

## Invited Commentary: Risk Factors for Autism—Perinatal Factors, Parental Psychiatric History, and Socioeconomic Status

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Received for publication October 8, 2004; accepted for publication January 20, 2005.

The paper by Larsson et al. (1) in this issue of the *Journal* adds to an accumulating body of evidence from relatively large, population-based observational studies (2, 3) suggesting that pregnancy complications and adverse birth outcomes are associated with subsequent risk of autism. As the struggle to understand the etiology of this devastating neurodevelopmental disorder continues, this growing literature offers promising opportunities for future research.

In their discussion, Larsson et al. (1) touch on the challenge of determining whether an observed association between obstetric suboptimality and autism risk reflects an independent causal contribution or whether it arises merely as a by-product of genetic susceptibility. Should the former be true, it implies that adverse pre- and perinatal events are autism risk factors and may be amenable to prevention and intervention efforts. Prior to Larsson et al., few studies collected data informing this distinction between causal effects of obstetric suboptimality and genetic susceptibility (4, 5). As more large epidemiologic studies of autism risk factors are developed, careful consideration should be given to addressing this critical question.

To foster this work, we present some simple causal diagrams (i.e., directed acyclic graphs (6)) to formalize and contrast competing causal models relating genetic susceptibility, obstetric suboptimality (the general term we will use to refer to adverse pre- or perinatal events), and autism. Figure 1 shows four basic causal diagrams; the arrows represent direct causal effects. These diagrams are obvious simplifications of a complex world. Such simplifications can be useful to the extent that they do not omit important common causes of exposure and outcome, as well as important common causes of any mediating variable(s) and outcome.

Model 1 depicts etiologic heterogeneity, with both genetic susceptibility and obstetric suboptimality having independent direct causal effects on the risk of autism. Although

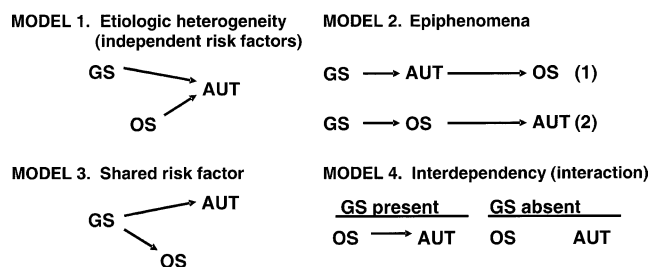
model 1 involves causal effects between both genetic susceptibility and obstetric suboptimality with autism, there is no causal relation between genetic susceptibility and suboptimality.

Model 2 shows two epiphenomenon, or mediation, models in which genetic susceptibility is causally associated with an intermediate outcome that, in turn, is causally associated with a distal outcome. If genetic susceptibility led to the early pathologic changes underlying autism and these then reduced pregnancy optimality, it would be consistent with the first of the two epiphenomenon models. The second epiphenomenon model would apply if, for example, genetic susceptibility triggered a prenatal event that then caused autism. When either of these epiphenomenon models holds, crude associations will exist between all three variables.

Model 3 illustrates shared risk factors, or confounding of the relation between obstetric suboptimality and autism due to genetic susceptibility. Under this model, genetic susceptibility is causally associated with both obstetric suboptimality and autism, but there is no causal association between obstetric suboptimality and autism.

Model 4 depicts interdependency of causes or effect-measure modification. Under this model, there is an association between obstetric suboptimality and autism only in the presence of genetic susceptibility.

Table 1 summarizes key statistical associations expected under each of the alternative causal models presented in figure 1, assuming no selection bias, no measurement error, and no unmeasured confounding. If the true causal model were one of etiologic heterogeneity, then genetic susceptibility would be associated with autism even after adjusting for obstetric suboptimality. Similarly, obstetric suboptimality remains associated with autism even after adjustment for genetic susceptibility. Genetic susceptibility would not appear to be associated with obstetric suboptimality in crude



**FIGURE 1.** Simple causal models relating genetic susceptibility (GS), obstetric suboptimality (OS), and autism (AUT).

analyses, but if analyses are conducted by using just cases (essentially stratification on the outcome, as discussed by Hernán et al. (7)), genetic susceptibility may be inadvertently associated with obstetric suboptimality.

In the epiphenomena model, under certain assumptions (8), adjustment for the intermediate variable, either statis-

tically or through stratification, blocks the association between genetic susceptibility and the more distal outcome. If the second epiphenomenon model were true, then adjustment for suboptimality would remove the association between genetic susceptibility and autism. Under the first epiphenomenon model, if analyses were restricted to cases, there would be no association between genetic susceptibility and obstetric suboptimality.

Under the shared risk factor model, genetic susceptibility is associated with autism regardless of adjustment for obstetric suboptimality. Genetic susceptibility also is a confounder, creating an apparent association between suboptimality and autism in unadjusted analyses. Adjustment for genetic susceptibility would correct for this confounding, and, after adjustment, suboptimality would no longer be associated with autism.

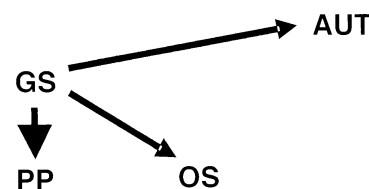
Because, under the interdependency model, suboptimality is associated with autism for only those with genetic susceptibility, an estimate of the association between obstetric suboptimality and autism in the full sample is essentially an average of two separate causal effects, weighted by the proportion of the sample with the genetic susceptibility. This summary of the data would often be misleading. In addition, under the interdependency model, the estimate of the crude association between genetic susceptibility and suboptimality is not likely to be particularly useful in identifying the underlying causal model.

In the paper by Larsson et al. (1), associations between various pre- and perinatal events were found to persist even after adjustment for parental psychiatric history. The authors are careful not to equate parental psychiatric history with genetic susceptibility to autism, but the discussion suggests, and evidence supports (9, 10), that mental illness in parents is connected to autism in children via genetic links, which implies a modification to the causal diagrams in figure 1. Specifically, one would redraw each diagram by adding a parental psychopathology variable that is associated with genetic susceptibility. The implication for the etiologic heterogeneity model is slight. However, the implication for the shared risk factor model is noteworthy (refer to figure 2). Parental psychopathology can be viewed as an imperfect measure of genetic susceptibility. Assuming that this mis-measurement is nondifferential and random, unless the relation between underlying genetic susceptibility and reported parental psychopathology is quite strong, we would expect associations between obstetric suboptimality and

**TABLE 1.** Statistical associations expected to be observed under different statistical models

Model	Associations
Etiologic heterogeneity	GS* associated with AUT* regardless of adjustment for OS* OS associated with AUT regardless of adjustment for GS GS and OS unassociated
Epiphenomena	Model 1 GS associated with AUT regardless of adjustment for OS OS associated with AUT regardless of adjustment for GS GS and OS associated
	Model 2 GS associated with AUT, but GS not associated with AUT after adjustment for OS OS associated with AUT regardless of adjustment for GS GS and OS associated
	Shared risk factor GS associated with AUT regardless of adjustment for OS OS associated with AUT, but OS not associated with AUT after adjustment for GS GS and OS associated
	Gene-environment interaction OS associated with AUT for only those with GS GS may or may not be associated with OS

\* GS, genetic susceptibility; AUT, autism; OS, obstetric suboptimality.



**FIGURE 2.** Shared risk factor model with parental psychopathology (PP) added as an imperfect measure of genetic susceptibility (GS). AUT, autism; OS, obstetric suboptimality.

autism to persist after adjustment for parental psychopathology because of residual confounding by genetic susceptibility. Therefore, the persistent observed association between suboptimality and autism after adjustment for parental psychopathology should not be interpreted as irrefutable evidence in favor of the etiologic heterogeneity model.

Although Larsson et al.'s analysis (1), in the end, does not prove that prenatal and perinatal events are independent risk factors for autism, it does add to the growing body of evidence suggesting that these events do occur more commonly among children with autism and that they should be studied further. To determine whether these events are independent risk factors, measures of genetic susceptibility should be included in studies of suboptimality and autism. The challenge, of course, is to find adequate measures. In the absence of known genes for autism risk, more detailed family histories (i.e., those assessing not only psychopathology but also behavioral features typical of autism in a variety of family members) may provide the best option. Inclusion of more extensive family history measures, followed by analyses that are informed by a conceptual framework, may offer the best hope for addressing this important autism research question.

## REFERENCES

1. Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol* 2005;161:916–25.
2. Hultman CM, Sparén P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology* 2002;13:417–23.
3. Glasson EJ, Bower C, Petterson B, et al. Perinatal factors and the development of autism. *Arch Gen Psychiatry* 2004;61:618–27.
4. Bolton PF, Murphy M, MacDonald H, et al. Obstetric complications in autism: consequences or causes of the condition? *J Am Acad Child Adolesc Psychiatry* 1997;36:272–81.
5. Zwaigenbaum L, Szatmari P, Jones MB, et al. Pregnancy and birth complications in autism and liability to the broader autism phenotype. *J Am Acad Child Adolesc Psychiatry* 2002;41:572–9.
6. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10:37–48.
7. Hernán MA, Hernández-Díaz S, Werler MM, et al. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol* 2002;155:176–84.
8. Cole SR, Hernán MA. Fallibility in estimating direct effects. *Int J Epidemiology* 2002;31:163–5.
9. Micali N, Chakrabarti S, Fombonne E. The broad autism phenotype. *Autism* 2004;8:21–37.
10. Bolton A, Palferman S, Heavey L, et al. Autism: the phenotype in relatives. *J Autism Dev Disord* 1998;28:369–92.