Comorbidity and vascular risk factors associated with Idiopathic Normal Pressure Hydrocephalus

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Umeå University 2016
Comorbidity and vascular risk factors associated with idiopathic normal pressure hydrocephalus:

The INPH-CRasH Study

Hanna Israelsson Larsen
Framför allt som skall bevaras må du bevara ditt hjärta, ty därifrån utgår livet.

Ords. 4:23 (1917)
Keep thy heart with all diligence; for out of it are the issues of life.

Proverbs 4:23 (KJV)
...imagination is thus a constitutive part of all thinking. There is no sharp distinction between the region of poetry and the region of science. Both alike are not ends in themselves, but means to higher ends.

Henry Havelock Ellis, 1859-1939
British physician, psychologist and author

...and above all, watch with glittering eyes the whole world around you because the greatest secrets are always hidden in the most unlikely places. Those who don’t believe in magic will never find it.

British author
ABSTRACT

Idiopathic normal pressure hydrocephalus (INPH) is a dementia treatable by insertion of a cerebrospinal fluid shunt. It has been suggested that INPH has similar pathophysiological mechanisms as cerebrovascular disease, but the vascular risk factor (VRF) profile of INPH patients has not been assessed using a modern epidemiological approach. The cognitive symptoms of INPH resemble the symptoms of depression, but the prevalence of depression among INPH patients is unknown. In addition, few studies investigate the impact of shunting on the quality of life (QoL), and no study has investigated the impact of comorbidity on QoL in INPH patients.

The objective of this dissertation was to present the VRF profile of INPH and to investigate the hypothesis that INPH may be a subgroup of vascular dementia. Additional objectives were to assess the prevalence of depression in INPH patients and to investigate the impact of shunting and comorbidities on QoL in INPH.

In the first cohort, the prevalence of possible INPH was assessed through clinical and radiological examinations in patients with a transient ischemic attack (TIA), consecutively admitted to the same hospital during 2006-2008. In the second cohort, VRFs, vascular disease and QoL were analysed in INPH patients consecutively shunted 2008-2010 in five out of six neurosurgical centres in Sweden. Patients remaining after inclusion (n=176, within the age-span 60-85 years and not having dementia) were compared to population-based age- and gender-matched controls (n=368, same inclusion criteria as for the INPH patients). Assessed VRFs were: hypertension, diabetes, obesity, hyperlipidemia, psychosocial factors (stress and depression), smoking, alcohol intake, physical activity and, dietary pattern. Cardiovascular, cerebrovascular and peripheral vascular disease as well as QoL were also assessed. Parameters were assessed through questionnaires, clinical examinations, measurements, ECG and, blood samples.

In the first cohort, 4% of the TIA patients had clinically and radiologically verified INPH. In the second cohort, VRFs were overrepresented among the INPH patients compared with the controls. The VRFs independently associated with INPH were: hyperlipidemia (Odds ratio (OR): 2.4, 95%CI: 1.4-4.0), diabetes (OR: 2.2, 95%CI: 1.2-3.9), obesity (OR: 5.4, 95%CI: 2.5-11.8) and, psychosocial factors (OR:
5.3, 95%CI: 3.2-8.9). When adding the VRFs that were overrepresented in INPH, although not independently (physical inactivity and hypertension), these six VRFs accounted for 24% of the INPH cases in the elderly population (population attributable risk %: 24). Depression was overrepresented in shunted INPH patients compared to the controls (46% vs. 13%, p<0.001) and the main predictor for low QoL was a coexisting depression (p<0.001).

In conclusion, the results of the INPH-CRasH study are consistent with a vascular pathophysiological component of INPH and indicate that INPH may be subgroup of vascular dementia. In clinical care and research, a complete risk factor analysis as well as screening for depression and a measurement for quality of life should be included in the work-up of INPH patients. The effect of targeted interventions against modifiable VRFs and anti-depressant treatment in INPH patients should be evaluated.
Idiopatisk normaltryckshydrocefalus (INPH, från engelskans ”idiopathic normal pressure hydrocephalus”) är en neurokirurgiskt behandlingsbar demens. Behandlingen är att operera in en shunt som dränerar cerebrospinalvätska från ventriklarna. Det har föreslagits att INPH skulle kunna orsakas av liknande patofysiologiska mekanismer som vid cerebrovaskulär sjukdom, men den vaskulära riskfaktorprofilen hos INPH-patienter har aldrig undersömts i en modern epidemiologisk studie. De kognitiva symtomen vid INPH påminner om symtomen vid depression, men prevalensen av depression hos INPH-patienter är okänd. Få studier undersöker hur shuntning påverkar livskvalitet och ingen studie har undersökt hur komorbiditet påverkar livskvaliteten vid INPH.

Syftet med den här avhandlingen var att undersöka den vaskulära riskfaktorprofilen hos INPH-patienter samt att utforska hypotesen att INPH skulle kunna vara en undergrupp till vaskulär demens. Ytterligare ett syfte med avhandlingen var att undersöka hur många INPH-patienter som har depression samt undersöka hur shunting och komorbiditet påverkar livskvalitet vid INPH.


I den första kohorten hade 4% av TIA-patienterna kliniskt och radiologiskt verifierad INPH. I den andra kohorten var vaskulära riskfaktorer överreprenteade hos INPH-patienterna jämfört med
normalpopulationen. Hyperlipidemi (OR: 2.4, 95%CI: 1.4-4.0), diabetes (OR: 2.2, 95%CI: 1.2-3.9), fetma (OR: 5.4, 95%CI: 2.5-11.8) och psykosociala faktorer (OR: 5.3, 95%CI: 3.2-8.9) var associerade med INPH oberoende av kön, ålder och de andra riskfaktorerna. Hypertension och fysisk inaktivitet var också associerade med INPH, dock inte oberoende av övriga riskfaktorer. Sammanlagd PAR% (från engelskans: population attributable risk %) för de här sex riskfaktorerna var 24%. INPH-patienterna hade depression i högre utsträckning än kontrollerna (46% vs. 13%, p<0.001), och depression var den viktigaste prediktorn för låg livskvalitet.

Resultaten tyder på att vaskulär sjukdom och vaskulära riskfaktorer är involverade i den patofysiologiska mekanismen vid INPH. INPH kan vara en undergrupp till vaskulär demens. En fullständig riskfaktoranalys och screening för depression bör ingå i den preoperativa utvärderingen såväl som i forskning på INPH-patienter, och ett mått på livskvalitet bör införas. Effekten av riktade insatser mot såväl vaskulära riskfaktorer som depression vid INPH bör utvärderas.
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<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimers Disease</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Life</td>
</tr>
<tr>
<td>ApoA</td>
<td>Apolipoprotein A</td>
</tr>
<tr>
<td>ApoB</td>
<td>Apolipoprotein B</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CRasH</td>
<td>Co-morbidity and Risk factors ASsociated with Hydrocephalus</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CVD</td>
<td>Cerebrovascular Disease</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>EI</td>
<td>Evans Index</td>
</tr>
<tr>
<td>EQ5D5L</td>
<td>EuroQol Five Dimensions Five Levels</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial Pressure</td>
</tr>
<tr>
<td>INPH</td>
<td>Idiopathic Normal Pressure Hydrocephalus</td>
</tr>
<tr>
<td>LVD</td>
<td>Large vessel disease</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
</tr>
<tr>
<td>N/A</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NPH</td>
<td>Normal Pressure Hydrocephalus</td>
</tr>
<tr>
<td>NS</td>
<td>Non significant</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PAR%</td>
<td>Population Attributable Risk Percent</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>R\text{\textsubscript{out}}</td>
<td>Resistance to outflow</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SHQR</td>
<td>Swedish Hydrocephalus Quality Register</td>
</tr>
<tr>
<td>SVD</td>
<td>Small Vessel Disease</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>VaD</td>
<td>Vascular Dementia</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>VP shunt</td>
<td>Ventriculoperitoneal shunt</td>
</tr>
<tr>
<td>VRF(s)</td>
<td>Vascular Risk Factor(s)</td>
</tr>
<tr>
<td>WML</td>
<td>White Matter Lesions</td>
</tr>
<tr>
<td>WTH</td>
<td>Waist-To-Hip</td>
</tr>
</tbody>
</table>
ORIGINAL PAPERS

This dissertation is based on the following papers, which are referred to by their Roman numerals in the text:


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** Reprinted with permission from Wolters Kluwer Health Lippincott Williams & Wilkins.
INTRODUCTION

Idiopathic normal pressure hydrocephalus (INPH) is a disease occurring in the elderly population\(^1\)\(^-\)\(^3\). The cause is unknown but most likely multifactorial. Vascular disease and its risk factors in combination with disturbances of the cerebrospinal fluid (CSF) hydrodynamics have been suggested as causative agents\(^2\)\(^-\)\(^7\). The cardinal symptoms of INPH are disturbances in gait and balance, urinary incontinence and cognitive deterioration\(^1\). The symptoms are relieved in 60-80\% of INPH patients by the insertion of a shunt that drains CSF from the ventricles of the brain\(^8\)\(^-\)\(^12\). The disease is probably both underdiagnosed and undertreated\(^13\)\(^-\)\(^16\). A recent review reported the pooled prevalence of INPH to be 1.3\% in the elderly population, while the prevalence of shunting was much lower\(^13\). According to reports from the World Health Organization (WHO), the number of elderly is expected to escalate rapidly and nearly triple from 524 million to about 1.5 billion in 2050, representing 16\% of the world’s population\(^17\). Accordingly, the number of elderly with INPH is likely to increase, with unnecessary suffering for the patients and rapidly increasing health-care expenditures for society if the disease is not acknowledged and treated appropriately\(^16\).

INPH occurs in the elderly, who are prone to several coexisting diseases and conditions\(^18\). In addition, the clinical symptoms of INPH resemble those of many other conditions that frequently occur among the elderly\(^1\), \(^3\), \(^18\). Thus, the differential diagnostic process and assessment of comorbidities are essential aspects of both research and clinical care to optimize the treatment of the patients\(^1\), \(^3\), \(^18\).

Vascular dementia (VaD) is one of the most important differential diagnoses and comorbidities when considering INPH\(^1\), \(^18\)\(^-\)\(^21\). Vascular disease is common in INPH patients, and it has been hypothesized that vascular disease may be involved in the pathogenesis of INPH\(^4\), \(^7\), \(^19\), \(^22\)\(^-\)\(^25\). Vascular disease is normally preceded by vascular risk factors (VRFs). However, the VRF profile in INPH is not well understood. The few studies investigating risk factors in INPH included too few participants and did not use representative controls\(^5\), \(^6\), \(^26\), \(^27\). The small sample size and the lack of population-based controls represent two of the major shortcomings in most research regarding INPH. Although the results of such small studies may be interesting and hypotheses-generating, large epidemiological studies are needed to further our understanding of
INPH. Such studies should be hypotheses-driven, with correct epidemiological design, and include large enough cohorts of patients to reach sufficient power to prove or reject the investigated hypotheses. Recently, there was a call for large risk factor studies in INPH\textsuperscript{(18)}.

Another short-coming in research regarding INPH is that many studies only investigate specific separate entities, and thus fail to acknowledge the multifactorial aspects of the disease. For example, depression is one of the most common and underdiagnosed comorbidities in the general elderly population and is even more common among elderly with dementia\textsuperscript{(28-31)}. However, the prevalence of depression in INPH patients is unknown. Few studies focused on the cognitive aspects of INPH have assessed the prevalence of coexisting depression. If a patient with INPH is also suffering from depression, this will logically also affect the patient’s cognitive state, the results of different cognitive tests, and his/her cognitive outcome after surgery.

In this dissertation, a large number of shunted INPH patients are compared with age- and gender matched representative controls from the normal elderly population. Comorbidities such as depression and cerebrovascular, cardiovascular and peripheral vascular disease are presented, as well as an extensive VRF profile. In addition, the impact of these diseases and risk factors on the quality of life (QoL) in INPH patients is investigated.

I hope that you will enjoy reading the dissertation; I certainly enjoyed writing it.
BACKGROUND

Vascular risk factors and disease

Overview

Worldwide, cardiovascular disease is the main cause of death, followed by cerebrovascular disease (CVD)\(^{32-34}\). Two of the largest risk factor studies, INTERHEART and INTERSTROKE, demonstrated that nine VRFs account for 90% of all myocardial infarctions, and ten VRFs account for 90% of all strokes\(^{33,34}\). The VRFs are as follows: smoking, hypertension, diabetes, high alcohol intake, abdominal obesity, low physical activity, hyperlipidemia, psychosocial factors, dietary pattern and, cardiac causes (risk factor solely for stroke).

Risk factors

In general, a risk factor is defined as a factor/determinant or predisposing condition that influences or enhances the probability of a specific disease or outcome\(^{35}\). Determinants that can be modified by intervention may be referred to as “modifiable risk factors”\(^{36}\). Coexisting risk factors often act synergistically\(^{32}\). Thus, when describing risk factors it may be more meaningful to refer to a “global” or “total” risk factor profile or score, rather than just individual risk factors\(^{18}\).

When an individual develops a vascular disease such as myocardial infarction or stroke, the disease process starts insidiously, with exposure to various VRFs over the course of several years. Eventually this exposure leads to subclinical organ damage, and it ultimately manifests itself as organ damage and an established vascular disease (figure 1)\(^{18,32}\). Thus, when symptoms appear, the vascular disease is often already at an advanced stage\(^{32}\). Most VRFs are modifiable, either through changes in life style or medication. The best and most cost-effective possibility to intervene and stop the disease progression is at the risk factor level, before the organs get damaged, i.e. primary prevention\(^{32,36}\). However,
secondary and tertiary prevention also reduces the progression of the disease and prevents the organs from becoming more severely damaged\(^{(37)}\).

**Large and small vessel disease**

Ischemic CVD can be subdivided into large vessel disease (LVD; caused by damage to the arteries, e.g. stroke, transient ischemic attack (TIA)) and small vessel disease (SVD; caused by damage to the arterioles and capillaries, e.g. lacunar infarctions, microbleeds, deep white matter lesions (WML))\(^{(38-40)}\) (figure 1). The pathophysiology of LVD, with atherosclerosis of the large vessels precipitated by VRFs, is well described in the literature. Since several manifestations of SVD (especially WML) are common comorbidities in idiopathic normal pressure hydrocephalus (INPH)\(^{(18)}\), the suggested pathophysiology of SVD will now be described in more detail.

In SVD, the role of VRFs is not completely understood. Age, LVD, diabetes and hypertension are reported as strong risk factors, and there is also an association with hyperlipidemia and chronic kidney disease (CKD)\(^{(39, 41-45)}\). The suggested underlying multifactorial pathophysiological mechanisms of SVD is that damage to the endothelium of the capillaries and arterioles in the frontal subcortical areas of the deep white matter in the brain leads to an increased vascular permeability and impaired autoregulation, which causes a chronic leakage of fluid into both the vessel walls and the deep white matter\(^{(39, 42, 45)}\). This excess fluid triggers an inflammatory response in the vessels and the surrounding environment which causes the small vessels to thicken and stiffen, leading to an impaired blood flow\(^{(39, 42, 44)}\). Subsequently, less oxygen and nutrients are transported to the brain, creating a state of chronic ischemia and reduced metabolism in the deep white matter. Additionally, less toxic metabolites and waste products are transported away from of the brain, leading to the accumulation of toxic waste products, which exacerbates the inflammatory response and endothelial failure even further\(^{(39, 40)}\). In the later disease stages, luminal narrowing and occlusion occurs, precipitating even worse ischemia and infarction\(^{(39, 42)}\). Patients with SVD may present as subcortical VaD, with lacunar infarctions, extensive amounts of WML and microbleeds, preferably in the prefrontal subcortical circuit\(^{(38, 40)}\). In subcortical VaD, the clinical symptoms resemble the symptoms of INPH\(^{(18, 38, 46)}\), and depression is common\(^{(38)}\).
The CSF system

The brain is contained in a cavity of approximately 1500 ml and surrounded by cerebrospinal fluid (CSF). The intracranial space contains 100-150 ml CSF\(^{(47)}\). CSF is produced primarily by the choroid plexus in the lateral ventricles, and is traditionally thought to be reabsorbed into the venous blood through the arachnoid granulations, located in the sinus sagittalis superior and lateral lacunae\(^{(47)}\). Several more sites may be involved in the absorption and clearance of CSF, such as the spinal arachnoid villi and lymphatic pathways (cervical and spinal)\(^{(47, 48)}\). Reabsorption may even occur at the cellular level of the blood-brain-barrier\(^{(48,50)}\). It has been suggested that the capillaries in the brain tissue may be a major site of CSF absorption\(^{(51)}\). For the traditional view of the CSF flow, see figure 2.

![CSF circulation diagram](image)

**Figure 2. Schematic overview of the CSF circulation.**

CSF flows from the lateral ventricles into the third ventricle via the foramen of Monro, to the fourth ventricle via the aqueduct of Sylvius and into the spinal cavity and the subarachnoid space via the foramina of Luschka the foramen of Magendie\(^{(47)}\).

Approximately 500 ml CSF is both produced and reabsorbed per day\(^{(52, 53)}\). The reabsorption of CSF is regulated by the intracranial pressure (ICP) and venous pressure, as well as the resistance to outflow \(R_{\text{out}}\)\(^{(53)}\).
(small panel, figure 2), thus maintaining a steady state ICP, as described by Davson’s equation:\(^{(54)}\):

\[
CSF \text{ absorption rate} = \frac{(ICP - \text{Venous pressure})}{R_{\text{out}}}
\]

In addition to this steady state ICP, there is a pulsatile flow of CSF, originated in the cardiac cycle. The Monroe-Kellie doctrine states that a volume increase in any of the components in the intracranial compartment (blood, CSF, brain tissue) must be compensated for by a reduction in the other volumes\(^{(53)}\). The ability of the intracranial compartments to accommodate an increase in volume by redistribution is called compliance. For each heartbeat, the volume changes in the vessels are transmitted to the CSF, generating ICP pulsations of different amplitudes, which drive the CSF circulation and redistribution\(^{(53)}\). In healthy blood vessels, this pulse wave originated in the heart is dampened by elasticity in the aorta and vessel walls. The large vessels expand in systole, thus storing a small fraction of blood, and return to their original size in diastole, thus passing along the stored blood and maintaining blood flow all the way along the vessel tree through the entire cardiac cycle. This is referred to as the Windkessel effect. Through the capillaries in the brain, blood flow is more or less continuous\(^{(55)}\).

**Hydrocephalus – a disturbance in the CSF system**

**Historical overview**

The word hydrocephalus is originated from the Greek words υδωρ (hydor, water) and κεφαλη (kephalos, head)\(^{(56)}\). The term is used for conditions where there is an excess accumulation of CSF within the ventricles of the brain. Hippocrates (466-377 BC) was the first to describe and name the disease. He and other early and medieval physicians believed that hydrocephalus was caused by an extracerebral accumulation of fluid\(^{(56)}\).

In the Renaissance, dissection on humans was permitted after a 2000-year prohibition, and the first known illustration of the ventricular system in the human brain was published by Leonardo da Vinci (1452-
1519) (figure 3). One generation later, Andreas Vesalius (1514–1564) described that the excess fluid in hydrocephalus was deposited in an intra- rather than extracerebral manner\(^{(56, 57)}\). In 1914, Dandy and Blackfan were the first to classify hydrocephalus as communicating or non-communicating\(^{(57)}\) (figure 4). The first shunt draining CSF from the ventricles was inserted in 1905, but it was not until in the 1950s that the first silicone shunt with a unidirectional shunt valve was introduced, representing a significant advancement in the treatment of hydrocephalus\(^{(56, 57)}\).

Among neurosurgeons, hydrocephalus was considered to be a disorder of high ICP and acute onset. However, in 1965, Hakim and Adams described three cases of patients with normal ICP, ventriculomegaly and symptoms of gait disturbance, urinary incontinence and cognitive deterioration who improved after the insertion of a shunt\(^{(58)}\). All of these cases had hydrocephalus due to a known cause, i.e. secondary hydrocephalus. The term idiopathic normal pressure hydrocephalus (INPH) was introduced in 1975 by Shenkin et al\(^{(59)}\).

**Classification**

![Figure 4. Classification of hydrocephalus.](image)

Hydrocephalus is still commonly divided into communicating and non-communicating (figure 4). In non-communicating hydrocephalus, there is a macroscopic obstruction somewhere along the CSF route, causing an elevated ICP. With communicating hydrocephalus, there is no such obstruction and the ICP is normal, thus the term normal pressure hydrocephalus (NPH). Reference values for normal ICP in elderly have been suggested to be between 8-14 mmHg\(^{(52)}\). Idiopathic NPH is by definition normal pressure hydrocephalus without a previous known
cause\(^{(1)}\). However, since almost all hydrocephalus cases have a somewhat obstructive component even though it may not be radiologically visible, an alternate definition has been suggested, describing hydrocephalus as “an active distension of the ventricular system of the brain resulting from inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation”\(^{(60)}\).

**Idiopathic Normal Pressure Hydrocephalus (INPH)**

**Clinical features**

INPH affects elderly individuals and is equally common in both sexes. The disease onset is insidious and the mean age at onset is about 70 years\(^{(1-3, 10, 61)}\). The first and most prominent symptom is a gradually developing symmetrical gait and balance disturbance\(^{(1, 2)}\). INPH patients have a hypokinetic gait with a broad base and toes pointing outward, short steps and low foot-floor elevation, as if the patient’s feet are “glued to the floor”. The patients’ movements are hesitant, and they often have difficulties in turning and may tend to sway and fall\(^{(1, 2, 18, 62)}\). The second typical symptom is cognitive decline, which may vary from very subtle changes to manifest dementia. The cognitive profile in INPH is characterized by mental slowness, psychomotor slowing, executive dysfunction and impaired information processing, learning and memory, indicating that the frontal-subcortical pathways are affected\(^{(1, 18, 63, 64)}\). This pattern is similar to that observed in VaD, indicating a possible vascular genesis of the cognitive aspect of INPH\(^{(18)}\). The third symptom of INPH is urinary problems, manifesting as urgency, increased frequency and incontinence\(^{(1, 2)}\). The disease is progressive, with worsening of the clinical symptoms over time\(^{(65)}\).

**Diagnosis**

In 2005, the international guidelines for diagnosing INPH were developed and published\(^{(1)}\). The guidelines suggest that INPH should be considered as a differential diagnosis of any unexplained disturbance in gait, continence or cognition with insidious onset in adults, and recommend that INPH should be classified as “probable”, “possible” or “unlikely” based on the patient history, physical examination and radiological features\(^{(1)}\). In 2008, the Japanese guidelines, using somewhat different criteria, were published\(^{(66)}\) (in English 2012\(^{(67)}\)), but they have not reached the same level of global acceptance as the 2005 international guidelines.
Radiological features
For all individuals clinically presenting as possible INPH, computed tomography (CT) or magnetic resonance imaging (MRI) (preferable) of the brain should be performed. Radiologically, INPH patients present with ventriculomegaly (Evans Index (EI) >0.3, defined as the ratio of the maximal diameter of the frontal horns to the maximal internal diameter of the skull\(^{(66)}\) not attributable to atrophy or congenital enlargement\(^{(1,2)}\). There should be no radiologically visible obstruction to CSF circulation\(^{(1)}\). Almost all INPH patients have WML\(^{(3)}\). A pattern of disproportionally enlarged subarachnoid space hydrocephalus (DESH) where the sylvian fissures are widened out of proportion to the cortical sulci have been described\(^{(69)}\).

Predictive tests for outcome of surgery
After confirming an INPH diagnosis, there are several predictive tests to investigate whether a patient is likely to benefit from a shunt. Specific supplementary tests may increase the predictive accuracy to greater than 90\%\(^{(70)}\). These tests can roughly be divided in two categories\(^{(2,53)}\):

1. Tests that measure parameters describing the CSF dynamic system (e.g. infusion tests measuring \(R_{\text{inf}}\)\(^{(53)}\)).
2. Tests that simulate shunting and evaluate clinical response (short- or long-term drainage of CSF\(^{(53)}\)).

Predictive tests should not be used for the diagnosis of INPH\(^{(4)}\), and for patients with a clinical and radiological picture typical of INPH, predictive tests may not be necessary. Predictive test results may be more important in atypical cases\(^{(2)}\). Clinically, the burden of comorbidity is also important to evaluate in the pre-operative decision-making.

Differential diagnoses
Identifying other possible explanations for the clinical or radiological appearance of INPH is essential in the diagnostic process\(^{(4)}\). VaD is one of the most important differential diagnoses\(^{(1,18-20)}\), but the symptoms of INPH can resemble several other common conditions in the elderly population\(^{(1,18)}\). Other important differential diagnoses include neurodegenerative disorders (e.g. AD and Parkinson’s disease), other hydrocephalic disorders (e.g. aqueductal stenosis), and several others conditions (e.g. musculoskeletal conditions, urinary conditions, and psychiatric disorders)\(^{(1,18)}\).
**Treatment**

INPH is considered the only neurosurgically treatable dementia. Treatment is insertion of a shunt that drains CSF from the ventricles to a cavity with lower pressure\(^{(2, 71)}\). A ventriculoperitoneal (VP) shunt is the most commonly used system (figure 5)\(^{(3)}\). Another type of shunt is the lumbo-peritoneal shunt, most frequently used in Japan\(^{(72)}\). There is no common pharmacological treatment for INPH. Interestingly some small studies have reported a positive outcome in INPH patients after treatment with acetazolamide\(^{(73, 74)}\).

**Outcome of surgery**

The outcome after surgery in INPH patients is most commonly measured by improvements in gait, which is the symptom with the highest improvement potential, improved in 60-80% of the patients\(^{(8-11)}\). Although all of the symptoms of INPH may improve following shunt surgery\(^{(5)}\), improvements in cognition are often somewhat less\(^{(75, 76)}\). A recent review investigated neuropsychological performance after shunting and found that while shunting improved global cognition, learning, memory and psychomotor speed, improvements in executive function was more uncertain\(^{(77)}\). A recently published practice guideline recommend that shunting may be offered as a treatment for subjective problems in gait, but since the procedure is associated with potential complications (recent studies describe complication rates of 15-28%, with a risk of 11% for serious adverse events), a thorough risk-benefit analysis must be performed before shunting\(^{(12)}\).

There is no consensus regarding the long-term outcome of shunting in INPH patients. Some studies have reported a poor long-term improvement rate of 20-40%\(^{(8, 9, 63)}\), while other studies have noted a sustained positive outcome in 74-87% of the patients for as long as seven years after shunting\(^{(78, 79)}\). Severe or long-standing dementia is a predictor for poor response to shunt surgery\(^{(2)}\). The more severe the symptoms, the less likely they are to improve with a shunt\(^{(80)}\).
Quality of life after shunting in INPH patients

QoL is a subjective, multidimensional concept, defined as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns”\(^{(81)}\). Most physicians agree that one of the main goals of surgery should be to improve QoL, and in recent years, dementia research has highlighted the importance of measuring QoL to evaluate the effect of a treatment in elderly individuals\(^{(82-85)}\). However, QoL in INPH patients is seldom assessed. One population-based study reported that INPH patients before surgery have a lower QoL than the general elderly population\(^{(86)}\) but very little is known about QoL after shunting. Before the INPH-CRasH study was conducted, there were some indications that surgery might improve QoL, based on the results from one small QoL study and some studies assessing indirect QoL parameters\(^{(20, 87, 88)}\). Since then, two more studies have been published\(^{(89, 90)}\) (table 1).

### Epidemiology

The exact number of elderly individuals with INPH is unknown. Prevalences of 0.02-14% have been reported in different populations (table 2). Most authors agree that INPH is probably both an underdiagnosed and undertreated condition\(^{(13-16)}\). A recent review found a pooled prevalence of 1.3% of INPH in people >65 years and an incidence of 0.12%, while the pooled incidence of shunt surgery was only 0.002%/year\(^{(13)}\).

<table>
<thead>
<tr>
<th>First author, year</th>
<th>INPH</th>
<th>Controls</th>
<th>Follow-up</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katzen, 2011(^{(87)})</td>
<td>n=12</td>
<td>n=9</td>
<td>6 months.</td>
<td>Surgery may improve QoL (not significant).</td>
</tr>
<tr>
<td>Lemcke, 2013(^{(90)})</td>
<td>n=145</td>
<td>-</td>
<td>6 months</td>
<td>Surgery improves QoL.</td>
</tr>
<tr>
<td>Petersen, 2014(^{(89)})</td>
<td>n=37</td>
<td>UK norm data.</td>
<td>6 months</td>
<td>Surgery improves QoL.</td>
</tr>
</tbody>
</table>

**Table 1. Summary of studies assessing QoL after shunting in INPH patients.**

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Subjects</th>
<th>% INPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brean, 2008(^{(82)})</td>
<td>Probable INPH in the whole Norwegian population.</td>
<td>0.02%</td>
</tr>
<tr>
<td>Iseki, 2009(^{(91)})</td>
<td>Probable INPH in the Norwegian population &gt; 65 years.</td>
<td>0.12%</td>
</tr>
<tr>
<td>Hiraoka, 2008(^{(92)})</td>
<td>Possible INPH in the Japanese population &gt;61 years</td>
<td>0.51%</td>
</tr>
<tr>
<td>Jaraj, 2014(^{(14)})</td>
<td>Possible INPH in the Japanese population ≥ 65 years.</td>
<td>2.9%</td>
</tr>
<tr>
<td>Marmarou, 2007(^{(15)})</td>
<td>Probable INPH in the Swedish population 70-79 years.</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>Probable INPH in the Swedish population ≥ 80 years.</td>
<td>5.9%</td>
</tr>
<tr>
<td></td>
<td>Suspected INPH in patients living in health-care facilities.</td>
<td>9-14%</td>
</tr>
</tbody>
</table>

**Table 2. Prevalence of INPH in different populations.**
Vascular comorbidity in INPH

Vascular disease in INPH

An association between INPH and CVD is well supported\(^{(18)}\). Vascular disease is the most common cause of death in INPH patients\(^{(8, 9, 93-95)}\) and INPH patients often present radiologically with large amounts of WML, both periventricular and subcortical in the deep white matter (figure 6). A number of studies report CVD to be overrepresented in INPH, particularly typical signs of SVD such as periventricular and deep WML and microbleeds\(^{(2, 7, 18, 19, 96, 97)}\). Subcortical VaD (so-calledBinswanger’s disease or subcortical atherosclerotic encephalopathy (SAE)) is perhaps the most important differential diagnosis to INPH\(^{(18, 21)}\), and is characterized by extensive, progressive WML as well as enlarged ventricles and hydrocephalic symptoms\(^{(18, 38, 46)}\). Both post-mortem studies and biopsies taken during surgery demonstrate similarities between INPH patients and patients with subcortical VaD\(^{(7, 98, 99)}\).

![Figure 6. MRI of three patients diagnosed with INPH and shunted with a VP shunt.](image)

A: Ventriculomegaly and some periventricular white matter lesions.
B: Ventriculomegaly and moderate periventricular and deep white matter lesions.
C. Ventriculomegaly, extensive amounts of degenerative vascular white matter lesions and microbleeds. Radiologically fulfilling criteria for both INPH and subcortical VaD.

Vascular risk factors in INPH

Vascular disease is normally preceded by a large number of VRFs\(^{(32)}\). However, little research on VRFs for INPH has been performed\(^{(18)}\). It is not known if risk factors for vascular disease are also risk factors for INPH, nor is it known how or if existing VRFs affect INPH. It is also unclear whether risk factors and subsequent vascular disease merely coexist with INPH or have a significant role in the pathogenesis and progression of the disease\(^{(18)}\). When the INPH-CRasH study was initiated, some old case reports\(^{(100, 101)}\) and four small studies regarding
VRF in INPH were found in the literature\(^5\), \(^6\), \(^{26}\), \(^{27}\) (table 3). Since then, two more VRF studies have been published\(^{102}\), \(^{103}\). Hypertension is considered the single most important VRF for INPH, and there are some indications that high cholesterol levels, diabetes and ischemic heart disease\(^6\), \(^{27}\) also might be overrepresented.

<table>
<thead>
<tr>
<th>First author</th>
<th>INPH</th>
<th>Controls</th>
<th>Significant VRF(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs, 1977(^{26})</td>
<td>n=33</td>
<td>n=33(^h)</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Graff-Radford, 1987(^5)</td>
<td>n=19</td>
<td>a) n=122(^h)</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) approximated(^p)</td>
<td></td>
</tr>
<tr>
<td>Casmiro, 1989(^{27})</td>
<td>n=17</td>
<td>n=51(^hp)</td>
<td>Hypertension, Diabetes, Hyperlipidemia</td>
</tr>
<tr>
<td>Krauss, 1996(^6)</td>
<td>n=65</td>
<td>n=70(^h)</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Table 3. Summary of VRF studies before the INPH-Crash study was initiated.
*Abbreviations: *\(^h\)=hospital based, *\(^p\)=population based.*

**Influence of vascular comorbidity on outcome of shunting**

The amount of comorbidity and the extent of vascular disease are important predictors of prognosis and the postoperative long-term outcome of shunting\(^18\)-\(^20\), \(^{34}\). Patients with a high burden of vascular comorbidity have less short- and long-term improvements after shunt surgery\(^{19}\), \(^{20}\), \(^{94}\), \(^{104}\). However, even patients with a high degree of CVD may benefit from surgery\(^{21}\), and most authors agree that even patients with extensive amounts of CVD should not be excluded from treatment\(^{18\-21}, \(^{104}\). Few studies have investigated the effect of VRFs on shunting, and the results are inconclusive. In some studies, coexisting VRFs do not influence outcome of surgery\(^{10}\), \(^{19}\), \(^{105}\). However, another study showed that of the INPH patients who showed no improvement after surgery, 67% had hypertension, whereas of the patients with slight improvement and marked improvement, 50% and 47%, respectively, had hypertension\(^{106}\). A recent review regarding co-morbidity in INPH called for large, population-based studies on the subject\(^{18}\).

**Depression in INPH**

Depression is one of the most frequent mental disorders in elderly\(^30\), \(^31\). It affects overall morbidity and mortality, lowers QoL and is a large socioeconomic burden\(^28\)-\(^31\). The prevalence of major depression is reported to be as high as 16% among the elderly, and the prevalence of minor depression and dysthymia is probably considerably higher\(^30\). In
patients with neurological impairment, the diagnosis may be difficult since the symptomatology of depression may be mistaken for symptoms of their neurological disease. The cognitive symptoms of INPH are somewhat similar to the symptoms of depression, and when comparing the typical vascular depression and INPH, the similarities are even more striking, with the typical frontal-subcortical executive dysfunction in both diagnoses. Depression is known to be overrepresented in dementias such as AD (depression present in 20-30% (28)) and VaD (depression present in 30-60% (113)), but very little is known about depression in INPH. Before the INPH-CRasH study was initiated, there were a few case reports but only two studies that assessed depression in a group of INPH patients (114-121). Since then, two more studies have been published (122, 123) (table 4).

<table>
<thead>
<tr>
<th>First author</th>
<th>INPH</th>
<th>Controls</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Markianos, 2009</td>
<td>n=19 (no report on how many shunted)</td>
<td>a) n=19h</td>
<td>INPH had higher depression score than controls.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) n=19p</td>
<td></td>
</tr>
<tr>
<td>Kito, 2009</td>
<td>n=64 (no report on how many shunted, only 10 available for follow-up after shunting)</td>
<td>n=126h</td>
<td>Less symptoms of depression in INPH than in Alzheimers' (14% vs. 37%).</td>
</tr>
<tr>
<td>Oliveira, 2014</td>
<td>n=35 (no report on how many shunted)</td>
<td>-</td>
<td>Depression-anxiety syndrome in 49%.</td>
</tr>
<tr>
<td>Behrens, 2014</td>
<td>n=40 (26 fulfilling criteria for INPH, no report on how many shunted)</td>
<td>a) n=44h</td>
<td>INPH had higher depression score than controls.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) n=28p</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Summary of studies conducted on depression in INPH patients
Abbreviations: h = hospital based, p = population based.

Neurodegenerative diseases in INPH

Alzheimer’s disease (AD) is the most common cause of dementia among the elderly and except for VaD, the most important differential diagnosis when considering INPH. In addition, VaD and AD may coexist, and VRFs may be important risk markers for AD (128, 129). INPH patients with AD findings (in the CSF or through cortical brain biopsy) may still improve after shunting, although the improvement may be less than that experienced by patients without AD (18, 95, 98). Specifically, cognitive long-term outcome is negatively affected by a coexisting AD pathology.
Pathophysiology of INPH

The underlying pathophysiological mechanisms for INPH are largely unknown and probably have multifactorial causes\(^2\),\(^{130}\). The two most widely accepted hypothesized underlying mechanisms are as follows:

1) A disturbance in the CSF dynamic system.
2) Vascular aspects/vascular comorbidity.

Traditionally, INPH is viewed as a CSF dynamic disorder. One of the most clinically important measures of the CSF dynamics in INPH is \(R_{\text{out}}\)\(^{(52, 53)}\) (figure 2, small panel). \(R_{\text{out}}\) is increased in INPH patients compared with both healthy adults and those with other dementias, indicating a disturbance in the CSF dynamics on the reabsorption side\(^2\),\(^{52, 53, 106}\). After shunting, \(R_{\text{out}}\) decreases in INPH patients\(^{(53)}\).

It has also been hypothesised that INPH and ischemic CVD share some of the same pathophysiological mechanisms\(^{4, 7, 19, 22-25, 131}\). Periventricular and deep WML are associated with more severe symptoms in INPH\(^{19, 20, 94, 104}\), and INPH patients have been proven to have a reduced cerebral blood flow, both in the periventricular and frontal subcortical areas of the brain\(^{(132-134)}\). Since the disturbances in gait and cognition are thought to arise from disturbances in the periventricular/subcortical/frontal areas of the brain\(^{(3)}\), this links the symptomatology to possible vascular changes.

Another suggested pathophysiological explanation is the “waterhammer theory”, which relates to atherosclerotic disturbances of the Windkessel effect and links the disturbance of the CSF system to vascular disease. When an individual ages and the burden of atherosclerosis and arteriosclerosis grow heavier, the stiffness of the blood vessels increases. This leads to a reduction in the normal dampening of arterial blood pressure by the Windkessel effect\(^{(55)}\). Thus, each cardiac cycle transmits a stronger systolic pulse into the intracranial compartment and CSF\(^{(135)}\), and further into the small arterioles and capillaires\(^{(43)}\). In healthy individuals, high arterial pulse pressure seems to contribute to the expansion of brain ventricles by creating a “water hammer”, which in time wears out the brain and causes ventricular dilatation\(^{(18,136)}\). Testing in INPH patients has revealed that individuals with a greater reduction in pulse-wave amplitude after shunting are more likely to improve in gait\(^{(137)}\). These findings indicates a possible causal relationship between \(R_{\text{out}}\), increased pulse-wave amplitudes and INPH\(^{(52)}\).
Epidemiological concepts

Comorbidity or cause, association or causation?

An association or coexistence between a certain factor and a disease or outcome does not prove a causal relationship. When determining if a coexisting factor is a risk factor for the outcome in question, biological, clinical, epidemiological and social factors must be considered and interpreted in addition to performing a purely statistical analysis. In 1965, Sir Bradford Hill presented nine items to consider when discussing causality:\(^{36,138,139}\):

1. **Strength**: The statistical strength of the association.
2. **Consistency**: The replicability of the association.
3. **Specificity**: The particularity of which one variable predicts the occurrence of another.
4. **Temporality**: That the exposure must precede the effect.
5. **Biological gradient**: If a dose-response curve can be demonstrated.
6. **Plausibility (biological)**: If the association is explainable with established biological/pathophysiological processes.
7. **Coherence**: If the association is compatible with various existing theories and knowledge.
8. **Experiment**: If the effect can be modified by altering the cause.
9. **Analogy**: If an association can be logically derived from another on the basis of a known similarity in other aspects

A decade later, Rothman presented the Pie-Chart model (figure 7). This model stresses the multifactorial pathogenesis of disease, involving multiple factors and diverse disease\(^{140}\). A cause may be **sufficient**, i.e. it is in itself enough for initiating the disease (very rare), **necessary**, i.e. without this factor, there is no disease, or **contributing**,

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**Figure 7.** Rothman's Pie-Chart model. Factor A-D represents four different contributing causes for developing the disease (the whole pie). In this particular model no necessary or in itself sufficient causes are present.
i.e. not in itself enough for initiating the disease but enhancing the probability for the disease (very common). Both Hill’s Criteria and Rothman’s pie-chart model are commonly used as conceptual frameworks when investigating causality.

**Common sources of error**

The trustworthiness of the data in epidemiological studies depends on the level of **reliability** (precision/repeatability) and **validity**. Precision is to which extent repeated measurements give the same answer. In a study with high precision, the influence of random error is small\(^{(36)}\). When too few participants are included in a study, precision is usually low. This is unfortunately common in research regarding INPH. Validity is to which extent the findings in the study reflect the truth. In studies with high validity, the influence of systematic error (bias) is low\(^{(35)}\). Common errors inducing low validity are selection bias (how the participants are included and/or excluded), information bias (how the data are collected) and confounding (mixing the effect of an extraneous variable with the effects of the exposure and outcome of interest)\(^{(35)}\). Validity may be divided in internal validity, i.e. to which extent the results of the study reflect the true situation of the population studied, and external validity or generalizability, i.e. to which extent the results of the study are applicable to other populations\(^{(35)}\).
RATIONALE OF RESEARCH

INPH patients represent a frail, underdiagnosed and undertreated group of elderly individuals. Comorbidity has a negative influence on shunting, and multiple risk factors may act synergistically and worsen the hydrocephalic symptoms. To understand the multifactorial nature of INPH and to optimize treatment for INPH patients, it is important to detect and, if possible, treat coexisting diseases and risk factors. A recent evidence-based task force report regarding co-morbidity in INPH patients concluded that there is a need for large, population-based studies regarding both VRFs and depression in INPH patients\(^{(18)}\).

There is a well-known association between INPH and vascular disease, but the VRF profile in INPH is poorly understood. No study to date has applied an extensive VRF template similar to that found in INTERHEART or INTERSTROKE on a large cohort of INPH patients. In existing studies, the number of participants is small\(^{(5, 27, 103)}\), the controls are not population-based\(^{(5, 6, 27)}\), or VRFs are assessed using different methods for cases and controls\(^{(102)}\). In addition, four out of five existing VRF studies examine the frequency of VRFs in INPH patients from over 15 years ago\(^{(5, 6, 27, 103)}\). The results of such studies may not be applicable today since during this time period, new international guidelines regarding the diagnosis and treatment of INPH have been developed\(^{(1)}\), and the definition and treatment of VRF have changed\(^{(32)}\).

Depression affects cognitive function and is a risk factor for both dementia and vascular disease. However, no study has focused on the prevalence of depression in shunted INPH patients, and the few studies that have assessed pre-operative depression either lack population-based controls\(^{(123, 124)}\) or include only a small number of subjects\(^{(122, 124, 125)}\).

QoL is considered one of the most important measurements when evaluating the effectiveness of a treatment but a measurement of QoL is rarely included in studies regarding INPH. In some studies, QoL is considered to be improved based on improvements in other parameters\(^{(20, 88)}\). However, when measuring QoL, an instrument specifically designed for the assessment of health status and subjective well-being must be used\(^{(83, 141, 142)}\). The few studies that report QoL in INPH patients either lack representative controls\(^{(89, 90)}\), or include only a small number of subjects\(^{(87)}\). No study investigates QoL in INPH patients on a long-term basis, and no study has investigated the impact of comorbidity on QoL in INPH patients.
AIMS

The overall primary objectives of this dissertation was to assess vascular disease and vascular risk factors in INPH, and to investigate the hypothesis that INPH may be a subgroup of vascular dementia. Additional objectives were to assess depression in INPH patients, and investigate the impact of coexisting comorbidities on quality of life in INPH.

The specific aims for the papers included in this dissertation (I-IV) were as follows:

I. To investigate the frequency of ventriculomegaly, with or without symptoms, in a population of elderly individuals with vascular disease and thus determine how many of these patients might suffer from possible INPH.

II. To present the modern vascular risk factor profile of INPH patients compared with that of the normal elderly population.

III. To investigate the prevalence of depression in shunted INPH patients compared with that found in the normal elderly population and to investigate possible causes for depression in INPH patients.

IV. To compare quality of life among shunted INPH patients and the normal elderly population and investigate which factors influence quality of life in INPH patients.
SUBJECTS AND METHODS

Summary

In **paper I**, the methodological approach was a retrospective prevalence study. The medical files of TIA patients consecutively admitted to the neurology department in Umeå during two years were scrutinized regarding clinical symptoms and radiological features to determine how many patients fulfilled the radiological and clinical criteria for possible INPH. All of the statistical analyses were conducted using SPSS (version 20, SPSS Inc., IL, USA).

In **papers II-IV**, the methodological approach was a case-control study. INPH patients consecutively shunted during three years (2008-2010) from five out of six neurosurgical centres in Sweden were compared with population-based gender- and age-matched controls. The participants (176 cases, 368 controls) first answered an extensive questionnaire and then visited their nearest health-care provider (INPH patients: the doctor at their local health care centre, controls: a doctor at the University Hospital of Umeå) for a per-protocol clinical examination, an electrocardiography (ECG) and to leave a blood sample. To confirm and extend the information from the questionnaires, blood samples and measurements, information regarding diagnoses and medications for all of the participants was assessed from registries held by the National Board of Health and Welfare in Sweden. All of the statistical analyses were conducted using SPSS (version 21-23, SPSS Inc., IL, USA).

Power

Since hypertension is the VRF traditionally thought to be the most important in INPH, the frequency of hypertension was used to calculate power for the INPH-CRasH study (**papers II-IV**). The primary objective was to test the null hypothesis that the two proportions (cases and controls) were equal. The test is 2-tailed, which means that an effect in either direction will be interpreted. The criterion for significance (alpha) was set at 0.050. Since the results from older VRF studies may not be applicable to today’s patients, it was instead assumed that the mean percentage of hypertension would be 45% in INPH patients and 32% in the normal population. When performing power calculations on these percentages with a proposed approximated sample size of 200 and 400 for the two groups, the study would have a power of 87% to yield a statistically significant result.
Subjects

TIA patients in paper I

Umeå municipality has a catchment area of approximately 140,000 inhabitants (2008). All of the TIA patients within that area are admitted to the University Hospital. All of the patients diagnosed with a TIA (ICD-10: G45.0, G45.1, G45.3, G45.8 or G45.9) consecutively admitted between 31 of May 2006 and 31 of May 2008 to the neurology department in the University Hospital of Umeå were considered possible cases. TIA was defined as a minor ischemia in a vascular area of the brain, generating temporary focal symptoms not lasting longer than 24 hours \(^{(144)}\).

Since many patients were expected to have more than one exclusion criteria, the order in which the exclusion criteria were applied was pre-specified. First, the patients who did not have a TIA for that specific admission were excluded (i.e patients admitted to the hospital from the region for screening of A. carotis). Second, patients with age <50 or >85, a previous stroke, or patients that had been incorrectly diagnosed with a TIA (i.e. symptoms lasted longer than 24 h) were excluded. Then, medical files and CT images of the remaining patients were scrutinized. The causes for further exclusion were conditions possibly influencing the results of the balance tests, i.e.: previous neurosurgery, Parkinson’s disease or AD, patients too sick to test properly, patients who had undergone knee or hip surgery, multiple TIA, or patients declining further balance- and gait examination. See figure 8 for the complete patient-flow. For the demographics, see table 5.
**INPH patients in papers II-IV**

Before surgery, all of the patients with suspected INPH in Sweden undergo a thorough evaluation by an experienced INPH team, typically consisting of a neurologist, a neurosurgeon, a physiotherapist and a nurse, and sometimes including a neuropsychologist and a medical engineer. Methodical interviews regarding symptoms, clinical examinations, brain imaging, and appropriate additional diagnostic tests are performed in all patients to confirm the diagnosis, according to the international guidelines of INPH\(^1\). All of the patients who undergo shunt surgery in Sweden are nowadays registered in the Swedish Hydrocephalus Quality Register (SHQR). In the INPH-CRasH study, all of the INPH patients who were consecutively shunted in Sweden from 1 January 2008 to 31 December 2010 and registered in the SHQR were considered possible cases. During 2008-2010, five out of six neurosurgical centres (Umeå, Uppsala, Linköping, Lund and Göteborg) in Sweden participated in the register, covering approximately 80% of the Swedish population. All participants were contacted in 2011.

A total of 396 INPH patients were registered in the SHQR from 2008 to 2010. The exclusion criteria for participation in the study were age <60 or >85 at the date of surgery, a known preoperatively mini mental state estimation (MMSE) <23 and, death. After exclusion, 239 patients were contacted for participation, and 176 chose to participate in the study. See figure 9A for the complete patient-flow. For demographics, see table 5.

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Papers II-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>TIA patients</td>
<td>n=76</td>
</tr>
<tr>
<td>Years of age, mean ± SD (range)</td>
<td>68±8 (51-82)</td>
<td>74±6 (61-86)</td>
</tr>
<tr>
<td>Gender, % females (n)</td>
<td>47% (n=36)</td>
<td>42% (n=73)</td>
</tr>
<tr>
<td>Months from shunting to study participation, mean ± SD (range)</td>
<td>-</td>
<td>21±10 (6-45)</td>
</tr>
</tbody>
</table>

**Table 5. Demographic characteristics of subjects in papers I-IV.**

**Controls in papers II-IV**

The controls were individually matched to the cases according to age and gender and continuously enrolled when confirmation of study participation from the cases arrived. The name and social security number for the controls were found in the Swedish population index, where all Swedish citizens are registered. All controls lived within the
admission area of the University Hospital of Umeå. The goal was to receive two controls for each case. Assuming a response-rate of 50% among the controls, four controls per case were contacted (except for five of the cases who were late in confirming participation in the study and were not individually matched with any controls). The same exclusion criteria as for the cases were applied to the controls (MMSE was assessed at the clinical examination). The initial plan was to exclude controls who had been diagnosed with INPH but had not yet undergone surgery or had not been selected to undergo surgery, but this exclusion criterion was not applicable to any of the controls.

Of the 684 controls who were contacted, 373 chose to participate in the study. After exclusion, the study population of the controls consisted of 368 individuals. See figure 9B for the complete control-flow. For demographics, see table 5.

Figure 9. Case-control flow for the INPH-Crash study (papers II-IV).
Assessment of data

*Data assessment paper I*

Stroke physicians, physiotherapists and occupational therapists systematically examine all TIA patients in Umeå by testing balance, gait and cognition. Each patient is examined by at least three independent professionals. The final tests are performed 24 hours after admission, at which point a physician confirms or excludes the diagnosis of TIA. Hence, any unexpected findings regarding balance, gait and/or cognition should be representative of the patient’s habitual state. In addition, all of the patients admitted for a TIA undergo a CT scan and/or a MRI.

In *paper I*, the medical files of the included TIA patients were retrospectively scrutinized according to a protocol (appendix 2), and the CT scans of the patients’ brains were measured and graded according to the ventricular size, WML and atrophy.

*Data assessment papers II-IV*

All of the included INPH patients and controls in *papers II-IV* received a letter by post, which included the following items:

a. A structured questionnaire.

b. An informative letter in which the study participant was asked to complete the questionnaire and send it back to Umeå if he/she wanted to participate in the study.

c. A pre-addressed, stamped envelope to be used to mail the completed questionnaire back to the University Hospital of Umeå.

If the questionnaire was not returned within one month, the participant received a reminder letter. This procedure was repeated two times before the participant was registered as “not interested in participation”. In the questionnaire, the cases/controls answered questions regarding VRFs and other parameters as described in the section “investigational parameters”. For some parameters in the questionnaire, the cases were asked to answer twice: first regarding their current health status and then how they recalled their health status to be before surgery.

Regarding the INPH patients, after a patient’s completed questionnaire was received at the University Hospital of Umeå, thus confirming
participation in the study, another package was sent to the patient. This package included the following items:

a. An informative letter in which the patient was asked to go to the local health care centre for measurements and to have blood drawn.

b. An instructional letter for the local health care centre.

c. An instructional protocol for the local health care centre to complete and return to Umeå (appendix 3).

d. A pre-addressed, stamped padded envelope containing two test tubes for blood samples to fill with blood and return to the University Hospital of Umeå.

Regarding the controls, approximately one week after the completed questionnaire was returned to Umeå, a follow-up call was made. If the participant was willing to continue to participate in the study, an appointment was made for him/her at the neurological department. There, the same structural protocol was followed as for the cases (appendix 3).

During the clinical examination of both the patients and controls, the following parameters were measured: the distance around the waist and hip, height and weight. The individual's blood pressure was measured three consecutive times after at least five minutes rest, and an ECG was performed. For the controls, an MMSE was performed. Blood samples (non-fasting, 15 ml.) were drawn. In addition, data regarding diagnoses for in- and outpatient care as well as prescribed medication were assessed through registries held by the Swedish National Board of Health and Welfare, and the data regarding baseline symptoms and outcome of surgery were extracted from the SHQR

**Handling of data papers II-IV**

All of the ECGs and blood samples were sent to the University Hospital of Umeå for analyses. The ECGs were first interpreted by the computer executing the ECGs, and then by an experienced physician at the University Hospital of Umeå interpreted. When there were difficulties regarding the interpretation, another experienced specialist in internal medicine was consulted. A study-specific database was constructed. After the primary data entry, all of the data were checked for consistency at least twice.
Investigational parameters

**Investigational parameters paper I**

**Clinical parameters**
First, a comprehensive anamnesis was taken from the medical files based on each patient’s own description of his/her daily life before admission to the hospital, including a history of previous problems with gait, balance, cognition and incontinence. VRFs were noted. A complete list of previous diagnoses was included. The second part of the examination was based on tests performed after admission to the hospital: Rombergs (feet together, side-by-side), tandem standing (feet together heel-to-toe), standing on one leg, and tendency to fall. The patient’s mental state was evaluated, and dementia was graded as none, mild or severe. In the medical files, both the physiotherapist and the occupational therapist had written a detailed review of the patient’s habitual state, evaluating balance, gait and ability to function in daily life. This information made it possible to retrospectively classify each patient’s functional state according to the mRS and Katz ADL scale. For detailed protocol, see appendix 2.

**Radiological parameters**
To measure the ventricular size, EI was used. Ventriculomegaly was defined as EI>0.3, and very large ventricles were defined as EI>0.33. EI was measured by the first author of paper I (HI), with a previous interrater reliability of 0.97 for EI compared to an experienced neuroradiologist. To grade the amount of WML, the scale presented by van Swieten et al. was used. To grade the amount of atrophy, the method presented by Simoni et al. was used. An experienced neuroradiologist graded atrophy and WML.

**Diagnosis of possible INPH**
Possible INPH was defined according to the international guidelines of INPH. For the patients with ventriculomegaly and an unexplained, objectively verified disturbance in balance/gait, five experienced INPH physicians blinded to the patient’s clinical symptoms independently examined the CT scans to see if they would diagnose the patient as possible INPH.
Investigational parameters papers II-IV

Using the SHQR, the questionnaire, the blood test results, the clinical examination, the anthropometrical measurements and, the register data from the National Board of Health and Welfare, the following parameters were assessed:

- The 10 VRFs that have been proven to account for approximately 90% of the risk for myocardial infarction or stroke worldwide\(^{33,34}\) (smoking, hypertension, diabetes mellitus, abdominal obesity, dietary pattern, physical activity, alcohol intake, hyperlipidemia, psychosocial factors and cardiac disease). For a complete list of assessed VRFs see table 6.

- Vascular comorbidity. For a complete list of assessed vascular comorbidities, see table 6.

- Quality of life (assessed by the EuroQol Five Dimension Five Level (EQ5D5L) instrument)\(^{149}\).

- Demographic data (age, gender, occupation).

- Independency (measured by accommodation and the need for in-home care).

- Falling and fear of falling.

- Complications after surgery (headache, stomach ache, epilepsy).

- Baseline symptoms of INPH (gait, mRS, MMSE) and outcome of surgery (the same parameters as baseline). Gait was measured on a scale of 1-8, where 1 represented normal gait, and 8 represented wheelchair bound. Improvement after surgery was defined as 1 point on the gait scale, 1 point on the mRS and 3 points on the MMSE.

- Previous and current medication.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Definition</th>
<th>Assessed by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Current or former smoker.</td>
<td>Q</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Blood pressure ≥140/90 mmHg or the use of anti-hypertensive drugs.</td>
<td>M + Q</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>History of treated diabetes mellitus or non-fasting p-glucose ≥11.1 mmol/l (198 mg/dl).</td>
<td>BS + Q</td>
</tr>
<tr>
<td>Obesity</td>
<td>- Abdominal obesity: WTH-ratio ≥0.85 (females) or ≥0.90 (males)</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>- General obesity: Body Mass index (BMI) &gt;30.0</td>
<td>Q</td>
</tr>
<tr>
<td>Dietary pattern</td>
<td>- Prudent: A daily intake of fruits or vegetables.</td>
<td>Q</td>
</tr>
<tr>
<td></td>
<td>- Unhealthy: A high intake (daily) of salty snacks/pastry/lemonade/candy in combination with a low intake (less than one time/week) of fruits/berries/vegetables/roots/fish/shellfish</td>
<td>Q</td>
</tr>
<tr>
<td>Physical activity</td>
<td>- Physically active: Moderate/strenuous exercise ≥4 h/week.</td>
<td>Q</td>
</tr>
<tr>
<td></td>
<td>- Physically inactive: Physically active &lt;1h/week.</td>
<td>Q</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>- Moderate: Drinker of 1-30 drinks/month.</td>
<td>Q</td>
</tr>
<tr>
<td></td>
<td>- High: Drinker of &gt;30 drinks/month or binge drinker (≥5 drinks/day, at least once per month).</td>
<td>Q</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>- Hyperlipidemia: ApoB/ApoA1 &gt;0.9 (male) or &gt;0.8 (female)</td>
<td>BS</td>
</tr>
<tr>
<td></td>
<td>- High ApoB: ApoB &gt;1.2</td>
<td>BS</td>
</tr>
<tr>
<td></td>
<td>- Low ApoA1: ApoA1 &lt;1.15 (male) or &lt;1.25 (female)</td>
<td>BS</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td>Depression (≥5 points on the Geriatric Depression Scale 15 (GDS-15) or a high burden of stress (permanent or several periods of stress, i.e. feeling irritable, filled with anxiety or having sleeping difficulties) at home or in general</td>
<td>Q</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>- Ischemic heart disease: Previous myocardial infarction, left bundle blockage, angina pectoris.</td>
<td>ECG + Q</td>
</tr>
<tr>
<td></td>
<td>- All cardiac disease: Ischemic heart disease, atrial fibrillation/flutter, left ventricular hypertrophy, right bundle blockage or other pathologies.</td>
<td>Q</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>History of TIA or ischemic stroke.</td>
<td>Q</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Stenosis of extra cranial cerebral arteries, claudication intermittents, renal dysfunction (GFR&lt;90), chronic kidney disease (GFR&lt;60) (GFR calculated by the CKD-EPI equation)</td>
<td>BS + Q</td>
</tr>
</tbody>
</table>

Table 6. Definition and assessment of vascular risk factors and comorbidities.
Abbreviations: Q=Questionnaire, M=Measurement, BS=Blood sample, P=protective factor, ApoB=Apolipoprotein B, ApoA1=Apolipoprotein A1, GFR=Glomerular filtration rate.
Statistical considerations

Missing values
The handling of missing values was parameter-dependent. In paper I, the patients with missing values were excluded from the analyses. For the questionnaire used in papers II-IV, most unanswered questions were coded as missing values. However, if a participant had refused to answer a question but instead had written a comment in the margin clearly answering the question or had answered a supplementary question (e.g. not answered yes or no on a direct question but in a supplementary question specified the answer on the first question), these answers were considered as answering the original question as well. Regarding depression, when there were unanswered questions in the GDS-15, the results of the missing answers were calculated based on the result of the answered questions and imputed in the final score\(^{(155)}\), and if less than 75% of the questions were answered, the individual was excluded from the analyses. When building multivariable models in papers II-IV, only the participants with answers in all of the investigated parameters (for depression: calculated score) were included.

Resolved matching
In papers II-IV, when conducting the comparative case-control analyses, the matching was resolved. This was done for two main reasons. First, five of the INPH patients had data arriving just a few days before the recruitment period ended and did not receive any individually matched controls. Second, the distribution of the controls to the cases was unequal, and for as many as 33 cases (19% of all cases), all of the controls declined to participate. Strictly matched analyses would have excluded all of these cases from the analyses. Thus, the findings presented are for models adjusted for the original matching criteria (age and gender), similar to INTERHEART/INTERSTROKE.

Sub-analyses to control for the lack of geographical matching
The controls were matched to the cases by gender and age but not geographical location. Thus, to investigate if the lack of geographical matching had any effect on the main results in papers II-IV, sub-analyses were performed in which only the participants from the same hospital catchment area (the University Hospital of Umeå) were included. The same proportions of cases to controls as found in the large analyses were used. The statistical program randomly selected controls for these sub-analyses.
Ethics

Ethical approval
The Regional Ethical Review Board in Umeå approved all of the studies presented in this dissertation. All of the procedures were performed according to the Declaration of Helsinki. The INPH-CRasH study was registered in clinicaltrials.gov (NCT 01850914). Since paper I was a retrospective review of the TIA patients’ medical files, informed consent from each participating individual was not considered necessary by the ethical review board. For the INPH-CRasH study (papers II-IV), informed consent was obtained from each participant by returning the completed questionnaire.

Handling of pathological test results
Regarding the blood tests, all of the participants were informed of their test results in a letter. If a previously unknown pathology was found, the participant was recommended to schedule an appointment at his/her local health care centre for follow up. For the controls, any abnormal ECG findings were discussed immediately with the individual, and checked for in the medical file. If an unknown pathology was found, the individual was referred to the cardiology department for further evaluation. Regarding depression, the controls presenting with high scores on the GDS-15 were referred to the psychiatric ward in Umeå for further evaluation. Regarding the cases, since the ECGs were performed at the health care centre in the INPH patient’s respective hospital district, any abnormal findings (except for the blood tests) were considered the responsibility of their physician in charge.
RESULTS

INPH in TIA patients

As shown in paper I, the mean EI in the patients who had had a TIA was 0.28±0.03 SD. Ventriculomegaly was observed in 20% of the TIA patients (n=15), and the patients with a history of gait/balance disturbance were more likely to have ventriculomegaly than those without (58% vs. 12%, p<0.001). Five of the patients with ventriculomegaly had an unexplained gait and/or balance disturbance. After further examination of the CT scans (figure 10), three (4%) TIA patients fulfilled the radiological and clinical criteria for possible INPH(1). When applying the radiologically more strict Japanese criteria(69), 3% of the TIA patients scored as INPH.

Outcome of surgery in INPH

The outcome parameters for the shunted INPH patients in papers II-IV were assessed 3 and 12 months after surgery. No significant differences were found between the two different time points. Since more patients participated in the 3 months outcome measurements (n=175 vs. n=121), the outcome data assessed after 3 months were used in the further analyses (table 7).
Vascular disease

Paper II demonstrated that PVD and CVD but not ischemic heart disease were overrepresented in the INPH patients compared with the controls (table 8).

<table>
<thead>
<tr>
<th>Table 7. Outcome of surgery in INPH patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviations: I=improved after surgery, NI=not improved after surgery (unimproved or worse), U=unchanged after surgery, W=worse after surgery.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8. Vascular disease in INPH and the population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviations: KD=GFR&lt;90, CKD=GFR&lt;60, ECG=seen on ECG, reported=self reported.</td>
</tr>
</tbody>
</table>

Vascular risk factors

As shown in paper II, the INPH patients had a higher mean number of VRFs than the controls (4.4±1.5 SD vs. 3.3±1.5 SD, p<0.001). For data regarding the number of VRFs for patients and controls, see figure 11.
Of the patients, 73% had four or more VRFs, compared with 43% of the controls (p<0.001). The higher the number of VRFs, the higher the OR (≈1.6 additional OR/additional number of VRFs, see figure 12).
Six of ten VRFs were overrepresented in INPH, and the protective factors were overrepresented among the controls (table 9). The population attributable risk percent (PAR%) for a model containing all of the VRFs associated with INPH was 24% (95% CI: 20-28%).

<table>
<thead>
<tr>
<th>Frequency for each variable</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/total n of probands</td>
</tr>
<tr>
<td>INPH</td>
<td>Controls</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83% (131/157)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>37% (52/140)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27% (38/142)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>91% (128/140)</td>
</tr>
<tr>
<td>Smoking</td>
<td>55% (95/172)</td>
</tr>
<tr>
<td>Physical activity</td>
<td>33% (53/160)</td>
</tr>
<tr>
<td>Active</td>
<td>24% (40/166)</td>
</tr>
<tr>
<td>Inactive</td>
<td>48% (83/172)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>23% (32/138)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>46% (65/143)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>54% (92/170)</td>
</tr>
<tr>
<td>Moderate</td>
<td>20% (34/170)</td>
</tr>
<tr>
<td>High</td>
<td>74% (128/173)</td>
</tr>
<tr>
<td>Dietary pattern</td>
<td>18% (31/173)</td>
</tr>
</tbody>
</table>

Table 9. The total VRF profile of INPH patients and controls.

All odds ratios were adjusted for age and gender.

Four VRFs remained independently associated with INPH after adjustment for each other, age and gender: abdominal obesity, psychosocial factors hyperlipidemia and diabetes (table 10). The Nagelkerke R² for the final multivariable model was 0.28.

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Gender</td>
<td>1.7 (1.0-2.9)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2.4 (1.4-4.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.2 (1.2-4.0)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>5.4 (2.5-11.8)</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td>5.3 (3.2-8.7)</td>
</tr>
</tbody>
</table>

Table 10. The final multivariable logistic regression model for VRF in INPH.

All odds ratios adjusted for all variables in the model. For the variable “gender”, male gender was used as reference.
When separately analyzing the lipid profile of INPH patients compared with the population, all of the parameters were significant except the prescription of lipid-lowering drugs (table 11).

<table>
<thead>
<tr>
<th>Value or frequency for each variable (n/total n of probands)</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INPH</strong></td>
<td><strong>Controls</strong></td>
</tr>
<tr>
<td>Mean ApoB (g/L)</td>
<td>1.12±0.26SD</td>
</tr>
<tr>
<td>High ApoB</td>
<td>38% (53/140)</td>
</tr>
<tr>
<td>Mean ApoA1 (g/L)</td>
<td>1.43±0.26 SD</td>
</tr>
<tr>
<td>Low ApoA1</td>
<td>17% (24/140)</td>
</tr>
<tr>
<td>Mean ratio ApoB/ApoA1</td>
<td>0.81±0.25SD</td>
</tr>
<tr>
<td>High ratio ApoB/ApoA1</td>
<td>37% (52/140)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>7% (12/176)</td>
</tr>
<tr>
<td>High ratio ApoB/ApoA1 or lipid-lowering drugs</td>
<td>43% (62/143)</td>
</tr>
</tbody>
</table>

Table 11. The lipid profile of INPH patients and controls.
Abbreviations: <sup>a</sup>=analyzed with ANCOVA (covariates: age and gender), <sup>b</sup>=analyzed with logistic regression (OR adjusted for age and gender).

When separately analyzing the VRF traditionally thought to be the most important in INPH (i.e. hypertension), only the variables “hypertension: systolic or diastolic” and “systolic or diastolic hypertension or anti-hypertensive medication” were associated with INPH (table 12).

<table>
<thead>
<tr>
<th>Value or frequency for each variable (n/total n of probands)</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INPH</strong></td>
<td><strong>Controls</strong></td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>139±20SD</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>79±11 SD</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Systolic (&gt;140)</td>
<td>48% (67/140)</td>
</tr>
<tr>
<td>Diastolic (&gt;90)</td>
<td>20% (28/140)</td>
</tr>
<tr>
<td>Systolic or diastolic</td>
<td>51% (71/140)</td>
</tr>
<tr>
<td>Anti-hypertensive medication</td>
<td>64% (108/169)</td>
</tr>
<tr>
<td>Systolic or diastolic hypertension or anti-hypertensive medication</td>
<td>83% (131/157)</td>
</tr>
</tbody>
</table>

Table 12. Blood pressure in INPH patients and controls.
Abbreviations: <sup>a</sup>=analyzed with ANCOVA (covariates: age and gender), <sup>b</sup>=analyzed with logistic regression (OR adjusted for age and gender).
Depression

Among the psychosocial factors described in paper II, depression was the one most strongly correlated with INPH. Paper III showed that compared with the controls, shunted patients were more likely to experience both depression (46% vs. 13%, OR adjusted for age, gender, blood pressure and CVD: 6.4, 95%CI: 3.8-10.9, p<0.001) and severe depression (OR adjusted for the same potential confounders: 14.4, 95%CI: 3.0-68.6, p=0.001) (figure 13). The shunted patients also had a higher mean GDS-15 score than controls (4.9±3.7SD vs. 1.9±2.3 SD, p<0.001). More patients had depression before than after surgery (56% vs. 46%, p=0.04) (figure 13, small panel), and similarly, patients had a higher mean depression score before than after surgery (p<0.005, preoperative score: 5.9±3.8SD).

Figure 13. Scoring on GDS-15 and severity of depression in INPH patients and controls. Abbreviations: **=p-value <0.001, *=p-value <0.05.

The more impaired gait and the more severe disability, the more likely the patient was to have a high GDS-15 score and/or a coexisting depression. Outcome of surgery regarding gait or MMSE did not correlate with depression, but the patients who did not improve in mRS were more likely to have depression (table 13). However, both the improved and unimproved patients (in both gait and mRS) still had a
higher mean GDS-15 score than the controls (p<0.001) and were more likely to have suspected depression than the controls (p<0.001).

<table>
<thead>
<tr>
<th>Outcome of surgery in:</th>
<th>Gait</th>
<th>mRS</th>
<th>MMSE</th>
<th>OR (95% CI) / Corr. coeff.</th>
<th>p-value</th>
<th>Gait</th>
<th>mRS</th>
<th>MMSE</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
<td>(0.9-1.0)</td>
<td>0.80</td>
<td>1.0</td>
<td>0.4</td>
<td>1.0</td>
<td>(0.5-2.0)</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>(0.8-1.0)</td>
<td>0.01</td>
<td>(0.9-1.2)</td>
<td>0.87</td>
<td></td>
<td>(0.2-0.9)</td>
<td>0.02</td>
<td>(0.4-4.1)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Severity of symptoms:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.32</td>
<td>0.28</td>
<td>-0.20</td>
<td>&lt;0.001</td>
<td></td>
<td>1.3</td>
<td>1.5</td>
<td>0.9</td>
<td>(1.0-1.5)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.1-2.0)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.8-1.0)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Table 13. GDS-15 and postoperative hydrocephalic symptoms in shunted INPH patients. Logistic regression analyses were used except for severity of symptoms vs. mean score, where Spearman’s Rank correlation coefficient was used.

Quality of life

As shown in paper IV, shunting improved the patients’ self-perceived QoL (p<0.001), even though the INPH patients still did not reach the same QoL level as the general population (figure 14).

![Figure 14. Mean values on quality of life in INPH patients and controls. Abbreviations: ** = p-value <0.001.](image-url)
The amount of time after surgery had no impact on QoL (see figure 15 and table 14).

When analysing the five dimensions in the EQ5D5L instrument, shunted INPH patients had more problems than controls in all dimensions ($p<0.001$) except for pain/discomfort. In addition, the INPH patients perceived that they had more problems in all dimensions of QoL before than after surgery ($p<0.005$) (figure 16).
For specific details regarding how the separate most important risk factors and comorbidities from papers II-III influenced QoL in the shunted INPH patients and the controls, see table 14.

<table>
<thead>
<tr>
<th>EQ5D5L index</th>
<th>INPH</th>
<th>Controls</th>
<th>EQ-VAS</th>
<th>INPH</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>-0.06 (0.42)</td>
<td>-0.18 (&lt;0.001)</td>
<td>-0.04 (0.65)</td>
<td>-0.09 (0.07)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.13 (0.08)</td>
<td>-0.29 (&lt;0.001)</td>
<td>-0.16 (0.05)</td>
<td>-0.30 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>-0.43 (&lt;0.001)</td>
<td>-0.40 (&lt;0.001)</td>
<td>-0.46 (&lt;0.001)</td>
<td>-0.45 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>-0.23 (0.07)</td>
<td>-0.15 (0.008)</td>
<td>-0.12 (0.17)</td>
<td>-0.19 (0.001)</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>-0.09 (0.30)</td>
<td>-0.12 (0.02)</td>
<td>-0.07 (0.40)</td>
<td>-0.19 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>-0.07 (0.41)</td>
<td>-0.18 (0.001)</td>
<td>-0.12 (0.18)</td>
<td>-0.18 (0.001)</td>
<td></td>
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<tr>
<td>Vascular risk factors:</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Hypertension</td>
<td>0.01 (0.92)</td>
<td>-0.17 (0.001)</td>
<td>0.07 (0.42)</td>
<td>-0.17 (0.002)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
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<td>-0.09 (0.27)</td>
<td>-0.23 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity</td>
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<td>0.04 (0.49)</td>
<td>0.09 (0.33)</td>
<td>-0.13 (0.02)</td>
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<tr>
<td>Hyperlipidemia</td>
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<td>-0.04 (0.52)</td>
<td>-0.24 (0.006)</td>
<td>0.03 (0.61)</td>
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</tr>
<tr>
<td>Outcome of surgery in:</td>
<td></td>
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<td></td>
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<tr>
<td>Gait</td>
<td>0.15 (0.06)</td>
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<td>0.05 (0.57)</td>
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</tr>
<tr>
<td>mRS</td>
<td>0.19 (0.02)</td>
<td>N/A</td>
<td>-0.12 (0.15)</td>
<td>N/A</td>
<td></td>
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<tr>
<td>MMSE</td>
<td>0.04 (0.65)</td>
<td>N/A</td>
<td>0.004 (0.97)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Symptom severity:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait</td>
<td>-0.44 (&lt;0.001)</td>
<td>N/A</td>
<td>-0.19 (0.02)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td>-0.32 (&lt;0.001)</td>
<td>N/A</td>
<td>-0.17 (0.04)</td>
<td>N/A</td>
<td></td>
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<tr>
<td>MMSE</td>
<td>0.31 (&lt;0.001)</td>
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<td>0.07 (0.46)</td>
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<td></td>
</tr>
<tr>
<td>Independency</td>
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<td>N/A</td>
<td>-0.11 (0.17)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Year of surgery</td>
<td>0.10 (0.17)</td>
<td>N/A</td>
<td>0.15 (0.06)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Months from shunting to QoL assessment</td>
<td>-0.13 (0.13)</td>
<td>N/A</td>
<td>-0.16 (0.08)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Table 14. Factors possibly influencing quality of life.
Linear regression was used, with the scale variable as dependent. All presented β coefficient were standardized. For the variable “gender”, male gender was used as reference.

Depression was the main predictor of low QoL in shunted INPH patients, independent of age, gender and other factors table 15). Outcome of surgery did not have an independent influence on QoL. In the controls, somewhat different factors affected QoL, but depression remained the most important predictor of QoL.
When comparing the INPH patients with depression with those without depression, the patients with depression had a lower QoL as measured by both the EQ5D5L (0.50±0.24 SD vs. 0.73±0.24 SD, p<0.001) and the EQ-VAS (57±22 SD vs. 76±15 SD, p<0.001).

### Sub-analyses

When performing the sub-analyses to investigate if the lack of geographical matching had any effect on the main results (including only patients from Umeå (n=30) and a random sample of controls (n=73)), some parameters in paper II lost their significance (hypertension, physical activity and moderate alcohol intake). The remaining significant factors were hyperlipidemia, diabetes, abdominal obesity, physical inactivity and psychosocial factors. When building a multivariable logistic regression model (adjusted for age and gender) containing these five VRFs, two remained independently associated with INPH: hyperlipidemia (OR: 8.2, 95% CI: 2.6-25.4) and psychosocial factors (OR: 6.4, 95% CI: 1.8-22.4).

---

### Table 15. Factors independently influencing quality of life in INPH patients and controls.

The final linear regression model for INPH regarding the EQ5D5L index had an adjusted $R^2=0.31$ (adjusted $R^2$ solely for depression=0.18). Regarding the EQ-VAS, the final model had an adjusted $R^2=0.24$ (adjusted $R^2$ solely for depression=0.20). Abbreviations: NS=not significant, N/A=not applicable.

<table>
<thead>
<tr>
<th></th>
<th>EQ5D5L index</th>
<th></th>
<th>EQ-VAS</th>
<th></th>
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<tr>
<td></td>
<td>INPH</td>
<td>Controls</td>
<td>INPH</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>$\beta$ coefficient</td>
<td>(p-value)</td>
<td>$\beta$ coefficient</td>
<td>(p-value)</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.35 (&lt;0.001)</td>
<td>-0.32 (&lt;0.001)</td>
<td>-0.45 (&lt;0.001)</td>
<td>-0.32 (&lt;0.001)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>-0.19 (0.02)</td>
<td>NS</td>
<td>-0.17 (0.03)</td>
<td>NS</td>
</tr>
<tr>
<td>Severity of gait</td>
<td>0.26 (0.001)</td>
<td>N/A</td>
<td>NS</td>
<td>N/A</td>
</tr>
<tr>
<td>disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>-0.11 (0.04)</td>
</tr>
<tr>
<td>disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>NS</td>
<td>-0.15 (0.02)</td>
<td>NS</td>
<td>-0.11 (0.03)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>-0.11 (0.03)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>-0.11 (0.001)</td>
</tr>
</tbody>
</table>
DISCUSSION

Main Findings

INPH is probably more common than previously thought, and even more common among people with CVD. In paper I, 4% of the population with TIA had possible INPH, and paper II showed that both stroke and PVD (i.e. stenosis of the extra cranial cerebral arteries, kidney disease and CKD) were overrepresented in INPH patients compared with the general population. In addition, paper II showed that INPH patients had more VRFs than the normal population. The most important VRFs that were independently associated with INPH were: abdominal obesity, psychosocial factors (mainly depression), hyperlipidemia and diabetes. In addition, hypertension and physical inactivity were associated with INPH, although not independently. These six VRFs together accounted for 24% of INPH in the elderly population.

Paper III showed that depression was more common among shunted INPH patients than the normal population (46% vs. 13%). The main predictor for depression in INPH was severity of the hydrocephalic symptoms, not outcome of surgery. Paper IV showed that shunted INPH patients perceived their QoL to improve after shunting and that this self-perceived improvement was long-lasting. However, shunted INPH patients still scored their QoL lower than the normal population. The main predictor of low QoL in shunted INPH patients was a coexisting depression, followed by severity of the gait disturbance. Outcome of surgery was not related to low QoL in INPH patients.

Vascular disease in INPH

Vascular comorbidity in INPH

Comparison to previous VRF studies in INPH

Paper II showed that VRF are more common among INPH patients than in the normal elderly population, and that the six VRFs associated with INPH together account for almost one quarter of INPH. The complete modern VRF profile has not previously been investigated in INPH with representative cases and controls using an adequate epidemiological design. An association between VRFs and INPH has previously been suggested, and the results in paper II expand and confirm the knowledge from the previously conducted case-control studies in INPH (table 3).
Since the INPH-CRasH study was initiated, two more case-controlled VRF studies have been published\(^{102, 103}\). The most recent VRF study retrospectively investigated VRF in a sample of 26 patients from 1986-2000 compared with the general population\(^{103}\). The individuals considered to have INPH had ventriculomegaly and clinical findings of INPH (thus fulfilling the same diagnostic criteria as the TIA patients in paper I). Associations between CVD (stroke/TIA and WML) and INPH were found, similar to the results in paper II and in agreement to what have previously been shown\(^{2, 7, 18, 19, 96, 97}\). The only VRF that was associated with INPH was hypertension, but the association was not significant in the multivariable analyses. This lack of any significant association between VRFs and INPH is probably due to the small sample size of INPH patients, which reduces precision. In addition, there was a risk for information bias reducing internal validity, since the definition and treatment for several VRFs have changed during 1986-2000. In paper II, hypertension did not remain an independent VRF in the multivariable analyses, in agreement to this recent study. However, several other VRFs were shown to be independently associated with INPH, such as: hyperlipidemia, psychosocial factors, diabetes and physical inactivity. The INPH-CRasH study had enough power and was specifically designed for assessing the VRF profile of INPH, and compared a large sample of adequately diagnosed INPH patients with representative age- and gender matched population-based controls. Thus, the results in paper II should be more accurate.

The other recently published VRF study investigated 440 patients with possible/probable INPH compared with the general population\(^{102}\). That study showed that cardiovascular disease (angina pectoris: 11% vs. 4%, myocardial infarction: 9% vs. 4%) as well as hypertension and diabetes were overrepresented in the INPH group compared with the controls and also noted some differences between genders. A large sample of representative patients and controls were investigated, adding high precision to the study. However, the VRFs were assessed in different ways for the cases and controls. For the INPH patients, a physician, the patient, or the relatives of the patient reported the diagnoses, while all parameters assessed for controls were assessed solely by a questionnaire to the patients/relatives. This likely induced an information bias. In paper II, all of the parameters were assessed similarly for cases and controls by using a questionnaire, a clinical examination and an ECG, and the INPH patients did not have myocardial infarction in a higher degree than the general elderly population. Even though self-reported
angina pectoris and myocardial infarction among the INPH patients were seen in approximately the same percentages in both studies (11-13% in the INPH-CRasH study), the self-reported percentages for the same diagnoses among the controls were much higher (7-12%). When the ECG results were added to the analyses, the prevalence of ischemic heart disease was much higher for both cases (23%) and controls (21%).

One of the most interesting results in paper II was the strong association between hyperlipidemia and INPH, measured by apolipoproteins. A high level of lipids has previously been shown to be associated with SVD, particularly periventricular WML. A possible association between high cholesterol levels and INPH has previously been suggested, but the levels of apolipoproteins have not previously been described in INPH patients. ApoB and ApoA1 are considered better indicators of the lipid profile than the more commonly assessed cholesterol (HDL cholesterol, LDL cholesterol and total cholesterol) and are also better risk-predictors for both cardiovascular and cerebrovascular events. As shown in paper II, INPH patients consistently had a more unhealthy apolipoprotein profile than the general population (higher ApoB, lower ApoA1, higher ratio ApoA1/ApoB), and the difference was not attributable to a difference in the prescription of lipid-lowering drugs.

Renal dysfunction and CKD were also overrepresented in INPH patients compared with the general population: This association have not previously been described in INPH. Decreased renal function and especially CKD are also risk factors for both dementia and CVD, particularly SVD. Interestingly, CKD is also associated with increased plasma concentrations of ApoB. The combined findings of high levels of apolipoproteins and CKD in the INPH patients in paper II, suggest a possible SVD pathophysiological pathway.

**Preventive strategies**

A couple of years ago, the American Heart Association and American Stroke Association emphasized the importance of vascular disease and risk factors for cognitive impairment and dementia. In paper III, diabetes, hyperlipidemia, obesity and psychosocial factors (particularly depression) were the strongest VRFs for INPH. An association with INPH was also found for physical inactivity as well as hypertension. These results correspond well to VRF studies in other dementias. A recent review that assessed the major modifiable risk factors for
dementia identified these same six risk factors as well as smoking as the most important modifiable VRFs for dementia prevention \(^{(128)}\).

The few studies investigating how coexisting VRFs affect outcome of surgery in INPH patients present conflicting results \(^{(10, 19, 105, 106)}\) and an association between less improvement after shunting and VRFs has not been found. However, VRFs inevitably lead to vascular disease, and INPH patients presenting with vascular disease are less likely to improve after surgery \(^{(19, 20, 94, 104)}\). In most neurosurgical centres, when an INPH patient is selected for surgery, no VRF analysis is performed, and existing risk factors are not specifically addressed and treated. In clinical care, the most important VRFs, as identified in paper II, should be screened for as part of the preoperative evaluation of INPH patients. Existing VRFs should be optimized in addition to surgery according to modern guidelines for vascular disease and risk factors \(^{(32, 37)}\). The effect of such interventions should be evaluated.

**Hypothesising SVD as the pathophysiological pathway in INPH**

It has been emphasised that a “grand unifying hypothesis” for the underlying pathophysiological processes of INPH must explain (figure 17) \(^{(2, 3)}\):

a) The disturbed brain function (e.g. the clinical symptoms, the radiologic findings of WML).

b) The disturbed CSF dynamics (e.g. the ventriculomegaly, the increased \(R_{	ext{max}}\), the possibly increased amplitudes in the ICP pulsations).

a) Why the clinical symptoms improve after shunting.

Several theories regarding a pathophysiological pathway of possible vascular origin in INPH have been proposed \(^{(4, 7, 22-25)}\). As discussed in paper II, SVD may be the underlying pathophysiological explanation of most findings.

**Vascular aspects of brain function and CSF dynamics in INPH**

Hypertensive vascular disease with multiple deep white matter infarctions reducing periventricular tensile strength has been suggested to cause communicating hydrocephalus \(^{(4, 7)}\). Radiological signs of SVD
are common in INPH, primarily periventricular and subcortical WML, but microbleeds and lacunar infarctions also occur (2, 4, 7, 18, 19, 96, 97, 160). INPH patients also present with a reduced cerebral blood flow pattern and WML in the periventricular and frontal subcortical areas of the brain (22, 23, 133, 134, 161, 162). End arteries (arterioles and capillaries) are the vessels supplying these areas with oxygen and nutrients, and these areas are sensitive to vascular changes, both ischemia originating from the large vessels and SVD. The clinical manifestations of INPH are thought to be of frontal/subcortical origin (3, 22), linking the symptomatology to a possible vascular pathway originated in the areas supplied by the small vessels. Regarding SVD, it has been suggested that a dysfunctional endothelium with damage to the blood brain barrier causes impairment in the metabolism in the deep white matter as well as chronic ischemia, accumulation of toxic waste products and inflammation (39, 42). Biomarkers of axonal damage and chronic ischemia have been found in the CSF of INPH patients, (18, 143, 163) and most studies investigating metabolism in INPH report a decreased cerebral metabolism (162). After CSF drainage, an increase in cerebral metabolism has been reported (131).

$R_{\text{out}}$ is a measure of the total resistance to CSF outflow, including all possible sites of reabsorption of CSF (see Davson’s equation and figure 2). Why $R_{\text{out}}$ is elevated in INPH patients on group level remains unclear. Some INPH patients do not have an elevated $R_{\text{out}}$ and may still improve after shunting (53, 106), and elderly individuals without INPH may also have a high $R_{\text{out}}$ (52), indicating that $R_{\text{out}}$ is not the only pathophysiologic factor in INPH. Increased $R_{\text{out}}$ can be caused by the narrowing of CSF flow channels along the pathways of CSF circulation as a consequence of any inflammatory or degenerative process (164). It has been proposed that clinical symptoms and large ventricles in a subject with high $R_{\text{out}}$ may develop during special circumstances, such as vascular disease (52). Paper II showed that VRFs are overrepresented in patients with INPH. VRFs cause SVD, and SVD may cause chronic inflammation, providing a possible explanation for the increased $R_{\text{out}}$ in INPH patients. Another possible association between increased $R_{\text{out}}$ and vascular disease may be found in recent discoveries regarding the CSF circulatory system. On a microvascular level in mice, it has been shown that CSF flows in spaces surrounding perforating arteries and continues to follow the arterioles all the way to the brain capillary bed, continuously exchanging water and solutes with the venous blood flow via the interstitial fluid (48-50). This is referred to as the “glymphatic pathway” (49, 50). In mice, ischemic brain injury hinders this exchange (50). If the glymphatic pathway is also valid in
humans, it could be interrupted by an endothelium damaged by SVD, possibly causing the increased $R_{\text{out}}$ seen in INPH patients.

Increased pulsatile stress has also been suggested to cause INPH\cite{24,25}. In normal senescence, the vessels become less elastic, and there is a reduction of the normal dampening of systolic blood pressure by the Windkessel effect and an increased pulse pressure\cite{55}. In a population with atherosclerotic plaque in the large vessels and a large amount of VRFs, the vessels are stiffer, and the pulsations even heavier\cite{55,135}. This increased pulsatility is transmitted into the microcirculation, exposing the small vessel walls to increased pulsations. The effect is worst in the sensitive areas of the brain and kidney, causing severe lesions\cite{55}. In addition to the previously described common signs of SVD in INPH patients\cite{2,4,7,18,19,96,97,160}, paper II showed that CKD is overrepresented in INPH. In otherwise healthy elderly, it has been suggested that this stronger pulse pressure is transduced into the CSF, creating a water hammer that in time may wear out the brain, causing ventricular dilatation\cite{136}. In addition, ventricular enlargement has been shown to correlate with periventricular WMH\cite{165}. A brain already affected by comorbidity might be even more vulnerable to this “water hammer”, not only through multiple deep white matter infarctions that reduce periventricular tensile strength, as previously suggested\cite{4,7}, but also through the complex multifactorial pathophysiological processes seen in SVD.

**Vascular aspects regarding the effect of shunting in INPH**

In SVD, it is hypothesized that the downward spiralling of a damaged endothelium no longer able to clear toxic metabolites from the brain leads to even more inflammation and endothelial damage, causing the small vessels to thicken and stiffen\cite{39,42}. These events reduces cerebral blood flow, leading to even more accumulation of toxic metabolites, more chronic ischemia, a higher degree of impaired metabolism, and an even more impaired cerebral blood flow\cite{39,42}. After shunting, cerebral blood flow in INPH patients has been reported to increase, and patients with increased cerebral blood flow after shunting are more likely to improve\cite{162}. In addition, most studies that have investigated cerebral metabolism in INPH patients report it to increase after shunting\cite{162}. If a shunt not only produces an alternate route for the CSF outflow (and thus reduces $R_{\text{out}}$ and increases compliance) but also facilitates the transportation of waste products and toxic metabolites out of the brain, it is possible that this would moderate the vicious cycle of SVD, leading
to less accumulation of toxic waste products, less inflammatory effect and possibly increased cerebral blood flow and increased metabolism.

Thus, SVD, in combination with LVD, could hypothetically explain most of the pathological findings in INPH (see figure 18). This hypothesis motivates research proving the link between the CSF dynamic disturbance and manifestations of vascular disease in INPH.

**Figure 18. A possible heterogeneous vascular pathophysiological pathway in INPH**

*In SVD, VRFs may cause endothelial damage, leading to increased permeability of the vessel walls, and leakage of material into vessel walls and perivascular tissue. This leads to inflammation, demyelination, glial scarring, thickening and stiffening of the vessel wall as well as impaired autoregulation. This might affect absorption of CSF in the microcirculation, which in combination with increased pulsations (caused by LVD) may lead to the typical disturbance in the CSF dynamic system seen in INPH. In addition, both LVD and SVD (as well as VRFs) increase the vulnerability of the brain. This increased vulnerability of the brain in combination with the disturbed CSF-dynamics may cause the clinical features of INPH. Since most VRFs are modifiable, this could add new possibilities to the treatment of INPH.*

**INPH in vascular disease**

INPH is an underdiagnosed and undertreated condition\(^\text{13, 16}\) and is probably even more underdiagnosed among frail elderly\(^\text{15}\). An interesting question is if the results from paper I (4% possible INPH in
a TIA population) are applicable to the general elderly population. When comparing the included TIA patients in paper I with the INPH patients and controls in papers II-IV, the INPH patients had a higher mRS than the TIA patients (meaning a higher grade of disability). When comparing the VRFs assessed for the TIA patients in paper I with the same VRFs among the INPH patients in paper II, it is interesting to note that the INPH patients had VRFs in a higher degree than the TIA patients: hypertension (83% vs. 79%), diabetes (27% vs. 13%) and smoking (55% vs. 43%). The VRF profile of the TIA patients (as shown in paper I) was somewhat more similar to the controls than to the INPH patients. It is also noteworthy that when the Japanese radiological criteria were applied, the prevalence of possible INPH was exactly the same as in one of the Japanese prevalence studies. This could suggest that the results in paper I may be generalizable to the general elderly population.

The prevalence of 4% of possible INPH in a population ≥50 years of age is very high compared with the results reported in most population-based prevalence studies. When comparing this result with the prevalence reported in the most recent review regarding prevalence, possible INPH was three times more common among patients with TIA than in the general elderly population >65 years of age (4% vs. 1.3%). In addition, paper II showed that both CVD and VRFs are overrepresented in INPH patients, and CVD has previously been shown to be associated with INPH. Thus, the confounding effect of CVD must be taken into account and the results in paper I should not be generalized to the entire elderly population. However, the prevalence of 4% of possible INPH among patients with CVD should probably be regarded as a minimum number, since the investigated TIA patients represent a quite healthy subpopulation of CVD patients. INPH is an underdiagnosed condition, and as shown in paper I, the disease may be even more underdiagnosed in a population with CVD. INPH is a treatable condition, and the high number of TIA patients with possible INPH motivates further screening for INPH among patients presenting with stroke and/or TIA and a history of unexplained gait/balance disturbance in combination with ventriculomegaly.

Is INPH a vascular dementia?

**Summary and hypothesis testing through Hills’ criteria**

It is unquestionable that obstructive hydrocephalus and secondary hydrocephalus are caused by disturbances in the CSF dynamic system.
Since the obvious symptom of ventriculomegaly and the treatment (insertion of a shunt) is the same, INPH is traditionally coupled with the rest of the subgroups of hydrocephalus. However, it is possible that this association may lead to a misclassification. Since the insidious onset of clinical symptoms, the typical age span and the high level of comorbidity differentiates INPH from the rest of the hydrocephalus group, there may be other causes for INPH. A disturbance of the CSF circulation is probably not sufficient for developing INPH\textsuperscript{162} and it is possible that the disturbance of the CSF dynamic system may be a symptom rather than a cause of INPH.

A grand unifying theory, suggesting just one factor in itself sufficient for causing INPH according to Rothman’s pie-chart model, is highly unlikely. A disturbance of the CSF dynamic system is necessary for the diagnosis of INPH. However, the cause for INPH is most likely multifactorial, involving several contributing causes such as vascular comorbidity, disturbances in the CSF dynamic system and normal senescence. When applying Hill’s criteria, vascular disease, particularly SVD and its risk factors, may form a biologically plausible pathophysiological pathway for both the disturbances in the CSF dynamics and the disturbed brain function, coherent to the known natural history and possible biology of the disease.

**Paper II** demonstrated strong associations between INPH and both VRFs and CVD, altogether fulfilling Hill’s strength criteria. Multiple lines of evidence have previously linked WML and CVD to INPH\textsuperscript{(2, 7, 18, 19, 21, 46, 96-99)}, adding consistency to the association. When comparing the results in paper I with other prevalence studies, INPH was three times more common in a healthy subpopulation with CVD than in the normal population. In addition, paper II showed that the higher the number of VRFs, the more likely the individual was to have INPH. This to some extent fulfils the biological gradient criteria, but these results need to be replicated.

Subcortical VaD, i.e. Binswangers disease or SAE, is probably the most common differential diagnosis when diagnosing INPH. Patients with VaD often have a larger number of WML and are somewhat older than patients with INPH. In contrast with INPH, VaD is considered incurable. However, the clinical symptoms of INPH and VaD are similar, the ventriculomegaly is present in both conditions, and WML is common in INPH patients\textsuperscript{(2, 7, 18, 19, 96, 97)} and can sometimes not be
distinguished from the WML in VaD\(^{(166)}\). INPH has been proven to be a progressive disease, with symptoms only partly reversible after shunting\(^{(65)}\), and VaD may improve after insertion of a shunt\(^{(21)}\). In summary, these findings fulfil the analogy criteria linking INPH to VaD.

The SVD vascular hypothesis does not fulfil the specificity criterion. Patients may present with a heavy amount of VRFs and CVD without having INPH, and some INPH patients do not have any typical signs of CVD. An association and possible causal relationship between vascular disease and INPH have previously been suggested\(^{(4, 7, 22-25)}\). The INPH-CRasH study provides additional support of that theory. However, the temporality criteria, the most important criteria to prove causation, have not been fulfilled. To prove a causal relationship between VRFs, vascular disease and INPH, prospective studies that investigate the exposure to VRFs and the development of vascular disease before the manifestation of INPH need to be conducted. In addition, case-controlled studies that investigate the hypothesised association between vascular disease and the CSF dynamic disturbance in INPH are needed. To fulfil the experiment criteria, the effect of VRF treatment in INPH needs to be evaluated, and the effect of shunting in subcortical VaD/Binswangers disease/SAE needs to be replicated in larger studies.

Nevertheless, considering all of the available evidence, it may no longer be beneficial to look at INPH and VaD as two separate entities but rather as two manifestations of the same disease, where patients with VaD have had a longer disease duration and accordingly, more irreversible brain damage. For a schematic overview of Hill’s criteria regarding the vascular hypothesis in INPH, see table 16.

<table>
<thead>
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<th>Criteria</th>
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<th>Not fulfilled</th>
</tr>
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<td>Strength</td>
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<td></td>
</tr>
<tr>
<td>Consistency</td>
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<tr>
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<td>Coherence</td>
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<td>Analogy</td>
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</table>

Table 16. Schematic overview of fulfilment of Hills criteria for the vascular hypothesis in INPH.
Depression and quality of life in INPH

Both depression and INPH are underdiagnosed conditions among the elderly. In a recent review regarding modifiable VRFs for dementia, depression was considered one of the most important risk factors. As shown in paper III, the shunted INPH patients presented with a remarkably higher prevalence of depression than the normal elderly population (46% vs. 13%). In addition, the INPH patients had more severe symptoms of depression than the normal population. Even when compared with the frequency of depression in other dementias, the percentage of depression in INPH patients was high, more in line with the frequency of depression in patients with VaD or stroke than in patients with AD.

Depression among the elderly often has physiological or organic reasons. There is increasing evidence of a two-way relationship between CVD and depression as well as an association between VRFs and depression. CVD, especially subcortical SVD manifesting itself as deep WML, is associated with a heightened risk for depression, and depression is also a risk factor for both stroke and TIA. WML are a frequent comorbidity in INPH, and the patients in paper III had both CVD and VRFs to a greater extent than the general population (as shown in paper II). This indicates a possible connection between vascular disease and depression in INPH patients. Providing further support for such a connection is the striking similarity between typical vascular depression and the cognitive symptoms of INPH. Both are characterized by executive dysfunction, apathy and cognitive impairment, indicating a frontal-subcortical pathway.

The executive symptoms are the ones least likely to improve after shunting in INPH. Depression severely affects cognitive function among the elderly. Thus, it may be hypothesised that a lack of improvement in cognition after surgery may partly be explained by a coexisting, undiagnosed and untreated depression. If the depression in INPH has somewhat vascular causes, optimizing the VRF profile of INPH patients, as suggested in paper II and figure 18, may also improve the symptoms of depression, similar to what has been suggested regarding vascular depression. However, the hypothesis that VRF treatment may have a positive effect on the cognitive symptoms and depression in INPH must be investigated further in future studies.
Few studies that investigate the neuropsychological profile of INPH report the frequency of depression. In the recently launched INPH scale\(^{(169)}\), no measurement of depression is included in the neuropsychological test battery. This means that a coexisting depression would act as a huge confounder, making the results of the neuropsychological tests unreliable. Recently, a computerized neuropsychological test battery specifically designed for INPH was presented, CoGNIT (COMputerized General Neuropsychological INPH Test), incorporating a depression scale\(^{(125)}\).

In dementia research, the importance of measuring QoL in elderly has been emphasized\(^{(82-85)}\). Applying a risk-benefit as well as cost-utility perspective, QoL is an important instrument to include when evaluating the effect of a specific treatment. However, very few studies have included QoL as an outcome measure after shunting in INPH. In paper IV, it was shown for the first time that INPH patients perceive that shunting improves their QoL on a long-term basis. This is in accordance with what has previously been suggested in short-term studies\(^{(87, 89, 90)}\). Paper IV also demonstrated that the most important predictor for low QoL was a coexisting depression, corresponding to what has been found in INPH patients before shunting\(^{(86)}\). Paper III showed that almost half of shunted INPH patients might suffer from a depression. Thus, to optimize care and QoL, it is important to screen for depression in both research and the clinical care of INPH patients. If needed, adequate treatment for depression should be initiated as soon as possible.

Paper III also showed that the severity of the hydrocephalic symptoms was one of the main predictors for depression in shunted INPH patients, and paper IV showed that next to depression, the severity of gait disturbance was the other main independent predictor for low QoL. The severity of the hydrocephalic symptoms was more important than outcome of surgery regarding both depression and QoL. Thus, in addition to treating a coexisting depression, it may be beneficial to add a physical exercise program to the rehabilitation of INPH patients, as was done in the SINPHONI study\(^{(72)}\).
Reliability and validity of the data

**General methodological considerations**

*Paper I*

In *paper I*, detailed examinations were performed on a reasonably large number of participants (n=76) by experienced professionals or by investigators with high interrater reliability compared with experienced professionals. These factors minimize the risk of random error and increase the reliability/precision of the study. Regarding internal validity, all of the TIA patients were thoroughly examined in a similar manner, and all of the patients underwent a CT scan. In addition, all of the symptoms of the TIA were confirmed to have vanished within 24 hours (but most often within minutes or one hour), meaning that the results of the final clinical examinations should reflect the habitual state of the patient. This approach minimizes the risk for information bias and confounding. Thus, the study should have high internal validity.

Regarding external validity, the results presented in *paper I* cannot be generalized to the elderly population as a whole since TIA patients cannot be considered to represent the general population. A large number of TIA patients were excluded due to other concomitant medical conditions, most likely inducing a selection bias of the healthier TIA patients and increasing the probability of a type 2 error. Thus, the finding that 4% of patients have possible INPH is probably an underestimate, and 4% should be regarded a minimum percentage. With precaution for this type 2 error, the results can in part be generalized to elderly patients with CVD, although the true percentage of patients with possible INPH in a population with CVD is probably higher.

*Papers II-IV*

In *papers II-IV*, shunted INPH patients (n=176) were compared to age- and gender-matched controls from the normal population (n=368). The INPH-CrAsH study represents one of the largest research cohorts of INPH patients, thus minimizing the risk of random error and providing good reliability. Internal validity should also be high. All of the information was prospectively assessed in similar ways for both the patients and the controls, including similar questionnaires, a per-protocol standardized visit to the nearest health-care provider and biological markers (blood samples, ECG and anthropometrical measurements). All self-ratings in the questionnaires were assessed using well-known, validated instruments. For the comparisons between patients and
controls, this altogether minimizes the risk for information bias. A possible limitation is that different examiners throughout the country examined the patients, whereas the same examiner investigated all of the controls. This might have induced some bias in the data collection. However, since all of the visits followed the same protocol, this risk should be small. Regarding confounding, patients and controls were first matched according to age and sex. Second, to avoid confounding in the analyses, a multitude of parameters were collected, and all variables that proved significant in the univariable analyses were analysed controlled for confounders in the multivariable models.

The included cases were the majority of non-demented INPH patients properly diagnosed with INPH and consecutively shunted during a three-year period in Sweden. There is no reason to believe that the patients that were assigned to the sixth neurosurgical centre (which did not participate in the study) differed from the rest of the patients in any way. Thus, the included patients should be representative of non-demented shunted INPH patients. It should however be noted that since one of the exclusion criteria was a preoperative MMSE<23, this might have induced a selection bias of the healthier patients. Thus, the reported results should probably be regarded as minimum numbers, and some of the associations might have been stronger if patients with MMSE<23 had been included. The controls were population-based and from the same source population as the patients. There was no selection of “healthy” controls (except for the same exclusion criteria as the patients). This means that the controls should be representative of the general non-demented elderly population. In summary, this means that the external validity or generalizability of the results presented in papers II-IV should be reasonably high.

**Some specific methodological concerns**

*Causality*

The main limitation of the INPH-CRasH study is that the VRFs were assessed after the INPH diagnosis, which means that causality was not possible to determine. However, in the typical vascular disease process, VRFs accumulate over the course of several years, eventually leading to the disease state. In *paper II*, it was shown that there were no differences in the VRFs when comparing the patients from the three years of surgery, and it has been shown previously that the frequency of neither hypertension nor diabetes increases with the duration of INPH\(^6\). Furthermore, there are no biologically plausible explanatory models for
INPH acting as a risk factor for VRF, while there are several possible models presenting VRFs as risk factors for INPH, as previously discussed. Thus, there is little reason to believe that the assessed VRFs in the shunted INPH patients did not exist before the diagnosis.

**Comparisons before-after surgery**
For some of the parameters, the patients were asked to recall how they had felt before surgery. Since these pre-operative answers suffer from an uncontrolled recall-bias, they should be cautiously interpreted even though they provide information on how the patients perceive their life to be before shunting.

**Outcome of surgery**
In papers II-IV, there were no significant differences in outcome of surgery between 3 and 12 months for any of the included outcome parameters. Since there were more participants in the 3-month postoperative follow-up, those values were used. However, since there was a discrepancy in time between when outcome of surgery and the other investigated parameters were assessed, the comparisons involving the outcome parameters should be interpreted with some precaution.

**Geographical matching**
Some differences were noted between the results of the primary analysis and those of the sub-analyses, and it cannot be completely precluded that these differences were due to an unknown parameter distinguishing the controls’ geographical area from the other geographical areas. However, all of the participants in papers II-IV came from the same country and had similar living conditions. Thus, the loss of some of the significances in the sub-analyses was probably due to the smaller sample sizes.
Suggestions to improve clinical care in INPH

An advanced differential diagnostic perspective is essential in the clinical care of all elderly patients. This is even more important in INPH patients since the symptoms of INPH may resemble many other common conditions. Such a multifactorial approach is equally important for neurologists and neurosurgeons, who need to consider and perhaps screen for other conditions that may coexist with INPH, as well as for primary care physicians and geriatricians, who need to consider INPH as a differential diagnosis along with other common conditions among the elderly. When providing clinical care for elderly patients, it is unacceptable to miss common, possibly treatable, coexisting conditions that may severely impact daily life and QoL for patients during their final years of life.

Specific suggestions generated from the work in this dissertation are as follows:

✔ Patients with CVD and ventriculomegaly in combination with an unexplained disturbance in gait or balance existing before the TIA/stroke should be referred to a hydrocephalus centre or a specialist with an interest in INPH for further evaluation if the symptoms of stroke are not too pronounced.

✔ Depression should be screened for as part of the clinical routine in INPH patients. If the screening reveals a possible coexisting depression, the diagnosis needs to be adequately confirmed and treatment should be considered.

✔ A VRF profile screening should be part of the preoperative evaluation of INPH patients. Coexisting risk factors should be optimized according to modern guidelines for vascular disease and risk factors (32, 37).

✔ Since the severity of the gait disturbance is one of the most important predictors for both low QoL and depression in INPH patients, it may be beneficial to add physical exercises after surgery (72).
Further directions of research

One of the major shortcomings in INPH research is that many studies include only a small number of patients and lack representative controls, thus reducing precision and possibly inducing bias. In addition, many studies only investigate a single variable or a few variables, which makes them vulnerable to confounders. INPH is a disease of interest to neurologists, neurosurgeons, neuroradiologists and physicists, reflecting the multifactorial aspects of the disease. To properly investigate the pathophysiological processes involved in INPH, a multidisciplinary approach is needed, combining hypotheses generated from different fields and investigating them in studies with correct epidemiologic design and sufficient power to prove or reject the hypotheses.

Specific suggestions generated from the work in this dissertation are as follows:

- In neuropsychological studies investigating the cognitive aspects of INPH, a screening instrument for depression should be included, such as in the recently launched computerized neuropsychological test battery CoGNIT(125).

- To prove a causal relationship between INPH and VRFs/vascular disease, a large prospective population-based study should be conducted with a similar design as the INPH-CRasH study, investigating if VRFs and CVD exist before the diagnosis of INPH.

- The effect of VRF treatment in INPH patients should be evaluated.

- The effect of coexisting VRFs and CVD on the CSF dynamic disturbance seen in INPH should be investigated.

- Measurements of QoL should be included in studies investigating outcome of surgery in INPH patients, facilitating both risk-benefit and cost-utility analyses.
CONCLUSIONS

Ventriculomegaly and symptoms of INPH are common among elderly individuals with cerebrovascular disease. Among patients with cerebrovascular disease, one in twenty-five may also have INPH.

INPH patients have more vascular risk factors than the normal elderly population. The most important vascular risk factors in INPH are diabetes, hyperlipidemia, obesity, psychosocial factors, physical inactivity and hypertension. Together, these risk factors account for almost one quarter of INPH in the elderly population. Vascular disease, particularly cerebral small vessel disease, may be the underlying pathophysiological cause of INPH. In the clinical care of INPH patients, vascular risk factors should be screened for, and coexisting risk factors should be optimized.

Depression is overrepresented in INPH patients compared with the normal elderly population. Screening for depression should be included in the clinical routine and in neuropsychological testing of INPH patients.

INPH patients perceive that their quality of life improves after shunting. This perceived improvement is long-lasting, even though shunted INPH patients still have a lower quality of life than the normal elderly population. The main predictor for low quality of life among shunted INPH patients is a coexisting depression.
APPENDIX

1. Authors’ contributions
Contributions by Hanna Israelsson Larsen to each paper included in this dissertation.

<table>
<thead>
<tr>
<th>The author’s responsibility</th>
<th>Paper</th>
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<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Conception and/or design</td>
<td>-</td>
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<tr>
<td>Planning of the study</td>
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<td>Acquisition of data</td>
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<tr>
<td>Analysis and interpretation</td>
<td>b</td>
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<tr>
<td>Drafting the paper</td>
<td>a</td>
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<td>Journal correspondence</td>
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a. main responsibility
b. contributed to high extent
c. contributed
Basic information
1. Code
2. Age at admission to hospital
3. Gender
4. ICD-10
5. Year and date for admission to hospital

History: life before admission to hospital
1. Previous stroke
2. Disturbances in balance/gait (yes/no)
   • If disturbances: known cause (yes (=exclusion)/no)
   • Help for walking (no/walking stick/walker/wheelchair)
3. Physically active (yes (describe)/no/impossible to determine)
4. mRS
5. Cause of high mRS (balance/gait/other)

Investigation: during stay at hospital
1. Cause of admission to hospital (if other than TIA=exclusion)
2. Any additional focal neurological symptoms during stay at hospital, if so=exclusion
3. Disturbance in balance (no/mild/severe)
   • Able to carry out Rombergs
   • Able to carry out tandem stance
   • Able to stand on one leg
   • Tendency to fall
4. Disturbances in gait (no/mild/severe)
   • If gait disturbance – describe
5. Aphasia (yes/partly/no)
6. Oriented and understand instructions (yes/partly/no)

History + investigations
1. Dementia (no/mild (small amount of cognitive decline but can still manage ADL)/severe (large amount of cognitive decline, ADL is affected))
2. Incontinence (yes/no)
3. ADL according to Katz

Risk factors
1. Diabetes (yes/no)
2. Hypertension (treated (yes/no)
3. Smoker (yes/previously/no)
4. Heart disease (healthy/myocardial infarction/angina/congestive heart failure/atrial fibrillation/other)
5. Previous diagnoses (complete list)
6. Angiocardiology performed (yes/no)
   • Carotid stenosis (yes (above 50% in one artery, comment if less)/no)
Vascular risk factors in patients with idiopathic normal pressure hydrocephalus

INSTRUCTIONS:
1. Let the patient sit down and rest for 5 minutes.
2. Fill in the form at the back of this paper.
3. Perform an ECG. Print a stripe.
4. Draw a blood sample. Pipes and referrals available in the enclosed brown padded envelope.

**Sampling:**
5 ml venous blood should be drained into each of the three supplied Li-hep tubes.

**Further handling of blood samples:**
The tubes should be marked with the enclosed labels. Each blood sample should be centrifuged for 30 minutes, then placed into the transport sleeves.

5. Put this form, the ECG stripe and the three tubes with blood in the prefilled envelope. Send the letter back the same day.

Thank you for your help!

FORM
(for health care professionals at the health care center)

Name of the patient: ........................................
Social security number: ....................................
Length (cm): ...................................................
Weight (kg): ...................................................
Circumference of waist (cm): ............................
Circumference of hips (cm): ..............................

(Waist: measure at narrowest circumference or 2 cm above the navel. Measure without clothes. Hips: Measure over light clothing at widest circumference. See picture to the right.)

Blood pressure:
(After 5 min rest, measure resting blood pressure three times at the level of the heart in the right arm with the patient seated. 1 min rest between each measurement).
1. ....................... 
2. ....................... 
3. ....................... 

ECG
Connect an ECG. Print a stripe, and enclose the printed stripe in the letter that is sent back to University hospital of Umeå.
Idiopatisk normaltryckshydrocefalus, kallad INPH från engelskans “Idiopathic Normal Pressure Hydrocephalus” är en demenssjukdom som drabbar äldre. Medelålder vid insjuknande är runt 70 år. Den “klassiska symtomtriaden” vid INPH är:

1. gång- och balanssvårigheter,
2. demens,
3. urininkontinens.


Det är inte helt klarlagt hur många individer i befolkningen som har INPH. Mellan 0.02-14% har rapporterats i olika sorters populationer. Orsaken till sjukdomen är oklar, men det finns teorier kring att INPH skulle kunna orsakas av liknande mekanismer som vaskulär sjukdom (alltså t.ex. hjärtinfarkt och stroke). Vaskulär sjukdom brukar föregås av vaskulära riskfaktorer (faktorer som ökar risken för att få vaskulär sjukdom, t.ex. högt blodtryck, diabetes eller en ogylnsam blodfettsprofil). Det finns några få tidigare studier som tyder på att INPH-patienter har fler vaskulära riskfaktorer än normalbefolkningen, men de flesta tidigare studier är gjorda på ett för litet patientmaterial för att kunna fastställa ett säkert samband.

Depression är vanligt hos äldre och ännu vanligare hos individer med demens. Dessutom är depression i sig både en riskfaktor för vaskulär sjukdom samt en riskfaktor för svårare demens. De symtom på demens som INPH-patienter oftast uppvisar påminner om symtomen på depression. En samtidig depression hos en INPH-patient skulle troligtvis påverka hur bra patienten svarar på shuntoperationen. Trots det är det okänt hur många patienter med INPH som samtidigt lider av depression, och idag utförs ingen screening för depression innan kirurgi.
Syftet med avhandlingen
Det primära syftet med den här avhandlingen var att beskriva vaskulär sjukdom och den vaskulära riskfaktorprofillen hos en stor grupp INPH patienter, och jämföra med en ålders- och könsmatchad normalpopulation (i artikel II). Ytterligare ett syfte var att undersöka hur stor andel av de patienter som har vaskulär sjukdom som också skulle kunna ha INPH (i artikel I). Två ytterligare syften var att utforska hur stor andel av shuntade INPH-patienter som har depression (i artikel III), samt att undersöka hur shuntoperationen och andra möjliga faktorer påverkar livskvalitén hos shuntade INPH patienter (i artikel IV).

Metoder

Artikel I
Här undersöks de medicinska journalerna från de patienter som hade haft en TIA (från engelskans Transient Ischemic Attack) 2006-2008 i Umeå. En TIA är en vaskulär sjukdom och kan sägas vara en mini-stroke, där symtomen ska ha avklingat inom 24 timmar (men vanligtvis har avklingat inom några minuter eller en timme). Alla TIA patienter undersöks grundligt med gång- och balanstester och radiologiska undersökningar när de kommer in till sjukhuset, vilket gör det möjligt att göra en noggrann journalgenomgång i efterhand. Journalerna och de radiologiska bilderna på totalt 76 TIA-patienter undersöktes i detalj för att se hur stor mänga som skulle kunna ha INPH.

Artiklarna II-IV

**Resultat och slutsatser**

I artikel I hade 4% av TIA-patienterna möjlig INPH. Det är tre gånger fler än vad som tidigare rapporterats i normalbefolkningen (1.3%). TIA är en vaskulär sjukdom och resultatet tyder på att det kan finnas vaskulära komponenter i INPH.

I artikel III visades att INPH-patienter led av depression i mycket högre utsträckning än normalbefolkningen (46% mot 13%). I artikel IV visades att INPH-patienterna tyckte att deras livskvalité förbättrades efter shuntoperationen, och att förbättringen höll i sig över tid. Trots det, hade INPH-patienterna lägre livskvalité än normalbefolkningen. Den största anledningen till låg livskvalité hos INPH-patienterna var depression. Sammantaget innebär det här att man bör screena för depression i vården av INPH-patienter. Om depression förekommer tillsammans med INPH bör man överväga behandling, och utvärdera effekten av behandlingen både kliniskt och i forskning.
ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to all of you who have helped and encouraged me along the way. Especially, I would like to thank:

**Jan Malm**, my main supervisor. You are the best mentor anyone could wish for. Thank you for your never-ending support, for gradually letting me take more and more responsibility and grow as a researcher, for continuously encouraging me and believing in me, for answering my e-mails in the middle of the night and for your enthusiasm and honesty. You are an amazing professor and supervisor and I am deeply grateful for the privilege of working with you.

**Anders Eklund**, my co-supervisor. Thank you for believing in me, for your intelligent, to-the-point suggestions and comments, for your patience and availability, for your continuous encouragement and for sharing your statistical knowledge.

My co-authors: **Richard Birgander** for explaining and sharing the joy of MRI and teaching me how to interpret radiological pictures. **Khalid Ambarki** who, when I entered the research group as a medical student on the second semester, with great tutorship learned me about ventricular volume and measurements. **Per Allard**, in memorandum, for your great enthusiasm, for your valuable comments and suggestions and for teaching me a lot about depression in elderly. **Bo Carlberg** for your invaluable support all through the INPH-CRasH project; providing helpful suggestions and references as well as taking time for discussing vascular risk factors in detail. **Carsten Wikkelso**, **Katarina Laurell**, **Babar Kahlom** and **Göran Leijon** for valuable comments on the paper and support during conference meetings.

I also want to thank **Lars-Owe Koskinen**, for letting me attend to my first craniotomy. I will never forget the feeling of amazement and wonder. Thanks also to **Hans Stenlund** and **Anna Myléus** for statistical help and epidemiological advice.

All the staff at the neurological department in Umeå. You are the best. **Kristin Nyman**, research nurse – without you there would have been no controls in the INPH-CRasH study. Thank you for providing structure, for booking appointments for all the controls, and thank you for helping out with the measurements. **Jörgen Andersson**, without you I would
not have been able to calculate anything. Thank you for constructing the filemaker database and for helping me with thousand and one technical questions. You’re a computer magician. Thank you Sonja Edvinsson and Hanna Ackelind for your help with the blood samples. Thank you Sara Widmark, Birgitta Nordin and Kerstin Gruffman for administrative support and for helping me out of with a lot of last-minute crises. I also want to thank Erika Strålberg and Anton and Sanna for helping me put data into the database.

Colleagues and staff during my time at the neurosurgical clinic in Gothenburg. I learned a lot and enjoyed working with you! Special thanks to Magnus Tisell who hired me, and Dan Farahmand, Andreas Bartley and Katrin Rabie for letting me assist you during shunt surgery.

Colleagues in the research group and/or fellow PhD-students for good laughs, “fika” breaks, for interesting discussions and a great deal of fun at conference meetings: Nina Sundström, Jennifer Frankel, Anders Wählín, Tora Dunäs, Tomas Bäckström, Kennet Andersson, Laleh Zarrinkoob and Petter Holmlund. Special thanks to Sara Qvarlander for interesting discussions, for much needed coffee breaks and for teaching me a lot about CSF dynamics – sometimes even without using any formulas ;). Special thanks also to Anders Behrens who helped proof-reading the dissertation.

My friends: I love you. I would never have been able to do this without you. Kerstin, thank you for always being a wonderful friend. Thank you Erik, Jennifer, Sandra, Simon and Elisabeth, Anny, Mattias and Hans; you gave me a place to sleep on during long days and nights of writing when I was not at home, reminded me that I needed to eat, fed me and helped me relax, let me complain and then cheered me up. Thanks to Daniel Rinnström for the CRaSH acronym (and for the cave fish and the weird heads) and to Pernilla Israelsson who helped proof-reading the dissertation. Also thanks to the whole TG (you know who you are), to MESK (and the spex and the city crew) who gave me friends for life. Special thanks to Skalman who helped me through a lot of computer crises (among other things saved one of my lectures with only hours to go before the lecture…)

Thank you Adam Stolterman, for listening to my idea for cover, and painting the picture even more beautiful than I could imagine.
Mother, thank you for your love and rock-hard belief in that I can do anything I want. Thank you for teaching me how to fight and never give up, thank you for being a true role-model, and thank you for the luxurious chocolate... Father, you taught me the importance of truth, and the importance of being honest, in work and in life. I know you watches over me, and will continue to do so all through my life. TOBIAS, MIN ÄLSKADE LILLEBROR! DU ÄR BÄST!

And last... and first... and always: Robert, my love, my husband, the one who makes my heart sing. Thank you for your continuous support, patience and love. Thank you for sometimes forcing me to take breaks away from work. Thank you for boosting me and taking care of me, and thank you for loving me when I am not even the slightest bit loveable.
REFERENCES


