



A few more questions for suicide prevention



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Despite decades of prevention and research efforts, hundreds of thousands of people die by suicide each year. Although incidence of suicide has declined in many countries, others are confronted with large increases.¹ Even in countries with decreasing overall suicide incidence, particular cohorts, such as those of middle-aged men, appear to be resistant to preventive interventions as shown by their stable or increasing incidence of suicide. Effective prevention of suicide is hampered by a paucity of knowledge of its causes, which is reflected in two major obstacles to prevention: the inability to predict the occurrence of suicide and the absence of a target for treatment. For example, many suicides will occur during a depressive episode, but not all depressed individuals consider suicide as a means to end their emotional pain and feelings of hopelessness. Even with any certainty about a risk, how this risk can be eliminated is unclear. The beneficial effects of available pharmacological or psychotherapeutic treatments on the occurrence of suicide are scarce, not to mention their potential harmful effects. To effectively prevent suicide, psychological and neurobiological markers are desperately needed for risk identification and targeted treatment.^{2,3}

Such markers can be identified via the study of the causes of suicidal behaviour. Suicide is never the consequence of a single cause. The evidence-based stress-diathesis model of suicidal behaviour⁴ takes the multiplicity of causes into account by stating that suicide is the consequence of an interaction between proximal and distal characteristics. Proximal factors include psychiatric disorders, such as depression. Two causes are known for the development of a distal vulnerability for suicide: genetic factors and early life adversities, such as childhood abuse. In *The Lancet Psychiatry*, Massimiliano Orri and colleagues⁵ report the findings of a systematic review and meta-analysis of a potential third cause—ie, antenatal and perinatal characteristics. Using data from 42 population-based longitudinal or nested case-control cohort studies (involving 21 different cohorts with sample sizes ranging from 140 to over 3 million and with follow-up periods ranging from 2 to 70 years), they report associations between in-utero and perinatal (<1 year of age) conditions and suicide. Major study findings include an association between

an increased risk of suicide and family characteristics (high birth order, having a teenage or single mother), socioeconomic position (low parental education), and indices of fetal growth (low birthweight and small-for-gestational-age at birth), independently of parental psychopathology. Given the scarce available evidence, no firm conclusions could be drawn regarding associations between early life factors and an increased risk of suicide attempts or suicidal ideation. Nevertheless, the findings add to the observations that childhood or adolescence risk factors for suicidal thoughts might differ from those for suicidal behaviour.⁶

The findings of Orri and colleagues⁵ provide new support for a developmental origin of health and disease (DOHaD) hypothesis of suicidal behaviour.⁷ Consequently, suicide prevention requires a few more questions to be asked, thereby targeting the two major obstacles to prevention (described above). First, the accumulation of evidence in support of the DOHaD hypothesis has reached a level at which the evidence should be used to inform practice.⁸ Evidence-based suicide risk assessment will need to include an investigation of antenatal and perinatal circumstances as a potential marker of suicide risk. Thus, in addition to questions about a familial history of suicide and a history of childhood adversities, risk assessment needs to address the identified family characteristics and indices of fetal growth to gain insight into the vulnerability to suicide. Moreover, the findings are relevant for a primary prevention approach to suicide, in which educational programmes and interventions should engage individuals during the preconceptional period, pregnancy, childhood, and adolescence.^{8,9} Second, the acceptance of the DOHaD concept can be delayed by insufficient insights into underlying mechanisms. Many questions with regard to causal mechanisms indeed remain. The dose-response relationship between birth order and suicide risk suggests such a causal mechanism, but future research will have to answer questions about underlying neurobiological mechanisms to define targets for treatment of suicide risk. Such mechanisms could include the disturbed development of particular brain areas, oxidative stress, and epigenetics.¹⁰ If causality can be shown, further research will need to investigate the reversibility of such mechanisms via an enriched environment, be it neurobiological, psychological, or social.

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I declare no competing interests.

- 1 WHO. Preventing suicide: a global imperative. Geneva: World Health Organization, 2014.
- 2 Van Heeringen K. The neuroscience of suicidal behavior. New York, NY: Cambridge University Press, 2018.
- 3 Holmes EA, Ghaderi A, Harmer CJ, et al. The Lancet Psychiatry Commission on psychological treatments research in tomorrow's science. *Lancet Psychiatry* 2018; **5**: 237–86.
- 4 Van Heeringen K, Mann JJ. The neurobiology of suicide. *Lancet Psychiatry* 2014; **1**: 63–72.

- 5 Orri M, Gunnell D, Richard-Devantoy S, et al. In-utero and perinatal influences on suicide risk: a systematic review and meta-analysis. *Lancet Psychiatry* 2019; published online April 24. [http://dx.doi.org/10.1016/S2215-0366\(19\)30077-X](http://dx.doi.org/10.1016/S2215-0366(19)30077-X).
- 6 Mars B, Heron J, Klonsky ED, et al. What distinguishes adolescents with suicidal thoughts from those who have attempted suicide? A population-based cohort study. *J Child Psychol Psychiatry* 2019; **60**: 91–99.
- 7 Turecki G, Ernst C, Jollant F, et al. The neurodevelopmental origins of suicidal behavior. *Trends Neurosci* 2012; **35**: 14–23.
- 8 Oyamada M, Lim A, Dixon R, Wall C. Development of understanding of DOHaD concepts in students during undergraduate health professional programs in Japan and New Zealand. *J Developm Origins Health Dis* 2018; **9**: 253–59.
- 9 Britto PR, Lye SJ, Proulx K, et al. Nurturing care: promoting early childhood development. *Lancet* 2016; **389**: 91–102.
- 10 Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev* 2014; **94**: 1027–76.

Mapping genotype to phenotype in neurodevelopmental copy number variants



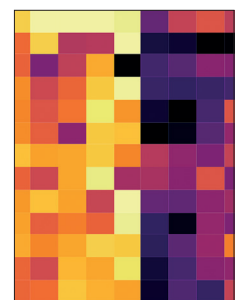
The first studies that identified an association between copy number variants (CNVs) and neurodevelopmental conditions were published over a decade ago.¹ Several studies since then have confirmed the validity of these results, and individuals with neurodevelopmental conditions have an excess of de novo and rare CNVs compared with their siblings or the general population.^{2,3} These CNVs span multiple genes, but seem to converge on specific pathways—eg, synaptic transmission, chromatin modification, and transcriptional regulation in autism.⁴ These studies typically investigate whether CNVs are enriched in specific neurodevelopmental conditions such as autism and attention-deficit hyperactivity disorder (ADHD); a phenotype-first approach. In *The Lancet Psychiatry*, Samuel Chawner and colleagues⁵ ask the opposite question: do CNV carriers have phenotypes that differ by genotype?

To investigate this question, the authors conducted the largest systematic investigation of phenotypic differences in 258 CNV carriers aged 6–19 years and 106 sibling controls in the IMAGINE-ID cohort. Participants were phenotyped for a range of neurodevelopmental, cognitive, and psychiatric phenotypes; a non-trivial task. Focusing on 13 CNVs associated with neurodevelopmental conditions, they first investigated if CNV carriers differed from the sibling controls for multiple psychiatric conditions and across the phenotypes measured. In line with previous research, CNV carriers had significantly higher odds of being diagnosed with a psychiatric condition (odds ratio [OR]

13.8, 95% CI 7.2–26.3), and higher impairment across all phenotypes tested, with attention-deficit hyperactivity disorder (OR 6.9, 3.2–15.1), and autism spectrum disorder traits (OR 44.1, 15.3–127.5) being particularly high.

They next investigated whether CNV carriers differed in their phenotypic presentation according to their genotype. The results support a model in which CNV carriers have broadly overlapping phenotypes, with some genotype-specific effects. Notably, phenotypes associated with intelligence and conduct problems differed between CNV genotypes, whereas sleep and mood difficulties were similarly impaired across the 13 CNV genotypes.

These results support a systemic vulnerability model. According to this model, neuropsychiatric conditions and behaviour are emergent properties of complex systems. Genes disrupted by neurodevelopmental CNVs affect several neural networks leading to broad phenotypic alterations. Studies investigating common variant,^{6,7} rare variant,⁸ and transcriptomic overlap⁹ have identified substantial but differing shared biology between various neuropsychiatric conditions, blurring diagnostic boundaries. Together, these findings point to the immense complexity in mapping genotypes to phenotypes across neurodevelopmental and neuropsychiatric conditions. CNVs need not map onto a unique constellation of phenotypes, and substantial shared biology exists between phenotypes. Clearly, delineating the association between genotype and phenotype is non-trivial, and the challenge ahead is to



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