
The Foetal Origins of Adult Disease: Interpreting the Evidence From Twin Studies

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Twin studies have a contribution to make to the debate concerning the foetal origins of adult disease. Twins are growth retarded compared to singletons and experience post-natal catch-up growth. However, there is no evidence that twins are at increased risk of cardiovascular disease. Studying whether discordance in size at birth within monozygotic twin pairs is predictive of discordance in later life disease should help resolve whether the association between size at birth and later disease is due to common genetic factors. Results from studies of blood pressure in childhood and adult life looking at these within twin effects are far from conclusive. There are, however, methodological problems in the interpretation of these results, not least of which is the relatively small numbers of twin pairs studied. Studies exploring the effect of zygosity and chorion type on later disease provide may provide a useful extension of the research agenda. In summary, twin studies to date have raised more questions about the foetal origins hypothesis than they have resolved.

The hypothesis, first advanced by Barker over 15 years ago (Barker & Osmond, 1986) that a number of important adult diseases including cardiovascular disease, hypertension and non-insulin dependent diabetes have their origin in foetal life (Barker, 1998) remains a controversial one. This is despite the accumulating body of observational evidence that now exists showing broadly consistent inverse associations between size at birth and these later conditions that cannot be simply explained by artefact, bias or confounding with socio-economic factors. (Eriksson et al., 1999; Frankel et al., 1996; Huxley et al., 2000; Leon et al., 1998)

Twin studies have been identified as providing a potentially highly informative contribution to assessing the foetal origins hypothesis (Paneth & Susser, 1995). Two areas stand out as being of particular interest. Firstly, twins are growth retarded compared to singletons and thus it is of direct interest to know whether they also are at increased risk of cardiovascular disease and other conditions linked in observational studies of singletons to size at birth. Secondly, resolving whether the association between size at birth and later disease is due to common genetic factors (Hattersley & Tooke, 1999) appears to be tractable by studying whether discordance in size at birth within monozygotic twin pairs is predictive of discordance in later life disease. This issue of *Twin Research* adds to the growing literature in this field. It brings together a series of papers involving

studies of twins around the theme of the early origins of later disease that address these two questions as well as several others of importance.

Twins Compared to Singletons

Compared to singletons twins are born of lower birth weight and have shorter average gestations. On average they are 0.8–0.9 kg lighter than singletons at birth and are delivered 2–3 weeks earlier. Shorter gestation only accounts for a small part of the size deficit at birth of twins compared to singletons: at term twins still being 0.6–0.7 kg lighter than singletons. Twin size at birth is also reduced compared to singletons with respect to other birth dimensions, including crown-heel length and head circumference (Wilson, 1974).

Twins are not only appreciably smaller than singletons at birth, they also are subject to very substantial catch-up growth. By 9 years of age twins on average have almost converged with singletons in terms of height and weight with much of the catch-up growth occurring in the first two years of life (Wilson, 1979). A recent study of nearly 4900 twins and 2500 singletons in Finland found no differences in height at age 17 years and almost no difference in weight (Pietilainen et al., 1999). In the context of the foetal origins hypothesis this feature of twin growth is intriguing as small size at birth followed by catch-up growth in singletons has been proposed as an important risk factor for coronary heart disease (Eriksson et al., 1999; Eriksson et al., 2001). This distinctive catch-up growth in twins provides a further reason for enquiring about whether they have a higher risk of coronary heart disease or have raised blood pressure compared to singletons.

The first analysis of twin mortality from coronary heart disease was based on routine Swedish data covering almost 15 thousand twins. Mortality from coronary heart disease in female twins was almost exactly the same as that for the Swedish population as a whole, while male twins had a mortality rate that was 0.85 of the national rate (Vågerö & Leon, 1994). A similar analysis of all cause mortality from age 6 years, based on data from the Danish Twin Registry,

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showed twins to have very similar rates to that of the general population regardless of zygosity (Christensen et al., 1995). A new analysis of more extensive data from the Danish Twin Registry is presented in this issue of *Twin Research* (Christensen et al., 2001). This paper, based on the adult mortality experience of almost 20 thousand twins, again fails to detect any difference between twins and the general population either with respect to all causes or cardiovascular mortality.

Turning to blood pressure a New Zealand study (Williams & Poulton, 1999) found that twins in fact had a significantly lower systolic blood pressure than singletons at age 9 years after adjustment for a range of potential confounding factors. This negative finding is again supported by a study reported in this issue of *Twin Research* from the Netherlands Twin Registry (de Geus et al., 2001). It was found that adult twins do not have a different mean systolic or diastolic blood pressure or prevalence of use of anti-hypertensive medication than singletons. What is particularly convincing about this study is not only the care with which blood pressure was measured, but also the fact that the results were the same when comparisons were made between twins and singletons within the same families.

The evidence to date, therefore, is completely consistent in failing to find any evidence that twins are at higher risk of cardiovascular disease or raised blood pressure compared to singletons despite their appreciably impaired growth in utero and the rapid and substantial catch-up growth they undergo in childhood. In their contribution to this issue of *Twin Research*, Phillips et al. (2001) argue that the intra-uterine growth retardation of twins is not the same as that experienced by singletons, thus explaining the absence of an effect on cardiovascular risk in twins. While this may be true there remains considerable uncertainty about the nature of down regulation of foetal growth in twin pregnancies compared to that suffered by singletons. Even the point in gestation at which growth is down regulated in twin pregnancies is not clear. From studies of twin deliveries it appears that it is only after 30–32 weeks that there is a measurable deficit in twins compared to singletons delivered at the same age (McKeown & Record, 1952). More recent ultrasound studies, however, suggest that growth velocity in twins may be depressed earlier than 30 weeks (Taylor et al., 1998).

Further work is required to better understand the distinctive nature of reduced growth in twin pregnancies. Evidence that the primary process is environmental comes from observations made by McKeown and Record (1952) in the early 1950s. Their studies of outcomes of singleton, twin, triplet and quadruplet pregnancies suggest that the point in gestation when down regulation of growth occurs in different types of multiple pregnancy is when the total weight of all the foetuses in the pregnancy exceeds a certain common threshold.

Variation Within Twin Pairs

The variation in birth weight within twin pairs offers a number of important opportunities to test aspects of the foetal origins hypothesis (Leon, 1999). The most obvious is that if variation in size at birth within monozygotic (MZ) twin pairs is correlated with some later outcome, this pro-

vides rather powerful evidence for foetal programming in that the association cannot be explained by genetic factors. Studies of within twin pair differences in size at birth have looked at later blood pressure (Baird et al., 2001; Dwyer et al., 1999; Ijzerman et al., 2000; Nowson et al., 2001, Poulter et al., 1999) and non-insulin dependent diabetes (Poulsen et al., 1997) and most recently acute myocardial infarction (Hübinette et al., 2001).

The results of the first studies (Dwyer et al., 1999; Poulsen et al., 1997; Poulter et al., 1999) suggested that within pair differences in birth weight were inversely associated with raised blood pressure and non-insulin dependent diabetes. However, the most recent studies of blood pressure (Baird et al., 2001; Ijzerman et al., 2000) together with a paper in this issue of *Twin Research* (Nowson et al., 2001) provide little evidence for such an effect within MZ twins. The recent study of acute myocardial infarction (Hübinette et al., 2001) also fails to provide good evidence of an effect within MZ twins. However, their results show that the MZ twin who has suffered an acute myocardial infarction to be on average lighter at birth than their co-twin who has not had an acute myocardial infarction. In contrast within DZ twins cases tend to be heavier than their unaffected co-twin.

One of the difficulties in interpreting the evidence in this area is that the studies tend to be based on relatively small numbers. Two of the blood pressure studies have 16 MZ twin pairs each, one has 58 and the largest 167 pairs. The study of acute myocardial infarction (Hübinette et al., 2001) is based on only 40 MZ twin pairs and 72 DZ twin pairs. The effects are thus not measured with much precision, suggesting that it is a priority to undertake a meta-analysis of all available data in order to make further progress.

It has been suggested that obesity could be related to undernutrition in utero. This possibility was first raised by a study of offspring of women subject to severe nutritional deprivation during the Dutch Hunger Winter at the end of the Second World War. At 17 years of age male offspring of mothers who experienced famine conditions while they were in their first trimester of pregnancy were found to be more obese than those who were subject to famine at later stages of gestation (Ravelli et al., 1976). However, a follow-up of this cohort at age 50 years failed to find this effect in men, although it was found in women (Ravelli et al., 1999).

The possibility that in utero circumstances may be related to adult height, weight and body mass index has been investigated using twins. In a study of 699 adult twins from the Minnesota Twin Registry (Allison et al., 1995) birth weight and gestational age were obtained from obstetric records and adult height and weight were self-reported. The correlation of within-pair differences in birth weight with adult height in MZ twins was 0.32 ($p < 0.0005$) and with adult weight was 0.136 ($p < 0.0005$), while there was little correlation of birth weight differences with differences in body mass index. This study concluded that the intra-uterine period has an “enduring impact on adult height but not relative weight”. The strength of the study was that it was large enough to detect such an effect despite the fact that as MZ twins grow up they become very similar in weight and height. A classic US study found that the correlation coefficient for height/length in MZ twins increased progressively

from 0.62 at birth to 0.94 at 8 years of age (Wilson, 1979). However, studies of MZ twin pairs highly discordant in size at birth, in which one of the twins was extremely small (< 1750g), have found that appreciable differences in size persist in childhood (Babson & Philips, 1973; Keet et al., 1986).

The paper by Ijzerman et al., (2001) in this issue of *Twin Research* also reports evidence of an in utero programming effect on adult height. They find that differences in height within 68 MZ twin pairs at age 17 years were directly related to differences in birth weight ($p = 0.01$) and to differences in birth length ($p < 0.01$). Similar but slightly stronger associations were also found for dizygotic (DZ) twin pairs. The weakness of this study is that birth weight and birth length were gathered from maternal reports which, as discussed later, could be biased by knowledge of postnatal differences in body size.

A similar use of twin studies to look at in utero determinants of body mass index has been made in two other papers in this issue of *Twin Research* (Johansson & Rasmussen, 2001; Whitfield et al., 2001). Using the Australian Twin Registry Whitfield et al., (2001) studied 1800 MZ and 2000 DZ twin pairs aged 17 to 87 years. Birth weight and adult height and weight were based on self and co-twin reports obtained through a questionnaire survey. In an analysis to partition genetic and environmental influences they concluded that there was a weak positive relationship between birth weight differences and body mass index within twin pairs having accounted for genetic influences. Johansson and Rasmussen (2001) employed a more transparent approach to the analysis of twin data to look at the question of in utero influences on body mass index. They analysed Swedish routine data in which information on size at birth of each member of 400 MZ and 284 DZ twin pairs from the Medical Birth Registry was linked to height and weight measured at the time of military conscription at 18 years of age. They also found evidence of a weak positive correlation between differences in birth weight and differences in body mass index within MZ twin pairs, but not within DZ pairs. On this basis they conclude that environmental circumstances in utero may influence later body mass index.

Finally, a similar design and logic is applied by Räsänen et al. (2001) in a paper on hay fever in relation to size at birth published in this issue of *Twin Research*. The study using a recent cohort of Finnish twins found only very weak evidence that difference in size at birth within MZ or DZ twin pairs was related to discordance in hay fever. The weakness of this study was that both birth weight and hay fever prevalence were as reported by parents.

In summary, the current literature in which within twin variation in foetal growth (notably in MZ twin pairs) is used to test the hypothesis that there is in utero programming of childhood and adult characteristics and disease risk is not as definitive as one might hope. The studies of blood pressure are not consistent in their findings and there is a major problem in terms of most of the studies being relatively small, and the one study of coronary heart disease fails to find a significant effect either within MZ or DZ twin pairs. However, the two studies looking at in utero influences on height both suggest that there is a real effect of foetal growth

that cannot be attributable to foetal genotype, while the studies of body mass index are less consistent. More independent studies are clearly needed in this area, and again pooled analyses are desirable in which the data from different sources are combined.

Aside from the issue of statistical power there are two important sources of bias that are not adequately addressed in any of the studies. The first applies to those studies in which birth weight was reported by the subjects or by their mother (Ijzerman, et al., 2001; Nowson et al., 2001; Rasanen et al., 2001; Whitfield et al., 2001). Here there is the concern that even if the birth weights of the twin pairs are recalled correctly, their post-natal size may lead to a biased assignment at recall of the two birth weights. To this extent the use of obstetric records to obtain size at birth data appears to be the best option. However, even here there may be problems. As Johansson and Rasmussen (2001) briefly mention, there may be “cross-over” effects, whereby the birth details of one member of a twin pair is erroneously associated with the post-natal “identity” of their co-twin. This problem does not arise in the more conventional types of twin studies where discordance in phenotype by zygosity is of principle interest. The distinctive feature of the studies discussed here is that there is an attempt to relate discordance in size at birth with that in later life. In most, if not all countries, the names of twins and any national identity number they may be given are formally assigned and registered some days if not weeks after birth. Unless reliable information on order of birth is taken into account there is a prima facie case for suggesting that cross-over may occur as defined above. On the assumption that cross-over would be random with respect to later outcomes, the effect on the sort of twin studies reported here would be to attenuate the strength of any real association. Future reports of these sorts of studies should discuss the extent to which cross-over may be a problem in their data.

Zygosity and Chorion Type

The possibility that circumstances in utero may be causally related to later disease provides a challenge to the conventional use of twin studies that aim to partition sources of variation in phenotype into those that are genetic and those that are environmental (Phillips, 1993). This was clearly recognised over 50 years ago before the advent of the foetal origins hypothesis. In a classic paper published in 1950 entitled *Primary Biases in Twin Studies*, Price (1950) argued that the “very severe” in utero environment of twins may result in underestimation of the strength of genetic effects. His argument was based on consideration of the particularly discordant pre-natal experiences that monochorionic MZ twins can be subject to. This subgroup of MZ twins share one placenta and have therefore to share the limited nutrients available through the single foetal supply line. They may also suffer more severe problems due to inequitable blood circulation between co-twins as occurs which in its most extreme form results in twin-twin transfusion syndrome. Price’s critical point is that MZ twins as a whole may have a more discordant in utero experience than DZ twins — thus potentially undermining the validity of the classic twin method. This bias may be becoming more serious in the

most recent cohorts of twins due to advances in neonatal care which is leading to the survival of more highly discordant MZ twin pairs, a point discussed in Sadrzadeh et al. (2001) in this issue of *Twin Research*.

This potential bias in the conventional twin design has been turned on its head by several investigators and used as a basis for exploring the foetal origins hypothesis. At a mechanistic level, Gardiner (2001) in this issue of *Twin Research*, explores the way in which twin-twin transfusion syndrome (that can occur in monochorionic MZ twins) may provide a model for exploring the long term consequences on vascular structure of patterns of in utero blood. Epidemiological studies have also attempted to exploit this “primary bias”. Using the Danish Twin Registry, Poulsen et al. (1999) looked to see whether zygosity was associated with metabolic variables involved in the pathophysiology of non-insulin dependent diabetes. They found evidence that MZ twins were more insulin resistant than DZ twins, even after excluding those with impaired glucose tolerance. They concluded that “excluding a genetic cause, ...and assuming a comparable postnatal environment, differences may be attributable to differences in the intrauterine environment.” These data are discussed again in a paper from the same group in this issue of *Twin Research* (Poulsen & Vaag, 2001) that reviews the utility of twin studies for investigating the effect of the intrauterine environment on insulin metabolism.

Phillips in his critique of twin studies (Phillips, 1993; Phillips et al., 2001) suggests that it was essential that chorion type was taken into account if proper inferences were to be drawn from them. However, studies of twins in which chorion type is known are uncommon. One exception is the East Flanders Twin Registry whose data has been analysed by Loos et al., (2001) in a paper in this issue of *Twin Research*. They studied 424 pairs of twins born in 1964 for whom detailed data on size at birth, gestational age and placental structure and chorionicity had been abstracted from delivery records. These twins were followed up when they were in their mid-30s. Detailed anthropometric measurements were obtained using a standardised examination protocol. The results of the study failed to find evidence of any association between adult obesity and body fat distribution and zygosity and chorion type, or of differences in MZ concordance in adult characteristics according to chorion type. Their interpretation of these findings was that any effect of foetal programming of these adult characteristics is small, and is unlikely to undermine the validity of the classic twin method, at least when used to study determinants of adult obesity and body fat distribution.

Conclusions

The relatively small number of twin studies of the foetal origins hypothesis of adult disease have raised more questions that they have answered. The fact that twins per se do not appear to have an increased risk of cardiovascular disease despite their considerably smaller size at birth and the substantial catch-up growth they are subject has yet to be explained. While there are only a few studies in which this question has been addressed, the evidence appears to be relatively firm and unambiguous and not subject to the sorts of biases that may affect other uses of twin data in this area.

There are two potential explanations for this absence of an effect of being a twin on cardiovascular risk. Phillips et al. (2001) argue that the factors which determine size at birth in twins differ fundamentally from those operating in singletons. However, the absence of an effect is what would be expected if the association seen between size at birth and cardiovascular disease in unrelated singletons is due to a common genetic factor.

There is a definite research agenda that starts from the absence of a twin effect on cardiovascular disease. More attention needs to be given to understanding the way in which down regulation of growth in twins and subsequent catch-up differs from that in observed in singletons. At a simple level more could be done to characterise the state of twins at birth compared to small singletons at birth. This should include more detailed anthropometric comparisons at birth, particularly with respect to differences in fat and lean (muscle) tissue — a factor that may well be important in terms of later disease (Yajnik, 2000) — regardless of whether the underlying mechanism involves in utero programming or is due to a common genetic factor.

The studies of differences within twin pairs have been the most disappointing. Many of the studies are very small and may be subject to a range of biases including self-report of birth weight as well as the problem of cross-over described above. The hope that this design could clearly establish whether or not the association between size at birth and later characteristics and disease rates could be due to a common genetic factor has not been realised. The results of studies are inconsistent and not coherent. If a common genetic factor was important, then one would expect to fail to see an association between differences in size at birth and later disease/characteristics in MZ twins but observe it instead in DZ twins. However, some studies that fail to find an effect within MZs also fail to find one within DZs. The small size of individual studies in this area clearly points to the importance of undertaking a meta-analysis. This will help with precision, but concerns about biases in the data are not going to be so easily overcome.

The exploration of the effect of zygosity and chorion type on later disease and characteristics is intriguing as it exploits what has been identified as the potential Achilles heel of classic twin studies — that is the assumption of equal effects of the prenatal environments of MZ and DZ twins. Unfortunately however there are only a very small number of studies that have used this approach. Further studies of this sort should be undertaken, which would have the merit of not depending upon the analysis of birth weights of individual twins, although there may be problems of statistical power given the relatively small average discordance in size at birth according to zygosity or chorion type.

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