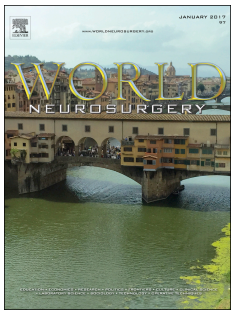
Accepted Manuscript



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

Junkkari Antti, Roine Risto P, Luikku Antti, Rauramaa Tuomas, Sintonen Harri, Nerg Ossi, Koivisto Anne M, Häyrinen Antti, Viinamäki Heimo, Soininen Hilkka, Jääskeläinen Juha E, Leinonen Ville

PII: S1878-8750(17)31480-8

DOI: 10.1016/j.wneu.2017.08.170

Reference: WNEU 6420

To appear in: *World Neurosurgery*

Please cite this article as: Antti J, Risto P R, Antti L, Tuomas R, Harri S, Ossi N, Anne M K, Antti H, Heimo V, Hilkka S, Juha E J, Ville L, Why does the health-related quality of life in idiopathic normal pressure hydrocephalus fail to improve despite the favorable clinical outcome?, *World Neurosurgery* (2017), doi: 10.1016/j.wneu.2017.08.170.

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

AUTHORS (12)
Junkkari, Antti* [a]; Roine, Risto P. [b,c]; Luikku, Antti [d]; Rauramaa, Tuomas [e]; Sintonen, Harri [f]; Nerg, Ossi [d]; Koivisto, Anne M. [d]; Häyrinen, Antti [a]; Viinamäki, Heimo [g]; Soininen, Hilkka [h]; Jääskeläinen, Juha E. [a]; Leinonen, Ville [a].

AFFILIATIONS
[a]Neurosurgery of NeuroCenter, Kuopio University Hospital and University of Eastern Finland, POB 100, 70029 Kuopio, Finland; [b]Research Centre for Comparative Effectiveness and Patient Safety, University of Eastern Finland, Kuopio, POB 1627, 70211 Kuopio,Finland; [c]Group Administration, Helsinki and Uusimaa Hospital District, HUS, POB 705, 00029 Helsinki, Finland; [d]Neurology of NeuroCenter, University of Eastern Finland and Kuopio University Hospital, POB 100, 70029 Kuopio, Finland;[e]Department of Pathology, Kuopio University Hospital and University of Eastern Finland, POB 100, 70029 Kuopio, Finland;[f]Department of Public Health, University of Helsinki, Mannerheimintie 172, 00014 Helsinki, Finland; [g]Department of Psychiatry, Kuopio University Hospital and University of Eastern Finland, POB 100, 70029 Kuopio, Finland ; [h]Department of Neurology, University of Eastern Finland, POB 1627, 70211 Kuopio, Finland.

*Corresponding author: *For quick contact: tel.+358400680368, Fax: +358-17-173-916, Email: antti.junkkari@kuh.fi.*

Highest academic degress and email addresses: Junkkari, Antti (MD, antti.junkkari@kuh.fi); Roine, Risto P. (MD PhD, risto.roine@uef.fi); Luikku, Antti (BM, antti.luikku@uef.fi); Rauramaa, Tuomas (MD PhD, tuomas.rauramaa@kuh.fi); Sintonen, Harri (PhD, harri.sintonen@helsinki.fi); Nerg, Ossi (MD, ossi.nerg@kuh.fi); Koivisto, Anne M. (MD PhD, anne.koivisto@kuh.fi); Häyrinen, Antti (BM, anthay@student.uef.fi); Viinamäki, Heimo. (MD PhD, heimo.viinamaki@kuh.fi); Soininen, Hilkka (MD PhD, hilkka.soininen@uef.fi); Jääskeläinen, Juha E. (MD PhD, juha.e.jaaskelainen@kuh.fi); Leinonen, Ville. (MD PhD, ville.leinonen@kuh.fi)

Manuscript in numbers: Manuscript Word count 2713; Abstract word count 250; 1 figure; 4 Tables. Supplementary material: 3 supplementary tables (Tables A.1, A.2 and A.3) and 1 supplementary figure (Fig A.1).

Key words (6): health-related quality of life, comorbidity, discrepancy, 15D, iNPHGS, normal pressure hydrocephalus, patient reported outcome

ABBREVIATIONS (24)

Abeta/Aβ	Amyloid-beta
AD	Alzheimer's disease
BDI	Beck Depression Inventory
BMI	Body mass index
CACI	Charlson Age Comorbidity Index
CDR	Clinical Dementia Rating
CI	Confidence interval
ClinRO	Clinician reported outcome
CSF	Cerebrospinal fluid
Hptau/HPт	Hyperphosphorylated tau
HRQoL	Health-Related Quality of Life
ICP	Intracranial pressure
iNPH	idiopathic Normal Pressure Hydrocephalus
iNPHGS	idiopathioc Normal Pressure Hydrocephalus Grading Scale
KUH	Kuopio University Hospital
MI	Multiple Imputation
MICE	Multiple Imputation by Chained Equations
MMSE	Mini-Mental State Examination
NA	Not applicable
OR	Odds ratio
pmm	Predictive mean matching
PRO	Patient Reported Outcome
sNPH	Secondary Normal Pressure Hydrocephalus
SPSS	Statistical Package for Social Sciences

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 disease-specific 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.

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.[1] The few studies conducted on this topic suggest that physicians tend to estimate the efficacy of treatment better than patients.[1-3] This might be due to the information asymmetries between the physician and the patient,[1, 2] unmet expectations,[3] or the 'response shift' phenomenon.[4] On the other hand, PRO's, such as Health-Related Quality of Life (HRQoL), may appreciate aspects not captured by ClinROs.[5-9]

Recently we published a prospective 1-year follow-up study of HRQoL outcome in patients with idiopathic normal-pressure hydrocephalus (iNPH),[9] a progressing condition of the elderly which characteristically impairs the gait, cognition and urinary continence of the affected.[10-12] The so far unknown origin has been contemplated to cause various abnormalities in the cerebral spinal fluid (CSF) physiology and hydrodynamics which ultimately lead to the symptoms and signs observed in patients with iNPH.[11,12] 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.[11,12] The only available treatment, the CSF shunt surgery, has been reported to relieve some of the symptoms in a majority of patients with iNPH.[13]

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.[7,8] 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.[7,8] 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.[7,8,14,15] Only little is known about HRQoL in iNPH,[9] and there are no guidelines for the measurement of HRQoL in iNPH.

In our study,[9] 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 1, Fig. A.1].

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 cognition impairment, depressive symptoms or neurodegenerative comorbidity.

MATERIALS AND METHODS

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) in computed tomography or magnetic resonance imaging.[11]

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 1). 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 1), the primary prospective 1-year follow-up study was performed with 189 participants, of whom 145 (77 %) completed the HRQoL follow-up (Figure 1).[9] Regarding this study population, the selection procedure for the CSF shunts has been described in detail previously.[9] Information on the CSF shunt types and prognostic tests used can be found from (Tables 1 and 2).

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 1). As a result, 141 participants were included in the analysis (Figure 1). 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 [Fig A.1, Tables 1 & 2] 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 1].

EVALUATION OF INPH SYMPTOMS AND THE CLINICAL OUTCOME MEASURE

To classify the triad of symptoms featuring iNPH (cognitive impairment, impaired gait and urinary disturbance) we used a modified Finnish version of the 12-point iNPH Grading Scale (iNPHGS),[16] which is a clinician-rated scale to separately assess the severity of each symptom with scoring based on observations by the physician and interviews with the patients or their caregivers.[16] Subscores for each dimension range from 0 to 4, with higher scores representing worse symptoms.[16] A minimum clinically important decrease in the iNPHGS score has been estimated to be one point.[17]

THE HRQOL INSTRUMENT

The generic HRQoL instrument used in our study, the 15D, contains 15 dimensions of health: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity.[18] Each dimension has five ordinal levels; one must choose the most suitable level portraying one's state of health at the moment.[18] The 15D instrument produces dimension level values and a single index score (15D score) by using set of population-based preference weights acquired from the Finnish population.[18] The 15D score that combines all the dimensions to one index on a 0 to 1 scale, with 0 referring to being dead and 1 being at full health.[18] The minimum clinically important change/difference in the 15D score has been estimated to be ≥ 0.015.[19]

CHARACTERISTICS AND COMORBIDITIES

Comorbidities and attributes were recorded from all the patients undergoing surgery in the KUH. The Charlson Age Comorbidity Index (CACI) was used to estimate the burden caused by coexisting conditions (Table 3).[20] CACI combines 19 medical conditions so that each comorbidity corresponds to a weighted number, a higher number representing greater burden.[20] By adding up all the numbers, and one point for each decade over the age of 40, a final CACI score can be calculated.[20]

EDUCATION

As the primary education in Finland lasts for nine years, patients were dichotomized according to the educational years achieved in life-time: those with nine years or less of education and to those with more.

BIOPSY PROCEDURE & IMMUNOHISTOCHEMISTRY

Preceding the insertion of the CSF shunt's ventricular catheter (approximately 3 cm from the midline and near to the coronal suture of the scalp), biopsy forceps or needle were used to retrieve one to three cylindrical cortical brain biopsies of 3– 7 mm in length and 2–5 mm in diameter. The details of the biopsy and its immunohistochemistry analysis have been previously described.[21, 22] From all samples, the cellular or neuritic immunoreactivity for amyloid-beta (Abeta) and hyperphosphorylated tau (HPtau) were evaluated by light microscopy and were graded as present or absent by a neuropathologist (Tables 1,2).[22] Patients were then further divided by the presence of pathology of any kind, the Abeta or HPtau observed in the frontal cortical biopsy.

COGNITIVE EVALUATION

Mini-Mental State Examination (MMSE) was used to evaluate patients' cognitive function.[23] MMSE ranges from 0 to 30, with higher scores representing better cognitive function.[23] The preoperative MMSE score was converted to dementia staging in accordance with the Clinical Dementia Rating (Table 2).[24]

ASSESSMENT OF DEPRESSIVE SYMPTOMS

Depressive symptoms were assessed with the self-administered 21-item Finnish version of the Beck Depression Inventory (BDI) (Table 3).[25] 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.[25] The gathering of BDI from all consecutive patients started first in January 2011, consequently, BDI data are missing from some patients.

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 (Table 4, Table A.1).[26] The potential effect of missing data on the regression results was estimated with multiple imputation by chained equations (Table 4, Table A.2).[27] Variables were included in the multivariate model if they reached a moderate tendency towards significance in univariate analyses ($p \leq 0.25$) (Table 4),[26] and those excluded were recorded (Table A.1). 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.

RESULTS

52 patients (37%) had inconsistency between their 1-year 15D and iNPHGS scores (Figure 1, Tables 1 and 2): 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 2). 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 (Fisher's exact test, p = 0.034, 41% vs 21%) than those without discrepancy (Table 3).

A secondary statistical analysis was performed for patients with positive discrepancy (Table A.3). 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 A.3).

REGRESSION ANALYSIS

Multivariate binary logistic regression analysis was performed with negative discrepancy (yes = 1, no = 0) as the dependent variable (Table 4). 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 4) 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.

DISCUSSION

LIMITATIONS AND GENERALISABILITY

There are no universally agreed diagnostic criteria for iNPH.[11,12] 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.[7,8] 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.

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.[3] As old patients affected by a condition with poor prognosis are at an increased risk for misunderstanding the goals of the treatment/study,[28] 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 may cause unimproved HRQoL despite of otherwise improved functionality and thus negate the favorable outcome.[9] It could be argued that similarly patients with co-existing chronic pulmonary disorder or any non-metastatic tumors 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.[29] These findings are in accordance with the conceptual model of HRQoL presented Wilson & Cleary,[30] 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.[30] 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.[5-9, 30]

An exciting finding was that neither the absence of Abeta and HPtau pathology in the frontal cortical biopsy (indicating the absence of comorbid Alzheimer's disease pathology, 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.[7, 8] 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[7, 8]. 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,[5,31] 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[32], and it detects health status changes in various surgical conditions, such as in spinal stenosis[33]. 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 1). These participants had less severe iNPHGS symptoms at baseline, but were otherwise very similar to the rest of the study population (Table A.3), suggesting that there might be psychological or nonmedical factors influencing the HRQoL outcome even though these attributes could not be captured by our study.[4,30] 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.[5] 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 Abeta and HPtau 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.

ACKNOWLEDGMENTS

We want to thank Tuomas Selander (Science Service Center of KUH) for providing statistical assistance and Marita Parviainen (Research Nurse) for collection of data and performing data entry.

COMPETING INTERESTS & STUDY FUNDING

Dr Sintonen has developed the 15D, which is a commercial product. Other authors report no disclosures. This study was sponsored by Kuopio University Hospital, State Research Funding (VTR Fund), University of Eastern Finland, Finnish Medical Foundation and Finnish Cultural Foundation.

REFERENCES

1. Mühlbacher AC, Juhnke C. Patient preferences versus physicians' judgement: does it make a difference in healthcare decision making?. *Appl Health Econ Health Policy*. 2013;11:163.

2. Carlson HA, Pellettieri L. Doctors' versus patients' evaluation of results after neurosurgery. *J Neurol Neurosurg Psychiatry*. 1989;52:153-5.

3. Lattig F, Grob D, Kleinstueck FS, Porchet F, Jeszenszky D, Bartanusz V,et al. Ratings of global outcome at the first post-operative assessment after spinal surgery: how often do the surgeon and patient agree?. *Eur Spine J.* 2009;18:386-94.

4. Schwartz CE, Finkelstein JA. Understanding inconsistencies in patient-reported outcomes after spine treatment: response shift phenomena. *Spine J.* 2009;9:1039-1045.

5. Petersen J, Hellström P, Wikkelsø C, Lundgren-Nilsson Å. Improvement in social function and health-related quality of life after shunt surgery for idiopathic normal-pressure hydrocephalus. *J Neurosurg*. 2014;121:776-784.

6. Spinou A, Fragkos KC, Lee KK, Elston C, Siegert RJ, Loebinger MR, et al. The validity of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. *Thorax*. 2016;71:683-694.

7. Banerjee S, Samsi K, Petrie CD, Alvir J, Treglia M, Schwam EM, et al. What do we know about quality of life in dementia? A review of the emerging evidence on the predictive and explanatory value of disease specific measures of health related quality of life in people with dementia. *Int J Geriatr Psychiatry*. 2009;24:15-24.

8. Bowling A, Rowe G, Adams S, Sands P, Samsi K, Crane M, et al. Quality of life in dementia: a systematically conducted narrative review of dementia-specific measurement scales. *Aging Ment Health*. 2015;19:13-31.

9. Junkkari A, Häyrinen A, Rauramaa T, Sintonen H, Nerg O, Koivisto AM, et al. Health-related quality-of-life outcome in patients with idiopathic normal-pressure hydrocephalus–a 1-year follow-up study. *Eur J Neurol.* 2017;24:58-66.

10. Andrén K, Wikkelsø C, Tisell M, Hellström P. Natural course of idiopathic normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry.* 2014;85:806-810.

11. Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, et al. Guidelines for management of idiopathic normal pressure hydrocephalus. *Neurol Med Chir (Tokyo)*. 2012;52:775-809.

12. Relkin N, Marmarou A, Klinge P, Bergsneider M, Black PM. Diagnosing idiopathic normal-pressure hydrocephalus. *Neurosurgery*. 2005;57:S4-S16.

13. Kazui H, Miyajima M, Mori E, Ishikawa M, SINPHONI-2 Investigators. Lumboperitoneal shunt surgery for idiopathic normal pressure hydrocephalus (SINPHONI-2): an open-label randomised trial. *Lancet Neurol*. 2015;14:585-594.

14. Perales J, Cosco TD, Stephan BC, Haro JM, Brayne C. Health-related quality-of-life instruments for Alzheimer's disease and mixed dementia. *Int Psychogeriatr*. 2013;25:691-706.

15. Missotten P, Dupuis G, Adam S. Dementia-specific quality of life instruments: a conceptual analysis. *Int Psychogeriatr*. 2016;28:1245-1262.

16. Kubo Y, Kazui H, Yoshida T, Kito Y, Kimura N, Tokunaga H, et al. Validation of grading scale for evaluating symptoms of idiopathic normal-pressure hydrocephalus. *Dement Geriatr Cogn Disord*. 2008;25:37-45.

17. Kanno S, Saito M, Kashinoura T, Nishio Y, Iizuka O, Kikuchi H, et al. A change in brain white matter after shunt surgery in idiopathic normal pressure hydrocephalus: a tract-based spatial statistics study. *Fluids Barriers CNS*. 2017;14:1. https://doi.org/10.1186/s12987-016-0048-8.

18. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. *Ann Med.* 2001;33:328-336.

19. Alanne S, Roine RP, Räsänen P, Vainiola T, Sintonen H. Estimating the minimum important change in the 15D scores. *Qual Life Res*. 2015;24:599-606.

20. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47:1245-1251.

21. Koivisto AM, Alafuzoff I, Savolainen S, Sutela A, Rummukainen J, Kurki M, et al. Poor cognitive outcome in shunt-responsive idiopathic normal pressure hydrocephalus. *Neurosurgery.* 2012;72:1-8.

22. Seppälä TT, Nerg O, Koivisto AM, Rummukainen J, Puli L, Zetterberg H, et al. CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings. *Neurology*. 2012;78:1568-1575.

23. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.

24. Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. Mapping scores onto stages: mini-mental state examination and clinical dementia rating. *Am J Geriatr Psychiatry.* 2006;14:139-144.

25. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561-571.

26. Stoltzfus JC. Logistic regression: a brief primer. *Acad Emerg Med*. 2011;18:1099-1104.

27. Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Stat Softw*. 2011;45.

28. Lidz CW, Appelbaum PS. The therapeutic misconception: problems and solutions. *Med Care*. 2002;40:V55-56.

29. Peters E, Schulz LM, Reuss-Borst M. Quality of life after cancer—How the extent of impairment is influenced by patient characteristics. *BMC cancer*. 2016;16:787.

30. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. *JAMA*. 1995;273:59-65.

31. Meier U, Stengel D, Muller C, Fritsch MJ, Kehler U, Langer N, et al. Predictors of subsequent overdrainage and clinical outcomes after ventriculoperitoneal shunting for idiopathic normal pressure hydrocephalus. *Neurosurgery*. 2013;73:1054-1060.

32. Martinez-Martin P, Jeukens-Visser M, Lyons KE, Rodriguez-Blazquez C, Selai C, Siderowf A, et al. Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. *Mov Disord*. 2011;26:2371-2380.

33. Räsänen P, Ohman J, Sintonen H, Ryynänen OP, Koivisto AM, Blom M, et al. Cost-utility analysis of routine neurosurgical spinal surgery. *J Neurosurg Spine*. 2006;5:204-209.

FIGURE LEGENDS

FIGURE 1. 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[12]; CSF, Cerebrospinal fluid.

APPENDIX

FIG A.1.

LEGEND: Title: 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.

TABLE 1. 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*	62	44	
Favorable INPHGS outcome[†]	68	48	
Discrepancy	52	37	
Negative discrepancy[‡]	29	21	
Positive discrepancy[§]	23	16	
Comorbidity			
Comorbidity burden (Median CACI score)	5	4,7[‖]	
Histology in frontal cortical biopsy			
Aβ - and HPт –	68	48	
Aβ + and HPт -	49	36	
Aβ + and HPт+	20	15	
Aβ - and HPт +	1	1	
Biopsy/staining unsuccessful	*3*		
Grouping for statistical analyses: Absence of Aβ or HPт found in the frontal cortical biopsy	68	49	138
INPH probability[¶] (modified criteria)			
Probable iNPH	129	92	
Possible iNPH	12	8	
Unlikely iNPH	0	0	
INPH probability[#] (unmodified criteria)			
Probable iNPH	33	23	
Possible iNPH	108	77	
Unlikely iNPH			
Types of valves used in the study population**			
PS Medical (Medtronic) Strata***	138	98	
PS Medical (Medtronic) Delta****	3	2	
CSF shunt location			
Ventriculo-peritoneal shunt	140	99	
Ventriculo-atrial shunt	1	1	

LEGEND: *Favorable HRQoL outcome, Positive and clinically important change in HRQoL (∆15D score ≥ 0.015); [†]Favorable INPHGS outcome, Severity of iNPH symptoms relieved (iNPHGS decreased at least 1 point); [‡]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 (∆15D score < 0.015 and ∆INPHGS ≤ -1); [§]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); [‖]25th and 75th percentile; [¶]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; [#]Diagnostic criteria by Relkin et al. 2005[12]; **All including a siphon-control device; ***Adjustable pressure setting, initial pressure setting set at 1.5 performance level of the valve; ****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.

TABLE 2. Comparison between the participants with and without negative discrepancy*

	141 STUDY PARTICIPANTS WITH BOTH 15D AND INPHGS OUTCOMES						COMPARISONS	
VARIABLES	29 Patients with negative discrepancy*			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 ‡						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 HPт found in the frontal cortical biopsy	13	45		55	49	109		0.678§
Comorbidity burden (Median CACI score)	6‖	5,8¶		5‖	4,7¶		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§
Sex (Female)	15	52		50	45			0.535§
Diagnostics								
INPH probability # (modified criteria)								0.127§
Probable iNPH	29	100		100	89			
Possible iNPH	0	0		12	11			
INPH probability** (unmodified criteria)								0.624§
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§
CSF tap & Infusion –tests	7	25		26	24			1.000§
CSF tap & Infusion -tests & ICP-monitoring	1	4		4	4			1.000§
ICP -monitoring	7	25		25	23			0.808§
Potential outcome modifying follow-up factors								
Subjective hearing impairment after shunting***	12	41		23	21			**0.029**§
Surgical complications (revision)	3	10		9	7.1			0.712§
CSF shunt valve settings adjusted externally during the follow-up	11	38		42	38			1.000§
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. *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). †U-value in the Mann–Whitney U test; ‡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); [§]Fisher's Exact Test; [ll]Median score ; [¶]25th and 75th percentile; [#]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; **Diagnostic criteria by Relkin et al. 2005[12]; ***Worsening of hearing-dimension of 15D one year after the shunting. 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.

TABLE 3**.** Charlson age-comorbidity index (CACI) of the study population

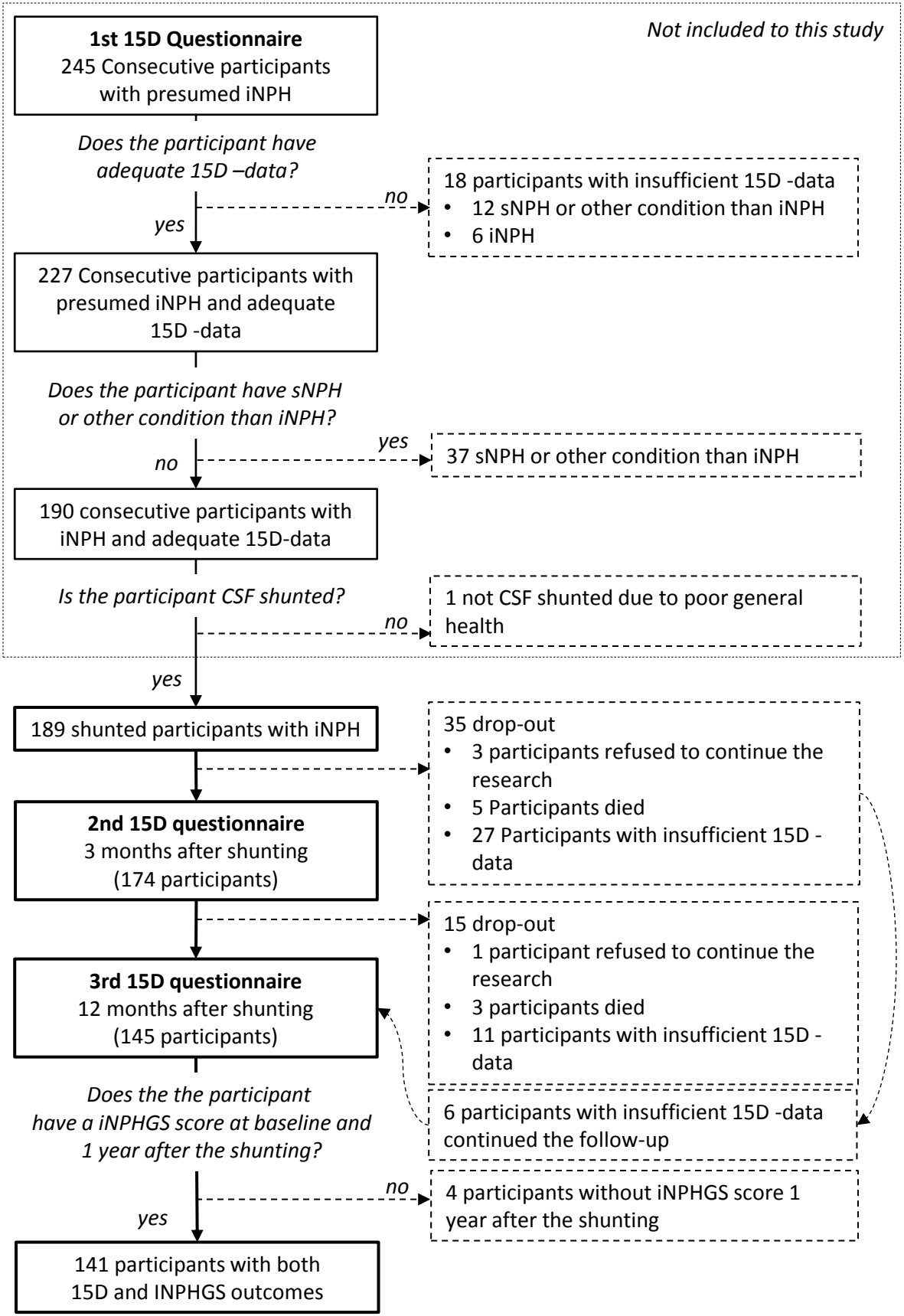
Weight	Comorbid condition	29 Patients with negative discrepancy*		112 Patients without negative discrepancy		Comparisons (Fisher's exact test)
		N	%	N	%	p-value
6	Acquired immune deficiency syndrome	0	0	0	0	N/A
	Metastatic solid tumor	1	3	1	1	0.370
3	Moderate or severe liver disease	0	0	0	0	N/A
2	Any 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.*a failure to show at least minimum clinically important improvement in HRQoL (15D) while having at least minimum clinically important improvement in the iNPHGS (∆15D score < 0.015 and ∆INPHGS ≤ -1). ABBREVIATIONS: N/A, not applicable.

TABLE 4. 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*	NA	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*	NA	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*	NA	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*	NA	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*	NA	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*	NA	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*	NA	-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*	NA	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*	NA	-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.*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; NA, not applicable.


Not included to this study
1st 15D Questionnaire
245 Consecutive participants with presumed iNPH
Does the participant have adequate 15D –data?
no
18 participants with insufficient 15D -data
• 12 sNPH or other condition than iNPH
• 6 iNPH
yes
227 Consecutive participants with presumed iNPH and adequate 15D -data
Does the participant have sNPH or other condition than iNPH?
yes
37 sNPH or other condition than iNPH
no
190 consecutive participants with iNPH and adequate 15D-data
Is the participant CSF shunted?
1 not CSF shunted due to poor general health
no
yes
189 shunted participants with iNPH
35 drop-out
• 3 participants refused to continue the research
• 5 Participants died
• 27 Participants with insufficient 15D -data
2nd 15D questionnaire
3 months after shunting
(174 participants)
15 drop-out
• 1 participant refused to continue the research
• 3 participants died
• 11 participants with insufficient 15D -data
3rd 15D questionnaire
12 months after shunting
(145 participants)
6 participants with insufficient 15D -data continued the follow-up
Does the the participant have a iNPHGS score at baseline and 1 year after the shunting?
no
4 participants without iNPHGS score 1 year after the shunting
yes
141 participants with both 15D and INPHGS outcomes

Highlights

(i) Worse starting point predicts negative discrepancy between PRO and CliNRO
(ii) Certain comorbidities may negate the clinical response in terms of HRQoL
(iii) Absence of AD pathology does not protect from the negative discrepancy
(iv) Better cognitive function does not protect from the negative discrepancy
(v) PROs should be a part of outcome evaluation in patients with cognition impairment

Dr Sintonen has developed the 15D, which is a commercial product. Other authors report no disclosures.