**EFFECT OF LOW BIRTH WEIGHT AND GENDER ON THE NEED
FOR ADULT PSYCHIATRIC HOSPITALIZATION**

BY

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Abstract

Background: Low birth weight is associated with increased rates of psychiatric symptomology in childhood but less is known about the risk of adult psychiatric hospitalization. The primary objective of this study is to examine the relationship between low birth weight (< 2500 g) and gender on the lifetime prevalence (evaluated to 47 years of age) of psychiatric hospitalization in a large Danish birth cohort. A secondary objective is to examine in greater detail the selective effects of low birth weight and gender on the risk for alcoholism.

Method: Subjects were born at the Copenhagen University Hospital between 1959 and 1961 (N=9,125). A comprehensive series of measures were obtained for each of the 8,109 surviving and eligible infants at the time of birth. Lifetime psychiatric outcomes were defined as any ICD 10 group F diagnosis (*Mental and Behavioral Disorders*) or an equivalent ICD 8 diagnosis found in the Danish Central Psychiatric Register by 2007. Bivariate analyses stratified by gender are used to compare the prevalence of psychiatric diagnoses among low birth weight infants. Logistic regression models examine the relationship between low birth weight and alcoholism while adjusting for comorbid psychiatric illness.

Results: For males and not for females, low birth weight is associated with an overall increased rate of lifetime psychiatric hospitalization and the specific risk of the development of alcoholism, anxiety, and personality disorders. The association between low birth weight and male alcoholism is retained after sequential logistic regression modeling with low birth weight adjusted for social class and other comorbid psychiatric illness.

Conclusions: The results support our previous findings that low birth weight is associated with the increased prevalence of adult psychiatric illness. Selective gender effects suggest the greater

likelihood of psychopathology among low birth weight males than females, especially for

alcoholism.

Acknowledgements

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Introduction

Perinatal Neurodevelopment and Psychiatric Illness

Premature birth (< 38 weeks gestational age) and low birth weight (< 2500g) are associated with an increased risk of a variety of neurodevelopmental problems including, learning disabilities, severe cognitive impairment and behavioral deregulation (Gaddin, 2011; Taylor et al, 2011; Vanderbilt, 2010). Behavioral characteristics, cognitive disabilities and developmental disorders associated with premature birth and/or low birth weight probably result from early developmental events that disrupt brain growth such as exposure to perinatal hemorrhage or hypoxia (Bhutta and Anand, 202a; Buonocore et al., 2001; Kaindl, 2009; Taylor et al, 2011). The neurobiological sequellae of prematurity are likely to affect brain structures and functions important for behavioral regulation and implicated in the development of psychiatric illness (Aylward, 2005; Back et al., 201, 2007; Manzardo et al. 2006, 2011; Miller et al., 2005; Taylor et al, 2011; Volpe, 2009). These neurobiological changes are expected to influence vulnerability to the development of psychiatric illness later in life. Children born prematurely appear to experience higher rates of impulse control behavioral disorders such as the attention deficit hyperactivity disorder as well as neuropsychiatric symptoms of anxiety and depression (Bhutta and Anand, 2002a; Bhutta et al., 2002b; Botting et al. 1997; Nomura et al., 2007; Indredavik, 2004; Stjernqvist and Svenningsen, 1999). More recent study has reported increased symptomology suggestive of Autism and Asperger's Disorders among extremely low birth weight children (Hack et al., 2009). Longitudinal follow up of individuals who were born prematurely have identified increased rates of psychiatric hospitalization in adolescence and young adulthood (Lindstrom, 2009).

Perinatal Neurodevelopment and the Risk for Alcoholism

Several perinatal markers of brain development have been identified that predict the development of alcoholism in adulthood (Goodwin et al., 1999; Knop et al., 2003; Manzardo 2005a; 2005b; 2011). These markers include delayed achievement of developmental motor milestones (i.e. walking and standing; Manzardo et al. 2005a) as well as perinatal factors commonly associated with premature birth including low birth weight, shorter birth length and smaller head circumference (Knop et al. 2003; Manzardo et al, 2011). We were the first to show the effect of gender on the relationship between prematurity and alcoholism may be limited to an effect in males (Manzardo et al, 2011) This gender selectivity is consistent with reports of a heightened intrinsic vulnerability of males over females to the deleterious effects of low birth weight and premature birth (Anderson and Doyle, 2004; Ingemarsson, 2007; Johnson, 2007).

Gender and Psychiatric Illness

Consistent gender differences are also found worldwide in the pattern of psychiatric illnesses with males having more substance use and antisocial disorder and females showing more mood, anxiety, eating and somatoform disorders (Kessler et al., 1997). The diagnosis of Alcohol Dependence is associated with especially high rates of additional, "comorbid", psychiatric illness in men and women (Grant et al., 2007; Hasin et al., 2007; Kessler et al., 1997; Penick et al., 1994; Regier et al., 1990; Weissman et al, 1980). Alcoholism is commonly linked to anxiety and mood disorders as well as personality disorders, especially antisocial personality disorder in males (Hasin et al., 2007; Regier et al., 1990). This parallels increases in mood, and anxiety symptoms and conduct problems observed among those born preterm or with very low birth weight (Botting et al. 1997; Indredavik, 2004; Stjernqvist and Svenningsen, 1999).

Substance Use Disorders and Comorbid Psychiatric Illness

The level of psychiatric comorbidity contributes measurably to the overall burden of illness, predicting greater functional impairment, more frequent psychiatric hospitalizations, greater chronicity and increased mortality (Wu et al., 1999). Individuals with substance use disorders (SUDs) comorbid with other psychiatric disorders are much more likely to receive specialized mental health care than individuals who suffer from alcoholism or SUDs alone (Grant et al., 2007; Hasin et al. 2007; Wu et al., 1999). A disproportionate share of mental health care resources is spent on a relatively small number of individuals who present with high levels of psychiatric comorbidity that is often complicated by alcohol or substance use problems. Because of the relatively high prevalence of alcohol use disorders in the general population and their strong association with other non-substance related psychiatric illnesses, a focused systematic examination was conducted of the relationship between premorbid risk factors, such as low birth weight, and the diagnosis of alcoholism in a large, psychiatrically hospitalized group. The present study uses a Danish birth cohort that contains both male and female subjects to examine the relationship between low birth weight and lifetime psychiatric outcomes through 47 years of age. We propose that low birth weight will be associated with an increase in risk of psychiatric illness in general and that low birth weight will predict alcoholism and psychiatric comorbidities among male but not female subjects.

Materials and Methods

Subject Population

The study sample consists of male and female subjects obtained from a large Danish birth cohort of 9,125 consecutive deliveries (over 20 weeks gestation) from 1959 through 1961(Villumsen, 1970, Zachau-Christiansen, 1972). All births took place in the maternity ward

of the State University Hospital (Rigshospitalet) in Copenhagen. The sample overrepresents mothers from a slightly lower social class and a predominantly urban environment. Participants were also at a modestly increased risk of pregnancy and birth complications (Baker and Mednick, 1984). Of the original 9,125 babies enrolled in the cohort, 728 died in the first year and were therefore excluded from follow-up. Another 288 subjects did not have personal identification numbers, and therefore could not be linked to the Central Psychiatric Register or other Danish archival sources. These subjects are presumed to have died or emigrated from Denmark as children.

Perinatal Measures

Information obtained before, during and shortly after birth include: indices of the social and medical status of the mother during pregnancy, complications during pregnancy and birth, birth weight and the infant's condition at birth (Villumsen, 1970; Zachau-Christiansen, 1972). Two neonatal examinations were carried out (Day 1 and Day 5), and a one-year postnatal examination was performed that included development and diet during the first year of life and ratings of the general physical condition of the child at 1 year of age. Despite the range of detailed information collected about the mothers and babies in this cohort, no information was collected about the mother's alcohol consumption either before or during pregnancy. Due to limitations of computer capacity at the time of the original study (1959–1961), the data were not always recorded as discrete numerical values and were on occasion coded categorically as ordinal levels or categorical ranges. In some instances, it was possible only to approximate a mean value for a tested variable.

Predictive Measures:

- **Birth Weight** – The weight of the newborn subjects in grams was also recorded as
  levels: 1= <1000g; 2= 1000–1500g; 3= 1501–2000g; 4= 2001–2500g; 5= 2501–3000g;
  6= 3001–3500g; 7= 3501–4000g; 8= 4001–4500g; 9= 4501–5000g, 10= >5000g with a
  mean (SD) level of 5.8(1.25) which approximately 2800 grams or 6.2 pounds.
  Categorical analyses divided subjects into lower birth weight (levels 1–4, less than 2500
  grams, N =1046) and higher birth weight (levels 5–10, more than 2500 grams, N =7082)
  groups.

- **Gestational Age at Delivery**- The gestational age at the time of delivery, in weeks, was
  recorded in levels: 1= <28 weeks; 2= 28-29 weeks; 3= 30-31 weeks; 4= 32-33 weeks; 5=
  34-35 weeks; 6= 36-37 weeks; 7= 38-39 weeks; 8= 40-41 weeks; 9= 42-43 weeks; 10=
  44-45 weeks; 11= >45 weeks. The frequency data as coded approximates a normal
  distribution with a mean (SD) of 7.30 (1.32) that approximates 38.3 weeks (9.5 months).
  Categorical analyses divided subjects into two groups: premature (levels 1–6, less than 38
  weeks, N =1251) and full term (levels 7–11, 38 weeks or greater, N =5268) to
  approximate Centers for Disease Control guidelines, which define premature birth as a
  birth stage <37 weeks (Center for Disease Control and Prevention. Retrieved from
  http://www.cdc.gov/features/prematurebirth/). Full term birth is 40 weeks.

- **Infant Gender** – The sample population consisted of 4114 (51%) males and 3995(49%)
  females. Duplicate sources within the perinatal data base were cross-checked against the
  Danish Central Person Register to ensure accuracy in gender designations

- **Parental Social Status at 1 year** – Lower socioeconomic status and social standing have
  been associated with an increased risk of both premature birth (Morgen et al., 2008) and

the development of substance use disorders (Dohrenwend et al., 1992). Data about

parental social status were obtained from an interview with the mother when the child

was 1 year old. The 1-9 point Social Status Scale was based on the breadwinner's

occupation, education, type of income, and quality of housing. The distribution of the

sample population is slightly skewed toward the lower social class with a mean (SD)

level of 4.0(1.85).

Adult Outcome Measures

Over the period surveyed, hospital diagnoses in Denmark were based upon the

International Classification of Diseases, Edition 8 (ICD-8) until 1994 when the ICD-10 system

was adopted (Denmark never formally adopted the ICD-9 system). In order to standardize study

procedures, all ICD-8 diagnoses were first converted to ICD-10 diagnoses according to a

crosswalk published by the World Health Organization (1992). Only the ICD-10, group F codes,

that classify *Mental and Behavioral Disorders* were considered for this study. A total of 376

separate and distinct ICD-10, F diagnostic codes were assigned to the sample of 1,247

hospitalized psychiatric patients. Because many of the ICD-10 F diagnostic codes overlapped

beneath major mental illness groups, they were organized in 14 mutually exclusive summary

diagnostic categories as indicated in Table 1. The organization of the ICD-10, F, *Mental and

Behavioral Disorder* codes into 14 overarching, but separate and distinct categories largely

followed the schema of the international classification system with some exceptions made to

increase its compatibility with the DSM-IV-TR (2000).

Table 1. Fourteen Summary Diagnostic Categories Created from ICD-10 F Codes

1. Organic Mental Disorder (F 00.0 to F 09.0)

2. Alcohol Use Disorder (F 10.00 to F 10.99)

3. Any Non-Alcohol Psychoactive Substance Use Disorder (F 11.00 to F 19.99)

4. Any Schizophrenia, Schizoaffective, Schizotypical or Delusional Disorder (F 20.00 to F 29.99)

5. Any Mood (Affective) Disorder (F 30.0 to F39.9, F 48.0)

6. Any Anxiety or Stress Related Disorder (F 40.00 to F 43.99, F 48.1 to F 48.9)

7. Any Somatoform Disorder (F 45.00 to F 45.99)

8. Any Eating Disorder (F 50.0 to F 50.9)

9. Any Adult Personality Disorder Excluding Dissocial and Unstable Personality Disorder (F 60.0-F 60.1, F 60.5 to 60.9, F 61.0 to F 61.9, F 62.0 to 62.9, F 68.0 to F 68.8, F 69.0)

10. Dissocial Personality Disorder (F 60.2, F 63.0 to F 63.2, F 63.8 to F 63.9)

11. Unstable Personality Disorder (F 60.30, F 60.31, F 60.4)

12. Any Mental Retardation Diagnosis (F 70.0 to F 79.9)

13. Any Developmental Disorder (F 80.0 to F89.9)

14. Any Other Mental and Behavior Disorder (Group F) (F 44.0 to F 44.9, F 49, F 51.0 to F52.9, F55.9, F58, F 59, F63.3, F64.0-F67, F 90.0 to F 90.9, F 91.0 to F 91.9, F 92.0 to F 92.9F 95.0 to F 95.9, F 98.0 to F 98.9, F 99.0, Z03.2)

Data Analysis

Primary Analyses

Statistical analyses were performed using SAS software version 9.1. Frequencies were generated for demographic data. Bivariate analyses were conducted using the Chi Square test to examine the prevalence of diagnoses in the 14 diagnostic categories among low birth weight infants. Analyses were stratified by gender to account for gender-based differences in the frequency of psychiatric diagnoses as well as gender-selective effects of low birth weight on psychiatric outcomes such as alcoholism (Manzardo et al, 2011).

Secondary Analyses

Secondary analyses examined the influence of low birth weight on alcoholism diagnoses using logistic regression modeling. These analyses were conducted sequentially in order to assess the relationship between low birth weight and alcoholism while adjusting for the effects of social class and increasing levels of comorbid psychiatric illness. Model 1 considered the effect of low birth weight on alcoholism. In model 2, the relationship is adjusted for social class and the presence of at least one other psychiatric condition. In model 3, the relationship is further adjusted for psychiatric illnesses linked to low birth weight in our bivariate analyses. The fit for each of the models is assessed using the Hosmer-Lemshow Goodness of Fit Test.

Sensitivity Analyses

Low birth weight and premature birth are partially overlapping conditions that may differentially influence the risk of developing alcoholism. Therefore, logistic regression modeling was performed in a subset of full term infants to assess the effects of small size while excluding the influence of premature gestational stage. Because the effect was not found for female babies, the three models described previously were examined in a subset of full term males.

Results

Approximately 65% of study subjects were delivered at term or later and about 13% were categorized as low birth weight (Table 2). These rates were similar for both male and female subjects. Of the 8,109 eligible subjects, 1,216 or 24.3% received formal treatment at a state-run psychiatric facility at some point in their lifetime with an approximately equal proportion of male (618) and female (598) admissions.

Table 2: Demographic Characteristics of the Overall Cohort

Characteristic	Males (N=4114) n (%)/x(sd)	Females (N=3995) n (%)/x(sd)	Total (N=8109) n (%)/x(sd)
Social Class at Birth	4.00(1.85)	3.98(1.84)	3.99 (1.85)
Preterm Birth (<38 weeks)	649 (20%)	602 (18%)	1251(19%)
Low Birth Weight (<2500g)	490(12%)	556(14%)	1046(13%)
Any Psychiatric Admission	618 (15%)	598 (15%)	1216 (15%)

Social class is presented as mean level on a scale of increasing economic status from 1 to 9 points.

Bivariate Examination of Psychiatric Diagnostic Category

The results of the bivariate analysis of low birth weight on the diagnosis of psychiatric illness by diagnostic category are shown in Table 3. Low birth weight is associated with an overall increase in the likelihood of psychiatric hospitalization (OR=1.38, 95%CI=1.16-1.63) and significantly associated with a diagnosis of alcoholism, mood disorder, anxiety disorder, personality disorder and mental retardation. When these findings are stratified by gender a selective pattern is observed.

Table 3: Low Birth Weight by Psychiatric Diagnostic Category and Gender among Members of the Danish Perinatal Cohort

Diagnostic Categories	Male (N=4114) Low	High	p	Females (N=3995) Low	High	p	Total (N=8109) Low	High	p
	n (%)	n (%)	p	n (%)	n (%)	p	n (%)	n (%)	p
Psychiatric Admission	102 (20.8)	516 (14.24)	0.0001	95 (17.1)	503 (14.6)	0.1314	197(18.8)	1019 (14.4)	0.0002
Organic Brain	9 (1.84)	38 (1.05)	0.1235	7 (1.26)	41 (1.19)	0.8933	16 (1.53)	79 (1.12)	0.2490
Substance Abuse	21 (4.29)	127 (3.51)	0.3841	17 (3.06)	66 (1.92)	0.0808	38 (3.63)	193 (2.73)	0.1025
Alcohol Abuse	51(10.4)	196 (5.41)	0.0001	20 (3.60)	101 (2.94)	0.3993	71 (6.79)	297 (4.21)	0.0002
Schizophrenia	23 (4.69)	123(3.39)	0.1447	18 (3.24)	85 (2.47)	0.2905	41 (3.92)	208 (2.95)	0.0883
Mood	14 (2.86)	83 (2.29)	0.4382	29 (5.22)	123 (3.58)	0.0609	43 (4.11)	206 (2.92)	0.0367
Anxiety	42 (8.57)	190 (5.24)	0.0027	54 (9.71)	292 (8.49)	0.3421	96 (9.18)	482 (6.83)	0.0058
Somatoform	0	1	.	4 (0.72)	11 (0.32)	0.1529	4 (0.38)	12 (0.71)	0.1484
Eating Disorder	0	1	.	2 (0.36)	12 (0.35)	0.9682	2 (0.19)	13 (0.18)	0.9601
Personality	36 (7.35)	155 (4.28)	0.0024	28 (5.04)	165 (4.80)	0.8081	64 (6.12)	320 (4.53)	0.0241
Dissocial Personality	5 (1.02)	23 (0.63)	0.3300	2 (0.36)	7 (0.20)	0.4711	7 (0.67)	30 (0.42)	0.2737
Unstable Personality	1 (0.20)	15 (0.41)	0.4835	10 (1.80)	45 (1.31)	0.3575	11 (1.05)	60 (0.85)	0.5128
Mental Retardation	5 (1.02)	21 (0.58)	0.2479	8 (1.44)	23 (0.67)	0.0549	13 (1.24)	44 (0.62)	0.0252
Develop Disorder	4 (0.82)	26 (0.72)	0.8096	4 (0.72)	6 (0.17)	0.0170	8 (0.76)	32 (0.45)	0.1794
Other Mental Illness	22 (4.49)	102 (2.82)	0.0419	10 (1.80)	52 (1.51)	0.6121	32 (3.06)	154 (2.18)	0.0765

All ICD-8 and ICD-10 diagnoses, across all admissions, assigned to perinatal birth cohort subjects (N=1247) located in the Danish Central Psychiatric Register were classified into one of 13 summary categories shown above. The columns do not add up to 100% because patients were typically assigned multiple diagnoses. Chi-squared analysis of diagnostic category by birth weight, stratified by gender.

Bivariate Analyses Stratified by Gender

Low birth weight in male babies is associated with an increased rate of psychiatric admission (OR= 1.6, 95%CI= 1.2-2.0) compared to males who had normal birth weights (Table 3). Low birth weight males also have significantly higher rates of the specific diagnostic categories of alcoholism (OR= 2.0, 95%CI= 1.5-2.8); anxiety disorders (OR= 1.7, 95%CI= 1.2-2.4), personality disorders (OR= 1.8, 95%CI= 1.2-2.6) and other disorders (OR= 1.6, 95%CI= 1.0-2.6). In contrast, female babies show significantly increased rates of mental retardation (OR= 2.2, 95%CI= 0.96-4.9) and developmental disorders (OR= 4.1, 95%CI= 1.2-14.7) as compared to females who had normal birth weights.

Relationship of Low Birth Weight to Alcoholism Outcome

As described above, alcohol and substance use disorders are commonly associated with comorbid psychiatric problems including anxiety, depression, and personality disorders. We use logistic regression to consider the effect of low birth weight on the development of alcoholism while controlling for the presence of increasing levels of comorbid psychiatric illness (Table 4). These analyses are also stratified by gender to account for expected gender-selective effects. As indicated above, low birth weight approximately doubles the risk for developing alcoholism among males (OR= 2.0; 95% CI= 1.5-2.8) but has no effect on the risk for alcoholism in females (OR= 1.2; 95% CI= 0.7-2.0). Model 2 considers this relationship while adjusting for the effect of social class and the presence of any additional comorbid psychiatric illness. The results show that the effect of low birth weight on alcoholism in males is retained. Model 3 considers this relationship while further adjusting for select diagnostic categories previously linked to low birth weight: anxiety disorders, mood disorders, personality disorders and mental retardation. Again, the effect of low birth weight on alcoholism in males is retained. The Hosmer-Lemeshow test

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indicates that there is no lack of fit for model 2 (p= 0.65) or model 3 (p= 0.20) in males, or

model 2 (p=0.34) in females. However, this is not true for model 3 (p= 0.0004) in females unless

mood disorders are removed from the model (p= 0.29). The relationship between birth weight

and alcoholism in females is not affected by this change.

Table 4: Logistic Regression - Model of Birth Weight and Psychiatric Comorbidity on Alcoholism

Males (N=3302, 80%)	Model 1		Model 2		Model 3	
	OR	CI	OR	CI	OR	CI
Low Birth Weight	**2.03**	1.47-2.81	**1.78**	1.16-2.72	**1.74**	1.13-2.68
Social Class			0.82	0.82-1.01	**0.83**	0.75-0.92
Any Psychiatric Comorbidity			**24.2**	17.0-34.40		
Anxiety Disorders					**4.68**	3.03-7.23
Mood Disorders					**7.34**	4.11-13.10
Personality Disorders					**7.54**	4.78-11.90
Mental Retardation					1.18	0.354-3.93

Females (N=3173, 79%)	Model 1		Model 2		Model 3	
	OR	CI	OR	CI	OR	CI
Low Birth Weight	1.23	0.76-2.01	0.95	0.50-1.80	1.01	0.51-1.97
Social Class			0.93	0.81-1.06	**0.86**	0.75-1.00
Any Comorbidity			**73.2**	35.1-153.0		
Anxiety Disorders					**9.29**	5.38-16.0
Mood Disorders					**3.14**	1.71-5.78
Personality Disorders					**4.16**	2.34-7.40
Mental Retardation					**4.42**	1.42-13.8

Modeling Full Term Infants

As stated, low birth weight and premature birth are overlapping conditions that may

differentially influence the risk of developing alcoholism. In an effort to distinguish the effects of

low birth weight and premature birth, we examined the relation between low birth weight and

alcoholism among males born at term (Table 5). These analyses test the independence of the

effect of low birth weight on male alcoholism in the absence of any confounding influence

associated with premature gestational stage. The results show that low birth weight among full

term male subjects is associated with a significantly increased likelihood of developing

alcoholism (OR= 3.4, 95%CI= 1.9-6.1). This effect is retained when this relationship is adjusted

for social class and the presence of at least one other comorbid psychiatric condition (Model 2).

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And the effect is retained when the relationship is further adjusted for selected psychiatric diagnoses: anxiety disorders, mood disorders, personality disorders and mental retardation (Model 3). The Hosmer-Lemeshow test indicates that there is no lack of fit for model 2 (p= 0.76) or model 3 (p= 0.38) in this subset of subjects.

Table 5: Model of Birth Weight and Psychiatric Comorbidity on Alcoholism among Full Term Males

Males (N=2124, 52%)	Model 1		Model 2		Model 3	
	OR	CI	OR	CI	OR	CI
Low Birth Weight	**3.39**	1.87-6.15	**3.08**	1.39-6.83	**2.45**	1.10-5.43
Social Class			**0.85**	0.74-0.98	**0.78**	0.68-0.90
Any Psychiatric Comorbidity			**25.7**	16.1-41.1		
Anxiety Disorders					**5.02**	2.84-8.87
Mood Disorders					**8.47**	3.86-18.6
Personality Disorders					**8.69**	4.87-15.5
Mental Retardation					0.40	0.036-4.54

Discussion

Low birth weight is associated with an increased rate of lifetime psychiatric hospitalizations by age 47 among members of a large Danish birth cohort. Increased rates of anxiety disorders, mood disorders, personality disorders and mental retardation are observed. The relationship between low birth weight and psychiatric illness may be stronger among low birth weight males who show significantly increased rates of a psychiatric admission; alcoholism; anxiety disorders and personality disorders than normal birth weight males. Sensitivity analyses support the contribution of small size toward the risk of alcoholism rather than premature gestational stage per se. Low birth weight females show increased rates of mental retardation and developmental disorders relative to normal birth weight females. Low birth weight nearly doubled the risk of alcoholism among males even after controlling for the effects of psychiatric comorbidity and social class.

Assessment of Adult Psychiatric Illness among Low Birth Weight Individuals

Increased rates of behavioral and neurodevelopmental problems in childhood have been well characterized among premature and low birth weight babies (Gaddin, 2011; Taylor et al,

2011; Vanderbilt, 2010). Research to date has emphasized childhood and adolescent outcomes of the preterm with follow up extending into early adulthood, up to the mid 20s (Lindstrom et al., 2009; Nomura et al., 2007). Previous studies have relied mainly upon parental reports of psychiatric symptomology and self- assessment questionnaires rather than diagnostic interviews or clinical assessments. Increased rates of psychiatric hospitalization have been reported among children and young adults who were born prematurely (Lindstrom et al., 2009). And increased psychological distress has been observed among low birth weight infants once they reach middle age (Thompson et al., 2001; Westrupp et al., 2011; Wiles et al., 2005). The longest reported follow-up of psychiatric outcomes of low birth weight infants used an historical cohort born in Hertfordshire, England in the 1920's (Osmond et al, 1993). The study examined rates of geriatric depression among men and women at age 68 years (Thompson et al, 2001) and found that birth weight was inversely correlated with depression scores among men, but not among women. Men < 6.5 pounds at birth were 3 times more likely to report depression at age 68 years than men who were > 8.5 pounds at birth. The present study uses a longitudinal follow-up of 47 years to provide the longest follow up to consider clinical psychiatric outcomes and including a comprehensive assessment of all reported psychiatric diagnoses. The results are consistent with previous findings suggesting increased lifetime psychiatric illness among low birth weight individuals.

Male Vulnerability to Psychiatric Illness

The observed gender differences in the effects of low birth weight on psychiatric outcomes may be influenced by several factors. Female infants are normally smaller than male infants at birth and may be resistant to some of the deleterious effects of low birth weight. The overall rate of psychiatric hospitalization is also typically higher among females than males;

although this was not true for the present study which showed an approximately equal representation of male and female admissions. Strong sex differences may be observed in the diagnostic rates of specific psychiatric illnesses which may be attributable to both natural prevalence as well as diagnostic bias. We accounted for these various influences by stratifying our analyses and considering males and females separately.

Consistent with our previous findings, low birth weight males, but not low birth weight females, are more likely to develop psychiatric illnesses including alcoholism. Neuroanatomical injuries typically identified among premature and low birth weight infants include reductions of cortical white matter and lesions in frontal lobe structures associated with executive functions which have also been linked to psychiatric illness. The gender selectivity of the identified relationship between low birth weight and the particular group of psychiatric illnesses: anxiety disorders, personality disorders and alcoholism among males suggest the possibility of a common etiological root for the grouping. The observed association may result from developmental injuries acquired at birth that are associated with low birth weight, of which males appear to be more vulnerable than females. It is possible that exposure to the sequellae of low birth weight increases vulnerability of developing this cluster of disorders in adulthood among males. The predictive relationship between low birth weight and alcoholism among males is retained even after the effects of psychiatric comorbidity and social class are controlled and thus the relationship is not solely a function of increased psychiatric comorbidity.

Study Strengths and Limitations

The large number of study subjects and long duration of follow-up are major strengths of the present study. The cohort is also taken from a genetically and culturally homogenous population of Copenhagen, Denmark. However, the sample represents a slightly lower

socioeconomic class than the general Danish population with an elevated risk for premature birth and low birth weight. As a consequence, the mean birth weight for this cohort (~2800 grams) is slightly lower than the recorded average (3,300grams) for all of Denmark in 1959 (Matthiessen et al., 1967). Lower social class is also associated with an increased rate of psychiatric problems and could increase the likelihood of psychiatric hospitalization. The association between low birth weight and increased risk of psychiatric outcomes reported in this study is retained even after controlling for the effects of social class supporting the overall generalizability of study findings to the Danish population in this historical time frame. However, technological advancements in neonatal care and infant mortality would likely prevent a direct comparison with more recent cohorts.

The use of national archival data resources permits the systematic evaluation of all psychiatric admissions accumulated over the lifetime of the subject. Previous studies have shown that a significant number of subjects with diagnosable psychiatric illness will not seek treatment in their lifetime, and therefore, would not be identified in archival searches of treated subjects. Increased access to psychiatric care associated with the socialized health care system in Denmark may partly compensate for this effect. Never-the-less, archival data sources from the Danish Central Psychiatric Register may differentially represent subjects with severe and comorbid psychiatric problems.

Alcohol use and smoking in pregnancy have been associated with an increased risk of fetal growth problems including low birth weight and premature birth (Ornoy & Ergaz, 2010; Nomura et al., 2011). It is also possible that the teratogenic effects of fetal alcohol or tobacco exposure or could differentially influence the risk of developing psychiatric problems in males and females who are exposed (Haley et al, 2006). We previously reported that the effect of low

birth weight on male alcoholism in this cohort persisted even after the influence of maternal

tobacco use in pregnancy was controlled (Manzardo et al. 2011). We do not have specific

information regarding the mothers' alcohol use during pregnancy, but the level of alcohol use by

Danish women in general during this historical time frame is estimated to be very low. The

present study also does not consider the possible influence of other psychiatric illness among the

parents.

Implications

Our findings suggest that the rates of lifetime psychiatric illness may be modified by

efforts to reduce the occurrence of low birth weight births, especially among male babies.

Improved neonatal care for low birth weight infants might also help to offset some of the

acquired risk of developing psychiatric problems by decreasing the scope of neurological injury

and promoting repair. Further, early detection and treatment of psychiatric symptomology

exhibited in childhood may be predicted to improve adult outcomes. Targeted interventions to

improve childhood developmental outcomes may prove to be a useful strategy to reduce

psychiatric illness among males. A different early intervention strategy may be needed to address

psychiatric problems in women.

Conclusion

The present study supports previous findings that low birth weight is associated with

increased rates of adult psychiatric illness in a gender selective pattern. Low birth weight appears

to have greater impact on psychiatric outcomes in males who show increased rates of alcoholism

and psychiatric disorders commonly comorbid with alcoholism. The results support the theory

that developmental insults acquired around the time of birth may increase the vulnerability

toward alcoholism-related comorbid disorders among men.

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