

The validity of twin studies

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Abstract

The classical twin study is the most popular method for assessing the relative contribution of genes and environment to traits in human populations. Critics argue that several assumptions of the twin method are unjustified, and therefore results from twin studies are misleading. Specifically, it has been suggested that twins differ in important aspects from singletons, that monozygotic (MZ) and dizygotic (DZ) twins are not matched in their degree of environmental similarity, and that MZ twins are neither matched genetically nor in their prenatal environments. These criticisms are addressed and it is suggested that they do not provide serious impediments to the validity of the twin study.

Keywords assumptions, equal environments assumption, methodology, twins.

Are twins the same as singletons?

One criticism of the twin method is that twins differ from singletons in several important aspects, and therefore results from twin studies do not generalize to the population as a whole. Twins tend to have lower birth weights, experience shorter gestation times, and are at greater risk of perinatal complications (e.g. cerebral palsy) and mortality than singletons.^{1–3} This risk is particularly pronounced for monochorionic MZ twins who share a common placenta and are at increased risk of vascular complications. Several studies have also found lower childhood IQs for twins compared to singletons,⁴ although not all studies agree.⁵ Record, McKeown and Edwards⁴ found lower verbal reasoning scores in twins compared to singletons and even lower scores in triplets. These differences were independent of maternal age, birth weight, gestational age, zygosity and birth order. There was a much smaller difference between singletons and twins whose co-twin had died *in utero*, suggesting that this effect was due to post-natal competition for resources rather than an effect *in utero*.

Most studies that have found differences between singletons and twins have examined young twins. A host of studies comparing older twins with singletons have failed to find differences in physical characteristics and cognitive abilities,⁶ suggesting that any differences between twins and singletons are 'washed out' by five years of age. In addition, most studies have not matched twins with singletons in terms of genetic background nor early environmental experiences.

A recent study comparing twins with their siblings (who are matched in both genetic background and early environmental experiences) in Dutch WAIS (Wechsler Adult Intelligence Scale) scores, failed to detect any differences between twins and their siblings in cognitive abilities.⁵

Another line of evidence arguing against differences between twins and singletons is that twins exhibit similar means, frequencies and prevalences as singletons for most traits and adult diseases.⁷ Twins do not consistently differ from singletons in the rate of schizophrenia, affective illnesses or any other type of psychiatric illness.⁸ The exception appears to be cancers of the breast and testis, where there is evidence that DZ twins are at an increased risk as compared to MZ twins and singletons.^{9–11} The hypothesis is that DZ twins are exposed to particularly high levels of hormones *in utero* (e.g. oestrogen, follicular stimulating hormone) which have been associated with the development of breast and testicular cancers.

Are MZ and DZ twins treated the same? The equal environments assumption

The classical twin design assumes that MZ twin pairs experience the same degree of environmental similarity as DZ twin pairs. Critics point out that, if MZ twin pairs are exposed to more similar environments than DZ pairs, then any excess similarity between MZ pairs compared to DZ pairs, may be the result of environmental rather than genetic factors.

There is overwhelming evidence that MZ twins are treated more similarly than their DZ counterparts. As children, MZ twins are more likely to have the same playmates, share the same room and dress alike.¹² As adults, MZ twins are more likely to keep in contact, than same-sex DZ twins.¹² However, it is questionable whether this environmental similarity causes

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increased phenotypic concordance. Environmental similarity during childhood does not predict twin similarity in personality, attitudes, intelligence, nor a range of psychiatric disorders (cf. Kendler *et al.*¹³ for a review). Even though parents do appear to treat MZ twins more similarly than DZ twins,¹⁴ this similarity of treatment is uncorrelated with twin similarity for personality, vocational interests and cognitive abilities.¹⁵ Additionally, it appears that the more similar parental treatment of MZ vs. DZ twins occurs *in response to* the greater similarity of actions initiated by MZ pairs.¹⁶

Results from a variety of other study designs are inconsistent with violations of the equal environment assumption. A number of studies have examined the relationship between physical similarity and trait similarity. If trait resemblance between twins is influenced by the similarity with which they are treated, after controlling for zygosity, trait similarity should correlate with physical similarity between twins. Physical similarity is not correlated with similarity in intelligence, personality or schizophrenia.^{17–19} A number of studies have also examined the impact of actual vs. perceived zygosity on trait similarity.^{13,14} If there is some preconceived notion that MZ twins are more alike than DZ twins, and therefore should be treated more similarly, then trait similarity should be a function of perceived zygosity. As Kendler *et al.*¹³ point out, this method has the advantage of effectively testing all sources of environmental similarity that are a consequence of attitudes and expectations about zygosity. Studies using this method have failed to find any consistent influences of perceived zygosity on a range of traits and conditions including intelligence, attitudes, hyperactivity, major depression, generalized anxiety disorder, phobia, bulimia and alcoholism.¹³ In contrast, it appears that twins are treated according to their *actual* zygosity, rather than their *perceived* zygosity.

The results of all these studies suggest that the increased similarity of treatment of MZ twins is not due to their greater phenotypic similarity, nor expectations of social environment. Rather it seems more likely that the increased similarity in treatment of MZ twins is a consequence of their genetic identity and the more similar responses this elicits from the environment.

How identical are MZ twins?

There are many reasons why MZ twins may be less than fully identical. A wide variety of prenatal genetic and environmental influences may cause phenotypic and genotypic divergence. Reconvergence may occur after birth because the twins do not passively undergo differing experiences. On the contrary, it now seems likely that they actively seek, select, and perceive similar environments because of similarities in brain physiology.²⁰

The very low concordance rates of MZ twins for some disorders (e.g. autoimmune disorders), and the failure to find specific environmental factors responsible for this discordance, has prompted closer scrutiny of the assumption that MZ

twins are indeed genetically identical. Unequal allocation of blastomeres during twinning may contribute to differences between MZ twins. As critical numbers of cells may be necessary for normal development, deficits may occur in the smaller twin, in extreme cases leading to acardia, vanishing twin syndrome, etc.²¹ Skewed X-inactivation has been found in a number of female MZ twins who are discordant for X-linked disorders including colour blindness, Duchenne's muscular dystrophy and G6PD deficiency.²² Twins may exhibit 'reciprocal skewing', or one twin may exhibit skewed and the other random X-inactivation. This pattern may be caused by sequestration in the twinning process of a number of blastomeres that exhibit nonrandom patterns of X-inactivation. Uneven cytoplasmic distribution of DNA methylases following zygote splitting could result in differences between MZ twins in DNA methylation patterns and consequently differential imprinting.²² For example, several MZ twin pairs who are discordant for disorders where imprinting is involved (e.g. Beckwith–Wiedemann Syndrome) have been reported.²³ Postzygotic nondisjunction may result in MZ twins with different chromosomal constitutions.²¹ This can even result in rare cases of MZ twins who are phenotypically discordant in sex. Differential trinucleotide repeat expansion has been reported in MZ twin pairs, but no cases of twins discordant for single-gene diseases due to postzygotic single-gene mutation have been convincingly demonstrated.²⁴

MZ twin pairs are also exposed to differing prenatal environments. Differences in the site of placental implantation may produce differences in twins. As there is only one optimal site of implantation, it is unlikely that both twins will be able to benefit from this site. Monochorionic MZ twins, who share a common placenta are more likely to experience complications due to shared interfetal vasculature and have unequal distribution of nutrients. On the other hand, dichorionic MZ twins who do not share a placenta are less likely to receive similar doses of transplacental transmitted agents such as teratogens and infections. Finally, different modes of delivery, delays in delivery of one twin, and differences in perinatally acquired infections (e.g. chorioamnionitis, HIV) may contribute to differences between MZ twins.

Conclusions

The twin study remains the best method for assessing the relative contribution of genes and environment to traits in human populations. Many of the criticisms of twin studies are unjustified. Twins are indeed representative of the general population for a wide range of traits and diseases, and available evidence strongly suggests that twin studies do not violate the equal environments assumption. Future studies need to address the impact of epigenetic influences and differing prenatal environments on twin discordance. Such information is likely to yield rich rewards in understanding human genetic development and insight into the twinning process itself.

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