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## Article

# Nick Martin and the Genetics of Depression: Sample Size, Sample Size, Sample Size

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## Abstract

Nick Martin is a pioneer in recognizing the need for large sample size to study the complex, heterogeneous and polygenic disorders of common mental disorders. In the predigital era, questionnaires were mailed to thousands of twin pairs around Australia. Always quick to adopt new technology, Nick's studies progressed to phone interviews and then online. Moreover, Nick was early to recognize the value of collecting DNA samples. As genotyping technologies improved over the years, these twin and family cohorts were used for linkage, candidate gene and genome-wide association studies. These cohorts have underpinned many analyses to disentangle the complex web of genetic and lifestyle factors associated with mental health. With characteristic foresight, Nick is chief investigator of our Australian Genetics of Depression Study, which has recruited 16,000 people with self-reported depression (plus DNA samples) over a time frame of a few months — analyses are currently ongoing. The mantra of sample size, sample size, sample size has guided Nick's research over the last 30 years and continues to do so.

**Keywords:** Major depressive disorder; genome-wide association study; twin study

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Major depressive disorder is common, affecting 10% of men and 20% of women in their lifetime. Its etiology is heterogeneous, with both genetic and nongenetic risk factors. With this level of complexity, most studies of the genetics of depression call for collection of larger sample size. Nick Martin was early to recognize this, and more to the point, to do something about it. As early as 1984, he published on 3810 twin pairs (Jardine et al., 1984), when prior to this, the largest published sample size for these traits was 587 twin pairs (Jardine et al., 1984). This sample size was a massive feat in the predigital era. Nick implemented standardized interviews (the famous 1981 white, 1989 green, 1991 yellow booklets), and his success might be attributed to his attention to detail and the personal touch — *hand*-written birthday cards, prints of flowers by his mother Beryl Martin, an acclaimed water color artist, and always posted with a proper stamp not a postmark! In designing these questionnaires, he recognized the value of recording quantitative measures of depression-related traits, such as anxiety and depression symptoms and neuroticism. Quick to adopt study designs that give best bang for buck, one study for depression and anxiety used a clinical phone interview of 2470 twins selected for their extreme scores for neuroticism in order to increase statistical power for a linkage study (Kirk et al., 2000). Given the need for an even larger sample, these data were combined with similar measures obtained in Dutch twins. Nick generously provided me (CMM) with the

opportunity to come to Brisbane and analyze those data (Middeldorp et al., 2005; Middeldorp et al., 2009; Middeldorp et al., 2006). By the time I (NRW) joined the group at the Queensland Institute of Medical Research (QIMR) in 2005, there were 12,772 twin pairs from 5000 families, with up to four longitudinal measures of neuroticism (Lake et al., 2000; Wray et al., 2007; Wray, Middeldorp et al., 2008). These data provided many important research contributions beyond the traditional variance component modelling: (1) genetic contribution to variation between people in neuroticism and depression symptoms was far more important than the shared environmental factors (Lake et al., 2000; Middeldorp et al., 2005); (2) despite differences between the sexes in prevalence of depression, the genetic factors are mostly shared (Middeldorp et al., 2006); (3) that the association between childhood sexual abuse and psychopathology arises at least in part through the influence of shared familial factors on both risk of victimization and risk of psychopathology (Dinwiddie et al., 2000); (4) the relationship between postpartum and lifetime depression (Treloar et al., 1999). Nick was never one to steer away from difficult or thorny problems, such as the complex relationship between marital problems and depressive symptoms (Beam et al., 2011), nicely put in this way:

> The study of marital relationships and depression is not unlike a game of cat's cradle: an interactive two-person game that can produce multiple outcomes, many tied up in a frustrating knot. However, behavior genetic studies disentangle one substantial knot — the realistic possibility that genetic and environmental selection account for part of the association between marital problems and depressive symptoms.... This is because twin

analyses control for measured and unmeasured genetic selection into having an unhappy marriage or feeling depressed. (p. 342)

They showed that poor marital support is associated with depressive symptoms after accounting for the genetic factors that contribute to the cat's cradle. Nick's foresight in collection of endophenotypes and subtypes of depression such as postpartum depression (Byrne, Carrillo-Roa et al., 2014), seasonal affective disorder (Byrne et al., 2015) and insomnia (Byrne et al., 2013; Byrne, Heath et al., 2014) which has proven fertile ground for me (EMB) to dissect the heterogeneity of depression.

Not surprisingly, these bold and evidence-based well-powered studies earned Nick a well-deserved international reputation and a high citation index. It was a realization that the most highly cited researcher in psychiatry was a geneticist (and very generous and inquisitive colleague) led me (IBH) to establish a now 20-year collaboration through the Brisbane Adolescent and Twin Study (Wright & Martin, 2004). Our shared passion for the importance of longitudinal data over this critical developmental period is a healthy population. Adolescents aged 12–14 years were recruited over the period 1992–2016 (N~3800 with personality data), with up to five waves of data collection (Couvy-Duchesne et al., 2018), with our report on the 25Up (25 years and older) study just published (Mitchell et al., 2019).

Nick has always been ahead of the times, first in data collection in twin studies and then in establishing a wet lab in collaboration with Grant Montgomery for generating the genotype data for linkage studies (Middeldorp et al., 2009; Wray, Middeldorp et al., 2008) and candidate gene studies (Wray, James et al., 2008; Wray, James et al., 2007). Of course, with the benefit of hindsight, we now understand why these studies failed (the traits are highly polygenic), but still an important stepping stone to where we are today. Next, came the genome-wide association studies (GWAS) and Nick's QIMR samples contributed to one of the first consortium studies, the MDD2000+ study, so named because of the goal to achieve a sample of 2000 cases (Wray et al., 2012), still massive in 2010. Our (NRW and EB) careers were boosted significantly by our entry card into international consortia provided by the QIMR depression samples. In 10 short years from the MDD2000+, the international Psychiatric Genomics Consortium (PGC) has accumulated genomic data on >175 K depression cases (Howard et al., 2019). Recognizing the need for large single cohort data sets recorded not only for case–control status but with measures of a wide range of symptom, lifestyle, comorbid disorder and drug response data, Nick applied for and was awarded one of the largest NHMRC Project grants to date, AU$2.5 for the Australian Genetics of Depression Study (AGDS; NRW, IBH and EMB are all coinvestigators). Nick used the skills well-learned in recruitment of twin cohorts to generate a new approach of direct-to-consumer case cohort collection, with the strong belief that individuals are well capable of self-reporting and indeed can report over a longer period of time than can be achievable in clinical cohorts. After small pilot trials (do not run before you can walk), over 15,000 people completed the online surveys and provided a DNA sample in a 6-month campaign that heavily used radio and TV interviews and social media (yes NGM is a very presentable media tart). The resulting data are rich, and the first publications (Byrne et al., 2019) are starting to come out. The UK GLAD (Genetics Links to Anxiety and Depression) study was modeled on AGDS and recruited 40,000 cases of anxiety/depression (Davies et al., 2019), providing useful reciprocal replication data.

Nick is well known for the welcome provided to new recruits and visitors, both scientifically and socially. It is because of him that many working in the field of quantitative and psychiatric genetics are proud to call Brisbane, Australia, home (NRW, EB and CM all moved countries to work here). In the month before his 70th birthday, Nick Martin started his NHMRC Leadership 3 Fellowship, and he is fired up for 5 more years of data collection and new research results. Over his career, Nick has had an uncanny talent for collecting world-recognized data sets that seem to have grown exponentially over time and are able to answer increasingly complex problems. In recognizing sample, sample, sample size, particularly when it comes to genetic studies of depression, we wait with anticipation what this new funding will bring.

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