Project Number: CC012

Title: Hypothesis-driven and hypothesis-free Mendelian randomization analyses to identify potentially modifiable risk factors for cleft and cleft-related outcomes

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Scientific Outline:

The aim of this study is to carry-out hypothesis-driven and hypothesis-free Mendelian randomization to identify potentially modifiable risk factors for cleft and cleft-related outcomes

Maternal lifestyle factors that been implicated in causing cleft include smoking, alcohol intake, mother's BMI and folic acid intake. However, for many of these potential risk factors the evidence is still conflicting. Major limitations in identifying risk factors for cleft are measurement error, recall bias and confounding. For example, data on maternal nutrition is often ascertained from food frequency questionnaires, which may be a blunt tool for measuring nutrient intake and could lead to associations appearing weaker than they truly are. Measurement error and recall bias is particularly problematic for exposures known to be harmful in pregnancy, such as smoking and drinking, because mothers are likely to under-report their exposures. This is even more problematic among parents of children with birth defects who systematically report their exposures differently to other parents. Even where associations are observed between exposures and orofacial cleft, these correlations do not necessarily represent causation. Instead, these associations might arise due to confounding by other lifestyle factors that also correlate with the exposure of interest.

One way to infer causal associations from observational studies is to use an approach known as Mendelian randomization (MR), which uses genetic data as 'proxies' for exposures of interest. These analyses can help overcome the problems of measurement error, bias and confounding and identify causal risk factors for cleft (Davey Smith and Ebrahim 2003). For example, Tyrell et al (2016) have shown that maternal glucose levels during pregnancy have a causal effect on offspring birthweight using a genetic risk score for glucose levels in mothers. Similarly, we have previously shown some evidence that genotypes associated with low levels of maternal vitamin B12 in pregnancy lead to a reduced cognitive score in children at age 8 (Bonilla et al, 2012 and Caramaschi et al, 2017). In the context of cleft, common genetic variants in mothers of children born with a cleft can be used as surrogates for specific maternal lifestyle factors to infer whether those modifiable factors have a causal impact on cleft.

We plan to identify risk factors which have previously been identified as potential being risk factors for cleft. We will identify genetic instruments for these risk factors and carry-out a two samples MR analysis of the risk factor on cleft using the Cleft collective to test the SNP-outcome association.

In addition, thanks to the work of colleagues in our department at the University of Bristol, we are able to apply for funding to carry out hypothesis-free MR analyses using MRbase (www.mrbase.org), which is a platform that stores data from a huge number of GWAS studies and uses this to define proxies for several hundred potential exposures (Hemani et al, 2016). MRbase will be used to explore associations between thousands of potential exposures (for which there is GWAS data in MRBase) against the risk of cleft using data from the Cleft collective. In doing this we hope to identify new modifiable risk factors for cleft and identify important biological pathways.

Bonilla C et al.Vitamin B-12 status during pregnancy and child's IQ at age 8: a Mendelian randomization study in the Avon longitudinal study of parents and children.

PLoS One. 2012;7(12):e51084

Caramaschi D et al. Exploring a causal role of DNA methylation in the relationship between maternal vitamin B12 during pregnancy and child's IQ at age 8, cognitive performance and educational attainment: a two-step Mendelian randomization study.Hum Mol Genet. 2017;26(15):3001-3013.

Davey Smith G and Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003;32(1):1-22.

Hemani G et al. MR-Base: a platform for systematic causal inference across the phenome using billions of genetic associations. Biorxiv 2016: doi: https://doi.org/10.1101/078972

Tyrrell J et al.Genetic Evidence for Causal Relationships Between Maternal Obesity-Related Traits and Birth Weight.JAMA. 2016 Mar 15;315(11):1129-40.