Recruitment and Attrition in Twin Register Studies of Childhood Behavior: The Example of the Australian Twin ADHD Project

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There are a growing number of large-scale initiatives for twin registers of children. The Australian Twin ADHD Project (ATAP) is used to illustrate two key limitations which may arise with such studies, namely (1) the importance of including or possibly excluding families in which one or both twins have significant developmental disability, and (2) the selective failure to recruit and/or the selective attrition of families in which parents and children share behavioral difficulties. Initially ATAP excluded 1 in 6 of families whose twins were enrolled in the volunteer-based Australian Twin Registry (ATR), and as more children with significant problems were identified, these families were sequentially excluded. With longitudinal data over ten years, two points about retention were identified: the difficulty of retaining the twins in late adolescence, and the loss of the families whose twins had more ADHD symptoms. We discuss strategies for limiting the loss of families and for ensuring comparability of data across registers with similar interests but different methods of recruitment and exclusion.

Quantitative genetic methodology is requiring ever larger sample sizes to ensure sufficient power. In her recent review of European Twin Registers, Boomsma (1998) calculates that together they include over 350,000 twin pairs. But does bigger necessarily mean better? We use 10 years of longitudinal data from the Australian Twin ADHD Project ATAP (Hay et al., 2001a, b) to illustrate two particular problems for childhood register studies in general, and behavioral registers in particular. These are:

1. Child twins are enrolled by their parents and not by themselves. Given the high rates of morbidities such as cerebral palsy and intellectual disability in multiples (Bryan, 1992), a significant number of children may be enrolled who are inappropriate for behavioral studies. Their involvement may not be problematic in twin studies of physical traits, but for behavior, one needs to ensure that similarity of behavior in MZ twins relates primarily to genes, rather than to pre- or perinatal insults. Also, if one twin has a significant disability, behavioral problems in the other twin may result from the demands of the disabled child on the family, and the lack of attention to the non-disabled child. This point was made by Shere (1959) in her study of twins discordant for cerebral palsy and her claim that cerebral palsy has more behavioral impact on the unaffected than the affected twin raises an issue that has not received enough attention
2. If there is a genetic component to the behavioral problems of interest, then parental ability to respond may be limited. The influences may be as straightforward as the parent with reading disability being less able to comprehend, for instance, questionnaire items on language and reading development of the twins. ADHD has a particularly high genetic component (Levy & Hay, 2001) and consequently problems may be more subtle. For example, the disorganization that is a feature of adult ADHD (Hay et al., 2001b) can lead to parents forgetting appointments or misplacing questionnaires

This selective loss of more dysfunctional families may significantly impair the ability to generalize results of any genetic analysis across the range of behaviors. This may be especially serious for longitudinal studies with selective attrition of such families. They may be more likely to move or to divorce (Barkley, 1997), making it more difficult to find them for follow-up studies.

Our Australian Twin ADHD Project (ATAP) was first described by Levy et al. (1996, 1997) and Hay et al. (2001a). Discussion of the genetic analysis of *DSM-IV* Inattention and Hyperactivity-Impulsivity in ATAP can be found in Levy et al. (2001a). Many previous studies of ADHD had collected data on attentional problems as adjuncts to wider surveys of childhood behavior, using measures that often did not translate to the (then) *DSM-III-R* criteria. The need for a more focussed study led to us in 1990 to establish ATAP, which derives from the Australian Twin Registry (ATR) with recruitment through sources such as media campaigns, and in particular maternity services and the very active parents organization, the

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https://doi.org/10.1375/twin.5.5.324 Published online by Cambridge University Press

Australian Multiple Birth Association (AMBA). In 1991, parents of all eligible, contactable, 4- to 12-year-old twin pairs on the ATR were asked to complete a questionnaire about twins and similar-aged siblings. This included ADHD questions from *DSM-III-R*, plus birth details, history of medical, language and educational interventions, as well as zygosity. Many of the families had joined the ATR at the birth of their twins, and several years later had been lost to contact or had lost interest, despite our following the Dillman protocol (Dillman, 1991) of reminder cards, then resending the questionnaire for completion, and finally phone calls. The first contact resulted in families with significantly lower rates ($p < 0.01$) of ADHD symptomatology than those who subsequently agreed to participate. Figure 1 summarizes the stages of ATAP.

The initial response rate of 2350 of 3215 eligible families compares well with the UK-based Twins Early Development Study (TEDS) in which only 3442 of 7756 twin pairs identified and approached returned the background and test booklets containing vocabulary questions (Dale et al., 1998). Rarely reported in studies was our decision to exclude 412 families of the initial 2350 who indicated a major disability. Each decision was reviewed by the MD and child psychiatrist in our team — F. Levy — who has considerable experience of childhood diseases. Some of these disabilities were conditions such as cerebral palsy, major cardiac malformations, and intellectual disability, for which twins are at high risk (Bryan, 1993), as well as such common conditions as epilepsy, which is no more common in twins than in singletons (Berkovic, 1998). Others conditions were muscular dystrophy, leukemia, autism, Down syndrome plus rare genetic conditions including mucopolysaccridoses such as Hunter and Hurler syndromes, and specific environmental disorders such as meningitis. (Also excluded was one family in which the mother completed the behavioral questionnaire for the twin as she thought he would have been had he not died soon after birth. This illustrates what can happen in large-scale surveys where there is no direct contact with the family.)

The decision was made to exclude the entire family, even if only one child had a significant disability. Usually one of the twins was the affected family member, and more rarely a sibling. There is sufficient evidence now of the impact of a disabled child on the behavioral development of siblings, including the development of both internalizing and externalizing behavioral problems (Cuskelly et al., 1998). These make it sensible that a longterm behavioral study exclude these families. One of the most difficult dilemmas was whether or not to include the extremely preterm and exceptionally low birth weight multiples. And there were children as small as 24 weeks and 650 gms. Because of the possible relationship of these problems to later learning and ADHD difficulties, such children were only excluded if there were clear physical problems associated with preterm birth such as retinopathy.

At our second wave of data collection in 1994–95, we excluded a further 27 families. In some cases an early suspicion of pervasive developmental disorder was finally confirmed. Other instances concerned developmental conditions such as Duchenne muscular dystrophy in which prodromal signs may have affected the earlier data on this child.

Testing for Zygosity

The logistics of DNA assessment of zygosity make it impractical for large-scale surveys, and it is usual to rely on questionnaire assessment of zygosity. Whilst studies of adult twins have found that reliable information is obtained with use of only a few questions, we have found this not to be the case with children. At the time of the first assessment in 1991, we relied on only six questions but found that not only was there ambiguity in many cases, but also that parents were using behavioral similarity in their assessment of zygosity. Thus in wave 2 we moved to 12 questions (listed in Table 3 of Hay et al., 2001a), six on similarity and features, and six on confusion by others. We then used a Discriminant Function Analysis-DFA (Cohen et al., 1975) to combine these to maximize the adequacy of diagnosis. We also considered two common causes of confusion, namely placentation and blood group polymorphisms such

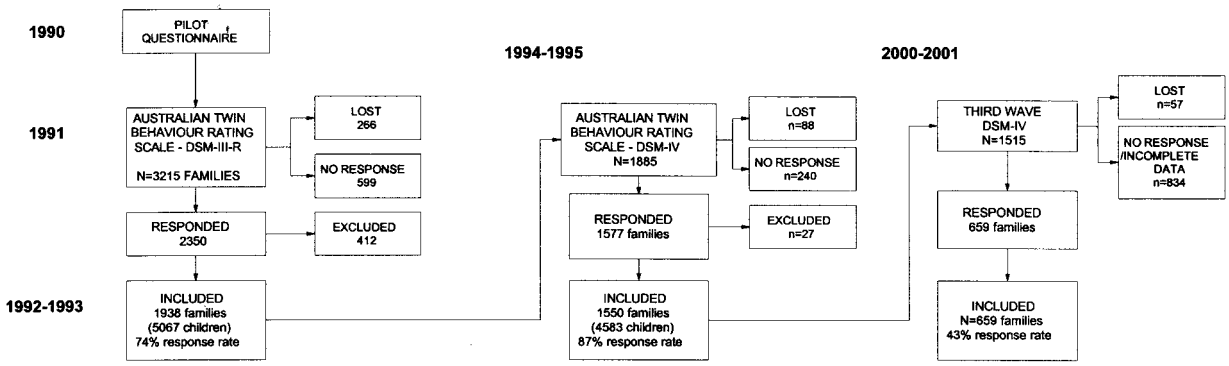

Figure 1
The Australian twin ADHD project

https://doi.org/10.1375/twin.5.5.324 Published online by Cambridge University Press

as ABO and Rhesus. The old myth that all MZ twins have one placenta is still common (Bryan, 1993), and parents may not recognize that being the same on common blood group systems does not mean the twins are necessarily MZ. Almost all twins whose parents were uncertain of zygosity were rated MZ by the DFA. Small differences in MZ twins led parents to uncertainly as to whether their children were MZ, yet they were reluctant to call them DZ.

Changes Over Time

ATAP has two complete waves of assessment, and a third almost complete. Figure 1 shows that the response rate was much worse in the third wave, when the twins were aged 12–20 and were providing self-report data (the main reason for information being incomplete). The response rates were fairly constant in the first two waves when the children were aged 4–12 and 8–16. In the third wave, it was families with the younger twins who continued to participate. Those with complete data across all three waves had twins who at Wave 1 were some six months younger ($p < 0.05$). A more serious issue is shown in Figure 2.

Families who completed all three waves had children with significantly fewer symptoms at Wave 1, the first assessment. This result was consistent across all DSM-III-R symptoms, as well as when these were sub-divided into the symptom groups of Inattention and Hyperactivity-Impulsivity. This may be an underestimate of the actual effect. ADHD is a contentious diagnosis in Australia, and a significant number of families at Wave 3 sent back blank questionnaires with a note indicating that ADHD was not a problem for their family. Thus we may be undersampling both the low as well as the high ADHD symptom families.

Conclusions

We cannot be the only group who have faced the dilemma of whether to exclude families with significantly disabled children from their large-scale twin studies of behavior. Yet this is rarely reported, though it is an issue to be considered in any register, especially ones in which there is little face-to-face contact with the families. We suggest that the extent of exclusion and the criteria for exclusion be clearly spelled out, as disability may be a significant source of differences in results between studies. Although 5% is the commonly cited figure for the percentage of children with a major disability, such disabilities are more common in multiples (Bryan, 1993), and if one takes into account both twins and singleton siblings, the chance of at least one child in a family having a disability is significant. In the past, some well-known twin longitudinal studies, such as the Louisville Twin Study (Wilson, 1983) chose to use very strict criteria which excluded a significant proportion of twins with lower birthweight and gestational age to make them more comparable to singletons. But is this the most appropriate way to deal with twin-singleton differences?

As well as differences in exclusion criteria, registers may differ in participation rates, and these are often difficult to identify. Just because a register is population-based, it is very unlikely to imply total involvement unless all the information is obtained by record linkage. The West Australian Twin Child Health (WATCH) study, commenced in 1997, was undertaken to establish a population-based

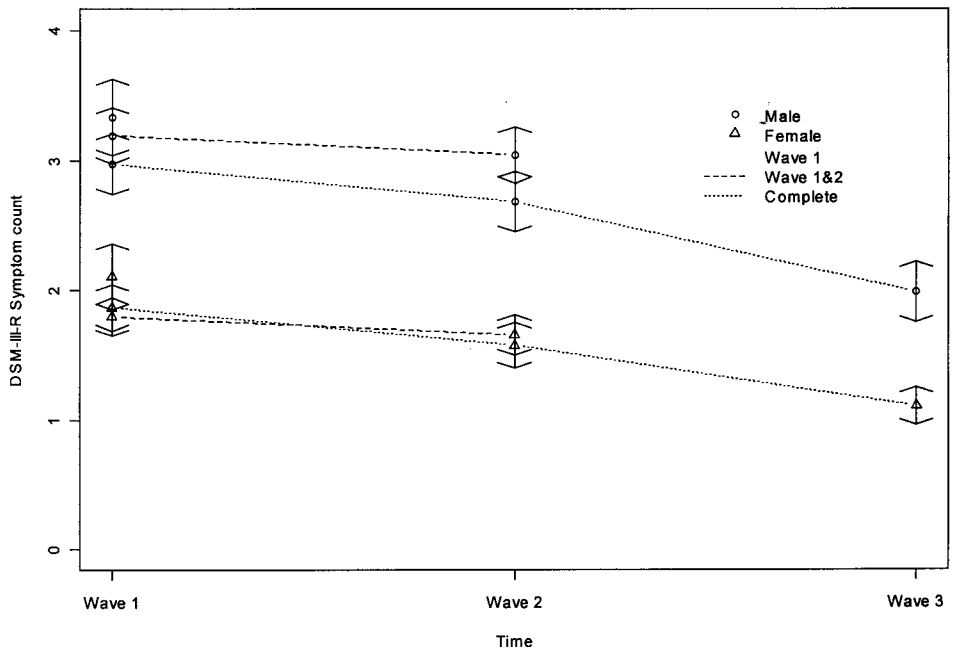

Figure 2

DSM-III-R symptom count at three waves for 3 participation groups W1, W1,2 and All.

https://doi.org/10.1375/twin.5.5.324 Published online by Cambridge University Press

twin register including all twins born in the state 1980–1992 (see Croft et al., this issue). All multiples born in WA over this period were identified using the WA Maternal and Child Health Research database, with linkage to other health-related databases such as the WA Death Register, WA Hospital Morbidity Database, and Birth Defects and Cerebral Palsy Registers. The WATCH databases included no information on ADHD symptomatology, but this was obtained subsequently by mailed questionnaire. The national volunteer registry (the ATR from which ATAP was derived) overlaps with WATCH since it includes those WA families who had previously volunteered for the ATR, before being identified and formally approached several years later for WATCH. There were no differences in patterns of ADHD symptoms between these cohorts.

This highlights that the key issue may not be how families are identified from population or volunteer sources, but in how they are encouraged to participate after identification. Strachan (1999) emphasizes advantages and disadvantages to each potential source of twins. While each method of subject selection has the potential to bias estimates both of prevalence and of genetic effects, too few studies to date have compared data from different recruitment methods. Ultimately data only come if families agree to give it. What are the best strategies for getting and retaining cooperation by parents of twins, especially in ADHD, where some failure to respond may originate in the parent's own psychopathology, and symptoms of disorganization and of reading difficulty? The ATR has reminder initiatives, such as fridge magnets (so that when you move you think about the ATR and notify them of change of address) which may be especially relevant to ADHD.

Our data show that considerable effort must be focused on retaining families at adolescence/early adulthood. Our web site, http://www.twinsandmultiples.org, provides much information for families of preschool and primary school age multiples. Far fewer resources are available for older twins, though the forum available on the web site may help them share experiences with other multiples of the same age. Some successful workshops for adolescent twins have been run in Australia, but such initiatives are labour-intensive and may not help retain the involvement of those twins with ADHD.

Some 12 years ago we suggested (Gleeson et al., 1990) that some basic measures routinely be collected in all twin studies, to check comparability across studies. Not only has this failed to happen, but it remains very difficult to find such information on most registers as the distribution of birthweights and gestational age, far less such basic data as the performance of twins compared with singletons. This may matter less for adult traits but needs to be considered in children with obvious twin-singleton differences in development (Wilson, 1983).

Implications for Molecular Genetics

In the case of childhood developmental disorders such as ADHD, twins are crucial for the developing EDAC approach of extremely discordant and concordant sibling pairs. They are the same age. As we have discussed elsewhere (Hay et al., 2001b) there are major changes in ADHD symptomatology during adolescence that may confound studies of singleton siblings. Whilst ADHD is slightly more common in twins than in singletons (Levy et al., 1996), we have shown that the aetiology is the same in twins and singletons and in both genders (Rhee et al., 1999) and also that ADHD is inherited as a continuum across the entire population (Levy et al., 1997). The issue is even more complex with the recognition in *DSM-IV* of ADHD subtypes and the implications this has for the definition of affected sib pairs. Given the number of successful and replicated linkages shown for ADHD, it is an ideal candidate behavior for collaborative research and so has been an NIH focus with its ADHD Molecular Genetics Network. But sampling problems are significant, as illustrated by the DRD4 association with comorbidity of ADHD with conduct disorder (Holmes et al., 2002). If ADHD families are difficult to identify, then families with ADHD plus conduct disorder are going to be even more difficult to find, simply as a consequence of the symptomatology. Holmes et al. got around this problem by redefining conduct disorder in terms of oppositional defiant disorder plus one conduct symptom, but is this an appropriate solution? What are the implications for sampling when one does include the very intrusive conduct disorder symptoms that concern such topics as mugging and rape?

Is there something that is peculiar to ADHD that lends itself to such research? While Simonoff et al. (1998) suggest that there may be biases in parental report that lead to DZ twins being reported as extremely different in ADHD symptomatology, this is generally not the case when the more customary *DSM-IV* items are used. Our recent paper by Rasmussen et al. (in press) indicates a remarkable similarity between our ATAP data and the data from St Louis, despite the fact that the two studies used different recruitment techniques, and in St Louis ADHD information was obtained by phone interview rather than by questionnaire. While there has been much discussion of biases on the reporting on internalising symptoms in children, ADHD may be more robust and given its high heritability an obvious focus for molecular initiatives in the future.

Clearly there is a challenge in twin registry studies to include adequate consideration of several issues, especially inclusion/exclusion criteria and attrition.

Acknowledgments

This work was supported initially by the Government Employees' Medical Insurance Fund and subsequently by the National Health and Medical Research Council (Australia).

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