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ANTTI JUNKKARI

HEALTH-RELATED QUALITY OF LIFE IN PERSONS WITH IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

Health-related quality of life in persons with idiopathic normal pressure hydrocephalus

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ABSTRACT:

Idiopathic normal pressure hydrocephalus (iNPH) is a relatively rare progressive condition of the aged population, often featuring impairment of gait and cognition, as well as urinary incontinence and enlarged brain ventricles. The diagnosis of iNPH is challenging due to other conditions with overlapping symptomology. Cerebrospinal fluid (CSF) shunting remains the only available treatment for iNPH, relieving some of the symptoms in the majority of patients. iNPH patients who are not treated have been estimated to deteriorate. A larger comorbidity burden, coexisting Alzheimer's disease (AD)-related pathology, older age, and a longer duration of the disease have been associated with a worse outcome, but do not exclude a favorable response to CSF shunt therapy. While the etiology of iNPH is still mostly unknown, our knowledge of the pathophysiology of iNPH has increased.

Health-related quality of life (HRQoL) is relatively new concept that has during the past decades been used in medicine, for example, to estimate the efficacy of an intervention. HRQoL has attracted considerable interest in AD research, but not in iNPH. Consequently, no guidelines exist on how to measure HRQoL in patients with iNPH, and little is known about the factors contributing to the HRQoL of patients with iNPH. This doctoral thesis is based on a unique prospective cohort study, the objective of which was to identify factors affecting and predicting patient-reported HRQoL, measured using the generic 15D HRQoL instrument, in patients with iNPH prior to and after CSF shunting. In our study, more severe iNPH and the presence of depressive symptoms predicted lower HRQoL in persons with iNPH prior to treatment. Patients with iNPH have significantly lower HRQoL scores compared to the general population. During a one-year follow-up after CSF shunting, less than half of the patients with iNPH experienced a significant improvement in their HRQoL. The absence of AD-associated pathology in the frontal cortical biopsy and a lower body mass index were associated with an improvement in HRQoL (one year after CSF shunting). Subjective hearing loss following CSF shunting in persons with iNPH was more common than previously thought. This study revealed that a small proportion of persons with iNPH treated with a CSF shunt do not experience an improvement in HRQoL, despite a favorable clinical outcome. This discrepancy is partly explained by the severity of iNPH-related symptoms, co-existing chronic pulmonary disorder, or the existence of any non-metastatic cancer.

In conclusion, the 15D instrument is potentially a reliable tool for measuring HRQoL in patients with iNPH. Less than half of the patients with iNPH experience a significant improvement in HRQoL one year after CSF shunting. A small proportion of

persons with iNPH who are treated with a CSF shunt do not experience an improvement in HRQoL, despite a favorable clinical outcome.

National Library of Medicine Classification: W30, W74, W950, WL300, WL203, WM 220, WT150, WT155
Medical Subject Headings: Normal Pressure Hydrocephalus; Alzheimer's disease; Quality of Life; Depression; Cohort studies; Comorbidity; Cerebrospinal Fluid; Biopsy; Risk Factors;

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TIIVISTELMÄ:

Idiopaattinen normaalipaineinen hydrokefalia (iNPH) on hiipien alkava, tuntemattomasta syystä aiheutuva aivorappeumasairaus, joka luonteenomaisesti heikentää etenevästi kävely- ja virstanpidätyskykyä sekä tiedonkäsittelyä (kognitiota), esiintyen yleisimmin ikääntyneessä väestössä. Oireisilla henkilöillä havaitaan laajentuneet aivokammiot aivojen magneetti- tai tietokonekuvissa. Taudin diagnostiikkaa hankaloittavat muut sairaudet, jotka imitoivat iNPH:lle tyypillistä taudinkuvaa. Ainoan saatavilla olevan hoidon, aivo-selkäydinnestesuntin, on raportoitu lievittävän osaa sairauteen liittyvistä oireista suurimmalla osalla potilaista. Sairauden on arvioitu etenevän hoitamattomilla potilailla. Hoidon ennustetta huonontavat muut samanaikaisesti esiintyvät sairaudet, kuten Alzheimerin tauti (AT), korkea ikä ja sairauden pitkä kesto, mutta ne eivät poissulje suotuisaa hoitovastetta. Vaikka sairauden syy on edelleen tuntematon, tunnetaan iNPH:n patofysiologiaa nykyisin paremmin.

Terveyteen liittyvä elämänlaatu (Health-Related Quality of Life, HRQoL) on suhteellisen uusi käsite, joka on kasvattanut suosiota lääketieteessä viime vuosikymmeninä. HRQoL on ollut erityisenä mielenkiinnon kohteena AT:ssa, mutta iNPH-tutkimukseen HRQoL on ilmaantunut vasta viime vuosina. Tämä selittää sen, ettei elämänlaadun mittaamiseen iNPH:ssa ole kansainvälisiä suosituksia ja HRQoL:llään vaikuttavista tekijöistä iNPH:ssa tiedetään vain vähän.

Tämä väitöstutkimus perustuu vuoden mittaiseen seurantatutkimukseen, jonka tarkoituksena oli tunnistaa, 15D-elämänlaatumittarin avulla, iNPH potilaan itse arvioimaan elämänlaatuun vaikuttavia tekijöitä ennen aivo-selkäydinnestesunttia ja sen jälkeen. Vakavampi iNPH-sairaus ja samanaikaiset masennusoireet ennustavat matalampaa elämänlaatua ennen leikkausta. iNPH potilaiden elämänlaatu on huomattavasti matalampi kuin samanikäisellä verrokkiväestöllä. Seurannassa alle puolet potilaista kokee itse elämänlaatunsa merkittävästi parantuneen sunttihoidon jälkeen. Jos potilaalla ei ollut aivobiopsiassa AT-muutoksia tai hänellä oli pienempi painoindeksi, elämänlaatuvaste sunttihoidolle oli parempi. Subjektiivinen kuulonalenema leikkauksen jälkeen saattaa olla yleisempää kuin aikaisemmin on ajateltu. Pienellä osalla elämänlaatu ei parane huolimatta kliinisten oireiden helpottumisesta. Tätä ristiriitaa selittävät osittain potilaan sairauden vaikeusaste ja potilaan muut sairaudet, kuten samanaikaisesti esiintyvä krooninen keuhkosairaus tai sairastettu (etäpesäkkeetön) syöpä.

Näyttää siltä että 15D-elämänlaatumittari soveltuu HRQoL:n itsearviointimittauksiin iNPH – potilailla. Alle puolet iNPH-potilaista koki elämänlaatunsa

parantuneen vuoden kuluttua sunttihoidosta. Pienellä osalla iNPH:n kliinisten oireiden helpottuminen ei johtanut itse koettuun elämänlaadun paranemiseen.

Luokitus: W30, W74, W950, WL300, WL203, WM 220, WT150, WT155

Yleinen suomalainen asiasanasto: Normaalipaineinen hydrokefalia; hydrokefalia; Alzheimerin tauti; elämänlaatu; seurantatutkimus; masennus; komorbiditeetti; aivo-selkäydinneste; Kudosnäyte; Riskitekijät

To my brother

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Kuopio, November 27th 2017

List of the original publications

This dissertation is based on the following original publications:

I Junkkari A, Sintonen H, Nerg O, Koivisto AM, Roine RP, Viinamäki H, Soininen H, Jääskeläinen JE & Leinonen V. Health-related quality of life in patients with idiopathic normal pressure hydrocephalus. *European Journal of Neurology 22:1391-1399, 2015.*

II Junkkari A, Häyrinen A, Rauramaa T, Sintonen H, Nerg O, Koivisto AM, Roine RP, Viinamäki H, Soininen H, Luikku A, Jääskeläinen JE & Leinonen V. Health-related quality-of-life outcome in patients with idiopathic normal-pressure hydrocephalus - a 1-year follow-up study. *European Journal of Neurology 24:58-66, 2017.*

III Junkkari A, Roine RP, Luikku A, , Rauramaa T, Sintonen H, Nerg O, Koivisto AM, Häyrinen A, Viinamäki H, Soininen H, Jääskeläinen JE & Leinonen V. Why does the health-related quality of life in idiopathic normal pressure hydrocephalus fail to improve despite the favorable clinical outcome? *World Neurosurgery, In Press, 2017.*

Contents

Abbreviations

AD	Alzheimer's disease
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADL	Activities of daily living
AUC	Area under the curve
Aβ	Amyloid beta
BD	Binswanger's disease
BDI/BDI-21	Beck Depression Index
BMI	Body mass index
CACI	Charlson Age Comorbidity Index
CA	Callosal angle
CBF	Cerebral blood flow
CBD	Corticobasal degeneration
CDR	Clinical Dementia Rating
CI	Confidence interval
ClinRO	Clinician-reported outcome
CSF	Cerebrospinal fluid
CT	Computed tomography
CVD	Cerebrovascular disease
DESH	Disproportionately enlarged subarachnoid space hydrocephalus
DLB	Dementia with Lewy's bodies
DSI	Disease State Index
ELD	External lumbar drainage
HPτ	Hyperphosphorylated tau
HRQoL	Health-related quality of life
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
iNPH	Idiopathic normal pressure hydrocephalus
iNPHGS	iNPH Grading Scale
KUH	Kuopio University Hospital
LPS	Lumbo-peritoneal shunt
MAR	Missing at random
MCI	Mild cognitive impairment
MI	Multiple imputation
MICE	Multiple imputation by chained equations
MMSE	Mini-Mental State Examination
MNAR	Missing not at random
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
n/N	Number of observations
NA	Not applicable
NPH	Normal pressure hydrocephalus
OR	Odds ratio

PD	Parkinson's disease
PET	Positron emission tomography
pmm	Predictive mean matching
PROM	Patient-reported outcome measure
PSP	Progressive supranuclear palsy
QALY	Quality-adjusted life years
QoL	Quality of life
SE	Standard error
SAH	Subarachnoid hemorrhage
SD	Standard deviation
sNPH	Secondary normal pressure hydrocephalus
SPECT	Single-photon emission computed tomography
SPSS	Statistical Package for Social Sciences
SVD	Small vessel disease
T2D	Type 2 diabetes mellitus
UEF	University of Eastern Finland
VA	Ventriculo-atrial
VaD	Vascular dementia
VCI	Vascular cognitive impairment
WML	White matter lesions
VP	Ventriculo-peritoneal

1 Introduction

The first scientific description of the characteristics of normal pressure hydrocephalus (NPH) was published by Hakim and Adams in 1965 (1). In a summary, after the presentation of three case reports, they stated: "*The patients had exhibited mental dullness, inattentiveness, psychomotor retardation, unsteadiness of gait, and incontinence of urine, ...*", later to be called Hakim's triad or the NPH triad (1,2). In each patient, enlarged brain ventricles (ventriculomegaly) without obstruction of cerebrospinal fluid (CSF) flow were seen by using pneumoencephalography (1), an imaging technique that was later replaced by computed tomography (CT) and magnetic resonance imaging (MRI) (3). Hakim and Adams also observed that despite the ventriculomegaly, these three patients did not have elevated intracranial pressure (ICP) measured through a lumbar puncture (1), and consequently the syndrome was henceforth referred to in the nomenclature as NPH.

Shortly after the discovery of NPH, associations were found between heterogeneous events prior to the onset of NPH, mainly subarachnoid hemorrhage (SAH), but also other events such as trauma, intracerebral hemorrhage (ICH), malignancy, meningitis and stroke (4,5). In these cases, NPH was regarded as a result of other conditions and was thus named as a secondary NPH (sNPH). However, in half of the cases, no prior event leading to NPH could be identified, which led to the naming of the other NPH sub-group as idiopathic normal pressure hydrocephalus (iNPH) (2,5,6) (Figure 1).

iNPH is a chronic disease that has an insidious onset late in life and is progressive in nature, impairing the gait of the affected, while other symptoms, such as cognitive impairment or urinary incontinence, are also commonly seen (2,7-9) (Appendices 1 and 2). iNPH is a diagnostic challenge, with patients being classified according to the increasing probability of having the condition rather than having or not having the disease (2,9) (Appendices 1 and 2). The diagnosis of iNPH is further complicated by other conditions with overlapping symptomology (10). While the etiology of iNPH is still mostly unknown, our knowledge of the pathophysiology of iNPH has increased (see section 2.1.7).

CSF shunting remains the only available treatment for iNPH, relieving some of the symptoms in the majority of patients (7,11). iNPH patients who are not treated have been estimated to deteriorate (7,8) and have increased mortality (12). The variety of comorbid conditions (see section 2.8.3) and their overall burden (13-16), older age (17-19), and a longer duration of the disease (20-22) have been associated with a worse outcome, but do not exclude a favorable response to CSF shunt therapy (2,13,17,19,23-29).

Health-related quality of life (HRQoL) is a relatively new concept that has during the past decades been used in medicine, for instance to estimate the efficacy of an intervention (30,31). While many definitions of HRQoL exist, it has been considered to be a multidimensional concept (31,32). HRQoL was developed partly due to an urgent need for more patient-oriented outcome indicators and health status measurements (30,31), and it has remained an important instrument in numerous study settings (31) and conditions, such as Alzheimer's disease (AD) (33-36). While numerous tools to measure HRQoL exist, they can be divided into two different categories: I) general and II) disease-specific HRQoL instruments (31). The choice between the two depends on the purpose of the study, as

generic HRQoL measurements are used for investigating the HRQoL impairment caused by the condition, while disease-specific HRQoL instruments might be more suited to clinical trials, or to a specific condition, as they can potentially be more sensitive to a change in the health state (31,33,34,37,38).

The validity of patient-reported outcome measures (PROMs), such as HRQoL, have, however, been questioned in patients with progressive neurodegenerative disorder, as in persons with dementing illness, insight is often impaired (39), and this may affect the results of the PROMS (33,34,40-44). Formal or informal caregiver (proxy)-rated HRQoL scores are usually lower than the self-reported HRQoL (33,34,40-44).

There are only four reports focusing on HRQoL in patients with iNPH, all of which used a generic HRQoL instrument (45-48). Consequently, no guidelines exist on how to measure HRQoL in patients with iNPH, and little is known about the factors contributing to the HRQoL of patients with iNPH.

The objective throughout the present study was to identify factors affecting and predicting self-reported HRQoL, measured using the generic 15D HRQoL instrument (49) in patients with iNPH prior to and after CSF shunting. This information is required for further understanding of this condition and the aspects that are important for the HRQoL of patients in different stages of the disease. The study may help clinicians to try to modify factors impairing HRQoL and to estimate which patients will benefit from CSF shunt surgery.

2 Review of the literature

2.1 IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

2.1.1 Clinical classification

In addition to the classification of sNPH and iNPH (see section 1), a Japanese research group identified by MRI in 1998 a characteristic alteration in the subarachnoideal spaces of NPH patients (50); the majority of iNPH patients showed enlarged Sylvian fissures, while the midline surface (also called high convexity) was disproportionately narrow (50). This finding, DESH, was soon adopted in Japanese iNPH guidelines as a supporting sign of the condition and as a subclassification of iNPH (2,51) (Figure 1, Appendix 1). Recently, a study introduced a familial subgroup of iNPH (52), the role of which in the clinical classification of iNPH remains to be determined (Figure 1). The occurrence of possible familial iNPH might be as high as 16% (52).

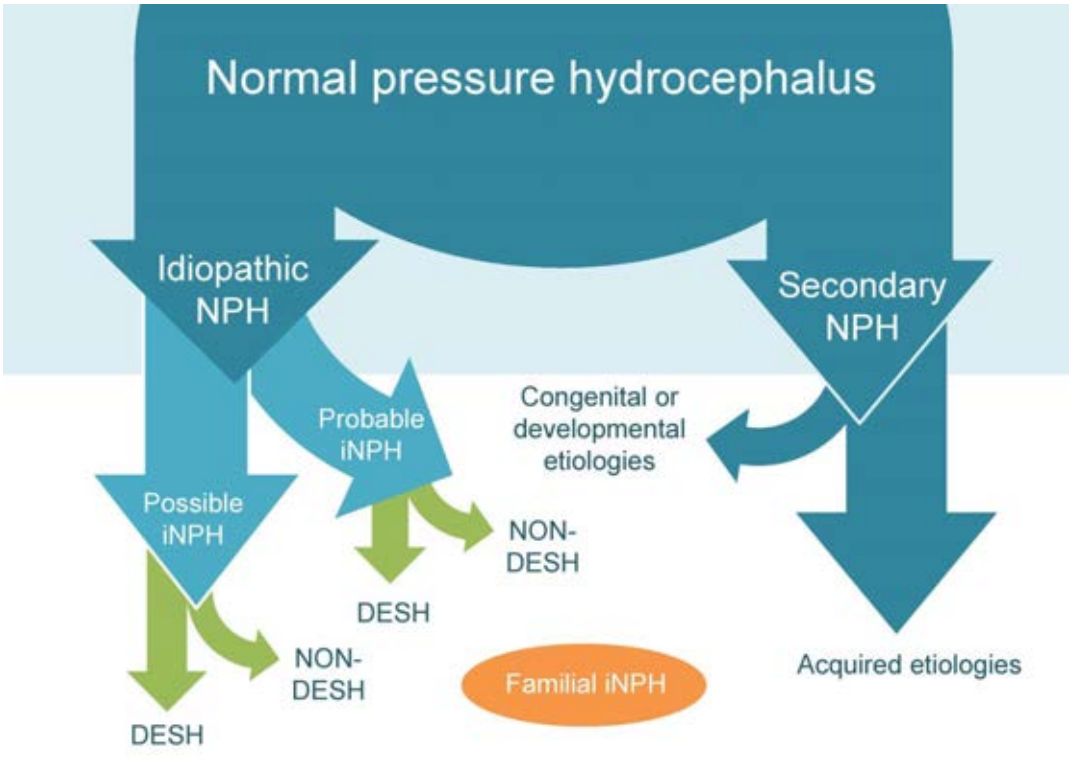

Figure 1. Clinical classification of normal pressure hydrocephalus (NPH) adapted from Mori et al. 2012. (2). The arrow size is not proportional to the frequency of the condition. Abbreviations: DESH, disproportionately enlarged subarachnoid space hydrocephalus.

2.1.2 Epidemiology

iNPH has been estimated to cause less than 5% of all dementia cases (53) (Figure 2).The incidence of iNPH is dependent on the study setting and the population (54); in hospital-based studies, the incidence is lower, on average 2.49 per 100 000 inhabitants per year, ranging from 0.22 to 5.80 per 100 000 inhabitants per year (55-62). There have been only two population-based studies reporting the incidence: the first reported a significantly higher incidence of 1.2/1000 per year among inhabitants aged 70 years or older (63) than the second, in which an incidence of 0.011/1000 per year was recorded in a nationwide population (64), which is reasonable, as the incidence of iNPH increases with age (Martin-Laez et al. 2015).

According to the latest review, the prevalence of iNPH in the general population is 1.30% globally (54), ranging from 0.42% to 2.94% in different studies (54,63,65-70). It has been noted that due to the characteristics of the two distinct guidelines for the diagnosis of iNPH, epidemiological studies using a particular set of guidelines may observe different frequencies of iNPH compared to studies using other diagnostic criteria (71).

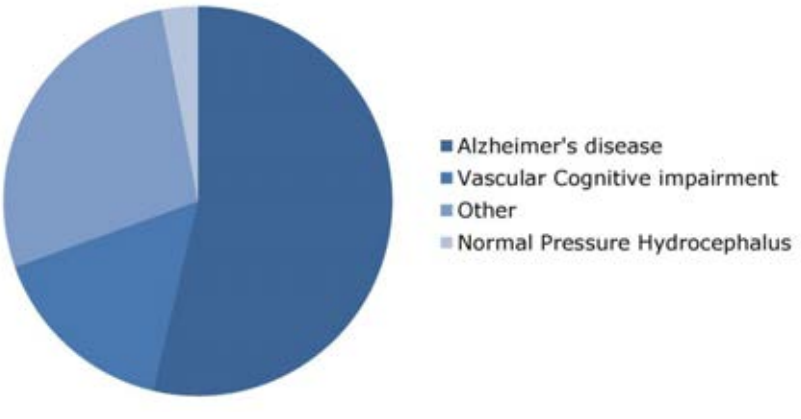

Figure 2. Distribution of the main dementia syndromes. Adapted from Lobo et al. 2000 (72) and Moorhouse et al. 2008 (73). The category 'other' includes all other causes of dementia, such as frontotemporal degeneration, Lewy body dementia, or vascular cognitive impairment with other neurodegenerative and hereditary diseases. Abbreviations: NPH, normal pressure hydrocephalus.

2.2 DIAGNOSTIC CRITERIA

Two internationally recognized diagnostic guidelines have been developed: the second edition of the Japanese iNPH guidelines (2) (Appendix 1) and the international iNPH guidelines (9) (Appendix 2). Both classify patients according to the increasing probability of having iNPH, rather than having or not having the illness. The more components of the diagnostic criteria are fulfilled, the more likely iNPH is to be present (2,9). Both of these guidelines describe essentially identical core characteristics of iNPH: a chronic disease that has an insidious onset later in life, usually in the 70s, and is progressive in nature, impairing the gait, while other symptoms are commonly also seen, such as cognitive impairment or urinary incontinence (2,9) (Appendices 1 and 2). These findings are

accompanied by enlarged ventricles, either in computed tomography CT or MRI imaging (2,5,9). Diagnosis is supported by the findings in procedures investigating or mechanically altering the hydrodynamics of the CSF (2,5,9). However, the suspect should not have other conditions explaining the symptomatology, such as sNPH caused by SAH (2,5,9) (Appendices 1 and 2). As the clinical diagnosis of iNPH requires a detailed medical history, differential diagnostics, and a neurological examination accompanied by brain imaging with CT or MRI (2,9,10), it is to be expected that diagnoses are mainly set in hospitals where specialized, multidisciplinary neurological and/or neurosurgical expertise is available. The clinical features of iNPH and differential diagnostics are described in detail in the later other chapters (see chapters 2.3 and 2.6)

However, the probability classifications and the requirements to fulfill them differ between the two sets of guidelines: the Japanese iNPH guidelines (2) use tests considered to be prognostic in nature, such as the CSF tap test (10), and the outcome of CSF shunting as diagnostic criteria. In addition, the Japanese iNPH guidelines recognize two subtypes of iNPH identified in brain imaging by MRI: patients displaying disproportionately enlarged subarachnoid space hydrocephalus (DESH) and non-DESH (2) (Figure 1, Figure 3, Appendix 1) (see chapters 2.1.3 and 2.1.6). According to the Japanese iNPH guidelines, only individuals who develop their symptoms in their 60s or later may have possible iNPH, whereas in the international iNPH guidelines, onset may occur at any age after childhood to reach the same likelihood category (2,9) (Appendices 1 and 2). These differences have been noted in the literature, as the number of patients diagnosed with iNPH in the same study population has differed depending on the guidelines used. Consequently, harmonization to form one common diagnostic system has been suggested (71).

2.3 CLINICAL CHARACTERISTICS

While the classical triad was observed in all three cases described in the first original publication (1), it was later found that only half of the patients exhibited the full symptomatology (19,20,74), and the triad is not therefore required for the diagnosis of iNPH (2,9,10) (Appendices 1 and 2). However, gait or balance problems are present in nearly all of the affected (at least 90%) (19,20,74), followed by cognitive impairment in 80% (20,74), and urinary problems in 74% of the affected on average (19,20,74,75).

2.3.1 Gait impairment

Characteristically, patients with fully developed iNPH have gait impairment consisting of problems in the initiation of walking, standing up and sitting down. Furthermore, they often have to take multiple steps while turning, suffer from poor balance and postural instability, and have a broad walking stance with a small-stepped gait. (2,10,76-78) The current Japanese iNPH diagnostic guidelines describe the characteristic gait as '*small stride, shuffle, instability during walking, and an increase in instability on turning*.' (2) (Appendix 1). The international iNPH guidelines describe the gait impairment as a decreased step height or length, slow walking speed, increased trunk swaying while walking, widened standing base, toes turned outward on walking, retropulsion, multiple steps in turning, or impaired

walking balance. At least two of all the abovementioned have to be present (9) (Appendix 2).

2.3.2 Cognitive impairment and neuropsychiatric symptoms

Persons with iNPH often have reduced psychomotor speed, impaired attention and concentration, as well as impaired memory, learning, and executive functions (79-81). Furthermore, iNPH patients with cardio- and cerebrovascular risk factors have even worse performance in neuropsychological testing than other patients with iNPH (79). The type of cognitive defect in iNPH is commonly regarded as frontosubcortical, due to the neuropsychological profile and results from imaging studies showing defects in that particular area (79-82). In iNPH, some cognitive functions are impaired in a similar way as in other neurodegenerative conditions (2,10,81). Half of patients with iNPH develop dementia, despite the treatment (17).

In association with cognitive impairment, patients with iNPH often express varying neuropsychiatric symptoms, ranging from depressive to psychotic symptoms (83-91). Depressive symptoms or apathy are most frequently present and can be partly explained by the associated brain damage (89,91). Apathy in iNPH could arise from dysfunction in the anterior cingulate cortex, thalamus, and damage to the subcortical white matter due to a hypoperfusion in these areas (89).

2.3.3 Urinary symptoms

Many iNPH patients experience lower urinary tract symptoms that are similar to those in other disorders and more common in older age (10,92). Storage symptoms, such as an increased frequency or urgency of urination, are those most frequently present in iNPH patients, followed by voiding symptoms such as the feeling of incomplete emptying of the bladder or incontinence (75,92). However, detrusor overactivity is present in almost all iNPH patients suffering from urinary incontinence, which is also a common finding in other brain diseases altering the autonomic control of urination (75,92). On the other hand, impaired mobility or cognition caused by iNPH may cause functional incontinence, as a person is bedridden or unable to use the restroom facilities (92,93).

2.3.4 Assessment scales

Different scales have been developed for assessing the severity of symptoms in iNPH and for the outcome assessment of CSF shunting, such as the iNPH Grading Scale (iNPHGS), iNPH scale, or Kiefer Score (11,94-98). However, there is no consensus on which of these instruments should be primarily used, a dilemma similar to that regarding diagnostic guidelines (see 2.1.2 Diagnostic criteria) (11,71). In addition to this, there have been a variety of methods and attempts to characterize iNPH with instruments designed for specific symptoms/impairments (2,9,11).

To evaluate cognitive functions in iNPH, guidelines have suggestions for the instrument to be used: "*With respect to cognition, there must be documented impairment (adjusted for age and educational attainment) and/or decrease in performance on a cognitive screening instrument (such as the Mini Mental State Examination) or evidence of at least two of the following,"* after which the characteristic cognitive changes in clinical examination are presented in the international guidelines (9) (Appendix 2). In the Japanese iNPH guidelines, this is simply mentioned as "*Cognitive impairment is detected on cognitive tests*," but does not

specify the instruments (2) (Appendix 1). There are also a variety of ways that gait impairment can be (99) and is measured in patients with iNPH (2,11).

2.4 NEUROIMAGING

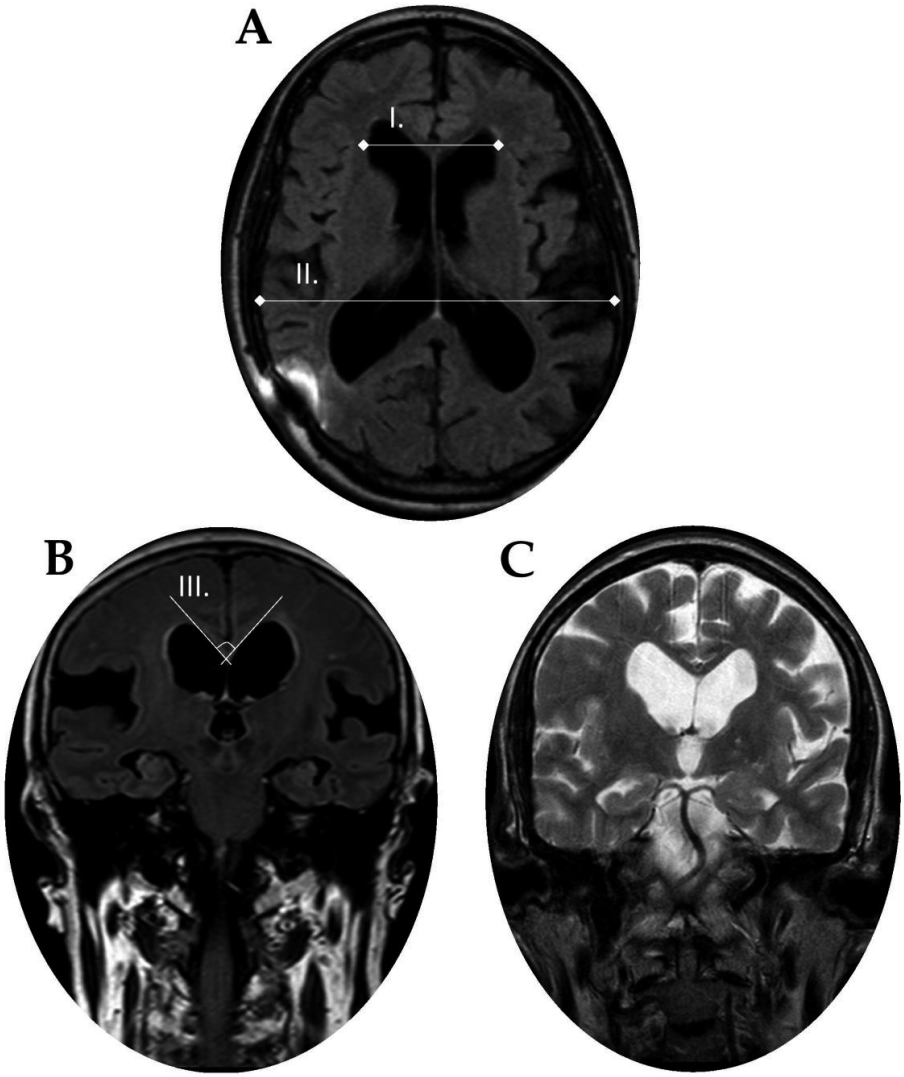

Figure 3. The radiological presentation of iNPH in two patients (AC, B) using axial (A) and coronal (B and C) magnetic resonance imaging. Line I, maximal width of the frontal horns of the lateral ventricles; line II, maximum inner diameter of the skull; line III, callosal angle; B, disproportionately enlarged subarachnoid space hydrocephalus (DESH); C, non-DESH.

As mentioned in the previous two chapters (2.1.3 and 2.1.4), brain imaging studies displaying ventriculomegaly without macroscopic evidence of an obstruction of CSF flow still form the foundation for the diagnosis of iNPH (1,2,9) (Appendices 1 and 2). According to both iNPH guidelines, ventriculomegaly should be estimated using the Evans index (2,9)

(Appendices 1 and 2), which is the ratio between the maximal width of the frontal horns of the lateral ventricles and the maximum inner diameter of the skull, in which proportions of three or greater are considered pathological (2,9,100) (Figure 3). While a person cannot have iNPH without ventriculomegaly, ventriculomegaly alone does not indicate iNPH, as dilated ventricles can be seen in the normal population (63,100) and in other conditions, such as atrophy caused by AD or by frontotemporal degeneration (FTD) (2,9,10,12,74,101,102). Dilated ventricles are also seen in patients suffering from alcohol abuse, relating to the loss of white brain matter (103). As such, numerous radiological measures have been introduced to differentiate iNPH from other processes (2,10,12,74,101,102,104) and to support the diagnosis of iNPH (2,50,74).

DESH is widely regarded as the most feasible radiological marker for iNPH (50,102,105,106). This morphology has been suggested to be caused by an obstruction of CSF flow between the arachnoid granulations and basal cisterns (50,107). The absence of DESH, however, does not exclude the diagnosis of iNPH (2,107).

In AD, the increased width of temporal horns of the lateral ventricles has been used as a marker for temporal atrophy, distinguishing AD patients from the normal population (102,108). This temporal atrophy is seen to a much lesser degree in patients with iNPH, and as such, narrow temporal horns may support the diagnosis of iNPH over AD in patients with ventriculomegaly (102).

The callosal angle (CA) (Figure 3) has also been used to differentiate AD and iNPH, with a narrower angle indicating the presence of iNPH (104) and predicting a positive CSF shunting outcome (105). However, these associations with CA were not reproduced in a larger study setting (102). Curiously, the international iNPH guidelines consider a CA of 40 degrees or more as a supportive finding in brain imaging (Appendix 2) (9), rather than 40 degrees or less, which might be a clerical error.

Similarly, in MRI imaging, a sign of increased flow of CSF through the cerebral aqueduct, the flow void phenomenon, was suggested to predict the CSF shunt outcome (102,109), and was included in the international guidelines as a supportive radiological feature of iNPH (Appendix 2) (9). It was, however, later found to be unuseful in this regard, and as such was disputed (102,110).

White matter lesions (WMLs) are frequently present in persons with iNPH (2,111-114) and their significance will be described in detail later (see section 2.5).

Persons with ventriculomegaly, but without other symptoms, have attracted considerable attention in recent years. Iseki et al. (63) found that a small proportion of the normal population (1.1%) developed ventriculomegaly during a prospective follow-up. One-third of those presenting with asymptomatic ventriculomegaly developed possible iNPH within the next ten years (63). In addition to this, ventriculomegaly has been reported to increase the risk of dementia in patients without iNPH (12,101). It has been suggested that this asymptomatic ventriculomegaly could represent a preclinical stage of iNPH in some of the affected (63,66).

2.5 ETIOLOGY

While the etiology of iNPH is still unknown, various abnormalities in CSF physiology and hydrodynamics, in particular a disturbance in CSF homeostasis, have been contemplated to cause the symptoms and signs observed in patients with iNPH (1,2,115). The current literature still supports this hypothesis, as numerous studies in different settings have observed abnormalities in the hydrodynamics of CSF in patients with iNPH, such as abnormal cardiac-related pulsations of ICP or occasional rises in CSF pressure (B waves), which are more frequent while sleeping (2,53,115-117) (see section 2.8.4). The other hypothesis-supporting argument is that the mechanical alteration of CSF hydrodynamics has been shown to ease some of the neurological symptoms of iNPH in the majority of patients (7,11). Some of these abnormalities have been suggested to be caused by aberrant vascular mechanisms and pulsations (117,118). Cardiovascular risk factors, such as dyslipidemia or type 2 diabetes mellitus (T2DM), have been proposed to play an even greater role in the pathophysiology of iNPH (2,13,27,28,70,111,119-122), as they, and the conditions that they are associated with, such as cerebro-vascular disease (CVD), are frequently present in persons with iNPH (2,13,27,28,70,111,119-122).

While many studies have suggested a common pathology (2,13,27,70,111,119-121), some have gone even further, suggesting iNPH to be a sub-type of vascular dementia (VaD) (121). Both of these hypotheses are in accordance with or supported by other findings (111,121), as the same vascular risk factors have been associated with the pathophysiology of WMLs (123), which are seen in some patients with iNPH (2,111-114). Similarly, a reduced cerebral blood flow (CBF) causing critical and sub-critical ischemia in the regional white matter has been observed in patients with iNPH (2,124-126). In addition to ischemia, this sub-optimal perfusion accompanied by impaired CSF drainage has been theorized to result in the accumulation of toxic/metabolite substances, such as amyloid beta (Aβ), leading to neural damage (124,127). One of the intriguing observations is that subcortical ischemic vascular disease (also called Binswanger's disease, BD), a sub-type of small vessel disease (SVD) (73,128-130), clinically resembles iNPH (13,111,121,131,132). From the perspective of metabolite accumulation, the new discovery of a dural lymphatic system (133,134) opens new windows for etiological research on iNPH.

On the other hand, there is promising new evidence that iNPH could be a unique neurodegenerative entity with a potentially specific pathogenesis: a recent study (135) established a preliminary connection between patients with features of iNPH on MRI and a segmental copy number loss of the *SFMBT1* gene. Although the *SFMBT1* protein is mainly localized in areas playing a crucial role in CSF circulation, such as the choroid plexus, the exact function of the protein is unknown (135). Furthermore, there is emerging evidence of a familial background of iNPH (52,136-138). Due to all of the presented potential theoretical backgrounds, and because only nonconforming neuropathological changes have been found in persons with iNPH (2,27,139), the condition has been proposed to be multi-factorial (2,27,139).

2.6 DIFFERENTIAL DIAGNOSTICS AND COMORBIDITIES

Differentiating iNPH from other conditions is challenging, as they are known to produce similar symptoms and at the same time co-exist with iNPH (2,9,13,56,99,107). Parkinson's disease (PD), medication side effects and other conditions can potentially mimic all the classical symptoms of iNPH, while some disorders only have one to two overlapping symptoms, such as the cognitive impairment associated with AD (107). As such, clinicians may have to conduct several additional tests for differential diagnostics, such as spinal MRI to rule out gait impairment caused by spinal stenosis (2,99,107).

2.6.1 Vascular diseases

Similarly to cardiovascular risk factors (2,13,28,70,111,119-122) (see section 2.5 etiology), different manifestations of vascular disease, such as peripheral vascular disease or CVD, are highly common in patients with iNPH (13,27,28,121,122), and interestingly, iNPH might be overrepresented in patients with CVD (140). Some patients with CVD have varying stages of cognitive impairment, ranging from mild cognitive impairment (MCI) to dementia (previously named vascular dementia, VaD) due to different heterogeneous vascular etiologies, all of which are grouped under the term vascular cognitive impairment (VCI) (73). Of patients with iNPH, 5% have been estimated to develop dementia stage VCI (17). One form of VCI, BD, can be nearly impossible to differentiate from iNPH, as it features the same symptoms as iNPH and is accompanied by ventriculomegaly at later stages, possibly due to the ischemic periventricular WMLs (13,130-132), which on the other hand have been seen in patients with iNPH (2,111-114).

2.6.2 Alzheimer's disease

AD is the most common form of dementia (72), characterized by an insidious and progressive deterioration in cognition (141,142). Neuropathologically, AD classically features the extracellular accumulation of Aβ aggregates and intraneuronal neurofibrillary tangles formed from hyperphosphorylated tau (HPτ) protein prior to the onset of cognitive symptoms (141-144). However, the disease itself is multifactorial (142,145), and neuroinflammatory processes can potentially also play a role in the pathophysiology of AD (142,146,147). In addition to the detected objective gradual impairment of cognitive functions, the diagnostic criteria of AD include the use of CSF biomarkers, such as Aβ1–42, and imaging studies, such as MRI to detect medial temporal lobe atrophy or positron emission tomography (PET) to detect amyloid deposits, all of which reflect the ongoing pathological process of AD in the brain tissue (141,142,148).

According to neuropathological findings in post-mortem autopsies or small frontal cortical brain biopsies obtained during the CSF shunt placement or during pre-operative recording of ICP, pathological findings related to AD, abnormal depositions of Aβ and HPτ, can be found in roughly half of the brains of persons with iNPH (13,27,29,149-153). Due to these findings, AD and iNPH have been suggested to share pathological pathways through Aβ accumulation (127,154), and on the other hand, AD is considered to be a comorbidity (iNPH-AD) (2,9,10,13,17). AD is also considered to be a differential diagnosis, as AD patients may express ventriculomegaly related to the characteristic cortical atrophy (10,13,74,148) (see section 2.1.5).

2.6.3 Parkinsonian disorders

In a clinical examination, hypokinetic-rigid gait impairment caused by other parkinsonian disorders, such as PD, dementia with Lewy's bodies (DLB), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and multiple system atrophy (MSA) can be challenging to differentiate from that caused by iNPH, especially in their early stages (13,99). Therefore, CT or MRI imaging and supplementary diagnostic testing are required (2,10,13,99). Supplementary diagnostic tests may include single-photon emission computed tomography (SPECT) or PET to investigate dopamine transporter activity in the brain to exclude DLB (2,10,13,99). Identifying specific symptoms that are not usually present in patients with iNPH, such as the asymmetry of symptoms in PD, may be useful, but does not exclude the co-existence of both conditions (2,10,13,99).

2.7 PROGRESSION OF INPH

The natural course of iNPH is mostly unknown (8,155) and there have only been a couple of studies regarding selected untreated persons with iNPH. However, it appears that on average, untreated patients will deteriorate during the follow-up without CSF shunt therapy (7,8,131,155). How untreated iNPH progresses on an individual level varies significantly, ranging from spontaneous improvement to severe deterioration (8,155). Untreated iNPH is linked to at least two times higher mortality compared to the general aged population, while it is unknown whether CSF shunt surgery reduces mortality among iNPH patients (12). In addition to this, the response rate for CSF shunting seems to decrease on average six months after the surgery (156), possibly indicating the progression of the condition (see Chapter 6). In the general population, asymptomatic ventriculomegaly could represent a preclinical stage of iNPH (63,66) (see section 2.4). Ventriculomegaly has also been associated with an increased risk of dementia, even when the patient does not have iNPH (12,101)

2.8 TREATMENT

Diversion of CSF from the brain ventricles to the right atrium of the heart to relieve the symptoms of iNPH was successfully performed in three patients by Hakim & Adams using a ventriculo-atrial (VA) shunt (1) (Figure 4). Subsequently, different types of CSF shunt valve systems and surgery techniques have been developed (2,10) (see sections 2.8.1 and 2.8.3). The operation itself with some variations described below remains the only available treatment for iNPH and relieves some of the symptoms in the majority (on average 70%) of patients with iNPH (7,11). Gait impairment responds to shunt treatment more frequently than other symptoms (2,20), although the recovery of cognition (157) and urinary continence (2) can be seen in some patients (see section 2.8.2). However, half of patients with iNPH develop dementia despite the treatment (17).

2.8.1 Structure of CSF shunts

VA shunting has largely been replaced during the past decades by a ventriculo-peritoneal (VP) shunt (1,2,10) (Figure 4). VP shunting guides the CSF to the peritoneal cavity instead of the right atrium of the heart (2,10). A CSF shunt commonly consists of three parts: a proximal catheter, usually located in the right lateral ventricle; a distal catheter, inserted into either the peritoneal cavity or the right atrium; and the CSF shunt valve in the middle

connecting the two compartments (2,10) (Figure 4).

Proximal catheter can be inserted to the lateral ventricle through a surgical bur hole, made approximately 3 cm from the midline and close to the coronal suture of the skull. Alternatively, an occipital entry-point to the proximal catheter can be made from the posterior parieto-occipital region of the skull. While VP is the most typical way of placing a CSF shunt, the proximal catheter can in the lumboperitoneal shunt (LPS) also be inserted into the lumbar CSF space (2,10).

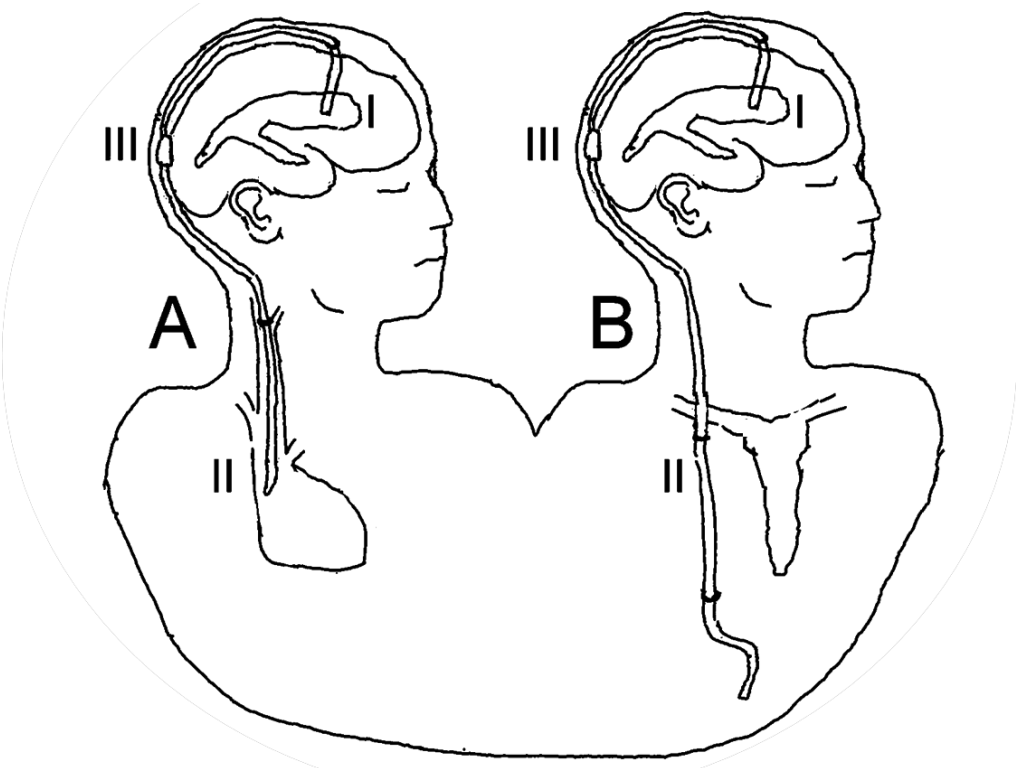

Figure 4. The cerebrospinal fluid (CSF) shunt system. A, ventriculo-atrial shunt; B, ventriulo-peritoneal shunt; I, proximal catheter; II, distal catheter; III, CSF shunt valve.

Valves operate so that when a certain level of pressure is exceeded in the lateral ventricle, the valve opens passively due to the pressure difference between the two compartments, and CSF is thus routed unidirectionally to the extracranial space until the pressure is lowered/normalized and the valve closes (2,10). Two main valve types exist: one in which the pressure requirement for the valve to open can be adjusted post-operatively in a non-invasive manner using an extracorporeal magnetic programming device (programmable valves), and another that cannot be adjusted (fixed pressure valves) (2,10). Programmable valves have in recent years displaced fixed pressure valves due to their flexibility, such as in case of CSF overdrainage (see section 2.7.5 complications) (2,10). It appears that the initial pressure at which the CSF shunt valve is set to open does not affect the clinical outcome (10,158). Thus, selection between the valves is based on the preference and clinical experience of the neurosurgeon (10,158). However, there might be differences

in complication rates when using varying CSF shunt parts, such as valve safety mechanisms and catheter materials (see section 2.8.5).

While the opening pressure of the valve is usually lowered until there is a reduction in iNPH symptomatology (10,159), there have been no studies regarding the lowering of the opening pressure of the valve if and when the iNPH symptoms reappear after the initial response to the CSF shunt (see section 2.7). There is, however, some evidence to support starting with a slightly higher opening pressure level; gradually lowering it until a clinical response is achieved may help to avoid overdrainage, and if overdrainage is observed, the opening pressure of the valve should be increased (159,160) (see section 2.8.5).

2.8.2 Patient selection

While there has been no sham surgery to test the efficacy of CSF shunting, and a request for this has been presented (161,162), some authors have argued that enough evidence has been acquired in other study settings to justify the usage of CSF shunt surgery in iNPH (7,8,11,25). In the light of the progressive nature of the condition (see section 2.7), sham surgery is considered unethical by some authors, as a delay in treatment could potentially cause irreversible harm to those left unshunted (8). In addition, it has proven extremely challenging to preoperatively identify those who will have a favorable clinical outcome (2,9,25,53,163-166). Although numerous patient-related attributes and operation-related variables have been recognized (see 2.8.3), no exclusion criteria have been introduced to date for persons who have iNPH and are physically qualified for the surgery (2,9,10,25,53,163,165,166). This patient selection issue is further obscured by the nonuniformity of diagnostic and assessment criteria for iNPH (see sections 2.2 and 2.3.4), which, together with various methods for using different prognostic tests (see sections 2.2 and 2.8.3), has led to the observed diversity in favorable outcome rates. These challenges may cause difficulty for clinicians in generalizing iNPH studies to different patient populations (167).

From clinical and research perspectives, strict patient selection produces good outcomes for patients who fulfill the requirements, and lower complication rates for those who are operated on (167). However, too strict selection may unjustifiably discriminate against patients who could potentially benefit from the shunt treatment, but who are excluded due to patient characteristics (167), such as their age or comorbidity burden. Excluding patients from research settings due to age or the comorbidity burden makes it nearly impossible to generalize the acquired study results to real life, as most of the aged population are affected by coexisting conditions. On the other hand, in practice, relaxed selection criteria may produce unfavorable outcomes and predispose more people to the risks of the operation (168) (see section 2.8.5). In the case of iNPH, patients who are left unshunted are considered to have the worst prognosis (see section 2.7).

2.8.3 Prognostic and outcome-modifying factors

It appears that the longer the duration of iNPH before shunt therapy, causing irreversible damage, the less likely it is for the symptoms of iNPH to be relieved by CSF shunt surgery (20-22) (Table 1). While age has been identified as an independent risk factor for post-operative morbidity in the older population (169), and while older age has been reported to negatively affect the CSF shunting outcome (17-19), there are no recommendations to

Table 1. Prognostic factors of the outcome of CSF shunt treatment.

Prognostic factor	Effect on the outcome of CSF shunt treatment	Excludes a favorable clinical outcome
Longer duration of untreated iNPH	-	No
Younger age	+	No
Increased comorbidity burden	-	No
Co-existing CVD	-	No
iNPH-AD/iNPH patients with Aβ or HPτ pathology	-	No
DESH	+/-	No
Narrower CA	+/-	No
Presence of Lunberg A or B waves in ICP monitoring	+/-	No

+ indicates a positive and – a negative effect on the outcome of CSF shunt treatment. +/- indicates conflicting results between studies. A favorable clinical outcome is usually focused on the improvement of gait, but the definition of a positive clinical outcome varies (11). Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; CVD, cerebro-vascular disease; AD, Alzheimer's disease; iNPH-AD, iNPH patients with coexisting AD; Aβ, amyloid beta; HPτ, hyperphosphorylated tau; DESH, disproportionately enlarged subarachnoid space hydrocephalus; CA, callosal angle.

exclude the aged population from CSF shunting, as they can potentially benefit from the operation similarly to younger patients (19,23,25). An increased comorbidity burden (the number and severity of comorbidities combined) has been associated with a poorer prognosis following CSF shunting in iNPH (13-16), and co-existing vascular diseases such as CVD (28,122) have been associated with a poorer prognosis.

In addition, persons with iNPH usually die due to cardio- and cerebrovascular causes, similarly to the older general population (28,122,170). However, patients with these comorbidities should not be excluded from treatment, as they may have a favorable outcome, like those patients without comorbidities (13,28). Likewise, persons with iNPH-AD or iNPH presenting Aβ or HPτ pathology have been reported to have a worse outcome than those without, but should not be left untreated (13,17,24,26,27,29,149,150,171). From the radiological markers (see section 2.4), DESH (105) and a narrower CA (172) have been associated with a favorable shunting outcome, while some studies have not observed any predictive value with these markers (102). Lundberg A and B waves are discussed in next section.

2.8.4 Prognostic tests

Temporary emulation of the function of a CSF shunt has been used to predict the outcome of treatment (2,10,173,174) (Table 2). This is done, for example, by examining the gait in a standardized manner, such as measuring how much time it takes for the patient to walk 10 meters repeatedly (175). This is done before and two to four hours after the removal of 30 to 50 ml CSF lumbarly, also known as the tap test (2,10,174). Another option is to continuously drain CSF over several days, removing a total of 300–500 ml of CSF, also known as external lumbar drainage (ELD) (2,174). Similarly to other issues with iNPH, it has been challenging to determine what the minimal clinically significant change after a CSF tap test or ELD is when different standardized gait evaluations are used (174).

However, while mimicking the function of a CSF shunt seems to predict the outcome, it has been criticized as being highly insensitive, and thus patients with negative tests should not be excluded from CSF shunting, but undergo other ancillary testing

Table 2. Prognostic and diagnostic tests for predicting the outcome of CSF shunt treatment.

Prognostic or diagnostic test	Continuous measurement of ICP	Infusion test	ELD	Tap test
Performance	24-hour intraventricular measurement of ICP. Is as invasive as placing a CSF shunt.	Estimating CSF outflow resistance by measuring changes in ICP in the lumbar CSF space, caused by continuous or pulsatile infusion of artificial CSF (for example with Ringer solution)	Examining the gait repeatedly in a standardized manner before and after continuous draining of CSF over several days, removing total of 300–500 ml of CSF	Examining the gait repeatedly in a standardized manner before and two to four hours after the removal of 30–50 ml CSF lumbarly
Positive result	Positive if: a) a basal intracranial pressure above 10 mmHg or b) the presence of any A waves, or c) more than 30% B waves during the monitoring	Positive[b] if: outflow resistance ≥ 12 mmHg/ (ml/min)	Positive[a] if: improvement of gait/ gait speed/ fewer steps taken	Positive[a] if: improvement of gait/ gait speed/ fewer steps taken
Interpretation	If positive, the patient is likely to suffer from iNPH, and thus may benefit from CSF shunt treatment. If the test is negative, the patient is unlikely to have iNPH, but some patients with iNPH may have normal findings.	If positive, the patient is likely to suffer from iNPH, and thus may benefit from CSF shunt treatment. If the test is negative, the patient is unlikely to have iNPH, but some patients with iNPH may have normal findings.	If positive, the patient is likely to benefit from CSF shunt treatment. A negative test does not exclude a favorable CSF shunt treatment outcome.	If positive, the patient is likely to benefit from CSF shunt treatment. A negative test does not exclude a favorable CSF shunt treatment outcome.

[a]There are no uniform guidelines on how to measure and what is the minimal clinically significant gait improvement after CSF removal (Appendices 1 & 2). [b]Stricter outflow resistance limits exist (174,176,177). Abbreviations: ELD, external lumbar drainage; CSF, Cerebrospinal fluid; iNPH, idiopathic normal pressure hydrocephalus; ICP, Intracranial pressure; ml, milliliter; min, minute; mmHg, millimeters of mercury.

(10,173,174). These tests investigate abnormalities in CSF hydrodynamics typical of iNPH, such as the infusion test to measure elevated CSF outflow resistance (174,176,177). Even though this test is used as a differential diagnostic tool and as a prognostic test, there are persons with iNPH who could potentially benefit from CSF shunting but do not express elevated CSF outflow resistance and cannot therefore be excluded from shunting (173,174,177).

Continuous measurement of ICP has been used in a similar manner to infusion testing, but the prognostic value of the different abnormalities observed during monitoring, such as Lundberg A and B waves or pulsatile ICP, are still under debate (2,174,178). The Lundberg A waves are steep rises in ICP lasting at least five minutes, which are thought to reflect the risk of reduced CBF due increased ICP (179,180). The Lundberg B waves refer to a signal during ICP monitoring with frequencies of 0.3–3 cycles per minute, which results from the fluctuations in the CBF (180,181). While some have considered an increased frequency of Lundberg B waves during sleep to correlate with the outcome (179), these findings have been criticized for lacking controls from the normal population (174). Raftopoulos et al. (179) state that the amplitude and a longer duration of Lundberg A and B waves during ICP monitoring predict the shunt response, but opposing results have also been reported (174,182).

Like different combinations of known prognostic factors and tests, even more sophisticated computerized methods have been presented that merge multimodal data, such as the Disease State Index (DSI) (164). However, even the DSI has problems in predicting the outcome of CSF shunting with the currently known variables and prognostic tests (164). This, again, speaks for the need to develop new biomarkers and indicators for iNPH and CSF shunt treatment, as none of the currently known prognostic factors, or diagnostic and prognostic tests, is able to reliably differentiate responders from non-responders (164).

2.8.5 Complications

Complications, ranging from minor (such as mild overdrainage) to severe (such as subdural hematoma (SDH), intracerebral hemorrhage (ICH), or death), may emerge after CSF shunting (2,11,183). In a systematic review pooling outcome data from multiple studies that had used different CSF shunt placements in patients with iNPH (11), a complication rate of 10% and a mortality rate of 1% were observed (see section 2.8). A recent large retrospective cohort study focusing on the complications related to VP shunting in various conditions, including iNPH, reported a complication rate of 24% (183). The reason for the contrasting results is that the latter study (183) included reoperation (revision) of any part of the CSF shunt system as a complication, while the systematic review (11) only regarded SDH, infections, and seizures as complications, and revision was kept as a separate entity, affecting 16–30% of patients with iNPH (10,11).

A common reason for the revision of a VP shunt is obstruction of the distal catheter due to withdrawal from the abdominal cavity (2,10). VA shunts do not suffer from obstruction problems as often, but rarer renal and cardiopulmonary complications have been reported (2,184). The total malfunction of the CSF shunt system may be detected, for example, using an infusion test (2,177,183) (see section 2.8.4). The administration of antibiotics just prior to the operation has reduced the rate of infections (2,185).

Overdrainage means that sometimes the CSF shunt valve opening pressure is

set to too low, or changing the position of the body causes more CSF to be guided to the extracranial space than is needed, which may cause a variety of symptoms depending on the pressure difference (2,10,183). While minor overdrainage is fairly common and presents as postural headache or as a minor non-traumatic SDH in radiological imaging, the frequency of more severe forms of overdrainage, such as SDH requiring surgical treatment, have decreased, possibly because of the introduction of antisiphon devices and adjustable valves (2,10,11,183,186). Mild overdrainage can be managed by increasing the opening pressure of the valve (2,10,183).

2.9 QUALITY OF LIFE

After the mid-20th century, medical professionals and the society as a whole were the first to experience the luxury and the cost of advancing technology, as life-preserving technologies started to exceed those preserving health (30,36); pediatric renal patients who had previously perished were now able to survive due to renal dialysis, but as a result were hospitalized and had to pay the cost of living (30). This was similar to the first cancer patients treated with chemotherapy having to endure the severe and sometimes permanent side effects (30). Together with the enormous socioeconomic changes in society, the number of persons with chronic conditions increased, and the indicators that were previously used to assess the quality of health care, such as mortality, suddenly became inappropriate (30,32,36). In parallel to the medical sciences, social science tried to identify indicators of social change, because despite economic growth, society appeared to increasingly suffer from different social issues, such as substance abuse and crime (30,32). In the 1970s, these dilemmas gave birth to the concept of '*quality of life*', QoL, which was quickly adopted in clinical practice ethics, and to social and health-care programs across the political field, and spurred exponential growth in scientific publications (30,36).

The reason for the broad adoption of QoL was the urgent need for more patient-oriented outcome indicators and health status measurements, but also the ambiguousness of the concept, which has led to varying definitions of QoL and instruments to measure it, all of which have changed over time (30,31,36). While different definitions of QoL exist, it is uniformly regarded as a multidimensional concept in which '*health*' is only one dimension, but that is inseparably intertwined with the other domains of QoL, well-being, and happiness (31,32). The World Health Organization has defined QoL as "*individuals' 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.*" (187). In medical research, '*health-related*' was added as a prefix to QoL to emphasize the effect of health-rendering conditions on QoL and, on the other hand, to make the concept of QoL narrower in an attempt to control the influence of non-medical factors, and thus the concept of health-related quality of life (HRQoL) was formed (31,32).

One of the best-known models for HRQoL in medical research was presented by Wilson and Cleary (32) (Figure 5), portraying the relationship of clinical and subjective outcome measurements. In this concept, biological and physiological factors together with characteristics of the individual, and of the environment, create the observed and experienced symptom status. This symptom status is also modified by psychological factors. For example, pain related to the pathological process of cancer can be modified by

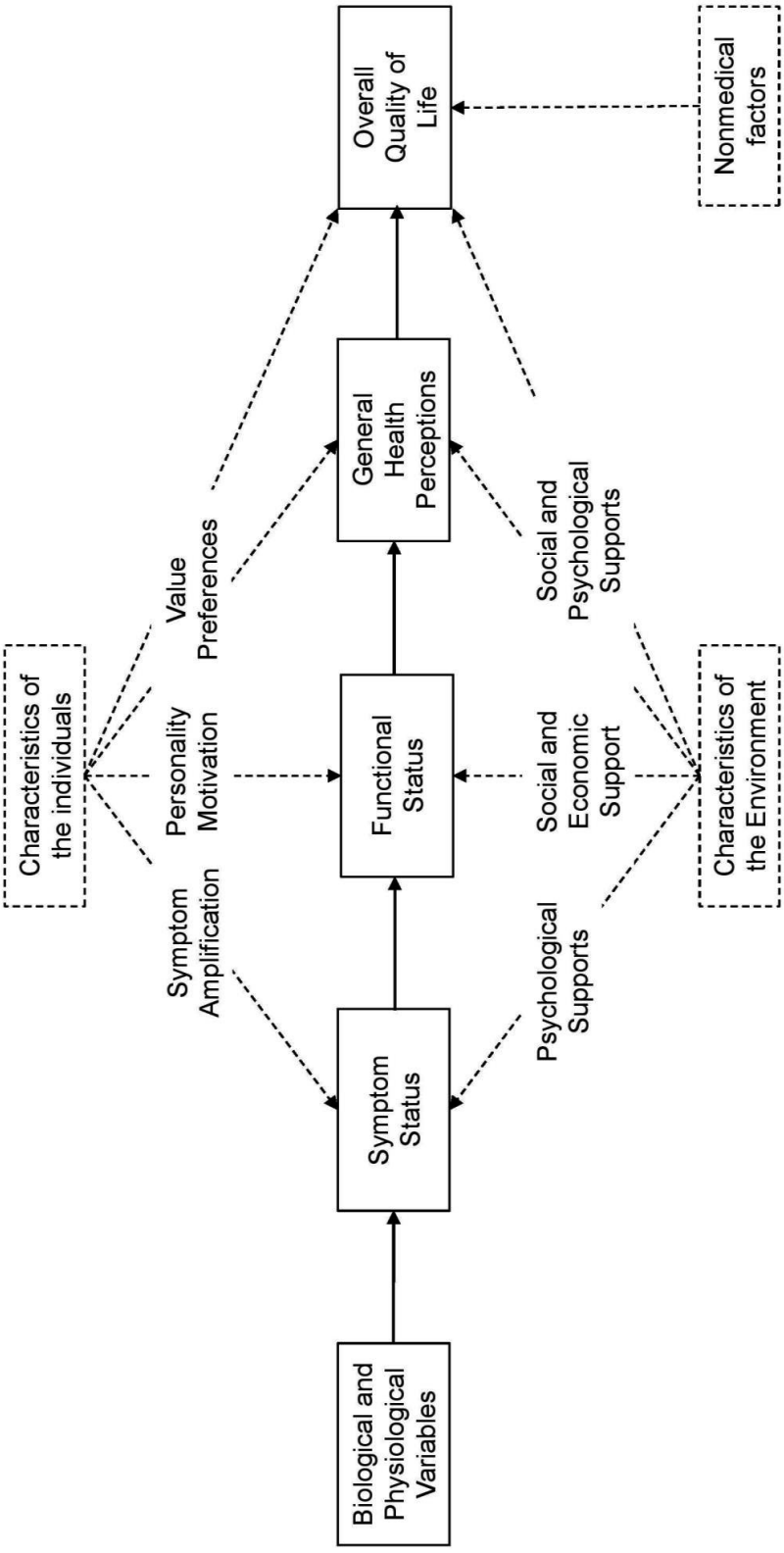

Figure 5. Conceptual model for health-related quality of life showing the relationships among different patient outcome measures, adapted from Wilson & Cleary (32).

the individual's emotions, such as fear. Similarly, these symptoms can be modified by the surrounding culture. For example, pain can be underexpressed if a person's culture does not support the showing of vulnerabilities.

Symptoms, such as pain, may affect the functionality of the person, for example the ability to walk. Functionality, such as the ability to walk, can be influenced by individual and environmental factors, such as adherence to pain medication or what rehabilitation services and aids are available, such as rollators.

Functionality, together with factors related to the individual and the environment, affect the perceptions of one's health. For example, a person may not mind losing a little finger or can adapt to it (a value preference). However, if the person has a certain role in society, e.g. a violist, and loses a finger, the person's perception of health is drastically modified. This perception, combined with the preferences of the individual, reflected in the background of the environment, and merged with past experiences and life lived (nonmedical factors), forms the overall QoL (32) (Figure 5).

2.9.1 Instruments for measuring health-related quality of life

While numerous tools to measure HRQoL exist, they can be divided into two different categories: I) generic and II) disease-specific HRQoL instruments (31). The former can be applied to measure HRQoL in every population and condition, while disease-specific HRQoL instruments are designed to capture the characteristics of a specific condition and cannot be used in a general manner (31). Generic HRQoL instruments used in patients with AD or iNPH are presented in detail in Table 3. Studies on HRQoL in patients with iNPH are presented later (Chapter 2.9.4).

Utility measurements are a sub-type of generic HRQoL instruments that use a certain descriptive system (questionnaire) and utility formula to convert the questionnaire's dimensions of health into a single number (31,188). One example of generic utility measurement is the 15D instrument, including 15 dimensions of health: mobility, vision, eating, hearing, breathing, sleeping, speech, excretion, usual activities, mental function, discomfort, depression, distress, vitality, and sexual activity (49) (Table 3, Appendix 3). The 15D is visually presented in the first two publications of this thesis (see Figures 6 & 8). Each dimension has five ordinal levels; one must choose the most suitable level describing one's state of health at that particular moment (49). From each dimension level value, a single index score (15D score) can be obtained by using a set of population-based preference weights acquired from the Finnish population (49). The 15D score combines all the dimensions in one index on a scale of 0 to 1, with 0 referring to being dead and 1 to being in full health (49,188). The minimum clinically important change, the smallest difference that a person can reasonably feel in the 15D score, has been estimated to be ≥0.015 (189). The applications and limitations of the 15D are presented later (see section 2.9.5).

Generic HRQoL measurements are good for investigating the HRQoL impairment caused by the condition or disease (31). Disease-specific HRQoL instruments might be better suited to detecting changes in HRQoL following an intervention, and as such are commonly used in clinical trials (31). General HRQoL measurements may produce complimentary information on previously unknown complications, and offer a way to compare the effects of different conditions on HRQoL with the HRQoL of the general population (31). However, it has been suggested that HRQoL utility instruments should be preferred that use preference weights obtained from the local general population (190).

HRQoL instruments can be further classified into three categories depending on how the HRQoL evaluation is performed: 1) self-rated HRQoL instruments, 2) formal or informal caregiver (proxy)-rated HRQoL tools, and 3) tools that can be applied by either one (31) (Table 3).

2.9.2 Measuring HRQoL in progressive neurodegenerative disorders

One of the fundamental questions in measuring HRQoL is whether patients with cognitive decline have enough insight for patient-reported outcome measures (PROMs), such as HRQoL, as insight in persons with cognitive impairment is often impaired (39) and it may affect the results of the PROMs (33,34,40-44). Formal or informal caregiver (proxy)-rated HRQoL scores are usually lower than the self-reported HRQoL (33,34,40-44). Lawton (35) stated that a person with cognitive impairment completely lacks the capability for self-judgement, and that proxies would be better able to estimate the HRQoL of the affected indirectly by different means of observation. This view has, however, been challenged over time, and PROMs, such as the self-rated HRQoL, are currently seen to also be important in dementia research. Many guidelines suggest using both self- and proxy-evaluated HRQoL if possible (33,34,198). Reports concerning the required cognitive function for PROMs are scarce (33,34).

Interestingly, while insight and cognition are commonly regarded as parallel constructs, insight may be preserved in the earlier stages of cognitive impairment (199). Preserved insight during the progression of the condition has been hypothesized to lead to impaired HRQoL at first, but as the insight is gradually diminished, the HRQoL is expected to improve, because the patient becomes blissfully ignorant of his/her condition (40,199,200). However, this hypothesis of preserved awareness causing decreased HRQoL has been questioned (201). The preserved awareness may, however, affect HRQoL indirectly through depressive symptoms (201). Depressive symptoms are internationally acknowledged factors affecting HRQoL in persons with cognitive impairment (34,41,202,203) (see sections 2.9.3 & 2.9.4). However, if the hypothesis holds even partly true, an ethical dilemma emerges when it comes to the decision to treat the individual person; if an intervention improves the cognitive impairment or delays its progression, it may unintentionally enable the person to suffer from the condition through increased awareness (199). Nevertheless, the benefit of treating a neurodegenerative condition, such as AD, outweighs its costs, as earlier treatment supports daily functioning (142), and prevents the increase in neuropsychiatric symptoms (204) reducing the HRQoL of both the person with AD (34,202,203) and his/her caregiver (205).

Despite two decades of research, investigators have found very little common ground when it comes to choosing the HRQoL instrument for patients with cognitive impairment (33-35,206,207). There are disagreements on the optimal way to administer the HRQoL instrument and what dimensions and qualities the instrument should have when used in patients with impaired cognitive function (33-35,206,207). The development of optimal HRQoL measurement has been seen as challenging, because the importance of certain dimensions of HRQoL may vary in different stages of dementia or they may lose their value completely (198).

Table 3. Generic HRQOL instruments used in patients with AD or iNPH.

Author	Instrument, rater	Items/domains	Collection, disease state	Used in AD	Used in iNPH
The EuroQoL Group 1990 (191)	EQ-5D, patient and/or caregiver	Consist of two parts: a self-administered health index and a VAS. 5 domains: mobility, self-care, pain/discomfort, usual activities, and anxiety/depression	Interview or Self-administered questionnaire, mild to moderate AD	Yes	Yes
Selai et al. 2001(192)	QOLAS, patient	10 items. Questions (two for each domain) are personally modified for each patient by asking what is important to his/her QoL. Domains: physical, psychological, social/family, work, and cognitive	Interview, mild to moderate AD	Yes	No
Sintonen et al. 2001(49)	15D, patient	15 domains: mobility, vision, eating, hearing, breathing, sleeping, speech, excretion, usual activities, mental function, discomfort, depression, distress, vitality, and sexual activity	Self-administered questionnaire, mild to moderate AD	Yes	No
WHOQOL Group 1995 (187)	WHOQOL 100, patient	100 items. 6 domains: physical health, psychological, levels of independence, social relations, environment, and spirituality/ religion/ personal beliefs	Self-administered questionnaire mild to moderate AD	Yes	No
Kaplan et al. 1988 (193)	QWB, patient	Domains: self-care, usual/social activities, mobility and physical activities. Two to eight items per domain. Incorporates 21 symptom complexes pertaining to physical and emotional health, cognitive and sensory function, speech, general weakness, limbic function, and pain	Self-administered questionnaire, mild to moderate AD	Yes	No
Neumann et al. 2000 (194)	HUI 2, caregiver	7 domains: sensation, mobility, emotion, cognition, self-care, pain, and fertility	Interview, all AD stages	Yes	No
Neumann et al. 2000 (194)	HUI 3, caregiver	8 domains: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain	Interview, all AD stages	Yes	No
Ware et al. 1999 (195)	SF-36, patient	36-item questionnaire having eight domains: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy and vitality, pain, and general perception of health. These comprise two summary measures: the physical component summary and the mental component summary	Interview or self-administered questionnaire	Yes	Yes
Jenkinson et al. 1997(196)	SF-12, patient	A 12-item questionnaire having eight domains: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. These comprise two summary measures: the physical component summary and the mental component summary.	Interview or Self-administered questionnaire	Yes	Yes

This table was adapted and modified from the thesis of Kristiina Hongisto (PhD) with the permission of the author (197). Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; AD, Alzheimer's disease

Disease-specific HRQoL instruments have been seen as a preferred option: they are thought to capture changes caused by interventions, as well as the important HRQoL aspects of dementia, that generic HRQoL measurements cannot (see section 2.2.1). Furthermore, they are seen as more reliable and valid for patients with cognitive impairment, as they were developed for this population (33,34,37,38). However, even for these instruments, the definition of HRQoL and the domains perceived to be important for HRQoL in dementia differ according to the instrument, and have changed over time (33,206,207). One of the core disagreements is whether the HRQoL instrument should portray dimensions of health that are important to the respondent, or whether the dimensions should be selected by the scientific community (198). In their recent review of dementia-specific HRQoL measurement scales, Bowling et al. (33) stated that persons and patients might have a broader perspective of HRQoL than experts, and they contemplated an ideal HRQoL measure as follows (bold used to emphasize issues regarded as important by the author (I)):

"So, what might an ideal (QoL) measure be like? We suggest ***an ideal measure would reflect the views and priorities of the person with dementia****. As there has been no large-scale, representative study to elicit the views of those with mild to moderate dementia,* ***one cannot specify the domains in advance****."*

2.9.3 Factors associated with HRQoL in persons with cognitive impairment

Table 4. Factors influencing self-rated HRQoL in persons with cognitive impairment

Factors	Effect on self-evaluated HRQoL
Neuropsychiatric symptoms (such as depressive symptoms)	-
Performance of activities of daily living	+/-
Sex	+/-
Education level	+/-
Polypharmacy	-
Comorbidity burden	-

- indicates a negative effect on self-evaluated HRQoL. +/- indicates conflicting results between studies. Abbreviations: HRQoL, health-related quality of life.

Despite the methodological disagreements, multiple factors that might be important for the self-rated HRQoL of patients with cognitive impairment have been identified (Table 4): neuropsychiatric symptoms, such as depressive symptoms, have been found in numerous studies to heavily impair HRQoL in patients with AD or cognitive impairment (34,40,41,202,203,208). According to a recent review, lower performance in activities of daily living (ADL) is not associated with lower HRQoL (34). Conflicting results, however, have been recently presented (208,209). Similarly, there are dissimilar findings when it comes to different demographic variables and HRQoL in persons with cognitive impairment, as some factors, such as a higher educational level and sex (male), have been suggested both to have (41) and not to have (34) an association with better HRQoL. Polypharmacy (210) and a greater comorbidity burden (211) have been associated with poorer HRQoL in persons with cognitive impairment. In addition to this, persons with cognitive impairment might perceive their health as poorer than cognitively healthy patients with otherwise the same comorbidity burden (212), which might relate to the conflict between desired and present health states (32,199) (see section 2.9).

Most of the studies focusing on the relationship between self- and proxy-rated HRQoL and impaired cognition and various other variables have been performed in patients with AD (33,34,40). The progression of HRQoL during the natural course of dementia may vary, and HRQoL does not necessarily worsen, despite impaired cognition (40,213-215) (see section 2.9.2). Recent studies have reported that even if a patient's cognition improved through different interventions, HRQoL of the patient did not improve (216,217).

Proxy-rated HRQoL evaluations, however, are usually lower than self-rated evaluations (33,34,40-44) and gradually deteriorate as the patient's memory disorder progresses (40,215,217). Three parallel theories have sought to explain this observation: the caregivers are underestimating the patient's HRQoL, partly explained by the burden of the caregiving and the increased neuropsychiatric symptoms of the patient, which in turn have an effect on the evaluator's ratings (34,43,203,214,215), or persons with cognitive impairment lose insight (40,41,199,200) (see section 2.9.2), or patients adapt to their condition and thus self- and proxy evaluations vary (199).

The inability to remember the past may cause the self-evaluation of HRQoL in a person with cognitive impairment to be highly situational: The feelings and symptoms, or their absence, at the time of the HRQoL interview may have a greater impact on self-rated HRQoL than in a person without cognitive impairment (197).

2.9.4 Health-related quality of life in iNPH

There have only been four studies on HRQoL in patients with iNPH, all of which have used a generic HRQoL instrument (45-48). However, the study of Gelling et al. (45), using the SF-36 HRQoL instrument (195,218), holds limited value for iNPH research, as the patients with NPH were grouped with those having benign intracranial hypertension (BIH) or congenital hydrocephalus, and because universally acknowledged diagnostic guidelines for iNPH were not available in 2004 when the study was performed (see section 2.2). Consequently, current knowledge of HRQoL in iNPH is based on only three existing studies that used generic HRQoL measurements at baseline and after CSF shunt surgery in patients with iNPH (46-48): one using the EQ-5D (48,191) and the two others using the brief QoL inventory SF-12 (46,47,196). A literature search of HRQoL studies in iNPH has been published in the 2nd publication of this thesis (Chapter 5, Table 12).

In iNPH, we may detect similar changes in HRQoL as in AD (see sections 2.9.2 & 2.9.3) and PD (219) through shared symptomatology. However, this type of comparison has not been performed. As dementia and psychiatric comorbidities are associated with an increased risk of complications and a poorer HRQoL outcome after major spinal surgery (220), one might also suspect persons with iNPH to be at higher risk of unfavorable surgical and HRQoL outcomes.

Prior to CSF shunt surgery, a higher self-rated HRQoL correlated with better performance of activities of daily living (ADL) in persons with iNPH (48). Self-rated HRQoL did not differ between iNPH patients with different demographic variables, such as age and sex (48). The self-rated HRQoL seems to be lower in patients with iNPH when compared to EQ-5D reference values acquired from the general population of the UK (48).

The HRQoL results following CSF shunt therapy are conflicting, as one study did not observe a significant change in HRQoL (46), but two others reported a significant improvement (14,48). Patients with complications following CSF shunting, such as

overdrainage, may report a lower HRQoL than those without complications (14,48). Changes in the generic outcome measures appear to reflect changes in some of the clinical variables following CSF shunting (14,48). The dimensions of HRQoL that are reported to improve after CSF shunting using the EQ-5D are 'mobility', 'self-care', 'usual activities of daily living' and 'anxiety' (48). When it comes to improvement in the individual dimensions of HRQoL, demographic factors may play a role, as older age has been reported to be associated with a lower gain in 'physical functioning', and females are more likely to benefit in terms of 'mental health' measured by the SF-12 (14). In addition, there are a few patients whose HRQoL has improved despite their poor clinical outcome, and it has been hypothesized that in these patients, HRQoL captures subtle changes caused by CSF shunting that are not portrayed by objective measurements (48). A larger comorbidity burden predicts a worse HRQoL outcome following CSF shunting (14). Surprisingly, none of the three published studies evaluated the effect of cognition on HRQoL. For instance, Katzen et al. (46) performed a detailed neuropsychological evaluation of all of the 12 iNPH participants in their study, but did not evaluate or publish its effect on HRQoL.

2.9.5 The use and limitations of the 15D instrument

While the 15D has been used in varying study settings in over 100 different conditions/diseases/health problems (221) and discussed in over 400 publications (222), only a relatively small number of studies have used the 15D instrument in patients with cognitive impairment, all of which have been performed in Finland (40,203,223-226). Preliminary evidence, based on the previous conceptual view of AD, indicates that the 15D captures the essential dimensions of HRQoL that are important for patients with AD (227). However, as stated before (see section 2.9.2), one should interpret this result cautiously, as the conceptual framework for AD is diverse (207). The 15D might have only limited sensitivity in detecting the change in health (e.g. progression of the disease) of persons with AD, and, consequently, disease-specific HRQoL instruments are recommended (33,40). In contrast, the 15D has been successfully used to measure generic HRQoL in Finnish patients with PD (228). The latest international review of the usage of HRQoL instruments in PD, approves the use of 15D instrument in the affected persons (229). Similarly, the 15D has performed well in detecting changes in the health status in numerous surgical conditions (221), such as hip or knee replacement surgery (230), microdiscectomy for lumbar disc herniation (231), or neurosurgical spinal surgery, including persons with lumbar spinal stenosis (232).

One of the core strengths of the 15D is the usage of preference weights obtained from the local Finnish general population, making it more robust when used in persons from this area (49,190). In addition, the 15D, like other generic measures, enables comparisons with the general population and with other conditions (31,49,228).

As self-rated generic HRQoL instruments (SF-12, EQ-5D) can detect changes in the health status of patients with iNPH (14,48) (see section 2.9.4), and because the 15D has been successfully used in PD (228) and detects health status changes in various surgical conditions (221,230-232), the 15D is a potentially reliable tool to measure HRQoL in persons with iNPH. However, its sensitivity in iNPH patients with cognitive impairment needs to be evaluated.

2.9.6 Health economics in iNPH

Quality-adjusted life years (QALYs) is a concept combining both the length and the HRQoL of the life lived (233). Originally, QALYs were developed to measure the cost-effectiveness of different interventions, so that society's limited resources could be potentially allocated more effectively (233). The core principle is that each person has a number-weighted health state, a utility value that may be affected by different health conditions (234). The total QALYs that patient has in his/her lifetime can be calculated by adding the amounts of time spent in these different health states (234). The cost of QALYs has been widely used to compare different health interventions (233). It has been estimated that treatment producing one QALY, costing less than £20,000 to £30,000, is cost-effective (234).

A reasonable QALY gain following CSF shunting in patients with iNPH has been observed (167,235). However, these studies have been based on utility simulations, which have made assumptions concerning the progression rate of iNPH in untreated patients, as there have been no studies on this topic (see section 2.7). Stein et al. (167) estimated iNPH patients to gain 1.7 QALYs from CSF shunting, basing the progression rate of the utility value (-10%/year) in patients with iNPH on a 65-year-old patient with AD, while Kameda et al. (235) based their utility predictions on patients with ICH. While Stein et al. (167) did not report an estimation of the QALY cost, Kameda et al. (235) concluded that CSF shunting is cost-effective, as in the first year after CSF shunting, the price for one QALY was at minimum USD 29,934 (~£22,400) (235).

3 Aims of the Study

3.1 OBJECTIVES & SCOPE

3.1.1 Overall objective

The objective throughout the present study was to elucidate and identify factors affecting and predicting the self-rated HRQoL in persons with iNPH. This information is required for further understanding of the condition and what is important to the patient's HRQoL in different stages of treatment. The study may help clinicians to try to modify factors that cause a deterioration in HRQoL and to estimate which patients will benefit from shunt surgery.

3.1.2 Specific aims of the study

I) To evaluate whether a generic utility instrument, the 15D, is a suitable tool for HRQoL assessment in patients with iNPH. This was studied by investigating whether 15D portrays iNPH in a similar way to broader assessment batteries that are known to be of importance in iNPH and cognitive impairment. A further aim was to identify clinical factors predicting self-rated HRQoL in persons with untreated iNPH. In addition, our aim was to investigate the HRQoL impairment caused by iNPH by comparing the HRQoL of the study population with that of an age- and gender-matched sample of the general population.

II) To investigate the rate of a favorable HRQoL outcome after CSF shunt surgery and to identify individual factors predicting the one-year HRQoL outcome. Furthermore, we aimed to study how comorbidities, especially Alzheimer's disease, affect the self-rated HRQoL. In addition, our aim was to investigate whether there is concordance between the changes in the 15D and the other outcome variables.

III) To conduct a pilot study evaluating the cost-effectiveness of CSF shunting in patients with iNPH.

IV) To determine how often patient-reported outcomes (measured by the 15D) and clinician-reported outcomes (measured by the iNPH Grading Scale (iNPHGS)) differ in persons with iNPH. Another aim was to investigate whether patient-related factors, such as cognitive impairment, depressive symptoms, or neurodegenerative comorbidity, predict the discrepancy between patient- and clinician-rated outcomes.

4 Health-related quality of life in patients with idiopathic normal pressure hydrocephalus

4.1 ABSTRACT

Background and purpose
Factors affecting health-related quality of life (HRQoL) were explored in patients with idiopathic normal pressure hydrocephalus (iNPH).

Methods
Using the 15D instrument HRQoL was evaluated in 132 patients diagnosed with iNPH by clinical and neuroradiological examinations. The severity of iNPH symptoms was measured with the iNPH grading scale (iNPHGS), depressive symptoms with the Beck Depression Inventory (BDI-21) and cognitive impairment with the Mini-Mental State Examination.

Results
The mean (SD) 15D score (on a 0–1 scale) of patients with iNPH was significantly lower than that of an age- and gender-matched sample of the general population [0.718 (0.103) vs. 0.870 (0.106); $P < 0.001$]. The mean 15D score was lower in iNPH patients with moderate or severe depressive symptoms than in patients without depressive symptoms ($P = 0.003$). According to stepwise multiple linear regression analysis, a higher total iNPHGS score (b= 0.62, $P < 0.001$) and a higher BDI-21 total score (b= 0.201, $P = 0.025$) predicted a lower 15D score; in combination, these explained 51% of the variance in the 15D score ($R^2 = 0.506$, $P < 0.001$).

Conclusions
Idiopathic normal pressure hydrocephalus impairs patients' HRQoL on multiple dimensions, similarly to other chronic diseases. Potentially treatable depressive symptoms contribute greatly to the HRQoL impairment of iNPH patients, but only if they are moderate or severe. The 15D portrayed HRQoL dimensions affected by iNPH in a similar way to broader assessment batteries and thus is a potentially useful tool for treatment evaluation and cost utility analysis.

4.2 INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a disorder of elderly patients; it typically features ventriculomegaly, impaired gait, urinary incontinence and cognitive impairment (236). Although iNPH can be treated with shunting surgery (237,238), its status as a curable dementia has been questioned owing to varying outcomes of shunt replacement (2,9,17,115). The identification of comorbidities that may potentially hamper the efficacy of treatment has been considered vital in the clinical management of iNPH (13).

Although there is no agreement regarding the optimal tool with which to measure health-related quality of life (HRQoL) in patients with cognitive deficits (33,34), it is considered as an important part of evaluating health service outcome and cost-effectiveness (33). The inability to perform activities of daily life (ADL) is the main cause of HRQoL deterioration in patients with cognitive impairment (239). Depression and other psychiatric symptoms are assumed to impair HRQoL in dementia (34,240), and they are frequently present in iNPH (83,86,89,90). Psychiatric symptoms related to iNPH can be partly explained by the related brain damage (89).

Only few studies have measured HRQoL amongst iNPH patients (14,45,46,48). Our primary aim was to compare the HRQoL of iNPH patients with that of an age- and gender-matched sample of the general population. The components that affect HRQoL in iNPH patients were also explored as well as the usefulness of the generic 15D HRQoL instrument in the evaluation of symptoms of iNPH.

4.3 METHODS

4.3.1 Study design and participants

The study was performed in the Neurosurgery Department of the Kuopio University Hospital (KUH). Permission for the study was obtained from the KUH Research Ethics Board. A neurologist conducted the primary examination. Patients were referred for further neurosurgical examinations if they exhibited one to three symptoms potentially related to NPH (impaired cognition, gait or urinary continence) together with enlarged brain ventricles disproportionate to the size of the sulci of cerebral convexities (Evan's index >0.30) (241) in computed tomography or magnetic resonance imaging.

The first 36 consecutive patients (27%) were selected for the shunting procedure according to the results of 24-h monitoring of intraventricular pressure (IVP) (17). For the rest of the patients, final selection for shunting was based on the following three-step protocol: 55 (35%) patients were shunted based on a positive tap test (at least 20% improvement in gait speed in two 10-m tests); 31 (24%) patients with a negative tap test underwent lumbar infusion testing, and those with a pathological finding (conductance ≤10) were shunted; and 10 (8%) patients with a negative finding in both of the above tests were shunted based on 24-h monitoring of IVP.

Health-related quality of life was measured between April 2009 and April 2013 in all consecutive patients providing informed consent and with possible iNPH. The HRQoL questionnaires were completed by the patients themselves or by an interviewing nurse. The clinical information and questionnaires were recorded prior to the shunting. In total, data were collected from 177 consecutive patients and stored in the NPH Registry of KUH (www.uef.fi/nph). Forty-five patients were excluded from the final analysis: 39 patients because their clinical condition was found to be noniNPH or secondary NPH, and six patients because of incomplete HRQoL questionnaire data (>3 missing answers on the 15D). Finally, the mean 15D score of 132 possible iNPH patients (Table 5) was compared with that of an age- and gender-matched sample (n = 3372) from the general population (242).

4.3.2 The HRQoL measure

The 15D instrument has been described in section 2.9.5. (Figure 6, Table 6, Appendix 3).

4.3.3 Evaluation of comorbidities

Coronary heart disease, chronic atrial fibrillation, other cardiac arrhythmias, chronic heart failure and hypertension were classified as cardiovascular comorbidities. Patients were classified into two groups: patients with and patients without one or more cardiovascular comorbidities. Because musculoskeletal comorbidities were not systematically explored in this study, their effects on HRQoL were estimated indirectly; medications of iNPH patients were explored and patients with regular pain medication were compared with those without regular pain medication.

Depressive symptoms were assessed with the selfadministered 21-item Finnish version of the Beck Depression Inventory (BDI-21) (243). Each item includes four statements that have a numerical value from 0 to 3. The questionnaire's total score ranges from 0 to 63, with higher scores indicating more severe depressive symptoms. iNPH patients were classified into three groups: patients without (BDI < 10), with minor (10 ≤ BDI ≤ 16) or with moderate or severe depressive symptoms (BDI ≥ 17).

4.3.4 Evaluation of cognition

The Mini-Mental State Examination (MMSE, range 0–30) (244) was used to evaluate patients' cognitive function. Patients were classified into three groups: no significant cognitive impairment (27 ≤ MMSE ≤ 30), minor cognitive impairment (23 ≤ MMSE ≤ 26) or moderate or severe cognitive impairment (MMSE ≤ 22).

4.3.5 Evaluation of iNPH symptoms

Evaluation of iNPH symptoms to classify the triad of symptoms a modified Finnish version of the 12-point iNPH grading scale (iNPHGS) was used (95). The iNPHGS is a clinician-rated scale to separately assess the severity of each of the three symptoms, with scoring based on observations by the physician and interviews with the patients or their caregivers. Subscores for each dimension range from 0 to 4, with higher scores representing worse symptoms.

4.3.6 Activities of daily life

Activities of daily life were measured using the Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory (ADCS-ADL) (245). The ADCS-ADL is a proxy/informant-rated questionnaire and was administered by the study nurse. Lower total scores (scale 0–78) indicate worse ADL performance.

4.3.7 Education

Patients were dichotomized according to years of education: patients with ≤9 years of education and patients with >9 years of education

Table 5. Characteristics of 132 iNPH patients

VARIABLE	Mean/N	Mean 15D score (SD)	p[a]
OVERALL	[132] (100)	0.718 (0.10)	
GENDER			0.802
Male	65 (52)	0.715 (0.11)	
Female	68 (49)	0.720 (0.10)	
AGE	75.1 (8.9)		
INPHGS SCORE (0-12)	6.2 (2.8)		
Impaired gait (0-4)	2.2 (1.1)		
Impaired cognition (0-4)	1.7 (1.1)		
Urinary incontinence (0-4)	2.4 (1.5)		
CARDIOVASCULAR COMORBIDITIES			0.805
No Cardio-vascular comorbidities	36 (27)	0.722 (0.13)	
≥1 Cardio-vascular comorbidity	96 (73)	0.716 (0.93)	
PAIN MEDICATION			0.009
Regular usage	46 (35)	0.701 (0.11)	
No regular usage	86 (65)	0.750 (0.08)	
MMSE SCORE (0-30)	21.9 (5.1) [130]	0.718 (0.10)	0.233
No significant cognitive impairment (27≤ MMSE≤30)	24 (18)	0.739 (0.08)	
Minor cognitive impairment (23≤MMSE≤26)	40 (31)	0.731 (0.10)	
Moderate or severe cognitive impairment (MMSE≤22)	66 (51)	0.702 (0.01)	
EDUCATION LEVEL	[127]		0.805
≤9 years of education	86 (68)	0.718 (0.10)	
>9 years of education	41 (32)	0.713 (0.11)	
BDI-21 SCORE (0 – 63)	12.2 (8.6) [74]	0.714 (0.10)	0.003
No depressive symptoms (BDI-21 < 10)	39 (53)	0.747 (0.09)	
Minor depressive symptoms (10 ≤ BDI-21 ≤ 16)	17 (23)	0.703 (0.08)	
Moderate or severe depressive symptoms (17 ≤ BDI-21 ≤ 63)	18 (24)	0.654 (0.12)	
ADCS-ADL SCORE (0-78)	49.1 (3.3) [40]	0.723 (0.09)	

iNPH, idiopathic normal pressure hydrocephalus; iNPHGS, iNPH grading scale; MMSE, Mini-Mental State Examination; BDI-21, Beck Depression Index; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory. Values are expressed as number of cases or mean, with percentage or SD in parentheses. The number of observations is given in braces. [a]t test or ANOVA. Statistically significant differences (P < 0.05) are in bold.

4.3.8 Statistics

The data were analyzed using the Statistical Package for Social Sciences (SPSS® 19 for Windows). The independent samples t test and Mann–Whitney U test were applied to test the differences between the two groups' mean and median 15D scores and dimension level values. One-way analysis of variance (ANOVA) was used in multiple comparisons. The linear association between variables was measured using Pearson's correlation coefficient. Stepwise multiple linear regression analysis was done. All tests for significance were two-sided, with probabilities of <0.05 accepted as significant. The Bonferroni corrections of P values were used to adjust for multiple comparisons.

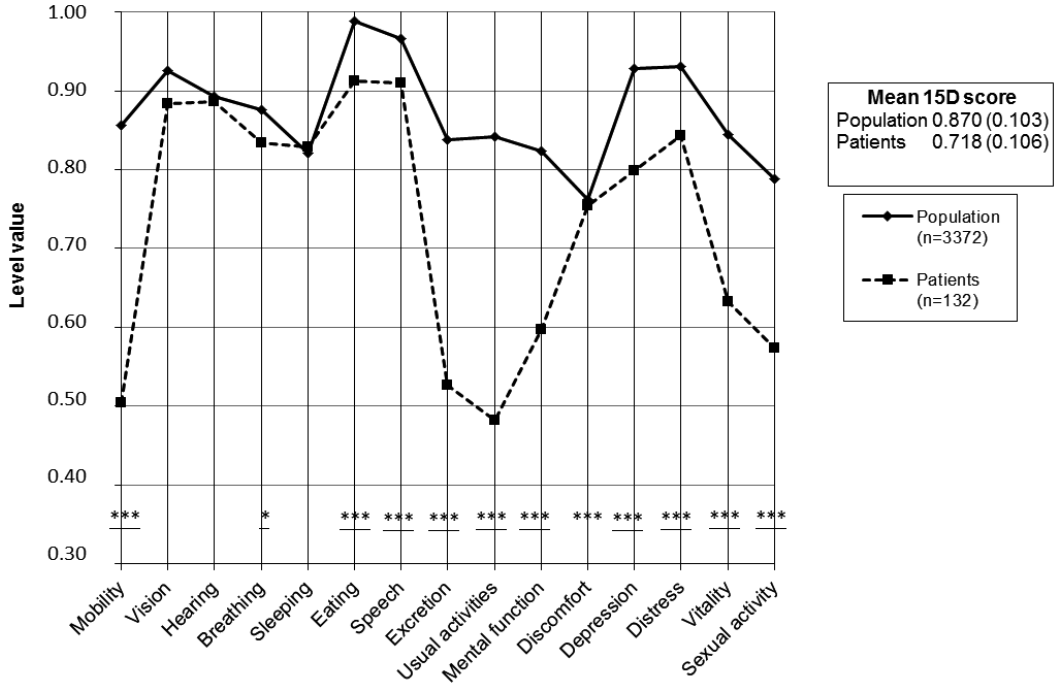

Figure 6. The mean 15D profile of the study population and of an age- and gender-matched sample of the general population. *P < 0.05 and ***P < 0.001 in the Mann–Whitney U test; a clinically significant difference (|D15D| ≥ 0.015) is underlined; data are mean (SD) scores.

4.4 RESULTS

The mean (SD) 15D score and the majority of 15D dimensions of patients with iNPH were significantly lower than those of the age- and gender-matched sample of the general population [0.718 (0.103) vs. 0.870 (0.106); P < 0.001] (Figure 6, Table 6).

4.4.1 Factors affecting the HRQoL of iNPH patients

There was a strong negative correlation between iNPH patients' 15D and iNPHGS scores (r = 0.69, P < 0.001). Detailed 15D and iNPHGS correlations are presented in Table 7. Of the 132 iNPH patients, 46 (35%) used pain medication regularly and had significantly lower 15D score (P = 0.009) than those with no regular use (Tables 5 and 8). Of the 74 iNPH patients for whom BDI-21 was available, 17 (23%) patients had minor and 18 (24%) moderate or severe depressive symptoms (Table 5). iNPH patients with moderate or severe depressive symptoms had a lower 15D score (P = 0.003) than patients without depressive symptoms (Table 9).

Seven variables were used in stepwise multiple linear regression analysis, with 15D score as the dependent variable (Table 10). ADCS-ADL was removed from the stepwise multiple linear regression analysis because ADCS-ADL data were available for only a small patient population. The highest variance inflation factor was 1.13 (MMSE) and the lowest tolerance was 0.83 (MMSE) suggesting that multicollinearity does not have a significant effect on our model. Stepwise multiple linear regression analysis (Table 10) indicated that a higher total iNPHGS score (b = 0.62, P < 0.001) and a higher total BDI-21

score (b = 0.201, P = 0.025) predicted a lower 15D score; in combination, they explained 51% of the variance in the 15D total score (R2 = 0.506, P < 0.001).

Table 6. The Mean 15D scores and dimension level values, Comparison between the study population with age- and gender-matched general population.

VARIABLE	iNPH patients [132]	General population [3372]	Mean difference[b] (95% CI)	p*
15D score[a]	0.718 (0.10)	0.870 (0.11)	0.153 (0.13, 0.17)	< 0.001
Moving	0.505 (0.18)	0.856 (0.19)	0.351 (0.32, 0.38)	< 0.001
Seeing	0.883 (0.18)	0.925 (0.15)	0.042 (0.01, 0.07)	0.44
Hearing	0.886 (0.19)	0.892 (0.17)	0.006 (-0.02, 0.04)	0.77
Breathing	0.834 (0.24)	0.876 (0.20)	0.042 (-2.1E-4, 0.08)	0.032
Sleeping	0.829 (0.22)	0.821 (0.19)	-0.008 (-0.05, 0.03)	0.08
Eating	0.913 (0.17)	0.988 (0.10)	0.076 (0.05, 0.10)	< 0.001
Speech	0.910 (0.15)	0.966 (0.10)	0.056 (0.03, 0.08)	< 0.001
Secretion	0.527 (0.30)	0.838 (0.21)	0.311 (0.26, 0.36)	< 0.001
Usual activities	0.483 (0.26)	0.842 (0.22)	0.359 (0.31, 0.40)	< 0.001
Mental function	0.598 (0.24)	0.824 (0.21)	0.226 (0.19, 0.26)	< 0.001
Discomfort and symptoms	0.755 (0.25)	0.762 (0.21)	0.008 (-0.04, 0.05)	< 0.001
Depression	0.799 (0.20)	0.928 (0.13)	0.129 (0.09, 0.16)	< 0.001
Distress	0.843 (0.18)	0.930 (0.13)	0.088 (0.06, 0.12)	< 0.001
Vitality	0.633 (0.18)	0.845 (0.16)	0.212 (0.18, 0.24)	< 0.001
Sexual activity	0.574 (0.36)	0.788 (0.28)	0.215 (0.15, 0.28)	< 0.001

[a]Data are mean (SD) scores. The scale is 0-1, worst to best, [ ] number of observations, [b]Positive difference indicates better score and negative difference indicates worse score for population controls than for patients. Clinically significant difference (|Δ15D |≥ 0.015) is bolded, *Mann-Whitney U-test

4.5 DISCUSSION

Compared with other chronic conditions, iNPH patients' mean 15D score (0.718, mean age 75) was similar to the previously reported 15D scores of patients with other neurological disorders (0.729, mean age ≥75 years) and psychiatric patients (0.721, mean age ≥75 years) (246). The HRQoL of iNPH patients has been measured previously using SF-36 and QoL-10; however, it was not stated whether any secondary NPH patients were included in their study group (45). In addition, the brief QoL inventory SF-12 (14,46) and EQ-5D (48) have been used to estimate HRQoL at baseline and after shunt surgery in iNPH patients. Health-related quality of life was affected on a variety of dimensions – far more than only in mobility, mental function or excretion; iNPH patients were worse off than the control sample on 12 of the 15 dimensions. The dimensions of 'usual activities', 'moving', 'excretion', 'mental status', 'vitality', 'sexual activity' and 'depression' were the most impaired.

The results from multivariate and univariate regression analyses and the strong correlations betweenmultiple variables (iNPHGS, MMSE, BDI and ADCSADL) and dimensions of the 15D show that a rather simple generic utility measurement, the 15D, indicates very much the same results as the broader batteries regarding iNPH. Thus, it is a potentially useful tool with which to evaluate the effectiveness of treatment in patients with

iNPH and enables cost utility analysis. However, the self-reported HRQoL of patients with iNPH who have a different severity of cognitive impairment must be evaluated separately. Our results may only be applicable to iNPH patients with comparable cognitive deficit. Our study revealed no significant differences in the mean 15D score between patients without cognitive deficits and those with minor, moderate or severe cognitive impairment.

Depressive symptoms are significant and potentially treatable symptoms that cause the deterioration of HRQoL in iNPH. Proper treatment of depressive symptoms in patients with iNPH might potentially improve the HRQoL of affected patients. Even though depressive and other psychiatric symptoms are common in patients with iNPH (83,86,89,90), very little is known about the prevalence of depression in iNPH (13). In our study, nearly one-half of iNPH patients [35 of 74 (47%)] reported depressive symptoms of some severity. It is debatable to what extent the symptoms of iNPH or the cognitive impairment itself explain and/or contribute to the elevated BDI scores of iNPH patients (Table 11). One might assume that longer duration of the iNPH would increase the BDI score. In our study a significant difference was not observed in BDI scores between iNPH patients whose iNPH related symptoms had begun less than a year from the clinical examination and those whose iNPH related symptoms had existed for more than a year.

Regular use of analgesics was associated with lower HRQoL in iNPH patients. This association might be because of pain-causing musculoskeletal comorbidities. Nevertheless, the results of stepwise multiple linear regression analysis suggest that pain is not the main cause of HRQoL impairment in these patients, as other conditions – iNPH itself and depressive symptoms – have a more severe impact.

Poor performance in ADL may be the major cause of HRQoL deterioration in patients with iNPH. Lower ADL performance was associated with lower HRQoL in iNPH patients. There was a strong negative correlation between the ADCS-ADL and iNPHGS scores; according to the multinomial linear regression analysis, the latter was the main explanatory factor for impairment of HRQoL in patients with iNPH.

There are some limitations to this study. It lacks a proxy-rated HRQoL measure. However, recently the reliability and validity of the proxy-rated HRQoL have been criticized (33). The criteria for exclusion of patients with severe dementia from the self- and proxy-reported questionnaires remain unresolved (33). According to an earlier study (247), proxy-rated disease-specific HRQoL measurement (Quality of Life – Alzheimer's Disease) provided results similar to selfreported HRQoL if the patient scored >10 on the MMSE. In our sample, 131 of 132 patients fulfilled this criterion. It was also observed that patients without regular pain medication were more likely to have missing BDI or ADCS-ADL values. No other tendencies between missing and observed data were observed. Not all comorbidities were recorded in this study, leaving open the question of whether iNPH alone decreases the HRQoL as much as observed.

Table 7 Pearson's correlation between domains of 15D and characteristic variables

Urinary Incontinence	Impaired Cognition	Impaired Gait	INPHGS SCORE	Sexual activity	Vitality	Distress	Depression	Discomfort and symptoms	Mental function	Usual activities	Secretion	Speech	Eating	Sleeping	Breathing	Hearing	Seeing	Moving	15D SCORE	
-0.20 (0.02)	0.11 (0.22)	-0.08 (0.36)	-0.09 (0.29)	**-0.24 (0.005)**	-0.05 (0.58)	0.07 (0.40)	0.17 (0.05)	0.05 (0.60)	0.12 (0.17)	0.03 (0.78)	0.11 (0.22)	0.11 (0.20)	-0.06 (0.50)	0.05 (0.55)	-0.01 (0.92)	-0.10 (0.24)	0.10 (0.25)	0.08 (0.37)	-0.02 (0.80)	GENDER
0.13 (0.15)	**0.19 (0.029)**	**0.21 (0.016)**	**0.22 (0.010)**	0.06 (0.49)	0.04 (0.67)	0.09 (0.29)	0.07 (0.40)	0.02 (0.82)	-0.10 (0.25)	-0.04 (0.61)	-0.13 (0.13)	0.08 (0.38)	0.08 (0.38)	-0.03 (0.72)	-0.06 (0.48)	-0.10 (0.24)	0.07 (0.43)	-0.12 (0.11)	-0.05 (0.56)	AGE
0.04 (0.68)	0.04 (0.69)	0.07 (0.42)	0.06 (0.49)	-0.11 (0.20)	-0.01 (0.93)	0.08 (0.39)	0.09 (0.30)	-0.06 (0.51)	0.03 (0.72)	-0.01(0.93)	0.02 (0.85)	0.04 (0.68)	0.14 (0.10)	2.2E-4 (0.99)	-0.05 (0.56)	-0.14 (0.11)	-0.05 (0.53)	-0.050 (0.57)	-0.03 (0.78)	CARDIO-VASCULAR COMORBILIDITY
0.12 (0.18)	0.15 (0.09)	**0.20 (0.027)**	**0.20 (0.024)**	**-0.18 (0.038)**	**-0.17 (0.046)**	-0.11 (0.21)	-0.14 (0.12)	-0.11 (0.20)	-0.05 (0.54)	-0.17 (0.05)	-0.17 (0.06)	-1.9E-3 (0.985)	**-0.21 (0.014)**	-0.09 (0.32)	-0.03 (0.77)	-0.04 (0.61)	-0.08 (0.38)	-0.10 (0.28)	**-0.23 (0.009)**	REGULAR PAIN MEDICATION
-0.22 (0.014)	**-0.57 (<0.001)**	**-0.24 (0.005)**	**-0.44 (<0.001)**	0.04 (0.66)	0.13 (0.16)	0.06 (0.49)	0.14 (0.11)	0.06 (0.53)	**0.48 (<0.001)**	**0.30 (0.001)**	**0.27 (0.002)**	0.01 (0.93)	**0.21 (0.017)**	-0.02 (0.79)	-0.01 (0.92)	-0.05 (0.61)	-0.05 (0.54)	**0.23 (0.010)**	**0.28 (0.001)**	MMSE [130]
2.1E-3 (0.98)	**-0.18 (0.038)**	0.10 (0.28)	-0.04 (0.69)	-0.05 (0.61)	-0.01 (0.91)	-0.09 (0.34)	-0.04 (0.63)	0.07 (0.42)	0.11 (0.21)	0.01 (0.95)	-0.04 (0.69)	-0.11 (0.20)	-0.03 (0.74)	0.04 (0.63)	-0.07 (0.46)	-0.15 (0.09)	0.01 (0.87)	-0.01 (0.89)	-0.02 (0.80)	EDUCATION LEVEL [127]
0.07 (0.56)	**0.28 (0.014)**	0.22 (0.06)	**0.25 (0.029)**	**-0.23 (0.046)**	**-0.31 (0.006)**	**-0.48 (<0.001)**	**-0.44 (<0.001)**	-0.14 (0.24)	-0.22 (0.07)	-0.18 (0.13)	-0.11 (0.13)	0.09 (0.126)	-0.18 (0.13)	**-0.33 (0.004)**	-0.12 (0.31)	-0.05 (0.64)	-0.18 (0.13)	0.07 (0.549)	**-0.39 (0.001)**	BDI [74]
-0.28 (0.08)	**-0.53 (<0.001)**	**-0.51 (0.001)**	**-0.59 (<0.001)**	0.04 (0.79)	0.17 (0.30)	0.21 (0.19)	-0.03 (0.863)	0.02 (0.90)	**0.37 (0.020)**	**0.36 (0.022)**	0.24 (0.14)	-0.01 (0.95)	0.30 (0.06)	0.14 (0.39)	-0.21 (0.201)	0.27 (0.09)	0.31 (0.05)	**0.42 (0.007)**	**0.36 (0.02)**	ADCS-ADL [40]
0.82 (<0.001)	**0.67 (<0.001)**	**0.77 (<0.001)**	1	**-0.24 (0.006)**	**-0.40 (<0.001)**	-0.12 (0.183)	**-0.21 (0.014)**	-0.163 (0.062)	**0.49 (<0.001)**	**-0.58 (<0.001)**	**-0.70 (0.001)**	**-0.25 (0.004)**	**-0.35 (<0.001)**	-0.096 (0.271)	-0.10 (0.24)	**-0.18 (0.043)**	-0.02 (0.84)	**-0.62 (<0.001)**	**-0.69 (<0.001)**	INPHGS
0.47 (<0.001)	**0.32 (<0.001)**	**1**	**0.77 (<0.001)**	**-0.23 (0.009)**	**-0.32 (<0.001)**	-0.03 (0.71)	-0.09 (0.29)	**-0.19 (0.027)**	**-0.27 (0.002)**	**-0.58 (<0.001)**	**-0.50 (<0.001)**	**-0.22 (0.013)**	**-0.35 (<0.001)**	-0.04 (0.62)	-0.10 (0.28)	**-0.19 (0.029)**	-0.04 (0.62)	**-0.68 (<0.001)**	**-0.59 (<0.001)**	Impaired Gait
0.26 (0.002)	**1**	**0.32 (<0.001)**	**0.67 (<0.001)**	**-0.24 (0.005)**	**-0.37 (<0.001)**	-0.16 (0.06)	**-0.19 (0.032)**	0.10 (0.27)	**-0.65 (<0.001)**	**-0.40 (<0.001)**	**-0.25 (0.004)**	**-0.26 (0.003)**	**-0.35 (<0.001)**	-0.05 (0.56)	-0.05 (0.57)	**-0.19 (0.031)**	-0.05 (0.59)	**-0.30 (<0.001)**	**-0.54 (<0.001)**	Impaired Cognition
1	**0.26 (0.002)**	**0.47 (<0.001)**	**0.82 (<0.001)**	-0.10 (0.28)	**-0.25 (0.004)**	-0.07 (0.43)	**-0.19 (0.029)**	-0.09 (0.29)	**-0.22 (0.010)**	**-0.36 (<0.001)**	**-0.77 (<0.001)**	-0.11 (0.21)	-0.14 (0.11)	-0.11 (0.20)	-0.09 (0.31)	-0.05 (0.57)	0.03 (0.69)	**-0.45 (<0.001)**	**-0.46 (<0.001)**	Urinary Incontinence

MMSE, Mini-Mental State Examination; BDI-21, Beck Depression Index; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; iNPHGS, iNPH grading scale.Statistically significant correlation is in bold. P values are in parentheses. The number of observations is in braces. Statistically significant differences (P < 0.05) are in bold

In conclusion, iNPH reduces patients' general HRQoL in a manner similar to many other chronic conditions. Potentially treatable depressive symptoms contribute greatly to the HRQoL impairment of iNPH patients, but only if they are moderate or severe. The ability to perform ADL may also have a major impact on the HRQoL of iNPH patients. In addition, regular use of analgesics is associated with reduced HRQoL in iNPH patients. No significant differences in HRQoL between groups separated by level of cognition, as measured with the MMSE, were observed. The 15D portrayed HRQoL dimensions affected by iNPH in a way similar to broader assessment batteries. Therefore, it is a potentially useful tool for treatment evaluation and cost utility analysis.

Table 8. The mean 15D scores and dimension level values: comparison within the study population between patients regularly using pain medication and those without regular pain medication

VARIABLE	iNPH patients without regular pain medication [46]	iNPH patients with regular pain medication [86]	Mean difference (95% CI)	p[a]
15D score[a]	0.750 (0.08)	0.701 (0.11)	**0.049 (0.02, 0.08)**	**0.009**
Moving	0.528 (0.16)	0.492 (0.19)	0.036 (-0.03, 0.10)	0.28
Seeing	0.903 (0.17)	0.873 (0.19)	0.030 (-0.04, 0.10)	0.38
Hearing	0.898 (0.18)	0.880 (0.20)	0.018 (-0.05, 0.09)	0.61
Breathing	0.842 (0.25)	0.829 (0.25)	0.013 (-0.08, 0.10)	0.77
Sleeping	0.855 (0.21)	0.816 (0.22)	0.040 (-0.04, 0.12)	0.32
Eating	0.962 (0.11)	0.887 (0.19)	**0.075 (0.02, 0.13)**	**0.014**
Speech	0.911 (0.16)	0.910 (0.14)	5.1E-4 (-0.05, 0.05)	0.99
Secretion	0.594 (0.30)	0.491 (0.29)	0.103 (-3.1E-3, 0.21)	0.06
Usual activities	0.542 (0.24)	0.451 (0.26)	**0.092 (-5.0E-5, 0.18)**	**0.050**
Mental function	0.616 (0.24)	0.588 (0.25)	0.028 (-0.06, 0.12)	0.54
Discomfort and symptoms	0.793 (0.23)	0.734 (0.25)	0.058 (-0.03, 0.15)	0.20
Depression	0.836 (0.19)	0.780 (0.21)	0.057 (-0.02, 0.13)	0.12
Distress	0.869 (0.15)	0.829 (0.19)	0.041 (-0.02, 0.11)	0.21
Vitality	0.674 (0.16)	0.611 (0.18)	**0.064 (1.1E-3, 0.13)**	**0.046**
Sexual activity	0.661 (0.35)	0.527 (0.35)	**0.134 (7.2E-3, 0.26)**	**0.038**

iNPH, idiopathic normal pressure hydrocephalus; CI, confidence interval. The number of observations is given in braces. Clinically and statistically significant differences ($|\Delta 15D| \geq 0.015$) are in bold. [a]t test; bdata are mean (SD) scores; the scale is 0–1, worst to best; ca positive difference indicates a better score and a negative difference indicates a worse score for iNPH patients without regular use of pain medication than for patients with regular use of pain medication. Statistically significant differences ($P < 0.05$) are in bold.

Table 9. The mean 15D scores and dimension level values: comparison within the study population between patients without depressive symptoms, with minor depressive symptoms and those with moderate or severe depressive symptoms

Dependent variable	iNPH patients without depressive symptoms [39]	iNPH patients with minor depressive symptoms [17]	iNPH patients with Moderate or severe depressive symptoms [18]	p-value ANOVA	p-value (Bonferroni) Patients without depressive symptoms vs with minor depressive symptoms	p-value (Bonferroni) Patients without depressive symptoms vs with moderate or severe depressive symptoms	p-value (Bonferroni) Patients with minor depressive symptoms vs with moderate or severe depressive symptoms	Mean difference[b] (95% CI) Patients without depressive symptoms - with moderate or severe depressive symptoms
15D score[a]	0.747 (0.07)	0.703 (0.08)	0.654 (0.12)	**0.003**	0.33	**0.003**	0.38	**0.093 (0.03, 0.15)**
Moving	0.515 (0.18)	0.551 (0.20)	0.469 (0.19)	0.44	1.00	1.00	0.60	0.046 (-0.09, 0.18)
Seeing	0.902 (0.18)	0.806 (0.23)	0.835 (0.24)	0.23	0.35	0.79	1.00	0.066 (-0.08, 0.21)
Hearing	0.905 (0.19)	0.836 (0.16)	0.827 (0.20)	0.24	0.61	0.43	1.00	0.078 (-0.05, 0.21)
Breathing	0.827 (0.25)	0.824 (0.25)	0.734 (0.30)	0.44	1.00	0.66	0.96	0.093 (-0.09, 0.29)
Sleeping	0.896 (0.16)	0.778 (0.21)	0.737 (0.24)	**0.010**	0.12	**0.016**	1.0	**0.159 (0.02, 0.29)**
Eating	0.946 (0.13)	0.875 (0.17)	0.850 (0.20)	0.08	0.40	0.12	1.00	0.095 (-0.01, 0.21)
Speech	0.894 (0.16)	0.930 (0.13)	0.918 (0.14)	0.67	1.00	1.00	1.00	-0.023 (-0.12, 0.07)
Secretion	0.577 (0.28)	0.516 (0.28)	0.494 (0.31)	0.55	1.00	0.93	1.00	0.082 (-0.11, 0.28)
Usual activities	0.522 (0.27)	0.484 (0.25)	0.423 (0.24)	0.43	1.00	0.58	1.00	0.097 (-0.08, 0.28)
Mental function	0.652 (0.22)	0.612 (0.20)	0.562 (0.26)	0.38	1.00	0.51	1.00	0.090 (-0.07, 0.25)
Discomfort and symptoms	0.763 (0.26)	0.700 (0.21)	0.707 (0.22)	0.57	1.00	1.00	1.00	0.056 (-0.11, 0.22)
Depression	0.885 (0.14)	0.777 (0.13)	0.671 (0.24)	**<0.001**	0.10	**<0.001**	0.21	**0.214 (0.09, 0.33)**
Distress	0.922 (0.13)	0.716 (0.16)	0.690 (0.20)	**<0.001**	**<0.001**	**<0.001**	1.00	**0.232 (0.12, 0.34)**
Vitality	0.690 (0.15)	0.664 (0.16)	0.564 (0.17)	**0.022**	1.00	**0.019**	0.19	**0.126 (0.02, 0.24)**
Sexual activity	0.560 (0.36)	0.548 (0.32)	0.439 (0.35)	0.46	1.00	0.68	1.00	0.121 (-0.12, 0.36)

CI, confidence interval. The number of observations is in braces. Clinically and statistically significant differences ($|\Delta 15D| \geq 0.015$) are in bold. [a]A positive difference indicates a better score and a negative difference indicates a worse score for iNPH patients without depressive symptoms than for patients with moderate or severe depressive symptoms; [b]data are mean (SD) scores; the scale is 0–1, worst to best. Statistically significant differences ($P < 0.05$) are in bold.

Table 10. Multivariate predictors of HRQoL of iNPH patients

Variables	R^2	F	B (Std. error)	β	t	p
REGRESSION MODEL [73]	0.506	35.9				**< 0.001**
iNPHGS score			-0.024 (0.003)	-0.616	-7.08	**< 0.001**
BDI-21 score			-0.0024 (0.001)	-0.190	-2.28	**0.025**
EXCLUDED VARIABLES						
Age				(0.021)	0.24	0.725
Gender				(-0.030)	-0.36	0.728
Educational level				(-0.031)	0.48	0.719
MMSE score				(0.043)	-0.02	0.635
Regular pain medication				(-0.002)	-0.35	0.986

HRQoL, health-related quality of life; iNPH, idiopathic normal pressure hydrocephalus; iNPHGS, iNPH grading scale; BDI-21, Beck Depression Index; MMSE, Mini-Mental State Examination. The b value that would result if the variable was put back into the model is given in parentheses. The number of observations is given in braces. Statistically significant differences ($P < 0.05$) are in bold.

Table 11. The Mean BDI-21 Scores and subscore values of the study population

	Item	All patients [74]	Patients without depressive symptoms [39]	Patients with minor depressive symptoms [17]	Patients with moderate or severe depressive symptoms [18]
1	Sadness	0.49 (0.60) [73]	0.18 (0.39)	0.59 (0.51) [16]	1.06 (0.64)
2	Pessimism	0.46 (0.74)	0.15 (0.37)	0.47 (0.72)	1.11 (0.96)
3	Feelings of Failure	0.22 (0.42) [73]	0.08 (0.27)	0.24 (0.44) [16]	0.50 (0.51)
4	Dissatisfaction	0.62 (0.79)	0.15 (0.37)	0.94 (0.66)	1.33 (0.91)
5	Guilt	0.15 (0.43)	0.00 (0.00)	0.18 (0.39)	0.44 (0.70)
6	Punishment	0.16 (0.50)	0.00 (0.00)	0.18 (0.53)	0.50 (0.79)
7	Self-Hate	0.12 (0.37)	0.00 (0.00)	0.12 (0.33)	0.39 (0.61)
8	Self-Accusation	0.43 (0.70)	0.08 (0.35)	0.59 (0.62)	1.06 (0.87)
9	Suicidal Thoughts	0.08 (0.27)	0.00 (0.00)	0.00 (0.00)	0.33 (0.49)
10	Crying	0.30 (0.68)	0.08 (0.27)	0.29 (0.47)	0.78 (1.11)
11	Irritability	0.50 (0.73)	0.21 (0.57)	0.65 (0.49)	1.00 (0.91)
12	Social Withrawal	0.50 (0.78)	0.23 (0.63)	0.53 (0.62)	1.06 (0.94)
13	Indecision	0.77 (0.91)	0.41 (0.68)	0.82 (0.88)	1.50 (0.99)
14	Change in self-awarness	0.47 (0.71)	0.15 (0.49)	0.59 (0.62)	1.06 (0.80)
15	Work Difficulties	1.76 (0.98)	1.41 (0.99)	2.12 (0.86)	2.17 (0.79)
16	Imsomnia	0.65 (0.93)	0.28 (0.72)	0.88 (0.93)	1.22 (1.00)
17	Tiredness	1.31 (0.86)	0.90 (0.64)	1.65 (0.79)	1.89 (0.90)
18	Loss of Appetite	0.26 (0.55)	0.08 (0.27)	0.29 (0.59)	0.61 (0.78)
19	Loss of Weight	0.23 (0.61)	0.08 (0.35)	0.18 (0.39)	0.61 (0.98)
20	Somatic Worries	0.61 (0.77)	0.28 (0.46)	0.82 (0.64)	1.11 (1.08)
21	Loss of Libido	1.70 (1.26)	1.23 (1.25)	2.06 (1.14)	2.39 (0.98)
	Total	12.2 (8.57)	6.0 (2.9)	14.2 (1.55)	23.9 (7.49)

Data are mean (SD) scores, [ ] number of patients, BDI-21 questionnaire's each item includes four statements that have a numerical value from 0 to 3. The questionnaire's total score ranges from 0 to 63, with higher scores indicating more severe depressive symptoms. iNPH patients were classified into three groups according to their depressive symptoms: patients without ($BDI < 10$), with minor ($10 \leq BDI \leq 16$), or with moderate or severe depressive symptoms ($17 \leq BDI \leq 63$)

5 Health-related quality-of-life outcome in patients with idiopathic normal-pressure hydrocephalus – a 1-year follow-up study

5.1 ABSTRACT

Background and purpose
This prospective study explored the factors affecting the health-related quality-of-life (HRQoL) outcome in patients with idiopathic normal-pressure hydrocephalus (iNPH) 1 year after the installation of the cerebrospinal fluid shunt.

Methods
Sed The HRQoL outcome was evaluated using a 15D instrument, in which the minimum clinically significant change/difference has been estimated to be ±0.015. The follow-up data (15D, Mini-Mental State Examination, Beck Depression Inventory, iNPH Grading Scale), frontal cortical biopsy, Charlson Age Comorbidity Index and body mass index of 145 patients diagnosed with iNPH by clinical and radiological examination were analyzed.

Results
At 1-year follow-up, 63 (43%) patients had experienced a clinically significant improvement in HRQoL. Multivariate binary logistic regression analysis indicated that the absence of amyloid-β and hyperphosphorylated tau pathology in the frontal cortical biopsy (53% vs. 33%; absolute risk difference, 20%; adjusted odds ratio, 2.27; 95% confidence interval, 1.07–4.84; $P < 0.05$) and lower body mass index (adjusted odds ratio, 0.90, 95% confidence interval, 0.82–0.98; $P < 0.05$) predicted favorable HRQoL outcome 1 year after the shunting.

Conclusions
Less than half of the patients with iNPH experienced clinically significant favorable HRQoL outcome, partly explained by the patient's characteristics and comorbidities. The HRQoL approach reveals aspects that are important for the patient's well-being, but may also improve the quality of the outcome assessment of cerebrospinal fluid shunting. Study results may help clinicians to estimate which patients will benefit shunt surgery.

5.2 INTRODUCTION

Idiopathic normal-pressure hydrocephalus (iNPH) is a disorder that causes severe deterioration of healthrelated quality of life (HRQoL) amongst those affected (248). This impairment is partly due to the wellknown features of iNPH (2,248) but also to the frequently present comorbidities (13) and psychiatric symptoms (18,89,91,248). Vascular cognitive impairment and especially Alzheimer's disease are common comorbidities, and patients with these comorbidities have been reported to have poorer outcome (17,24,101,149). Although some of the symptoms of iNPH can be relieved with

cerebrospinal fluid shunt surgery (11), there is barely any knowledge in the current literature about the predictors of the HRQoL outcome (Table 12). Our primary aim was to investigate factors and comorbidities that may have an effect on the 1-year HRQoL outcome of the shunting surgery.

Table 12. Results of the literature search of the relevant studies

	STUDY		
Search words used	[Quality of Life] and [NPH] or [Quality of life] and [Normal Pressure Hydrocephalus]		
Articles found from MEDLINE/Pubmed	36		
Articles included*	3		
	Katzen H et al. 2011	Meier U et al. 2013	Petersen J et al. 2014
Country	USA	Germany	Sweden
Study type	Prospective cohort	Randomized trial	Prospective cohort
Patients	12	143	37
HRQoL measurement	SF-12	SF-12	EQ-5D
Follow-up time	6 months	6 - 12 months	6 months
Favourable quality of life outcome			31 (86%)
Comorbidities evaluated		Charlson Comorbidity Index	
Predictors of the quality of life outcome		Charlson Comorbidity Index score	
Statistical analysis	Anova, paired t-test	Univariate mixed-effects linear regression model	Wilcoxon signed-ranks test, Mann-Whitney U-test/Kruskal-Wallis
PubMed Identifier	21135747	24257332	25036194

The inclusion criteria were: 1) standardized quality of life questionnaire and 2) a shunting outcome follow-up. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life.

5.3 METHODS

5.3.1 Study design and participants

The study was performed in the Neurosurgery Department of the Kuopio University Hospital (KUH). Permission for the study was obtained from the KUH Research Ethics Board. A neurologist conducted the primary examination. Patients were referred for further neurosurgical examinations if they exhibited one to three symptoms potentially related to normal-pressure hydrocephalus (NPH) (impaired cognition, gait or urinary continence) together with enlarged brain ventricles disproportionate to the size of the sulci of cerebral convexities (Evan's index >0.30) (2) in computed tomography or magnetic resonance imaging.

Collection of HRQoL baseline measurement data started in April 2009 from all

consecutive patients providing written informed consent and with suspected iNPH. The HRQoL questionnaires were completed by the patients themselves or by an interviewing nurse. By February 2015, data had been collected from 245 consecutive patients and stored in the NPH Registry of KUH (www.uef.fi/nph) (Figure 7). As 56 patients were excluded from further research (Figure 7), a total of 189 patients with iNPH were included in the study (Table 13). The clinical information and questionnaires were recorded prior to the shunting and 3 and 12 months post-operatively (Figure 7, Tables 13 and 14).

The first 41 consecutive patients (22%) were selected for the shunting procedure according to the results of 24-h, intraventricular monitoring of the intracranial pressure: (i) a basal intracranial pressure above 10 mmHg or (ii) the presence of any A waves or more than 30% B waves during the monitoring were indications for the shunt (17). Four patients (2%) were shunted based on clinical decision as spine tap could not be performed. For the rest of the patients, final selection for shunting was based on the following three-step protocol: 89 (47%) patients were shunted based on a positive tap test (at least 20% improvement in gait speed in two 10-m tests); 46 (24%) patients with a negative tap test underwent lumbar infusion testing, and those with a pathological finding (conductance ≤10) (176) were shunted; and 9 (5%) patients with a negative finding in both of the above tests were shunted based on 24-h monitoring of intraventricular pressure.

5.3.2 The HRQoL measure

The 15D instrument has been described in section 2.9.5 (Appendix 3). Patients were dichotomized according to the change in the 15D score 3 months and also 1 year after the shunting (Figure 7, Table 14): patients who had experienced at least a minimum clinically important improvement in HRQoL (Δ15D score ≥0.015), and patients whose HRQoL deteriorated or remained the same (Δ15D score <0.015) compared with the baseline. The 15D results of an age- and gender-standardized sample (n = 3372) from the general population were used as a reference (Figure 8) (242).

5.3.3 Evaluation of cognition

Cognitive evaluation has been described in section 4.3.3. MMSE scores were converted to dementia staging in accordance with the Clinical Dementia Rating (249) (Table 14). Education level determination has been described in section 4.3.7

5.3.4 Evaluation of depressive symptoms

Evaluation of depressive symptoms has been described in section 4.3.4. (Table 14). The collection of BDI from all consecutive patients started in January 2011, which is the main reason for missing depression data.

5.3.5 Evaluation of iNPH symptoms

The evaluation of iNPH symptoms has been described in section 4.3.5 (Table 14).

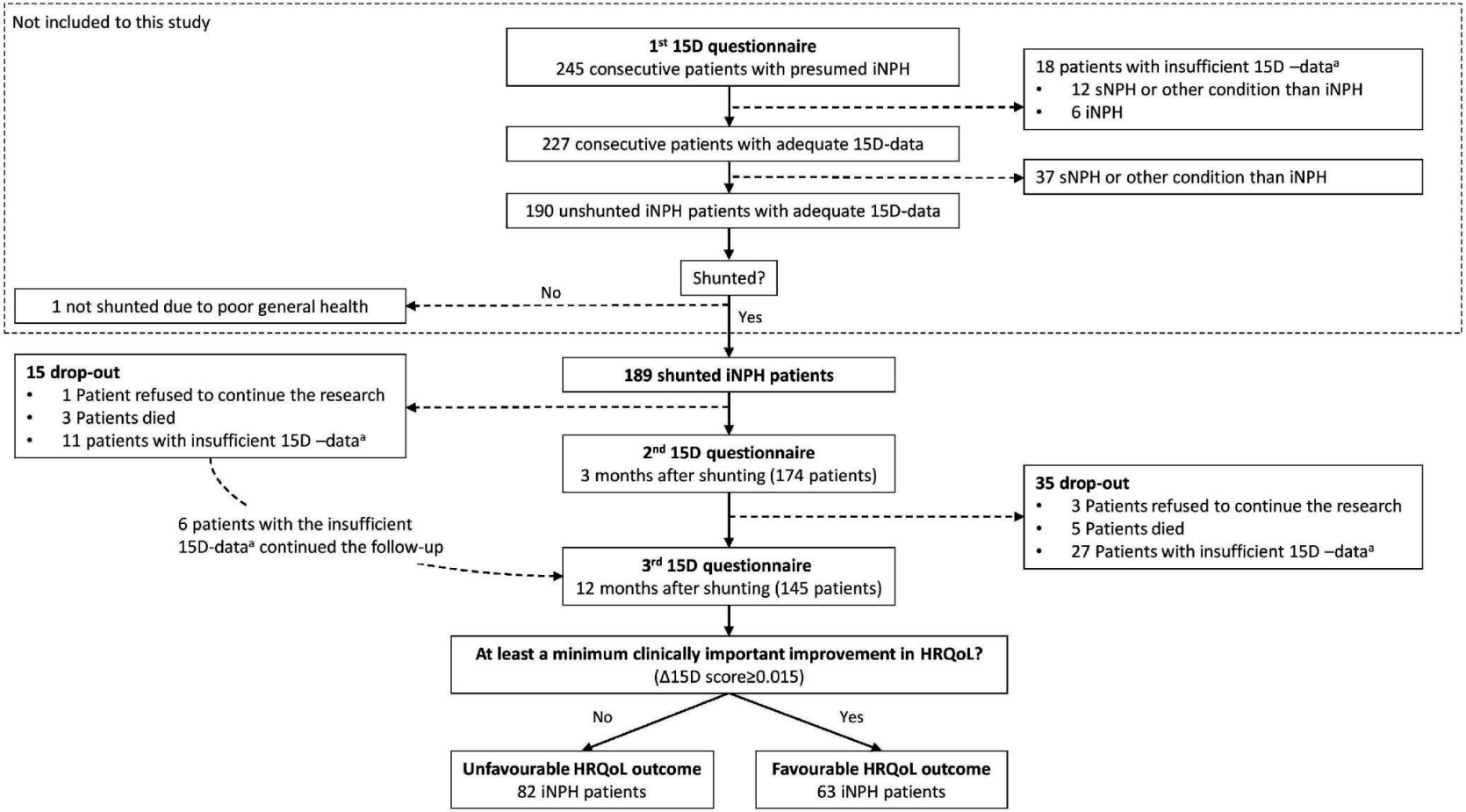

Figure 7. Flowchart of the study population. *≥4 dimensions missing in the 15D questionnaire or the questionnaire is missing completely. HRQoL, health-related quality of life; iNPH, idiopathic normal-pressure hydrocephalus; sNPH, secondary NPH (2).

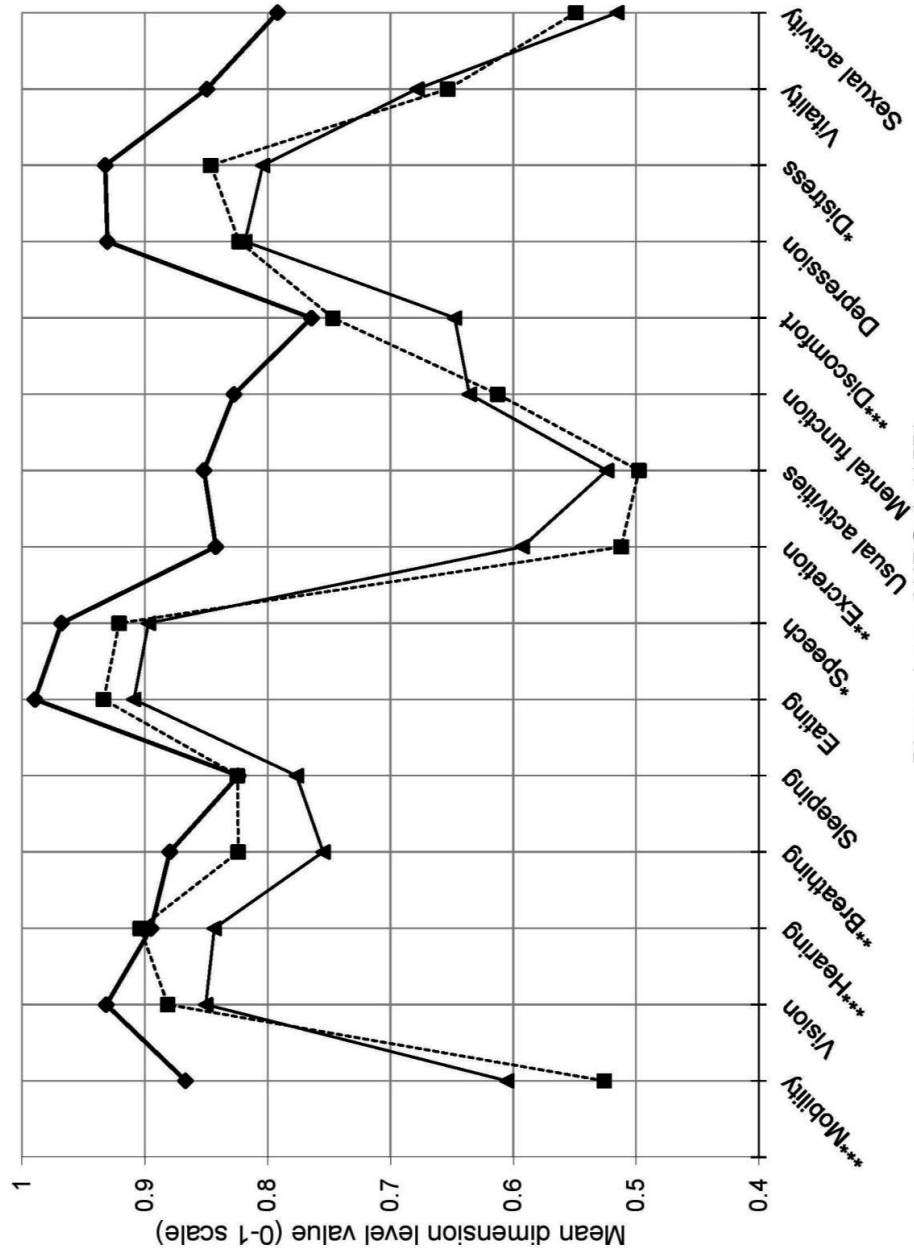

Figure 8 The health-related quality of life (HRQoL) dimensions of the 15D instrument. Comparison of the baseline with 1-year follow-up. Significant change in the Wilcoxon signed-rank test from the baseline to the 1-year follow-up: *P < 0.05, **P < 0.01 and ***P < 0.001.

5.3.6 Characteristics and comorbidities

Patient characteristics and comorbidities were recorded from all patients undergoing surgery in the KUH. To evaluate the burden caused by the coexisting conditions we used the Charlson Age Comorbidity Index (CACI) (250) (Tables 13 and 15), which combines 19 medical conditions so that each comorbidity corresponds to a weighted number, higher number representing greater burden. By adding all of the numbers, including 1 point for each decade over the age of 40, a final CACI score can be determined.

5.3.7 Biopsy procedure and immunohistochemistry

Prior to insertion of the ventricular catheter (approximately 3 cm from the midline and close to the coronal suture of the skull), between one and three cylindrical cortical brain biopsies of 2–5 mm in diameter and 3–7 mm in length were obtained with biopsy forceps. The details of the biopsy and its immunohistochemistry analysis have been previously described (17,101). The cellular or neuritic immunoreactivity for amyloid-b (Aβ) and hyperphosphorylated tau (HPτ) were evaluated by light microscopy in all samples and were graded as present or absent by a neuropathologist (251) (Table 13). For statistical analyses, the patients were then further grouped by the presence of pathology of any kind: Aβ or HPτ found in the frontal cortical biopsy.

5.3.8 Statistics

The data were analyzed using the Statistical Package for Social Sciences (SPSS® 19 for Windows, Version 19.0. IBM Corp., Armonk, NY, USA) and the R language and environment for statistical computing (R- 3.2.4 for Windows; R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). The primary outcome variable was the 15D. The paired-samples t-test or the Wilcoxon signed-rank test was applied to test differences in the means or the ranks of the repeated measurements in multiple comparisons, respectively. The multivariate binary logistic regression analysis was performed using the enter method (252) and the potential effect of missing data was estimated with multiple imputation by chained equations (253) (Tables 16 and 17). The odds ratios (ORs) were calculated with 95% confidence intervals (CIs). All tests for significance were two-sided, with probabilities of <0.05 accepted as statistically significant.

5.4 RESULTS

At 1 year, 63 patients (43%) had experienced a clinically important improvement in HRQoL (Table 14). There were no significant changes in the follow-up variables in the 1-year follow-up (Table 14), but there were significant changes in the health dimensions of the 15D (Figure 8): 35 (24%) of the patients experienced more hearing loss 1 year after the shunting than at baseline and 40 (28%) of the patients reported more respiratory problems 1 year after the shunting. There was a correlation (Pearson correlation -0.58, $P < 0.001$) between the changes in the iNPHGS and 15D scores in the 1-year follow-up.

Table 13. Characteristics and comorbidities of the study population

VARIABLE	Observed
CHARACTERISTICS	Mean/n
Age (at shunting) (SD)	74 (7.1)
BMI (at shunting) (SD) [n]	27 (4.8) [180]
Education level (>9 years of education) (%) [n]	63(35) [180]
Sex (Female) (%)	95 (50)
Gait apraxia prior shunting (%)	185 (98)
INPH PROBABILITY* (modified criteria)	
Probable iNPH (%)	173 (91)
Possible iNPH (%)	16 (9.0)
Unlikely iNPH (%)	0 (0.0)
INPH PROBABILITY (unmodified criteria)**	
Probable iNPH (%)	48 (25)
Possible iNPH (%)	141 (75)
Unlikely iNPH (%)	0 (0.0)
HISTOLOGY IN FRONTAL CORTICAL BIOPSY	
Aβ - and HPτ –	82 (45)
Aβ + and HPτ -	69 (38)
Aβ + and HPτ+	28 (15)
Aβ - and HPτ +	3 (2)
Biopsy/staining unsuccessful	7
Grouping for statistical analyses	[182]
Absence of Aβ or HPτ found in the frontal cortical biopsy	80 (44)
COMORBIDITIES	
Median CACI score (25th, 75th percentile)	5 (4,7)
TYPES OF VALVES USED IN THE STUDY POPULATION* **	
PS Medical (Medtronic) Strata[a]	186 (98)
PS Medical (Medtronic) Delta[b]	3 (2)
CSF SHUNT LOCATION	
Ventriculo-peritoneal shunt	188 (99)
Ventriculo-atrial shunt	1 (0.5)

Values are expressed as numbers of cases or mean, (% or SD), number of observations [n], *Diagnostic criteria by Relkin et al. 2005 [15], from which the physiological criteria (IV) for probable iNPH was not included, as CSF opening pressure was measured only from patients going through infusion tests in our study population. **Diagnostic criteria by Relkin et al. 2005 [15]. ***All including a siphon-control device. [a]Adjustable pressure setting, initial pressure setting set at 1.5 performance level of the valve. [b]Fixed pressure setting, set at 1.5 performance level of the valve. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; CSF, Cerebrospinal fluid; BMI, Body mass index [kg/m^2]; Aβ Amyloid-β; HPτ, Hyperphosphorylated tau; CACI, Charlson Age Comorbidity Index.

Table 14. The Follow-up of the study population

	FOLLOW-UP			COMPARISONS		
VARIABLE	Baseline	3 months after the shunting	One year after the shunting	p value baseline vs. 3 months after the shunting	p value 3 months vs. one year after the shunting	p value baseline vs. one year after the shunting
	Mean/n	Mean/n	Mean/n			
Mean 15D score (0-1 scale)	0.715	0.739	0.716	**0.022**[a]↑	**0.008**[b] ↓	0.461[b]
(SD)	(0.10)	(0.12)	(0.13)		(-2.64)[c]	(-0.74)[c]
[n]	[189]	[174]	[145]	[174]	[139]	[145]
Favorable HRQoL outcome (yes)		97	63			
(%)		(56)	(43)			
[n]		[174]	[145]			
INPHGS score (0-12 scale)	6.1	5.3	5.5	**<0.001**[b]↓	0.099[b]	0.153[b]
(SD)	(2.7)	(3.0)	(2.9)	(-3.89)[c]	(-1.65)[c]	(-1.43)[c]
[n]	[186]	[175]	[146]	[172]	[140]	[144]
Favorable INPHGS outcome (yes)		83	69			
(%)		(49)	(48)			
[n]		[169]	[144]			
BDI-21 score (0–63)	11	12	11	0.986[b]	0.518[b]	0.326[b]
(SD)	(7.6)	(7.6)	(7.6)	(-0.02)[c]	(-0.65)[c]	(-0.98)[c]
[n]	[127]	[132]	[100]	[114]	[95]	[95]
MMSE score (0-30 scale)	22	23	-	0.779[b]		
(SD)	(4.7)	(4.8)		(-0.28)[c]		
[n]	[183]	[161]		[159]		
No dementia (MMSE 30, CDR 0) (%)	1 (1.0)	-	-			
Mild cognitive impairment (MMSE 26-29, CDR 0.5) (%)	50 (27)	53 (33)	-			
Mild dementia (MMSE 21-25, CDR 1) (%)	79 (43)	63 (39)	-			
Moderate dementia (MMSE 11-20, CDR 2) (%)	49 (27)	41 (26)	-			
Severe dementia (MMSE 0-10, CDR 3) (%)	4 (2.0)	4 (2.0)	-			
POTENTIAL MODIFYING FOLLOW-UP FACTORS	**N (%)**	**Mean time (months) after the shunting (SD)**		**Most common reason for the modification (%)**		
CSF shunt valve settings were adjusted externally during the follow-up	80 (42)	2.9 (2.6)				
The opening pressure of the CSF valve was lowered	64 (80)			Persisting iNPH symptoms (100)		
The opening pressure of the CSF valve was increased	16 (20)			Overdrainage (100)		
SURGICAL COMPLICATIONS						
Chronic subdural hematoma required surgery (trepanation)	2 (1)					
Shunt infection*	2 (1)					
Fatal intraventricular hemorrhage**	1 (0.5)					
Status epilepticus	1 (0.5)					
Revision of the CSF shunt	*19 (10)*	*2.5 (2.9)*		*Peritoneal catheter displacement (60)*		

Values are expressed as numbers of cases or mean, (% or SD), number of observations [n], [a]Paired samples test, [b]Wilcoxon Sign Test, [c]Z-score for the Wilcoxon Sign Test, the up (↑) and down (↓) arrows indicate the direction of the statistically significant change, Favorable HRQoL outcome: Positive and clinically significant change in HRQoL (Δ15D ≥ 0.015), Favorable INPHGS outcome: Severity of iNPH symptoms relieved (iNPHGS decreased at least 1 point),*Removal of infected shunt and later new shunt was administered, **After starting anticoagulation due to artificial aortic valve and the immediate post-operative computed tomography was normal; Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; iNPHGS, iNPH Grading Scale; BDI-21, Beck Depression Index; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; CSF, Cerebrospinal fluid.

Table 15: Charlson age-comorbidity index (CACI) of the study population

Weight	Comorbid condition	Patients, n (%)
6	Acquired immune deficiency syndrome	0 (0.0)
	Metastatic solid tumor	3 (1.6)
3	Moderate or severe liver disease	0 (0.0)
2	Any non-metastatic solid tumor	16 (8.5)
	Malignant lymphoma	3 (1.6)
	Leukemia	0 (0.0)
	Diabetes with end organ damage	40 (21.1)
	Moderate or severe renal disease	31 (16.4)
	Hemiplegia	3 (1.6)
1	Diabetes without end organ damage	27 (14.3)
	Mild liver disease	5 (2.6)
	Ulcer disease	1 (0.5)
	Connective tissue disease	15 (7.9)
	Chronic pulmonary disease	17 (9.0)
	Dementia	134 (70.9)
	Cerebrovascular disease	24 (12.7)
	Peripheral vascular disease	4 (2.1)
	Congestive heart failure	14 (7.4)
	Myocardial infarction	50 (26.5)
	Each decade of age ≥50 years is equivalent to a 1-point increase in comorbidity	
1	50 ≤ Age <60	7 (3.7)
2	60 ≤ Age <70	36 (19.0)
3	70 ≤ Age <80	94 (49.8)
4	80 ≤ Age <90	52 (27.5)

Table 16: Multiple imputation info

GENERAL INFORMATION				
Missingness	• 14 variables (32%) had missing data • 81 (43%) of the cases had missing data • When all the variables, including the outcome variables, were analyzed at the same time to detect systematic tendencies (Little's Missing Completely at Random –test; p =0.159) there was no clear indication that there would be any			
Imputation	• 42 variables (listed below) were included to the imputation model, including the outcome variable (Favorable HRQoL outcome 1 year after shunting, 1=yes,0=no). • MI was performed with the R language and environment for statistical computing (R-3.2.4 for Windows, R Core Team 2015) using the mice-package [26], in which the default settings were kept • Number of imputations was 50 • No transformations of the data were performed • The distribution of observed and imputed data were examined with a density plot for each variable			
IMPUTED VARIABLES	N missing (%)	Normality assumption satisfied	Normality Test used (p-value)	Imputation model
FOLLOW-UP VARIABLES				
Favorable HRQoL outcome (yes)				
3 months after the shunting	15 (7.9)	N/A	N/A	pmm
1 year after the shunting	44 (23.2)	N/A	N/A	pmm
Mean 15D score (0-1 scale)				
Baseline	0 (0.0)	Yes	Shapiro-Wilk-test (>0.45)	N/A
3 months after shunting	15 (7.9)	Yes	Shapiro-Wilk-test (>0.32)	pmm
1 year after shunting	44 (23.2)	Yes	Shapiro-Wilk-test (>0.16)	pmm
Favorable iNPHGS outcome (yes)				
3 months after shunting	15 (7.9)	N/A	N/A	pmm
1 year after shunting	45 (23.8)	N/A	N/A	pmm
INPHGS score (0-12 scale)				
Baseline	3 (1.6)	Yes	Shapiro-Wilk-test (p>0.14)	pmm
3 months after shunting	14 (7.4)	No	Shapiro-Wilk-test (<0.01)	pmm
1 year after shunting	43 (22.8)	No	Shapiro-Wilk-test (<0.01)	pmm

MMSE Score (0-30 scale)				
Baseline	6 (3.2)	Yes	Shapiro-Wilk-test (0.08)	pmm
3 months after shunting	28 (14.8)	No	Shapiro-Wilk-test (0.04)	pmm
Revision of the CSF shunt	0 (0.0)	N/A	N/A	N/A
CSF shunt valve settings adjusted during the follow-up (yes)	0 (0.0)	N/A	N/A	N/A
COMORBIDITIES				
Histology in frontal cortical biopsy				
Presence of Aβ and/or HPτ found in the frontal cortical biopsy	7 (3.7)	N/A	N/A	pmm
CACI Score	0 (0.0)			
CACI condition (yes/no)				
Acquired immune deficiency syndrome	0 (0.0)	N/A	N/A	N/A
Metastatic solid tumor	0 (0.0)	N/A	N/A	N/A
Moderate or severe liver disease	0 (0.0)	N/A	N/A	N/A
Any non-metastatic solid tumor	0 (0.0)	N/A	N/A	N/A
Malignant lymphoma	0 (0.0)	N/A	N/A	N/A
Leukemia	0 (0.0)	N/A	N/A	N/A
Diabetes with end organ damage	0 (0.0)	N/A	N/A	N/A
Moderate or severe renal disease	0 (0.0)	N/A	N/A	N/A
Hemiplegia	0 (0.0)	N/A	N/A	N/A
Diabetes without end organ damage	0 (0.0)	N/A	N/A	N/A
Mild liver disease	0 (0.0)	N/A	N/A	N/A
Ulcer disease	0 (0.0)	N/A	N/A	N/A
Connective tissue disease	0 (0.0)	N/A	N/A	N/A
Chronic pulmonary disease	0 (0.0)	N/A	N/A	N/A
Dementia	0 (0.0)	N/A	N/A	N/A
Cerebrovascular disease	0 (0.0)	N/A	N/A	N/A
Peripheral vascular disease	0 (0.0)	N/A	N/A	N/A
Congestive heart failure	0 (0.0)	N/A	N/A	N/A
Myocardial infarction	0 (0.0)	N/A	N/A	N/A
CHARACTERISTICS				
Sex (Female)	0 (0.0)	N/A	N/A	
Age (at shunting)	0 (0.0)	Yes	Shapiro-Wilk-test (0.31)	pmm
BMI	9 (4.8)	No	Shapiro-Wilk-test (<0.001)	pmm
Education level (Nine years or less of acquired education)	9 (4.8)	N/A	N/A	pmm
iNPH probability [12]	0 (0.0)	N/A	N/A	N/A
Gait apraxia prior shunting	0 (0.0)	N/A	N/A	N/A
DIAGNOSTIC TESTS				
Shunting decision based on TAP-test	0 (0.0)	N/A	N/A	N/A
Shunting decision based on TAP & Infusion –tests	0 (0.0)	N/A	N/A	N/A
Shunting decision based on TAP & Infusion & ICP-monitoring	0 (0.0)	N/A	N/A	N/A
Shunting decision based on ICP-monitoring	0 (0.0)	N/A	N/A	N/A

Abbreviations: Favorable HRQoL outcome: Positive and clinically significant change in HRQoL (Δ15D ≥ 0.015), Favorable INPHGS outcome: Severity of iNPH symptoms relieved (iNPHGS decreased at least 1 point); pmm, predictive mean matching; iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; MMSE, Mini-Mental State Examination; iNPHGS, iNPH Grading Scale; ICP, Intracranial pressure; BMI, Body mass index [kg/m2]; Aβ Amyloid-β; HPτ, Hyperphosphorylated tau; CACI, Charlson Age Comorbidity Index.

5.4.1 Regression analysis

Multivariate binary logistic regression analysis was performed with clinically significant, favorable change in 15D score 1 year after the shunting (yes = 1, no = 0) as the dependent variable. The model had good calibration demonstrated by the Hosmer–Lemeshow test (Table 17) and the overall percentage accuracy rate for the model was 64%. The highest variance inflation factor was 1.14 (CACI score) and the lowest tolerance was 0.88 (CACI score), suggesting that multicollinearity did not have a significant effect on the model. According to the model, absence of Aβ and HPτ pathology in the frontal cortical biopsy (53% vs. 33%; absolute risk difference, 20%; adjusted OR, 2.27; 95% CI, 1.07–4.81; P = 0.033) and lower body mass index (adjusted OR, 0.90; 95% CI, 0.82–0.98; P = 0.014) predicted favorable HRQoL outcome 1 year after the shunting. Multiple imputation by chained equations confirmed that study findings were robust to the missing data.

5.5 CONCLUSIONS

5.5.1 Limitations and generalizability

Our study lacks a non-operated control group and a more detailed neuropsychological test. A proxy-rated HRQoL measure or the 1-year Mini-Mental State Examination was not gathered. The study was geographically restricted to the Eastern Finnish population and the results can only be applied to similar patients (40). There are no universally accepted criteria for iNPH (2,9).

5.5.2 Interpretation

There is a large contrast between our study and the literature (11,14,46,48) when it comes to favorable outcome rate, and this might be due to the differences in the methods for assessing and classifying the outcome. In our study the HRQoL outcome was classified as 'unfavorable' if the HRQoL deteriorated or remained the same. It could be argued that because iNPH itself is a naturally progressing condition (8), and a significant proportion of patients with iNPH may also have other progressive neurodegenerative comorbidities (17,24,101,149), the stability of HRQoL could be considered as a favorable outcome. However, the unaffected HRQoL could also be partly explained by cognitive impairment that often causes affected patients to lack insight into their own condition (40). In our study, the absence of Aβ or HPτ pathology in the frontal cortical biopsy predicted the HRQoL outcome 1 year after the shunting (Figure 9), which is logical, as the neurodegenerative comorbidities (17,24,101,149) and patients' old age (17,18) are associated with poorer outcome (Figure 10, Table 18). However, we could not identify any definite age that would exclude a beneficial shunt response.

The 15D includes some dimensions of health that are important in terms of HRQoL but are not commonly investigated in the iNPH literature (Figure 10). In our study the majority of these dimensions remained impaired or even worsened. It has been suggested that post-operative changes in the cerebrospinal fluid hydrodynamics cause hearing loss in some patients with NPH (254,255) and they have also been reported to have effects on sleeping (112,256,257). However, sleep disordered breathing might also be connected with NPH (112,256-258) and could also explain our observation.

Table 17. Logistic regression analysis iNPH patients for the prediction of a favorable HRQoL outcome one year post-operatively.

Predictors	Model	n	Unstandardized coefficient B	S.E.	Wald's χ^2 (t-value)	df	p-value	Adjusted OR (95% CI)
Absence of Aβ and HPτ pathology in the frontal cortical biopsy (= 1, otherwise 0)	Univariate	142	0.74	0.35	4.60	1	**0.032**	**2.10 (1.07-4.12)**
	Multivariate	132	0.82	0.38	4.56	1	**0.033**	**2.27 (1.07-4.81)**
	Imputed Multivariate[a]	-	0.82	0.38	(2.14)	124.03	**0.035**	**2.27 (1.06-4.84)**
Baseline MMSE score	Univariate	141	0.06	0.04	2.85	1	0.092	1.06 (0.99-1.14)
	Multivariate	132	0.03	0.04	0.47	1	0.492	1.03 (0.95-1.12)
	Imputed Multivariate[a]	-	0.03	0.04	(0.69)	124.03	0.494	1.03 (0.95-1.12)
BMI score	Univariate	138	-0.11	0.04	7.00	1	**0.008**	**0.90 (0.83-0.97)**
	Multivariate	132	-0.11	0.04	6.23	1	**0.013**	**0.90 (0.82-0.98)**
	Imputed Multivariate[a]	-	-0.11	0.04	(-2.50)	124.03	**0.014**	**0.90 (0.82-0.98)**
CACI score	Univariate	145	-0.18	0.08	4.93	1	**0.026**	**0.84 (0.71-0.98)**
	Multivariate	132	-0.10	0.10	1.12	1	0.289	0.28 (0.03-3.16)
	Imputed Multivariate[a]	-	-0.10	0.10	(-1.06)	124.03	0.291	0.90 (0.74-1.09)
Presence of gait apraxia prior shunting (=1, otherwise 0)	Univariate	145	-1.40	1.17	1.44	1	0.231	0.25 (0.03-2.43)
	Multivariate	132	-1.26	1.23	1.05	1	0.306	0.28 (0.03-3.16)
	Imputed Multivariate[a]	-	-1.26	1.23	(-1.02)	124.03	0.308	0.28 (0.02-3.24)
Constant	Multivariate	132	3.35	2.05	2.67	1	0.102	28.40
	Imputed Multivariate[a]	-	3.35	2.05	(1.64)	124.03	0.105	28.40
Multivariate model evaluation					χ^2	**df**	**p-value**	
Overall model evaluation					16.83	5	0.005	
Goodness-of-fit test (Hosmer & Lemeshow)					4.78	8	0.780	
Variables excluded from the multivariate model*								
Age**	Univariate	145	-0.07	0.02	6.97	1	**0.008**	**0.94 (0.89-0.98)**
Baseline BDI score	Univariate	96	0.02	0.03	0.68	1	0.409	1.02 (0.97-1.08)
Baseline iNPHGS score	Univariate	143	-0.07	0.07	1.24	1	0.265	0.93 (0.82-1.06)
Baseline 15D score	Univariate	145	-1.95	1.76	1.23	1	0.268	0.14 (0.01-4.47)
Nine years or less of acquired education (=1, otherwise 0)	Univariate	138	0.41	0.36	1.27	1	0.260	1.50 (0.74-3.04)
iNPH probability* (2 =probable, 1=possible)**	Univariate	145	0.11	0.40	1.11	1	0.791	1.11 (0.51-2.43)
Sex (0=female, 1 = male)	Univariate	145	-0.10	0.34	0.09	1	0.765	0.90 (0.47-1.75)
Shunting decision based on TAP-test (=1, otherwise 0)	Univariate	145	-0.39	0.34	1.31	1	0.253	0.68 (0.35-1.32)
Shunting decision based on TAP & Infusion –tests	Univariate	145	0.26	0.40	0.44	1	0.507	1.30 (0.60-2.84)
Shunting decision based on TAP & Infusion & ICP-monitoring	Univariate	145	0.69	0.93	0.56	1	0.455	2.00 (0.32-12.35)
Shunting decision based on ICP-monitoring	Univariate	145	0.19	0.39	0.24	1	0.628	1.21 (0.56-2.62)

Favorable HRQoL outcome: Positive and clinically significant change in HRQoL (Δ15D ≥ 0.015, yes = 1, otherwise = 0), [a] Pooled results of 50 imputations. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; S.E., Standard Error; Aβ, Amyloid-β; HPτ, Hyperphosphorylated tau; MMSE, Mini-Mental State Examination; iNPHGS, iNPH Grading Scale; BMI, Body mass index; CACI ,Charlson Age Comorbidity Index. *Variable was excluded if p>0.25 in univariate statistics (252) or it **had strong correlation with other included variable (Age correlates with CACI score, Pearson correlation 0.53, p<0.001).The reason why age was excluded instead of CACI score was that the CACI score itself includes age as a comorbid condition.***Diagnostic criteria by Relkin et al. 2005.

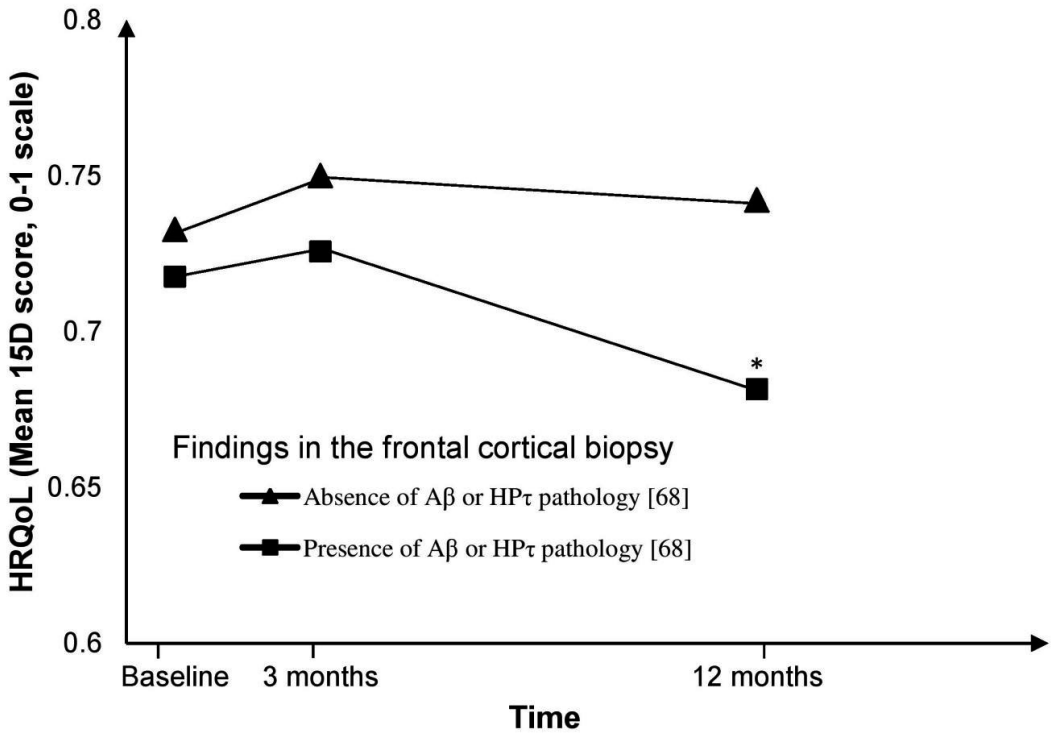

Figure 9. Repeated HRQoL measurements of patients dichotomized according to the findings in the frontal cortical biopsy. *[Number of observations], *Denotes significant change from the baseline at the p < 0.05 level in the Wilcoxon Sign test. Abbreviations: iNPH, idiopathic Normal Pressure Hydrocephalus; HRQoL, Health-Related Quality of Life; Aβ, Amyloid-β; HPτ, Hyperphosphorylated tau.*

Surprisingly, body mass index predicted the HRQoL outcome but the comorbidity burden did not. It is possible that the complications could be associated with the overweight (259) and thus explain the poorer outcome, but it is also possible that the body mass index is associated with other comorbidities and a longer follow-up might elucidate the potential differences between patients with different comorbidity burdens.

In conclusion, less than half of the patients with iNPH experienced a clinically significant favorable HRQoL outcome, partly explained by the preoperative characteristics and comorbidities. The HRQoL approach reveals aspects that are important for the patient's well-being, but may also improve the quality of the outcome assessment of cerebrospinal fluid shunting. Study results may help clinicians to estimate which patients will benefit from shunt surgery.

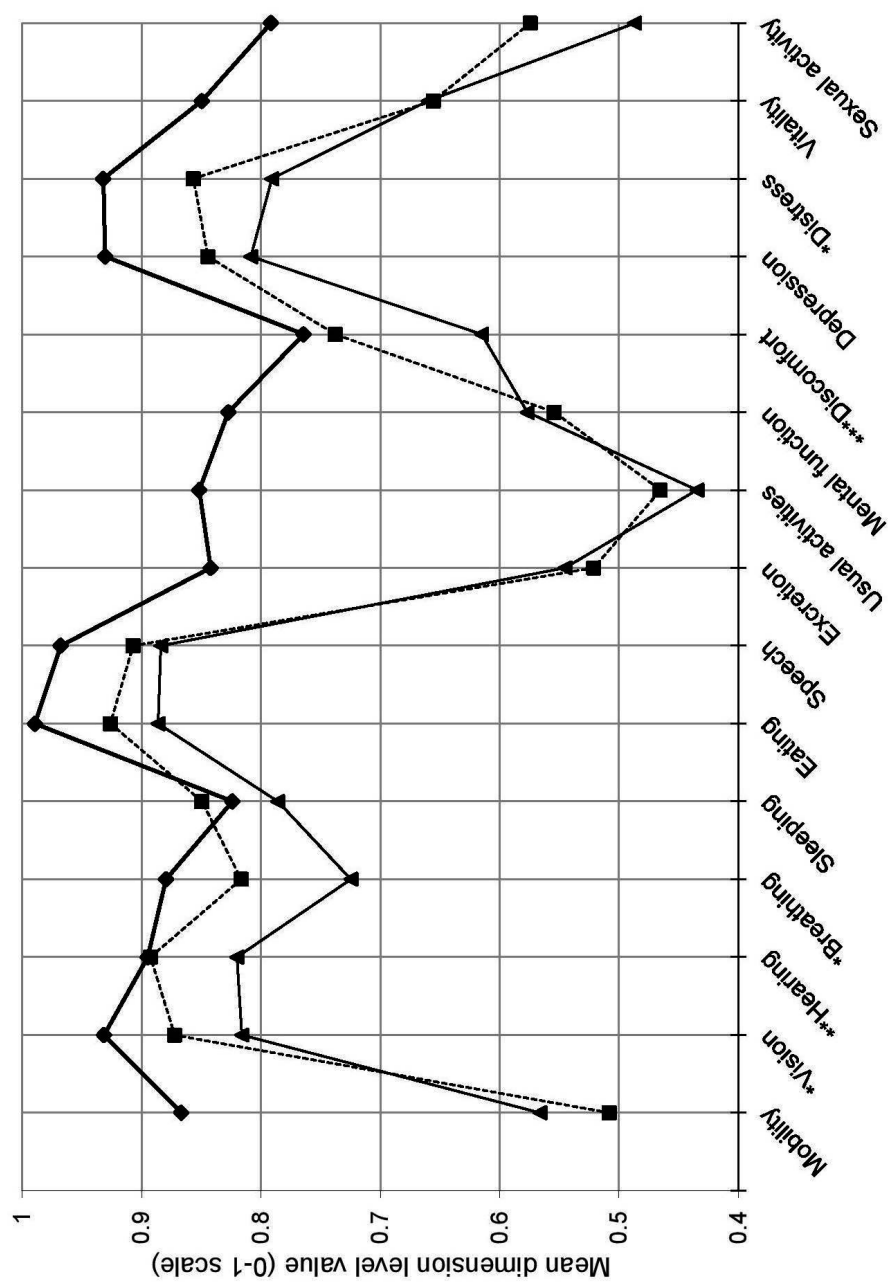

Figure 10. The HRQoL dimensions of the 15D instrument of patients with presence of Aβ or HPτ found in the frontal cortical biopsy. Comparison of the baseline with one year follow-up. [Number of observations], *Denotes significant change in the Wilcoxon Sign test from the baseline to the one-year follow-up at the $p < 0.05$ level, ** at the $p < 0.01$ level, and the *** at the $p < 0.001$ level. Abbreviations: iNPH, idiopathic Normal Pressure Hydrocephalus; HRQoL, Health-Related Quality of Life; Aβ, Amyloid-β; HPτ, Hyperphosphorylated tau.

Table 18: Comparison of change in the clinical variables between iNPH patients with and without Aβ or HPτ pathology in the frontal cortical biopsy.

Variable	Findings in the frontal cortical biopsy											
	Aβ -,HPτ -						Aβ +, HPτ - or Aβ +, HPτ +					
	Baseline	3 months	1 year	p[a] value baseline vs 3 months after the shunting	p[a] value 3 months vs one year after the shunting	p[a] value baseline vs one year after the shunting	Baseline	3 months	1 year	p[a] value baseline vs 3 months after the shunting	p[a] value 3 months vs one year after the shunting	p[a] value baseline vs one year after the shunting
15D score	0.732	0.753	0.743	0.052[a]	0.484[a]	0.371[a]	0.705	0.727	0.684	0.052[a]	**0.002[a]↓**	**0.037[a]↓**
(0-1 scale)	(0.10)	(0.11)	(0.12)	-1.943[b]	-1.700[b]	-0.894[b]	(0.11)	(0.12)	(0.13)	-1.946[b]	-3.067[b]	-2.086[b]
	[80]	[75]	[69]	[75]	[68]	[69]	[102]	[93]	[73]	[93]	[68]	[73]
iNPHGS	5.5	4.6	4.7	**0.001[a]↓**	0.597	**0.035[a]↓**	6.5	5.8	6.3	**0.015[a]↓**	0.077[a]	0.831[a]
score (0-12	(2.4)	(2.6)	(2.5)	-3.259[b]	-0.528[b]	-2.112[b]	(2.8)	(3.1)	(2.7)	-2.424[b]	-1.768[b]	-0.214[b]
scale)	[78]	[75]	[68]	[73]	[67]	[67]	[101]	[94]	[75]	[93]	[70]	[74]
Impaired	2.0	1.7	1.7	**0.022[a]↓**	0.922[a]	0.105[a]	2.2	2.1	2.2	0.278[a]	0.142[a]	0.418[a]
gait (0-4)	(1.0)	(1.1)	(1.2)	-2.298[b]	-0.098[b]	-1.619[b]	(1.1)	(1.2)	(1.0)	-1.085[b]	-1.470[b]	-0.810[b]
Impaired	1.3	1.3	1.1	0.692[a]	0.241[a]	0.130[a]	1.7	1.7	2.0	0.754[a]	0.159[a]	0.186[a]
cognition	(1.0)	(1.0)	(0.9)	-.396[b]	-1.173[b]	-1.513[b]	(1.2)	(1.2)	(1.3)	-0.313[b]	-1.410[b]	-1.322[b]
(0-4)												
Urinary	2.2	1.6	2.0	**0.002[a]↓**	0.237[a]	0.165[a]	2.5	2.1	2.2	**0.010[a]↓**	0.359[a]	0.311[a]
incontinence	(1.4)	(1.4)	(1.3)	-3.094[b]	-1.182[b]	-1.388[b]	(1.4)	(1.5)	(1.5)	-2.580[b]	-0.918[b]	-1.014[b]
(0-4)												
MMSE	23	23 (4.3)		0.304[a]			22	22		0.811[a]		
score (0-30	(3.9)	[71]		-1.388[b]			(5.3)	(5.1)		-0.239[b]		
scale)	[78]			[71]			[98]	[83]		[81]		
BDI-21	12	12 (7.7)	12	0.942[a]	0.428[a]	0.925[a]	10.4	10.8	11.3	0.558[a]	**0.038[a]↑**	0.090[a]
score (0-63)	(7.3)	[62]	(7.7)	-0.073[b]	-0.792[b]	-0.094[b]	(7.7)	(7.1)	(7.6)	-0.586[b]	-2.073[b]	-1.698[b]
	[57]		[46]	[57]	[62]	[46]	[64]	[64]	[51]	[55]	[46]	[48]

Values are expressed as numbers of cases or mean, (SD), [number of observations], [a]Wilcoxon Sign Test, [b]Z-score for the Wilcoxon Sign Test, up (↑) and down (↓) arrows indicate the direction of the statistically significant change. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; MMSE, Mini-Mental State Examination; iNPHGS, iNPH Grading Scale; BDI-21, Beck Depression Index; Aβ , Amyloid-β; HPτ, Hyperphosphorylated tau.

6 Health economics of iNPH: results

6.1 STUDY POPULATION

For this thesis, our aim was to predict the HRQoL progression of untreated and treated iNPH patients, analyze the average QALY gain resulting from the treatment, and determine the price for one QALY. In 27 of the 189 iNPH patients analyzed for the 2nd publication [Table 13] (see section 5), HRQoL was measured twice prior to treatment. On average, the measurements were carried out two months apart while the patients were waiting for the insertion of the CSF shunt. These patients did not differ from the rest of the study population in terms of the comorbidity burden, severity of iNPH, BMI, cognitive impairment, age, or sex. Our primary hypothesis was that between iNPH diagnosis and CSF shunt insertion, iNPH naturally progresses (7,8), which could be seen as a decrease in HRQoL. In addition, from the 2nd publication (see section 5), we were able to record the average proportional progression of HRQoL impairment in treated iNPH patients by comparing the HRQoL utility values 3 and 12 months after shunting (Figure 11, see section 6.2).

6.2 METHODS

The progression rates were determined by calculating the percentual change in HRQoL between the two time points. For this simulation, the progression rate of iNPH in treated iNPH patients was calculated for each individual by dividing the 15D score 12 months after shunting with the 15D score three months after shunting. These values were obtained directly from the follow-up data used in the 2nd publication (260). From these, the mean progression rate was calculated (-0.3% HRQoL/month), and was then extrapolated over several years:

$HRQoL_{tn} = P^n a_0$, where HRQoL at a certain time point (t) is equal to the baseline 15D score (a_0) multiplied by the progression rate (P) to the power of time in months (n).

For example, a two-year 15D score for a treated iNPH patient having a baseline value of 0.70 would be 0.997^{24} x 0.70 = 0.65. To simulate how iNPH would progress in hypothetical untreated iNPH patients, a progression value (-2.5% HRQoL/month) was obtained from the 27 patients who had two HRQoL measures prior to treatment. Using this progression model, two curves were drawn to simulate the progression of iNPH in untreated and treated patients (Figure 11). The curve endpoint was set to the average life expectancy of iNPH patient following a CSF shunt (5.1 years) (170), and a dotted line was drawn to represent the HRQoL progression of a patient who would live longer than the average iNPH patient.

From these estimates, a polynomial function was fitted for both the treated (y = -7E-05x2 + 0.0012x + 0.7166) and hypothetically untreated iNPH patients (y = 1E-04x2 – 0.0156x + 0.7439). By integrating the polynomial functions to the time period of 5.1 years, the area under the curve (AUC) was calculated. In this concept, the AUC for each of the two curves represents the average QALYs that the person in that patient group has in his/her

lifetime. To calculate the price of one QALY, the cost of CSF shunting was obtained from 151 iNPH patients who were operated on at KUH between January 2013 and July 2014. The overall total cost included salaries of operating staff, instruments, and equipment used in the operation, hospital days, and all additional costs incurred by laboratory and radiological investigations.

6.3 RESULTS

The rate of progression was estimated to be on average -0.3% HRQoL/month for treated iNPH patients and -2.5% HRQoL/month for hypothetical untreated iNPH patients. The average QALY difference was estimated to be 1.4 QALYs (3.4 vs. 2.0 QALYs) when the AUC difference between the simulated treated and untreated iNPH patients was determined. On average, the cost of CSF shunting was 13 200 euros, and the estimated price of one QALY was 9 400 euros.

6.4 DISCUSSION

See discussion in chapter 8.4.

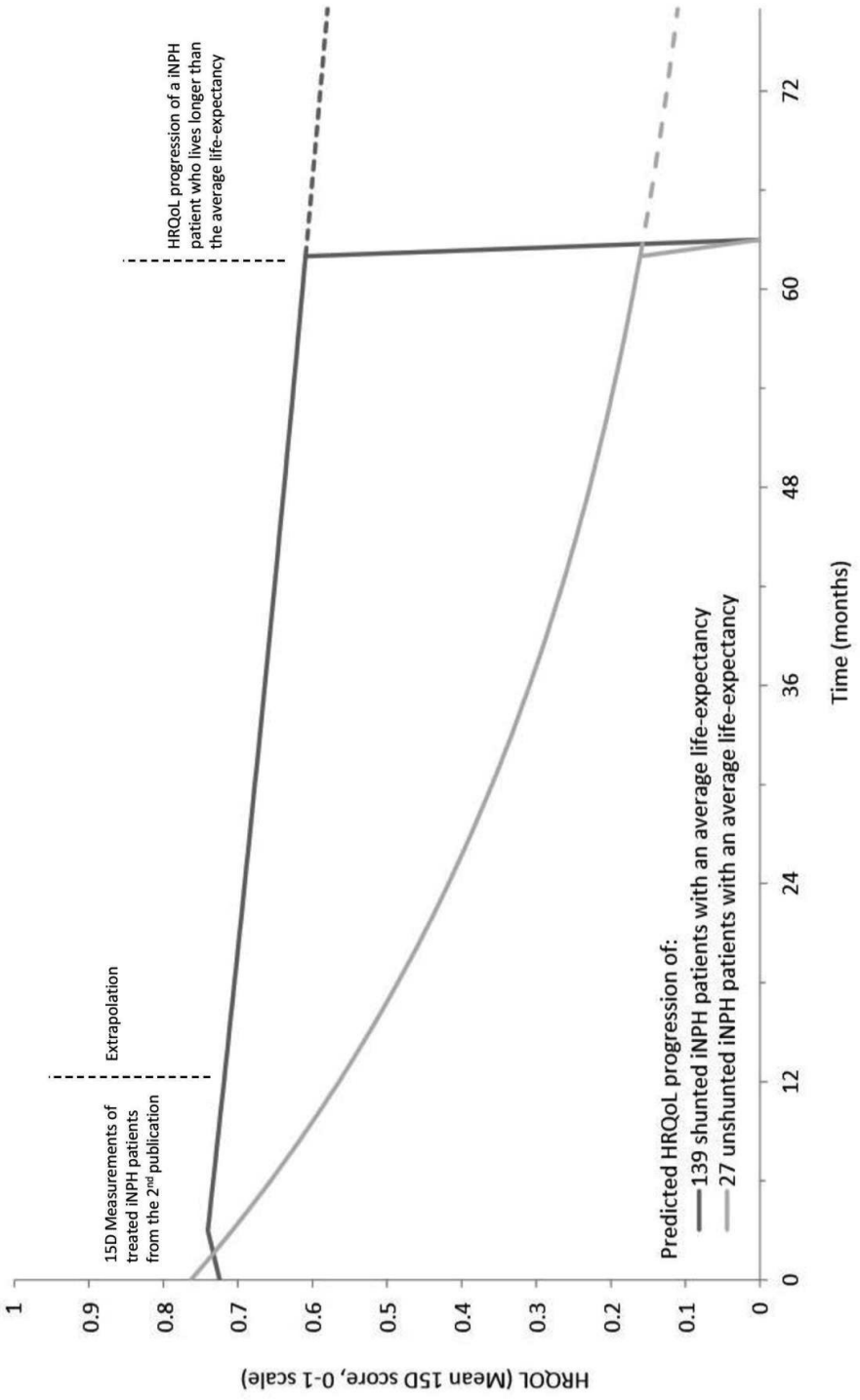

Figure 11. The predicted HRQoL progression of untreated and treated iNPH patients. For shunted patients, the equation for the curve is y = -7E-05x2 + 0.0012x + 0.7166, and for unshunted patients: y = 1E-04x2 – 0.0156x + 0.7439.

7 Why does the health-related quality of life in idiopathic normal pressure hydrocephalus fail to improve despite the favorable clinical outcome?

7.1 ABSTRACT

Objective
Occasionally a favorable clinical disease-specific outcome does not reflect into improved generic health-related quality of life (HRQoL) in patients with idiopathic normal pressure hydrocephalus (iNPH) one year after the installation of the cerebrospinal fluid (CSF) shunt. Our aim was to identify factors causing this discrepancy.

Methods
The one-year HRQoL outcome of 141 iNPH patients was evaluated using the generic 15D instrument, in which the minimum clinically important change/difference on the 0-1 scale has been estimated to be ± 0.015. A 12-point iNPH grading scale (iNPHGS) was used as a clinical diseasespecific outcome measure, in which one point decrease is considered to be clinically important. We identified 29 (21%) iNPH patients from our prospective study, whose HRQoL deteriorated or remained the same despite of a favorable iNPHGS outcome. We analyzed this discrepancy using patients' clinical variables and characteristics.

Results
Multivariate binary logistic regression analysis indicated that a higher (worse) iNPHGS score at baseline (adjusted OR, 1.7; 95% CI, 1.3-2.3; $p < 0.001$), comorbid chronic pulmonary disease (40% vs. 20%; adjusted OR, 17.8; 95% CI, 3.6-89.9; $p < 0.001$) and any comorbid non-metastatic tumor (62% vs. 17%; adjusted OR, 11.5; 95% CI, 1.5-85.3; $p = 0.017$) predicted discrepancy between iNPHGS and 15D outcomes.

Conclusions
Frail patients suffering from certain pre-existing comorbidities may not experience improvement in generic hrqol despite of a favorable clinical disease-specific response. Acknowledging the comorbidity burden of the patient may help clinicians and the patients to understand the conflict between patient reported and clinical outcomes.

7.2 INTRODUCTION

There is an occasional discrepancy between the patient reported (PRO) and clinician reported (ClinRO) outcomes, but the extent of this phenomenon, its etiology and how it behaves in different patient populations are largely unknown (261). The few studies conducted on this topic suggest that physicians tend to estimate the efficacy of treatment better than patients (261-263). This might be due to the information asymmetries between the physician and the patient (261,263), unmet expectations (262) or the 'response shift' phenomenon (264). On the other hand, PRO's, such as Health-Related Quality of Life

(HRQoL), may appreciate aspects not captured by ClinROs (33,34,48,260,265).

Recently we published a prospective 1-year follow-up study of HRQoL outcome in patients with idiopathic normal-pressure hydrocephalus (iNPH) (260), a progressing condition (8) of the elderly which characteristically impairs the gait, cognition and urinary continence of the affected (2,9). The so far unknown origin has been contemplated to cause various abnormalities in the cerebral spinal fluid (CSF) physiology and hydrodynamics, in particular a disturbance in CSF homeostasis, which ultimately lead to the symptoms and signs observed in patients with iNPH (2,9). iNPH itself is a diagnostic challenge, where patients are by the current guidelines classified by the increasing probability to have the condition, rather than having or not having the illness (2,9). The only available treatment, the CSF shunt surgery, has been reported to relieve some of the symptoms in a majority of patients with iNPH (7).

Another unresolved question is the usage of PROs in patients with cognitive impairment, who are suspected to lack insight for self-evaluation as the illness progresses (33,34). Reports concerning the required cognitive function for PROs are rare, and it has been speculated, if participants should be excluded from PRO's if they reach certain stage of dementia (33,34). Despite of two decades of research, investigators have found very little of common ground to choosing a HRQoL instrument for patients with dementia, what is the optimal way of administrating it, and what dimensions and qualities it should or should not have (33,34,206,207). Only little is known about HRQoL in iNPH (260) and there are no guidelines for the measurement of HRQoL in iNPH.

In our study (260), a PRO (15D HRQoL instrument) and a ClinRO (iNPH Grading Scale, iNPHGS) seemed to match, as the favorable outcome rate using both instruments was alike (44% vs 48%). When investigated further, a lack of strong correlation between the changes in the 15D and the iNPHGS scores raised the question of possible discrepancy between the two [Table 19, Figure 12].

This led to the current study aiming to determine 1) how common is the discrepancy between the PRO and the ClinRO in iNPH patients measured by HRQoL (15D) and iNPHGS, respectively, 2) do patients with discrepancy differ from the rest of the study population and 3) are there explanatory factors for the discrepancy, such as cognitive impairment, depressive symptoms or neurodegenerative comorbidity.

7.3 METHODS

7.3.1 Study design & participants

The permission for the research was received from the Research Ethics Board of the Kuopio University Hospital (KUH), a hospital that geographically serves neurosurgery to the Eastern Finnish population of about 900 000 inhabitants. Patients suspected to have iNPH in this epidemiological area were primarily examined by a neurologist and referred for further neurosurgical investigations, if they displayed one to three symptoms possibly related to NPH (impaired cognition, impaired gait or urinary continence) accompanied with enlarged brain ventricles disproportionate to the size of the sulci of cerebral convexities (Evan's index >0.30) (2) in computed tomography or magnetic resonance imaging.

Between April 2009 and February 2015 data were collected in the Neurosurgery Department of KUH from 245 consecutive patients with suspected iNPH providing a

written informed consent (Figure 13). The HRQoL questionnaires were completed by an interviewing nurse or by participants themselves and stored in the NPH Registry of KUH (www.uef.fi/nph).

As 56 patients were excluded from further research due insufficient data, not having iNPH or not having CSF shunt (Figure 13), the primary prospective 1-year follow-up study was performed with 189 participants, of whom 145 (77 %) completed the HRQoL follow-up (Figure 13) (260). Regarding this study population, the selection procedure for the CSF shunts has been described in detail previously (260). Information on the CSF shunt types used can be found from (Table 19).

As both 1-year iNPHGS and 15D scores were essential for analyzing the discrepancy between the two, four patients missing a 1-year iNPHGS score were excluded (Figure 13). As a result, 141 participants were included in the analysis (Figure 13). Participants were classified to have a negative discrepancy, if they did not have a clinically important improvement in HRQoL despite of having at least a minimum clinically important improvement in the iNPHGS score 1-year after the shunting [Figure 13, Tables 19 & 20] and a positive discrepancy if they had experienced at least a minimum clinically important improvement in the 15D score, but the iNPHGS score did not show a clinically important improvement [Table 19].

7.3.2 Evaluation of iNPH symptoms and the clinical outcome measure

The evaluation of iNPH symptoms has been described in section 4.3.5. A minimum clinically important decrease in the iNPHGS score has been estimated to be one point (266).

7.3.3 The HRQoL instrument

The 15D instrument has been described in section 2.9.5 (Appendix 3).

7.3.4 Evaluation of charasteristics and comorbidities

Evaluation of comorbidities and CACI has been described in section 5.3.6 (Table 21).

7.3.5 Education

The education level determination has been described in section 4.3.7.

7.3.6 Biopsy procedure & immunohistochemistry

the biopsy procedure and immunohistochemistry has been described in section 5.3.7 (Tables 19,20).

7.3.7 Evaluation of cognition

Cognitive evaluation has been described in section 4.3.4 and CDR in section 5.3.3 (Table 20).

7.3.8 Assesment of depressive symptoms

Assesment of depressive symptoms has been described in section 4.3.3 (Table 20).

TABLE 19. Characteristics and comorbidities of the 141 study participants

Variables	Number of participants or Mean	SD or %	Number of observations if any missing data
CHARACTERISTICS			
Age (at shunting)	74	7.4	
BMI (at shunting)	27	4.8	134
Education level (≤9 years of education)	85	63	136
Sex (Female)	65	46	
Gait apraxia prior to shunting	137	97	
1-year outcome			
Favorable HRQoL outcome[a]	62	44	
Favorable INPHGS outcome[b]	68	48	
DISCREPANCY	52	37	
Negative discrepancy[c]	29	21	
Positive discrepancy[d]	23	16	
COMORBIDITY			
Comorbidity burden (Median CACI score)	5	4,7[e]	
Histology in frontal cortical biopsy			
Aβ - and HPτ –	68	48	
Aβ + and HPτ -	49	36	
Aβ + and HPτ+	20	15	
Aβ - and HPτ +	1	1	
Biopsy/staining unsuccessful	*3*	*n/a*	
Grouping for statistical analyses: Absence of Aβ or HPτ found in the frontal cortical biopsy	68	49	138
INPH PROBABILITY[F] (MODIFIED CRITERIA)			
Probable iNPH	129	92	
Possible iNPH	12	8	
Unlikely iNPH	0	0	
INPH PROBABILITY[G] (UNMODIFIED CRITERIA)			
Probable iNPH	33	23	
Possible iNPH	108	77	
Unlikely iNPH			
Types of valves used in the study population[h]			
PS Medical (Medtronic) Strata[i]	138	98	
PS Medical (Medtronic) Delta[j]	3	2	
CSF shunt location			
Ventriculo-peritoneal shunt	140	99	
Ventriculo-atrial shunt	1	1	

LEGEND: [a]Favorable HRQoL outcome, Positive and clinically important change in HRQoL (Δ15D score ≥ 0.015); [b]Favorable INPHGS outcome, Severity of iNPH symptoms relieved (iNPHGS decreased at least 1 point); [c]Negative discrepancy, a failure to show at least a minimum clinically important improvement in HRQoL (15D) while having at least a minimum clinically important improvement in the iNPHGS (Δ15D score < 0.015 and ΔINPHGS ≤ -1); [d]Positive discrepancy, patients who experienced at least a minimum clinically important improvement in HRQoL (15D) while the iNPHGS score remained the same or increased (Δ15D score ≥ 0.015 and ΔINPHGS ≥ 0); [e]25th and 75th percentile; [f]Diagnostic criteria by Relkin et al. 2005 [12], from which the physiological criterion (IV) for probable iNPH was not included, as CSF opening pressure was measured only from patients going through infusion tests in our study population; [g]Diagnostic criteria by Relkin et al. 2005 [12]; [h]All including a siphon-control device; [i]Adjustable pressure setting, initial pressure setting set at 1.5 performance level of the valve; [j]Fixed pressure setting, set at 1.5 performance level of the valve. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; CSF, Cerebrospinal fluid; HRQoL, Health Related Quality of Life; iNPHGS, iNPH Grading Scale; BMI, Body mass index [kg/m^2]; Aβ Amyloid-β; HPτ, Hyperphosphorylated tau; CACI, Charlson Age Comorbidity Index.

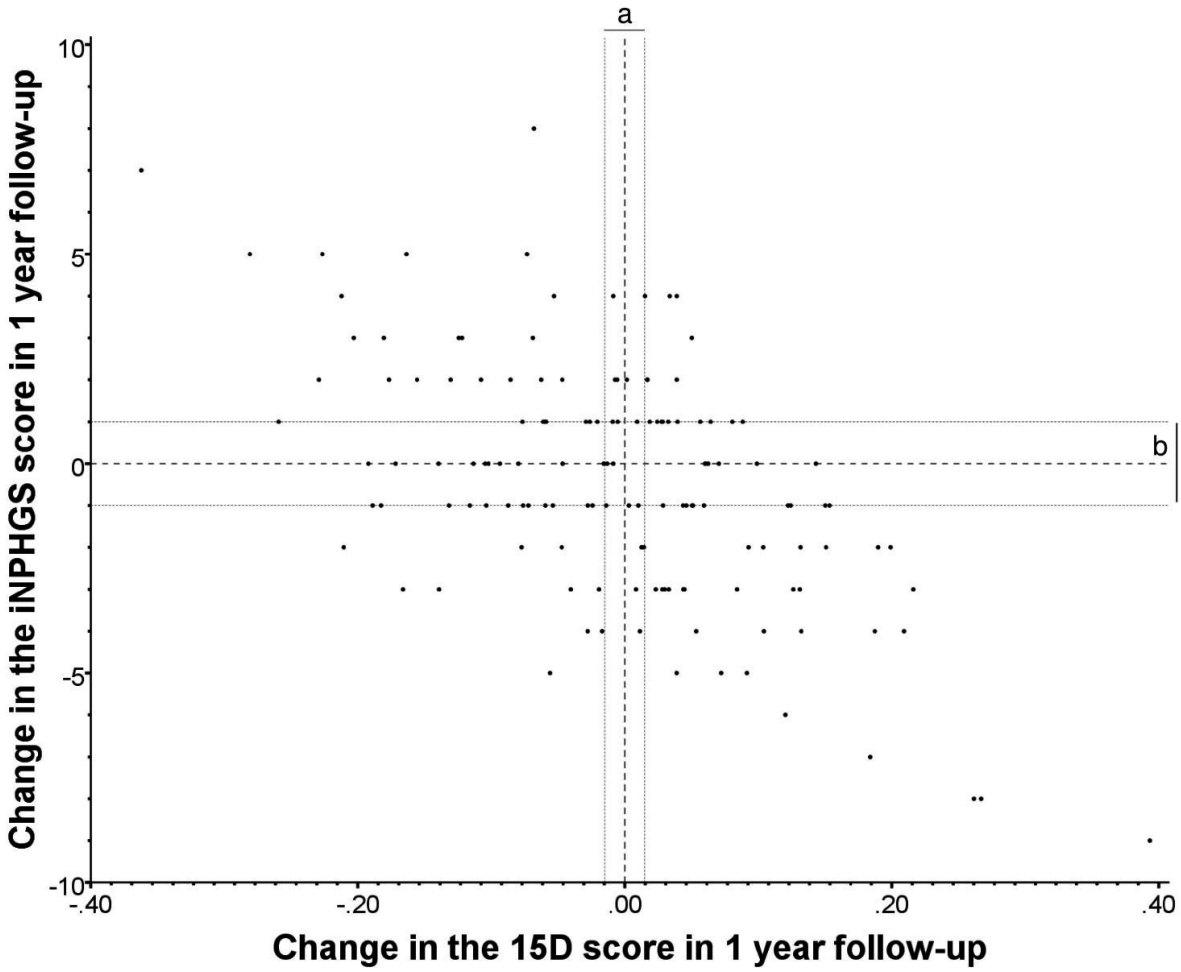

Figure 12. Pearson correlation between the changes in INPHGS and 15D scores one year post-operatively in 141 study participants. LEGEND: Each dot represents data from one person; Pearson correlation (R=-0.58, p<0.001); a, clinically insignificant change in the 15D score (|Δ15D score| < 0.015) [19]; b, clinically insignificant change in iNPHGS score (|ΔINPHGS| < 1) [17]. Patients were identified to have negative discrepancy if they did not show at least a minimum clinically important improvement in HRQoL (15D score) while having at least a minimum clinically important improvement in the iNPHGS (Δ15D score < 0.015 and ΔINPHGS ≤ -1) and similarly to have positive discrepancy if they experienced at least a minimum clinically important improvement in 15D score while the iNPHGS score remained the same or increased (Δ15D score ≥ 0.015 and ΔINPHGS ≥ 0). ABBREVIATIONS: INPHGS, iNPH Grading Scale; iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life.

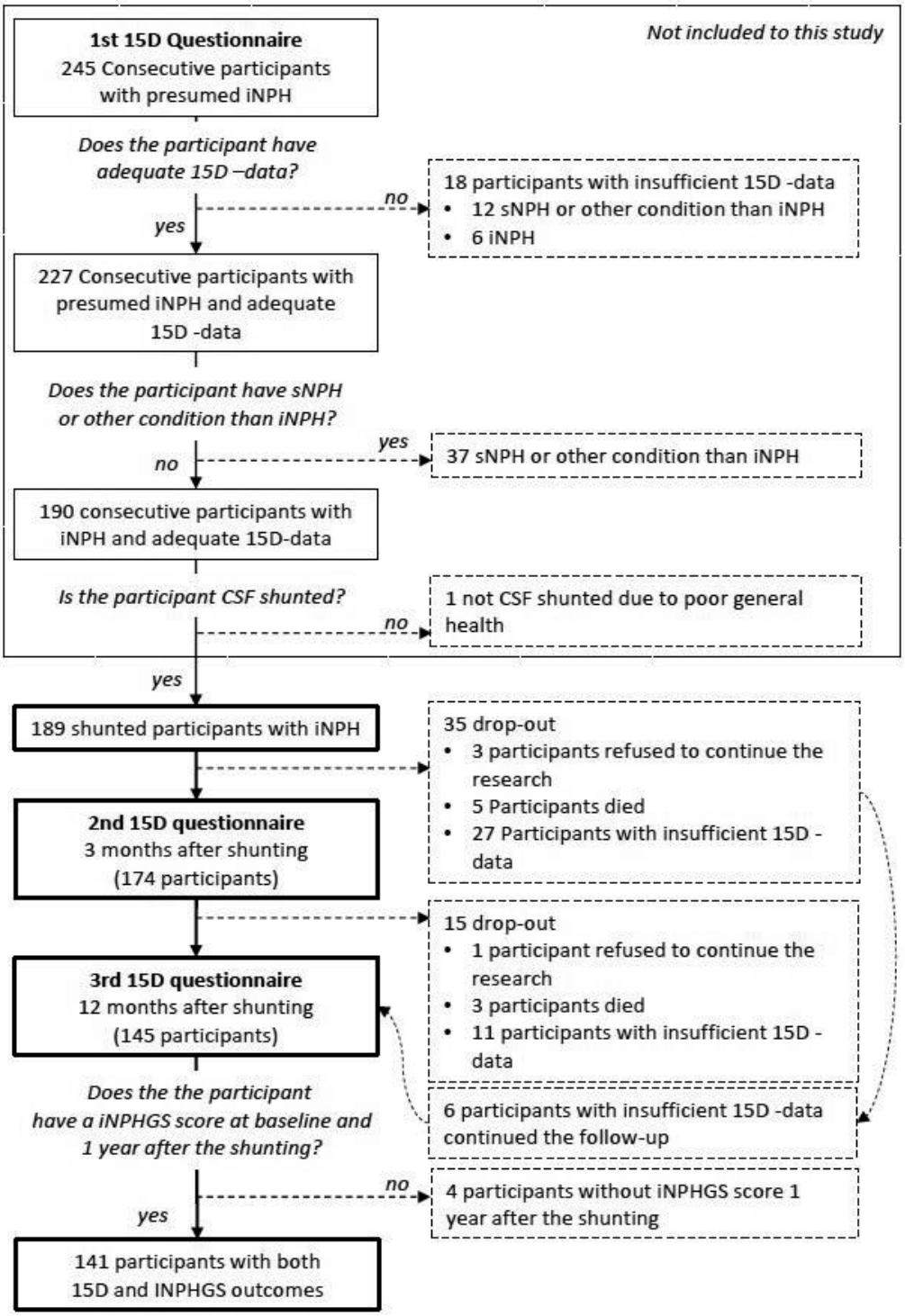

FIGURE 13. Title: Flowchart of the study population. LEGEND: insufficient 15D data, ≥4 dimensions missing in the 15D questionnaire or the questionnaire is missing completely [18]; ABBREVIATIONS: HRQoL, health-related quality of life; iNPH, idiopathic normal-pressure hydrocephalus; sNPH, secondary NPH [11]; CSF, Cerebrospinal fluid.

TABLE 20. Comparison between the participants with and without negative discrepancy[e]

	141 STUDY PARTICIPANTS WITH BOTH 15D AND INPHGS OUTCOMES						COMPARISONS	
VARIABLES	29 Patients with negative discrepancy[e]			112 Patients without negative discrepancy			Mann-Whitney U	p-value
	Mean or Number of participants	SD or %	Number of observations if any missing data	Mean or Number of participants	SD or %	Number of observations if any missing data		
PREOPERATIVE CONDITION								
HRQoL (15D score, 0-1 scale)	0.707	0.1		0.728	0.1		1351	0.163
Severity of iNPH symtoms (INPHGS score, 0-12 scale)	7.6	2.0		5.3	2.1		823	**<0.001**
Severity of depressive symptoms (BDI score, 0-63 scale)	12	8.1	18	11	7.0	76	617	0.519
Cognition level (MMSE score, 0-30 scale)	21	5.3		23	4.7	109	1316	0.166
MMSE score converted to Clinical Dementia Rating[1]						109		
No dementia	0	0		1	1			
Mild cognitive impairment	7	24		33	30			
Mild dementia	12	42		44	40			
Moderate dementia	9	31		29	27			
Severe dementia	1	3		2	2			
COMORBIDITY								
Absence of Aβ or HPτ found in the frontal cortical biopsy	13	45		55	49	109		0.678[d]
Comorbidity burden (Median CACI score)	6[b]	5,8[c]		5[b]	4,7[c]		1160	**0.016**
Characteristics								
Age (at shunting)	75	6.9		74	7.6		1368	0.190
BMI (at shunting)	29	5.4	28	26	4.5	106	1053	**0.018**
Education level (≤9 years of education)	17	59		68	64	107		0.669[d]
Sex (Female)	15	52		50	45			0.535[d]
DIAGNOSTICS								
INPH probability[2] (modified criteria)								0.127[d]
Probable iNPH	29	100		100	89			
Possible iNPH	0	0		12	11			
INPH probability[3] (unmodified criteria)								0.624[d]
Probable iNPH	8	28		25	22			
Possible iNPH	21	72		87	78			
PROGNOSTICS TESTS USED PRELIMINARY TO CSF SHUNT								
CSF tap test	13	46		55	49			0.835[d]
CSF tap & Infusion –tests	7	25		26	24			1.000[d]
CSF tap & Infusion -tests & ICP-monitoring	1	4		4	4			1.000[d]
ICP -monitoring	7	25		25	23			0.808[d]
POTENTIAL OUTCOME MODIFYING FOLLOW-UP FACTORS								
Subjective hearing impairment after shunting[4]	12	41		23	21			**0.029[d]**
Surgical complications (revision)	3	10		9	7.1			0.712[d]
CSF shunt valve settings adjusted externally during the follow-up	11	38		42	38			1.000[d]
The opening pressure of the CSF valve was lowered	9	82		32	76			
The opening pressure of the CSF valve was increased	2	18		10	24			

LEGEND: Statistically significant difference is bolded.[1]MMSE score converted to Clinical Dementia Rating, No dementia (MMSE 30, CDR 0), Mild cognitive impairment (MMSE 26-29, CDR 0.5), Mild dementia (MMSE 21-25, CDR 1, Moderate dementia (MMSE 11-20, CDR 2), Severe dementia (MMSE 0-10, CDR 3); [2]Diagnostic criteria by Relkin et al. 2005 [12], from which the physiological criterion (IV) for probable iNPH was not included, as CSF opening pressure was measured only from patients going through infusion tests in our study population; [3]Diagnostic criteria by Relkin et al. 2005 [12]; [4]Worsening of hearing-dimension of 15D one year after the shunting. [a]U-value in the Mann–Whitney U test; [b]Median score ;[c]25th and 75th percentile; [d]Fisher's Exact Test; [e]Negative discrepancy, a failure to show at least minimum clinically important improvement in HRQoL (15D score) while having at least minimum clinically important improvement in the iNPHGS (Δ15D score < 0.015 and ΔINPHGS ≤ -1). ABBREVIATIONS: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; iNPHGS, iNPH Grading Scale; BDI, Beck Depression Index; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; CSF, Cerebrospinal fluid; ICP, Intracranial pressure.

7.3.9 Statistics

The data were analyzed using the Statistical Package for Social Sciences (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and the R language and environment for statistical computing (R- 3.2.4 for Windows; R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). The linear association between the changes in the iNPHGS and 15D scores at the 1-year follow-up was analyzed using Pearson's correlation coefficient. The significance of the differences in the clinical variables between participants with and without a negative discrepancy, were tested with Mann–Whitney U test for continuous and Fisher's Exact test for non-continuous variables, respectively.

The reason to focus on negative discrepancy was made on clinical basis; as such a discrepancy can be seen as an unpredicted and unfavorable phenomenon unlike the positive discrepancy. To predict the negative discrepancy, uni- and multivariate binary logistic regression analyses were performed using the enter method (252)(Tables 22 & 23). The potential effect of missing data on the regression results was estimated with multiple imputation by chained equations (253) (Tables 22 & 24). Variables were included in the multivariate model if they reached a moderate tendency towards significance in univariate analyses ($p \leq 0.25$) (252) (Table 22), and those excluded were recorded (Table 23). The odds ratios (ORs) were calculated with 95% confidence intervals (CIs). All tests for significance were two-sided, with probabilities of <0.05 accepted as statistically significant.

7.4 RESULTS

52 patients (37%) had inconsistency between their 1-year 15D and iNPHGS scores (Figure 12, Tables 19 and 20): 29 (21%) had a negative and 23 (16%) a positive discrepancy. Patients with a negative discrepancy had higher comorbidity burden (Mann-Whitney U-test, $p = 0.016$), Body Mass Index (Mann-Whitney U-test, $p = 0.018$) and iNPHGS (Mann-Whitney U-test, $p < 0.001$) scores and had higher frequency of subjective hearing loss (Fisher's exact test, $p = 0.029$, 41% vs 21%) than those without a negative discrepancy (Table 20). Patients with a negative discrepancy had also a higher prevalence of comorbid chronic pulmonary disease (Fisher's exact test, $p = 0.001$, 28% vs 5%) and history of myocardial infarctions

TABLE 21. Charlson age-comorbidity index (CACI) of the study population

Weight	Comorbid condition	29 Patients with negative discrepancy[a]		112 Patients without negative discrepancy		Comparisons (Fisher's exact test)
		N	%	N	%	p-value
6	Acquired immune deficiency syndrome	0	0	0	0	N/A
	Metastatic solid tumor	1	3	1	1	0.370
3	Moderate or severe liver disease	0	0	0	0	N/A
2	Any non-metastatic solid tumor	4	14	6	5	0.215
	Malignant lymphoma	0	0	1	1	1.000
	Leukemia	0	0	0	0	N/A
	Diabetes with end organ damage	6	21	22	20	1.000
	Moderate or severe renal disease	6	21	19	17	0.597
	Hemiplegia	0	0	3	3	1.000
1	Diabetes without end organ damage	4	14	17	15	1.000
	Mild liver disease	1	3	2	2	0.502
	Ulcer disease	0	0	1	1	1.000
	Connective tissue disease	2	7	9	8	1.000
	Chronic pulmonary disease	8	28	5	5	**0.001**
	Dementia	22	76	75	67	0.500
	Cerebrovascular disease	4	14	13	12	0.752
	Peripheral vascular disease	0	0	3	3	1.000
	Congestive heart failure	4	14	5	5	0.086
	Myocardial infarction	12	41	24	21	**0.034**
	Each decade of age ≥50 years is equivalent to a 1-point increase in comorbidity					
1	50 ≤ Age <60	0	0	7	6	0.345
2	60 ≤ Age <70	5	17	22	20	1.000
3	70 ≤ Age <80	13	45	54	48	0.836
4	80 ≤ Age <90	11	38	29	26	0.248

LEGEND: Statistically significant difference is bolded. aa failure to show at least minimum clinically important improvement in HRQoL (15D) while having at least minimum clinically important improvement in the iNPHGS (Δ15D score < 0.015 and ΔINPHGS ≤ -1). ABBREVIATIONS: N/A, not applicable.

TABLE 22. Logistic regression analysis for the prediction of a negative discrepancy 1 year post-operatively

Predictors	Model	n	Unstandardized coefficient B	S.E.	Wald's χ^2 (t-value)	p-value	Adjusted OR (95% CI)
Age	Univariate	141	0.04	0.03	1.39	0.236	1.04 (0.98-1.10)
	Multivariate	132	0.03	0.05	0.45	0.502	1.03 (0.94-1.13)
	Imputed Multivariate[a]	N/A	0.03	0.05	(0.67)	0.504	1.03 (0.94-1.13)
Baseline iNPHGS score	Univariate	141	0.38	0.10	14.82	**<0.001**	**1.46 (1.20-1.77)**
	Multivariate	132	0.55	0.15	14.57	**<0.001**	**1.74 (1.31-2.31)**
	Imputed Multivariate[a]	N/A	0.55	0.15	(3.82)	**<0.001**	**1.74 (1.31-2.32)**
Baseline MMSE score	Univariate	138	-0.57	0.04	1.90	0.168	0.94 (0.87-1.02)
	Multivariate	132	0.07	0.06	1.43	0.232	1.08 (0.95-1.21)
	Imputed Multivariate[a]	N/A	0.07	0.06	(1.20)	0.234	1.08 (0.95-1.21)
BMI score	Univariate	134	0.10	0.04	4.90	**0.027**	**1.10 (1.01-1.20)**
	Multivariate	132	0.06	0.06	1.09	0.297	1.06 (0.95-1.18)
	Imputed Multivariate[a]	N/A	0.06	0.06	(1.04)	0.299	1.06 (0.95-1.18)
Comorbid Any non-metastatic solid tumor (1 = yes, 0 = no)	Univariate	141	1.04	0.68	2.32	0.128	2.83 (0.74-10.78)
	Multivariate	132	2.44	1.02	5.67	**0.017**	**11.45 (1.54-85.28)**
	Imputed Multivariate[a]	N/A	2.44	1.02	(2.38)	**0.019**	**11.45 (1.51-87.03)**
Comorbid Chronic pulmonary disease (1 = yes, 0 = no)	Univariate	141	2.10	0.62	11.53	**0.001**	**8.15 (2.43-27.38)**
	Multivariate	132	2.88	0.82	12.26	**<0.001**	**17.89 (3.56-89.87)**
	Imputed Multivariate[a]	N/A	2.88	0.82	(2.38)	**0.001**	**17.89 (3.50-91.35)**
Comorbid Congestive heart failure (1 = yes, 0 = no)	Univariate	141	1.23	0.71	3.03	0.082	3.42 (0.86-13.68)
	Multivariate	132	-0.28	1.26	0.05	0.821	0.75 (0.06-8.87)
	Imputed Multivariate[a]	N/A	-0.28	1.26	(-0.23)	0.822	0.75 (0.06-9.09)
Comorbid Myocardial infarction (1 = yes, 0 = no)	Univariate	141	0.95	0.44	4.63	**0.031**	**2.59 (1.09-6.15)**
	Multivariate	132	0.81	0.60	1.81	0.179	2.25 (0.69-7.36)
	Imputed Multivariate[a]	N/A	0.81	0.60	(1.34)	0.182	2.25 (0.68-7.45)
Constant	Multivariate	132	-11.26	4.59	6.03	**0.014**	1.30E-5
	Imputed Multivariate[a]	N/A	-11.26	4.59	(-2.46)	**0.015**	1.28E-5
Multivariate model evaluation					χ^2	**p-value**	
Overall model evaluation					43.87	<0.001	
Goodness-of-fit test (Hosmer & Lemeshow)					8.05	0.429	

LEGEND: Statistically significant difference is bolded.a Pooled results of 50 imputations. Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; S.E., Standard Error; MMSE, Mini-Mental State Examination; iNPHGS, iNPH Grading Scale; BMI, Body mass index; N/A, not applicable.

TABLE 23. Variables excluded from the multivariate model

Variables excluded from the multivariate model[1]	Model	n	Unstandardized coefficient B	S.E.	Wald's χ^2 (t-value)	p-value	Adjusted OR (95% CI)
Absence of Aβ and HPτ pathology in the frontal cortical biopsy (= 1, otherwise 0)	Univariate	138	-0.23	0.42	0.29	0.590	0.80 (0.35-1.82)
Baseline BDI score	Univariate	94	0.02	0.04	0.45	0.505	1.02 (0.96-1.10)
Baseline 15D score	Univariate	141	-2.31	2.19	1.12	0.290	0.10 (0.00-7.20)
CACI score[2]	Univariate	141	0.24	0.09	6.41	**0.011**	**1.27 (1.06-1.52)**
Comorbid Diabetes with end organ damage (1 = yes, 0 = no)	Univariate	141	0.07	0.52	0.02	0.900	1.07 (0.39-2.94)
Comorbid Moderate or severe renal disease (1 = yes, 0 = no)	Univariate	141	0.24	0.52	0.22	0.640	1.28 (0.46-3.56)
Comorbid Diabetes without end organ damage (1 = yes, 0 = no)	Univariate	141	-0.11	0.60	0.04	0.852	0.89 (0.28-2.90)
Comorbid Connective tissue disease (1 = yes, 0 = no)	Univariate	141	-0.17	0.81	0.04	0.839	0.85 (0.17-4.16)
Comorbid Dementia (1 = yes, 0 = no)	Univariate	141	0.44	0.48	0.84	0.359	1.55 (0.61-3.96)
Comorbid Cerebrovascular disease (1 = yes, 0 = no)	Univariate	141	0.20	0.61	0.10	0.748	1.22 (0.37-4.06)
Nine years or less of acquired education (=1, otherwise 0)	Univariate	136	-0.21	0.43	0.24	0.627	0.81 (0.35-1.88)
INPH probability[3] , unmodified criteria (2 =probable, 1=possible)	Univariate	141	0.28	0.47	0.36	0.551	1.33 (0.52-3.35)
Sex (0=female, 1 = male)	Univariate	141	-0.28	0.42	0.46	0.496	0.75 (0.33-1.71)
Shunting decision based on CSF Tap-test (=1, otherwise 0)	Univariate	141	-0.17	0.42	0.17	0.681	0.84 (0.37-1.91)
Shunting decision based on CSF Tap & Infusion –tests (1 = yes, 0 = no)	Univariate	141	0.05	0.49	0.01	0.917	1.05 (0.40-2.74)
Shunting decision based on CSF Tap & Infusion tests & ICP-monitoring (1 = yes, 0 = no)	Univariate	141	-0.04	1.14	0.00	0.975	0.96 (0.10-8.97)
Shunting decision based on ICP-monitoring(1 = yes, 0 = no)	Univariate	141	0.10	0.49	0.04	0.835	1.11 (0.42-2.89)

LEGEND: [1]Variable was excluded from multivariate model (Table 22) if p>0.25 in univariate statistics [25] or [2]The regression model was better (accuracy rate 86% vs 82%, 8 vs 4 variables) when the singular dimensions of CACI (the comorbidities without their weights, Table 21) were used instead of the weighted CACI score. In addition to this, CACI score had moderate correlation to age which was included to the model (Pearson correlation 0.52, p<0.001). [3]Diagnostic criteria by Relkin et al. 2005 [12]. ABBREVIATIONS: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; S.E., Standard Error; Aβ, Amyloid-β; HPτ, Hyperphosphorylated tau; MMSE, Mini-Mental State Examination; iNPHGS, iNPH Grading Scale; BMI, Body mass index; CACI ,Charlson Age Comorbidity Index; BDI, Beck Depression Inventory; CSF, Cerebrospinal fluid; ICP, Intracranial pressure.

TABLE 24: Multiple imputation info

GENERAL INFORMATION				
Missingness	• 17 variables (33%) had missing data • 81 (43%) of the cases had missing data • When all the variables, including the outcome variables, were analyzed at the same time to detect systematic tendencies (Little's Missing Completely at Random –test; p =0.159) there was no clear indication that there would be any			
Imputation	• 50 variables (listed below) were included to the imputation model, including the outcome variable (Negative discrepancy[a] 1 year after shunting, 1=yes,0=no). • MI was performed with the R language and environment for statistical computing (R-3.2.4 for Windows, R Core Team 2015) using the mice-package [27], in which the default settings were kept • Number of imputations was 50 • No transformations of the data were performed • The distribution of observed and imputed data were examined with a density plot for each variable			
IMPUTED VARIABLES	N missing (%)	Normality assumption satisfied	Normality Test used (p-value)	Imputation model
OUTCOME VARIABLE				
Negative discrepancy[a] 1 year after shunting, 1=yes, 0=no).	48 (25.4)	N/A	N/A	pmm
Discrepancy classification (0=positive discrepancy[b], 1=no discrepancy, 2=negative discrepancy)	48 (25.4)	N/A	N/A	pmm
FOLLOW-UP VARIABLES				
Favorable HRQoL outcome (yes)				
3 months after the shunting	15 (7.9)	N/A	N/A	pmm
1 year after the shunting	44 (23.2)	N/A	N/A	pmm
Mean 15D score (0-1 scale)				
Baseline	0 (0.0)	Yes	Shapiro-Wilk-test (>0.45)	N/A
3 months after shunting	15 (7.9)	Yes	Shapiro-Wilk-test (>0.32)	pmm
1 year after shunting	44 (23.2)	Yes	Shapiro-Wilk-test (>0.16)	pmm
Favorable iNPHGS outcome (yes)				
3 months after shunting	15 (7.9)	N/A	N/A	pmm
1 year after shunting	45 (23.8)	N/A	N/A	pmm
INPHGS score (0-12 scale)				
Baseline	3 (1.6)	Yes	Shapiro-Wilk-test (p>0.14)	pmm
3 months after shunting	14 (7.4)	No	Shapiro-Wilk-test (<0.01)	pmm
1 year after shunting	43 (22.8)	No	Shapiro-Wilk-test (<0.01)	pmm
MMSE Score (0-30 scale)				
Baseline	6 (3.2)	Yes	Shapiro-Wilk-test (0.08)	pmm
3 months after shunting	28 (14.8)	No	Shapiro-Wilk-test (0.04)	pmm
POTENTIAL OUTCOME MODIFYING FOLLOW-UP FACTORS				
Revision of the CSF shunt	0 (0.0)	N/A	N/A	N/A
CSF shunt valve settings adjusted during the follow-up (yes)	0 (0.0)	N/A	N/A	N/A
Subjective hearing impairment after	44 (23.3)	N/A	N/A	pmm

shunting[c] (1=yes, 0=no)				
COMORBIDITIES				
Histology in frontal cortical biopsy				
Presence of Aβ and/or HPτ found in the frontal cortical biopsy	7 (3.7)	N/A	N/A	pmm
CACI Score	0 (0.0)			
CACI condition (yes/no)				
Acquired immune deficiency syndrome	0 (0.0)	N/A	N/A	N/A
Metastatic solid tumor	0 (0.0)	N/A	N/A	N/A
Moderate or severe liver disease	0 (0.0)	N/A	N/A	N/A
Any non-metastatic solid tumor	0 (0.0)	N/A	N/A	N/A
Malignant lymphoma	0 (0.0)	N/A	N/A	N/A
Leukemia	0 (0.0)	N/A	N/A	N/A
Diabetes with end organ damage	0 (0.0)	N/A	N/A	N/A
Moderate or severe renal disease	0 (0.0)	N/A	N/A	N/A
Hemiplegia	0 (0.0)	N/A	N/A	N/A
Diabetes without end organ damage	0 (0.0)	N/A	N/A	N/A
Mild liver disease	0 (0.0)	N/A	N/A	N/A
Ulcer disease	0 (0.0)	N/A	N/A	N/A
Connective tissue disease	0 (0.0)	N/A	N/A	N/A
Chronic pulmonary disease	0 (0.0)	N/A	N/A	N/A
Dementia	0 (0.0)	N/A	N/A	N/A
Cerebrovascular disease	0 (0.0)	N/A	N/A	N/A
Peripheral vascular disease	0 (0.0)	N/A	N/A	N/A
Congestive heart failure	0 (0.0)	N/A	N/A	N/A
Myocardial infarction	0 (0.0)	N/A	N/A	N/A
CHARACTERISTICS				
Sex (Female)	0 (0.0)	N/A	N/A	
Age (at shunting)	0 (0.0)	Yes	Shapiro-Wilk-test (0.31)	N/A
BMI	9 (4.8)	No	Shapiro-Wilk-test (<0.001)	pmm
Education level (Nine years or less of acquired education)	9 (4.8)	N/A	N/A	pmm
INPH PROBABILITY	0 (0.0)	N/A	N/A	N/A
Unmodified criteria[d] [12]	0 (0.0)	N/A	N/A	N/A
Modified criteria[e]	0 (0.0)	N/A	N/A	N/A
Gait apraxia prior shunting	0 (0.0)	N/A	N/A	N/A
DIAGNOSTIC TESTS				
Shunting decision based on CSF Tap-test	0 (0.0)	N/A	N/A	N/A
Shunting decision based on CSF Tap & Infusion –tests	0 (0.0)	N/A	N/A	N/A
Shunting decision based on CSF Tap & Infusion tests & ICP-monitoring	0 (0.0)	N/A	N/A	N/A
Shunting decision based on ICP-monitoring	0 (0.0)	N/A	N/A	N/A

LEGEND: [a]a failure to show at least minimum clinically important improvement in HRQoL (15D score) while having at least minimum clinically important improvement in the iNPHGS (Δ15D score < 0.015 and ΔINPHGS ≤ -1);[b]Positive discrepancy, patients who experienced at least a minimum clinically important improvement in HRQoL (15D score), while the iNPHGS score remained the same or increased (Δ15D score ≥ 0.015 and ΔINPHGS ≥ 0);[c]Worsening on hearing dimension of 15D one year after the shunting; [d]Diagnostic criteria by Relkin et al. 2005 [12]; [e]Diagnostic criteria by Relkin et al. 2005 [12], from which the physiological criterion (IV) for probable iNPH was not included, as CSF opening pressure was measured only from patients going through infusion tests in our study population; [d]Worsening of hearing-dimension of 15D one year after the shunting. ABBREVIATIONS: N/A, not applicable; Favorable HRQoL outcome: Positive and clinically important change in HRQoL (Δ15D ≥ 0.015), Favorable INPHGS outcome: Severity of iNPH symptoms relieved (iNPHGS decreased at least 1 point); pmm, predictive mean matching; iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; MMSE, Mini-Mental State Examination; iNPHGS, iNPH Grading Scale; ICP, Intracranial pressure; CSF, Cerebrospinal fluid; BMI, Body mass index [kg/m2]; Aβ Amyloid-β; HPτ, Hyperphosphorylated tau; CACI, Charlson Age Comorbidity Index.

(Fisher's exact test, p = 0.034, 41% vs 21%) than those without discrepancy (Table 21).

A secondary statistical analysis was performed for patients with positive discrepancy (Table 21). Patients with a positive discrepancy had lower iNPHGS score at

baseline (Mann-Whitney U-test, $p < 0.001$) than those without a positive discrepancy (Table 25).

7.4.1 Regression analysis

Multivariate binary logistic regression analysis was performed with negative discrepancy (yes = 1, no = 0) as the dependent variable (Table 22). According to the model, baseline INPHGS score (adjusted OR, 1.7; 95% CI, 1.3–2.3; $p < 0.001$), comorbid chronic pulmonary disease (40% vs. 20%; absolute risk difference, 20%; adjusted OR, 17.9; 95% CI, 3.6–89.9; $p < 0.001$) and comorbid non-metastatic tumour (62% vs. 17%; absolute risk difference, 42%; adjusted OR, 11.5; 95% CI, 1.5–85.3; $p = 0.017$) predicted negative discrepancy between INPHGS and 15D outcomes 1 year after the shunting. The model had good fit as demonstrated by the Hosmer–Lemeshow test (Table 22) and 86% of the patients were classified correctly. The highest variance inflation factor was 1.2 (baseline iNPHGS score) and the lowest tolerance was 0.8 (baseline iNPHGS score), suggesting that multicollinearity did not have a significant effect on the model. Multiple imputation by chained equations confirmed that analysis results were robust to the missing data.

7.5 CONCLUSIONS

7.5.1 Limitations and generalizability

There are no universally agreed diagnostic criteria for iNPH (2,9). Proxy- rated HRQoL data were not gathered. The study was restricted to one geographical area and the results can be only applied to a similar population. A generic HRQoL measure with potentially lower sensitivity to detect a change in patients with cognitive impairment was used instead of a disease-specific HRQoL measure (33,34). The study lacks a more detailed neuropsychological test and validated evaluation of daily functions. There is a possibility of small variation between the physicians when it comes to the usage of a clinician-rated iNPHGS scale. The significance of different radiological variables used in the diagnostics of iNPH was not evaluated.

7.5.2 Interpretation

In our study, a participant with poor starting point (High iNPHGS score) was more likely to experience unimproved generic HRQoL while having a favorable clinical disease-specific outcome. It could be that in these cases the participant's wish to become fully functioning after the operation is unmet, which may explain the unimproved HRQoL (262). As old patients affected by a condition with poor prognosis are at an increased risk for misunderstanding the goals of the treatment/study (267), one might justifiably say that in these terms patients with cognitive impairment are very vulnerable. An unfortunate complication, such as hearing impairment following CSF shunting (260) may cause unimproved HRQoL despite of otherwise improved functionality and thus negate the favorable outcome. It could be argued that similarly patients with co-existing chronic pulmonary disorder or any non-metastatic cancer are more likely to find themselves where they left in terms of HRQoL as the CSF shunting does not affect the severe generic HRQoL impairment caused by these comorbidities (268) . These findings are in accordance with the conceptual model of HRQoL presented Wilson & Cleary (32), where not only the symptom

status and disease process but the characteristics of the individual and the environment influence the perception of general health and HRQoL (32). This observed discrepancy between the PRO and PROM rationalizes, in its very essence, the use of both measurements and elucidates the limitations if used alone (32-34,48,260,265).

An exciting finding was that neither the absence of Aβ and HPτ pathology in the frontal cortical biopsy (indicating the absence of comorbid Alzheimer's disease, AD) nor a better cognitive function, decreased the likelihood of discrepancy. However, our results should be interpreted cautiously, as generic utility measurements, such as the 15D instrument, might have limited sensitivity to detect health status changes in persons with cognitive impairment (33,34). While many patients lack full insight already early on in the cognitive impairment, self-rated HRQoL has unique value, but should always be accompanied with other outcome measures (33,34). While some self-rated generic HRQoL instruments (SF-12, EQ-5D) have been reported to be able to detect change in the health status of patients with iNPH (14,48), more evidence is warranted. The 15D instrument is potentially reliable tool to measure HRQoL in persons with iNPH, as it has been successfully used in patients with Parkinson's disease (229), and it detects health status changes in various surgical conditions, such as in spinal stenosis (232). It can be hypothesized that the physical symptoms present in iNPH could help the patient with cognitive impairment to differentiate his/her heath states better than a patient with cognitive decline only.

Interestingly, a small percentage of patients experienced a minimum clinically important improvement in HRQoL while the iNPHGS score remained the same or increased (got worse) (Table 19). These participants had less severe iNPHGS symptoms at baseline, but were otherwise very similar to the rest of the study population (Table 25), suggesting that there might be psychological or nonmedical factors influencing the HRQoL outcome even though these attributes could not be captured by our study (32,264). Similarly, it has been hypothesized, that in these iNPH patients HRQoL captures subtle improvements caused by CSF shunting and that are not portrayed by objective measurements (48). In future studies, the potential effect of CSF shunt valve adjustments to ClinRo and PROM outcomes would be undoubtedly worthy of further research.

In conclusion, frail patients suffering from certain pre-existing comorbidities may not experience improvement in generic HRQoL despite of a favorable clinical disease-specific response to CSF shunt surgery. The absence of Aβ and HPτ pathology in the frontal cortical biopsy, or a better cognitive function, do not protect from the negative discrepancy. Acknowledging the comorbidity burden of the patient may help clinicians and the patients to better understand the conflict between patient-reported and clinical outcomes.

Table 25. Comparison between the participants with and without positive discrepancy[e]

	141 STUDY PARTICIPANTS WITH BOTH 15D AND INPHGS OUTCOMES						COMPARISONS	
VARIABLES	23 Patients with positive discrepancy[e]			118 Patients without positive discrepancy			Mann-Whitney U	p-value
	Mean or Number of participants	SD or %	Number of observations if any missing data	Mean or Number of participants	SD or %	Number of observations if any missing data		
Preoperative condition								
HRQoL (15D score, 0-1 scale)	0.75	0.1		0.72	0.1		1558	0.263
Severity of iNPH symtoms (INPHGS score, 0-12 scale)	3.9	2.0		6.2	2.6		665	**<0.001**
Severity of depressive symptoms (BDI score, 0-63 scale)	9.6	5.7	16	11	7.5	78	577	0.632
Cognition level (MMSE score, 0-30 scale)	23	3.6		22	0.5	115	1443	0.490
MMSE score converted to Clinical Dementia Rating[1]						115		
No dementia	0	0		1	1			
Mild cognitive impairment	7	30		33	29			
Mild dementia	11	48		45	38			
Moderate dementia	5	22		33	29			
Severe dementia	0	0		3	3			
Comorbidity								
Absence of Aβ or HPτ found in the frontal cortical biopsy	14	61		54	47	115		0.258
Comorbidity burden (Median CACI score)							1274	0.637
Characteristics								
Age (at shunting)	73	7.8		74	7.4		1263	0.597
BMI (at shunting)	26	3.8		27	4.9	111	1038	0.158
Education level (≤9 years of education)	17	77	22	68	60	114		0.151
Sex (Female)	10	44		55	47			0.823
Diagnostics								
INPH probability[2] (modified criteria)								**0.027**
Probable iNPH	18	78		111	94			
Possible iNPH	5	22		7	6			
INPH probability[3] (unmodified criteria)								0.789
Probable iNPH	6	26		27	23			
Possible iNPH	17	74		91	77			
Prognostics tests used preliminary to CSF shunt								
CSF tap test	7	30		61	52			0.071
CSF tap & Infusion –tests	9	40		24	20			0.062
CSF tap & Infusion -tests & ICP-monitoring	1	4		4	3			1.000
ICP -monitoring	6	26		26	22			0.786
Potential outcome modifying follow-up factors								
Subjective hearing impairment after shunting[4]	3	13		32	27			0.193
Surgical complications (revision)	4	17		8	7			0.108
CSF shunt valve settings adjusted externally during the follow-up	12	52		41	35			0.157
The opening pressure of the CSF valve was lowered	7	58						
The opening pressure of the CSF valve was increased	5	42						

LEGEND: Statistically significant difference is bolded.[1]MMSE score converted to Clinical Dementia Rating, No dementia (MMSE 30, CDR 0), Mild cognitive impairment (MMSE 26-29, CDR 0.5), Mild dementia (MMSE 21-25, CDR 1, Moderate dementia (MMSE 11-20, CDR 2), Severe dementia (MMSE 0-10, CDR 3); [2]Diagnostic criteria by Relkin et al. 2005 [13], from which the physiological criterion (IV) for probable iNPH was not included, as CSF opening pressure was measured only from patients going through infusion tests in our study population; [3]Diagnostic criteria by Relkin et al. 2005 [13]; [4]Worsening on hearing dimension of 15D one year after the shunting. [a]U-value in the Mann–Whitney U test; [b]Median score ;[c]25th and 75th percentile; [d]Fisher's Exact Test; [e]Positive discrepancy, patients who experienced at least a minimum clinically important improvement in HRQoL (15D score) while the iNPHGS score remained the same or increased (Δ15D score ≥ 0.015 and ΔINPHGS ≥ 0). ABBREVIATIONS: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, Health Related Quality of Life; iNPHGS, iNPH Grading Scale; BDI, Beck Depression Index; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; CSF, Cerebrospinal fluid; ICP, Intracranial pressure.

8 General Discussion

8.1 HRQOL AT BASELINE

To the best of our knowledge, ours is the largest published comparison of HRQoL between patients with iNPH and the general population (see section 2.9.4, Chapter 4, Table 12). Our results are in accordance with those of Petersen et al. (48), reporting the self-rated HRQoL to be impaired in patients with iNPH when compared to EQ-5D reference values from the general UK population (48). The model of HRQoL by Wilson and Cleary (32) (Figure 5) makes it easier to understand why iNPH has a considerable impact on self-rated HRQoL: Increased symptoms (more severe iNPH) (see chapter 4) lead to impaired functionality (48). This impaired functionality, together with individual factors such as depressive symptoms (34,41,202,203,208), has an effect on a person's perceptions of their health, and ultimately their HRQoL.

Depressive symptoms are significant and potentially treatable symptoms causing a deterioration in HRQoL in iNPH. While the impact of depressive symptoms on HRQoL in different neurodegenerative diseases is known (34,41,202,203,208) and their treatment is encouraged (269), there are only two sets of evidence-based guidelines on how these symptoms should be treated (270-272). Psychological and other non-pharmacological interventions can reduce depressive symptoms in people with dementia, but how psychological intervention should be performed is unclear (271). There is limited evidence supporting the use of antidepressant drugs to treat depressive symptoms in patients with dementia (272).

Another reason for impaired HRQoL iNPH patients is urinary incontinence (see section 2.3.3), which impairs self-rated HRQoL cross-culturally (273). If urinary incontinence remains problematic after CSF shunting, the management of urinary incontinence should be tailored according to the pathophysiology of the symptom (see section 2.3.3) (274). For example, if detrusor overactivity is present (see section 2.3.3), patients might benefit from bladder-relaxing drugs (274).

The more severe the iNPH-related symptoms were, the greater was the impairment of HRQoL (see Chapter 4). This finding indicates that the 15D can differentiate the health states of iNPH. Thus, the 15D is a potentially useful tool with which to evaluate HRQoL in patients with iNPH.

8.2 HRQOL OUTCOME

Less than half of the patients with iNPH in our material experienced a clinically significant, favorable HRQoL outcome one year after CSF shunting (see Chapter 5). Petersen et al. (48) reported much better HRQoL outcomes: in their study, self-rated HRQoL improved in 31/37 (86%) iNPH patients during a six-month follow-up. In two other studies on HRQoL in iNPH (14,46), a favorable HRQoL outcome was not reported (see Table 12). One reason for the difference may be the different follow-up times, as the positive response to a CSF shunt seems to decrease on average six months after the surgery (156). In our study, the HRQoL response to a CSF shunt decreased on average somewhere between three and 12 months after the surgery (see Figures 8 & 9, Table 14 - pages 42, 45 and 51). It could be argued that

because iNPH itself is a naturally progressing condition (8), and a significant proportion of patients with iNPH may also have other progressive neurodegenerative comorbidities (17,24,101,149), a gradual decrease in HRQoL during follow-up after CSF shunting is to be expected. Thus, HRQoL remaining on a stable level could be considered as a favorable HRQoL outcome in patients with iNPH.

On the other hand, the progression of HRQoL impairment during the natural course of memory disorder or in iNPH may vary, and HRQoL does not necessarily worsen, despite impaired cognition (40,213-215). The individual differences in HRQoL progression or the stability of HRQoL could partly be explained by different comorbidity burdens (see Table 1), lost insight (40,41,199,200) (see section 2.9.2), or by adaptation (199).

The absence of Aβ or HPτ pathology in the frontal cortical biopsy predicted a favorable HRQoL outcome one year after the shunting (Figure 9), which is in accordance with previous studies (13,17,24,26,27,29,149,150,171). Surprisingly (see Table 1), the body mass index also predicted a favorable HRQoL outcome, whereas comorbidity was not associated with the outcome. It is possible that the complications after surgery (see section 2.8.5) may be related to overweight (259) and thus explain the poorer outcome in those with a higher BMI.

The 15D instrument produced complimentary information on previously unknown complications: hearing loss following CSF shunting in patients with iNPH appears to be more common than previously thought. It has been suggested that post-operative changes in the cerebrospinal fluid hydrodynamics can cause hearing loss in some patients with NPH (254,255). For this reason, the patient's hearing should be objectively measured prior to and after CSF shunting.

8.3 HEALTH ECONOMICS

In comparison to the literature, it can be argued that our estimations of the speed at which iNPH progresses in treated patients might be too optimistic, as it is known that the proportion of patients who have a favorable outcome declines in a longer follow-up (see section 2.7). A slightly slower progression rate (-0.6%/month in the iNPH scale, range 0–100) can be calculated from a recent study investigating the natural course of iNPH using a disease-specific scale in untreated participants (8), while in our study, untreated iNPH patients deteriorated faster (-2.5% HRQoL/month on average). Our model is a rough generalization on the group level, and individual AUCs would potentially better represent the reality, as they allow the formation of unique HRQoL trajectories for each person

While Stein et al. (167) did not report an estimation of the QALY cost, Kameda et al. (235) concluded that CSF shunting is cost-effective, as in the first year after CSF shunting, the price for one QALY was at minimum USD 29,934 (~£22,400) (235), which is slightly higher than our estimation. The differences between studies are probably due to the differences in the progression rate in each model and how financial costs were calculated. With the limited evidence based on simulations using different utility estimates, CSF shunting in patients with iNPH might be cost-effective.

8.4 DISCREPANCIES BETWEEN PATIENT- AND CLINICIAN-REPORTED OUTCOME MEASURES

Some patients with iNPH who are treated with a CSF shunt do not experience a favorable self-rated HRQoL improvement, despite a favorable clinical outcome (23/141, 16%). In these cases, a patient usually has severe iNPH-related symptoms prior to the operation. It could be that factors related to the individual (32), such as unmet expectations, affect the HRQoL outcome, and may thus explain the conflict between ClinRO and PROM. It is also possible that if a certain stage of severity is reached in iNPH, small improvements in symptoms do not convert to improved functionality, and HRQoL thus remains unimproved (32).

Similarly, as HRQoL is a multidimensional concept (31,32), an unfortunate complication, such as hearing impairment following CSF shunting (260), despite otherwise improved functionality, might negate the HRQoL improvement. It could be argued that patients with a co-existing chronic pulmonary disorder or any non-metastatic cancer are similarly more likely to find themselves where they started in terms of HRQoL, as CSF shunting does not affect the severe generic HRQoL impairment caused by these comorbidities (268). The observed discrepancy between the ClinRO and PROM rationalizes, in its very essence, the use of both measurements and elucidates the limitations of using them alone (32-34,48,260,265).

An exciting finding was that neither the presence of Aβ or HPτ pathology in the frontal cortical biopsy (indicating the presence of comorbid AD pathology) nor a lower cognitive function increased the likelihood of the discrepancy. This supports previous studies, which have recommended the inclusion of PROs as a part of outcome evaluation, even in patients with cognitive impairment (33,34).

The ability of iNPH patients to sense a change in their HRQoL may differ from those suffering from AD or other neurodegenerative conditions (see sections 2.9.2, 2.9.4 & 2.9.5). It can be hypothesized that the physical symptoms present in iNPH could help a patient with cognitive impairment to differentiate his/her health states better than a patient with a mainly cognition impairing condition. (see sections 2.9.2, 2.9.4 & 2.9.5).

8.5 STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of this study include the large representative population samples of both people with iNPH and the general aged population. The drop-out rate was relatively low, and a sophisticated statistical method (MICE) indicated that it did not have an effect on our results. Due to the cross-sectional setting, we are unable to draw direct conclusions on the causal relationships between iNPH and CSF shunt outcomes. A proxy-rated HRQoL measure, non-operated control group, one-year cognitive evaluation, a more detailed neuropsychological test such as CERAD (40,275), and knowledge of the caregiver burden would have further strengthened the study.

The lack of universally agreed diagnostic criteria for iNPH may be seen as a limitation (2,9). A generic HRQoL measure with potentially lower sensitivity to detect a change in patients with cognitive impairment was used instead of a disease-specific HRQoL measure (33,34). There is a possibility of slight variation between physicians in the

usage of a clinician-rated iNPHGS scale. The significance of different radiological variables used in the diagnostics of iNPH was not evaluated.

For the pilot study regarding the health economics (see section 6), the HRQoL progression model did not take into account the rate of decline in HRQoL with age (246), the comorbidity burden, or the cognitive status of the affected. The rate of progression of HRQoL remained proportionally the same in our model, which is an unlikely scenario (8). One can suspect that at some point, the disease renders the functionality of a person to a state where normal activities of daily living become impossible, after which HRQoL, or other utility indicators, stagnate (235). The HRQoL progression model also assumes that all patients survive to the end of their average life expectancy, which clearly is not true. Similarly, the mortality was set as the same for treated and untreated patients, which can be questioned. The cost of CSF shunting is not uniformly based on the study population, and may not therefore be exactly correct. Due to the small sample size, short follow-up, and the potential selection bias, the presented results of this pilot study must be viewed with caution.

8.6 IMPLEMENTATION AND FUTURE PERSPECTIVES

This doctoral thesis study pinpointed some of the factors influencing and predicting HRQoL in persons with iNPH prior to and after treatment. Similarly, the thesis study eludicated the differences between and limitations of patient- and clinician-reported outcome measures, emphasizing the need to use them simultaneously.

While the concept of HRQoL has been of interest for decades (30,31), especially in AD (33-36), the role of HRQoL in iNPH (45-48,248,260) and the iNPH itself (2,9,10) (see sections 2.2, 2.6 and 2.8.2) are still defining themselves. One could presume that as such, HRQoL research in iNPH will be guided by the AD- and PD-related HRQoL literature and their guidelines, but the very conceptual characterization of HRQoL in iNPH needs to be determined by the persons with the condition and those investigating it.

Due to the late recognition of HRQoL tools (45-48,248,260) and the lack of literature and HRQoL guidelines, iNPH researchers are in an ambiguous position. This, however, creates a possibility to adapt the most recent HRQoL practices from the start. Nevertheless, bridging the scientific vacuum with the limited available information may be a tremendous task for researchers, as iNPH and HRQoL, both shrouded with uncertainties, await further research. We have aimed at transparency in the methods and documentation, so our findings can be applied in the future, regardless of the potentially resolved uncertainties.

In the light of the progressive nature of the condition (see section 2.7), those left untreated by surgery could potentially suffer from irreversible damage during a longer follow-up (8). Therefore, it can be argued that, for now, there can be no exclusion of persons with iNPH who are physically fit for the surgery (see section 2.8.2). Studies should not exclude patients on the basis of comorbidity, either, as it makes the generalization of the results to the aged population nearly impossible (see section 2.8.2). In the future, more uniform diagnostic criteria, as well as new specific and sensitive diagnostic tests and tools, are likely to be developed. Unification of the diagnostic criteria for iNPH is essential for

future iNPH research. Exclusion criteria for studies and clinical practice alike may hopefully be introduced based on the unified diagnostic criteria.

For future studies, it would be interesting to compare the observed HRQoL progression to other, objective outcome measures in a longer follow-up. The longer follow-up of treated iNPH patients might better elucidate the natural course of iNPH in terms of HRQoL, and shed light on how HRQoL progresses in different sub-groups and on the individual level. We have already planned a five-year follow-up for our study population. It is unlikely that the research community will obtain actual utility values from untreated patients in a prospective study setting with a longer follow-up, as there are ethical limitations to performing such a study (see sections 2.7 & 2.8.2).

While acknowledging the limitations above, this thesis demonstrates the severe impairment of HRQoL in patients with iNPH before and after CSF shunting (248,260). However, the life of a person with iNPH can be fulfilling and worth living, despite the HRQoL impairment (32,36). There are multiple theoretical ways in which the HRQoL of patients with iNPH can be improved (32,36) (see Figure 5). Improved HRQoL can be potentially obtained by increasing the functionality of a person with iNPH, for example providing gait and balance supports or improving access to treatment. An intervention changing the preferences and values of persons with iNPH could help them to adapt to the situation and thus improve their HRQoL (199). Linked to this, adequate treatment of depressive symptoms or apathy may improve HRQoL in patients with iNPH through a change in perspective, and relieving the HRQoL impairment caused by other coexisting conditions may similarly be beneficial (32,34,36,248). However, the extent to which and by what means the depressive symptoms or apathy can be relieved in persons with iNPH is beyond the scope of this thesis. Our results suggest that hearing should be measured objectively from iNPH patients prior to and after CSF shunt treatment.

In terms of HRQoL, the outcome of CSF shunting varies (46-48,260), and at worst, less than half of the persons with iNPH will experience subjective improvement. For most, HRQoL will remain the same or deteriorate (260). It could be that due to the varying progressive nature of the condition (7,8,131,155), a slower decline or stagnation of HRQoL impairment could be considered a favorable outcome (260). Clinicians and patients alike may have to accept the limited HRQoL improvement that the treatment provides, but should also acknowledge that even in the case of an unsatisfactory HRQoL outcome, a patient's condition could be significantly worse if left untreated. The outcome of CSF shunting may be different depending on the evaluation tools used and on who evaluates the outcome, and thus one can expect occasional discrepancies between PROMs and ClinROs (see sections 2.3.4 and 2.8.2). Acknowledging HRQoL as a multifactorial concept and recognizing the comorbidity burden and the severity of iNPH in the affected may help clinicians and persons with iNPH understand their different perceptions when evaluating the treatment outcome.

To help clinicians and researchers make informed decisions concerning the use of HRQoL instruments, the scientific community needs a prospective study on the priorities and preferences of HRQoL dimensions in persons with cognitive impairment, and a review study of both generic and disease-specific measurements used in the affected. To date, neither of these studies has been performed. Numerous generic HRQoL instruments have recently been presented and increasingly used in patients with cognitive impairment in various study settings (33) since the original critique of generic HRQoL instruments was

presented (37,38). In addition, the dimensions of HRQoL currently deemed to be important in cognitive impairment may have captured only a partial truth (33).

Due to the above-mentioned reasons, one could speculate that there will be updates to the existing dementia-specific HRQoL instruments and more interest in combining a generic HRQoL measure with a dementia-specific one in future studies. For this reason, iNPH studies should include both generic and dementia-specific HRQoL instruments for patients with iNPH (see section 2.9.4). It may be that HRQoL measurements with generic utility, such as the 15D, have the ability to capture changes in the health status associated with iNPH due to the physical symptoms, as in PD (see section 2.9.5). However, the stage of cognitive impairment, and its effect on HRQoL, must also be addressed in persons with iNPH (see section 2.9.4).

Missing data, such as that resulting from drop-outs, is an important source of bias in medical literature. It is still often ignored, and statistical analyses are carried out as complete case analyses without addressing whether or how data are missing (276,277). A systematic reason for the missing data, such as patients dropping out due to complications associated with the treatment, causes a flawed data set and produces biased results, regardless of the power of the study (number of participants) (276,277). It is, however, challenging to avoid missing data, and even more challenging to know whether the data are missing completely at random or if there is a systematic mechanism (277). There are several ways to handle missing data (277). One of these is multiple imputation (MI) (276-278), which was used in our study. While it is still uncommon, as the most common statistical software packages do not offer MI, its popularity is rapidly increasing (278). It is essential to emphasize the importance of addressing missing data, as well as the availability of freeware MI packages that have been published (253). The R code for this procedure is included in the appendices for future studies to consider (Appendix 4).

It can be hypothesized that as vascular risk factors may play a significant role in the pathophysiology of iNPH (2,13,28,70,111,119-122) (see section 2.5 etiology), their adequate treatment by medical and non-medical interventions could potentially prevent some cases of iNPH and thus lead to the avoidance of HRQoL impairment. However, as no studies regarding such interventions exist, one cannot know how many patients, if any, would potentially benefit from such interventions and what would be the cost-effectiveness of such life-long primary prevention. It would be interesting to investigate whether aggressive treatment of vascular risk factors in patients with asymptomatic ventriculomegaly (63,66) could prevent cases of iNPH. Likewise, the potential identification of genetic factors associated with iNPH (135) and their application to similar interventions would be exciting.

Assessment of HRQoL in persons with iNPH is challenging due to uncertainties regarding the natural course of the disease and the measurement issues in patients with cognitive impairment (see sections 2.7 and 2.9.2): should the patients be excluded from study if they reach a certain stage of cognitive impairment? What is the required cognition for self- and proxy-rated HRQoL measurements? Reports concerning the required cognitive function for PROMs are scarce (33,34). This challenge is further complicated by the attempt to control for all the HRQoL-influencing factors (32,36), which can be time- and resource-consuming. The author recommends the following for future iNPH HRQoL studies to consider (Table 26).

Table 26. Recommendations by the author.

No.	Topic	Recommendation
I.	HRQoL instrument	The use of AD-specific and generic HRQoL utility measurement due to the lack of a specific HRQoL measure for iNPH.
II.	HRQoL instrument	If we wish to design a HRQoL instrument specific for iNPH, we need the introduction of a conceptual HRQoL model based on preferences of the iNPH population acquired by quantitative and qualitative research methods. Before this, however, the very diagnostic concept of iNPH must be defined.
III	HRQoL measurement	The use of both self- and proxy evaluations of HRQoL.
IV.	Factors affecting HRQoL	Consideration of depressive symptoms (both in self- and proxy assessment of HRQoL).
V.	Factors affecting HRQoL	Consideration of cognitive impairment measured by a standardized instrument and estimation of its impact on self-evaluated HRQoL.
VI.	Factors affecting HRQoL	Consideration of the severity of iNPH-related symptoms (e.g. incontinence) and their effect on HRQoL.
VII.	Factors affecting HRQoL	Consideration of the performance of activities of daily living and its effect on self-evaluated HRQoL.
VIII.	Relationship between ClinRo and PROM	Inclusion of objective indicators of the outcome (for example, a gait assessment using electronic documentation devices attached to the patient) and investigating their relationship with the subjective outcome.
IX.	Generalization of the results/ Factors affecting HRQoL	Detailed documentation of the comorbidity burden of the study population and its inclusion in statistical analyses.
X.	Generalization of the results	Detailed documentation of diagnostic and exclusion criteria, as well as the prognostic tests used.
XI.	Avoidance of missing data	If possible, using live interviews or at least telephone interviews instead of mailed questionnaires to avoid missing data.
XII.	Handling of missing data	The use of MICE/MI or comparable methods for assessing the effect of missing data.

Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; HRQoL, health-related quality of life; PROM, patient-reported outcome measure; CLinRo, clinician-reported outcome measure; MICE, multiple imputation by chained equations; MI, multiple imputation; AD, Alzheimer's disease.

9 Conclusions

In conclusion:

I.
- i. The 15D instrument is a potentially reliable tool for measuring HRQoL in patients with iNPH.
- ii. The severity of iNPH and the severity of existing depressive symptoms predict HRQoL in persons with iNPH at baseline.
- iii. iNPH severely impairs the HRQoL of the affected when compared to the general population.

II.
- i. Less than half of patients with iNPH experience a clinically significant, favorable HRQoL outcome one year after CSF shunting.
- ii. The absence of Aβ and HPτ pathology in the frontal cortical biopsy and lower BMI predict a favorable HRQoL outcome one year after CSF shunting.
- iii. Hearing loss following CSF shunting in patients with iNPH appears to be more common than previously thought.

III.
- i. A small proportion of persons with iNPH who are treated with a CSF shunt do not experience a favorable HRQoL outcome, despite having a favorable clinical outcome (negative discrepancy).
- ii. More severe iNPH-related symptoms at baseline and co-existing chronic pulmonary disorder or the presence of cancer predict the negative discrepancy.
- iii. The absence of Aβ and HPτ pathology in the frontal cortical biopsy, or a better cognitive function, do not prevent the negative discrepancy.

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APPENDICES

Appendix 1. Diagnostic criteria for idiopathic normal pressure hydrocephalus (iNPH) according to the Japanese iNPH guidelines. Adapted from Mori et al. 2012.

POSSIBLE INPH		
Meets all of the following five features:	(1) Individuals who develop the symptoms in their 60s or older (2) More than one of the clinical triad: gait disturbance, cognitive impairment, and urinary incontinence. (3) Ventricular dilation (Evans' index > 0.3). (4) Above-mentioned clinical symptoms cannot be completely explained by other neurological or non-neurological diseases. (5) Preceding diseases possibly causing ventricular dilation are not obvious, including subarachnoid hemorrhage, meningitis, head injury, congenital hydrocephalus, and aqueductal stenosis.	
Possible iNPH supportive features	(a) Small stride, shuffle, instability during walking, and increase of instability on turning. (b) Symptoms progress slowly; however, sometimes an undulating course, including temporal discontinuation of development and exacerbation, is observed. (c) Gait disturbance is the most prevalent feature, followed by cognitive impairment and urinary incontinence. (d) Cognitive impairment is detected on cognitive tests (e) Sylvian fissures and basal cistern are usually enlarged. (f) Other neurological diseases, including Parkinson's disease, Alzheimer's disease, and cerebrovascular diseases, may coexist; however, all such diseases should be mild (g) Periventricular changes are not essential. (h) Measurement of CBF is useful for differentiation from other dementias.	
Possible iNPH with MRI support	Possible iNPH with MRI support indicates the condition fulfilling the requirements for possible iNPH, where MRI shows narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH). This class of diagnosis can be used in circumstances wherea CSF examination is not available, for example, in a population-based cohort study.	
PROBABLE INPH		
Meets all of the following three features	(1) Meets the requirements for possible iNPH.	
	(2) CSF pressure of 200 mmH_2O or less and normal CSF content	
	(3) One of the following three investigational features	(a) Neuroimaging features of narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface (DESH) under the presence of gait disturbance. (b) Improvement of symptoms after CSF tap test. (c) Improvement of symptoms after CSF drainage test
DEFINITE INPH	Improvement of symptoms after the shunt procedure.	

Abbreviations; CBF: cerebral blood flow, CSF: cerebrospinal fluid, DESH: disproportionately enlarged subarachnoid space hydrocephalus, MRI: magnetic resonance imaging

Appendix 2. Diagnostic classification of idiopathic normal pressure hydrocephalus (iNPH) according to the international iNPH guidelines. Adapted from Relkin et al. 2005.

PROBABLE INPH	**The diagnosis of probable iNPH is based on clinical history, brain imaging, physical findings, and physiological criteria.**
I. History	
Reported symptoms should be corroborated by an informant familiar with the patient's premorbid and current condition, and must include	a. Insidious onset (versus acute) b. Origin after age 40 yr c. A minimum duration of at least 3 to 6 months d. No evidence of an antecedent event such as head trauma, intracerebral hemorrhage, meningitis, or other known causes of secondary hydrocephalus e. Progression over time f. No other neurological, psychiatric, or general medical conditions that are sufficient to explain the presenting symptoms
II. Brain imaging	
A brain imaging study (CT or MRI) performed after onset of symptoms must show evidence of	a. Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evans' index > 0.3 or comparable measure) b. No macroscopic obstruction to CSF flow c. At least one of the following supportive features 1. Enlargement of the temporal horns of the lateral ventricles not entirely attributable to hippocampus atrophy 2. Callosal angle of 40 degrees or more 3. Evidence of altered brain water content, including periventricular signal changes on CT and MRI not attributable to microvascular ischemic changes or demyelination 4. An aqueductal or fourth ventricular flow void on MRI
Other brain imaging findings may be supportive of an iNPH diagnosis but are not required for a Probable designation	1. A brain imaging study performed before onset of symptoms showing smaller ventricular size or without evidence of hydrocephalus 2. Radionuclide cisternogram showing delayed clearance of radiotracer over the cerebral convexities after 48–72 h 3. Cine MRI study or other technique showing increased ventricular flow rate 4. A SPECT-acetazolamide challenge showing decreased periventricular perfusion that is not altered by acetazolamide

III. Clinical	By classic definitions (Fisher 1977, Hakim and Adams 1965), etc., findings of gait/balance disturbance must be present, plus at least one other area of impairment in cognition, urinary symptoms, or both.
With respect to gait/balance, at least two of the following should be present and not be entirely attributable to other conditions	a. Decreased step height b. Decreased step length c. Decreased cadence (speed of walking) d. Increased trunk sway during walking e. Widened standing base f. Toes turned outward on walking g. Retropulsion (spontaneous or provoked) h. En bloc turning (turning requiring three or more steps for 180 degrees) i. Impaired walking balance, as evidenced by two or more corrections out of eight steps on tandem gait testing
With respect to cognition, there must be documented impairment (adjusted for age and educational attainment) and/or decrease in performance on a cognitive screening instrument (such as the Mini Mental State Examination), or evidence of at least two of the following on examination that are not fully attributable to other conditions	a. Psychomotor slowing (increased response latency) b. Decreased fine motor speed c. Decreased fine motor accuracy d. Difficulty dividing or maintaining attention e. Impaired recall, especially for recent events f. Executive dysfunction, such as impairment in multistep procedures, working memory, formulation of abstractions/similarities, insight g. Behavioral or personality changes
To document symptoms in the domain of urinary continence, either one of the following should be present	a. Episodic or persistent urinary incontinence not attributable to primary urological disorders b. Perrsistent urinary incontinence c. Urinary and fecal incontinence Or any two of the following should be present: a. Urinary urgency as defined by frequent perception of a pressing need to void b. Urinary frequency as defined by more than six voiding episodes in an average 12-hour period despite normal fluid intake c. Nocturia as defined by the need to urinate more than two times in an average night
IV. Physiological	CSF opening pressure in the range of 5–18 mm Hg (or 70–245 mm H_2O) as determined by a lumbar puncture or a comparable procedure. Appropriately measured pressures that are significantly higher or

	lower than this range are not consistent with a probable iNPH diagnosis.
POSSIBLE INPH	A diagnosis of possible iNPH is based on historical, brain imaging, and clinical and physiological criteria
I. History	
Reported symptoms may	a. Have a subacute or indeterminate mode of onset b. Begin at any age after childhood c. May have less than 3 months or indeterminate duration d. May follow events such as mild head trauma, remote history of intracerebral hemorrhage, or childhood and adolescent meningitis or other conditions that in the jugment of the clinician are not likely to be causally related e. Coexist with other neurological, psychiatric, or general medical disorders but in the judgment of the clinician not be entirely attributable to these conditions f. Be nonprogressive or not clearly progressive
II. Brain imaging	
Ventricular enlargement consistent with hydrocephalus but associated with any of the following	a. Evidence of cerebral atrophy of sufficient severity to potentially explain ventricular size b. Structural lesions that may influence ventricular size
III. Clinical	
Symptoms of either	a. Incontinence and/or cognitive impairment in the absence of an observable gait or balance disturbance b. Gait disturbance or dementia alone
IV. Physiological	Opening pressure measurement not available or pressure outside the range required for probable iNPH
UNLIKELY INPH	1. No evidence of ventriculomegaly 2. Signs of increased intracranial pressure such as papilledema 3. No component of the clinical triad of iNPH is present 4. Symptoms explained by other causes (e.g. spinal stenosis)

Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; SPECT, single-photon emission computed tomography.

Appendix 3. The 15D questionnaire: a generic HRQoL utility measurement. Adapted from (49) 15D©/Harri Sintonen (www.15D-instrument.net).

QUALITY OF LIFE QUESTIONNAIRE (15D©)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes **your present health status**. Continue through all 15 questions in this manner, giving only **one** answer to each.

QUESTION 1. MOBILITY

1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION

1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING

1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING

1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible, even with full use of sleeping pills, or stay awake most of the night.

QUESTION 6. EATING

1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

1 ( ) I am able to speak normally, i.e. clearly, audibly, and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering, or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. EXCRETION

1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, freetime activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

1 ( ) I am able to think clearly and logically, and my memory functions well
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION

1 ( ) I do not feel at all sad, melancholic, or depressed.
2 ( ) I feel slightly sad, melancholic, or depressed.
3 ( ) I feel moderately sad, melancholic, or depressed.
4 ( ) I feel very sad, melancholic, or depressed.
5 ( ) I feel extremely sad, melancholic, or depressed.

QUESTION 13. DISTRESS

1 ( ) I do not feel at all anxious, stressed, or nervous.
2 ( ) I feel slightly anxious, stressed, or nervous.
3 ( ) I feel moderately anxious, stressed, or nervous.
4 ( ) I feel very anxious, stressed, or nervous.
5 ( ) I feel extremely anxious, stressed, or nervous.

QUESTION 14. VITALITY

1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired, or feeble.
3 ( ) I feel moderately weary, tired, or feeble.
4 ( ) I feel very weary, tired, or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired, or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY

1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.

3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

Appendix 4. R code to perform MI and logistic regression analysis using datasets with and without MI. R language and environment for statistical computing (R- 3.2.4 for Windows; R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). MI was used to investigate whether missing data had a significant effect on our results from logistic regression analysis, which was conducted to predict the HRQoL outcome 1 year after the installation of a CSF shunt.

```
#1. Setting up the working directory:
setwd("Z:/ file location ")

#2. Installing the required statistical packages
library (mice)
library (VIM)
library (lattice)
library(ggplot2)
library (MASS)
library (QuantPsyc)
library(aod)
library(epitools)
library(pastecs)
library(miceadds)
library (memisc)

#3. Setting up the data frame
data<-as.data.set(spss.system.file("Z://file location //file_name.sav"))
dat<-as.data.frame(data)

#4. Describing missing data
md.pattern(dat)

#5. Logistic regression without MI
mylogit<- glm(15D_outcome~ CACI_score_presunt + MMSE_presunt + abcense_of_any_amyloid_or_tau_pathology + BMI + existing_gait_apraxia,data=dat, family = "binomial")

#6. Multiple imputation
mi.dat<- mice(dat,m=50,maxit=20)

#7. Description and analysis of the MI dataset
mi.dat
head(mi.dat$15D_outcome)
bwplot(mi.dat)
densityplot(mi.dat)
summary(mi.dat)

#8. Investigating whether missing data had an effect on our regression analysis

fit<-with(mi.dat, glm(15D_outcome~ CACI_score_presunt + MMSE_presunt + abcense_of_any_amyloid_or_tau_pathology + BMI + existing_gait_apraxia,data=dat, family = "binomial")
fit
pooled<-pool(fit)
```

```
pooled
round(summary(pooled),3)
```

ANTTI JUNKKARI

Idiopathic normal pressure hydrocephalus (iNPH) is a progressive condition of the aged population. Cerebrospinal fluid (CSF) shunting remains the only available treatment for iNPH, relieving some of the symptoms in the majority of patients. Health-related quality of life (HRQoL) is relatively new concept and only little is known about the factors contributing to the HRQoL of patients with iNPH. This thesis is based on a unique prospective cohort study, describing factors affecting and predicting patient-reported HRQoL in patients with iNPH prior to and after CSF shunting.

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