Commentary: Twins, worms and life course epidemiology

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Scientists can be remarkably flexible when investigating the nature of health and survival, taking advantage of populations from roundworms to humans to gain insight. Yet, flexibility can foster concern over generalizability. In this issue of \textit{IJE}, Öberg \textit{et al.}\textsuperscript{1} provide evidence on the generalizability of findings with twins, one of epidemiology’s most popular special populations, by showing that morbidity and mortality patterns in more than 49,000 Swedish twins born in the middle third of the 20th century are similar to those of non-twins. Specifically, they found that twins had the same risk of cardiovascular disease, overall cancer and death as the background population and as their non-twin siblings. The unique methodological strengths of this study make it an important addition to a growing body of research showing that twins are unremarkable with respect to a broad array of medical, cognitive and psychological outcomes.

Whereas twin studies have long been recognized within genetics and genetic epidemiology as one of a few valuable research designs to assess or control for the influence of familial factors on various phenotypes, there has been considerable scepticism towards the use of twins in life course epidemiological research. Among the main concerns is that twins could be non-representative of the source population due to their third trimester intrauterine growth restriction, potentially leading to fetal programming.\textsuperscript{2,3} Furthermore, the higher occurrence of prematurity, some cognitive malformations and neonatal death, as well as the unique experience of being reared with an age-matched sibling and, at least for dizygotic twins, having parents who are on average older, have encouraged the view that twins surviving to adulthood may be different. Concerns over the uniqueness of twins may have been further heightened over the past 30 years, as artificial reproduction techniques have accounted for an ever-larger proportion of twin births, leading to the characterization of twins as being on average socially advantaged (e.g. having older and better educated parents), but maybe biologically disadvantaged (e.g. having less fertile parents).\textsuperscript{4}

The Swedish finding that being a twin does not affect late-life health is in agreement with other large-scale studies of twin–singleton differences in cardiovascular disease, diabetes and mortality. For example, a recent study of diabetes found no difference in 10-year period prevalence in over 77,000 twins and 215,000 controls.\textsuperscript{5} One of the major strengths of the new study by Öberg \textit{et al.}\textsuperscript{1} is the comparison with siblings who are exposed to the same socio-economic and genetic background as the twins, enabling a more sensitive test of the potential adult health consequences of being a twin. The failure to find twin–sibling differences despite this increased sensitivity provides the most convincing demonstration of the typicality of twins.

The study by Öberg \textit{et al.}\textsuperscript{1} does not address twin functioning prior to adulthood, nor does it consider the more recent cohorts that may have been influenced by assisted reproduction. Other research, however, suggests the absence of twin–singleton differences in these instances as well. For example, it has recently been shown that twins born in Denmark in the late 1980s have academic performance in adolescence similar to singletons,\textsuperscript{6} whereas a recent study of US-born twins suggests that they have normal brain development.\textsuperscript{7}

For the vast majority of twin births, the apparent absence of long-term health consequences is in many ways remarkable. Twins have markedly reduced birthweight, and twin pregnancies and births are known to carry excess pre- and perinatal risk.\textsuperscript{8} In this case, a developmental origins hypothesis might lead to the expectation that twins would show excess rates of cardiovascular disease and mortality in adulthood. The consistent failure to find increased...
twin risk, however, suggests that reduced fetal growth, at least the reduced fetal growth twins generally experience, may not be the basis for the developmental origins of adult cardiovascular disease.

In addition to its theoretical significance, research on twin–singleton differences also has potential clinical and practical significance. Firstly, twins comprise 2–5% of birth cohorts and the ‘prognosis’ for twins, who are often born premature and small-for-gestational-age compared with singletons, is therefore of considerable interest for many families. They should be reassured by these findings. Secondly, if twins had adult health trajectories different to those of singletons, then results from twin studies may not generalize to the population of non-twins. This is of importance, because several of the nationwide twin studies were initiated very early in the modern epidemiological era and hence constitute many decades of data collection, follow-up and research on very large cohorts. These investments in time and resources are supported by findings such as those by Öberg et al.1

The persistent concerns about the external validity of life course epidemiological studies on twins are puzzling considering the many powerful studies showing no twin–singleton differences in adult health. Even when differences ‘are’ present, e.g. slightly lower mean adult height in older cohorts of twins, it seems likely that factors affecting variation around the mean would be the same in a population of twins as in a population of singletons. Twins are by no means the only ‘special population’ used in epidemiological research; the study of populations as diverse as nurses, Mormons, conscientious objectors, Catholic nuns and British bureaucrats has provided important insights into disease morbidity and mortality. And although we agree that the validity of all research designs needs to be continuously and rigorously evaluated, concerns over external validity should be put in a reasonable perspective. For example, in ageing research, the mortality pattern of the 959-cell nematode, Caenorhabditis elegans (a rather ‘special population’ when compared with humans) has been key to understanding the contribution of stochasticity to mortality patterns. Of course findings on C. elegans need to be validated against human populations, which in this case they have by reference to another special population, Scandinavian twins.9,10

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**References**


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