Idiopathic Intracranial Hypertension in Sweden – Epidemiological studies focused on Incidence and Risk factors
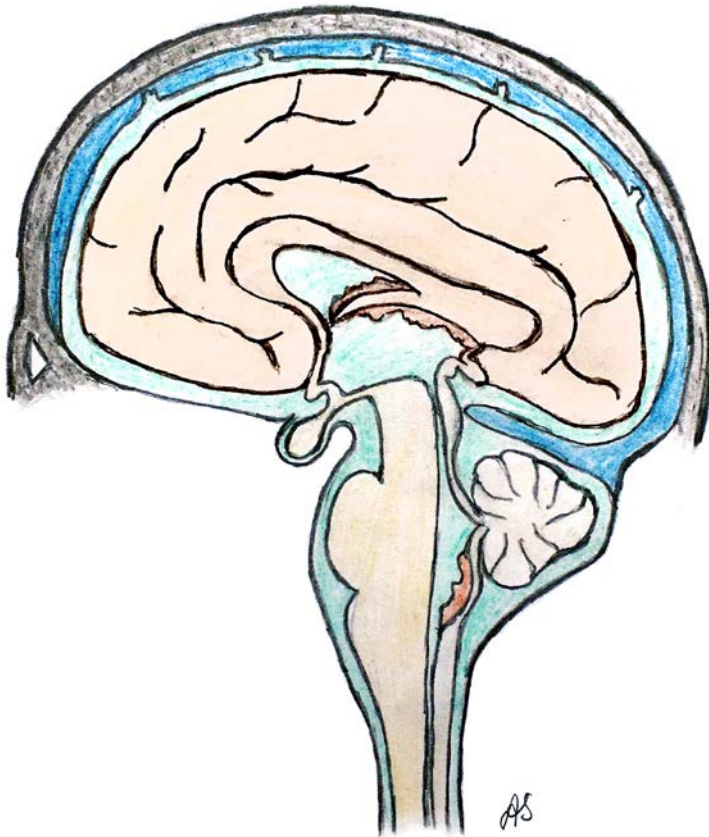
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IDIOPATHIC INTRACRANIAL HYPERTENSION IN SWEDEN – EPIDEMIOLOGICAL STUDIES FOCUSED ON INCIDENCE AND RISK FACTORS

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*"You've got to get up every morning with determination
if you're going to bed with satisfaction."*

George H Lorimer

ABSTRACT

Idiopathic intracranial hypertension (IIH) is a disorder which is not that unusual for neurologists and ophthalmologists to meet in clinical practice even though it only affects around 1 per 100,000 individuals. It gives rise to symptoms of headache and visual disturbances caused by high intracranial pressure (ICP). The first recorded patient with this disorder was described by Quicke in 1893, followed by 22 cases reported by Dandy in 1937, who later summarized the common diagnostic characteristics of the disorder (1). Even though we have known about this disorder for far more than 100 years and several studies have been performed to investigate its origin, we still don't know what causes the increased pressure. We know that it more commonly affects females of reproductive age, in particular those who are obese. But why this is the case is not known. Several hypotheses have been suggested and studied over the years. Additionally, several risk factors that could be involved in the development of high intracranial pressure have been proposed. However, since the disorder and some of its risk factors are rare, there have been conflicting findings as to the strength of some of the proposed associations between such risk factors and IIH development.

The intension of this thesis was to conduct studies investigating the incidence of IIH in Sweden as well as describing a Swedish cohort to shed light onto potential different risk factors. We used Swedish large national registers to investigate if risk factors were more common in IIH cases compared to controls prior to diagnosis.

Study I is a descriptive study of all patients with a diagnosis code for IIH in Stockholm County during 2006-2013. We included 207 individuals ≥18 years of age with the diagnosis code G93.2 registered in the national patient register during these years. We validated the diagnosis coding by review of medical records and found that only 65% fulfilled the modified Dandy diagnostic criteria for IIH. The incidence was 0.65 per 100,000 individuals, in the lower range of most reported incidence studies on IIH. Among those fulfilling IIH diagnosis criteria, as reported in other studies, most patients were females (F/M ratio of 6:1) and females were slightly younger than men at time of diagnosis (mean age women 31 (CI 29-33) compared to 43 (CI 36-50) in men).

These results provided the motivation to improve finding correctly diagnosed IIH patients to include in register studies. In study II we therefore developed algorithms, that included parameters thought to improve prediction by using data which are possible to extract from registers, to better predict which patients to include as "true" IIH cases. We developed the algorithms by testing these parameters using a stepwise logistic regression model on a randomized one half of study I individuals and then tested how well they predicted on the other half. By using parameters age,

receiving 3 or more registrations of the diagnosis code G93.2, and in the second algorithm also adding acetazolamide treatment (needing use of drug register data) prediction of true cases improved to 86% and 88%, respectively.

With use of the developed algorithms we continued to do the national case-control register studies looking at exposure to risk factors in the year prior to the first IIH diagnosis to undertake study III and IV. We looked at the whole population over 18 years during 2000-2016. In study III and IV 902 IIH cases and 4510 matched general population (GP) controls and 4510 obese controls were included. Matching factors were age, sex, and region of residence at the time the IIH patient in the matched group was diagnosed. When analyzing drug dispensations, we had 654 IIH cases and 3270 corresponding GP and obese controls, respectively included. In study I, we found that conditions causing an inflammatory response were common. In study III we therefore wanted to analyze this in a larger population. The results from study III showed increased OR for both infectious (OR = 4.3; 95% CI 3.3-5.6) and inflammatory disorders (OR = 3.2; 95% CI 2.4-4.3) the year prior to the first IIH diagnosis compared to GP controls. Similarly, OR were significantly increased though of slightly lower magnitude compared to the obese controls.

In Study IV we investigated the incidence of IIH in Sweden and evaluated risk factors previously proposed in the literature. The mean incidence in the adult population over the study period was similar to study I; 0.71 per 100,000 individuals. The incidence showed however a steady increase which we believe is related to increasing obesity worldwide, as well as in Sweden. Regarding risk factors we could conclude that we saw a significant increased risk of exposure to several disorders, especially kidney failure, SLE, PCOS, tetracyclines, and lithium and systemic corticosteroid treatments. We also found surprisingly high OR for arterial hypertension which in recent years has not been considered a risk factor although it has been described. Equally important, our results confirm that hormonal contraceptives and pregnancy are not likely to be risk factors for IIH. In this study and this thesis, we discuss common denominators regarding risk factors for IIH and proposed three main hypotheses; an inflammation theory, an androgen theory and an ICP regulatory mechanism theory to be of interest for further research.

LIST OF PUBLICATIONS

I.   Population-based incidence and clinical characteristics of idiopathic intra-cranial hypertension. **Anna Sundholm**, Sarah Burkill, Olafur Sveinsson, Fredrik Piehl, Shahram Bahmanyar, A Ingela M Nilsson Remahl.

Published in Acta Neurol Scand. 2017 Nov;136(5):427-433

II.   Improving identification of idiopathic intracranial hypertension patients in Swedish patient register. **Anna Sundholm**, Sarah Burkill, Shahram Bahmanyar, A Ingela M Nilsson Remahl.

Published in Acta Neurol Scand. 2018 Mar;137(3):341-346

III.   Infectious and inflammatory disorders might increase the risk of developing idiopathic intracranial hypertension – a national case-control study. **Anna Sundholm**, Sarah Burkill, Elisabet Waldenlind, Shahram Bahmanyar, A Ingela M Nilsson Remahl.

Accepted for publication in Cephalalgia

IV.   Idiopathic intracranial hypertension, a national Swedish study of incidence and risk factors. **Anna Sundholm**, Sarah Burkill, Elisabet Waldenlind, Shahram Bahmanyar, A Ingela M Nilsson Remahl.

Submitted manuscript

These articles will be referred to in the text by their roman numbers (I-IV).

CONTENTS

LIST OF ABBREVIATIONS

ATC	Anatomic Therapeutic Chemical Classification
ATPase	adenosine triphosphate synthase
AQP	aquaporins
BBB	blood brain barrier
BMI	body mass index
CD	correct diagnosis of IIH
CI	confidence interval
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
DAG	directed acyclic graphs
DIIH	drug-induced intracranial hypertension
GP	general population
11β-HSD1	11β-hydroxysteroid dehydrogenase type 1
ICD-10-SE	International Statistical Classification of Diseases and Related Health Problems – Tenth Revision – Swedish version
ICP	intracranial pressure
IIH	idiopathic intracranial hypertension
ISF	interstitial fluid
LPS	lumbo-peritoneal shunt
MPR	Swedish Medical Birth Register (SE: medicinska födelseregistret)
MRI	magnetic resonance imaging
NBHW	National Board of Health and Welfare (SE: Socialstyrelsen)
NPR	Swedish National Patient Register (SE: Patientregistret)
NPV	negative predictive value
ONSF	optic nerve sheath fenestration
OR	odds ratios
PCOS	poly-cystic ovarian syndrome
PDR	The Swedish Prescribed Drug Register (SE: Läkemedelsregistret)
PIN	personal identity number (SE: personnummer)
PPV	positive predictive value

PTCS	pseudotumor cerebri syndrome
sIH	secondary intracranial hypertension
SLE	systemic lupus erythematosus
SS	Statistics Sweden (SE: SCB – Statistiska centralbyrån)
TPR	The Swedish Total Population Register (SE: Folkbokföringsregistret)
VPS	ventriculo-peritoneal shunt

1   BACKGROUND

Idiopathic intracranial hypertension (IIH) is an uncommon disorder with symptoms caused by elevated intracranial pressure (ICP) of unknown cause. It mainly affects obese women of childbearing age (2). The symptoms include headache, visual disturbances (vision field defects, acuity or double vision), pulsatile tinnitus, and nausea.

1.1   Terminology and clinical diagnosis

The disorder IIH has over the years been described with different terms; pseudotumor cerebri syndrome, benign intracranial hypertension, but in recent years idiopathic intracranial hypertension is the most frequently used term. The first description of the syndrome with a presentation of various cases was published by Dandy in 1937 (1). The diagnostic criteria mainly used over the years for IIH diagnosis was formulated by Smith in 1985, the so called modified Dandy Criteria (3), see table 1.

Table 1. Diagnostic criteria for IIH – the modified Dandy Criteria (3, 4)

	The modified Dandy Criteria
1.	Signs and symptoms of increased intracranial pressure (headaches, nausea, vomiting, transient obscurations of vision, papilledema).
2.	No localizing neurologic signs otherwise, with the single exception being unilateral or bilateral VI nerve paresis.
3.	CSF can show increased pressure, but no cytologic or chemical abnormalities otherwise.
4.	No evidence of hydrocephalus, mass, structural, or vascular lesion on MRI or contrast-enhanced CT for typical patients, and MRI and MR venography for all others.

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

However, new criteria for this syndrome as well as a new name for this disorder was proposed by Friedman et al (5). The name pseudotumor cerebri syndrome was then reused and the criteria subdivided the disorder into primary pseudotumor cerebri syndrome (primary PTCS) and secondary pseudotumor cerebri syndrome (secondary PTCS). Primary PTCS was proposed to comprise traditional IIH criteria with a typical clinical picture and no associated risk factors apart from obesity, recent weight gain, and poly-cystic ovarian syndrome (PCOS). Secondary PTCS was proposed to include patients with underlaying disorders such as cerebral venous trombosis, as well as a syndrome clinically similar to primary PTCS but in association with certain risk factors (various comorbidities and medications

further specified in chapter 1.4 on risk factors and in table 3 and 4)). Friedman also divided the syndrome into pseudotumor cerebri with or without papilledema. Friedman's criteria are not universally accepted, and many studies still use the old modified Dandy Criteria which we also chose to do.

There are some recent data on typical radiological findings (5) in IIH and it has been suggested that improved magnetic resonance imaging (MRI) diagnostics should be used when setting the diagnosis, especially in uncertain cases. For example, the new proposed criteria involve MRI criteria for diagnosis in probable cases (5) and suggests the following radiological diagnostics to be used in the investigation for IIH:

- MRI with and without gadolinium enhancement

- MRI venography for atypical patients

- If MRI is contraindicated contrast-enhanced computer tomography (CT)

- If the patient does not have papilledema or six nerve palsy indicating long-standing increase intracranial pressure (ICP), then signs of high ICP should be evident on MRI to set a final diagnosis (5), see table 2.

Table 2. Signs/findings on MRI indicating high intracranial pressure (5)

MRI findings of high ICP should include at least three of the following:
i.   Empty sella
ii.   Flattening of the posterior aspect of the eye bulb
iii.   Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
iv.   Transverse venous sinus stenosis.

It is important to bear in mind however that these radiological findings are not specific for IIH and lack of them does not exclude high ICP. For example, empty sella (*i.e.* the pituitary gland is flattened and sella turcica filled with cerebrospinal fluid instead of gland material) has sensitivity (80%) and specificity (83%) therefore being commonly seen also in normal persons (6). Sinus stenosis on gadolinium enhanced MRI however has both high sensitivity and specificity (>93%)(6, 7).

1.2 Epidemiology of IIH

1.2.1 Age distribution, sex, and socioeconomic factors

IIH usually affects patients in the age of 15 to 45 years (8, 9). A large proportion of those affected are overweight/obese, or have a recent weight gain (10). It is also more common among females (approximately nine times more frequent in

females than males) in this age group (15-45) (11). IIH is also seen in the pediatric population, however prior to reaching adolescent age, the association with female sex and obesity is not present (12). The disorder is also shown to greatly affect patients' lives, their families, and impact on society. For example, it has been shown that the IIH disorder causes loss of income for patients, substantial health-care costs for society (13, 14) and high emergency department utilization (15). IIH also has negative effects on quality of life (16-18). Some studies have also shown an association to cognitive dysfunction in IIH patients (19, 20); these studies described cognitive dysfunction most noted in the domains visual spatial, global cognitive score, reaction time, and processing speed compared to normal controls. These are factors that may indirectly affect income and sick leave compensations with consequences to both the individual and the society.

1.2.2 Incidence and prevalence

The yearly incidence of IIH has been described within a wide range in different regions of the world varying between 0.03-4.7 per 100,000 (14, 21). In a recent metanalysis the pooled incidence of IIH was 1.2 per 100,000. Large studies performed in USA, Libya, Israel, Northern Ireland, Scotland and England report incidences between 0.9 and 4.7 per 100,000 individuals (8, 14, 22-26). There are however also reports of much lower incidence; for example in a relatively large cohort in Japan the incidence was only 0.03 per 100,000 (21) and in Italy (Parma) 0.3 per 100,000 inhabitants (27). Several studies speculated that the differences seen in incidence in these studies to a large extent could be due to differences in obesity prevalence, but other factors (e.g. genetic) could play an important role as well. Rising incidence of IIH in several regions has been reported (14, 23-26, 28) and has been proposed to be correlated to the increase in obesity prevalence. The incidence of IIH in a Scandinavian population has never been investigated.

Prevalence is less commonly reported but studies in England and Ireland have calculated the prevalence during the respective study period to be 10.9-14.3 per 100,000 inhabitants (23, 28).

1.2.3 Register data on IIH

A correct (diagnosis) coding of IIH in registries has been shown to be low. Fisayo (29) showed that 40 percent with an initial diagnosis of IIH got a changed diagnosis on follow up visit. Koerner et al (30) only found a positive predictive value (PPV) of 55% when they evaluated all diagnoses given in inpatient and emergency hospital settings. Also, a correct diagnosis of IIH can be associated with difficulties due to ophthalmological misinterpretation of a proposed papilledema (29). Increased intracranial pressure can also be misinterpreted if measured incorrectly or if the patient is not relaxed during the lumbar puncture procedure.

1.3   Pathophysiology

The pathophysiology of IIH is largely unknown even though there are several theories suggesting various mechanisms that could be involved. As the skull represents a rigid volume space this means that disorders causing high ICP must originate from increased amount of some of the brain constituents such as the cerebrospinal fluid (CSF), the interstitial fluid (ISF), the blood, or the brain cells. The basic principle to explain the intracranial pressure physiology is the Monroe-Kellie Doctrine, see figure 1. In neurointensive care we have primarily focused on ICP in relation to the arterial blood pressure, measuring mean arterial pressure (MAP), cerebral perfusion pressure (CPP) and ICP. But changes in vascular pressure on the venous side might be more important as ICP regulatory mechanisms as there is less resistance compared to on the arterial side (31). Cerebral blood both in and outflow seems to be important when regulating ICP but other factors affecting other brain constituents might also be involved in the pathogenesis of IIH causing impaired ICP homeostasis (32).

Figure 1. The Monroe-Kellie doctrine (31).
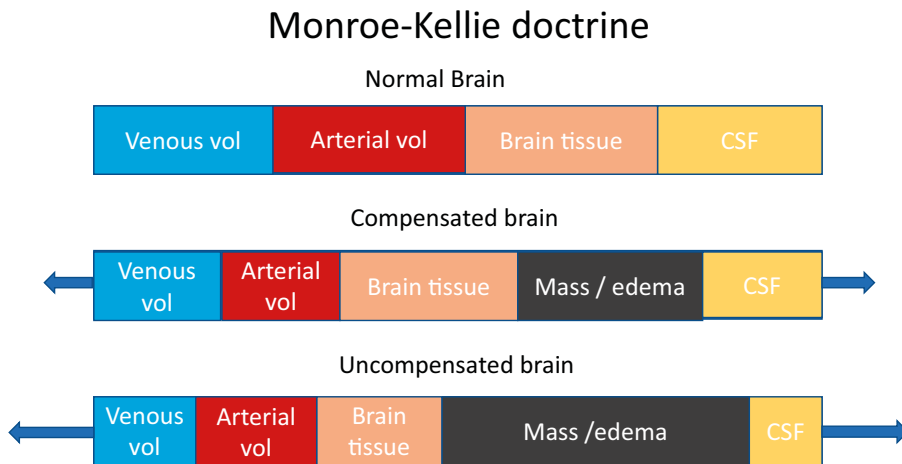
1.3.1   Increased CSF production

The average human produces approximately 600ml of CSF per day (the majority from the choroidal epithelium, and < 10% from ISF) which is about three to four times the total CSF volume (33). The production of CSF is shown to reduce with age (33) which may be an explanation why IIH only affects younger to middle aged persons. It has been shown that CSF production is relatively independent of ICP (34).

1.3.1.1 Aquaporins

Aquaporins (AQP) are water permeable channels in the central nervous system (CNS) that facilitate water movement across cell membranes in supporting cells of the CNS. Nine different kinds have been described and two of them have been especially interesting regarding IIH. AQP1 is expressed in the choroid plexus cells and thought to be involved in the production of CSF. AQP4 is mainly expressed in glial cells throughout the brain and spinal cord and is responsible for much of the water flow in and out of the brain over the blood brain barrier (BBB) and the blood-CSF barrier (35). Interestingly acetazolamide (which is used as first line treatment regime for IIH) has been shown to inhibit AQP4 activity (36) and modulate AQP1 activity (37). Eide et al (38) have shown histopathological alterations with cortical patchy astrogliosis in combination with AQP4 being increasingly expressed in the brain of IIH patients undergoing shunt procedures. As opposed to this study, one genetic study sequencing the gene AQP4 on chromosome 18 did not find any difference between 28 IIH patients compared with controls (39). Another negative study measured serum neural and glial antibodies but did not find any antibodies against AQP4 in IIH patients (40).

1.3.2 Decreased CSF absorption

CSF is absorbed by transportation to the subarachnoidal space where the majority is absorbed to a large extent by the arachnoid granulations/arachnoid villi in the sagital sinus. Previously it was thought that all CSF was absorbed this way, but in recent years evidence points towards CSF being absorbed in several parts of the CNS. Edsbagge et al showed that up to 50% of CSF may be absorbed by spinally located arachnoid villi (41). It has also been shown that CSF is likely to be absorbed into the lymphatic system, probably primarily through the cribriform plate where olfactory nerves pass as well as CSF sheath and dura (42). It has also been shown that persons with IIH more commonly also have problems with hyposmia (ability to smell/detect odors) (43-45). It has been speculated that this pathway (through the cribriform plate) of CSF absorption might be important. There is also some evidence in CSF infusion studies for increased resistance of CSF absorption in IIH patients (46, 47).

1.3.3 Increased central venous pressure and outflow resistance

Hypotheses have over the years discussed a possible pathophysiological mechanism with increased central venous pressure as an explanation behind increased ICP in IIH patients (7, 48-50). Different aspects have been proposed to be important in ICP regulations with aspects from the venous system both intra- and extra-cranially in general both regarding IIH and other disorders causing intracranial hypertension (31), see figure 2. Central (abdominal) obesity is proposed causing

increased intra-abdominal pressure that via raised pleural pressure and cardiac filling pressure would impair venous blood return and cause increased venous pressure in the CNS (48, 51). An association with jugular valve impairment has also been demonstrated in IIH patients possibly contributing to this phenomenon (49). Resistance to venous outflow by stenosis of the venous sinuses (7) has also been shown to be common in IIH patients.

Figure 2. Venous outflow restrictions that can affect ICP (31).
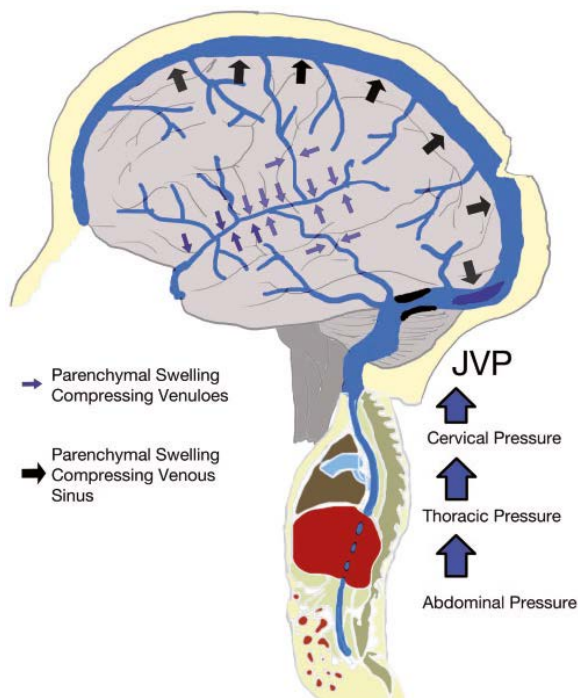
Showing potential venous outflow restrictions that can affect ICP both intracranially (obstruction/compression) or extracranially (cervical, thoracic and abdominal pressure). Figure originally published by Mark Wilson in J of Cerebral Blood Flow & Metabolism 2016, volume 36, issue 8, p1338-50. Published with permission according to Creative Commons license; https://creativecommons.org/licenses/by-nc/3.0/

1.3.3.1 The venous sinuses

In recent years a lot of focus has been towards resistance to venous outflow by stenosis in the transverse sinus. Farb et al (7) showed that bilateral venous sinus stenosis is common in IIH patients. They observed this phenomenon in 27 out of 29 IIH patients but only 4 out of 59 control patients. It is debated whether the stenosis seen is a cause or a consequence of high ICP. It has been suggested that

the stenosis is caused by a collapse of the sinus walls due to the high ICP. Some studies have shown the stenosis to resolve with intensive treatment and normalization of the ICP by CSF diversion procedures (52, 53), while other studies have not (despite a normalization of the ICP under a longer time span with medical treatment – the stenosis still remained (54)). It's increasingly recognized that the stenosis is symptomatic and could benefit from treatment. Surgical treatment with venous sinus stenting is described in the literature where expansion of the compressed area with a stent was shown to be favorable in patients with IIH not responding to medical treatment or to cases with fulminant IIH with acute progress of symptoms (55-57).

1.4   Risk factors

There are many factors proposed to be associated with IIH (58, 59). However, evidence for a true association for many of these risk factors are lacking as most studies are based on small case-control studies (involving 20-60 cases) (60-64) or case reports that do not have enough sample size to draw strong conclusions. Only one recent case-control study exploring cycline antibiotics in association to IIH included as many as 339 IIH cases (65). Suggested risk factors need verification compared to what would be expected as "normal /coincidental" exposure in large case-control studies.

1.4.1   Female predominance

Female sex is highly associated with an increased risk of IIH after puberty (11, 60). Only 8-19% of the IIH cases are male (11). Factors that cause this sex difference are unknown. Female predominance after puberty suggests that hormones play an important part in the development of IIH, however studies have not been able to prove this relationship (66).

1.4.1.1 Suggested androgen theory

It has been proposed that increased testosterone levels in women and lower testosterone levels in males could be a risk factor for IIH (67). In support of this theory female IIH patients seem to have a different androgen endocrine profile compared to both obese female controls with polycystic ovary syndrome (PCOS) and obese female controls without PCOS (68). This previous study showed a statistically significant difference with increased serum testosterone levels and CSF androgen levels in female IIH patients compared with controls. PCOS is known to be associated to hyperandrogenism and has been reported to be a risk factor associated with IIH and to obesity(69). It has also been shown that males with IIH seem to have a higher risk than controls for having signs of testosterone deficiency (61). A case study describes development of secondary IIH in a man with prostate cancer and

previous anti-androgen treatment in combination with weight gain (70). In women hyperandrogenism has been described as associated with earlier onset of IIH (71). There are also several case reports of females and males that during transsexual treatments have developed IIH (72-75). Yet another study showed an association to visceral obesity and androgens with a similar pattern as described above (low androgen/testosterone levels in males and high levels in females) (76). These studies propose evidence of androgens playing a role in IIH development.

1.4.2   Obesity

There is a lot of evidence that obesity is very highly associated with IIH (17, 58, 60, 62, 77), and it is believed to be the most common risk factor for IIH development. The majority of IIH patients are overweight or obese (10). The risk increases in relation to Body Mass Index (BMI) (17). Additionally, in patients with a BMI <30 kg/m^2, recent weight gain is shown to be common before development of IIH disorder (17, 77). Weight gain is also associated with recurrence of the disorder (77) and weight loss is shown to improve symptoms of IIH (78-81). However how obesity interacts with IIH is incompletely understood. As presented before (see section 1.3.3) there have been theoretical hypotheses that abdominal obesity in IIH patients causes increased intra-abdominal pressure, which is a possible explanation for the high intracranial pressure in IIH (48). This hypothesis is challenged, however, since most obese persons with abdominal obesity do not develop IIH. Distribution of fat tissue might also be of importance. The findings of a small cohort study found significantly lower waist-to-hip ratio in IIH patients compared with obese controls (82). The effect of obesity on IIH risk could possibly also have an the association with androgen theory described above (76).

1.4.2.1 Cytokines and chemokines

The adipose tissue is known to be a neuroendocrine organ secreting many biological factors which result in a pro-inflammatory state (83, 84). This has been speculated as an explanation behind IIH pathophysiology. Altered serum or CSF levels of certain cytokines and chemokines have been demonstrated, but there have also been conflicting results, with some studies showing significant differences (85-88) and other not (89). Leptin has been of interest, but results are conflicting. Some studies have shown significantly higher levels of leptin compared with controls (86, 89, 90) suggesting a hypothalamic leptin resistance impairing appetite control (89) and it has been suggested that central leptin resistance could have a role in epithelial choroidal plexus cells causing increased CSF secretion (32).

1.4.2.2 *Glucocorticosteroids and 11β-HSD1*

Glucocorticoid withdrawal as well as Cushing's and Addison's disease have been proposed to be associated with IIH development pointing towards some association between corticosteroids and IIH (91-93). Previously corticosteroids were used in the treatment for IIH but are nowadays not recommended due to side effects, especially weight gain, no evidence of a sustained effect, and a risk of worsening when tapering the treatment (94). The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) has been demonstrated to be dysregulated in obesity (95). The pathophysiological explanations in IIH suggests that cytokines expressed in the obese activate 11β-HSD1. As a result, increased levels of 11β-HSD1 in IIH patients cause activation of cortisone to cortisol, which might affect ICP. The proposed mechanism for this is through the effect on the choroid plexus cells (possibly through effect on the Na+-K+-ATPase pump) and on arachnoid granulation cells thereby causing CSF dysregulation by means of increased CSF production and decreased CSF absorption (32, 96, 97). Furthermore, 11β-HSD1 activity has been shown to be reduced after introduction of a low-calorie diet with weight loss in IIH patients (96), which could be an important factor explaining the improvement of ICP after weight loss in IIH patients. A new treatment is currently being investigated for IIH using 11β-HSD1 inhibitor (phase II study) (98).

1.4.3 Other proposed associated comorbidities

There are several comorbidities that over the years have been associated with IIH. For some comorbidities the level of evidence is higher than for others. Comorbidities described as highly associated with IIH are for example Addison's disease, hypoparathyroidism, and hypervitaminosis A (58). The recently proposed Friedman criteria for the diagnosis suggest that presence of any of these risk factors (comorbidities and medications) should alter the diagnosis from IIH to secondary pseudotumor cerebri syndrome (5). On the other hand since many of these comorbidities have not been proven truly associated with IIH as pointed out by Chen et al (58) further studies are recommended. Many risk factors in their review were categorized as "possible risk factors" such as iron deficiency anemia, obstructive sleep apnea syndrome or "probable risk factors" such as uremia. Those risk factors are also included as causing secondary pseudotumor cerebri in the new proposed criteria. See table 3 for risk factors causing secondary pseudotumor cerebri syndrome in the new proposed criteria (5). Prior to the studies included in this thesis, large scale studies comparing these risk factors with the prevalence in a control population were lacking.

Table 3. Comorbidities proposed to cause secondary pseudotumor cerebri syndrome (5)

Cerebral venous abnormalities:	Medical conditions:

Cerebral venous sinus thrombosis	Endocrine disorders:
	    Addison's disease
	    Hypoparathyroidism

Bilateral jugular vein thrombosis or surgical ligation	Hypercapnia:
	    Sleep apnea syndrome
	    Pickwickian syndrome

Middle ear or mastoid infection	Anemia
Increased right heart pressure	Renal failure
Superior vena cava syndrome	Turner's syndrome
Arteriovenous fistulas	Down's syndrome
Decreased CSF absorption from previous intracranial infection or subarachnoid hemorrhage	
Hypercoagulable states	

1.4.4 Medications proposed as being associated with IIH

Medications strongly associated with IIH are substances containing retinoid and tetracycline derivatives, growth hormone used in children and steroid withdrawal. Also other medications with less strong evidence have been described as being associated with IIH, such as lithium, corticosteroids, and sulpha antibiotics among others (58). Regarding association with medications the new proposed criteria by Friedman also suggest most of the above-mentioned drugs are likely a cause of secondary pseudotumor cerebri (5). See table 4 for medications and exposures causing secondary pseudotumor cerebri syndrome in the new proposed criteria (5).

Table 4. Medications and exposures proposed to cause secondary pseudotumor cerebri syndrome (5)

Medications and exposures:
Antibiotics: Tetracycline, minocycline, doxycycline, nalidixic acid, sulpha drugs
Vitamin A and retinoids: Hypervitaminosis A, isotretinoin, all-trans retinoic acid for promyelocytic leukemia, excessive liver ingestion
Hormones: Human growth hormone, thyroxine (in children), leuprorelin acetate, levonorgestrel (Norplant system), anabolic steroids
Withdrawal from chronic corticosteroids
Lithium
Chlordecone (insecticide)

1.5   Adverse health outcomes

IIH is a disorder that often causes symptoms of longstanding headache and visual deficits. In a Danish study by Yri *et al* some 40% had remaining headache fulfilling criteria for chronic headache one year after diagnosis (99). Permanent visual damage has been shown to be common. Around 40% of patients improve without visual symptoms, with most patients experiencing generally minor visual field defects, however 5-10% are at risk of obtaining more severe permanent visual defects, including blindness (3, 100). Cognitive dysfunction is also described among patients with IIH (19, 20) as well as decreased quality of life (16, 17). Preventing complications in patients with IIH often requires frequent contacts with healthcare providers (ophthalmologists, neurologists and sometimes neurosurgeons). Friesner *et al* (13) report that the IIH disorder causes a substantial cost both for society and the individual due to direct healthcare costs (check-ups, high need of hospital admissions and sometimes surgical procedures such as ventriculoperitoneal (VP) shunt and shunt revisions) and personal costs (loss of income) as well as indirect costs (change of work due to impaired health). A recent British study by Mollan *et al* also revealed substantial and increasing health care costs (a five-folded increase over 13 years) in this patient group (14). Indirect costs for the disorder have however not been addressed in European settings.

1.6   Treatment

Until recently, there was no consensus on how IIH should be optimally treated. Randomized trials are very scarce (101). Historically, there have been few trials available that compare different treatment regimes. To date there are however some trials ongoing and in the past years some consensus guidelines have been published (102-104). There is consensus on IIH that investigation and treatment of an eventual underlying cause is of major importance (obesity if present and eventual other causes or risk factors that might be present). Also, symptomatic treatment of the high intracranial pressure and its symptoms as well as securing/ preserving vision is the focus when dealing with this patient group, with rapid surgical intervention if vision is threatened.

1.6.1   Acetazolamide

The first line treatment for IIH is acetazolamide. It is often started as soon as a patient is diagnosed with the disorder and shows symptoms of affected vision. It is titrated to high doses in order to lower intracranial pressure. The first randomized trial on 165 IIH patients with mild visual loss, the (NORDIC) IIH study, investigated the effect of acetazolamide treatment plus diet versus placebo and diet (105). This study showed a significant though modest improvement in visual function and provides the first evidence that acetazolamide is effective in lowering ICP in IIH patients. Acetazolamide works as a carbonic anhydrase inhibitor

and effects the choroid plexus reducing CSF production and thereby lowering ICP (94). Treatment with acetazolamide however renders frequent side effects which often affects patient compliance. Common side effects are paresthesias in hands and feet, loss of appetite (often resulting in weight loss), altered taste, nausea, metabolic acidosis, and fatigue.

1.6.2 Topiramate

Topiramate is also recommended for treatments of IIH and has a similar mechanism of action as acetazolamide. As a mild carbonic anhydrase inhibitor, it possibly reduces CSF production as well as improving IIH symptoms by weight loss (a common side effect of the treatment). There is one randomized small study (20 patients in each arm) comparing the effectiveness of topiramate and acetazolamide which showed no significant difference at 3, 6 and 12 months follow up (106). The most common side effects of topiramate are distal paresthesias, concentration difficulties/cognitive impairment and weight loss. As topiramate also has the indication prophylactic treatment for migraine, patients with both disorders might benefit from this treatment. Studies in rats have shown that topiramate lowered intracranial pressure more efficiently than other treatments such as acetazolamide and furosemide (107).

1.6.3 Other oral medications in IIH

Sometime use of acetazolamide in combination with other diuretics have been tried, for example furosemide, however such treatments have not been evaluated in controlled studies. Short term treatment with corticosteroids in patients with severe visual disturbances has been reported and sometimes used but is nowadays uncommon due to side effects including weight gain, which might in the long term worsen the IIH presentation (94).

1.6.4 Weight reduction

Weight loss is the most important aspect of IIH treatment in obese IIH patients. It is shown that weight loss is associated with improvement of IIH symptoms (78, 79, 81, 108-110). All overweight IIH patients should be advised and supported to lose weight and preferably be referred to dieticians or specialist centers with a focus on weight reduction.

1.6.5 Surgical treatment

Today surgical procedures should be strongly considered if there is risk of visual damage due to high ICP. The most commonly and traditionally used surgical treatments for IIH are CSF diversion procedures and optic nerve sheath fenestration (ONSF). Recently, stent procedures of the sinus transverses have raised hope of new treatment for IIH, as well as gastric bypass to induce weight loss.

1.6.5.1 Shunt procedures

Of the available CSF diversion procedures, ventriculo-peritoneal shunt (VPS) procedure or lumbo-peritoneal shunt (LPS) are the most common. VPS procedure is associated with less complications and revisions compared to LPS procedures (111, 112); while the effect on headache and visual symptoms seems to be equal. Shunt procedures are regarded as effective treatment for high intracranial pressure and are most effective for treatment of acute visual symptoms. The most effective treatment for intractable headache and visual symptoms was if shunting was performed within two years of diagnosis and/or with obvious papilledema (112). The complication rate is however high with over 40% requiring additional surgery. A major complication rate was seen in 8% (for example shunt infection, tonsillar herniation, subdural hematoma, CSF fistula) and minor complications in 33% (56).

1.6.5.2 Optic nerve sheath fenestration

ONSF is used to reduce papilledema-related visual loss; it does not lower ICP and therefore thought to be less effective on the headache component of the disorder. It shows good effectiveness on visual symptoms. It is a less invasive procedure than the CSF diversion procedures and does not have a high complication rate. In a review by Satti *et al* (56) they analyzed reported ONSF procedures in over seven hundred patients. Improvement of papilledema occurred in 80%, improvement of headache in 44% and visual improvement occurred in 59%. Major complications (eye muscle paralyses, retrobulbar/orbital hemorrhage et al) were only seen in 1.5% of cases reported. Minor complications were reported in 16% of patients.

1.6.5.3 Stent procedure of the venous sinus

Treatment with venous sinus stenting is a new promising treatment for refractory IIH first described by Higgins in 2002 (113). The procedure has since been performed and results reported in many studies. In a recent meta-analysis (114), some 473 patients from 24 studies were evaluated. Symptoms were generally shown to improve; for example, headache (76%), papilledema (86%), visual acuity (70%) and tinnitus (85%) all showed substantial improvements in reporting of symptoms. Major complications were observed in less than 2% of patients (subdural hematoma).

1.6.5.4 Bariatric surgery

Bariatric surgery has been proposed as an effective treatment option to help patients lose weight to improve IIH symptoms (78, 81, 110). In a review by Handley et al (115) summarizing the effect of bariatric surgery in IIH patients they saw improvement of IIH symptoms in 95% of patients with data available suggesting bariatric surgery is a promising treatment regime for patients with IIH. However, bariatric surgery is not straightforward, so patients must be willing to implement dietary changes and fulfill the criteria for bariatric surgery prior to this treatment.

1.7 Epidemiological studies – Methodological considerations

Epidemiological studies help us study the natural cause of a disease and identify trends of a disease occurring. With epidemiological methods we also determine incidence and prevalence of a disorder in a population. We also use epidemiological studies to identify possible etiologies behind a disorder and allows for the study of effect and safety of treatments or disease prevention. We often study whether there is a connection between an exposure and the outcome. There are different types of epidemiological studies: observational or experimental. This thesis is comprised of only observational studies. The types and uses of observational studies are discussed in this chapter.

1.7.1 Types of observational epidemiological studies

1.7.1.1 Descriptive studies

In a descriptive study one observes and describes a specific phenomenon, for example describe a condition or disease. It could be case reports, case series, or incidence studies. It is often useful if not much is known about a phenomenon, to identify patterns, and help create hypotheses for further studies.

1.7.1.2 Cross sectional studies/prevalence studies

Cross sectional studies take measurements at one point in time and can be used for a variety of research questions. For example, assessment of whether associations between risk factors and disease can be undertaken. Cross-sectional studies are, however, limited in that temporality cannot be assessed, and therefore cannot give information on cause and effect.

1.7.1.3 Case-controls studies

Case-control studies can be described as retrospective observational studies in that those with and without the outcome are identified (cases and controls respectively), and previous exposure to certain risk factors are then examined. It is important that the cases and controls are as similar as possible except for their outcome/disease. With case control studies it is possible to study several exposures. This type of study is most convenient when investigating rare disorders because all cases are identified from study start, which is not the case for cohort studies. Several controls can be chosen per case.

1.7.1.4 Cohort studies

Cohort studies are also observational but can be both retrospective (the exposure and outcome have already happened) or prospective (cohorts are identified through their exposure to an outcome/disease). Persons are defined as exposed or non-exposed and are followed over time to determine whether the outcome occurs. In cohort studies it is important that included participants are similar except for the exposure status.

These types of studies are generally considered better for rare exposures but can be underpowered when considering rare outcomes.

1.7.2   Systematic errors

Bias is what we call systematic errors and can occur in any phase of the research, both in the study design phase, during data collection and when interpreting and analyzing the results. Publication bias could also be a factor when analyzing research as negative study results might be less commonly published. It is important to identify and avoid bias when performing studies. There are mainly three broad types of bias; information bias, selection bias and confounding.

1.7.2.1   Information bias

Information bias is when the information we collect about or from the study participants is incorrect. Example of information bias could be: measurement errors, recall bias and interviewer bias. Non-differential misclassification bias is bias at random and is believed to affect both investigated groups similarly; in most cases affect our results by moving the point estimate towards the null. Differential misclassification however is non-random affecting for example exposed and non-exposed differently and can give both an over- or under estimation of the association, thereby resulting in either hiding or creating an association that is not valid.

1.7.2.2   Selection bias

Selection bias appears when the selection of study participants is done in a way that it is not randomized, or the sample is not representative of the populations intended to study. Example of selection bias is: volunteer bias, loss to follow up, selection bias by death, healthy worker effect. This type of bias is common in case-control studies and can appear for example by the way study participants are selected or if they during inclusion not randomly choose to be included or to remain during the whole study period. For example, if we study the effect of a vaccine but included study participants that are mostly young healthy adults we include selection bias as the population that will probably most benefit from the vaccination are an older population with multiple comorbidities.

1.7.2.3   Confounding

A confounder is a factor that interferes with the study. It needs to be associated to the exposure and a risk factor for the outcome studied and cannot be in the causal pathway. A confounder cannot be caused by the exposure. If the factor however is in the causal pathway, it is called a mediator. A common example of confounding is for example if we are studying the relationship between alcohol consumption and cardiovascular disorder. Smoking would then be the confounder needing to adjust for as smoking is correlated to alcohol consumption but not caused by this exposure and smoking is a risk factor for cardiovascular disorder (the outcome),

see figure 3. Confounders could be known prior to study start and we should then try to adjust for them. Also, some confounders could be known to the researcher but not possible to adjust for, and we might also have unknown confounders.

Figure 3. Example of confounding.
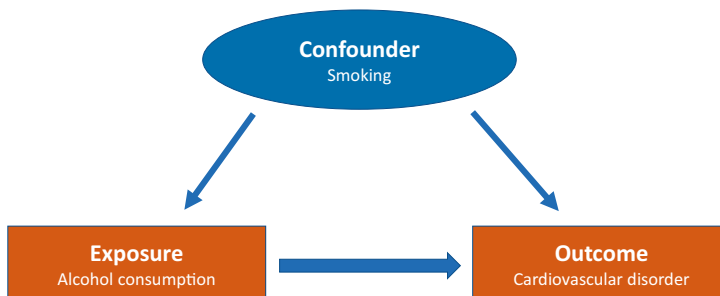
To adjust for confounders, we can do this from study start by study design or at the end by different analyzing methods. From the start we can use technics such as randomization (in for example randomized trials) or adjust for confounders by means of how we choose our study participants. This we can do by using restriction (only including for example women of certain age, or only non-smokers, a method that however affects the study's generalizability) or by matching cases with controls on certain factors. We can also at end of study investigate whether we have confounding by doing:

- stratification analyses (by age, gender or by other possible confounders that we suspect)

- regression analyses (statistical analyses adding other variables that we think might affect the factor we are investigating)

- sensitivity analyses (sub-group analyses)

- standardization (making exposure categories comparable by for example weighting the groups to the suspected confounder factor. Weighting is done against a standardized rate of how common that factor in the specific population we investigate).

1.7.3 Random errors

When we measure research data we get a point estimate. However, we do know that a point estimate is affected by variability in exposure and might be due to chance. To estimate random errors, we use statistical methods and often describe this variation by p-values or confidence interval to interpret the statistical variation. In our studies we use 95% confidence intervals.

2   AIMS

The overarching aim of this thesis was to investigate risk factors associated with IIH to improve the knowledge base on which individuals may be at risk of disease development. A secondary aim was to evaluate IIH (incidence and clinical characteristics) in a Swedish context.

The specific aims of each study:

I.   Validation of the IIH diagnosis (G93.2) in the Swedish National Patient Registry (NPR) as well as investigate the incidence and clinical characteristics of IIH in a Swedish County sub-population.

II. Developing algorithms that with higher probability finds correctly diagnosed IIH patient in NPR, making registry studies more reliable.

III. Investigating if conditions causing inflammatory activation are more frequent among IIH patients compared to matched controls the year prior to the diagnosis of idiopathic intracranial hypertension (IIH).

IV. Investigating the incidence of IIH in Sweden over time as well as studying if IIH patients are more frequently exposed to previously reported risk factors (comorbidities and treatments) the year prior to diagnosis compared to matched controls.

3 METHODOLOGICAL CONSIDERATIONS

3.1 Setting and study populations

3.1.1.1 Study I and II

All patients (≥18 years) with a diagnosis code of G93.2 registered for benign intracranial hypertension that had contact with specialized healthcare departments within the Stockholm County between Jan 1, 2006 to Dec 31, 2013 were included. Medical records were collected and reviewed with information gathered on year of diagnosis, presence of comorbidities and medication use the year prior to first diagnosis, presenting symptoms, age, sex, and investigation results. The diagnosis was validated according to the modified Dandy Criteria (3, 4).

3.1.1.2 Study III and IV

All patients (≥18 years) with a diagnosis code of G93.2 registered for benign intracranial hypertension that had contact within specialized healthcare departments in Sweden during the years 2000 to 2016 and for whom the algorithms developed in study II predicted a correct diagnosis were included as IIH cases. For every case we selected five matched general population (GP) controls and five obese controls (that also had a diagnosis code for obesity (ICD-10-SE E66) in NPR). Matching factors were age, sex, region and vital status on the index date. Index date was defined as the date of IIH diagnosis for the case and same date used within the matched group. Cases were excluded if they had received a diagnosis of IIH prior to the year 2000. Controls were also excluded if they received a diagnosis code of IIH prior to index date.

3.2 Data sources

3.2.1 Swedish registers

Registers have a long tradition in Sweden. As early as the seventeenth century, people in Sweden were registered in church books to keep a record of parish members, and in the eighteenth century this was further formalized into an official authority to produce population statistics, the first of its kind in the world (116).

In Sweden every citizen is assigned a unique ten-digit personal identity number (PIN) (*Swedish: personnummer*) since the year 1947 (117). The PIN enables linkage between many national registers and forms a unique base for medical research.

3.2.1.1 The total population register (TPR)

The Total Population Register (TPR, *in Swedish: Folkbokföringsregistret*) started collecting data from 1968. It contains data on PIN, name, place of birth (country,

county and parish), citizenship, place of residence, sex, age, registration of migration (date, country, ground for settlement), death, and relations (marital status, child-parent information, guardian, adoption) (40). This register is part of Statistics Sweden (SS, *in Swedish: Statistiska centralbyrån*).

3.2.1.2 The Swedish National Patient Register (NPR)

In 1964 the NPR (*Swedish: Patientregistret*) was founded. It has national coverage from 1987 regarding inpatient care and from the year 2000 it also includes outpatient data. Today it registers all specialized inpatient and outpatient contacts, but not primary care contacts. Studies of the inpatient register validity is generally good with a PPV of 85-95 % for most diagnoses, although accuracy is variable depending on the diagnosis (118). In the inpatient register a missing primary diagnosis is ≤1% (118, 119). The proportion missing is higher in the outpatient register. Initially, in 2001, 25-30% of main diagnosis were missing, however in recent years only about 3% are missing (119).

The register contains data on PIN, age, sex, date of admission and date of discharge, hospital, clinic, main and secondary diagnoses, and procedure codes (119). ICD-10-SE coding has been used since 1997 (118). The register is held by the National Board of Health and Welfare (NBHW) in Sweden (*Swedish: Socialstyrelsen*).

3.2.1.3 The Swedish Prescribed Drug Register (PDR)

The PDR (*Swedish: Läkemedelsregistret*) started July 2005 and contains information on pharmacological prescriptions sent to pharmacies in Sweden including prescribed care-related consumables. The register contains data on PIN, sex, age, place of residence, item (name of pharmacological drug, ATC-code, dose, number of items prescribed), prescription information (amount of prescribed drug, date of prescription, date of collected drug from pharmacy), costs, and information on type of clinical setting, including the profession of the prescriber (120). This register is also held by the NBHW in Sweden.

3.2.1.4 The Swedish Medical Birth Register (MBR)

The MBR (*in Swedish: Medicinska födelseregistret*) started in 1973. 97-99% of all births in Sweden are reported in the register. It provides data on the mother (among other data PIN, age, smoking habits, cohabitation status, previous pregnancies), pregnancy length (full weeks + number of days over full weeks), date of delivery (year + month), and information on the infant (121). MBR is administered by the NBHW in Sweden.

3.3 Study designs

3.3.1 Diagnostic criteria for IIH

We chose to use the modified Dandy Criteria (3, 4) in our studies (see table 1 in background section 1.1). The new proposed criteria by Friedman (5) were not adopted in our studies for four main reasons:

1. the criteria are still under debate

2. other reference studies have used the old criteria

3. the new criteria include radiological descriptive terms not regularly described in older radiology reports, which would result in lots of missing data

4. the main purpose of our study was to investigate whether associated comorbidities and medications truly is associated with IIH.

The modified Dandy Criteria were used when validating the diagnosis code in Study I by reviewing medical records.

3.3.2 Study design study I

Study I was a validation and descriptive study on patients with an IIH diagnosis in Stockholm County 2006-2013. All patients with a diagnosis code of G93.2 in the NPR were included and the diagnosis was validated by medical record review. As a quality control, 10% of the records were randomly selected and reviewed by a second neurologist blinded to the valuation.

3.3.3 Study design study II

Patients from study I (≥18 year of age for whom the diagnosis code had been validated, n=207)) were included and randomized into two groups; one used to produce the algorithm (n=105) and one for validation (n=102). We tested variables that was possible to extract from registries that we thought could be useful to better predict which patients should be included in registry studies.

3.3.4 Study design study III + IV

These studies used a case-control study design, including all IIH patients diagnosed 2000-2016 as cases. Exposures were risk factors for IIH development. Exposure were identified using register codes the year prior to index date (first diagnosis of IIH). ICD-10-SE diagnosis codes were used to identify diagnoses in the NPR, and ATC-codes on drug composition were used to identify prescriptions within the PDR. Study IV also investigated incidence of IIH over time. Risk factors that we investigated were disorders causing inflammatory activation (study III) as well as previously reported risk factors for IIH (study IV).

3.3.4.1 Choosing of risk factors for study III

The reason for choosing inflammation was related to the results of study I (in this study we found many exposures related to disorders causing inflammation) and inflammation had been a hypothesized factor in the literature. From study I alone, we did not know if exposure to disorders causing inflammation in IIH patients differs relative to what would be an expected exposure rate. We therefore speculated that inflammation could act as a risk factor and decided to investigate this. (See included diagnoses by ICD-10-SE coding and treatments by ATC coding in appendix 9.1).

3.3.4.2 Choosing of risk factors study IV

Previously reported risk factors were chosen based on review articles, results from previous case-control studies, case reports of risk factors and proposed secondary causes (5, 58-62, 122). One risk factor that we would have liked to investigate, apart from those included, was obstructive sleep apnea syndrome (OSAS) since this diagnosis was seen in 21% of male patients in study I. Unfortunately, this diagnosis code was missed on the acquisition of diagnosis codes from NPR and therefore not available to us. (See included risk factors by ICD-10-SE coding and ATC coding in Appendix 9.2).

3.4   Statistical analyses

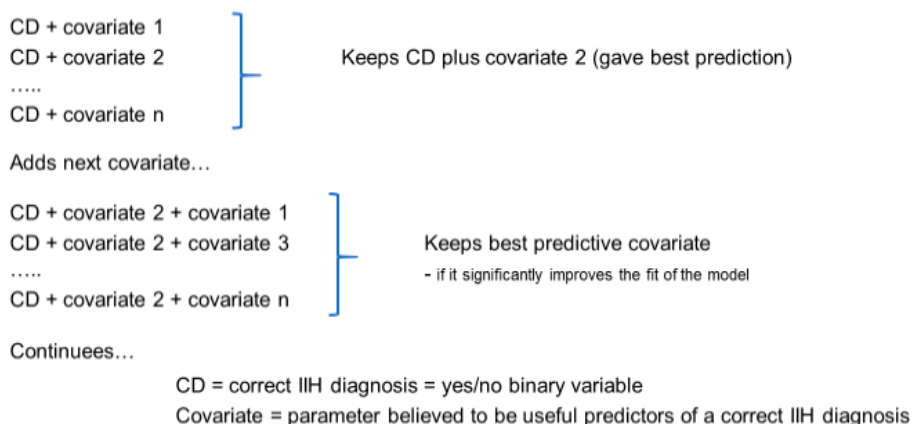### 3.4.1   Incidence and age differences (study I and IV)

Incidence was calculated by dividing new onset cases per year with the total Stockholm County population ≥18 years old (study I) or the total populations ≥18 years old (study IV) in Sweden at the end of December that year (official statistics available from Statistics Sweden) and multiplied by 100,000. In study I we calculated the confidence interval for the mean incidence using the variance for the time-period 2006-2013. Age differences by sex were calculated using a univariate linear regression model using age as a continuous outcome and sex as the independent variable.

3.4.2   Development of algorithms (study II)

The binary variable for a correct or incorrect diagnosis was used as the outcome in a forward stepwise logistic regression model (figure 4). The variables available in the national registers (NPR and PDR) which we believed to be useful predictors of a correct IIH diagnosis were included as covariates. This approach meant that variables which did not significantly improve the fit of the model were removed. We tested the following covariates to produce algorithm 1 (variables that could be drawn from both the NPR and the PDR): age, sex, number of diagnosis codes being recorded (at least two, three or five times), and if patients had received Acetazolamide treatment. Algorithm 2 contained the same variables except for Acetazolamide treatment making us independent of the PDR for this algorithm. We constructed

numerous models and selected the one which most frequently correctly predicted whether the patient had true IIH or not. We obtained predicted probabilities using the outcome of the model for the algorithm group and applied predicted probabilities to the test group based on patient characteristics for the variables included in the algorithm. The different algorithms produced were evaluated by calculating how well they were predicting both true and incorrect IIH combined (predictive probability value). Positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CI) were also evaluated.

Figure 4. Forward stepwise logistic regression model.

CD + covariate 1
CD + covariate 2
.....
CD + covariate n

Keeps CD plus covariate 2 (gave best prediction)

Adds next covariate…

CD + covariate 2 + covariate 1
CD + covariate 2 + covariate 3
.....
CD + covariate 2 + covariate n

Keeps best predictive covariate
- if it significantly improves the fit of the model

Continuees…

CD = correct IIH diagnosis = yes/no binary variable
Covariate = parameter believed to be useful predictors of a correct IIH diagnosis

3.4.3   Case-controls studies on risk factors (study III and IV)

If at least one of the two algorithms predicted correct diagnosis of IIH they were included as IIH cases in the register studies. Patients were excluded if they had a previous IIH diagnosis recorded (1997-1999). Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) comparing IIH to GP controls as well as comparing IIH to obese controls. This model assumes clustering within the matched groups and the variance is adjusted accordingly. The frequency was reported. As a proxy for socioeconomic status the adjusted model included educational level (categorized as level 1: ≤ 9 years of compulsory school, level 2: > 9 year of compulsory school and $\leq$ high school, level 3: $>$ higher education after high school).

3.5   Ethical approval

All studies were approved by the ethical committee in Stockholm. In study I additional local approval was given by each head of the different clinical departments before receiving permission to review medical records.
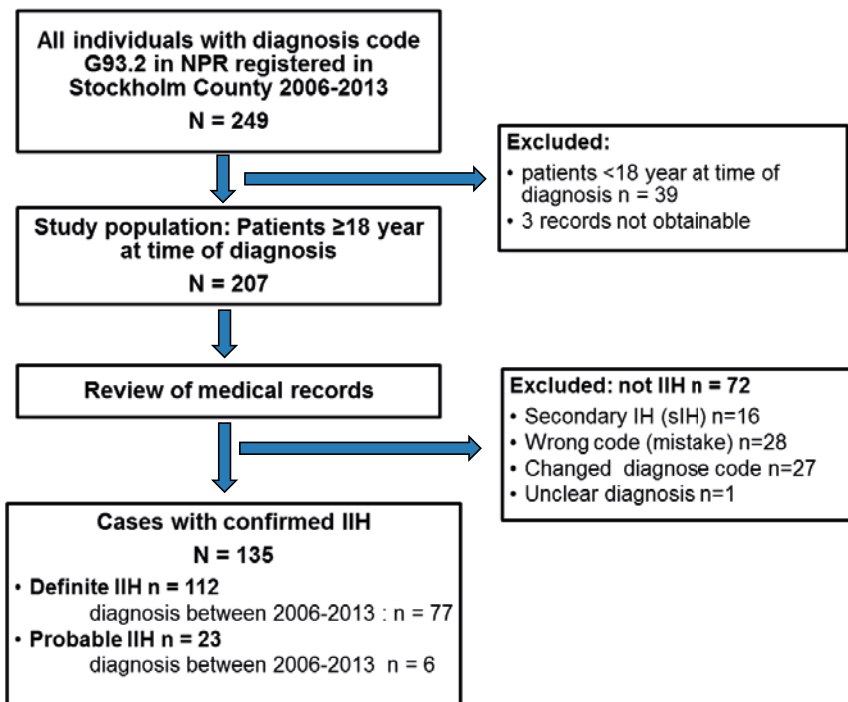
4   RESULTS

4.1   Validation of IIH diagnosis

Study I focused on validation of the IIH diagnosis coding in the NPR, using the modified Dandy Criteria. See inclusion chart, figure 5.

We found a low PPV of 65.2% (95% CI: 58.4-71.4) of a correct IIH diagnosis when validating the registered codes for IIH in the NPR by medical record review. As many as 14% had a wrong code (given by mistake), 13% were initially suspected as being IIH but later received a different diagnosis code, and 8% received the code for IIH but had an obvious cause explaining the high intracranial pressure, so called secondary intracranial hypertension (sIH). 0.5% had an unclear diagnosis which was not possible to validate from records.

Figure 5. Inclusion chart study I.

4.2 Incidence and onset of IIH

4.2.1 Increasing incidence

In study I the average yearly incidence in Stockholm county was 0.65 (CI 0.57-0.73) per 100,000 adult inhabitants. Results were similar for the whole of Sweden when looking at the national register data in study IV with an average yearly incidence of 0.71 per 100,000 adult inhabitants. When looking at the incidence over time in study IV we saw an increasing incidence overall, especially evident among females age 18-45, shown in figure 6 and table 5.

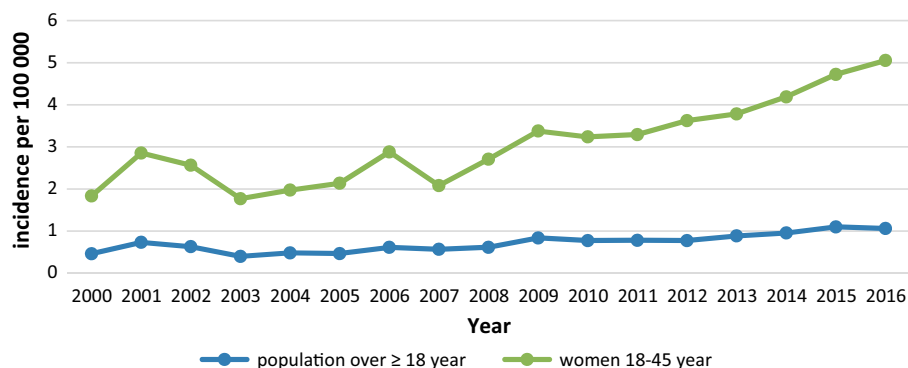**Figure 6.** Incidence of IIH per 100,000 inhabitants.

Table 5. Incidence by time-period in the adult population, and for females 18-45

Population:	Mean incidence / time-period:			Mean incidens:
	2000–2005	2006–2011	2012–2016	2000–2016
Population over ≥18	0.53	0.70	0.95	0.71
Women aged ≥ 18 to ≤ 45	1.66	2.23	3.32	2.35

4.2.2 Obesity

In study I obesity was common. Unfortunately, a precise value of BMI was missing in many medical records (in 30% of definitive and 83% of probable IIH). Mean BMI in those with precise values were 34.4 kg/m^2 (definite IIH), and 38.1 kg/m^2 (probable IIH). However, when including subjective definitions such as obese or overweight we found that 92% of patients with an IIH diagnosis were overweight or obese (data available for 103 out of 135 patients).

4.2.3 Age at diagnosis and sex difference

In study I when evaluating IIH in Stockholm County a female to male ratio of 6.1:1 was observed. Women were also on average younger than men at the time of diagnosis; the mean age at diagnosis for females was 31.0 (CI 28.8-33.1), and for males 42.9 (CI 36.4-49.5), p<0.001. Similar results were seen in the large national register study with a female to male ratio of 6.6:1 and mean age at time of diagnosis for women of 31.5 (CI 31.3-31.7) with males slightly older at 36.2 (CI 35.5-36.9).

4.2.4 Educational level

Educational level differed significantly among IIH patients compared to GP controls. The educational level of IIH patients was more similar to the obese controls, see table 6. We analyzed education as a proxy for socioeconomic status and used this data in the adjusted model for the odds ratios (OR).

Table 6. Information on achieved highest educational level

Information on achieved highest educational level n (%)	IIH 887 (98.3%)	GP controls 4454 (98.8%)	Obese controls 4453 (98.7%)
Compulsory school (≤ 9 years)	163 (18.4%)	439 (9.9%)	766 (17.2%)
Upper secondary (high school)	447 (50.4%)	1853 (41.6%)	2408 (54.1%)
University (level above high school)	277 (31.2%)	2162 (48.5%)	1279 (28.7%)

4.3 Algorithm

We tested different covariates possible to extract from registers that we believed could be helpful in better predicting which patients had a correct IIH diagnosis. The forward stepwise logistic regression model kept the following covariates that significantly improved model fit: age, number of times the diagnosis code G93.2 was recorded, and acetazolamide treatment. We chose to produce two algorithms (one without and one including drug register data). See table 7 below for information on how well the algorithms predicted whether a patient was true IIH according to number of recorded diagnosis codes. We chose to use three or more G93.2 as the covariate in our defined algorithms.

Table 7. Algorithms tested according to times of recorded diagnosis code

Prediction of correct diagnosis Patient and prescription registry* (Algorithm 1):		Algorithm given correct prediction % (95% CI)	PPV% (95% CI)	NPV% (95% CI)
A	2 or more codes	88.2 (80.3-93.2)	89.7 (79.8-95.0)	85.3 (69.0-93.8)
B	3 or more codes	88.2 (80.3-93.2)	89.7 (79.8-95.0)	85.3 (69.0-93.8)
C	5 or more codes	80.4 (71.5-87.0)	82.4 (71.3-89.7)	76.5 (59.4-87.8)
Prediction of correct diagnosis Patient registry only** (Algorithm 2):		**Algorithm given correct prediction % (95% CI)**	**PPV% (95% CI)**	**NPV% (95% CI)**
D	2 or more codes	85.3 (77.0-91.0)	91.2 (81.6-96.0)	73.5 (56.3-85.7)
E	3 or more codes	86.3 (78.1-91.7)	91.2 (81.6-96.0)	76.5 (59.4-87.8)
F	5 or more codes	82.4 (73.6-88.6)	83.8 (73.0-90.9)	79.4 (62.5-89.9)

PPV = positive predictive value, NPV = negative predictive value, CI = 95% confidence interval.
* Models contain variables: age, ever exposed to Acetazolamide treatment and specified number of times receiving ICD-10 code G93.2. ** Models contain age, specified number of times receiving ICD-10 code G93.2.

The algorithms predicted our definite IIH patients very well and was good at identifying those with a wrong diagnosis code or just an initial suspicion that later changed to another diagnosis (see table 8). However, the algorithms only predicted correctly in 60% of the sIH patients and had difficulty predicting probable IIH.

Table 8. Correct prediction IIH diagnosis (yes or no) according to validated diagnosis results

Validated diagnosis results:	Algorithm 1 correctly predicted IIH status % (95% CI)	Algorithm 2 correctly predicted IIH status % (95% CI)
Definite IIH	94.7 (84.4-98.4)	93.0 (82.3-97.4)
Probable IIH	63.6 (28.8-88.3)	81.8 (42.0-96.6)
sIH	60.0 (8.1-96.2)	60.0 (8.1-96.2)
Wrong diagnosis code* or initial suspicion**	90.9 (46.3-99.2)	81.8 (42.0-96.6)

Algorithm 1 comprise of variables: age + receiving diagnosis code G93.2 three or more times and exposure to Acetazolamide treatment. Algorithm 2 comprise of variables: age + receiving diagnosis code G93.2 three or more times. CI = 95% confidence interval. Definite IIH, idiopathic intracranial hypertension fulfilling modified Dandy Criteria; Probable IIH, overall clinical description in great concordance with IIH but with some missing data in medical records; sIH, secondary intracranial hypertension. *Patients seeking medical attention for another diagnosis but received code G93.2 (IIH). **Initial suspicion of IIH that later changed to other diagnosis or not sufficient workup.

4.4 Risk factors in association to IIH

4.4.1 Descriptive study I

In study I we found obesity and female sex to be the most common risk factors (see above). According to frequency we also found that having recently been exposed to an infection was common (present in 21%). Both obesity and infections cause inflammatory activation. Other disorders associated with inflammation, such as asthma, allergy, systemic lupus erythematosus (SLE), pancreatitis, inflammatory bowel disorders, and psoriasis were also common as comorbid disorders at IIH presentation. In men with IIH comorbidities such as hypertension (42%), diabetes (26%), and OSAS was common (21%).

4.4.2 Case-control studies III and IV

In the case-control studies (study III and study IV) we included after use of algorithms: 902 IIH cases and 4510 matched GP controls and 4510 obese controls. In the analyzes performed to study drug dispensing's, 654 IIH cases were included and a corresponding 3270 GP and obese controls, respectively. Study III investigated infectious and inflammatory disorders as possible risk factors for IIH development while study IV investigated factors previously proposed in the literature as risk factors for IIH development (disorders, drugs and pregnancy). Included ICD-10-SE diagnosis codes and ATC codes are shown in appendix section 9.1-9.2.
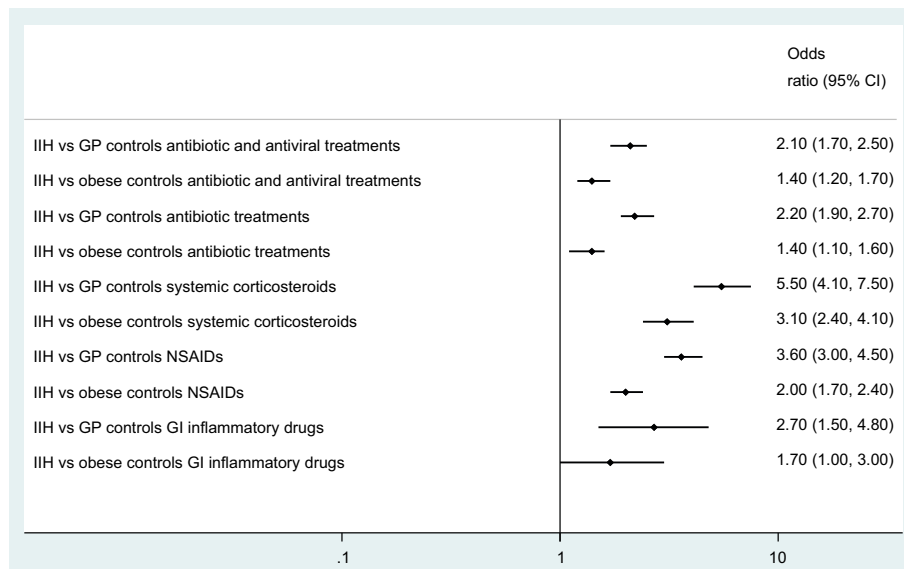
4.4.3 Infectious and inflammatory disorders

Both exposure to inflammatory and infectious disorders were significantly more common in IIH patients compared to both control groups the year prior to the first diagnosis of IIH. When comparing IIH patients to GP controls, the odds for exposure to infections were: $OR_{adjusted}$=4.3 (95% CI 3.3-5.6) and for inflammatory conditions $OR_{adjusted}$=3.2 (95% CI 2.4-4.3). Compared to obese controls IIH patients also had increased odds, however the magnitude of the effect was reduced: infectious disorders $OR_{adjusted}$=2.6 (95% CI 2.1-3.3) and inflammatory disorders $OR_{adjusted}$=2.4 (95% CI 1.8-3.2). When doing sensitivity analyses on exposure to any infectious or inflammatory disorders and how many times they received any of these codes in the preceding year we found that the OR for developing IIH increased with having received three or more codes compared to only one code (see figure 7). Sensitivity analyses looking at drug dispensing for drugs used to treat inflammatory and infectious disorders supported our findings with increased OR for exposure to these drugs in IIH patients compared to controls, see figure 8. We also performed a sensitivity analyzes by looking at exposure to antibiotics when excluding antibiotics reported to be risk factors for IIH (i.e. excluding tetracyclines, sulfonamides and fluoroquinolone antibiotics) but our results did not change materially in this analysis.

Figure 7. Frequency of receiving a code for any infectious or inflammatory disorder in the preceding year before index IIH code.
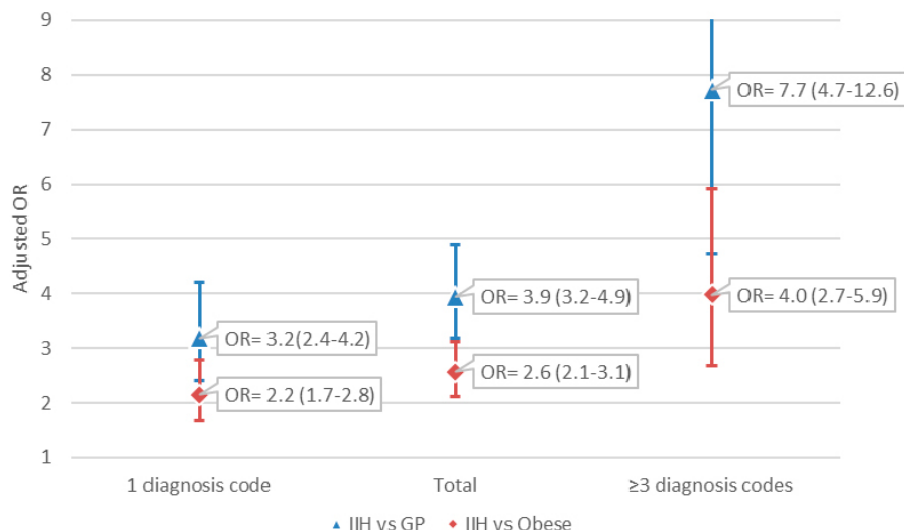
Adjusted OR with 95% CI in parenthesis. Adjustments made for educational level.

Figure 8. Odds ratio of dispensations from pharmacies one year prior to diagnosis (index date) in IIH patients compared to GP controls and compared to obese controls.
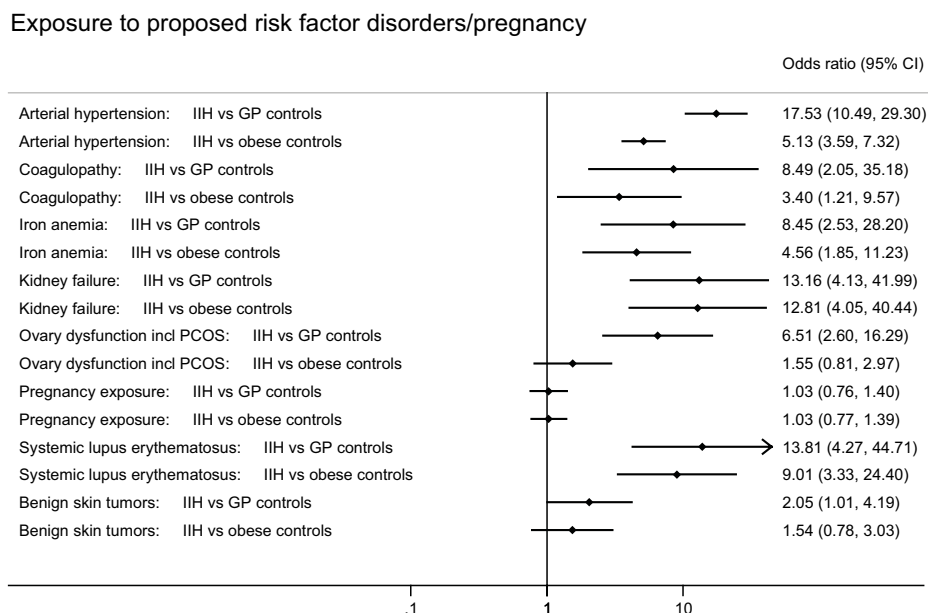

	Odds ratio (95% CI)
IIH vs GP controls antibiotic and antiviral treatments	2.10 (1.70, 2.50)
IIH vs obese controls antibiotic and antiviral treatments	1.40 (1.20, 1.70)
IIH vs GP controls antibiotic treatments	2.20 (1.90, 2.70)
IIH vs obese controls antibiotic treatments	1.40 (1.10, 1.60)
IIH vs GP controls systemic corticosteroids	5.50 (4.10, 7.50)
IIH vs obese controls systemic corticosteroids	3.10 (2.40, 4.10)
IIH vs GP controls NSAIDs	3.60 (3.00, 4.50)
IIH vs obese controls NSAIDs	2.00 (1.70, 2.40)
IIH vs GP controls GI inflammatory drugs	2.70 (1.50, 4.80)
IIH vs obese controls GI inflammatory drugs	1.70 (1.00, 3.00)

Adjusted OR with 95% CI. Adjustments made for educational level.

4.4.4   Proposed risk factor disorders and pregnancy exposure

Looking at previously reported risk factors we found a significantly increased risk of exposure to most of these disorders. The ORs were greater when comparing with GP controls relative to obese controls in all disorders except for kidney failure where results were similar for IIH patients compared to both control groups. In ovary dysfunction including PCOS the OR compared to obese controls did not reach significance as compared to GP controls. There was no difference in pregnancy exposure when comparing IIH patients with both control groups (see figure 9). Benign skin tumors were analyzed as a sensitivity analysis being a disorder that we did not expect to have any association to either IIH, inflammation nor obesity. Benign skin disorders were slightly more common in IIH patients but did not reach significance compared to obese controls and borderline significance compared to GP controls, see figure 9.

Figure 9. Forest plots visualizing adjusted ORs in IIH cases compared to GP and obese controls.
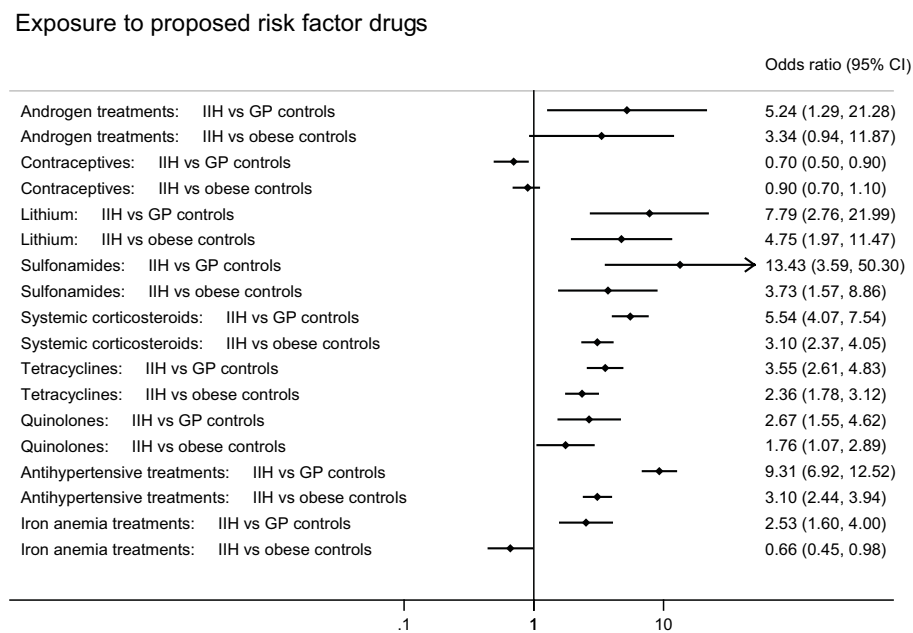
Exposure to proposed risk factor disorders/pregnancy

	Odds ratio (95% CI)
Arterial hypertension: IIH vs GP controls	17.53 (10.49, 29.30)
Arterial hypertension: IIH vs obese controls	5.13 (3.59, 7.32)
Coagulopathy: IIH vs GP controls	8.49 (2.05, 35.18)
Coagulopathy: IIH vs obese controls	3.40 (1.21, 9.57)
Iron anemia: IIH vs GP controls	8.45 (2.53, 28.20)
Iron anemia: IIH vs obese controls	4.56 (1.85, 11.23)
Kidney failure: IIH vs GP controls	13.16 (4.13, 41.99)
Kidney failure: IIH vs obese controls	12.81 (4.05, 40.44)
Ovary dysfunction incl PCOS: IIH vs GP controls	6.51 (2.60, 16.29)
Ovary dysfunction incl PCOS: IIH vs obese controls	1.55 (0.81, 2.97)
Pregnancy exposure: IIH vs GP controls	1.03 (0.76, 1.40)
Pregnancy exposure: IIH vs obese controls	1.03 (0.77, 1.39)
Systemic lupus erythematosus: IIH vs GP controls	13.81 (4.27, 44.71)
Systemic lupus erythematosus: IIH vs obese controls	9.01 (3.33, 24.40)
Benign skin tumors: IIH vs GP controls	2.05 (1.01, 4.19)
Benign skin tumors: IIH vs obese controls	1.54 (0.78, 3.03)

Adjusted OR with 95% CI. Adjustments made for educational level. Results also for sensitivity analysis done on benign skin tumors.

4.4.5 Proposed risk factors in drug treatments

When looking at the exposure to previously reported possible risk factor drugs we found significantly increased ORs for exposure to lithium, corticosteroids, antibiotics (tetracyclines, sulpha drugs, quinolones). Exposure to androgen treatments was rare with large confidence intervals but significantly increased compared to GP controls and border significant compared to obese controls. Exposure to contraceptives were in fact lower than in the control groups. As a sensitivity analysis we also analyzed exposure to drugs used to treat arterial hypertension and iron anemia deficiency due to that these disorders often are being diagnosed and treated in primary care settings. Increased odds in arterial hypertension treatments confirmed our results on arterial hypertension diagnosis, however results for iron anemia treatments were divergent with higher odds compared to GP controls but lower odds compared to obese controls. Results are shown in figure 10.

Figure 10. Forest plots visualizing adjusted ORs in IIH cases compared to GP and obese controls on exposure to risk factor drugs.

Exposure to proposed risk factor drugs

	Odds ratio (95% CI)
Androgen treatments: IIH vs GP controls	5.24 (1.29, 21.28)
Androgen treatments: IIH vs obese controls	3.34 (0.94, 11.87)
Contraceptives: IIH vs GP controls	0.70 (0.50, 0.90)
Contraceptives: IIH vs obese controls	0.90 (0.70, 1.10)
Lithium: IIH vs GP controls	7.79 (2.76, 21.99)
Lithium: IIH vs obese controls	4.75 (1.97, 11.47)
Sulfonamides: IIH vs GP controls	13.43 (3.59, 50.30)
Sulfonamides: IIH vs obese controls	3.73 (1.57, 8.86)
Systemic corticosteroids: IIH vs GP controls	5.54 (4.07, 7.54)
Systemic corticosteroids: IIH vs obese controls	3.10 (2.37, 4.05)
Tetracyclines: IIH vs GP controls	3.55 (2.61, 4.83)
Tetracyclines: IIH vs obese controls	2.36 (1.78, 3.12)
Quinolones: IIH vs GP controls	2.67 (1.55, 4.62)
Quinolones: IIH vs obese controls	1.76 (1.07, 2.89)
Antihypertensive treatments: IIH vs GP controls	9.31 (6.92, 12.52)
Antihypertensive treatments: IIH vs obese controls	3.10 (2.44, 3.94)
Iron anemia treatments: IIH vs GP controls	2.53 (1.60, 4.00)
Iron anemia treatments: IIH vs obese controls	0.66 (0.45, 0.98)

Adjusted OR with 95% CI. Adjustments made for educational level. Results also for sensitivity analysis on antihypertensive and iron anemia treatments.

5 DISCUSSION

Epidemiological studies are important in gaining understanding into rare disorders such as IIH. They are used to improve our knowledge on for example incidence, describe characteristics of a disorder, and provide hypotheses on factors that influence the disorder. It can also be used to evaluate outcome and changes over time.

5.1 Descriptive part – the patient cohort and validation

5.1.1 IIH cohort – variation in disease course and healthcare

Study I, the retrospective descriptive study, by evaluating medical records of large numbers of IIH patients with this rare disorder gave an important understanding of the complexity of the IIH disorder.

There were large variations in both how long patients had ongoing symptoms before receiving the diagnosis, and regarding the disease course between individual patients. It was also obvious that investigations, treatments, and follow-up routines differed. These decisions varied between doctors in charge and there were large variations in medical actions taken, even when it appeared that cases were quite similar. This could be due to both a lack of evidence-based guidelines for IIH, and that it is a rare diagnosis with few cases to gain experience from for the individual physician. Furthermore, the combination of the varied disease presentations, and the fact that several disciplines are involved in the patient's care (neurologists, ophthalmologists, neurosurgeons) is a challenge for equal care.

Because of this we saw a need for better guidelines for the IIH disorder in Sweden. We organized a multidisciplinary meeting at Karolinska University hospital with specialists in neurology, neurosurgery, neuroradiology, neuroophthalmology, and neuropediatrics attending. Subsequently, this resulted in the development of the first Swedish national guidelines for IIH (103). Simultaneously other countries were doing similar work resulting in new published guidelines in recent years (102, 104). Guidelines are important to improve clinical management and equal care for this patient group as well as help to evaluate current care regimes and facilitate improvements for this group of patients in the future.

5.1.2 Age and sex difference

We found an interesting age difference with males being older compared to females at time of diagnosis. This was most evident in study I but remained significant in study III. Some studies have also reported a similar significant age difference when comparing females to males (14, 123), others with a tendency to similar results (11, 26) and a few without this finding (124, 125).

In study I males had much higher frequency of cardiovascular disorders such as hypertension (42% in men and 8% in women) and diabetes (26% in men and 3% of women) as well as OSAS (21% in men compared to 0 cases among females). Regarding the seen differences among females and men in study I we speculate that risk factors of importance for IIH development might vary between the sexes and would be of interest for further studies.

OSAS has previously been associated with IIH in men (11, 61) and has been speculated to have pathophysiological implications in the IIH disorder (126). One small study however did not find that the prevalence of OSAS in IIH patient was higher than controls (127). Looking into OSAS and comparing to matched controls would have been of high interest in study IV but unfortunately, we did not have that data available.

Arterial hypertension is described to be common in IIH patients over age of 40 (128) and this could partly explain the differences seen in study I. We did analyze a possible sex difference on arterial hypertension on our data in study IV. In both females and men respectively, arterial hypertension was found to be much more common in IIH patients compared to matched controls. The results for females compared to GP controls for arterial hypertension was OR=16.1 (95% CI 9.0-29.0) and for men (OR=27.4 (95% CI 9.4-79.3). Compared to obese controls OR for arterial hypertension was for women (OR=5.4 (3.5-8.2)) and for men (OR=4.6 (2.4-8.7)). As confidence intervals are overlapping we could not conclude that sex influence this risk factor.

5.1.3 Educational level

Educational level differed among IIH patients compared to GP controls. As it was more similar compared to obese controls we believe that this appears to indicate some type of relationship between obesity and educational level. To our knowledge educational level in comparison with controls has not been investigated before in IIH patients, however living in socially deprived areas has been studied. Both living in socially deprived areas and educational level are often used in studies as a proxy for socioeconomic status. In the study by Mollan *et al* (14) it has been shown that IIH patients to a much larger extent were living in what has been described as socially deprived areas; as many as 53% of diagnosed patients were living in the quantile 1 or 2 = the most social deprived areas in a scale of five quintiles. We believe this likely reflects that persons living in socially deprived areas have a higher prevalence of obesity and therefore have higher incidence of IIH. Living in a socially deprived surrounding is likely to provide less resources to achieve higher education. However, we cannot rule out that longstanding symptoms (headache, cognitive function) before receiving a diagnosis in some individuals might have affected ability to perform in school.

5.1.4   Female sex and obesity

Female sex and obesity are the main two risk factors associated with IIH. This was also confirmed in our studies. Regarding female sex, 85% (study I) and 86% (study III/IV), of IIH patients were females. Similar results with female predominance with a variation between 76-98% have been reported in other descriptive studies (8, 14, 22-26). We could only study obesity in study I and unfortunately a precise value of BMI was missing in many medical records. However, if including subjective definitions such as obese or overweight we found that 92% of patients with an IIH diagnosis were overweight or obese (data on 103 out of 135 patients). Other studies confirm the strong association with obesity/overweight among those with information on weight (71-100%) (22, 23, 26).

5.1.5   Validation

Study I was primarily a validation study of the registered IIH diagnosis in the NPR. We found that only 65% had a correct code according to the modified Dandy Criteria. Problems with validity of registered diagnosis codes and change of diagnosis codes during investigation and follow-up of patients have been demonstrated before as mentioned in the background section (1.2.3) (29, 30). Therefore, there was a need for a method to enable better choosing which patients to include in our registry studies. This challenged us to produce the algorithms that we then applied in studies III and IV to improve probability of which patients to include as correct IIH cases. The algorithms improved prediction to 86-88%.

The algorithms performed best in correctly selecting patients with definite IIH (93-95%) and discarding cases with just a wrong diagnosis code or with an initial suspicion that later received another diagnosis (82-91%). In study I both incident and prevalent/previously diagnosed cases were included. The results showed that the algorithms worked less well in probable IIH maybe because 74% of the probable cases in study I were prevalent cases with the majority (57%) of those cases having less than 3 codes registered and therefore less contacts with healthcare, (showing only 64-82% correct prediction). As we only included incident cases in study III and IV we believe the algorithms might have worked better at selecting IIH patients.

The algorithms were the least successful in predicting sIH (60%). We believe this is due to these patients often having similar symptoms and treatments as IIH patients and often a more precise diagnosis code for their repeated visits is lacking in ICD-10-SE.

Altogether, validation of registered diagnoses and algorithms were found to be useful when performing register studies on a diagnosis such as IIH that initially may be difficult to diagnose correctly. In IIH, given that both the outcome of the

eye examination and ICP examination can be heterogenous depending on experience and sometimes uncertain results, and that several causes resulting in a sIH diagnosis might not be obvious on first visit, this is especially important to consider. The IIH disorder almost certainly causes multiple contacts with healthcare. Therefore, we believe the most evident parameter that should be used in register studies in this patient group is having received the diagnosis code on several occasions to be included as an IIH patient.

5.2   Incidence of IIH

Our results showed an increase in IIH incidence over the years from 2000 to 2016 with an 80-100% increase in overall incidence among all adults 18-45 years old. A similar increase has been reported in many recent studies (14, 24-26). However, Sweden seems to have a somewhat lower incidence with a mean incidence of 0.71 per 100,000 inhabitants. This lower incidence seems to be related to lower reported prevalence of obesity in Sweden compared to the other nations that also have reported higher IIH incidence. A meta-analysis found an almost linear correlation between incidence of IIH and obesity prevalence when analyzing data from several regions (129).

As in other studies the highest incidence in the Swedish cohort was found among young females of reproductive age, 2.35 per 100,000. Unfortunately, we do not have data on BMI/overweight in Swedish registers, but other studies have shown that the incidence increases substantially if only looking at obese females of reproductive age, with incidence between 22-38 per 100,000 (24-26). Since our study used algorithms to analyze the incidence we cannot exclude that some cases with IIH might not have been included and our results could therefore be an underestimation. However, considering results of previous validation studies of correctness of IIH diagnosis (see discussion above) this might well apply to other incidence reports with a possible reverse problem (overestimation).

5.3   Risk factors for IIH

Better understanding of factors that might trigger IIH is of great importance in a disorder with an apparent multifactorial pathogenesis such as IIH where the pathophysiological processes remain unknown. To summarize and discuss our results according to common denominators and in relation to possible hypotheses in the literature, see the modified directed acyclic graph (DAG) (figure 11).

Possible pathways in developing IIH:

1) The confirmed risk factors found to be associated with IIH in themselves are in the causal pathway (not knowing the physiological explanation)

2) The underlying hypothesized disturbances explain or are part of the following proposed causal mechanisms
   a. inflammatory activation
   b. androgen changes
   c. intracranial pressure regulations

3) Both 1) and 2) (multifactorial pathogenesis)

To visualize the uncertainties the DAG has orange arrows for previously proposed pathways and blue for newly proposed underlying pathways.

Figure 11. Modified DAG over proposed risk factor pathways.
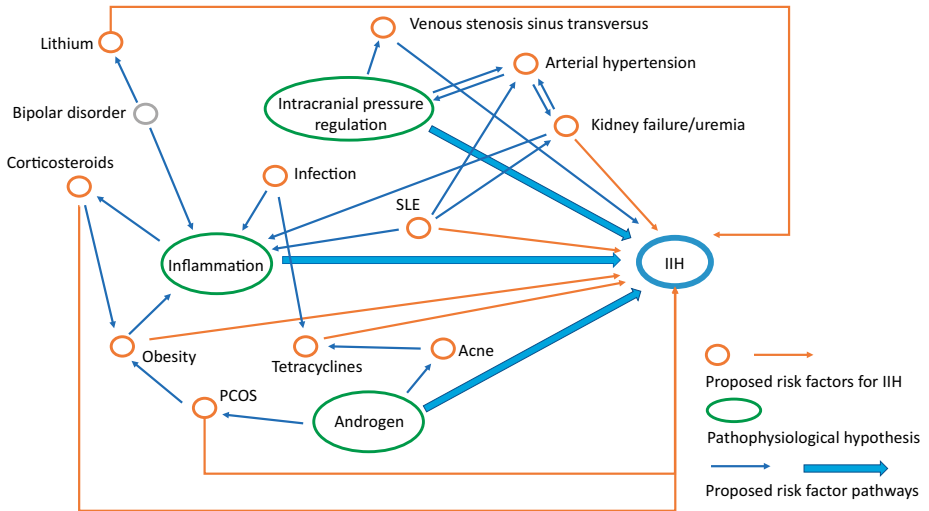
Abbreviations: SLE = systemic lupus erythematosus, PCOS = polycystic ovarian syndrome

5.3.1   Inflammation hypotheses

In study I we described which comorbidities were found in the IIH population at the time of diagnosis. A common denominator was disorders causing inflammatory activation, such as infectious disorders, and other disorders such as asthma, pancreatitis, appendicitis, inflammatory bowel disease and so forth. Also, obesity (being the most common risk factor with the strongest association to IIH) is a disorder known to cause inflammatory activation (84) which provided the impetus for us to investigate this hypothesis. In study III we investigated how common

conditions causing inflammatory activation were in IIH cases compared to controls and found that overall there was a significantly increased OR for having any infectious or inflammatory condition recorded. Even higher increased ORs were seen for having ≥3 number of codes of any infectious or inflammatory diagnosis registered compared to only one code the year prior to index date. One speculation explaining this could be that having several codes could possibly implicate a more severe inflammatory activation needing repeated contacts with health care or having multiple disorders with inflammatory activation that could increase the risk of IIH development. Increased ORs were seen with both infectious and inflammatory conditions compared to both GP and obese controls. However, among obese controls the effect size was lower. We also evaluated inflammatory conditions from different organ systems and found increased OR in all except for infectious and inflammatory conditions of the female reproductive organs that did not turn out to be significant compared to either of the two control groups. We therefore do not think that it is of relevance where the infection/inflammation is localized.

In study IV which considered various previously reported risk factors, we found not only significantly increased ORs among disorders causing inflammatory activation but also of treatments used to treat infections/inflammatory disorders. Among those disorders systemic lupus erythematosus (SLE) is a systemic inflammatory disorder. It is also reported that inflammatory activation is seen in the adipose tissue regardless of obesity level in kidney failure/uremia (130). Additionally, in several pharmacological treatments the conditions for why the drug is dispensed is associated with disorders causing inflammatory activation and this could be the pathophysiological explanation behind the association. For example, the antibiotics associated with IIH (tetracyclines, sulphonamides and quinolones) are used to treat infections causing inflammatory activation, and corticosteroid treatment are used for treating conditions causing inflammatory activation. Even the risk factor lithium treatment could potentially have an increased risk associated with inflammatory activation since bipolar disorders, for which lithium primarily is used, have been proposed to be associated with inflammatory activation (131). Which pathophysiological processes might be involved in an association of the inflammatory activation and IIH development need to be further investigated.

5.3.2 Androgen hypotheses

A common denominator to some of the risk factors previously associated with IIH are also associated with changes in androgen levels, which has been proposed as a risk for IIH development (see background). Factors that can be coupled to androgen levels are: PCOS (associated with an excess androgen state in women), androgen treatments, tetracyclines that are often used to treat acne (acne being associated with hyperandrogenism (132)) and vitamin A treatments used to treat acne (however not prevalent enough for us to study). The proposed mechanism in

association to IIH is low levels in men and high levels in women (67). Our results supported this hypothesis in that we saw a tendency towards higher OR in ovary dysfunction and androgen treatments (significant compared to GP controls but only a tendency compared to obese controls). However, as the number of exposed cases and controls is low this renders large confidence intervals and a large uncertainty. Results from other studies support our findings, i.e. that testosterone deficiency was more prevalent in men with IIH than in controls (61), that PCOS was shown to be more prevalent in IIH women (69, 133), and that hyperandrogenism is associated with earlier onset of IIH in women (71). Therefore, we believe our results could give further support to the androgen hypothesis.

5.3.3   Arterial hypertension and intracranial pressure regulation

Our results confirm the findings in prior minor case-control studies where arterial hypertension was more frequently seen compared to controls (60, 62). It is also reported to be a common comorbidity in IIH patients over 40 years of age (128). The descriptive study I revealed that arterial hypertension was a common comorbidity, especially among men, where 42% had this comorbidity compared to only 8% of the women. In study IV, arterial hypertension stood out with an $OR_{adjusted}$ as high as 17.5 (10.5-29.3) compared to GP controls and 5.1 (3.6-7.3) compared to obese controls. An increased risk of development of new cardiovascular events and arterial hypertension has also been described after diagnosis of IIH compared to matched controls (also BMI matched) (134).

Previous discussions have rendered that arterial hypertension is a confounder of known risk factors such as obesity, but our results also implicate that it might be a risk factor *per se* for IIH development. Supposing this to be true, other risk factors associated with IIH such as SLE and kidney failure known to cause increased arterial blood pressure could trigger IIH disorder by means of blood pressure. A potential pathophysiological hypothesis could be through intracranial pressure regulatory mechanisms. There is some experimental evidence of a correlation between raised ICP and raised blood pressure by means of sympathetic activity (135). Other pathophysiological mechanisms involved in ICP regulations seems to be stenosis of the transverse venous sinus (136) that could also be involved in mechanisms keeping the cerebral perfusion stable. Sinus transversus stenosis is something we know to be common in IIH patients (7). Further studies are needed to address whether arterial hypertension is a risk factor involved in IIH development.

5.3.4   Oral contraceptives and pregnancy

As IIH is so strongly associated with females of reproductive age, using contraceptives and becoming pregnant is something that often needs to be considered during patient/physician consultations. Our results showed no increased risk of

hormonal contraceptives and that exposure to pregnancy is not a risk factor for IIH development. This is consistent with recent studies and opinions (63, 137) but important to be verified in a large-scale study. Regarding pregnancy of course some might still develop or have the disorder while going through a pregnancy and thereby will need follow-up and treatment considerations. For women having had IIH prior to a pregnancy it is important they are provided with dietary advice and regular weight controls to avoid additional weight gain that increases the risk of recurrence/worsening of IIH (137).

5.3.5 Pharmacological risk factors

As described above, the proposed risk factors in study IV that showed significant association to IIH, need to be further investigated to determine whether it is the underlying condition for the treatments or the treatment itself that is the major risk in driving the development of IIH. This type of knowledge will be of importance in guiding the clinician on whether a specific treatment should be changed or if it is the underlying condition that needs to be treated.

A recent review article addressing drug-induced intracranial hypertension (DIIH) analyzed this using the following proposed criteria (138):

The patient meets the diagnostic criteria for IIH and at least four of the following:

A. Signs or symptoms of increased ICP are not due to any pre-existing clinical condition

B. Signs or symptoms of increased ICP developed within a reasonable time interval of drug administration

C. Upon discontinuation of suspected drug, signs or symptoms of increased ICP improved after five half-lives with subsequent resolution

D. Signs or symptoms of increased ICP recurred on re-challenge of suspected drug

E. The suspected drug has been previously reported to be associated with increased ICP

The conclusion from this review using these criteria was that some drugs such as vitamin A derivatives, tetracyclines, recombinant growth hormone, and lithium treatments were the most strongly associated drugs with a direct drug-induced effect while the association with corticosteroids was moderate and quinolones, oral contraceptives and several others were weakly associated with IIH (138). This is consistent with our results, particularly increased OR for lithium and tetracyclines. Regarding the antibiotics all of our studied antibiotic groups had

significantly increased OR for exposure the year prior to index date compared to controls, but to a higher extent in tetracyclines (IIH vs GP OR = 3.6 (2.6-4.8)) with almost significant (only slightly overlapping) difference in confidence intervals compared to the total antibiotic treatment group (IIH vs GP OR= 2.2 (1.9–2.7)). This was also the case when analyzing the sulpha antibiotic exposure group, but CIs were wider due to less frequent usage, so these results should be interpreted with some uncertainty. We believe that the reason that antibiotics as a group all have higher OR could be explained by the inflammatory hypothesis with the underlying infectious disorder/inflammation as a main driving mechanism. However, since the tetracyclines have even higher OR than all antibiotics combined this could implicate also a specific drug-induced effect. The same mechanism could apply to corticosteroidal use but as OR were moderately increased its hard to say whether it supports a specific drug-induced action. Therefore, our results suggest a drug specific effect by tetracyclines and lithium and possibly to some extent also by sulpha drugs and corticosteroidal drugs.

It is important to know how certain drugs function to impose specific patho-physiological effects associated with increased ICP and this needs to be further evaluated. Some hypotheses have been proposed over the years. One hypothesis discussed in the literature is that some treatments associated with IIH such as corticosteroids and vitamin A might upregulate the expression of AQP1 (139, 140).

5.4   Strengths and limitations

5.4.1   Register studies

Sweden's unique national registers make it possible to collect data on a national level, which can provide a decent sized sample even when investigating rare diseases. The source population studied the year 2000 was 6,945,013 individuals and increased over the study period to 7,918,746 in the year 2016 (population over 18 years of age at the end of December the particular year). When performing studies on the whole population and a population with this magnitude the risk of a selection bias by including a certain group with certain characteristics is thereby considered to be low.

IIH patients will have contact with specialized care when receiving their diagnosis and therefore we think that the majority of IIH patients should be captured in the Swedish NPR register. An additional strength is that the controls used in study III and IV came from the same population and were matched with the cases according to region of residence as well as age and sex to control for confounding.

5.4.2   Available information in retrospective studies

There are several limitations when doing retrospective register studies. Firstly, the data are collected prior to the study start meaning that we may lack information on potentially important variables/factors. In this case there was no information on BMI (height or weight) available in Swedish registries which is of great importance when investigating a disorder like IIH which is so strongly associated with obesity.

Other data such as smoking status and alcohol consumption could have been useful in the adjusted model, but these data are not available in any of the national Swedish registers.

Lack of clinical data of importance was a clear problem also in study I when looking retrospectively in medical records. Many times, useful parameters such as precise weight and height (BMI), a precise descriptive eye status, smoking status and so forth were missing, and we had to rely on terms such as overweight, normal eye status or papilledema. This problem became more evident in those IIH cases in study I with a code for IIH during the study time-period that were prevalent cases. Many of those had received their first diagnosis many years earlier, which meant we were unable to get firsthand information from case records at the time of diagnosis. Therefore, the diagnosis had to be evaluated from data found in more recent reports, resulting in many of these patients receiving a probable IIH diagnosis.

5.4.3   Use of obese controls in study III and IV

When evaluating risk factors in a disorder such as IIH with close association to obesity we knew that this was an important variable to consider. Unfortunately, BMI is not recorded in any national registers apart from MBR. We were therefore not able to include this parameter when matching cases with controls. To overcome this major limitation, we included a second control group having had a recorded ICD-10-SE code of obesity diagnosis registered in NPR. This was of great importance to the study to be able to evaluate the data comparing also to a control group being obese. However, receiving an obesity diagnosis in the NPR is uncommon and probably only represents patients that are severely obese and seek medical attention because of their obesity or its complications. This could mean that the groups are not entirely similar with respect to BMI and comorbidities if the obese controls are more severely obese than the IIH patients and thereby have a more complex health situation even though they are age and sex matched. The same can apply to the GP controls in that we believe this group to be less obese than the IIH cases. Therefore, we believe it was important to display results both for comparison with GP controls and obese controls. We believe that the "true results" if it would have been possible to obtain BMI matched controls probably would be somewhere in between.

5.4.4 Validity of registers

An additional strength to our register studies (study III and IV) is that prior to this we did a validation study (study I) looking at how valid the IIH diagnosis was in the NPR and then proceeded with constructing and testing algorithms (study II) to better predict "true IIH cases" from the NPR diagnosis. In study I, only 65% had a correct diagnosis code according to established diagnostic criteria. To overcome this limitation, we made the algorithms (study II) that better predicted which patients to include in register studies as correct IIH cases. However, this is still only a prediction and incorrect IIH cases will to some extent be included and there are probably also IIH cases which fulfil diagnosis criteria that our algorithms have identified as likely not IIH and therefore is not included in the analysis. We do however believe this is the best way to do register studies and the only way to perform large scale studies on such a rare disorder which is often misdiagnosed.

Limitations with validity of registered diagnosis codes might apply to the exposures that we are investigating in study III and IV. The validity of register data on specific diagnosis codes is often not done, but overall validity is considered good. Some misclassification bias of exposure codes is to be expected but we believe this to be non-differential, i.e. this happens randomly and is expected to affect cases and controls similarly.

The validity of the PDR is very good since it is an automatized system recording all prescriptions and their dispensing from pharmacies. However, we lack the information on whether patients actually were taking the drug.

The MBR is very good with coverage of 97-99% of all births in Sweden (121).

5.4.5 Surveillance and selection bias

We cannot rule out that IIH cases due to their symptoms might have been more prone to seek help from specialized healthcare than GP's resulting in surveillance bias. Physicians might have done investigations resulting in diagnosis of concomitant disorders that might otherwise have been undetected. Consequently, chronic or uncomplicated disorders that usually are diagnosed and treated in primary care, might have been coded in specialized care more often in IIH cases than in controls. As a sensitivity analysis, we therefore investigated the ICD-10-SE codes for such disorders as a primary analysis and as a secondary analysis looked at the drug dispensing on drugs used to treat these same disorders to investigate if we would get corresponding results. The purpose of this was also to overcome the limitation that the NPR does not contain data on diagnoses from primary care contacts.

In study III we did sensitivity analysis looking at the number of codes for infectious and inflammatory disorders during three-month intervals the year prior to

diagnosis to see if our results were due only to surveillance bias. We found higher OR in the period closest to diagnosis but otherwise stable and increased OR over the investigated 3-month periods. We believe that this could be due to surveillance bias, but we cannot rule out that a recent inflammatory activation pushes the patient to worsening of symptoms and therefore subsequent diagnosis of IIH.

We suspect that the obese control group could be more severely obese compared to IIH cases as this is a rare diagnosis in the registries. This might make them more prone to other health problems and could result in a selection bias with the obese control group possibly being sicker compared to IIH patients.

5.4.6 Limitations with the algorithms

When validating the algorithms produced in study II we found that these algorithms were poor predictors of sIH. In our cohort in study I, 8% of patients had a validated diagnosis of sIH and they often had similar symptoms as IIH patients, many with longstanding need for ICP lowering treatments and several follow-ups. In fact, there is no unique code for sIH in ICD-10-SE, making G93.2 the best choice for clinicians for follow-up visits when the underlying cause is treated and no longer present. This points to a limitation of the ICD-10-SE code system; however, this will be possible to code in the new coming ICD-11 coding system. It would have been useful to know if these sIH patients also had a registered diagnosis code for the primary cause in close relationship with the IIH diagnosis code, but we did not have that data available as we only received information on code G93.2 in study I.

Another factor that might have improved the algorithms would have been the code for papilledema (H47.1) – but we did not have that data and can only speculate to what extent that might or might not have affected the validity of the algorithms.

5.5 Generalizability

The results in study I describe an IIH cohort in one county dominated by a big city and its suburbs. This might affect generalizability and results might have looked different in another setting. However, study III and IV are national population studies and we therefore believe that results could apply to other similar populations. Regarding risk factor analyses we believe this could apply to other western counties with a similar range of comorbid disorders. The difference in obesity prevalence between countries, however, is likely to affect the degree of exposure to obesity related risk factors and IIH incidence.

6   CONCLUSIONS

These studies add new input to the research field of the IIH disorder:

Study I:

- Our validation study showed that the diagnosis code for IIH in NPR was incorrect in 35% of the cases, mostly due to patients not fulfilling the diagnostic criteria. Thus, when planning for register based studies of IIH or any other disorder, it is of utmost importance to evaluate the validity of a registered diagnosis by cross checking with data from an adequate number of case records.
- The incidence of IIH in Sweden is in the lower range compared to what is reported in recent studies in northern Europe.
- In the case records obesity/overweight was reported in 92% of the true IIH cases, and in 61% of the patients for whom BMI was recorded the mean BMI was 34.7. These findings are in line with other studies indicating that obesity is likely to be part of the pathophysiological process or an important risk factor.

Study II:

- We found that construction and testing algorithms was a good tool to better predict which cases to include in register studies on IIH. We found that patients having had several visits with the same diagnosis code improved the diagnostic prediction.

Study III and IV:

- The incidence of IIH was shown to be rising in Sweden, and this also seems to be related to the reported increase of obesity prevalence in Sweden and in other countries. As obesity is a major risk factor for IIH, body weight needs to be closely monitored in these patients. On a national level it is important to use health resources wisely to prevent comorbidities and health problems that are associated with obesity, IIH being one of them.
- Our two case-control studies on risk factors increase the evidence that there are associations between IIH and infectious/inflammatory conditions and other previously suspected risk factors such as arterial hypertension, SLE, kidney failure, PCOS that can not only be explained by obesity.
- Associations with tetracyclines, lithium and corticosteroids exposures were also evident.
- Anticonception and pregnancy – did not show association to IIH development.
- Altogether, our findings give support for a multifactorial pathogenesis of IIH.
- We discuss our results in relation to 3 hypotheses on possible pathophysiological mechanisms that could be involved in IIH development: inflammatory hypothesis, androgen hypothesis and the hypothesis of disturbed ICP regulatory mechanisms. Further studies are necessary to address these hypotheses.

7   FUTURE PERSPECTIVES

IIH is a disorder affecting primarily obese females of reproductive age, and often give rise to longstanding symptoms and a potential risk for irreversible visual deficits. Our studies show that the incidence is increasing and as we know that IIH has a large impact on patients' quality of life and gives rise to substantial costs for the society – it is important to continue the efforts to better treat and help this patient group.

Our findings also support the theory that the disorder has a multifactorial origin and accordingly needs to be individualized. Epidemiological studies help us show associations and develop hypotheses but cannot explain the pathophysiological and causal relationships. Considering this, other studies are needed to improve knowledge on the pathophysiological level. As well as evidence-based knowledge on best treatment and healthcare regime for this patient group, both on an individual level as well as structural levels (chain of structured healthcare actors). The most important research areas in the future are:

7.1   Understanding pathophysiology

To understand the pathophysiological processes behind what causes the increased ICP development in IIH and which pathophysiological processes are involved are of great importance. Today several studies in IIH have been performed and knowledge is being continually generated. I believe more studies looking into how inflammatory activation could be involved in IIH development would be interesting to perform. Also, what precise mechanisms could be involved that could explain an increasing risk of IIH if exposed to for example lithium and tetracyclines. With greater knowledge on the pathophysiological mechanisms we might improve preventative initiatives to lower disease prevalence. This could improve treatments in use today but also develop new more specific treatments. This would also help us better guide our patients in risk factor managements and treatment choices.

7.2   Treatment for IIH

I see a need for more randomized comparison studies regarding treatments to provide evidence-based guidelines for IIH treatment to provide guidance for clinicians in handling this quite complex patient group. Studies are ongoing on new treatments as well as comparative studies on treatments already in use today, so hopefully we have better evidence and better treatments to offer our patients in the future. Working with this patient group and during my research studies I have gained a greater understanding of the complexity of this disorder, its likely multifactorial pathogenesis and that we most certainly will continue to need individually adjusted treatment regimes.

7.3 Quality of life, headache and cognitive function

After normalization of ICP some IIH patients continue having complex problems with headache, fatigue, concentration and possibly impaired cognitive function which reduce their quality of life and affect work performance. There are only a few studies on these aspects. The outcome of IIH in the long perspective is sparsely known. These factors need to be more investigated in the future. This is of importance to guide patients and health providers on how to best use our health resources and rehabilitation needs.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Idiopatisk intrakraniell hypertension (IIH) är en relativt ovanlig sjukdom som ffa drabbar unga överviktiga kvinnor. Vi vet väldigt lite om vad det är som orsakar IIH, därav namnet idiopatisk. Sjukdomen kännetecknas av högt intrakraniellt tryck som i sin tur ofta orsakar symtom som huvudvärk, synpåverkan, illamående och pulserande ljud i öronen. Många gånger är symtomen långvariga, kräver många kontroller inom sjukvården och höga doser trycksänkande läkemedel med besvärande biverkningar. Det finns också flera studier som visar på risk att dessa patienter drabbas av permanent synskada och kronisk huvudvärksproblematik, men också att de kanske får påverkan på sk kognitiva funktioner som minne och processhastighet.

För att kunna utveckla bättre behandlingar krävs ofta att man vet de bakomliggande mekanismerna till sjukdomen. Idag vet vi att det finns en stark association mellan IIH och exempelvis kvinnligt kön, fertil ålder och övervikt. Men frågorna varför och hur har vi inte besvarat. Långt ifrån alla överviktiga kvinnor drabbas ju av denna sjukdom.

Syftet med denna avhandling var att bättre kartlägga sjukdomsförekomsten i Sverige och de faktorer som verkar öka risken att insjukna i sjukdomen. Varför är detta intressant? För det första kan en kartläggning av sjukdomens incidens och samsjuklighet ge oss kunskap om hur mycket ohälsa sjukdomen skapar (hur många drabbas, ökning eller minskning av sjukdomsförekomst, vilka drabbas primärt och hur ser dessa ut gällande sin hälsosituation). Man kan också utifrån detta i ett längre perspektiv dra slutsatser kring kostnader, behov av vårdresurser osv.

Vi fann att incidensen av IIH i Stockholms län under 2006–2013 var 0,65 per 100 000 personer över 18 år. Sjukdomen var sex gånger vanligare hos kvinnor och majoriteten av dessa var överviktiga. I den större registerstudien var medelincidensen i stort sett densamma 0,71 per 100 000 men jämför man över hela perioden så ses en stadig och tydlig ökning som vi bedömer sannolikt beror på den rapporterade ökningen av fetma i världen och i Sverige.

Det vi fann i studie I var att många patienter (hela 35%) som fått diagnoskoden för IIH inte uppfyllde diagnoskriterierna. För att kunna genomföra registerstudier var vi därför tvungna att hitta en metod som med större sannolikhet kunde identifiera rätt patienter att undersöka. Utifrån materialet i studie I skapade vi algoritmer (statistisk metod) som genom att använda faktorer som ålder, att man fått diagnoskoden flera gånger samt i den ena av algoritmerna även läkemedel som används för behandling av sjukdomen (Diamox® = acetazolamid) ökade sannolikheten för att vi inkluderade rätt personer, dvs patienter med IIH.

Vidare ville vi studera om IIH patienterna var mer exponerade för vissa misstänkt utlösande faktorer före utvecklingen av IIH jämfört med matchade kontroller. Vi tittade bland annat på faktorer som man tidigare misstänkts varit associerade med sjukdomen. Vi använder oss av våra stora svenska register. Detta innebär att vi kan studera misstänkta utlösande faktorer i en mycket större grupp patienter (IIH fall) och kontroller än vad man tidigare kunnat göra. Totalt inkluderade vi 902 fall och 4510 kontroller från befolkningen matchade på ålder, kön och bostadsort och lika många matchade personer som även hade en fetmadiagnos. I den del där vi tittade på läkemedelsuttag från apotek inkluderades 654 IIH fall och 3270 matchade kontroller i båda kontrollgrupperna.

Vi fokuserade på om infektion och inflammation var associerat till ökad risk för att insjukna i IIH och fann att risken var 3–4 gånger större att man hade varit exponerad för dessa sjukdomstillstånd året innan man fick sin IIH diagnos bekräftad. Vi tittade också på de tidigare föreslagna riskfaktorerna njursvikt, inflammatoriska sjukdomen SLE, polycystiskt ovariesyndrom, samt högt blodtryck. Våra resultat bekräftade att dessa tillstånd verkar öka risken att utveckla IIH. Likaså förefaller behandling med vissa läkemedel som tetracycliner, litium och kortisonanvändning vara betydligt vanligare hos IIH patienter året innan sjukdomsdebut jämfört med kontrollgrupperna. Intressant var också att vår studie bekräftade att graviditet och p-pilleranvändning inte verkar vara en riskfaktor för IIH utveckling.

Fortfarande är de bakomliggande mekanismerna för dessa riskökningar inte klarlagd men vi presenterar hypoteserna att 1.) inflammation kan vara en viktig gemensam pusselbit, 2.) hormonella förändringar i androgenregleringen och 3.) faktorer som påverkar den intrakraniella tryckkontrollen kan vara av betydelse för utvecklingen av IIH sjukdomen. Dessa teorier behöver vara fokus för framtida studier när det gäller IIH sjukdomen och dess mekanismer med förhoppning om att kunna ge mer kunskap och nyare och bättre behandlingar för denna drabbade patientgrupp.

9 APPENDIX

9.1 ICD-10-SE codes and ATC codes used for Analyses study III

ICD-10-SE codes used for the analyses:

All infectious and inflammatory disorders:	All A+B diagnosis, J00-22, L00-08, N10, N12, N70-71, K35, K81, K85, M00-03, J40-46, N00-01, N03, N05, N11, M05-14, M30-36, K50-52, K90, L20-30
Infectious disorders:	All A+B diagnosis, J00-22, L00-08, N10, N12, N70-71, K35, K81, K85, M00-03
Inflammatory disorders:	J40-46, N00-01, N03, N05, N11, M05-14, M30-36, K50-52, K90, L20-30
Specific infections:	A + B diagnoses
Respiratory inflammation/infections:	J00-22, J40-46
Kidney inflammation/infections:	N00-01, N03, N05, N10-12
Female genital inflammation/infections:	N70-77
Systemic inflammatory disorder:	M30-36, M05-14
GI inflammation/infections:	K20, K29, K50-52, K35-37, K61, K73, K75, K80-81, K85, K90
Skin inflammation/infections:	L00-08, L20-30

ATC codes used for the analyses:

Antibiotic+antiviral treatments:	J01, J05, D06, P
Antibiotic treatments:	J01
Systemic corticosteroids:	H02
Non-steroidal antiinflammatory drugs:	M01
GI drugs:	A07

9.2 ICD-10-SE codes and ATC codes used for Analyses study IV

ICD-10-SE codes used for the analyses:

Addison's disorder	E27
Arterial hypertension	I10-15
Benign skin tumors	D22-23
Coagulopathy	D65-68
Cushing disorder	E24
Hyperparathyroidism	E21
Hyperthyroidism	E05
Iron anemia	D50
Kidney failure	N17-19
Ovary dysfunction incl PCOS in females	E28
Sarcoidosis	D86
SLE	M32
Turner and Downs syndrome	Q96+Q90

ATC codes used for the analyses:

Androgen treatments	G03B
Antihypertensive treatments	C02-03, C07-09
Hormonal contraceptives (systemic use)	G03A
Iron anemia treatments	B03A
Lithium	N05AN
Retinoidal derivatives for acne	D10BA
Sulphonamides	J01EB-E
Systemic corticosteroids	H02
Tetracycline derivatives	J01A
Quinolone derivatives	J01M

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