

Critical Need for Family-Based, Quasi-Experimental Designs in Integrating Genetic and Social Science Research

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Researchers have identified environmental risks that predict subsequent psychological and medical problems. Based on these correlational findings, researchers have developed and tested complex developmental models and have examined biological moderating factors (e.g., gene-environment interactions).

In this context, we stress the critical need for researchers to use family-based, quasi-experimental designs when trying to integrate genetic and social science research involving environmental variables because these designs rigorously examine causal inferences by testing competing hypotheses.

We argue that sibling comparison, offspring of twins or siblings, in vitro fertilization designs, and other genetically informed approaches play a unique role in bridging gaps between basic biological and social science research. We use studies on maternal smoking during pregnancy to exemplify these principles. (*Am J Public Health*. 2013;103:S46–S55. doi:10.2105/AJPH.2013.301252)

RECENT RESEARCH HAS

focused on early risks, such as prenatal factors, for later cognitive, behavioral, and health outcomes.^{1–7} This life course framework has been aided by recent advances in developmental theories and analyses of cascade models.⁸ These approaches have been complemented by a growing interest in understanding how biological factors moderate the influence of environmental risks by studies of gene-environment interaction (G×E).^{9,10} Researchers ultimately are trying to understand how genetic and biological influences, environmental risks, and behavior act and interact across development to result in psychological and physical health problems.^{11,12} In this context, the present article stresses the critical advantages of using family-based, quasi-experimental research designs when integrating genetic and social science research because these approaches allow for strong tests of causal inferences regarding hypothesized risks that are critical in developmental models and G×E studies. We use recent quasi-experimental studies on maternal smoking during pregnancy (SDP) as an exemplar.

MATERNAL SMOKING DURING PREGNANCY

SDP is associated with increased likelihood of various offspring problems, including preterm birth and low birth weight,¹³ infant mortality,¹⁴ cognitive

deficits,^{15,16} obesity,¹⁷ and social and behavioral difficulties (e.g., childhood conduct problem, adolescent delinquency, and substance use problems).^{18,19} Several literature reviews have concluded that fetal exposure to maternal SDP causes these problems^{13,18,19} because the statistical associations are well-replicated, robust to the use of statistical controls for measured confounds, and consistent with basic research on SDP conducted in animals.^{20,21} Other researchers have hypothesized mechanisms through which maternal SDP influences offspring outcomes.²² For instance, researchers have postulated that maternal SDP alters the development of brain systems responsible for stress reactivity,²³ reward sensitivity,^{19,24} and decision-making,²⁵ which subsequently influence behavior and substance use problems.

However, all of the analytic models used to study mediating variables, including developmental cascade models, are based on strong causal assumptions.²⁶ In particular, the models assume that there are no other causes of the associations among initial risks, the mediating variables, and the outcome of interest. It is clear, however, that maternal SDP is correlated with numerous environmental risks across multiple domains (e.g., maternal and paternal intellectual abilities, psychiatric problems, substance use problems, socioeconomic status, etc.) that also predict offspring problems.²⁷ In addition, maternal SDP

is influenced by genetic factors,^{28–30} with the genetic risk being correlated with both women's liability for nicotine dependence problems²⁹ and criminality,³⁰ consistent with the finding that genetic factors often influence multiple behavioral traits.^{31,32} The fact that genetic factors influence SDP, therefore, means that genetic confounding factors could account for the association between SDP and offspring health and behavior problems.^{33,34} Given the inability of human research to adequately account for all environmental and genetic selection factors, numerous researchers have cautioned against drawing causal inferences regarding maternal SDP^{18,28,35–37} or, for that matter, all prenatal risks.^{38,39}

Correctly identifying the processes through which genetic and environmental factors interact, therefore, requires that researchers appropriately rule out environmental and genetic confounds of the causal relation. The assumptions concerning causal inferences have profound implications for studies that explore G×E of SDP with measured genotypes,^{40,41} because all models assume that the putative environmental factor reflects purely environmental processes.^{9,42,43} Researchers must rule out genetic confounding of environmental variables when conducting G×E studies, because genetic selection factors caused by gene-environment correlations (rGE; a related but distinct set of mechanisms we describe in the following section)

can confound the study of G×E.^{44,45} Correctly understanding how genetic factors interact with environmental risks, therefore, requires rigorously testing competing causal hypotheses about the environment. Improper conceptualization of environmental risks is a key limitation in current genomic studies of psychiatric problems.⁴⁶

CONFOUNDING IN OBSERVATIONAL STUDIES

Typically, observational studies are composed of 1 person per family. This means that environmental risks can be correlated with—confounded by—all differences among families in genetic factors, environmental influences that make family members similar, and environments that make family members dissimilar. Confounds between genetic variants and environments that are pervasive^{47–49} can arise systematically through 2 basic types of rGE.^{33,50,51}

Passive Gene–Environment Correlations

Correlations between genetic variants and environments can arise passively (i.e., the behavior and characteristics of the offspring do not cause the correlation). This occurs because parents provide both their children's segregating genes and home environments. When an allele (version) of a genetic variant in parents is associated with their child rearing, the same allele in the offspring is passively correlated with their experienced child rearing.

Active and Evocative Gene–Environment Correlations

Genes and environments also become correlated when the genetically influenced behavior and

characteristics of individuals actively select them into, or evoke changes in, their environments.

QUASI-EXPERIMENTAL DESIGNS

Numerous designs can be used to strengthen causal inferences regarding environmental risks by ruling out specific forms of confounding, including confounding because of rGE. Quasi-experiments are based on individuals who are not randomly assigned to conditions but use design features that rule out many plausible alternative explanations for an association.⁵² Family-based, quasi-experimental designs vary in their internal validity (ability to make strong causal inferences) and external validity (generalizability). These designs thus provide rigorous (but not probative) tests of causal

inferences and help identify the mechanisms through which risks are associated with outcomes, which is critical for integrating genetic and social science research that relies on strong causal inferences.

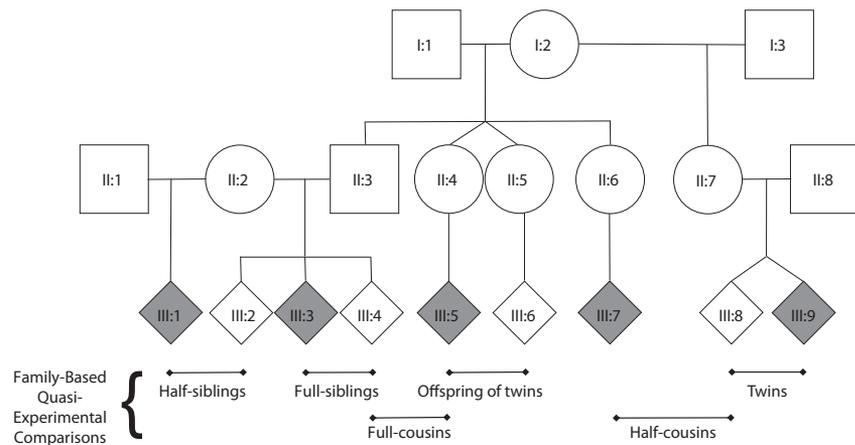
Family-based, quasi-experiments use “natural experiments” based on family relationships. When a study includes multiple family relationships that differ in their environmental exposure and genetic risk, quantitative genetic models can specifically test competing causal hypotheses.^{28,53–55} Although there are numerous family-based, quasi-experimental designs,^{34,56,57} we focus on the subset used to study SDP (e.g., we do not review adoption studies⁵⁸). Figure 1 presents a family pedigree to illustrate several quasi-experimental designs.

We briefly describe the various designs in the following, but Table 1

presents the major advantages and limitations or assumptions of each design, including the traditional comparison of unrelated individuals. In the following section, we also explain how combining multiple quasi-experimental designs enables researchers to further specify the mechanisms responsible for correlations between environmental risks and outcomes (e.g., SDP and offspring functioning).

Sibling-Comparison Designs

Comparisons of differentially exposed siblings can help account for certain types of confounding. Comparisons of siblings raised in the same family automatically exclude confounding of the exposure with all environmental factors that are shared in common by the siblings. Comparisons of siblings can also help rule out genetic confounding.^{59–61} The process of



Note. I = first generation; II = second generation; III = third generation. Squares represent males. Circles represent females. Diamonds represent either males or females. Horizontal lines represent mating and sibling relationships. Vertical lines represent parent-child relationships. Inverted Vs represent twin pairs. Shaded diamonds represent individuals exposed to a risk factor (e.g., maternal smoking during pregnancy). Examples of differentially exposed siblings are presented, including half-siblings (III:1 and III:2, who share 25% of their genes); full-siblings (III:3 and III:4, who share 50% of their genes); and twins (III:8 and III:9, either fraternal twins, who share 50% of their genes, or identical twins, who share 100% of their genes). Differentially exposed cousins are also presented, including half-cousins (III:7 and III:8, who share 6.25% of their genetic factors); full-cousins (III:4 and III:5, who share 12.5% of their genetic factors); and offspring of twins (III:5 and III:6). If the twins (II:4 and II:5) are fraternal, their offspring (III:5 and III:6) would share 12.5% of their genetic factors. If the twins (II:4 and II:5) are identical, their offspring (III:5 and III:6) would share 25% of their genetic factors.

FIGURE 1—Schematic of extended family pedigree with examples of several family-based, quasi-experimental comparisons.

TABLE 1—Descriptions of Major Advantages and Limitations/Assumptions of Family Based Quasi-Experimental Designs for Examining Environmental Risks

Research Design	Major Advantages	Major Limitations/Assumptions
1. Traditional comparison of unrelated individuals	Economical; many samples exist that can be analyzed in this way.	Can only be used to assess correlations; cannot support any degree of causal inference. Confound all genetic and environmental differences among individuals with the environmental factor. Statistical covariates can help control for these factors if they are measured and meet assumptions of statistical control. Assume no carry-over effects.
2. All sibling comparisons ⁵⁹⁻⁶³	Account for all selection factors that make the siblings similar (without having to include measured covariates of selection factors). These include genetic and environmental factors that are shared by siblings. Relatively easy to obtain large samples when all siblings, or a random selection of siblings, are assessed.	Do not rule out environmental selection factors that (1) vary among siblings, (2) are correlated with the environmental factor within families, and (3) are correlated with the outcome. Statistical covariates can be added to help control for such factors within the limits of statistical control. Do not account for factors correlated with age, birth order, and sex of siblings. Statistical covariates can be added to help control for such factors within the limits of statistical control. Are particularly sensitive to measurement unreliability. Assume no carry-over effects from the environmental exposure of 1 sibling to the outcome of another. Assume results generalize to other populations (e.g., singletons and families with no within-family variability). Cannot examine influence of outcome of 1 sibling on outcome of another. Cannot study risks that are shared by siblings. Requires large samples for adequate statistical power.
2A. Half-sibling comparisons (e.g., maternal half-siblings)	Account for all genetic selection factors passed down from 1 parent (e.g., mothers) that make siblings similar. Half-siblings share 25% of their genes. Account for environmental selection factors that make siblings similar.	Do not rule out genetic factors passed down from 1 parent (e.g., mothers) that make sibling dissimilar, which could influence exposure to the environmental risk. Do not rule out any genetic factors passed down from or the environmental factors associated with 1 parent (e.g., different fathers of maternal half-siblings). Assume results generalize to families with full-siblings.
2B. Full-sibling comparisons	Account for all genetic selection factors passed down from both mothers and fathers that make siblings similar. Full-siblings share 50% of their genes. Account for environmental selection factors that make siblings similar.	Do not rule out genetic factors that make siblings dissimilar, which could influence exposure to the environmental risk. Assume results generalize to families with half-siblings.
2C. Fraternal twin comparisons	Account for all genetic selection factors passed down from both mothers and fathers that make siblings similar. Fraternal twins share 50% of their genes. Account for environmental selection factors that make siblings similar. Account for all confounds associated with offspring age. Account for shared prenatal factors that make twins similar.	Do not rule out genetic factors make sibling dissimilar, which could influence exposure to the risk. Assume results generalize to other populations (e.g., nontwins). Cannot study prenatal and other risks that cotwins share. Requires access to twin samples.
2D. Identical twins comparisons (co-twin control design) ⁶⁴	Account for all genetic selection factors. Identical twins share 100% of their genes. Account for environmental selection factors that make siblings similar. Account for all confounds associated with offspring age. Account for shared prenatal factors that make twins similar. Account for factors correlated with sex.	Assume results generalize to other populations (e.g., nontwins). Cannot study prenatal and other risks that co-twins share. Requires access to twin samples.

Continued

TABLE 1—Continued

2E. Quantitative genetic analysis of multiple sibling comparison designs ^{54,65,66}	<p>Allow researchers to estimate the degree to which the association between an environmental risk and outcome is because of shared genetic liability and environmental factors that make siblings similar (both selection factors), as well as environmental factors that make siblings unique (consistent with a causal inference).</p> <p>Can increase the statistical power of the estimate of environmental factors that make siblings unique (consistent with a causal inference).</p>	<p>Requires assumptions about assortative mating and equal environmental influences across sibling types are met.</p> <p>Requires assumptions about equal variability in measures across sibling types are met.</p> <p>Requires access to large samples with multiple types of siblings.</p>
2F. Sibling comparisons in a bidirectional case-crossover design ⁶⁷ (i.e., comparison of subsets of sibling pairs with different patterns of exposure across birth order)	Can examine whether carry-over effects associated with timing of the risk account for a reduced sibling-comparison estimate.	<p>Requires even larger samples of differentially exposed siblings (i.e., to compare families with exposure of the first-born offspring to families with exposure of the second-born offspring).</p> <p>Cannot rule out all carry-over effects (e.g., those that influence all siblings in a family regardless of timing).</p>
3. All offspring of siblings/twins comparisons (e.g., maternal cousin comparisons) ^{28,34,68–72}	<p>Account for all factors that make the cousins similar. These include environmental factors and genetic factors that are shared by cousins.</p> <p>Can explore environmental risks that are shared by siblings/twins.</p>	<p>Do not rule out selection factors that vary within an extended family. These include environmental factors unique to each nuclear family, such as the influence from spouses of the adult siblings (e.g., fathers). In addition, these include all genetic factors passed down from the spouses of the adult siblings (e.g., fathers).</p> <p>Are particularly sensitive to measurement unreliability.</p> <p>Assume no carry-over effects.</p> <p>Assume results generalize to other populations (e.g., extended families with no cousins).</p> <p>Requires large samples for adequate statistical power.</p>
3A. Offspring of half-siblings comparisons (e.g., offspring of maternal half-siblings)	<p>Account for part of the genetic selection factors passed down from 1 parent (e.g., mothers) that make cousins similar. These half-cousins share 6.25% of their genetic makeup.</p> <p>Account for environmental selection factors that make cousins similar.</p>	<p>Do not rule out genetic factors passed down from 1 parent (e.g., mothers) that make cousins dissimilar, which could influence exposure to the risk.</p> <p>Assume results generalize to families with offspring of full-siblings.</p> <p>Limited advantages because of minimal sharing of genetic factors.</p>
3B. Offspring of full-siblings comparisons (e.g., offspring of maternal full-siblings)	<p>Account for part of the genetic selection factors passed down from 1 parent (e.g., mothers) that make cousins similar. These half-cousins share 12.5% of their genetic makeup.</p> <p>Account for environmental selection factors that make cousins similar.</p>	<p>Do not rule out genetic factors passed down from 1 parent (e.g., mothers) that make cousins dissimilar, which could influence exposure to the risk.</p> <p>Assume results generalize to families with offspring of half-siblings.</p> <p>Limited advantages because of minimal sharing of genetic factors.</p>
3C. Offspring of fraternal twins comparisons	<p>Account for part of the genetic selection factors passed down from 1 parent (e.g., mothers) that make cousins similar. These half-cousins share 12.5% of their genetic makeup.</p> <p>Account for environmental selection factors that make cousins similar.</p> <p>Account for prenatal and age factors of the adult twins, which influence their offspring.</p>	<p>Do not rule out genetic factors passed down from 1 parent (e.g., mothers) that make cousins dissimilar, which could influence exposure to the risk.</p> <p>Assume results generalize to families with offspring of nontwins.</p> <p>Requires access to twin samples.</p>
3D. Offspring of identical twins comparisons ⁷³	<p>Account for part of the genetic selection factors passed down from 1 parent (e.g., mothers) that make cousins similar. These half-cousins share 25% of their genetic makeup.</p> <p>Account for environmental selection factors that make cousins similar.</p> <p>Account for prenatal and age factors of the adult twins, which influence their offspring.</p>	<p>Do not rule out genetic factors passed down from 1 parent (e.g., mothers) that make cousins dissimilar, which could influence exposure to the risk.</p> <p>Assume results generalize to families with offspring of nontwins.</p> <p>Require access to twin samples.</p>

Continued

TABLE 1—Continued

3E. Quantitative genetic analysis of multiple offspring of siblings designs ^{28,34,68-71}	<p>Allow researchers to estimate the degree to which the association between a shared environmental risk and outcome is because of shared genetic liability and environmental factors that make cousins similar (both selection factors), as well as environmental factors that make cousins unique (consistent with a causal inference).</p> <p>Can increase the statistical power of the estimate of environmental factors that make cousins unique (consistent with a causal inference).</p>	<p>Requires assumptions about equal environmental influences across cousin types.</p> <p>Requires assumptions about equal variability in measures across cousin types.</p> <p>Requires access to large samples with multiple types of adult siblings.</p>
3F. Quantitative genetic analysis of the combination of sibling-comparisons and multiple offspring of siblings designs ⁷⁴⁻⁷⁷	<p>Can help identify the background selection factors when sibling comparisons find no within-family estimate. The approach estimates the degree to which the association between an individual-level environmental risk and outcome is because of genetic liability (shared by parent and all offspring), environmental factors that make cousins similar, or environmental factors that make cousins unique (all selection factors).</p>	<p>Requires large sample of siblings nested within multiple types of adult siblings.</p> <p>Requires advanced multilevel modeling to accurately distinguish intergenerational processes.</p> <p>Require assumptions about equal environmental influences across cousin types.</p> <p>Require assumptions about equal variability in measures across cousin types.</p> <p>Are particularly sensitive to measurement unreliability.</p>
4. In vitro fertilization (IVF) comparisons ⁷⁸	<p>Use an adoption study “in utero” to separate genetic influences passed down from parents to offspring from environmental factors, including those in pregnancy.</p>	<p>Assume results generalize to other populations (e.g., families who didn’t go through fertility treatment).</p> <p>Assume fertility treatments do not influence outcome of interest.</p> <p>Requires large samples, especially when comparing subgroups of IVF.</p> <p>Difficult to recruit large samples.</p> <p>Potential restricted range in environmental risks.</p> <p>Require access to fertility treatment samples.</p>
4A. Genetically related offspring comparisons (e.g., to mothers; homologous IVF or sperm donation).	<p>Provide a group of mother-offspring pairs (similar to the comparison of unrelated individuals) who have gone through IVF treatment.</p>	<p>Have all of the limitations of the traditional comparison of unrelated individuals.</p>
4B. Genetically unrelated offspring comparisons (e.g., to mothers; embryo donation, egg donation, and gestational surrogacy).	<p>Account for all genetic selection factors passed down from both mothers and fathers.</p>	<p>Do not rule out genetic factors that could influence exposure to the environmental risk.</p> <p>Do not rule out environmental factors that correlate with the exposure.</p>
4C. Quantitative genetic analysis of multiple in vitro designs	<p>Combination of genetically related and unrelated offspring allow researchers to estimate the degree to which the association between an environmental risk and outcome is because of shared genetic liability (a selection factor) or environmental factors correlated with the exposure (consistent with a causal inference).</p>	<p>Requires large samples to accurately estimate genetic and environmental estimates.</p>

Note. The table does not include every advantage and limitation/assumption. References to articles that more fully describe advantages and disadvantages of the methods are included in the text and in the table. The designs described in the table can be combined with other methods (e.g., longitudinal assessments and the use of statistical covariates) to help test and rule out competing explanations for the results.

meiosis (the type of cell division that produces eggs and sperm) randomly distributes alleles from parents to each offspring. Although siblings differ in their genetic makeup, the random process of meiosis rules out systematic confounding between genetic variants and environmental exposures because of passive rGE. As such, the comparison of

differentially exposed half-siblings, who share 25% of their genes on average (i.e., III:1 and III:2 in Figure 1), accounts for genetic factors passed down from 1 parent that make siblings similar. The comparison of full-siblings, who share 50% of their genes (i.e., III:3 and III:4), rules out the possibility that genetic factors passively passed down from either parent account

for the association between the exposure and the outcome. If the probability of exposure cannot be influenced by the genetic characteristics of the offspring (e.g., random events or events that occur before conception), active and evocative rGE are also ruled out. To rule out genetic confounding arising from active or evocative rGE when studying other risks, the

differentially exposed siblings have to be identical twins, who share 100% of their genetic sequences (i.e., III:8 and III:9).⁶⁴ Because the twins must be discordant for the exposure, they cannot be used to study risks that are shared by twins, such as SDP.^{79,80} Like all quasi-experimental designs, sibling comparisons have a number of assumptions. For

instance, sibling-comparison designs cannot rule out confounded environmental factors that vary within siblings that are highly correlated with both the exposure and the outcome. Comparisons of any type of siblings cannot always identify the selection factors responsible for associations between risks and outcomes.^{59,61} However, when combining different sibling-comparison designs (e.g., full- and half-siblings⁶⁵ or fraternal and identical twins⁶⁶), researchers can use quantitative genetic models to explore the degree to which an association is the result of genetic and shared environmental influences (selection factors) or environments that make siblings unique (consistent with a causal inference).⁵⁴

There are also assumptions about the generalizability of the findings from the comparison of differentially exposed siblings.^{59,62} In addition, sibling comparisons are based on strict assumptions about carry-over effects (i.e., the possibility that exposure of 1 sibling influences the outcome of another).^{59–61,62,63} Fortunately, asking the same scientific question using different quasi-experimental approaches with different limitations in sequence allows researchers to robustly test causal hypotheses. For instance, with large enough samples, researchers can test the assumption of no carry-over effects by conducting bidirectional case-cross studies that explore differentially exposed sibling pairs who vary in their exposure across birth order (i.e., when the mother smoked more during the first or second pregnancy).⁶⁷

Offspring of Siblings or Twins Designs

The comparison of differentially exposed cousins similarly

helps to account for unmeasured genetic and environmental selection factors when examining a specific risk. Cousin comparisons account for all environmental factors shared by cousins that make them similar. Cousin comparisons also can help account for genetic selection, with the degree to which a cousin comparison accounts for genetic factors depending on their genetic relatedness. The offspring of half-siblings (i.e., III:7 and III:8, maternal half-cousins), for instance, share 6.25% of genetic variants, whereas the offspring of full-siblings (i.e., III:4 and III:5, maternal full-cousins) and fraternal twins (i.e., III:5 and III:6) share 12.5%. The offspring of identical twins design is a special case of a cousin comparison—the cousins share 25% of their genetic factors with each other (i.e., socially, the offspring are cousins, but genetically they are half-siblings).^{28,34,68–73}

The advantage of the offspring of siblings or twins designs is that it can answer questions about risks that are almost always shared by siblings, like parental divorce. However, the design cannot account for all genetic and environmental confounds, especially the genetic and environmental influences passed down from the spouses of the twin parents.⁷² When studying individual-level risks, such as SDP, the design rules out fewer confounds than sibling comparisons (e.g., cousin comparisons do not account for as much genetic confounding as the comparison of full-siblings). However, the offspring of siblings or twins design has different assumptions and threats to its internal and external validity, making it a useful complement to sibling comparisons. For example, the comparison of differentially exposed first-born offspring of

twins could be used to study a environmental risk free of the effects of birth order, which could confound sibling-comparison studies.^{59,61,63}

When offspring of multiple types of adult siblings are included in a study (e.g., offspring of identical and fraternal twins), researchers can infer the extent to which environmental and genetic influences confound the statistical associations between an environmental risk and outcome.^{28,34,68–71} Again, one of the primary advantages of the offspring of siblings or twins designs is the ability to examine risks that are shared by siblings. However, researchers can combine siblings comparisons and offspring of siblings or twins designs to explore the degree to which genetic and environmental factors shared by siblings account for the associations between an individual-level risk factor and outcome.^{74–76} This is an important advantage, because sibling comparisons by themselves cannot identify the mechanisms responsible for a statistical association between a risk and an outcome when the comparison of differentially exposed siblings suggests no causal influence.^{59,61}

In Vitro Fertilization Designs

The in vitro fertilization (IVF) design is a quasi-experimental approach that takes advantage of new reproductive technologies to conduct “cross fostering” studies in humans. The design includes both offspring who are genetically related to mothers (e.g., through homologous IVF) and not genetically related to their birth mothers (e.g., through embryo donation).⁷⁸ The key test of a putative environmental risk factor, such as maternal SDP, is whether the risk is associated with an offspring outcome in

families in which the women gave birth to genetically unrelated offspring. When IVF studies include both offspring who are genetically related to their mothers and offspring who are not genetically related, behavior genetic models can test whether genetic influences account for the statistical association between a risk factor and outcome.⁷⁸ A limitation of this design is concern about the generalizability of findings from a sample of women who have had IVF.

STUDIES OF MATERNAL SMOKING DURING PREGNANCY

Many studies of SDP using family-based, quasi-experimental designs suggest causal environmental effects on some outcomes, but not on others.⁸¹

Birth-Related and Perinatal Problems

Comparisons of siblings differentially exposed to maternal SDP have consistently found robust associations with birth-related complications, such as restricted fetal growth, preterm birth, and placental abruption, which support a causal inference.^{13,81} In particular, recent sibling-comparison studies with large representative samples have supported the hypothesis that maternal SDP causes low infant birth weight^{79,82,83} and infant mortality.¹⁴ Offspring of twins²⁹ and IVF studies^{84,85} have reported commensurate results regarding maternal SDP and offspring birth weight, which provides converging evidence for this causal hypothesis.

Psychosocial or Cognitive Outcomes

Sibling-comparison studies of SDP and childhood conduct and

oppositional problems,^{76,82} attention or impulsivity problems,^{76,86} intellectual abilities,^{16,82} academic achievement or grades,^{15,77,82} psychological functioning during adolescence,^{75,87} suicidal behavior,⁸⁸ substance use and substance problems,⁸³ adolescent antisocial behavior,⁸⁹ and adolescent and young adult criminal convictions^{87,89} have all reached the opposite conclusion—familial selection factors account for all of the associations. Although there is a robust correlation between maternal SDP and behavioral outcomes in between-family studies, differentially exposed siblings do not differ in the measured behaviors. Although there were concerns about the measurement of child functioning in some early sibling-comparison studies,^{60,90} all published sibling-comparison studies of behavioral outcomes to date, including studies predicting normative traits, have concluded that familial selection factors, not exposure to maternal SDP, account for the associations. This conclusion is reinforced by the fact that bidirectional case-cross studies⁶⁷ of intellectual abilities¹⁶ suggest that some assumptions inherent in the sibling-comparison design (e.g., carry-over effects) were not violated and do not account for the findings.

Recent studies combined different quasi-experimental designs to test other assumptions in sibling comparisons and helped identify the confounded selection factors that actually account for the association between maternal SDP and offspring psychosocial or cognitive problems. In a study that included half- and full-siblings, as well as half- and full-cousins, the authors found that confounded genetic influences accounted for part of the association between SDP and offspring intellectual abilities and

academic achievement.⁷⁷ IVF studies likewise suggested that genetic factors passed down from women accounted for the statistical associations of SDP with offspring conduct problems⁸⁴ and attention deficit or hyperactivity problems.⁸⁵ Those results were also consistent with an offspring of twins study of SDP and offspring attention deficit or hyperactivity problems.⁹¹ Finally, a recent study that combined sibling comparisons with an offspring of siblings design found that genetic liability shared by parents and offspring accounted for the association between SDP and offspring stress-coping.⁷⁵ The results of the quasi-experimental research was further supported by studies comparing unrelated individuals that included strong measured covariates in the analyses^{36,92} or propensity score matching.⁹³ The converging evidence from studies using multiple designs, therefore, provides strong evidence that selection factors, including genetic confounds, account for the statistical associations between SDP and offspring psychosocial or cognitive problems.

STUDIES OF MOLECULAR GENETIC RISKS

It is notable that similar types of quasi-experimental designs are performed to identify both environmental and genetic risk for outcomes. Transmission Disequilibrium Tests⁹⁴ and similar within-family approaches^{95,96} have long been conducted in molecular genetic studies to account for several forms of confounding. The designs compare relatives (e.g., parent-offspring, siblings, etc.) to examine whether a proposed allele is segregating together with the disease more often than the other allele(s).

Price et al.⁹⁷ recently used a similar family-based, quasi-experimental design to study women who SDP and who gave birth to fraternal twins who were discordant for specific genes. The study suggested that a variant in a gene coding enzymes that metabolize xenobiotic (foreign) substances in the fetus was significantly associated with fetal growth, even within fraternal twins (i.e., the twin with the susceptibility allele had less fetal growth). They also found that the magnitude of the association between SDP and offspring fetal growth was moderated by this genetic variant, suggesting a fetal genotype-by-maternal SDP interaction for fetal growth (an example of G×E).

INTEGRATING GENETICS AND SOCIAL SCIENCE RESEARCH

Family-based, quasi-experimental designs have profound implications for numerous research fields, although such studies are relatively new for many environmental risks. First, quasi-experimental studies have important ramifications for epidemiologic research. It is clear that observational studies that rely solely on including measured covariates in an analysis to control for selection factors do not adequately test alternative hypotheses, which has had severe consequences for the field.⁹⁸ Rather, researchers must identify plausible alternative explanations for statistical associations ahead of time and use multiple designs to test competing causal hypotheses.^{34,52} This will often involve moving away from the standard practice of conducting observational designs using 1 person from each family. A number of such

samples already exist. For example, nationally representative studies in the United States that included assessments of multiple siblings in families^{99–102} have enabled researchers to use several family-based, quasi-experimental designs. Far more family-based samples are needed in the future, however. Such research will require interdisciplinary efforts to combine quasi-experimental designs with more precise measurements of risks, confounding factors, mediating processes, and outcomes.

Second, quasi-experimental designs are of great value to prevention or intervention scientists. Conducting studies that support a credible degree of causal inference regarding environmental exposures can provide guidance and justification for randomized controlled trials that increase or decrease desirable or undesirable exposures.^{103–105} That is, quasi-experimental research can identify modifiable environmental risks that are associated with offspring development independent of genetic confounds and many environmental selection factors, consistent with a causal association. For example, quasi-experimental research strongly suggests that public health initiatives should aim to further reduce SDP because of its apparent causal effect on low birth weight, pre-term birth, and infant mortality. Quasi-experimental research can also identify risks that are not causal, but instead are markers for other causal agents. As such, quasi-experimental research suggests that solely reducing maternal SDP is unlikely to reduce offspring psychosocial or behavior problems. Translating the findings from quasi-experimental studies into prevention and intervention efforts certainly will

require more collaboration across traditionally disparate fields.¹⁰⁶

Third, the use of family-based, quasi-experimental designs also can inform the burgeoning field of G×E.^{9,10} As discussed previously, research exploring the interaction between environments and genes is necessarily based on strong causal assumptions about the environmental influence.^{9,42,43}

Given the quasi-experimental research to date, G×E studies with SDP are more justified when exploring pregnancy-related outcomes, such as low birth weight.⁹⁷ By contrast, the growing body of quasi-experimental research suggests that researchers cannot assume that SDP has an environmentally mediated influence on psychosocial and cognitive problems. Recent G×E studies of maternal SDP,^{40,41} therefore, may have incorrectly interpreted the statistical interaction; the statistical interaction could represent gene-by-gene interactions instead of a G×E.

Finally, quasi-experimental research can help integrate genetic and social science research by informing clinical neuroscience research, an example of translational epidemiology.^{107–110} We certainly endorse integration of experimental methods in basic animal research with findings from human studies.^{111,112} There are limitations to the generalizability of animal studies,¹⁰⁶ however, especially when studying pregnancy, because of the enormous biological differences across species.¹¹³ As such, the quasi-experimental studies of maternal SDP can help specify the mechanisms that clinical neuroscience research should explore further.¹¹⁴ Quasi-experimental studies can be seen as a critical bridge between basic neuroscience and epidemiology.

Neuroscience research with animals has excellent internal validity because of the ability to conduct randomized controlled studies but somewhat limited external validity to human behavior. In contrast, traditional epidemiological studies have limited internal validity but stronger external validity.

SUMMARY

Researchers have identified environmental exposures that are correlated with psychological and medical problems. Based on these findings, researchers have developed complex developmental models and have tested biological moderating factors for these outcomes. We still know little about the true causes of these outcomes, however, because it remains unclear whether environmental risks are truly causal or whether part—or most—of the associations with these risks are attributable instead to familial confounding.^{115,116} It is important to stress that this is true of both social science research, which has typically focused on environmental risks, and genetic research with susceptibility genes or other biomarkers.⁹⁶

In this article, we show examples of when genetic and environmental selection factors have been neglected, and causation may have been claimed erroneously. We also describe how family-based, quasi-experimental methods can help integrate genetics and the behavioral and social sciences to inform our understanding of the true causes of human health and development. We argue that rigorous translational epidemiological approaches—studies employing quasi-experimental methods—play a unique position in bridging gaps between basic biological research and social

science research because the approaches rigorously test causal hypotheses.^{107–110} We used studies on maternal SDP to exemplify these principles.

Our advocacy for quasi-experimental designs in integrating genetic and social research parallels the calls to use these approaches by leading researchers in medicine,^{115,116} psychiatry,^{117,118} sociology,¹¹⁹ psychology,^{34,52} family studies,¹²⁰ epidemiology,^{39,61} and economics.¹²¹ Ultimately, integrating genetic and social science research will require researchers to incorporate measures across multiple levels of analysis with strong quasi-experimental designs in a developmental context.¹²⁰ ■

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