Epidemiology of Normal Pressure Hydrocephalus

Prevalence, Risk Factors, Diagnosis and Prognosis

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To my beloved Rebecka, Mother, Father and brother David
ABSTRACT

The number of older persons and individuals with cognitive impairment is expected to increase dramatically in most parts of the world. It is therefore important to learn more about disorders that affect cognition. Idiopathic normal pressure hydrocephalus (iNPH) mainly occurs in older persons and symptoms include cognitive impairment, gait disturbance and urinary symptoms. The aim of this thesis was to examine various aspects regarding the epidemiology of iNPH.

The sample comprised data from the Gothenburg population studies. Study participants underwent comprehensive clinical and neuropsychiatric examinations between 1986 and 2009. iNPH was diagnosed in concordance with criteria from international consensus guidelines.

Study I: The prevalence of iNPH was higher than previously reported. More than one in twenty, among 80-year-olds, had signs and symptoms consistent with probable iNPH. Study II: Vascular risk factors and markers of cerebrovascular disease were associated with iNPH. Hypertension was related to an almost three-fold increased chance of having imaging signs of iNPH. For diabetes, it was more than four-fold. The strongest relation to iNPH was for cerebral white matter lesions, which were associated with a more than six-fold increased chance. Study III: More than one fifth of the sample had ventricular enlargement, defined by current cut-off values for Evans Index. In addition, men aged 80 years or more, had on average, values equal to or higher than what is currently considered pathological. Study IV: Persons who fulfilled criteria for probable iNPH had an almost four-fold increased risk of death. In those with radiological signs of iNPH, the risk of dementia was almost three-fold increased.

iNPH is probably more common than previously supposed. Many older persons have clinical and imaging signs consistent with iNPH. These findings are important considering that iNPH is a treatable disorder. Vascular factors are probably involved in the pathophysiology. Current cut-off values for ventricular enlargement, using Evans Index, ought to be reappraised in order to improve diagnostic possibilities. Untreated iNPH is associated with a poor prognosis with a high risk of death or dementia. Radiological signs of iNPH may have a greater prognostic importance than previously presumed.

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SAMMANFATTNING PÅ SVENSKA

Antalet äldre och personer med nedsatt kognitiv förmåga förväntas öka dramatiskt de kommande åren. Det är således av stor vikt att studera sjukdomar som påverkar intellektuella funktioner. Idiopathisk normaltryckshydrocefalus (iNPH) drabbar framförallt äldre personer. Symptomen innefattar försämrad kognitiv funktion, gångsvårigheter och vattenkastningsbesvär. Syftet med denna avhandling var att undersöka epidemiologiska aspekter av denna sjukdom.


Delstudie I: Förekomsten av iNPH var högre än vad man tidigare uppskattat. Mer än var tjugonde 80-åring uppvisade kliniska och radiologiska fynd förenliga med iNPH. Delstudie II: Vaskulära riskfaktorer och markörer för cerebrovaskulära sjukdom var kopplat till iNPH. Hypertoni ökade sannolikheten att ha radiologiska fynd förenliga med iNPH nästan trefaldigt. Gällande diabetes var sannolikheten mer än fyrfaldigt ökad. Starkast koppling var till vitsubstansförändringar som gav en mer än sexfaldigt ökad sannolikhet. Delstudie III: Mer än en femtedel av alla hade förstorade ventriklar enligt gällande definition, baserat på Evans Index. Dessutom hade män, i åldrarna 80 år och äldre, i genomsnitt ett värde på Evans Index som utifrån dagens kriterier skulle klassas som sjukligt. Delstudie IV: De som uppfyllde kriterierna för iNPH hade en nästan fyrfaldigt ökad risk för död. Dessutom var risken för demens nästan trefaldigt ökad hos de som hade radiologiska fynd förenliga med iNPH.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.


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Hydrocephalus –

From the Greek words
“Hydor”= water and “Kéfale”= skull
1 NORMAL PRESSURE HYDROCEPHALUS - AN INTRODUCTION

Classification of Hydrocephalus

Hydrocephalus is a term for various conditions characterized by impaired cerebrospinal fluid (CSF) dynamics. Enlargement of the cerebral ventricles is one of the main hallmarks.\(^1\) Hydrocephalus includes several different disorders with varying causes and clinical presentations, and can therefore occur in all ages.\(^2\) The topic of this thesis is idiopathic normal pressure hydrocephalus, which is an adult form.

The classification of the hydrocephalic disorders is largely based on the anatomy and physiology of the central nervous system (figure 1). Hydrocephalus can be classified into two main forms: non-communicating (obstructive) hydrocephalus, and communicating (non-obstructive) hydrocephalus. Non-communicating hydrocephalus is characterized by an obstruction of the CSF flow, somewhere between the point of production and absorption. Causes can include congenital malformations, hemorrhage, tumors and various other intracranial mass lesions. Non-communicating hydrocephalus can affect persons of all ages and have an acute or chronic onset. Clinical features depend on the underlying cause.\(^2\) Because CSF flow is obstructed, intracranial pressure (ICP) can be increased. In contrast, in the communicating form of hydrocephalus, there are no visible obstructions of CSF flow, and the underlying mechanisms are not fully understood. There is no increase in intracranial pressure, hence the name normal pressure hydrocephalus (NPH).\(^3\) NPH affects adults, and is further divided into two groups. When it is caused by certain precipitants, such as trauma, meningitis or subarachnoid hemorrhage, NPH is classified as secondary (sNPH). In cases where no identifiable cause can be found, NPH is labeled idiopathic (iNPH).\(^3,4\) This thesis involves iNPH and discussions regarding other forms of hydrocephalus are beyond the scope of the present work.
Epidemiology of Normal Pressure Hydrocephalus

Figure 1. Classification of hydrocephalus.

Examples include congenital disorders in children, malformations, tumors and other mass lesions.

Can be caused by trauma, intracranial hemorrhage and CNS infections.

The main topic of this thesis is idiopathic normal pressure hydrocephalus (iNPH).
In order to fully understand the present, we must first have knowledge about the past.
History of iNPH

The first modern description of iNPH was made by the Colombian neurosurgeon Salomón Hakim in 1965. In the original publications, two cases of secondary NPH, following traumatic brain injury, and one case of idiopathic NPH were described. The patients presented with cognitive impairment, gait disturbance and urinary incontinence and were noted to have distended ventricles on angiography and pneumoencephalogram. Lumbar puncture was performed and intracranial pressure was found to be within normal limits. Interestingly, after the lumbar puncture, clinical improvement was noted. Shunt surgery was performed and further improvement occurred.

After having published his original finding, Salomón Hakim devoted himself to further research on NPH and its potential causes. In particular, he was interested in intracranial biomechanics. Thus, he spent much time on the hydrodynamic aspects of CSF and the cerebral ventricles. He theorized that, because pressure is defined as force per unit area, the ventricles in NPH could be enlarged due to increased force acting on the brain tissue while the CSF pressure remains constant.

Although, neither change in intracranial pressure nor ventricle size have subsequently been found to relate to postoperative improvement, much of the research has so far been focused on pressure-volume relationships. However, it might be that the complexities involved in the CSF circulation have been underestimated. Also, compared to the hydrodynamic aspects, other research areas in iNPH, such as the overlap between other neurodegenerative disorders have thus far received less attention.

Clinical Features

iNPH mainly affects older persons and symptoms often develop insidiously. Core signs and symptoms include gait and balance disturbance, cognitive impairment and urinary symptoms. These are summarized in figure 2. The symptoms are sometimes referred to as the “typical triad”. However, this is
probably not an appropriate description for several reasons. Approximately half of all patients might only have one or two of these symptoms. Thus, the constellation of clinical characteristics is likely more complex than implied by the term “triad”. Furthermore, there is uncertainty regarding the exact distinctive features for each symptom. Gait and balance problems, cognitive dysfunction and urinary symptoms are common in older persons and may sometimes be due to comorbidities. Therefore, ascribing these symptoms to patients with suspicions of iNPH should be made in a thoughtful manner.

**Gait and Balance**

Gait disturbance is common in iNPH. It is often stated to be the first symptom to develop, and the most characteristic. However, it is not known whether this is truly the case. For example, it might be that walking difficulties are more easily detected at an initial stage than subtle cognitive symptoms. Nevertheless, gait disturbance is an important part of the clinical picture. Typically the abnormal gait pattern is characterized as broad-based, magnetic with reduced cadence, step height and step width. In classic literature, the gait is sometimes described as apraxic. Sometimes the gait pattern can have features of Parkinsonism, such as hesitation, freezing and reduced arm-swing. However, iNPH-patients more typically have retropulsion, i.e. a tendency towards a backward-extended posture.
The balance and posture dysfunction seems to be related to a backward-displaced center of pressure and a defective vertical visual perception.\textsuperscript{14} Other characteristics of the gait pattern include outward rotation of the feet, and difficulties turning.\textsuperscript{11} Impaired balance often coexists with gait disturbance in iNPH, and can result in an increased risk of falls. Although the mechanisms underlying gait and balance disturbance in iNPH are not precisely known, these symptoms may be similar to those seen in patients with vascular cognitive impairment.\textsuperscript{15}

Cognitive impairment
Symptoms and signs of cognitive impairment are common among patients with iNPH. Often cognitive impairment in iNPH is of the frontal-subcortical type. Thus, common features include psychomotor slowing, inattention,
forgetfulness and impaired executive functions.\textsuperscript{1, 16} In a study comparing iNPH with patients with Alzheimer’s disease, those with iNPH had more frontal lobe symptoms.\textsuperscript{17} They were found to have a more pronounced impairment regarding attention and psychomotor speed, whereas the patients with Alzheimer’s disease had worse memory. It was speculated that the frontal lobe symptoms in iNPH might be secondary to subcortical, periventricular, white matter disease. In another study, compared to healthy individuals, iNPH patients had impaired functions in several domains, as described above, and also exhibited signs of impaired dexterity and fine motor skills.\textsuperscript{18} It was also found that neuropsychological impairment was associated with gait disturbance, incontinence and increased daily sleep.\textsuperscript{18} iNPH patients with concomitant vascular risk factors performed worse on neuropsychological tests. Several of these findings were later confirmed in a rather large, multicenter study.\textsuperscript{19} The authors speculate that the signs and symptoms in iNPH might be due to multifocal periventricular hypometabolism in combination with impaired connectivity in cortical-subcortical circuits. It was also theorized that the reduced wakefulness might be caused by dysfunction in the ascending activating systems.

Urinary Symptoms
Urinary symptoms are common in iNPH. It is said that patients often experience increased frequency and urgency early on, and develop incontinence at later stages.\textsuperscript{1} However, urinary symptoms are very common in both men and women in the general population. Thus, it can be difficult to differentiate these symptoms of iNPH from other causes. Urgency and incontinence in iNPH is thought to occur from a central disinhibition leading to hyperactivity of the detrusor, as this has been found in urodynamic studies.\textsuperscript{20, 21} Impaired cognition and locomotion may however also contribute.
Anatomy and Physiology of the CSF Circulation

CSF (Liquor cerebrospinalis) is a clear and colorless fluid that surrounds the central nervous system. CSF has several vital physiological functions, such as protective cushioning, regulation of intracranial pressure and transport of metabolites and waste products. The total volume of CSF (surrounding the brain and spinal cord) is approximately 200 ml. Turnover is rather high given that the production rate is around 500 ml per day (20 ml per hour). Thus, daily formation is two to three times higher than the total CSF volume. The basic anatomy of the ventricular system is shown in figure 3.

The arachnocentric view on CSF circulation

The traditional approach to CSF circulation is largely based on anatomical descriptions and experiments made in the nineteenth century and beginning of twentieth century, i.e. more than 100-150 years ago. Much emphasis has been placed on the absorptive pathways through the arachnoid villi. Therefore, the traditional view on CSF circulation could be said to have an arachnocentric focus. Accordingly, the main production site of CSF is the choroid plexus. CSF flows in a pulsatile manner with each cardiac cycle. A net flow occurs from the lateral ventricles, through the foramina of Monro to the third ventricle, from there, through the aqueduct of Sylvius down to the fourth ventricle and eventually exits through foramen of Magendie and Luschkae. The CSF enters the subarachnoid space of the cisterna magna. Traditionally CSF is said to travel down the subarachnoid space of the spinal cord and also directly up along the cerebral convexities where it is absorbed into the venous blood of sinuses through the arachnoid granulations.
A more contemporary approach to CSF dynamics
The traditional view on CSF circulation is rather straightforward and easy to grasp. However, recent findings indicate a more complex process, and there is now increasing evidence that the traditional view on CSF circulation is over-simplified and outdated. For example, the brain parenchyma, capillaries including perivascular spaces and interstitial fluid might be more important for CSF production and absorption than the choroid plexus and arachnoid granulations.\textsuperscript{22, 26, 27} In upright active individuals up to two thirds of CSF absorption can occur through the spinal subarachnoid space.\textsuperscript{28} Furthermore, perineural sheaths of pia and arachnoid mater along cranial- and spinal nerves have been found to constitute important pathways of lymphatic CSF
Several studies have shown that CSF tracers readily enter extra-cranial lymphatics, such as the cervical lymph nodes, and ultimately the blood stream. In one study performed on sheep, the cribriform plate was obstructed, blocking absorption to the nasal mucosa lymphatics. This led to an increased intracranial pressure and an almost three-fold increase in CSF outflow resistance.

To complicate things further…

In 2013, a landmark paper was published in Science that provided a possible explanation for the function of sleep. As it turns out, the findings may also have implications for our understanding of the CSF circulation, and possibly the pathophysiology of iNPH.

Real-time imaging was made, in vivo, using fluorescent tracers, injected into the CSF. This was performed in asleep and awake mice and in anesthetized mice. Intriguingly, in the sleeping and anesthetized mice, a substantial influx of CSF occurred along the para-arterial spaces into the brain parenchyma. Upon arousal, however, this influx decreased by approximately 95 %. This was then repeated using radiolabeled amyloid beta (Aβ). It was found that during sleep, Aβ was cleared from the interstitial space two-times faster than during the awake state. Furthermore, cortical interstitial volume was also measured and found to increase almost twofold during sleep.

These findings indicate that during sleep, the interstitial volume shrinks. This in turn, allows influx of CSF along the para-arterial spaces, and clearance of metabolites and waste products. The pathway of waste clearance, from the extracellular space, occurred as a convective flow through a complex astroglial network referred to as the glymphatic system.

^ The lymphatic system has an important role in the clearance of metabolic waste. In almost all organs, the number of lymphatic pathways is proportional to the metabolic activity. The brain is however an exception. It is interesting that despite having the highest metabolic activity, and thus an enormous need for waste clearance, the CNS itself lacks lymphatic vessels.
These processes are believed to require a high energy expenditure, which cannot be accommodated in the aroused state. While awake, the brain has to take in, filter, and process vast amounts of new data. Therefore, maintenance and household functions in the brain, i.e. elimination of waste, takes place during sleep.

The glymphatic system is composed of three main parts, a para-arterial influx of CSF from the subarachnoid space, a trans-parenchymal passage route through an astroglial system, where the CSF mixes with interstitial fluid, and finally a para-venous clearance route. The process is mediated by aquaporin 4 (AQP4) channels located on the endfeet of the astrocytes (Figure 4).

It is believed that the glymphatic system can be disrupted by vascular injury and traumatic brain injury. This could lead to reactive astrogliosis with resulting displacement of the AQP4 channels.\textsuperscript{32, 33} As the glymphatic system fails, clearance of waste products decrease and potentially neuro-toxic proteins, such as Tau and amyloid may accumulate ultimately leading to further brain injury and neurodegeneration. In the context of iNPH, it is interesting that decreased wakefulness is a frequently occurring symptom among patients. Also, AQP4 seem to be involved in regulation of brain water content, and levels of AQP4 have been found to be altered in hydrocephalus.\textsuperscript{34}
Figure 4. The Glymphatic system (The figure is a simplified representation. In actuality, the end-feed of astrocytes cover almost the entire capillary surface.)
Pathophysiology

It is often believed that iNPH is primarily caused by an alteration of CSF dynamics, such as decreased absorption.\(^{35}\) This might very well be true. However, there is so far little evidence that directly supports this notion. Indeed CSF diversion does improve symptoms. Though, it is theoretically possible that the effect of shunt surgery is due to secondary changes in the cerebral microcirculation. It might be that the previously oversimplified concepts of CSF circulation have led to an underestimation of the actual complexities involved in the pathophysiology.

Morphological changes of CSF outflow tracts, such as arachnoid fibrosis have been noted in some patients on autopsy.\(^{36}\) This might implicate an impaired outflow as a pathological basis. However, most studies included only a few cases, and more recent papers have provided contradictory results.\(^{37}\) Also, patients with iNPH are said to have an increased resistance to CSF outflow.\(^{38}\) However, most patients with iNPH are older, and it is known that both production and absorption of CSF decreases with age.\(^{39, 40}\) Furthermore, values of CSF outflow resistance (\(R_{\text{out}}\)) that are considered pathological may be found in as many as 25 % of healthy elderly.\(^{41}\) Moreover, other measures of CSF dynamics, such as continuous monitoring of intracranial pressure and radionuclide cisternography, that are often said to show characteristic features of iNPH, lack evidence-based support.\(^{42}\) For example, intermittent alterations of intracranial pressure have been reported to be diagnostic of iNPH and useful as a prognostic marker in terms of shunt surgery.\(^{43, 44}\) However, similar findings are seen in healthy individuals and might actually be physiological occurrences.\(^{28, 45}\) Thus, regarding the pathophysiology, mechanisms other than those involving CSF dynamics should also be considered.

The role of vascular disease
There are numerous reports linking iNPH to various vascular risk factors including hypertension, diabetes mellitus and heart disease.\(^{46-50}\) These studies were made using hospital-based samples. Thus population-based epidemiological studies have so far been lacking. Also, in a review issued by
a task force for the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders (ISHCSF), it was noted that the previous studies were based on small samples and were more than twenty years old. Furthermore, these papers do not provide data for a direct causal relation. Nevertheless, a possible causal association between vascular disease processes and iNPH is further supported by several additional studies.

Arterial hypertension is more common in patients with iNPH, and a previous prospective cohort study found that systolic blood pressure and pulse pressure were related to development of increased ventricle size. Interestingly, the relation between hypertension and ventricular enlargement is also supported by animal studies. Spontaneously hypertensive rats have been found to develop enlarged ventricles. In addition, another study on sheep found that hydrocephalus developed quickly after that balloons were inserted into the ventricles and set to inflate during systole and deflate during diastole, thereby increasing the pulse pressure.

Small vessel disease has also been implicated in the pathogenesis of iNPH. Neuropathological examinations have revealed signs of cerebrovascular disease in patients with iNPH. In addition, cerebral white matter lesions (WMLs), which are associated with small vessel disease and white matter ischemia, have been found to be more common in iNPH compared to controls. Furthermore, WMLs are related to similar subcortical symptoms, such as gait disturbance, urinary incontinence and cognitive impairment. Moreover, WMLs have been found to decrease after shunt surgery, with reductions correlating with clinical improvement. Additional support for a vascular pathology underlying iNPH comes from numerous studies that have found reduced blood flow in several areas including the periventricular white matter. Also, cerebral blood flow has been found to increase after CSF removal via lumbar puncture or shunt surgery.

Some authors have reported that WMLs in iNPH might be associated with a poor response to shunt surgery. However, this may be contradicted by a randomized, double-blinded sham-controlled study that included iNPH patients with severe white matter disease, who also fulfilled criteria for
Binswanger’s disease. Half of the patients received a standard ventriculoperitoneal shunt, and half received a ligated shunt. After three months, the patients in the treatment group improved while no improvement was noted in the control group. After the three months, the ligated shunts were opened in the control patients, after which they to improved.

Further support for a vascular disease mechanism might come from a recent study in which iNPH patients were found to have a higher number of cerebral microbleeds than healthy controls. The association between iNPH and cerebral microbleeds might be due to small vessel disease.

Two studies have reported interesting results regarding the reduction of white matter hyperintensities and clinical improvement in iNPH patients treated with Acetazolamide. Acetazolamide, a carbonic anhydrase inhibitor, is the only potential pharmacological treatment that has been proposed for iNPH. It is currently approved for treatment of glaucoma, idiopathic intracranial hypertension and acute mountain sickness. Acetazolamide is a diuretic and has been shown to reduce CSF production. More importantly, Acetazolamide is also a vasodilator that has been shown to increase cerebral blood flow. Among eight, non-shunted, iNPH patients treated with Acetazolamide, five responded positively with improved gait. Furthermore, a significant reduction in periventricular hyperintensities was seen. In another study, non-shunted iNPH patients, treated with Acetazolamide underwent repeated MRI and clinical assessments. These were compared to iNPH patients who underwent external lumbar drainage (ELD) and controls consisting of iNPH patients without intervention. White matter changes decreased in those treated with Acetazolamide and in the patients who underwent ELD, but not among controls. It is important to note that WMLs in iNPH might have other causes than ischemia, such edema or CSF stagnation, and the authors state the positive effects of Acetazolamide might be due to decreased interstitial brain water, reduced transependymal CSF flow, or increased cerebral blood flow. Regardless, the findings of these studies are highly intriguing, and a

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B Of interest, Acetazolamide has also been suggested to be a blocker of aquaporin channels (Owler et al. Cerebrospinal Fluid Research 2010, 7:15)
randomized controlled trial on Acetazolamide in iNPH would probably be of value.

As mentioned in the previous section, it is conceivable that vascular disturbances and ischemia might contribute to partially reversible changes in the microcirculation. However, the exact mechanisms linking vascular disease to iNPH are currently not clear.

Other potential causes
Interestingly, iNPH patients have been found to have larger head size than healthy controls.\textsuperscript{73, 74} This might suggest that iNPH is a congenital disorder that becomes symptomatic in late life. Given these findings, it has been hypothesized iNPH might be a “two-hit disease”.\textsuperscript{75, 76} Accordingly it was theorized that iNPH begins with benign external hydrocephalus during infancy (the first hit), which causes an increased head size and ventricle size. After this, the person may be asymptomatic until late-life, when white matter disease develops (the second hit). The authors state that white matter ischemia, with resulting myelin loss, may give rise to a more hydrophilic environment that impedes CSF flow through the extracellular space. This process ultimately leads to further decrease of CSF absorption with clinical decompensation causing the person to become symptomatic.

However, another study found that head circumference was only increased in a subset of iNPH patients.\textsuperscript{77} The authors found that the number of patients with iNPH who had a head circumference above the 90\textsuperscript{th} percentile was significantly increased compared to controls. Though, this was not the case for the rest of the iNPH sample. The distribution among those with a head circumference below the 90\textsuperscript{th} percentile was similar to that of the control population. These results imply that a congenital cause of iNPH might be the case only in a minority of the patients. Of further importance, it has been suggested that iNPH, in fact is a rather heterogeneous syndrome with many potential causes and that persons with suspected iNPH might also have other neurodegenerative disorders or various concomitant comorbidities.\textsuperscript{10, 78} This might be true, at least to some extent, given the considerable overlap between iNPH and other neurodegenerative diseases.
Cerebral amyloid pathology in iNPH and overlapping features with Alzheimer’s disease

iNPH and Alzheimer’s disease have several common features. These include clinical, radiological and biochemical findings. For example, patients with Alzheimer’s disease often have enlarged ventricles, gait disturbance and urinary problems. Also, patients with iNPH have reduced levels of Amyloid-β (Aβ42) in CSF, similar to those with Alzheimer’s disease. In addition, Amyloid-β is frequently found in cortical brain biopsies in iNPH. In fact the two diseases are thought to often coexist. Some authors have therefore hypothesized that iNPH and Alzheimer’s disease might have a common etiological mechanism. It was previously postulated that both diseases are the result of hydrodynamic disturbances of CSF flow. Alzheimer’s disease was theorized to be due reduced CSF production, with decreased turnover of CSF ultimately leading to accumulation of Aβ42 and in turn causing neurodegeneration. iNPH, on the other hand was thought to occur from a decreased CSF absorption which would also lead to decreased turnover of CSF and accumulation of Aβ42 giving rise to a similar syndrome as Alzheimer’s disease. Based on this, a pilot study was conducted in order to examine the possible therapeutic effects of shunt surgery in patients with Alzheimer’s disease. However, despite initially promising results, a randomized, double-blinded, sham-controlled trial later showed no benefit of CSF shunting in patients with Alzheimer’s disease.

There might also be other explanations for the existence of cerebral amyloid pathology in iNPH. It might be that the development of iNPH is related to interstitial CSF stagnation with reduced periventricular metabolism leading to decreased CSF clearance and accumulation of Aβ42. A study conducted in Gothenburg, Sweden found that patients with iNPH, compared to healthy individuals, had not only low levels of Aβ42 but also other types of amyloid proteins (Aβ38, Aβ40, sAPPα and sAPPβ) were low. This finding is typically not seen in Alzheimer’s disease. The authors found also increased levels of neurofilament light protein (NFL), which might be due to degeneration of periventricular axons. Moreover, all amyloid proteins increased in ventricle CSF after shunt surgery. It has, since then, been theorized that that the low
levels of CSF Aβ42, in iNPH, are not due to deposition (as in Alzheimer’s disease) but instead caused by decreased clearance via the glymphatic system.\textsuperscript{85}

In a study from Finland, cortical biopsies were obtained, during shunt surgery or postmortem, from patients with iNPH and Alzheimer’s disease.\textsuperscript{86} iNPH patients with amyloid pathology had higher levels of y-secretase activity compared to iNPH patients without amyloid pathology. Patients with Alzheimer’s disease, on the other hand, are known to have increased activity of β-secretase. These findings might indicate different pathophysiological mechanisms. In addition, in a relatively large cohort of iNPH patients from the same registry, no association was found between Apolipoprotein E-status and iNPH.\textsuperscript{87} Furthermore, patients with iNPH seem to have larger hippocampus volumes than those with Alzheimer’s disease.\textsuperscript{88} Another study is also worth mentioning. Positron emission tomography (PET) imaging was made, using \textsuperscript{11}C-labeled radiotracer Pittsburgh compound B imaging (PIB) to detect cerebral amyloid pathology and compare patients with iNPH and those with Alzheimer’s disease.\textsuperscript{89} Three out of ten iNPH patients had increased cortical amyloid. However, the amyloid distribution was different in those with iNPH compared to those with Alzheimer’s disease. Those with Alzheimer’s disease showed increased levels in the frontal and temporoparietal areas, while those with iNPH had a distribution limited to the high convexity and parasagittal areas. The authors state that these regions might be mechanically more compressed in iNPH, resulting in decreased clearance of Amyloid-β.

Although both patients with iNPH and Alzheimer’s disease may have cerebral amyloid pathology, altogether, previous results suggest that the pathophysiological mechanisms are different. Nevertheless, many of the common features are interesting and perhaps worthy of further investigation.

Why are the ventricles enlarged?
In obstructive hydrocephalus intracranial pressure (ICP) is increased and the reason for ventricular enlargement could be regarded as rather intuitive.
However, in iNPH ICP appears to be within normal range and the cause of ventricular enlargement has puzzled the scientific community for decades.

Originally it was postulated that an increase in ventricle size might result in a concomitant decrease in pressure.\(^7\) This reasoning was partly based on Pascal’s principle, in which pressure is equal to force per unit area. Thus ICP could be normal due to having an increased area (ventricle volume) and increased force acting on the ventricle walls. Owing to this, it has been theorized that iNPH might be due to microscopic obstructions of CSF flow such as scarring or fibrosis of the arachnoid granulations. However, histopathological studies have been unable to confirm this.\(^{37}\) Furthermore, attempts to predict response to shunt surgery based on pressure-volume variables have been futile. Some patients have normal resistance to CSF outflow, but improve after CSF diversion while others have elevated outflow resistance but remain unchanged.\(^{90}\) These findings are difficult to explain using the previous models. Therefore, the exact reason for ventricular enlargement remains highly unclear.

It is well known that patients with cerebral atrophy can have enlarged ventricles (a condition sometimes termed hydrocephalus ex vacuo). However, not all patients with brain atrophy have enlarged ventricles. Therefore, it is theoretically possible that ventricular enlargement in some patients with Alzheimer’s disease and vascular dementia is not entirely attributable to loss of brain parenchyma. For instance, it might be that there are concurrent changes in the cerebral microcirculation similar to that in iNPH. This could possibly also explain part of the overlap regarding symptoms. However, other typical radiological signs of iNPH such as narrowing of high convexity sulci and subarachnoid space do not seem to be common in other neurodegenerative disorders. Although, this has, so far, not been investigated using population samples.

As mentioned earlier, hypertension and diabetes are common in iNPH. It might also be that stiffening of large vessels, due to atherosclerotic processes, lead to an increased pulse-pressure. This could, in turn, result in increased mechanical force acting on the brain parenchyma leading to
ventricular enlargement. However, in order to gain knowledge on this topic, epidemiological studies using population-based samples with longitudinal data are needed. For example, the order of events regarding development of different radiological signs and clinical features are currently not known.

Prevalence and Incidence

Epidemiological studies in iNPH are scarce and there are few population studies on the prevalence and incidence. Most previous studies were made using smaller samples and included few people above age 80 years. Also, several authors have stated that iNPH is a rare disorder.\textsuperscript{91, 92} Although, there is some uncertainty regarding prevalence estimates\textsuperscript{C}, existing data does not support the notion that iNPH is uncommon.

In Germany, a door-to-door survey was conducted in order to examine the prevalence of Parkinsonism.\textsuperscript{93} The authors found a prevalence of iNPH, in persons above age 65 years, of 0.4%. However, because iNPH was only examined in those who screened positive for Parkinsonism, the study probably underestimated the prevalence. A study from Norway reported a prevalence of probable iNPH of approximately 0.1% in persons older than 65 years.\textsuperscript{94} However, this study was not populations based. Participants were recruited from an advertisement campaign directed to the general population and primary care physicians. It is thus possible that the low prevalence was due to recruitment bias.

A population-based study in Tajiri, Japan found a prevalence of NPH of 2.9% among 170 men and women aged 65 years or older.\textsuperscript{95} Another population-based study from the same area examined 497 persons aged 65 years or more and reported a prevalence of possible iNPH of 1.4%\textsuperscript{.96} A third population-based study from Japan included 790 persons and found that

\textsuperscript{C} One of the reasons for having uncertainty in the prevalence estimates might be that iNPH, like many other neurological diseases is rather difficult to diagnose. The brain is a highly complex organ shielded by thick bone and isolated from the rest of the body by a blood-brain-barrier. Advanced imaging techniques and extensive workup are often needed to make an accurate diagnosis. Thus, making a precise diagnosis on a population-level is difficult and may require substantial resources.
1.5% had features of NPH on MRI, and 0.5% met the criteria of possible iNPH. These studies included mainly younger elderly. A study, conducted in Umeå, Sweden examined the occurrence of ventricular enlargement and symptoms of iNPH among patients with TIA admitted to a stroke unit. The authors found that 3.9% of the patients fulfilled radiological and clinical criteria for possible iNPH. Several other studies have been aimed to assess the prevalence of iNPH. However, these were not population-based. Instead, they were conducted on specific samples, such as patients from memory clinics or nursing homes and thus had inherent limitations. A recent systematic review pooled prevalence data from earlier population studies and found that the prevalence of iNPH, among persons aged 60 years or more, was 1.3% (95% CI; 0.96-1.71).

Two previous studies have examined the incidence of iNPH, one of which was population-based. The first study was conducted in Norway and estimated the incidence among all ages to 5.5/100,000. The second one, conducted in Japan followed a cohort of 70-year-olds for ten years and estimated the incidence to 120/100,000. In Sweden, the annual incidence of shunt surgery for hydrocephalus is 3.33/100,000 (of which approximately half are for iNPH). The incidence of shunt surgery in Norway has been reported to be 1.09/100,000. Thus, extrapolating from earlier studies, existing data suggests that iNPH is highly underdiagnosed and undertreated. Using even the most modest estimates, it seems that less than 20% of patients receive treatment. However, it should be pointed out that the number of shunt surgeries seems to have increased, at least in Japan, since these studies were published.

Diagnosis

The diagnosis of iNPH is mainly based on the combination clinical signs and brain imaging findings from CT or MRI. Certain additional tests of CSF dynamics may sometimes also be applied. Evidence-based guidelines for the diagnosis of iNPH have previously been developed in order to aid clinicians and provide consensus in research.
The first guidelines were created by several experts from Japan and published in 2004 (The English version was published in 2008). A second edition was made in conjunction with the Japanese Ministry of Health, and was published in 2011 (The English version, published in 2012).

In 2005, researchers from the USA and Europe also created separate guidelines for management of iNPH. According to these, iNPH should be diagnosed by careful review of the patient history, possibly also from a close informant, thorough clinical examination and neuroimaging. If diagnostic uncertainty remains, additional tests of CSF dynamics can be performed. However, despite meticulous review of the literature, the authors acknowledge the uncertainty and difficulties in diagnosing iNPH. For this reason, a classification system of “probable”, “possible” and “improbable” iNPH was proposed. The main signs and symptoms and diagnostic criteria are summarized in figure 5.

Overall, the Japanese and American-European guidelines are rather similar. One differences is that gait disturbance is not mandatory for the classification of “probable iNPH” according to the Japanese guidelines. Also, according to the Japanese criteria, persons who improve after shunt surgery can be labeled “definite iNPH”. This is not the case in the American-European guidelines.

So far, the guideline criteria have not been validated regarding reliability, validity, sensitivity and specificity. Nevertheless, they have been of value in providing consensus and an evidence-based approach to the management of iNPH. Also, it is worth mentioning that in Japan, the number of shunt surgeries for iNPH seems to have increased dramatically after the publication of the guidelines in 2004.

Patient history
Clinical features of iNPH are also discussed in previous sections. Signs and symptoms of iNPH typically develop gradually. A more acute onset should prompt the clinician to consider other diagnoses. Patients often present with gait and balance difficulties, unsteadiness and or increased number of falls.
They may also present with signs of cognitive dysfunction, such as inattention, forgetfulness, drowsiness, increased sleep, lack of motivation as described earlier. Obtaining a medical and surgical history from a relative or other close informant is often of value considering that patients can sometimes have trouble recalling. Urinary symptoms, such as urgency and or incontinence are also common. However, urinary problems frequently occur in older persons without iNPH, due to other reasons. It is therefore important to distinguish symptoms in iNPH, which are thought to occur from overactivity of the detrusor, from other causes such as benign prostatic hyperplasia or stress incontinence. One should also bear in mind that some patients may find it difficult to discuss these types of symptoms. In addition, it is important to consider causes of secondary NPH, such as previous head trauma, meningitis or subarachnoid hemorrhage. Thus, past episodes of possible precipitants should be inquired. The possibility of congenital causes should also be considered. Treating physicians can therefore ask about neurological symptoms during childhood. Finally, there are several somatic and psychiatric disorders that can mimic iNPH. The presence of any comorbidities should thus be carefully reviewed.
**Figure 5. Overview and summary of the American-European guidelines for the diagnosis of iNPH.**

**MAIN SIGNS AND SYMPTOMS ACCORDING TO GUIDELINES**

**Patient History**
- Progressive symptoms with onset after the age of 40. Minimum duration of 3 months. No evidence of secondary NPH. No other concurrent conditions can sufficiently explain symptoms.

**Neuroimaging**
- Ventricular enlargement (Evans Index > 0.3). No obstruction of CSF flow. In addition, at least one of the following features: Enlargement of the temporal horns. Periventricular signal changes. Flow void on MRI.

**Clinical Features**
- Cognition: Decreased psycho-motor speed, fine motor skill. Decreased attention, recall, and executive dysfunction.
- Urinary symptoms: Episodic or persistent incontinence, not attributable to urological disease.

**SUMMARY OF GUIDELINE CRITERIA**

**PROBABLE iNPH**
- Gait and Balance disturbance + Cognitive Impairment or Urinary Incontinence or both

**POSSIBLE iNPH**
- At least one of the following: Gait and Balance disturbance, Cognitive Impairment or Urinary Incontinence

**UNLIKELY iNPH**
- No signs of ventricular enlargement, Signs of increased intracranial pressure, none of the classic symptoms present, signs and symptoms attributable to other conditions

Imaging signs consistent with iNPH must be present
Assessment of gait and neuropsychology

Gait and balance can be assessed in several ways. A clinical examination, in which a physician examines gait, including tandem gait and Romberg's test, is of value. Additional examination by a physiotherapist may probably add more information. Also, formal testing, by measuring gait speed and number of steps is important in order to compare pre- and postoperative values. There are also many ways in which neuro-psychological evaluations can be done. Often the MMSE is performed. More specific testing of frontal-subcortical, executive functions and fine motor skills can be performed using the Stroop test, Grooved Pegboard test and the Rey Auditory Verbal Learning Test.18 Several other similar cognitive tests can also be applied.108

Imaging in iNPH

All patients with suspected iNPH must undergo imaging of the brain in order to examine ventricle size and exclude possible obstructions. A normal scan probably rules out iNPH rather effectively. According to the guidelines, ventricular enlargement is a mandatory criterion.1 16 It is stated in the guidelines that ventricular enlargement should be evidenced by an Evans Index greater than 0.3, or by an equivalent measure of ventricles size. However, no such alternative measure is suggested.

Regarding the choice of imaging, MRI is superior to CT in many ways. Although the guidelines do state that CT is probably sufficient for routine diagnosis of iNPH. Nevertheless, MRI allows for a better visualization of small obstructive lesions, including possible thin membranes.109 More advanced imaging techniques, such as measurements of cerebral perfusion by CT, MRI, SPECT, PET or pseudo-continuous arterial spin labeling (pCASL) have also been described.110-113 These have provided interesting results from an academic standpoint, but are currently not clinically applied. Additional methods, such as isotope cisternography114, have previously also been advocated, but currently lack evidence.1

One of the major radiological hallmarks of iNPH is the presence of ventricular enlargement disproportional to subarachnoid space volume, i.e. ventricular enlargement not due to atrophy.8, 115 More specifically, the radiological
findings in iNPH have been described as a tightness of high convexity sulci and medial subarachnoid space, together with ventriculomegaly and enlarged Sylvian fissures (Figure 6). These findings have been termed DESH (disproportionately enlarged subarachnoid space hydrocephalus). According to studies based on clinical samples and population data, findings of DESH might differentiate iNPH from normal aging and vascular dementia. Although, previous studies have provided promising results, additional research is needed to elucidate the exact diagnostic value. Dilation of the lateral ventricles is probably the most prominent sign, but most other parts of the ventricular system can also be enlarged. Optic nerve sheath diameter, which can be increased in conditions with increased intracranial pressure, has not been studied in iNPH.

Another radiological finding in iNPH that has recently gotten more attention is the narrowing of the corpus callosum angle on coronal sections. The first paper that measured the corpus callosum angle on MRI was published in 2008. In that study, the angle was measured perpendicular to the antero-posterior commissure plane, at the level of the posterior commissure. A sharp angle, less than 90°, differentiated iNPH patients from normal controls and those with Alzheimer's disease. However, the patients with iNPH were pre-selected based on clinical features and other imaging signs. Thus, the exact sensitivity and specificity cannot be determined, and further studies are needed to determine the exact prognostic value.

White matter changes are also frequent imaging findings in iNPH. These may be both periventricular or located in the deep white matter. White matter changes are associated with small vessel disease and ischemia. However, it sometimes also stated that the white matter changes in iNPH are caused by edema due to hydrodynamic disturbance of CSF circulation. Thus, the exact cause of these imaging findings is still the subject of some debate. However, the fact that iNPH is strongly associated with other vascular conditions probably indicates that ischemic processes are at least partly involved in the disease mechanisms. It should also be stated that cerebral ischemia may cause axonal demyelination, which can in turn, give rise to increased interstitial fluid.
Figure 6. Morphological changes in iNPH

An increased CSF flow through the cerebral aqueduct, termed flow void, can sometimes be seen on MRI. This has been said to be suggestive of iNPH and have prognostic importance. However, previous studies have been contradictory and the exact value of this radiological sign is therefore not known. Regardless, the presence of a flow void is probably useful in differentiating communicating, from non-communicating hydrocephalus.

Evans Index is an estimate of ventricle size, and is probably one of the most common imaging markers in the diagnosis of iNPH. It is defined as the ratio between the maximum width of the frontal horns of the lateral ventricles and the maximum width of the inner diameter of the skull (Figure 7). Values
higher than 0.3 are regarded pathological, and are currently required by international consensus guidelines for the diagnosis.\(^1\)\(^6\) However, despite the fact that Evans Index is used extensively in both research and clinical practice, exact values in the adult population are not precisely known. Earlier studies reporting values on Evans Index were made using small samples or non-representative populations. Despite having a major role in the diagnosis of iNPH, no previous population-based epidemiological studies have reported reference values.

Evans Index was first described in 1942 in children, using sagittal views on pneumoencephalograms.\(^{122}\) Later, in 1976, it was adapted for CT images.\(^{124}\) In the original paper, Evans examined 53 children and concluded that a value, using the ratio between the frontal horns and the inner diameter of the skull, higher than 0.3 represents ventricular enlargement. Since then, this cut-off value has been applied for the diagnosis of iNPH in older adults. Also, of interest, in the original paper Evans stated that there was less variation in ratio between the frontal horns and the skull, as apposed to just measuring the frontal horns. However, subsequently it was found that this was merely due to a miscalculation and that in fact the opposite was true.\(^{125}\)

In studies on healthy elderly, mean values for Evans Index have varied between 0.25 and 0.31.\(^{119, 126-128}\) In addition, population-based studies have reported prevalence values, of Evans Index higher than 0.3, varying between 6.5 and 16.1 \%.\(^{95-97, 116}\) However, these studies included mainly younger elderly and did not report mean values.

Of further note, the exact method of measuring Evans Index has not been specified. In a study comprising ten iNPH patients, Evans Index was measured at different angles and sections in each patient and a considerable variation was noted.\(^{129}\) Another limitation regarding Evans Index is that it is not a direct measure ventricular volume, instead it might be regarded a surrogate marker. A previous study found that although Evans Index correlated highly with ventricular volume, it was not a reliable estimate of ventricle volume due to a wide prediction interval.\(^{126}\)
Overall, it might be that more advanced imaging of brain- and CSF spaces, such as volumetric analysis using MRI, would be of greater value in the diagnosis of iNPH. In an interesting study, a large representative, population-based sample from Iceland was examined with MRI and clinical evaluations. Ventricle volume and subarachnoid space volume were measured. A large ratio between these two measures was associated with gait disturbance and cognitive impairment. These results suggest that the specific morphology of disproportional ventricular enlargement in relation to the high convexity sulci might better indicate iNPH (As opposed to just measuring ventricle size, which may also capture patients with atrophy to a large extent). Additional studies, using smaller samples, have shown that
measurement of ventricular volume in relation to cortical thickness and subarachnoid space volume might be of value in differentiating iNPH from other neurodegenerative diseases.\cite{130, 131}

Finally it is important to discuss the fact that ventricle size does not appear to correlate with improvement after CSF diversion.\cite{132, 133} If this is true, then it might not be meaningful at all to have a certain defined cut-off for either Evans Index or any other measure of ventricle size. For example, it is not known whether patients with symptoms of iNPH who have values of Evans Index less than 0.3 could respond to treatment.

CSF tap-test
The CSF tap test is a well-known diagnostic test for iNPH. CSF is removed through a lumbar puncture after which the patient is evaluated for possible improvement.\cite{134} The CSF tap test has been used for the diagnosis of iNPH, and prediction of who will benefit from treatment, for several decades. However, the predictive value of the CSF tap test is not precisely known. The exact way of carrying out the test has not been standardized.\cite{42} For example, the amount of CSF removed has varied between 30 and 50 ml. Also, the specific types of clinical evaluations and time between CSF removal and clinical evaluation have varied. Different authors have also used different cut-off criteria for the classifying patients as improved or not. According to a recent systematic review\cite{135} the average sensitivity, for a favorable treatment outcome, was 58 % (ranging from 26 % to 87 %). The average specificity was 75 % (ranging from 33 % to 100 %). Thus, current data suggests that the CSF tap test is not suitable for ruling out patients from treatment and has, an overall, rather limited clinical value.

CSF Infusion tests
Various aspects of CSF dynamics can be measured using so-called infusion tests. More precisely, the resistance of CSF outflow ($R_{\text{out}}$) can be calculated by infusing saline through a lumbar puncture. Increased CSF outflow resistance, i.e. a high $R_{\text{out}}$, has been said to be an important diagnostic marker and predictor of shunt response.\cite{38} It is thus often used in the clinical work-up of iNPH. However, when considering existing data, CSF infusion
studies are probably not reliable for diagnosing iNPH and should not be used for selecting candidates for shunt surgery. Values of $R_{\text{out}}$ that are believed to indicate iNPH, may be found in as many as 25% of healthy elderly. In addition, a more recent, large prospective cohort study found no relation between CSF outflow resistance and outcome after shunt surgery. Therefore, similar to the tap-test, measurement of CSF outflow resistance is probably of limited value.

**Treatment**

Diversion of CSF by a surgically placed shunt catheter is currently the only evidence-based treatment of iNPH. Different methods of CSF drainage can be applied. The most common include placement of a ventriculo-peritoneal shunt, in which the proximal catheter tip is inserted in the lateral ventricles and the distal end within the peritoneal cavity. Similarly, in ventriculo-atrial shunts the proximal tip is within the lateral ventricles, but the distal end is placed in the right atrium of the heart. In lumbo-peritoneal shunts, the proximal end of the catheter is placed within the dura mater in the spinal canal, and the distal end within the peritoneal cavity. Many other locations for shunt placement have previously been described, but have not gained acceptance.

So far most studies on the treatment in iNPH have been non-blinded and made without control groups. High-level evidence, such as randomized controlled trials (RCT’s), has so far been scarce. However, several well-conducted observational studies have indicated that iNPH patients may benefit substantially from shunt surgery. It might also be of interest to point out that the difference between observational studies and RCT’s may possibly be overstated. RCT’s are often considered to be the gold standard of evidence. However, two earlier papers have compared RCT’s to observational studies by examining several different disorders in various research areas. The studies found that the effects estimated by RCT’s and those estimated by observational studies were highly similar.
Of further note, there is one previous RCT that has compared ventriculoperitoneal shunting to placebo. However, the study has so far received surprisingly little attention. In that study, iNPH patients with concomitant Binswanger’s disease were randomized to receive either a standard ventriculoperitoneal shunt, or a ligated shunt. Both patients and caregivers were blinded to the intervention. Three months post-randomization, patients in the treatment arm improved while no improvement was noted in the control group. When the ligated shunts were opened in the control patients they too improved. Despite the fact that only fourteen patients were included, significant differences were detected. The study was stopped early after interim analysis.

One important observational study has provided further evidence for CSF diversion. The study sample consisted of 33 iNPH patients who were inadvertently subjected to a severe delay of treatment (more than six months, due to a major administrative failure of the hospital). These were compared to 69 patients who were treated in normal fashion, within three months. A substantial deterioration occurred in those with delayed treatment, while those treated within three months improved. Although the study actually intended to examine the natural history of iNPH, it may also be regarded as a study on the effect of treatment based on a within-subject design. It is reasonable to assume that that the administrative failure leading to delayed treatment affected patient groups at random. Therefore, the study could be considered a natural experiment, which might allow for causal inference, at least to some extent.

A systematic review, published in 2013, examined 64 studies comprising more than 3,000 patients. According to the results of this paper, the percentage of patients improving after shunt surgery has increased considerably over the past decades. According to the studies published

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D Natural experiments can be described as studies in which randomization is not performed by the researchers, but instead occurs due to an exogenous, chance phenomenon. They can provide important information and allow for causal inference in circumstances when randomization is not ethical or impractical for various other reasons. These types of studies are common in economics.
during the last five years, an estimated 82 % of patients improved after treatment. Moreover, during the past decades, shunt-related mortality, morbidity and revision rates have decreased substantially.

Improved cognition after shunt surgery has been reported in several studies\textsuperscript{43, 148, 149} including a recent meta-analysis\textsuperscript{150} that showed improved global cognitive function as well as enhanced memory and psychomotor speed.

In a European multicenter study, 142 iNPH patients, from thirteen centers in nine countries were included\textsuperscript{151}. All patients were treated with shunt. At follow-up, after one year, 69 % had improved at least one level on the modified Rankin scale\textsuperscript{152} (mRS). Almost one third of the sample improved two or three levels. The percentage of patients being able to live independently increased from 53 %, before surgery to 82 % after. Based on the outcome of an iNPH-scale\textsuperscript{153}, 84 % of the patients were classified as improved (≥ 5 points).

In the SINPHONI-study\textsuperscript{8}, another large multicenter study, consisting of 26 centers in Japan, 100 iNPH patients were treated with a ventriculo-peritoneal shunt. The primary outcome was improvement of the mRS. Secondary outcome measures were based on an iNPH grading scale\textsuperscript{140}, timed “Up & Go” test, and the mini mental state examination (MMSE). Follow-up examinations were conducted at 3, 6 and 12 months after shunt surgery. Almost 70 % of the patients improved at least one level on the mRS. The percentage of patients who improved to mRS ≤ 1 (i.e. no functional impairment) increased from 7 % to 44 % after treatment. The mean value of MMSE increased from 23 to 25 after treatment. Significant improvement was also noted in all other secondary outcome measures.

The SINPHONI-2, a subsequent study, was a prospective randomized controlled trial that included 93 patients from 20 different centers\textsuperscript{154}. Study participants were randomly assigned to receive shunt surgery or conservative management over a three-month period. At follow-up, three months after randomization, 65 % of those treated with a lumbo-peritoneal shunt improved
≥ 1 level on the mRS, compared to only 5% in those with conservative therapy. Almost all other tests of gait, cognition and caregiver burden also indicated significant improvement in the treatment arm. However, it is important to note that the study was neither sham-controlled nor blinded. Nevertheless the findings are important and indicate that CSF diversion is beneficial. Comparing results from the SINPHONI and SINPHONI-2 trials, lumbo-peritoneal shunts seem to have a slightly higher revision rate, but similar safety and efficacy compared to ventriculo-peritoneal shunts.\textsuperscript{155} Head-to-head studies have however so far not been conducted.

Assessment of outcome after shunt surgery

There is no standard measure of outcome in iNPH. Thus improvement after treatment has been defined in different ways in different studies. A commonly used method to evaluate outcome is the mRS. However, it is important to bear in mind that change in mRS is a rather crude outcome measure. This implies that only substantial changes can be detected. It is therefore plausible that the mRS is less prone to placebo-effect and observer bias. Evaluation can also be made using a specific outcome scale for iNPH.\textsuperscript{153} This covers four symptom domains (gait, balance, cognition and urinary incontinence) and includes both ordinal and continuous variables. The scale is calibrated and norm-based. Several other scales\textsuperscript{156, 157} have also been developed, but have not gained acceptance.

Prognosis

Mortality in iNPH patients, treated with shunt, has been found to be approximately two to three times higher than in the general population, and similar to patients with stroke.\textsuperscript{158-160} So far, almost all studies regarding the prognosis in iNPH have been based on convenience samples.\textsuperscript{161-163} Furthermore, there is little data on the natural course, i.e. prognosis in untreated patients.\textsuperscript{164}

As mentioned in the previous section, an earlier study examined the progression of hydrocephalic symptoms in a group of iNPH patients who were unable to undergo treatment due to a severe delay by the hospital.\textsuperscript{144}
The study found that untreated patients deteriorated considerably, with worsening gait and cognition. However, there are currently no epidemiological studies regarding the natural course. Furthermore, it is not known whether treatment with shunt surgery increases survival.

Although cognitive impairment is one of the main symptoms in iNPH, the risk of developing dementia is not precisely known. A recent study from a large registry-based sample consisting of patients with suspected iNPH showed a high risk of cognitive impairment and dementia in both shunted and non-shunted individuals during a follow-up period of over 4 years (46% of shunt responders were eventually diagnosed with dementia).\textsuperscript{165} However, all patients who were diagnosed with iNPH received shunts. Thus, the non-shunted patients had other diagnoses, such as Alzheimer’s disease or vascular dementia. Also, the decision to shunt was based on results from intracranial pressure monitoring which might have biased the results. Nevertheless, the findings indicate that iNPH is an important cause of dementia. Early diagnosis and treatment is probably crucial.
Never before in human history has the population been as aged as currently. Over the last fifty years, the number of older persons has tripled. Furthermore, the number of older persons is expected to triple again over the next fifty years.
2 THE AGING SOCIETY AND THE AGING BRAIN

The world’s older population is increasing rapidly in almost all countries. Currently, approximately 12% of the world’s population is aged 60 years or more. By 2050, this number is expected to increase to more than 21% (Figure 8). Furthermore, the older population is aging as well. The number of persons aged 80 years or more, is projected to triple over the next thirty to forty years. Several major challenges lie ahead for societies throughout the world. However, given improved health and increased longevity, population aging can also be viewed as a success for mankind.

The causes of population aging include decreased mortality, in particular due to decreased tobacco use and decreased mortality from cardiovascular diseases. Declining fertility is also an important cause. Interestingly, there seems to be a continuing trend for decreasing mortality and current data does not support the theory that humans are reaching a theoretical upper age-limit. For more than 160 years, life expectancy in the record-holding countries has been increasing by almost three months per year. Also, based on long-term trends, there is no indication that the increase in life expectancy is abating. Indeed, this raises an intriguing question. What is the maximum life span of a human being?

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E In the year 1800, average life expectancy in Sweden was less than 40 years. In 1900, this number had increased to slightly higher than 50 years. Today, the average life expectancy is more than 80 years (Source: UN Demographic yearbook and Statistics Sweden, SCB).
Potential Social and Economic Consequences

Increased longevity and population aging poses several important economic and societal challenges. Indeed, major interventions are needed to cope with these concerns. Such interventions might be to raise retirement age, decrease benefits or increase taxes. However, the rapid increase in population age is historically unprecedented. Therefore, fundamental reforms with innovative reorganization of health care policies and welfare systems are required.

Population aging has been described as a major threat to societies with potential devastating consequences such as increased suffering and possible
economic collapse. However, some of these worries are probably somewhat overstated. It is important to emphasize that several factors could attenuate the cost of having an older population. For example, decreased fertility can result in an increased workforce. Immigration may possibly also lessen the burden of a diminishing workforce. Similarly, increased retirement age might be an option for at least parts of the population. Another option could be to allow persons to work fewer hours per week in exchange for working more years. Moreover, adherence to healthier lifestyles, including smoking cessation and reduced alcohol intake, might reduce the incidence and cost of various non-communicable diseases. Improved education, and prevention of diseases could further augment healthy aging, reduce disability and associated healthcare costs. Future technological advances can also act to increase health and well-being at lower costs. Also, it seems that individuals are not merely becoming older, but are reaching old age with better health. Furthermore, regardless of economic implications, societies would probably benefit from changing the perceptions on high age, abandon stereotypical views and eliminate discrimination.

Dementia and the aging brain
Dementia and cognitive impairment mainly affects older persons and is one of the most important causes of disability and global burden of disease. Progressive cognitive deterioration with loss of independence has catastrophic consequences for both patients and relatives. Alzheimer’s disease and vascular dementia are the most common causes of dementia. However, there are probably many other neurological disorders (including iNPH) that, in total, also account for a large number of cases of cognitive impairment. Currently, approximately 40 million people around the world suffer from dementia, and the number is expected to double every twenty

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F "Contraception and the Celtic Tiger" is the title of a paper published in 2003, by the Harvard economists David Bloom and David Canning. In 1979, the Irish government lifted their ban on contraception. As a result, fertility decreased suddenly and the dependency ratio, i.e. proportion non-working individuals to working individuals, accordingly decreased. The number of active persons in the workforce rose substantially and the country witnessed a remarkable economic growth.
years, reaching more than 115 million by 2050.\textsuperscript{175} The cost of dementia, in 2010, was estimated to be equivalent of 1 \% of the world's GDP.\textsuperscript{176, 177} However, there are reasons for optimism. For example, the occurrence of dementia seems to be decreasing despite population aging.\textsuperscript{178, 179} Also, more recently possibilities for primary and secondary prevention have been emerging.\textsuperscript{180} As we continue to fill knowledge gaps, hopefully lifestyle changes and enhanced living conditions as well as increase in education and socioeconomic reforms may lead us to a better future with improved well-being throughout higher age.
3  AIM

The overall aim of this thesis was to examine the epidemiology of iNPH. This included the prevalence, risk factors, estimated ventricle size in the general population, and long-term outcome among untreated individuals. The thesis is based a representative population-based sample of men and women aged 70 years or more.

Paper 1
The aim of the first paper was to determine the prevalence of probable iNPH, and occurrence of radiological signs consistent with iNPH.

Paper 2
The aim of the second paper was to examine vascular risk factors and WMLs in relation to clinical and imaging signs of iNPH, using a nested case-control analysis.

Paper 3
In paper three, the aim was to examine ventricle size and provide reference values for Evans Index (a diagnostic marker for iNPH).

Paper 4
The aim of the fourth paper was to study long-term outcome among untreated individuals with probable iNPH and persons with imaging signs of iNPH. Outcomes were mortality, dementia and progression of hydrocephalic symptoms.
4 METHODS AND STUDY DESIGN

Study sample - The Gothenburg Population Studies

The Gothenburg population studies include several representative cohorts, followed for almost fifty years. The studies consist of detailed examinations designed to investigate aging and age-related disorders. All participants were systematically obtained from the Swedish population register based on birth dates, and included people living in private households and in residential care. The examinations comprised physical and psychiatric examinations including laboratory and radiological work-up. Also, house-visits, telephone interviews, close-informant interviews and non-respondent analyses were made. In addition, the studies were complemented with data from the Swedish national inpatient register and Swedish cause of death register. For the present thesis, data from the following cohorts were included.

The Population Studies of Women

The Population studies of women (PPSW)\textsuperscript{181,182} began in 1968 and baseline examinations included women aged 38 to 65 (born between 1914 and 1930). The PPSW is currently still ongoing.

The Longitudinal Gerontological and Geriatric Population Studies and H85 Studies in Gothenburg

The Longitudinal Gerontological and Geriatric Population Studies (H70) and H85-cohorts\textsuperscript{183-186} are population-based cohort studies that began in 1971. Similar to the PPSW, the examinations included comprehensive assessments of somatic and psychiatric disorders, physical examinations including blood test, lumbar puncture, ECG, radiological examinations, anthropometric measurements and data on psychosocial background factors and psychometric tests. The first examinations included 70-year old men and women born in 1901-02. Follow-up examinations have been conducted at various ages. In 1986, a follow-up examination was conducted and the prevalence of dementia was determined with the help of CT imaging of the
At the time, the sample included approximately half of all 85-year-olds in Gothenburg. The cohort examined in 2000 (70-year-olds born in 1930) was merged with PPSW cohort, i.e. they were examined together.

The Nordic Research on Ageing Studies
The Nordic Research on Ageing (NORA)\textsuperscript{187} studies began in 1990 and were conducted in Gothenburg, Sweden, and additional sites in Denmark and Finland. The sample included 75-year-olds at baseline, and follow-up was made five years later at age 80. For the present thesis, only those examined in Gothenburg were included.

Study population in papers I-VI
We merged data from the studies described above, and included all persons who underwent one or more CT examination of the brain between 1986 and 2000. All participants were aged 70 years or more at baseline. An overview of the cohorts is shown in the figure 9.

A total of 3246 individuals were invited to take part and 2182 accepted (response rate 67 %), with no significant difference in response rate between men and women (65 % versus 68 %; p=0.107). Of those who took part in the clinical examinations, 1238\textsuperscript{G} underwent a CT scan of the brain (response rate 58 %; 60 % for men and 56 % for women; p=0.067). The selection of study participants is shown in figure 10. Participants in the CT study were on average slightly younger and performed better on the Mini Mental State Examination (MMSE). There were no significant differences in the prevalence of dementia or major depression between the CT group and non-CT group (table 1). Also, the participants in each cohort were similar to non-participants regarding several demographic factors such as age, sex, marital status, mortality and various psychiatric illnesses. Thus, the sample can considered

\textsuperscript{G} Correction: Subsequently it was noted that two persons had undergone CT imaging but had no other clinical data. These were therefore excluded. Also, one person was found to be less than 70 years at the time of CT. This person was therefore also excluded. After re-analyzing the data, these changes were did not alter any results significantly. However, in paper I results are presented based on a sample of 1238 while subsequent studies included 1235 participants.
representative of the population. However, due to having merged individual cohorts, unbalance occurred in the total data set, in particular regarding age groups and sex. The distribution of the merged sample is shown in table 2.

The sample comprised data from four prospective cohort studies. **NORA = Nordic Research On Ageing, PPSW = Prospective Population study of Women, H85-H90 and H70 = Longitudinal Gerontological and Geriatric Population Studies in Gothenburg, Sweden.** Baseline examination was considered at time of first CT. All persons were aged 70 years or more at baseline. Data from the Swedish National Inpatient Register and the Population Register was available until 2012.

**Figure 9.** Gothenburg population studies, overview of the cohorts included in this study
Figure 10. Selection of study participants (three CT-participants were subsequently excluded)
Table 1. Comparison between CT participants and non-CT participants

<table>
<thead>
<tr>
<th></th>
<th>Non-CT Group (N=944)</th>
<th>CT Group (N=1235)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, %</td>
<td>76.4</td>
<td>72.9</td>
<td>0.067</td>
</tr>
<tr>
<td>Dementia (DSM-III-R), %</td>
<td>12.0</td>
<td>10.8</td>
<td>0.401</td>
</tr>
<tr>
<td>Major depression, %</td>
<td>8.4</td>
<td>6.7</td>
<td>0.136</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>77.2 (6.4)</td>
<td>74.7 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean MMSE score (SD)</td>
<td>26.1 (5.9)</td>
<td>26.8 (5.0)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Legend: DSM-III-R=Diagnostic And Statistical Manual of Mental Disorders, 3rd edition revised, MMSE= Mini-Mental State Examination, SD=Standard Deviation. 
*Two persons were excluded due to complete lack of data. In addition, one individual was subsequently noted to be less than 70 years at baseline. This person was therefore also excluded.
Table 2. Distribution of study participants according to gender and cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Women % (n)</th>
<th>Men % (n)</th>
<th>Total % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H85 Studies (85-year-olds)</td>
<td>18.0 (162)</td>
<td>22.0 (74)</td>
<td>19.1 (236)</td>
</tr>
<tr>
<td>H88 Studies (88-year-olds)</td>
<td>2.6 (23)</td>
<td>2.7 (9)</td>
<td>2.6 (32)</td>
</tr>
<tr>
<td>H90 Studies (90-year-olds)</td>
<td>0.2 (2)</td>
<td>1.8 (6)</td>
<td>0.6 (8)</td>
</tr>
<tr>
<td>NORA Studies (75-year-olds)</td>
<td>1.9 (17)</td>
<td>5.4 (18)</td>
<td>2.8 (35)</td>
</tr>
<tr>
<td>NORA Studies (80-year-olds)</td>
<td>4.4 (40)</td>
<td>11.4 (38)</td>
<td>6.3 (78)</td>
</tr>
<tr>
<td>PPSW/H70 Studies (Ages 70+)</td>
<td>35.7 (321)</td>
<td>0.0 (0)</td>
<td>26.0 (321)</td>
</tr>
<tr>
<td>PPSW/H70 Studies (Ages 70+)</td>
<td>37.2 (335)</td>
<td>56.7 (190)</td>
<td>42.5 (525)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (900)</td>
<td>100 (335)</td>
<td>100 (1235)</td>
</tr>
</tbody>
</table>

Radiological Examinations

Between 1986 and 2000, study participants underwent CT imaging of the brain. All scans were in the transverse plane, and no contrast was used. Three observers, a medical student H, a resident in neurosurgery I, and a consultant in neurology J, collectively made an initial screening assessment of all CT images. The observers were, at the time of the image assessments, unaware of clinical data. Each case was evaluated for hydrocephalic ventricular enlargement, i.e. radiological findings consistent with iNPH. This was based on previous descriptions in the literature 1, 8, 59, 188, and was defined as enlargement of all four ventricles without equivalent widening of cortical sulci or obstruction of CSF flow or structural lesions. Persons with extracerebral mass lesions or other pathologies influencing ventricular morphology were excluded. The presence of WMLs was not considered for the diagnosis. Cases in which ventricular dilation was caused by conditions other than NPH, such as brain atrophy, obstructive hydrocephalus or loss of brain parenchyma were not considered as hydrocephalic ventricular enlargement. Evans Index was measured in all cases, and defined as the ratio between the largest width of the frontal horns and the largest inner diameter of the skull. Occluded sulci at the high convexity (OccSul) was defined as not having any sulcus extending to the midline at the falx cerebri on the two uppermost CT slices. A consultant neuroradiologist K re-evaluated all images that in the initial assessment screened positive for hydrocephalic ventricular enlargement or had uncertain findings. The neuroradiologist made the final diagnosis in all cases.

Diagnosis of iNPH

The diagnosis of iNPH was based on the results of the imaging findings, clinical examinations and data from interviews. This was made in concordance with criteria from the American-European iNPH guidelines. 1

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H Daniel Jaraj (Then medical student, now licensed physician)
I Katrin Rabiei (Then Neurosurgical resident, now specialist in Neurosurgery)
J Carsten Wikkelsø (Consultant physician and Professor of Neurology)
K Christer Jensen (Consultant physician, specialist in Neuroradiology)
History of severe head trauma, meningitis or subarachnoid bleeding were exclusion criteria.

Gait disturbance was assessed by evaluating data from clinical examinations and interviews. Physicians, specializing in geriatrics, performed physical examinations in which a general assessment of gait was made. The examiner graded walking difficulties as non-existent, slight or extensive. Participants had also been asked questions regarding gait and walking difficulties on interviews. Gait disturbance was defined as presence of any walking difficulty on examination and/or presence of self-reported walking difficulty. Cognitive function was evaluated with the Mini Mental State Examination (MMSE). A score of 25 or less was defined as cognitive impairment. Urinary incontinence was assessed by self-report, and defined as involuntary leakage of urine occurring more than once per week.

Probable iNPH was diagnosed in participants who had hydrocephalic ventricular together with gait disturbance and one of either MMSE ≤ 25 or urinary incontinence. Possible iNPH was diagnosed in persons with hydrocephalic ventricular enlargement and at least one other core clinical sign of iNPH, i.e. gait disturbance, MMSE ≤ 25 or urinary incontinence.

Papers I – IV

Paper I
The prevalence of probable iNPH, and radiological signs of iNPH, was calculated by dividing the number of persons with each finding by the total number of study participants. Crude prevalence rates regarding age group and sex were compared using the Fisher’s exact test. In addition, the association between radiological signs, and symptoms of iNPH were examined using multiple binary logistic regression models adjusting for age and sex.
Paper II

In the second paper the relation between WMLs, vascular risk factors and iNPH was examined. Radiologists, unaware of the clinical data, evaluated WMLs on CT. This was made independently of the evaluations for hydrocephalic ventricular enlargement (i.e. by different radiologists). WMLs were defined as low-density areas in the periventricular and subcortical white matter and graded as not present, mild, moderate or severe. In the analyses for the present paper, WMLs were classified as moderate to severe vs not present or only mild. Data on vascular risk factors was obtained from clinical evaluations, interviews and the Swedish National Inpatient Register. This is a validated national health care register that currently records more than 99 % of all hospital discharges in Sweden. Hypertension, diabetes mellitus (type 1 or type 2), stroke/TIA, and coronary artery disease were defined as present if a person had a diagnosis in the national inpatient register, or a self-reported diagnosis as told by a physician. In addition, smoking was classified as past or present cigarette smoking vs never having smoked. Overweight was defined as a body mass index > 25 kg/m².

In the analyses, two groups of cases were defined: Those with hydrocephalic ventricular enlargement (labeled HVe), i.e. imaging findings consistent with iNPH, and those who fulfilled criteria for probable iNPH (labeled suspected iNPH). A nested case-control design was applied. Thus for each case, in both groups, five controls were randomly selected from the total sample. These were matched for age, sex and cohort. The controls consisted of persons without imaging signs of iNPH. Cases and controls were compared using Pearson’s $\chi^2$ test, the Cochran-Mantel-Haenszel test. In addition, in order to examine independent associations for each risk factor, conditional logistic regression models were made.

Paper III

In all cases, the size of the frontal horns of the lateral ventricles was assessed and Evans Index was measured. This was made by the three observers, as described previously. Evans Index was defined as the ratio between the maximum width of the frontal horns and the maximal width of the inner diameter of the skull. Images were also evaluated for findings
consistent with iNPH as described above. All uncertain cases were reevaluated by a neuroradiologist.

Descriptive statistics were examined for the total sample and subgroups based on sex and age. Mean and median values as well as dispersion, distribution and outliers were assessed using the descriptive data, histograms and box-plots. Independent sample t-tests were used to compare mean values between groups. Evans Index was also dichotomized as > 0.3 vs < 0.3 and differences were tested using the Pearson’s $\chi^2$ test. Statistical analyses were made using SPSS version 22.0 (SPSS Inc., Chicago, IL) and R version 3.2.2.\textsuperscript{190}

Paper IV
Baseline examinations were performed between 1986 and 2000. One, or more, follow-up examination was made for all cohorts until 2009 (figure 9). Median follow-up time was 11.5 years (interquartile range 6.5 years) with a maximum follow-up of 25 years. Data was obtained from the somatic and psychiatric examinations, interviews, close-informant interviews and complemented with data from the Swedish National Inpatient Register.

Possible iNPH and probable iNPH was diagnosed in accordance with criteria from international consensus guidelines, as described previously. Dementia was diagnosed by geriatric psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders (third edition, revised) criteria. Date of death was obtained from the Swedish Population Register (National Board of Health and Welfare’s Cause of Death Register). This is a national register that is complete regarding mortality among all Swedish residents both in Sweden and abroad.\textsuperscript{191}

Progression to probable iNPH, from possible iNPH or asymptomatic hydrocephalic ventricular enlargement, was evaluated using criteria the American-European iNPH guidelines. This was made using data from the clinical examinations and the Swedish National Inpatient Register. The development of gait disturbance cognitive impairment or urinary incontinence was also assessed in those with hydrocephalic ventricular enlargement who
were asymptomatic at baseline.

Among those with hydrocephalic ventricular enlargement (n=55), two persons had previously been treated with shunt surgery and were therefore excluded from all analyses. In the analyses, outcomes were examined for all those with hydrocephalic ventricular enlargement. In addition, they were divided into the following subgroups: those with probable iNPH (n=24), and those with possible iNPH or asymptomatic ventricular enlargement (n=29).

The date of the first CT examination was considered as baseline. All comparisons were made with individuals without hydrocephalic ventricular enlargement (n=1180). Crude five-year mortality was compared between groups using the Pearson’s $\chi^2$ test. Mortality and risk of dementia was also examined using Kaplan-Meier survival curves, the Log-rank test and Cox proportional hazard models for each group. The models were adjusted for baseline age, sex, and cohort. In addition, a binary logistic regression models was made to examine the association between hydrocephalic ventricular enlargement (all cases, n=53) and risk of dementia at any time during the study, i.e. baseline and follow-up. Adjustment was made for baseline age, sex and cohort. Statistical analyses were made using SPSS version 22.0 (SPSS Inc., Chicago, IL) and R version 3.2.2.
5 RESULTS AND DISCUSSION

Paper I
The prevalence of iNPH, in the total sample (n=1238) was 2.1 %. Stratifying by age groups, the prevalence was 0.2 % in those aged 70-79 years, and 5.9 % in those aged 80 years or more (Table 3). There was no difference in the prevalence regarding sex. However, the prevalence was strongly related to being older than 80 years (OR 35.5; 95 % CI 4.8-262.7). The prevalence of imaging findings of iNPH is shown in table 4. The relation between symptoms of iNPH and radiological findings is shown in table 5.
Paper I
PREVALENCE

**2.1 %**
PREVALENCE OF PROBABLE iNPH IN THE TOTAL SAMPLE

---

PREVALENCE OF PROBABLE iNPH BY AGE GROUPS

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-79 years</td>
<td>0.2 %</td>
</tr>
<tr>
<td>80 years or more</td>
<td>5.9 %</td>
</tr>
</tbody>
</table>

MORE THAN 1 IN TWENTY AMONG 80-YEAR-OLDS HAD PROBABLE iNPH

---

4.5 % OF THE TOTAL SAMPLE HAD A CT IMAGE CONSISTENT WITH iNPH (HcVe)
Table 3. Prevalence of probable iNPH by age group and gender (N=1238)

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Men % (n/N)</th>
<th>Women % (n/N)</th>
<th>Total % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-79</td>
<td>0.5 (1/208)</td>
<td>0.2 (1/626)</td>
<td>0.2 (2/834)</td>
</tr>
<tr>
<td>80+</td>
<td>7.1 (9/127)</td>
<td>5.4 (15/277)</td>
<td>5.9 (24/404)</td>
</tr>
<tr>
<td>Total</td>
<td>3.0 (10/335)</td>
<td>1.8 (16/903)</td>
<td>2.1 (26/1238)</td>
</tr>
</tbody>
</table>

Legend: n= The number of persons with probable iNPH. N= The number of persons included in this study. Prevalence in 70-79 vs 80+ p <0.001, Prevalence in men vs women p = 0.186

Table 4. Prevalence of Hydrocephalic Ventricular Enlargement (HcVe), Evans Index (EI) > 0.3, and Occluded sulci by sex and age groups (N=1238)

<table>
<thead>
<tr>
<th></th>
<th>Men % (n=335)</th>
<th>Women % (n=903)</th>
<th>Total % (n=1238)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70-79</td>
<td>80+ Tot.</td>
<td>70-79</td>
</tr>
<tr>
<td>HcVe</td>
<td>5.3 (11)</td>
<td>11.0 (9)</td>
<td>23.6 (49)</td>
</tr>
<tr>
<td></td>
<td>(14)NS</td>
<td>(9)</td>
<td>(22)</td>
</tr>
<tr>
<td></td>
<td>(25)</td>
<td>(22)</td>
<td>(31)</td>
</tr>
<tr>
<td>EI&gt;0.3</td>
<td>6.3 (13)</td>
<td>11.0 (14)</td>
<td>23.6 (49)</td>
</tr>
<tr>
<td></td>
<td>(14)NS</td>
<td>(27)</td>
<td>(24)</td>
</tr>
<tr>
<td></td>
<td>(27)</td>
<td>(24)</td>
<td>(16)</td>
</tr>
<tr>
<td></td>
<td>(13)</td>
<td>(24)</td>
<td>(16)</td>
</tr>
</tbody>
</table>

Legend: Data are in percentages

\(a = p<0.005, \quad b = p<0.001: \) differences between sex,
\(NS = p \geq 0.05, \quad c = p < 0.05, \quad d = p<0.001: \) differences between age groups
Table 5. The relation between clinical and CT features of iNPH

<table>
<thead>
<tr>
<th></th>
<th>Gait disturbance</th>
<th>Cognitive impairment</th>
<th>Urinary incontinence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/N)</td>
<td>% (n/N)</td>
<td>% (n/N)</td>
</tr>
<tr>
<td>Reference group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>12.1 (114/941)</td>
<td>8.6 (81/942)</td>
<td>10.3 (77/745)</td>
</tr>
<tr>
<td></td>
<td>HeVe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>61.1 (33/54)</td>
<td>55.6 (30/54)</td>
<td>45.8 (22/48)</td>
</tr>
<tr>
<td>OR (CI)</td>
<td>9.9 (5.2–18.9)</td>
<td>10.1 (4.9–20.7)</td>
<td>7.6 (3.9–14.7)</td>
</tr>
<tr>
<td></td>
<td>EI &gt; 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>34.1 (86/252)</td>
<td>32.1 (81/252)</td>
<td>31.8 (68/214)</td>
</tr>
<tr>
<td>OR (CI)</td>
<td>3.1 (2.2–4.5)</td>
<td>3.5 (2.3–5.3)</td>
<td>4.1 (2.7–6.2)</td>
</tr>
<tr>
<td></td>
<td>Occluded sulci</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>36.9 (24/65)</td>
<td>30.2 (19/63)</td>
<td>25.5 (14/55)</td>
</tr>
<tr>
<td>OR (CI)</td>
<td>4.2 (2.4–7.6)</td>
<td>4.3 (2.1–8.8)</td>
<td>3.3 (1.7–6.4)</td>
</tr>
</tbody>
</table>

Legend: HeVe = Hydrocephalic ventricular enlargement, EI = Evans Index, OccSul = Occluded sulci, n= The number of persons within each CT category with corresponding clinical feature of NPH, N= The number of persons within each CT category examined for the corresponding clinical feature of NPH. Reference group= All persons without radiological features of iNPH. Odds ratios show results from multiple binary logistic regressions of each CT feature on outcome adjusting for age and gender.
This is, to date, the largest population-based study on the prevalence of iNPH. According to the results, more than one in twenty, among 80-year-olds have signs and symptoms consistent with probable iNPH. Furthermore, 4.5 % of the total sample, and almost 9 % of 80-year-olds, had hydrocephalic ventricular enlargement, i.e. radiological findings consistent with iNPH. This finding is important considering that ventricular enlargement might be the earliest sign of iNPH.\textsuperscript{103}

If the results of this study are true, an estimated 700,000 persons in the United States, and two million persons in Europe might be suffering from iNPH. Earlier estimates have shown that less than one in twenty are being treated\textsuperscript{94,104} and the results from this study further indicate that iNPH is highly underdiagnosed and undertreated.

The most important limitation of this study concerns the diagnosis of probable iNPH. The diagnosis was made retrospectively, in a rather crude way, using data from interviews and clinical examinations. Although cases were diagnosed using criteria from international consensus guidelines, there were several important clinical features that were not assessed. Gait disturbance, cognitive impairment and urinary incontinence are common among older persons and often non-specific. Therefore, data on more detailed and specific examinations would have been desirable. However, the diagnostic bluntness might have also lead to an underestimation of the prevalence, as some iNPH patients might only have subtle symptoms. Furthermore, all cases diagnosed with probable iNPH had a rather characteristic CT image, i.e. enlarged ventricles disproportional to the subarachnoid space. In addition, the association between symptoms of iNPH and CT findings were rather strong.

Additional limitations of this study include those that pertain to observational studies in general. These include issues such as low participation rate and possible selection bias. Indeed, these factors might have influenced the results. However, a selection bias and a low participation rate would probably have led to an underestimation of the prevalence. Another limitation is the use of CT. The image quality was not optimal in some of the older scans. This is due to the technical standard at the time they were made. MRI might
have been somewhat better, but was unavailable. Nevertheless, despite several limitations, the results of this study indicate that many older persons have clinical and imaging features of iNPH and are in need of further evaluations. iNPH is probably more common than previously supposed. Given the progressive nature and debilitating symptoms, it is crucial to increase the possibilities for early diagnosis and treatment.
Paper II
In this population-based study, WMLs, Hypertension, diabetes, stroke/TIA and overweight were more common in cases with hydrocephalic ventricular enlargement and suspected iNPH compared to matched controls (Table 6). In the regression models, suspected iNPH was associated with moderate to severe WMLs, while hydrocephalic ventricular enlargement was related to history of hypertension, moderate to severe WMLs, and diabetes (Table 7). Among cases with hydrocephalic ventricular enlargement, all but four persons (51/55, 93%) had hypertension, diabetes, or WMLs on CT. Of those with suspected iNPH, all but two persons (24/26, 92%) had hypertension, diabetes, or WMLs on CT.
Paper II
RISK FACTORS

---

**HVe (Radiological iNPH)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.7 (1.1-6.8)</td>
</tr>
<tr>
<td>WMLs</td>
<td>6.5 (2.1-20.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.3 (1.1-16.3)</td>
</tr>
</tbody>
</table>

**Suspected iNPH (Probable iNPH)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMLs</td>
<td>5.2 (1.1-6.8)</td>
</tr>
</tbody>
</table>

---

**Among cases with radiological iNPH, all but 4 persons, i.e. 97% had hypertension, diabetes or WMLs**
Table 6. Frequency WMLs and vascular risk factors in cases with hydrocephalic ventricular enlargement and suspected iNPH compared to controls

<table>
<thead>
<tr>
<th></th>
<th>Suspected iNPH</th>
<th>HVe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=26)</td>
<td>Controls (n=130)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42.9 (9/21)</td>
<td>21.2 (25/118) (^a)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.0 (3/23)</td>
<td>7.6 (9/118) (^NS)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19.0 (4/21)</td>
<td>30.8 (36/117) (^NS)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>56.5 (13/23)</td>
<td>24.4 (29/119) (^a)</td>
</tr>
<tr>
<td>CAD</td>
<td>18.2 (4/22)</td>
<td>11.0 (13/118) (^NS)</td>
</tr>
<tr>
<td>Overweight</td>
<td>60.0 (3/5)</td>
<td>44.8 (43/96) (^NS)</td>
</tr>
<tr>
<td>Moderate-Severe WMLs</td>
<td>66.7(16/24)</td>
<td>17.5 (21/120) (^b)</td>
</tr>
</tbody>
</table>

HVe=Hydrocephalic ventricular enlargement, iNPH=Idiopathic Normal Pressure Hydrocephalus, TIA=Transient Ischemic Attack, CAD=Coronary Artery Disease, WMLs=White Matter Lesions. 

\(^a\) p<0.05, \(^b\) p<0.001, \(^NS\) p>0.05, \(^*\) p<0.1. p-values are results of Pearson chi-square, cases vs controls. Data are % (n/N): n=Number of persons with corresponding risk factor, N=Number of persons examined for the corresponding risk factor. WMLs were graded on the Gothenburg scale, 0-3 (Not present or only mild = 0-1 vs moderate-severe=2-3).
Table 7. Multivariable analysis of vascular risk factors in hydrocephalic ventricular enlargement and suspected iNPH

<table>
<thead>
<tr>
<th></th>
<th>Suspected iNPH (n=26)</th>
<th></th>
<th></th>
<th>HVe (n=55)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.1 (0.5-8.7)</td>
<td>0.286</td>
<td>2.7 (1.1-6.8)</td>
<td>0.039</td>
<td>2.7 (1.1-6.8)</td>
<td>0.039</td>
</tr>
<tr>
<td>WMLs</td>
<td>5.2 (1.5-17.6)</td>
<td>0.009</td>
<td>6.5 (2.1-20.3)</td>
<td>0.001</td>
<td>6.5 (2.1-20.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2.3 (0.7-7.8)</td>
<td>0.178</td>
<td>0.8 (0.2-3.3)</td>
<td>0.741</td>
<td>0.8 (0.2-3.3)</td>
<td>0.741</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-</td>
<td>-</td>
<td>4.3 (1.1-16.3)</td>
<td>0.031</td>
<td>4.3 (1.1-16.3)</td>
<td>0.031</td>
</tr>
<tr>
<td>Overweight</td>
<td>-</td>
<td>-</td>
<td>1.8 (0.6-5.4)</td>
<td>0.293</td>
<td>1.8 (0.6-5.4)</td>
<td>0.293</td>
</tr>
</tbody>
</table>

HVe=Hydrocephalic ventricular enlargement, iNPH=Idiopathic Normal Pressure Hydrocephalus, OR=Odds Ratio, CI=Confidence Interval, WMLs=White Matter Lesions. WMLs graded on the Gothenburg scale, 0-3 (Not present or only mild = 0-1 vs moderate-severe=2-3). OR’s and p-values show results of conditional logistic regression models. The model for suspected iNPH included history of hypertension WMLs and stroke/TIA. For HVe, the model included History of hypertension, WMLs, Stroke/TIA, Diabetes mellitus and Overweight.
The results of this study suggest that vascular mechanisms might be involved in the pathophysiology of iNPH. The fact that vascular risk factors are common in iNPH might also be important from a clinical standpoint. Health care professionals ought to be aware of the high occurrence of vascular risk factors in iNPH, considering that they are treatable.

The main strength of this study is the population-based sample. Previous investigations regarding the risk factors in iNPH have been made using hospital-based samples. These studies might have included more severe cases and had a higher risk of selection bias, given that cases and controls were selected separately. In the present study, a large representative sample was examined, and a nested case-control analysis was performed. Thus, cases and controls were obtained from the same population. Furthermore, exposure data was collected prospectively from comprehensive clinical examinations and the Swedish National Inpatient Register. Nevertheless there are several important sources of potential bias that should be considered. Similar to the first study in this thesis, there was a diagnostic bluntness regarding the cases. This might have led to bias and confounding. However, the persons included in this study were not scanned due to symptoms or suspicions of iNPH, yet a strong association between imaging signs of iNPH and several vascular factors was found. The group with hydrocephalic ventricular enlargement should theoretically have been subjected to less bias, considering that they were selected solely on the basis of imaging findings by blinded observers. Also, the number of cases was relatively small. A larger sample would probably have provided more precise outcome estimates. Furthermore, the use of CT is an important limitation, in particular regarding analysis of WMLs. MRI would have been better. Although, it has been suggested that CT might be more specific for detection of clinically relevant WMLs. Another important limitation is the fact that the study design does not allow for causal inference. It is not known whether the WMLs cause iNPH, or vice versa. For example, it might be that white matter changes in iNPH are not merely due to small vessel disease, but could also be caused by CSF stagnation or edema due to iNPH. However, it is not particularly common for any single study to, by itself, provide causal
evidence. Thus, it is important to view the results in context. When taking into consideration that several previous, clinical and animal, studies have provided concurring data, the results of this study suggest that vascular disease processes are probably involved in the mechanisms underlying iNPH.
Paper III
Evans Index ranged between 0.11 and 0.46, in the total sample. The mean value was 0.28 (SD 0.04). Descriptive statistics are shown in Table 8. The distribution of Evans Index in the total sample is shown in figure 11.

On average, men had higher values than women, 0.29 vs 0.27 (p<0.001). Also, higher age was associated with larger values of Evans Index in age groups 70-79 years vs 80 years or older (0.27 vs 0.29, p<0.001). The mean value of Evans Index, in men aged 80 years or more was 0.3 (SD 0.03). The number of persons with Evans Index > 0.3, in the total sample was 255 (20.6%). These findings are shown in table 9 and figure 12. The mean value of Evans Index among those with hydrocephalic ventricular enlargement (n=55) was 0.36 (SD 0.04).
More than 1 in 5 individuals above the age of 70 fulfilled current criteria for ventricular enlargement.

The frequency of Evans Index > 0.3 in those aged 85 years or more:

- 70-74 years: 0.27
- 75-79 years: 0.27
- 80-84 years: 0.28
- 85+ years: 0.30

The frequency of Evans Index > 0.3 in the total sample: 20.6%
Figure 11. Distribution of values of Evans Index in the study population
Figure 12. Values of Evans Index by age groups and sex
Table 8. Descriptive statistics for Evans Index in a population-based sample of 1235 men and women aged 70 years or more

<table>
<thead>
<tr>
<th>Descriptive variable</th>
<th>Value (Total sample n=1235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.275</td>
</tr>
<tr>
<td>95 % CI</td>
<td>0.273-0.277</td>
</tr>
<tr>
<td>Median</td>
<td>0.270</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.05</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>0.04</td>
</tr>
<tr>
<td>Minimum-Maximum value of EI</td>
<td>0.11-0.46</td>
</tr>
<tr>
<td>Percentiles</td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>0.22</td>
</tr>
<tr>
<td>10th</td>
<td>0.23</td>
</tr>
<tr>
<td>25th</td>
<td>0.25</td>
</tr>
<tr>
<td>50th</td>
<td>0.27</td>
</tr>
<tr>
<td>75th</td>
<td>0.30</td>
</tr>
<tr>
<td>90th</td>
<td>0.33</td>
</tr>
<tr>
<td>95th</td>
<td>0.35</td>
</tr>
</tbody>
</table>

CI= Confidence Interval, Std. Deviation= Standard Deviation, EI=Evans Index.
Table 9. Mean values of Evans Index and frequency of values higher than 0.3 by sex and age group in a population based sample of 1235 men and women

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>85+</th>
<th>Total sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Evans Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (SD)</td>
<td>0.28 (0.04)</td>
<td>0.29 (0.04)</td>
<td>0.30 (0.03)</td>
<td>0.31 (0.05)</td>
<td>0.29 (0.05)</td>
</tr>
<tr>
<td>Women (SD)</td>
<td>0.26 (0.03)</td>
<td>0.27 (0.04)</td>
<td>0.28 (0.04)</td>
<td>0.29 (0.05)</td>
<td>0.27 (0.04)</td>
</tr>
<tr>
<td>Total (SD)</td>
<td>0.27 (0.03)</td>
<td>0.27 (0.04)</td>
<td>0.28 (0.04)</td>
<td>0.30 (0.05)</td>
<td>0.28 (0.04)</td>
</tr>
<tr>
<td><strong>Evans Index &gt;0.3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men % (n)</td>
<td>23.7 (45)</td>
<td>22.2 (4)</td>
<td>42.5 (17)</td>
<td>48.3 (42)</td>
<td>32.2 (108)</td>
</tr>
<tr>
<td>Women % (n)</td>
<td>10.0 (52)</td>
<td>9.4 (10)</td>
<td>21.4 (18)</td>
<td>35.1 (67)</td>
<td>16.3 (147)</td>
</tr>
<tr>
<td>Total % (n)</td>
<td>13.7 (97)</td>
<td>11.3 (14)</td>
<td>28.2 (35)</td>
<td>39.2 (109)</td>
<td>20.6 (255)</td>
</tr>
</tbody>
</table>
This is the first population-based study to report reference values on Evans Index. Evans Index is extensively used in both research and clinical practice, despite the fact that normal values in adults are not precisely known. A correct, and early diagnosis of iNPH is crucial considering the progressive nature of the disorder. The results of this study indicate that the current cut-off criterion, of 0.3, has a low specificity. The mean value of Evans Index, in the total sample was close to what is currently considered pathological. Also, more than one fifth of the study population would be classified as having ventricular enlargement if the definition of Evans Index > 0.3 is used. Moreover, men aged 80 years or more, had on average, values equal to or higher than 0.3.

One of the main limitations of this study is the fact that Evans Index was measured by non-radiologists. However, considering that Evans Index is a simple linear measure based on rather obvious anatomical structures, it could reasonable to suppose that even non-specialists, i.e. persons with basic training in neurology and neuroradiology, can perform the measurement correctly. Other potential sources of bias may be unbalance in the data and possible cohort effects. In addition, it is important to mention the possibility of selection bias. Among those in the original sample, many did not undergo CT imaging. This might have affected the results. However, when comparing CT-participants vs non-CT-participants, only small differences were noted.
Crude 5-year mortality was higher in those with probable iNPH, compared to individuals without iNPH (87.5 % vs 19.1 %, p<0.001). The crude five-year mortality and adjusted hazard ratios for each group is shown in table 10. Figure 13 shows the Kaplan-Meier survival curves for each group. Mortality was increased in those with probable iNPH (n=24), and in the total group with hydrocephalic ventricular enlargement (n=53) in Cox proportional hazard models. There was no significant difference in mortality between those with possible iNPH/asymptomatic hydrocephalic ventricular enlargement (n=29) and those without imaging signs of iNPH.

The risk of dementia during follow-up, among those with possible iNPH or asymptomatic hydrocephalic ventricular enlargement (n=29), was also examined. In total, 40.0 % of those with possible iNPH or asymptomatic hydrocephalic ventricular enlargement developed dementia, compared to 20.6 % of those without (p=0.019). The estimated hazard ratio for dementia, adjusted for baseline age, sex and cohort, was 2.8 (95% CI: 1.5-5.2). Among all those with hydrocephalic ventricular enlargement (n=53), 68 % (n=36) had dementia at baseline, or developed dementia during follow-up (adjusted odds ratio 4.9; 95% CI: 2.5-9.6, compared to those without imaging findings of iNPH).

Regarding the progression of symptoms, 45 % of those with possible iNPH or asymptomatic hydrocephalic ventricular enlargement developed probable iNPH during follow-up. Only two persons (3.8 %) with hydrocephalic ventricular enlargement remained asymptomatic throughout follow-up.
Paper IV
LONG-TERM OUTCOME

5-YEAR MORTALITY

The hazard ratio for developing dementia during follow-up in those with possible INPH or asymptomatic hydrocephalic ventricular enlargement:

- 2.8 (1.5-5.2)
- 68% of those with hydrocephalic ventricular enlargement had dementia at baseline or at the end of follow-up:
  - Adjusted odds ratio 4.9 (2.5 - 9.6)

- 3.8% of those with hydrocephalic ventricular enlargement, only two persons (3.8%) remained asymptomatic during follow-up.
### Table 10. Mortality among study participants

<table>
<thead>
<tr>
<th>Hydrocephalic ventricular enlargement (HVe)</th>
<th>Individuals without iNPH n=1180</th>
<th>Probable iNPH n=24</th>
<th>Possible iNPH &amp; Asymptomatic HVe n=29</th>
<th>All cases with HVe n=53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted five-year mortality, % (n)</td>
<td>19.1 (225)</td>
<td>87.5 (21)***</td>
<td>27.6 (8) ns</td>
<td>54.7 (29)***</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>-</td>
<td>3.8 (2.4-5.8)</td>
<td>1.2 (0.7-1.8)</td>
<td>1.9 (1.4-2.5)</td>
</tr>
</tbody>
</table>

Legend: iNPH=idiopathic Normal Pressure Hydrocephalus, HVe=Hydrocephalic ventricular enlargement, HR=Hazard ratio, *** p<0.001, ns: p=0.251, p-values show results of Pearson Chi-square test compared to individuals without iNPH. Hazard ratios were estimated using Cox proportional hazard models including age at baseline, sex and study cohort. The group with possible iNPH and asymptomatic hydrocephalic ventricular enlargement included 4 persons who had hydrocephalic ventricular enlargement but missing data regarding symptoms of iNPH.

**Figure 13.** Unadjusted survival curves (Kaplan-Meier), comparing individuals without iNPH (Reference group), persons with possible iNPH (also including those with asymptomatic hydrocephalic ventricular enlargement and missing clinical data) (p=0.284), and individuals with probable iNPH (p<0.001). Groups were compared using the Log rank test.
According to the results of this study, untreated individuals with signs and symptoms of iNPH have a substantially increased risk of mortality and dementia. Furthermore, almost all persons with imaging signs of iNPH developed dementia or other symptoms of iNPH. These findings indicate that imaging signs of iNPH are important markers for cognitive impairment and neurological disability. The results of this study suggest that clinical and radiological signs of iNPH are associated with a markedly poor prognosis with a high risk of death and dementia among untreated persons.

The results of this study also suggest that radiological signs of iNPH might precede clinical symptoms. This has previously been indicated by a study that examined six cases.\textsuperscript{103} If it is true that radiological signs are the first to develop, then current diagnostic criteria might only capture individuals at a later stage when the disorder has manifested with more severe symptoms. Therefore, the results of this study might also have implications regarding the diagnosis of iNPH.

There are no previous epidemiological studies on long-term outcome in iNPH. Previous studies have mainly used hospital-based samples and there is very little data on the natural course. Furthermore, the risk of dementia and progression of symptoms over time is not precisely known.

Main strengths of this study include the population-based sample, comprehensive examinations and duration of follow-up. There are, however, also several important limitations that should be discussed. As described previously, the diagnostic uncertainty regarding iNPH is important to consider. Although this may have influenced the validity of the study, it is also reasonable to suppose that there might have been less bias regarding the associations between imaging signs of iNPH and outcomes. The reason for this is that those with hydrocephalic ventricular enlargement were diagnosed by a consultant neuroradiologist, unaware of clinical data. Therefore, results of this study suggest that imaging findings of iNPH are associated with a poor prognosis regardless of symptoms. Other limitations, that have also been discussed earlier, include unbalance in the data, possible cohort effects and small number of cases. The group with possible iNPH and asymptomatic
hydrocephalic ventricular enlargement (n=29) did not have a significantly increased mortality. These persons were, on average, younger and part of the more recent cohorts, thus having less follow-up time. It is plausible that significant differences might have been detected using a larger sample with longer follow-up. Cases were diagnosed with CT, and MRI would probably have been somewhat better. However, this was not available at the time of baseline examinations. Small obstructive lesions can be missed on CT. Nevertheless, it can be argued that CT imaging allows for an overall sufficient assessment of the ventricles and high convexity sulci.
6 CONCLUSIONS AND FUTURE PERSPECTIVES

iNPH is probably more common than previously supposed. Furthermore, a large number of older persons have imaging features consistent with iNPH. This finding is important considering that radiological features might be an early sign of iNPH.

Many elderly are in need of further evaluations. However, despite being a treatable disorder, the number of persons being diagnosed and treated is likely far less than the actual number of person suffering from iNPH. Considering that life expectancy is rising, the number of patients with iNPH might also increase. There is a need for future studies to improve diagnosis and selection of candidates for shunt surgery.

Vascular factors, such as cerebral WMLs, hypertension and diabetes are rather strongly associated with iNPH. The findings indicate that vascular disease mechanisms are involved in the pathophysiology. Considering also earlier data, a causal association may be supposed. Clinicians ought to be aware of the high occurrence of vascular diseases in iNPH since concurrent management of risk factors is important. The findings may also have importance from a perspective of preventive measures. Future studies should aim to further elucidate the role of vascular mechanisms in iNPH. This might not only improve understanding of the pathophysiology but also provide insight into disease features that might be of diagnostic importance. It is also important to learn more about potential causes in order to improve treatment. Also, future investigations regarding other mechanisms including non-vascular risk factors would be of value.

Mean values of Evans Index, among older persons in the general population, are higher than previously reported. Current criteria for ventricular enlargement might capture as many as one in five, of those aged 70 years or more. Thus, the current cut-off value of 0.3 probably has a low specificity for
the diagnosis of iNPH. Persons with hydrocephalic ventricular enlargement had, on average, values above the 95th percentile. However, it is difficult to determine diagnostic cut-off values. For example, it is not known whether or not persons with Evans Index below 0.3 could still have iNPH. Considering that ventricle size does seem not predict outcome after shunt surgery, more advanced imaging such as volumetric assessment of the ventricles, subarachnoid space and cortical thickness might be of greater value. Given the risks of shunt surgery, a correct diagnosis of iNPH is crucial. However, previous attempts to predict shunt response based on various hydrodynamic characteristics have so far been rather futile. Further research on clinical variables and other imaging features, such as white matter changes, blood flow and metabolism might add more knowledge and insight. Also, considering the high degree of overlap between iNPH and other neurodegenerative conditions, future studies on diagnostic measures should include not only iNPH patients and healthy controls, but also patients with other diagnoses such as Alzheimer’s disease and vascular dementia. It is also important for future studies to have adequate power given the heterogeneity of iNPH.

Untreated individuals who fulfill criteria for probable iNPH have substantial excess mortality. Considering these findings, individuals with signs and symptoms of iNPH should be thoroughly evaluated and treated without delay if the diagnosis is confirmed. Furthermore, persons with radiological signs of iNPH appear to have a very high risk of developing dementia or other symptoms. Radiological signs are therefore probably more important than previously thought. It remains to be elucidated whether pre-symptomatic iNPH should be treated. Additional epidemiological studies, using population-based data, are needed in the field. However, given the estimated prevalence of iNPH, even relatively large samples would likely yield a somewhat small number of cases. One way to circumvent this problem might be to merge population data from several centers.
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