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Research report

Perinatal depression and omega-3 fatty acids: A Mendelian randomisation study

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ABSTRACT

Background: There have been numerous studies investigating the association between omega-3 fatty acids (FAs) and depression, with mixed findings. We propose an approach which is largely free from issues such as confounding or reverse causality, to investigate this relationship using observational data from a pregnancy cohort.

Methods: The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort collected information on FA levels from antenatal blood samples and depressive symptoms at several time points during pregnancy and the postnatal period. Conventional epidemiological analyses were used in addition to a Mendelian randomisation (MR) approach to investigate the association between levels of two omega-3 FAs (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) and perinatal onset depression, antenatal depression (AND) and postnatal depression (PND).

Results: Weak evidence of a positive association with both EPA (OR=1.07; 95% CI: 0.99–1.15) and DHA (OR=1.08; 95% CI: 0.98–1.19) with perinatal onset depression was found using a multivariable logistic regression adjusting for social class and maternal age. However, the strength of association was found to attenuate when using an MR analysis to investigate DHA.

Limitations: Pleiotropy is a potential limitation in MR analyses; we assume that the genetic variants included in the instrumental variable are associated only with our trait of interest (FAs) and thus cannot influence the outcome via any other pathway.

Conclusions: We found weak evidence of a positive association between omega-3 FAs and perinatal onset depression. However, without confirmation from the MR analysis, we are unable to draw conclusions regarding causality.

1. Introduction

Several studies have investigated the association between omega-3 fatty acids (FAs) and depressive disorders, with mixed results. Although it has long been established that docosahexaenoic acid (DHA), a member of the omega-3 family, can affect brain function and behaviour (Simopoulos, 2009), the precise relationship with depression is unknown. Evidence from several observational studies shows an inverse relationship between fish consumption and depression which would appear to lend support to this hypothesis, as fish is a major source of omega-3 FAs (Hibbeln, 1998, 2002; Tanskanen et al., 2001; Silvers and Scott, 2002). However, observational studies are subject to issues such as confounding and reverse causation, and intervention trials attempting to establish whether depression can be treated with omega-3 FAs have met with mixed success (Freeman et al., 2006; Rondanelli et al., 2011; Su et al., 2008; Makrides et al., 2010; Carney et al., 2009).

It has been suggested that the lack of association in some intervention studies could be due to the investigation of the wrong FAs, or even the wrong ratios and dosages of FAs included in the interventions (Martins, 2009). Alternative criticisms focus on the broad inclusion criteria around diagnosis and the range of scales used to measure depression, both of which can lead to a heterogeneous mix of cases (Martins et al., 2012; Mischoulon, 2011). Meta-analyses of these intervention studies fail to reach a consensus on the association between omega-3 FAs and depression (Appleton et al., 2008, 2010; Bloch and Hannestad, 2012; Martins, 2009; Martins et al., 2012), and difficulties arise when attempting to combine studies due to heterogeneity among the range of study

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designs, types and doses of FAs investigated. Alternative methods of investigating the relationship between FAs and depression have not, as of yet, been explored.

It is possible that any association between FA levels and depressive symptoms are absent other than in challenging conditions, such as during pregnancy. Due to the increased nutritional demands on the body and the suspected resultant decrease in levels of highly unsaturated brain FAs during the antenatal and postnatal periods, women may be especially at risk of developing depressive symptoms at this time (Su et al., 2008; Kendall-Tackett, 2010). The potential range of symptoms and diagnostic criteria used when assessing depression can result in a heterogeneous mix of cases with varying symptoms, which can make discovering associations problematic and findings difficult to generalise. Perinatal onset depression can be thought of as a more homogenous subgroup of depression cases. In addition to sex, these cases are likely to be more similar in terms of age and other characteristics, as well as all undergoing a similar stress event (i.e. labour). In this situation, we should have greater power to detect an association between depression and levels of FAs, assuming such a relationship exists.

The omega-3 family of FAs are thought to be particularly relevant to depression as these are involved in brain development (McNamara and Carlson, 2006; Stahl et al., 2008). In particular, reduced levels of DHA are associated with impairments in both cognitive and behavioural performances (Innis, 2007). Alpha-linolenic acid (ALA) and linoleic acid (LA), from the omega-3 and omega 6 families respectively, are described as essential FAs because the body lacks the enzymes to synthesise them and so both must be obtained through diet. Due to the inefficient conversion of ALA to the longer chain omega-3 FAs, such as DHA, an adequate supply of dietary omega-3 FAs is important, however the modern Western diet tends to consist predominantly of omega-6 FAs. DHA and arachidonic acid (AA), an omega-6 FA, are known to be vital during pregnancy for foetal brain development, as well as during lactation and throughout the life cycle (Simopoulos, 2009). During the last trimester, the foetal brain undergoes rapid growth and requires increased levels of DHA. As such, maternal FA status is likely to deteriorate while the foetal demand for DHA is high (Steer et al., 2012; Hornstra, 2000; Kendall-Tackett, 2010). Eicosapentaenoic acid (EPA) is a precursor to DHA, and beneficial effects in several conditions, such as schizophrenia and depression, have been linked to this FA (Emsley et al., 2002; Marshall and Rathbone, 2011). In studies investigating the association of omega-3 FAs and depression, randomised controlled trials have tended to focus on supplementation with EPA, or EPA administered in parallel with DHA (Appleton et al., 2010), making it difficult to tease apart the effect of either FA. Arguments in support of both EPA and DHA as the more beneficial FA have been put forward, with a meta-analysis by Martins (2009) concluding that EPA has a greater effect in alleviating depression. However, other studies have focused on DHA, given its role as the major FA constituent of brain phospholipids, and the fact that it is the predominant omega-3 FA obtained through fish consumption (Sinn et al., 2012; Meyer et al., 2013).

In this study we investigate the association between antenatal FA levels and perinatal depression using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. ALSPAC is uniquely placed to investigate the causality of any association with data collected on both FA levels throughout pregnancy and depressive symptoms at several time points during pregnancy and the postnatal period. In this study, we use a Mendelian Randomisation (MR) approach within the analysis to investigate whether there is a causal link between levels of two omega-3 FAs (DHA and EPA) and perinatal depression.

MR is a method of assessing causality from observational data through the use of instrumental variables. MR uses genetic variants, or scores constructed based on an individual's genotype across several variants, as a proxy for some modifiable risk factor associated with an outcome of interest, this process is illustrated in Fig. 1. The MR principle relies on both Mendel's first and second laws, which imply that genotypes transmit across conception to a viable conceptus, independent of both environment and other genetic variants (Davey Smith, 2011). Given these assumptions and, assuming the genetic variants are not associated with the outcome other than through the risk factor they act as a proxy for, we can make much stronger inferences about the causal nature of any association between the risk factor and the outcome (Davey Smith and Ebrahim, 2003). The effects given by the MR analysis should therefore be free from the problems of confounding and reverse causality to which observational epidemiology is prone. To our knowledge, this is the first study to investigate the association between FA levels and depression using an instrumental variable approach.

2. Methods

2.1. Sample

The ALSPAC study is a prospective cohort located in the South West of England. All women with an expected due date between April 1991 and December 1992 were eligible to join the study and 14,541 were initially recruited, resulting in 14,062 live births. Detailed information was collected on the mothers throughout pregnancy, and information has continued to be collected on the children, mothers and partners enroled in the study (Fraser et al., 2013; Boyd et al., 2013). Details of all available data are contained on the website through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

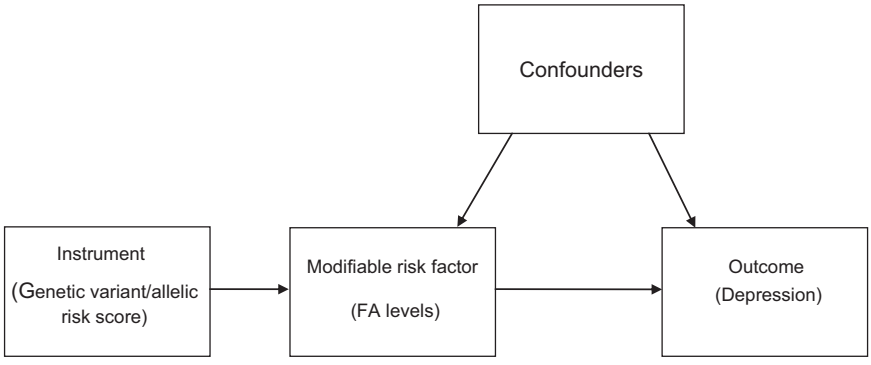

Fig. 1. Directed acyclic graph illustrating Mendelian randomisation. In this model, allelic risk scores associated with FA levels are calculated and used to assess the association of both EPA and DHA with perinatal depression.