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Opposite risk patterns for autism and schizophrenia are associated with normal variation in birth size: phenotypic support for hypothesized diametric gene-dosage effects

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1. Introduction

Autism and schizophrenia are complex disorders that remain difficult to explain with currently identified risk factors, which include genetic, developmental and environmental influences (for recent reviews, see [1–4]). Heritability estimates place the familial component between 50 and 80% for autism and schizophrenia [5–8], but only a fraction of the contributing genetic variants have been identified [9–11], and such estimates are often inflated [12]. Recent work has begun to uncover the potential importance of imprinted genes with parent-of-origin effects on autism, schizophrenia and other neuropsychiatric disorders [13–15]. In 2008, Badcock and Crespi [16,17] hypothesized that autism and schizophrenia are diametric opposites joined by a spectrum of less severe disorders and normal cognition (figure 1).

Genomic imprinting, also known as parent-of-origin imprinting, normally involves the expression of only one copy of a bi-parentally inherited gene because it is tagged for expression by one parent and silenced by the other parent during early development [18–21]. Genetic mechanisms for achieving parent-of-origin expression are deletion, loss of imprint and obtaining two rather than one copy from one of the parents (uniparental disomy) [18,19]. For example, insulin-like growth factor (IGF2) is a mammalian gene with diametric gene-dosage effects. When perturbed, IGF2 can cause opposite outcomes in fetal development, birth size and subsequent behavioural syndromes [22,23] because the maternal copy is normally silenced and the paternal copy expressed. When both copies are expressed...
Gene dosage effects in utero are diametrically associated with phenotypic proxies of diametric and residents, to test whether autism and schizophrenia are containing three decades of data for roughly 5 million nationals affected by imprinting imbalances.

Provisioning, but can also be expected to affect the mental maternal resource allocation during pregnancy and infant the phenotypic effects of imprinting apply not only to caregivers, but also to the risk of these disorders.

Gardner [18,19] later extended the theory, emphasizing that autism and schizophrenia are diametrically connected, we asked four questions: (1) Is there an opposite pattern of risk present between autism and schizophrenia within ±1 s.d. of mean birth size (to avoid confounding pathological effects at distribution extremes)? That is, does above-average birth weight/length predict increased autism (but not schizophrenia) risk, and does below-average birth weight/length predict increased schizophrenia (but not autism) risk? (2) If this diametric risk pattern exists, does it increase as average birth size deviates beyond ±1 s.d., as expected if these disorders are linked by a spectrum of small-to-large diametric gene-dosage effects? (3) Are these patterns supported across the range of autistic versus schizophrenic disorders? (4) Do other known risk factors affect the hypothesized axis between autism and schizophrenia?

2. Material and methods
To answer questions (1) and (2), we focused on comparing risk patterns between autism spectrum (AS) and schizophrenia spectrum (SS) disorders based on deviations from average birth weight and length. Other autistic, schizophrenic and related disorders were included largely to answer question (3). We used Cox regression (proportional hazards) to model the risk of autism and schizophrenia as a function of birth weight and length. Covariates...
included to control for known familial and environmental effects on these disorders were also used to answer question (4).

(a) Study population
We identified all singleton live births (n = 1,787,447) between January 1978 and January 2009 in the Danish Fertility Database, which contains identification of parents and other birth-related information. We used unique personal identification numbers (de-identified from central-person register numbers) to link information about individuals between different registries to near completion, including the Danish National Patient Registry (which holds nationwide data on all admissions to any Danish hospital since 1977), the Danish Psychiatric Central Register (with recorded diagnoses for all psychiatric inpatient admissions since 1969), the Danish Civil Registration System and the Danish Cause of Death Registry (which contains records of changes in vital status, date of death, migration and socioeconomic status). Of the initial 1,787,447 singleton births, 29,677 (1.6%) were removed due to missing data and removal of outliers (to ensure normality), reducing the sample size to 1,757,770. Of these, 95,345 (5.42%) had an autistic or schizophrenic (or related) disorder (see study sample characteristics, electronic supplementary material, table S1).

(b) Birth size as a phenotypic marker of gene-dosage variation in utero
We assumed that normal population-level variation in birth size should (after accounting for other factors that influence birth size) contain a detectable signal of underlying deviations from average gene-dosage variation in utero. This assumption is based on the demonstrated effects of disrupted imprinted genes on birth size and subsequent postnatal behaviour (see the electronic supplementary material, Material and Methods, for details). We explored the validity of this assumption in the Danish population by examining variation in birth size for individuals with BWS, SRS, PWS and ANS (figure 2). This showed that adjusted birth sizes differ significantly depending on whether the imprinting disorder was maternally or paternally biased, strongly so for BWS, SRS and PWS, and less pronounced for ANS. This confirms that population-wide variation in birth size has the potential to capture perturbations to imprinted genes and copy number variation, and supported the use of birth size as a phenotypic marker when investigating whether autism and schizophrenia might be linked to putative diametric gene-dosage deviations in utero.

(c) Removing confounding effects from birth size
We removed the effect of gestation length on birth weight and length by taking residuals from generalized additive models (c) Removing confounding effects from birth size
We removed the effect of gestation length on birth weight and length by taking residuals from generalized additive models of birth weight and length prior to running t-tests, residuals were taken from a generalized additive model (red line in plots).

(d) Defining autistic and schizophrenia disorder groups
Our two main disorder groups were AS disorders and a broad SS disorder group. AS included autism (infantile and atypical), Asperger’s syndrome and pervasive developmental disorder not otherwise specified. SS included schizophrenia, bipolar disorder and major depression (see ICD codes and structure, electronic supplementary material, table S2 and figure S1). Both spectra have been described before [44,45], have overlapping genetic risk loci [46], and were chosen specifically to test questions (1) and (2) because they cover the range of autistic and schizophrenic behaviours well while avoiding smaller sample sizes associated with more specific diagnoses.

The use of spectra is becoming increasingly accepted due to overlapping aetiology and behaviours, but we recognized that their definitions continue to be debated and revised [47]. We therefore also did separate analyses that used narrower and broader disorder groups related to both AS and SS (electronic supplementary material, table S2 and figure S1) to address question (3). Narrower groups derived from AS included infantile autism and infantile and atypical autism. Narrower groups derived from SS included bipolar disorder, major depression and schizophrenia. Broader groups related to AS included disorders of psychological development (as both AS and autism are derivatives from this
broader group; electronic supplementary material, figure S1) and behavioural and emotional disorders with onset in childhood and adolescence. This group was chosen for the typical early onset and self-oriented behaviours, which ultimately make these individuals demanding on their carers (usually the mother) and thus functionally similar to autistic behaviours associated with the paternally biased gene-dosage effects described by Badcock & Crespi [16,17]. Broader groups related to SS included schizophrenia, plus schizotypal and delusional disorders, chosen because schizophrenia is derived from this broader group (electronic supplementary material, figure S1). For details of data validation, see the electronic supplementary material, Material and Methods.

(e) Statistical analyses and comparisons of risks
We used Cox regression in R v. 15 to estimate relative risks (RRs) of AS, SS and related disorders in offspring depending on birth weight or length grouped as defined above. Other influences were controlled for by adding them as covariates in Cox regressions; they included known familial effects, pre-existing conditions, pregnancy- and birth-related factors, and environmental and socioeconomic effects (for details on covariates, see the electronic supplementary material, Material and Methods, and table S3). To directly test for diatmatic risks between AS and SS disorders within ±1 s.d. of the mean, we compared Cox regression coefficients and standard errors within groups 3 or 4 with Student’s t-tests (for dependent samples, survcomp package in R). Specifically, we tested whether AS risk was significantly higher than SS risk for larger babies (group 4) and vice versa for smaller babies (group 3). To test for broader cumulative risk patterns within AS or SS, we used survcomp to compare Cox regression coefficients and standard errors, specifically asking whether AS risk was significantly lower in group 4 than 5 and lower in group 5 than 6, and whether SS risk was significantly lower in group 3 than 2 and lower in group 2 than 1.

Figure 3. Risk of AS and SS disorders by birth weight (a) and birth length (b). Points show relative risks (RRs) obtained from Cox regression for each disorder (see the electronic supplementary material, table S4, for corresponding risk ratios, confidence intervals and p-values). Risk for other disorders related to AS and SS are also shown. Grey histogram bars represent the majority of birth data within approximately ±1 s.d. of the mean, including groups 3 (2891–3290 g or 49.7–51.2 cm), central (3291–3690 g or 51.3–52.7 cm) and 4 (3691–4090 g or 52.8–54.3 cm). Smaller babies beyond ±1 s.d. included groups 1 (1850–2490 g or 45–48.0 cm) and 2 (2491–2890 g or 48.1–49.6 cm). Larger babies included groups 5 (4091–4490 g or 54.4–55.9 cm) and 6 (4491–5400 g or 56.0–59 cm). Histograms represent birth weight and length distributions by frequency (>1000) on the right y-axis.
3. Results

(a) Autism spectrum and schizophrenia spectrum disorders

(i) Relative risk patterns within ±1 s.d. of mean birth size
For larger-born babies (group 4 in figure 3), AS risk was significantly higher (6% for birth weight and 18% for birth length) and SS risk was significantly lower (6% for both weight and length at birth) relative to the central group (figure 3; electronic supplementary material, table S4). Risk for AS for these above-average babies was significantly higher than risk for SS disorders (birth weight, \( t = 20.03, p < 0.001 \); birth length, \( t = 41.6, p < 0.001 \)). For smaller-born babies (group 3 in figure 3), AS risk was significantly lower (8% for birth weight and 11% for birth length) and SS risk was significantly higher (8% for birth weight and 12% for birth length) relative to the central group (figure 3). For these below-average babies, SS risk was significantly higher than AS risk (birth weight, \( t = 19.3, p < 0.001 \); birth length, \( t = 26.4, p < 0.001 \)).

(ii) Relative risk patterns across all birth sizes
Considering the full birth size range (groups 1 to 6 in figure 3; electronic supplementary material, table S4) an opposing pattern of risks between AS and SS persisted for all groups when considering birth length and for all groups except group 1 when considering birth weight. The magnitude of AS risks increased cumulatively across groups 4–5–6 (weight, 6–23–53%; length 18–31–56%; figure 3) as babies were born increasingly larger, with each risk significantly larger than the previous for weight (group 4 < 5, \( t = 3.12, p < 0.001 \); group 5 < 6, \( t = 3.03, p = 0.001 \)) and length (group 4 < 5, \( t = 2.21, p < 0.013 \); group 5 < 6, \( t = 2.71, p = 0.003 \)). The magnitude of SS risks across groups 4–5–6 remained below average with a significant monotonic decrease with increasing birth length (figure 3). Across groups 3–2–1 (figure 3), the magnitude of SS risks increased as babies were born increasingly smaller (weight, 8–21–25%; length, 12–24–34%), with all risks significantly larger than the previous for length (group 3 < 2, \( t = 2.94, p = 0.001 \); 2 < 1, \( t = 1.73, p = 0.041 \)) and between one of the two group comparisons for weight (group 3 < 2, \( t = 3.35, p < 0.001 \); group 2 < 1, \( t = 0.59, p = 0.277 \)).

(b) Other disorders related to the autism and schizophrenia spectra
Within ±1 s.d. of mean birth size (groups 3 and 4 in figure 3; electronic supplementary material, table S4), patterns of RR for narrower and broader disorder groups displayed a similar pattern of risk to those found for AS and SS disorders. Larger-born babies (group 4) were at increased risk for most disorders related to AS (birth weight, 3 out of 4; birth length, 4 of 4) and at decreased risk for 2 of 4 disorders related to SS for both birth size predictor variables (figure 3). Smaller-born babies (group 3) were at increased risk for all disorders related to SS (both predictor variables, 4 out of 4) and decreased risk for most disorders related to AS (both predictor variables, 3 of 4). Considering the entire birth size range (groups 1 to 6; figure 3), RR patterns for the narrower and broader disorder groups were likewise largely consistent with those found for AS and SS. For larger-born babies (groups 4–5–6), risks were higher for autistic-related relative to schizophrenic-related disorders, with autistic risks tending to increase in magnitude when further from the mean (figure 3). For smaller-born babies (groups 3–2–1), risks tended to be larger for schizophrenic-related disorders relative to autistic-related disorders between groups 3 to 2. However, the clarity of this separation disappeared at the smallest birth size in group 1, indicating that only considering the smallest babies does not provide encompassing insight in the overall trends that underlie risk for mental disorders across all birth sizes.

(c) Other risk factors
Patterns of RR related to covariates (figure 4; electronic supplementary material, tables S5–S14) showed that autistic disorders tended to be higher in male offspring and schizophrenic disorders more prevalent in female offspring, except for two groups (schizophrenia, schizophrenia—schizotypal-delusional disorders) that were higher in males. This may be due to differences in severity [16] and age at detection [48,49] between the sexes, where schizophrenia is more often severe in males (and perhaps obvious earlier in life) with onset delayed in females, including a second peak for women aged 45–79 [49]. The 30 years of follow-up available for this study (electronic supplementary material, figure S2) may thus not have allowed sufficient time to capture all cases of these disorders in females, especially for those born closer to 2009.

Offspring born from older fathers had increased risks for all disorders, with risks for 8 of 10 disorders significantly increased. These risks tended to be larger for autistic than schizophrenic disorders. By contrast, increasing maternal age decreased risk for four out of five schizophrenic-related disorders and one autistic-related group, but increased risk for three autistic-related groups. Compared with first-born children, second- and later-born children had relatively lower risk for autistic disorders but higher risk for schizophrenic disorders (figure 4).

4. Discussion

(a) Opposite risk patterns present for autism and schizophrenia
The results of our study consistently support the Badcock and Crespi hypothesis [16,17] that autism and schizophrenia are opposite extremes of a single gradient of mental disorders. This is remarkable, for the inclusive fitness theory that produced these predictions [18,19,21,32,34–36] was initially blind to any clinical applications and remains at present the only theory that predicts the diametrically opposed risk patterns that our study uncovered. The evolutionary logic and our results for normal birth sizes within ±1 s.d. (which answered the first question that we posed) underscore that, in an evolutionary sense, our physical and mental health is always at risk of being compromised by deep kinship conflicts that we share with most other animals [21,32–34,50].

Our results lend credibility to Badcock & Crespi’s [16,17] idea that the opposed risk factors will at least partly be due to diametric gene-dosage deviations caused by disrupted genomic imprinting or copy number variants. However, this support is indirect. We still lack most of the genetic evidence needed to understand which genes became subject to parent-of-origin imprinting and why other genes escaped that fate, but the evidence available so far seems encouraging.
risks for smaller and larger babies, respectively. Using a on eight birth weight groups, indicating higher and lower trend in risk for schizophrenia and affective disorders based in Stockholm County from 2001 to 2007, Abel singleton births between 1973 and 1986 from Denmark and depending on birth size. Using a sample of 1.49 million previous work examining risk of autism or schizophrenia similarly rather than diametrically [26].

in three other regions affected autism and schizophrenia between autism and schizophrenia. However, CNV variation and duplications contributed to the diametric association found across the entire birth size range examined here, but they examined autism and schizophrenia independently, and their aim was not to test for presence or absence of a diametric association between both disorders in the same population and for normal birth sizes. Other epidemiological studies [38,40,41] have also examined risk of either autism or schizophrenia based on birth size, but most were limited by very small sample sizes and were likewise not testing for opposite patterns of risk between autism and schizophrenia.

For example, reciprocal deletions and duplications at two loci 1q21.1 and 16p11.2 appear to be linked with diametric phenotypes in the autistic–schizophrenic spectrum [28,51]. Duplications of 1q21.1 and deletions of 16p11.2 are correlated with larger head size in childhood and increased risk of autism, whereas deletions of 1q21.1 and duplications of 16p11.2 are associated with smaller head size and higher risk of schizophrenia [52,53]. A recent analysis of CNVs found four chromosomal regions where reciprocal deletions and duplications contributed to the diametric association between autism and schizophrenia. However, CNV variation in three other regions affected autism and schizophrenia similarly rather than diametrically [26].

It is important to note that our results are consistent with previous work examining risk of autism or schizophrenia depending on birth size. Using a sample of 1.49 million singleton births between 1973 and 1986 from Denmark and Sweden, Abel et al. [39] found an overall significant negative trend in risk for schizophrenia and affective disorders based on eight birth weight groups, indicating higher and lower risks for smaller and larger babies, respectively. Using a sample of 589,114 children aged 0–17 who resided in Stockholm County from 2001 to 2007, Abel et al. [37] later found a significant nonlinear trend in risk for AS disorders based on nine birth weight z-score groups, indicating higher risks in very small and large babies relative to those born of average size. Both studies support the risk patterns found across the entire birth size range examined here, but they examined autism and schizophrenia independently, and their aim was not to test for presence or absence of a diametric association between both disorders in the same population and for normal birth sizes. Other epidemiological studies [38,40,41] have also examined risk of either autism or schizophrenia based on birth size, but most were limited by very small sample sizes and were likewise not testing for opposite patterns of risk between autism and schizophrenia.

(b) Larger deviations in birth size increase risks for most disorders

The second question that we addressed concerned Badcock and Crespi’s prediction [16,17] that disturbances in paternal

Figure 4. Risks patterns for autistic (left) and schizophrenic (right) disorders based on covariates. Red shades indicate magnitudes of increased risk and blue shades decreased risks (see the electronic supplementary material, tables S5 – S14, for detailed values). Blank panels represent coefficients that could not be calculated due to lack of variation. White dots (centre of square) indicate significance \( p < 0.05 \).
and maternal gene-dosage deviations should directionally increase or decrease risks of specific psychiatric disorders outwards from the centre of average birth size and normal cognition. Our results testing the full birth size range mostly supported this prediction. AS risk (and other related behaviours) continued to increase with increasing birth weight and length, and SS risk (and related behaviours) continued to increase with decreasing birth weight and length. This pattern was consistent across the entire birth length range, but at extremely low birth weight (group 1, figure 3), the separation between AS and SS became less clear. This is consistent with earlier findings that abnormal gestations resulting in very low birth sizes may be harmful for brain development in general, increasing the risks for many psychiatric disorders [37,39] irrespective of imprinting or copy number predispositions that may bias risk in a specific direction when birth size is closer to the population mean.

The third question we asked was whether risk patterns would consistently support the Badcock and Crespi hypothesis whether diagnoses were grouped broadly or narrowly. As figure 3 illustrates, this appeared to be the case, with remarkably few exceptions. This level of coherence also suggests that the results that we obtained are robust in spite of ongoing discussions among clinicians on how best to categorize and refine diagnoses of mental disease [47].

(c) Effects of parental age, maternal hypertension and parity

We found a consistent effect of paternal age on risk of both autistic- and schizophrenic-related disorders, which relates to predictions from previous studies suggesting that age-related increases in the mutational load of male sperm may negatively impact offspring psychiatric health [1,54]. Errors in sperm production could increase risk for either autism or schizophrenia, for example through duplication of paternally expressed genes or expression of normally paternally silenced genes with effects on neurodevelopment. Such age effects are not expected for maternal gametes as they are mostly produced while the female is still in her mother’s womb. In light of this, the effects of maternal age in our analyses are interesting, for they appear to be directional, with largely increasing risks of autistic and decreasing risks of schizophrenic disorders in offspring. However, our finding that first-born children have an elevated risk of autistic diagnoses later in life suggests that the relationship between risk of psychiatric disorders and maternal age may be U-shaped. Maternal hypertension during pregnancy significantly increased risk for all autistic (but not schizophrenic) disorders, consistent with autistic-type disorders being related to paternally induced higher demands on fetal provisioning that require higher maternal metabolism during pregnancy [32,55].

(d) Caveats and perspectives

Two main caveats should be noted. First, the diametric pattern predicted by Badcock and Crespi (supported by figure 3) is only one, albeit a very coherent, factor contributing to the causation and prevalence of autism and schizophrenia. The finding that many other variables we included also contributed significant risk to both disorders (figure 4; electronic supplementary material, tables S5–S14) echoes this. Second, the statistical trends we uncovered represent relatively modest changes in absolute disease risk, which were 0.65% (or 10 890 of 1 673 315) for AS disorders and 1.23% (or 20 672 of 1 683 097) for SS disorders. Thus, for example, the 53% enhanced AS relative risk of group 6 babies (birth weights 4491–5400 g) increased their absolute risk to 1% and the 25% increased SS relative risk of group 1 babies (1850–2490 g) increased their absolute risk to 1.54%.

These reservations notwithstanding, the shifts that we found in RR of being diagnosed with autism or schizophrenia (or related) disorders were remarkably consistent. This robustness of correlative evidence suggests that it will be worthwhile to extend large-scale genomic studies [5,11] with epigenetic studies that could clarify which genes are involved in parent-of-origin expression, and how their imprints and copy numbers are established. Collecting enough brain samples to make meaningful connections between disorders and differential imprinting or copy numbers of genes that affect fetal provisioning and the behaviour of children and young adolescents will be challenging. Our results make clear, however, that such studies deserve priority given the enormous significance of neuropsychiatric illnesses for the human condition.

Ethics statement. Approval for our study was obtained from the Danish Data Protection Agency, the Danish National Board of Health, the Danish Psychiatric Central Research Registry and Statistics Denmark.

Data accessibility. Data for this study are regulated by public authorities in accordance with The Danish Act on Processing of Personal Data (Act No. 429 of 31 May 2000). Data have been deposited under terms of a contract at Statistics Denmark (www.dst.dk) and cannot leave the servers at Statistics Denmark. Access to the data used in this study can be granted to other researchers through an affiliation with Centre for Social Evolution, University of Copenhagen, if approved by Statistics Denmark. For further information please contact Professor Jacobus J. Boomsma, Centre for Social Evolution (J.Boomsma@bio.ku.dk) and the Head of Division for Research Services, Ivan Thaulow (ITH@DST.dk), Statistics Denmark.

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