Schizophrenia Bulletin vol. 41 no. 2 pp. 513–521, 2015
doi:10.1093/schbul/sbu110
Advance Access publication July 25, 2014

Somatic Diseases and Conditions Before the First Diagnosis of Schizophrenia: A Nationwide Population-based Cohort Study in More Than 900 000 Individuals

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Objective: **Schizophrenia is associated with excess physical comorbidity. Yet, to our knowledge, large studies are lacking on the associations with somatic diseases before the onset of schizophrenia. The authors conducted a nationwide study of the full spectrum of treated somatic diseases before the first diagnosis of schizophrenia.** ***Method:*** **Nationwide sample of the Danish population consisting of singletons (*n* = 954 351) born 1977–1993 and followed from birth to 2009, during which period 4371 developed schizophrenia. Somatic diagnoses at all general hospital contacts (admitted or outpatient care at a somatic hospital) from 1977 to 2009 were used as exposures. The incidence rate ratio (IRR) of schizophrenia was calculated using Poisson regression adjusted for confounders.** ***Results:*** **Among the 4371 persons who developed schizophrenia from 1992 to 2009, a total of 4180 (95.6%) persons had a previous somatic hospital contact. A history of any somatic hospital contact was associated with an elevated risk of schizophrenia (IRR = 2.04, 95% CI = 1.77–2.37). A wide range of somatic diseases and conditions were associated with an increased risk of schizophrenia, including epilepsy (IRR = 2.26, 95% CI = 1.93–2.62), nutritional or metabolic disorders (IRR = 1.57, 95% CI = 1.39–1.77), circulatory system diseases (IRR = 1.63, 95% CI= 1.38–1.92), and brain injury (IRR = 1.58, 95% CI = 1.45–1.72).** ***Conclusions:*** **A wide range of potential etiological factors could have contributed to the observed associations, including genetic or physiological overlaps between conditions, and interacting immunological, behavioral, and neurodevelopmental factors.**

Key words: schizophrenia/risk factors/physical illness

Introduction

Physical comorbidity and excess mortality is well documented in people with schizophrenia[1] and is commonly ascribed to poor health habits, medication side effects and poorer access to health care. However, a somatic (physical) disease or condition might also precipitate the onset or be associated with increased risk of schizophrenia. Increased risk of schizophrenia has been associated with exposure to a range of somatic diseases including common infections,[2,3] autoimmune diseases,[4,5] atopic disorders,[6] epilepsy,[7] and head injury.[8] Many somatic diseases leading to hospital contacts are associated with immune responses,[9] and some patients with schizophrenia have elevated levels of inflammatory markers in the blood and cerebrospinal fluid.[10–12] Furthermore, studies suggest that a subset of people with schizophrenia have displayed signs of abnormal neurodevelopment.[13] Young children who are later diagnosed with schizophrenia show subtle motor deficits,[14–16] and by middle childhood, some of them report psychotic-like experiences[17] or display additional cognitive and neuromotor deficits.[17–19] Subtle central nervous system symptoms or signs could be associated with a somatic disease or condition before the first diagnosis of schizophrenia. However, it is unknown if, and to what degree, a wide range of somatic diseases are associated with the first diagnosis of schizophrenia.

The Danish registers provide advantages when it comes to systematic investigation of associations between physical diseases and risk of subsequently developing schizophrenia. These include elimination of recall bias and comparison of specific physical diagnoses with the background population. Additionally, the registers provide the possibility of adjusting for various confounders, including family history of psychiatric disorder and sociodemographic variables. Using Danish nationwide registers,[20,21] we examined the full spectrum of treated somatic disorders in relation to first diagnosis of schizophrenia. This investigation could provide important new knowledge about possible shared risk factors of a wide range of physical diseases and schizophrenia.

Methods

Registers

The Danish Civil Registration System[20] was established in 1968, where all persons alive and living in Denmark were registered. Among other variables, it includes information on personal identification number, sex, date, and place of birth; continuously updated information on vital status; and the parent's personal identifiers. The personal identification number is used in all national registers enabling accurate linkage between registers. Inpatient psychiatric contacts are registered in the Danish Psychiatric Central Register,[21] which was computerized in 1969. In 1995, outpatient psychiatric contacts and emergency room contacts were also included. The Danish National Hospital Register[22] has existed since 1977 and contains information on physical (somatic) inpatient hospital contacts. Since 1995, this register also contains outpatient and emergency room contacts. All registered diagnoses are defined according to World Health Organization International Classification of Diseases (ICD) codes: ICD-8 was used until 1993 and ICD-10 from 1994 onward. The Danish registers do not fully cover all aspects of private medical specialist treatment. There are no private psychiatric hospitals in Denmark.

Study Population

The national registers enabled us to create a cohort of individuals (n = 954 351) born in Denmark from January 1, 1977 to December 31, 1993. The individuals were identified by their personal identification number and followed to identify onset with schizophrenia from the 15th birthday until death, emigration, or June 30, 2009, whichever came first.

Exposures

All individuals were traced in the Danish National Hospital Register to examine if they had been admitted or been in outpatient care at a somatic hospital in Denmark. The time of first exposure was defined as the first day of the first contact with the diagnosis in question. Prior to the initiation of the project, physical diseases or disorders were grouped into 19 categories: (1) infectious and parasitic diseases; (2) neoplasms; (3) diseases of the blood (forming) organs, immunological disorders; (4) endocrine, nutritional and metabolic diseases; (5) diseases of the nervous system and the sense organs; (6) epilepsy; (7) cerebral palsy; (8) diseases of the circulatory system; (9) diseases of the respiratory system; (10) diseases of the digestive system; (11) diseases of the skin and subcutaneous tissue; (12) diseases of the musculoskeletal system/connective tissue; (13) diseases of the genitourinary system; (14) complications of pregnancy, childbirth, and puerperium; (15) certain condition originating in the perinatal period; (16) congenital malformations and chromosomal abnormalities; (17) symptoms, signs, abnormal findings, ill-defined causes; (18) injury, poisoning, and certain consequences of external causes; and (19) brain (head) injury. Each person could have a history of more than 1 disease.

Outcome

Cohort members were classified with schizophrenia if they had been admitted to a psychiatric hospital or had been in outpatient care with a diagnosis of schizophrenia, either ICD-8 code 295.x or ICD-10 code F20.x (a small minority of those included could have received a schizoaffective [ICD-8 code 295.7] or schizophreniform disorder [ICD-8 code 295.4] diagnosis before 1994 but were included as cases of schizophrenia). Date of onset was defined as first day of first contact (in- or outpatient) with a diagnosis of schizophrenia.

Covariates

Parents were categorized hierarchically according to either a history of schizophrenia, schizophrenia-like psychoses, or other mental disorders (any ICD-8 or ICD-10 diagnosis), respectively, if they had been admitted to a psychiatric hospital or in outpatient care with one of these diagnoses. Information on maternal and paternal age at birth and parental loss was obtained from the Danish Civil Registration System; second-generation immigration status was defined as follows: second-generation immigrants by both parents (mother and father born abroad), second-generation immigrants by mother (mother born abroad), second-generation immigrants by father (father born abroad), and native Danes (both parents born in Denmark), as previously.[23] Unknown father, maternal age, paternal age, second-generation immigration status, and parental death were coded as described elsewhere.[24–26]

Statistical Analyses

The incidence rate ratio (IRR) of schizophrenia was estimated by Poisson regression. All relative risks were adjusted for calendar year, age, and its interaction with sex. In addition, we adjusted for a slight change in the age and sex-specific incidence during the study period. We used Poisson regression as an approximation of a Cox regression. IRRs were first adjusted for calendar year, age, and its interaction with sex, and the second (final) model adjusted additionally for unknown father, maternal age, paternal age, second-generation immigration status, parental mortality, and psychiatric family history. Persons with no diagnosis of the disease in question were chosen as reference category. Age, calendar year, history of mental illness in parents, time since onset with a physical disease, and parental loss were treated as time-dependent variables,[27] whereas all other variables were considered time independent.

To distinguish potential short-term consequences of somatic diseases on the risk of schizophrenia from potential long-term consequences of somatic diseases on the risk of schizophrenia, time since physical disease was categorized as 0–4 completed years ("concurrent") and 5 or more completed years ("delayed"). *P* values were based on likelihood ratio tests.

Results

A total of 954 351 persons born in Denmark 1977–1993 were followed for the development of schizophrenia from the 15th birthday until 2009 and 4371 persons developed schizophrenia during follow-up. Among the 4371 persons diagnosed with schizophrenia, 4180 (95.6%) persons had a general hospital contact before the first diagnosis of schizophrenia. Table 1 shows the crude incidence rate and IRRs of schizophrenia for persons with a history of any general hospital contact and also for each of the studied main somatic categories. The IRR of developing schizophrenia was 2.04 (95% CI 1.77–2.37) for persons with a history of any general hospital contact, compared with persons with no history of any somatic hospital contacts. The IRR of schizophrenia associated with the various somatic categories ranged from the lowest estimate of 1.07 (95% CI 0.94–1.22) for pregnancy complications and complications of the puerperium to the highest estimate of 2.26 (95% CI 1.93–2.62) for epilepsy. Most of the estimates were significantly elevated; however, complications of pregnancy and puerperium cerebral palsy and immunological diseases were only associated with marginally elevated risk estimates. The table also shows the number of exposed cases with schizophrenia for each main somatic category. The significantly elevated risk estimates observed for symptoms, signs, abnormal findings, ill-defined causes, brain injury, injury, poisoning, certain other consequences of external causes, and the broad somatic categories (including endocrine, nutritional and metabolic diseases, diseases of the circulatory system, diseases of the respiratory system, conditions originating in the perinatal period, and congenital malformations) ranged from 1.14 (95% CI 1.03–1.25) for congenital malformations to 1.63 (95% CI 1. 1.38–1.92) for diseases of the circulatory system.

In table 2, we present IRRs of schizophrenia for each of the studied physical diseases according to time since onset of the physical disorder in question, classified as concurrent (0–4 years) and delayed (≥5 years). Epilepsy was associated with significantly elevated risk estimates in the "concurrent (IRR = 5.08 (95% CI 3.95–6.41) and the "delayed" (IRR = 1.87 (95% CI 1.53–2.26) period. For diseases of the circulatory system, digestive system, skin and subcutaneous tissue, or genitourinary system; complications of pregnancy, childbirth and puerperal diseases; and symptoms, signs, and abnormal findings of ill-defined causes, we found significantly elevated IRRs in both "concurrent" and "delayed" categories.

In table 3, we show the three most common conditions among cases within each main somatic category subgrouped according to the ICD-8 and ICD-10 classification. It should be pointed out that the table only shows the *first* somatic diagnosis (not the cumulative incidences) during the subject's lifetime.

The majority of cases (n = 3535) had had a hospital contact due to "injury, poisoning and certain consequences of external causes." The most common first-contact diagnoses were leg distortions and other common orthopedic injuries. Few had a first-contact diagnosis of intoxication. For "symptoms, signs, abnormal finding, ill-defined causes" (n = 1574), the top 3 first diagnoses were "febrile convulsions," "abdominal conditions not otherwise specified," and "observation not otherwise specified." The most common first-contact diagnoses of the third largest somatic category, "diseases of the respiratory system" were pharyngitis/rhinitis, adenoid hypertrophy and pneumonia. A variety of infections codes were among the top 3 diagnoses in several main somatic categories (ie, otitis media in the category of diseases of the nervous and sense organs). Anemia was among the top 3 diagnoses within "diseases of the blood (forming) organs, immunological disorders." Malnutrition, overweight, and spontaneous hypoglycemia were common diagnoses within the main category of "endocrine, nutritional and metabolic diseases." Only 27 cases with schizophrenia had a first diagnosis within the circulatory system, and heart rhythm disorders were among the most common first diagnoses. In addition to infection codes, the most common first-contact diagnoses for "diseases of the nervous system and sense organs" were migraine and tension headache. The category "certain condition originating in the perinatal period" almost entirely consisted of ICD-8 diagnoses and neonatal hyperbilirubinemia was the most common first diagnosis.

Discussion

The main findings were moderate associations between a large and varied range of apparently preexisting physical diseases and conditions and the later risk of schizophrenia. Any preexisting somatic hospital diagnosis was associated with a 2-fold increased risk of onset of schizophrenia. Generally, risks for schizophrenia were higher within the first years after a somatic contact but remained clearly elevated several years after. These findings suggest that schizophrenia could be associated with a wider range of preexisting somatic conditions.

The strengths of this study include the prospective design and the population-based nationwide registers in Denmark, ensuring that all exposures were recorded prospectively and independently of the outcome and therefore not subject to selection or recall bias. The extensive

Table 1. Incidence Rate Ratio for Schizophrenia by General Hospital Contacts Among 954 351 People Born 1977–1993 of Which 4371 Developed Schizophrenia 1992–2009

	ICD-10	ICD-8	Number of Cases	Incidence Rate[a]	Incidence Rate Ratios (95% CI) First Adjustment[b]	Incidence Rate Ratios (95% CI) Full Adjustment[c]
Overall			4180	5.72	2.30 (95% 1.99–2.67)	2.04 (1.77–2.37)
Infectious and parasitic diseases	A00-B-99	000–136	706	7.65	1.47 (1.36–1.60)	1.29 (1.09–1.40)
Neoplasms	C00-D48	140–239	153	6.69	1.24 (1.05–1.45)	1.22 (1.04–1.43)
Diseases of the blood (forming) organs, immunological disorders	D50-D89	280–289	109	7.09	1.33 (1.09–1.60)	1.18 (0.97–1.42)
Endocrine, nutritional, and metabolic diseases	E00-E90	240–279	292	9.16	1.78 (1.58–2.01)	1.57 (1.39–1.77)
Diseases of the nervous system and the sense organs[d]	G00-H95	320–389	867	7.76	1.51 (1.40–1.62)	1.36 (1.26–1.46)
Epilepsy[d]	G40-G41	345–345.99	169	13.43	2.49 (2.13–2.90)	2.26 (1.93–2.62)
Cerebral Palsy	G80	343.99–344.99	22	8.04	1.46 (0.93–2.16)	1.30 (0.83–1.94)
Diseases of the circulatory system	I00-I99	390–441.1, 444.3–458, 782.4	144	9.80	1.72 (1.45–2.02)	1.63 (1.38–1.92)
Diseases of the respiratory system	J00-J99	460–519	1456	6.91	1.41 (1.32–1.50)	1.27 (1.19–1.35)
Diseases of the digestive system	K00-K93	520–577, 444.2	976	7.67	1.47 (1.37–1.58)	1.39 (1.29–1.49)
Diseases of the skin and subcutaneous tissue	L00-L99	680–709	503	8.54	1.55 (1.41–1.70)	1.42 (1.29–1.56)
Diseases of the musculoskeletal system/ connective tissue	M00-M99	710–738	828	7.18	1.30 (1.20–1.40)	1.26 (1.17–1.36)
Diseases of the genitourinary system	N00-N99	580–629, 792	653	8.17	1.56 (1.43–1.70)	1.47 (1.35–1.59)
Complications of pregnancy, childbirth and puerperium	O00-O99	630–678	320	5.54	1.31 (1.15–1.50)	1.07 (0.94–1.22)
Certain condition originating in the perinatal period	P00-P96	760–779	963	6.60	1.27 (1.18–1.37)	1.16 (1.08–1.25)
Congenital malformations and chromosomal abnormalities	Q00-Q99	740–759	465	6.38	1.16 (1.06–1.28)	1.14 (1.03–1.25)
Symptoms, signs, abnormal findings, ill-defined causes	R00-R99	780, 782.3, 782.5–791, 293–796	1574	8.34	1.97 (1.85–2.10)	1.75 (1.65–1.87)
Injury, poisoning, and certain consequences of external causes	S00-T99	800–999	3535	9.33	1.65(1.53–1.79)	1.54 (1.42–1.66)
Brain injury	S06, S06.1–S06.9, S02–S02.1, S02.7, S02.9	850.99, 851.29–584.99, 800.99–801.09, 803.88	591	9.33	1.73 (1.59–1.89)	1.58 (1.45–1.72)

[a]Number of new cases per 10 000 person years at risk.
[b]Adjusted for calendar year, age and its interaction with gender. Persons with no diagnosis of the disease in question were chosen as reference category.
[c]Adjusted for calendar year, age and its interaction with gender as well as for all other variables in table 1.
[d]Only contacts after 28 days were used.
[e]Only contacts after 1826 days were used.

Danish registers allowed the examination of a wide range of physical illnesses, and we were able to adjust for a wide range of confounding factors. The major limitation of the study is that the onset of schizophrenia has to be identified through first hospital contact. If cases had been registered with another psychiatric contact before the first diagnosis of schizophrenia,[28] general hospital contacts prior to a diagnosis of schizophrenia could have been due to psychopharmacological treatment initiated before first diagnosis of schizophrenia. The limitations also include lack of randomization and lack of data on smoking, diet, exercise, and stress. However, it is unlikely that these unregistered variables could explain the observed associations. The use of broadly defined exposure categories

Table 2. Incidence Rate Ratio (IRR) for Schizophrenia According to Time Since First Somatic Diagnosis Among 954 351 People Born in Denmark Between 1977–1993

	Concurrent 0–4 years			Delayed ≥5 years			
	No. of cases	Incidence Rate[a]	IRR (95% CI)	No. of Cases	Incidence Rate	IRR (95% CI)[b]	*P* Value[c]
Overall	371	3.95	1.81 (1.52–2.16)	3809	5.98	2.38 (2.06–2.77)	≤.00001
Infectious and parasitic diseases	145	8.39	1.60 (1.35–1.89)	561	7.48	1.44 (1.32–1.58)	.26
Neoplasms	61	6.92	1.33 (1.02–1.70)	92	6.55	1.18 (0.95–1.44)	.47
Diseases of blood (forming) organs, immunological disorders	17	8.11	1.62 (0.97–2.53)	92	6.93	1.29 (1.04–1.57)	.39
Diseases of endocrine, nutritional, metabolic diseases	87	8.88	1.94 (1.56–2.39)	205	9.29	1.73 (1.50–1.98)	.36
Diseases of the nervous system and sense organs[d]	179	8.77	1.69 (1.45–1.95)	688	7.54	1.47 (1.35–1.59)	.10
Epilepsy[d]	67	24.83	5.08 (3.95–6.41)	102	10.32	1.87 (1.53–2.26)	<.001
Cerebral palsy	—	—	—	22	8.6	1.53 (0.98–2.27)	—
Diseases of the circulatory system	89	12.09	2.11 (1.70–2.59)	55	7.50	1.32 (1.00–1.70)	.006
Diseases of the respiratory system	172	6.89	1.45 (1.24–1.68)	1284	6.92	1.40 (1.31–1.50)	.69
Diseases of the digestive system	298	9.19	1.81 (1.61–2.04)	678	7.15	1.36 (1.25–1.48)	<0.001
Diseases of the skin and subcutaneous tissue	210	10.26	1.83 (1.59–2.10)	293	7.63	1.40 (1.24–1.57)	.003
Diseases of the musculoskeletal/ connective tissue system	397	6.89	1.27 (1.14–1.40)	431	7.47	1.33 (1.20–1.47)	.48
Diseases of the genitourinary system	274	9.51	1.91 (1.68–2.15)	379	7.41	1.38 (1.24–1.53)	<.001
Complications of pregnancy, childbirth, and puerperium[e]	217	5.42	1.22 (1.05–1.41)	103	5.83	1.65 (1.32–2.05)	.02
Condition orig. in the perinatal period	—	—	—	960	6.60	1.27 (1.18–1.37)	—
Congenital malformations/ chromosomal abnormalities	58	6.81	1.49 (1.13–1.91)	407	6.32	1.13 (1.02–1.25)	.06
Symptoms, signs, abnormal finding, ill-defined causes	480	11.62	2.66 (2.41–2.93)	1094	8.00	1.77 (1.65–1.90)	<.001
Injury, poisoning/other consequences of external causes	915	5.46	1.58 (1.43–1.73)	2620	6.79	1.69 (1.56–1.84)	.08
Brain injury	207	11.67	2.16 (1.87–2.48)	384	8.43	1.56 (1.40–1.73)	<.001

[a]The incidence rate measures the number of new cases per 10 000 person years at risk.
[b]The IRRs were adjusted for calendar year, age, and its interaction with gender. Person with no diagnosis of the disease in question were chosen as reference category.
[c]*P* value indicates whether there is a difference between the concurrent and the delayed period.
[d]Only contacts after 28 days were used.
[e]Only contacts after 1826 days were used.

was due to considerations concerning statistical power but may have resulted in that more severe or complicated cases were included. We examined the temporal relationships between somatic diseases and risk of developing schizophrenia but cannot exclude reverse causality. Furthermore, some cohort members have not passed through the entire risk period for schizophrenia because the oldest individuals were 32 years of age. The relatively young cohort implies that the risk period for many cancers and for most cardiovascular diseases was not covered. Another issue is the clinical diagnoses of somatic and psychiatric diseases. For a clinical diagnosis of schizophrenia, the reliability in Denmark has been shown to be high.[29] For some common somatic diagnoses (such as anemia), the introduction of the ICD-10 classification captured more diagnoses than the ICD-8 classification.

Several of our findings are new, whereas others are replications of previous research results. Our findings with respect to epilepsy and increased risk of schizophrenia are in keeping with previous studies.[7,30,31] Also our findings regarding traumatic brain injury and increased risk of schizophrenia are consistent with the literature.[32,33] A marginally elevated risk estimate for diseases of the blood (forming) organs or immunological disorders may reflect associations between a range of autoimmune diseases and increased risk of schizophrenia.[4,5] An elevated risk estimate for the broad and diagnostically heterogeneous categories of endocrine, nutritional, and metabolic diseases; digestive system diseases; respiratory system diseases; genitourinary system diseases; and skin diseases can partly be attributed to a large and varied range of diagnoses including infections, autoimmune diseases,

Table 3. List of the Three Most Common Conditions Among Cases Within Each Main Somatic Category Subgrouped According to the ICD-8 and ICD-10 Classification

Main Diagnostic Group	Three Most Common Conditions
Infectious and parasitic diseases	
ICD-8: 000–136 (*n* = 427)	427 (100%)
Gastroenteritis (*n* = 166)	166 (38.88%)
Viral infections nonspecified (*n* = 39)	39 (9.31%)
Septicaemia (*n* = 20)	20 (4.68%)
ICD-10: A00-B99 (*n* = 279)	279 (100%)
Diarrhea/gastroenteritis (*n* = 62)	62 (22.22%)
Venereal warts ano-genital region (*n* = 25)	25 (8.96%)
Viral infection nonspecified (*n* = 21)	21 (7.52%)
Neoplasms	
ICD-8: 140–239 (*n* = 44)	44 (100%)
Hemangioma or lymphangioma (*n* = 7)	7 (15.9%)
Neoplasms in lower extremities (bone or cartilage; *n* = 3)	3 (6.82%)
Neoplasm of the kidney (*n* = 2)	2 (4.55%)
ICD-10: C00-D48	109 (100%)
Naevus nonspecified (*n* = 11)	11 (10.09%)
Neoplasm of the breast (*n* = 7)	7 (6.42%)
Neoplasm of the ovarium (*n* = 7)	7 (6.42%)
Diseases of the blood (forming) organs, immunological disorders	
ICD-8: 280–289 (*n* = 80)	80 (100%)
Anemia (iron deficiency; *n* = 21)	21 (26.25%)
Anemia nonspecified (*n* = 12)	12 (15.00%)
Mesenteric lymphadenitis (*n* = 11)	11 (13.75%)
ICD-10: D50-D89 (*n* = 29)	29 (100%)
Anemia nonspecified (*n* = 5)	5 (17.24%)
Allergic purpura (Henoch-Schonlein; *n* = 4)	4 (13.79%)
Thrombocytopenia nonspecified (*n* = 2)	2 (6.90%)
Endocrine, nutritional, and metabolic diseases	
ICD-8: 240–279 (*n* = 128)	128 (100%)
Malnutrition, cachexia (*n* = 46)	46 (35.94%)
Hypoglycemia, spontaneous (*n* = 29)	29 (22.66%)
Adiposity (*n* = 15)	15 (11.72%)
ICD-10: E00-E90 (*n* = 164)	164 (100%)
Adiposity due to large calorie intake (*n* = 23)	23 (14.02%)
Adiposity nonspecified (*n* = 21)	21 (12.80%)
Dephydration (*n* = 12)	12 (7.32%)
Diseases of the nervous system and the sense organs	
ICD-8: 320–389 (*n* = 485)	485 (100%)
Otitis media viral (*n* = 154)	154 (31.75%)
Otitis media acute purulent (*n* = 101)	101 (20.82%)
Otosalpingitis (*n* = 53)	53 (10.92%)
ICD-10: G00-H95 (*n* = 382)	382 (100%)
Conjunctivitis acute nonspecified (*n* = 20)	20 (5.23%)
Migraine nonspecified (*n* = 13)	13 (3.40%)
Tension headache (*n* = 13)	13 (3.40%)
Diseases of the circulatory system	
ICD-8: 390–441.1, 444.3–458, 782.4 (*n* = 27)	27 (100%)
Lung emboli/infarction (*n* = 3)	3 (11.11%)
Heart rhythm disorder (Atrioventricular dissociation; *n* = 2)	2 (7.41%)
Heart function disorder, other type (*n* = 2)	2 (7.41%)
ICD-10: I00-I99 (*n* = 117)	117 (100%)
Hemorroides nonspecified (*n* = 8)	8 (6.84%)
Supraventricular tachycardia, paroxyxmal (*n* = 7)	7 (5.98%)
Tachycardia paroxysmal nonspecified (*n* = 7)	7 (5.98%)
Diseases of the respiratory system	
ICD-8: 460–519 (*n* = 1033)	1033 (100%)
Pharyngitis and rhinitis acute (*n* = 189)	189 (18.30%)
Adenoid hypertrophy (*n* = 176)	176(17.04%)
Pneumonia with or without pleural affection (*n* = 138)	138 (13.36%)
ICD-10: J00-J99	423 (100%)
Tonsillitis chronic (*n* = 72)	72 (17.02%)
Astma nonspecified (*n* = 69)	69 (16.31%)
Tonsillitis acute nonspecified (*n* = 38)	38 (8.98%)
Diseases of the digestive system	
ICD-8: 520–577, 444.2 (*n* = 427)	427 (100%)
Inguinal hernia unilateral (*n* = 110)	110 (25.76%)
Gastroenteritis noninfectious (*n* = 38)	38 (8.90%)
Obstipation (*n* = 36)	36 (8.43%)
ICD-10: K00-K93	549 (100%)
Appendicitis acute nonspecified (*n* = 102)	102 (18.58%)
Obstipation (*n* = 37)	39 (7.10%)
Inguinal hernia unilateral (*n* = 32)	32 (5.83%)
Diseases of the skin and subcutaneous tissue	
ICD-8: 680–709 (*n* = 161)	161 (100%)
Allergic prurigo/eczema (Prurigo-Besnier; *n* = 29)	29 (18.00%)
Abscess, phlegmon, lymphangitis (*n* = 29)	9 (5.59%)
Urticaria nonspecific (*n* = 8)	8 (4.96%)
ICD-10: L00-L99 (*n* = 342)	342 (100%)
Incarnated nail (*n* = 28)	28 (8.18%)
Localized infections of skin and subcutaneous tissue (*n* = 24)	24 (7.02%)
Phlegmon of finger, hand or foot (*n* = 23)	23 (6.72%)
Diseases of the musculoskeletal system/connective tissue	
ICD-8: 710–738 (*n* = 65)	65 (100%)
Bunions (feet (*n* = 6)	6 (9.23%)
Arthritis acute infectious of the elbow (*n* = 4)	4 (6.15%)
Purulent arthritis (*n* = 4)	4 (6.15%)
ICD-10: M00-M99 (*n* = 763)	763 (100%)
Pain in an extremity (leg or arm; *n* = 69)	69 (9.04%)
Chondromalacia patella (patellofemoral syndrome; *n* = 54)	54 (7.07%)
Myosis (*n* = 51)	51 (6.68%)
Diseases of the genitourinary system	
ICD-8: 580–629, 792 (*n* = 229)	229 (100%)
Phimosis (*n* = 67)	67 (29.26%)
Hydrocele of testicles (*n* = 35)	35 (15.28%)
Pyelonephritis, pyelitis and cystopyelitis (*n* = 32)	32 (13.97%)
ICD-10: N00-N99 (*n* = 424)	424 (100%)
Phimosis and paraphimosis (*n* = 45)	45 (10.61%)
Cystitis (*n* = 42)	42 (9.90%)
Breast hypertrophy (*n* = 17)	17 (4.00%)
Complications of pregnancy, childbirth and puerperium	
ICD-8: 630–678 (*n* = 2)	2 (100%)
Induced abortion with septicemia (*n* = 1)	1 (50%)
Spontaneous abortion with septicemia (*n* = 1)	1 (50%)

Table 3. Continued

Main Diagnostic Group	Three Most Common Conditions
ICD-10: O00-O99	318 (100%)
Induced abortion non otherwise specified (*n* = 173)	173 (54.40%)
Imminent abortion (*n* = 11)	11 (3.46%)
Inertia of labor (weakened labor; *n* = 8)	8 (2.52%)
Certain condition originating in the perinatal period	
ICD-8: 760–779 (*n* = 959)	959 (100%)
Neonatal hyperbilirubinemia (non-erythroblastosis; *n* = 376)	376 (39.21%)
Immature infant (*n* = 175)	175 (18.25%)
Other diseases of the newborn after complicated birth (*n* = 64)	64 (6.67%)
ICD-10: DP00-DP96 (*n* = 2)	2 (100%)
Bleeding from vagina of the infant (*n* = 1)	1 (50%)
Congenital hydrocele (*n* = 1)	1 (50%)
Congenital malformations and chromosomal abnormalities	
ICD-8: 740–759 (*n* = 300)	300 (100%)
Retained testis (unilateral; *n* = 41)	41 (13.67%)
Protruding ears (*n* = 23)	23 (7.67%)
Congenital testicular hydrocele (*n* = 16)	16 (5.33%)
ICD-10: Q00-Q99 (*n* = 165)	165 (100%)
Protruding ears (*n* = 24)	24 (14.55%)
Retained testis (unilateral; *n* = 17)	17 (10.30%)
Congenital curvature of the penis (penis arcuatus; *n* = 9)	9 (5.45%)
Symptoms, signs, abnormal finding, ill-defined causes	
ICD-8: 780–782.3, 782.5–791, 793–796 (*n* = 728)	728 (100%)
Febrile convulsions (*n* = 166)	166 (22.80%)
Nonspecific observation (*n* = 147)	147 (20.19%)
Fever not specified (*n* = 53)	53 (7.28%)
ICD-10: R00-R99 (*n* = 846)	846 (100%)
Abdominal condition nonspecified (*n* = 164)	164 (19.39%)
Acute abdomen (*n* = 118)	118 (13.95%)
Syncope (*n* = 75)	75 (8.87%)
Injury, poisoning and certain other consequences of external causes	
ICD-8: 800–999 (*n* = 573)	573 (100%)
Contusion of face, head, neck (excluding eye cavity; *n* = 28)	28 (4.89%)
Intoxications with predominantely non-pharmaceutical drug (*n* = 23)	23 (4.02%)
Fracture of the antebrachium (*n* = 20)	20 (3.49%)
ICD-10: S00-T99 (*n* = 2962)	2962 (100%)
Leg distorsion (*n* = 187)	187 (6.31%)
Hand injury (*n* = 135)	135 (4.56%)
Finger injury (*n* = 105)	105 (3.54%)

asthma, and atopic diseases.[4,5] Our findings with respect to anemia being a frequent first diagnosis in schizophrenia may reflect associations with autoimmune disorders or nutritional deficiencies. Associations between nutritional deficiencies during pregnancy and offspring schizophrenia spectrum disorders have been found,[34–38] and serum iron markers might also be linked with schizophrenia.[39]

Associations between the broad category of congenital malformations and increased risk of schizophrenia have previously been observed.[40] Our findings of a marginally elevated risk of later schizophrenia for the major somatic category of congenital malformations appear to corroborate these findings. We did not specifically examine whether differential effects were present for rare syndromes[41] or minor physical anomalies.[42,43] The findings regarding neonatal hyperbilirubinemia point in the same direction as trends found in an older Danish birth cohort.[44] Also, our findings with respect to febrile convulsions point in the same direction as previous research.[45] The elevated risk estimate associated with hospital contacts with diagnoses of the circulatory system is based on rather few cases and a large and varied range of circulatory system diagnoses contributed to the overall risk estimate. However, the possibility of shared genetic risk factors[39,46] should be examined further, and the possibility of higher thrombo-embolic disease risk in schizophrenia could be examined further. Infections were coded differently from the procedure of a recent study on the same cohort that focused on individual exposure to infections and risk of schizophrenia.[47] This study only included the narrow definition of infection within the diagnostic category of "infectious and parasitic diseases." This will probably underestimate the effect of this particular category and overestimate the effects of other somatic categories because infection codes are also distributed throughout several of the 18 other categories included.

The uniformity of the associations observed in this study could potentially reflect many possible mechanisms. These might include genetic or physiological overlap, interacting immunological, behavioral, experiential, or social factors. A proportion of the somatic diagnoses in our sample might have been secondary to childhood psychiatric disorders, some of which have an increased risk of traumatic injury.[48] A wider range of somatic disorder could have played a role in people with a low psychosis threshold, and, for instance, abnormal or delayed neurodevelopment could have increased the risk of certain somatic illnesses and the risk for schizophrenia. Schizophrenia might share risk factors with some somatic diseases or be a systemic disease as suggested by some authors.[49] We also cannot rule out that the risk of developing schizophrenia and for developing some somatic conditions (eg, impaired glucose tolerance) is influenced by factors associated with suboptimal growth and weight gain in infancy.[50–56] Moreover, adverse influences in childhood including prolonged stress and abuse might contribute to the association between the large and varied range of somatic hospital contacts and the risk of schizophrenia.

As this is the first study to investigate the full spectrum of treated somatic diseases before the first diagnosis of schizophrenia, more research should be conducted in the area to elucidate the present findings. For instance, further modeling with fewer somatic categories and using cumulative incidences of somatic diseases before first

diagnosis of schizophrenia could be helpful in delineating which etiologic mechanisms were most strongly associated with increased point estimates. Future research could further examine the hypothesis that there are systemic underpinnings of schizophrenia and that some physical diseases might precipitate the onset or be associated with increased risk of schizophrenia.

Funding

Stanley Medical Research Institute and the independent Lundbeck Foundation.

Acknowledgments

The funders had no influence on data analysis or the study content what so ever. The authors wish to thank Jakob Christensen MD, PhD for valuable comments.

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