Does intra-uterine growth discordance predict differential risk for adult psychiatric disorder in a population-based sample of monozygotic twins?

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The study of discordant monozygotic twins may identify important developmental risk factors for adult psychiatric disorder. Differential experience in utero is one candidate environmental risk factor that may distinguish monozygotic twins. In this report, we examine whether intra-pair differences in birth weight predicts discordance for adult psychiatric disorders in 527 female monozygotic twin pairs from a population-based twin registry. Twins were personally interviewed about their lifetime history of DSM-III-R alcoholism, anorexia nervosa, bulimia nervosa, generalized anxiety disorder, major depression, panic disorder, social phobia and simple phobia. Birth weight was estimated from birth certificates, or from retrospective maternal, paternal and self-reports. Conditional logistic regression is used to characterize the association between intra-pair differences in birth weight and discordance for psychiatric disorder in monozygotic twins. The twin with the heavier birth weight in discordant pairs is insignificantly more likely to have a history of alcoholism or bulimia. The twin with the lighter birth weight in discordant pairs is (insignificantly) more likely to have a history of major depression, panic disorder, social phobia and simple phobia. For all psychiatric disorders examined, the lighter (or heavier) cotwin at birth is not systematically the affected twin within discordant pairs.

INTRODUCTION

The study of discordant monozygotic twins may identify important developmental risk factors for adult psychiatric disorder. Differential experience in utero is one candidate environmental risk factor that may distinguish monozygotic twins. It is widely recognized that variation in the quality and similarity of the intra-uterine environment experienced by monozygotic twins is influenced by factors associated with placentation. Monozygotic twins may be subdivided into three placental classes: dichorionic-diamniotic, monochorionic-diamniotic and monochorionic-monoamniotic. Monozygotic twins that divide within 72 h of fertilization have two placentae, two amnions and two chorionic membranes, and are therefore dichorionic-diamniotic. The proximity with which the two embryos are implanted in the uterine wall determines whether their placental membranes are completely separate, partially shared or fused (Baldwin, 1994). Monozygotic twins that split within 3–4 days share a single placenta and are therefore monochorionic-diamniotic. If twinning takes place after some cells are committed to amniogenesis, at days 8–9, then both twins are in the same amniotic sac and are monochorionic-monoamniotic. Later twinning leads to incomplete separation of the embryos and conjoined twins (Baldwin, 1994). Dizygotic twins arise from the fertilization of two separate ova, and each embryo therefore has the full complement of amniotic and chorionic membranes. All dizygotic twins are therefore dichorionic-diamniotic, but the relative separation of the placental membranes varies (as it does in monzygotic dichorionic-diamniotic twins). In Caucasian populations, monochorionic-diamniotic twins comprise approximately 63%, monochorionic-monoamniotic twins comprise approximately 2% and dichorionic-diamniotic twins comprise approximately 35% of live monozygotic
twin births (Baldwin, 1994). The proportion of dichorionic twins with separate or shared/fused amniotic (placental) membranes is roughly equal.

Dichorionic monozygotic and dizygotic twins have, in general, similar developmental and gestational risks. Monozygotic monochorionic twins, however, are at additional risk because of blood vessels that connect the circulation of one twin to the circulation of the other (inter-twin vascular anastomoses). This may create an imbalanced blood flow between the twins, resulting in the twin transfusion syndrome, which may affect between 7.5 and 17.5% of monozygotic monochorionic twins (Bernischke, 1961; Tan et al., 1979). Although a transfusion syndrome may also occur in dichorionic twins with partially fused placenta (Corney, 1975), such placental vascular communications are very rare. Monozygotic monochorionic-monoamniotic twins are at risk from inter-twin (cord) entanglements, although inter-twin vascular anastomoses are relatively less frequent. The well-documented excess mortality and morbidity of monozygotic twins is largely due to the complications of monochorionic (monoamniotic) placentaion (Baldwin, 1994; Machin and Still, 1995).

Given such differential patterns and sources of risk between monochorionic (monoamniotic) and dichorionic twins, the possibility that systematic differences in twin similarity may arise as a function of variable placentaion has been widely canvassed. To date, placentaion has been reported to influence twin resemblance for birth weight (Corey et al., 1979; Buzzard et al., 1983; Ramos-Arroyo et al., 1988), (cord) plasma cholesterol levels (Corey et al., 1976), cognitive abilities (Melnick et al., 1978; Rose et al., 1981; Spitz et al., 1996), personality (Sokal et al., 1995), red blood cell mass (Bulmer, 1970) and immunoglobulin (IgG) type (Byron and Slavin, 1974), but not laterality (Carlier et al., 1996). Putative indices of placentaion, such as the dermatoglyphics index proposed by Reed and colleagues (Reed et al., 1978; Rose et al., 1987; Bogle et al., 1994), have also been reported to predict differential similarity between putative monochorionic-monozygotic and dichorionic-monozygotic twin pairs for type A behavior (Reed et al., 1991) and schizophrenia (Davis et al., 1995). Although the mechanisms underlying placental influences on twin similarity are unclear, it has been suggested that certain placental features may provide the requisite threshold for differential phenotypic expression. Cord anomalies, for example, may function as a threshold for the expression of cleft palate and anencephaly in discordant monozygotic twins, leading Baldwin (1994) to postulate that other (polygenic/multifactorial) traits could also have their threshold provided by intra-uterine experiences associated with placentaion.

The systematic collection of placental data on large population-based samples of twins is rare (Derron et al., 1995). Evaluation of the impact of placentaion on behavioral variation both within and between monozygotic and dizygotic twins has therefore been largely restricted to studies conducted with small, well-characterized samples. Consideration of the role that variation in placentaion plays in twin similarity for risk of adult psychiatric disorder has been limited (Davis et al., 1995). In the absence of reliable placental data, however, other indices of a differential prenatal environment — such as intra-pair birth weight differences in monozygotic twins — have been examined (Kringlen, 1967; Shields and Gottesman, 1977; Lewis et al., 1987; Hyde et al., 1992; Onstad et al., 1992). Such differences reflect the differential effect of an unequal, albeit shared, prenatal environment. Prenatal growth discordance in monozygotic twins is not a measure of placentaion per se, however, as such growth discordance may reflect a multiplicity of prenatal experiences and factors. These may include: (i) chorialvic effects (Corey et al., 1979; Vlietinck et al., 1989; Machin, 1997) and/or differential placental proximity (in dichorionic twins) and competition for nutrients (Benirschke, 1965; Corey et al., 1979; Blickstein and Lancet, 1988; see also, Eberle et al., 1993); (ii) the insertion and number of cord vessels (Ramos-Arroyo et al., 1988; Machin, 1997) and/or differential prenatal growth in the uterus; (iii) the moderating influence of maternal factors (Nance et al., 1978; Hemon et al., 1982). Intra-uterine growth discordance in monozygotic twins therefore affords an opportunity to examine the impact of a composite of prenatal influences on differential risk of psychiatric disorder. In this report, we aim to determine whether intra-pair differences in birth weight predicts discordance for adult psychiatric disorders in 527 female monozygotic twin pairs from a population-based twin registry.

METHODS

Subjects

The data analyzed for this report were collected as part of a longitudinal study of the genetic and environmental risk factors for common psychiatric disorders in women (Kendler et al., 1992a). The first contact with these twins comprised a mailed survey,
to which 64% of individuals responded. The true cooperation rate is likely to be higher, however, because an unknown proportion of nonrespondents never received the mailed questionnaire due to an incorrect mailing address, incorrect forwarding of mail, etc. Of the 1176 female twin pairs who returned the questionnaire, 529 monozygotic and 372 dizygotic pairs subsequently completed an interview about their lifetime history of psychiatric disorder. Zygosity was determined blindly by standard questions (Eaves et al., 1989), photographs and DNA analysis (Spence et al., 1988). As described in detail elsewhere (Kendler et al., 1994), all living biological parents of these 1031 twin pairs were identified during the course of the personal interview with the twins. Of the 1698 parents thus identified, 855 mothers and 617 fathers of twins also completed an interview that included questions about the birth of the twins. The sample who are the subject of the present report comprise the 527 monozygotic female twin pairs for whom interviews were conducted with both twins and at least one biological parent.

**Measures**

**Assessment of a lifetime history of psychiatric disorder**

Twins were personally interviewed at home by field staff with 2 weeks of formal training, and a Masters degrees in Social Work or at least 2 years of clinical experience. Different interviewers were assigned to each twin in a pair to ensure that field staff were blind to the psychopathologic status of the co-twin. Twins were interviewed about their lifetime history of alcoholism, anorexia nervosa, bulimia nervosa, generalized anxiety disorder, major depression and panic disorder using an adapted version of the Structured Clinical Interview for DSM-III-R American Psychiatric Association, 1987; Spitzer et al., 1987). Phobias (simple, social and agora-phobia) were assessed using an adaptation of the phobic disorders section of the Diagnostic Interview Schedule Version III-A (Robins and Helzer, 1985). Psychiatric diagnoses were based on a blind diagnostic review of the personal interview by an experienced psychiatric diagnostician. The inter-rater reliabilities (κ) of these diagnostic assignments are 0.96 for major depression, 0.73 for generalized anxiety disorder, 0.95 for the rating of any unreasonable fear and 0.81 for rating that such a fear interfered with the subject’s life, and 0.86 for alcoholism (Kendler et al., 1992a–c, 1994). The κ values could not be computed for panic disorder, anorexia nervosa or bulimia nervosa due to their low lifetime prevalence in this sample.

**Assessment of birth weight and weeks gestation**

During the personal interview conducted with the mothers and fathers of twins, each parent was asked about the length of the twin pregnancy and each twin’s birth weight. Interviews with the twins also included a question inquiring about their own birth weight. These interviews yielded 989 maternal, 683 paternal and 1003 twin reports of the twin’s birth weight, and 994 maternal and 718 paternal reports of gestation length. In addition, birth certificates noting weeks of gestation and birth weight were available for 446 and 113 individual twins. The Pearson correlation between mother’s, father’s, and twin’s reports of birth weight and those recorded on birth certificates is 0.89 (n = 97), 0.73 (n = 74) and 0.64 (n = 110), respectively. The Pearson correlation between mother’s and father’s reports of weeks gestation and that recorded on birth certificates is 0.66 (n = 416) and 0.64 (n = 248), respectively. All correlations are significant at P < 0.0001. Based on these findings, and the greater number of twin versus father reports, the following data hierarchy was used to assign (1) birth weight, and (2) weeks of gestation: (1) birth certificate over mother’s report over the twin’s self-report over father’s report; and (2) birth certificate over mother’s report over father’s report. This hierarchy yielded birth weight and gestation data for all 1054 individual twins. Pair-wise growth discordance was calculated as the ratio of the twins birth weights [largest birth weight – lowest birth weight/largest birth weight × 100].

**Statistical analysis**

Discordant monozygotic twins may be viewed as a special form of the 1:1 matched case–control design because each case (the twin with a history of disorder) may be matched with a cotwin control (the twin without a history of disorder). Analysis of this kind of data requires conditional logistic regression to condition the likelihood function for the null model (without risk factors) and the full model (with risk factors) on the total number of matched pairs included in each analysis. Conditional logistic regression is used here to characterize the association between intra-pair differences in birth weight and discordance for psychiatric disorder using procedure PHREG in SAS version 6.12 (SAS Institute Inc., 1995). The risk ratio estimated by these analyses is the expected change in the risk ratio of having a history of disorder versus not having a history of disorder that is associated with a per-unit change in the risk factor (i.e. per-gram difference in birth weight within matched pairs). A risk ratio > 1 indicates that the twin who is heavier at birth is more...
likely to have a history of disorder. Conversely, a risk ratio < 1 indicates that the twin who is lighter at birth is more likely to have a history of disorder. The significance of the expected change in the risk ratio reflects the difference between the null and the full model. This is assessed by the Wald statistic, and the associated two-tailed $P$ value indicates the significance of the risk factor in the model.

**RESULTS**

The twins birth weights ranged between 879 and 4054 g (mean, 2412.87 g; SD, 515.97 g), and weeks of gestation ranged between 28 and 41 weeks (mean, 37.98 weeks; SD, 2.64 weeks). Growth discordance ranged between 0 and 65% (mean, 9.62%; SD, 9.02%). Examined categorically, 195 pairs (39%) were 0–5%, 120 pairs (24%) were 6–10%, 66 pairs (13.2%) were 11–15%, 57 pairs (11.4%) were 16–20%, 29 pairs (5.8%) were 21–25%, 16 pairs (3.2%) were 26–30% and 17 pairs (3.4%) were >30% growth discordant. The remaining 27 pairs had the same estimated birth weight. The absolute weight difference within pairs ranged between 0 and 1729 g (mean, 248.48 g; SD, 246.70 g).

Twins were aged between 18 and 51 years (mean, 29.03 years; SD, 7.44 years) at the time of interview. The estimated lifetime prevalence (uncorrected for age) of alcoholism is 10.8%, that of anorexia nervosa 3%, that of bulimia nervosa 4.2%, that of generalized anxiety disorder (of at least 6 months duration) is 8.4%, that of major depression 30.2%, that of panic disorder/agoraphobia 13.7%, that of simple phobia 11.5% and that of social phobia 18%. Fifty-seven pairs are discordant for a life-time history of alcoholism, 16 for anorexia nervosa, 22 for bulimia nervosa, 44 for generalized anxiety disorder, 159 for major depression, 72 for panic disorder/agoraphobia, 131 for simple phobia and 95 for social phobia.

The mean percentage growth discordance in discordant and concordant monozygotic twins is presented in Table 1. Psychiatric disorder is not significantly associated with intra-pair differences in birth weight in discordant monozygotic twins (Table 2). Positive associations (at $P > 0.05$) are found for bulimia and alcoholism. A negative association (i.e. a risk ratio < 1.00) indicates that the twin with the heavier birth weight in discordant pairs is (insignificantly) more likely to have a history of these disorders. Among depressed twins from discordant pairs ($n = 159$), for example, 97 were lighter at birth and 62 were heavier at birth.

**DISCUSSION**

We aimed to determine whether intra-pair differences in birth weight are associated with discordance for psychiatric disorder in a population-based sample of adult female twins. The twin with the heavier birth weight in discordant pairs is (insignificantly) more likely to have a history of alcoholism or bulimia. The twin with the lighter birth weight in discordant pairs is (insignificantly) more likely to have a history of major depression, simple phobia, panic disorder, anorexia nervosa, social phobia or generalized anxiety disorder. For all psychiatric disorders examined, the lighter (or heavier) cotwin at birth is not systematically the affected twin within discordant pairs.

There is no previously published work on the relationship between intra-uterine growth discordance and risk for nonpsychotic psychiatric disorders in unselected samples of adult twins. It is of interest, however, that Hettema et al. (1995) reported that (adult) physical similarity significantly influenced twin resemblance for bulimia. This finding was interpreted as suggesting that a greater degree of physical resemblance, and perhaps a similar level of body image dissatisfaction and appearance-based self-esteem, increases co-twin risk for bulimic behaviors. Although the association between intra-uterine growth discordance and bulimia is not statistically significant here (at $P = 0.08$), further consideration of physical similarity as a risk factor for bulimia in twins may be warranted.

Our findings do not suggest that all complications of pregnancy and delivery necessarily produce a measurable continuum of risk (Pasamanick et al., 1956) that is manifest as an increased risk for any psychiatric disorder. Brown et al. (1996) note, however, that the same risk factor could produce different outcomes depending on the timing or degree of exposure, genetic predisposition, concomitant exposures (e.g. viral infection) or subsequent events (e.g. birth trauma). We were able to examine the impact of differential birth trauma and postnatal complications (full results available on request), and con-
<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Twin pairs discordant for disorder</th>
<th>Twin pairs concordant for disorder</th>
<th>Twin pairs concordant for no disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Range</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>11.19</td>
<td>11.5</td>
<td>0–65</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>9.62</td>
<td>11.5</td>
<td>0–43</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>13.95</td>
<td>12.27</td>
<td>0–38</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>12.23</td>
<td>12.68</td>
<td>0–65</td>
</tr>
<tr>
<td>Major depression</td>
<td>8.65</td>
<td>7.61</td>
<td>0–39</td>
</tr>
<tr>
<td>Panic disorder/</td>
<td>9.37</td>
<td>8.17</td>
<td>0–38</td>
</tr>
<tr>
<td>agoraphobia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social phobia</td>
<td>8.81</td>
<td>8.26</td>
<td>0–38</td>
</tr>
<tr>
<td>Simple phobia</td>
<td>9.58</td>
<td>9.11</td>
<td>0–65</td>
</tr>
</tbody>
</table>

Note: Growth discordance is the % intra-pair difference in birthweight.
TABLE 2. Association between birth weight and risk for adult psychiatric disorder in discordant monozygotic twins

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Number of discordant pairs</th>
<th>Risk ratio (95% confidence interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>57</td>
<td>1.036 (0.995, 1.080)</td>
<td>0.09</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>16</td>
<td>0.909 (0.665, 1.243)</td>
<td>0.55</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>22</td>
<td>1.066 (0.993, 1.144)</td>
<td>0.08</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>44</td>
<td>0.999 (0.965, 1.035)</td>
<td>0.97</td>
</tr>
<tr>
<td>Major depression</td>
<td>159</td>
<td>0.979 (0.951, 1.008)</td>
<td>0.16</td>
</tr>
<tr>
<td>Panic disorder/agoraphobia</td>
<td>72</td>
<td>0.984 (0.938, 1.034)</td>
<td>0.53</td>
</tr>
<tr>
<td>Simple phobia</td>
<td>95</td>
<td>0.982 (0.956, 1.008)</td>
<td>0.17</td>
</tr>
<tr>
<td>Social phobia</td>
<td>131</td>
<td>0.999 (0.966, 1.033)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Note: The risk ratio is the expected change in the risk ratio of having a history of disorder versus not having a history of disorder that is associated with a per-unit change in the risk factor (i.e. per-gram difference in birth weight within twin pairs).

LIMITATIONS

These results should be interpreted in light of certain limitations. First, males and females may be differentially affected by growth discordance (O’Brien and Hay, 1987), and the present findings therefore apply only to female twins. Second, data extracted from birth records and retrospective maternal, paternal and twin reports were not always in agreement, and we therefore utilized a hierarchy of birth certificate data over maternal over twin over paternal retrospective reports to assign a best estimate of birth weight in an attempt to minimize reporting error. Although none of these data sources is likely to be error free, the accuracy of both abstracted medical record data and retrospective maternal reports have generally been found to be adequate (Hewson and Bennett, 1987; O’Callaghan et al., 1990). Finally, it is important to reiterate that placentaion is not reliably indexed by prenatal growth discordance. Growth discordance may index many different intra-uterine factors. A study examining associations with placental type (or indices that better estimate placental type such as the dermatoglyphics index proposed by Reed and colleagues) or fluctuating asymmetry may therefore yield different results to those reported here.

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Introduction, paras. 3 + 4 — Full details of Davis et al. (1995) for reference list.

Corney (1975) — First six editor names (all or all if seven in total).

Derom et al. (1995) — First six editor names (all or all if seven in total).

Eaves et al. (1989) — First six author names (all or all if seven in total).

Heifetz (1983) — Letter or abstract?

Jorgersen et al. (1992) — First six author names (all or all if seven in total).

Machin and Still (1995) — First six editor names (all or all if seven in total).

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