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ORIGINAL RESEARCH

Mental Health Disorders in Patients with Inflammatory Bowel Disease Onset in Childhood or Youth – A Nationwide Cohort Study from Denmark

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Purpose: The study aims to explore the association between patients diagnosed with inflammatory bowel disease (IBD) in childhood or youth and mental health disorders.

Methods: The study is a register-based cohort study of patients with IBD-onset before 25 years of age and matched references. They were followed until 30 years of age. The incidence rate and incidence rate ratio (IRR) for a wide spectrum of mental health disorders were assessed based on diagnostic codes from the Danish National Patient Registry, reimbursed prescriptions for psychotropic medications, and composite measures combining diagnosis and medication. Furthermore, the relative excess risk due to interaction (RERI) for parental educational level and parental mental health disorders were estimated.

Results: A total of 4904 patients with Crohn's disease (CD), 5794 with ulcerative colitis (UC), and 94,802 matched references were identified. Patients with CD-onset before age 18 had a higher risk of anxiety disorders (IRR 1.58 (CI95%: 1.33–1.86)), while patients with CD-onset between age 18 to 24 had a higher risk of both anxiety and mood disorders. Patients with UC-onset before age 18 had a higher risk of anxiety disorders (IRR: 1.39 (CI95%: 1.19–1.64)). In general, patients with IBD had a higher risk of receiving psychotropic medication. Parental education had a subadditive interaction with the risk of emotional disorders for both patients with CD and UC, while maternal mental health disorders had a subadditive interaction for patients with UC.

Conclusion: Patients with CD and UC have a higher risk of mental health disorders, primarily due to an elevated risk of emotional disorders and a higher use of psychotropic medication. Surprisingly, the study demonstrated subadditive effect of parental education and for patients with UC maternal mental health disorders on the risk of emotional disorders.

Keywords: Crohn's disease, ulcerative colitis, psychiatric disorders, psychotropic medication

Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a group of immune mediated gastrointestinal diseases that are characterized by inflammation of the intestines. IBD is often diagnosed in adolescence or early adulthood and has a fluctuating course with periods of relapse and remission. The disease course ranges from mild disease with few or no symptoms to severe disease with need of surgery, treatment with biological therapy, or hospitalization. The etiology is unknown, but genetic and environmental factors are thought to play a role.[1]

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Adolescence is a period characterized by rapid somatic, psychological, and social development,[2] and being diagnosed with a chronic disease in this time period or in early adulthood may impact mental health. A growing body of evidence supports an association between IBD and anxiety and mood disorders.[3,4] In patients with IBD, anxiety and depression have been linked to an increased risk of escalation of IBD treatment, hospitalization, and emergency department visits due to IBD activity.[5] Patients diagnosed with depression also had an increased risk of flares and IBD-related surgery.[5] The mechanism of anxiety and depression in children and youth is a complex interplay of psychological, genetic, and environmental factors, and can be linked to stressful life events.[6–8] In a systematic review an increased risk of both anxiety and depression following IBD diagnosis was found, and individuals with depression showed a 2-fold increased risk of IBD indicating a bi-directional association between IBD and mental health.[4] This may be further supported by the findings of patients diagnosed with depression also had an increased risk of flares and IBD-related surgery.[5]

In patients with onset of IBD in childhood or youth, recent cohort studies have shown an increased risk of mood[9–12] and anxiety disorders.[9,11] Furthermore, some have also found an increased risk of other mental health disorders,[11] including attention deficit hyperactivity disorder (ADHD) but contradicting results have been found in other studies.[10,13] The conflicting results may be due to differences in the definition of mental health disorders.

Parental mental health disorders[14,15] as well as parental socioeconomic status (SES)[16–18] are important risk factors for mental health disorders in offspring. The mechanisms are not fully understood, but both genetic and environmental factors are thought to play a role for the association between parental mental health disorders and mental health disorders in offspring,[19,20] while parental SES may be part of the social selection hypothesis or the social causation hypothesis.[16] In patients with IBD (13–17 years of age) parental stress has been linked to the development of depression.[21] However, the role of parental mental health disorders or parental socioeconomic status in studies on IBD and mental health disorders in adolescents has not been examined.

While different theories on the mechanism behind anxiety and depression have been described, there is a need for further studies to explore if an association with other mental health disorders exist. Therefore, the primary aim of this study was to describe the incidence rate and incidence rate ratio for a wide spectrum of mental health disorders (including neurodevelopmental disorders) in patients with IBD onset in childhood or youth and explore whether a potential association was modified or confounded by parental mental health disorders or socioeconomic position.

Method

Study Design and Setting

The study was a register-based cohort study using information from the Danish administrative registers. All citizens are given a ten-digit personal identification number, making linkage between the different registers possible. Information on the parents' personal identification number was retrieved from the Fertility Database.[22] Information on admissions and outpatient treatment was collected from the Danish Psychiatric Central Research Register[23] (DPCR) and The Danish National Patient Registry (DNPR). Information on medication was collected from The Danish National Prescription Registry.[24] Furthermore, information on contacts to private practicing psychiatrists and psychologists was collected from The Nation Health Service Registry,[25] and information on educational level from the Population Education Register.[26]

Denmark has a universal and tax-funded healthcare system that provides free access to a comprehensive package of health services, including treatment for IBD at the hospital.[27] Mental health services for children and adolescents (<18 years of age) are organized on two administrative levels. The administrative regions are responsible for the specialized mental health services (private practicing child and adolescent psychiatrists and child and adolescent psychiatric departments at the hospitals) and general practitioners (GPs). The municipalities are responsible for educational and social services. Mental health services for children and adolescents are organized in a stepped care approach.[28]

For children and adolescents (<18) referral to specialized mental health services can either be done by a GPs, educational services, social services, or other hospital departments. Minor mental health disorders or intellectual disabilities which require no specialized psychiatric assessment or treatment can be managed in the educational or social services or at the GP. However, guidelines stipulate that only licensed child and adolescent psychiatrists should initiate

treatment with psychotropic medicine – either from child and adolescent psychiatric departments or private practicing child and adolescent psychiatrists.

Mental health services for adults (>18 years of age) are also organized between the municipalities and the regions. Referrals to specialized mental health services (private practicing psychiatrists or psychiatric departments) are done by GPs or other hospital departments.

Even though most health services in Denmark are free of charge, including private practicing psychiatrists, a growing number of private practitioners have no reimbursement agreements with the region and require self-payment. They often have shorter waiting times for assessment than in the regional specialized mental health services.

In most cases, treatment by private practicing psychologists is not covered by the public health insurance. However, youth (18–24 years of age) with depression (from 2008) and anxiety (from 2011) are covered, and patients with psychological distress due to "severe disease" can be entitled to a subsidy after referral by the GP.[29]

Participants

Patients with a first-time diagnosis of Crohn's disease (CD) or Ulcerative colitis (UC), below the age of 25 years in the DNPR and diagnosed between 2002 and 2018 were included. The diagnostic ICD-10 code K50 was used for Crohn's Disease and ICD-10 code K51 for ulcerative colitis. Information on the patient's maternal personal identification number had to be known, and the patient had to be living in Denmark at the time of inclusion. To have information on mental health disorders before diagnosis we excluded patients living outside of Denmark for more than 15 months. For each patient, ten references were matched on age (birth year) and sex assigned at birth. References had the same inclusion criteria as patients as well as not having an IBD diagnosis (CD: ICD-8 code 563.01, or ICD-10 code K50. UC: ICD-8 codes 563.19, 569.04 or ICD-10 code K51) at the time of inclusion (Figure 1).

When studying incident mental health disorders, patients with mental health disorders (including neurodevelopmental disorders) prior to the index date and their matched references, as well as references with prior mental health disorders were excluded (Incident cohort- Figure 1).

Exposure

The exposure was having a CD or a UC diagnosis. Analyses of incident mental health disorders were stratified according to patients being diagnosed before 18 years of age or between the ages of 18 and 24 years.

Outcome

Mental Health Disorders

When examining mental health disorders, we examined diagnoses of mental health disorders and prescriptions for psychotropic medication separately and as composite measures.

Information on mental health disorders was retrieved from the DPCR[23] and the DNPR.[30] Diagnosis codes were from the ICD-10 and grouped according to Dalsgaard et al[31] (Figure 2). For patients diagnosed before 1994, the diagnostic codes were ICD-8 codes (used to exclude patients with prior mental health disorders). They were converted into ICD-10 codes (Supplementary Table 1). We identified the first date of a new primary diagnosis (A-diagnosis). Information from in- and outpatients visits and primary diagnoses in somatic hospitals or emergency departments were included.

Information on psychotropic medicine was retrieved from The Danish National Prescription Registry,[24] which contains information on all redeemed prescriptions since 1997. The following Anatomical Therapeutic Chemical (ATC) categories were included: Central nervous system (CNS) stimulants (ATC: N06BA), antipsychotics (ATC: N05A), antidepressants (ATC: N06A), anxiolytics (ATC: N05B), and sedative (ATC: N05C) (Supplementary Table 1). Patients needed two redeemed prescriptions to be categorized as receiving medication. The date of the first prescription was used in the analysis.

By combining information from hospital data and the use of medicine we constructed four composite groups (neurodevelopmental, psychotic disorders, emotional disorders, and other mental health disorders) as done by Janssons et al[12] (Figure 2).

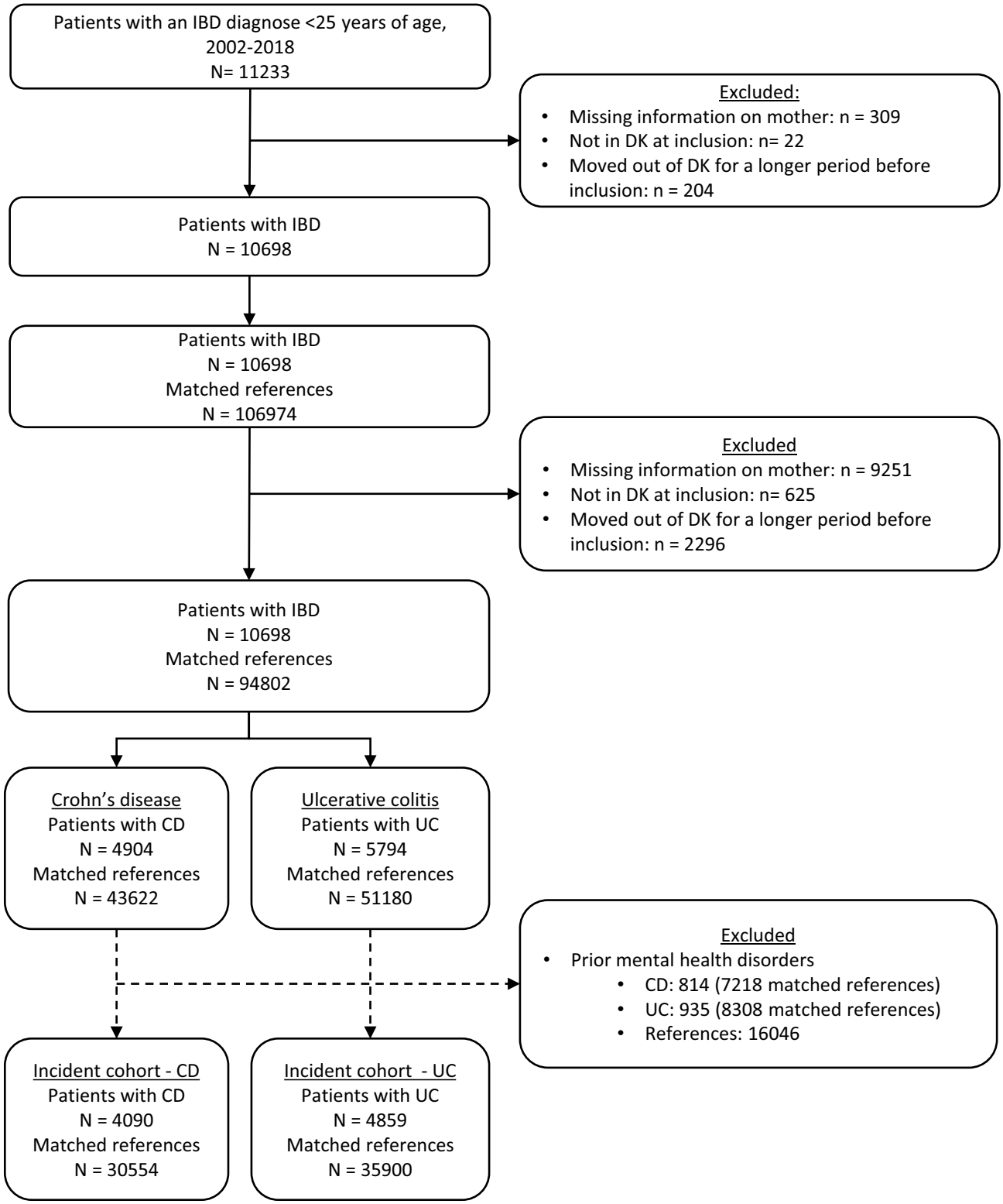

Figure 1 Flowchart.

Composite group	Subgroup	ICD-10 / ATC
Neurodevelopmental disorders	Intellectual disability	F70-F79
	Other developmental disorders	F80-83
	Autism spectrum disorders	F84.x excluding F84.2-84.4
	ADHD	F90.0 F98.8
	Central nervous system stimulants	N06BA
Psychotic disorders	Schizophrenia spectrum disorders	F20-F29
	Antipsychotic	N05A
Emotional disorders	Mood disorders	F30-F39
	Anxiety disorders	F40-F48+F93
	Antidepressants	N06A
	Anxiolytics	N05B
Diagnosis of other mental health disorders	Substance use disorders	F10-19
	Eating disorders	F50
	Personality disorders	F60-69
	Attachment disorders*	F94.x excluding F94.1
	ODD/CD*	F91 + F90.1
	Tic disorders*	F95
	Sedatives	N05C

*Not reported separately but part of the diagnosis of other mental health disorders

Figure 2 Overview of composite groups and subgroups of mental health disorders.

Neurodevelopmental disorders (eg, intellectual disability, autism, and ADHD) were evaluated separately as their pathogenesis differs from the other mental health disorders. They are characterized by being either congenital or developed in early childhood although they may be diagnosed later in life.

Contacts

Contact to psychiatric hospitals (in- or outpatient) was retrieved from the DNPR using codes 50 (psychiatry) and 52 (child and adolescent psychiatry) for Specialty. Contacts to psychologists or private practicing psychiatrists were retrieved from The National Health Insurance Service Registry, using the Specialty codes: 24 (psychiatrist), 26 (child and adolescents' psychiatrist), or 63 (psychologist) to identify the contacts. On a weekly basis the National Health Insurance Service Registry records activities of health professionals contracted within the public healthcare system, making it possible to identify visits, but not diagnostic codes.[25] The date of the contact was set to the Monday in the week the contact was recorded. Contacts were categorized as "yes" or "no" on a yearly basis from 5 years before to 5 years after the date of inclusion.

Follow-up

Participants were followed from the index date (date of diagnosis for the patients with IBD and their matched references) until the date of mental health diagnosis/first prescription, death, moving out of Denmark, when turning 30 years,

31.12.2019, or for references date of later IBD diagnosis whichever came first. When analyzing the composite endpoint, the date of the first diagnosis or the first prescription was used.

Covariates

Parental Education

Information on parental educational status was retrieved from the Population Education Register,[26] which contains information on the highest educational level achieved. The educational level was categorized using International Standard Classification of Education (ISCED)[32] into "low" (ISCED1-4 corresponding to primary education to upper secondary/Post-secondary non-tertiary education) and "high" (ISCED 5–8) (corresponding to short-cycle tertiary education to a doctoral or equivalent level).

Parental Mental Health Disorders

Parental mental health disorders were defined as having a psychiatric diagnosis: (ICD-8: 290.00–319.90 or ICD-10: F00-99) in DNPR up to 5 years prior to the index day. Separate variables for mother and father were constructed and categorized as "yes" or "no".

Statistical Analysis

To examine the incidence rates (IR) and incidence rate ratios (IRR) of mental health disorders and medicine use we used the incident cohorts where patients with prior mental health disorders (including neurodevelopmental disorders) were excluded. We performed the analyses separately for patients diagnosed with IBD in childhood and adolescence (<18 years) and in young adulthood (18–24), except for neurodevelopmental disorder where all patients with CD or UC were examined together. The IRR was calculated using Cox proportional hazard regression models with robust variance estimation and retaining information on matching groups by analyzing data in strata based on inclusion year and sex, thereby securing conditioning on sex, calendar time, and age at diagnosis.[33,34]

Depending on the mechanism behind the association between parental mental health disorder[19,35,36] or parental educational level[16,17] and mental health disorders, they can be either a confounder or effect modifier. Mechanisms such as shared genetics for IBD and mental health disorders[37] as well as socioeconomic position and IBD[38] have been suggested. Potential confounding was assessed by including the potential confounding factor in the model and comparing the IRR with the model solely adjusting for matching variables. To examine if parental mental health disorders or parental education modified the association between IBD and emotional disorder, we assessed the additive effect by calculating the relative excess risk due to interaction (RERI). Both analyses were performed with emotional disorders as the outcome, as this was the most common group of mental health disorders. The analyses were done separately for CD and UC.

To secure that the estimated results were not due to different contact patterns to mental health services for patients with IBD and references, we calculated the proportion of participants who had contacts with either psychiatric hospitals, private practicing psychiatrists, or psychologists 5 years prior to and 5 years after diagnosis on a yearly basis.

The data was collected through the Danish administrative registers. According to Danish legislation registry-based studies do not need approval from the Danish Health Research Ethics Committee. The study was registered in North Denmark Region's record of processing activities (2021–104). Other approvals are not necessary according to Danish laws when doing register-based cohort studies[39,40] (§14.2Health science questionnaire studies and health science registry research projects must only be notified to the scientific ethics committee system if the project includes human biological material.[40]). Data was analyzed in a pseudonymized form on Statistics Denmark's research machine, thereby complying with the General Data Protection Regulation.

All analysis was performed using STATA 18. The artwork was done in R.

Results

A total of 10,698 patients and 94,802 references were identified. Of the patients with IBD 4904 were diagnosed with CD and 5794 with UC. (Figure 1).

Crohn's Disease

The 4904 patients with CD were matched with 43,622 matched references. Of the patients with CD 2015 were diagnosed before 18 years of age and 2889 from 18 to 24 years of age. The median age was 14.6 for both patients and references in the group with patients diagnosed before 18 years of age, and 21.5 in the group between 18 and 24 years of age. Among patients diagnosed before 18 years of age, 198 (9.8%) had a mental health disorder (including neurodevelopmental disorders) before the IBD diagnosis compared to 1877 (10.2%) of references. For patients diagnosed from 18 to 24 years of age, the corresponding figures were 616 (21.3%) and 5472 (21.6%), respectively (Table 1).

A total of 202 (4.1%) patients with CD and 2258 (5.2%) CD references had neurodevelopmental disorders before the index day. The incidence rate of neurodevelopmental disorders after the index day was 3.35/1000 person-years (py) (CI95%: 2.74–4.09/1000py) for patients and 4.27/1000py (CI95%: 4.00–4.56/1000py) for references, and an incidence rate ratio of 0.81 (CI95%: 0.66–1.00). The overall lower risk of having a neurodevelopmental disorder was primarily due to a lower risk of receiving CNS stimulants (Table 2).

Excluding patients with prior mental health disorders, their matched references, and references with prior mental health disorders left 4090 patients with CD and 30,554 references in the analysis (Incident cohort). (Supplementary Table 2)

Patients with CD had a higher risk of being diagnosed with mental health disorders. Patients diagnosed before 18 years of age had a higher risk in the composite groups: emotional disorders and other disorders. This was primarily due to an elevated risk of anxiety disorders (IRR 1.58 (CI95%: 1.33–1.86)) and sedatives (IRR: 1.80 (CI95%: 1.45–2.24). (Figure 3; Supplementary Table 3). Patients with CD diagnosed from 18 to 24 years of age had a higher risk of all composite groups (psychotic disorders, emotional disorders, and other disorders). This was due to a higher risk of mood disorders (IRR: 1.55 (CI95%: 1.18–2.04)), anxiety (IRR: 1.40 (CI95%: 1.14–1.72)) for emotional disorders, and use of all types of psychotropic medication in all composite groups (Figure 3; Supplementary Table 3).

When examining the influence of parental mental health disorders or parental education on the most prevalent condition, emotional disorders, including each of the covariates (parental mental health disorder/parental education) in the model did not change the estimates (Supplementary Table 4). There was a negative additive interaction between lower parental education and CD (RERI: −0.35 (CI05%: (−0.65:-0.05)) (Supplementary Table 5).

For contacts to mental health services, there were no differences in admissions to psychiatric hospitals. Patients with CD had an increase in outpatient contact with psychiatric hospitals and contacts with private practicing psychiatrists 2 to 3 years after diagnosis. The contact with psychologists rose already in the years before diagnosis and peaked 2 years after diagnosis (Figure 4).

Ulcerative Colitis

A total of 5794 patients with UC and 51,180 matched references were identified. Of the patients with UC, 2009 were diagnosed before 18 years of age and 3785 from 18 to 24 years of age. The median age was 14.9 for patients and 14.8 for references in the groups with patients diagnosed before 18 years of age, and 21.7 and 21.6, respectively, in the groups from 18 to 24 years of age. In the group diagnosed before 18 years of age, 184 (9.2%) of patients with UC had a mental health disorder before the IBD diagnosis, while 1698 (9.4%) of references had a mental health disorder before the index date. For the age groups from 18 to 24 years of age, it was 751 (19.8%) and 6999 (21.2%), respectively (Table 1).

A total of 233 (4.0%) patients with UC and 2351 (4.6%) UC references had neurodevelopmental disorders before the index day. The incidence rate of neurodevelopmental disorders after the index day was 2.30/1000py (CI95%: 1.85–2.85/1000py) for patients and 3.94/1000py (CI95%: 3.70–4.18/1000py) for references, and the incidence rate ratio was 0.60 (CI95% 0.48–0.75). The overall lower risk of having a neurodevelopmental disorder was primarily due to a lower risk of being diagnosed with ADHD or receiving CNS stimulants (Table 2).

Excluding patients with prior mental health disorders, their matched references, and references with prior mental health disorders left 4859 patients with UC and 35,900 references in the analysis (Supplementary Table 2).

Patients with UC had a higher risk of being diagnosed with mental health disorders. Patients diagnosed before 18 years of age had a higher risk in the composite groups: emotional disorders and other disorders. This was primarily due to

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Table 1 Baseline Characteristics of Patients With Crohn's Disease and Ulcerative Colitis and Their Matched References (Cohort A) Divided Into Age Groups at Diagnosis: Diagnosed Before 18 years of Age or Diagnosed Between 18 and 24 years of Age. Figures are n and (Proportion) Unless Otherwise Stated

		Crohn's Disease				**Ulcerative Colitis**			
		Under 18		**18–24**		**Under 18**		**18–24**	
Factor	Level	Patient	Reference	Patient	Reference	Patient	Reference	Patient	Reference
N		2015	18,316	2889	25,306	2009	18,102	3785	33,078
Sex	Male	1070 (53.1%)	9768 (53.3%)	1171 (40.5%)	10,184 (40.2%)	990 (49.3%)	8909 (49.2%)	1713 (45.3%)	14,904 (45.1%)
	Female	945 (46.9%)	8548 (46.7%)	1718 (59.5%)	15,122 (59.8%)	1019 (50.7%)	9193 (50.8%)	2072 (54.7%)	18,174 (54.9%)
Age at inclusion, median (IQR)		14.6 (11.5, 16.6)	14.6 (11.4, 16.5)	21.5 (19.8, 23.0)	21.5 (19.8, 23.0)	14.9 (11.7, 16.7)	14.8 (11.6, 16.6)	21.7 (19.9, 23.3)	21.6 (19.9, 23.3)
Parent educational level	High	869 (43.5%)	7801 (43.0%)	1079 (37.7%)	9758 (39.1%)	937 (47.0%)	7561 (42.2%)	1502 (40.1%)	12,539 (38.5%)
	Low	1127 (56.5%)	10,338 (57.0%)	1786 (62.3%)	15,199 (60.9%)	1055 (53.0%)	10,362 (57.8%)	2243 (59.9%)	20,052 (61.5%)
Maternal mental health disorders		133 (6.6%)	1459 (8.0%)	145 (5.0%)	1838 (7.3%)	117 (5.8%)	1354 (7.5%)	178 (4.7%)	2296 (6.9%)
Paternal mental health disorders		82 (4.1%)	1111 (6.1%)	123 (4.3%)	1316 (5.2%)	80 (4.0%)	1066 (5.9%)	156 (4.1%)	1709 (5.2%)
Mental health disorders before index day		198 (9.8%)	1877 (10.2%)	616 (21.3%)	5472 (21.6%)	184 (9.2%)	1698 (9.4%)	751 (19.8%)	6999 (21.2%)

Table 2 The Number of Cases (n), and Person-years (Py) and the Incidence Rate Ratio (IRR) of Having Neurodevelopmental Disorder for Patients With Crohn's Disease (CD) or Ulcerative Colitis (UC). Neurodevelopmental Disorders are Based on the First Diagnosis/or Prescription of the Specific Disorders or Medication. Participants Can Be Present in More Than One Category

	CD	**CD - References**		**UC**	**UC - References**	**IRR UC**
Before index day						
Neurodevelopmental disorders	202 (4.1%)	2258 (5.2%)		233 (4.0%)	2351 (4.6%)	
After index day						
	CD	CD - Ref		UC	UC - Ref	
	n (person time/1000 person-years)	n (person time/1000 person-years)	IRR CD	n (person time/1000 person-years)	n (person time/1000 person-years)	IRR UC
Neurodevelopmental disorders	96(28,675)	922(215,835)	0.81 [0.66,1.00]	82(35,724)	1,048(266,278)	0.60 [0.48,0.75]
Intellectual disability	12(29,069)	56(219,837)	1.68 [0.90,3.14]	7(36,062)	55(271,027)	1.01 [0.46,2.22]
Other developmental disorders	5(29,088)	31(219,915)	1.32 [0.52,3.37]			-
Autism spectrum disorders	24(29,019)	167(219,409)	1.18 [0.77,1.81]	15(36,024)	164(270,613)	0.75 [0.44,1.27]
ADHD	35(28,974)	347(218,612)	0.79 [0.56,1.12]	29(35,944)	413(269,382)	0.55 [0.38,0.80]
Central stimulating medicine	56(28,848)	665(217,054)	0.65 [0.49,0.85]	62(35,849)	774(267,707)	0.61 [0.47,0.79]

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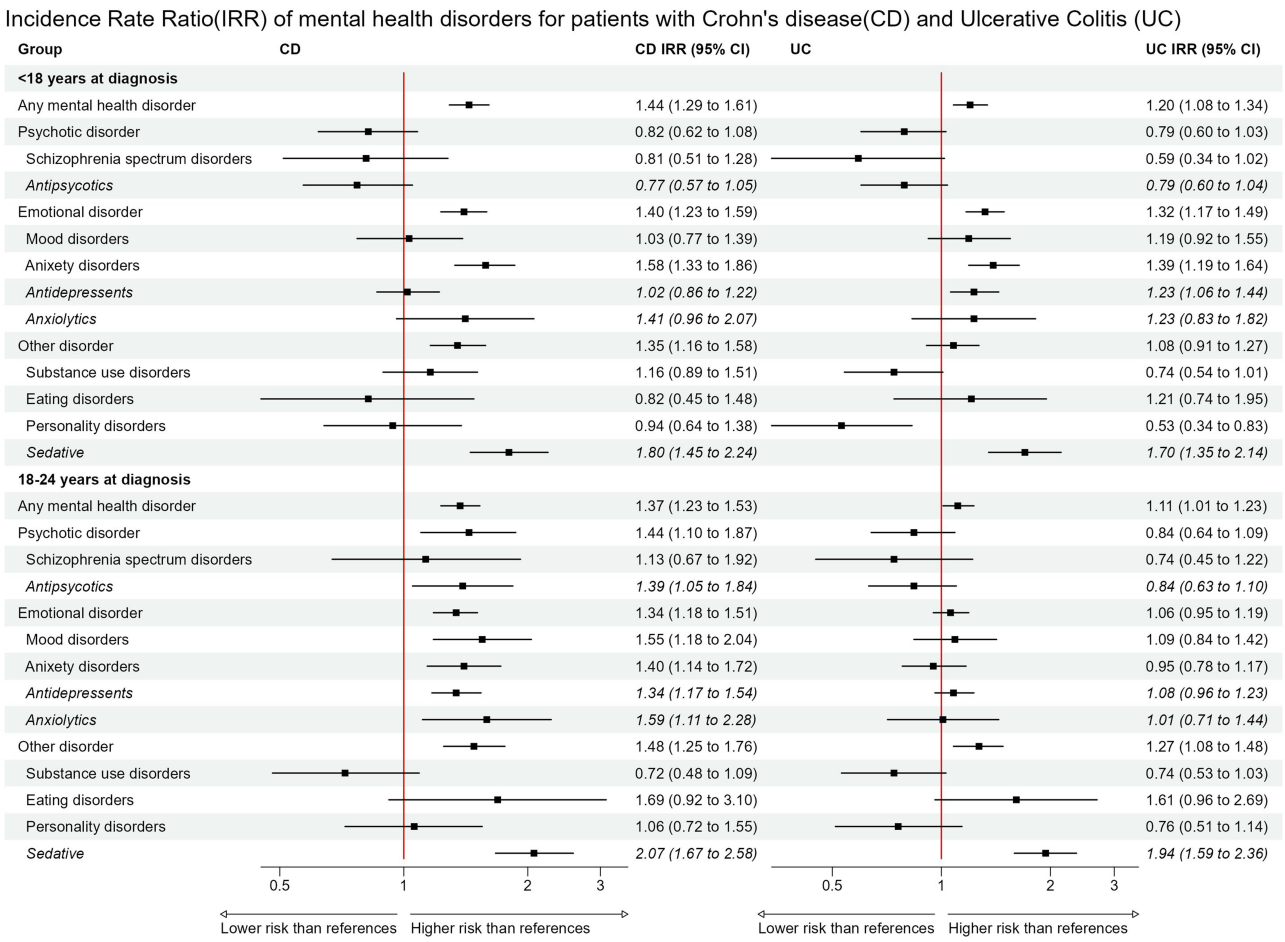

Figure 3 Incidence rate ratios of mental health disorders for patients with Crohn's disease and Ulcerative Colitis in the patients diagnosed before 18 years of age and between 18–24 years of age. The following groups were composite measures based on medication and diagnoses: any mental health disorders, psychotic disorders, emotional disorders, and other disorders. Medication is shown in italic.

an elevated risk of anxiety disorders (IRR: 1.39 (CI 95%: 1.19–1.64)) and higher use of antidepressants (IRR 1.23 (CI 95%: 1.06–1.44)) and sedatives (IRR: 1.70 (CI 95%: (1.35–2.14)). Patients with UC before 18 years of age had a lower chance of personality disorders (IRR: 0.53 (CI 95%: 0.34–0.83)) (Figure 3; Supplementary Table 3).

Patients with UC diagnosed from 18 to 24 years of age only had a higher risk in the composite group: other disorders. This was due to an increased risk of having sedatives (IRR 1.94 (CI 95%: 1.59–2.36)) (Figure 3; Supplementary Table 3).

When examining the influence of parental mental health disorders or parental education on the association between UC and emotional disorders, including each of the covariates (parental mental health disorder/parental education) in the model, it did not change the estimates (Supplementary Table 4). There was a negative additive interaction between lower parental education and UC (RERI −0.31 (CI95%: −0.54:-0.07), p = 0.05) and maternal mental health disorders (RERI: −0.74 (CI95%: −1.24:-0.24)) (Supplementary Table 5).

For contacts to mental health services, there were no differences in admissions to psychiatric hospitals. Patients with UC seemed to have fewer outpatient contacts, with a slight increase a year after diagnosis. The contact with psychologists rose after diagnosis, with a peak 2 years after diagnosis (Figure 4).

Discussion

In all groups patients with IBD had an increased risk of being diagnosed with mental health disorders. The main reason for this elevated risk was different for CD, UC, and the two age groups. A substantial proportion could also be attributed to a higher use of different medications. For patients with CD, diagnosed before 18 years of age, anxiety was the most

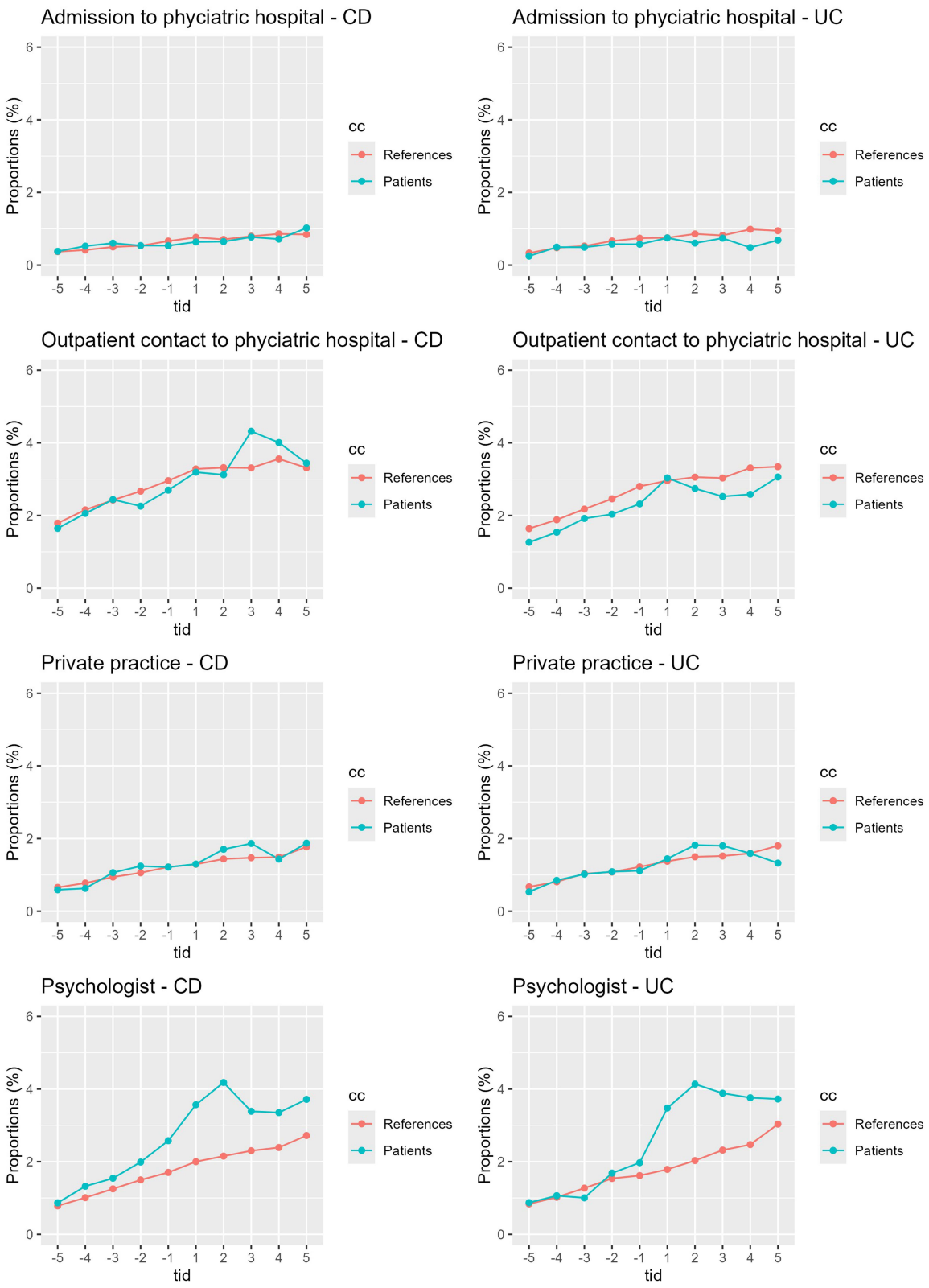

Figure 4 Proportion of patients with CD, UC or references that had contact with psychiatric hospitals (admission and outpatient) or with private practicing psychiatrists or psychologists in a period of 5 years before to 5 years after inclusion.

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predominant mental health disorder. Patients with CD, diagnosed between 18 and 24 years of age, were primarily diagnosed with all types of emotional disorders. For patients with UC anxiety was the predominant mental health disorder for patients diagnosed before 18 years of age, while patients diagnosed between 18 and 24 solely had an increased risk of receiving sedatives. There was a negative additive interaction for low parental education for both CD and UC and for maternal mental health disorders in the UC cohort.

The finding of an overall increased risk of mental health disorders in patients with CD and UC in both age groups is comparable to previous studies[9,11,12] There were some differences between CD and UC, especially in the group diagnosed from 18 to 24 years of age. When looking at the group of emotional disorders, both patients with CD and UC had elevated risk of anxiety except patients with UC diagnosed between 18 and 24 years of age. This is in line with Butwicka et al who in a Swedish nationwide register-based cohort study also found an elevated risk of anxiety in patients diagnosed before 18 years of age, using the same broad definition of anxiety.[11] In a Danish register-based cohort study Kappel et al did not find an association, but they used a more restricted definition of anxiety disorder limiting it to F41 "Other anxiety disorder", only.[10] In a cohort study using data from GPs, Cooney et al found an elevated risk for patients diagnosed with CD before 25 years of age, but not for patients with UC which is in line with our study for patients with UC diagnosed from 18 to 24 years of age.

We only found an increased risk of mood disorders in patients with CD diagnosed from 18 to 24 years of age. Cooney et al also found an elevated risk of depression in CD patients diagnosed before 25 years of age.[9] In contrast to other previous studies[10,11] we did not find an increased risk of mood disorders in patients diagnosed with CD or UC under 18 years of age compared to references. Kappel et al found an increased risk of depression[10] in patients with CD and UC diagnosed before 18 years of age, but the difference might be due to different definitions and that Kappel et al included both A and B diagnoses, while we only included A diagnoses. This means that Kappel et al also included patients seen at the hospital, where the primary reason for the visit was not depression. This might give a more correct estimate of the number of patients affected but more likely overestimates the association between disease and depression since patients more often have contact with the hospital than references. Using a composite measure (anxiety disorders, mood disorders, and antidepressants and anxiolytic medicine) Jansson et al found an increased risk of emotional disorders in both patients with CD and UC.[12] When making a composite measurement we also found an increased risk in all groups except for patients with UC diagnosed after 18 years of age.

Both patients with CD and UC had a decreased risk of being diagnosed with neurodevelopmental disorders, primarily due to a lower risk of ADHD and receiving CNS stimulants. Previous studies have shown no difference in neurodevelopmental disorders[12] or in ADHD.[10]

We did not find an increased risk of schizophrenia spectrum disorders in either patients with CD or UC. This is in line with Butwicka et al who did not find higher IRR for patients with IBD based on diagnosis for patients under 18 years of age.[11] In contrast to our study, Jansson et al using composite measures (diagnosis and medication) found an increased risk for children diagnosed before 18 years of age.[12] We only found an increased risk for the composite measure psychotic disorders in patients with CD diagnosed from 18 to 24 years of age for CD due to higher use of antipsychotics, where the use could be for another indication than schizophrenia spectrum disorders.

For a range of other conditions, we did not find an overall higher risk of being diagnosed with a mental health disorder, but a higher risk of receiving sedatives which resulted in a higher risk in the composite measurement of "Other disorder", like Jansson et al found.[12]

Patients with IBD in general had a higher risk of receiving psychotropic medicine than references, except for CNS stimulants. Similar results have been found among adult patients with IBD.[41] Especially in the therapeutic group Sedatives there was an elevated risk for both CD and UC in both age groups. Sedatives include melatonin, benzodiazepine-like drugs (Z-drugs), and benzodiazepine. The prevalence of sleep disturbances in patients with IBD is high,[42] however, in children it may not be more common in children with IBD than in healthy children.[43] Sleep disturbances in patients with IBD have been linked to anxiety, depression, and disease severity, but the direction of the association is unknown.[43] Our findings of an increased use might be due to higher levels of sleep disturbances, either secondary to emotional disorders or due to IBD-related symptoms. However, the increased use of psychotropic medication in patients with IBD including patients with UC who did not have other mental health disorders calls for further investigation.

There were no signs of confounding from parental mental health disorders or parental education. However, there were subadditive interactions for parental educational level for both CD and UC and for maternal mental health disorders in UC indicating that the combined effect of IBD and low parental education or mental health disorders, respectively, is less than expected in an additive model. This is surprising as we expected a positive additive effect for the combination of having IBD and parents with low education/mental health disorders since parental stress or few resources might increase the risk of mental health problems for the children. This study does not provide an explanation for this. It could be speculated whether patients with IBD whose parents have low education or have mental health disorders might be underdiagnosed, as only registered diagnosis or reimbursed medicine is included. However, this finding needs further investigation.

Patients with IBD did not have more frequent admission to psychiatric hospitals. There was a small peak in outpatient contacts for patients with CD, but a lower level for patients with UC, indicating that the higher number of diagnoses was not due to patients having easier access to psychiatric hospitals or differences in referral patterns among GPs. Patients with IBD had more contacts with psychologists, which may be explained by the reimbursement possibility for patients with severe disease or a higher incidence of minor mental health disorders. However, patients with CD had a rise in contacts prior to IBD diagnosis, suggesting symptoms of minor mental health disorders before diagnosis.

Strengths and Weaknesses

This study has several strengths. The Danish registers are regarded as high quality and allow for a long period of follow-up, with low levels of missing and loss to follow-up.[30,44] The information is gathered independently of the study question, minimizing differentiated misclassification of the outcome.

Even though the study design has many strengths there are some weaknesses. No studies have validated IBD diagnosis in children in the DNPR, but in a small subsample of patients in the validation study by Lo et al the validity of using one diagnosis with either CD or UC was high (For CD the positive predictive value was 0.86 and 0.93 for UC).[45]

Only patients seeking help would have a diagnosis or a prescription for medicine. Furthermore, intellectual disabilities and other minor mental health disorders not requiring specialized assessment or medical treatment, could have been managed by educational services or GPs, where the diagnosis do not appear in the DNPR. Therefore, there might be an underestimation of the incidence. The validity of diagnosis of psychiatric diagnoses in the DNPR for children and adolescents ranges[46–49] from 75% (depression)[46] to 86% (hyperkinetic disorders),[49] meaning that some patients would be misclassified as having a mental health disorder. However, these patients had contact with psychiatric hospitals indicating some degree of psychiatric symptoms.

It could be hypothesized that patients to a higher degree than references would be referred to psychiatric departments or diagnosed with eg, anxiety. However, we also examined the contact patterns for the two groups and found that patients with IBD were not more likely to be seen at the hospital. Furthermore, as we only included A-diagnosis (primary diagnosis of a visit), B-diagnosis for patients with IBD, who had a diagnosis from the educational services or in the private or primary sector would not be included, minimizing the risk of differential misclassification.

When using the registers, the time of diagnosis is not the same as the time of onset. Therefore, it is possible that some individuals would have had symptoms of debut of disease before they were included in the study. In the child and adolescent psychiatry the time from first symptoms to a visit to the hospital and a diagnosis can be very long, with delays in diagnosis of emotional disorders up to three years,[50] however, the waiting time would probably not depend on the IBD. Furthermore, the indication for use of psychotropic medication was not available and information on medicine only contains information on reimbursed medication. There is a risk that patients who had a prescription issued but did not redeem it at the pharmacy would be misclassified as not having a mental health disorder. However, this proportion is expected to be low, and it would only be the milder cases of mental health disorders. The misclassification would be non-differential.

Conclusion

Patients with CD and UC have a higher risk of any mental health disorders, primarily due to an elevated risk of emotional disorders and a higher use of psychotropic medication. Further investigation of the high use of psychotropic medication and the subadditive interaction of parental education level on the risk of emotional disorders is needed. It is important to recognize comorbid mental health disorders in the future treatment of patients with IBD – especially in patients with CD.

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