Hannu Tiri

COMORBIDITIES AND MORTALITY OF HIDRADENITIS SUPPURATIVA IN FINLAND
Abstract

Hidradenitis suppurativa (HS) is a chronic inflammatory disease of hair follicles, characterized by subcutaneous inflammatory nodules and abscesses, typically on the axillary, genitofemoral, and perianal skin. Symptoms of HS, such as foul-smelling discharge from the inflamed lesions, pain, and disease location in sensitive areas, markedly diminish patients’ quality of life.

Smoking and obesity are associated with HS, which also has several common comorbidities. While there is a growing body of evidence of somatic comorbidities in HS, psychiatric comorbidities have received less attention. Furthermore, literature on comorbidities in young patients with HS is scarce, and no systematic evaluation of mortality in HS has yet been undertaken.

This study aimed to clarify the associations between HS and mental disorders, to explore both somatic and psychiatric comorbidities of HS in children and adolescents, and to determine the life expectancy and cause-specific risks of death in patients with HS.

The study population comprised over 4300 cases with HS diagnosed in Finnish hospitals between 1987 and 2014. Age- and sex-matched patients with psoriasis and melanocytic nevi served as controls. Patient data were obtained from the statutory Finnish Care Register for Health Care. Information on dates and causes of death of the cases and controls were acquired from Statistics Finland.

This study showed a heavy psychiatric disease burden in patients with HS. The prevalence rates and risks of all studied psychiatric comorbidities were higher in the HS than in the control groups. This was also evident in children and adolescents with HS, not only in adults. Furthermore, younger patients also had elevated risks for many somatic disorders including inflammatory bowel and joint diseases. Remarkably, the mean age at death in the HS group was only 60.5 years. The most common causes for death in the order of likelihood were: cardiovascular diseases, neoplasms, ‘accidents, suicides or violence’ and alcohol-related diseases. Suicide risk was elevated in women with HS.

HS patients should be cautiously monitored for possible somatic and psychiatric comorbidities. It is clear that these patients require effective, comprehensive and multidisciplinary care to improve their quality of life and prevent premature death.

Keywords: adolescent, cause of death, child, comorbidity, hidradenitis suppurativa, life expectancy, mental disorders, mortality, neoplasms, nevus, patient care team, psoriasis, quality of life, suicide
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Tiivistelmä

Hidradenitis suppurativa (HS) on krooninen tulehduksellinen karvatuppien sairaus, joka heikentää elämänlaatua merkittävästi. Kivuliaat kyhmyt ja paiseet sekä vuotavat käytävät, jotka sijaitsevat useimmiten kainaloissa, nivusissa, genitaalialueella ja pakaravaossa, ovat sen tyyplöissä ilmenemismuotoja.

HS-potilailla on moninaisia terveysongelmia, joita ovat mm. tupakointi, lihavuus ja suurentunut riski useisiin somaattisiin sairauksiin. Tutkimustieto HS-potilaisten psykiatrissista sairauksista on kuitenkin vähäistä eikä liitännäissairauksista lapsilla ole juuri lainkaan tietoa. Tämän lisäksi HS-potilaisten kuolemansyitä tai eliniäntodetta ei ole perusteellisesti selvitetty.

Tällä tutkimuksella haluttiin määrittää psykiatristen sairauksien riski HS-potilailla ja selvitää sekä somaattisten että psykiatristen liitännäissairauksien todennäköisyyttä lapsuudessa ja nuoruudessa. Tutkimuksen tavoitteena oli myös tutkia, mihin sairauksiin HS-potilailla on suurenpunut riski kuolla ja minkä ikäisillä he menehtyvät.


Tämän tutkimuksen perusteella HS-potilailla on runsaasti psykiatria liitännäissairauksia. Sekä somaattisten että psykiatristen sairauksien riski onkin pitettävä mielessä aina HS-potilaista hoidettaessa. Tekohka, kokonaisvaltainen ja moniammatillinen hoito on tärkeää potilaisten elämänlaadun parantamiseksi ja ennenaikaisen eliniänoidotuksen ehkäisemiseksi.

Asiasanat: elinajan odote, elämänlaatu, hoitoitimi, itsemurha, kasvaimet, komorbiditeetti, kuolinsyy, kuolleisuus, lapsi, mielenterveyshäiriöt, märkivä hikirauhastulehdus, neevus, nuori, psoriasis
To my father (1940–2018)
Acknowledgements

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What we miss, we never lose.
The one we loved we always miss.
We never lose the one we loved.
The one we loved we always love.

Claes Anderson

To my beloved son Onni, who was born during early days of this study. You bring so much happiness to my life. I am so proud of you, you mean the world to me.

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Where words fail, music speaks.

Hans Christian Andersen

Oulu, October 2019

Hannu Tiri
**Abbreviations**

APP amyloid precursor protein  
C5a complement factor C5a  
CD Crohn’s disease  
CI confidence interval  
CRHC The Finnish Care Register for Health Care  
CV cardiovascular  
HR hazard ratio  
HS hidradenitis suppurativa  
IBD inflammatory bowel disease  
ICD International Classification of Diseases  
IHS4 International Hidradenitis Suppurativa Severity Score System  
IL interleukin  
IRR incidence rate ratio  
OR odds ratio  
SpA spondyloarthopathy  
Th T helper cell  
TNF tumor necrosis factor  
WHO World Health Organization  
yHS youth-onset hidradenitis suppurativa
Original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:


*equal contribution
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1 Introduction

The word ‘stigma’ is of Greek origin. Initially it meant a mark made by a sharp instrument, but, later on, it has received various other meanings. Historically, slaves and criminals were marked with stigmas, cut or burned signs on the skin, to proclaim their social status. (Scambler, 2009; Weiss, Ramakrishna, & Somma, 2006) The word ‘stigma’ may also be used to refer to wounds that resemble those that Jesus Christ suffered in his crucifixion (Gray, 2002). Currently, a stigma is usually defined as a physical or social mark that disrupts social interactions. It may lead to alienation and social discrimination. (Dimitrov & Szepietowski, 2017)

Dermatologic diseases are commonly regarded as stigmatizing because they are so visible to other people (Ongenae, Dierckxsens, Brochez, van Geel, & Naeyaert, 2005). However, a dermatologic condition can be highly stigmatizing even in the absence of visible skin lesions (Richards, Fortune, Griffiths, & Main, 2001). Hidradenitis suppurativa (HS) is a chronic inflammatory disease characterized by painful abscesses, which are most commonly located on the axillary, inframammary, inguinal and anogenital skin (Alikhan, Lynch, & Eisen, 2009). These locations are easy to hide with clothes in ordinary life. However, discharge from the active lesions and chronic sinus tracts typical of HS stains clothes easily, creating a false impression of poor hygiene (Esmann & Jemec, 2011). The other symptoms of HS also cause immense psychological distress (Matusiak, 2018). The severe pain of inflamed lesions, disease location on intimate areas of the body, and fear of body odor can be disastrous to patients. The lack of understanding and public knowledge of HS further exacerbates the patients’ suffering. Physical exercise is important for the health of these patients, but they are often unable to do sports because of the pain and suppuration. (Esmann & Jemec, 2011) These symptoms may also lead to frequent absences from work (Tzellos, Yang, Mu, Calimlim, & Signorovitch, 2018). Furthermore, obesity, another stigmatizing condition (Puhl & Heuer, 2010), is a risk factor for, and a very common comorbidity in patients with HS (Alikhan et al., 2009). All the above-mentioned symptoms and factors are stigmatizing, and together they cause substantial distress to patients with HS.

The key reasons that prompted this study were the unmet needs and frustration of patients with HS seen in the daily dermatological practice. At the onset of HS, abscesses are often misdiagnosed as common boils, which leads to non-efficacious treatments and diagnostic delays of unbearable lengths (Alikhan et al., 2009; Jemec, 2012). Consequently, having experienced unsatisfactory medical care, patients may
even incise their own abscesses rather than seek help from physicians. Furthermore, multimorbidity in patients with HS is often seen in daily practice (Andersen & Jemec, 2017). Based on clinical experience, not only somatic comorbidities but also various psychiatric problems may be overrepresented in these patients compared to those with other dermatologic conditions. Since psychiatric disorders are particularly associated with high levels of stigma and decreased quality of life (ESEMeD/MHEDEA 2000 Investigators et al., 2004a; Hinshaw & Stier, 2008; Spitzer et al., 1995), this aspect of the present study was especially important.

Scientific research on HS has been infrequent, even neglected, although HS has recently gained more attention and has been the subject of an increasing number of studies around the world (van der Zee, Laman, Boer, & Prens, 2012). Moreover, new treatment options have become available (van Straalen, Schneider-Burrus, & Prens, 2018). Although things have developed in the right direction, more studies are required in many areas of HS management. The present study aimed to increase understanding of the characteristics of HS, with particular emphasis on its comorbidities and mortality. Better knowledge of HS is essential to improve the quality and comprehensiveness of care of this highly stigmatizing disease that has a profound negative impact on patients.
2 Review of the literature

Velpeau (1839) first described a patient with a peculiar inflammatory disease located in the flexural areas of the skin. The French surgeon Aristide Verneuil gave a name hidradenitis suppurativa to this disease in 1854 (Verneuil, 1854). He thought that HS was a bacterial infection of the sweat glands, as the name of the disease implies (Greek: hidros=sweat, aden=gland, -itis=inflammation; Latin: suppurato=to form pus). The apocrine type of sweat gland was first described much later, in 1922, by Schiefferdecker. For a long time, the intertriginous location of apocrine glands led to the theory of their association with HS. It was not until 1975 Plewig and Kligman suggested that the primary event in HS was actually follicular occlusion, a theory that was confirmed in 1990 by Yu and Cook. Therefore, the term HS is a misnomer. Despite this, the term is still widely used, although in some countries the name acne inversa is preferred (Boer & Weltevreden, 1996).

2.1 Epidemiology

Although several studies have attempted to evaluate it in different settings, the prevalence of HS in the general population is currently, at best, an estimate (Jemec & Kimball, 2015). A population-based study that represented about 15% of the population of the United States reported the prevalence to be only 0.1% (Garg, Kirby, Lavian, Lin, & Strunk, 2017). A Danish study found a prevalence of 4%, but the study population consisted only of young women (Jemec, 1988). Recent studies, including one based on a representative sample of the French population, have estimated the prevalence to be 1% or less (Jemec & Kimball, 2015; Revuz et al., 2008). A prevalence of 1% is generally accepted to be the most accurate estimate (Zouboulis, Desai et al., 2015).

Few previous studies have examined the incidence of HS. In a registry-based Italian study the overall age-standardized incidence of HS was 3.2/100,000 persons/year (Bettoli et al., 2016). Two studies from U.S. reported higher annual incidences (6.0 and 11.4/100,000 persons/year) (Garg, Lavian, Lin, Strunk, & Alloo, 2017; Vazquez, Alikhan, Weaver, Wetter, & Davis, 2013). None of these studies was nationwide.

Females are more frequently affected by HS than males in the ratio of 3:1 (Jemec, 2012), but ratios ranging from 2:1 to 5:1 have been reported, too (Wiseman, 2004). Premenstrual flares, the alleviation of HS symptoms during pregnancy and the efficacy of antiandrogen therapy led to a hypothesis of sex hormones playing a
pathogenic role in HS (Riis, Ring, Themstrup, & Jemec, 2016). However, the exact mechanisms behind the sex difference in prevalence remain unknown.

HS occurs most commonly after puberty, usually in the second or third decade of life (Alikhan et al., 2009; Liy-Wong, Pope, & Lara-Corrales, 2015). The onset of the disease later in life is infrequent (von der Werth & Williams, 2000). Although HS has been considered a rare disease in children with approximately 2% of cases occurring before puberty (Liy-Wong, 2015), recent studies suggest that early-onset HS may be more common than previously thought (Braunberger et al., 2018). In a Dutch study, 7.7% of patients with HS reported that their first symptoms developed before they turned thirteen (Deckers, van der Zee, Boer, & Prens, 2015).

2.2 Pathophysiology of hidradenitis suppurativa

2.2.1 Pathogenesis

The primary event in HS is considered to be the occlusion of the hair follicle (Zouboulis et al., 2015), which may be preceded by infundibulofolliculitis and shrinkage of the sebaceous gland (Boer & Weltevreden, 1996). The occlusion is caused by infundibular keratosis and hyperplasia of the follicular epithelium, which leads to accumulation of cellular debris and dilatation of the hair follicle (von Laffert, Stadie, Wohlrab, & Marsch, 2011). Eventually the follicle will rupture. The rupture allows hair fragments, microbes and keratin to spread into the surrounding tissue, causing a foreign body reaction, a massive local immune response and inflammation. The inflammation may induce abscess formation followed by scarring in later stages. (Alikhan et al., 2009) In addition, it is hypothesized that unphagocytosed keratinocytes or stem cells from the hair follicle may have the capability to epithelialize the abscess cavity, creating tunnels and sinus tracts (van der Zee et al., 2012).

The exact pathogenic pathway of HS is not fully understood, but it seems that a wide range of cytokines are involved (Zouboulis et al., 2015). Investigations suggest that the key inflammatory mediators of HS include tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), T helper cell (Th) 1, Th17, interleukin (IL)-1\(\beta\), IL-6, IL-8, IL-12, IL-17, IL-23, and interferon gamma (Vossen, van der Zee, & Prens, 2018). Recently, the IL-36 family was also found to be upregulated (Hessam et al., 2018). Additionally, complement system is activated in HS. Plasma levels of complement factor C5a (C5a) and membrane attack complex C5b-9 are higher in patients with
HS than in healthy controls. C5a may be the priming component in the production of TNF-α in monocytes. (Kanni, Zenker, Habel, Riedemann, & Giamarellos-Bourboulis, 2018) The events that drive the activation of complement remain unknown, although antimicrobial peptides have been suggested to play a significant role in the initiation and progression of HS (Prens & Deckers, 2015).

2.2.2 The role of bacteria

Patients with HS experience symptoms that are usually associated with bacterial skin infections, such as pain, swelling, redness and suppuration with foul-smelling discharge (Zouboulis et al., 2015). Furthermore, 73% of sinus tracts contain live bacteria (Ring et al., 2017a), and many antibiotics are used to treat HS (Zouboulis et al., 2019). Regardless of that, HS is not a classic infectious disease (Alikhan et al., 2009).

HS lesions may be sterile or may contain numerous bacteria species (Zouboulis et al., 2015). Coagulase-negative staphylococci are the bacteria most often found in HS lesions, but they are also a part of the normal flora of hair follicles (Ring et al., 2015). In fact, fewer bacteria are found in the non-affected skin of patients with HS than in that of healthy controls, suggesting that alterations in the composition of the biofilm may be involved in the disease’s etiology. These alterations could reduce the protective capabilities of the biofilm or activate a dysregulated immune response to other bacteria. (Ring et al., 2017b)

The role of microbes in the pathogenesis of HS is still unclear (Alikhan et al., 2009). Bacteria could be only commensals (Nikolakis et al., 2015). On the other hand, commensal bacteria are hypothesized to have a secondary or opportunistic role, because bacteria are trapped inside the hair follicle when it is occluded (Naik et al., 2019). Trapped microbes may trigger an inflammatory process, especially in individuals with genetic or immune defects (Ring & Emtestam, 2016; van der Zee et al., 2012). Such defects, which predispose to aberrant immune responses, are probably present in patients with HS (Nazary, van der Zee, Prens, Folkerts, & Boer, 2011). In these patients, normally harmless bacteria may multiply and become pathogenic (Park & Lee, 2018). As a consequence, biofilms may form and attach to epithelialized sinus tracts (Kathju, Lasko, & Stoodley, 2012). Biofilms are difficult to eliminate, which makes treatment difficult (Costerton, Lewandowski, Caldwell, Korber, & Lappin-Scott, 1995). In general, biofilm-driven diseases respond unpredictably to antibiotic treatments, heal poorly, and feature prolonged
inflammation (Ring et al., 2017a). These all are typical features of HS (Kathju et al., 2012).

2.2.3 Genetics

More than 30% of first-degree relatives of patients with HS also have the disease, indicating that HS pathology has a genetic component (Alikhan et al., 2009). In particular, patients with early-onset disease tend to have a positive family history (Deckers et al., 2015).

Genetic investigations of HS have demonstrated different heterozygous mutations in subunits of the gamma secretase gene, leading to impaired function (Pink, Simpson, Desai, Trembath, & Barker, 2013). Gamma secretase is a part of the Notch signaling pathway, which is necessary in hair follicle differentiation. It has been proposed that a defect in the pathway impairs the epidermal barrier, disrupts the hair growth cycle, and turns hair-follicles into follicular keratin-rich epidermal cysts. (Pan et al., 2004)

Gamma secretase mutations with an autosomal dominant mode of inheritance have been found in patients with familial HS (Wang et al., 2010). However, these patients comprise only a minority of all patients with HS, most have been reported in China, and their HS disease characteristics are often atypical (Ingram, 2016). Therefore, the significance of the gamma secretase mutations in the etiology of HS has been disputed. Other mutations such as those in PSTPIP1 gene are under investigation, but the genetic background of HS is still unexplained for the most part. As yet, it can only be stated that the HS phenotype may manifest in genetically susceptible individuals with aberrant innate immunity in the presence of environmental triggers. (Vosson et al., 2018) These triggers include skin friction and probably microbes, but the best characterized risk factors for HS are smoking and obesity (Prens & Deckers, 2015).

2.2.4 Smoking and obesity

The etiology of HS is multifactorial (Vosson et al., 2018). Cigarette smoking and obesity are the most important environmental factors. They are both strongly associated with HS: as many as 70–89% of patients with HS are smokers and 30–75% obese. (Alikhan et al., 2009; Sartorius, Emtestam, Jemec, & Lapins, 2009)

A highly significant association between the prevalence of HS and current smoking (odds ratio [OR] 12.55) and overweight (OR 1.1 for each body mass index
unit) has been reported (Revuz et al., 2008). Smoking increases the probability of HS by promoting hyperplasia of the epidermis and stimulating follicular keratosis and occlusion. It also creates a more proinflammatory environment in the skin. (Kelly & Prens, 2016)

Adipocytes (fat cells), which are present in excessive quantities in obese individuals, secrete adipokines. Adipokines are metabolically active proinflammatory cytokines that facilitate inflammation. (Ouchi, Parker, Lugus, & Walsh, 2011) In addition to inflammation, obesity increases skin friction in the flexural areas of the body. Repetitive mechanical friction of the skin is thought to stimulate follicular keratosis, thereby enhancing the risk for HS. Combined with an occlusive, warm, and humid climate in the skinfolds, friction can lead to follicular microtraumas. (de Winter, van der Zee, & Prens, 2012) The skin of individuals with defective follicular support is thought to be particularly vulnerable to such microtraumas, thus predisposing for HS. In patients with HS, the skin is hypothesized to be fragile around the sebofollicular junction. (Danby, Jemec, Marsch, & von Laffert, 2013) Ruptures in that area may trigger the horizontally spreading inflammatory process characteristic of HS in the dermis and subcutis (von Laffert et al., 2011).

2.3 Clinical presentation

The onset of HS is often insidious (Wiseman, 2004). Initial lesions are typically tender and erythematous papules or nodules in intertriginous areas of the skin. Patients with HS gradually develop larger and deeper nodules and deep-seated abscesses that may rupture. (Slade, Powell, & Mortimer, 2003) These painful lesions often extrude a purulent and foul-smelling discharge through multiple openings (Alikhan et al., 2009). As the inflammatory process continues, nodules tend to coalesce and form a subcutaneous honeycomb of abscesses and sinus tracts (Poli, Jemec, & Revuz, 2006). If untreated, draining sinuses persist for long periods of time discharging pus intermittently and repeatedly. Chronic inflammation and iterative healing of the abscesses lead to fibrosis and scarring, dermal contractures and ropelike elevations of the skin (Zouboulis et al., 2015). (Figure 1)

In some patients, HS lesions can spread widely beyond the intertriginous areas of the skin (Alikhan et al., 2009). Patients with early-onset HS are particularly prone to a form of disease that is more widespread, but not necessarily more severe than that of those with adult-onset HS (Deckers et al., 2015). In the most severe
cases, HS may penetrate into deeper structures including muscle, the lymph nodes, urethra and bowel (Alikhan et al., 2009; Slade et al., 2003). Although HS is more common in women, men have a greater tendency for severe disease (Matusiak, Bieniek, & Szepietowski, 2009b). Perianal and perineal disease, which can cause treatment problems, is particularly predominant in men (Makris et al., 2017). Men are also more likely to have HS lesions in atypical locations (Canoui-Poitrine et al., 2009).

2.4 Diagnostics

No pathognomonic test exists for HS (van der Zee & Jemec, 2015); its diagnosis is based on a set of clinical criteria known as the modified Dessau definition (Revuz & Jemec, 2016). According to this definition, three criteria must be met for a positive diagnosis. Firstly, typical lesions such as deep-seated painful nodules or abscesses, draining sinuses, or bridged scars must be present. Secondly, these lesions must occur in the areas typical of HS: the axillae, groin, perineal region, buttocks and infra- and intermammary folds. Thirdly, there must be a clear history of chronicity or recurrence. (Zouboulis, Del Marmol et al., 2015) In other words, a diagnosis of HS can be made when a patient has recurrent inflammation with
lesions typical of HS in the flexural areas of the body, occurring more than twice in a six-month period (van der Zee & Jemec, 2015).

Despite their distinct clinical appearance, HS lesions are often misinterpreted as common boils (Jemec & Kimball, 2015). This results in a considerable diagnostic delay, which has been estimated in previous studies to last an average of 7–14 years (Kluger, Ranta, & Serlachius, 2017; Saunte et al., 2015).

### 2.5 Classification of disease stage

The severity of HS has traditionally been graded using the Hurley clinical staging system (Table 1) (Hurley, 1989). This system is well suited for classification of the disease stage, and useful when planning surgical interventions (Alharbi, Kauczok, & Pallua, 2012). However, it is a static tool and not suitable for monitoring and evaluating the success of medical therapy (Zouboulis et al., 2015).

<table>
<thead>
<tr>
<th>Hurley stage</th>
<th>Extent of the disease</th>
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<tr>
<td>I</td>
<td>Single or multiple abscesses, no scars, no sinus tracts</td>
</tr>
<tr>
<td>II</td>
<td>Recurrent abscesses, scars, sinus tracts, widely separated lesions</td>
</tr>
<tr>
<td>III</td>
<td>Diffuse or almost diffuse involvement or multiple interconnected tracts and abscesses throughout an entire regional area of which hidradenitis has a predilection for</td>
</tr>
</tbody>
</table>

With application of the Hurley system, 68% of patients with HS patients are classified as having stage I (mild) disease. Stage II (moderate disease) is found in 28%, and stage III (severe), in 4% of patients. (Canoui-Poitrine et al., 2009)

There are several other instruments that can be used for classification of HS, including the Sartorius score (Sartorius, Lapins, Emtestam, & Jemec, 2003; Sartorius et al., 2009), the Physician’s Global Assessment (PGA) (Zouboulis et al., 2015), the Hidradenitis Suppurativa Severity Index (HSSI) (Grant, Gonzalez, Montgomery, Cardenas, & Kerdel, 2010), and the Hidradenitis Suppurativa Clinical Response score (HiSCR) (Kimball et al., 2016). However, these systems are inconvenient to use in the real-world clinical setting and their use is mostly limited to clinical trials (van der Zee & Jemec, 2015). A tool that combines the clinical picture with treatment options has also been developed. This refined Hurley staging system divides Hurley stages into subcategories depending on the severity of the disease, and proposes treatment strategies for each category separately. (Horváth et al., 2017; Rondags et al., 2019)
The recently developed International Hidradenitis Suppurativa Severity Score System (IHS4) is a validated tool for scoring the severity of HS dynamically. A patient’s IHS4 is calculated as the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining sinuses or fistulas (multiplied by 4). A total score of ≤3 signifies mild, 4–10 moderate, and ≥11 severe disease. The IHS4 is easy and quick to use, and can be used to monitor disease progression and treatment efficacy. (Zouboulis et al., 2017)

2.6 Associated diseases

HS is associated with several other diseases and there is a growing body of evidence regarding its somatic comorbidities (Kohorst, Kimball, & Davis, 2015; I. M. Miller, McAndrew, & Hamzavi, 2016; Shlyankevich, Chen, Kim, & Kimball, 2014). However, studies on psychiatric comorbidities are scarce, particularly with regard to conditions other than depression (Shavit et al., 2015). Moreover, population-based studies on comorbidities are lacking especially in pediatric patients, and the literature comprises mainly of case reports and series (Liy-Wong et al., 2015; Mengesha, Holcombe, & Hansen, 1999; R. A. Palmer & Keefe, 2001).

2.6.1 Somatic comorbidities

Cardiovascular disease risk

Hidradenitis suppurativa is a chronic inflammatory disease (Alikhan et al., 2009). Other such diseases, including psoriasis, inflammatory bowel diseases (IBDs) and rheumatoid arthritis are associated with an elevated risk of cardiovascular (CV) diseases, independently of CV risk factors (Abuabara et al., 2010; Dregan, Chowienczyk, & Molokhia, 2017; Svedbom et al., 2015). Similarly, patients with HS also carry an elevated risk for CV morbidity. In a Danish study, the risk for major CV adverse events in patients with HS was comparable to that in those with severe psoriasis. (Egeberg, Gislason, & Hansen, 2016) Similar findings among all these chronic inflammatory diseases imply that they might, to some extent, share the same inflammatory mechanisms (E. Bianchi & Rogge, 2019; Speeckaert et al., 2016; Vossen et al., 2018).

The elevated risk for CV diseases in HS is independent of smoking and comorbidities (Egeberg et al., 2016). On top of that, excessive smoking is very
common in patients with HS (Alikhan et al., 2009). Additionally, diabetes, obesity, hypertension and dyslipidemia, which are significant comorbidities of HS, are also components of metabolic syndrome as well as risk factors for CV diseases (Tzellos et al., 2015). As a consequence, patients with HS are likely to carry a particularly high risk of atherosclerosis.

**Autoimmune diseases**

Clustering of autoimmune diseases with HS has been observed (Kohorst et al., 2015). HS is strongly associated with IBDs, especially Crohn’s disease (CD), and spondyloarthopathies (SpAs) (Fauconier et al., 2018; van der Zee, van der Woude, Florencia, & Prens, 2010).

The association of HS with IBDs has been shown in various studies. Studies from Denmark and The Netherlands reported that the prevalence of IBDs is approximately two- to eight-fold greater in patients with HS than in the general population (Deckers et al., 2017; Egeberg et al., 2017). Another study from The Netherlands found that HS was present in 6.8% to 10.6% of patients with IBD. It is noteworthy that concomitant HS was associated with early onset of intestinal symptoms in patients with IBD, which led more frequently to anti-TNF-α treatment and surgery. (Janse et al., 2015)

Interestingly, HS and CD have several similarities (van der Zee, Horvath, Jemec, & Prens, 2016). Firstly, the cutaneous lesions of HS and CD have analogous clinical and histological features, which can complicate the diagnosis in some patients (Church, Fazio, Lavery, Oakley, & Milsom, 1993). Secondly, the efficacy of the same anti-TNF-α treatments in both diseases suggests shared inflammatory pathways (Roussomoustakaki et al., 2003). Thirdly, the IL-23/Th-17 pathway is likely to be involved in the pathogenesis of both diseases (Abraham & Cho, 2009; Schlapbach, Hänni, Yawalkar, & Hunger, 2011). Lastly, tobacco use triggers and aggravates both HS and CD but not ulcerative colitis (Cosnes, 2008; Kelly & Prens, 2016). Notably, the association between ulcerative colitis and HS is not as strong as that between CD and HS (van der Zee et al., 2010).

Back pain is a common symptom in patients with HS; it was present in 71% of patients in a German study (Schneider-Burrus et al., 2016). Such pain may be the result of concomitant SpA, which is significantly more common in patients with HS than in the general population, with prevalence rates ranging from 3.7% to 56.5% (Fauconier et al., 2018; Kohorst et al., 2015; Richette et al., 2014; Schneider-Burrus et al., 2016; Shlyankevich et al., 2014). The highest rate of SpA was found in a
study that included only patients with moderate to severe HS affecting the genitofemoral, perianal or gluteal skin (Schneider-Burrus et al., 2016). An explanation for this association between HS and SpA might be the fact that they share some features, such as the elevated risk for IBDs and increased levels of IL-17 and TNF-α (Kohorst et al., 2015; Smith & Colbert, 2014; Stolwijk et al., 2015). Curiously, SpA patients with concomitant HS have a higher level of axial SpA disease activity than patients without HS (Rondags, Arends, Wink, Horváth, & Spoorenberg, 2019).

Other associations

Several other diseases and syndromes have also been linked to HS. For example, thyroid diseases and polycystic ovarian disease are more frequent in patients with HS than in the general population (Garg, Neuren, & Strunk, 2018; Shlyankevich et al., 2014). Pyoderma gangrenosum, acne conglobata and pilonidal sinus are also more common, although the clinical presentation of HS may resemble all of them, making the distinction difficult (Hsiao et al., 2010; Jansen & Plewig, 1998; Poli, Wolkenstein, & Revuz, 2010).

Anaemia, amyloidosis and lymphedema are possible secondary findings or complications of severe HS (Deckers, van der Zee, & Prens, 2016; Faye et al., 2007; Girouard, Falk, Rennke, & Merola, 2012). Likewise, squamous cell carcinoma of the skin is a feared complication of HS, usually in persistent cases of perianal disease (Maclean & Coleman, 2007).

HS is linked to many syndromes. Patients with Down syndrome have an increased risk for HS, especially for early-onset HS (Denny & Anadkat, 2016). HS is also a part of PASH (pyoderma gangrenosum, acne, HS) and PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, HS) syndromes, and it has been reported in patients with SAPHO (synovitis, acne, palmoplantar pustulosis, hyperostosis, osteitis) (Gasparic, Riis, & Jemec, 2017). In addition, patients with pachyonychia congenita and Dowling-Degos disease, both diseases with keratin defects exposing to follicular occlusion, and patients with KID (keratitis, ichthyosis, deafness) syndrome are more prone to HS (Fimmel & Zouboulis, 2010; Zouboulis et al., 2015).
2.6.2 Psychiatric comorbidities

Dermatologic patients in general are more susceptible to psychiatric problems than healthy population (Dalgard et al., 2015; Picardi, Abeni, Melchi, Puddu, & Pasquini, 2000). Among all dermatological conditions, HS is one of those with the most negative effects on the patient’s life (Matusiak, Bieniek, & Szepietowski, 2010a; Wolkenstein et al., 2007). The symptoms of HS cause high levels of emotional distress and may be devastating to patients (Goodeham & Papp, 2015). In addition, a recent study reported an association between HS and alcohol, opioid and cannabis dependence, all of which predispose towards mental disorders (Garg, Papagermanos, Midura, Strunk, & Merson, 2018; Schneider, 2009). As a consequence, it is unsurprising that patients with HS tend to have psychiatric problems. However, until recently, there were relatively few studies on the psychiatric comorbidities of HS (Machado et al., 2019; van der Zee et al., 2012).

Although many reports highlight the psychological burden borne by patients with HS, studies on psychiatric comorbidities have yielded inconsistent results (Onderdijk et al., 2013; Shlyankevich et al., 2014). Furthermore, these studies have mainly focused on depression and many have been limited by small sample sizes (Shavit et al., 2015).

Although depression appears to be more common in patients with HS than in otherwise healthy populations, the prevalence of depression in patients with HS is not exactly known. Depression rates from 1.6% to 42.9% have been reported, with such a wide range being contradictory. (Crowley et al., 2014; J. S. Kirby, Butt, Esmann, & Jemec, 2017; Onderdijk et al., 2013; Thorlaciuc, Cohen, Gislason, Jemec, & Egeberg, 2018; Vazquez et al., 2013) In a study by Onderdijk et al. (2013), quality of life and mood were significantly impaired in patients with HS, and, as measured using the Major Depression Inventory questionnaire, depression was significantly more frequent in patients with HS than controls who had other dermatologic diseases ($p = 0.006$). However, the same study found that when depression was defined using the International Classification of Diseases (ICD), Tenth Revision, criteria, its rate was higher in HS patients than in the controls, but not significantly so (9% vs. 6%; $p = 0.34$). A large Danish study found that the association between HS and depression could be explained by confounding factors such as low socioeconomic status, smoking, alcohol overuse and healthcare consumption (Thorlaciuc et al., 2018). A significant association between HS and depression was found in a registry-based study from Israel, which showed that depression and anxiety are more common among patients with HS (Shavit et al., 2015).
Also, inpatients with HS were more likely to have psychiatric disorders than HS-free controls in a claims data analysis of almost 90 million hospital admissions in the United States (K. R. Patel et al., 2018). The results of previous studies on risks for psychiatric comorbidities in patients with HS are summarized in Table 2.

Table 2. Recent and major studies on the risk for psychiatric disorders in patients with hidradenitis suppurativa.

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Study</th>
<th>Country</th>
<th>Sample size</th>
<th>Prevalence1 vs. control</th>
<th>OR (95% CI)3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Thorlacius et al. 2018</td>
<td>Denmark</td>
<td>7732</td>
<td>1.6% vs 0.8%</td>
<td>1.13 (0.87–1.47)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Thorlacius et al. 2018</td>
<td>Denmark</td>
<td>7732</td>
<td>0.8% vs 0.3%</td>
<td>1.73 (1.23–2.41)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Shavit et al. 2015</td>
<td>Israel</td>
<td>3207</td>
<td>1.5% vs 1.1%</td>
<td>1.3 (0.9–1.9)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Shavit et al. 2015</td>
<td>Israel</td>
<td>3207</td>
<td>0.4% vs 0.1%</td>
<td>2.1 (0.9–4.7)</td>
</tr>
</tbody>
</table>

1Number of patients with hidradenitis suppurativa (HS), 2Data given as prevalence in HS patients vs. controls, 3Data given as Odds ratio (95% confidence interval), 4Number of hospital admissions

In addition to the studies shown above, another from the United States systemically evaluated the prevalence rates of various mental disorders separately in mild and severe HS. The results suggested that the burden of psychiatric comorbidities increases with the severity of HS. However, although the study population comprised over 5000 patients with HS, it included only privately-insured patients from 60 large employers. (Kimball et al., 2018)

2.7 Mortality

Several of the comorbidities of HS are potentially life-threatening (Kohorst et al., 2015; Reddy, Strunk, & Garg, 2019). Patients with HS carry elevated risks for all-cause mortality and adverse CV outcomes (Egeberg et al., 2016). Furthermore, a 50% higher cancer incidence is reported in patients with HS compared with the general population (Lapins, Ye, Nyrên, & Emtestam, 2001), and suicides are also reported to be more common among patients with HS (K. R. Patel et al., 2018; Thorlacius et al., 2018). However, there has not yet been a systematic cause-specific evaluation of mortality in patients with HS.
2.8 Treatment

The European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa from the year 2015 states that HS “should be treated based on its individual subjective impact and objective severity” (Zouboulis et al., 2015). However, decentralization of healthcare provision and a lack of interdisciplinary treatment policies have resulted in a highly variable approach to the signs and symptoms of HS (Jemec & Kimball, 2015). Furthermore, proper treatment of HS is often delayed by late diagnosis, which further hampers the outcome (Saunte et al., 2015).

2.8.1 Medical treatment

Because the exact pathogenesis of HS is not clear (Vossen et al., 2018), medical treatment for HS remains suboptimal (Deckers & Prens, 2016; Gulliver, Zouboulis, Prens, Jemec, & Tzellos, 2016). Inflammation in HS is often severe and difficult to suppress (Riis, Søeby, Saunte, & Jemec, 2015). Although HS is not a classic bacterial disease, patients often benefit from antibiotics. Treatment guidelines usually recommend topical clindamycin, perioral tetracycline and combinations of clindamycin and rifampicin (Clemmensen, 1983; Gener et al., 2009; Mendonça & Griffiths, 2006; Revuz, 2010). Dapsone may be used as well (Kaur & Lewis, 2006; Yazdanyar, Boer, Ingvarsson, Szepietowski, & Jemec, 2011). Recently, intravenous ertapenem and various combinations of different antibiotics have been administered in more severe cases (Bettoli, Join-Lambert, & Nassif, 2016; Deckers & Prens, 2016; Join-Lambert et al., 2015; Matusiak, Bieniek, & Szepietowski, 2014). HS has also been treated with oral retinoids such as acitretin, alitretinoin and isotretinoin (Deckers & Prens, 2016). Of these, acitretin has yielded the best evidence of efficacy, but small studies have also reported positive responses to alitretinoin (Boer & Nazary, 2011; Verdolini, Simonacci, Menon, Pavlou, & Mannello, 2015). On the contrary, there are reports of low efficacy and HS flares during isotretinoin treatment (Poli & Revuz, 2019; Soria et al., 2009). Therefore, isotretinoin should be only administered if the patient with mild HS has severe concomitant acne vulgaris (Deckers & Prens, 2016; Huang & Kirchhof, 2017).

Because of their side effects in long-term use, systemic immunosuppressive agents like prednisolone and cyclosporin A are rarely used in patients with HS (Buell & Koo, 2008; Deckers & Prens, 2016; Oray, Abu Samra, Ebrahimiadib, Meese, & Foster, 2016). There are only limited data on the efficacy of cyclosporin A (L. Bianchi, Hansel, & Stingeni, 2012; Buckley & Rogers, 1995; Rose, Goodfield,
but prednisolone suppresses the inflammation of HS and may, for example, be used temporarily to reduce inflammation prior to surgery (Danby, Hazen, & Boer, 2015; Zouboulis et al., 2015). Intrallesional corticosteroids are much more widely used. Inflamed nodules can be treated with intrallesional injections of corticosteroids, generally triamcinolone acetonide. Lesion pain tends to be relieved only a few days after the injection and as a consequence, surgery may be avoided or replaced with a minor procedure to remove the residual of the nodule. (Riis et al., 2016) There is also some evidence that superficial and short sinus tracts could be treated with triamcinolone injections instead of surgery (Álvarez, García-Martínez, Poveda, & Pascual, 2019).

Recently, biologic agents, especially adalimumab and infliximab, have proven to be effective against HS (Deckers & Prens, 2016; Matusiak, Bieniek, & Szepietowski, 2009a; Matusiak, Szczęch, Bieniek, Nowicka-Suszko, & Szepietowski, 2017). The data concerning ustekinumab and anakinra are also promising, but limited (Lim & Oon, 2019). Unfortunately, medical therapy, even with biologics, seldom results in a lasting response, especially in more severe cases (Andersen & Jemec, 2017). However, there are many ongoing clinical trials on various different drugs and new biologic treatments for HS. These medications include IL-17, IL-23, C5a, IL-1α and Janus kinase 1 inhibitors, apremilast and hydroxychloroquine. (Kerdel et al., 2019; Matusiak, Jemec, & Szepietowski, 2019; van Straalen et al., 2018; Yao, Jørgensen, & Thomsen, 2019).

Adjunctive treatments are frequently used to enhance the efficacy of the medical treatment. These include metformin and hormonal therapies such as spironolactone, cyproterone acetate and finasteride (Arun & Loffeld, 2009; Farrell, Randall, Vafaee, & Dawber, 1999; Joseph, Jayaseelan, Ganapathi, & Stephen, 2005; Lee & Fischer, 2015; Mortimer, Dawber, Gales, & Moore, 1986; Sawers, Randall, & Ebling, 1986; Verdolini, Clayton, Smith, Alwash, & Mannello, 2013).

### 2.8.2 Surgical treatment

Surgical treatment of HS is common (Kohorst et al., 2016). However, it is always recommended to use medical therapy to minimize inflammation before elective surgery (Blok, Spoo, Leeman, Jonkman, & Horvath, 2015; Horváth et al., 2017; Janse, Bieniek, & Horváth, 2016; Yazdanyar & Jemec, 2010). When the inflammation is suppressed, it is easier to accurately define the borders of the lesions that need to be removed. As a consequence, the size of the surgical wound can be reduced, allowing for faster recovery. Furthermore, pre-treatment to reduce
inflammation increases the success rate of surgical operations because it mitigates
the interference of inflammation with wound healing. (Danby et al., 2015)

There are many surgical options for the treatment of HS. Depending on the
type of lesions, as well as the severity and the extent of HS, procedures such as
incision and drainage, punch debridement, deroofing, and limited or wide excision
may be appropriate (Zouboulis et al., 2015). Acute pain in abscesses can be treated
with incision and drainage, which gives short-term relief from intense pain (Jemec,
2012). Deroofing (also called unroofing) is a procedure in which the entire roof of
a sinus tract or an abscess is removed, and the wound is left open for secondary
intention healing (van Hattem, Spoo, Horváth, Jonkman, & Leeman, 2012). Punch
debridement (also called miniunroofing) is a comparable but easier method suitable
for early or small lesions (Danby et al., 2015).

Small HS lesions can be treated with limited excision and side-to-side closure
(Jemec, 1988), but procedures involving secondary intention healing or large skin
flaps or transplantations are often needed (Bieniek, Matusiak, Okulewicz-Gojlík,
& Szepietowski, 2010; Rompel & Petres, 2000). Operations can be performed with
traditional cold steel, electrosurgery or lasers, usually carbon dioxide lasers (Janse
et al., 2016; Zouboulis et al., 2015). The mandatory indications for surgery are:

- sinus tracts and fistulas (other than small)
- accordion-like scars
- contracted scars
- mutilating HS
- suspected malignancy (Blok et al., 2015; Constantinou, Widom, Desantis, &
  Obmann, 2008).

An alternative to wide excision is skin-tissue sparing excision with electrosurgical
peeling (STEEP), a procedure in which all lesional tissue is removed step-by-step
without trying to achieve wider margins of healthy skin. The wound is left open for
secondary intention healing or covered with a skin graft. (Blok et al., 2015)
Alternatively, a carbon dioxide laser may be used instead of electrosurgical
equipment to perform a similar tissue-sparing procedure (Lapins, Sartorius, &
Emtestam, 2002).
2.8.3 Other aspects

Patients with HS may benefit from lifestyle changes (Zouboulis et al., 2015). They should be encouraged to stop smoking and lose weight, not only because tobacco use and obesity are known to worsen HS (Sartorius et al., 2009), but also because smoking and overweight are key risk factors for many comorbidities, like atherosclerosis and diabetes (Erhardt, 2009; Guh et al., 2009; Willi, Bodenmann, Ghali, Faris, & Cornuz, 2007).

Pain and superinfections are important to consider when treating HS (Horváth, Janse, & Sibbald, 2015; Matusiak et al., 2014; Z. S. Patel et al., 2017; Scheinfeld, 2013). They should be effectively managed. Chronic pain is one of the most important symptoms of HS (Wolkenstein et al., 2007). It not only decreases the patient’s quality of life, but is also known to be related to sleep disturbances and mental disorders (Kaaz, Szepietowski, & Matusiak, 2018). Importantly, before prescribing opioids to treat pain in patients with HS, the physician must carefully consider the risk of drug dependence (Garg et al., 2018; Z. S. Patel et al., 2017).

2.8.4 Multidisciplinary and individualized treatment

Patients with HS frequently have multiple health problems such as obesity, smoking, pain, chronic wounds, psychological distress, and many somatic and psychiatric comorbidities (Andersen & Jemec, 2017). Because of the heterogeneity of HS and the multiplicity of its comorbidities, patients with HS should ideally be treated by multidisciplinary teams (Persaud et al., 2017; Scuderi et al., 2017). Such teams provide the most comprehensive and efficacious levels of care by utilizing the expertise of different specialties (W. B. Kim et al., 2016).

No single optimal treatment algorithm exists for patients with HS (Alikhan et al., 2009; Isak, Feldman, & Pichardo, 2018). The treatment plan has to be individualized to suit each patient (Zouboulis et al., 2015). Frequently, a combination of multiple treatment modalities is required to achieve the best possible results (Alikhan et al., 2009).
3 Aims of the study

This study was designed to add to the existing body of knowledge on comorbidity burden and mortality in patients with HS, thereby contributing to more comprehensive care for patients with HS. The specific aims of the study were:

1. To clarify in detail the associations between HS and mental disorders.
2. To explore the risk for both somatic and psychiatric comorbidities of HS in children and adolescents.
3. To determine the life expectancy and the cause-specific risks of death in patients with HS.
4. To investigate whether suicide risk is elevated in patients with HS.
4 Materials and methods

This registry-based study was designed to evaluate psychiatric and somatic comorbidities as well as mortality in patients with HS in a nationwide retrospective case-control setting. The case-control setting is well suited for investigating several different disease associations simultaneously. This type of analysis usually provides sufficient statistical power, even when used to study rare associations. (Song & Chung, 2010)

4.1 Patient data from the Finnish Care Register for Health Care (I–IV)

Registries have proven to be excellent sources of information in comorbidity research (Jemec & Kimball, 2015). Therefore, patients for this study were identified using the Finnish Care Register for Health Care (CRHC; previous name The Finnish Hospital Discharge Register). The CRCH is a statutory and nationwide registry maintained by the Finnish National Institute of Health and Welfare. The CRHC contains comprehensive patient data, including the identification number of the patient, their date of birth and sex as well as the dates and codes for primary and subsidiary diagnoses. According to Finnish laws and regulations, data in the CRHC are confidential, but permission to use them for purposes of scientific research can be granted on a case-by-case basis. The CRHC covers all public hospitals and the largest private hospitals in Finland. Data from outpatient clinics have been included in the registry since 1998. (National Institute for Health and Welfare, a)

4.2 Mortality data from Statistics Finland (III, IV)

In order to investigate mortality, information on deaths was obtained from two registries: the CRHC and Statistics Finland. Statistics Finland is the main producer of official statistics in Finland, and it has mortality data dating back to 1936. Almost 100% of all deaths of Finnish citizens are recorded in its database. Information on causes of death is gained from death certificates, which are issued by patient’s personal doctor or the physician who confirmed the death. The death certificate form is ratified by the Ministry of Social Affairs and Health. If an autopsy is necessary to determine the cause of death, the death certificate is issued by a forensic pathologist. During the study period, all death certificates were verified at
the National Institute of Health and Welfare, usually by a forensic pathologist, and then forwarded to Statistics Finland. (Statistics Finland, a)

4.3 Study populations (I–IV)

The CRHC database was queried to obtain records of three study populations: the HS group, and two control groups, comprising patients with either psoriasis or melanocytic nevi. All of the inclusion diagnoses were made between 1st Jan 1987 and 31st Dec 2014, and were identified by diagnostic codes based on the World Health Organization’s (WHO’s) ICD, Ninth Revision, Finnish version (ICD-9), and Tenth Revision (ICD-10) (World Health Organization, a). ICD codes have proven to be helpful in scientific research, particularly if the studied disease has a simple definition and easily recognized symptoms (O’Malley et al., 2005). ICD-9 was utilized in Finland in 1987, which was the starting year of the patient search, and ICD-10 replaced it in 1996. All patients with at least one diagnostic code for the case or control diagnosis were included in the study (Table 3).

Table 3. International Classification of Diseases (ICD) codes for hidradenitis suppurativa, psoriasis and benign melanocytic nevi used in the study.

<table>
<thead>
<tr>
<th>Disease</th>
<th>ICD-9 code</th>
<th>ICD-10 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidradenitis suppurativa</td>
<td>7058C</td>
<td>L73.2</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>6918B, 6961A</td>
<td>L40.0</td>
</tr>
<tr>
<td>Melanocytic nevi</td>
<td>2160–9A</td>
<td>D22</td>
</tr>
</tbody>
</table>

4.3.1 Inclusion and exclusion criteria (I, II, IV)

The investigation of psychiatric comorbidities included patients aged 10 years or more, because the mental disorders studied are rare in young children (I) (Merikangas, Nakamura, & Kessler, 2009). Additionally, suicides are particularly uncommon in young children (Sheftall et al., 2016). Therefore, the same age criterion was applied when studying suicide risk (IV). However, a different age profile was used when somatic and psychiatric comorbidities were evaluated in children and adolescents. It is known that infantile forms of HS resolve early in life, and HS has not been described in children less than 5 years old (Liy-Wong et al., 2015; R. A. Palmer & Keefe, 2001). Thus, this analysis included patients who were
diagnosed with HS between their 5th and 18th birthdays (II). This subgroup of young patients with HS was designated as youth-onset HS (yHS).

Although psychiatric disorders are not associated with nonmelanoma skin cancer (Balieva, Lien, Kupfer, Halvorsen, & Dalgard, 2016), they can be associated with malignant melanoma (Beesley et al., 2015). Therefore, patients with in situ or invasive melanoma (ICD-9 code 172, ICD-10 codes C43 and D03) were excluded from the nevi control group (I, II, IV). Furthermore, the age distribution of patients with HS and psoriasis varies markedly. The onset of psoriasis is bimodal: It occurs frequently in young adulthood but its incidence peaks again in older age groups unlike in HS (Alikhan et al., 2009; Parisi, Symmons, Griffiths, & Ashcroft, 2013). Thus, young patients with HS were only compared with nevi controls when comorbidities in yHS group were investigated (II).

4.3.2 Matching (I, II)

For the purpose of investigating psychiatric comorbidities, each HS case was matched by sex and age (±5 years) with controls from the psoriasis and melanocytic nevi groups in a ratio of 1:4 (I). However, when comorbidities were evaluated in children and adolescents, matching by age between cases and nevi controls was more restrictive (±1 years) (II). In the matching process, one HS case at a time was selected by a computer, and the data of controls were then automatically searched through in random order until a control that fulfilled the criteria for the matching variables was found. After a match was found, the data of the case and match were written to a new data set and removed from the source data. This process was rerun four times per every HS case to achieve the preselected patient-control ratio. The 1:4 ratio was chosen, because it enhances the precision of the risk estimate compared to the ratios between 1:1 and 1:3. Furthermore, it has been shown that adding more than four or five controls per case does not improve statistical power in most situations. (Hennessy, Bilker, Berlin, & Strom, 1999)

4.4 Evaluation of comorbidities (I, II)

To investigate possible associations between HS and psychiatric disorders, a comprehensive approach with a variety of psychiatric disorders was chosen for this study. The psychiatric disorders that were included in the study are presented in Table 4. Bipolar disorder and manic episodes were merged into one group because bipolar disorder may first manifest with mania (Baldessarini, Tondo, & Visioli,
As a consequence, the diagnostic code for ‘manic episode’ is the first diagnosis recorded in the patient’s file, only later being clarified with the correct code for bipolar disorder.

**Table 4. International Classification of Diseases (ICD) codes for psychiatric disorders included in the study.**

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>ICD-9 code</th>
<th>ICD-10 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia and schizotypal disorder</td>
<td>295</td>
<td>F20–F21</td>
</tr>
<tr>
<td>All psychotic disorders</td>
<td>295, 2971A, 2973A, 2988A, 2989X</td>
<td>F20–F29</td>
</tr>
<tr>
<td>Bipolar disorder and manic episodes</td>
<td>2962–2964, 2967A</td>
<td>F30–F31</td>
</tr>
<tr>
<td>Major depression</td>
<td>2961, 2968A, 3004A</td>
<td>F32, F33, F34.1</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>3000A–C, 3002B–D, 3002X, 3003A</td>
<td>F40–F42</td>
</tr>
<tr>
<td>Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders</td>
<td>3002, 3090A, 3092C–E, 3093A, 3094A, 3098A, 3098X, 3099X</td>
<td>F40–F45, F48</td>
</tr>
<tr>
<td>Disorders of adult personality and behavior</td>
<td>301</td>
<td>F60–F69</td>
</tr>
</tbody>
</table>

1The Finnish version of the Ninth Revision of the International Classification of Diseases, 23004A excluded

Prevalence rates of the selected psychiatric disorders were evaluated in HS cases as well as in age- and sex-matched psoriasis and melanocytic nevi controls, and ORs for these disorders were calculated between the study groups. In addition, a gender-stratified analysis was performed to investigate whether there was a sex-based difference in the strength of the association between HS and psychiatric diseases. In this analysis, ORs for mental disorders between patients with HS and those with psoriasis were compared separately in women and men.

To further explore the comorbidity burden, prevalence rates of the above-mentioned psychiatric disorders, except disorders of adult personality and behaviour, were analyzed in patients in the yHS group. Age- and sex-matched patients from melanocytic nevi group served as controls. The analysis was performed twice, first before the age of 18 years, and then again before the age of 23 years. The somatic diseases shown in Table 5 were also explored in these young patients.
Table 5. International Classification of Diseases (ICD) codes for somatic disorders included in the study.

<table>
<thead>
<tr>
<th>Somatic disorder</th>
<th>ICD-9 code</th>
<th>ICD-10 code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>7061A–7061C, 7061E, 7061X</td>
<td>L70.0, L70.1, L70.8, L70.9</td>
</tr>
<tr>
<td>Adrenal or adrenal cortical hyperplasia</td>
<td>2552A, 2553A</td>
<td>E25.01, E27.0</td>
</tr>
<tr>
<td>Diabetes, type 1</td>
<td>250B</td>
<td>E10</td>
</tr>
<tr>
<td>Diabetes, type 2</td>
<td>250A</td>
<td>E11</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>7580A</td>
<td>Q90</td>
</tr>
<tr>
<td>Hypertension</td>
<td>401–404</td>
<td>I10–I13</td>
</tr>
<tr>
<td>Inflammatory bowel diseases</td>
<td>555, 556</td>
<td>K50, K51</td>
</tr>
<tr>
<td>Inflammatory joint diseases</td>
<td>6960A, 7111, 7113, 7131A, 7140–7143, 7148X, 7165A, 7166A, 7168A, 7169X, 7200A, 7202A, 7209X</td>
<td>M02, M03, M05–M09, M13, M45, M46.1</td>
</tr>
<tr>
<td>Dermatomyositis, lupus, Sjögren syndrome, scleroderma</td>
<td>6954, 7100A, 7101A, 7101B, 7101X</td>
<td>M32, M33, M34, M35.0, M35.1, L93, L94.0, L94.1</td>
</tr>
<tr>
<td>Metabolic syndrome2</td>
<td>-</td>
<td>E66.00</td>
</tr>
<tr>
<td>Obesity</td>
<td>2780A</td>
<td>E66.01, E66.1, E66.2, E66.8, E66.9</td>
</tr>
<tr>
<td>Pilonidal sinus</td>
<td>685</td>
<td>L05.0, L05.9</td>
</tr>
<tr>
<td>Polycystic ovarian disease</td>
<td>2564A</td>
<td>E28.2</td>
</tr>
<tr>
<td>Premature adrenarche</td>
<td>2591A</td>
<td>E22.80, E30.1</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>242, 244, 2451</td>
<td>E03.4–E03.9, E05, E064</td>
</tr>
</tbody>
</table>

1The Finnish version of the Ninth Revision of the International Classification of Diseases, 2Diagnostic code for metabolic syndrome has been utilized in Finland since the late 1990s, 32440X, 2442A, 2443X, 2454A excluded, 4E05.3, E05.4, E05.81, E06.4 excluded

4.5 Evaluation of mortality (III, IV)

In order to evaluate possible risks for all-cause and cause-specific mortality, the dates and causes of death of patients in all study groups who had died by the end of 2015 were obtained from Statistics Finland. These data are based on death certificates that contain the ICD codes for underlying, intermediate and immediate causes of death as well as the codes for contributing causes. The statistical analyses of this study used the code for the underlying cause of death.

Since 1969 in Finland causes of death have been classified into 54 different categories based on ICD codes. Although there are a few other classification methods, this 54-group classification has been utilized throughout the study period in Finland. It complies with the European shortlist classification applied by the European Union and Eurostat. The 54-category classification was used as a basis
Table 6. Categorization and International Classification of Diseases (ICD) codes for causes of death.

<table>
<thead>
<tr>
<th>Cause of death (54-category classification number1)</th>
<th>ICD-10 codes2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms (4–22)</td>
<td></td>
</tr>
<tr>
<td>Lip, oral cavity and pharynx cancers (4)</td>
<td>C00–C14</td>
</tr>
<tr>
<td>Gastrointestinal cancers (5–8)</td>
<td>C15–C16, C18–C21</td>
</tr>
<tr>
<td>Liver, bile duct and pancreatic cancers (9–10)</td>
<td>C22, C25</td>
</tr>
<tr>
<td>Respiratory tract cancers (11)</td>
<td>C32–C34</td>
</tr>
<tr>
<td>Melanoma of the skin (12)</td>
<td>C43</td>
</tr>
<tr>
<td>Breast cancer (13)</td>
<td>C50</td>
</tr>
<tr>
<td>Female reproductive cancers (14–16)</td>
<td>C53–C56</td>
</tr>
<tr>
<td>Prostate cancer (17)</td>
<td>C61</td>
</tr>
<tr>
<td>Kidney and bladder cancers (18–19)</td>
<td>C64, C67</td>
</tr>
<tr>
<td>Lymphatic and hematopoietic cancers (20)</td>
<td>C81–C96</td>
</tr>
<tr>
<td>Other (21–22)</td>
<td>C17, C23–C24, C26–C31, C37–C41, C44–C49, C51–C52, C57–C60, C62–C63, C65–C66, C68–C80, C97, D00–D48</td>
</tr>
<tr>
<td>Endocrine, nutritional and metabolic diseases (23–24)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (23)</td>
<td>E10–E14</td>
</tr>
<tr>
<td>Other (24)</td>
<td>E00–E09, E15–E90</td>
</tr>
<tr>
<td>Diseases of the nervous system (25–26)</td>
<td></td>
</tr>
<tr>
<td>Dementia, Alzheimer’s disease (25)</td>
<td>F01, F03, G30, R54</td>
</tr>
<tr>
<td>Other (26)</td>
<td>G00–G29, G31.0–G31.1, G31.8–G62.07, G62.2–G72.0, G72.2–H95</td>
</tr>
<tr>
<td>Diseases of the circulatory system (27–30)</td>
<td></td>
</tr>
<tr>
<td>Ischemic heart diseases (27)</td>
<td>I20–I25</td>
</tr>
<tr>
<td>Cerebrovascular diseases (29)</td>
<td>I60–I69</td>
</tr>
<tr>
<td>Other (28, 30)</td>
<td>I00–I15, I26–I28, I30–I42.5, I42.7–I52, I70–I99</td>
</tr>
<tr>
<td>Diseases of the respiratory system (31–35)</td>
<td>J00–J99</td>
</tr>
<tr>
<td>Diseases of the digestive system (36)</td>
<td>K00–K93</td>
</tr>
<tr>
<td>Diseases of the genitourinary system (37)</td>
<td>N00–N99</td>
</tr>
<tr>
<td>Congenital malformations (38)</td>
<td>Q00–Q99</td>
</tr>
<tr>
<td>Alcohol-related diseases (41)</td>
<td>F10, G31.2, G40.51, G62.1, G72.1, I42.6, K29.2, K70, K86.0, K85.2, 035.4, P04.3, X45</td>
</tr>
<tr>
<td>Accidents, suicides and violence (42–53)</td>
<td>V01–X44, X46–Y89</td>
</tr>
<tr>
<td>Certain infectious and parasitic diseases, other</td>
<td>A00–A09, A15–B99, D50–D89, F00, F02, F04–</td>
</tr>
<tr>
<td>diseases, ill-defined and unknown causes of death (01–03, 39–40)</td>
<td>F09, F11–F99, J65, L00–M99, O00–O35.3, O35.5–P04.2, P04.4–P05.2, R00–R53, R55–R99</td>
</tr>
<tr>
<td>No death certificate (54)</td>
<td>-</td>
</tr>
</tbody>
</table>

1Division of causes of death into 54 categories as classified by Statistics Finland, 2The corresponding ICD-9 codes are included in the study, 3G40.51 not included, 4K85.2 not included
of the analyses in this study, but some categories were merged together to achieve more illustrative results (Table 6). (Statistics Finland, a)

4.6 Statistical analyses

The crude incidence rates for HS and psoriasis were ascertained by dividing the number of new HS patients in one year by the number of individuals at risk. An indirect method was used to calculate the age-standardized incidence rates. The age distribution of the general Finnish population for different age groups between 1987 and 2014, provided by Statistics Finland, was utilized as a reference (Statistics Finland, b).

Odds ratios for somatic and psychiatric disorders between HS cases and age- and sex-matched controls were evaluated using a conditional logistic regression model. The potential association between HS and suicide was examined using a Cox regression model separately for women and men. To assess possible mediation by mental disorders of the association between HS and suicide risk, mediation analyses based on a single-mediator model were carried out using the SAS macros as described by Jasti, Dudley and Goldwater (2008).

Cox proportional hazard analysis and models adjusted for age and sex were used to calculate hazard ratios (HRs) for overall and cause-specific mortality in the study populations. The proportional hazards assumption was tested graphically and by using a statistical test based on the distribution of Schoenfeld residuals.

Age and sex characteristics of the study populations are shown as means with standard deviations and proportions. All results are presented as ORs or HRs with 95% confidence intervals (CIs), and two-sided p-values less than 0.05 are considered statistically significant.

Statistical analyses were performed using STATA Data Analysis and Statistical Software (MP 13, StataCorp LP, College Station, TX, USA) and the SAS software package (version 9.4, SAS Institute Inc., Cary, NC, USA).

4.7 Permissions and ethical aspects

The National Institute of Health and Welfare and the Statistics Finland granted permission to use the national data of their registries for this study. A statement of the ethical committee was not required, because the registry-based data of the study populations were obtained without any information regarding the patients’ identity. Furthermore, the patients were not contacted in any way.
5 Results

5.1 Characteristics of the study populations (I–IV)

The initial CRHC database query yielded data for 4,381 patients with HS, 40,406 with psoriasis, and 49,214 with melanocytic nevi. Of these, 4372 patients with HS and 39,497 with psoriasis were ≥10 years of age at the time of diagnosis. Furthermore, 43,248 patients aged 10 years or more with melanocytic nevi but without melanoma were found.

Four matches from the nevi group were found for each HS patient, but 44 (1.0%) patients with HS had fewer than four psoriasis matches and another 35 (0.8%) patients with HS had no psoriasis match at all. (Table 7)

Table 7. Characteristics of cases with hidradenitis suppurativa (HS) and controls with psoriasis and benign melanocytic nevi aged ≥10 years.

<table>
<thead>
<tr>
<th>Patients</th>
<th>HS</th>
<th>Psoriasis</th>
<th>Nevi</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N)</td>
<td>4372</td>
<td>39497</td>
<td>43248</td>
</tr>
<tr>
<td>Females</td>
<td>58.6%</td>
<td>44.6%</td>
<td>63.8%</td>
</tr>
<tr>
<td>Age in years¹</td>
<td>39.6 (±13.5)</td>
<td>49.6 (±17.6)</td>
<td>43.8 (±20.0)</td>
</tr>
<tr>
<td>Males</td>
<td>42.0 (±14.0)</td>
<td>48.9 (±16.5)</td>
<td>44.1 (±22.1)</td>
</tr>
</tbody>
</table>

1Shown as mean ± standard deviation, 2Matched by age and sex in a 1 to 4 ratio, 3There was no psoriasis match for 35 cases with HS

5.1.1 Patients with youth-onset hidradenitis suppurativa (II)

Of all cases with HS, 153 patients were aged ≥5 and <18 years at diagnosis. From the benign melanocytic nevi controls, 8475 of patients belonged to the corresponding age group. Of those patients, 612 subjects formed the control group for the present study after age and sex matching. The age and sex characteristics of these patients are presented in Table 8.
Table 8. Characteristics of cases with youth-onset hidradenitis suppurativa (yHS) and controls with benign melanocytic nevi.

<table>
<thead>
<tr>
<th></th>
<th>yHS</th>
<th>Nevi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>153</td>
<td>8475</td>
</tr>
<tr>
<td>Girls</td>
<td>72.6%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Age in years¹</td>
<td>15.6 (±2.1)</td>
<td>11.1 (±3.9)</td>
</tr>
<tr>
<td>Matched patients²</td>
<td>153</td>
<td>612</td>
</tr>
<tr>
<td>Girls</td>
<td>72.6%</td>
<td>72.6%</td>
</tr>
<tr>
<td>Age in years¹</td>
<td>15.6 (±2.1)</td>
<td>15.4 (±2.2)</td>
</tr>
</tbody>
</table>

¹Shown as mean ± standard deviation, ²Matched by age and sex in a 1 to 4 ratio

5.2 Incidence of hidradenitis suppurativa and psoriasis in Finland (I)

The age-adjusted incidence of HS, which was most frequently (26.1%) diagnosed in individuals between 30 and 39 years of age, was 3.0/100,000 persons/year. For psoriasis, the age-adjusted incidence was 27.8/100,000 persons/year. It was most commonly (28.8%) diagnosed in individuals older than 60 years. (Figure 2)

Fig. 2. Age at diagnosis in patients with hidradenitis suppurativa and those with psoriasis.
5.3 Psychiatric comorbidities of hidradenitis suppurativa (I)

All of the mental disorders that were studied were more common in patients with HS than in the controls. Almost one-fourth (24.1%) of patients with HS had at least one mental disorder compared with 19.1% of psoriasis patients and 13.5% of patients with melanocytic nevi. Major depression was the most frequent mental disorder in all three patient groups, and again, it was most commonly found in patients with HS (15.3% vs. 12.1% vs. 8.3%, respectively). The risks for all studied psychiatric disorders were significantly higher in patients with HS than control groups (Table 9).

Table 9. Comorbidities in patients with hidradenitis suppurativa (N=4337 for psoriasis and N=4372 for melanocytic nevi) vs. matched psoriasis (N=17318) and melanocytic nevi (N=17488) controls.

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any psychiatric disorder</td>
<td>1044 (24.1)</td>
<td>3315 (19.1)</td>
</tr>
<tr>
<td>Major depression</td>
<td>663 (15.3)</td>
<td>2099 (12.1)</td>
</tr>
<tr>
<td>ADSSO</td>
<td>484 (11.2)</td>
<td>1529 (8.8)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>301 (6.9)</td>
<td>866 (5.0)</td>
</tr>
<tr>
<td>Any psychotic disorder</td>
<td>203 (4.7)</td>
<td>566 (3.3)</td>
</tr>
<tr>
<td>Schizophrenia¹</td>
<td>103 (2.4)</td>
<td>267 (1.5)</td>
</tr>
<tr>
<td>Personality disorders²</td>
<td>141 (3.3)</td>
<td>404 (2.3)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>135 (3.1)</td>
<td>301 (1.7)</td>
</tr>
</tbody>
</table>

¹Includes schizotypal disorder, ²Includes disorders of adult personality and behavior, HS = hidradenitis suppurativa, OR = odds ratio, CI = confidence interval, ADSSO = anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders

5.3.1 Sex differences

Psychiatric disorders were more common in female than male patients with HS (25.5% and 22.0%, respectively). In fact, aside from psychotic disorders, every psychiatric disorder studied was more frequent in women. The prevalence rate of ‘any psychotic disorder’ was equal between sexes (present in 4.7%), but ‘schizophrenia or schizotypal disorder’ was more common in men.

A similar sex pattern was found in patients with psoriasis: women were more likely than men to have psychiatric disorders. At least one psychiatric diagnosis was found in 21.2% of women and in 16.3% of men. All psychiatric disorders were more frequent in women than men except psychotic disorders, ‘schizophrenia or
schizotypal disorder’ and ‘bipolar disorder or manic episodes’ which were present in similar proportions of patients by sex.

The sex-stratified analysis revealed a significantly stronger association between HS and mental disorders in men than in women (OR 1.46 vs. 1.28, respectively; \( p = 0.02 \)). When analyzing the psychiatric disorders separately, men with HS had a significantly higher risk (OR 1.70) for anxiety disorders than women with HS (OR 1.29; \( p = 0.003 \)). Additionally, a borderline significant sex-based difference was found for ‘schizophrenia or schizotypal disorder’ (OR 1.88 in men vs. 1.36 in women; \( p = 0.05 \)). (Figure 3)

**Fig. 3.** Sex-stratified odds ratios for psychiatric disorders in patients with hidradenitis suppurativa. (Reprinted with permission from Elsevier.)

### 5.4 Psychiatric comorbidities of hidradenitis suppurativa in children and adolescents, and in early adulthood (II)

Young patients with HS had a markedly higher comorbidity burden than the nevi group at the age of 18 years. To elucidate the possible further accumulation of comorbidities in young adulthood, the prevalence of comorbidities was evaluated again at 23 years of age. Between the ages of 18 and 23, the prevalence of
psychiatric disorders in the yHS group increased from 15.7% to 23.5%. In controls with nevi, the increase was subtle, from 5.6% to 8.7%. (Table 10)

Table 10. Prevalence rates of psychiatric comorbidities in the study groups, and risks of psychiatric disorders between the groups evaluated at the ages of 18 and 23 years.

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Group</th>
<th>&lt;18 years old</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
<th>&gt;23 years old</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any psychiatric disorder</td>
<td>yHS</td>
<td>24 (15.7)</td>
<td>3.31 (1.86–6.90)</td>
<td>36 (23.5)</td>
<td>3.31 (2.05–5.36)</td>
<td>Nevi</td>
<td>34 (5.6)</td>
</tr>
<tr>
<td>Major depression</td>
<td>yHS</td>
<td>13 (8.5)</td>
<td>2.68 (1.29–5.58)</td>
<td>24 (15.7)</td>
<td>3.64 (2.04–6.49)</td>
<td>Nevi</td>
<td>21 (3.4)</td>
</tr>
<tr>
<td>ADSSO</td>
<td>yHS</td>
<td>14 (9.2)</td>
<td>2.61 (1.30–5.28)</td>
<td>21 (13.7)</td>
<td>3.00 (1.64–5.48)</td>
<td>Nevi</td>
<td>23 (3.8)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>yHS</td>
<td>9 (5.9)</td>
<td>3.43 (1.39–8.47)</td>
<td>14 (9.2)</td>
<td>3.87 (1.84–8.14)</td>
<td>Nevi</td>
<td>11 (1.8)</td>
</tr>
<tr>
<td>Any psychotic disorder</td>
<td>yHS</td>
<td>3 (2.0)</td>
<td>6.00 (1.00–35.9)</td>
<td>3 (2.0)</td>
<td>2.40 (0.57–10.0)</td>
<td>Nevi</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

OR = odds ratio, CI = confidence interval, yHS = youth-onset hidradenitis suppurativa, ADSSO = anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders

5.5 Somatic comorbidities of hidradenitis suppurativa in children and adolescents (II)

Approximately one third of patients with yHS (34.0%) had at least one of the somatic comorbidities studied compared with 4.9% of controls with melanocytic nevi. In addition, at least one somatic and psychiatric comorbidity was found concomitantly in 9.2% of yHS patients vs. in 1.3% nevi controls. (Figure 4)
Of the somatic comorbidities, acne, obesity, IBDs and inflammatory joint diseases were the most strongly associated with HS. Down syndrome was found in seven patients (4.6%) in the yHS group, but the OR could not be calculated, because there were no controls with Down syndrome. The diagnostic codes for type 2 diabetes, polycystic ovarian disease, premature adrenarche, adrenal hyperplasia, lupus, dermatomyositis, scleroderma and Sjögren syndrome were also searched for but not found in the yHS group. The risks for somatic comorbidities in patients with yHS compared with nevi controls are presented in more detail in Table 11.

Somatic comorbidities were analyzed again before the age of 23 years. In contrast to the psychiatric comorbidities, no significant further accumulation of somatic diseases was observed between the ages of 18 and 23 years (data not shown).
Table 11. Somatic comorbidities in the youth-onset hidradenitis suppurativa group (yHS) compared with the nevi group.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>N (%)</th>
<th>OR (95% CI) yHS vs. Nevi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yHS</td>
<td>Nevi</td>
</tr>
<tr>
<td>Acne</td>
<td>21 (13.7)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Diabetes, type 1</td>
<td>4 (2.6)</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>7 (4.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory bowel diseases</td>
<td>5 (3.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Inflammatory joint diseases(^1)</td>
<td>8 (5.2)</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>3 (2.0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Obesity</td>
<td>9 (5.9)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Pilonidal sinus</td>
<td>2 (1.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>4 (2.6)</td>
<td>3 (0.5)</td>
</tr>
</tbody>
</table>

\(^1\)Includes reactive, rheumatoid and psoriatic arthritis, ankylosing spondylitis and undifferentiated spondyloarthropathies, OR = odds ratio, CI = confidence interval

5.6 Mean age at death (III)

By the year 2015, 498 (11.4%) patients in the HS group had died. Even though there was a higher proportion of women than men in the group, the majority of deaths (59.8%) were among men. The mean age at death in the HS group was 60.5 years compared with 71.1 years in the psoriasis group and 75.2 years in the nevi group (Table 12). The distribution of age at death in all study groups is graphically illustrated in Figure 5.

Table 12. Age and sex of deceased patients in study groups.

<table>
<thead>
<tr>
<th>Study group</th>
<th>All patients</th>
<th>Women (%)</th>
<th>Deceased patients</th>
<th>Women (%)</th>
<th>Age at death(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS</td>
<td>4379</td>
<td>2568 (58.6%)</td>
<td>498</td>
<td>200 (40.2%)</td>
<td>60.5 (±13.3)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>40406</td>
<td>18061 (44.7%)</td>
<td>8620</td>
<td>3255 (37.8%)</td>
<td>71.1 (±14.2)</td>
</tr>
<tr>
<td>Neviri</td>
<td>49214</td>
<td>30507 (62.0%)</td>
<td>4041</td>
<td>2137 (52.9%)</td>
<td>75.2 (±15.7)</td>
</tr>
</tbody>
</table>

\(^1\)Shown as mean age in years (± standard deviation), HS = hidradenitis suppurativa
5.7 Causes of death (III)

Causes of death were analyzed systematically in all study groups. The risk for all-cause mortality was highest in patients with HS (HR 1.22; 95% CI 1.12–1.34 vs. psoriasis and HR 2.63; 95% CI 2.39–2.90 vs. nevi controls). In patients with HS, CV diseases, neoplasms, ‘accidents, suicides and violence’ and alcohol-related diseases were the most common main categories of causes of death. On the subcategory level, the risk of dying from respiratory tract cancers was particularly high in patients with HS compared with both control groups (HR 2.56; 95% CI 1.86–3.53 vs. psoriasis and HR 4.53; 95% CI 3.19–6.43 vs. nevi controls).

Tables 13 and 14 show the numbers and proportions of deceased patients, and age- and sex-adjusted HRs for mortality between the HS group and the control groups. The sex-stratified analysis found no major differences in cause-specific risks of mortality in patients with HS (data not shown).
**Table 13.** Cause-specific mortality and risk of death in patients with hidradenitis suppurativa (HS) compared with patients with psoriasis and melanocytic nevi.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>N (%)</th>
<th>HS</th>
<th>Psoriasis</th>
<th>Nevi</th>
<th>HS vs. Psoriasis</th>
<th>HS vs. Nevi</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>498</td>
<td>8620</td>
<td>4041</td>
<td></td>
<td>1.22 (1.12–1.34)</td>
<td>2.63 (2.39–2.90)</td>
</tr>
<tr>
<td>Neoplasm/cancer</td>
<td>139 (27.9%)</td>
<td>168 (81.1%)</td>
<td>1304 (32.3%)</td>
<td></td>
<td>1.79 (1.50–2.13)</td>
<td>1.90 (1.59–2.28)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (2.6%)</td>
<td>133 (81.9%)</td>
<td>52 (1.3%)</td>
<td></td>
<td>1.82 (1.01–3.29)</td>
<td>3.73 (1.98–7.02)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.4%)</td>
<td>35 (81.9%)</td>
<td>8 (26.6%)</td>
<td></td>
<td>0.91 (0.21–3.87)</td>
<td>3.83 (0.76–19.5)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>19 (3.8%)</td>
<td>609 (81.9%)</td>
<td>419 (32.3%)</td>
<td></td>
<td>1.29 (0.81–2.05)</td>
<td>2.11 (1.32–3.39)</td>
</tr>
<tr>
<td>Dementia</td>
<td>10 (2%)</td>
<td>473 (81.9%)</td>
<td>343 (32.3%)</td>
<td></td>
<td>1.19 (0.63–2.25)</td>
<td>1.88 (0.99–3.56)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.8%)</td>
<td>136 (81.9%)</td>
<td>76 (32.3%)</td>
<td></td>
<td>1.18 (0.59–2.35)</td>
<td>2.03 (0.99–4.17)</td>
</tr>
<tr>
<td>Circulatory</td>
<td>168 (33.7%)</td>
<td>3455 (81.9%)</td>
<td>1479 (32.3%)</td>
<td></td>
<td>1.31 (1.12–1.54)</td>
<td>3.59 (3.03–4.25)</td>
</tr>
<tr>
<td>IHD</td>
<td>100 (20.1%)</td>
<td>2109 (81.9%)</td>
<td>822 (32.3%)</td>
<td></td>
<td>1.29 (1.06–1.59)</td>
<td>3.97 (3.18–4.94)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (7.0%)</td>
<td>736 (81.9%)</td>
<td>320 (32.3%)</td>
<td></td>
<td>1.16 (0.82–1.64)</td>
<td>3.18 (2.20–4.60)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>18 (3.6%)</td>
<td>550 (81.9%)</td>
<td>181 (32.3%)</td>
<td></td>
<td>0.99 (0.62–1.59)</td>
<td>2.99 (1.80–4.97)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9 (1.8%)</td>
<td>269 (81.9%)</td>
<td>93 (32.3%)</td>
<td></td>
<td>0.75 (0.38–1.47)</td>
<td>2.74 (1.33–5.62)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>4 (0.8%)</td>
<td>85 (81.9%)</td>
<td>40 (32.3%)</td>
<td></td>
<td>1.72 (0.62–4.79)</td>
<td>3.47 (1.18–10.2)</td>
</tr>
<tr>
<td>Congenital</td>
<td>2 (0.4%)</td>
<td>18 (81.9%)</td>
<td>15 (32.3%)</td>
<td></td>
<td>1.02 (0.23–4.46)</td>
<td>1.41 (0.32–6.17)</td>
</tr>
<tr>
<td>Alcohol-related</td>
<td>47 (9.4%)</td>
<td>864 (81.9%)</td>
<td>89 (32.3%)</td>
<td></td>
<td>0.67 (0.50–0.90)</td>
<td>5.86 (4.09–8.38)</td>
</tr>
<tr>
<td>Accidents/violence</td>
<td>56 (11.2%)</td>
<td>654 (81.9%)</td>
<td>274 (32.3%)</td>
<td></td>
<td>1.05 (0.80–1.39)</td>
<td>2.29 (1.71–3.06)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (3.6%)</td>
<td>242 (81.9%)</td>
<td>84 (32.3%)</td>
<td></td>
<td>1.23 (0.75–2.01)</td>
<td>3.38 (1.99–5.75)</td>
</tr>
</tbody>
</table>

1Includes endocrine, nutritional and metabolic diseases, 2Includes Alzheimer's disease, 3Congenital malformations, 4Includes suicides, 5Includes certain infectious and parasitic diseases, other diseases, and ill-defined and unknown causes of death, HR = hazard ratio, CI = confidence interval, IHD = ischemic heart diseases
Table 14. Risk of death from neoplasms in patients with hidradenitis suppurativa compared with controls with psoriasis and melanocytic nevi.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>N (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Lip/oral/pharynx</td>
<td>4 (2.9%)</td>
<td>46 (2.7%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (11.5%)</td>
<td>206 (12.2%)</td>
</tr>
<tr>
<td>Hepatobiliary/pancreas</td>
<td>14 (10.1%)</td>
<td>236 (13.9%)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>45 (32.4%)</td>
<td>387 (22.9%)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0 (0.0%)</td>
<td>26 (1.5%)</td>
</tr>
<tr>
<td>Breast</td>
<td>10 (7.2%)</td>
<td>89 (5.3%)</td>
</tr>
<tr>
<td>Female reproductive</td>
<td>4 (2.9%)</td>
<td>62 (3.7%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>7 (5.0%)</td>
<td>93 (5.5%)</td>
</tr>
<tr>
<td>Kidney/bladder</td>
<td>6 (4.3%)</td>
<td>114 (6.7%)</td>
</tr>
<tr>
<td>Hematopoietic</td>
<td>12 (8.6%)</td>
<td>184 (10.9%)</td>
</tr>
<tr>
<td>Other neoplasm²</td>
<td>21 (15.1%)</td>
<td>250 (14.8%)</td>
</tr>
</tbody>
</table>

¹Shown as N (percent of all cancer deaths), ²Includes non-melanoma skin cancer, HS = hidradenitis suppurativa, HR = hazard ratio, CI = confidence interval

5.7.1 Risk of suicide (IV)

Of patients with HS, 22 (4.4%) had died by suicide. In comparison, suicide was the cause of death in 2.1% of patients with psoriasis and in 1.8% of melanocytic nevi. In the HS group, the majority (63.6%) of suicides were women. In addition, 7.0% of all deaths in women with HS were suicides compared with 2.7% in men. In the control groups, suicide was less frequent in women than in men.

In the sex-stratified analysis, the risk for suicide was significantly more elevated in women with HS than in women with psoriasis or melanocytic nevi. However, no such increased risk was found in men (Table 15).

Table 15. Hazard ratios for suicide in patients with hidradenitis suppurativa compared with patients with psoriasis or benign melanocytic nevi.

<table>
<thead>
<tr>
<th>Gender</th>
<th>N (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Both</td>
<td>22</td>
<td>181</td>
</tr>
<tr>
<td>Women</td>
<td>14 (63.6%)</td>
<td>35 (19.3%)</td>
</tr>
<tr>
<td>Men</td>
<td>8 (36.4%)</td>
<td>146 (80.7%)</td>
</tr>
</tbody>
</table>

HS = hidradenitis suppurativa, HR = hazard ratio, CI = confidence interval
In the mediation analysis, depression was not an important mediator of suicide in women with HS. It was involved in only 11.7% of suicides. In contrast, 44.9% of male suicides were mediated by depression, showing it to be an influential mediator. The results were similarly skewed towards males in another mediation analysis, which took all psychiatric disorders into account. The proportions of suicides in the HS group that were mediated by ‘any psychiatric disorder’ were 17.7% in women with HS and 58.9% in men. Prevalence rates of psychiatric disorders of patients died by suicide are summarized in Table 16.

Table 16. Psychiatric comorbidities of patients who died by suicide in the study groups.

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>HS (N=22)</th>
<th>Psoriasis (N=181)</th>
<th>Nevi (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any psychiatric disorder</td>
<td>12 (54.5%)</td>
<td>91 (50.3%)</td>
<td>30 (41.1%)</td>
</tr>
<tr>
<td>Major depression</td>
<td>9 (40.9%)</td>
<td>57 (31.5%)</td>
<td>20 (27.4%)</td>
</tr>
<tr>
<td>ADSSO</td>
<td>6 (27.3%)</td>
<td>35 (19.3%)</td>
<td>13 (17.8%)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>3 (13.6%)</td>
<td>21 (11.6%)</td>
<td>6 (8.2%)</td>
</tr>
<tr>
<td>Any psychotic disorder</td>
<td>2 (9.1%)</td>
<td>23 (12.7%)</td>
<td>6 (8.2%)</td>
</tr>
<tr>
<td>Schizophrenia or schizotypal disorder</td>
<td>0</td>
<td>9 (5.0%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Bipolar disorder or manic episodes</td>
<td>0</td>
<td>11 (6.1%)</td>
<td>9 (12.3%)</td>
</tr>
<tr>
<td>Disorders of adult personality and behavior</td>
<td>1 (4.5%)</td>
<td>18 (9.9%)</td>
<td>5 (6.8%)</td>
</tr>
<tr>
<td>Mental and behavioral disorders due to psychoactive substance use(^1)</td>
<td>6 (27.3%)</td>
<td>60 (33.1%)</td>
<td>16 (21.9%)</td>
</tr>
</tbody>
</table>

\(^1\)Not included in ‘any psychiatric disorder’, includes abuse, dependence, withdrawal state and withdrawal state with delirium of the following substances: alcohol, opioids, cannabinoids, sedatives or hypnotics, cocaine, other stimulants, hallucinogens, volatile solvents and multiple drugs or other psychoactive substances, HS = hidradenitis suppurativa, ADSSO = anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders
6 Discussion

This study was one of the first to demonstrate the heavy psychiatric burden of HS in both young and adult patients. At least one psychiatric diagnosis was found in approximately one of every four patients with HS. Remarkably, psychiatric disorders were already frequent comorbidities in patients less than 18 years of age, and their prevalence increased rapidly during early adulthood. This study was also among the first to report an elevated prevalence of somatic comorbidities in children and adolescents with HS on a nationwide level.

6.1 Increased risk of psychiatric disorders in the hidradenitis suppurativa group (I)

In the present study, the prevalence of every psychiatric disorder studied was higher in the HS group than in the psoriasis or nevi control groups. Notably, among dermatologic diseases, psoriasis is generally considered to have one of the strongest associations with mental disorders (Dalgard et al., 2015; Rieder & Tausk, 2012). However, in this study, the risk for psychiatric disorders was significantly greater in patients with HS than in those with psoriasis.

6.1.1 Depression and anxiety

In this study, major depression (15.3%) was the most common psychiatric disorder in the HS group. In previous studies on HS, prevalence rates of depression have varied considerably: the highest prevalence reported is 42.9%, but not all studies have found a clear association between HS and depression (Onderdijk et al., 2013; Thorlacius et al., 2018; Vazquez et al., 2013). In an Israeli study of 3207 patients with HS, depression was found in 5.9% of patients (Shavit et al., 2015). Although that prevalence seems low in comparison with the present study, the risk for depression was still significantly 1.7-fold higher in patients with HS than in non-HS controls. Unlike in the present study, the Israeli group did not have access to patient data from psychiatric hospitals, which may explain the lower prevalence rate in their study. The highest prevalence rate for depression (42.9%) was based on a relatively small sample of 268 patients with HS in one county in the United States (Vazquez et al., 2013). In contrast with this present hospital-based study, it included diagnoses that were set at all levels of health care, which could explain the higher rate.
In a Danish cohort of over 7000 patients with HS, an age- and sex-adjusted analysis found a risk of depression in patients with HS that was double that of a background population of over 4 million Danes (Thorlacius et al., 2018). However, in a fully-adjusted analysis, where socioeconomic status, smoking, alcohol overuse and health care consumption were taken into consideration, the significance was lost (OR 1.13; 95% CI 0.87–1.47). On the other hand, as the authors of the Danish study point out, HS may be a cause of low socioeconomic status. For example, HS symptoms and absenteeism may hinder patient’s career progress (Matusiak et al., 2010a). Because low socioeconomic status is associated with depression (Rojas-Garcia et al., 2015), the comprehensive adjustments performed in the Danish study may have masked the degree of association between HS and depression. However, the Danish group did find a significant association between HS and antidepressant drug use, which implies that depression is a true comorbidity of HS. Notably, prevalence rates of depression were surprisingly low in the Danish study as only 1.6% of patients with HS and 0.8% of controls had a diagnosis of depression. According to data from the WHO, in 2015 the proportion of people suffering from depression was 4.4% globally, 5.0% in Denmark, and 5.6% in Finland (World Health Organization, b).

Anxiety is often concurrent with depression (Stahl, 1997). Therefore, it is rational that anxiety disorder was the second most common psychiatric disorder in patients with HS. In the present study, 6.9% of patients suffered from anxiety disorder, a clearly higher prevalence than those of the above mentioned Israeli and Danish studies (3.9% and 0.8%, respectively) (Shavit et al., 2015; Thorlacius et al., 2018). Although their prevalence rates vary, the results of all these three studies indicate a significant risk for anxiety disorder in patients with HS.

Understandably, the symptoms of HS have profound emotional impacts (Jemec, 2012; Wolkenstein et al., 2007). Malodorous discharge, pain and the visual appearance of HS lesions can cause distress and preclude the physical exercise that is important for mental health (Matusiak, 2018). Pain may also cause insomnia, which can become chronic and further predispose to depression (Kaaz et al., 2018; Tsuno, Besset, & Ritchie, 2005). Moreover, HS often manifests in intimate areas of the skin, which may worsen the distress and lead to sexual problems, in turn negatively affecting the patient’s mental state (Esmann & Jemec, 2011). Furthermore, patients with HS are often multimorbid (Andersen & Jemec, 2017). It is known that the probability of a psychiatric disorder increases with the number of chronic diseases affecting the individual (Piane & Smith, 2014). The lack of public knowledge and understanding of the disease adds to the stigma borne by
patients with HS (Esmann & Jemec, 2011). All these negative factors may result in alienation and major psychiatric problems, including depression and anxiety (Matusiak, 2018).

From a pathogenetic point of view, the chronic systemic inflammation of HS may be involved in the association between HS and psychiatric disorders (Fond et al., 2014; Riis et al., 2015). At the moment, the exact pathogeneses of HS, depression and anxiety remain largely unknown, but chronic inflammation probably plays a role in all of them (Kelly & Prens, 2016; Köhler et al., 2017; A. H. Miller & Raison, 2016; Renna, O'Toole, Spaeth, Lekander, & Mennin, 2018). One indication of this is that anti-TNF-α medications have proven efficient in HS therapy, and have also shown anti-depressive features (Matusiak et al., 2009a; N. Patel et al., 2017). These drugs may normalize stress hormone levels and improve serotonergic or noradrenergic neurotransmission (Krügel, Fischer, Radicke, Sack, & Himmerich, 2013). Additional shared pathogenic pathways may be found, when more information about the pathomechanisms of HS and depression is obtained.

6.1.2 Schizophrenia and bipolar disorder

The present study was the first to demonstrate the association between HS and both ‘schizophrenia or schizotypal disorder’ and ‘bipolar disorder or manic episodes’. Before this study, only the previously mentioned group from Israel had reported a possible association between these diseases (Shavit et al., 2015). Their results were not statistically significant, possibly due to a lack of data from psychiatric hospitals. More recently, researchers from the United States reported that psychoses were more frequent in inpatients with HS than those without (K. R. Patel et al., 2018). Additionally, another group from the United States found that psychoses were more common in patients with severe forms of HS than in those with mild disease (Kimball et al., 2018).

In the current study, patients with HS had a higher risk for schizophrenia and bipolar disorder compared with the psoriasis group, which in turn showed a higher risk for both disorders than the nevi group. Psoriasis has previously been shown to be associated with both of these disorders (Chen et al., 2012; Han, Lofland, Zhao, & Schenkel, 2011). The heavy inflammatory load of HS may explain these elevated risks because, as with depression, chronic inflammation is thought to be an important component in the pathogenesis of both schizophrenia and bipolar disorder (Goldstein, Kemp, Soczynska, & McIntyre, 2009; B. J. Miller, Buckley, Sebolt, Mellor, & Kirkpatrick, 2011; Riis et al., 2015). In patients with
schizophrenia, raised levels of IL-17 and IL-23, which are also the key cytokines in HS and psoriasis, have been reported (Debnath & Berk, 2017; Schlapbach et al., 2011).

Another explanation for the association between HS and mental disorders is excessive smoking, which is common in patients with HS and in those with mental disorders, especially schizophrenia and bipolar disorder (Alikhan et al., 2009; Dickerson et al., 2013; Lasser et al., 2000). Constituents of tobacco smoke relieve psychiatric symptoms by affecting the dopamine system (Mackowick et al., 2014). Alleviation of symptoms and the feeling of being better generates an urge to smoke repeatedly. The resultant heavy smoking may lead to activation or worsening of HS (Kelly & Prens, 2016).

6.1.3 Sex differences in the frequency of psychiatric disorders

In the HS group, women were more frequently affected by psychiatric disorders than men (25.5% vs. 22.0%), a finding that is in line with the previous Israeli study (Shavit et al., 2015). Notably, although the overall prevalence of psychotic disorders was 4.7% in both sexes, ‘schizophrenia or schizotypal disorder’ was more often found in men (2.7% vs. 2.1%). This is remarkable, because schizophrenia is usually equally common in men and women (Perälä et al., 2007). One possible explanation for this is the fact that men suffer from severe HS more often than women (Canoui-Poitrine et al., 2009). Therefore, it follows that the inflammatory load of HS may be heavier in men than in women. This could, in turn, result in a higher risk for schizophrenia in men, because, as mentioned above, the key cytokines of HS may also be involved in the inflammatory mechanisms of schizophrenia.

Notably, although psychiatric disorders were more common in women with HS, sex-stratified analysis found that the association between HS and psychiatric disorders was stronger in men when compared between patients with HS and those with psoriasis. The risks of schizophrenia and anxiety disorders were particularly more elevated in men with HS compared with women with HS. Different perception between sexes of HS and psoriasis symptoms could explain this. The negative influence of psoriasis on mental health is found to be milder in men than in women (Böhm et al., 2013). In HS, no such difference has been reported. Moreover, HS affects the quality of life of patients equally in both sexes (Matusiak, Bieniek, & Szepietowski, 2010b).
6.2 Increased risk of psychiatric disorders in the youth-onset hidradenitis suppurativa group (II)

This study showed that the risk of psychiatric disorders alongside HS is already present when patients are less than 18 years old. The prevalence rate of psychiatric disorders was almost three-fold higher in the yHS group (15.7%) than in the age- and sex-matched patients with melanocytic nevi (5.6%). The steepest increase in prevalence occurred between the ages of 14 and 16 years. Unlike in the whole HS cohort, ‘anxiety, dissociative, stress-related, somatoform, and other nonpsychotic mental disorders’ was the most common group of mental disorders in young patients with HS. It was more frequently found in the yHS group than depression. It is possible that anxiety evolves into depression in children and adolescents, which could explain this result (Cole, Peeke, Martin, Truglio, & Seroczynski, 1998).

Remarkably, by the time patients in yHS group had reached 23 years of age, the prevalence of depression had nearly doubled from 8.5% to 15.7%. With the same 5-year advance, the proportion of patients in this group with any psychiatric disorder increased to 23.5%, which is almost identical to that seen in the whole HS cohort. Only the prevalence of psychotic disorders did not increase during that time, and the risk for this group of disorders was not significantly higher in the yHS group than in the nevi group.

The high prevalence of psychiatric disorders in the yHS group could have two different explanations. Firstly, it could reflect the devastating impact of HS on the mental health of young patients (Esmann & Jemec, 2011). Secondly, because both psychiatric diseases and HS occur at such a young age, they may have shared pathogenic pathways (Kelly & Prens, 2016; Köhler et al., 2017). Therefore, it would be of special interest to evaluate the temporal relationships between these diseases. However, the long diagnostic delay of HS precluded a reliable evaluation of which condition occurred earlier in the present study setting (Kluger et al., 2017; Saunte et al., 2015).

Additionally, it is known that HS is more common in patients with Down syndrome (Denny & Anadkat, 2016), who are also more vulnerable to psychiatric problems (Alexander et al., 2016). In this study, 7 of 153 yHS patients had Down syndrome, but none of them had a diagnosis of any mental disorder. Therefore, the results of the present study are not biased by Down syndrome.
6.3 Increased risk of somatic comorbidities in the youth-onset hidradenitis suppurativa group (II)

Although there is a growing body of literature on somatic comorbidities in adult patients with HS, the evidence of comorbidities in young patients with HS is scarce (Mikkelsen & Jemec, 2014). In one study of 66 patients with HS symptoms occurring before the age of 13 years, the prevalence rates of associated acne, rheumatoid arthritis and IBD were similar to those in patients with normal-onset HS (Deckers et al., 2015). Additionally, a few case reports suggest a link between prepubertal HS and metabolic syndrome, as well as between HS and hormonal imbalances, such as premature adrenarche and adrenal hyperplasia (Jourdain, Le, Mourier, Ploussard, & Roussel, 1988; Lewis, Messenger, & Wales, 1993; Mengesha et al., 1999). However, in the present study, no cases with these hormonal imbalances were found in the yHS group.

The current study showed that patients in the yHS group had a clearly higher risk for IBDs than nevi controls. Although IBDs usually first manifest between the ages of 20 and 40 years (Ananthakrishnan, 2015), 3.3% of the young patients with HS had a diagnosis of IBD compared with 0.3% of the controls. In Finland, the prevalence of IBDs in the general population is one of the highest in the world (0.8%) (Ventola et al., 2017), but still markedly lower than that found in the yHS group. Thus, the results of this study support the idea of shared pathogenic pathways between HS and IBDs (Abraham & Cho, 2009; Roussomoustakaki et al., 2003; Schlapbach et al., 2011). When treating young patients with HS, it is essential to keep the risk of IBD in mind, because the early onset of IBD may indicate an increased risk for more severe bowel disease and, consequently, even intestinal cancer (Duricova et al., 2014).

The risk of inflammatory joint diseases was significantly higher in the yHS cases than in controls. Therefore, young patients with HS should be actively screened for musculoskeletal symptoms. Possible signs of inflammatory joint diseases should not be misinterpreted as growing pains, since the association of these diseases is already strong in childhood and adolescence.

Patients in the yHS group were more likely to be obese than those in the nevi control group. However, the prevalence of obesity (5.9%) was relatively low compared with the results from previous studies in adult populations (Alikhan et al., 2009). The result of this study may be an underestimation, because obesity is a sensitive issue, particularly in young patients. Therefore, physicians might not
record a diagnosis code of obesity in young patients’ files for fear of stigmatizing them.

Down syndrome was found in 4.6% (7/153) of patients in the yHS group. This could be expected, because HS usually occurs earlier in life in patients with Down syndrome than on average (Denny & Anadkat, 2016). In any case, the proportion of patients in the yHS group with Down syndrome is striking, because Down syndrome was present in only 0.13% of all live births in Finland during the study period (National Institute for Health and Welfare, b). The association of Down syndrome with HS is hypothesized to result from the overexpression of the amyloid precursor protein (APP), whose gene is located in the chromosome 21. In trisomy 21, this gene is more likely to be overexpressed, which leads to higher levels of APP. APP stimulates keratinocytes and is suggested to cause follicular occlusion, which is the primary pathogenic event in HS. (Blok, Jonkman, & Horvath, 2014)

Down syndrome is associated with thyroid disorders (Alexander et al., 2016). In the yHS group, a thyroid disorder was diagnosed in two patients with both HS and Down syndrome. Therefore, the association between yHS and thyroid disorders should not be interpreted as significant in this study, even though the statistical analysis suggested a high risk (OR 6.97; 95% CI 1.25–38.8).

The prevalence and risk of acne were clearly higher in the yHS group than in the nevi controls. However, this might be an overestimation. Although acne conglobata is known to be associated with HS (Poli et al., 2010), some of the patients with early-onset HS may have been primarily misdiagnosed with acne instead of HS.

### 6.4 Markedly reduced life-span in patients with hidradenitis suppurativa (III, IV)

In this study, patients with HS died at a markedly younger age than controls with psoriasis or melanocytic nevi. The mean age at death was only 60.5 years in patients with HS. That was 10.6 years younger than the average in patients with psoriasis and 14.7 years younger than in those with nevi. Although the elevated risk for all-cause mortality in patients with HS was previously known (Egeberg et al., 2016), no previous study had examined age at death in patients with HS and such a low mean was unexpected.

Several previous studies have linked psoriasis with an increased mortality risk (Abuabara et al., 2010; Prodanovich et al., 2009; Springate et al., 2017; Svedbom et al., 2015), but in the present study the overall risk of death was higher with HS
than with psoriasis. The high intensity and long duration of systemic inflammation in HS may explain this elevated risk. Systemic inflammation is usually longer-lasting in HS than in psoriasis, because, on average, HS manifests earlier in life (Alikhan et al., 2009; Parisi et al., 2013). Furthermore, it has been suggested that patients with HS carry a heavier systemic inflammatory load than patients with other dermatological disorders (Riis et al., 2015). Chronic inflammation is linked to increased risks for other conditions such as atherosclerosis, stroke and cancer as well as all-cause mortality (Coussens & Werb, 2002; Dregan et al., 2017; Emerging Risk Factors Collaboration, 2010; Libby, Ridker, & Maseri, 2002; McColl, Allan, & Rothwell, 2009).

Previously, an increased incidence rate ratio (IRR 1.35; 95% CI 1.15–1.59) for all-cause mortality has been reported in Danish patients with HS compared with the general population (Egeberg et al., 2016), which is in line with the results of the present study. However, the Danish study found no statistically significant difference in the risk of death between patients with HS and those with severe psoriasis (IRR 1.09; 95% CI 0.94–1.28). It is likely that, as well as patients with severe psoriasis, the present registry-based study also included patients with psoriasis of moderate severity, which may explain the different findings. Additionally, the calculations of the present study are not as comprehensively adjusted as those of the Danish study.

6.4.1 Cause-specific risks of death in patients with hidradenitis suppurativa (III)

This study was the first systematically performed evaluation of mortality risks for all causes of death in patients with HS. Although HS is associated with smoking and obesity as well as with a variety of other potentially life-threatening conditions (Kohorst et al., 2015; Reddy et al., 2019), few studies on mortality have been conducted previously. According to those studies, patients with HS carry elevated risks for all-cause mortality and adverse CV outcomes. The risk of CV death has been found to be even higher in patients with HS than in those with severe psoriasis. (Egeberg et al., 2016) Patients with HS also have an elevated risk of malignant neoplasms (Lapins et al., 2001).

In the present study, CV diseases, neoplasms, ‘accidents, suicides or violence’ and alcohol-related diseases were the four most frequent causes of death in patients with HS. Of those, diseases of the circulatory system were the most common causes of death, and the risk of patients with HS dying from these diseases was higher than
those in the control groups. Obesity is an important risk factor for CV diseases because it causes systemic inflammation (Fontana, Eagon, Trujillo, Scherer, & Klein, 2007; Gustafson, 2010). It is also associated with several other diseases such as type 2 diabetes, obstructive sleep apnea and dyslipidemia, and also with increased CV mortality (Peeters et al., 2003; Vgontzas et al., 1994). Obesity is strongly associated with HS (Alikhan et al., 2009), but, unfortunately, in this registry-based study setting, it was impossible to explore reliably the true prevalence of obesity in the HS group. Nevertheless, it is likely that obesity plays a major part in increasing the risk for a shortened life-span in patients with HS.

The second most common cause of death in patients with HS was cancer, and the risk of dying from cancer was significantly greater in the HS group than in the control groups. The risk of dying from cancers of the respiratory tract was particularly elevated – these usually smoking-related neoplasms (Hecht, 2006), caused 45/139 (32.4%) of all cancer deaths. It is noteworthy that the risk of death from cancers of the respiratory tract was highest in patients with HS, although, similarly to HS, psoriasis is associated with excessive tobacco use (Armstrong, Harskamp, Dhillon, & Armstrong, 2014). As with smoking, obesity is a common condition in both HS and psoriasis patients (Alikhan et al., 2009; Armstrong, Harskamp, & Armstrong, 2012). Obesity is linked with cancer development and poorer cancer survival (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003; Calle & Kaaks, 2004). Notably, 70–89% of patients with HS are smokers and 30–75% obese, which are higher proportions than have been reported in patients with psoriasis (Alikhan et al., 2009; Armstrong et al., 2014; Augustin, Reich, Glaeske, Schaefer, & Radtke, 2010). Therefore, tobacco use and obesity are likely to cause more health problems in patients with HS than in those with psoriasis. Furthermore, it is possible that the heavy chronic inflammatory load of HS plays a crucial role in increasing the risk of cancer deaths, because inflammation induces tumor growth. Inflammation is also involved in malignant conversion of tumors and dissemination of cancers. (Todoric, Antonucci, & Karin, 2016)

Previously, a Swedish registry-based study found that patients with HS had an incidence of all cancers 50% greater than that of the general population (Lapins et al., 2001). It also found a 4.6-fold greater incidence of non-melanoma skin cancer in patients with HS. Malignant transformation to cutaneous squamous cell carcinoma in anogenital regions of the skin is one of the most feared complications of HS since it carries a high risk for metastasis and mortality, but it is an infrequent manifestation (Jourabchi, Fischer, Cimino-Mathews, Waters, & Okoye, 2017; Makris et al., 2017). In this study, HRs for the risk of death from non-melanoma
skin cancer were higher in patients with HS than the controls, but the low number of patients (HS 4, psoriasis 9, nevi 12) led to wide CIs and low statistical power (HR 12.3; 95% CI 3.49–43.2 vs. psoriasis and HR 8.38; 95% CI 2.46–28.6 vs. nevi controls).

Patients with HS had a clearly greater risk for death from alcohol-related diseases than the nevi controls (HR 5.86; 95% CI 4.09–8.38), which strengthens the previous findings that alcohol abuse is associated with HS (Garg et al., 2018). The death risk from ‘accidents, suicides and violence’ was also greater in patients with HS than in nevi controls, which is likely to be at least partly a consequence of hazardous drinking habits. The risk for dying from ‘accidents, suicides or violence’ was almost equal in patients with HS and those with psoriasis. However, with alcohol-related diseases, the risk was higher among patients with psoriasis. Alcohol consumption is known to be greater than average in patients with psoriasis (B. Kirby et al., 2008), but the extent of it is difficult to compare between them and those with HS.

Naturally, CV diseases and neoplasms are the most frequent causes of death in the general population in Finland, not only in patients with HS (Statistics Finland, a). Neurologic diseases, especially dementia and Alzheimer’s disease, are becoming increasingly common causes of death (Thies & Bleiler, 2012), but in this study such deaths were uncommon in patients with HS. Even though both Alzheimer’s disease and HS have been linked to gamma secretase mutations, it seems that different mutations are involved (Riis, Egeberg, Gislaso, & Jemec, 2017). Previous studies have not found Alzheimer’s disease to be associated with HS (Garg & Strunk, 2017; Riis et al., 2017). Furthermore, dementia is a disease of elderly people. Patients with HS, who often have a reduced life span, are at heightened risk of death before the typical age of Alzheimer’s disease onset.

6.4.2 Women with hidradenitis suppurativa carry an elevated suicide risk (IV)

Suicides accounted for 4.4% (22/498) of all deaths in the HS group, a proportion more than two-fold higher than both the psoriasis and nevi groups. In a previous study, a Danish group reported an elevated risk for suicide in patients with HS (HR 2.42, 95% CI 1.07–5.45) (Thorlacius et al., 2018). In their study, no sex-stratified analysis was performed, possibly because of the relatively small occurrence of suicide (N=11). Notably, in the present study, 14/22 (63.6%) of suicides in the HS group were women, whereas the majority of suicides were men in both control
groups. As a consequence, women with HS had a significantly higher risk for suicide than women in the control groups, but the corresponding risks were not significantly elevated in men with HS. This is surprising, because suicides are clearly more common in men than in women in Finland (Titelman et al., 2013). In addition, although patients with HS have poor quality of life, it is not thought to affect either sex disproportionately (Matusiak et al., 2010b).

HS occurs in sensitive areas of the skin and causes discomfort, chronic pain, suppuration and odor, all of which may lead to anxiety, depressive mood and isolation of patients (Matusiak, 2018). Systemic inflammation may also increase the patient’s risk of mental disorders (Fond et al., 2014). Suicide may be considered the most extreme manifestation of mental disorders, especially of depression (Cavanagh, Carson, Sharpe, & Lawrie, 2003; Nordentoft, Mortensen, & Pedersen, 2011). Psychotic disorders are also associated with increased suicide risk (B. A. Palmer, Pankratz, & Bostwick, 2005). Because psychiatric problems are more common in women (ESEMeD/MHEDEA 2000 Investigators et al., 2004b), as was also the case in this study, one would easily think that mental disorders are responsible for the increased suicide risk. However, only 11.7% of suicides in women with HS were mediated by depression. Similarly, other mental disorders were not especially common in women who died by suicide, because ‘any psychiatric disorder’ was diagnosed in only 17.7% of them. On the contrary, in men with HS, depression and other psychiatric disorders were important mediators as they were involved in high proportion of suicides (44.9% and 58.9%, respectively).

Suicide attempts are more likely the more somatic diseases a depressed individual has (Goodwin, Marusic, & Hoven, 2003). In addition to chronic somatic diseases, substance misuse may also negatively affect mental health (Schneider, 2009). The association between HS and many chronic diseases is well established (Kimball et al., 2018), and alcohol, opioid and cannabis misuse are reported to be more common in patients with HS (Garg et al., 2018). However, in the present study, neither the most common chronic somatic diseases (including respiratory and CV diseases, stroke, diabetes, and inflammatory joint and bowel diseases), nor substance misuse were over-represented in patients with HS who died by suicide.

The symptoms of HS may predispose for isolation and unwillingness to leave the home (Esmann & Jemec, 2011; Matusiak, 2018), which could result in patients with HS not seeking help for depression and anxiety. This could, in turn, contribute to the numbers of patients with HS who also have undiagnosed mental disorders. However, this does not explain the sex difference in suicide risk. Taking all of the above into consideration, the factors that lead to suicide in women with HS remain
largely unknown. It is possible that in Finland the gravity of hopelessness and suicidal ideation are not recognized in women with HS, because suicide is usually associated with male sex (Titelman et al., 2013).

6.5 Strengths and limitations of the study

Finnish registries are known to be solid sources of information. Data in the CRHC database are considered reliable, and the diagnostic codes accurate with high positive predictive values. (Sund, 2012) Furthermore, the cause of death validation process has been shown to be appropriate for epidemiological studies on mortality (Lahti & Penttilä, 2001). These facts were the major strengths of this study along with the reasonably large and nationwide study populations. However, although the yHS group was one of the largest cohorts of young patients with HS, it comprised no more than 153 patients, which limited the study’s statistical power.

Because the CRHC captures data only from patients treated at hospitals, patients with mild HS or psoriasis may have been omitted, since some such cases may not have been referred to hospital care. This may have resulted in underestimation of the incidence rates of those two diseases. Furthermore, HS has been a poorly recognized disease especially during the early part of the study period (van der Zee et al., 2012), which could have further lowered the incidence rate of HS in this study. The hospital-generated data used in this study probably also resulted in an over-representation of more severe HS cases that may have had a heavier comorbidity burden. This may, in turn, have led to over-estimation of the risk for premature death. Nevertheless, it is likely that, for the same reason, the psoriasis controls also had above average disease severity, which improves comparability between the study groups and enhances the reliability of the results of this study.

In a registry-based study, it is not possible to verify the accuracy of the diagnoses or the ICD codes, a fact that may weaken the analyses of this study. However, previous hospital-based studies from the United States have shown that the diagnostic code for HS has a high positive predictive value, especially when set by a dermatologist (G. E. Kim, Shlyankevich, & Kimball, 2014; Shlyankevich et al., 2014). Because of the hospital-based data utilized in this study, it is likely that most of the HS diagnoses were set by dermatologists or plastic surgeons familiar with HS.

The CRHC contains no data on clinical findings, disease severity, behavioral matters, socioeconomic status or risk factors for HS such as obesity and smoking.
This limited the ability to analyze differences between the HS and control populations in more detail or to refine the adjustments of the study groups further. Additionally, the temporal relationship between the occurrence of HS and the comorbidities would have been interesting to explore. Unfortunately, this was not possible because the register data would have not been reliable due to the long diagnostic delay of HS (Saunte et al., 2015).

Because this study was based on Finnish registries, it included a mainly Caucasian population. Thus, results are generalizable only to similar populations. However, suicide and intoxication-oriented drinking of alcohol are relatively common in Finland (Titelman et al., 2013; World Health Organization, c), which may also weaken the generalizability of the results concerning deaths from ‘accidents, suicides or violence’ and alcohol-related diseases.

### 6.6 Clinical implications

This study showed that the burden of psychiatric disease is heavier in patients with HS than previously thought. This burden consists not only of depression and anxiety but also of other mental disorders including psychotic disorders. Notably, an accumulation of both psychiatric and somatic comorbidities was evident in patients with HS from a young age. Furthermore, the mortality risk was elevated in patients with HS. Suicide contributed to the mortality in women, which reflects the devastating nature of HS.

Treating physicians should aim to improve the quality of life of the patients with HS. Firstly, HS symptoms should be recognized as early as possible and treated effectively: Chronic inflammation should be reduced with medical therapy to minimize its adverse impacts, and surgery should always be administered when necessary. Secondly, during each appointment, treating staff should consider the possibility of both psychiatric and somatic comorbidities. Because patients with HS often suffer from many concomitant diseases, it is recommended to use screening tools for conditions such as depression, IBDs and SpAs as well as regular questionnaires regarding quality of life (Dauden et al., 2018). Also, risks for a variety of other comorbidities, cancers and shortened life-span should be kept in mind. Thirdly, it is crucial to take sleep quality into account. Because sleep may be impaired by the itching and pain associated with HS, these symptoms should be treated as well as possible to prevent insomnia (Kaaz et al., 2018). Chronic insomnia is known to be associated with many diseases such as depression, hypertension, metabolic syndrome and type 2 diabetes (Ohayon, 2002).
Furthermore, the risk for accidents and suicide increases with insomnia (Daley et al., 2009; McCall, 2011). The sleep of patients with HS may be disturbed also by sleep apnea, the risk of which is increased due to obesity (Meurling, Kelly, Kirby, & Garvey, 2019; Thomas, Gordon, & Mortimer, 2014). Sleep apnea should be recognized in time, as it is an additional factor that increases mortality (He, Kryger, Zorick, Conway, & Roth, 1988).

The nature of HS is multidimensional. Patients may need help from several fields of medicine. Regardless of this, the treatment of HS in Finland tends not to follow a multidisciplinary approach. It is carried out without close collaboration between health care professionals from different fields, and without one physician taking the lead in treatment. To produce the most effective and comprehensive care, it would be optimal for patients with HS to be treated by multidisciplinary teams (W. B. Kim et al., 2016; Persaud et al., 2017; Scuderi et al., 2017). In that way, the competence of each specialist could be utilized to help these patients. Dermatologists have an essential role in treating patients with HS because they are familiar with the comorbidity risks, medical treatment and also with at least minor surgical procedures. However, they should work closely with general practitioners and surgeons to deal with comorbidities and problems that demand major surgical intervention. In addition to these three specialties, professionals of many other fields are often required to effectively treat patients with HS and help them cope with their lives (Figure 6).
Fig. 6. A multidisciplinary model for the treatment of hidradenitis suppurativa.
6.7 Future prospects

Further studies are required to explore the pathogenesis of HS in detail. Novel data could clarify not only the treatment strategies but also the associations between HS and other diseases and their temporal relationships. New studies are also required to investigate whether HS truly is an independent risk factor for shortened life span or if the results of this study can be explained by the comorbidities, obesity and unhealthy lifestyle associated with HS. To increase statistical power, the suicide risk of HS and the comorbidity burden in young patients with HS should be investigated in larger populations.

Interestingly, a recent study from the United States found that the incidence of HS is increasing (Garg et al., 2017). This may be due to a true increase of incidence, growing awareness of HS or both. In Finland, physicians are now more familiar with HS than before. Even so, HS needs to be recognized even earlier in order to provide patients with proper treatment from the beginning of the disease. In that way, disease progression to more severe forms could be prevented. Additionally, the comorbidities and risks related to HS could be considered at an early stage. As a result, patients with HS could have a better quality of life, and the risk of early death could be minimized. This cannot be emphasized enough, especially if the incidence of HS is truly increasing.
7 Conclusions

The findings of this study increase the knowledge about the morbidity and mortality of patients with HS. With better understanding of the disease characteristics, physicians are more able to monitor patients for possible somatic and psychiatric comorbidities. This allows comorbidities to be treated early with better outcomes, or even prevented. In other words, the better HS is understood, the more comprehensive care can be delivered to the patient.

The following conclusions can be drawn based on studies I–IV:

1. The psychiatric disease burden in patients with HS is heavy. HS is associated with several psychiatric disorders, including depression and anxiety, and also psychotic disorders and bipolar disorder. These disorders are more strongly associated with HS than with psoriasis.

2. The risks for both somatic and psychiatric comorbidities are present in children and adolescents with HS.

3. HS markedly shortens life expectancy. The most important causes of death, in order of likelihood, are: CV diseases, neoplasms, ‘accidents, suicides and violence’ and alcohol-related diseases. The risk of dying from respiratory tract cancers is particularly elevated.

4. Suicide risk is elevated in women with HS.
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Original publications


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1530. Sirniö, Kai (2019) Distal radius fractures : Epidemiology, seasonal variation and results of palmar plate fixation


1536. Terho, Henri (2019) Electrocardiographic risk markers for cardiac events in middle-aged population


1538. Ylönen, Susanna (2019) Genetic risk factors for movement disorders in Finland


Hannu Tiri

COMORBIDITIES AND MORTALITY OF HIDRADENITIS SUPPURATIVA IN FINLAND