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Children of Twins Design

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Keywords: *behavior genetics, adoption studies, cotwin control, gene-environment correlation, intergenerational transmission, causal processes*

Abstract: Because parents provide the environmental context for the family and transmit genetic makeup to their offspring, the genetic and environmental processes responsible for associations between family risk factors and offspring adjustment are confounded. Social scientists typically use statistical controls to account for 'third' variables that influence both characteristics, but family studies cannot account for unmeasured genetic or environmental confounds. The Children of Twins (CoT) Design can separate co-occurring genetic and environmental developmental mechanisms because the design utilizes control groups that vary in genetic and environmental risk. As a result, the design can delineate intergenerational associations into (a) environmental processes specifically related to the risk factor, (b) genetic factors that influence the risk factor and offspring characteristic, and (c) common environmental factors that vary between families. The CoT approach offers advantages over traditional family studies that assume genetic factors are not important; rather, the genetically informed design explores the manner in which genetic and environment processes act to influence offspring adjustment.

One of the first lessons in all statistics classes for the social sciences is that correlation does not mean causation (*see* **Correlation Issues in Genetics Research**). In spite of this premise, most disciplines have historically assumed that associations between parental and offspring characteristics are due to direct environmental causation [15]. However, third variables, or selection factors, may influence both generations and account for the intergenerational relations. Social scientists typically try to statistically control for environmental selection factors in their studies, but unmeasured confounds may also influence the associations. These cannot be controlled statistically. However, unmeasured selection factors can be taken into account by carefully selecting comparison groups, thus moving researchers closer to being able to make causal statements.

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This article was originally published online in 2005 in Encyclopedia of Statistics in Behavioral Science, © John Wiley & Sons, Ltd and republished in Wiley StatsRef: Statistics Reference Online, 2014.

Genetic factors are critical to take into account in intergenerational studies, because parents provide the environmental context and transmit their genes to their offspring. Therefore, any statistical association between parents and children may also be due to similar genetic backgrounds. Genetic confounds in intergenerational associations are referred to as passive **gene-environment correlation (passive rGE)**. Passive rGE occurs when common genotypic factors influence parental behaviors, which are considered to be environmental risk factors, and child outcomes [14, 18]. Although genetic confounds render most typical research, such as family studies, uninterruptible, researchers have largely ignored the role of passive rGE [16].

There are a number of behavior genetic designs that delineate between the genetic and environment processes that are responsible for relations between parental characteristics and child outcomes [3, 7, 17]. The most well-known genetically informed design is the **adoption study** because of the clear separation between the genetic risk transmitted to the child by the biological parents and the environment that is provided by the adopting family. However, the adoption study is becoming increasingly difficult to conduct and suffers from a number of methodological assumptions and limitations [17]. The **co-twin control design** can also help separate genetic and environmental processes through which environmental risk factors influence one's behavior, but the design cannot include risk factors that both twins share [3]. Therefore, other behavior genetic designs are necessary.

The Children of Twins (CoT) Design is a genetically informed approach that also explores the association between environmental risk factors and outcomes in offspring. The offspring of identical twins have the same genetic relationship with their parents and their parents' cotwin because each twin is genetically the same. However, only one twin provides the environment for his/her children. As a result, the genetic risk associated with the parental behavior can be inferred from the cotwin [7, 13]. Using children of identical twins can determine if a parental characteristic has an environmental association with a child behavior or whether the intergenerational relation is confounded by selection factors. When children of fraternal twins are included, the design is able to reveal whether confounds are genetic or environmental in origin [5].

The CoT Design is best known for its use with studying dichotomous environmental risk factors, such as a diagnosis of a psychiatric disorder [6]. For example, the children of schizophrenic parents are at higher risk for developing the disorder than the general population. In order to elucidate the genetic and environmental mechanisms responsible for the intergenerational association, researchers compare the rates of schizophrenia in the offspring of discordant pairs of twins (one twin is diagnosed with the disorder and one is not). A comparison between the children of affected (diagnosed with schizophrenia) identical twins and their unaffected (no diagnosis) cotwins is the initial step in trying to understand the processes through which the intergenerational risk is mediated. Because offspring of both identical twins share the same genetic risk associated with the parental psychopathology from the twins, any difference between the offspring is associated with environmental processes specifically related to the parental psychopathology (see below for a discussion of the influence of the nontwin parent). Effectively, the CoT Design provides the best control comparison group because children with schizophrenia are compared with their cousins who share the same genetic risk associated with schizophrenia and any environmental conditions that the twins share. If offspring from the unaffected identical twin have a lower prevalence of schizophrenia than offspring of the affected identical twin, the results would suggest that the experience of having schizophrenic parent has a direct environmental impact on one's own risk for schizophrenia.

If the rates of the disorder in the offspring of the affected and unaffected identical cotwins are equal to each other, the direct causal role of the parental psychopathology would be undermined. However, such results do not elucidate whether shared genetic or environmental processes are responsible for the intergenerational transmission. A comparison of the rates of psychopathology in the children of the unaffected identical and fraternal cotwins highlights the nature of the selection factors. Children of the unaffected identical twins only vary with respect to the environmental risk associated with schizophrenia, whereas offspring of the unaffected fraternal twin differs with respect to the environmental *and* genetic

risk (lower). Therefore, higher rates of schizophrenia in the children of the unaffected identical cotwins than in children of the unaffected fraternal cotwins suggest that genetic factors account for some of the intergenerational covariation. If the rates are similar for the children in unaffected identical and fraternal families, shared environmental factors would be of most import because differences in the level of genetic risk would not influence the rate of schizophrenia.

The most well-known application of the design explored the intergenerational association of schizophrenia using discordant twins [6]. Offspring of schizophrenic identical cotwins had a morbid risk of being diagnosed with schizophrenia of 16.8, whereas offspring of the unaffected identical cotwins had a morbid risk of 17.4. Although the offspring in this later group did not have a parent with schizophrenia, they had the same risk as offspring with a schizophrenic parent. The results effectively discount the direct causal environmental theory of schizophrenia transmission. The risk in the offspring of the unaffected identical twins was 17.4, but the risk was much lower (2.1) in the offspring of the unaffected fraternal cotwins. This latter comparison suggests that genetic factors account for the association between parental and offspring schizophrenia. Similar findings were reported for the transmission of bipolar depression [1]. In contrast, the use of the CoT to explore transmission of alcohol abuse and dependence from parents to their offspring highlighted role of the family environment [8].

One of the main strengths of the design is its ability to study different phenotypes in the parent and child generations. For example, a study of divorce using the CoT Design reported results consistent with a direct environmental causal connection between parental marital instability and young-adult behavior and substance abuse problems [4]. Similar conclusions were found with CoT Design studies of the association between harsh parenting and child behavior problems [9] and between smoking during pregnancy and child birth weight [3, 11]. However, a CoT analysis found that selection factors accounted for the lower age of menarche in girls growing up in households with a stepfather, results that suggest the statistical association is not a causal relation [12]. These findings suggest that underlying processes in intergenerational associations are dependent on the family risk factors and outcomes in the offspring.

In summary, selection factors hinder all family studies that explore the association between risk factors and child outcomes. Without the ability to experimentally assign children to different conditions, researchers are unable to determine whether differences among groups (e.g., children from intact versus divorced families) are due to the measured risk factor or unmeasured differences between families. Because selection factors may be environmental or genetic in origin, researchers need to use quasi-experimental designs that pull apart the co-occurring genetic and environmental risk processes [17]. The CoT Design is a behavior genetic approach that can explore intergenerational associations with limited methodological assumptions compared to other designs [3]. However, caution must be used when interpreting the result of studies using the CoT Design. Similar to all nonexperimental studies, the design cannot definitely prove causation. The results can only be consistent with a causal hypothesis because environmental processes that are correlated with the risk factor and only influence one twin and their offspring may actually be responsible for the associations.

The CoT Design can also be expanded in a number of ways. The design can include continuously distributed risk factors [3, 7] and measures of family level environments. Associations between parental characteristics and child outcomes may also be due to reverse causation, but given certain assumptions, the CoT Design can delineate between parent-to-child and child-to-parent processes [19]. Because the design is also a quasi-adoption study, the differences in genetic and environmental risk in the approach provides the opportunity to gene-environment interaction [8]. When the spouses of the adult twins are included in the design, the role of assortative mating and the influence of both spouses can be considered, an important consideration for accurately describing the processes involved in the intergenerational associations [7]. Finally, the CoT Design can be combined with other behavior genetic designs to test more complex models of parent–child relations [2, 10, 20]. Overall, the CoT Design is an important genetically informed methodology that will continue to highlight the mechanisms through which environmental and genetic factors act and interact.

Related Articles

Twins Reared Apart Design, Twin registers, Twin concordance, Statistical Genetics, Path analysis in genetics

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