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Risk of neurological, eye and ear disease in offspring to parents with schizophrenia or depression compared with offspring to healthy parents

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Abstract

Background. Neurological, visual and hearing deviations have been observed in the offspring of parents with schizophrenia. This study test whether children to parents hospitalized with schizophrenia have increased the likelihood of childhood neurological disorder.

Methods. Among all parents in Sweden born 1950–1985 and with offspring born 1968–2002: 7107 children with a parent hospitalized for schizophrenia were compared to 172 982 children with no parents hospitalized for schizophrenia or major depression, as well as to 32 494 children with a parent hospitalized for major depression as a control population with another severe psychiatric outcome. We estimated relative risks (RR) and two-sided 95% confidence intervals calculated from Poisson regression.

Results. Children to parents with schizophrenia were more likely than controls to have been hospitalized before the age of 10 with a diagnosis of cerebral palsy, RR = 1.76 (95% CI: 1.15–2.69); epilepsy, RR = 1.78 (95% CI: 1.33–2.40), combined neurological disease, RR = 1.33 (95% CI: 1.11–1.60) and certain diseases of the eye, RR = 1.92 (95% CI: 1.17–3.15) and ear, RR = 1.18 (95% CI: 1.05–1.32). Similar disease-risk-pattern was found for children to parents hospitalized with a diagnosis of major depression. A specific risk increase for strabismus RR = 1.21 (95%CI: 1.05–1.40) was found for off-spring with parental depression.

Conclusions. Compared with children to healthy parents, children to parents with schizophrenia have increased risk of a variety of neurological disorders as well as visual and hearing disorders at an early age. The risk increase was not specific to schizophrenia but was also seen in children to parents with a diagnosis of major depression.

Introduction

Schizophrenia is a disturbance of mind and brain characterized by psychotic symptoms including delusions and hallucinations, with worldwide estimates of incidence ranging from 7.7 to 43 per 100 000 individuals (McGrath et al. 2004). It has been well documented that a substantial portion of individuals with schizophrenia or schizophrenia spectrum disorder (e.g. schizoaffective disorder, schizophreniform) show subtle neurological abnormalities including impairments in motor function and sensory integration, and persistence of primitive reflexes (Neelam et al. 2011).

Similar neurological deviations have been observed in the offspring of parents with schizophrenia during childhood (Fish, 1957, 1959; Schubert & McNeil, 2004, 2005; Prasad et al. 2009; Neelam et al. 2011), and both visual dysfunction (Erlenmeyer-Kimling, 2000; Schubert et al. 2005; Yeap et al. 2006; Haraldsson et al. 2008) and auditory system abnormalities have been described in offspring of mothers with a history of psychosis prospectively assessed with vision tests at 4 years, neurological examinations at 6 years, and follow-up at 22 years (Schubert et al. 2005). The first of these studies of 'high-risk' offspring (Fish, 1957) had an especially strong impact, as it showed that neurological abnormality in the offspring the first year of life predicted the development of schizophrenia or related personality disorders later in life. Fifty years later, the Swedish High-Risk Study (Schubert & McNeil, 2004, 2005) obtained a similar finding of early visual dysfunction as a predictor of schizophrenic disorders. In general, the associations between parental psychosis and offspring neurological abnormality in that study appeared specific to schizophrenia, as increased neurological abnormality was found only in offspring of mothers with schizophrenia (and not offspring of

mothers with affective disorders), and such neurological abnormality specifically predicted schizophrenia- (and not affective-) related disorder in the offspring (Schubert & McNeil, 2004, 2005).

As these abnormalities occur early in the offspring's life, the findings are of considerable relevance for theoretical understanding of inherited genetic components,

However, these findings remain uncertain as samples studied to date have generally been small, and not necessarily representative, and few studies have performed a direct comparison of subjects at risk for schizophrenic *v.* affective disorders. The goal of the present study was to test the strength and specificity of the association between parental psychosis type and offspring neurological disease, using a population-based cohort design and comprehensive registers of in-hospital treatment of various forms of neurological disease early in the offspring's life.

Methods

Study population

The Swedish Multi-Generation Register contains information on first degree relatives registered in Sweden since 1961 and born 1932 or later and their biological and adoptive parents when applicable (*Multi-generation register 2011. A description of contents and quality – Statistiska centralbyrån* n.d.). The Swedish National Patient Register contains all hospital admissions for any somatic or psychiatric disorder in Sweden from 1973. For each hospital admission in the register, there is a recorded admission and discharge date as well as the International Classification of Diseases (ICD) diagnostic code for the primary discharge diagnosis as well as up to eight secondary diagnoses made by the treating physician (Lichtenstein et al. 2009). The study population was defined as all parents in the Swedish Multi-Generational Register born between 1950 and 1985 and with an offspring born between 1968 and 2002 who fell into one of three groups: (1) Hospitalized at least once with a primary diagnosis of schizophrenia (primary exposed group); (2) Never hospitalized with a diagnosis of schizophrenia spectrum disorder or major depression (control group); (3) Hospitalized at least once with a primary diagnosis of major depression (secondary exposed group); as recorded in the National Patient Register. For each person with a primary diagnosis of schizophrenia, 20 individuals were selected into the control group. The population of offspring to parents with major depression was stratified and matched to schizophrenia offspring by sex and birth year of the parents. The size of the major depression population (smallest stratum) did not allow us to include more than four controls for each case. The secondary exposed group, major depression, was chosen to enable a comparable comparison using another non-related major psychiatric disorder, with the potential of better understanding if associations between parental schizophrenia and neurological, eye and ear disease in the offspring are specific to schizophrenia or rather related to psychiatric hospitalization more generally.

Classification of schizophrenia and major depression in the parents

Individuals with schizophrenia were defined as those identified in the National Patient Register as having been hospitalized at least once with the discharge diagnosis of schizophrenia or schizoaffective disorder (ICD-8 295; ICD-9 295; ICD-10 F20 and F25). The previous study using this register gave almost identical estimates of familial risks of schizophrenia compared with the literature (Lichtenstein et al. 2006) and the diagnosis of schizophrenia in the registry has been validated previously (Dalman et al. 2002). Individuals with major depression were defined as those with one or more inpatient admissions for major depression (ICD-8 296.0, 296.2, 298.0, 300.4; ICD-9 296B, 296X, 298A, 311; ICD-10 F32, F33, F34). These diseases were diagnosed with a hierarchical diagnostic structure. Thus, if an individual had the discharge diagnosis of both schizophrenia and major depression, he was considered to have schizophrenia and grouped accordingly.

Classification of neurological, eye and ear disease in the offspring

After selecting the parents based on the aforementioned criteria, all of their children born between 1968 and 2002 were evaluated for hospitalization with the discharge diagnosis of an eye, ear or neurological disease prior to the age of 10. The full coverage of lifetime diagnosis according to ICD-8, ICD-9 and ICD-10 in the Swedish Patient Register allowed us to include all hospitalizations with diagnoses of neurological, eye and ear diagnoses from birth to ten years of age. The 10-year-old cut-off limit was chosen to increase the likelihood that the neurological, eye or ear disease would be an early characteristic of the child. Diseases of the nervous system included ICD-10 Chapter VI G00–G99 (Diseases of the nervous system). This is a large number of diagnoses subcategorized in Inflammatory diseases of the nervous system (Meningitis, Encephalitis), Systemic atrophies (Huntington, Ataxia), Extrapyramidal movement disorder (Parkinson, Dystonia), Other degenerative diseases, Demyelinating diseases (MS), Episodic and paroxysmal disorders (Epilepsy), Nerve, nerve root disorders (Facial and Cranial nerves, Cerebral Palsy and others. We also included Chapter XVII Q00–Q07.9 Congenital malformations in the nervous system (Brain malformations, Microcephaly, Hydrocephalus). Comparable diagnoses in ICD-8 and ICD-9 were identified (ICD-8 320–358, 740–743.9, 780.6, 293; ICD-9 320–359 excluding 338.1–338.3, 740–742.9, 780.5, 294.1). The diagnoses of cerebral palsy (ICD-10 G80–G80.9; ICD-9 343–343.9; ICD-8 343) and epilepsy (ICD-10 G40–G41.9; ICD-9 345–345.9; ICD-8 345–345.9) were considered separately.

The eye diseases where defined as ICD-10 Chapter VII diagnoses and grouped into two eye disorder categories: (1) Category one which includes eye structures: disorders of the sclera, cornea, iris, ciliary body, lens, choroid, retina vitreus body and globe as well as glaucoma (ICD-10 H15–H45) and (2) category two which includes eye muscles and pathways: diseases of the optic nerve and visual pathway, ocular muscles, binocular movement, accommodation and refraction as well as visual disturbances and blindness (ICD-10 H46–H57). Category one can be considered as a disease in the eye itself and category two as a disease in muscles and pathways connecting to the eye. Strabismus was considered separately. Comparable diagnoses in ICD-8 were 363–365, 371–371.9, 374–377 excluding 377.3, 378.5–378.8 and ICD-9 361–366, 379.0–379.3.

Diseases of the ear were defined as ICD-10 Chapter VIII H60–H95 Diseases of the ear and mastoid process. Subcategories are diseases of the external ear (ex. Otitis externa), diseases of middle ear and mastoid (ex Otitis media, Perforation of tympanic membrane), diseases of the inner ear (Otosclerosis, Vestibular

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function), hearing loss, deaf mutism. Comparable diagnoses in ICD-8 were 384.0, 385, 386, 388–389.9 and in ICD-9 386.0–389.0.

Statistical analysis

The risk of neurological disease in the offspring between the three groups was analysed by fitting Poisson regression models for each child outcome separately. Each child was followed up for the disease until 31 December 2012. The child's age was used as the time scale, categorically, in 1-year-bands. Generalized estimating equations (Liang & Zeger, 1986) were used with parents as cluster variable, to adjust for the possible correlations between offspring within parents and for the fact that different parents have different numbers of offspring. Besides 'crude models', models, with covariates adjusting only for offspring age and parents' diagnosis, models were also fitted adjusting for parent's sex, child's sex, parent's birth year and child's birth year, all categorically. The children who had parents with schizophrenia and the children whose parents were diagnosed with depression were compared with control individuals by calculating the relative risk (RR) estimated by the incidence rate ratios and associated two-sided 95% Wald-type confidence intervals. Disease rate (cases per 10 000 person-years) was calculated for descriptive purposes. All calculations were made conditional on couples with at least one child.

In complementary models, to examine the specificity of the association by parental sex, we allowed separate parameters for maternal and paternal schizophrenia or major depression diagnosis, both parents or none. We performed additional complementary analyses increasing the specificity of exposure by using a more stringent definition of schizophrenia and major depression. First, we restricted the exposure groups to parents hospitalized for the first time for schizophrenia or major depression prior to the birth of the child. In the second set of analyses, the parents in the two exposed groups were required to have had at least two hospital admissions for schizophrenia or major depression as opposed to only one admission.

Statistical tests of hypotheses were made on the two-sided 5% level of significance. We did not perform any adjustment for multiple statistical tests. The SAS software 9.2 (PROC GENMOD) was used for all the analyses.

Results

We identified 2 173 273 unique individuals in Sweden born between 1950 and 1985 who had children born between 1968 and 2002, of whom 4827 were parents hospitalized at least once for schizophrenia. 19 312 parents who had been hospitalized with a diagnosis of major depression were randomly chosen from a group of 31 067. 94 702 parents with no hospitalization for either schizophrenia-related disorders or major depression were selected from a group of 2 137 378 and matched to the schizophrenia group based on sex and birth year of the parent (Table 1). The parents with schizophrenia had (mean) 1.47 children per parent, the parents with depression 1.68 children per parent and the general population sample had 1.79 children per parent.

Table 2 shows the number of offspring diagnosed with neurological, eye or ear disease based on the parents' diagnosis. Of the 212 583 children in the study, 3.3% had parents who had been hospitalized with schizophrenia, 15.3% had parents who had been hospitalized for major depression and 81.4% belonged to parents with neither diagnosis. When examining the number of children hospitalized for neurological, eye or ear disease prior to the age of 10, it was apparent that both the children of parents with schizophrenia and major depression had higher incidence rates of hospitalizations compared with children of parents who had neither diagnosis. By graphical inspection, these hospitalizations were most frequent in the first two years of life, then started to decrease and in general levelled out by age 10. The pattern was identical for the offspring of all three groups of parents, i.e. those with schizophrenia, major depression or neither diagnosis as can be seen in Fig. 1. We examined if families had more than one child with the disease and found that 1.75% (neurological disease), 2.12% (eye disease) and 4.78% (ear disease) of the families fulfilled this criterion.

Compared to the no-diagnosis group, children who had a parent with schizophrenia were statistically significantly more likely to have been hospitalized with a diagnosis of cerebral palsy RR: 1.76 (CI: 1.15–2.69); epilepsy RR: 1.78 (CI: 1.33–2.40) and combined neurological disease RR: 1.33 (CI: 1.11–1.60); the eye from category one, RR: 1.92 (CI: 1.17–3.15); and disease of the ear RR:1.18 (CI: 1.05–1.32). Compared with the no-diagnosis

Table 1. Cohort description

	Parental Schizophrenia	Parental major depression	Healthy controls
Number of diseased parents	4827	19 312	94 702
Number of children	7107	32 493	172 982
% Male offspring	51.47%	51.59%	51.54%
Parental disease exposure			
Mother only	2802	11 208	N.A.
Father only	2025	8104	N.A.
Both parents	0	0	N.A.
Maternal birth year, median (min,max)	1958 (1950–1983)	1958 (1950–1983)	1958 (1950–1983)
Paternal birth year, median (min,max)	1958 (1950–1983)	1958 (1950–1983)	1958 (1950–1983)
Offspring year of birth	1987 (1968–2002)	1987 (1968–2002)	1987 (1968–2002)

Note: Birth years obtained through matching.

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Table 2. Relative risk (incidence rate ratio, IRR) of eye, ear and neurological disease in offspring comparing the offspring of parents with schizophrenia or major depression with the offspring of parents with neither diagnosis (controls)

	Parental schizophrenia		Parental major depression		Controls
Disease in offspring	Cases (per 10 000 person-years)	IRR (95% CI) *p* value	Cases (per 10 000 person-years)	IRR (95% CI) *p* value	Cases (per 10 000 person-years)
Neurological disease	119 (18.1)	**1.33 (1.11–1.60) *p* = 0.0025**	602 (19.9)	**1.46 (1.33–1.60) *p* < 0.0001**	2191 (13.0)
Cerebral palsy (CP)	23 (3.5)	**1.76 (1.15–2.69) *p* = 0.0090**	87 (2.9)	**1.45 (1.14–1.84) *p* = 0.0022**	313 (2.0)
Epilepsy	47 (7.1)	**1.78 (1.33–2.40) *p* = 0.0001**	203 (6.7)	**1.67 (1.07–1.96) *p* < 0.0001**	645 (4.1)
Eye disease	64 (9.7)	1.14 (0.88–1.47) *p* = 0.3077	311 (10.2)	**1.23 (1.08–1.40) *p* = 0.0013**	1256 (7.9)
Category one	17 (2.6)	**1.92 (1.17–3.15) *p* = 0.0097**	54 (1.8)	1.32 (0.98–1.79) *p* = 0.0696	218 (1.4)
Category two	48 (7.2)	0.98 (0.73–1.31) *p* = 0.8878	265 (8.7)	**1.21 (1.05–1.38) *p* = 0.0068**	1077 (6.8)
Strabismus	44 (6.6)	1.00 (0.74–1.37) *p* = 0.9832	237 (7.8)	**1.21 (1.05–1.40) *p* = 0.0094**	952 (6.0)
Ear disease	316 (49.1)	**1.18 (1.05–1.32) *p* = 0.0051**	1776 (60.7)	**1.47 (1.39–1.55) *p* < 0.0001**	6268 (40.5)

Bold = the *p* value <0.05 (for the statistical test of hypothesis, H0: RR = 1 *v.* the alternative hypothesis, Ha: RR≠1); IRR = Incidence Rate Ratio; CI = Confidence Interval; Category one = diseases of the sclera, cornea, iris, ciliary body, lens, choroid, retina, vitreus body and globe as well as glaucoma; Category two = diseases of the optic nerve and visual pathway, ocular muscles, binocular movement, accommodation and refraction as well as visual disturbances and blindness. For a joint statistical test involving all the eight tests in column 1, or column 2, simultaneously, the *p* values in the table column should be sorted in increasing order and instead of the value 0.05 the *p* values should be compared with 0.00625, 0.0071429, 0.0083333, 0.01, 0.01250, 0.016667, 0.025 and 0.05 according to the Holm's procedure (Holm, 1979).

group, children who had a parent with depression were statistically significantly more likely to have been hospitalized with a diagnosis of cerebral palsy RR: 1.45 (CI: 1.14–1.84); epilepsy RR: 1.67 (CI: 1.07–1.96) and combined neurological disease RR: 1.46 (CI: 1.33–1.60); category two eye disease, RR: 1.21 (CI: 1.05–1.38); a combination of category one and two eye disease RR: 1.23 (CI: 1.08–1.40); strabismus RR: 1.21 (CI: 1.05–1.40); and ear disease RR: 1.47 (CI: 1.39–1.55).

Complementary analyses of psychiatric diagnosis in the parents specific to either the father or the mother did not reveal any differences related to parental sex (Table 3).

All the analyses were also performed using more stringent grouping classifications thereby increasing the specificity of the analyses. In the first set of such analyses, the only offspring selected were the ones whose parents had been hospitalized for the first time for schizophrenia or major depression prior to the birth of the child. In the second set of analyses, the parents in the two exposed groups were required to have had at least two hospital admissions for schizophrenia or major depression as opposed to only one admission. The RR generally increased in magnitude but the pattern observed in the relationships did not change (eAppendix 1).

Discussion

In summary, we found evidence of an increased risk of neurological and eye and ear diseases at an early age among offspring of parents with schizophrenia compared with the offspring of parents from the general population. These children had a markedly increased risk of having been hospitalized with a variety of neurological diseases with an especially highly increased risk of hospitalization for cerebral palsy and epilepsy, prior to the age of 10. The uniqueness of our study rests on the population-based data with national linkage of parental diagnosis and off-spring diagnoses.

The increased risk for neurological disorders, primarily epilepsy and cerebral palsy, among the children of parents diagnosed with schizophrenia compared with those with parents who did not carry either this diagnosis or the diagnosis of major depression are supported by previous findings indicating a strong association between schizophrenia and epilepsy (Mäkikyrö et al. 1998; Danielyan & Nasrallah, 2009; Weber et al. 2009) as well as a potentially shared risk factor with cerebral palsy (Rehn & Rees, 2005). When considering the offspring of individuals with the diagnosis of schizophrenia, there are a limited number of studies that have specifically explored the prevalence of epilepsy or cerebral palsy among them. An Australian study (Morgan et al. 2012) explored, among other things, epilepsy in the offspring of mothers diagnosed with schizophrenia. Any comparison with the results of that study regarding the incidence of epilepsy among these children is not warranted since only three children were reported to carry this diagnosis. The study does, however, show an increased risk for epilepsy among the offspring of mothers with unipolar depression which is in accordance with the results of our study. The results of our study are also in accordance with the notion that the genetic risk for schizophrenia may increase the risk for disorders such as epilepsy (Williams et al. 2009) or cerebral palsy (Rehn & Rees, 2005).

We did not adjust for multiple statistical comparisons. The overall study objective of testing for a difference between children to parents with schizophrenia and children to healthy parents is built from a composite hypothesis involving 8 statistical tests (Table 2) of which 5 had unadjusted *p* values below the 0.05 limit. After adjusting for multiplicity using the Holm's procedure (Holm, 1979), all 5 remained statistically significant. For inference involving mean differences not only for children to parents with schizophrenia compared with children to healthy parents, but also for children to parents with major depression compared to children to healthy parents, a composite hypothesis involving 16 statistical tests, eight of the 11 tests statistically significant on the unadjusted 0.05 limit, remained statistically significant (Table 2).

Our finding of an increased risk for eye pathology could be seen in a setting with schizophrenia-associated changes in basic sensory processing and abnormalities in low-level sensory processes. A number of studies have shown the connection between schizophrenia and impairment of the visual sensory system (Yeap et al. 2006; Viertiö et al. 2007) and eye movement deficits

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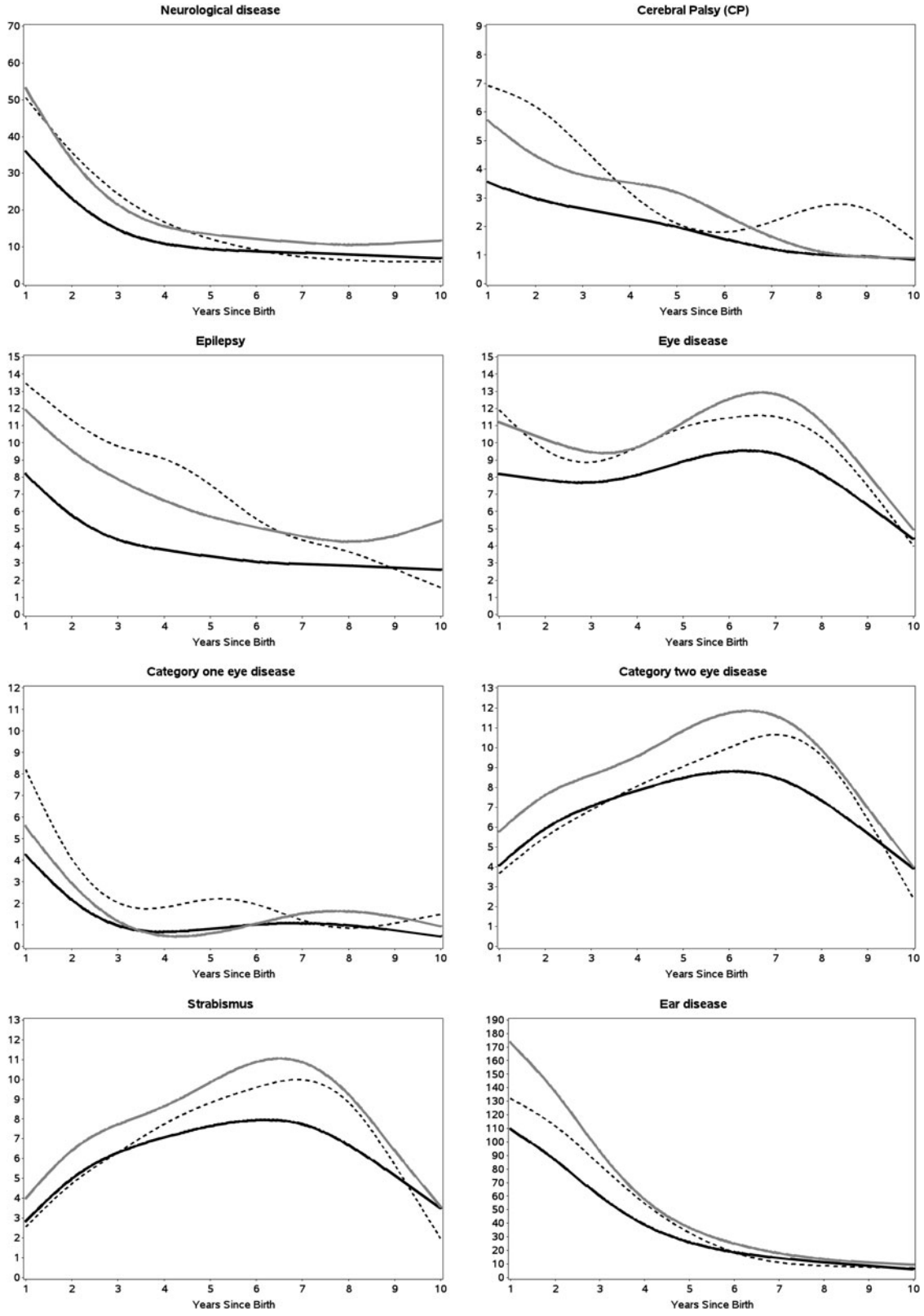

Fig. 1. Age-specific incidence rates (cases per 10 000 person-years) of Neurological disease (CP, Epilepsy), Eye disease (categories one and two and strabismus) and ear disease for children to parents with a diagnosis of Schizophrenia (grey), Major depression (dashed) or Healthy controls, i.e. neither Schizophrenia nor Major depression (black).

(Haraldsson et al. 2008). Contrary to previous studies, we did not find an increased risk among the offspring of individuals diagnosed with schizophrenia when specifically looking at eye disease in muscles and pathways connecting to the eye, as well as ocular movement, visual disturbance and blindness/low vision (our 'category one'). Instead, we found an increased risk for eye

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Table 3. Paternal and maternal-specific relative risk (incidence rate ratio, IRR) of eye, ear and neurological disease when comparing the offspring of parents (father or mother) with schizophrenia or major depression with the offspring of parents with neither diagnosis (controls)

	Parental schizophrenia IRR (95% CI) *p* value		Parental major depression IRR (95% CI) *p* value	
Disease in offspring	Father diagnosed	Mother diagnosed	Father diagnosed	Mother diagnosed
Neurological disease	**1.59 (1.23–2.07) *p* = 0.0004**	1.13 (0.87–1.47) *p* = 0.3549	**1.45 (1.26–1.67) *p* < 0.0001**	**1.47 (1.30–1.65) *p* < 0.0001**
Cerebral palsy (CP)	1.09 (0.48–2.46) *p* = 0.8429	**2.25 (1.37–3.71) *p* = 0.0014**	**1.63 (1.15–2.32) *p* = 0.0060**	1.32 (0.95–1.82) *p* = 0.0955
Epilepsy	**2.06 (1.36–3.13) *p* = 0.0007**	**1.57 (1.03–2.38) *p* = 0.0372**	**1.56 (1.22–1.99) *p* = 0.0004**	**1.76 (1.43–2.17) *p* < 0.0001**
Eye disease	1.26 (0.85–1.86) *p* = 0.2545	1.07 (0.76–1.49) *p* = 0.7083	1.19 (0.97–1.45) *p* = 0.1006	**1.26 (1.07–1.48) *p* = 0.0047**
Category one	**2.22 (1.07–4.57) *p* = 0.0314**	1.72 (0.87–3.38) *p* = 0.1162	1.51 (0.96–2.36) *p* = 0.0724	1.20 (0.79–1.80) *p* = 0.3929
Category two	1.08 (0.68–1.71) *p* = 0.7432	0.91 (0.62–1.34) *p* = 0.6403	1.09 (0.87–1.37) *p* = 0.4524	**1.28 (1.08–1.52) *p* = 0.0043**
Strabismus	1.17 (0.73–1.87) *p* = 0.5228	0.90 (0.60–1.35) *p* = 0.6068	1.15 (0.91–1.45) *p* = 0.2507	**1.25 (1.04–1.50) *p* = 0.0162**
Ear disease	1.15 (0.96–1.37) *p* = 0.1183	**1.20 (1.03–1.40) *p* = 0.0189**	**1.28 (1.18–1.40) *p* < 0.0001**	**1.60 (1.49–1.72) *p* < 0.0001**

Bold = the *p* value <0.05 (for the statistical test of hypothesis, H0: RR = 1 *v.* the alternative hypothesis, Ha: RR≠1); IRR = Incidence rate ratio; CI = Confidence interval; Category one = diseases of the sclera, cornea, iris, ciliary body, lens, choroid, retina, vitreus body and globe as well as glaucoma; Category two = diseases of the optic nerve and visual pathway, ocular muscles, binocular movement, accommodation and refraction as well as visual disturbances and blindness.

disease that focused on disease in the eye itself but not on later visual processing among these offspring. There is not much previous research on this connection between schizophrenia and early visual processing or disease of the eye. There is, however, some evidence that the earliest stage of visual information processing occurring at the retinal level is impaired in patients with schizophrenia, although this impairment may be state dependent during the acute phase of the disorder (Balogh et al. 2008). Other studies that have focused on visual information processing by using the backward visual masking task have shown marked impairment among both schizophrenic patients (Cadenhead et al. 1998) and unaffected sibling of schizophrenic patients (Green et al. 2006), but this impairment is likely the result of processing at later stages of the visual pathway. Given the limited number of studies on the role of visual information processing at the earliest retinal stage in schizophrenia, it may be important to explore this connection further in light of our results. At this point the actual underlying reason for the increased risk of disease of the eye among the offspring of parents diagnosed with schizophrenia is unclear. Previous research has provided substantial evidence that the development of schizophrenia is antedated by increased rates of minor physical anomalies in the eye, ear and head regions (Cantor-Graae et al. 1998), deviant head circumference at birth (McNeil et al. 1993) and changes in craniofacial shape (Henriksson et al. 2006), all witnessing deviant prenatal development. It has been argued that the visual abnormalities in schizophrenia might be due to infectious agents in the eye or central nervous system *in utero* or later and thus a consequence of for instance congenital Toxoplasmosis or Herpes viruses such as cytomegalovirus, varicella-zoster virus that is associated both with later psychoses and ocular symptoms (Torrey & Yolken, 2017). In a recent review, Silverstein & Rosen (2015) argue that there are multiple structural and functional disturbances of the eye in schizophrenia, all of which could be factors in the visual disturbances of patients. We do not know which visual abnormalities are illness-related or due to medication and comorbid conditions. However, our high-risk study is based on visual pathology at birth or early infancy and childhood, which is an advantage.

When the results of our study are interpreted, it is important to note that the diagnoses used to categorize both the parents and the diseases in the offspring are based on hospital discharge diagnoses. Because of this the study is based on the most severely ill patients and excludes those who may be more mildly affected by the disease. Therefore, the generalizability of the results may be limited to those individuals who have a severe enough psychiatric condition to warrant hospitalization and even more importantly, severe enough eye, ear and neurological diseases so that the children required hospitalization at a young age. As a consequence, the increased risk for the offspring of individuals with schizophrenia observed in this study may actually be more of an underestimation of the real risk for these diseases among the offspring given that a large number of people may have never been hospitalized for their disease but managed successfully as out-patients. Future studies should focus on children with neurological diseases not requiring hospitalization, as well as a milder form of the eye and the ear to explore the connection between these diseases and schizophrenia further.

Although the results indicate that the children of parents with schizophrenia have a markedly increased risk of being hospitalized with neurological diseases, cerebral palsy and epilepsy prior to the age of 10 and diseases of the eye and ear, when compared with the children of healthy parents, it is important to note that similar pattern was observed in the children of individuals with major depression. This lack of specificity may indicate that the vulnerability for a variety of diseases observed in this study is not due to a specific psychiatric disorder but to severe parental psychiatric disorders in general. The similar findings in schizophrenia and major depression and offspring diseases might reflect a common genetic aetiology, but could also result from non-optimal lifestyle characteristics like smoking during and after pregnancy, or factors associated with psychiatric hospitalization and medication. The (relative) risk for neurological disease in the offspring increased in magnitude when limited to the subgroup of parents first hospitalized for mental disorder prior to the birth of the offspring, and in the subgroup of parents with especially severe illnesses as well. Schizophrenia and major depression are equally likely affected by surveillance bias. While the results could potentially reflect differences in fertility or factors associated with the fertility, only small differences were observed in number of live-born children. As in most observational studies, we can also not rule out residual confounding

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contributing to the consistent findings for schizophrenia and major depression. Factors associated with socioeconomic status may have confounded our results.

Future studies could explore this relationship further in an attempt to better understand the underlying cause of this vulnerability.

Conclusion

Our results indicate that, compared with children to healthy parents, children to parents with schizophrenia have increased risk of a variety of neurological disorders as well as visual and hearing disorders at an early age. The risk increase was not specific to schizophrenia but was also seen in children to parents with a diagnosis of major depression.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718000338

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References

Balogh Z, Benedek G and Kéri S (2008) Retinal dysfunctions in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **32**(1), 297–300.

Cadenhead KS, Serper Y and Braff DL (1998) Transient versus sustained visual channels in the visual backward masking deficits of schizophrenia patients. *Biological Psychiatry* **43**(2), 132–138.

Cantor-Graae E, Ismail B and McNeil TF (1998) Neonatal head circumference and related indices of disturbed fetal development in schizophrenic patients. *Schizophrenia Research* **32**(3), 191–199.

Dalman C, Broms J, Cullberg J and Allebeck P (2002) Young cases of schizophrenia identified in a national inpatient register--are the diagnoses valid? *Social Psychiatry and Psychiatric Epidemiology* **37**(11), 527–531.

Danielyan A and Nasrallah HA (2009) Neurological disorders in schizophrenia. *The Psychiatric Clinics of North America* **32**(4), 719–757.

Erlenmeyer-Kimling L (2000) Neurobehavioral deficits in offspring of schizophrenic parents: liability indicators and predictors of illness. *American Journal of Medical Genetics* **97**(1), 65–71.

Fish B (1957) The detection of schizophrenia in infancy; a preliminary report. *The Journal of Nervous and Mental Disease* **125**, 1–24.

Fish B (1959) Longitudinal observations of biological deviations in a schizophrenic infant. *The American Journal of Psychiatry* **116**, 25–31.

Green MF, Nuechterlein KH, Breitmeyer B and Mintz J (2006) Forward and backward visual masking in unaffected siblings of schizophrenic patients. *Biological Psychiatry* **59**(5), 446–451.

Haraldsson HM, Ettinger U, Magnusdottir BB, Sigmundsson T, Sigurdsson E and Petursson H (2008) Eye movement deficits in schizophrenia: investigation of a genetically homogenous Icelandic sample. *European Archives of Psychiatry and Clinical Neuroscience* **258**(6), 373–383.

Henriksson KM, Wickstrom K, Maltesson N, Ericsson A, Karlsson J, Lindgren F *et al.* (2006) A pilot study of facial, cranial and brain MRI morphometry in men with schizophrenia: part 2. *Psychiatry Research* **147** (2–3), 187–195.

Holm S (1979) A simple sequentially rejective multiple test procedure. *Scandinavian Journal of Statistics* **6**, 65–70.

Liang K-Y and Zeger SL (1986) Longitudinal data analysis using generalized linear models. *Biometrika* **73**(1), 13–22.

Lichtenstein P, Björk C, Hultman CM, Scolnick E, Sklar P and Sullivan PF (2006) Recurrence risks for schizophrenia in a Swedish national cohort. *Psychological Medicine* **36**(10), 1417–1425.

Lichtenstein P, Yip BH, Björk C, Pawitan Y, Cannon TD, Sullivan PF *et al.* (2009) Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* **373**(9659), 234–239.

Mäkikyrö T, Karvonen JT, Hakko H, Nieminen P, Joukamaa M, Isohanni M *et al.* (1998) Comorbidity of hospital-treated psychiatric and physical disorders with special reference to schizophrenia: a 28 year follow-up of the 1966 northern Finland general population birth cohort. *Public Health* **112**(4), 221–228.

McGrath J, Saha S, Welham J, Saadi OE, MacCauley C and Chant D (2004) A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine* **2**, 13.

McNeil TF, Cantor-Graae E, Nordström LG and Rosenlund T (1993) Head circumference in "pre schizophrenic" and control neonates. *The British Journal of Psychiatry: The Journal of Mental Science* **162**, 517–523.

Morgan VA, Croft ML, Valuri GM, Zubrick SR, Bower C, McNeil TF *et al.* (2012) Intellectual disability and other neuropsychiatric outcomes in high-risk children of mothers with schizophrenia, bipolar disorder and unipolar major depression. *The British Journal of Psychiatry: The Journal of Mental Science* **200**(4), 282–289.

Multi-generation register (2011) *A description of contents and quality – Statistiska centralbyrån* (n.d.). Statistiska Centralbyrån.

Neelam K, Garg D and Marshall M (2011) A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia. *BMC Psychiatry* **11**, 139.

Prasad KM, Sanders R, Sweeney J, Montrose D, Diwadkar V, Dworakowski D *et al.* (2009) Neurological abnormalities among offspring of persons with schizophrenia: relation to premorbid psychopathology. *Schizophrenia Research* **108**(1-3), 163–169.

Rehn AE and Rees SM (2005) Investigating the neurodevelopmental hypothesis of schizophrenia. *Clinical and Experimental Pharmacology & Physiology* **32**(9), 687–696.

Schubert EW, Henriksson KM and McNeil TF (2005) A prospective study of offspring of women with psychosis: visual dysfunction in early childhood predicts schizophrenia-spectrum disorders in adulthood. *Acta Psychiatrica Scandinavica* **112**(5), 385–393.

Schubert EW and McNeil TF (2004) Prospective study of neurological abnormalities in offspring of women with psychosis: birth to adulthood. *The American Journal of Psychiatry* **161**(6), 1030–1037.

Schubert EW and McNeil TF (2005) Neuropsychological impairment and its neurological correlates in adult offspring with heightened risk for schizophrenia and affective psychosis. *The American Journal of Psychiatry* **162** (4), 758–766.

Silverstein SM and Rosen R (2015) Schizophrenia and the eye. *Schizophrenia Research: Cognition.* **2**(2), 46–55.

Torrey EF and Yolken RH (2017) Schizophrenia and infections: the eyes have it. *Schizophrenia Bulletin* **43**(2), 247–252.

Viertiö S, Laitinen A, Perälä J, Saarni SI, Koskinen S, Lönnqvist J *et al.* (2007) Visual impairment in persons with psychotic disorder. *Social Psychiatry and Psychiatric Epidemiology* **42**(11), 902–908.

Weber NS, Cowan DN, Millikan AM and Niebuhr DW (2009) Psychiatric and general medical conditions comorbid with schizophrenia in the National Hospital Discharge Survey. *Psychiatric Services* **60**(8), 1059–1067.

Williams HJ, Owen MJ and O'Donovan MC (2009) Schizophrenia genetics: new insights from new approaches. *British Medical Bulletin* **91** (1), 61–74.

Yeap S, Kelly SP, Sehatpour P, Magno E, Javitt DC, Garavan H *et al.* (2006) Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Archives of General Psychiatry* **63**(11), 1180–1188.