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Letter to the Editor

Low birth weight and adult depression: eliciting their association

Theories supporting fetal origins of adult health and disease are nowadays widely accepted regarding some psychiatric conditions (Losh *et al.* 2012; Eide *et al.* 2013). However, whether genetic or environmental factors disrupting fetal growth might constitute a risk factor for depressive and/or anxious psychopathology remains still controversial.

A recent meta-analysis (Wojcik *et al.* 2013) evaluated the current evidence for an association between low birth weight (BW) and adult depression or psychological distress in the general population, and found no conclusive association between them. Remarkably, the systematic literature search performed by the authors allowed them to identify a couple of recent health register studies with positive results (Abel *et al.* 2010; Larsen *et al.* 2010). Although they were discarded from the statistical analyses of Wojcik *et al.* (2013) after considering that depression could be largely undiagnosed in the populations included therein, these important cohort designs – alongside the results from the meta-analysis itself – leave the door open to further scrutiny and debate.

Besides, despite the comprehensiveness of the above-mentioned meta-analysis, it is worth taking into account that fetal growth and psychopathology may share both genetic and environmental aetiological factors. In view of this, twin methodology can contribute to disentangle the putative origins of the controversial association discussed herein. Importantly, as heritability estimates of depression are relatively low (h^2 about 37%) and individual-specific environmental effects have a substantial influence on depressive phenotypes (Sullivan *et al.* 2000), it is likely that intra-uterine environmental factors affecting each of the co-twins' BW may play a role in engendering this psychopathology. In addition, previous epidemiological studies using twins have taken as their starting point inconclusive associations between low BW and later outcomes, to corroborate that non-genetic influences on BW may underlie the presence of disease (Villamor *et al.* 2009).

As monozygotic (MZ) twins are nearly identical at the DNA sequence level, their differences in BW provide a measure of non-genetic effects on fetal growth. Hence, a twin design constitutes an appropriate methodology to approach the current issue controlling for potential genetic confounders. Along these lines, if the BW–depression link were exclusively due to intra-uterine environmental impact on BW, this analysis would help to clarify the aetiology of this association and may possibly assist in the identification of at-risk individuals during early stages.

Here, the authors aimed to assess the presence of a link between BW and depression or anxiety and to determine whether the association can be explained by either familial factors (genetic plus shared environment) or within-pair differences in size at birth (i.e. unique environmental influences: does the twin with the lower BW have a higher risk for psychopathology than his co-twin?).

The variables of interest have been studied here using information from a representative sample of adult twins from the University of Barcelona Twin Registry (n=121 pairs). The presence of lifetime mental disorders was assessed in a face-to-face interview using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) by a trained clinical psychologist (X.G.). After excluding duos where at least one co-twin presented a neurological or psychiatric diagnosis other than depression or anxiety, 210 individuals (85 MZ and 20 dizygotic pairs; mean age=31 years, S.D.=13 years, 33% male) were selected for analysis. Taking into account the increasing evidence of shared aetiopathology and diagnostic criteria overlap for depressive and anxious disorders (Lowe *et al.* 2008), and given that previous reports have widely used instruments that measure symptoms of depression and anxiety together (Wojcik *et al.* 2013), patients with any of both lifetime diagnoses were grouped in a single set: D/A (affected by depression and/or anxiety). In all, 51 individuals (24% of the sample) had at least one of these lifetime diagnoses. Information on BW (and obstetric history) was collected by interviewing the twins' mothers (Walshe *et al.* 2011), using the Lewis–Murray Scale for Obstetric Complications (Lewis *et al.* 1989). BW distribution by gestational age of all subjects in the sample was in accordance with a previous report of twins (Glinianaia *et al.* 2000). In the overall sample, the mean BW was 2522 (S.D.=626, range 800–4150) g, and the observed mean intra-pair difference in BW was 279 (S.D.=254) g.

Corrections for sex, age and weeks of gestation of the twins were included in all the analyses. Participants gave their written informed consent, and

all procedures were carried out in accordance with the Declaration of Helsinki.

As a preliminary step, a logistic regression was performed in the above-mentioned subsample (n=210 individuals) to test for a potential direct relationship between BW and adult D/A. Huber–White estimators were applied to adjust for non-independence of the observations. No such association was found (β=0.31, S.E.=0.32, p=0.34).

It is worth noting that Pearson's correlation for BW of the MZ twin subset was r=0.83, which means that approximately 17% of the BW variance could be attributed to unique intra-uterine factors not shared by MZ twins. Thus, despite the previous (null) result, separating the variance of BW into familial and unique environmental factors was likely to provide additional information. This would clarify if the putative BW–D/A link was only due to one of these features and had been confounded by the other. In order to assess this hypothesis, a multivariate regression model solved by generalized estimating equations with an exchangeable correlation structure was applied using data from the group of 85 MZ twin pairs (15 D/A concordant, 14 D/A discordant and 56 healthy duos).

For the current aim, the logistic regression $\text{logit}(\pi_{ij}) = \beta_0 + \beta_B \mu_{i.} + \beta_W (X_{ij} - \mu_{i.})$ gives an estimate of both (i) genetic and shared environmental factors (β_B) and (ii) unique environmental events affecting each co-twin (β_W) (Begg & Parides, 2003) that confer risk for disease. Subindexes $i \in \{1, \ldots, n\}$ and $j \in \{1, 2\}$, respectively, stand for pair number (here, n=85 MZ pairs) and co-twin number (an arbitrarily assigned number within a pair: 1 or 2); π_{ij} represents the probability that co-twin j from the ith pair has of being affected by D/A; β_0 is the regression intercept; $\mu_{i.} = (X_{i1} + X_{i2})/2$ is the mean BW value of the ith pair; and $X_{ij} - \mu_{i.}$ represents the deviation of co-twin j from the pair's mean.

The so called unique environmental events ($X_{ij} - \mu_{i.}$) allow the quantification of the degree of (dis)advantage that each co-twin had during the pregnancy, as reflected in BW. In pairs where both twins had the same BW, $X_{ij} - \mu_{i.}$ equals 0, whereas positive or negative values of this term signify, respectively, that a co-twin had the higher or lower BW in his pair. Thus, β_B allows testing whether the twin with the lower BW has a higher risk for D/A than his heavier co-twin, which might indicate a role for a unique environment.

Results of this regression indicate no association between either genetic plus common environmental (β_B) or unique environmental events (β_W) and D/A (β_B=0.53, S.E.=0.37, p=0.15; β_W=–0.2, S.E.=0.79, p=0.79).

Although the sample size used for the current calculations was modest, all results were far from statistical significance, suggesting that they were not just related to lack of statistical power. They argued against a considerable effect size of the evaluated risk factors. Remarkably, demographic characteristics of this sample are representative of the general population for both obstetric and psychopathological profiles (both BW profile and sex distribution of D/A in the whole set of twins were in good agreement with the literature), which might render associations detectable.

The current results indicate that neither BW by itself nor environmental influences on BW are associated with adult depression. Thus, pregnancy factors associated with discordant BW in twins seem to not predispose to adult D/A. Remarkably, this latter finding is in agreement with a previous independent twin study indicating no differential risk for D/A diagnosis in MZ twins discordant for BW (Foley *et al.* 2000). Altogether, these research reports suggest that controversial results on the topic are probably not due to environmental influences on BW.

As stated by Wojcik *et al.* (2013), factors such as severity of symptoms may underlie the fact that both positive and negative results have been reported on the BW–depression association, particularly considering the fact that earlier studies have been based on heterogeneous research designs. In effect, the present analyses lacked the possibility of evaluating diverse disease severities, and advocate for further research on this issue as a putative means to clarify the controversial results. The relative contribution of genetic and/or environmental factors that may underlie the (potential) relationship between fetal growth and adult D/A should also be elucidated taking this fact into consideration, in order to gain more epidemiological insights.

Further data are available on request.

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Declaration of Interest

None.

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