVERALL QUALITY ASSESSMENT	
ANY SIGNIFICANT STUDY STRENGTHS? :	
MOST IMPORTANT DESIGN FLAW? **:**	
Overall, do the results appear internally valid (free from bias)?	☐ Yes ☐ Somewhat / partially ☐ No
Overall, do the results appear externally valid (generalizable)?	☐ Yes ☐ Somewhat / partially ☐ No
OVERALL QUALITY SCORING RANGE: Scoring range = 0-16	☐ High (11-16) ☐ Average (6-10) ☐ Low (5 or less)
OVERALL QUALITY IMPRESSION:	☐ Good ☐ Fair ☐ Poor
ADDITIONAL COMMENTS? ANY KEY FEATURES OR RESULTS FROM THIS STUDY?	