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## Discussion

## The twin representativeness assumption

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The papers in this special NBR-issue on twin studies of brain, cognition and behavior are based on the assumption that results from twin research generalize to singletons. There are a number of reasons why we should consider this assumption critically: Twins are on average born prematurely and 1 kg lighter than singletons; twins grow up with an age-matched sibling; dizygotic twins tend to have older mothers and, in the last four decades, a considerable proportion of dizygotic twins are conceived with the help of fertility treatment. Thus, being a dizygotic twin is associated with parental health (for which infertility may be a symptom) and socioeconomic conditions.

Enormous progress has been made in reducing perinatal and infant mortality for twins. In the Danish 1870–1900 birth cohorts, which were the first to be included in the Danish Twin Registry, both twins survived to age 6 in only one third of the pairs. Today, 98 % of twins make it to age 6. However, the concern has been whether the disadvantaged beginning of life with a high frequency of prematurity, low birth weight and a delivery that is often difficult would leave “scars” on the twins affecting their health and functioning later in life. In particular, the big scientific influence of “the fetal origins hypothesis” launched in the 1990s, which hypothesized that intrauterine and infant growth were strong determinants of later life health, propelled an increasing interest in testing twin-singleton differences and their potential impact on the interpretation of twin studies even though the mechanism of low birth weight is fundamentally different in singletons and twins

Generally, studies of twin-singleton differences in mortality and disease incidence including cardiovascular diseases and type 2 diabetes, assessed through national mortality and hospitalization records with virtually no selection bias, have shown no or small differences between twins and singletons after the infant period – even when the singleton comparison group is comprised of the siblings to the twins (Öberg et al., 2012). In the domains covered in this special NBR-issue, the results are less consistent. European studies of twin cohorts born in the 1930s to the 1950s found substantially lower mean IQs for twins than for singletons, but studies of IQ and academic achievement including test scores showed that this twin-singleton difference had vanished in the 1980s birth cohorts, probably as a result of better maternal health and living conditions as well as improvements in obstetrics and pediatrics (Christensen et al., 2006). Many smaller studies have found twin-

singleton differences in the cognitive and behavioral domain, but here a potential publication bias should be kept in mind.

For behavioral studies, a potential challenge is that the twins grow up with an age-matched sibling. It has been hypothesized that twins could benefit from the socializing effects experienced by their co-twins (the Adaptive hypothesis), while, alternatively, the divided attention of the parents could lead to intra-pair competition and dissociating. A large Finnish study of peer reports of adaptive behavior in 11–12 year-old twins and singletons (Pulkkinen et al., 2003) found no evidence that individual twins differ from singletons in externalizing problem behaviors (hyperactivity-impulsivity, inattention, aggression) or internalizing problem behaviors (depressive symptoms, social anxiety). Regarding adaptive behaviors (constructive, compliant, and active behavior), the same-sexed twins had a small advantage compared to singletons, whereas the advantage was substantial in the opposite-sexed twins.

Many other studies have focused on differences between opposite-sexed and same-sexed twins motivated by findings from animal studies that intrauterine androgen hormone transfer from male fetuses to their female siblings may have a masculinizing effect on the female fetus. However, as pointed out by Ahrenfeldt et al. (Ahrenfeldt et al., 2020) in a review in this NBR-issue, positive findings on behavioral differences between opposite-sexed and same-sexed twins have generally failed to replicate. Cognition is the trait for which there is most support for this Twin Testosterone Transfer hypothesis, but also here the results are very divergent.

Many of the twin registries around the world have, for decades, collected data and biological material from a large number of twins. This makes the twin registries ideal for entering consortia that need very large sample sizes, e.g. GWAS-studies of complex traits. Ganna et al. (Ganna et al., 2013) sought to identify SNPs associated with being a twin *per se* and found no difference between twins and singletons in the main analysis that combined monozygotic and dizygotic twins and compared them with singletons. However, stratifying for zygosity, the authors found two SNPs that were genome-wide significant in dizygotic twins. This supports that twin samples can be used without bias in genetic trait-specific studies, together with non-twins, if there are no genetic variants associated with both the trait under investigation and

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being a dizygotic twin, as monozygotic twinning is a random event.

Twins are unique, and for some studies this is a factor that needs to be taken into consideration, e.g. in studies of congenital malformations where the intertwined intrauterine environment can result in malformations (e.g. acardia) that only occur in monozygotic twins. However, for understanding the determinants of the variation in cognition and behavior, the advantages of twin studies clearly outweigh the potential disadvantages and biases. Even in traits for which there is a mean difference between twins and singletons, e.g. IQ in older cohorts, it seems plausible that it is the same factors in twins and singletons that cause variation around their respective mean IQ. Finally, results from twin studies should be interpreted together with results from other designs and study populations that have other strengths and weaknesses, to provide a triangulation and thereby a better understanding of the trait under study.

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