# COMMENTARY



How can population cohort

studies contribute to our understanding of low prevalence clinical disorders? The case of autism spectrum disorders

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## **Practice points**

- When interpreting research in autism for clinical applications, always look carefully at the nature of the sample.
- There are very high levels of problem behaviors in children with autism, and differences emerge early.
- Positive psychological well-being in mothers of children with autism is intact.
- In early childhood, the risk for mental health problems in these mothers is not higher than in other mothers. The risk, however, may increase in later years.
- Up to the age of 5 years, the direction of influence is primarily one way: from mothers' well-being to later child behavior problems.

**SUMMARY** In this paper, we describe how secondary data analyses of large populationrepresentative surveys can be used to refine methodological designs on the prevalence of behavior problems and maternal mental health problems in families with a child with an autism spectrum disorder. We also suggest that prospective repeated measures usually available in cohort studies are extremely useful for understanding complex interrelationships between the broader autism phenotype and parental variables, in a way that is more relevant to the entire autism spectrum disorder population and not just those families with the highest levels of difficulties.

Research interest in autism spectrum disorders (ASDs) has soared during the past decade with substantial research activity focusing on trying to understand the reasons behind the reported increased prevalence of ASD [1]. Parallel to this, the interest in environmental factors related to the broader autism phenotype has increased partly because we are more aware of the systemic nature of clinical disorders and, most

importantly, because we acknowledge the importance of environmental factors for designing interventions targeting a clinical disorder, such as ASD, of unknown etiology which is only diagnosed symptomatically.

In large part, these environmental factors relate to family variables, especially parental mental health, and its association with core autism features and associated problem

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behaviors. ASDs are present in approximately 1% of the population [2,3], although more recent figures suggest that prevalence may actually be higher [4]. The core features of this disorder, which underlie most diagnostic systems, suggest impairments in social interaction and communication and a restricted repertoire of interests and behaviors. Although not part of the autism features, ASDs in children are associated with very high levels of behavior problems (such as hyperactivity, aggression, self-injury and emotional problems), and a number of case-cohort studies that have compared children with ASD to children with Down's syndrome, fragile X, intellectual or developmental disabilities, psychiatric disorders or typical development tend to conclude that behavior problems are more prevalent in the ASD population [5-7]. In similar case-cohort designs, the well-being of these children's parents is shown to be at a disadvantage compared with parents of other groups of children, especially in terms of increased psychological distress, depression and increased levels of physical health problems [5,7,8]. Case-cohort studies typically rely on referred or self-referred samples for participation and one advantage of this approach is the ability to include large numbers of participants from a population with a relatively low prevalence.

However, there is a methodological complication that threatens the validity of findings of increased difficulties for children with ASD and their parents because psychiatric problems tend to be overestimated in clinical populations [9]. In addition, ASDs are often accompanied by the presence of an intellectual disability (ID; present in ~50% of this population) and it is difficult to separate the effects of ID from those of the ASD on children's behavior. There are several reasons for this, including the heterogeneity of ASD symptomatology and its overlap with behaviors frequently observed in children with an ID, especially those at the lowest spectrum of intellectual ability (e.g., repetitive and stereotypic behaviors). To control for this, case-cohort studies either exclude children with an ID from their ASD samples, or include ASD children with specific ID levels to compare them to children with similar levels of ID without the associated ASD. In either case, findings of elevated levels of problems are not representative of the entire ASD population. We propose that large population-representative studies can be used to examine levels of behavior problems in children

with an ASD and their parents' well-being. This research approach addresses the issue of sampling bias, while at the same time allowing us to control for any ID effects on behavior.

In line with this proposal, we conducted two studies using data from large studies which included participants randomly selected to be representative of the entire UK population. In our first study, we examined the levels of behavior problems (hyperactivity, emotional symptoms and conduct problems) in 5-16 year-old children drawn from a survey designed to measure psychiatric morbidity in children and adolescents in the UK (Office of National Statistics 1999, 2004 Mental health survey of children and adolescents [10]). ASD was diagnosed, in the context of the survey, using a standardized psychiatric clinical interview-based assessment, and the presence of ASD was independent of the probability of being included in the study. This independence was achieved because participants were randomly selected from a child benefit register, which, in the UK, is a no-means tested benefit given to the parents of all children residing in the country. We compared children with ASD (n = 51) to those with ASD and ID (n = 47), children with ID only (n = 590) and children with neither condition (comparison group; n = 17,727). Borderline and abnormal levels of hyperactivity, emotional symptoms and conduct problems were highest among children with ASD with or without an associated ID, and the same pattern was evident for the mothers' emotional disorders (although maternal positive mental health was not different among groups) [11]. To examine the independent association of ASD and ID, multivariate regression models showed that controlling for child gender, age, family socioeconomic position, maternal mental health (emotional disorder and positive wellbeing) and the moderating role of socioeconomic position, the presence of ASD and ID significantly and independently increased the odds for behavior problems in children.

As this study included children of different ages, we applied the same design in a group of children who were all 5 years of age to control for any developmental effects on behavior [12]. Participants were drawn from the third survey of the Millennium Cohort Study (MCS), an ongoing birth cohort study designed to prospectively capture the development of approximately 19,000 children representative of the UK population. Comparing children with ASD with those with ASD and ID, ID only, and a comparison group that was typically developing, the highest levels of behavior problems (hyperactivity, emotional symptoms and conduct problems) were present in children with ASD with and without ID, although, with the exception of hyperactivity, they were not significantly different from behavior problems in children with an ID only. Similar to the previous study, after controlling for child gender, family socioeconomic position and maternal mental health, the presence of an ASD and the presence of ID significantly and independently increased the odds for all three types of problem behaviors. In this study, we were able to examine more aspects of maternal well-being, including the presence of serious mental illness, low quality of life because of psychological distress and physical health problems, and life satisfaction. Similar to the previous survey, there were no group differences in positive adaptation (i.e., life satisfaction), but unlike the previous survey, the measures of negative psychological adaptation did not suggest that mothers of children with an ASD were systematically worse off than the mothers of the other groups of children [12].

While this discrepancy in results between two population studies could be related to the younger age of the children in the MCS, the more robust and detailed aspects of maternal well-being examined here seem to question the disadvantage evident in most case-cohort studies. While a further advantage of case-cohort studies is the better ascertainment of ASD and ID status, this is not always possible in large population representative samples, such as the ones used in these studies. Most such studies rely on parental report and this was the case for our second study too. However, the prevalence of parental report of ASD (0.92% [12]) was very similar to current known estimates [2,3,10], and the identification of ID using information from the surveys - as opposed to clinical ascertainment - avoids potential over-identification of ID in clinical ASD samples [13].

A further advantage of population surveys is the potential for longitudinal research, especially research that can capture problems as they emerge (i.e., prospective designs). This advantage comes into play mainly when we wish to investigate risk and resilience factors. We found that, after controlling for the presence of ASD and ID, children's behavior problems significantly increased the odds for negative psychological adaptation in mothers, and vice versa [11,12]. Looking at the association between behavior problems and parental mental health within ASD families, other researchers also consistently identify children's behavior problems as significant predictors of parental well-being, even after controlling for the severity of the autism symptoms [14–16].

However, it is impossible to infer causality in the context of cross-sectional designs. To test whether child behavior problems are significant risk factors for decreased parental well-being, we need longitudinal studies with repeated measures of parental well-being, ideally before children's behavior problems emerge. This is extremely difficult to achieve when relying on clinical populations, as children and families will have accessed services precisely because of emerging difficulties. Longitudinal research in referred ASD populations in mid-childhood suggested that the relationship is bidirectional, with changes in child behavior affecting changes in maternal well-being [17]. However, the assumption of causality relies on temporal precedence [18], and this is where prospective birth cohort studies can be very useful in allowing researchers to follow up a population with a clinical disorder (such as ASD) as behavior problems emerge. In our latest analysis, we examined the development of behavior problems in 132 children with ASD (identified at age 5 in the third survey of the MCS) at 9 months, 3 and 5 years, and its association with maternal well-being also measured at the same time points [19]. The bidirectionality of the longitudinal relationship was examined by modeling maternal and child outcomes simultaneously to allow for concurrent associations (which all previous studies indicate are significant) when examining longitudinal effects. Findings suggested that some aspects of earlier maternal well-being (namely psychological distress at age 3 years, life satisfaction at 9 months and at age 3 years, and physical health limitations at age 3 years) had significantly affected children's later problem behaviors, but in none of the models did children's problem behaviors show any longitudinal effects on later maternal well-being.

The absence of reciprocal long-term effects might be associated with the fact that maternal and child behaviors had not become more intertwined through longitudinal exposure by the time the children were 5 years of age. However, recent findings from studies modeling longitudinal change in behavior problems in older children with ID also suggest a lack of reciprocal change [20], indicating that it may not be the young age of the children in our sample but that children's behavior problems may not necessarily be a causal risk factor for long-term maternal mental health problems. Our findings also identify significant longitudinal effects of maternal well-being, which suggest that negative outcomes (such as psychological distress and physical health limitations) may be causal risk factors for increases in later behavior problems, while positive adaptation (such as high life satisfaction) could strengthen families' resilience by decreasing later behavior problems.

#### Conclusion

We believe that population cohort studies have several methodological advantages: better sampling design, larger sample size affording sufficient numbers of low prevalence clinical samples to be identified, and potentially repeated measurements. These strengths allow the refinement of our knowledge of the broader phenotype of ASD and its interactions with environmental variables in a way that is potentially more useful for developing interventions and policies relevant to the entire ASD population. Secondary analyses of existing data can be considered as research of secondary importance by the research community and by funding bodies, but we think that the methodological refinement of a well-designed population survey can often outweigh some of the limitations.

Of course, secondary data analyses are not suited to all research questions. In our case, there was a good match because we were looking to examine well-researched relationships using better identified samples. Should our findings be replicated, these secondary analyses carry some important messages for the families of children with an ASD. Despite difficulties, positive wellbeing in mothers remains intact, and, at least in the early years, mothers of children with an ASD do not consistently present the highest levels of psychological difficulties. Their children's difficult behaviors are indeed present at high levels and they are associated with parental well-being in the short-term, but they may not be the main driver of adverse long-term mental health problems. While reductions in children's behavior problems should be targeted early for reduction, more systemic intervention approaches should also consider increasing family resilience by boosting positive adaptation (e.g., increasing life satisfaction) and decreasing psychological distress.

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