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In reply

We thank Dr van Os for his thoughtful comments and careful reading of our work. In addition, his letter provides us with a welcome opportunity to demonstrate that social class confounding cannot account for our result from the Dutch famine study.[1]

First, if there were confounding due to social class of origin, it would most likely have diminished the association between prenatal exposure to famine and the risk of hospitalization for schizophrenia. As Dr van Os rightly indicates, the lower class was underrepresented in the exposed cohorts. Most studies suggest that individuals in the lower class are at an increased risk of hospitalization for schizophrenia; therefore, the effect would be to reduce the observed risk in the exposed cohort and to reduce the relative risk of hospitalization for schizophrenia. The result of the Dutch study[2] *to which Dr van Os refers was atypical. That study included only a small number of patients with schizophrenia (N=34) and was conducted in a university town; the authors noted these limitations and did not infer from their results that individuals in the upper class in Holland were at a higher risk for schizophrenia.*

Second, in the unlikely circumstance that upper social class were associated with schizophrenia, the confounding would have been minimal. To see this, consider an example. Assume that we have 5000 exposed and 100 000 unexposed individuals and that the risk of schizophrenia is the same in the exposed and unexposed groups within a given social class (ie, there is no effect of exposure on risk). Next assume that the risk of schizophrenia is twice as high in the upper class (0.5%) than in the lower class (0.25%). Allow the ratio of upper to lower class births to be 3:2 in the exposed group and 1:1 in the unexposed group, as it actually was in the data of our study.[1] *The risk of schizophrenia in the exposed group can be computed as a weighted average of the risk in the upper and lower class, ie, [(0.5% × 3000)+(0.25% × 2000)]/5000=4/1000, and the risk of schizophrenia in the unexposed group can be computed in the same way to be 3.75/1000. The relative risk is 4/3.75=1.07. This example shows that, while being born into the upper class is assumed to have a strong effect on schizophrenia, even if prenatal famine exposure is assumed to have no effect on schizophrenia, the artifactual relative risk due to social class confounding is barely detectable and cannot account for a relative risk of the magnitude that we observed.*

Third, a subsequent study has provided empirical evidence that social class was not a confounding factor.[3] *This study examined the related outcome of schizophrenia spectrum personality disorder in men aged 18 years in the same exposed and unexposed birth cohorts. Unlike the schizophrenia study, that study included data about the social class of origin of the subjects. The effect was found to be the same among individuals in the upper and lower classes. Finally, we were unable to verify the decrease in ICD-9 affective psychoses in the exposed birth cohort that is noted by Dr van Os. It seems that he has made some errors in the data analysis (eg, by the omission of female cases). Nevertheless, it should be underscored that had this decrease in affective psychoses been real, it would not by any means indicate that the result we have reported for schizophrenia was due to social class confounding.*

In summary, social class confounding does not explain the increased risk of schizophrenia after early prenatal exposure to famine.

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N-Methyl-D-Aspartate Receptor Hypofunction in Schizophrenia Could Arise From Reduced Cortical Connectivity Rather Than Receptor Dysfunction

An article by Olney and Farber[1] outlines an intriguing theory of schizophrenia based on studies of the glutamate *N*-methyl-D-aspartate (NMDA) receptor. Their model relies on the observation that NMDA antagonists such as phencyclidine hydrochloride can induce psychoticlike symptoms in human subjects and has demonstrated neurotoxic reactions in animals. The latter could provide an explanation for the downhill course of many patients with schizophrenia. Their model also notes that dopamine is known to inhibit glutamate release, an observation that suggests a possible therapeutic action, namely, disinhibition of glutamate release, of dopamine-blocking antipsychotic drugs. The authors postulate that NMDA receptor dysfunction underlies the pathology of schizophrenia.

Other recent studies suggest that NMDA receptor hypofunction in schizophrenia may derive not from re-