Age at Migration and Risk of Schizophrenia Among Immigrants in Denmark: A 25-Year Incidence Study

To the Editor: In the December 2011 issue, Veling et al. (1) report on a study from the Netherlands that the risk of psychotic disorders in immigrants decreased with age at the time of immigration. The authors suggest that early life is an important risk period for the development of psychosis in immigrants. We sought to replicate their findings using data from the Danish nationwide population-based registers.

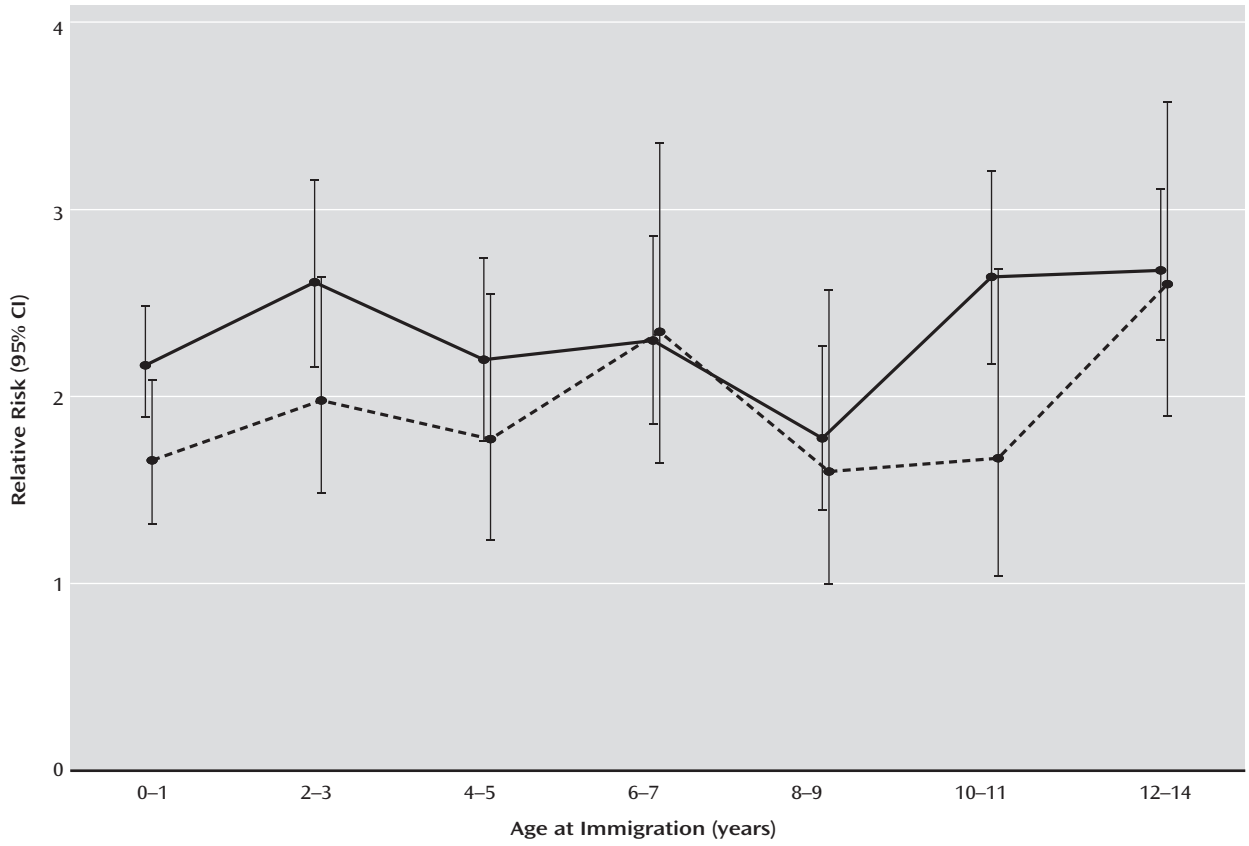
Data on persons who were born between 1971 and 1995 and who resided in Denmark by the age of 15 were followed for the development of schizophrenia (ICD-10:F20, ICD-8:295) from age 15 until December 31, 2010, using survival analysis techniques. Immigrants were identified as persons born abroad; developmental level of country of origin was categorized as "developing" or "developed" (2). Age at migration was identified as age at the time of first permanent residence in Denmark.

During the study period, 809 immigrants from developing countries, 248 immigrants from developed countries, and 8,767 Danes developed schizophrenia. After adjusting for age, sex, and calendar year, immigrants from developing countries had a 2.34-fold greater risk for schizophrenia (95% confidence interval [CI]=2.17–2.51); immigrants from developed countries had a 1.90-fold greater risk (95% CI=1.67–2.15).

The incidence rate ratio of schizophrenia, by country of origin as well as by age at the time of immigration to Denmark, compared with Danish-born individuals, is depicted graphically in Figure 1. For example, individuals from developed countries who immigrated to Denmark before their second birthday had a 1.66-fold significantly greater risk of schizophrenia (95% CI=1.30–2.07), and individuals from developing countries who immigrated to Denmark before their second birthday had a 2.16-fold significantly greater risk of schizophrenia (95% CI=1.88–2.48). When including age at migration as a trend in the model, the incidence rate ratio of schizophrenia increased by 1.02 (95% CI=1.00–1.05) for every 1-year increase in the age at migration from developed countries and increased by 1.01 (95% CI=1.00–1.03) for every 1-year increase in the age at migration from developing countries.

Although the majority of immigrants in our sample originated from developing countries, subdividing the developmental status of country of origin yielded no differences in the impact of age at immigration. Thus, the differences observed between the two studies are not due to any differential impact of age at migration in relation to degree of "Westernization" of the country of origin, a factor that Veling et al. (1) suggest may be important. We found no evidence that risk of schizophrenia decreases with age at the time of immigration to Denmark. Our Danish study investigated the potential effect of age at immigration before the 15th birthday,

FIGURE 1. Adjusted Relative Risks Associated With Immigrants' Origin and Age at Immigration to Denmark[a]



[a] The solid line represents immigrants to Denmark from developing countries, and the punctuated line represents immigrants from developed countries. Estimates of relative risks were adjusted for age, sex, and calendar year.

while the Veling et al. Dutch study investigated the potential effect up until approximately age 30. However, because the greatest impact in the Dutch study was observed in individuals migrating early in life, this cannot explain the differences in the observed results.

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Deficiency of the Odds Ratio for Common Outcomes

TO THE EDITOR: The article by Chen et al. (1) in the July issue provides a fascinating account of the interaction by genotype in the context of a smoking cessation trial. Participating smokers were randomly assigned either to placebo (N=132) or to various combinations of active treatments (N=941). The authors then reported the proportion with confirmed 7-day abstinence after 8 weeks, stratified by three common haplotypes (defined by two single-nucleotide polymorphisms on chromosome 15 that have established associations with nicotine and cocaine dependence). Despite clear evidence of statistical interaction between haplotype group and successful smoking cessation, the authors' stated conclusion that "[s]mokers with the high-risk haplotype were three times as likely to respond to pharmacologic cessation treatments as were smokers with the low-risk haplotype" is not correct. As shown in Figure S4 of the online data supplement that accompanies the Chen et al. article, treatment approximately doubled (not tripled) the 8-week abstinence proportion in the high-risk haplotype group, from about 24% to about 50%. In contrast, there was no treatment effect in the low-risk haplotype group.

The explanation for this large discrepancy is that the authors made the common error of interpreting odds ratios from logistic regression models as relative risks. This interpretation is not valid for outcomes that are not rare. It has been repeatedly noted in the biomedical literature that this is a serious deficiency of the odds ratio (2, 3), and many authors have therefore urged that for cohort analyses such as those used in the Chen et al. study, the odds ratio is not a parameter of interest and should be avoided (4). It is simple in these settings to estimate risk ratios or differences (5), and this also facilitates useful calculations such as the number needed to treat (i.e., the inverse risk difference) (6). For example, manipulation of these absolute risks shows that the number needed to treat in order to prevent one relapse among the high-risk haplotype subpopulation is approximately four. This is an impressive finding that is completely obscured in the published analysis.

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Response to Kaufman and Harper Letter

TO THE EDITOR: A great deal of research shows that the *CHRNA5-CHRNA3-CHRNB4* haplotypes are associated with measures of smoking quantity (1–4). However, earlier research presented inconsistent results with regard to the association of these haplotypes with smoking cessation likelihood. Our findings show that these haplotypes can predict cessation success and also that their association with cessation likelihood differs depending on the use of smoking cessation pharmacotherapy in the quit attempt. In essence, we obtained a significant interaction effect between haplotype and treatment condition such that individuals with haplotypes that confer a heightened risk of relapse benefited much more from cessation pharmacotherapy than did individuals without such haplotypes.

In our study, we used both the Cox proportional hazards model to estimate the likelihood of smoking relapse over time and the logistic regression model to estimate the odds of smoking abstinence, and both showed greater benefit from pharmacotherapy in individuals with risk haplotypes than in those without such haplotypes. However, at one point in the article, we discussed the odds ratio generated by the logistic regression as if it reflected relative risk. In their letter, Kaufman and Harper note that the odds ratio and the relative risk ratio diverge for analyses of common events.

We agree with Kaufman and Harper's observation and appreciate their pointing out that the results of our research appear even more striking when portrayed in terms of number needed to treat. In our study, the number needed to treat