Editorial: Closing in on causal links between environmental exposures and human development using observational data - “Confound those confounders!”

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A central goal of developmental psychopathology research is to understand the mechanisms linking environmental exposures in childhood to variations in mental health and development across the lifespan. The Journal of Child Psychology & Psychiatry has featured many influential studies and reviews addressing this important topic. It has been at the heart of ensuing discussions about the strengths and limitations of different designs to bolster causal interpretations, what these have told us so far and what the mechanisms of action might be (Sonuga-Barke, 2019). There has also been consideration of how these research findings might be used to improve prevention and/or treatment by changing environmental circumstance and experiences. Indeed, there is considerable pressure, both from within the field and outside, to move from basic science into translation as quickly as possible - and quite rightly. But of course, at the same time, researchers are cautious not to overstate claims from their studies, being acutely aware of how challenging questions about causal processes can be to answer given the methodological tools we have at our disposal and the complexity of the phenomena we seek to understand. Furthermore, apparent breakthroughs can too often slip away when they are subjected to rigorous replication attempts or when new and more exacting study designs challenge the assumptions earlier studies were predicated on (Rutter & Pickles, 2016). This month’s issue of the journal presents a series of papers that are powerful illustrations of these matters. The papers address several specific environmental exposures, including prenatal factors, parenting and adverse childhood experiences, and illustrate important principles that should be used as a basis for taking the field forward.

The research review by *Scorza* et al sets the scene nicely – detailing some of the prospects and challenges in understanding the role of epigenetic mechanisms in the association between early life (including prenatal) exposures and biobehavioural development. Their particular target is to understand the intergenerational transmission of disadvantage. Through what mechanisms, they ask, does poverty impact on children’s brain development, physical and mental health, cognitive development and scholastic achievement, and how might these perpetuate cycles of disadvantage? They outline a substantial body of animal experimentation which seems to clearly show that early exposures in utero or in the early postnatal period may bring about long-term changes in neurodevelopment via gene regulation. Demonstrating such effects in humans has turned out to be far from straightforward, although there are quite a number of intriguing leads, including possible influences of early adverse childhood experiences on pregnancy outcomes and antenatal stress effects on birth and childhood development. However you look at it, there is no getting away from the fact that there is a stark gap between what animal studies show and what we can convincingly demonstrate in humans. The authors note a series of critical design considerations for future research in this area, including gathering prospective data, sampling populations with plenty of variation in levels of disadvantage and obtaining direct measurements of brain development. I would add to that the need to disentangle genetic from environmental sources of variation. The all-too-obvious competing explanation for ‘intergenerationality’ is of course genetics, and although there is some excitement about

mechanisms like methylation for shedding light on the biological effects of the environment, and of intergenerational transmission (Sonuga‐Barke & Fearon, 2018) we know that patterns of methylation are themselves partially heritable or may be influenced by genes via gene-environment correlation (Chiarella, Tremblay, Szyf, Provençal, & Booij, 2015). So, simple associations between methylation status and child outcome are not easy to interpret on their own. And of course, we are never able to do experimental work with humans in which individuals are randomly assigned to adverse environmental circumstances, which might otherwise resolve many of these issues. So, we rely in large part on observational studies, natural experiments and counterfactual logic to narrow down the search for causes as best we can.

Axelsson et al present a very interesting study that illustrates some of these challenges. They investigated the hypothesis that variation in the gut microbiota in early life might alter risk for later ADHD diagnosis. Although this idea has been floated and investigated in a small number of studies, Axelsson et al.'s study is extremely important because it leverages data from a very large Danish registry, which includes sibling groups. The large sample (N=671.5k; nearly 18k ADHD diagnoses) provides a lot of statistical power, which is crucial for detecting what might be small effects, and—by comparing siblings within the same family—it provides tight control on both measured and unmeasured confounders. Although they did not have direct measures of infant gut microbiota, they collected proxy data on this: mode of delivery at birth (caesarean versus vaginal delivery) and antibiotic use, both of which have persistent impacts on the microbiota. The results were sobering, as they showed that confounders had quite an impact: an apparently substantial association drifted away when confounders were carefully controlled. A great deal of the reduction in association reflected the impact of unmeasured confounders – shared, family-level differences in both rates of the exposure (caesarean delivery and antibiotic use) and ADHD. In other words, while families with caesarean delivery or high antibiotic use were more likely to have children with ADHD, it was not necessarily the exposed child within that family who received the diagnosis (it was just about as often the unexposed sibling). Further evaporation of the association occurred when measured confounders were adjusted.

In addition to highlighting the importance of applying careful control for confounders, the paper also illustrates another critical point: the great value of routinely collected health data for addressing questions like this. There may never be a specific grant-funded research project that will collect data on this scale, so routine health data, when collected with sufficient rigour, is absolutely invaluable when statistical power is a limiting factor. Of course, there are limitations of routinely collected data, so the key is to obtain convergent evidence from different sources. For example, one might question the quality of the diagnoses obtained in this way, the role of referral bias, or the lack of direct biological assays, so studies with representative sampling and more intensive measurement will be crucial to complement the limitations of larger-scale routine datasets like this. It seems self-evident that wherever possible such efforts at triangulation should be as closely aligned as possible, for example by employing common measurement standards and protocols, so that joint analyses might be feasible and discrepancies in findings can be more easily spotted and interpreted.

Using similarly powerful population data from Scandinavia, involving more than a million routine health records, *Ginsberg and colleagues* deployed very much the same approach to the question of the association between ADHD and maternal infection during pregnancy. In this case, much like the previous paper, the unadjusted association between antenatal infection and ADHD was quite marked. However, once within-family confounds were examined by comparing exposed and non-exposed siblings the association disappeared altogether. Just like the Axelsson study, Ginsberg et al find that antenatal exposure and ADHD commonly aggregate in the same families, but when you look within a family, the exposed child is not more likely to receive a diagnosis of ADHD than a non-exposed sibling, which suggests that the exposure may be confounded with other factors and not a cause. The authors point out that much the same story had already been seen for the association between smoking during pregnancy and ADHD, although even that issue has not been fully resolved (see for example Dolan et al., 2016). A recent paper by Hannigan et al (2018) used a variant of the Children of Twins design to decompose the causes of intergenerational association between antenatal maternal depression and child internalizing and externalizing problems, and drew similar conclusions. A large proportion of the association between maternal antenatal depression and child internalizing problems (86%) was accounted for by common genes. The remaining 14% that was seemingly accounted for by environmental transmission disappeared altogether when *postnatal* maternal depressive symptoms were also controlled. These studies considered together are crucial in providing stringent tests of possible causal effects.

In all these cases, the puzzle is that animal experiments, which can definitively establish the existence of causal mechanisms, do show that antenatal exposures adversely affect foetal brain development, but we struggle to find compelling evidence that the same applies in humans. I am reminded of Moffitt, Caspi & Rutter's (2006) point that animal studies clearly show the importance of gene-environment interaction but establishing this in humans has been difficult. What certainly seems to come through much of this work is that a considerable amount of the 'action' is happening at the family level, and because a lot of genetic and social factors get intermingled at that level it is challenging, to say the least, to disentangle them. For some of these exposures, it could be that the signals we get from the data at the family level are indeed indicating some causal processes are at work, but measurement error (in the exposure and the outcome) makes it very difficult to discern which child is affected by which exposure within the same family. Heterogeneity and interwoven risk factors make this very hard to resolve. Another possibility is that within-family moderators disrupt the simple exposure-outcome association in ways that are not currently well accounted for. One can't help wondering whether cumulatively large genetic effects (of the kind identified in twin or family studies) are simply dwarfing more subtle environmental mechanisms, or that most of the business end of development is in gene-environment interplay. It would certainly be far too soon to conclude that antenatal exposures are not important.

When thinking about confounding variables it is critical to consider the fact that most causal influences have time-specific effects, but we rarely capture these. Even when we do take into account both time-varying confounders and time-varying causal influences we face major analytical challenges and the risk that we control out effects of interest (so called over-adjustment bias, see Mansournia, Etminan, Danaei, Kaufman, & Collins, 2017).

Handled appropriately though, longitudinal data can take us some way to addressing causal questions because individuals act as their own controls, ruling out a wide range of static confounders, potentially loosening the tight knot of risk factors that typically cluster at the level of the family when considered in aggregate.

Okuda et al adopt this sort of approach to address the role of parenting in antisocial behaviour in pre-adolescence. The authors present quite a large longitudinal study recruiting from two sites (one in the Bronx, New York and one in Puerto Rico), which examined the developmental relationship between parenting and antisocial behaviour repeatedly between ages 9, 10 and 11. The results demonstrated that earlier parenting predicted changes in subsequent antisocial behaviour, even when earlier antisocial behaviour and other confounders were controlled for. The authors also found that child sensation seeking traits interacted with parental monitoring – with a high level of association between sensation seeking and later antisocial behaviour in the context of low parental monitoring but not high parental monitoring. A similarly structured longitudinal study by *Zhang and colleagues* found evidence of bidirectional associations between academic achievement and externalizing problems in a sample of Chinese children across grades 5 to 9. In other words, deteriorating academic progress can lead to increases in externalizing problems, and externalizing problems can undermine academic progress. The data provide quite good evidence, within the limits of a correlational design, of potential causal influence. The implications of both these studies for intervention are quite clear.

One of the really big challenges in using longitudinal data to identify causal associations by ruling out unmeasured time-varying covariates is the substantial constraints imposed by measurement burden. In general, it can be very challenging to measure the processes of interest at sufficiently high temporal resolution, even when doing so might be critical for establishing meaningful patterning of development across time. Nowhere is this more evident than in the earliest stages of the lifecycle, where rapid change occurs. In their paper, *Pisch et al* measured infant sleep and memory function every two months from 4 to 10 months of age. Their data pointed to a potentially important connection between early memory performance and infant sleep. The study used sophisticated techniques to measure both of these variables – actigraph data for measuring sleep recorded over 7 consecutive nights, and eye tracking data during an experimental task to measure memory performance. The objective measurements and the high temporal resolution of the data collection were crucial in identifying developmental changes that would have been obscured by a single measurement or an overall average. Although not directly asking about causation, the study illustrates how some causal questions really need sophisticated and in-depth measurement and these are currently hard to scale up for use in the kinds of epidemiological studies discussed above. This is a serious impediment to progress in developmental science, and creative solutions, are, I hope, on the way, for example through the use of smartphone technology, wearable devices, AI-driven automated video and audio coding and the like.

Rasmussen and colleagues report fascinating findings from the Dunedin study tracing long-term connections between early-life indicators of adversity and inflammation in adulthood. The study taps into the rich seam of research exploring inflammation as a possibly critical mechanism linking psychosocial experience to physical (as well as mental) health. Inflammation of course is not a single biological entity, but a complex suite of regulatory

systems with diverse effects. Rasmussen and colleagues examined a novel marker of inflammation: soluble urokinase plasminogen activator receptor (suPAR). This marker of systemic inflammation is quite strongly linked to mortality and is thought to represent a more stable marker of chronic inflammation than some other commonly measured factors (such as IL-6, CRP). suPAR levels were quite consistently linked to indicators of ageing (measured from biomarkers and facial images) and self-reported health at age 38 years. Confounders loomed large again. For example, the association between early-life socio-economic status and suPAR was entirely removed when sex, BMI and smoking were controlled for, and indeed all of the early-life associations were substantially reduced by these covariates. Nevertheless, there remained a highly reliable association between adverse early experiences and suPAR (whereas all associations with CRP fell away after adjustments for confounds).

As we collect more detailed data, in higher volumes and with greater temporal resolution, and start to consider environmental exposures beyond the 'usual suspects' the challenge of sifting confounder from mediator and association from cause will grow ever more complex. Methodological and analytical innovation will be essential to keep pace with our improved technologies for capturing data (Zhao & Castellanos, 2016). Coordinated large-scale data collection efforts, and an informative mix of complementary natural experiments, experimental, longitudinal and genetically-informative designs, alongside rich measurements, will be essential to tackle the confounding problem and maximise the yield from these collective efforts.

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