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Using Epidemiologic Methods to Test Hypotheses Regarding Causal Influences on Child and Adolescent Mental Disorders

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Abstract

Epidemiology uses strong sampling methods and study designs to test refutable hypotheses regarding the causes of important health, mental health, and social outcomes. Epidemiologic methods are increasingly being used to move developmental psychopathology from studies that catalogue correlates of child and adolescent mental health to designs that can test rival hypotheses regarding causal genetic and environmental influences. A two-part strategy is proposed for the next phase of epidemiologic research. First, to facilitate the most informed tests of causal hypotheses, it is necessary to develop and test models of the structure of hypothesized genetic and environmental influences on mental health phenotypes. This will involve testing the related hypotheses that there are both (a) dimensions of psychopathology that are distinct in the sense of having at least some unique genetic and/or environmental influences, and (b) higher-order domains of correlated dimensions that are all apparently influenced in part by the same genetic and/or environmental factors. The resulting causal taxonomy would organize tests of causal hypotheses regarding both factors that may broadly increase risk for multiple dimensions of psychopathology and factors that may specifically increase risk for each individual dimension. Second, it is necessary to make greater use of a number of powerful epidemiologic designs that allow rigorous tests of rival hypotheses regarding genetic and environmental causes.

Keywords

Epidemiology; developmental psychopathology; taxonomy; causal models

Epidemiology is a set of methods developed to support inferences regarding the causes of health problems and other socially significant outcomes (Susser, Schwartz, Morabia, & Bromet, 2006). Epidemiologic studies often use population-based samples to avoid biases that may confound causal relations and often use longitudinal designs to measure putative causal risk factors prior to the onset of the disorder to strengthen causal inferences (Costello & Angold, 2006). Such methods helped define the modern scientific fields of child and adolescent psychiatry and clinical child and adolescent psychology. In particular, the landmark Isle of Wight Study (Rutter, 1989; Rutter, Tizard, & Whitmore, 1970) helped turn a generation of scholars from speculation to science. It did so by showing how strong methods and clear logic could answer important questions about mental health.

The subfield of developmental epidemiology uses both epidemiologic and longitudinal methods to study the development and origins of child and adolescent psychopathology and disabilities (Costello & Angold, 2006). Developmental epidemiology is still far from realizing its full potential, but an excellent start has been made. In recent years, important advances been made in defining the prevalence and distribution of mental disorders (Angold & Costello, 2006; Roberts, Roberts, & Xing, 2007) and describing patterns of comorbidity among mental disorders (Angold, Costello, & Erkanli, 1999). In addition, sound research designs have allayed concerns that alleged large secular increases in the prevalence of child and adolescent mental disorders (Costello, Erkanli, & Angold, 2006; Tick, van der Ende, & Verhulst, 2007) and that childhood vaccinations cause autism (Fombonne, 2008). Other important studies have identified factors in childhood and adolescence that predict whether stressful life events will lead to emotional disorders (Bourma, Ormel, Verhulst, & Oldehinkel, 2008; Copeland, Keeler, Angold, & Costello, 2007; Koenen, Moffitt, Poulton, Martin, Caspi, 2007) and have suggested that both processes of selection and causation may be involved in the association between socioeconomic status and mental disorders (Costello, Compton, Keeler, & Angold, 2003; Miech, Caspi, Moffitt, Wright, & Silva, 1999).

Developmental epidemiology is increasingly focusing on hypotheses regarding the genes and environments that jointly influence risk for child and adolescent mental disorders (Jaffee & Price, 2007; Moffitt, Caspi, & Rutter, 2005; Rutter, 2002). The pressing need is to continue to move from studies that merely catalogue *correlates* of mental disorders to studies that address causation (Rutter, 2007). A full understanding of the causes of child and adolescent mental disorders is an unattainable goal, of course. Science never proves causal hypotheses; hypotheses are always tentative. It can, however, subject rival causal hypotheses to extreme risk of refutation in well-designed studies to narrow down the number of plausible alternative hypotheses that are consistent with the data. As Karl Popper (1963) said, scientists learn from their mistakes (refuted hypotheses). Thus, in this paper, the term “causal influence” should be read as shorthand for “currently unrefuted causal hypothesis.” This position is not unique to developmental psychopathology. One could not, for example, conclusively *prove* that smoking cigarettes plays a causal role in the biological processes that give rise to lung cancer. Nonetheless, that causal hypothesis has withstood countless attempts at refutation and led to changes in policies that were followed by reductions in smoking and concomitant reductions in the incidence of lung cancer. Although a full understanding of causation is beyond our reach, progress based on stringent tests of refutable causal hypotheses is not.

In this paper, we describe two related strategies for the next phase of epidemiologic studies designed to test hypotheses regarding the causes of developing mental disorders. First, although not widely appreciated, some kinds of refinements in the operational definitions of child and adolescent mental health phenotypes are needed to facilitate studies of etiology. Second, it will be important to use quasi-experimental designs to test causal hypotheses regarding specific genetic and environmental influences on those phenotypes. We first describe two related empirical tactics for meeting the first goal of improving definitions of mental health phenotypes for the specific purpose of etiologic studies. We then describe a powerful but underutilized epidemiologic strategy to exemplify ways of meeting the second goal of stringently testing hypotheses regarding causal influences.

DEFINING MENTAL HEALTH PHENOTYPES FOR STUDIES OF ETIOLOGY

Although researchers often use definitions of mental health phenotypes that appear in ICD-10 and DSM-IV in studies of etiology, the promise of recent advances in methods for identifying causal risk factors for child and adolescent mental disorders may not be realized if we do not refine our definitions of mental health phenotypes specifically for the purpose of etiologic

research. This will require both studies of the correlational and the causal structure underlying child and adolescent psychopathology.

Correlational Structure of Psychopathology

Over many studies, and many diagnostic nomenclatures, a large vocabulary has emerged for referring to the specific symptomatic behaviors, emotions, and cognitions associated with personal distress and functional impairment. Because studies of risk factors are most informative when based on unbiased population-based samples, the most informative studies of the correlational structure of symptoms usually will be conducted using population-based samples.¹ That is, it is necessary to (a) identify correlated sets of symptoms that reflect underlying latent dimensions of psychopathology, (b) identify the symptoms that best define each of these dimensions, (c) identify the fewest dimensions that validly and exhaustively describe impairing mental health problems, and (d) understand the pattern of correlations among these dimensions of psychopathology to determine if a hierarchical structure exists that is important to the design of etiologic studies.

Hundreds of studies of the correlational structure of symptoms of child and adolescent mental disorders have been conducted (summarized by Lahey, Applegate, Waldman, Loft, Hankin, & Rick, 2004). Unfortunately, these do not provide all of the information needed to define the correlational structure of child and adolescent psychopathology for two reasons. First, few item pools included even the majority of the large vocabulary of symptoms used in DSM-IV, ICD-10, and relevant rating scales. Second, nearly all previous studies used unrepresentative samples with unknown biases.

In addition, a related unanswered question is whether the correlational structure of symptoms identified in empirical studies is consistent with the dimensional structures underlying ICD-10 and DSM-IV. Although these are categorical diagnostic nomenclatures, with few exceptions diagnoses of common mental disorders are made by first summing interchangeable symptoms and then applying cut-scores and other criteria (e.g., age of onset) to dichotomize the dimensional score into “normality” versus “diagnosis” (Boyle, Offord, Racine, Szatmari, Fleming, & Sanford, 1996). Therefore, one can evaluate the dimensional structures underlying ICD-10 and DSM-IV by testing both the assignment of symptoms to dimensions and the number of separate dimensions identified in each nomenclature. Although it is more complicated, one also can test the validity of diagnostic cut-scores to determine if they appear to identify the point on each continuum at which the risk of not treating exceeds the risks inherent in treating (Lahey et al., 2004).

Factor analytic studies—To begin to understand the correlational structure of DSM-IV symptoms of common child and adolescent mental disorders, Lahey et al. (2004) recruited a representative sample of 1,358 4–17 year olds. The item pool included items that operationalized DSM-IV and ICD-10 symptoms of anxiety disorders, depression, and the attention-deficit and disruptive behavior disorders. Some 60 items on attention problems, social problems, relational aggression, reactive and proactive aggression, and property crimes also were included that are similar to items in other nomenclatures and measures but that are not symptoms in DSM-IV or ICD-10. Because this large pool of items had never been studied together, exploratory factor analyses (EFAs) were conducted. For both parent and youth informants, the EFAs yielded factors similar to the dimensions underlying DSM-IV. The exception was that, consistent with previous studies (e.g., Ferdinand, van Lang, Ormel, &

¹It may be necessary to conduct studies of the dimensional structure of symptoms with low base rates by oversampling at-risk or clinic-referred youth.

Verhulst, 2006), correlations among anxiety symptoms were so high that only one or two broad dimensions of anxiety could be extracted using EFA.

In a second study of a population-based sample of 4,049 6–17 year old twins (Lahey et al., 2008), confirmatory factor analyses (CFAs) were conducted of both parent- and youth-rated DSM-IV and ICD-10 symptoms from the same instrument. The dimensional structure underlying DSM-IV was tested against the simpler model suggested by the EFAs and the model underlying ICD-10. The fit of the DSM-IV model was significantly better than for the simpler model based on the EFA (Lahey et al., 2004) that collapsed anxiety disorder dimensions. Again, however, many symptom dimensions were very highly correlated with other dimensions. Indeed, consistent with previous findings based on different methods (reviewed by Angold, Costello, and Erkanli 1999), the symptom dimensions corresponding to DSM-IV generalized anxiety disorder (GAD) and major depression (MDD) were so highly correlated that they were not distinguishable in CFA. In addition, the fit of the two-dimensional DSM-IV model of ADHD symptoms and the two-dimensional model distinguishing ODD and CD symptoms fit better than the three-dimensional ICD-10 model of hyperkinetic disorder and the one-dimensional model of ODD and CD implied by ICD-10 (Lahey et al., 2008).²

Hierarchical correlational structure of the dimensions of psychopathology—In both of these factor analytic studies (Lahey et al., 2004, 2008), the pattern of correlations among factors suggested a possible hierarchical factor structure. Figure 1 shows all correlations greater than $r = .40$ among the latent dimensions of parent-rated DSM-IV symptoms in the best fitting model in the TTS (Lahey et al., 2008). Very similar correlations were found among dimensions of youth-rated symptoms (Lahey et al., 2008). The hierarchical structure among the dimensions of parent-rated symptoms was formally tested using higher-order CFA. Consistent with many previous findings based on different item pools (e.g., Achenbach, 1966), the results suggested that symptom dimensions were hierarchically organized within second-order “externalizing” and “internalizing” domains (Lahey et al., 2008).

A new finding of this study, however, was that the dimension defined by symptoms of MDD and GAD loaded *equally* on both the “externalizing” and the “internalizing” dimensions in the best-fitting model (Lahey et al., 2008). This is important because it indicates the need to rethink the nature of these higher-order factors. Even though the symptoms of MDD and GAD clearly do not reflect what is meant by “externalizing” (i.e., “acting out”) psychopathology, MDD and GAD symptoms were strongly correlated with dimensions in the “externalizing” domain. Although this finding regarding the place of depression in the higher-order factor structure of psychopathology is revealing, it is not unprecedented. Indeed, many studies have shown that depression is correlated substantially with ADHD, ODD, and CD, both concurrently and longitudinally (Angold, Costello, & Erkanli, 1999; Capaldi, 1991; Fergusson, Lynskey, & Horwood, 1996).

Two additional findings from the Lahey et al. (2008) study also are potentially relevant to the goal of defining mental health phenotypes for etiologic research. First, the two second-order factors explained a considerable amount of the variance in each of the first-order dimensions of psychopathology (Lahey et al., 2008). For parent-rated symptoms, the second-order “internalizing” factor explained 44%–76% of the variance in each of the four first-order latent anxiety-fear dimensions. Similarly, the second-order “externalizing” dimension explained 68%–82% of the variance in each of the four first-order latent ADHD and disruptive behavior

²This does not necessarily mean that ICD-10 criteria for categorical diagnoses are less valid than those in DSM-IV, as categorical diagnoses are based on more than just assumptions about the underlying symptom dimensions. For example, there is evidence that the DSM-IV criteria for ODD under-identify impaired oppositional children and adolescents relative to the ICD-10 approach of counting both ODD and CD in making diagnoses of ODD (Rowe, Maughan, Costello, & Angold, 2005).

disorder symptom dimensions. A total of 76% of the variance in the latent MDD/GAD dimension was explained by the two second-order dimensions. Second, the two second-order “internalizing” and “externalizing” factors also were substantially correlated ($r = .54$). Therefore, these findings (Lahey et al., 2008) are consistent with previous studies of different item pools (e.g., Achenbach, 1966; Hartman et al., 2001) in indicating that child and adolescent mental disorders are far less differentiated than their categorical definitions in DSM-IV and ICD-10 imply.

Hypothesized Causal Structure of Psychopathology

Studies of the correlational structure of psychopathology provide a necessary but insufficient foundation for the definition of mental health phenotypes. For the purpose of etiologic research, however, it is essential to go beyond correlational studies and operationalize phenotypes in ways that optimize tests of hypotheses regarding the interplay of genetic and environmental causal influences. That is, the causal taxonomy of psychopathology needed for studies of etiology may differ in some ways from the taxonomy used for clinical purposes, even though the two clearly must be related.

To facilitate etiologic studies, a hypothesized causal taxonomy of mental health phenotypes must have two characteristics. First, it is necessary that each individual dimension of psychopathology be hypothesized to be influenced by at least some *unique* hypothesized genetic and/or environmental influences (Kendler, 2006). If studies consistently support the hypothesis that two or more correlated dimensions are influenced only by the same common genetic and environmental influences, there would be little justification for distinguishing them in studies of etiology. Although there could be valid reasons to distinguish dimensions with entirely shared causal influences for other purposes (e.g., differential response to treatments), it would be more efficient to consider them as constituting a single phenotypic dimension in etiologic studies. Second, it is essential to determine the extent to which there are higher-order domains in which multiple dimensions of psychopathology are all apparently influenced in part by the same genetic and/or environmental factors. This is important because, if there is substantial sharing of the same genetic and environmental influences on multiple dimensions of psychopathology, then we must understand the nature of that sharing and modify our research tactics to find the etiologic influences that generally increase risk for multiple dimensions of psychopathology.

Based on what is currently known about the correlational structure of psychopathology and the sharing of causal influences, it is possible to propose the working model of the causal structure of child and adolescent psychopathology illustrated in Figure 2. It is reasonable to hypothesize that at least two sets of ‘general risk’ genetic and/or environmental factors influence risk for the multiple dimensions of psychopathology within the broad “externalizing” and “internalizing” domains. In addition, disorder-specific etiologic factors differentiate each dimension of psychopathology to some extent (Dick, 2007; Kendler, Prescott, Myers, & Neale, 2003; Krueger, Hicks, Patrick, Carlson, Iacono, & McGue, 2002; Lahey & Waldman, 2003). Given the substantial correlation between latent “externalizing” and “internalizing” domains (Lahey et al., 2008), it also seems very likely that some general risk genetic and/or environmental influences influence both broad domains. That is, in contrast to current thinking about etiology, there are likely to be causal influences that increase risk for psychopathology in general.

Three strategies hold particular promise for elaborating and testing such hypothesized hierarchical causal taxonomies of psychopathology to facilitate etiologic research:

1. *Multivariate behavior genetic analysis.* It will be important to use genetically-informative samples, such as representative samples of twins, to conduct multivariate

behavior genetic analyses of the dimensions of psychopathology (Eaves, Rutter, Silberg, Shillady, Maes & Pickles, 2000). This is because differences between monozygotic and dizygotic twins in cross-twin, cross-trait correlations among the various dimensions of psychopathology allow estimates of the extent to which each dimension is influenced by the same or different genetic and/or environmental factors.

2. *Genetic and environmental factor analysis.* It will be important to examine the factor structure of DSM-IV symptoms based on the *genetic* and *environmental* correlations among these symptoms in genetically informative samples (Yamagata et al., 2006). In the factor analytic approaches described above (e.g., Lahey et al., 2004, 2008), the structure of child and adolescent disorders was based on analyses of the *phenotypic* correlations among symptoms. In order to develop a taxonomy that facilitates etiologic research, it is important to understand that such phenotypic correlations among symptoms exist because those symptoms share the same (or correlated) genetic or environmental influences (or correlated measurement error). Therefore, the symptoms that define a dimension at the phenotypic level could covary due to either common genetic or common environmental influences or both. To provide a foundation for etiologic studies, it is necessary to tease apart these hypothesized causal influences and separately identify dimensions of symptoms that share the same underlying genetic (or environmental) influences.

Fortunately, matrices of genetic and environmental covariances among symptoms can be estimated in genetically informative samples and subjected to factor analysis to examine their underlying hypothesized causal structure. If dimensions defined on the basis of genetic (or environmental) correlations differ from dimensions based on phenotypic correlations, the factor analyses of genetic (or environmental) correlations would identify symptom dimensions that appear to reflect relatively homogeneous sets of genetic or environmental influences. In principle, it should be easier to discover the genes related to phenotypes defined on the basis of shared genetic influences than dimensions based on simple phenotypic correlations (since those correlations could reflect primarily shared environmental influences).

3. *Trajectory analysis.* There is evidence of marked differences in the correlates of delinquent behavior depending on whether youth follow a childhood-onset or adolescent-onset developmental trajectory (Lahey et al., 2006; Moffitt, Caspi, Dickson, Silva, & Stanton, 1996; Raine, Moffitt, Caspi, Loeber, Stouthamer-Loeber, & Lynam, 2005). Moffitt (1993) hypothesized that the genetic and environmental influences on different trajectories of delinquency are distinct. This could mean that studies of the genetic and environmental influences on delinquency would be misleading if differences in developmental trajectories are not considered (Silberg, Rutter, Tracy, Maes, & Eaves, 2007). Although less research has been done on developmental trajectories of other mental health problems, there also is evidence of differences in developmental trajectories of depressive symptoms (Dekker, Ferdinand, van Lang, Bongers, van der Ende, & Verhulst, 2007) that should be investigated for the same reason.

Are Sex-Specific Causal Models Necessary?

Before causal taxonomies of mental disorders can be formalized and tested, one must decide if different causal hypotheses are necessary for youth of different ages, sexes, or race-ethnicities. Although each of these demographic factors is important, the greatest attention has been paid to potential sex differences in causal influences on mental disorders (Moffitt, Caspi, Rutter, & Silva, 2001). If sex-specific causal models are needed, that would dictate separate analyses of data from girls and boys. To date, most research has focused on sex differences in delinquent behavior. Longitudinal studies of representative samples found large sex differences

in the prevalence of childhood-onset delinquency, but few differences in its correlates (Lahey et al., 2006; Moffitt et al., 2001). In addition, no differences have been detected in genetic influences on delinquency in females and males, even though there is evidence that females could have a higher threshold for exhibiting delinquency given the same causal influences (Van Hulle, Rodgers, D'Onofrio, Waldman, & Lahey, 2007). This suggests that a single causal model can account for delinquency in both sexes, but it must explain both the sex difference in prevalence and the apparent sex difference in susceptibility to causal influences. Similarly, testable causal models of all mental disorders for which there are sex differences in prevalence (e.g., depression and substance abuse) must account for these differences before they can be considered to be comprehensive.

TESTING HYPOTHESES REGARDING CAUSAL RISK FACTORS

Clearly, an important goal for the next decades of research will be to test rival hypotheses regarding the interplay of measured genes and environments in the origins of child and adolescent mental disorders (Rutter, 2003, 2006). Because much has been written about gene finding in general (Rao, 2008; Vink & Boomsma, 2002), we focus in this paper on the equally important task of testing refutable causal hypotheses regarding specific environmental variables that may influence psychopathology through both main effects and gene-environment interactions (Rutter, 2007). It is important to note, however, that the major strategies for gene finding, such as genome-wide association studies (Hirschhorn, & Daly, 2005), require very large and representative samples (Rao, 2008), necessitating epidemiologic methods. Large sample sizes are needed because mental health phenotypes are almost certainly genetically complex, with many genes accounting for small amounts of variance in the phenotype. Large samples are particularly necessary to test gene-environment and gene-gene interactions among many polymorphisms. Representative samples are needed for such studies because even subtle variations in sample composition can obscure genetic associations (Rao, 2008). Strategies for pooling DNA across multiple population-based samples may be important in the future, but great care must be taken to avoid the introduction of confounding population stratification (Sham, Bader, Craig, O'Donovan, & Owen, 2002).

The testing of refutable causal hypotheses regarding measured environments will often require prospective longitudinal studies in which reverse causation is not possible—the candidate environment cannot be influenced by the outcome (Kraemer, Kazdin, Offord, Kessler, Jensen, & Kupfer, 1997; Susser et al., 2006). In addition, however, tests of causal hypotheses must directly confront the possibility that genetic and environmental selection factors account for non-random exposure to risk environments and thereby confound associations between environments and outcomes (Jaffee & Price, 2007). A number of research strategies are available for controlling such confounds in tests of hypotheses that address causation (Rutter, 2003, 2007). One class of strategies involves the use of natural experiments, such as adoption and twin births, to test hypotheses regarding the causal effects of measured candidate environments while controlling genetic confounds (D'Onofrio et al., 2003; Rutter, 2007). Only studies involving random assignment can rule out all alternative explanations for hypothesized causal effects, and even they are fallible. Nonetheless, well-designed quasi-experimental analyses can *greatly* reduce the number of plausible alternative explanations for what appear to be causal effects (Shadish, Cook, & Campbell, 2002). Moreover, when different quasi-experimental methods with different threats to their validity reach the same conclusions about a candidate environmental influence, the results may justify randomized controlled prevention trials (Dodge, 2001).

Many quasi-experimental strategies for studying putative causative environmental factors using natural experiments have been described (Rutter, 2007). Therefore, we highlight one particularly useful strategy that has received less attention than it deserves. Most natural

experiments are based on relatively rare events, such as the birth of twins. In contrast, sibling-comparison analyses depend only on the assessment of multiple children born to the same parents. These analyses provide simple but highly informative tests of causal environmental hypotheses, but only for certain kinds of measured environments. Sibling-comparison analyses are appropriate, however, only when exposure to the candidate environment varies among siblings. Variables such as the mother's immigrant status cannot be used because there is no variation among siblings on such variables. Fortunately, other quasi-experimental methods are available for testing causal hypotheses for candidate environments that cannot vary among siblings (D'Onofrio et al., 2003; Rutter, 2007).

Sibling-comparison analyses can often support strong causal inferences because they are based solely on comparisons among children born to the same parents within a nuclear family. That is, tests of causal effects of the candidate environment using sibling comparisons are not based at all on comparisons of children born to different families. Therefore, comparisons of siblings *within* families completely rule out as alternative explanations all environmental selection factors that differ *between* families and are shared by siblings within a nuclear family. In addition, for candidate environments that are characteristics of the parents (e.g., maternal alcohol consumption during pregnancy), sibling-comparison analyses can rule out all three types of gene-environment correlation as alternative explanations for findings (rGE; Plomin, DeFries, & Loehlin, 1977). *Passive* rGE occurs when *different parents* provide both different genes and different family environmental influences that are correlated with those genes. Because sibling comparison analyses compare offspring of the *same parents*, and because the process of meiosis randomly distributes alleles of polymorphic genes across siblings, passive rGE cannot systematically confound within-family tests of the candidate environment (Rutter, 2007). For some candidate environments, *active* and *evocative* rGE also can be ruled out using sibling-comparison analyses. Active and evocative rGE occur when individuals select or elicit features of their environments that both influence the disorder and are correlated with their genotypes. This confounds any effects of the child's genotype with the hypothesized effects of the candidate environment. Sibling comparisons can rule out active and evocative rGE, but only when exposure to the candidate environmental influence precedes the phenotype in time, making active and evocative effects of the child's phenotype on the candidate environment impossible. For example, because each offspring's heritable phenotype cannot select or evoke differential exposure to the age at which his or her mother conceived and gave birth (Harden et al., 2007), environments associated with variations in maternal age would be free of confounding due to active and evocative rGE.

Examples of candidate environments that precede the measurement of child mental health phenotypes and for which sibling-comparison analyses rule out active and evocative gene-environment correlation include maternal age at each child's birth and maternal substance use, stress, or nutrition during pregnancy. Sibling-comparison analyses also could be used with other candidate environments, but the analyses would require additional assumptions and greater uncertainty. For example, one could use them to test causal hypotheses regarding parenting practices during infancy, but one would need to assume that controlling for measured characteristics (e.g., infant temperament) would effectively rule out all active and evocative rGE created by genetically influenced aspects of infant behavior.

Sibling-comparison analyses with controls for multiple measured covariates have been used in large population-based samples to support (i.e., fail to refute) the hypothesis that maternal consumption of alcohol during pregnancy causally influences risk for conduct problems in her offspring through environmental processes (D'Onofrio, Van Hulle, Waldman, Rodgers, Rathouz, & Lahey, 2007). Such results do not necessarily mean that alcohol is the active environmental causal agent, of course. It is possible that some other *unmeasured* environmental variable closely associated with gestational alcohol consumption is the actual causal variable.

Fortunately, the only such alternative explanations that sibling-comparison analyses do not rule out are the effects of other environmental variables that were not measured and controlled and which (1) vary among siblings within families, (2) are associated with the phenotype, and (3) are highly correlated with the candidate environment within nuclear families. Because few environmental variables meet all of these requirements in most cases, sibling-comparison analyses considerably narrow the field of possible environmental causes. This will make it far easier to eventually formulate specific causal environmental hypotheses that can withstand repeated stringent attempts at refutation and, therefore, justify randomized control trials of manipulations of those variables to prevent adverse outcomes.

Sibling-comparison analyses are just one of many quasi-experimental strategies for testing causal hypotheses regarding “main effects” of candidate environmental variables. Using quasi-experimental methods in large and representative samples will do much to refine causal hypotheses regarding environmental influences on mental disorders in children and adolescents. It is very likely, however, that some youth are more vulnerable to environmental influences than other youth. One source of such differences in vulnerability is undoubtedly genetic variation (Rutter, 2002; Caspi & Moffitt, 2006; Reiss & Leve, 2006). Many recent papers have described viable strategies for studying the complex interplay among genetic and environmental factors (Eaves, Silberg, & Erkanli, 2003; Jaffee & Price, 2007; Johnson, 2007; Moffitt, Caspi, & Rutter, 2005; Rathouz, Van Hulle, Rodgers, Waldman, & Lahey, 2008). These strategies are of the utmost importance and should be incorporated in future studies addressing causal hypotheses within developmental epidemiology. This should include studies in which genetic influences are latent, as in twin studies, as well as studies incorporating measured genes.

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Figure 1.

Correlations among the latent dimensions of parent-rated DSM-IV symptoms in the best-fitting model defining the second-order structure of "internalizing" and "externalizing" dimensions. Only correlations > .40 among dimensions are shown. Based on Figure 5, Lahey et al. (2008), page 196.

Figure 2.

A testable working model of the hierarchical causal structure of child and adolescent psychopathology. Shared environmental influences are omitted to simplify illustration, but could be included in the model if needed.