

*Minna Kyllönen*

PROGNOSIS OF JUVENILE  
IDIOPATHIC ARTHRITIS:  
MORTALITY AND PSYCHIATRIC  
MORBIDITY AMONG CHILDREN,  
ADOLESCENTS AND YOUNG  
ADULTS FROM A CASE-  
CONTROL STUDY PERSPECTIVE

UNIVERSITY OF OULU GRADUATE SCHOOL;  
UNIVERSITY OF OULU,  
FACULTY OF MEDICINE





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**Kyllönen, Minna, Prognosis of juvenile idiopathic arthritis: mortality and psychiatric morbidity among children, adolescents and young adults from a case-control study perspective.**

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***Abstract***

During this millennium, the survival of juvenile idiopathic arthritis (JIA) has greatly improved. However, chronic illness such as JIA appears to have an impact on the psychosocial development and mental health of children and adolescents. The aims of this thesis were to evaluate mortality, causes of death, mental and behavioural disorders and the use of psychotropic medications in patients with recent-onset juvenile idiopathic arthritis (JIA) patients compared to population controls.

The research material of this case-control study was selected from national registers. The cases, JIA patients with the International Classification of Diseases (ICD-10) codes of M08.0–M08.9 or M09.0\*L40.5, were collected from the national reimbursement register. For each case, the National Population Registry picked three controls matched for age, sex and residence. Mortality data were picked from Statistics Finland, psychiatric diagnoses (ICD-10 codes F10–98) from the Care Register of National Institute for Health and Welfare, and psychotropic medication was collected from the national prescription register.

During the follow-up time, 4,180 JIA patients (62% females) received special reimbursement for JIA medications. Mean age at diagnosis was 8.3 years. The median follow-up time was 6.6 years (IQR 3.1–10.5). The patients were compared with 12,511 controls. The relative risk of death in the JIA group was not elevated compared to controls. However, the risk of psychiatric morbidity was higher among the JIA patients than the controls, especially in females. In addition, compared to controls, females with JIA purchased more antidepressants than males with JIA.

In conclusion, this study provides novel information on the prognosis of JIA. Mortality in patients with JIA is the same as in controls, but psychiatric morbidity is increased among children, adolescents and young adults compared to controls.

***Keywords:*** adolescent, antidepressants, chronic disease, juvenile arthritis, mental health, mortality, psychiatric disorders, psychotropic medication, suicide



# **Kyllönen, Minna, Lastenreuman ennuste: lasten, nuorten ja nuorten aikuisten kuolleisuus ja psykiatrinen sairastavuus tapaus-verrokki tutkimuksen näkökulmasta.**

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta

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## ***Tiivistelmä***

Lastenreuman eloonjäämisennuste on parantunut tämän vuosituhaten aikana. Kroonisella sairaudella kuten lastenreumalla on kuitenkin vaikutusta eri-ikäisten lasten ja nuorten psyykkiseen kehitykseen ja mielenterveyteen. Tämän tutkimuksen tarkoituksena oli kartoittaa lastenreumapotilaiden kuolleisuutta, kuolinsyitä, mielenterveyden- ja käyttäytymisen häiriöitä sekä psyykenlääkkeiden käyttöä verrokkiväestöön verrattuna.

Tutkimusmateriaali tähän tapaus-verrokkitutkimukseen kerättiin kansallisista rekistereistä. Tapaukset eli lastenreumapotilaat (diagnosikoodeilla M08.0–M08.9 tai M09.0\*L40.5) kerättiin Kansaneläkelaitoksen (Kela) erityiskorvattavuusrekisteristä. Jokaista tapausta kohti Väestörekisterikeskus poimi kolme väestöverrokkia, jotka oli kaltaistettu iän, sukupuolen ja asuinpaikan suhteen. Kuolleisuusdata saatiin Tilastokeskuksesta. Kaikki seuranta-aikana ilmaantuneet psykiatriset diagnoosit (ICD-10-koodit F10–98) kerättiin Terveys- ja hyvinvoinnin laitoksen hoitoilmoitusrekisteristä (Hilmo) ja psyykenlääkkeiden ostokerrat Kelan lääkeostorekisteristä.

Seuranta-aikana 4180 lastenreumapotilasta (62 % naisia) sai erityiskorvattavuuden reumalääkityksestä. Keski-ikä diagnosihetkellä oli 8,3 vuotta. Keskimääräinen seuranta-aika oli 6,6 vuotta (IQR 3,1–10,5). Potilaita verrattiin 12 511 verrokkiin. Kuoleman riskissä ei ollut eroa verrokkeihin, mutta lastenreumapotilailla, erityisesti naispotilailla, oli verrokkeja suurempi riski sairastua psykiatriseen sairauteen. Verrokkeihin verrattuna naispotilaat ostivat lisäksi enemmän masennuslääkkeitä kuin miespotilaat.

Tutkimus tarjoaa uutta tietoa lastenreumapotilaiden ennusteesta. Kuolleisuus ei ole lisääntynyt lastenreumapotilailla verrattuna verrokkiväestöön, mutta lapsilla, nuorilla ja nuorilla aikuisilla lastenreumapotilailla on enemmän psykiatrista sairastavuutta.

*Asiasanat:* antidepressantit, itsemurha, krooninen sairaus, kuolleisuus, lastenreuma, mielenterveys, nuoruusikä, psykiatriset häiriöt, psykiatri



*To all children and adolescents with juvenile idiopathic  
arthritis*



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Oulu, 6.12.2022

Minna Kyllönen



## Abbreviations

ACR	American College of Rheumatology
ADHD	Attention-Deficit/Hyperactivity Disorder
ANA	antinuclear antibody
APA	American Psychological Association
ATC	Anatomical Therapeutic Chemical Classification System
BASC	Behavior Assessment System for Children
BDI	Beck Depression Inventory
CARRA	Childhood Arthritis and Rheumatology Research Alliance Registry
CBCL	Child Behavior Checklist
CCP	cyclic citrullinated peptide
CDI	Children's Depression Inventory
CI	confidence interval
CTLA4	cytotoxic T-lymphocyte-associated protein 4
DMARD	Disease Modifying Antirheumatic Drugs
DSM	Diagnostic and Statistical Manual of Mental Disorders
EQ5D	EuroQol-5-Dimension
ERA	enthesitis-related arthritis
FOXP3	forkhead box P3
HAM-D	Hamilton Rating Scale for Depression
HLA	Human Leukocyte Antigen
HR	hazard ratio
ICD	International Classification of Diseases
IL	interleukin
ILAR	International League of Associations for Rheumatology
IQR	interquartile range
IRR	incidence rate ratio
JIA	juvenile idiopathic arthritis
JPFS	juvenile primary fibromyalgia syndrome
KSADS-PL	Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version
MFQ	Mood and Feeling Questionnaire
NSAID	non-steroidal anti-inflammatory drug
p	p-value
PID	pediatric primary immunodeficiency

PTPN22	protein tyrosine phosphatase nonreceptor type 22
RCMAS	Revised Children's Manifest Anxiety Scale
RF	rheumatoid factor
RR	risk ratio
SAFA-A	Self- Administered Psychiatric Scales for Children and Adolescents
SASK	Social Anxiety of Children
SCARED	Screen for Child Anxiety Related Emotional Disorders Questionnaire
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
SF-12	Short Form 12-item health questionnaire
SF-36	Short Form 36-item health questionnaire
SII	Social Insurance Institution of Finland
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TNF-alpha	tumor necrosis factor alpha
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

## List of original publications

- I Kyllönen M.S., Kautiainen H., Puolakka K., & Vähäsalo P. (2019). The mortality rate and causes of death among juvenile idiopathic arthritis patients in Finland. *Clinical and Experimental Rheumatology*, 37(3), 508–511.
- II Kyllönen M.S., Ebeling H., Kautiainen H., Puolakka K., & Vähäsalo P. (2021). Psychiatric disorders in incident patients with juvenile idiopathic arthritis-a-case-control cohort study. *Pediatric Rheumatology Online Journal*, 19(1). <https://doi.org/10.1186/s12969-021-00599-x>
- III Kyllönen M.S., Kautiainen H., Jääskeläinen E., Puolakka K., & Vähäsalo P. Use of Psychotropic Medication in Incident Juvenile Idiopathic Arthritis Patients from 2000–2014 — A Case-Control Cohort Study. *Clinical and Experimental Rheumatology*. In *press*.



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# 1 Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous inflammatory rheumatic disease with onset before the age of 16 years. It is classified into seven categories according to the criteria of ILAR (International League of Associations for Rheumatology)(Giancane et al., 2016). All seven subtypes of JIA vary phenotypically from each other and differ to some extent in their immunological and genetic mechanism of origin, but they also have similarities in their pathogenesis (Prakken et al., 2011; Ravelli & Martini, 2007). In addition to arthritis, manifestations such as uveitis can lead to reduced quality of life in patients with JIA (Glerup et al., 2020; Ravelli & Martini, 2007; Wallace, 2006).

During the last two decades, the mortality of JIA has decreased, but the numbers vary due to different research settings (Baum & Gutowska, 1977; Hashkes et al., 2010; Koivuniemi & Leirisalo-Repo, 1999; Krause et al., 2016; Laaksonen, 1966; Minden et al., 2002). In patients with JIA, accidental deaths have increased from the 1970s to the 2000s while amyloidosis-related deaths have decreased simultaneously with the increased use of more effective antirheumatic drugs (Immonen et al., 2008; Peden et al., 2008; Savolainen & Isomaki, 1993).

According to previous literature, children and adolescents with JIA are more likely to be at the risk of experiencing mental health problems than healthy children and adolescents of the same age (Barth et al., 2016; Bomba et al., 2013; Flato et al., 2003; Memari et al., 2016; Mullick et al., 2005; Vandvik, 1990). Previous studies based on psychiatric interviews (Mullick et al., 2005; Vandvik, 1990), self-reported questionnaires (Billings et al., 1987; Bomba et al., 2013; Ding et al., 2008; Hanns et al., 2018; Huygen et al., 2000; Margetic et al., 2005; Memari et al., 2016; Packham, 2002; Raab et al., 2013; Russo et al., 2012; Stevanovic & Susic, 2013; Tarakci et al., 2011; Vuorimaa et al., 2008) and quality of life studies (Arkela-Kautiainen et al., 2005; Barth et al., 2016; Flato et al., 2003; Foster et al., 2003; Oliveira et al., 2007; Ostile et al., 2010; Peterson et al., 1997) have reported different results on the mental and behavioral problems of JIA patients. The varying results are mostly due to differences in study methods and differences between research groups (disease state/disability, age, medication and disease duration).

According to two small clinical assessment studies depression and anxiety are the most common mental disorders in patients with JIA (Mullick et al., 2005; Vandvik, 1990). In addition, previous self-reported questionnaire-based studies have found high prevalence of anxiety and depression symptoms in JIA (Barth et al., 2016; Bomba et al., 2013; Flato et al., 2003; Hanns et al., 2018; Huygen et al.,

2000; Margetic et al., 2005; Memari et al., 2016; Packham, 2002; Russo et al., 2012; Stevanovic & Susic, 2013; Tarakci et al., 2011; Vuorimaa et al., 2008). These are common disorders in general population as well (Merikangas et al., 2009; Paananen et al., 2013). A few studies have evaluated behavioral problems and found increased numbers of these problems in JIA patients (Ding et al., 2008; Huygen et al., 2000; Memari et al., 2016; Russo et al., 2012).

Research data on the use of psychotropic medication in JIA patients is limited. One previous Finnish study on adolescent patients with JIA and pain showed that 8.7% had purchased antidepressants (Rebane et al., 2019). However, in general population, the use of antidepressants and antipsychotics has grown globally over the last ten years among children and, especially among adolescents (Bonati & Clavenna, 2005; Haapasalo-Pesu et al., 2016; Hálfðánarson et al., 2017; Hoffmann et al., 2014; Højlund et al., 2019; John et al., 2016; Kalverdijk et al., 2017; Sarginson et al., 2017; Steinhausen, 2015).

The research data on mental and behavioral disorders and psychotropic medication use in children and adolescents with JIA is scarce. However, it is important to get information about the extent of these issues because the information contributes to recognizing mental and behavioral disorders in patients and referral to treatment. It is also important to find out the mortality and causes of death among patients with JIA in this millennium, which will help to obtain fresh information on the prognosis of JIA. This longitudinal case-control study provides information on mortality and causes of death and new information on the whole spectrum of mental and behavioral disorders in JIA and the influence of gender and the age at JIA onset on psychiatric morbidity. In addition, it provides new information on the use of psychotropic medication in JIA.

## 2 Review of literature

### 2.1 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is defined as a heterogeneous group of arthritis with unknown cause that persists for more than 6 weeks, begins before 16 years of age and when other known conditions are excluded (Petty et al., 2004). History of arthritis in children dates back to the 19<sup>th</sup> century, when rheumatic fever, Still's disease and chronic arthritis were described (Schaller, 2005). The first publication mentioning children with chronic arthritis from 1897 was by Still (Schaller, 2005). Pediatric rheumatology as a subspeciality has developed since the 1970s (Schaller, 2005).

#### 2.1.1 Classification

The first classifications of JIA were published in the early 1970s by the American College of Rheumatology (ACR) and by the European Alliance of Associations for Rheumatology (formerly known as the European League Against Rheumatism) (Rumsey & Laxer, 2020). The International League of Associations for Rheumatology (ILAR) developed the first uniform criteria for JIA classes in the mid-1990s and since then, two updated versions have appeared; the latest is from the year 2001 (Petty et al., 2004; Rumsey & Laxer, 2020).

The ILAR classification criteria from 2001 currently in use, which also serve as diagnostic criteria, are shown in Table 1 (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007). The most frequent subtype is oligoarthritis (Giancane et al., 2016; Petty, 2001; Petty et al., 2004; Ravelli & Martini, 2007). All seven subtypes of JIA may manifest throughout childhood, but the incidence rates of enthesitis-related arthritis and polyarthritis (RF-positive) peak in late childhood or adolescence (Giancane et al., 2017; Petty et al., 2004; Ravelli & Martini, 2007). Females make up the majority in all subtypes except enthesitis-related arthritis and systemic arthritis (Giancane et al., 2016; Petty, 2001; Petty et al., 2004; Ravelli & Martini, 2007).

An international and multi-professional group has made new proposals for criteria which take into account some JIA category with similarity to some adult disease (Martini et al., 2019). In these criteria, JIA is divided into six groups of inflammatory disorders: (A) systemic JIA, (B) RF-positive JIA, (C) enthesitis-

related JIA, (D) early-onset ANA-positive JIA, (E) other JIA, (F) unclassified JIA; other known conditions that begin before the 18<sup>th</sup> birthday and persist for at least 6 weeks are excluded (Martini et al., 2019).

**Table 1. ILAR classification criteria for juvenile idiopathic arthritis (JIA) adapted according to Petty et al. 2004, Ravelli and Martini 2007 and Giancane et al. 2016.**

JIA class	The relative frequency	Onset age	Gender ratio
Systemic arthritis	4–7%	throughout childhood	F=M
Oligoarthritis (formerly called pauciarticular) <i>Persistent</i> (no additional joint involvement after the first six months of illness) <i>Extended</i> (more than four joints are ultimately affected after the first six months of illness)	27–56%	peak at 2–4 years	F>M
Polyarthritis RF-negative	11–28%	early peak at 2–4 years and later peak at 6–12 years	F>M
Polyarthritis RF-positive	2–7%	Late childhood or adolescence	F>M
Psoriatic arthritis	2–11%	early peak at 2–4 years and later peak at 9–11 years	F>M
Enthesitis-related arthritis	3–11%	Late childhood or adolescence	M>F
Undifferentiated arthritis	11–21%		F>M

F=female, M=male, RF= rheumatoid factor

### 2.1.2 Epidemiology

The most commonly reported prevalence of JIA varies between 16 and 150 per 100,000 in developed countries (Ravelli & Martini, 2007). In addition, a systematic review from Europe reported a prevalence from 3.8 to 400/100,000 children in 2010 (Thierry et al., 2014). The wide variance in numbers must be due to differences in study design/methods, such as patient selection based on different diagnostic criteria (Thierry et al., 2014).

The incidence of JIA varies in different countries, too. In 2010, the reported incidence of JIA was 1.6–23 per 100,000 children in Europe (Thierry et al., 2014).

A longitudinal population study from the Nordic countries found that the incidence was 15 per 100,000 children/year according to the ILAR criteria, varying from 7 in Iceland, 19–23 in Norway, 9–16 in Denmark, 15 in Sweden to 21 in Finland (Berntson et al., 2003). In addition, a Finnish study reported that the incidence was 22.7/100,000 in a region of southern Finland in 1995 and the number was higher than in earlier years (1980, 1985 and 1990) (Kaipiainen-Seppänen & Savolainen, 2001).

### **2.1.3 Etiopathogenesis**

JIA is an autoimmune disease, the origin of which is affected by multiple genetic, environmental and immunological factors (Horton & Sheno, 2019; Prahalad & Glass, 2008). There are some similarities but also differences in the pathogenesis of different subtypes of JIA (Prakken et al., 2011).

#### *Immunological mechanism*

A genetically predisposed person reacts inappropriately towards a self-antigen due to the influence of an unknown environmental factor (Prakken et al., 2011). This reaction causes the activation of adaptive specific immunity (B and T-lymphocytes) and innate (non-specific) immunity (Prakken et al., 2011; Prakken & Albani, 2009). The autoreactive immune response leads to tissue damage (Prakken et al., 2011). In addition, imbalance between proinflammatory T-helper cells and anti-inflammatory T-cells like FOXP3 regulatory cells is part of this autoimmune phenomenon (Pralhad & Glass, 2008; Prakken et al., 2011; Prakken & Albani, 2009). Proinflammatory cytokines such as interferons, interleukins and tumor necrosis factor alpha are seen in synovial fluid and plasma of patients with JIA (Pralhad & Glass, 2008; Prakken et al., 2011; Prakken & Albani, 2009). Cytokines such as tumor necrosis factor alpha and interleukin 1 and 6 (interleukins especially in systemic arthritis) are important treatment targets in modern biologic medication for JIA (Prakken et al., 2011).

In the autoimmune process, humoral immunity produces anti-CCP and rheumatoid factor (RF) which are an important part of pathogenesis and inflammation of RF-positive arthritis (Prakken et al., 2011; van Rossum et al., 2003; Zaripova et al., 2021). In addition, antinuclear antibodies (ANA) have been found in patients with JIA, with the exception of ERA and systemic arthritis (Zaripova et al., 2021).

Several interleukins such as 17 and 23 have been reported to play a relevant role in the pathogenesis of enthesitis-related arthritis (ERA) (Colbert, 2010). In addition, 60–90% of ERA patients have a genetic association with HLA-B27 (Colbert, 2010). HLA-B27-proteins are an important part of the immune system, helping the body to distinguish its own cells from foreign structures (Colbert, 2010). In addition, the pathogenesis of juvenile psoriatic arthritis may resemble enthesitis-related arthritis or antinuclear antibody positive oligoarthritis disease (Prakken et al., 2011).

### *Genetic factors*

Several studies have shown a strong genetic link to pathogenesis of JIA (Hinks et al., 2017; Prahalad & Glass, 2008; Prakken et al., 2011; Woo & Colbert, 2009). This genetic link is supported by twin and family studies (Prahalad & Glass, 2008; Woo & Colbert, 2009). Twin studies have reported that the probability of a monozygotic twin pair developing JIA is 25–40% (concordance rate) (Baum & Fink, 1968; Prahalad, 2006; Savolainen, 2000). A Finnish study reported an increased number of JIA cases in parents whose children had JIA (Säilä et al., 2003). In addition, another Finnish study found 41 multicase families with 88 affected siblings with JIA (Savolainen, 2000). Furthermore, a non-twin study showed an elevated risk for ANA and RF positivity in siblings of patients with JIA,  $p < 0.001$  (Moroldo et al., 2004).

Numerous non-HLA genes—CTLA4 (T-cell regulator), PTPN22 (B- and T-cell activity regulator), genes that code for IL-6, IL-1A, TNF-alpha cytokines etc. — have been found that influence the susceptibility to the etiopathogenesis of JIA (Palman et al., 2018; Prahalad & Glass, 2008; Prakken et al., 2011; Woo & Colbert, 2009). In addition, associations between JIA subtypes and HLA genes have been reported in several studies (Prahalad et al., 2000; Prakken et al., 2011; Thompson et al., 2004; Woo & Colbert, 2009). The genes encoding class I HLA (HLA A, B and C) molecules have been reported to associate with enthesitis-related arthritis (HLA-B27) and the JIA subtypes with early onset (HLA-A2) (Hinks et al., 2017; Prahalad & Glass, 2008). In addition, polyarticular JIA, systemic JIA, oligoarticular JIA and psoriatic arthritis are reported to associate with genes encoding class II HLA (HLA-DR, DP and DQ) molecules (Hinks et al., 2017; Prahalad & Glass, 2008). A worldwide genetics study on HLA molecules reported that juvenile RF-negative arthritis is genetically similar to juvenile oligoarthritis and both have genetic similarities to adult seronegative rheumatoid arthritis (Hinks et al., 2017).

In addition, juvenile RF-positive arthritis HLA genes are associated with some adult seropositive arthritis HLA genes (Hinks et al., 2017).

Genome-wide analysis reported that chromosome region 7q11 is associated with early polyarticular arthritis and 19p13 with pauciarticular arthritis (Thompson et al., 2004). In addition, chromosome 1 locus has been reported to relate to the pathogenesis of systemic arthritis (Ombrello et al., 2017).

### *Environmental factors*

Infectious agents and vaccination could be a trigger for an autoimmune reaction in JIA (Berkun & Padeh, 2010; Prakken et al., 2011). According to literature, influenza A, rubella, mumps, parvovirus B19, coxsackie and bacteria such as mycoplasma pneumoniae, borrelia burgdorferi and streptococcus group A have been suspected to initiate an autoimmune reaction (Berkun & Padeh, 2010; Prakken et al., 2011).

Antibiotics can change the microbiota in the gut due to an imbalance between good and harmful bacteria and inflammation in the mucosa (Arvonen et al., 2016). High levels of bacteria (such as Bacteroidetes) have been seen among some newly diagnosed JIA patients (Arvonen et al., 2016; Horton & Shenoi, 2019; Tejesvi et al., 2016). Increased risk of JIA has been reported before two years of age in children who have been exposed to one or more antibiotics, especially lincosamides and cephalosporins (Arvonen et al., 2015). In addition, a Finnish study reported that cow milk allergy was associated with JIA, especially in boys who were diagnosed with JIA before three years of age (Arvonen et al., 2017).

Stressful life events (adoption, family difficulties, divorce, death, separation) and perinatal factors (mother's smoking during pregnancy) could activate the immune system and act as a trigger for JIA (Berkun & Padeh, 2010).

However, breast feeding and numerous siblings in the family might modify the immunological system (Palman et al., 2018). The connection between these factors is not certain, but breast feeding and higher exposure to pathogens due to siblings seem to improve the immunological system (Palman et al., 2018).

#### **2.1.4 Clinical manifestation**

All seven subtypes of JIA vary phenotypically from each other. Usually, incidence is higher in females than in males (Table 1) (Ravelli & Martini, 2007).

Oligoarthritis disease is the most common subtype of JIA and it occurs in early childhood, more often in girls than in boys (Ravelli & Martini, 2007). It is divided

into two groups (Table 1) and presents as asymmetrical arthritis (during the first six months of disease or after the first six months of illness), high levels of positive antinuclear antibody and high risk of chronic and usually asymptomatic uveitis (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007).

Rheumatoid factor-negative polyarthritis is the second most common subtype of JIA and usually breaks out throughout childhood (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007). It is defined as a disease that affects five or more joints during the first six months of illness (Table 1) (Ravelli & Martini, 2007). It may be like oligoarthritis (antinuclear antibody positive, iridocyclitis, early age at onset, asymmetric arthritis) or like adult RF-negative disease (symmetric arthritis and later onset) (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007).

RF-positive arthritis, a rare subtype of JIA, breaks out most commonly in late childhood or in adolescence, and it is similar to adult rheumatoid arthritis (symmetrical arthritis) (Table 1) (Petty et al., 2004). The disease can lead to accelerated growth of the inflamed joint or retardation in general growth (B. Prakken et al., 2011). Early erosive bone changes and rheumatoid nodules are possible in this disease (Ravelli & Martini, 2007).

Among JIA subtypes, the relative frequency of psoriatic arthritis and enthesitis-related arthritis (ERA) is about 2–11% and they resemble each other in phenotype (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007).

Most patients with ERA are males and over six years of age (Table 1) (Ravelli & Martini, 2007). They usually have arthritis of the low extremities, hip arthritis, sacroiliitis, Achilles tendinitis, plantar fasciitis or other enthesitis (inflammation and tenderness at the point of insertion or at the ligaments) and acute uveitis in 24% of patients (Giancane et al., 2016; Hayworth et al., 2019; Petty et al., 2004; Ravelli & Martini, 2007). Usually, 60–90% of patients with ERA are HLA-B27 antigen positive, which predicts inflammation in small joints such as talar and subtalar joints and extended disease in boys and inflammation in the skeleton in both genders (Colbert, 2010). However, RF and antinuclear antibody are negative in these patients (Colbert, 2010; Giancane et al., 2016).

Psoriatic arthritis is a disease whose diagnosis requires a typical psoriatic rash, and in the absence of a rash, arthritis and any two of the following symptoms: dactylitis (sausage-like swelling in the fingers or toes), nail pitting, or family history of psoriasis in a first-degree relative (Table 1) (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007). Uveitis has been reported in 9% of psoriatic arthritis patients and HLA-B27 positivity in 12% of patients (Hayworth et al., 2019; Rumsey et al., 2021). It usually occurs in early or later childhood and resembles

RF-negative polyarthritis, oligoarthritis or enthesitis-related arthritis (ERA) in its symptoms (Ravelli & Martini, 2007).

Systemic juvenile arthritis is a rare and severe autoinflammatory disease which usually breaks out at any time in childhood in both genders (Ravelli & Martini, 2007). It differs from other subtypes in its symptoms and its pathogenesis (overrepresented IL 1 and 6) (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007). The most common features are periodic fever, lymphadenopathy, enlargement of the liver or spleen, serositis, erythematous, symmetrical and polyarticular arthritis (Giancane et al., 2016; Petty et al., 2004; Ravelli & Martini, 2007). It may lead to a life-threatening macrophage activation syndrome in 5–8% of those with systemic arthritis (Ravelli & Martini, 2007). In addition, it can lead to physical impairment due to arthritis and systemic inflammation (Shenoi et al., 2018).

About one-fifth of JIA patients are diagnosed with undifferentiated arthritis, which is defined as a disease whose category includes those patients who do not meet any criteria of the above classifications or who meet more than one (Giancane et al., 2016; Petty et al., 2004).

### **2.1.5 Uveitis**

Uveitis is an intraocular inflammation in the iris, ciliary body or/and choroids (Zeboulon et al., 2008). Iridocyclitis (anterior uveitis) is the most common subtype of uveitis in patients with JIA (Hayworth et al., 2019). Early onset arthritis, antinuclear antibody positivity and female gender are risk factors for this intraocular inflammation (Ravelli & Martini, 2007). A meta-analysis reported that uveitis was most common in Europe, with a prevalence of 14% (Hayworth et al., 2019). The corresponding percentages were 11% in North-America, 12% in the Middle East and 7% in Asia (Hayworth et al., 2019). In the Nordic countries, 20.5–22.1% of patients with JIA have been reported to have uveitis (Nordal et al., 2017, Rypdal et al. 2021). It can lead to eye complications: cataract, glaucoma and even blindness (Moorthy et al., 2010; Nordal et al., 2017; Ravelli & Martini, 2007; Rypdal et al. 2021; Wallace, 2006).

Research data on mental health and children with JIA-associated uveitis is limited to only one study. The study did not find clinically significant anxiety and depression among children (McDonald et al., 2022) .

### **2.1.6 Treatment**

Pharmacotherapy for JIA dates back to the 20<sup>th</sup> century when antimalarials, gold salts, phenylbutazone, salicylates and corticosteroids were used to treat active arthritis (Schaller, 2005). A Finnish study (n = 544) from the Rheumatism Foundation Hospital in Heinola during 1951–1961 reported that 70% of patients with JIA were treated with gold salts, 50% had used antimalarial therapy, and 38% had used corticosteroids (Laaksonen, 1966). Antimalarial and gold salt therapy did not improve the prognosis in aggressive disease (Laaksonen, 1966). Through research in the 1990s, methotrexate and the biologics drugs developed since then have improved the disease course (Immonen et al., 2011; Schaller, 2005). The medical treatment is an essential part of achieving remission of disease (Wallace, 2006). In addition to medical treatment, important treatment goals include prevention of eye and joint damage and promotion of normal psychosocial development and growth (Wallace, 2006).

To achieve uniform treatment of JIA patients, guidelines have been developed, most recently by the ACR in 2021 (Onel et al., 2022). Treat-to-target principle and the possibility to start DMARD treatment early are important in modifying the disease course (Onel et al. 2022, Ringold et al. 2019).

The first-line treatment for all arthritis are nonsteroidal anti-inflammatory drugs and glucocorticoids intra-articular injections (Cimaz et al., 2017; Giancane et al., 2016). It is recommended to start conventional disease-modifying antirheumatic drugs (DMARDs) if the disease is active, and to start it early for all with polyarticular disease (Cimaz et al., 2017; Giancane et al., 2016, Ringold et al. 2019). Conventional drugs include methotrexate *per os* or as injections, leflunomide, sulfasalazine and hydroxychloroquine (Cimaz et al., 2017; Giancane et al., 2016). Oral glucocorticoids are recommended as bridge therapy in moderate or high disease activity when initiating therapy. Biologic DMARDs (such as tumor necrosis factor alpha inhibitors, T-cell blockers and interleukin-1 and 6 blockers) have been added to treatment if remission is not achieved with conventional DMARDs within three months (Cimaz et al., 2017; Giancane et al., 2016).

## **2.2 Prognosis of JIA**

Despite the effective DMARDs, the disease can persist for many years after the onset of JIA (Ravelli & Martini, 2007; Wallace, 2006). The remission rate of the disease seems to increase during follow-up, and patients with oligoarthritis had a

better chance to achieve remission than patients with RF-positive arthritis (Flato et al., 2003; Shoop-Worrall et al., 2017). In addition, patients with oligoarthritis have fewer joint erosions than patients with polyarthritis and patients with RF and anti-CCP antibodies (Palman et al., 2018; Ravelli & Martini, 2007; Wallace, 2006). Uveitis can occur in 20–30% of patients with JIA and can remain active for more than 20 years and lead to eye complications: cataract, glaucoma and even blindness (Moorthy et al., 2010; Nordal et al., 2017; Ravelli & Martini, 2007; Rypdal et al. 2021; Wallace, 2006). A Nordic JIA cohort study reported that 18 years after the onset of JIA, 31.3% of patients (n = 80) had cataracts, 27.5% had glaucoma, and 2.5% had binocular blindness (Rypdal et al. 2021). Active disease can cause growth abnormalities, i.e., micrognathia and limb length inequality and corticosteroid treatment can cause osteoporosis (Ravelli & Martini, 2007; Wallace, 2006).

A large population-based cohort study (n = 434) on outcomes (remission rate, disease activity, damage, medication) of JIA from Denmark, Norway, Sweden and Finland reported that after 18 years of follow-up, 46% of patients had active disease (e.g., joint inflammation, elevated c-reactive protein, uveitis, morning stiffness >15 minutes) while 33% were in remission without medication (Glerup et al., 2020). Polyarthritis (RF-positive), psoriatic arthritis and ERA had poorer outcomes (about 60% of patients had active disease) than patients with oligoarthritis (about 46% of those with extended form of disease and about 32% of those with persistent form of disease had active disease), RF-negative polyarthritis (about 49% had active disease) or systemic arthritis (about 22% had active disease) (Glerup et al., 2020). In addition, an earlier study reported that patients with ERA had worse outcomes (poorer physical health and lower physical functioning) than patients with polyarthritis or oligoarthritis (Flatø et al., 2006).

Patients with JIA seem to have poorer quality of life than healthy controls (Flato et al., 2003; Moorthy et al., 2010; Peterson et al., 1997). Low quality of life is reported in enthesitis-related arthritis (Taxter et al., 2015; Tollisen et al., 2017), psoriatic arthritis (Barth et al., 2016; Foster et al., 2003; Taxter et al., 2015; Tollisen et al., 2017), polyarticular arthritis (Foster et al., 2003), undifferentiated arthritis (Oliveira Ramos et al., 2021; Taxter et al., 2015) and in systemic disease (Foster et al., 2003; Shenoj et al., 2018). According to literature, this phenomenon can to some extent be explained by active disease, disability and pain (Barth et al., 2016; Flato et al., 2003; Foster et al., 2003; Moorthy et al., 2010; Oliveira Ramos et al., 2021; Peterson et al., 1997; Rebane, 2020; Tollisen et al., 2017). In addition, patients with psoriatic arthritis and ERA have impaired quality of life due to active inflammation in enthesitis (Flatø et al., 2006; Rumsey et al., 2020; Taxter et al.,

2015). Several studies have reported poorer mental health in JIA compared to controls (Barth et al., 2016; Bomba et al., 2013; Memari et al., 2016; Mullick et al., 2005; Vandvik, 1990) , which has been found to be one factor contributing to the low quality of life in these patients (Anink et al., 2015; Kosola & Relas, 2021).

Social participation of patients with JIA varies according to research settings and decades. In previous decades, JIA has been reported to cause unemployment compared to general population (Packham, 2004). However, in this millennium employment and educational status have been comparable to that of general population (Anink et al., 2015; Moorthy et al., 2010; Ostile et al., 2010). In addition, education level has been reported to be higher than in general population in a study conducted in this millennium (Anink et al., 2015).

### **2.3 Mortality in JIA**

The life expectancy of JIA patients has improved and their mortality has decreased since the 1960s along with the increased use of more intensive antirheumatic drug treatment (DMARD and biologic drugs) (Immonen et al., 2008; Savolainen & Isomaki, 1993) .

Previous studies found varying numbers of deaths among JIA due to different follow-up times (Table 2). These studies did not include control groups, but two studies reported that the number of deaths among JIA patients was higher than in an expected age-and sex matched control population (French et al., 2001; Krause et al., 2016).

Three studies reported the age of death among JIA patients (Baum & Gutowska, 1977; French et al., 2001; Laaksonen, 1966). In a Finnish study, the mean age of death was 22.2 years (range 11–45 years) and in a US study from 2001, the mean age of death was 26.5 years (range 18–40 years) (French et al., 2001; Laaksonen, 1966). However, a large multinational study from 1977 reported a lower age of death than other studies (Baum & Gutowska, 1977) . The mean age of death was 15.2 years in this multinational study.

**Table 2. Studies reporting mortality in juvenile idiopathic arthritis patients over the last decades. Modified from (study I), (published with permission of Clinical and Experimental Rheumatology).**

Author	Country	Number of patients	Follow-up years, mean/median	Number of deaths	Number of deaths/ patients during follow-up as a percentage
Laaksonen, 1966	Finland	544	16/-	25	4.6
Baum & Gutowska, 1977	Europe, USA, Pacific area	6,290	9.2/-	184	2.9
Koivuniemi & Leirisalo-Repo, 1999	Finland	30	7.8/-	1	3.3
French et al., 2001	USA	57	25.6/-	4	7.0
Minden et al., 2002	Germany	215	-/16.5	0	0
Hashkes et al., 2010	USA	9,604	7.9/-	20	0.2
Krause et al., 2016	USA	71	-/7.5	0	0
		118	-	4	3.4
Tollisen et al., 2017	Norway	176	30	6	3.4
Tollisen et al., 2019	Norway	96	18.9/-	4	4.2
Glerup et al., 2020	Denmark, Norway, Sweden and Finland	434	17.5/-	1	0.2

## 2.4 Causes of death

Causes of death among JIA patients have varied over time. The main cause of death in studies from the last century was renal amyloidosis (Baum & Gutowska, 1977; Laaksonen, 1966). A multinational study (published in 1977) reported the following causes of death: infections, heart disease, trauma, adrenal failure, blood disorders, cerebral hemorrhage and complications of therapy (Baum & Gutowska, 1977).

Studies from this millennium have not reported any amyloidosis-related deaths in JIA. One US study (published in 2001) found that all four deaths were related to disease and its complications (autoimmune hepatitis, two immunodeficiency and one myocarditis), and another US study also found that deaths were most

commonly related to JIA itself or its treatment/complications (French et al., 2001; Hashkes et al., 2010).

## **2.5 Mental and behavioral disorders**

### **2.5.1 Classification**

Psychiatry developed into its own specialty in the 18<sup>th</sup> century, but child and adolescent psychiatry was not recognized until the 20<sup>th</sup> century (Manderscheid et al., 2010; Rutter, 2010). The development of new psychotropic medications and the emergence of neuroscience research led to the need to establish new, uniform and reliable diagnostic manuals: the International Classification of Diseases codes (ICD) (Table 3) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) in the late 20<sup>th</sup> century (International Advisory Group, 2011; Manderscheid et al., 2010; Stein et al., 2013). The ICD classification system was set up by the World Health Organization (WHO) and the DSM classification system is maintained by the American Psychological Association (APA), and they are usable from the age of five years onwards (Cantwell, 1996; International Advisory Group, 2011).

ICD-10 is currently in use in Finland for psychiatric diagnoses (Table 3). However, WHO approved the ICD-11 in 2019 (International Advisory Group, 2011). Based on the current (ICD-10) manual, mental and behavioral disorders are defined as follows:

*a clinically recognizable set of symptoms or behaviors associated in most cases with distress and with interference with personal functions* (International Advisory Group, 2011) .

In general population, the most common disorders in childhood (early childhood aged 0–5 years and childhood aged 6–11 years) are childhood behavioral and emotional disorders such as attention-deficit/hyperactivity disorder (ADHD), emotional disorders, separation anxiety, specific phobia, oppositional defiant disorders, sleeping disorders and psychological development disorders such as autism (Costello et al., 2006, 2011; Kessler et al., 2007). However, phobic, anxiety or mood disorders and disorders associated with substance use and physiological disturbances or physical factors such as eating disorders break out in adolescence (aged 12–19 years) (Costello et al., 2006; Kessler et al., 2007). Psychotic disorders usually start to occur from adolescence and schizophrenia from 15 to 35 years of

age (Kessler et al., 2007). In adulthood disorders, females have higher prevalence than males while males have higher prevalence of childhood disorders (Costello et al., 2006).

**Table 3. The International Classification of Diseases codes (ICD-10) on psychiatric diagnoses. Re-adapted CC BY 4.0 Licensed Image of Publication II © 2021, Kyllönen, Ebeling, Kautiainen, Puolakka and Vähäsalo.**

Psychiatric Diagnoses	ICD-10
Mental and behavioral disorders due to psychoactive (alcohol, opioids, cannabinoids, hypnotics, cocaine, stimulants, hallucinogens, tobacco) substance use	F10–19
Psychotic disorders	F20–29
Mood (affective) disorders	F30–39
Mania and bipolar disorders	
Depression and other mood disorders	
Neurotic, stress-related and somatoform disorders	F40–48
Phobic and anxiety disorders	
Obsessive-compulsive disorder	
Dissociative disorder	
Somatoform disorder (somatization, hypochondriacal, autonomic, pain)	
Others	
Behavioral syndromes associated with physiological disturbances and physical factors	F50–59
factorl factors	
Eating and sleeping disorders	
Others <sup>1</sup>	
Disorders of adult personality and behavior	F60–69
Mental retardation	F70–79
Disorders of psychological development	F80–89
Disorder of speech and language	
Disorder of scholastic skills	
Disorder of motor function (e.g., autism, Rett syndrome, Asperger syndrome)	
Childhood behavioral and emotional disorders	F90–98
Hyperkinetic and conduct disorders (e.g., aggressive, depression, unsocial, oppositional behavior)	
Emotional disorders (e.g., separation, phobic, social anxiety) specific to childhood onset	
Disorders of social functioning, tic disorders and others	

<sup>1</sup> Sexual dysfunction, behavioral disorders associated with puerperium, abuse of non-dependence-producing substances

### ***2.5.2 Prevalence of mental and behavioral disorders in childhood and adolescence in the general population***

The prevalence of mental and behavioral disorders varies according to research settings and classifications (Costello et al., 2006, 2011; Merikangas et al., 2009) and is affected by study population (selection bias) (Costello et al., 2006, 2011; Kessler et al., 2007).

The Finnish 1987 birth cohort (including 59,699 children and adolescents aged 0–21 years) found that 12.7% of the study population had been diagnosed with some psychiatric disorder (Paananen et al., 2013). The most common diagnoses were mood disorders (7%), neurotic, stress-related and somatoform disorders (5.6%) and behavioral and emotional disorders (3%) (Paananen et al., 2013).

According to a systematic review of 23 articles from 1997 to 2009, the average prevalence of any disorders in adolescence was 21.8% (Costello et al., 2011). The five most common disorders were drug abuse disorders (12.1%), anxiety disorders (10.7%), mood disorders (6.1%) and childhood behavioral disorders (3–4%), and less than 1% were rare disorders (psychosis, tic disorders, eating disorders) (Costello et al., 2011).

A large epidemiological study from the USA and UK at the beginning of this millennium showed varying results: the prevalence of mood disorders was 0.9–3.4%, that of anxiety disorders 2.2–9.5%, ADHD 0.9–8.7%, and of any conduct or oppositional disorders, 1.5–6.0% in children and in adolescents (Merikangas et al., 2009).

### ***2.5.3 Incidence of mental and behavioral disorders in childhood and adolescence in the general population***

A Danish cohort study (with 1.3 million individuals under the age of 18 years) found 99,926 (7.7%) new cases of any mental and behavioral disorders between 1995 and 2016 (Dalsgaard et al., 2020). The four most common incident diagnoses were anxiety disorder (2.6%), ADHD (2.4%), autism spectrum disorder (1.7%) and other developmental disorders (1.2%) (Dalsgaard et al., 2020). The cumulative incidence of mood disorders, depression, obsessive-compulsive disorder, eating disorder, schizophrenia and personality disorder began to increase after the age of 13 years and peaked in late adolescence in females. However, males had higher cumulative incidence of intellectual disability, autism spectrum disorders, developmental disorders, attachment disorders, tic disorders and ADHD than

females, especially under the age of 13 years. Mental disorders before the age of six years were rare in both genders.

According to a large Finnish birth cohort study (which followed adolescents from age 12 to 18), the cumulative incidence of any psychiatric disorders was 9.8% in females and 6.2% in males in the 1987 birth cohort, compared to 14.9% in females and 8.8% in males in the 1997 birth cohort (Gyllenberg et al., 2018). In females, the diagnoses of depression and anxiety increased in adolescence when comparing the 1987 cohort to the 1997 cohort, while in males, the diagnoses of autism spectrum disorders, learning and coordination disorders, attention deficit hyperactivity disorder, tic disorders, conduct and oppositional disorders increased.

In addition, another Finnish birth cohort study including individuals under the age of 27 years reported an increase in the cumulative incidence of all psychoses from the 1966 birth cohort to the 1986 birth cohort (1.0% in 1966 birth cohort and 1.9% in 1986 birth cohort) (Filatova et al., 2017). The cumulative incidence started to increase after 13 years of age in both females and males in the 1986 birth cohort while in the 1966 birth cohort it did not increase until after 15 years of age. The mean age of onset of psychosis was 21.5 years in the 1966 birth cohort and 20.9 years in the 1986 birth cohort. The authors explain the results by the fact that diagnostic practices may have changed or psychosis may now be recognized earlier.

## **2.6 Psychiatric morbidity (mental and behavioral disorders and symptoms) in physically ill children and adolescents compared to healthy controls or general population**

### ***2.6.1 Mental and behavioral disorders***

The literature search was based on articles, review articles or meta-analyses retrieved from PubMed using the keywords mental and behavioral disorders, all psychiatric disorders with ICD-10 codes F10–F98, children and adolescents, chronically illness. The articles that did not contain juvenile idiopathic arthritis or control group were excluded.

A systematic review article included 53 articles, which were picked from PubMed, PsycNET, Embase and a reference list of included studies from 1990–2018. Young patients under 18 years of age with chronic disease i.e., asthma, congenital heart disease, diabetes, epilepsy, inflammatory bowel disease, juvenile idiopathic arthritis or sickle cell disease have higher prevalence of any anxiety

disorders than general population (Cobham et al., 2020). According to this article, the prevalence of anxiety disorders varies between studies and disease groups: asthma 5.1–49.2%, type 1 diabetes 15.5–32.1%, epilepsy 23.8–50%, inflammatory bowel disease 25%, juvenile idiopathic arthritis 16.6%, and sick cell disease 10–27.5% (Cobham et al., 2020).

In a population study from Norway, a structured psychiatric interview was conducted for chronically ill children (n = 109) with asthma, epilepsy, diabetes, skeletal disorders, gastro-intestinal disorders, neurological disorders, cardiovascular disorders, endocrine disorders, kidney disorders, eczema, allergy, sensory impairment, hemophilia or arthritis (Hysing et al., 2007). Among children aged 4–16 years, 10% had some psychiatric diagnosis, compared to 6% of healthy controls (odds ratio 1.7, 95% CI 1.0–2.9) (Hysing et al., 2007).

In addition, a large (n = 4,640) study conducted in the United States found that 13% of children aged 5 to 17 years with chronic disease (juvenile idiopathic arthritis, asthma, epilepsy, diabetes mellitus, infantile cerebral palsy, spina bifida, congenital anomalies of the heart, sickle-cell disease, cystic fibrosis, blindness or low vision, color or night blindness, hearing loss, and common childhood cancers) had some mental and behavioral disorders and had greater risk compared to children without physical illness (odds ratio 1.8, 95% CI 1.5–2.1) (Suryavanshi & Yang, 2016).

### **2.6.2 Mental and behavioral symptoms**

The literature search was based on meta-analyses and review articles retrieved from PubMed using the keywords mental and behavioral symptoms, anxiety, depression, behavioral problems/symptoms, quality of life, children and adolescents, chronically ill children. Those meta-analyses or review articles that did not contain juvenile idiopathic arthritis or control group were excluded. According to this literature review, there are two meta-analyses and one review article that have reported mental and behavioral symptoms in children with chronic disease and one review article about the impact of childhood chronic illness on adult mental health (Barlow & Ellard, 2006; Pinquart & Shen, 2011a, 2011b; Secinti et al., 2017).

One review article from the United Kingdom focused on the psychosocial well-being of chronically ill children (aged 3–20 years), parents and siblings. Meta-analyses, systematic reviews and overviews on the subject were identified from MED, CINAHL, Cochrane Database, DARE, HTA, MEDLINE, NHS EED, PsycLIT, PsycINFO and PubMed from 1990 to 2004. Ten papers were selected

and four of these included JIA or chronic arthritis. The results showed that children with chronic disease, e.g., asthma, diabetes, cancer, inflammatory bowel disease, neurological and sensory disorders, hearing loss, JIA, rheumatic disease in general were more likely to have internalizing (e.g., anxiety, depression), externalizing problems (hyperactivity, aggression) and adjustment problems than healthy controls (Barlow & Ellard, 2006).

One meta-analysis about anxiety among children and adolescents with chronic physical illness compared to healthy peers or test norms included 322 studies, which were identified from electronic databases (PsycInfo, Medline, Google Scholar, Psyn dex) (Pinquart & Shen, 2011a). Of these articles, 18 included arthritis/rheumatism. The studies were published since the development of the scales up until November 2010. Participants were under 18 years of age. Studies in which young people had been referred to psychological services were excluded. The results indicated that patients with chronic disease reported elevated levels of anxiety symptoms, but children with arthritis (mean age 12.0 years) did not have significant levels of anxiety symptoms compared to controls. The levels of anxiety were higher in the first six years of life than in middle childhood or adolescence. Gender did not affect anxiety, but the level was influenced by source of information: the level was higher if the source was parent instead of the patient him/herself.

Another meta-analysis by the same authors focused on children and adolescents with chronic physical illness and behavior problems compared to healthy peer or test norms. It included 569 studies which were identified from electronic databases (PsycInfo, Medline, Google Scholar, Psyn dex) (Pinquart & Shen, 2011b). Of these articles, 27 included arthritis/rheumatism diseases ( $n = 1,746$  patients). The studies were published since the development of the scales up until May 2011. Studies in which young people had clinical levels of behavior problems were excluded. The mean age of patients was 10.6 years and the majority were girls. Total problem behavior, internalizing (e.g., anxiety) and externalizing (e.g., aggressive behavior) problems scores were increased in children with chronic disease including arthritis compared to controls or test norms. The level of problems was higher in males with JIA than in females with JIA and in teacher or parent reports than in children and adolescents with JIA reports.

A review from the United Kingdom included 34 studies, which were identified from MEDLINE, PsycARTICLES, PsycINFO and ScienceDirect from January 1980 to July 2016 (Secinti et al., 2017). Only one study included arthritis. Childhood chronic disease increased the risk for adult (between 19 and 30 years of age) anxiety and depression compared to healthy controls.

## 2.7 Psychiatric morbidity in JIA from a case-control study perspective

In the late 20<sup>th</sup> century, the development of screening questionnaires and structured interviews offered valuable tools to evaluate children's and adolescents' mental and behavioral symptoms in the scientific field (Rutter, 2010). These symptoms could now be scanned with several psychometrics tests which provide quantitative information from a wide perspective (Bomba et al., 2013; Ding et al., 2008; Huygen et al., 2000; Memari et al., 2016; Raab et al., 2013; Tarakci et al., 2011). Questionnaires used in earlier studies are shown in Table 4.

Register-based studies utilize various registry data collected for purposes other than the original study and are widely used in epidemiological research; they provide information on whole population level on mental and behavioral diagnoses, co-morbidity, service use, disease-related factors, etiopathogenesis and treatment (Gyllenberg et al., 2018; Jääskeläinen et al., 2015; Miettunen et al., 2019; Munk-Jørgensen & Dinesen Østergaard, 2011; Varimo et al., 2020, 2022; Vuori et al., 2020).

**Table 4. Questionnaires used in assessing symptoms of mental and behavioral disorders in earlier studies.**

Questionnaire study	Psychiatric symptoms to be assessed
Beck Depression Inventory (BDI)	depressive symptoms
Child Behavior Checklist (CBCL)	conduct, emotional, peer problems and hyperactivity and pro-social behavior (eight subscores and two composite internalizing and externalizing problem scores)
Children's Depression Inventory (CDI)	depressive symptoms among children and adolescents
Generic quality of life measurement (EQ5D)	mobility, self-care, usual activities, pain, anxiety/depression
Mood and Feeling Questionnaire (MFQ)	depressive symptoms
Hamilton Rating Scale for Depression (HAM-D)	depression state, feelings of guilt, insomnia, usual activities, decrease of ideational level, agitation, mental and somatic anxiety, gastrointestinal somatic symptoms and weight loss

Questionnaire study	Psychiatric symptoms to be assessed
Revised Children's Manifest Anxiety Scale (RCMAS)	anxiety symptoms among children and adolescents
Self- Administered Psychiatric Scales for Children and Adolescents (SAFA-A)	generalized, school, social and separation anxiety among children and adolescents
Social Anxiety of Children (SASK)	anxiety, social skills, physical skills, cognitive, physiological and emotional reactions (46 items)
Screen for Child Anxiety Related Emotional Disorders Questionnaire (SCARED)	panic/somatic, generalized, separation anxiety and school and social phobia
Short Form health questionnaire (SF-12 or 36)	physical functioning, pain, social functioning, general health, vitality, emotional problems and mental health

### **2.7.1 Mental and behavioral disorders**

Five previous studies evaluating psychiatric morbidity by mental disorder diagnosis in JIA are shown in Table 5.

A small Norwegian study of inpatient JIA children found that 16.7% patients with JIA had some anxiety disorder (separation anxiety, overanxious disorder or compulsive disorder), 29.2% had some depressive disorder (dysthymic disorder or major depression), and 15.6% had some behavioral disorder (oppositional disorder or attention deficit disorder) according to the DSM III classification (Vandvik, 1990). The patients were compared to siblings. According to parental assessment, the internalizing (depression, anxiety, withdrawal and somatic complaints) scores were higher in JIA children compared to healthy siblings (Vandvik, 1990). Vandvik found no statistical association between disease severity and psychiatric symptoms.

Another small study of outpatient JIA children from Asia reported that 20% of patients with JIA met the criteria for some anxiety disorder (somatoform disorder, adjustment disorder, mixed anxiety and depression) and 15% met the criteria for mood disorder (Mullick et al., 2005). Depressive disorders were more common in JIA compared to healthy controls.

One small longitudinal study found that the cumulative incidence of depression was 24.9% in children with JIA and 18.7% in young adults with JIA. In addition, the risk of depression was 2.5-fold higher among patients with JIA in childhood (95% CI 1.0–6.1), but no longer in adulthood, when it was only 0.5-fold higher (95% CI 0.5–4.7) compared to healthy controls (Krause et al., 2017). The mean

follow-up time in children with JIA was 6.3 years while being 8.0 years in adolescents with JIA.

Another small study from Turkey compared children with JIA (n = 32), children with pediatric primary immunodeficiency (PID) (n = 44) and healthy controls (n = 30) (Kayan Ocakoglu et al., 2018). In this study, 31% of JIA patients had mood disorder, 25% had anxiety disorder, and 22% had disruptive behavior disorder. These results did not differ between patients with JIA and PID, but there was a statistically significant difference between patients and healthy controls in mood disorders.

However, a Swedish study found no statistically significant difference between patients with JIA and healthy controls regarding depression and anxiety disorders (Berthold et al., 2022). During 1998–2019, 17.3 % of patients with JIA met the criteria for anxiety disorder (dysthymia or anxiety) and 14.5% met the criteria for depression. The study did not report association between JIA subclasses and depression or anxiety.

**Table 5. Previous studies of psychiatric disorders in JIA compared to controls.**

Authors	Diagnostics	Sample case/controls	Age in years mean/median	Disease duration in years mean/median
Vandvik, 1990	psychiatric interview DSM-III	75/47	-/10.6	-/0.6
Mullick et al., 2005	psychiatric interview ICD-10	40/40	13.2/-	2.7/-
Krause et al. 2017	medical records of depression diagnosis	89/89 (in childhood) 38/38 (in adulthood)	8.6/- 11.2/-	-/1.3
Kayan Ocakoglu et al., 2018	psychiatric interview (KSADS-PL)	32/30	14.2	-
Berthold et al., 2022	F32, F33, F34.1 and F41 ICD-10	640/3,200	-	-

DSM=the Diagnostic and Statistical Manual of Mental Disorders third edition, ICD-10=the International Classification of Diseases 10<sup>th</sup> edition, KSADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version

### **2.7.2 Mental and behavioral symptoms based on questionnaires**

Most questionnaire -based studies have focused only on anxiety (RCMAS, SCARED, SAFA-A questionnaires) or depression (HAM-D, SAKS, BDI, CDI, MFQ questionnaires) while few have reported behavioral problems (CBCL questionnaire) in JIA (Table 4 and Table 6). In all studies, females were in the majority (Bomba et al., 2013; Ding et al., 2008; Huygen et al., 2000; Kayan Ocakoglu et al., 2018; Kuburovic et al., 2014; Memari et al., 2016; Raab et al., 2013; Sur et al., 2021; Tarakci et al., 2011).

Bomba et al found a statistically significant difference in symptoms of anxiety and depression among patients with JIA compared to healthy controls and reported that patients had emotional difficulties and delayed psychological development leading to poor self-esteem (Bomba et al., 2013). The prevalence of anxiety was 53% in JIA and 10% in healthy controls. In addition, the prevalence of depression according to CDI was 23% in JIA and 8.3% in controls.

According to HAM-D, Sur et al found higher numbers of depression in JIA compared to healthy controls, 31% vs 5% (Sur et al., 2021). Kayan Ocakoglu et al. found higher CDI score in JIA patients compared to healthy controls, too (Kayan Ocakoglu et al., 2018). Patients with JIA had statistically significantly more somatization, social problems and rule-breaking behavior than controls according to CBCL, but not anxiety problems according to SCARED.

Using the CBCL questionnaire, Memari et al. also reported more social problems (13% in JIA vs. 1% in controls) and in addition, thought problems, e.g., obsessive thoughts (17% in JIA vs. 2% in controls) in JIA than controls (Memari et al., 2016). In addition, internalizing problems (e.g., anxious, withdrawal) and externalizing problems (e.g., aggressive, impulsive behavior) were more common in JIA than controls (internalizing problems in 70% of JIA patients vs. 19% of controls and externalizing problems in 5% in JIA vs. 8% in controls) (Memari et al., 2016).

Five studies – a small Turkish study from 2011, three European and one small UK study – reported no difference between children and adolescents with JIA and healthy controls regarding mental and behavioral symptoms (Ding et al., 2008; Huygen et al., 2000; Kuburovic et al., 2014; Raab et al., 2013; Tarakci et al., 2011). However, Raab et al. reported that 9.3% of JIA patients had self-reported psychiatric disorder (anxiety or depression), and depression was more common than anxiety (4.9% vs. 2.0%) (Raab et al., 2013). In addition, Kuburovic et al. found that 14.3% of JIA patients had significant anxiety symptoms and 10% had

depressive symptoms (Kuburovic et al., 2014). Tarakci et al. found a significant relationship between active joint count, disease duration, pain and anxiety and depression scores in patients with JIA (Tarakci et al., 2011).

Those studies that reported JIA classes did not evaluate the association between JIA subclasses and mental illness (Bomba et al., 2013; Huygen et al., 2000; Raab et al., 2013; Sur et al., 2021; Tarakci et al., 2011).

**Table 6. Previous questionnaire studies in JIA compared to controls.**

Authors	Country	Used questionnaire	Sample case/control	Mean age (range) in years	Mean disease duration (range) in years
Hyugen et al., 2000	Netherlands	self-report of depression SASK CBCL	47/52	(7–16)	-
Ding et al., 2008	United Kingdom	BDI RCMAS	60/general population	12.3	-
Taracki et al., 2011	Turkey	CDI SCARED	52/48	12.0	6.0
Raab et al., 2013	Germany	additional questionnaire of comorbidities	344/688	19.7	10.6
Bomba et al., 2013	Italy	SAFA-A CDI	39/80	11.4	3.0
Kuburovic et al., 2014	Serbia	SCARED MFQ	50/89	11.4	-
Memari et al., 2016	Iran	CBCL	51/75	11.2	-
Kayan Ocakoglu et al., 2018	Turkey	CDI SCARED CBCL	32/30	14.2	-
Sur et al., 2021	Romania	HAM-D	145/20	(8–18)	(0.5–16)

BDI=Beck Depression inventory, CBCL=Child behavior checklist, CDI=Children's Depression Inventory, HAM-D=Hamilton Rating Scale for Depression, MFQ= the Mood and Feeling Questionnaire, RCMAS=Revised Children's Manifest Anxiety Scale, SAFA-A=Self- Administered Psychiatric Scales for Children and Adolescent, SCARED=Screen for Child Anxiety Related Emotional Disorders, SASK=Social Anxiety of children

### 2.7.3 Mental health according to health-related quality of life studies

Using the health-related quality of life (physical, mental health, social interaction and role functioning) perspective, previous studies have not reported a statistically significant difference between JIA and healthy control population in the mental health section of SF-12 or the 36 Short Form Health Survey (the questionnaire contains questions on general health, physical and emotional health problems, limitation of activities, social activities, energy and motivation) (Table 7) (Arkela-Kautiainen et al., 2005; Barth et al., 2016; Flato et al., 2003; Foster et al., 2003; Ostile et al., 2010; Peterson et al., 1997; Tollisen et al., 2017, 2022). JIA patients still had more bodily pain, poor general health and physical functioning than controls (Flato et al., 2003; Foster et al., 2003; Peterson et al., 1997). However, a German study found that all EQ5D dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) were worse in JIA than in the general population and low EQ5D score was associated with disability, active disease, older age, low education and female gender (Barth et al., 2016). The prevalence of anxiety or depression per study population was 28% in JIA (n = 2,592) and 4.3% in controls (n = 3,552) (Barth et al., 2016). Östlie et al, also found that female gender was a predictor of mental health domain in SF-36 (Ostlie et al., 2010).

**Table 7. Previous health-related quality of life studies in JIA and controls assessing mental health.**

Authors	Country	Used questionnaire	Sample case/control	Age in years mean/median (range)	Disease duration in years mean/median
Peterson et al., 1997	USA	SF-36 mental health	50/102	33.5 /-	24.7/-
Flato et al., 2003	Norway	SF-36 mental health	258/258	-/22.1	-/14.9
Foster et al., 2003	United Kingdom	SF-36 mental health	82/ 82	-/30.0	-/21.0
Arkela-Kautiainen et al., 2005	Finland	SF-36 mental health	123/122	23.0/-	16.2/-
Östlie et al., 2010	Norway	SF-36 mental health	55/1184	27.4/-	-/18.8
Barth et al., 2016	Germany	EQ5D	2,592/3,552	(18–73)	-/27.0

Authors	Country	Used questionnaire	Sample case/control	Age in years mean/median (range)	Disease duration in years mean/median
Tollisen et al., 2017	Norway	SF-36 mental health	260/90	37.8/-	-
Tollisen et al., 2022	Norway	SF-12 mental health	79/79	25.1/-	-/19.2

EQ5D=generic quality of life measurement, SF-12=Short Form 12-item health questionnaire, SF-36 = Short Form 36-item health questionnaire

A Finnish study reported an association between JIA subclasses and mental health. They found that patients with extended oligoarthritis had lower physical and mental health than oligo- and polyarthritis patients (Arkela-Kautiainen et al., 2005).

#### **2.7.4 Meta-analysis on psychological adjustment in JIA**

One meta-analysis reviewed 21 original articles in the English language via a literature search in PsycInfo and Medline from 1887 and 1966 to July 2001. The database search focused on psychological adjustment (e.g., behavioral and emotional problems, low self-esteem), internalizing (e.g., anxiety, depression, social withdrawal) and externalizing (e.g., aggressive and oppositional behavior, hyperactivity) problems in JIA (LeBovidge et al., 2003). Ten studies did not recruit control groups and in the other studies the characteristics of control groups varied (healthy controls, chronic ill persons, siblings). The meta-analysis included children and adolescents with arthritis aged 1–20 years.

The results of parent reports and child self-reports indicated that young people with arthritis had an elevated risk for internalizing problems and adjustment problems compared to controls (LeBovidge et al., 2003).

## **2.8 Psychotropic medication**

### **2.8.1 Classification**

Psychotropic medications are classified by the Anatomical, Therapeutic, Chemical system (ATC) (WHO collaborating Center for Drug Statistics methodology, 2021). ATC classifies drugs into fourteen categories from A to V. Psychotropic drugs belong to the category of drugs acting on the nervous system (N) and further, into

the categories psycholeptics (NO5) and psychoanaleptics (NO6). Psycholeptics include antipsychotics (N05A), anxiolytics (N05B) and hypnotics and sedatives (N05C). Psychoanaleptics include antidepressants (N06A), psychostimulants, agents used for ADHD and nootropics (N06B), psycholeptics and psychoanaleptics in combination (N06C) and anti-dementia drugs (N06D). The system provides information on active substances and daily dose recommendations.

## **2.8.2 The use of psychotropic medication among children and adolescents in general population**

### *The number of psychotropic medication users by drug category*

Increased use of psychotropic medication among children and adolescents has been reported in several studies worldwide in this millennium (Bonati & Clavenna, 2005; Haapasalo-Pesu et al., 2016; Hálfðánarson et al., 2017; Hoffmann et al., 2014; Højlund et al., 2019; John et al., 2016; Kalverdijk et al., 2017; Sarginson et al., 2017; Steinhausen & Bisgaard, 2014; Varimo et al., 2020). In the USA, the use of psychotropic drugs among children and adolescents has increased by 0.6 percentage points during 2000–2014 (Lopez-Leon et al., 2018). The purchase of stimulants/other drugs to treat ADHD and anxiolytics increased while that of antidepressants and antipsychotics decreased (Lopez-Leon et al., 2018).

The use of psychotropic drugs in the Nordic countries also indicates an increased use of psychostimulants (Table 8) (Gómez-Lumbreras et al., 2021; Hálfðánarson et al., 2017; Zoëga et al., 2011). According to these Nordic studies on psychotropic medication use, their use increased in late adolescence with the exception of childhood-focused use of psychostimulants (Gómez-Lumbreras et al., 2021; Gyllenberg et al., 2011; Hálfðánarson et al., 2017; Vuori et al., 2020). The age of first purchase of antidepressants was 12–24 years in a Finnish study (Gyllenberg et al., 2011). The number of antipsychotics users was highest in 2008, 26 per 1,000 persons and in 2012, 36 per 1,000 persons, after which the numbers started to decline (Hálfðánarson et al., 2017).

Among antidepressants, sertraline was the most purchased drug in Norway, Sweden and Denmark while others (mirtazapine, venlafaxine) were most used in Finland (Gómez-Lumbreras et al., 2021). However, in a Finnish study, SSRIs (citalopram, paroxetine, fluoxetine) were the most commonly used antidepressants during 1994–2005 (Gyllenberg et al., 2011). In Finland, Sweden and Norway, the

most commonly used antipsychotics were risperidone and quetiapine and among hypnotics and sedatives, the most purchased drug in Sweden and Norway was melatonin (Gómez-Lumbreras et al., 2021; Hálfðánarson et al., 2017). These studies did not report the use of hypnotics and sedatives in Finland. Zoëga et al. reported that the most prevalent psychostimulant was methylphenidate in all these three Nordic countries, while according to Gómez-Lumbreras et al., dexamphetamine was the most common psychostimulant in Sweden and Norway (Gómez-Lumbreras et al., 2021; Zoëga et al., 2011).

**Table 8. Use of psychotropic medication per 1,000 persons among children and adolescents in the general population during follow-up or at the beginning and the end of follow-up.**

Research	Follow-up years	Age distribution, years	Antidepressants	Anti-psychotics	Anxiolytics, hypnotics and sedatives	Psychostimulants
Gyllenberg et al., 2011	1994–2005	13–24				
Finland			113			
Zoëga et al., 2011	2007	0–27				
Finland					1.2	
Sweden					2.5	
Norway					4.7	
Hálfðánarson et al., 2017	2005–2014	0–19				
Finland				2.5 to 8.0		
Sweden				2.5 to 2.7		
Norway				2.5 to 2.5		
Gómez-Lumbreras et al., 2021	2008–2017	0–19				
Sweden			5 to 14	1.8 to 2.5	10 to 20	7 to 23
Norway			4 to 6	2.2 to 3.0	10 to 35	10 to 15
Vuori et al., 2021	2008–2017	6–17				
Finland						6.5 to 27.6

### *The indications for use of psychotropic medication*

In Finland, evidence-based psychiatry treatment for child and adolescents includes, e.g., individual psychotherapy, family and child-parent interaction treatment and psychotropic medication (Lönnqvist, 2021). The drug therapies are treatments for severe symptoms in children and adolescents (Lönnqvist, 2021). There is concern about the side effects associated with the use of psychotropic medication in children worldwide (Rapoport, 2013). Compared to adults, young people using antipsychotics may more often get side effects from psychotropic medication such as tardive dyskinesia, obesity and cardiometabolic syndromes (Rapoport, 2013; Solmi et al., 2020). In addition, the use of antidepressants has been a global concern due to suicidality risk in young people (Rapoport, 2013; Solmi et al., 2020). SSRIs are safer in that respect, but they can cause side effects such as gastrointestinal effects and sexual dysfunction, too (Haapasalo-Pesu et al., 2003; Solmi et al., 2020).

Psychostimulants are the most studied in children worldwide and their effectiveness in the treatment of ADHD has been shown (Lönnqvist, 2021). In addition, the effectiveness of antidepressants in the treatment of obsessive-compulsive disorder has been reported (Lönnqvist, 2021), and SSRIs have an official indication for treatment of obsessive-compulsive disorder in addition to depression among children and adolescents (Haapasalo-Pesu et al., 2003; Rapoport, 2013). The use of antipsychotics has increased among children and adolescents in general while only aripiprazole has an official indication for treating schizophrenia (> 15 years old) and bipolar disorder (> 13 years old) in Finland (Haapasalo-Pesu 2016, Varimo et al, 2020). In addition, ziprasidone has an official indication for treating mania (10–17 years old), lurasidone for treating schizophrenia (13–17 years old), and clozapine for treating treatment-resistant schizophrenia (> 16 years old) (Haapasalo-Pesu 2016). Furthermore, risperidone and periciazine have an indication for treating behavioral disorders in children (> 5 years old) with mental retardation in Finland (Haapasalo-Pesu 2016, Varimo et al., 2020). Similar recommendations exist in the UK and the USA (Putignano et al., 2019). In addition, in the USA and the UK, antipsychotics have been licensed for use in the treatment of Tourette syndrome and autistic disorder. Furthermore, in the USA they are indicated for use in the treatment of major depression together with antidepressant medication (Olfson et al., 2012). In Finland, antipsychotics have been shown to be used off-label for the treatment of depression, anxiety, hyperkinetic and developmental disorders (Gyllenberg & Sourander, 2012; Haapasalo-Pesu et al., 2016; Varimo et al., 2020). Users of antipsychotics use concomitantly drugs such

as antidepressants, benzodiazepines and mood stabilizers to some extent (Gyllenberg et al., 2011; Gyllenberg & Sourander, 2012; Varimo et al., 2022).

According to a study from the US, stimulants are prescribed to treat symptoms such as depression and eating disorders in addition to deficit disorder (Olfson et al., 2013). In addition, anxiolytics have been prescribed to treat mood disorders and behavioral disorders (Olfson et al., 2013). However, this is neither recommended nor based on scientific evidence.

In addition, an increase in the use of SSRIs, SNRIs and tricyclic antidepressants has been reported in the treatment of pain and fibromyalgia among children and adolescents (Gmuca & Sherry, 2017; John et al., 2016; Mathew et al., 2016; Sarginson et al., 2017).

### ***2.8.3 The use of psychotropic medication among children and adolescents with JIA***

The literature search was based on articles retrieved from PubMed using the keywords psychotropic medication, antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, psychostimulants, psycholeptics, the active substances of all these five main groups according to the electronic version of Pharmaca Fennica, children and adolescents, juvenile idiopathic arthritis, chronic illness. Research data on the use of psychotropic drugs among JIA patients was limited and described mainly the use of antidepressants in pain treatment.

One Finnish study on adolescent JIA patients and pain (n = 195) reported that 8.7% of participants, especially females, used antidepressants, and their use was associated with pain (Rebane et al., 2019).

A registry study (n = 1,306) reported that 3.4% of young people with JIA used antidepressants and 1.5% used psycholeptic drugs (Montag et al., 2022). These numbers were slightly higher in females compared to males with JIA, but the difference was not statistically significant (Montag et al., 2022). Patients with systemic disease, psoriatic arthritis, enthesitis-related arthritis and extended oligoarthritis used antidepressants and psycholeptics more commonly than other JIA patients. A late start of biologic DMARD drug treatment was a risk factor for taking antidepressants and psycholeptics.

A randomized double-blinded pilot study (n = 6, aged 10.3–16.3) found that amitriptyline was not better than placebo in treating pain in active polyarticular JIA (Huber et al., 2007).

Secondary fibromyalgia has been reported in a small proportion (8.5%) of JIA patients (Teshler et al., 2022). In addition, a review article of pediatric pain syndromes in children and adolescents with rheumatic disease has reported that 25% of newly diagnosed patients had fibromyalgia, localized pain syndrome, complex regional pain syndrome or low back pain (Anthony & Schanberg, 2005). The authors recommended NSAIDs as first-line treatment for pain and tricyclic antidepressants for generalized pain with sleeping problems. SSRIs should only be used with caution in mood disorders (Anthony & Schanberg, 2005).



### **3 Aims of the study**

1. To evaluate mortality and causes of death in JIA patients in Finland compared with the general population.
2. To study mental and behavioural disorders in JIA patients compared to a control population.
3. To explore the use of psychotropic medications in patients with JIA compared to population controls.



## **4 Subjects and methods**

### **4.1 Subjects (Study I, II and III)**

All patients (cases) for this longitudinal case-control study with ICD-10 code M08.0–M08.9 or M09.0\*L40.5 were collected from 1<sup>st</sup> Jan 2000 to 31<sup>st</sup> Dec 2014 (index date) from the national reimbursement register maintained by the Social Insurance Institution of Finland (SII). In study I, II and III, the index day represents the day of the first reimbursement and the index day is used as a surrogate for date of JIA diagnosis. JIA patients who need medication such as conventional disease-modifying antirheumatic drugs, glucocorticoids or biologics drugs are entitled to special (higher) reimbursement of medication costs from the SII. To be entitled to special reimbursement and included in this national reimbursement register, the patient's pediatrician or (in most cases) pediatric rheumatologist must provide the SII with a certificate including diagnosis and treatment plan. Mild cases of JIA with no need for disease-modifying antirheumatic drugs are not included in the SII register and are therefore not included in this study. All patients in our study were given a code number which is the key to data aggregation and guarantees anonymity.

For each case, the National Population Registry identified three controls matched for age, sex and residence.

### **4.2 Causes of death (Study I)**

In this study, death data from the study population and control population (time, age at death, underlying causes of death and causes leading to death as International Classification of Diseases 10<sup>th</sup> Edition (ICD-10) codes) was obtained from the official death certificate statistics of Statistics Finland from 1<sup>st</sup> Jan 2000 to 31<sup>st</sup> Dec 2015.

### **4.3 Psychiatric diagnoses (Study II)**

In Finland, municipalities are responsible for organizing health services in their area including primary health care and hospitals for special outpatient and inpatient care. Every visit to any inpatient clinic (hospital) or outpatient clinic is recorded in the Care Register for Healthcare maintained by the National Institute for Health

and Welfare. The data includes, e.g., diagnoses, clinic visits and hospital treatment periods.

The Finnish law on personal registers obligates the service providers to produce information to the Care Register, which covers all hospital care since 1969 in Finland; in 1998, secondary care outpatient visits were added. The information includes personal identification code and diagnoses of the patient's medical problems as codes of the International Classification of Diseases 10<sup>th</sup> Edition (ICD-10).

In this study, all psychiatric diagnoses (ICD-10 codes F10–98) that occurred since 1<sup>st</sup> Jan 2000 to 31<sup>st</sup> Dec 2016 were obtained from this Care Register. These diagnoses were grouped into eight main categories (Table 3). Mental retardation (F70–79) was not included in the analysis.

#### **4.4 Psychotropic medication use (Study III)**

The information on psychotropic medication use (number of users) and the purchases of antidepressants was collected from the SII drug purchase register since 1<sup>st</sup> Jan 2000 to 31<sup>st</sup> Dec 2015. A single purchase indicated psychotropic medication use. The drug purchase register contains data on purchases of prescription medicines in pharmacies and detailed information on medication such as ATC codes, amount and date of purchase. Drugs supplied in hospitals or other facilities are not registered. The register covers all purchase of medicine data since 1995 in Finland.

Psychotropic medication was divided into six groups (ATC-code): 1) antipsychotics (N05A), 2) anxiolytics (N05B), 3) hypnotics and sedatives (N05C), 4) antidepressants (N06A), 5) psychostimulants, agents used for ADHD and nootropics (N06B), and 6) psycholeptics and psychoanaleptics in combination (N06C). The number of JIA patients and controls who purchased these drugs was analyzed.

Antidepressants were the most commonly purchased drugs and because of that, all antidepressant purchases per 1,000 person years during the follow-up were evaluated more specifically at five-digit level of ATC code (N06AA, N06AB, N06AF and N06AX) by gender. In addition, the number of JIA patients and controls who purchased antidepressants was analyzed at seven-digit level of ATC code (Table 9).

**Table 9. Antidepressants used in this study (five- and seven-digit level of ATC code). Reprinted with permission of Clinical and Experimental Rheumatology from Publication III © 2023 Springer.**

NO6AA	N06AB	N06AC	N06AX
Non-selective monoamine reuptake inhibitors	Selective serotonin reuptake inhibitors	Monoamine oxidase A inhibitors	Other antidepressants
Clomipramine	Fluoxetine	Moclobemide	Mianserin
Trimipramine	Citalopram		Trazadone
Amitriptyline	Paroxetine		Mirtazapine
Nortriptyline	Sertraline		Bupropion
Doxepin	Fluvoxamine		Venlafaxine
	Escitalopram		Milnacipran
			Reboxetine
			Duloxetine
			Agomelatine
			Vortioxetine

#### 4.5 Statistical methods and ethical aspects

The characteristics of the study population were presented as means with standard deviations (SD), as medians with interquartile range (IQR), or as counts with percentages, which were also used to present causes of deaths.

In study I, the cumulative mortality curves in patients with JIA and controls was calculated by Kaplan-Meier method. Cox proportional hazard model was used to estimate the mortality risk for the JIA patients and the control population. The mortality risk was presented as HR (hazard ratio) with 95% confidence intervals (CI)s. Analysis was performed using Stata 14.1 (Stata Corp LP, College Station, TX, USA).

In study II, the cumulative incidence of the first psychiatric diagnoses was investigated by the product limit estimate (Kaplan-Meier) of cumulative function, time from the index date to the first psychiatric diagnosis. The Cox proportional hazard model was used to estimate the psychiatric morbidity risk of the JIA patients and the control population. The risk of psychiatric morbidity in patients and controls was presented as hazard ratios (HR) with 95% CIs. The numbers and incidences of all psychiatric diagnoses were calculated assuming a valid Poisson distribution. Incidence rate and incidence rate ratios (IRR) of all psychiatric diagnoses during follow-up were calculated using Poisson regression model. The

incidences were presented by gender and the age at JIA onset. A Poisson regression model was tested using the goodness of fit of the model. Possible over-dispersion in the Poisson model was tested using the Lagrange multiplier test. In addition, a possible nonlinear relationship between incidences of psychiatric diagnoses and the age at diagnosis was assessed using a 4-knot-restricted cubic spline Poisson regression model. Stata 16.0 (Stata Corp LP, College Station, TX, USA) was used for the analysis.

In study III, the cumulative curves of probability of purchasing one's first antidepressant since the index date in patients with JIA and controls was calculated by Kaplan–Meier product limit estimate, with age as time scale. Cox proportional hazards regression models were used to estimate the risk of purchase of the first antidepressant and results were presented as hazard ratios (HRs) and 95% CIs in patients and controls. Rate ratios (RRs) of psychotropic medicine purchases since the index date between the cases and controls were estimated using generalized linear models with log link and binomial distribution. Purchases of antidepressant type drugs per 1,000 person years were evaluated by using a Poisson regression model. Stata 17.0 statistical package (StataCorp LP, College Station, TX, USA) was used for analysis. For all analyses,  $p < 0.05$  was considered significant.

Permission to use the databases was obtained from the SII and the National Institute for Health and Welfare. According to Finnish legislation, no ethical committee approval or patients' informed consent is required for register-based studies done without contacting the study subjects.

## 5 Results

### 5.1 Study population characteristics (Study I, II, III)

The cases in this study are presented in Table 10. There were 2,603 (62.3%) females and 1,577 males. The cumulative follow-up time among JIA patients was 28,941 years. The patients were compared with 12,512 population controls matched for age, sex and residence at the index date (7,793 females, 4,719 males).

**Table 10. Characteristics of incident juvenile idiopathic arthritis patients during 2000–2014 in Finland. Reprinted with permission of Clinical and Experimental Rheumatology from Publication I © 2019 Springer.**

	Females	Males	Total
Number	2,603	1,577	4,180
Mean age on the index day, years (SD)	8.4 (5.0)	8.3 (4.6)	8.3 (4.8)
Follow-up, person years	17.98	10.97	28.94
Median follow-up time, years (IQR)	6.5 (3.1–10.5)	6.7 (3.1–10.7)	6.6 (3.1–10.5)
Mean age at the end of follow-up, years (SD)	14.8 (6.4)	14.8 (6.3)	14.8 (6.4)

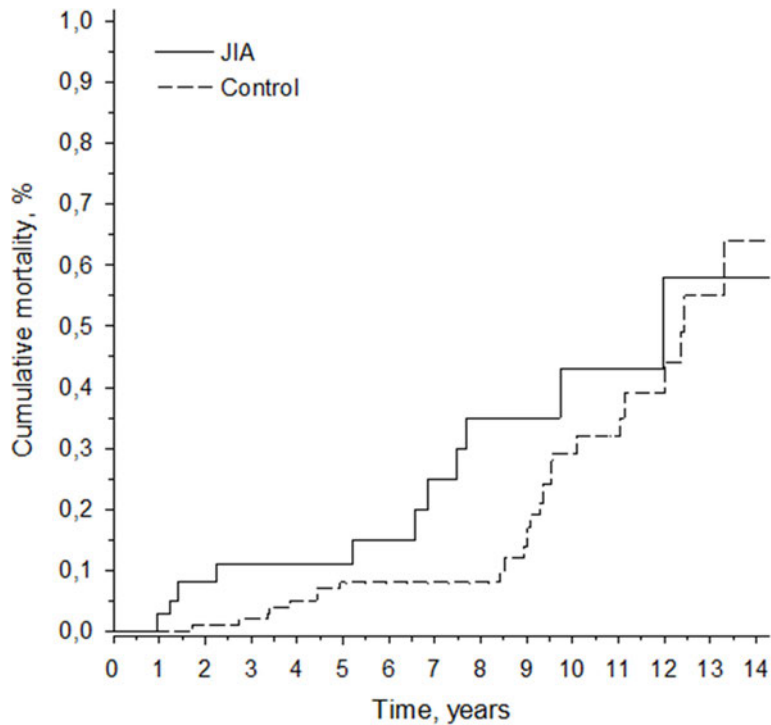
QR = interquartile range, SD = standard deviation

### 5.2 Mortality (Study I)

In study I, we found no difference in the incidence of deaths between JIA and controls or between genders. During the follow-up time, eleven JIA patients (6 females, 5 males) and 23 controls (12 females, 11 males) died. There was no difference in age at death between JIA and controls; mean age at death was 20.3 years (range 11–30) in JIA patients and 23.1 years (range 9–29) in controls ( $p = 0.17$ ).

The cumulative mortality is presented in Figure 1. The mortality did not differ between the JIA patients and controls. Ten-year cumulative mortality was 0.4% (95% CI 0.2–0.8) in the JIA group vs. 0.3% (95% CI 0.2–0.5) in the controls, and at the end of the follow-up, 0.6% (95% CI 0.3–1.2) vs. 0.6% (95% CI 0.4–1.0), respectively. The risk of death in the JIA group was not elevated compared to controls, with HR 1.4 (95% CI 0.7–3.0;  $p = 0.32$ ) or by gender perspective, being

1.5 in females with JIA (95% CI 0.6–4.0;  $p = 0.42$ ) and 1.4 in males with JIA (95% CI 0.5–3.9;  $p = 0.56$ ).



**Fig. 1. Cumulative mortality of the patients with incident juvenile idiopathic arthritis (JIA) and the control group. Reprinted with permission of Clinical and Experimental Rheumatology from Publication I © 2019 Springer.**

### 5.3 Causes of death (Study I)

There was no statistically significant difference in primary causes of death between JIA patients and controls (Table 11).

Among JIA patients, accidents were the most common (54%) cause of death, HR 2.6 (95% CI 0.9–7.3) compared to controls. During the follow-up time, JIA patients had six accidental deaths including two poisoning accidents, one skating accident, one drowning accident, one motor vehicle accident, and one riding accident. Correspondingly, the controls had seven accidental deaths, mainly motor vehicle accident deaths (71%).

However, suicide was the most common (39%) cause of death in the controls. There were only two suicide deaths in the JIA group, with HR 0.7 (95% CI 0.2–3.0). Psychiatric disorders such as depression, alcohol and drug abuse were the most common contributing causes of deaths in the controls (39%), but in only 1% in the JIA group,  $p = 0.053$ . Deaths due to infection, cancer and violence were rare.

There were only two deaths due to other causes of death among JIA patients and controls. In this group, JIA itself caused one death. This patient had systemic JIA and contributing causes to death were viral gastroenteritis and pneumonia. Down syndrome was recorded as the cause of one death, with seronegative JIA and diabetes as contributing causes. The reason for one death in the control group was unclear and one death was caused by mitochondrial muscle disease.

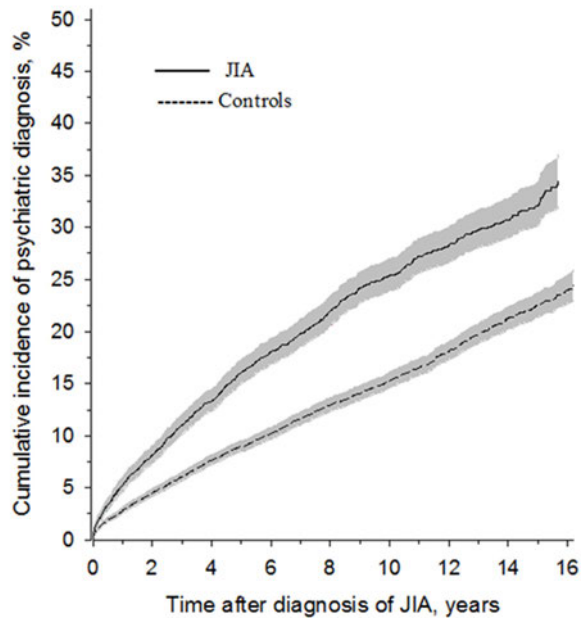
**Table 11. Causes of death among the JIA patients and controls during follow-up.**

Underlying causes of death	JIA 11 (%)	Controls 23 (%)
Accidents	6 (54)	7 (30)
Suicide	2 (18)	9 (39)
Infections	1 (1)	1 (4)
Cancer	0 (0)	3 (13)
Violence	0 (0)	1 (4)
Others	2 (1)	2 (9)

JIA = juvenile idiopathic arthritis

#### 5.4 Psychiatric morbidity (Study II)

In study II we evaluated all psychiatric disorders among JIA patients and controls and found that 959 (22.9%) JIA patients and 1,787 (14.3%) controls were diagnosed with some mental or behavioral disorder during the median follow-up time of 6.6 years (IQR 3.1–10.5). The cumulative incidence of psychiatric morbidity is shown in Figure 2. The risk of developing psychiatric disorders was higher among the JIA patients compared to controls,  $p < 0.001$ . Females with JIA had higher risk than males with JIA, HR 1.8 (95% CI 1.7–2.0) in females, HR 1.5 (95% CI 1.3–1.7) in males.



**Fig. 2. Kaplan-Meier-estimated psychiatric morbidity of the patients with incident juvenile idiopathic arthritis (JIA) and controls. Re-adapted CC BY 4.0 Licensed Image of Publication II © 2021, Kyllönen, Ebeling, Kautiainen, Puolakka and Vähäsalo.**

## 5.5 Incidence of mental and behavioral disorders (Study II)

In study II, we found that in both JIA patients and controls, the three most common disorders were neurotic, stress-related and somatoform disorders (F40–48); mood disorders (F30–39); and childhood behavioral and emotional disorders (F90–98) (Table 12).

Considering gender, females with JIA had higher incidence rates than males with JIA compared to controls. The incidence rate ratio of all diagnoses was 1.7 (95% CI 1.6–1.9) in females with JIA and 1.5 (95% CI 1.3–1.7) in males with JIA. In females, the risk of developing mental and behavioral disorder was significantly elevated in all other diagnosis groups except two minor groups: mental and behavioral disorders due to psychoactive substance use (F10–19) and disorders of adult personality and behavior (F60–69). However, in males the risk was increased in only three diagnosis groups: neurotic, stress-related and somatoform disorders (F40–48), behavioral syndromes associated with physiological disturbances and

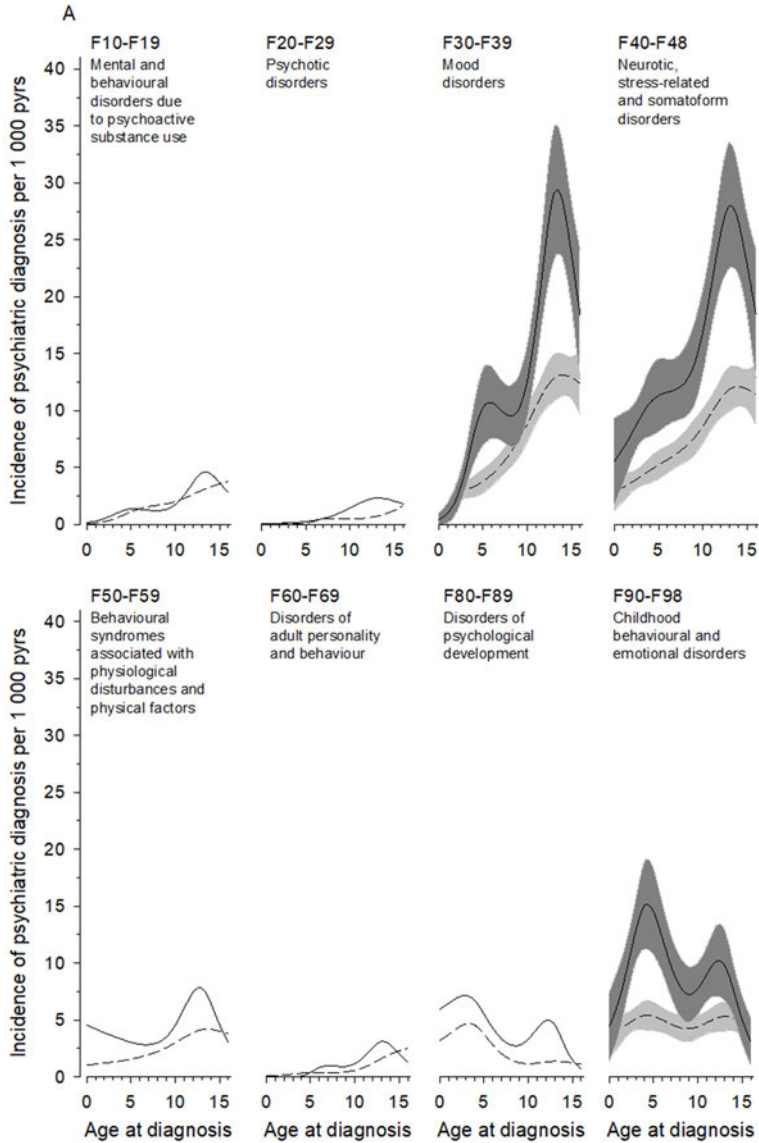
physical factors (F50–59) and childhood behavioral and emotional disorders (F90–98) (Table 12).

**Table 12. Incidence of psychiatric diagnoses per 1,000 person years (pyrs) and incidence rate ratios in juvenile idiopathic arthritis (JIA) patients compared to controls. Re-adapted CC BY 4.0 Licensed Image of Publication II © 2021, Kyllönen, Ebeling, Kautiainen, Puolakka and Vähäsalo.**

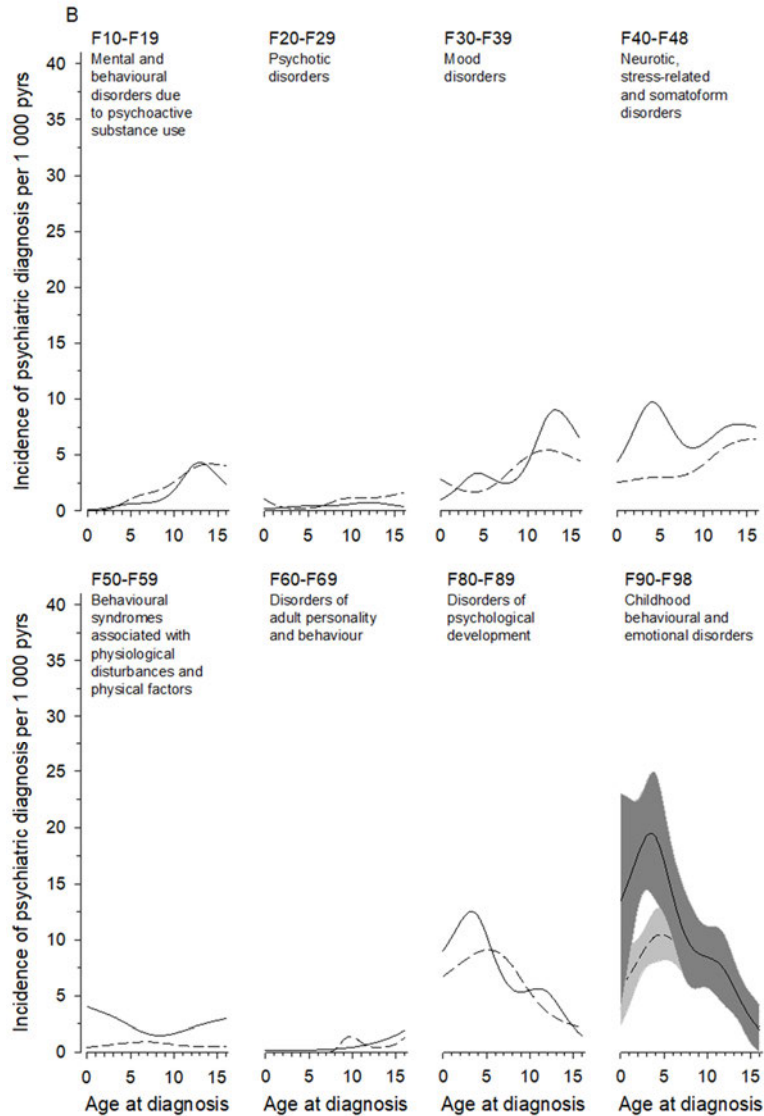
Psychiatric Diagnoses (ICD-10)	JIA Incidence/1,000 pyrs (95%CI)	Controls Incidence/1,000 pyrs (95%CI)	IRR (95%CI)
(F10–19)			
Females	2.0 (1.5– 2.7)	1.8 (1.5–2.1)	1.1 (0.8– 1,6)
Males	1.7 (1.1– 2.6)	2.1 (1.7–2.6)	0.8 (0.5– 1.3)
(F20–29)			
Females	1.0 (0.7–1.6)	0.5 (0.3–0.7)	2.2 (1.3– 3.7)
Males	0.5 (0.2–1.0)	0.8 (0.6–1.2)	0.6 (0.3– 1.4)
(F30–39)			
Females	12.9 (11.4–14.5)	7.3 (6.7–8.0)	1.8 (1.5– 2.0)
Males	4.6 (3.5–5.9)	3.6 (3.0–4.2)	1.3 (0.9– 1.7)
(F40–48)			
Females	15.5 (13.9–17.3)	7.6 (6.9–8.3)	2.0 (1.8– 3.5)
Males	7.3 (6.0– 8.9)	4.1 (3.5–4.8)	1.8 (1.4– 2.3)
(F50–59)			
Females	4.4 (3.6– 5.4)	2.6 (2.2–3.0)	1.7 (1.4– 2.2)
Males	2.5 (1.7–3.4)	0.70 (0.5–1.0)	3.6 (2.2– 5.8)
(F60–69)			
Females	1.1 (0.7–1.7)	0.9 (0.7–1.1)	1.3 (0.8– 2.0)
Males	0.6 (0.3–1.1)	0.5 (0.3–0.70)	1.3 (0.6– 2.9)
(F80–89)			
Females	4.5 (3.6–5.4)	2.5 (2.1–2.9)	1.8 (1.4– 2.3)
Males	7.1 (5.7–8.6)	6.0 (5.3–6.8)	1.2 (0.9– 1.5)
(F90–98)			
Females	9.2 (7.9–10.5)	4.8 (4.3–5.3)	1.9 (1.6– 2.3)
Males	10.9 (9.2–12.8)	7.4 (6.6–8.3)	1.5 (1.2– 1.8)

CI = confidence interval, ICD-10 = International Classification of Diseases 10th Revision, IRR = incidence

Children who contracted JIA in early childhood seemed to have the highest incidence rate of behavioral disorders while females who developed JIA in adolescence seemed to have the highest incidence rate of neurotic, stress-related and somatoform and mood disorders (Figure 3).



**Fig. 3. A** Incidence rate of psychiatric diagnoses in females with juvenile idiopathic arthritis (JIA) and in control females according to age in years at JIA onset in eight main psychiatric diagnostic categories (F10–F98). Incidence rate of JIA is indicated with a solid line and incidence rate of controls with a dashed line. Grey area represents 95% confidence intervals. Re-adapted CC BY 4.0 Licensed Image of Publication II © 2021, Kyllönen, Ebeling, Kautiainen, Puolakka and Vähäsalo.



**Fig. 3. B** Incidence rate of psychiatric diagnoses in males with juvenile idiopathic arthritis (JIA) and in control males according to age in years at JIA onset in eight main psychiatric diagnostic categories (F10–F98). Incidence rate of JIA is indicated with a solid line and incidence rate of controls with a dashed line. Grey area represents 95% confidence intervals. Re-adapted CC BY 4.0 Licensed Image of Publication II © 2021, Kyllönen, Ebeling, Kautiainen, Puolakka and Vähäsalo.

## 5.6 Psychotropic medication use (Study III)

In study III we found that psychotropic medication use was higher among JIA patient than controls,  $p < 0.001$ . There were 566 (13%) JIA patients who purchased some psychotropic drug at least once while the number in the control group was 1,294 (10%).

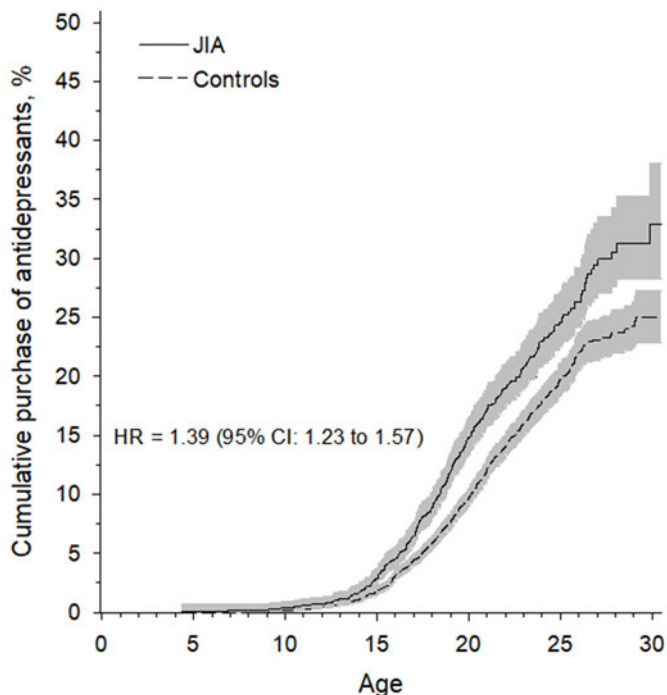
The psychotropic drug purchases and risk ratios in six drug groups are shown in Table 13. Both in JIA patients and in controls, the three most commonly purchased drugs were antidepressants, antipsychotics and anxiolytics.

**Table 13. The number of persons who purchased psychotropic drugs after the index date by drug category and the risk ratios between JIA patients and controls. Reprinted with permission of Clinical and Experimental Rheumatology from Publication III © 2023 Springer.**

Psychotropic medication (ATC code)	JIA (4,180) n(%)	Controls (12,512) n(%)	RR (95%CI)
1 Antidepressant (N06A)	393 (9.4)	890 (7.1)	1.3 (1.2–1.5)
2. Antipsychotics (N05A)	188 (4.5)	418 (3.3)	1.3 (1.1–1.6)
3. Anxiolytics (N05B)	127 (3.0)	265 (2.1)	1.4 (1.2–1.8)
4. Hypnotics (N05C)	93 (2.2)	214 (1.7)	1.3 (1.0–1.7)
5. Psychostimulants, agents used for ADHD and nootropics (NO6B)	68 (1.6)	205 (1.6)	1.0 (0.8–1.3)
6. Psycholeptics and psychoanaleptics in combination (N06C)	12 (0.3)	14 (0.1)	2.6 (1.2–5.5)

ATC code = Anatomical Therapeutic Chemical code, JIA = juvenile idiopathic arthritis, RR = risk ratio

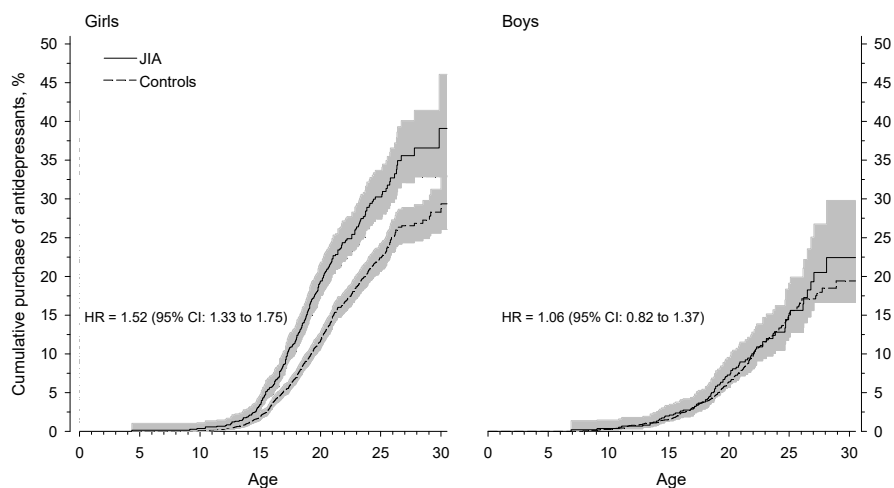
Among JIA patients antidepressant purchases were more frequent, 9.4% (393), than in controls, 7.1% (890),  $p < 0,001$  (Figure 4). The probability of purchase of the first antidepressant was higher among JIA patients, hazard ratio 1.4 (95% CI 1.2–1.6).



**Fig. 4. Cumulative purchases of first antidepressants in incident juvenile idiopathic arthritis (JIA) patients and in controls according to age. HR = hazard ratio, CI = confidence interval. Reprinted with permission of Clinical and Experimental Rheumatology from Publication III © 2023 Springer.**

Taking into account gender, in both study groups females purchased more antidepressants than males, 12% (308) of females with JIA vs. 5.4% (85) of males with JIA, whereas the numbers in the control group were 8.5% (659) and 4.9% (231), respectively. The difference between JIA females and control females was statistically significant.

The probability of purchasing the first antidepressant increased in late adolescence (after 15 years of age) in females but not in males compared to controls, hazard ratio 1.5 (95% CI 1.3–1.8) in females, 1.1 (95% CI 0.8–1.4) in males (Figure 5).



**Fig. 5. Cumulative purchases of the first antidepressant in incident juvenile idiopathic arthritis (JIA) patients and in controls according to gender and age. HR = hazard ratio, CI = confidence interval.**

We further analyzed antidepressants and reported results in four drug types (selective serotonin reuptake inhibitors (N06AB), monoamine oxidase A inhibitors (N06AG), non-selective monoamine reuptake inhibitors (N06AA) and other antidepressants (N06AX) (Table 14). We found that selective serotonin reuptake inhibitors (SSRIs) were the most commonly purchased drug group in both patients and controls (Table 14). When comparing patients with controls, females with JIA were more likely to purchase different antidepressant types than males with JIA (Table 15). In females, the use of these drugs was significantly elevated in two drug groups: other antidepressants and non-selective monoamine reuptake inhibitors. Among males with JIA, purchases of different antidepressant types were significantly increased in one drug group: non-selective monoamine reuptake inhibitors. The use of monoamine reuptake inhibitors was rare among the controls and none of the JIA patients purchased these drugs.

**Table 14. The number of persons who purchased antidepressants after the index date by seven-digit-level of ATC code.**

Antidepressants (ATC code)	JIA (4,180)	Controls (12,512)
Non-selective monoamine reuptake inhibitors (N06AA)		
Clomipramine	1 (0.0)	18 (0.1)
Trimipramine	1 (0.0)	9 (0.1)
Amitriptyline	27 (0.7)	33 (0.3)
Nortriptyline	4 (0.1)	12 (0.1)
Doxepin	4 (0.1)	15 (0.1)
Selective serotonin reuptake inhibitors (N06AB)		
Fluoxetine	96 (2.3)	660 (5.3)
Citalopram	86 (2.1)	522 (4.2)
Paroxetine	8 (0.2)	95 (0.8)
Sertraline	60 (1.4)	466 (3.7)
Fluvoxamine	2 (0.1)	9 (0.1)
Escitalopram	117 (2.8)	928 (7.4)
Monoamine oxidase A inhibitors (N06AG)		
Moclobemide	0 (0)	20 (0.2)
Other antidepressants (N06AX)		
Mianserin	2 (0.1)	23 (0.2)
Trazadone	5 (0.1)	23 (0.2)
Mirtazapine	122 (2.9)	679 (5.4)
Bupropion	21 (0.5)	118 (0.9)
Venlafaxine	63 (1.5)	369 (3.0)
Milnacipran	2 (0.1)	3 (0.0)
Reboxetine	0 (0.0)	9 (0.1)
Duloxetine	21 (0.5)	68 (0.5)
Agomelatine	5 (0.1)	18 (0.1)
Vortioxetine	2 (0.1)	21 (0.2)

ATC code = Anatomical Therapeutic Chemical code, JIA = juvenile idiopathic arthritis

**Table 15. Purchases of different antidepressant types per 1,000 person years among the JIA patients and the controls. Reprinted with permission of Clinical and Experimental Rheumatology from Publication III © 2023 Springer.**

Antidepressant type	JIA Mean (95%CI)	Control Mean (95%CI)	P-value
<b>Females</b>			
Selective serotonin reuptake inhibitors (NO6AB) *	72.4 (68.8–76.2)	65.2 (63.2–67.3)	0.34
Monoamine oxidase A inhibitors (NO6AG) *	0.0 (0.0–0.2)	0.1 (0.0–0.2)	0.021
Non-selective monoamine reuptake inhibitors (NO6AA)*	5.1 (4.1–6.1)	0.6 (0.4–0.9)	<0.001
Other antidepressants (NO6AX)*	50.9 (47.9–54.1)	27.6 (26.3–29.0)	<0.001
<b>Males</b>			
Selective serotonin reuptake inhibitors (NO6AB) *	20.1 (17.7–22.7)	30.7 (28.9–32.5)	0.055
Monoamine oxidase A inhibitors (NO6AG) *	0.0 (0.0–0.3)	2.5 (0.2–0.6)	0.001
Non-selective monoamine reuptake inhibitors (NO6AA) *	2.5 (1.7–3.5)	0.3 (0.2–0.6)	0.003
Other antidepressants (NO6AX) *	14.0 (12.0–16.2)	14.7 (13.5–16.0)	0.88

**CI = confidence interval, JIA = juvenile idiopathic arthritis; \*See Table 9.**



## 6 Discussion

### 6.1 Mortality and causes of death (Study I)

Mortality among JIA patients was not elevated compared to control population in Finland during the follow-up time in study I. In four studies published in this millennium, the results are similar to those in our study (Glerup et al., 2020; Hashkes et al., 2010; Krause et al., 2016; Minden et al., 2002).

Higher mortality in JIA patients has been shown in previous cohort studies with data collected in the last century and with follow-up periods longer than in study I (Baum & Gutowska, 1977; French et al., 2001; Krause et al., 2016; Laaksonen, 1966; Tollisen et al., 2017, 2019). In addition, two studies found that mortality in patients with JIA was higher than in general population (French et al., 2001; Krause et al., 2016).

The mean age of death among JIA patients in study I was lower than in the earlier studies with longer follow-up periods (French et al., 2001; Laaksonen, 1966) and higher than in the study conducted in an era when amyloidosis-related deaths were common (Baum & Gutowska, 1977). The incidence of amyloidosis among JIA patients has decreased simultaneously with the development of new DMARDs, which has improved the prognosis of JIA (Baum & Gutowska, 1977; Immonen et al., 2008; Laaksonen, 1966; Savolainen & Isomaki, 1993).

In study I, accidents were the main cause of death in JIA patients. A Finnish study from the last century reported similar results (Savolainen & Isomaki, 1993). The number of trauma deaths doubled from 1969–1979 to 1980–1990 among JIA patients, possibly due to their better physical condition and rare invalidity (Savolainen & Isomaki, 1993). The same trend has been shown in general both among Finnish children and worldwide: accident-related deaths have become the most common cause of death (Lantto et al., 2008; Peden et al., 2008).

The other causes of underlying death, e.g., infectious and underlying JIA disease-related deaths, were rare in JIA patients in study I. These results are in line with the research findings in this millennium (Hashkes et al., 2010). Studies from the last century have reported a higher number of underlying infectious deaths (Baum & Gutowska, 1977).

In study I, only two JIA patients committed suicide, and mental disorders due to psychoactive substance use were a contributing factor to the death in one JIA patient. However, Finnish studies found that suicide deaths increased among people

aged 15–19 in general and doubled among JIA patients in the last century (Lantto et al., 2008; Savolainen & Isomaki, 1993). One explanation for these results is thought to be the increased use of narcotics drugs and alcohol among young people (Gould et al., 2003). However, since the end of the last century, suicide numbers have been decreased, but at the same time, the use of antidepressants and mental health services has increased (Bonati & Clavenna, 2005; Comer et al., 2010; Gómez-Lumbreras et al., 2021; Gould et al., 2003; Gyllenberg et al., 2018; Haapasalo-Pesu et al., 2003; Karukivi & Haapasalo-Pesu, 2017; Steinhausen, 2015).

## **6.2 Mental and behavioral disorders (Study II)**

In the present study II, mental and behavioral disorders among children and adolescent with JIA were statistically significantly increased compared to the control population,  $p < 0.001$ . We reported all psychiatric diagnoses. The five most common disorders were neurotic, stress-related and somatoform disorders (F40–48); mood disorders (F30–39); behavioral syndromes associated with physiological disturbances and physical factors (F50–59); disorders of psychological development (F80–89), and childhood behavioral and emotional disorders (F90–98).

These results are in line with some self-reported questionnaire studies from recent years and with three small clinical assessment studies, although the research settings differ from our study and self-reported questionnaire studies are focused only on depression, anxiety and behavioral symptoms (Barth et al., 2016; Bomba et al., 2013; Kayan Ocakoglu et al., 2018; Krause et al., 2017; Memari et al., 2016; Mullick et al., 2005; Vandvik, 1990). However, a Swedish cohort study did not show statistically significantly more depression and anxiety disorders in patients with JIA than in controls (Berthold et al., 2022). According to the authors, one explanation for the results might be team-based care, which includes preventive psychological counselling for patients with JIA.

Furthermore, some small studies using self-questionnaires found no more psychiatric symptoms in children and adolescents with JIA than in healthy controls (Ding et al., 2008; Huygen et al., 2000; Tarakci et al., 2011). In addition, most previous quality of life studies on adult JIA patients do not report poorer mental health compared to controls (Arkela-Kautiainen et al., 2005; Flato et al., 2003; Foster et al., 2003; Ostile et al., 2010; Peterson et al., 1997; Raab et al., 2013; Tollisen et al., 2017).

### **6.2.1 Factors associated with mental and behavioral disorders/symptoms in JIA**

According to previous studies, psychiatric problems have been described as being associated with active disease, lack of adaptation to the disease, intra-family difficulties, peer problems and patient's poor mental maturity (Barth et al., 2016; Bomba et al., 2013; LeBovidge et al., 2005; Mullick et al., 2005; Vandvik, 1990). Vandvik et al, found a correlation between chronic family difficulties and child's psychosocial functioning, especially in polyarthritis patients' families (Vandvik, 1990). Mullick et al reported significantly higher distress, social impairment and perceived difficulties in patients with psychiatric disorders compared to patients without these disorders (Mullick et al., 2005). In addition, among patients with increased psychiatric morbidity, overprotection was observed on the part of the parents (Mullick et al., 2005). A few other studies have shown a connection between active joint count, high level of pain, increased anxiety and depression in JIA (Fair et al., 2022; Hanns et al., 2018; Kosola & Relas, 2021; Margetic et al., 2005; Ostile et al., 2010; Ostlie et al., 2009; Rebane, 2020; Tarakci et al., 2011; Vuorimaa et al., 2008). The onset of JIA can lead to anxiety and depression, which could predict disability and worse pain over the next four years after the diagnosis of JIA (Hanns et al., 2018; Vuorimaa et al., 2008). A Finnish study reported that high level of pain in patients with JIA was also associated with parental depressive symptoms, and pain interference was associated with antidepressants, opioids, non-steroidal anti-inflammatory drugs, disease modifying antirheumatic drugs, lower educational achievement, smoking and older age (Rebane, 2020).

One study from the United Kingdom has reported that children with JIA feel anxiety about issues related to the treatment of JIA such as injections and blood tests (Mulligan et al., 2013). In addition, corticosteroids can cause side effects, such as behavioral problems for children (Pinquart & Shen, 2011b). According to biological research, the association between the cytokines interleukin 6 and 1 and obsessive-compulsive disorders has been recognized in adolescence in the general population (Westwell-Roper et al., 2022). In addition, high acute phase protein levels and environmental stress have been reported to predict depression in childhood and in adolescence in general (Zajkowska et al., 2021). Finally, varying numbers of psychiatric symptoms in self-reported questionnaire studies have also been found to be associated with the data source: the numbers are higher for teacher or parent reports than for child and adolescent reports (Billings et al., 1987; Pinquart & Shen, 2011a, 2011b).

### **6.3 The effect of age at onset of JIA on mental and behavioral disorders (Study II)**

In study II we reported that early childhood onset of JIA increased the risk for behavioral disorders and that patients with disease onset in adolescence had increased risk for anxiety and depression compared to controls (Figure 3). Research on this topic is limited and the research settings differ. However, some previous study results are similar to our results. At the beginning of this millennium, a study focusing only on depression and anxiety reported that patients with age at onset in early adolescence seemed to have higher risk of depression and anxiety than patients who contracted JIA in childhood (Packham, 2002). In addition, an Italian study has found that children tend to have separation difficulties, behavioral problems and sleep disturbances while in adolescence, emotional lability is more common (Russo et al., 2012). Children with JIA were often concerned about their disease status and reported that pain disturbed their daily activities. However, adolescents reported that disease affected their body image (Russo et al., 2012). In addition, a multicenter study reported that according to their parents, the children with JIA who developed the disease before the age of five had less emotional and behavioral problems than older children (April et al., 2013).

According to psychological theories, children under the age of 7 years tend to react to the disease by expressing rage and aggression because of limited ego function, and this may lead to behavioral problems (D'Alborton et al., 2012). However, in adolescence, issues of normal personality development, sexuality, bodily changes and autonomy can give rise to anxiety, phobias and obsessive-compulsive disorders (D'Alborton et al., 2012; Turkel & Pao, 2007). In addition, lower self-identity and self-confidence and a sense of loss are risk factors for these disorders in adolescence, too (Packham, 2002). However, children's and adolescents' positive attitude to life, normal social participation, social competence and good social support by their parents and teachers are important factors in adjustment to disease (Huygen et al., 2000).

The incidence of mental and behavioral disorders is age-related also generally; adolescents have more anxiety than children, who for their part have more behavioral problems (Costello et al., 2006; Kessler et al., 2007; Miettunen et al., 2019).

## 6.4 The use of psychotropic medication (Study III)

In study III we evaluated the use of psychotropic medication in JIA. The risk of use of these drugs, especially antidepressants, antipsychotics and anxiolytics, was higher in patients with JIA compared to controls. In addition, further analysis showed that the most common antidepressants were SSRIs. The users were more often females than males among all psychotropics and among SSRIs, non-selective monoamine reuptake inhibitors and other antidepressants.

Studies evaluating psychotropic medication in patients with JIA are mainly limited to the use of antidepressants in the treatment of pain (Anthony & Schanberg, 2005; Huber et al., 2007; Rebane et al., 2019). A Finnish questionnaire-based study on adolescent JIA patients aged 18–30 years (n = 195) reported that 8.7% of the participants used antidepressants, and the use was significantly associated with greater experience of pain disturbance (Rebane et al., 2019). Furthermore, greater pain interference was associated with higher pain-related anxiety, older age and female gender. Another study showed that late start of biologic DMARDs was associated with antidepressant use (Montag et al., 2022).

SSRIs as first-line treatment in treating depression and official indication to treat anxiety disorders such as obsessive-compulsive disorders have been reported in Finnish birth cohort studies at the end of the 20<sup>th</sup> century and beginning of the 2000s (Gyllenberg et al., 2011; Haapasalo-Pesu et al., 2003). SSRIs have been found to be safer in terms of suicide risk than other antidepressants, which are usually second-line or third-line options in clinical use. (Finnish Medical Society Duodecim & Finnish Association of Psychiatrists, 2022; Haapasalo-Pesu et al., 2003; Solmi et al., 2020).

In addition, an increase in the use of antidepressants has been reported in the treatment of pain among children and adolescents (John et al., 2016; Sarginson et al., 2017). SSRIs, SNRIs and tricyclic antidepressants have been used to treat several pain syndromes and juvenile fibromyalgia in children (Gmuca & Sherry, 2017; Mathew et al., 2016). Tricyclic antidepressants are recommended to relieve chronic pain in children and adolescents in general population in the UK (Gmuca & Sherry, 2017; John et al., 2016; Mathew et al., 2016; Sarginson et al., 2017). A Finnish 1981 birth cohort study has shown that a child's own experience of pain at age eight was associated with emotional problems and predicted antidepressant use in adolescence (Luntamo et al., 2012). With reference to previous research and taking into account the results of study II, these may to some extent explain the

increased use of antidepressants in adolescent JIA patients compared to controls in study III.

In study III, the purchase of antidepressants was more common after 15 years of age than among younger JIA patients and controls (Figure 5). This result is in line with a previous Finnish birth cohort study evaluating antidepressant use in adolescence in general population (Gyllenberg & Sourander, 2012), an epidemiological study from the USA and Europe (Bonati & Clavenna, 2005), a UK national study of adolescents (Olfson et al., 2013) and a multi-national study from the Nordic countries, too (Gómez-Lumbreras et al., 2021). In addition, with reference to previous studies, severe depression and anxiety usually break out in adolescence (Berthold et al., 2022; Costello et al., 2011; Kessler et al., 2007; Miettunen et al., 2019; Rapoport, 2013; Russo et al., 2012; Turkel & Pao, 2007).

Due to the nature of our research, i.e., a register study, we were not able to analyze the exact underlying reason for the use of psychotropic drugs. However, psychotropic medication is often used off-label: some antipsychotics are used to treat depression, anxiety, hyperkinetic and developmental disorders (Gyllenberg & Sourander, 2012; Haapasalo-Pesu et al., 2016; Olfson et al., 2012; Varimo et al., 2020). In addition, users of antipsychotics simultaneously purchase antidepressants, mood stabilizers and benzodiazepines to some extent (Gyllenberg et al., 2011; Gyllenberg & Sourander, 2012; Varimo et al., 2022).

According to previous research, at the same time as the use of psychotropic drugs has increased, prescribing practices have changed (off-label use), the number of child and adolescent psychiatrists has increased, and psychological interventions have decreased (Hoffmann et al., 2014; Varimo et al., 2020). In addition, in the last millennium the use of specialized care for psychiatric disorders increased. The explanation for this might be a lower threshold for seeking help and increased need for diagnoses in order to get social, educational and financial support (Gyllenberg et al., 2018).

## **6.5 The effect of gender on mental and behavioral disorders and antidepressant use (Study II and III)**

In study II, the incidence rate of neurotic, stress-related and somatoform disorders and mood disorders seemed to be higher among females than males who developed JIA in adolescence as only few males have similar disorders (Figure 3). However, in study II, when JIA was diagnosed in childhood, disorders of psychological development and childhood behavioral and emotional disorders were more

common in males than in females (Figure 3). Some previous studies have also reported more depression and anxiety in adolescence in females with JIA than in males with JIA (Hanns et al., 2018; Margetic et al., 2005). A meta-analysis about behavioral problems in chronically ill children reported more of these problems in male participants (Pinquart & Shen, 2011b). However, in general, it is natural for boys to react with behavioral symptoms compared to girls (Hankin et al., 2015; Ostlie et al., 2009; Pinquart & Shen, 2011b).

A gender difference in psychiatric disorders has also been observed in the general population: females have more anxiety, depression and behavioral problems in adolescence while males have more of them in childhood (Costello et al., 2006; Hankin et al., 2015; Miettunen et al., 2019). In addition, females with chronic illness in adolescence seem to use mental health services and seek professional help for mood disorders more than males (Karukivi & Haapasalo-Pesu, 2017).

In study III we also reported more antidepressants use in females in adolescence than in males with JIA. With reference to previous research, in addition, a study on JIA and pain and a multicenter registry study on medication burden in patients with JIA reported more use of antidepressants in females than in males (Montag et al., 2022; Rebane et al., 2019). This gender difference in the use of antidepressants is also well known in the general population (Bonati & Clavenna, 2005; Gómez-Lumbreras et al., 2021; Gyllenberg et al., 2011; Haapasalo-Pesu et al., 2003; Olfson et al., 2013; Steinhausen & Bisgaard, 2014).

## **6.6 Strengths and limitations**

This study has multiple strengths. As far as I know, there are no previous longitudinal or cross-sectional studies on the use of all psychotropic medication in JIA or psychiatric diagnoses (ICD-10) in all new-onset JIA in this millennium. The cases for this study were obtained from the SII. Only patients who had diagnoses (ICD-10 codes M08.0–M08.9 or M09.0\*L40.5) and met the reimbursement decision criteria for appropriate diagnostic tests, diagnosis and treatment plan were included. In addition, the diagnosis for reimbursement decision is verified both by the physician treating JIA and by an SII official. For each case, the National Population Registry identified three controls matched for age, sex and place of residence. The controls were included in all analyses of all studies (I–III). The number of controls was three times that of cases, which is in line with good research

practice. This study has a large study population and therefore great statistical power.

The registers used in all studies I–III are comprehensive, nationwide and high-quality registers. The Care Register of the National Institute for Health and Welfare is systematically quality controlled and logical errors are algorithmically checked, and any detected errors are sent to hospitals for correction (Sund, 2012). Furthermore, the mortality data are based on a comprehensive death certificate. All death cases are immediately filed in the population information system (Finnish Digital Agency) and then forwarded to Statistics Finland. If the cause of death is or is suspected to result from an accident, suicide, crime or poisoning or if the reason is unknown, an autopsy is performed.

However, the registers used in this study have some limitations. The material may contain incorrect information, such as incorrect mental and behavioral diagnoses and incorrect causes of deaths. This could impact the results of study I and II. The SII has no clinical data available on JIA categories and the diagnoses of psychotropic medication use. Causality cannot be assessed between mental and behavioral disorders and the psychotropic medication used in this study. The study looked at the first purchase of psychiatric medication, so there is no information on long-term use, and therefore, on long-term mental and behavioral disorders.

Mild mental health problems which do not require specialized care are not included. In addition, the drug purchase register does not include medications used in inpatient care. Furthermore, register study as a research setting may cause bias when comparing mental and behavioral disorders and the use of psychotropic medication between cases and controls because it does not register those healthy controls who might have mental health problems but are less inclined to seek health services than JIA patients with a regular contact with health care. JIA patients might drift to increased use of mental health services due to parental concern about the child's active disease or due to physician's worries about the patient's emotional life.

There are some limitations regarding patient selection in this study. Mild cases or early stage of disease with no need of DMARD were not included in this study. The number of patients who do not need DMARDs varies between 11% and 62%, mostly due to differences in the year of diagnosis (1997–2019), follow-up time, and data source (register or hospital records) (Brunner et al. 2020; Glerup et al. 2020). According to the Finnish Rheumatology Quality Register preliminary report, approximately 20% of children with juvenile idiopathic arthritis diagnosed in the years 2016–2021 did not need DMARDs during the first year after diagnosis (P.

Vähäsalo, personal communication, March 1, 2023). It seems that the use of DMARDs for mild cases has increased in recent years. The reimbursement policy does not apply to inpatient care, so patients with a severe disease who receive only i.v. medication given at a rheumatic clinic were not included. Therefore, the study results, the increased number of mental and behavioral disorders and the increased use of psychotropic medication can be generalized to a selected group of JIA patients. Some JIA patients may also have died before applying for reimbursement for drug treatment. In studies I–III, the date of reimbursement decision defined the index day and also the age of onset, but in some of the cases the disease may have started earlier.

The limitation of this study is the shorter follow-up time than in previous mortality studies (Baum & Gutowska, 1977; French et al., 2001; Hashkes et al., 2010; Koivuniemi & Leirisalo-Repo, 1999; Krause et al., 2016; Laaksonen, 1966; Minden et al., 2002), which causes bias in the number of deaths and causes of deaths. In addition, the shorter follow-up time might not have been long enough for a psychiatric diagnosis in some patients.

## **6.7 Clinical implications and future studies**

Previous follow-up studies have reported that, e.g., patients with psoriasis arthritis, ERA and RF-positive arthritis have poorer outcome (active disease, damage and pain) than other JIA subclasses. However, there is a lack of information on causes of death according to JIA. We were also unable to evaluate this issue. It would be interesting to find out which causes of death occurred in the different JIA subclasses. Therefore, further research is needed on this subject in the future.

There is a lack of information on psychiatric disorders and JIA subclasses, too. Earlier studies have reported poorer quality of life in ERA, extended oligoarthritis and psoriarthritis patients than in other JIA subclasses. The association between ANA-positivity and anxiety or depression has also been studied, but none has been found. Further studies are needed to assess the possible role of JIA subclasses in all psychiatric disorders. In addition, earlier studies have shown comorbidity of psychiatric disorders in general population. Further studies addressing this issue among JIA patients are needed.

There are only few previous studies on the use of antidepressants and psycholeptics in JIA. These previous studies and the results of this study reflect the presence of clinically important pain and mental health problems in JIA patients. Further studies are needed to verify these findings. In addition, clinical assessment

studies are needed to deepen the knowledge about the indications for use of psychotropic medication among JIA patients.

This study and previous studies increase awareness of the psychiatric morbidity and mortality of JIA patients. They show that possible mood symptoms of JIA patients must be taken into account in primary or school health care and child health clinics. In addition, these results indicate that mental health assessment (anxiety and depression questionnaires) should be used in clinical practice for those who contracted JIA in adolescence, especially for females. There is a need for multiprofessional (rheumatologist, psychiatrist) collaboration in patient care, such as psychiatric assessment of patients who show anxiety or depression symptoms according to questionnaire answers.

## 7 Conclusions

1. Mortality did not differ between patients with JIA and controls in this study and in previous studies published in this millennium. Earlier studies reported deaths related to amyloidosis and infections. In this study, the main cause of death was accidents in patients with JIA while other causes of deaths were rare. Compared to controls, JIA patients had a trend towards higher risk of accidental deaths. The age of death was the same in both study groups. These results indicate that in the era of modern drug treatment (DMARDs and biologic DMARDs) for JIA, the life expectancy of the patients with JIA is as good as that of the controls, and fatal infections might be rare.
2. This study is the first to report the whole spectrum of mental and behavioral disorders among patients with JIA. There were more of these disorders in JIA patients compared to controls and the disorders were associated with the age at JIA onset and gender. Females with JIA had higher risk than males with JIA. Early childhood onset of JIA increased the risk for behavioral disorders, and onset in adolescence increased the risk for anxiety and depression compared to controls. These results show that patients with JIA should be evaluated in clinical practice for possible mental and behavioral disorders.
3. This study is the first to report six group of psychotropic medication among patients with JIA. The risk of purchasing antidepressants, antipsychotics and anxiolytics was higher in JIA patients compared to controls, particularly in females. The use of antidepressants began to increase in adolescence. These results reflect the presence of clinically important mental health problems in JIA patients.
4. During this millennium, the survival of JIA has improved, but psychiatric morbidity and the use of psychotropic medication has increased among patients with JIA. This is a fact that must be taken into account when treating these patients.



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## Original publications

- I Kyllönen M.S., Kautiainen H., Puolakka K., & Vähäsalo P. (2019). The mortality rate and causes of death among juvenile idiopathic arthritis patients in Finland. *Clinical and Experimental Rheumatology*, 37(3), 508–511.
- II Kyllönen M.S., Ebeling H., Kautiainen H., Puolakka K., & Vähäsalo P. (2021). Psychiatric disorders in incident patients with juvenile idiopathic arthritis-a-case-control cohort study. *Pediatric Rheumatology Online Journal*, 19(1). <https://doi.org/10.1186/s12969-021-00599-x>
- III Kyllönen M.S., Kautiainen H., Jääskeläinen E., Puolakka K., & Vähäsalo P. Use of Psychotropic Medication in Incident Juvenile Idiopathic Arthritis Patients from 2000–2014 — A Case-Control Cohort Study. *Clinical and Experimental Rheumatology*. *In press*.

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