Birth dimensions and risk of depression in adulthood: cohort study of Danish men born in 1953

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Background Two British cohort studies have reported birth weight to be associated with self-reported depression in adulthood, even after adjustment for socio-economic factors.

Aims To examine the relationship between birth dimensions and discharge from a psychiatric ward with a depression diagnosis in adulthood.

Method A cohort of 10 753 male singletons born in Copenhagen, Denmark in 1953 and for whom birth certificates had been traced in 1965 were followed from 1969 until 2002, with record linkage for date of first admission to a psychiatric ward that led to a discharge diagnosis of depression.

Results A total of 190 men, corresponding to 1.8% of the cohort, had a discharge diagnosis of depression. The Cox's regression analyses failed to show any association between birth dimensions (birth weight and ponderal index) and risk of psychiatric ward diagnosis of depression in adult life, before or after adjustment for social indicators at birth.

Conclusions This study does not support the existence of a relation between birth dimensions and psychiatric ward admission for depression in adult men.

Declaration of interest None.

Numerous studies have investigated the association between birth weight and health outcomes. Birth weight has been associated particularly with cardiovascular disease (Joseph & Kramer, 1996; Law & Shiell, 1996; Barker, 1998; Harding, 2001), and also with several other outcomes (Barker, 1998; Harding, 2001). Two British cohort studies have recently indicated that low birth weight might be associated with an increased risk of depression later in life after adjustment for socio-economic circumstances (Thompson *et al*, 2001; Gale & Martyn, 2004). These observations are compatible with the 'foetal origin of adult disease' hypothesis. Poor intrauterine growth could lead to permanent alterations of the neuroendocrine system and subsequently to an increased vulnerability to depression later in life. However, not all evidence concurs with the association between birth weight and depression. Thus, the first British cohort study failed to show an association in women (Thompson *et al*, 2001), and the later study found no relationship in men after multiple adjustments (Gale & Martyn, 2004). In our study we examined the association between size at birth and risk of psychiatric hospital discharge with a depression diagnosis during the years 1969–2003, in a cohort of Danish men born in 1953.

METHOD

Study population

According to official statistics, 12 270 boys were born within the metropolitan area of Copenhagen during 1953. These persons formed the population of the Danish longitudinal study (Project Metropolit) which has been described in detail elsewhere (Høgh & Wolf, 1981; Osler *et al*, 2004). Briefly, 11 376 of this population, who were alive and living in Denmark in 1968, were registered with a unique personal identification number when the Civil Registration System (CRS) was established.

Data sources and variables

Data from birth certificates, including information on date and place of birth, birth weight and birth length, singleton or multiple birth, mother's age and marital status, and father's occupational status at time of delivery, were manually collected for all members of the original study population in 1965. In January 2002, the Metropolit cohort was followed up to ascertain vital status through record linkage with the CRS Registry; if the person was not alive and living in Denmark, we obtained information on date of death or date of emigration/disappearance. Information on date of admission to psychiatric wards (from 1969 to December 2002) and diagnosis on discharge was obtained from the Danish Psychiatric Central Register. This register has compiled computerised data on admissions to psychiatric hospitals and to psychiatric departments in general hospitals in Denmark since April 1969, with coverage close to 100% (Munk-Jørgensen & Mortensen, 1997). The personal registration number ensured that a complete history of psychiatric hospitalisation could be established for each cohort member. A total of 230 boys born as twins and triplets and 393 boys with missing birth data were excluded, leaving 10 753 cohort members for the study analyses.

Birth weight was recorded in 100 g groups and analysed as a continuous variable and in the three categories < 2500 g, 2500–3499 g and ≥ 3500 g. Ponderal index used as a proxy measure for intrauterine growth was calculated as birth weight in kilograms ÷ (birth length in metres)^3, and entered into the models in quintiles. The marital status of the mother at time of delivery was treated in three categories: married, unmarried (single, divorced or widowed) and unknown. Fathers' occupation, which was recorded in 23 categories, was re-coded into three categories: employee (self-employed and salaried employed), worker (manual and non-manual workers) and unknown.

Diagnoses were classified according to ICD–8 (World Health Organization, 1967) during the years 1969–1993 and ICD–10 (World Health Organization, 1992) from 1994. The diagnoses included for this study were manic episode and bipolar affective disorder (code numbers

296.19, 296.39 and 298.19 in ICD–8 and F30, F31, F34.0 and F38.0 in ICD–10) and depressive disorders (code numbers 296.09, 296.29, 296.89, 296.99, 298.09, 300.49 and 301.19 in ICD–8 and F32, F33, F34.1 and F38.1 in ICD–10).

Statistical analysis

Associations between birth weight, other covariates and depression were analysed using Cox's proportional hazards regression models with age as the underlying time scale. Entry time was age at 1 April 1969 and follow-up ended at the age of first admission with a diagnosis of depression, death, emigration or 1 January 2002, whichever came first. The proportional hazards assumption was evaluated for all variables by comparing estimated −ln(−ln) survivor curves over the different categories of the variables being investigated v. ln (analysis time), and by tests based on the generalisation described by Grambsch & Therneau (1994). A power

calculation based on the birth weight distribution and estimated number of cases showed that the study would have adequate power (i.e. >80%) to detect a relative risk of 2.0 or greater. We performed the statistical analyses using STATA version 7 (Stata, 2001).

RESULTS

A total of 190 men had been discharged from a psychiatric ward with a diagnosis of depression between 1969 and 2002, of whom 39 were diagnosed as having a bipolar affective disorder. The distribution of birth dimensions and socio-economic indicators at birth for the cohort are shown in Table 1, together with the unadjusted hazard ratios for depression according to these characteristics. We found no association between birth weight or ponderal index and risk of depression from age 16 to 49 years. Indicators of disadvantaged parental social position at birth (father's occupation and mother's marital status)

were associated with increased risk of depression, with the strongest and significant estimate for single mothers. Entering the social indicators into the model changed the associations of birth weight and ponderal index with depression marginally. We repeated all analyses using data for psychiatric admission for bipolar affective disorder only. Because there were so few cases, birth weight was analysed in two categories, comparing the highest and the lowest half for this outcome. This gave nearly the same risk estimate: HR=1.02 (95% CI 0.53–1.95).

DISCUSSION

In this cohort of almost 11 000 Danish men born in 1953 we found no relation between birth weight or ponderal index and risk of psychiatric admission for depression in adult life, either before or after adjustment for father's occupation and mother's marital status at birth. The point estimates were close to 1.

Table 1 Crude and adjusted risk ratios of depression at age 15–49 years in relation to birth characteristics (n=10 753)

	Total n	Cases of depression n	Hazard ratios (95% CI)		
			Crude ratio	Adjusted for maternal marital status	Adjusted for paternal occupation[1]
Birth weight, g					
≤2499	461	8	1.03 (0.50–2.13)	0.98 (0.50–2.02)	1.01 (0.48–2.08)
2500–3499	5301	96	0.97 (0.72–1.31)	0.96 (0.91–1.29)	0.97 (0.71–1.30)
≥3500	4987	86	1 (reference)	1 (reference)	1 (reference)
Unknown	27	0			
Per 100 g increase			1.00 (0.98–1.03)	1.00 (0.98–1.03)	1.00 (0.98–1.03)
Ponderal index					
Quintile 5 (lowest)	2170	31	0.76 (0.41–1.23)	0.77 (0.48–1.24)	0.77 (0.84–1.98)
Quintile 4	2340	29	0.66 (0.40–1.09)	0.68 (0.40–1.09)	0.66 (0.67–1.65)
Quintile 3	1967	40	1.04 (0.66–1.65)	1.04 (0.66–1.65)	1.05 (0.67–1.65)
Quintile 2	2237	54	1.31 (0.86–2.00)	1.29 (0.85–1.98)	1.29 (0.84–1.98)
Quintile 1 (highest)	2012	36	1 (reference)	1 (reference)	1 (reference)
Unknown	4	0			
Per unit increase			1.02 (0.99–1.03)	1.02 (0.99–1.05)	1.02 (0.09–1.05)
Maternal marital status at birth					
Married	9826	163	1 (reference)		
Unmarried	914	27	1.83 (1.00–2.76)		
Unknown	13	0			
Paternal occupational status at birth					
Employee	4902	36	1 (reference)		
Worker	5138	85	0.93 (0.69–1.26)		
Unknown	713	19	1.56 (0.94–2.56)		

1. Adjusted for paternal occupational status at birth.

Strengths of the study

The study population consisted of all male singletons born in a well-defined area (covering a third of the Danish population) who survived to the age of 15 years. By using the population registers we managed to obtain complete follow-up information, and consequently these results are based on birth and psychiatric admission data for more than 95% of this non-selected population. We assume that our outcome measure is valid, since it was based on diagnoses confirmed by a psychiatrist and did not depend on the individual's ability to answer a questionnaire; we do not believe our study is subject to the selection biases that might occur when the outcome is based on self-report from a questionnaire.

Limitations

Birth weight has in this area of research been understood as a proxy measure of foetal growth. Birth weight is, however, a combined measure of at least two components: foetal growth rate and gestational age at birth (Wilcox, 2001). We had no information on gestational age, but ponderal index has been suggested as a measure of foetal growth which, in theory, should reflect intrauterine growth restriction (Joseph & Kramer, 1996). We did not find any clear indication of an association between quintiles of ponderal index and adult depression.

Depression is more common in women than in men, thus it is an obvious limitation of our study that women were not represented in the data-set. The risk of depression increases with age, and our study will not capture the presumed larger number of cases occurring later in life, although the follow-up covered a period of more than 30 years. On the order hand, depression at younger ages may have risk factors that differ from those of later-life depression. Some cases of bipolar disorder are first manifested and diagnosed as unipolar depression, and since our cohort was relatively young a number of diagnoses of unipolar depression will be changed to bipolar disorder at a later stage; consequently, we decided to analyse the two forms of depressive disorder together. Bipolar affective disorder is the most specific diagnosis, however, and therefore we repeated all the analyses for this outcome. The small number of cases in our study reduces the statistical power, in particular of the analyses with bipolar affective

disorder as outcome. However, the number of cases of this disorder will increase as the cohort matures, and at a later stage it will also be possible to make a register-based study of the total population, when the children recorded on the computerised medical birth register (started in January 1973) have become old enough to develop severe depression leading to hospitalisation.

We only had information about affective disorders diagnosed during admission to psychiatric hospital or the psychiatric department of a general hospital. A large proportion of patients with depression are treated solely as out-patients in community mental health centres, in private specialist practice or by their general practitioner. Furthermore, no information was available on possible confounders such as maternal depression.

Comparison with other studies

In the Hertfordshire birth cohort study the relation between birth weight and depression was examined in the late 1990s among 882 men and women born between 1920 and 1930; cases were identified by means of the Geriatric Depression Scale and the Geriatric Mental State Examination (Thompson *et al*, 2001). There was a strong association between lower birth weight and risk of depression in men, but no such relation in women. However, in the most recent study of 8000 male and female participants in the 1970 British Birth Cohort, lower birth weight was a significant risk factor for depression (assessed by Rutter's 24-item Malaise Inventory) at age 26 years in women, whereas there was no association between birth weight and risk of depression in men after adjustment for potential confounding factors (Gale & Martyn, 2004). In these two birth cohort studies psychiatric morbidity was assessed by means of self-completion scales. Although this approach might be more liable to misclassification than a register-based assessment of outcome, it might

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CLINICAL IMPLICATIONS

■ The risk of developing depression that required psychiatric hospital admission was 1.8% in men followed from age 15 years to 49 years.

■ Birth weight does not seem to influence the risk of depression leading to psychiatric ward admission in men.

■ Parental social class at birth was associated with an increased risk of depression in men before age 49 years.

LIMITATIONS

■ Depression is more common in women than in men, but women were not represented in the data-set.

■ Information was only available for affective disorders so severe that they lead to in-patient treatment in a psychiatric hospital or psychiatric department.

■ The number of cases was only 190 and no information was available on some possible confounders such as maternal depression.

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catch the less severe cases of depression treated in general practice. In two previous studies cases have been identified through hospital admission records. An Italian case–control study with 41 cases found that patients admitted to hospital with depression were more likely than controls matched by gender, age, maternal age and marital status to have been small for gestational age; cases had also lower mean birth weight, although this difference was of marginal significance (Preti *et al*, 2000). Further, Brown *et al* (2000), in an investigation of a birth cohort in The Netherlands, found that risk of major depression requiring hospitalisation was increased in groups of men and women who were exposed to famine during late gestation in the Dutch Hunger Winter of 1944–1945.

Interpretation

Our study provides no support for the existence of an inverse relationship between birth dimensions and discharge from a psychiatric ward with a diagnosis of depression in adult men. The fact that birth weight has been related to several unexpected outcomes points towards confounding factors as an explanation of the association (Weiss, 2001; Lawlor *et al*, 2004). The lack of association between birth weight and severe depressive disorders, which is known to be closely related to social circumstances during childhood, indicates that the relation found between birth size and other chronic diseases in adulthood is not just a result of residual confounding by factors related to social position.

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