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ORIGINAL PAPER

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Family aggregation of mental disorders in the nationwide Danish three generation study

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Abstract *Objective* The study of familial aggregation of major mental disorders in a national population. *Method* Within a Danish register-based cohort study, aggregation of mental disorders was analysed in all case-probands with first psychiatric contact before the age of 19 years in the time period between 1 April 1969 and 29 June 2004 followed up until the age of 35 years, their first-degree relatives, and a matched group of control-probands including their first-degree relatives. *Results* Hazard rate ratios were significantly elevated for cases as compared to controls for all diagnoses among probands, parents, and siblings. Among children of the probands, these ratios were significantly elevated for neurotic (anxiety) disorders, mental retardation, developmental disorders, behavioural and emotional disorders of childhood and adolescence, and miscellaneous disorders. Family aggregation of any diagnosis was significantly higher in probands with substance use disorder, schizophrenia, affective disorders, neurotic (anxiety) disorders, and miscellaneous disorders. There was specificity of familial transmission for affective and neurotic (anxiety) disorders. *Conclusion* This large nationwide study found some differential patterns of familial aggregation of major mental disorders.

Key words psychopathology · family aggregation · epidemiology · register study

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Introduction

Familial aggregation has been demonstrated for most of the major mental disorders. There is a considerably higher risk of schizophrenia in the first-degree relatives of schizophrenia patients (lifetime risk 1–16%) than in relatives of control probands from the general population (0–2%) [10, 18, 28]. This applies also to the families of patients suffering from schizoaffective disorders who show higher lifetime rates of the diagnoses within the group of the schizophrenias and related disorders and vice versa [8, 17]. Furthermore, there is a partial overlap in susceptibility for schizophrenia and bipolar disorder, in that relatives of probands with these disorders are at increased risk for schizoaffective and recurrent unipolar disorders [1]. The recurrence risk of bipolar disorder is 8.7% for first-degree relatives of bipolar probands and 14.1% for unipolar depression [26]. Prepubertal onset of bipolar disorder may represent a distinct subtype that is genetically related to ADHD, has a poorer response to lithium and a fourfold greater risk in first-degree relatives [26]. Various studies based on both adult and adolescent patients have also shown that major depression is a family disorder [14, 19, 23, 25, 27].

Various manifestations of substance dependence including alcohol, marijuana, and cocaine dependency and habitual smoking are all familial [12], and there is evidence of both common and specific addictive factors transmitted in the families [4] and in alcoholism alone there is an up to sevenfold increase of the disorder in the families of affected patients compared to controls [20]. From less extended research it is also clear that among the anxiety disorders, panic disorders, agoraphobia, and generalized anxiety disorders are recurrent in families [6, 11]. There is also evidence of a familial risk of suicidal ideation and suicidal behaviour in the general population [9].

Studies originating from either child and adolescent or adult index patients with ADHD have shown strong family loadings for various mental disorders including ADHD, antisocial disorders, and affective disorders [2, 3, 5, 7]. The familial risk of ADHD has been recorded to be two- to eightfold greater in first-degree relatives of ADHD probands [13]. In autism there is a recurrence rate in siblings of affected children that is much higher than the prevalence rate in the general population [21]. In addition, there is not only strong familial aggregation of autism-spectrum disorders [16] but also more frequently a broader phenotype including speech and learning disorders and intellectual deficits predominantly in the verbal domain that is specific to these families [15].

To date, there have been only few large scale studies of familial aggregation based on probands selected from general population samples. Few studies have exploited the potential of population registries to examine patterns of transmission of mental disorders across generations. In the present study, we use data from the Danish psychiatric central register (PCR) in order to study to our knowledge for the first time the family aggregation of major mental disorders across three generations in a nationwide population. Within this register-based cohort study, aggregation of all major mental disorders was analysed in all case-probands with first psychiatric contact during childhood and adolescence over an extended time period followed up until the age of 35 years, their first-degree relatives, and a matched group of control-probands including their first-degree relatives.

Methods

Sample

The sample for this study is based on linkage of data across registers of the population of Denmark. The Danish centralized civil register system (CRS) assigns a unique personal and life-lasting identification number but no names to all residents in Denmark. This unique personal identification number allows accurate linkage between various other registers and across generations. The sample for the present study was derived from the psychiatric central research register (PCR) of Denmark [22] which contains computerized data on all admissions to Danish inpatient facilities since 1 April 1969, and outpatients since 1995. All psychiatric admissions are represented in the register because there are no private psychiatric hospitals in the country. Both the CRS and the PCR contain all residents of the country, i.e. those born in the country as well as immigrants.

Cases

Cases for the present study included individuals with at least one psychiatric record with first contact before the age of 19 years in the period from 1 April 1969 to 29 June 2004. Only those born between 1 April 1969 and 29 June 1985 were included in the sample in order to obtain coverage for the entire period of childhood and adolescence (0–18 years) by the end of the study period in 29 June 2004 when the cohort had a maximum age of 35 years. Case-probands dying before the age of 19 years were excluded. Moreover, cases never admitted during the period of childhood and adolescence with a diagnosis among those shown in the Appendix were excluded. A total of 20,114 individuals remained after exclusions. The case-probands *index-time* is defined as the time of their first admission.

Controls

For each case-proband a total of three control-probands were obtained from the Danish centralized civil register (CRS) using risk-set sampling [24], that is they were alive and without registrations in the PCR at the case-probands index-time. Furthermore, control-probands were matched with regard to gender, age (same month and year of birth) and living in the same county at the case-probands index-time. Only control-probands born between 1 April 1969 and 29 June 1985 were included. Persons with PCR records during childhood and adolescence were excluded. Furthermore, control-probands were excluded if they died before the age of 19 years. This ensured total coverage of the period of childhood and adolescence.

For some case-probands, however, fewer than three control-probands were obtained (probably due to matching restrictions). Furthermore, some control-probands were excluded due to reasons mentioned above. The entire cohort of control-probands consisted of a total of 56,802 individuals.

First-degree relatives

For each proband (cases and controls) first-degree relatives including parents, siblings and children were identified in the CRS. The relatives were then identified in the PCR. The PCR data of the parents and the siblings of probands are taken into account with regard to the entire set of data during the observation period from 1 April 1969 to 29 June 2004. The PCR data of the children of the probands were included as far as childhood and adolescence were concerned. Note, however, that only three children of the probands among those included reached the age of 19 years before the end of the study period. Thus, the entire dataset includes three generations with the case-probands having a psychiatric contact during childhood and adolescence and being the index probands of the study.

Furthermore, a distinction was made between case-parents and control-parents. If a parent did have both case and control children, then this parent was defined as a case-parent only. This procedure was applied using the whole sample, i.e. the case/control status of the excluded probands was used when defining the case/control status of the parents. The same procedure applied also to the siblings and to the children of probands.

Table 1 Description of first-degree relatives of the probands (cases and controls). Proportions in percentage relate to the relevant total number (*N*) of subjects

	Cases (*N* = 20,114) (%)	Controls (*N* = 56,802) (%)	Both (%)
No of parents			
None	124 (0.6)	386 (0.7)	
One	586 (2.9)	1,096 (1.9)	
Both	19,404 (96.5)	55,320 (97.4)	
Case-parents (*N* = 39,855)	34,201 (85.8)	0 (0)	5,654 (14.2)
Control-parents (*N* = 104,169)	0 (0)	104,169 (100)	0 (0)
No of siblings			
None	5,984 (29.8)	10,983 (19.3)	
One	8,536 (42.4)	27,205 (47.9)	
Two	3,809 (18.9)	12,625 (22.2)	
Three or more	1,785 (8.9)	5,989 (10.5)	
Total	20,114 (100)	56,802 (100)	
Case-siblings (*N* = 22,872)	20,528 (89.8)	0 (0)	2,344 (10.2)
Control-siblings (*N* = 70,816)	0 (0)	70,816 (100)	0 (0)
No of children			
None	16,233 (80.7)	46,873 (82.5)	
One	2,333 (11.6)	5,216 (9.2)	
Two	1,130 (5.6)	3,704 (6.5)	
Three	322 (1.6)	845 (1.5)	
Four or more	96 (0.5)	164 (0.3)	
Total	20,114 (100)	56,802 (100)	
Case-children (*N* = 5,914)	5,709 (96.5)	0 (0)	205 (3.5)
Control-children (*N* = 15,495)	0 (0)	15,495 (100)	0 (0)

We identified a total of 39,855 case-parents (19,721 males and 20,134 females) and 104,169 control-parents (51,712 males and 52,457 females). Each individual is counted only once even if he or she is a parent of more than one proband. In addition, 22,872 case-siblings (11,668 males and 11,204 females), 70,816 control-siblings (36,481 males and 34,335 females), 5,914 case-children (2,991 males and 2,923 females), and 15,495 control-children (8,017 males and 7,478 females) were identified. Further details concerning the first degree relatives are shown in Table 1.

Diagnoses

The PCR data include date of birth, gender, admission and discharge date (including number of episodes), diagnoses (ICD-8 until 1993 and ICD-10 from 1994), type of admission (inpatients, outpatients and emergency cases). Date of death was taken from the Danish causes of death registry (CDR). Diagnoses differentiate between underlying disorder (main diagnosis) and the condition leading to the present admission (action diagnosis). In addition, the dataset contains auxiliary diagnoses and additional codes (mainly other diagnoses and medication codes). In order to match ICD-8 and ICD-10 categories a list of corresponding groups of included diagnoses was set up as shown in the Appendix. Data analysis was based on main diagnoses and action diagnoses. In general, the action diagnosis was used only if no main diagnosis was given.

Statistical analysis

Two different kinds of analyses were applied: (a) Cox regression analysis of time-to-event data considering the event of being diagnosed with a mental disorder (see below), and (b) familiality by examining the proportion of first-degree relatives having any or the same psychiatric diagnosis as their proband. These proportions were compared by use of a logistic regression with standard errors corrected for the correlation between multiple observations from subjects having more than one proband. The *P* value for the two-sided Wald test of no difference (odds ratio = 1) was calculated in order to cheque if the proportions found in relatives of cases were higher than those found in the relatives of controls. Testing was only done if all expected frequencies in the corresponding two by two table were greater than five.

For the Cox proportional hazards model, we first examined whether in general subjects from the case-cohorts were more prone to receive a psychiatric diagnosis. This was done by considering first contact ever as the event *psychiatric contact in general*, i.e. admission to either outpatient or inpatient psychiatric care. Secondly, we investigated whether the patterns differed with specific diagnoses by using the first event the specific diagnosis was given.

The Cox regression analyses were stratified by gender in order to prevent violations of the proportionality assumption. Birth cohorts for the parents were constructed by stratification of the parents by 20 quantiles, (i.e. 5, 10 and 15% percentiles) based on birth dates since 1 January 1960 (negative numbers if earlier than this date). Age was adjusted for by using age as time scale. Results are presented as hazard rate ratio with 95% confidence intervals, i.e. as the ratio between the hazard rate for the case-cohort and the hazard rate for the control-cohort.

Time limitations of the PCR induce left truncated observation time for most parents and also a few of the siblings. Therefore, entire or large parts of the childhood and adolescence period was missing for most of the parents and we decided to left censor this time period for the remaining parents. As a result of the exclusion criteria none of the probands have left truncated observations and, of course, neither do their children.

Dates of death were obtained from the CDR. The extract from CDR did, however, only include death until 31 December 2000. In the analyses, parents were censored at the date of death, at 31 December 2000 (latest date in CDR) or at the last date of discharge from a psychiatric admission later than 31 December 2000. For probands, siblings and children date of death was known until 31 May 2004 from the CRS and the censoring procedure was accordingly adjusted.

Analyses were carried out using Stata release 9.2 (StataCorp. 2005. *Stata Statistical Software: Release 9*. College Station, TX: StataCorp LP).

Results

Diagnoses of the case-probands

For each individual we identified the most severe diagnosis with respect to the hierarchy shown in the Appendix. Considering the entire study period, the frequencies (and proportions) of these diagnoses were: D0 brain disorders: 536 (2.7%); D1 substance use disorders: 1,649 (8.2%); D2 schizophrenic disorders: 1,947 (9.7%); D3 affective disorders: 1,726 (8.6%); D4 neurotic (anxiety) disorders: 5,169 (25.7%); D5 psychosomatic disorders: 1,570 (7.8%); D6 personality disorders: 1,659 (8.2%); D7 mental retardation: 469 (2.3%); D8 developmental disorders: 1,227 (6.1%); D9 emotional and behavioural disorders in childhood and adolescence: 3,674 (18.3%); D10 miscellaneous disorders: 488 (2.4%).

Findings of the Cox regression analyses

Frequencies and proportions of the most severe diagnosis given during the entire observation period

Table 2 Frequencies of subjects by most severe diagnosis during the time of observation in the various cohorts

Diagnosis	Case-probands	Control-probands	Case-parents	Control-parents	Case-siblings	Control-siblings	Case-children	Control-children
Number of subjects	20,114	56,802	39,855	104,169	22,872	70,816	5,914	15,495
Any	6,093 (30.3)	1,825 (3.2)	7,021 (17.6)	7,254 (7.0)	3,156 (13.8)	3,299 (4.7)	164 (2.8)	97 (0.6)
D0 brain disorders	281 (1.4)	34 (0.06)	405 (1.0)	447 (0.4)	103 (0.5)	67 (0.09)	0	0
D1 substance use disorders	825 (4.1)	214 (0.4)	1,883 (4.7)	1,873 (1.8)	324 (1.4)	367 (0.5)	0	0
D2 schizophrenic disorders	1,428 (7.1)	180 (0.3)	941 (2.4)	847 (0.8)	359 (1.6)	350 (0.5)	2 (0.03)	2 (0.01)
D3 affective disorders	750 (3.7)	405 (0.7)	936 (2.3)	1,224 (1.2)	395 (1.7)	511 (0.7)	2 (0.03)	1 (0.01)
D4 neurotic disorders	1,186 (5.9)	628 (1.1)	1,925 (4.8)	1,959 (1.9)	870 (3.8)	1,010 (1.4)	33 (0.6)	24 (0.2)
D5 psychosomatic disorders	387 (1.9)	155 (0.3)	40 (0.1)	59 (0.06)	128 (0.6)	244 (0.3)	0	2 (0.01)
D6 personality disorders	782 (3.9)	141 (0.2)	707 (1.8)	639 (0.6)	230 (1.0)	262 (0.4)	1 (0.02)	1 (0.01)
D7 mental retardation	110 (0.5)	12 (0.02)	23 (0.06)	11 (0.01)	58 (0.3)	53 (0.07)	8 (0.1)	6 (0.04)
D8 developmental disorders	154 (0.8)	10 (0.02)	7 (0.02)	8 (0.01)	137 (0.6)	121 (0.2)	29 (0.5)	21 (0.1)
D9 behav. and emot. disorders	75 (0.4)	5 (0.01)	5 (0.01)	10 (0.01)	451 (2.0)	223 (0.3)	81 (1.4)	37 (0.2)
D10 miscellaneous disorders	115 (0.6)	41 (0.07)	149 (0.4)	177 (0.2)	101 (0.4)	91 (0.1)	8 (0.1)	3 (0.02)

Proportions in percentage of the total number of subjects in each cohort in parentheses

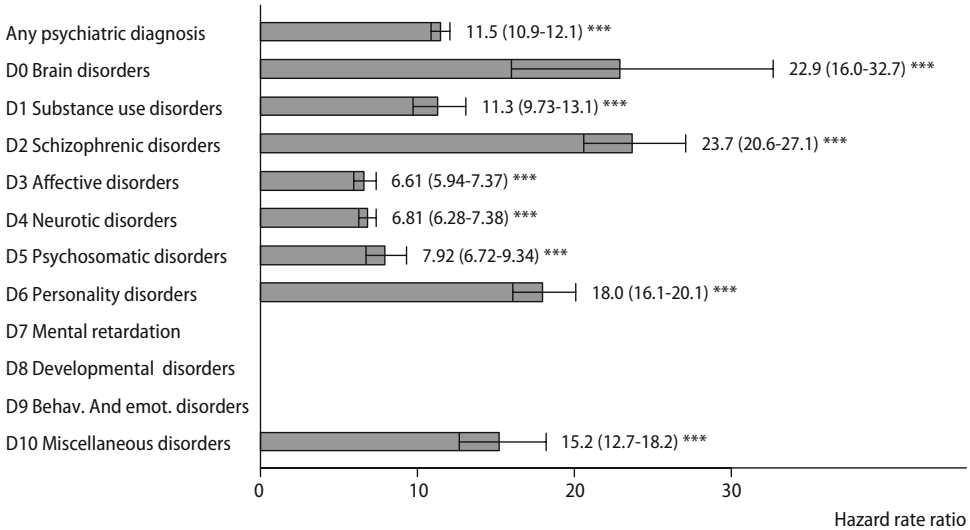

Fig. 1 Results from stratified Cox regression analyses showing the main differences in terms of the hazard rate ratio (HR) between the case- and control-probands. 95% Confidence intervals are given in *parentheses* after the HR

are shown in Table 2. In the cohort of probands the 76,916 subjects contributed a total of 371,507 person years and a total of 7,918 were diagnosed with a mental disorder from the hierarchy: 6,093 (30.3%) case-probands and 1,825 (3.2%) control-probands. Here, every proband was analysed from his or her 19th birthday and contributed risk time (person years) until first psychiatric contact as adult or until censoring. The latest observed exit was at the age of 35. In the cohort of parents, the 144,024 persons contributed a total of 3,864,926 person years and a total number of 14,275 had at least one psychiatric contact after their 19 years birthday with a diagnosis from the hierarchy: 7,023 (17.6%) of the case-parents and 7,255 (7.0%) of the control-parents. Mean age at entry was 21.1 years (SD = 4.0) but this distribution was highly skewed and the median age was 19.0 years whereas the 75% percentile was 21.9 years of age. The latest entry age was 67.6 years but 99% were 37.3 years or younger. In the cohort of siblings, the 93,688 persons contributed 2,194,015 years in total and 6,455 were diagnosed: 3,156 (13.8%) of the case-siblings and 3,299 (4.7%) of the control-siblings. Most siblings were observed from birth but the latest exit was at the age of 53, so a few had left truncated observations and entered the study on 1 April 1969. The 21,409 children contributed 85,246 person years but only 261 were diagnosed during the study period, so the data on the child-cohorts were somewhat sparse. In every cohort these numbers are different when specific diagnoses are considered because subjects then contribute risk time until the first contact with this diagnosis or until censoring.

The results of the Cox regression analyses for each of the four cohorts are shown in Figs. 1 and 2. In the cohort of probands, only the period after their 19th birthday was analysed as control-probands by design had no psychiatric contacts during childhood and adolescence. The parents were only assessed after age 19 so no information was available on earlier onset disorders. Because the sample of offspring of probands were only evaluated from birth to age 18, several adult disorders were too rare for meaningful analysis. In general, the number of subjects in the cohort of the probands' children is small and the confidence intervals are correspondingly wide.

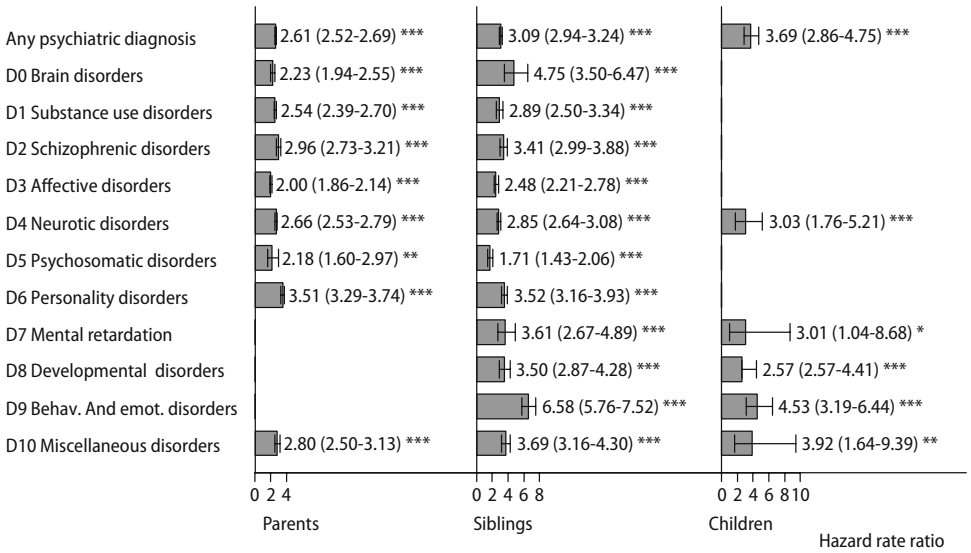

Fig. 2 Results from stratified Cox regression analyses showing the main differences in terms of the hazard rate ratio (HR) between the individual case- and control-cohorts (parents, siblings, children. 95% confidence intervals are given in *parentheses* after the HR

In the cases (Fig. 1) the probability of falling mentally ill as adults is 11.5 times higher for any diagnosis than in the controls. For the various diagnoses these hazard rate ratios vary between a low of 6.6 (affective disorders) to a high of 24 (schizophrenic disorders). All these ratios are highly statistically significant different from 1. Similarly, in the parents (Fig. 2) the hazard rate ratio for any disorder is 2.6, with a range from 2.0 to 3.5 for other disorders. In the siblings, the hazard rate ratio for any diagnosis is 3.1 and varies between 1.7 and 6.6 for other disorders. Even though the low frequencies of disorders in offspring precluded statistical analysis for many conditions in offspring, there are significantly increased hazard rates in the offspring of cases compared to those of controls, with a ratio of 3.7 for any disorder, and ratios ranging between 2.6 and 4.5 for those five diagnostic groups that were sufficiently prevalent in this cohort: neurotic (anxiety) disorders, mental retardation, developmental disorders, behavioural and emotional disorders in childhood and adolescence, and miscellaneous disorders.

Familiality

Familial aggregation of the various study diagnoses is shown in Table 3 that presents the frequencies of first-degree relatives of cases and controls who received *any* diagnosis or the *same* diagnosis as that of the proband. For the entire group of relatives as indicated in the column labelled 'all' and the aggregation of *any* diagnosis, there were significantly increased frequencies among first-degree relatives of cases for D1 substance use disorders, D2 schizophrenic disorders, D3 affective disorders, D4 Neurotic (anxiety) disorders, and D10 miscellaneous disorders. The same pattern also emerged for parents, whereas the association with any diagnosis was significantly elevated for D1 substance use, D3 affective and D4 neurotic disorders among the siblings. Almost all expected frequencies were less than five in the offspring of controls. Only a single test was done and this showed no significant difference in D4 neurotic disorders.

Probands and relatives were significantly more likely to exhibit the *same* diagnosis for D3 affective disorders and D4 Neurotic disorders. For siblings, specificity only emerged for D4 Neurotic disorders. The frequency of neurotic disorders was elevated among the control children. However, it should be noted that some of the relatively high proportions of diagnoses among the control children are seen in relatively small subsample sizes. Again, sample sizes in children were too small to analyse anything separately about familiality of *same* diagnoses in the offspring.

Discussion

This study is one of the largest studies of the familial aggregation of mental disorders based on a national register across three generations. The unique sampling of cases from a complete sample of individuals treated in the Danish National Health Service and selection of a large representative sample of controls from a centralized register afforded the opportunity to conduct the first study of the familial aggregation of mental disorders that is representative of the total population of Denmark. However, for the understanding of the results it has to be born in mind that the study is primarily based on patients with childhood onset disorders. Only in the parents, infor-

Table 3 Frequencies (proportions in percentage) of the most severe diagnosis observed in first-degree relatives of probands (cases and controls) during the study period

Proband's diagnosis	Relative's diagnosis	All		Parents		Siblings		Children	
		Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
D0 Brain Disorders	Any	376 (20.7)	19 (15.2)	248 (23.6)	15 (22.4)	121 (18.9)	4 (9.1)	7 (5.5)	0[a]
	Same	41 (2.3)	1 (0.8)[a]	26 (2.5)	0[a]	15 (2.3)	1 (2.3)[a]	0	0[a]
D1 substance use disorders	Any	1,084 (19.9)	110 (14.4)***	767 (23.9)	75 (17.9)**	293 (17.5)	32 (11.9)*	24 (4.3)	3 (3.9)[a]
	Same	339 (6.2)	34 (4.4)	277 (8.6)	29 (6.9)	62 (3.7)	5 (1.9)	0	0[a]
D2 schizophrenic disorders	Any	1,221 (18.8)	87 (13.8)**	794 (21.2)	50 (14.2)**	399 (16.9)	35 (15.2)	28 (7.2)	2 (4.2)[a]
	Same	252 (3.9)	18 (2.9)	158 (4.2)	10 (2.8)	92 (3.9)	8 (3.5)	2 (0.5)	0[a]
D3 affective disorders	Any	866 (14.6)	160 (11.0)***	590 (17.3)	112 (13.9)*	265 (12.6)	44 (9.1)*	11 (2.6)	4 (2.4)[a]
	Same	212 (3.6)	29 (2.0)**	142 (4.2)	20 (2.5)*	70 (3.3)	9 (1.9)	0	0[a]
D4 neurotic disorders	Any	2,620 (14.7)	241 (10.3)***	1,786 (17.7)	161 (13.1)***	802 (13.5)	70 (8.8)***	32 (1.8)	10 (3.1)
	Same	884 (5.0)	65 (2.8)***	571 (5.6)	40 (3.3)***	305 (5.2)	20 (2.5)**	8 (0.5)	5 (1.6)[a]
D5 psychosomatic disorders	Any	453 (8.4)	40 (7.3)	295 (9.5)	26 (8.5)	155 (8.1)	13 (7.2)	3 (0.9)	1 (1.6)[a]
	Same	21 (0.4)	2 (0.4)[a]	3 (0.1)	0[a]	18 (0.9)	2 (1.0)[a]	0	0[a]
D6 personality disorders	Any	867 (15.4)	72 (13.8)	625 (19.3)	52 (18.5)	222 (12.8)	18 (10.7)	20 (3.1)	2 (2.7)[a]
	Same	100 (1.8)	11 (2.1)	75 (2.3)	8 (2.8)	25 (1.4)	3 (1.8)[a]	0	0[a]
D7 mental retardation	Any	209 (13.6)	3 (6.8)	137 (14.9)	3 (12.5)[a]	71 (12.2)	0[a]	1 (3.2)	0[a]
	Same	14 (0.9)	0[a]	3 (0.3)	0[a]	11 (1.9)	0[a]	0	0[a]
D8 developmental disorders	Any	506 (13.1)	6 (21.4)[a]	345 (14.3)	4 (21.1)[a]	158 (11.6)	2 (22.2)[a]	3 (3.1)	–[b]
	Same	28 (0.7)	0[a]	0	0[a]	27 (2.0)	0[a]	1 (1.0)	–[b]
D9 behavioural and emotional dis.	Any	2,047 (16.5)	6 (28.6)[a]	1,418 (19.6)	4 (40.0)[a]	595 (15.7)	2 (20.0)[a]	34 (2.6)	0[a]
	Same	226 (1.8)	0[a]	5 (0.07)	0[a]	204 (5.4)	0[a]	17 (1.3)	0[a]
D10 miscellaneous disorders	Any	384 (22.0)	17 (11.3)**	276 (28.9)	13 (15.9)*	102 (18.7)	4 (7.8)	6 (2.5)	0[a]
	Same	42 (2.4)	1 (0.7)[a]	14 (1.5)	1 (1.2)[a]	28 (5.1)	0[a]	0	0[a]

Separate rows are showing the frequencies found in relatives having *any* of the diagnoses from the hierarchy and the *same* diagnosis as their proband. Proportions refer to the total number of first-degree relatives of probands having this diagnosis

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

[a]Expected frequency less than five (no test done)

[b]No control-probands with this diagnosis

mation on childhood onset disorders was not available.

The chief finding is that the first degree relatives of the cases are significantly more likely to receive treatment for any mental disorder as well as that manifest by the proband than those of control probands. These findings corroborate those from prior family studies of clinical and community samples of probands for all disorders including substance use disorders [4, 12, 20], the schizophrenias [10, 18, 28], affective disorders [2, 3, 14, 19, 23, 25–27], and anxiety disorders [6, 11]. We also found that there was strong specificity of familial aggregation of the probands' disorders, particularly in parents and siblings. This was particularly marked for affective and neurotic (anxiety) disorders. In contrast, other disorders like the schizophrenias did not show this pattern of aggregation. These disorders are very rare in childhood and adolescence. Thus, a relatively low base rate of these disorders in the present sample of case probands may be predominantly responsible for the lacking familial aggregation of the schizophrenias.

Significantly increased hazard rates in relatives were also obtained for some types of disorders for which there have not been prior studies of familial clustering, such as brain disorders, psychosomatic disorders, personality disorders, and mental retardation. The analysis of the familial aggregation of attention-deficit hyperactivity disorders or autism in the present cohort will need further analyses in order to evaluate findings of a small series of both clinical and population based family studies [2, 3, 5, 13, 15, 16].

As would be expected by the sampling of probands with childhood onset disorders, there was stronger familial aggregation among parents and their siblings than for offspring due to the restricted observation period and the smaller number in the study. Even though the magnitude was lower among offspring, there was still increased risk for early onset disorders including neurotic (anxiety) disorders, mental retardation, and developmental disorders.

Despite the unique and large sample, there are also limitations to the present study. First, our analyses did not include subjects or relatives with mental disorders who did not seek treatment and those who were treated abroad. However, in Denmark health service including psychiatry is free to the public following referral from general practitioners. All inpatient and outpatient services are in the public domain and there are no private hospitals available. The entire health service system is paid via taxes. Given this background, it may be assumed that the threshold for

getting into treatment is similar in the proband and control cohorts. It may also be assumed that both indigenous people and the small group of immigrants were represented to the same extent in the two cohorts because both are registered in the CPR. Thus, one may be rather sure that the large size and the representative nature of the treated samples may help to correct expected findings based on previous smaller and more biased clinical family aggregation study samples.

Second, we could not examine the reliability and validity of the findings because they were based on clinical records [16, 21]. However, the specialist education both in child and adult psychiatry has been organized always by the national psychiatric societies and surveyed by the National Board of Health so that all received the same education. When ICD-10 was launched in 1994, all psychiatrists were trained over a 2-year period including two follow-up courses. Since then, yearly nationwide courses in diagnoses and classification have been provided. Thus, the large group of physicians who provided diagnoses throughout the study period all received continuous education in assessment and classification within the same organization.

Third, diagnoses were partly based on the ICD-8 scheme of classification without any operationalized criteria for diagnoses and partly on the ICD-10 with a stronger adherence to descriptive diagnostic criteria. However, we attempted to minimize this limitation by using broader diagnostic categories instead of smaller specific diagnostic groups in the analyses. In addition, diagnostic correspondence between the two systems was not only established by the senior author alone but also controlled by another senior child and adolescent psychiatry chair person. Fourth, the left truncation of the parent data due to lacking information on mental disorders in childhood and adolescence is another limitation.

Despite these limitations, our findings confirm the importance of familial aggregation of mental disorders and suggest that future research will address the specific mechanisms of the specificity and consistency of this finding. We hope that future studies of the cohort of offspring using contemporary clinical and biologic measures may shed additional light on this important question.

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Appendix

See Table 4

Table 4 Main groups and subgroups of diagnoses and correspondence between ICD-8 and ICD-10 codes

Group number in data	Description	ICD-8 codes	ICD-10 codes
D0	Organic/brain disorders	290–294	F00–F09
D1	Substance use disorders	303, 304	F10–F19
D2	Schizophrenias, etc.	295, 297, 298	F20–F29
D3	Affective disorders	296	F30–F39
D4	Neurotic disorders, etc.	300, 307	F40–F48
D5	Psychosomatic disorders	305.09–305.99, 306.49, 306.50, 306.58, 306.59	F50–F59
D5a	Eating disorders	306.50, 306.58, 306.59	F50
D5b	Other psychosomatic disorders	305.09–305.99, 306.49	F51–F59
D6	Personality disorders	301	F60–F64, F66–F69
D7	Mental retardation	310–315	F70–F79
D8	Disorders of psychological development	299, 306.09–306.19, 306.39	F80–F89
D8a	-most equivalent to autism and Asperger's syndrome	299 except 299.09	F84–F89
D8b	-most equivalent to specific developmental disorders	306.09–306.19, 306.39	F80–F83
D9	Behavioural and emotional disorders in childhood and adolescence	306.29, 306.69, 306.79, 308	F90–F98
D9a	Externalising disorders including ADHD and attachment disorders	308.01, 308.07	F90, F91, F94
D9b	Internalising, emotional disorders	308.00, 308.02–308.06	F92–F93
D9c	Tics	306.29	F95
D9d	Elimination disorders	306.69, 306.79	F98.0, F98.1
D10	Miscellaneous disorders	302, 309, 793, 306.89, 306.99	F65, F99

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